



Review

Underneath the Gut–Brain Axis in IBD—Evidence of the Non-Obvious

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Abstract: The gut–brain axis (GBA) plays a pivotal role in human health and wellness by orchestrating complex bidirectional regulation and influencing numerous critical processes within the body. Over the past decade, research has increasingly focused on the GBA in the context of inflammatory bowel disease (IBD). Beyond its well-documented effects on the GBA–enteric nervous system and vagus nerve dysregulation, and gut microbiota misbalance—IBD also leads to impairments in the metabolic and cellular functions: metabolic dysregulation, mitochondrial dysfunction, cationic transport, and cytoskeleton dysregulation. These systemic effects are currently underexplored in relation to the GBA; however, they are crucial for the nervous system cells' functioning. This review summarizes the studies on the particular mechanisms of metabolic dysregulation, mitochondrial dysfunction, cationic transport, and cytoskeleton impairments in IBD. Understanding the involvement of these processes in the GBA may help find new therapeutic targets and develop systemic approaches to improve the quality of life in IBD patients.

Keywords: gut–brain axis; IBD; inflammation; metabolome; lipidome; mitochondrial function; cationic transport; cytoskeleton



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1. Introduction: The GBA Imbalance in IBD

The gut–brain axis (GBA) is a complex and bidirectional communication system driven by neural, hormonal, metabolic, immunological, and microbial signals, playing a crucial role in linking the state of the gastrointestinal tract with neural functions. The GBA can influence intestinal motility and secretion, cause visceral hypersensitivity, and induce cell modifications in the enteroendocrine and immune systems [1,2]. Numerous neurological disorders have been shown to be associated with changes in gut health [3,4]. Systematic data have shown that both brain–gut and gut–brain dysfunctions occur, with the former being particularly dominant in irritable bowel syndrome [5]. In patients with inflammatory bowel diseases (IBDs), the quality of life is significantly reduced, and eating behaviors and nutritional patterns often undergo inevitable changes [6,7]. IBD is characterized by chronic inflammation of the gastrointestinal tract, encompassing Crohn's disease and ulcerative colitis, which are differentiated by the location of the lesions. Crohn's disease is marked by inflammation and lesions along the entire length of the gastrointestinal tract, predominantly in the terminal ileum and proximal colon [8], whereas ulcerative colitis mainly affects the colon and rectum [9]. Regardless of injury location, both diseases share common symptoms: persistent diarrhea, abdominal pain, blood in stools, weight loss, and chronic fatigue [8,10]. Various factors contribute to the development of IBD: genetic predispositions (with several hundred associated genes identified [11–18]), immune response dysregulation [19–22], impaired intestinal microbiota (due to antibacterial and other drug administrations or

specific dietary patterns) [23–25], and changes in environmental factors (such as nutrition, stress, toxins, etc.) [26]. IBD is a serious global issue, as the number of diagnosed patients continues to rise [27–29]. Increasing evidence suggests a connection between IBD and neuroinflammatory as well as neurodegenerative diseases [30,31]. According to the meta-analysis results published in 2024, IBD is moderately associated with an increased risk of stroke, dementia of various etiologies, and Parkinson’s disease [32]. In addition, the risk for the development of depression and anxiety in patients and animal models with IBD has been found higher compared to the general population, and stress is a significant trigger that causes exacerbation of the disease [33,34]. Moreover, IBD-related negative effects including intestinal inflammation, dysbiosis, poor nutrition, physical and psychological discomfort, chronic fatigue, and stress are frequently self-reinforcing due to the GBA imbalance resulting from IBD [34–36].

1.1. The Current Gut–Brain Axis Paradigm

The GBA commonly accepted key components include the vagus nerve, the enteric nervous system (ENS), and the gut microbiota. The vagus nerve serves as the primary neural pathway connecting the gut and the brain, comprising sensory and motor fibers that facilitate bidirectional communication [37]. Sensory fibers transmit impulses from the gut to the brain, relaying signals related to satiety, nutrient availability, and gastrointestinal discomfort, while motor fibers convey instructions from the brain to modulate gut functions such as gastric secretion and motility [38]. This bidirectional communication ensures continuous feedback and regulation between the gut and the brain. The ENS is an extensive network of intrinsic neurons throughout the gastrointestinal tract, functioning independently of the central nervous system (CNS) and regulating essential gastrointestinal processes, including peristalsis, nutrient absorption, and gut motility [39]. Although numerous studies highlight the evident disruption of vagus nerve and ENS functions in IBD [40–42], the underlying molecular and cellular processes, as well as the involved signaling triggers, remain underexplored. In the following sections, we describe the relevant data on the processes significantly disrupted in IBD that have yet to be investigated in the context of GBA dysregulation. These underexplored areas may hold the key to understanding the intricate mechanisms linking gut and brain health in IBD.

The gut microbiota, a diverse community of microorganisms within the gastrointestinal tract, plays beneficial roles in metabolism, vitamin and essential metabolite synthesis, and pathogen inhibition [43–45]. As the result of inflammation in IBD, as a consequence of specific IBD treatments, gut microbiota undergoes dramatic changes, observed in both patients and animal models [46,47]. An imbalance in the gut microbiota reflected in the disproportion between pathogenic and symbiotic bacteria may occur in addition to the loss of bacterial diversity calling dysbiosis. Dysbiosis, through effects on certain cytokines like tumor necrosis factor, interleukin 6, and interleukin beta, can induce an inflammatory process associated with an increase in the permeability of the intestinal barrier due to the depletion of apical junction complexes’ (AJCs) proteins [48–50]. Animal and human studies have shown that dysbiosis can affect the onset and progression of IBD, as well as autism, diabetes, Alzheimer’s, and Parkinson’s diseases [51–57]. Animal studies have shown that microbiota can significantly impact brain function and behavior, with “germ-free” mice displaying deviations in brain volume, myelination, as well as CNS deficits, such as anxiety-like behaviors, memory and sociability impairments, and depressive symptoms [58–60]. Both animal and human studies demonstrate that individuals with depression often present a microbial imbalance characterized by reduced microbial abundance and species diversity. It has been demonstrated that the transfer of microbiota from patients with depression to rats induces depression-like behavior along with alterations in tryptophan metabolism in the recipient animals [61]. In another experiment involving the transfer of microbiota from patients to “germ-free” mice, not only were neurobehavioral changes observed, but there was also evidence of shifts in metabolic regulation [62]. Changes in the microbiota composition have been observed in patients with autism, and the ability of fecal super-

nant from autism spectrum disorder patients to induce gastrointestinal epithelium and ENS malfunctions in mice has also been demonstrated [63,64]. Therefore, symbiotic and pathogenic microbiota can also be involved in the GBA by producing biologically active metabolites: short-chain fatty acids and their precursors, particular neurotransmitters, and a variety of signaling molecules that can influence neural activity, immune response, as well as other physiological processes within the host organism [65,66]. In this review, we compile evidence regarding the currently underrated processes through which microbiota may contribute to the GBA imbalance in the course of IBD pathogenesis.

1.2. Diet Effects and Food Behavior in IBD

Studies exploring the involvement of diet in IBD patients have uncovered a significant impact of dietary preferences and food behavior both on neural functions and IBD progression. IBD patients with high food involvement tend to seek pleasurable food; however, individuals with high health engagement levels have a better emotional state and demonstrate lower hospitalization rates and relapses [7,67]. At the same time, avoidant eating behaviors common in IBD patients pose a high risk of avoidant/restrictive food intake disorder (ARFID). This, along with impaired absorption of nutrients in IBD, can result in supplemental deficits, digestive malfunction, and metabolic dysregulation [68]. Murine studies have found dietary effects on intestinal microbial diversity associated with changes in cognitive ability and behavior [69–71] and similar observations have been made in human studies [72,73]. Specific dietary schemes are now widely discussed as an approach to ameliorate mental health, with growing evidence from preclinical and clinical studies of the dietary impact on neurologic and psychiatric disorders, including neuroinflammation, cognitive decline, depression, autism spectrum disorder, epilepsy, Alzheimer's, and Parkinson's diseases [74,75].

Thus, the interrelation between gut microbiota, diet, and metabolism represents a finely balanced equilibrium that not only plays an essential role in the overall health but also in brain physiology, influencing behavior and mental health. In IBD, this equilibrium is inevitably imbalanced, along with chronic and recurrent inflammatory processes. Together, these factors lead to malfunctions of fundamental cellular mechanisms such as metabolic homeostasis, ion transport, and cytoskeletal and mitochondrial functions. In turn, these profound changes make IBD difficult to treat and cause associated disease complications, substantially involving GBA dysregulation [76,77]. The GBA in IBD has been the focus of recent research, with accumulating data on the impact of main IBD-related processes on the GBA, including inflammation, microbiome, and vagus nerve and ENS functions. At the same time, cellular and molecular processes essential for nervous system function that are impaired in IBD remain largely unexplored.

The purpose of this review is to summarize research data on metabolic homeostasis, mitochondrial function, ion transport, and cytoskeleton function involvement in IBD-related pathological processes concerning GBA imbalance (Figure 1) and consider in detail the possible pathways and cellular and molecular mechanisms that link these effects to each other, leading to the self-exacerbation of the negative effects of IBD. This review intends to put a research focus on these currently underexplored areas in regard to GBA. We believe that elucidating the role of these mechanisms in the GBA could open prospects for new systemic therapeutic approaches in IBD.

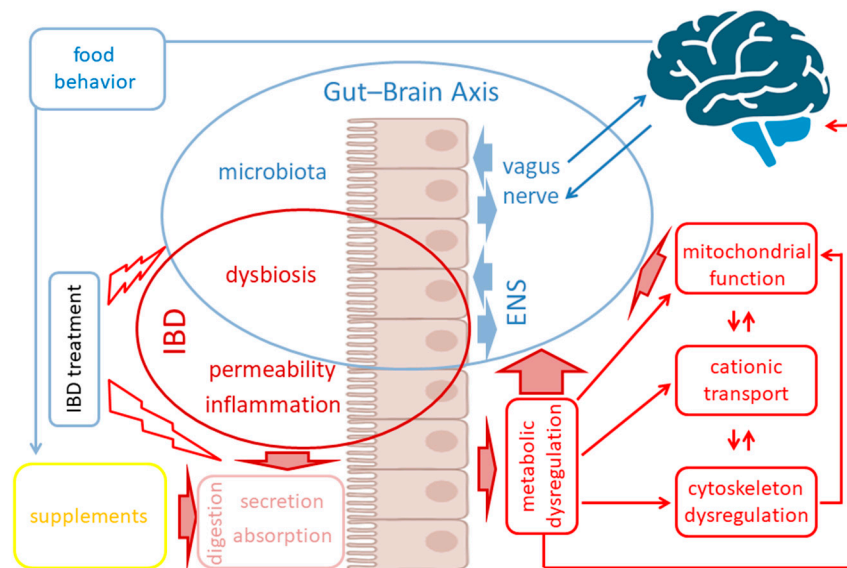


Figure 1. Schematic overview of metabolic dysregulation, mitochondrial function, cationic transport, and cytoskeletal dysregulation roles within GBA imbalance in IBD pathogenesis. Blue arrows indicate normal interactions; red arrows and broken arrows indicate negative effects of IBD-related processes and IBD treatment, accordingly.

2. Metabolic Dysregulation

In IBD patients, significant alterations in metabolic processes and pathways are commonly observed [78–80]. Metabolic profiling is currently being explored as a method for early identification of IBD [79–81]. Specific interrelationships have been established between changes in metabolite levels in IBD and the induction and development of immune responses, oxidative process dysregulation, mitochondrial malfunction [82–85], and remarkable lipidome deregulation [86,87]. In animal models of colitis, mass spectrometry assays have also revealed substantially altered lipid ratios and levels of enzymes that regulate major metabolic signaling cascades, including oxidative stress, β -oxidation, glycolysis, and the citric acid cycle [88–92] (Figure 2a). The lipidome homeostasis is fundamental to neural cell function and the nervous system makes great use of all classes of lipids (fatty acids, triglycerides, phospholipids, sterol lipids, and sphingolipids) and also contains the greatest proportion of lipids in the human body [93]. Lipids also play a key role in maintaining total metabolic homeostasis through cellular processes mediated by leukotriene, prostanoid, and endocannabinoid signaling; they also attenuate inflammation, regulate metabolic diseases, and control physiological processes [94–98]. The involvement of fatty acids and their derivatives in intracellular signaling is well documented [99–101]. Since phospholipids are main structural components of cellular and organelle membranes, dysregulation of the lipidome may contribute to mitochondrial dysfunction via membrane structure impairments [102–104]. Transmembrane proteins' conformation and functionality, including receptors and ion channels', are also highly dependent on membrane lipid composition [104,105]. Therefore, regarding metabolic dysregulation in IBD, the lipidome imbalance may play a key role in GBA dysregulation (Figure 2b). Despite the critical role of lipid metabolism and energy homeostasis in neural functions, the involvement of these processes in GBA dysregulation in IBD remains poorly understood.

2.1. PUFAs' Role and Therapeutic Potential in GBA Balance Restoration in IBD

Among major classes of lipids in CNS, polyunsaturated fatty acids (PUFAs) have the most well-defined regulatory role. n-3 PUFAs have been shown to be a limiting factor for proper neurodevelopment during the perinatal period [106]. PUFAs are implicated in neuronal signaling, neurogenesis control, vesicular processes, and central glucose homeostasis and are known for their ability to affect the mood and cognition [101,107]. Neural

tissue is enriched with two major PUFAs, arachidonic acid and docosahexaenoic acid, which are crucial for brain development and neural functions [108–110]. PUFAs' primary targets are fatty acid-activated receptors, the most studied of which are the peroxisome proliferator-activated receptors (PPARs). PPAR β and PPAR δ in the brain have been shown to regulate inflammatory responses and fatty acid metabolism [111]. PUFAs' involvement is also known in multiple distinct signaling pathways in neural cells. Anandamide and 2-arachidonoylglycerol, the arachidonic acid derivatives, are the major forms of endocannabinoids in the brain and are known to bind to cannabinoid receptor types 1 and 2 both in neuronal and glial cells to suppress neurotransmitter release [112,113]. This has been shown to mediate short-term synaptic plasticity and long-term depression in excitatory and inhibitory synapses [114]. A relationship between n-3 PUFAs and the gut microbiota has been shown: n-3 PUFAs intake alters the abundance and species composition of the microbiome. An imbalanced consumption of n-3/n-6 PUFAs in the diet can induce dysbiosis, in particular a significant increase in the *Firmicutes*/*Bacteroidetes* ratio, which was shown to be associated with metabolic imbalance [115]. An n-3 PUFA deficit has been shown to impair the microbiota composition in metabolic disorders. Conversely, the gut microbiota can also significantly affect the metabolism and absorption of PUFAs [116].

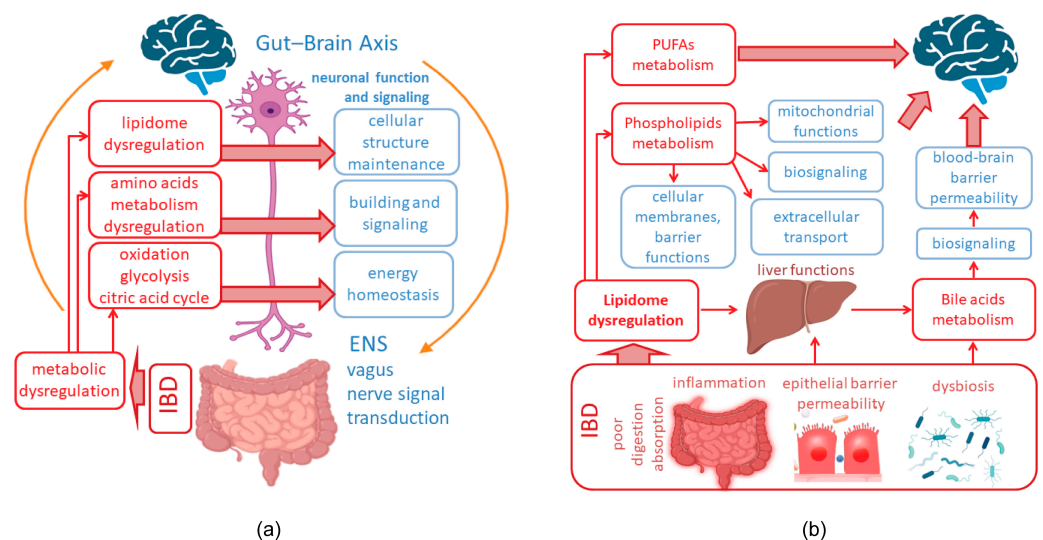


Figure 2. Schematic overview of mechanisms of metabolic dysregulation impact on GBA functions in IBD. **(a)** Schematic presentation of IBD-induced metabolic dysregulation effects on neural cells' functions and signaling within GBA. Red boxes indicate metabolic processes found impaired in IBD; blue boxes indicate neural cellular functions subject to metabolic dysregulation effects; red arrows indicate negative effects of IBD-related processes; **(b)** Schematic presentation of IBD-related lipidome dysregulation effects on cellular and organelle membranes and functions; biosignaling processes; and extracellular transport and blood-brain barrier permeability. Red boxes indicate classes of compounds whose metabolism is impaired in IBD; blue boxes indicate cellular functions subject to the corresponding lipidome dysregulation effects; red arrows indicate negative effects of lipidome dysregulation.

The beneficial effects of PUFAs on the GBA balance have been demonstrated in both murine models and clinical trials, leading to their consideration as a supportive supplement in the complex therapy of neuropsychiatric pathologies [117,118]. In IBD, the anti-inflammatory effects of PUFAs have been observed in murine colitis models [119–121], along with a preventive effect on liver inflammation and oxidative stress [120,122]. However, clinical studies on the effects of PUFAs intake in IBD have produced contradictory results [123,124]. PUFAs likely exert an indirect regulatory effect on IBD-related processes [125] and are possibly involved in the complex regulation of lipid homeostasis. Thus, PUFAs have been shown to downregulate Sterol Regulatory Element Binding Protein 1

(SREBP1) activity, which is a crucial actor in mitochondrial lipogenesis [126]. Studying specific PUFA supplements that may benefit GBA in IBD and understanding the involved regulatory pathways appear to be a promising direction for the research and therapeutic implication.

2.2. Phospholipid Involvement in GBA Misbalance in IBD

Lipidome dysregulation can lead to cellular membrane damage, as well as significant changes in crucial cell signaling, excitotoxicity due to excitatory amino acid production rise, and increased apoptosis [94]. A growing body of evidence highlights the importance of phospholipid (PL) metabolism dysregulation in the pathological changes associated with neuronal functions [127,128]. Dysregulation of PL metabolism is implicated in Alzheimer's and Parkinson's diseases, as well as other neural pathologies [102,129]. At the same time, PL play a significant role in the pathological processes related to IBD [130]. Inflammation-induced cell membrane destruction, a common trait of IBD, can affect both enterocytes and ENS cells during both acute and chronic phases of IBD. Consequently, receptor-mediated pathways involving PL cleavage into secondary messengers may substantially contribute to the GBA imbalance in IBD.

The catabolism of the major membrane phospholipid, phosphatidylcholine (PC), is associated with crucial regulatory pathways in both enteric epithelial and neural cells [130–132]. PC was found to have an effect in the IBD treatment by the gut barrier function modulation, polarization of macrophages regulation, and by reducing the inflammation and is also known to have a potential in remodeling gut microbiota [133–135]. Concurring mechanisms are known for PC hydrolysis, including protein kinase C (PKC)-dependent and independent pathways. The activation of M-cholinergic receptors due to an increased need for choline, the precursor of acetylcholine, induces the stimulation of PC-sensitive phospholipase D [136]. Cholinergic neuron hyperactivation reduces the concentration of extracellular choline, potentially limiting its entry into neighboring neurons and interfering with the synthesis of membrane PC [132]. Additionally, phospholipase D activation is mediated by adrenergic stimulation [137], glutamate, and metabotropic receptors' stimulation [138]. The PKC impact on phospholipase D catalytic activity is dual: stimulation via an ATP-independent pathway or inhibition under phosphorylation [139,140]. PC can also be utilized via the activation of phospholipase A2 that is mediated by the glutamate effect on NMDA receptors [141,142]. Notably, NMDA receptor stimulation, which mediates the cleavage of choline from PC, prevents its reutilization into PC by inhibiting choline phosphotransferase activity. This pathway of glutamatergic activation for acetylcholine synthesis can precede neuronal death [138]. Therefore, PC is a crucial component and biochemical regulator of neuronal functions, and its impaired levels and catabolism in IBD may act as a trigger in GBA imbalance.

Phosphatidylinositol (PI) and its metabolites also play a crucial role in neuronal functions, orchestrating the membrane transport of mediators, including processes like endocytosis, exocytosis, and vesicle binding [136,143]. PI metabolism and the formation of its derivatives have been shown to be impaired in IBD both in patients and in animal models [144–146]. Phosphorylated forms of PI are crucial regulators in neurotransmission through the mediators' release from presynaptic membranes modulation acting on postsynaptic receptors [147]. At least 15 cytoskeletal actin-binding proteins have been reported to interact with or being regulated by phosphoinositides, whose synthesis is regulated by extracellular signals [148]. Hyperinduction of phosphoinositides hydrolysis leads to calcium transport impairments that can result in neuronal damage and death [149]. The decrease in neuronal level PI metabolite, PI-(4,5)-diphosphate, enhances the formation of β -amyloid from APP, and this process is Ca^{2+} -dependent [150]. PI-(3,4,5)-trisphosphate has been found to be reduced in the brain of Alzheimer's disease patients and in mouse models, in association with endosomal system impairments [151]. Conversely, β -amyloid is known to affect transmembrane signaling, affecting the metabolism of PI and PI-(4,5)-diphosphate. PI and PI-(4)-monophosphate are thought to perform a neuroprotective role, since their ad-

dition to the culture of hippocampal neurons eliminated the toxic effect of β -amyloid [152]. Low concentrations of β -amyloid peptide were shown to stimulate, but high concentrations to inhibit, phospholipase C activity [153]. Decreased phospholipase C expression in the brain is associated with the terminal stage of dendrite degradation [154]. Catabolism of PI is under the control of phospholipase A2, which exhibits activity both under increased Ca^{2+} concentration (Ca^{2+} -dependent phospholipase A2) or in Ca^{2+} absence, the latter being limited by PL metabolites (Ca^{2+} -independent phospholipase A2) [155]. The activation of phospholipase A2 is responsible for the biosynthesis of secondary PL messengers: arachidonic acid, eicosanoids, PAF, and diglycerides [156]. Phospholipase A2 is also involved in processes associated with increased dendritic growth and neuronal differentiation during the nervous system development, as well as involved in cognitive functions [157,158].

Dietary modulation and therapeutic approaches towards normalizing PL metabolism, as far as the PL membrane composition maintaining the organelle health, may emerge as a novel approach in the systemic therapy of IBD and its related effects on the GBA.

2.3. Bile Acids' Shift in IBD and Their Regulatory Potential in GBA

Bile acids (BAs) are among key metabolic regulators of microbial origin in the intestine; primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in liver hepatocytes from cholesterol. The intestinal microflora is responsible for deconjugation, desulfation, conjugation with amino acids, and the formation of secondary BAs in the intestinal lumen [159,160]. Bacteria belonging to the phylum *Firmicutes*, such as *Clostridium cluster XIVa*, are responsible for the production of secondary BAs [161,162]. BAs perform a range of regulatory functions, acting as signaling molecules in cholesterol, lipid, steroid, and glucose metabolic cycles [163]. Changes in the composition of the microbiota and its enzymatic activity, characteristic of IBD, lead to alterations in the luminal pool of BAs and the range of functions they perform; this contributes to the maintenance of chronic inflammation and the formation of metabolic disorders [164–168] (Figure 2b). BA metabolism and signaling are substantially altered in IBD, with bacteria producing significant amounts of unusual BAs, whose roles remain to be fully elucidated [165,169]. In IBD patients, particularly those with Crohn's disease, the impairments in the deconjugation, transformation, and desulfation activities of the gut microbiota are observed. This disruption leads to increased levels of sphingolipids and the primary bile acids CA and CDCA in the stool, alongside a depletion of secondary bile acids (lithocholic acid (LCA) and deoxycholic acid (DCA)) [170]. Significant reductions in secondary BAs (LCA and DCA) have been observed in the stool and serum samples of Crohn's disease patients with psychological disorders. These patients' stool samples showed an enrichment of primary BAs (CA and CDCA), while their serum exhibited elevated concentrations of dehydrocholic acid (DHCA) compared to healthy volunteers [171]. Additionally, levels of taurodeoxycholic acid (TDCA), tauro lithocholic acid (TLCA), and tauro- β -muricholic acid (T β MCA) in feces positively correlated with anxiety scores [171,172]. High levels of sulfated fatty acids have also been identified in the feces of IBD patients, a characteristic trait of the disease [165]. Furthermore, Crohn's disease patients exhibit elevated levels of BAs conjugated with phenylalanine, tyrosine, or leucine [160]. Comprehensive omics analyses of fecal samples from patients with various types of IBD have shown shifts in bacterial taxa with marked sensitivity to BA-rich environments, including *Faecalibacterium prausnitzii*, *Gammaproteobacteria* u *Blautia* spp. [173,174]. IBD patients with significant depression or anxiety displayed markedly reduced fecal microbiota diversity and lower counts of *Faecalibacterium prausnitzii* compared to patients without psychological disorders [171]. Studies in rats have demonstrated that these bacteria possess therapeutic effects in alleviating depressive and anxious states, highlighting their potential role in managing psychological symptoms in IBD patients [175]. Recent clinical findings have confirmed the involvement of gut microbiota dysbiosis and altered BA metabolism in the psychological disorders associated with Crohn's disease [171].

BAs have been shown to penetrate the blood–brain barrier [176], and numerous studies have identified both primary and secondary BAs in the brains of humans and rats [177–180].

The unconjugated bile acids CA, CDCA, DCA, and ursodeoxycholic acid (UDCA) can pass through the phospholipid bilayer of the blood–brain barrier due to their hydrophobic properties [173,177], and their concentrations in the brain correlate with their concentrations in serum [141]. Conjugated BAs, due to their greater hydrophilicity and size, can pass through the blood–brain barrier via active transport. Expression of mRNAs of various bile acids transporters was found in the vascular plexus of rat brain ventricles [181]. It was shown that the increase in BA concentration in the blood serum in rats after bile duct ligation or intravenous injection of DCA and CDCA caused structural damage, increased blood–brain barrier permeability, and increased concentration of these BAs in the brain [182,183]. In vitro studies have demonstrated that BAs can disrupt tight junctions in monolayers of rat brain microvascular endothelial cells by causing phosphorylation of occludins and increasing permeability via a Rac1-dependent pathway [182]. In a mouse model of non-alcoholic steatohepatitis (NASH) combined with moderate chronic colitis, alterations in the composition and levels of BAs were observed. These changes were accompanied by an increase in the protein S100 β , a marker of brain permeability and glial cell activation, in the blood serum, along with a significant reduction in the tight junction proteins ZO-1 and occludins [184].

The most extensively studied bile acid receptors are the nuclear receptor farnesoid X receptor (FXR) and the membrane-bound receptor G protein-coupled bile acid receptor 1 (GPBAR1), also known as Takeda G protein-coupled receptor 5 (TGR5) [185,186]. These receptors are highly conserved in humans and mice [187]. FXR is the primary regulator of BA synthesis and enterohepatic circulation. The signaling pathways and molecular mechanisms through which FXR and TGR5 interact with BAs in the enterohepatic organs are comprehensively reviewed in [188]. These and other BA receptors have also been identified in the brains of humans and rodents [189]. Studies on FXR knockout mice have demonstrated that FXR plays a role in the homeostasis of glutamatergic, GABAergic, serotonergic, and noradrenergic neurotransmitter systems in the hippocampus and cerebellum, influencing locomotor and cognitive functions as well as behavior [190]. In mouse models of hepatic encephalopathy, the activation of FXR receptors in brain neurons by bile acids is associated with neurological decline [191]. Increased expression of FXR in the hippocampus of naïve rats induces depressive-like behavior and reduces the expression of brain-derived neurotrophic factor (BDNF) [192]. Conversely, the knockdown of hippocampal FXR completely prevents the negative effects of chronic unpredictable mild stress on rat behavior [192]. In cell culture studies, conjugates with the amino acids phenylalanine, tyrosine, or leucine have been identified as potent agonists of the human FXR. These conjugates are comparable in efficacy to CDCA, the most powerful natural FXR agonist. It was shown that the level of BAs conjugated with the three listed amino acids was significantly higher in the dysbiotic state of patients with Crohn's disease but not in patients with ulcerative colitis [160]. When mice were fed these compounds, there was a notable reduction in the expression of downstream FXR target genes responsible for bile acid synthesis in the liver. [160]. In the brain, the bile acid receptor TGR-5 is present on neurons, astrocytes, and microglial cells. Studies on a mouse model of hepatic encephalopathy, as well as in vitro studies on primary neurons and the mouse microglia cell line (EOC-20), have shown that the central activation via intracerebroventricular infusion of a TGR-5 agonist leads to reduced neuronal expression of chemokine ligand 2 (CCL-2), decreased production of pro-inflammatory cytokines, and reduced microglial proliferation [193]. Both in vitro and in vivo studies in mouse models of acute neuroinflammation have demonstrated that the binding of tauroursodeoxycholic acid (TUDCA) to TGR-5 exerts anti-inflammatory effects, influences microglial phenotype, reduces NF κ B activation, and induces the TGF β pathway [194]. Another bile acid receptor, sphingosine-1-phosphate receptor (S1PR2), is expressed by endothelial cells and neurons. In mice, S1pr2 $-/-$ knockout showed weaker disruption of the blood–brain barrier and reduced neutrophil infiltration during systemic inflammation induced by lipopolysaccharide compared to S1pr2 $+/-$ littermates, indicating S1PR2's role as a mediator of cerebrovascular inflammation [195]. In an azoxymethane-

induced mouse model of hepatic encephalopathy, high levels of the conjugated primary bile acid taurocholic acid in the blood led to the activation of S1PR2 in brain neurons (cortex and hippocampus), resulting in increased expression of mRNA and secretion of CCL2. This activation subsequently stimulated microglia, leading to increased expression of pro-inflammatory cytokines and sustained neuroinflammation [196]. The specific ways of brain-localized bile acid receptors' contribution to neurological changes remain largely unclear. However, many of these receptors are considered potential therapeutic targets for treating neurodegenerative diseases and psychiatric disorders [194,195,197,198].

Recently, the first clinical data confirming the involvement of gut dysbiosis and BA metabolism alteration in psychological disorders in Crohn's disease were obtained [171]. As our understanding of BAs' roles in neural functions grows, they are becoming perspective actors in the gut–brain axis in the context of IBD and gut microbiota misbalance.

Metabolic dysregulation is fundamentally involved in IBD and should be considered in relation to the GBA dysregulation. Currently, data are fragmentary, and specific pathways are poorly understood, necessitating a systematic approach to identify the metabolic pathways disrupted in IBD and their involvement in the GBA, as far as targeted strategies for their normalization are concerned. A promising avenue in diagnostics is a personalized metabolomics analysis approach. Potential methods for metabolic correction may include (i) the therapeutic and dietary compensation of supplementary deficiencies, addressing specific metabolic deficits defined, and (ii) the development of pharmaceuticals to modulate metabolic pathways and restore metabolic homeostasis.

3. Mitochondrial Functions

Currently, an increasing number of studies identify mitochondria as a crucial component of the GBA [199,200]. In IBD pathogenesis, mitochondrial dysfunction significantly contributes to the disruption of the intestinal epithelial barrier [90,201]. Mitochondria play a central role in cellular energy supply, ATP production, neural signal transduction, actin cytoskeleton dynamics (Figure 3); they are also involved in the homeostasis of cellular cations such as calcium and potassium, thereby participating in the regulation of various signaling pathways that either prevent or initiate inflammation and cell death [202–204]. Mitochondria are believed to adapt to intracellular changes in energy balance to maintain homeostasis. However, when metabolic dysregulations exceed the adaptive capabilities, mitochondrial dysfunction occurs, resulting in decreased energy production, the generation of reactive oxygen species (ROS), and oxidative stress-induced apoptosis [105,205]. Given the pivotal roles that mitochondria play in the physiology of neural cells, understanding the mechanisms of mitochondria involvement in GBA dysregulation in connection with IBD-related pathological processes, including metabolic dysregulation, could open new avenues for IBD research and therapy (Figure 3a).

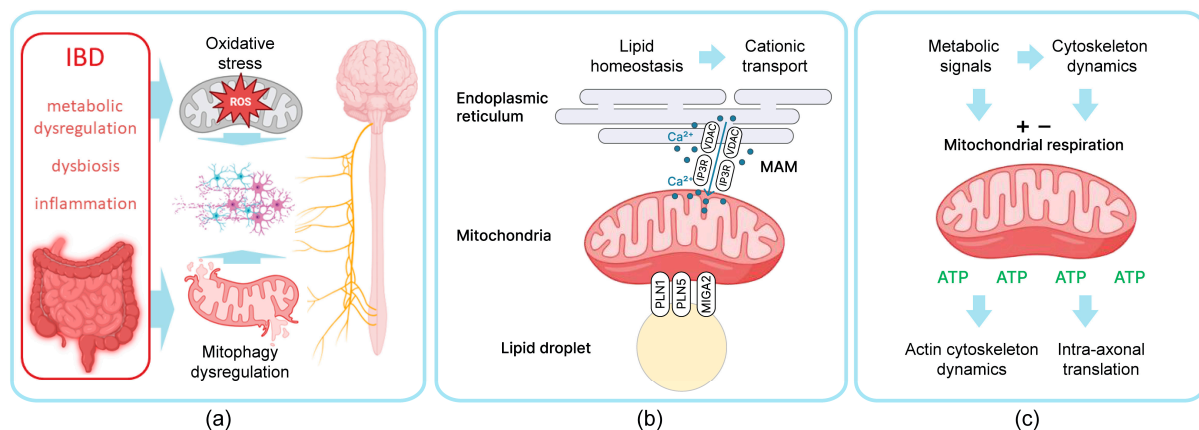


Figure 3. Mitochondrial functions' involvement in GBA imbalance in IBD. (a) Mitochondrial health is highly crucial for neural cells' function being subject to IBD-related pathological processes. (b) Lipid

droplets and mitochondrion-associated membranes' role in mitochondrial functions and calcium transport regulation. MAM—mitochondria-associated endoplasmic reticulum membrane, IP3R—inositol triphosphate receptor (a membrane glycoprotein complex that acts as a Ca^{2+} channel), VDAC—voltage-dependent anion channels, PLN1 and PLN5—surface proteins of lipid droplets involved in the contact of lipid droplets with mitochondria, MIGA2 is an outer mitochondrial membrane protein that directly links mitochondria to lipid droplets. (c) Mitochondria regulate actin filament dynamics that are crucial for intracellular junctions' integrity through ATP production. Mitochondrial respiration also promotes mitochondria-associated intra-axonal translation of actin regulatory proteins involved in axonal branching. Both the mitochondria-dependent regulation of actin dynamics and intra-axonal translation are regulated by the modulation of mitochondrial respiration by metabolic signals and cytoskeleton dynamics. Blue arrows indicate the directions of influence between the interconnected processes shown in the schemes.

3.1. Lipid Homeostasis Interrelation with Mitochondrial Functions

Lipid metabolism begins with the emulsification and absorption of lipids in the intestine and continues through their uptake and transport into cellular organelles, including mitochondria [130,206]. Depending on the availability of metabolic substrates, energy balance, and endocrine signaling, fats are either stored in lipid droplets within adipose tissue or oxidized in mitochondria and peroxisomes. Mitochondria are one of the main compartments for the synthesis of PL, such as phosphatidylethanolamine, which is the substrate for biosynthesis of PC, the main phospholipid of membranes and lipid droplets [104]. Unlike the transfer of free fatty acids (FFAs) from lipid droplets to mitochondria for energy production, mitochondria–lipid droplet contact can also facilitate the transfer of lipids from mitochondria to lipid droplets. Both mitochondria and lipid droplets are highly dynamic organelles. Contact sites between mitochondria and lipid droplets have been shown to support the expansion of lipid droplets by increasing ATP synthase-dependent triacylglycerol (TAG) synthesis or by stimulating lipid droplet transport [207,208]. It was hypothesized that atypical contacts between mitochondria and lipid droplets increased under conditions of high energy demand and were essential for both lipolysis and lipogenesis in response to various metabolic triggers [209]. Several members of the nuclear receptor superfamily influence all aspects of lipid metabolism [210]. PPARs and liver X receptors (LXRs), acting in concert with PPAR γ coactivator 1 α (PGC-1 α), regulate insulin sensitivity and lipid processing [211–213]. These receptors are the focus of intensive pharmacological research aimed at expanding the arsenal of small molecule ligands for the treatment of diabetes and metabolic syndrome [210].

Increasing evidence suggests that mitochondria, endoplasmic reticulum (ER), and lipid droplets are functionally interconnected to facilitate the exchange of small molecules and metabolites through membrane contact sites. These contact sites are critical for maintaining organelle function and overall cellular homeostasis, including lipid homeostasis [214,215]. Current research highlights the importance of contact sites between mitochondria and the ER, as well as between mitochondria and lipid droplets, in regulating cellular lipid metabolism [216]. For instance, under starvation conditions, cells adapt by switching their metabolism from glycolysis to fatty acid oxidation. This metabolic shift is primarily achieved through the breakdown of lipid droplets and the subsequent transport of FFAs into the mitochondria for β -oxidation [217]. Given the chronic digestion and absorption impairments in IBD [218], ENS cells may enter the starvation condition. Additionally, cells can activate autophagy as an adaptive response to starvation, breaking down organelles and cell membrane proteins to generate biomolecules, such as amino acids and FFAs, necessary for survival [219]. However, excessive FFAs can be toxic to cells, generating ROS and mitochondrial damage leading to cell death due to lipotoxicity [220,221]. In the nervous system, autophagy is the most important mechanism for regulating cellular functions and neuronal homeostasis; impairments in autophagy are associated with many neurodegenerative diseases [222–224]. Both constitutive and stress-induced autophagy in

neural cells is involved in the control and renewal of damaged mitochondria ER and other organelles [219]. Lipid homeostasis also has a significant impact on autophagy processes in neural cells [225], and the related mitochondrial dysfunction in IBD may be one of the clues to the GBA dysregulation in IBD.

3.2. The Role of Lipid Droplets and Mitochondrion-Associated Membranes in Mitochondrial Functions and Pathology

Mitochondria contain most of the enzymes necessary for triglyceride metabolism, emphasizing their close functional connection with lipid substrates. Lipid droplets are dynamic intracellular organelles that vary in size and primarily store TAG and sterol esters as sources of bioenergy [208]. Lipid droplets are typically located near the rough ER, and lately, their regulatory role is emerging, particularly in lipid metabolism and energy regulation [226]. Lipid droplet accumulation in nervous cells has been widely shown as the characteristic trait upon neuroinflammation and neurodegenerative processes [227]. Despite the lack of research on lipid droplets in IBD-related processes, lipid droplets in the enterocytes are considered as a functional link between lipid homeostasis and inflammatory processes [228]. Two types of interactions between lipid droplets and mitochondria are distinguished: dynamic contact, where lipid droplets bind to mitochondria via protein complexes, and stable contact, where proteins facilitate a strong and stable membrane attachment of mitochondria to lipid droplets [229]. Proteins involved in the contact between mitochondria and lipid droplets include the surface proteins of lipid droplets PLN1, PLN5, and the outer mitochondrial membrane protein MIGA2, which directly connects mitochondria with lipid droplets (Figure 3b). These contacts promote the synthesis of fatty acids, their conversion to triglycerides, and their accumulation in lipid droplets [209]. Peridroplet mitochondria, which are located in close proximity to lipid droplets, have a distinct biochemical profile compared to the rest of the cytosolic mitochondria population [209]. The fusion of lipid droplets with the mitochondrial matrix is thought not only to facilitate the use of lipids for metabolic needs but also their accumulation, as the mitochondrial matrix contains most of the enzymes of the tricarboxylic acid cycle, which remain active in peridroplet mitochondria [209,230]. The fusion of mitochondria with lipid droplets, observed in macula cells of the human vocal cords, suggests the use of triglycerides from lipid droplets for the cell's metabolic needs [231]. Impaired glycolysis, characteristic of intestinal tissues in IBD [232], can be assumed to secondarily inhibit mitochondrial metabolism due to a decrease in the amount of pyruvate entering the glycolytic pathway. This inhibition, in turn, may activate transcription factors and corresponding enzymes that promote more active oxidation of fatty substrates, as well as stimulate mitochondrial biogenesis necessary to restore ATP production and compensate for energy deficits [233]. Increased lipid droplet biogenesis was found in association with oxidative stress and elevated ROS production [234]. The recent elegant study in a mouse model demonstrating the involvement of the GBA showed an association between targeting ROS in the intestine and behavioral changes [235].

The outer membrane of mitochondria and the membrane of the adjacent ER can form common areas, known as mitochondrion-associated membranes (MAMs), which are essential for proper communication between these organelles (Figure 3b). Currently, MAM contacts are associated with the regulation of metabolism, autophagy, aging, and the production of ROS [236]. One of the primary functions of MAMs is the transport of calcium from the ER to mitochondria, allowing fine regulation of organelle activity and their role in executing physiological and pathological signals within the cell [237]. The protein composition of MAMs is dynamic and depends on the conditions and metabolic activity of the cell; according to proteomic data, MAMs can include more than 1000 proteins [238]. The structure and function of MAMs are critical for many cellular processes. Recent studies have shown that ion transport regulation is supported by the transmission of signals between the ER and mitochondria through MAMs by several proteins located within these structures. These proteins include those encoded by the PARK genes and some

proteins associated with neurodegeneration, such as huntingtin and presenilin [239]. The alteration of MAMs contributes to pathogenesis features such as autophagy dysregulation, mitochondrial dysfunction, oxidative stress, and more recently, neuronal death. These alterations are associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease [103,240,241].

3.3. The Mitophagy Regulation Importance in Neuronal Cell Health and Function

In neuronal cells, the efficient removal of damaged mitochondria through mitophagy, a highly conserved cellular process, is fundamental for maintaining mitochondrial and metabolic homeostasis, energy provision, and neuronal survival [242,243]. In healthy tissue, damaged and dysfunctional mitochondria are removed by mitophagy, preventing the accumulation of defective organelles and the development of pathological effects [242,244]. Maintaining mitochondrial function is crucial for cellular homeostasis and viability, and cells have developed a broad arsenal of quality control mechanisms to detect and eliminate defects in mitochondrial activity [244]. These mechanisms include mitochondrial biogenesis control, integrated stress response, fission and fusion events, and the selective autophagic removal of damaged or excess organelles via mitophagy. Defects in mitophagy, particularly in neuronal cells, have been found in association with neuropathology, including Alzheimer's, Parkinson's, and Huntington's diseases [245,246]. Mitophagy is mediated by the major proteins PTEN-induced kinase 1 (PINK1) and Parkin [247]. In normal mitochondria, PINK1 resides on the outer mitochondrial membrane but is degraded by the inner mitochondrial membrane protease PARL, suppressing the mitophagy signal [247]. However, in damaged mitochondria with reduced membrane potential, PINK1's amount was shown to be elevated and recognized by the Parkin protein, an E3 ubiquitin ligase, marking the mitochondria for subsequent degradation [248]. Most Parkin ubiquitination targets are localized within the mitochondria. During the early stage of mitophagy, Parkin translocates to dysfunctional mitochondria, activates PINK1, and ubiquitinates outer mitochondrial membrane (OMM) proteins [249]. During mitophagy induction, PINK1 accumulates on the OMM of damaged mitochondria, where it recruits and activates Parkin through phosphorylation. Subsequently, the factor p62 binds to ubiquitinated mitochondrial proteins, resulting in the encapsulation of mitochondria by LC3 autophagosomes, which are then degraded with the lysosomes involvement [250]. Animal models have shown that knockout of key genes responsible for mitophagy, particularly Atg5 or Pink1, leads to an increase in ROS levels [251]. The accumulation of a large number of dysfunctional mitochondria contributes to cell damage, a further increase in ROS levels, and a general inhibition of cellular energy production [219,243]. Impaired mitophagy results in the accumulation of damaged mitochondria and cellular dysfunction, contributing to neurodegeneration [244,246,252].

Mitophagy ensures the removal of dysfunctional mitochondria through several pathways that control, initiate, and facilitate this process. Mitophagy disruptions can adversely affect neuronal functions, as functional mitochondria are crucial for neurotransmitter synthesis, release, and reuptake at the synapse [243,244]. The accumulation of damaged mitochondria can lead to synaptic dysfunction and neurodegeneration, whereas mitophagy maintains synaptic integrity by eliminating damaged organelles. Damaged mitochondria can also be removed via autolysosomes, and if mitophagy is blocked, mitochondria can induce cell death (apoptosis and necrosis) [243,253]. Signal transduction between microglia, astrocytes, and neurons, which is essential for glial cell function, is also modulated by mitophagy-related pathways. Transcellular mitophagy, a process in which cells release mitochondria to be engulfed and degraded by neighboring cells, has been demonstrated in the brain [254]. For instance, glial cells can transfer mitochondria to neurons during a stroke. Dysregulation of this process can lead to neuroinflammation and loss of proteostasis [255]. Receptor-mediated transcellular mitophagy, activated under specific conditions, is driven by mitochondrial receptor proteins located on the outer or inner mitochondrial membrane containing various motifs. Although the process of transcellular mitophagy is not yet well understood and requires further study, it holds significant implications for neuronal health.

Mitophagy and mitochondrial health control are valuable questions requiring further research in the context of the GBA [202,256]. Maintaining a functionally active mitochondrial network and the approaches to regulate the population of these organelles in IBD-related conditions could be ultimately essential for the GBA function.

Thus, understanding the roles of mitochondrial functions in the GBA could reveal novel insights into the IBD pathophysiology and related dysfunctions, leading to the development of new therapeutic strategies aimed at preserving or restoring mitochondrial health in IBD. The interactions between lipid droplets and mitochondria, particularly through membrane contact sites, are believed to be crucial for the regulation of lipid metabolism and the maintenance of cellular homeostasis. Further research into the roles and regulation of these processes within the context of GBA may provide valuable insights into restoring metabolic pathways in IBD.

4. Cationic Transport Dysregulation

Dysregulation of cationic balance is a crucial factor in the pathogenesis of numerous diseases, including those affecting the nervous system. The study of the roles of cations (Zn^{2+} , Ca^{2+} , Na^+ , K^+ , Mg^{2+}) in CNS function remains highly relevant both under normal conditions and in pathological processes [257–260]. Calcium ions (Ca^{2+}) play a decisive role in maintaining physiological and biochemical processes within cells. As a vital intracellular messenger, Ca^{2+} is actively involved in numerous physiological functions, including neuronal excitation, muscle contraction, blood clotting, and enzyme activation. It also plays roles in cell differentiation, apoptosis, the immune response, and tumorigenesis. This broad range of functions necessitates a homeostatic regulatory system [261]. It is also involved in cell differentiation and apoptosis, in the immune response, and plays a significant role in tumorigenesis [262,263]. This broad range of functions necessitates a homeostatic regulatory system [264]. The CNS is particularly dependent on calcium homeostasis, and its deregulation is closely associated with several diseases, notably neurodegenerative and inflammatory diseases [260], including IBD [265]. It is highly plausible that Ca^{2+} homeostasis plays a significant role in the GBA (Figure 4).

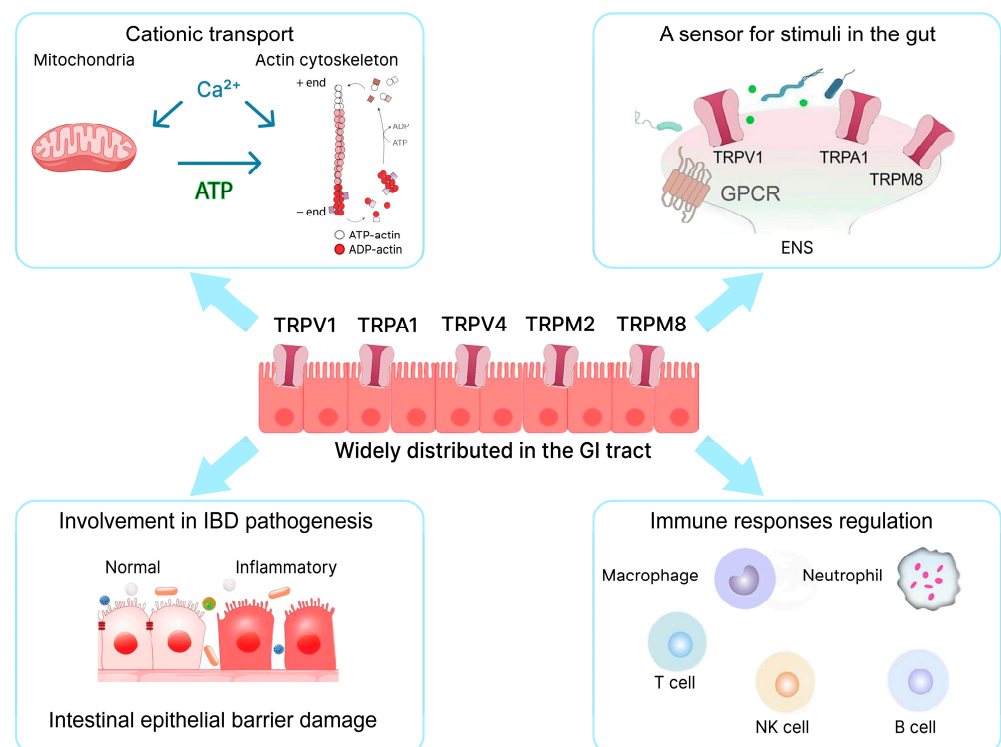


Figure 4. TRP ion channels' functions in the gut enterocytes and neurons. Blue arrows indicate the key effects of TRP-mediated cationic transport dysregulation: calcium transport and calcium deficit

significantly affects mitochondrial function's and actin dynamics in both enterocytes and neurons; TRP ion channels perform crucial functions in enteric nervous system (ENS) neurons and regulate calcium transport and response to various signals; calcium transport affects gut epithelial integrity, and calcium deficit induces "leaky gut" syndrome; TRP ion channels and cationic transport regulate immune responses via immune cells receptors' signaling.

Modulating calcium influx into cells and targeting calcium-mediated signaling pathways may represent promising therapeutic approaches for these diseases. In this context, calcium channels are considered potential targets in IBD [266–268]. Intracellularly, three major groups of channels are responsible for releasing calcium from the ER: ryanodine receptors (RyR) [269], inositol-3-phosphate receptors (IP3R) [264,269], and two-pore channels (TPC) [270]. Several calcium channels within the plasma membrane are also crucial for CNS cell function, including voltage-gated calcium channels (VGCC) [271], ionotropic glutamate receptors [272,273], calcium release-activated calcium (CRAC) channels [274], purinergic P2X receptors [275], and transient receptor potential (TRP) ion channels [276]. Understanding and targeting Ca^{2+} channels and their regulatory pathways could provide new insights and therapeutic opportunities for managing GBA function in IBD, underscoring the importance of maintaining cationic balance in both gut and mental health.

4.1. TRP Ion Channels' Role in the Inflammation and ENS Dysregulation in IBD

TRP ion channels are a large group of cation channels through which cells respond to various external stimuli. These channels are sensitive to temperature, tactile, and pain stimuli, are involved in mechanical and taste sensitivity, visual perception, and play an important role in the immune response and nociception. TRP ion channels are widely expressed in the central and peripheral nervous systems, as well as in non-neuronal cells such as those of the skin, bladder, pancreas, and spleen [277–281]. The currently known TRP ion channels form a large and heterogeneous superfamily, numbering more than 28 types and subdivided into subfamilies. In mammals, there are six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin) [280,282,283]. Accumulating evidence from clinical and animal studies supports the significant contribution of TRP ion channels to the pathophysiology of IBD. In this regard, they represent an attractive target for developing new therapeutic approaches [266,268,284–286]. TRPV1, TRPV2, TRPV4, TRPA1, TRPM2, and TRPM8 have been shown to be involved in the mechanisms of chronic inflammation and pain observed in IBD [287–291]. In the gastrointestinal tract, TRP ion channels are expressed in primary afferent sensory neurons and enteric neurons that jointly innervate the gastrointestinal tract [266,292,293]. TRP channels are also present in gastrointestinal non-neuronal cells, including enterocytes and enteroendocrine cells, such as enterochromaffin cells [294,295].

The activation of TRPV1, TRPA1, TRPV4, and TRPM8 have been shown to mediate the release of immunomodulatory neuropeptides by afferent neurons, including calcitonin-gene-related peptide (CGRP) and substance P (SP), which induce inflammatory responses [267,296,297]. The alterations of expression levels of these ion channels have been detected in IBD patients, as well as in mouse colitis models [267,268,289,298,299]. TRPV1 and TRPA1 ion channels are the most studied in the context of their involvement in intestinal inflammation. Both in IBD patients and rodent models, a significant change in the levels (both mRNA and protein) of TRPV1 and TRPA1 has been shown, which may indicate an important role of these ion channels in the inflammatory response regulation [300]. TRPV1 is hypothesized to be responsible for neuropathic inflammatory pain [300,301], as its activation promotes an increase in intracellular Ca^{2+} concentration and subsequent release of neuropeptides SP and CGRP from afferent sensory neurons, along with key proinflammatory cytokines [302]. TRPA1 is known to be involved in inflammatory reactions and the development of mechanical and chemical hypersensitivity in the colon [303]. The activation of TRPA1 may have a protective effect in IBD by reducing the expression of

some proinflammatory neuropeptides, cytokines, and chemokines [300]. TRPV4 mRNA expression is increased in IBD patients [304], and selective blockade of TRPV4 in a mouse model of ulcerative colitis reduced intestinal inflammation and relieved pain [305]. A review summarizing data of experimental and clinical studies concluded that the TRPV4 ion channel could be considered as a therapeutic target for IBD [306].

The members of the TRPM subfamily have also been shown to be involved in IBD. Heat-sensing TRPM2 is involved in inflammatory pain and promotes visceral hypersensitivity by stimulating a range of immune functions [307]. In the gastrointestinal tract, TRPM2 is expressed mainly in mucosal macrophages and mast cells [308]. In a rat model of ulcerative colitis, the increased expression of TRPM2 was detected in the colon, and TRPM2 inactivation reduced inflammation in a mouse model of DSS-induced colitis [288]. TRPM8 ion channel activation by the agonist icilin in a mouse colitis model demonstrated strong anti-inflammatory and analgesic effect [290]. These effects may also occur due to icilin suppressing activity on another ion channel, TRPV1, which is a nociceptor that can be co-expressed with TRPM8 [309].

4.2. TRP Ion Channels and Gut Microbiota

Due to their immunomodulatory function through neuropeptides and immune cells, TRP channels are associated with immunity and gastrointestinal inflammation. IBD is closely associated with changes in intestinal microbial composition and metabolism, suggesting that the interaction of the gut microbiota with the CNS may occur through receptors such as TRP ion channels [294,310,311]. ENS sensory neurons innervating the intestine abundantly express TRP channels [266]. An increasing number of studies aim to identify the relationship between TRP ion channels and the intestinal microbiota [311,312]. For instance, Perez-Burgos et al. found that *Lactobacillus reuteri* dose-dependently reduced capsaicin-induced activation of jejunal afferent nerves in mice [313], suggesting that TRP channels may interact with gut microbiota and related metabolites, thereby influencing intestinal homeostasis. Interestingly, TRPV1 denervation by high doses of resiniferatoxin caused a decrease in bacterial metabolites and affected bacterial abundance in the gut [312]. In a study examining the possible interaction of TRPA1 and TRPV1 ion channels (involved in pain perception) with the gut microbiota, Nagpal et al. showed that *Trpa1*^{-/-} and *Trpv1*^{-/-} knockout mice were as different in microbiota composition from each other and from wild-type mice [311]. Further research into the mechanisms of the relationship between TRP ion channels and the intestinal microbiota and microbial metabolites may provide new insight into the role of these channels in physiological processes in the intestine, the GBA, and the pathophysiology of pain that occurs in IBD.

TRP cation channels play a significant role in the pathogenesis of IBD, through cation transport regulation and interactions with the intestinal microbiota. Given this, as well as the established involvement of these ion channels in neurodegenerative and neuroinflammatory diseases, it is plausible that TRP ion channels constitute a crucial link in the regulation of the GBA. Understanding the specific mechanisms by which TRP ion channels influence both gut and brain function could provide valuable insights into the interconnected nature of gastrointestinal and neurological health. This underscores the potential of targeting TRP ion channels in developing therapeutic strategies for IBD and related GBA dysregulation.

5. Cytoskeleton Dysregulation

The actin cytoskeleton plays an essential role in enterocytes maintaining the integrity of the intestinal barrier and performs vital functions in neurons [314–319]. Actin is one of the highly conserved and abundant elements of the cytoskeleton that can form highly ordered and highly dynamic linear bundles, two-dimensional networks, and three-dimensional gels depending on cellular functions and signals [320,321]. Cytoskeletal F-actin is dynamically assembled from monomeric G-actin in an ATP-dependent manner, mediated by actin nucleators and crosslinkers such as formins, fascin, and ARP2/3 [322,323]. The dynamics

and stability of the actin cytoskeleton are closely related to mitochondrial health and cellular cationic transport process (Figure 5a). The dynamics of actin fibers is ATP-dependent, so mitochondrial processes have a substantial impact on cytoskeletal functions (Figure 3c). Cellular responses to environmental factors, in turn, largely occur through mitochondria-cytoskeleton interactions, involving mitochondrial dynamics, positioning, and function regulated by the cytoskeletal network [324,325]. F-actin also participates in the regulation of mitochondrial ROS production, dynamics, and positioning, with myosins implicated in mitochondrial fission events [324,326]. Cytoskeletal microtubules' growth suppresses the fission of bound mitochondria and provides transport and anchorage tracks, while PI-(4,5)-diphosphate INF2-mediated nucleation of actin filaments promotes mitochondrial fission and dynamics [327,328]. The actin cytoskeleton mediates a variety of cellular functions, especially important for both enterocytes and neuronal cells: the maintenance of cell shape and intercellular contacts, mitochondrial health and dynamics, and vesicle formation.

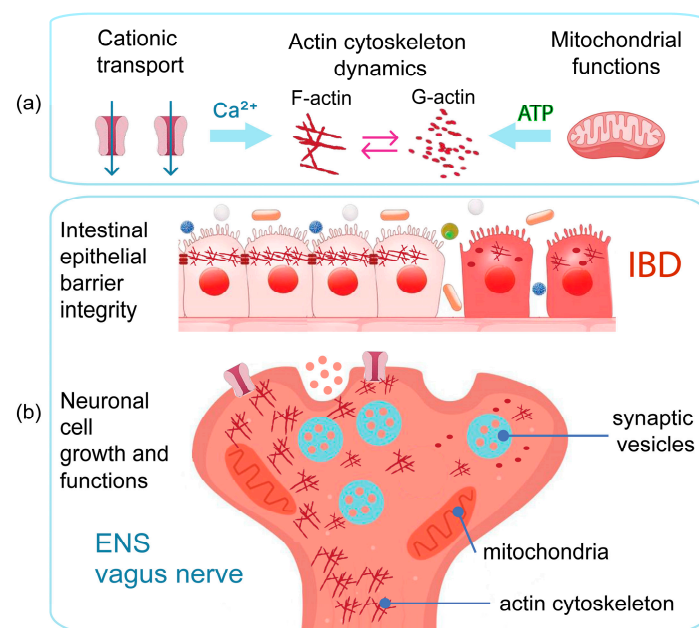


Figure 5. Actin cytoskeleton dynamics involved both in the intestinal barrier integrity maintenance and neuronal cell functions. (a) Actin cytoskeleton dynamics and actin filament formation depends on mitochondrial ATP production and sufficient Ca^{2+} cellular levels. Blue arrows show influence of ATP and Ca^{2+} levels on the assembly and disassembly of actin filaments (F-actin) from monomeric globular actin (G-actin). (b) Actin cytoskeleton involved in intestinal barrier integrity maintenance via intercellular junctions' stabilization. In neuronal cells, actin cytoskeleton is essential for proper vesicle formation, transmembrane receptors' positioning and action, axonal growth, mitochondrial movement within axons, and mitophagy.

5.1. Actin Cytoskeleton Role in Neuronal Cells and GBA Function

For proper neuronal function, the actin cytoskeleton is essential for axonal growth, mitochondrial movement within axons, and the process of mitophagy [253,329]. It is also crucial for the formation of synaptic vesicles and the reuptake of neurotransmitters [330,331]. As a result of inflammation, dysregulation of cation transport, and ATP production by mitochondria in IBD, the actin cytoskeleton may be disrupted not only in enterocytes but also in the cells of the ENS, also potentially affecting the functions of the vagus nerve (Figure 5b). Although these aspects have not been studied, they may offer promising directions for understanding ENS and vagus nerve dysfunctions within the GBA in the context of IBD. Deregulated cytoskeleton dynamics, in turn, may exacerbate mitochondrial movement and mitophagy impairments in neural cells [332]. These processes are critically important for neuronal health and proper nerve impulse transmission. Exploring therapeu-

tic approaches to restore actin cytoskeleton function in IBD may yield systemic positive effects. Besides restoring the integrity of the intestinal barrier by reestablishing intercellular contacts, it could also improve the functions of the ENS and vagus nerve within the GBA. Given the current lack of data in this area, but recognizing the existing premises, it makes sense to focus research on the role of neuronal actin cytoskeleton dysregulation in IBD. Understanding these mechanisms may provide new insights and potential therapeutic targets to alleviate GBA-related dysfunctions in IBD.

Another possible pathway of actin cytoskeleton involvement in GBA is circulating microbial metabolites, such as short-chain fatty acids, which include butyrate and propionate [333]. Gut microbiota is known to regulate gut epithelial barrier integrity in an actin-dependent manner with butyrate [334]. These compounds have also been shown to influence the integrity of the blood–brain barrier [335,336]. The brain endothelium, a major interface between circulating metabolic signals and the brain, is a critical component of the blood–brain barrier and also depends on the actin cytoskeleton state. In an *in vitro* model of the tight junctions, butyrate and propionate were shown to affect the actin cytoskeleton and the structure of tight junction proteins [337]. Both these short-chain fatty acids were shown to induce distinct changes in the orientation of F-actin bundles. Additionally, they increased the number of tight junction proteins and protected against LPS-induced degradation of tight junctions, thereby improving intercellular contacts integrity and also modulating mitochondrial network dynamics [337]. These findings provide a foundation for further research into the role of actin cytoskeleton function implications for the GBA in IBD.

5.2. Actin Cytoskeleton Dysregulation Involvement in Gut Epithelium Barrier Dysfunction in IBD

The idea of the actin cytoskeleton's important role in the gut epithelium barrier integrity is widely supported by findings that the destabilization of the actin network with cytoskeleton-disrupting toxins, inflammatory signaling molecules, or bacterial pathogens leads to the loss of AJC, along with an actin filament breakdown [317]. The intestinal barrier function is provided by intercellular junctions (adherent and tight junctions) of enterocytes accompanied with the mucous layer [338–341]. As a consequence of intestinal inflammation in IBD, an intestinal barrier disruption occurs [342–344]. Or conversely, intestinal barrier dysfunction may trigger immune activation [345–347]. Studies in IBD patients have revealed changes in the expression of genes of AJC proteins [348,349]. Mass spectrometry proteomic studies on human samples and animal models have also identified measurable changes in actin expression in the inflamed gut [350,351]. Several actin-binding proteins, such as cofilin, Arp3, and cortactin, colocalize with reorganized contractile rings in models of “leaky gut” induced by calcium depletion [352]. The motor protein myosin II, localized in these reorganized ring structures, is essential for AJC disassembly, as evidenced by the inhibition of its function with blebbistatin blocking that process, suggesting the involvement of actin-binding proteins in AJC regulation [353]. Recent studies have shown that the depletion of the actin-related protein (ARP2/3) inhibitor, ARPIN, alters the architecture of tight and adherent junctions while increasing actin content and epithelial barrier permeability [354]. This is supported by *in vivo* data in a mice model showing that ARPIN level decreases in response to DSS, and the suppression of ARPIN levels is also observed in highly inflamed areas of IBD patient samples [354]. Synaptopodin, found in actin stress fibers and tight junctions in epithelial cells, has been shown to exacerbate colitis in synaptopodin-deficient mice in response to dextran sodium sulfate [334]. There is substantial evidence of the association between calcium transport via TRP ion channels and the actin cytoskeleton, demonstrating the functional involvement of calcium transport [355,356]. Cationic transport through TRP ion channels has been shown to modulate cytoskeletal rearrangements [355,356].

In neural inflammation, calcium transport is also known to be impaired [357]. TNF- α is known to induce an F-actin rearrangement and additionally promotes the phosphorylation of the myosin light chain, leading to the disruption of tight junctions [358–361]. However, in chronic IBD, pro-inflammatory cytokine levels can be unelevated, and their effects can

be balanced by anti-inflammatory cytokines, raising questions about the mechanisms of intestinal permeability changes during chronic inflammation. Studies on Crohn's disease patients and their immediate family members have revealed genetically determined increased intestinal permeability in relatively healthy individuals, which cannot be solely explained by cytokine-induced permeability changes [362,363]. Increased intestinal permeability is also characteristic of various animal models of IBD. Animals with a null mutation in the *Nod2* gene exhibit increased intestinal permeability, mucin-2 secretion deficiency, and a predisposition to intestinal inflammation [364]. The *Il10*-deficient mouse strain, a popular model of IBD, also shows increased intestinal permeability, with mutations in the *Il10* gene associated with a predisposition to IBD in humans [365]. While the immune pathways inducing intestinal barrier loss have been extensively studied, the contribution of cytoskeletal dynamics and metabolism remains underexplored. Interestingly, mice with a predisposition to IBD due to mutations in the *Muc2* gene exhibit increased intestinal permeability, behavioral changes, metabolic dysregulation, and impaired mitochondrial function [366]. This suggests that immune activation mechanisms might not be the primary cause of intestinal barrier impairments in IBD.

The disruption of the intestinal barrier inevitably leads to an immune response due to the penetration of pathogenic factors, complicating the study of the actin cytoskeleton's role in IBD pathogenesis. However, restoring the balance of the actin cytoskeleton to recover the epithelial barrier function presents a promising direction for IBD therapy. Understanding and targeting the actin cytoskeleton dysregulation in IBD could provide novel insights and therapeutic opportunities for managing IBD and also restoring GBA functions. Regarding cytoskeletal modulation, new strategies may emerge to alleviate the chronic inflammation and neural dysfunctions associated with IBD.

6. Discussion: Clinical Applications and Translational Perspective

Considering recent data in patients with various forms and at different stages of IBD experiencing significant metabolic dysregulation [80,167,170,173,367,368], the extensive studies of pathophysiological mechanisms and regulatory pathway involved in the interrelations of these processes with GBA function become a highly relevant area. In this review, we systematically summarized the research data which shed light on the range of systemic effects of metabolic dysregulation in IBD on molecular and cellular processes critical for GBA functioning. The most significant effects of IBD in relation to metabolic dysregulation are the substantial lipidome deregulation [86,87] along with oxidative processes' dysregulation and mitochondrial malfunction [82–85]. Dysregulation of the lipidome entails multiple dramatic consequences, which consist not only in systemic processes' distortions, but also in basic cellular functions' lesions. Lipid metabolism is extremely important in biosignaling, since major classes of lipids, such as PUFAs and phospholipids, are precursors to a spectrum of messengers that mediate metabolic regulation and also the development and control of inflammation, as well as the regulation of nervous activity and signaling processes [368]. Along with this, the disproportions of phospholipids levels and phospholipid processing impairments lead to various crucial structural and signaling consequences [369]. Thus, changes in the composition and proportions of phospholipids play a significant role in the function of membrane cell structures and the integrity of the epithelial barrier (both intestinal and blood–brain barriers). Moreover, phospholipids perform important functions in intracellular transport and other intracellular membranous structures, in particular in the organelles' health, and to a significant extent, in mitochondrial health [369,370]. Data are just emerging identifying specific lipid indicators as clinical predictors for IBD [79,87,146]. However, this area has not yet been studied enough to offer specific targeted therapeutic approaches for metabolic dysregulation correction in IBD patients, in particular, lipidome dysregulation. However, it becomes clear that this direction contains great translational prospects, especially in relation to the GBA balance restoration in IBD.

The GBA, especially in the clinical context of IBD, is currently often considered to include the liver function, which is inevitably affected by pathological processes associated

with both chronic inflammation and metabolic dysregulation [371]. In particular, BAs are coming to the fore in the therapeutic perspective. Patients with different types and stages of IBD have different bile acid profiles [171–174]. As more clinical data accumulate, the composition of BAs in serum and feces may have a diagnostic or prognostic value [372]. The microbiota have long been and are currently undoubtedly considered the most important component of the GBA, and a great amount of research shows the clinical and prognostic significance and a great therapeutic potential of the microbiota in IBD. The imbalance in the gut microbiome found in patients with neurodegenerative diseases saw a rise in the exploration of the clinical application of microbiome-based therapies involving the GBA, including prebiotics, probiotics, and fecal microbiota transplant (FMT). This direction was supported by studies showing the human gut microbiome as a major determinant of the plasma metabolome, potentially playing a more dominant clinical role than the patients' genome [373–375]. Although significant overall positive effects have been shown from taking probiotics, as well as synbiotics and signaling substances produced by the microbiota, in particular on the mood and cognition in IBD and IBS patients, there is still a substantial lack of fundamental understanding of the underlying molecular pathways and cellular mechanisms to develop reliable therapeutic strategies [199,376–378]. As BAs perform a bactericidal function and are important components of the intestine's innate immunity participating in the control of its bacterial composition, they are promising in relation to the regulation of the GBA. It has been shown that primary taurocholic acid is required for the development of *Clostridioides difficile* [379], whereas secondary LCA and UDCA inhibit the growth of *C. difficile* [380]. Intestinal inflammation caused by this pathogen is often observed in patients with IBD [381]. Thus, in FMT in children with IBD as a treatment of recurrent *C. difficile* infection, only a temporary restoration of the diversity of bacterial microflora was observed and by 6 months it corresponded to the donor level, whereas in children with and without IBD, during the same time, there was a decrease in primary and an increase in secondary BAs, but only in children with IBD did the level reach the donor level [381]. Similar changes in secondary bile acid levels, as well as increases in short-chain fatty acid butyrate, acetate, and propionate levels, were observed after FMT in adult patients [382]. It is likely that the ratio changes of BAs in feces are one of the mechanisms of the therapeutic effect of FMT. Secondary bile acids are currently used in complex therapy of the nervous system pathologies, for example, TUDCA has a neuroprotective, anti-apoptotic effect, and also acts as a mitochondrial stabilizer in various brain disorders, including when taken orally [383]. In addition, secondary bile acids, for example, UDCA, have anti-inflammatory, cytoprotective, and anti-apoptotic effects and are applied in therapies for a wide range of neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease [383]. A number of studies in both animal models and patient data suggest that UDCA also may have a therapeutic role in IBD in regard to GBA influencing intestinal microbiota [384]. Thus, oral administration of UDCA or its taurine- or glycine-conjugated species to mice with experimental colitis reduced its severity, normalized the increased ratio of *Firmicutes* to *Bacteroidetes* associated with colitis, but did not restore bacterial diversity [385]. Currently, there is a lack of therapeutic observations of the effect of BAs on the condition of patients with IBD and nervous system disorders. At the moment, there is only one study that provides clinical results confirming the involvement of gut dysbiosis and BAs metabolic alteration in psychological disorders in Crohn's disease [171].

The next important interconnected links in the chain of GBA balance are the cation transport, actin cytoskeleton, and mitochondrial health (Figure 5). Regarding these basic cellular processes, there are currently few data that could prove their direct interconnection in IBD [386]. However, substantial impairments of all these anchors have been shown in animal models of IBD [85,89,90,387], as well as in several clinical studies [388,389]. To date, one of the well-studied candidates linking these processes within the GBA concept seems to be TRP ion channels families. TRP ion channels are widely expressed in the gastrointestinal tract and peripheral and central nervous systems, performing a number of important

functions there [268,294] (Figure 4). It is known that expression or activity changes, as well as mutations in TRP genes, are often associated with a wide range of intestinal epithelial disorders, including IBD, IBS, fibrosis, visceral hyperalgesia, and colorectal cancer [390]. Therefore, TRP channels are considered potential targets for new analgesics effective within the research and development of new approaches targeting TRP to reduce inflammation and relieve pain in IBD. It has now been shown that TRP channels play a significant role in the pathogenesis of IBD through the regulation of cation transport and interaction with the intestinal microbiota [391]. Currently, the most studied in this regard are TRPV1 and TRPA1, which are known as nociceptors [392,393]. TRPV1 has been shown to be responsible for neuropathic inflammatory pain [300,301] and hyperalgesia [394]. In this context, the interesting clinical study of biopsies from IBS showed that the number of nerve fibers expressing TRPV1 in the colon was markedly increased in relation to a healthy control group, and this increase was correlated with pain severity [395]. TRPA1 is also known to be involved in inflammatory responses and the development of mechanical and chemical hypersensitivity in the colon [303]. It has been shown that the activation of TRPA1 may have a protective effect in IBD by reducing the expression of certain pro-inflammatory neuropeptides, cytokines, and chemokines [300]. Meseguer et al. reported that bacterial lipopolysaccharides could activate TRPA1 channels, causing acute intestinal inflammation and visceral pain [396]. On the other hand, it has been shown that TRP ion channels play a critical role in the dynamics of the actin cytoskeleton [356]. Both the integrity of the intestinal barrier and mitochondrial health in the intestinal cells and neural cells depend on the actin cytoskeleton dynamics [85,317,397]. Mitochondrial functions also depend strictly on both the proper cytoskeleton functioning and calcium transport within the cell. In this review, we summarized data on the involvement and interrelations between these processes in the context of the GBA function imbalance in IBD. The search for new approaches to restore the function of each of these GBA links in IBD may offer ways to achieve long-term and self-sustaining positive therapeutic effects.

7. Conclusions

Numerous studies in both patients and animal models highlight the extensive involvement and importance of the GBA in IBD. Despite the significant interest in the GBA and the extensive research on its role and function in IBD, many aspects of this complex relationship remain unclear. Beyond the primary components of the GBA—vagus nerve function, ENS function, and microbiota—IBD leads to impairments in metabolic regulation, mitochondrial function, cationic transport, and cytoskeleton dynamics in intestinal cells. These mechanisms are also crucial for the proper functioning of neuronal cells. Acute and chronic inflammation, dysbiosis, and impaired digestion and absorption in IBD result in significant metabolic dysregulation. This dysregulation majorly affects the lipidome and cellular energy cycles, which are essential for the nervous system functions. Additionally, due to multiple changes in regulatory metabolic signals, cation transport and mitochondrial functions are disrupted in IBD. Consequently, actin cytoskeleton dysregulation might occur in both enterocytes and nervous system cells. Proper calcium transport is critical for neuronal and mitochondrial functions and is vital for maintaining the integrity of the epithelial barrier. Therefore, all the described processes are interconnected through direct and reverse regulatory pathways, potentially leading to the self-reinforcement of pathology. Deciphering these complex interrelations and their effects on the GBA is crucial. This knowledge may reveal new directions in the search for therapeutic targets and means to improve the quality of life for IBD patients. Despite the large number of studies, there is still a limited clinical arsenal for IBD treatment; mostly, a temporary alleviation of IBD symptoms is possible. Only a small percentage of patients stably respond to therapy, and only a small percentage achieves a complete cure, along with frequent relapses and self-reinforcement, in which GBA imbalance is shown to play a significant role. A further in-depth study of the systemic effects associated with GBA imbalance in IBD, summarized in this review, as well as the discovery of new therapeutic approaches to the restoration of

impaired metabolic, cellular, and organelle functions within the GBA in IBD patients could suggest great translational prospects.

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References

1. Mayer, E.A.; Nance, K.; Chen, S. The Gut-Brain Axis. *Annu. Rev. Med.* **2022**, *73*, 439–453. [[CrossRef](#)] [[PubMed](#)]
2. Barton, J.R.; Londregan, A.K.; Alexander, T.D.; Entezari, A.A.; Covarrubias, M.; Waldman, S.A. Enteroendocrine cell regulation of the gut-brain axis. *Front. Neurosci.* **2023**, *17*, 1272955. [[CrossRef](#)] [[PubMed](#)]
3. Wiley, N.C.; Dinan, T.G.; Ross, R.P.; Stanton, C.; Clarke, G.; Cryan, J.F. The microbiota-gut-brain axis as a key regulator of neural function and the stress response: Implications for human and animal health. *J. Anim. Sci.* **2017**, *95*, 3225–3246. [[CrossRef](#)] [[PubMed](#)]
4. Gunther, C.; Rothhammer, V.; Karow, M.; Neurath, M.; Winner, B. The Gut-Brain Axis in Inflammatory Bowel Disease—Current and Future Perspectives. *Int. J. Mol. Sci.* **2021**, *22*, 8870. [[CrossRef](#)]
5. Koloski, N.A.; Jones, M.; Kalantar, J.; Weltman, M.; Zaguirre, J.; Talley, N.J. The brain–gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. *Gut* **2012**, *61*, 1284–1290. [[CrossRef](#)]
6. Day, A.S.; Yao, C.K.; Costello, S.P.; Andrews, J.M.; Bryant, R.V. Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: A prospective multicentre observational study. *J. Hum. Nutr. Diet.* **2022**, *35*, 234–244. [[CrossRef](#)]
7. Palamenghi, L.; Usta, D.; Leone, S.; Graffigna, G. Food-Related Behavioral Patterns in Patients with Inflammatory Bowel Diseases: The Role of Food Involvement and Health Engagement. *Nutrients* **2024**, *16*, 1185. [[CrossRef](#)]
8. Dolinger, M.; Torres, J.; Vermeire, S. Crohn’s disease. *Lancet* **2024**, *403*, 1177–1191. [[CrossRef](#)]
9. Hendrickson, B.A.; Gokhale, R.; Cho, J.H. Clinical aspects and pathophysiology of inflammatory bowel disease. *Clin. Microbiol. Rev.* **2002**, *15*, 79–94. [[CrossRef](#)]
10. Baumgart, D.C.; Sandborn, W.J. Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet* **2007**, *369*, 1641–1657. [[CrossRef](#)]
11. Cleyne, I.; Boucher, G.; Jostins, L.; Schumm, L.P.; Zeissig, S.; Ahmad, T.; Andersen, V.; Andrews, J.M.; Annese, V.; Brand, S.; et al. Inherited determinants of Crohn’s disease and ulcerative colitis phenotypes: A genetic association study. *Lancet* **2016**, *387*, 156–167. [[CrossRef](#)] [[PubMed](#)]
12. Cleyne, I.; Vazeille, E.; Artieda, M.; Verspaget, H.W.; Szczypiorska, M.; Bringer, M.A.; Lakatos, P.L.; Seibold, F.; Parnell, K.; Weersma, R.K.; et al. Genetic and microbial factors modulating the ubiquitin proteasome system in inflammatory bowel disease. *Gut* **2014**, *63*, 1265–1274. [[CrossRef](#)] [[PubMed](#)]
13. Jostins, L.; Ripke, S.; Weersma, R.K.; Duerr, R.H.; McGovern, D.P.; Hui, K.Y.; Lee, J.C.; Schumm, L.P.; Sharma, Y.; Anderson, C.A.; et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* **2012**, *491*, 119–124. [[CrossRef](#)] [[PubMed](#)]
14. Liu, J.Z.; van Sommeren, S.; Huang, H.; Ng, S.C.; Alberts, R.; Takahashi, A.; Ripke, S.; Lee, J.C.; Jostins, L.; Shah, T.; et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat. Genet.* **2015**, *47*, 979–986. [[CrossRef](#)]
15. McCole, D.F. IBD candidate genes and intestinal barrier regulation. *Inflamm. Bowel Dis.* **2014**, *20*, 1829–1849. [[CrossRef](#)]
16. Momozawa, Y.; Dmitrieva, J.; Theatre, E.; Deffontaine, V.; Rahmouni, S.; Charlotiaux, B.; Crins, F.; Docampo, E.; Elansary, M.; Gori, A.S.; et al. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. *Nat. Commun.* **2018**, *9*, 2427. [[CrossRef](#)]

17. Stankey, C.T.; Bourges, C.; Haag, L.M.; Turner-Stokes, T.; Piedade, A.P.; Palmer-Jones, C.; Papa, I.; Silva Dos Santos, M.; Zhang, Q.; Cameron, A.J.; et al. A disease-associated gene desert directs macrophage inflammation through ETS2. *Nature* **2024**, *630*, 447–456. [[CrossRef](#)]
18. Minea, H.; Singeap, A.M.; Minea, M.; Juncu, S.; Muzica, C.; Sfarti, C.V.; Girleanu, I.; Chiriac, S.; Miftode, I.D.; Stanciu, C.; et al. The Contribution of Genetic and Epigenetic Factors: An Emerging Concept in the Assessment and Prognosis of Inflammatory Bowel Diseases. *Int. J. Mol. Sci.* **2024**, *25*, 8420. [[CrossRef](#)]
19. McCarthy, D.A.; Rampton, D.S.; Liu, Y.C. Peripheral blood neutrophils in inflammatory bowel disease: Morphological evidence of in vivo activation in active disease. *Clin. Exp. Immunol.* **1991**, *86*, 489–493. [[CrossRef](#)]
20. Somasundaram, R.; Nuij, V.J.; van der Woude, C.J.; Kuipers, E.J.; Peppelenbosch, M.P.; Fuhler, G.M. Peripheral neutrophil functions and cell signalling in Crohn's disease. *PLoS ONE* **2013**, *8*, e84521. [[CrossRef](#)]
21. Xavier, R.J.; Podolsky, D.K. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* **2007**, *448*, 427–434. [[CrossRef](#)] [[PubMed](#)]
22. Hanai, H.; Takeuchi, K.; Iida, T.; Kashiwagi, N.; Saniabadi, A.R.; Matsushita, I.; Sato, Y.; Kasuga, N.; Nakamura, T. Relationship between fecal calprotectin, intestinal inflammation, and peripheral blood neutrophils in patients with active ulcerative colitis. *Dig. Dis. Sci.* **2004**, *49*, 1438–1443. [[CrossRef](#)] [[PubMed](#)]
23. Singh, S.; Graff, L.A.; Bernstein, C.N. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am. J. Gastroenterol.* **2009**, *104*, 1298–1313. [[CrossRef](#)]
24. Felder, J.B.; Korelitz, B.I.; Rajapakse, R.; Schwarz, S.; Horatagis, A.P.; Gleim, G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: A case-control study. *Am. J. Gastroenterol.* **2000**, *95*, 1949–1954. [[CrossRef](#)]
25. Ungaro, R.; Bernstein, C.N.; Gearry, R.; Hviid, A.; Kolho, K.L.; Kronman, M.P.; Shaw, S.; Van Kruiningen, H.; Colombel, J.F.; Atreja, A. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: A meta-analysis. *Am. J. Gastroenterol.* **2014**, *109*, 1728–1738. [[CrossRef](#)]
26. Piovani, D.; Danese, S.; Peyrin-Biroulet, L.; Nikolopoulos, G.K.; Lytras, T.; Bonovas, S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. *Gastroenterology* **2019**, *157*, 647–659.e4. [[CrossRef](#)]
27. M'Koma, A.E. Inflammatory bowel disease: An expanding global health problem. *Clin. Med. Insights Gastroenterol.* **2013**, *6*, 33–47. [[CrossRef](#)]
28. Nishida, A.; Inoue, R.; Inatomi, O.; Bamba, S.; Naito, Y.; Andoh, A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin. J. Gastroenterol.* **2018**, *11*, 1–10. [[CrossRef](#)]
29. Carroll, M.W.; Kuenzig, M.E.; Mack, D.R.; Otley, A.R.; Griffiths, A.M.; Kaplan, G.G.; Bernstein, C.N.; Bitton, A.; Murthy, S.K.; Nguyen, G.C.; et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Children and Adolescents with IBD. *J. Can. Assoc. Gastroenterol.* **2019**, *2*, S49–S67. [[CrossRef](#)]
30. Kim, J.S.; Chen, M.H.; Wang, H.E.; Lu, C.L.; Wang, Y.P.; Zhang, B. Inflammatory Bowel Disease and Neurodegenerative Diseases. *Gut Liver* **2023**, *17*, 495–504. [[CrossRef](#)]
31. Kociszewska, D.; Vljakovic, S.M. The Association of Inflammatory Gut Diseases with Neuroinflammatory and Auditory Disorders. *Front. Biosci.* **2022**, *14*, 8. [[CrossRef](#)] [[PubMed](#)]
32. Zamani, M.; Ebrahimitabar, F.; Alizadeh-Tabari, S.; Kasner, S.E.; Elkind, M.S.V.; Ananthkrishnan, A.N.; Choden, T.; Rubin, D.T.; Malekzadeh, R. Risk of Common Neurological Disorders in Adult Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Inflamm. Bowel Dis.* **2024**, *30*, 2195–2204. [[CrossRef](#)] [[PubMed](#)]
33. Belei, O.; Basaca, D.G.; Olariu, L.; Pantea, M.; Bozgan, D.; Nanu, A.; Sirbu, I.; Marginean, O.; Enatescu, I. The Interaction between Stress and Inflammatory Bowel Disease in Pediatric and Adult Patients. *J. Clin. Med.* **2024**, *13*, 1361. [[CrossRef](#)]
34. Fairbrass, K.M.; Lovatt, J.; Barberio, B.; Yuan, Y.; Gracie, D.J.; Ford, A.C. Bidirectional brain-gut axis effects influence mood and prognosis in IBD: A systematic review and meta-analysis. *Gut* **2022**, *71*, 1773–1780. [[CrossRef](#)] [[PubMed](#)]
35. Suman, S. Enteric Nervous System Alterations in Inflammatory Bowel Disease: Perspectives and Implications. *Gastrointest. Disord.* **2024**, *6*, 368–379. [[CrossRef](#)]
36. Collins, S.M. Interrogating the Gut-Brain Axis in the Context of Inflammatory Bowel Disease: A Translational Approach. *Inflamm. Bowel Dis.* **2020**, *26*, 493–501. [[CrossRef](#)]
37. Powley, T.L. Brain-gut communication: Vagovagal reflexes interconnect the two “brains”. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2021**, *321*, G576–G587. [[CrossRef](#)]
38. Furness, J.B.; Callaghan, B.P.; Rivera, L.R.; Cho, H.J. The enteric nervous system and gastrointestinal innervation: Integrated local and central control. *Adv. Exp. Med. Biol.* **2014**, *817*, 39–71. [[CrossRef](#)]
39. Fleming, M.A., 2nd; Ehsan, L.; Moore, S.R.; Levin, D.E. The Enteric Nervous System and Its Emerging Role as a Therapeutic Target. *Gastroenterol. Res. Pract.* **2020**, *2020*, 8024171. [[CrossRef](#)]
40. Villanacci, V.; Bassotti, G.; Nascimbeni, R.; Antonelli, E.; Cadei, M.; Fisogni, S.; Salerni, B.; Geboes, K. Enteric nervous system abnormalities in inflammatory bowel diseases. *Neurogastroenterol. Motil.* **2008**, *20*, 1009–1016. [[CrossRef](#)]
41. De Giorgio, R.; Guerrini, S.; Barbara, G.; Stanghellini, V.; De Ponti, F.; Corinaldesi, R.; Moses, P.L.; Sharkey, K.A.; Mawe, G.M. Inflammatory neuropathies of the enteric nervous system. *Gastroenterology* **2004**, *126*, 1872–1883. [[CrossRef](#)] [[PubMed](#)]
42. Lindgren, S.; Stewenius, J.; Sjolund, K.; Lilja, B.; Sundkvist, G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. *Scand. J. Gastroenterol.* **1993**, *28*, 638–642. [[CrossRef](#)] [[PubMed](#)]

43. Adak, A.; Khan, M.R. An insight into gut microbiota and its functionalities. *Cell Mol. Life Sci.* **2019**, *76*, 473–493. [[CrossRef](#)] [[PubMed](#)]
44. Belizario, J.E.; Faintuch, J.; Garay-Malpartida, M. Gut Microbiome Dysbiosis and Immunometabolism: New Frontiers for Treatment of Metabolic Diseases. *Mediat. Inflamm.* **2018**, *2018*, 2037838. [[CrossRef](#)] [[PubMed](#)]
45. Afzaal, M.; Saeed, F.; Shah, Y.A.; Hussain, M.; Rabail, R.; Socol, C.T.; Hassoun, A.; Pateiro, M.; Lorenzo, J.M.; Rusu, A.V.; et al. Human gut microbiota in health and disease: Unveiling the relationship. *Front. Microbiol.* **2022**, *13*, 999001. [[CrossRef](#)]
46. Zuo, T.; Ng, S.C. The Gut Microbiota in the Pathogenesis and Therapeutics of Inflammatory Bowel Disease. *Front. Microbiol.* **2018**, *9*, 2247. [[CrossRef](#)]
47. Khan, I.; Ullah, N.; Zha, L.; Bai, Y.; Khan, A.; Zhao, T.; Che, T.; Zhang, C. Alteration of Gut Microbiota in Inflammatory Bowel Disease (IBD): Cause or Consequence? IBD Treatment Targeting the Gut Microbiome. *Pathogens* **2019**, *8*, 126. [[CrossRef](#)]
48. Kaminsky, L.W.; Al-Sadi, R.; Ma, T.Y. IL-1beta and the Intestinal Epithelial Tight Junction Barrier. *Front. Immunol.* **2021**, *12*, 767456. [[CrossRef](#)]
49. Longo, L.; Tonin Ferrari, J.; Rampelotto, P.H.; Hirata Dellavia, G.; Pasqualotto, A.; Oliveira, C.P.; Thadeu Schmidt Cerski, C.; Reverbel da Silveira, T.; Uribe-Cruz, C.; Alvares-da-Silva, M.R. Gut Dysbiosis and Increased Intestinal Permeability Drive microRNAs, NLRP-3 Inflammasome and Liver Fibrosis in a Nutritional Model of Non-Alcoholic Steatohepatitis in Adult Male Sprague Dawley Rats. *Clin. Exp. Gastroenterol.* **2020**, *13*, 351–368. [[CrossRef](#)]
50. Barbara, G.; Barbaro, M.R.; Fuschi, D.; Palombo, M.; Falangone, F.; Cremon, C.; Marasco, G.; Stanghellini, V. Inflammatory and Microbiota-Related Regulation of the Intestinal Epithelial Barrier. *Front. Nutr.* **2021**, *8*, 718356. [[CrossRef](#)]
51. Wallen, Z.D.; Demirkan, A.; Twa, G.; Cohen, G.; Dean, M.N.; Standaert, D.G.; Sampson, T.R.; Payami, H. Metagenomics of Parkinson's disease implicates the gut microbiome in multiple disease mechanisms. *Nat. Commun.* **2022**, *13*, 6958. [[CrossRef](#)] [[PubMed](#)]
52. Tan, A.H.; Chong, C.W.; Lim, S.Y.; Yap, I.K.S.; Teh, C.S.J.; Loke, M.F.; Song, S.L.; Tan, J.Y.; Ang, B.H.; Tan, Y.Q.; et al. Gut Microbial Ecosystem in Parkinson Disease: New Clinicobiological Insights from Multi-Omics. *Ann. Neurol.* **2021**, *89*, 546–559. [[CrossRef](#)] [[PubMed](#)]
53. Fritsch, J.; Garces, L.; Quintero, M.A.; Pignac-Kobinger, J.; Santander, A.M.; Fernandez, I.; Ban, Y.J.; Kwon, D.; Phillips, M.C.; Knight, K.; et al. Low-Fat, High-Fiber Diet Reduces Markers of Inflammation and Dysbiosis and Improves Quality of Life in Patients With Ulcerative Colitis. *Clin. Gastroenterol. Hepatol.* **2021**, *19*, 1189–1199.e30. [[CrossRef](#)] [[PubMed](#)]
54. Elzayat, H.; Mesto, G.; Al-Marzooq, F. Unraveling the Impact of Gut and Oral Microbiome on Gut Health in Inflammatory Bowel Diseases. *Nutrients* **2023**, *15*, 3377. [[CrossRef](#)]
55. Dash, N.R.; Al Bataineh, M.T.; Alili, R.; Al Safar, H.; Alkhayyal, N.; Prifti, E.; Zucker, J.D.; Belda, E.; Clement, K. Functional alterations and predictive capacity of gut microbiome in type 2 diabetes. *Sci. Rep.* **2023**, *13*, 22386. [[CrossRef](#)]
56. Mehra, A.; Arora, G.; Sahni, G.; Kaur, M.; Singh, H.; Singh, B.; Kaur, S. Gut microbiota and Autism Spectrum Disorder: From pathogenesis to potential therapeutic perspectives. *J. Tradit. Complement. Med.* **2023**, *13*, 135–149. [[CrossRef](#)]
57. Shoubridge, A.P.; Choo, J.M.; Martin, A.M.; Keating, D.J.; Wong, M.L.; Licinio, J.; Rogers, G.B. The gut microbiome and mental health: Advances in research and emerging priorities. *Mol. Psychiatry* **2022**, *27*, 1908–1919. [[CrossRef](#)]
58. Yeo, X.Y.; Chae, W.R.; Lee, H.U.; Bae, H.G.; Pettersson, S.; Grandjean, J.; Han, W.; Jung, S. Nuanced contribution of gut microbiome in the early brain development of mice. *Gut Microbes* **2023**, *15*, 2283911. [[CrossRef](#)]
59. Liu, W.H.; Chuang, H.L.; Huang, Y.T.; Wu, C.C.; Chou, G.T.; Wang, S.; Tsai, Y.C. Alteration of behavior and monoamine levels attributable to *Lactobacillus plantarum* PS128 in germ-free mice. *Behav. Brain Res.* **2016**, *298*, 202–209. [[CrossRef](#)]
60. Campos, A.C.; Rocha, N.P.; Nicoli, J.R.; Vieira, L.Q.; Teixeira, M.M.; Teixeira, A.L. Absence of gut microbiota influences lipopolysaccharide-induced behavioral changes in mice. *Behav. Brain Res.* **2016**, *312*, 186–194. [[CrossRef](#)]
61. Kelly, J.R.; Borre, Y.; O'Brien, C.; Patterson, E.; El Aidy, S.; Deane, J.; Kennedy, P.J.; Beers, S.; Scott, K.; Moloney, G.; et al. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *J. Psychiatr. Res.* **2016**, *82*, 109–118. [[CrossRef](#)] [[PubMed](#)]
62. Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol. Psychiatry* **2016**, *21*, 786–796. [[CrossRef](#)] [[PubMed](#)]
63. Gonzales, J.; Marchix, J.; Aymeric, L.; Le Berre-Scol, C.; Zoppi, J.; Bordron, P.; Burel, M.; Davidovic, L.; Richard, J.R.; Gaman, A.; et al. Fecal Supernatant from Adult with Autism Spectrum Disorder Alters Digestive Functions, Intestinal Epithelial Barrier, and Enteric Nervous System. *Microorganisms* **2021**, *9*, 1723. [[CrossRef](#)] [[PubMed](#)]
64. Hsiao, E.Y.; McBride, S.W.; Hsien, S.; Sharon, G.; Hyde, E.R.; McCue, T.; Codelli, J.A.; Chow, J.; Reisman, S.E.; Petrosino, J.F.; et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* **2013**, *155*, 1451–1463. [[CrossRef](#)]
65. Chen, Y.; Xu, J.; Chen, Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients* **2021**, *13*, 2099. [[CrossRef](#)]
66. Collins, S.M.; Surette, M.; Bercik, P. The interplay between the intestinal microbiota and the brain. *Nat. Rev. Microbiol.* **2012**, *10*, 735–742. [[CrossRef](#)]
67. Godala, M.; Gaszynska, E.; Durko, L.; Malecka-Wojcieszko, E. Dietary Behaviors and Beliefs in Patients with Inflammatory Bowel Disease. *J. Clin. Med.* **2023**, *12*, 3455. [[CrossRef](#)]

68. Yelencich, E.; Truong, E.; Widaman, A.M.; Pignotti, G.; Yang, L.; Jeon, Y.; Weber, A.T.; Shah, R.; Smith, J.; Sauk, J.S.; et al. Avoidant Restrictive Food Intake Disorder Prevalent Among Patients With Inflammatory Bowel Disease. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 1282–1289.e1. [[CrossRef](#)]
69. Li, W.; Dowd, S.E.; Scurlock, B.; Acosta-Martinez, V.; Lyte, M. Memory and learning behavior in mice is temporally associated with diet-induced alterations in gut bacteria. *Physiol. Behav.* **2009**, *96*, 557–567. [[CrossRef](#)]
70. Magnusson, K.R.; Hauck, L.; Jeffrey, B.M.; Elias, V.; Humphrey, A.; Nath, R.; Perrone, A.; Bermudez, L.E. Relationships between diet-related changes in the gut microbiome and cognitive flexibility. *Neuroscience* **2015**, *300*, 128–140. [[CrossRef](#)]
71. Beilharz, J.E.; Maniam, J.; Morris, M.J. Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats. *Brain Behav. Immun.* **2014**, *37*, 134–141. [[CrossRef](#)] [[PubMed](#)]
72. Martin, S.E.; Kraft, C.S.; Ziegler, T.R.; Millson, E.C.; Rishishwar, L.; Martin, G.S. The Role of Diet on the Gut Microbiome, Mood and Happiness. *medRxiv* **2023**. [[CrossRef](#)]
73. Salehi, Z.; Ghosn, B.; Rahbarinejad, P.; Azadbakht, L. Macronutrients and the state of happiness and mood in undergraduate youth of a military training course. *Clin. Nutr. ESPEN* **2023**, *53*, 33–42. [[CrossRef](#)]
74. Horn, J.; Mayer, D.E.; Chen, S.; Mayer, E.A. Role of diet and its effects on the gut microbiome in the pathophysiology of mental disorders. *Transl. Psychiatry* **2022**, *12*, 164. [[CrossRef](#)]
75. Ayten, S.; Bilici, S. Modulation of Gut Microbiota Through Dietary Intervention in Neuroinflammation and Alzheimer's and Parkinson's Diseases. *Curr. Nutr. Rep.* **2024**, *13*, 82–96. [[CrossRef](#)]
76. Gracie, D.J.; Hamlin, P.J.; Ford, A.C. The influence of the brain-gut axis in inflammatory bowel disease and possible implications for treatment. *Lancet Gastroenterol. Hepatol.* **2019**, *4*, 632–642. [[CrossRef](#)]
77. Peppas, S.; Pansieri, C.; Piovani, D.; Danese, S.; Peyrin-Biroulet, L.; Tsantes, A.G.; Brunetta, E.; Tsantes, A.E.; Bonovas, S. The Brain-Gut Axis: Psychological Functioning and Inflammatory Bowel Diseases. *J. Clin. Med.* **2021**, *10*, 377. [[CrossRef](#)]
78. Aldars-Garcia, L.; Gisbert, J.P.; Chaparro, M. Metabolomics Insights into Inflammatory Bowel Disease: A Comprehensive Review. *Pharmaceuticals* **2021**, *14*, 1190. [[CrossRef](#)]
79. Hua, X.; Ungaro, R.C.; Petrick, L.M.; Chan, A.T.; Porter, C.K.; Khalili, H.; Nurses' Health, S.; Collaborators, P. Inflammatory Bowel Disease Is Associated With Prediagnostic Perturbances in Metabolic Pathways. *Gastroenterology* **2023**, *164*, 147–150.e2. [[CrossRef](#)]
80. Santoru, M.L.; Piras, C.; Murgia, F.; Leoni, V.P.; Spada, M.; Murgia, A.; Liggi, S.; Lai, M.A.; Usai, P.; Caboni, P.; et al. Metabolic Alteration in Plasma and Biopsies From Patients With IBD. *Inflamm. Bowel Dis.* **2021**, *27*, 1335–1345. [[CrossRef](#)]
81. Bauset, C.; Gisbert-Ferrandiz, L.; Cosin-Roger, J. Metabolomics as a Promising Resource Identifying Potential Biomarkers for Inflammatory Bowel Disease. *J. Clin. Med.* **2021**, *10*, 622. [[CrossRef](#)] [[PubMed](#)]
82. Kinter, C.S.; Lundie, J.M.; Patel, H.; Rindler, P.M.; Szwedda, L.I.; Kinter, M. A quantitative proteomic profile of the Nrf2-mediated antioxidant response of macrophages to oxidized LDL determined by multiplexed selected reaction monitoring. *PLoS ONE* **2012**, *7*, e50016. [[CrossRef](#)] [[PubMed](#)]
83. Chiurchiu, V.; Maccarrone, M. Chronic inflammatory disorders and their redox control: From molecular mechanisms to therapeutic opportunities. *Antioxid Redox Signal.* **2011**, *15*, 2605–2641. [[CrossRef](#)] [[PubMed](#)]
84. Tian, T.; Wang, Z.; Zhang, J. Pathomechanisms of Oxidative Stress in Inflammatory Bowel Disease and Potential Antioxidant Therapies. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 4535194. [[CrossRef](#)]
85. Haberman, Y.; Karns, R.; Dexheimer, P.J.; Schirmer, M.; Somekh, J.; Jurickova, I.; Braun, T.; Novak, E.; Bauman, L.; Collins, M.H.; et al. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. *Nat. Commun.* **2019**, *10*, 38. [[CrossRef](#)]
86. Chen, H.; Li, W.; Hu, J.; Xu, F.; Lu, Y.; Zhu, L.; Shen, H. Association of serum lipids with inflammatory bowel disease: A systematic review and meta-analysis. *Front. Med.* **2023**, *10*, 1198988. [[CrossRef](#)]
87. Fan, F.; Mundra, P.A.; Fang, L.; Galvin, A.; Moore, X.L.; Weir, J.M.; Wong, G.; White, D.A.; Chin-Dusting, J.; Sparrow, M.P.; et al. Lipidomic Profiling in Inflammatory Bowel Disease: Comparison Between Ulcerative Colitis and Crohn's Disease. *Inflamm. Bowel Dis.* **2015**, *21*, 1511–1518. [[CrossRef](#)]
88. Noh, J.Y.; Farhataziz, N.; Kinter, M.T.; Yan, X.; Sun, Y. Colonic Dysregulation of Major Metabolic Pathways in Experimental Ulcerative Colitis. *Metabolites* **2024**, *14*, 194. [[CrossRef](#)]
89. Damiani, C.R.; Benetton, C.A.; Stoffel, C.; Bardini, K.C.; Cardoso, V.H.; Di Giunta, G.; Pinho, R.A.; Dal-Pizzol, F.; Streck, E.L. Oxidative stress and metabolism in animal model of colitis induced by dextran sulfate sodium. *J. Gastroenterol. Hepatol.* **2007**, *22*, 1846–1851. [[CrossRef](#)]
90. Borisova, M.A.; Achasova, K.M.; Morozova, K.N.; Andreyeva, E.N.; Litvinova, E.A.; Ogienko, A.A.; Morozova, M.V.; Berkaeva, M.B.; Kiseleva, E.; Kozhevnikova, E.N. Mucin-2 knockout is a model of intercellular junction defects, mitochondrial damage and ATP depletion in the intestinal epithelium. *Sci. Rep.* **2020**, *10*, 21135. [[CrossRef](#)]
91. Higuera, C.; Sainz, A.; Garcia-Sancho, M.; Rodriguez-Franco, F.; Rey, A.I. Faecal Short-Chain, Long-Chain, and Branched-Chain Fatty Acids as Markers of Different Chronic Inflammatory Enteropathies in Dogs. *Animals* **2024**, *14*, 1825. [[CrossRef](#)] [[PubMed](#)]
92. Baur, P.; Martin, F.P.; Gruber, L.; Bosco, N.; Brahmabhatt, V.; Collino, S.; Guy, P.; Montoliu, I.; Rozman, J.; Klingenspor, M.; et al. Metabolic phenotyping of the Crohn's disease-like IBD etiopathology in the TNF(DeltaARE/WT) mouse model. *J. Proteome Res.* **2011**, *10*, 5523–5535. [[CrossRef](#)] [[PubMed](#)]
93. Osetrova, M.; Tkachev, A.; Mair, W.; Gujjarro Larraz, P.; Efimova, O.; Kurochkin, I.; Stekolshchikova, E.; Anikanov, N.; Foo, J.C.; Cazenave-Gassiot, A.; et al. Lipidome atlas of the adult human brain. *Nat. Commun.* **2024**, *15*, 4455. [[CrossRef](#)] [[PubMed](#)]

94. Hornburg, D.; Wu, S.; Moqri, M.; Zhou, X.; Contrepois, K.; Bararpour, N.; Traber, G.M.; Su, B.; Metwally, A.A.; Avina, M.; et al. Dynamic lipidome alterations associated with human health, disease and ageing. *Nat. Metab.* **2023**, *5*, 1578–1594. [[CrossRef](#)]
95. Maccarrone, M. Deciphering Complex Interactions in Bioactive Lipid Signaling. *Molecules* **2023**, *28*, 2622. [[CrossRef](#)]
96. van Meer, G.; Voelker, D.R.; Feigenson, G.W. Membrane lipids: Where they are and how they behave. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 112–124. [[CrossRef](#)]
97. Serhan, C.N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* **2014**, *510*, 92–101. [[CrossRef](#)]
98. Levy, B.D.; Clish, C.B.; Schmidt, B.; Gronert, K.; Serhan, C.N. Lipid mediator class switching during acute inflammation: Signals in resolution. *Nat. Immunol.* **2001**, *2*, 612–619. [[CrossRef](#)]
99. Papackova, Z.; Cahova, M. Fatty acid signaling: The new function of intracellular lipases. *Int. J. Mol. Sci.* **2015**, *16*, 3831–3855. [[CrossRef](#)]
100. Hidalgo, M.A.; Carretta, M.D.; Burgos, R.A. Long Chain Fatty Acids as Modulators of Immune Cells Function: Contribution of FFA1 and FFA4 Receptors. *Front. Physiol.* **2021**, *12*, 668330. [[CrossRef](#)]
101. Falomir-Lockhart, L.J.; Cavazzutti, G.F.; Gimenez, E.; Toscani, A.M. Fatty Acid Signaling Mechanisms in Neural Cells: Fatty Acid Receptors. *Front. Cell. Neurosci.* **2019**, *13*, 162. [[CrossRef](#)] [[PubMed](#)]
102. Tong, B.; Ba, Y.; Li, Z.; Yang, C.; Su, K.; Qi, H.; Zhang, D.; Liu, X.; Wu, Y.; Chen, Y.; et al. Targeting dysregulated lipid metabolism for the treatment of Alzheimer’s disease and Parkinson’s disease: Current advancements and future prospects. *Neurobiol. Dis.* **2024**, *196*, 106505. [[CrossRef](#)] [[PubMed](#)]
103. Sammeta, S.S.; Banarase, T.A.; Rahangdale, S.R.; Wankhede, N.L.; Aglawe, M.M.; Taksande, B.G.; Mangrulkar, S.V.; Upaganlawar, A.B.; Koppula, S.; Kopalli, S.R.; et al. Molecular understanding of ER-MT communication dysfunction during neurodegeneration. *Mitochondrion* **2023**, *72*, 59–71. [[CrossRef](#)]
104. Mavuduru, V.A.; Vadupu, L.; Ghosh, K.K.; Chakraborty, S.; Gulyas, B.; Padmanabhan, P.; Ball, W.B. Mitochondrial phospholipid transport: Role of contact sites and lipid transport proteins. *Prog. Lipid Res.* **2024**, *94*, 101268. [[CrossRef](#)]
105. Bonora, M.; Giorgi, C.; Pinton, P. Molecular mechanisms and consequences of mitochondrial permeability transition. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 266–285. [[CrossRef](#)]
106. Leyrolle, Q.; Decoeur, F.; Briere, G.; Amadiou, C.; Quadros, A.; Voytyuk, I.; Lacabanne, C.; Benmamar-Badel, A.; Bourel, J.; Aubert, A.; et al. Maternal dietary omega-3 deficiency worsens the deleterious effects of prenatal inflammation on the gut-brain axis in the offspring across lifetime. *Neuropsychopharmacology* **2021**, *46*, 579–602. [[CrossRef](#)]
107. Bazinet, R.P.; Laye, S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.* **2014**, *15*, 771–785. [[CrossRef](#)]
108. Brenna, J.T.; Carlson, S.E. Docosahexaenoic acid and human brain development: Evidence that a dietary supply is needed for optimal development. *J. Hum. Evol.* **2014**, *77*, 99–106. [[CrossRef](#)]
109. Kyle, D.J.; Schaefer, E.; Patton, G.; Beiser, A. Low serum docosahexaenoic acid is a significant risk factor for Alzheimer’s dementia. *Lipids* **1999**, *34* (Suppl. 1), S245. [[CrossRef](#)]
110. Tokuda, H.; Kontani, M.; Kawashima, H.; Kiso, Y.; Shibata, H.; Osumi, N. Differential effect of arachidonic acid and docosahexaenoic acid on age-related decreases in hippocampal neurogenesis. *Neurosci. Res.* **2014**, *88*, 58–66. [[CrossRef](#)]
111. Tyagi, S.; Gupta, P.; Saini, A.S.; Kaushal, C.; Sharma, S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. *J. Adv. Pharm. Technol. Res.* **2011**, *2*, 236–240. [[CrossRef](#)] [[PubMed](#)]
112. Howlett, A.C.; Mukhopadhyay, S. Cellular signal transduction by anandamide and 2-arachidonoylglycerol. *Chem. Phys. Lipids* **2000**, *108*, 53–70. [[CrossRef](#)] [[PubMed](#)]
113. Kim, D.J.; Thayer, S.A. Activation of CB1 cannabinoid receptors inhibits neurotransmitter release from identified synaptic sites in rat hippocampal cultures. *Brain Res.* **2000**, *852*, 398–405. [[CrossRef](#)] [[PubMed](#)]
114. Kano, M.; Ohno-Shosaku, T.; Hashimoto-dani, Y.; Uchigashima, M.; Watanabe, M. Endocannabinoid-mediated control of synaptic transmission. *Physiol. Rev.* **2009**, *89*, 309–380. [[CrossRef](#)]
115. Lee, J.Y.; Plakidas, A.; Lee, W.H.; Heikkinen, A.; Chanmugam, P.; Bray, G.; Hwang, D.H. Differential modulation of Toll-like receptors by fatty acids: Preferential inhibition by n-3 polyunsaturated fatty acids. *J. Lipid Res.* **2003**, *44*, 479–486. [[CrossRef](#)]
116. Watson, H.; Mitra, S.; Croden, F.C.; Taylor, M.; Wood, H.M.; Perry, S.L.; Spencer, J.A.; Quirke, P.; Toogood, G.J.; Lawton, C.L.; et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut* **2018**, *67*, 1974–1983. [[CrossRef](#)]
117. Tung, T.H.; Chen, Y.C.; Lin, Y.T.; Huang, S.Y. N-3 PUFA Ameliorates the Gut Microbiota, Bile Acid Profiles, and Neuropsychiatric Behaviours in a Rat Model of Geriatric Depression. *Biomedicines* **2022**, *10*, 1594. [[CrossRef](#)]
118. Keller, L.; Dempfle, A.; Dahmen, B.; Schreiber, S.; Adan, R.A.H.; Andreani, N.A.; Danner, U.N.; Eisert, A.; Fetissov, S.; Fischmeister, F.P.S.; et al. The effects of polyunsaturated fatty acid (PUFA) administration on the microbiome-gut-brain axis in adolescents with anorexia nervosa (the MiGBAN study): Study protocol for a longitudinal, double-blind, randomized, placebo-controlled trial. *Trials* **2022**, *23*, 545. [[CrossRef](#)]
119. Charpentier, C.; Chan, R.; Salameh, E.; Mbodji, K.; Ueno, A.; Coeffier, M.; Guerin, C.; Ghosh, S.; Savoye, G.; Marion-Letellier, R. Dietary n-3 PUFA May Attenuate Experimental Colitis. *Mediat. Inflamm.* **2018**, *2018*, 8430614. [[CrossRef](#)]
120. Martin, F.P.; Lichti, P.; Bosco, N.; Brahmhatt, V.; Oliveira, M.; Haller, D.; Benyacoub, J. Metabolic phenotyping of an adoptive transfer mouse model of experimental colitis and impact of dietary fish oil intake. *J. Proteome Res.* **2015**, *14*, 1911–1919. [[CrossRef](#)]

121. Vargas Robles, H.; Citalan Madrid, A.F.; Garcia Ponce, A.; Silva Olivares, A.; Shibayama, M.; Betanzos, A.; Del Valle Mondragon, L.; Nava, P.; Schnoor, M. Experimental Colitis Is Attenuated by Cardioprotective Diet Supplementation That Reduces Oxidative Stress, Inflammation, and Mucosal Damage. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 8473242. [[CrossRef](#)] [[PubMed](#)]
122. Rohwer, N.; Jelleschitz, J.; Hohn, A.; Weber, D.; Kuhl, A.A.; Wang, C.; Ohno, R.I.; Kampschulte, N.; Pietzner, A.; Schebb, N.H.; et al. Prevention of colitis-induced liver oxidative stress and inflammation in a transgenic mouse model with increased omega-3 polyunsaturated fatty acids. *Redox Biol.* **2023**, *64*, 102803. [[CrossRef](#)] [[PubMed](#)]
123. Ajabnoor, S.M.; Thorpe, G.; Abdelhamid, A.; Hooper, L. Long-term effects of increasing omega-3, omega-6 and total polyunsaturated fats on inflammatory bowel disease and markers of inflammation: A systematic review and meta-analysis of randomized controlled trials. *Eur. J. Nutr.* **2021**, *60*, 2293–2316. [[CrossRef](#)] [[PubMed](#)]
124. Arslan, G.; Brunborg, L.A.; Froyland, L.; Brun, J.G.; Valen, M.; Berstad, A. Effects of duodenal seal oil administration in patients with inflammatory bowel disease. *Lipids* **2002**, *37*, 935–940. [[CrossRef](#)] [[PubMed](#)]
125. Bassaganya-Riera, J.; Hontecillas, R. CLA and n-3 PUFA differentially modulate clinical activity and colonic PPAR-responsive gene expression in a pig model of experimental IBD. *Clin. Nutr.* **2006**, *25*, 454–465. [[CrossRef](#)]
126. Infantino, V.; Iacobazzi, V.; De Santis, F.; Mastrapasqua, M.; Palmieri, F. Transcription of the mitochondrial citrate carrier gene: Role of SREBP-1, upregulation by insulin and downregulation by PUFA. *Biochem. Biophys. Res. Commun.* **2007**, *356*, 249–254. [[CrossRef](#)]
127. Shevchenko, A.; Simons, K. Lipidomics: Coming to grips with lipid diversity. *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 593–598. [[CrossRef](#)]
128. Wang, B.; Tontonoz, P. Phospholipid Remodeling in Physiology and Disease. *Annu. Rev. Physiol.* **2019**, *81*, 165–188. [[CrossRef](#)]
129. Leskova, G.F.; Kryzhanovskii, G.N. Dysregulation of phospholipid metabolism of neuronal membranes in the nervous system pathology. *Zhurnal Nevrol. I Psikiatrii Im. SS Korsakova.* **2010**, *110*, 102–106.
130. Boldyreva, L.V.; Morozova, M.V.; Saydakova, S.S.; Kozhevnikova, E.N. Fat of the Gut: Epithelial Phospholipids in Inflammatory Bowel Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 11682. [[CrossRef](#)]
131. Billah, M.M.; Anthes, J.C. The regulation and cellular functions of phosphatidylcholine hydrolysis. *Biochem. J.* **1990**, *269*, 281–291. [[CrossRef](#)] [[PubMed](#)]
132. Klein, J. Membrane breakdown in acute and chronic neurodegeneration: Focus on choline-containing phospholipids. *J. Neural. Transm.* **2000**, *107*, 1027–1063. [[CrossRef](#)] [[PubMed](#)]
133. Li, Q.; Chen, G.; Zhu, D.; Zhang, W.; Qi, S.; Xue, X.; Wang, K.; Wu, L. Effects of dietary phosphatidylcholine and sphingomyelin on DSS-induced colitis by regulating metabolism and gut microbiota in mice. *J. Nutr. Biochem.* **2022**, *105*, 109004. [[CrossRef](#)] [[PubMed](#)]
134. Stremmel, W.; Merle, U.; Zahn, A.; Autschbach, F.; Hinz, U.; Ehehalt, R. Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. *Gut* **2005**, *54*, 966–971. [[CrossRef](#)]
135. Treede, I.; Braun, A.; Sparla, R.; Kuhnel, M.; Giese, T.; Turner, J.R.; Anes, E.; Kulaksiz, H.; Fullekrug, J.; Stremmel, W.; et al. Anti-inflammatory effects of phosphatidylcholine. *J. Biol. Chem.* **2007**, *282*, 27155–27164. [[CrossRef](#)]
136. Bajjalieh, S.M.; Scheller, R.H. The biochemistry of neurotransmitter secretion. *J. Biol. Chem.* **1995**, *270*, 1971–1974. [[CrossRef](#)]
137. Llahi, S.; Fain, J.N. Alpha 1-adrenergic receptor-mediated activation of phospholipase D in rat cerebral cortex. *J. Biol. Chem.* **1992**, *267*, 3679–3685. [[CrossRef](#)]
138. Gasull, T.; Sarri, E.; DeGregorio-Rocasolano, N.; Trullas, R. NMDA receptor overactivation inhibits phospholipid synthesis by decreasing choline-ethanolamine phosphotransferase activity. *J. Neurosci.* **2003**, *23*, 4100–4107. [[CrossRef](#)]
139. Min, D.S.; Park, S.K.; Exton, J.H. Characterization of a rat brain phospholipase D isozyme. *J. Biol. Chem.* **1998**, *273*, 7044–7051. [[CrossRef](#)]
140. Bollag, W.B.; Zhong, X.; Dodd, M.E.; Hardy, D.M.; Zheng, X.; Allred, W.T. Phospholipase d signaling and extracellular signal-regulated kinase-1 and -2 phosphorylation (activation) are required for maximal phorbol ester-induced transglutaminase activity, a marker of keratinocyte differentiation. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 1223–1231. [[CrossRef](#)]
141. Rodriguez De Turco, E.B.; Jackson, F.R.; DeCoster, M.A.; Kolko, M.; Bazan, N.G. Glutamate signalling and secretory phospholipase A2 modulate the release of arachidonic acid from neuronal membranes. *J. Neurosci. Res.* **2002**, *68*, 558–567. [[CrossRef](#)] [[PubMed](#)]
142. Shen, Y.; Kishimoto, K.; Linden, D.J.; Sapirstein, A. Cytosolic phospholipase A(2) alpha mediates electrophysiologic responses of hippocampal pyramidal neurons to neurotoxic NMDA treatment. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6078–6083. [[CrossRef](#)] [[PubMed](#)]
143. Morgan, C.P.; Skippen, A.; Segui, B.; Ball, A.; Allen-Baume, V.; Larijani, B.; Murray-Rust, J.; McDonald, N.; Sapkota, G.; Morrice, N.; et al. Phosphorylation of a distinct structural form of phosphatidylinositol transfer protein alpha at Ser166 by protein kinase C disrupts receptor-mediated phospholipase C signaling by inhibiting delivery of phosphatidylinositol to membranes. *J. Biol. Chem.* **2004**, *279*, 47159–47171. [[CrossRef](#)] [[PubMed](#)]
144. Winkelmann, P.; Unterweger, A.L.; Khullar, D.; Beigel, F.; Koletzko, L.; Siebeck, M.; Gropp, R. The PI3K pathway as a therapeutic intervention point in inflammatory bowel disease. *Immun. Inflamm. Dis.* **2021**, *9*, 804–818. [[CrossRef](#)]
145. Thakur, P.C.; Davison, J.M.; Stuckenholtz, C.; Lu, L.; Bahary, N. Dysregulated phosphatidylinositol signaling promotes endoplasmic-reticulum-stress-mediated intestinal mucosal injury and inflammation in zebrafish. *Dis. Model. Mech.* **2014**, *7*, 93–106. [[CrossRef](#)]

146. Yang, Q.; Huang, Z.; Diao, N.; Tang, J.; Zhu, X.; Guo, Q.; Chao, K.; Gao, X. Lipidomics reveals significant alterations associated with exclusive enteral nutrition treatment in adult patients with active Crohn's disease. *Ann. Transl. Med.* **2022**, *10*, 1062. [[CrossRef](#)]
147. Cremona, O.; Di Paolo, G.; Wenk, M.R.; Luthi, A.; Kim, W.T.; Takei, K.; Daniell, L.; Nemoto, Y.; Shears, S.B.; Flavell, R.A.; et al. Essential role of phosphoinositide metabolism in synaptic vesicle recycling. *Cell* **1999**, *99*, 179–188. [[CrossRef](#)]
148. Wu, C.Y.; Lin, M.W.; Wu, D.C.; Huang, Y.B.; Huang, H.T.; Chen, C.L. The role of phosphoinositide-regulated actin reorganization in chemotaxis and cell migration. *Br. J. Pharmacol.* **2014**, *171*, 5541–5554. [[CrossRef](#)]
149. Castillo, M.R.; Babson, J.R. Ca²⁺-dependent mechanisms of cell injury in cultured cortical neurons. *Neuroscience* **1998**, *86*, 1133–1144. [[CrossRef](#)]
150. Berman, D.E.; Dall'Armi, C.; Voronov, S.V.; McIntire, L.B.; Zhang, H.; Moore, A.Z.; Staniszewski, A.; Arancio, O.; Kim, T.W.; Di Paolo, G. Oligomeric amyloid-beta peptide disrupts phosphatidylinositol-4,5-bisphosphate metabolism. *Nat. Neurosci.* **2008**, *11*, 547–554. [[CrossRef](#)]
151. Morel, E.; Chamoun, Z.; Lasiecka, Z.M.; Chan, R.B.; Williamson, R.L.; Vetanovetz, C.; Dall'Armi, C.; Simoes, S.; Point Du Jour, K.S.; McCabe, B.D.; et al. Phosphatidylinositol-3-phosphate regulates sorting and processing of amyloid precursor protein through the endosomal system. *Nat. Commun.* **2013**, *4*, 2250. [[CrossRef](#)] [[PubMed](#)]
152. Wu, B.; Kitagawa, K.; Yagy, K.; Zhang, N.Y.; Hattori, N.; Inagaki, C. Phosphatidylinositol and PI-4-monophosphate recover amyloid beta protein-induced inhibition of Cl⁻-ATPase activity. *Life Sci.* **2002**, *72*, 455–463. [[CrossRef](#)] [[PubMed](#)]
153. Wallace, M.A. Effects of Alzheimer's disease-related beta amyloid protein fragments on enzymes metabolizing phosphoinositides in brain. *Biochim. Biophys. Acta* **1994**, *1227*, 183–187. [[CrossRef](#)] [[PubMed](#)]
154. Sieber, F.E.; Traystman, R.J.; Martin, L.J. Delayed neuronal death after global incomplete ischemia in dogs is accompanied by changes in phospholipase C protein expression. *J. Cereb. Blood Flow Metab.* **1997**, *17*, 527–533. [[CrossRef](#)]
155. Hirabayashi, T.; Murayama, T.; Shimizu, T. Regulatory mechanism and physiological role of cytosolic phospholipase A2. *Biol. Pharm. Bull.* **2004**, *27*, 1168–1173. [[CrossRef](#)]
156. Norris, P.C.; Gosselin, D.; Reichart, D.; Glass, C.K.; Dennis, E.A. Phospholipase A2 regulates eicosanoid class switching during inflammasome activation. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 12746–12751. [[CrossRef](#)]
157. Schaeffer, E.L.; Gattaz, W.F. Cholinergic and glutamatergic alterations beginning at the early stages of Alzheimer disease: Participation of the phospholipase A2 enzyme. *Psychopharmacology* **2008**, *198*, 1–27. [[CrossRef](#)]
158. Sun, G.Y.; Xu, J.; Jensen, M.D.; Simonyi, A. Phospholipase A2 in the central nervous system: Implications for neurodegenerative diseases. *J. Lipid Res.* **2004**, *45*, 205–213. [[CrossRef](#)]
159. Gerard, P. Metabolism of cholesterol and bile acids by the gut microbiota. *Pathogens* **2013**, *3*, 14–24. [[CrossRef](#)]
160. Quinn, R.A.; Melnik, A.V.; Vrbanac, A.; Fu, T.; Patras, K.A.; Christy, M.P.; Bodai, Z.; Belda-Ferre, P.; Tripathi, A.; Chung, L.K.; et al. Global chemical effects of the microbiome include new bile-acid conjugations. *Nature* **2020**, *579*, 123–129. [[CrossRef](#)]
161. Juarez-Fernandez, M.; Porras, D.; Garcia-Mediavilla, M.V.; Roman-Saguillo, S.; Gonzalez-Gallego, J.; Nistal, E.; Sanchez-Campos, S. Aging, Gut Microbiota and Metabolic Diseases: Management through Physical Exercise and Nutritional Interventions. *Nutrients* **2020**, *13*, 16. [[CrossRef](#)] [[PubMed](#)]
162. Van den Abbeele, P.; Belzer, C.; Goossens, M.; Kleerebezem, M.; De Vos, W.M.; Thas, O.; De Weirtdt, R.; Kerckhof, F.M.; Van de Wiele, T. Butyrate-producing Clostridium cluster XIVa species specifically colonize mucins in an in vitro gut model. *ISME J.* **2013**, *7*, 949–961. [[CrossRef](#)] [[PubMed](#)]
163. Hylemon, P.B.; Zhou, H.; Pandak, W.M.; Ren, S.; Gil, G.; Dent, P. Bile acids as regulatory molecules. *J. Lipid Res.* **2009**, *50*, 1509–1520. [[CrossRef](#)] [[PubMed](#)]
164. Cai, J.; Rimal, B.; Jiang, C.; Chiang, J.Y.L.; Patterson, A.D. Bile acid metabolism and signaling, the microbiota, and metabolic disease. *Pharmacol. Ther.* **2022**, *237*, 108238. [[CrossRef](#)]
165. Duboc, H.; Rajca, S.; Rainteau, D.; Benarous, D.; Maubert, M.A.; Quervain, E.; Thomas, G.; Barbu, V.; Humbert, L.; Despras, G.; et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut* **2013**, *62*, 531–539. [[CrossRef](#)]
166. Eckburg, P.B.; Bik, E.M.; Bernstein, C.N.; Purdom, E.; Dethlefsen, L.; Sargent, M.; Gill, S.R.; Nelson, K.E.; Relman, D.A. Diversity of the human intestinal microbial flora. *Science* **2005**, *308*, 1635–1638. [[CrossRef](#)]
167. Franzosa, E.A.; Sirota-Madi, A.; Avila-Pacheco, J.; Fornelos, N.; Haiser, H.J.; Reinker, S.; Vatanen, T.; Hall, A.B.; Mallick, H.; McIver, L.J.; et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat. Microbiol.* **2019**, *4*, 293–305. [[CrossRef](#)]
168. Sokol, H.; Seksik, P.; Furet, J.P.; Firmesse, O.; Nion-Larmurier, I.; Beaugerie, L.; Cosnes, J.; Corthier, G.; Marteau, P.; Dore, J. Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflamm. Bowel Dis.* **2009**, *15*, 1183–1189. [[CrossRef](#)]
169. Fiorucci, S.; Carino, A.; Baldoni, M.; Santucci, L.; Costanzi, E.; Graziosi, L.; Distrutti, E.; Biagioli, M. Bile Acid Signaling in Inflammatory Bowel Diseases. *Dig. Dis. Sci.* **2021**, *66*, 674–693. [[CrossRef](#)]
170. Vich Vila, A.; Hu, S.; Andreu-Sanchez, S.; Collij, V.; Jansen, B.H.; Augustijn, H.E.; Bolte, L.A.; Ruigrok, R.; Abu-Ali, G.; Giallourakis, C.; et al. Faecal metabolome and its determinants in inflammatory bowel disease. *Gut* **2023**, *72*, 1472–1485. [[CrossRef](#)]
171. Feng, L.; Zhou, N.; Li, Z.; Fu, D.; Guo, Y.; Gao, X.; Liu, X. Co-occurrence of gut microbiota dysbiosis and bile acid metabolism alteration is associated with psychological disorders in Crohn's disease. *FASEB J.* **2022**, *36*, e22100. [[CrossRef](#)] [[PubMed](#)]

172. Sun, R.; Jiang, J.; Yang, L.; Chen, L.; Chen, H. Alterations of Serum Bile Acid Profile in Patients with Crohn's Disease. *Gastroenterol. Res. Pract.* **2022**, *2022*, 1680008. [[CrossRef](#)] [[PubMed](#)]
173. Gonzalez, C.G.; Mills, R.H.; Zhu, Q.; Saucedo, C.; Knight, R.; Dulai, P.S.; Gonzalez, D.J. Location-specific signatures of Crohn's disease at a multi-omics scale. *Microbiome* **2022**, *10*, 133. [[CrossRef](#)] [[PubMed](#)]
174. Connors, J.; Dunn, K.A.; Allott, J.; Bandsma, R.; Rashid, M.; Otle, A.R.; Bielawski, J.P.; Van Limbergen, J. The relationship between fecal bile acids and microbiome community structure in pediatric Crohn's disease. *ISME J.* **2020**, *14*, 702–713. [[CrossRef](#)]
175. Hao, Z.; Wang, W.; Guo, R.; Liu, H. Faecalibacterium prausnitzii (ATCC 27766) has preventive and therapeutic effects on chronic unpredictable mild stress-induced depression-like and anxiety-like behavior in rats. *Psychoneuroendocrinology* **2019**, *104*, 132–142. [[CrossRef](#)]
176. Kamp, F.; Hamilton, J.A.; Kamp, F.; Westerhoff, H.V.; Hamilton, J.A. Movement of fatty acids, fatty acid analogues, and bile acids across phospholipid bilayers. *Biochemistry* **1993**, *32*, 11074–11086. [[CrossRef](#)]
177. Higashi, T.; Watanabe, S.; Tomaru, K.; Yamazaki, W.; Yoshizawa, K.; Ogawa, S.; Nagao, H.; Minato, K.; Maekawa, M.; Mano, N. Unconjugated bile acids in rat brain: Analytical method based on LC/ESI-MS/MS with chemical derivatization and estimation of their origin by comparison to serum levels. *Steroids* **2017**, *125*, 107–113. [[CrossRef](#)]
178. Mano, N.; Goto, T.; Uchida, M.; Nishimura, K.; Ando, M.; Kobayashi, N.; Goto, J. Presence of protein-bound unconjugated bile acids in the cytoplasmic fraction of rat brain. *J. Lipid Res.* **2004**, *45*, 295–300. [[CrossRef](#)]
179. Pan, X.; Elliott, C.T.; McGuinness, B.; Passmore, P.; Kehoe, P.G.; Holscher, C.; McClean, P.L.; Graham, S.F.; Green, B.D. Metabolomic Profiling of Bile Acids in Clinical and Experimental Samples of Alzheimer's Disease. *Metabolites* **2017**, *7*, 28. [[CrossRef](#)]
180. Zheng, X.; Chen, T.; Zhao, A.; Wang, X.; Xie, G.; Huang, F.; Liu, J.; Zhao, Q.; Wang, S.; Wang, C.; et al. The Brain Metabolome of Male Rats across the Lifespan. *Sci. Rep.* **2016**, *6*, 24125. [[CrossRef](#)]
181. Choudhuri, S.; Cherrington, N.J.; Li, N.; Klaassen, C.D. Constitutive expression of various xenobiotic and endobiotic transporter mRNAs in the choroid plexus of rats. *Drug Metab. Dispos.* **2003**, *31*, 1337–1345. [[CrossRef](#)] [[PubMed](#)]
182. Quinn, M.; McMillin, M.; Galindo, C.; Frampton, G.; Pae, H.Y.; DeMorrow, S. Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms. *Dig. Liver Dis.* **2014**, *46*, 527–534. [[CrossRef](#)] [[PubMed](#)]
183. Lalic-Popovic, M.; Vasovic, V.; Milijasevic, B.; Golocorbin-Kon, S.; Al-Salami, H.; Mikov, M. Deoxycholic Acid as a Modifier of the Permeation of Gliclazide through the Blood Brain Barrier of a Rat. *J. Diabetes Res.* **2013**, *2013*, 598603. [[CrossRef](#)] [[PubMed](#)]
184. Fiaschini, N.; Mancuso, M.; Tanori, M.; Colantoni, E.; Vitali, R.; Diretto, G.; Lorenzo Rebenaque, L.; Stronati, L.; Negroni, A. Liver Steatosis and Steatohepatitis Alter Bile Acid Receptors in Brain and Induce Neuroinflammation: A Contribution of Circulating Bile Acids and Blood-Brain Barrier. *Int. J. Mol. Sci.* **2022**, *23*, 14254. [[CrossRef](#)]
185. Stanimirov, B.; Stankov, K.; Mikov, M. Pleiotropic functions of bile acids mediated by the farnesoid X receptor. *Acta Gastroenterol. Belg.* **2012**, *75*, 389–398.
186. Kawamata, Y.; Fujii, R.; Hosoya, M.; Harada, M.; Yoshida, H.; Miwa, M.; Fukusumi, S.; Habata, Y.; Itoh, T.; Shintani, Y.; et al. A G protein-coupled receptor responsive to bile acids. *J. Biol. Chem.* **2003**, *278*, 9435–9440. [[CrossRef](#)]
187. Fogelson, K.A.; Dorrestein, P.C.; Zarrinpar, A.; Knight, R. The Gut Microbial Bile Acid Modulation and Its Relevance to Digestive Health and Diseases. *Gastroenterology* **2023**, *164*, 1069–1085. [[CrossRef](#)]
188. Perino, A.; Demagny, H.; Velazquez-Villegas, L.; Schoonjans, K. Molecular Physiology of Bile Acid Signaling in Health, Disease, and Aging. *Physiol. Rev.* **2021**, *101*, 683–731. [[CrossRef](#)]
189. Fleishman, J.S.; Kumar, S. Bile acid metabolism and signaling in health and disease: Molecular mechanisms and therapeutic targets. *Sig. Transduct. Target. Ther.* **2024**, *9*, 97. [[CrossRef](#)]
190. Huang, F.; Wang, T.; Lan, Y.; Yang, L.; Pan, W.; Zhu, Y.; Lv, B.; Wei, Y.; Shi, H.; Wu, H.; et al. Deletion of mouse FXR gene disturbs multiple neurotransmitter systems and alters neurobehavior. *Front. Behav. Neurosci.* **2015**, *9*, 70. [[CrossRef](#)]
191. McMillin, M.; Frampton, G.; Quinn, M.; Ashfaq, S.; de los Santos, M., 3rd; Grant, S.; DeMorrow, S. Bile Acid Signaling Is Involved in the Neurological Decline in a Murine Model of Acute Liver Failure. *Am. J. Pathol.* **2016**, *186*, 312–323. [[CrossRef](#)] [[PubMed](#)]
192. Chen, W.G.; Zheng, J.X.; Xu, X.; Hu, Y.M.; Ma, Y.M. Hippocampal FXR plays a role in the pathogenesis of depression: A preliminary study based on lentiviral gene modulation. *Psychiatry Res.* **2018**, *264*, 374–379. [[CrossRef](#)] [[PubMed](#)]
193. McMillin, M.; Frampton, G.; Tobin, R.; Dusio, G.; Smith, J.; Shin, H.; Newell-Rogers, K.; Grant, S.; DeMorrow, S. TGR5 signaling reduces neuroinflammation during hepatic encephalopathy. *J. Neurochem.* **2015**, *135*, 565–576. [[CrossRef](#)]
194. Yanguas-Casas, N.; Barreda-Manso, M.A.; Nieto-Sampedro, M.; Romero-Ramirez, L. TUDCA: An Agonist of the Bile Acid Receptor GPBAR1/TGR5 with Anti-Inflammatory Effects in Microglial Cells. *J. Cell. Physiol.* **2017**, *232*, 2231–2245. [[CrossRef](#)]
195. Xiang, P.; Chew, W.S.; Seow, W.L.; Lam, B.W.S.; Ong, W.Y.; Herr, D.R. The S1P(2) receptor regulates blood-brain barrier integrity and leukocyte extravasation with implications for neurodegenerative disease. *Neurochem. Int.* **2021**, *146*, 105018. [[CrossRef](#)]
196. McMillin, M.; Frampton, G.; Grant, S.; Khan, S.; Diocares, J.; Petrescu, A.; Wyatt, A.; Kain, J.; Jefferson, B.; DeMorrow, S. Bile Acid-Mediated Sphingosine-1-Phosphate Receptor 2 Signaling Promotes Neuroinflammation during Hepatic Encephalopathy in Mice. *Front. Cell. Neurosci.* **2017**, *11*, 191. [[CrossRef](#)]
197. Xu, N.; Bai, Y.; Han, X.; Yuan, J.; Wang, L.; He, Y.; Yang, L.; Wu, H.; Shi, H.; Wu, X. Taurochenodeoxycholic acid reduces astrocytic neuroinflammation and alleviates experimental autoimmune encephalomyelitis in mice. *Immunobiology* **2023**, *228*, 152388. [[CrossRef](#)]

198. Wang, H.; Tan, Y.Z.; Mu, R.H.; Tang, S.S.; Liu, X.; Xing, S.Y.; Long, Y.; Yuan, D.H.; Hong, H. Takeda G Protein-Coupled Receptor 5 Modulates Depression-like Behaviors via Hippocampal CA3 Pyramidal Neurons Afferent to Dorsolateral Septum. *Biol. Psychiatry* **2021**, *89*, 1084–1095. [[CrossRef](#)]
199. Loh, J.S.; Mak, W.Q.; Tan, L.K.S.; Ng, C.X.; Chan, H.H.; Yeow, S.H.; Foo, J.B.; Ong, Y.S.; How, C.W.; Khaw, K.Y. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct. Target. Ther.* **2024**, *9*, 37. [[CrossRef](#)]
200. Zhu, Y.; Li, Y.; Zhang, Q.; Song, Y.; Wang, L.; Zhu, Z. Interactions Between Intestinal Microbiota and Neural Mitochondria: A New Perspective on Communicating Pathway From Gut to Brain. *Front. Microbiol.* **2022**, *13*, 798917. [[CrossRef](#)]
201. Ozsoy, M.; Stummer, N.; Zimmermann, F.A.; Feichtinger, R.G.; Sperl, W.; Weghuber, D.; Schneider, A.M. Role of Energy Metabolism and Mitochondrial Function in Inflammatory Bowel Disease. *Inflamm. Bowel. Dis.* **2022**, *28*, 1443–1450. [[CrossRef](#)] [[PubMed](#)]
202. Borbolis, F.; Mytilinaiou, E.; Palikaras, K. The Crosstalk between Microbiome and Mitochondrial Homeostasis in Neurodegeneration. *Cells* **2023**, *12*, 429. [[CrossRef](#)] [[PubMed](#)]
203. Austin, S.; Nowikovsky, K. LETM1: Essential for Mitochondrial Biology and Cation Homeostasis? *Trends Biochem. Sci.* **2019**, *44*, 648–658. [[CrossRef](#)] [[PubMed](#)]
204. Pain, P.; Spinelli, F.; Gherardi, G. Mitochondrial Cation Signalling in the Control of Inflammatory Processes. *Int. J. Mol. Sci.* **2023**, *24*, 16724. [[CrossRef](#)]
205. Schirmmayer, V. Mitochondria at Work: New Insights into Regulation and Dysregulation of Cellular Energy Supply and Metabolism. *Biomedicines* **2020**, *8*, 526. [[CrossRef](#)]
206. Iqbal, J.; Hussain, M.M. Intestinal lipid absorption. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *296*, E1183–E1194. [[CrossRef](#)]
207. Benador, I.Y.; Veliova, M.; Mahdavian, K.; Petcherski, A.; Wikstrom, J.D.; Assali, E.A.; Acin-Perez, R.; Shum, M.; Oliveira, M.F.; Cinti, S.; et al. Mitochondria Bound to Lipid Droplets Have Unique Bioenergetics, Composition, and Dynamics that Support Lipid Droplet Expansion. *Cell Metab.* **2018**, *27*, 869–885.e6. [[CrossRef](#)]
208. Olzmann, J.A.; Carvalho, P. Dynamics and functions of lipid droplets. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 137–155. [[CrossRef](#)]
209. Benador, I.Y.; Veliova, M.; Liesa, M.; Shirihai, O.S. Mitochondria Bound to Lipid Droplets: Where Mitochondrial Dynamics Regulate Lipid Storage and Utilization. *Cell Metab.* **2019**, *29*, 827–835. [[CrossRef](#)]
210. Alaynick, W.A. Nuclear receptors, mitochondria and lipid metabolism. *Mitochondrion* **2008**, *8*, 329–337. [[CrossRef](#)]
211. Barish, G.D.; Downes, M.; Alaynick, W.A.; Yu, R.T.; Ocampo, C.B.; Bookout, A.L.; Mangelsdorf, D.J.; Evans, R.M. A Nuclear Receptor Atlas: Macrophage activation. *Mol. Endocrinol.* **2005**, *19*, 2466–2477. [[CrossRef](#)] [[PubMed](#)]
212. Bookout, A.L.; Jeong, Y.; Downes, M.; Yu, R.T.; Evans, R.M.; Mangelsdorf, D.J. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* **2006**, *126*, 789–799. [[CrossRef](#)] [[PubMed](#)]
213. Hassan, F.U.; Nadeem, A.; Li, Z.; Javed, M.; Liu, Q.; Azhar, J.; Rehman, M.S.; Cui, K.; Rehman, S.U. Role of Peroxisome Proliferator-Activated Receptors (PPARs) in Energy Homeostasis of Dairy Animals: Exploiting Their Modulation through Nutrigenomic Interventions. *Int. J. Mol. Sci.* **2021**, *22*, 12463. [[CrossRef](#)] [[PubMed](#)]
214. Valm, A.M.; Cohen, S.; Legant, W.R.; Melunis, J.; Hershberg, U.; Wait, E.; Cohen, A.R.; Davidson, M.W.; Betzig, E.; Lippincott-Schwartz, J. Applying systems-level spectral imaging and analysis to reveal the organelle interactome. *Nature* **2017**, *546*, 162–167. [[CrossRef](#)]
215. Scorrano, L.; De Matteis, M.A.; Emr, S.; Giordano, F.; Hajnoczky, G.; Kornmann, B.; Lackner, L.L.; Levine, T.P.; Pellegrini, L.; Reinisch, K.; et al. Coming together to define membrane contact sites. *Nat. Commun.* **2019**, *10*, 1287. [[CrossRef](#)]
216. Ma, X.; Qian, H.; Chen, A.; Ni, H.M.; Ding, W.X. Perspectives on Mitochondria-ER and Mitochondria-Lipid Droplet Contact in Hepatocytes and Hepatic Lipid Metabolism. *Cells* **2021**, *10*, 2273. [[CrossRef](#)]
217. Rambold, A.S.; Cohen, S.; Lippincott-Schwartz, J. Fatty acid trafficking in starved cells: Regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics. *Dev. Cell* **2015**, *32*, 678–692. [[CrossRef](#)]
218. Hartman, C.; Eliakim, R.; Shamir, R. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World J. Gastroenterol.* **2009**, *15*, 2570–2578. [[CrossRef](#)]
219. Liu, S.; Yao, S.; Yang, H.; Liu, S.; Wang, Y. Autophagy: Regulator of cell death. *Cell Death Dis.* **2023**, *14*, 648. [[CrossRef](#)]
220. Bulow, M.H.; Wingen, C.; Senyilmaz, D.; Gosejacob, D.; Sociale, M.; Bauer, R.; Schulze, H.; Sandhoff, K.; Teleman, A.A.; Hoch, M.; et al. Unbalanced lipolysis results in lipotoxicity and mitochondrial damage in peroxisome-deficient Pex19 mutants. *Mol. Biol. Cell* **2018**, *29*, 396–407. [[CrossRef](#)]
221. Bosma, M.; Dapito, D.H.; Drosatos-Tampakaki, Z.; Huiping-Son, N.; Huang, L.S.; Kersten, S.; Drosatos, K.; Goldberg, I.J. Sequestration of fatty acids in triglycerides prevents endoplasmic reticulum stress in an in vitro model of cardiomyocyte lipotoxicity. *Biochim. Biophys. Acta* **2014**, *1841*, 1648–1655. [[CrossRef](#)] [[PubMed](#)]
222. Komatsu, M.; Waguri, S.; Chiba, T.; Murata, S.; Iwata, J.; Tanida, I.; Ueno, T.; Koike, M.; Uchiyama, Y.; Kominami, E.; et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* **2006**, *441*, 880–884. [[CrossRef](#)] [[PubMed](#)]
223. Friedman, L.G.; Lachenmayer, M.L.; Wang, J.; He, L.; Poulouse, S.M.; Komatsu, M.; Holstein, G.R.; Yue, Z. Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of alpha-synuclein and LRRK2 in the brain. *J. Neurosci.* **2012**, *32*, 7585–7593. [[CrossRef](#)] [[PubMed](#)]
224. La Barbera, L.; Vedele, F.; Nobili, A.; Krashia, P.; Spoletti, E.; Latagliata, E.C.; Cutuli, D.; Cauzzi, E.; Marino, R.; Viscomi, M.T.; et al. Nilotinib restores memory function by preventing dopaminergic neuron degeneration in a mouse model of Alzheimer's Disease. *Prog. Neurobiol.* **2021**, *202*, 102031. [[CrossRef](#)]

225. Hernandez-Diaz, S.; Soukup, S.F. The role of lipids in autophagy and its implication in neurodegeneration. *Cell Stress* **2020**, *4*, 167–186. [[CrossRef](#)]
226. Fan, H.; Tan, Y. Lipid Droplet-Mitochondria Contacts in Health and Disease. *Int. J. Mol. Sci.* **2024**, *25*, 6878. [[CrossRef](#)]
227. Mallick, K.; Paul, S.; Banerjee, S.; Banerjee, S. Lipid Droplets and Neurodegeneration. *Neuroscience* **2024**, *549*, 13–23. [[CrossRef](#)]
228. Wit, M.; Trujillo-Viera, J.; Strohmeyer, A.; Klingenspor, M.; Hankir, M.; Sumara, G. When fat meets the gut-focus on intestinal lipid handling in metabolic health and disease. *EMBO Mol. Med.* **2022**, *14*, e14742. [[CrossRef](#)]
229. Cui, L.; Liu, P. Two Types of Contact between Lipid Droplets and Mitochondria. *Front. Cell Dev. Biol.* **2020**, *8*, 618322. [[CrossRef](#)]
230. Fernie, A.R.; Carrari, F.; Sweetlove, L.J. Respiratory metabolism: Glycolysis, the TCA cycle and mitochondrial electron transport. *Curr. Opin. Plant Biol.* **2004**, *7*, 254–261. [[CrossRef](#)]
231. Sato, K.; Chitose, S.I.; Sato, K.; Sato, F.; Kurita, T.; Umeno, H. Metabolic activity of cells in the macula flava of the human vocal fold from the aspect of mitochondrial microstructure. *Laryngoscope Investig. Otolaryngol.* **2019**, *4*, 405–409. [[CrossRef](#)] [[PubMed](#)]
232. Xia, Y.; Zhang, L.; Ocansey, D.K.W.; Tu, Q.; Mao, F.; Sheng, X. Role of glycolysis in inflammatory bowel disease and its associated colorectal cancer. *Front. Endocrinol.* **2023**, *14*, 1242991. [[CrossRef](#)] [[PubMed](#)]
233. Cogliati, S.; Frezza, C.; Soriano, M.E.; Varanita, T.; Quintana-Cabrera, R.; Corrado, M.; Cipolat, S.; Costa, V.; Casarin, A.; Gomes, L.C.; et al. Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency. *Cell* **2013**, *155*, 160–171. [[CrossRef](#)] [[PubMed](#)]
234. Jin, Y.; Tan, Y.; Chen, L.; Liu, Y.; Ren, Z. Reactive Oxygen Species Induces Lipid Droplet Accumulation in HepG2 Cells by Increasing Perilipin 2 Expression. *Int. J. Mol. Sci.* **2018**, *19*, 3445. [[CrossRef](#)]
235. Ikeda, Y.; Saigo, N.; Nagasaki, Y. Direct evidence for the involvement of intestinal reactive oxygen species in the progress of depression via the gut-brain axis. *Biomaterials* **2023**, *295*, 122053. [[CrossRef](#)]
236. Simoes, I.C.M.; Morciano, G.; Lebedzinska-Arciszewska, M.; Aguiari, G.; Pinton, P.; Potes, Y.; Wieckowski, M.R. The mystery of mitochondria-ER contact sites in physiology and pathology: A cancer perspective. *Biochim. Biophys. Acta Mol. Basis Dis.* **2020**, *1866*, 165834. [[CrossRef](#)]
237. Rizzuto, R.; Duchen, M.R.; Pozzan, T. Flirting in little space: The ER/mitochondria Ca²⁺ liaison. *Sci. STKE* **2004**, *2004*, re1. [[CrossRef](#)]
238. Porter, G.A., Jr.; Beutner, G. Cyclophilin D, Somehow a Master Regulator of Mitochondrial Function. *Biomolecules* **2018**, *8*, 176. [[CrossRef](#)]
239. Vodickova, A.; Koren, S.A.; Wojtovich, A.P. Site-specific mitochondrial dysfunction in neurodegeneration. *Mitochondrion* **2022**, *64*, 1–18. [[CrossRef](#)]
240. Rodriguez-Arribas, M.; Yakhine-Diop, S.M.S.; Pedro, J.M.B.; Gomez-Suaga, P.; Gomez-Sanchez, R.; Martinez-Chacon, G.; Fuentes, J.M.; Gonzalez-Polo, R.A.; Niso-Santano, M. Mitochondria-Associated Membranes (MAMs): Overview and Its Role in Parkinson's Disease. *Mol. Neurobiol.* **2017**, *54*, 6287–6303. [[CrossRef](#)]
241. Parakh, S.; Perri, E.R.; Jagaraj, C.J.; Ragagnin, A.M.G.; Atkin, J.D. Rab-dependent cellular trafficking and amyotrophic lateral sclerosis. *Crit. Rev. Biochem. Mol. Biol.* **2018**, *53*, 623–651. [[CrossRef](#)] [[PubMed](#)]
242. Yoo, S.M.; Jung, Y.K. A Molecular Approach to Mitophagy and Mitochondrial Dynamics. *Mol. Cells* **2018**, *41*, 18–26. [[CrossRef](#)] [[PubMed](#)]
243. Han, S.; Jeong, Y.Y.; Sheshadri, P.; Su, X.; Cai, Q. Mitophagy regulates integrity of mitochondria at synapses and is critical for synaptic maintenance. *EMBO Rep.* **2020**, *21*, e49801. [[CrossRef](#)] [[PubMed](#)]
244. Lou, G.; Palikaras, K.; Lautrup, S.; Scheibye-Knudsen, M.; Tavernarakis, N.; Fang, E.F. Mitophagy and Neuroprotection. *Trends Mol. Med.* **2020**, *26*, 8–20. [[CrossRef](#)] [[PubMed](#)]
245. Martinez-Vicente, M. Neuronal Mitophagy in Neurodegenerative Diseases. *Front. Mol. Neurosci.* **2017**, *10*, 64. [[CrossRef](#)]
246. Cai, Q.; Jeong, Y.Y. Mitophagy in Alzheimer's Disease and Other Age-Related Neurodegenerative Diseases. *Cells* **2020**, *9*, 150. [[CrossRef](#)]
247. Lazarou, M.; Sliter, D.A.; Kane, L.A.; Sarraf, S.A.; Wang, C.; Burman, J.L.; Sideris, D.P.; Fogel, A.I.; Youle, R.J. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* **2015**, *524*, 309–314. [[CrossRef](#)]
248. Rakovic, A.; Shurkewitsch, K.; Seibler, P.; Grunewald, A.; Zanon, A.; Hagenah, J.; Krainc, D.; Klein, C. Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)-dependent ubiquitination of endogenous Parkin attenuates mitophagy: Study in human primary fibroblasts and induced pluripotent stem cell-derived neurons. *J. Biol. Chem.* **2013**, *288*, 2223–2237. [[CrossRef](#)]
249. Jin, S.M.; Youle, R.J. PINK1- and Parkin-mediated mitophagy at a glance. *J. Cell Sci.* **2012**, *125*, 795–799. [[CrossRef](#)]
250. Padman, B.S.; Nguyen, T.N.; Uoselis, L.; Skulsuppaisarn, M.; Nguyen, L.K.; Lazarou, M. LC3/GABARAPs drive ubiquitin-independent recruitment of Optineurin and NDP52 to amplify mitophagy. *Nat. Commun.* **2019**, *10*, 408. [[CrossRef](#)]
251. Kang, C.; Badr, M.A.; Kyrychenko, V.; Eskelinen, E.L.; Shirokova, N. Deficit in PINK1/PARKIN-mediated mitochondrial autophagy at late stages of dystrophic cardiomyopathy. *Cardiovasc. Res.* **2018**, *114*, 90–102. [[CrossRef](#)] [[PubMed](#)]
252. Subramaniam, S.R.; Chesselet, M.F. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Prog. Neurobiol.* **2013**, *106–107*, 17–32. [[CrossRef](#)] [[PubMed](#)]
253. Cardanho-Ramos, C.; Faria-Pereira, A.; Morais, V.A. Orchestrating mitochondria in neurons: Cytoskeleton as the conductor. *Cytoskeleton* **2020**, *77*, 65–75. [[CrossRef](#)] [[PubMed](#)]

254. Davis, C.H.; Marsh-Armstrong, N. Discovery and implications of transcellular mitophagy. *Autophagy* **2014**, *10*, 2383–2384. [[CrossRef](#)] [[PubMed](#)]
255. Swerdlow, N.S.; Wilkins, H.M. Mitophagy and the Brain. *Int. J. Mol. Sci.* **2020**, *21*, 9661. [[CrossRef](#)]
256. Li, F.; Wang, Y.; Zheng, K. Microglial mitophagy integrates the microbiota-gut-brain axis to restrain neuroinflammation during neurotropic herpesvirus infection. *Autophagy* **2023**, *19*, 734–736. [[CrossRef](#)]
257. Smart, T.G.; Hosie, A.M.; Miller, P.S. Zn²⁺ ions: Modulators of excitatory and inhibitory synaptic activity. *Neuroscientist* **2004**, *10*, 432–442. [[CrossRef](#)]
258. Brini, M.; Cali, T.; Ottolini, D.; Carafoli, E. Neuronal calcium signaling: Function and dysfunction. *Cell Mol. Life Sci.* **2014**, *71*, 2787–2814. [[CrossRef](#)]
259. Schwalfenberg, G.K.; Genuis, S.J. The Importance of Magnesium in Clinical Healthcare. *Scientifica* **2017**, *2017*, 4179326. [[CrossRef](#)]
260. Enders, M.; Heider, T.; Ludwig, A.; Kuerten, S. Strategies for Neuroprotection in Multiple Sclerosis and the Role of Calcium. *Int. J. Mol. Sci.* **2020**, *21*, 1663. [[CrossRef](#)]
261. Jedrzejewska-Szmeck, J.; Dorman, D.B.; Blackwell, K.T. Making time and space for calcium control of neuron activity. *Curr. Opin. Neurobiol.* **2023**, *83*, 102804. [[CrossRef](#)] [[PubMed](#)]
262. Moon, D.O. Calcium's Role in Orchestrating Cancer Apoptosis: Mitochondrial-Centric Perspective. *Int. J. Mol. Sci.* **2023**, *24*, 8982. [[CrossRef](#)] [[PubMed](#)]
263. Patergnani, S.; Danese, A.; Bouhamida, E.; Aguiari, G.; Previati, M.; Pinton, P.; Giorgi, C. Various Aspects of Calcium Signaling in the Regulation of Apoptosis, Autophagy, Cell Proliferation, and Cancer. *Int. J. Mol. Sci.* **2020**, *21*, 8323. [[CrossRef](#)] [[PubMed](#)]
264. Berridge, M.J. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. *Physiol. Rev.* **2016**, *96*, 1261–1296. [[CrossRef](#)]
265. Feske, S. Calcium signalling in lymphocyte activation and disease. *Nat. Rev. Immunol.* **2007**, *7*, 690–702. [[CrossRef](#)]
266. Holzer, P. Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. *Pharmacol. Ther.* **2011**, *131*, 142–170. [[CrossRef](#)]
267. Chen, Y.; Mu, J.; Zhu, M.; Mukherjee, A.; Zhang, H. Transient Receptor Potential Channels and Inflammatory Bowel Disease. *Front. Immunol.* **2020**, *11*, 180. [[CrossRef](#)]
268. Du, Y.; Chen, J.; Shen, L.; Wang, B. TRP channels in inflammatory bowel disease: Potential therapeutic targets. *Biochem. Pharmacol.* **2022**, *203*, 115195. [[CrossRef](#)]
269. Santulli, G.; Marks, A.R. Essential Roles of Intracellular Calcium Release Channels in Muscle, Brain, Metabolism, and Aging. *Curr. Mol. Pharmacol.* **2015**, *8*, 206–222. [[CrossRef](#)]
270. Patel, S.; Kilpatrick, B.S. Two-pore channels and disease. *Biochim. Biophys. Acta Mol. Cell Res.* **2018**, *1865*, 1678–1686. [[CrossRef](#)]
271. Schampel, A.; Kuerten, S. Danger: High Voltage-The Role of Voltage-Gated Calcium Channels in Central Nervous System Pathology. *Cells* **2017**, *6*, 43. [[CrossRef](#)] [[PubMed](#)]
272. Li, S.; Wong, A.H.; Liu, F. Ligand-gated ion channel interacting proteins and their role in neuroprotection. *Front. Cell Neurosci.* **2014**, *8*, 125. [[CrossRef](#)] [[PubMed](#)]
273. Connolly, C.N.; Wafford, K.A. The Cys-loop superfamily of ligand-gated ion channels: The impact of receptor structure on function. *Biochem. Soc. Trans.* **2004**, *32*, 529–534. [[CrossRef](#)] [[PubMed](#)]
274. Gwack, Y.; Srikanth, S.; Feske, S.; Cruz-Guilloty, F.; Oh-hora, M.; Neems, D.S.; Hogan, P.G.; Rao, A. Biochemical and functional characterization of Orai proteins. *J. Biol. Chem.* **2007**, *282*, 16232–16243. [[CrossRef](#)]
275. Del Puerto, A.; Wandosell, F.; Garrido, J.J. Neuronal and glial purinergic receptors functions in neuron development and brain disease. *Front. Cell. Neurosci.* **2013**, *7*, 197. [[CrossRef](#)]
276. Moran, M.M.; Xu, H.; Clapham, D.E. TRP ion channels in the nervous system. *Curr. Opin. Neurobiol.* **2004**, *14*, 362–369. [[CrossRef](#)]
277. Clapham, D.E. TRP channels as cellular sensors. *Nature* **2003**, *426*, 517–524. [[CrossRef](#)]
278. Toth, B.I.; Olah, A.; Szollosi, A.G.; Biro, T. TRP channels in the skin. *Br. J. Pharmacol.* **2014**, *171*, 2568–2581. [[CrossRef](#)]
279. Wyatt, A.; Wartenberg, P.; Candlish, M.; Krasteva-Christ, G.; Flockerzi, V.; Boehm, U. Genetic strategies to analyze primary TRP channel-expressing cells in mice. *Cell Calcium.* **2017**, *67*, 91–104. [[CrossRef](#)]
280. Zhang, M.; Ma, Y.; Ye, X.; Zhang, N.; Pan, L.; Wang, B. TRP (transient receptor potential) ion channel family: Structures, biological functions and therapeutic interventions for diseases. *Signal Transduct. Target. Ther.* **2023**, *8*, 261. [[CrossRef](#)]
281. Yan, Q.; Gao, C.; Li, M.; Lan, R.; Wei, S.; Fan, R.; Cheng, W. TRP Ion Channels in Immune Cells and Their Implications for Inflammation. *Int. J. Mol. Sci.* **2024**, *25*, 2719. [[CrossRef](#)] [[PubMed](#)]
282. Montell, C.; Birnbaumer, L.; Flockerzi, V.; Bindels, R.J.; Bruford, E.A.; Caterina, M.J.; Clapham, D.E.; Harteneck, C.; Heller, S.; Julius, D.; et al. A unified nomenclature for the superfamily of TRP cation channels. *Mol. Cell* **2002**, *9*, 229–231. [[CrossRef](#)] [[PubMed](#)]
283. Li, H. TRP Channel Classification. *Adv. Exp. Med. Biol.* **2017**, *976*, 1–8. [[CrossRef](#)] [[PubMed](#)]
284. Zielinska, M.; Jarmuz, A.; Wasilewski, A.; Salaga, M.; Fichna, J. Role of transient receptor potential channels in intestinal inflammation and visceral pain: Novel targets in inflammatory bowel diseases. *Inflamm. Bowel Dis.* **2015**, *21*, 419–427. [[CrossRef](#)]
285. Khalil, M.; Alliger, K.; Weidinger, C.; Yerinde, C.; Wirtz, S.; Becker, C.; Engel, M.A. Functional Role of Transient Receptor Potential Channels in Immune Cells and Epithelia. *Front. Immunol.* **2018**, *9*, 174. [[CrossRef](#)]
286. Koivisto, A.P.; Belvisi, M.G.; Gaudet, R.; Szallasi, A. Advances in TRP channel drug discovery: From target validation to clinical studies. *Nat. Rev. Drug Discov.* **2022**, *21*, 41–59. [[CrossRef](#)]

287. Massa, F.; Sibaev, A.; Marsicano, G.; Blaudzun, H.; Storr, M.; Lutz, B. Vanilloid receptor (TRPV1)-deficient mice show increased susceptibility to dinitrobenzene sulfonic acid induced colitis. *J. Mol. Med.* **2006**, *84*, 142–146. [[CrossRef](#)]
288. Yamamoto, S.; Shimizu, S.; Kiyonaka, S.; Takahashi, N.; Wajima, T.; Hara, Y.; Negoro, T.; Hiroi, T.; Kiuchi, Y.; Okada, T.; et al. TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. *Nat. Med.* **2008**, *14*, 738–747. [[CrossRef](#)]
289. D'Aldebert, E.; Cenac, N.; Rousset, P.; Martin, L.; Rolland, C.; Chapman, K.; Selves, J.; Alric, L.; Vinel, J.P.; Vergnolle, N. Transient receptor potential vanilloid 4 activated inflammatory signals by intestinal epithelial cells and colitis in mice. *Gastroenterology* **2011**, *140*, 275–285. [[CrossRef](#)]
290. Ramachandran, R.; Hyun, E.; Zhao, L.; Lapointe, T.K.; Chapman, K.; Hirota, C.L.; Ghosh, S.; McKemy, D.D.; Vergnolle, N.; Beck, P.L.; et al. TRPM8 activation attenuates inflammatory responses in mouse models of colitis. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 7476–7481. [[CrossRef](#)]
291. Issa, C.M.; Hambly, B.D.; Wang, Y.; Maleki, S.; Wang, W.; Fei, J.; Bao, S. TRPV2 in the development of experimental colitis. *Scand. J. Immunol.* **2014**, *80*, 307–312. [[CrossRef](#)] [[PubMed](#)]
292. Holzer, P.; Izzo, A.A. The pharmacology of TRP channels. *Br. J. Pharmacol.* **2014**, *171*, 2469–2473. [[CrossRef](#)] [[PubMed](#)]
293. Zernov, N.; Popugaeva, E. Role of Neuronal TRPC6 Channels in Synapse Development, Memory Formation and Animal Behavior. *Int. J. Mol. Sci.* **2023**, *24*, 15415. [[CrossRef](#)]
294. Boesmans, W.; Owsianik, G.; Tack, J.; Voets, T.; Vanden Berghe, P. TRP channels in neurogastroenterology: Opportunities for therapeutic intervention. *Br. J. Pharmacol.* **2011**, *162*, 18–37. [[CrossRef](#)]
295. Bellono, N.W.; Bayrer, J.R.; Leitch, D.B.; Castro, J.; Zhang, C.; O'Donnell, T.A.; Brierley, S.M.; Ingraham, H.A.; Julius, D. Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways. *Cell* **2017**, *170*, 185–198.e16. [[CrossRef](#)]
296. Engel, M.A.; Becker, C.; Reeh, P.W.; Neurath, M.F. Role of sensory neurons in colitis: Increasing evidence for a neuroimmune link in the gut. *Inflamm. Bowel Dis.* **2011**, *17*, 1030–1033. [[CrossRef](#)]
297. Yu, X.; Yu, M.; Liu, Y.; Yu, S. TRP channel functions in the gastrointestinal tract. *Semin. Immunopathol.* **2016**, *38*, 385–396. [[CrossRef](#)]
298. Yiangou, Y.; Facer, P.; Dyer, N.H.; Chan, C.L.; Knowles, C.; Williams, N.S.; Anand, P. Vanilloid receptor 1 immunoreactivity in inflamed human bowel. *Lancet* **2001**, *357*, 1338–1339. [[CrossRef](#)]
299. Rizopoulos, T.; Papadaki-Petrou, H.; Assimakopoulou, M. Expression Profiling of the Transient Receptor Potential Vanilloid (TRPV) Channels 1, 2, 3 and 4 in Mucosal Epithelium of Human Ulcerative Colitis. *Cells* **2018**, *7*, 61. [[CrossRef](#)]
300. Kun, J.; Szitter, I.; Kemeny, A.; Perkecz, A.; Kereskai, L.; Pohoczky, K.; Vincze, A.; Godi, S.; Szabo, I.; Szolcsanyi, J.; et al. Upregulation of the transient receptor potential ankyrin 1 ion channel in the inflamed human and mouse colon and its protective roles. *PLoS ONE* **2014**, *9*, e108164. [[CrossRef](#)]
301. Salas, M.M.; Hargreaves, K.M.; Akopian, A.N. TRPA1-mediated responses in trigeminal sensory neurons: Interaction between TRPA1 and TRPV1. *Eur. J. Neurosci.* **2009**, *29*, 1568–1578. [[CrossRef](#)] [[PubMed](#)]
302. Melnick, C.; Kaviany, M. Thermal actuation in TRPV1: Role of embedded lipids and intracellular domains. *J. Theor. Biol.* **2018**, *444*, 38–49. [[CrossRef](#)] [[PubMed](#)]
303. Lapointe, T.K.; Altier, C. The role of TRPA1 in visceral inflammation and pain. *Channels* **2011**, *5*, 525–529. [[CrossRef](#)] [[PubMed](#)]
304. Toledo Maurino, J.J.; Fonseca-Camarillo, G.; Furuzawa-Carballeda, J.; Barreto-Zuniga, R.; Martinez Benitez, B.; Granados, J.; Yamamoto-Furusho, J.K. TRPV Subfamily (TRPV2, TRPV3, TRPV4, TRPV5, and TRPV6) Gene and Protein Expression in Patients with Ulcerative Colitis. *J. Immunol. Res.* **2020**, *2020*, 2906845. [[CrossRef](#)]
305. Fichna, J.; Mokrowiecka, A.; Cygankiewicz, A.I.; Zakrzewski, P.K.; Malecka-Panas, E.; Janecka, A.; Krajewska, W.M.; Storr, M.A. Transient receptor potential vanilloid 4 blockade protects against experimental colitis in mice: A new strategy for inflammatory bowel diseases treatment? *Neurogastroenterol. Motil.* **2012**, *24*, e557–e560. [[CrossRef](#)]
306. Vergnolle, N. TRPV4: New therapeutic target for inflammatory bowel diseases. *Biochem. Pharmacol.* **2014**, *89*, 157–161. [[CrossRef](#)]
307. Jang, Y.; Cho, P.S.; Yang, Y.D.; Hwang, S.W. Nociceptive Roles of TRPM2 Ion Channel in Pathologic Pain. *Mol. Neurobiol.* **2018**, *55*, 6589–6600. [[CrossRef](#)]
308. Matsumoto, K.; Takagi, K.; Kato, A.; Ishibashi, T.; Mori, Y.; Tashima, K.; Mitsumoto, A.; Kato, S.; Horie, S. Role of transient receptor potential melastatin 2 (TRPM2) channels in visceral nociception and hypersensitivity. *Exp. Neurol.* **2016**, *285*, 41–50. [[CrossRef](#)]
309. Harrington, A.M.; Hughes, P.A.; Martin, C.M.; Yang, J.; Castro, J.; Isaacs, N.J.; Blackshaw, A.L.; Brierley, S.M. A novel role for TRPM8 in visceral afferent function. *Pain* **2011**, *152*, 1459–1468. [[CrossRef](#)]
310. Morreale, C.; Bresesti, I.; Bosi, A.; Baj, A.; Giaroni, C.; Agosti, M.; Salvatore, S. Microbiota and Pain: Save Your Gut Feeling. *Cells* **2022**, *11*, 971. [[CrossRef](#)]
311. Nagpal, R.; Mishra, S.K.; Deep, G.; Yadav, H. Role of TRP Channels in Shaping the Gut Microbiome. *Pathogens* **2020**, *9*, 753. [[CrossRef](#)] [[PubMed](#)]
312. Kumar, V.; Mahajan, N.; Khare, P.; Kondepudi, K.K.; Bishnoi, M. Role of TRPV1 in colonic mucin production and gut microbiota profile. *Eur. J. Pharmacol.* **2020**, *888*, 173567. [[CrossRef](#)] [[PubMed](#)]
313. Perez-Burgos, A.; Wang, L.; McVey Neufeld, K.A.; Mao, Y.K.; Ahmadzai, M.; Janssen, L.J.; Stanisz, A.M.; Bienenstock, J.; Kunze, W.A. The TRPV1 channel in rodents is a major target for antinociceptive effect of the probiotic *Lactobacillus reuteri* DSM 17938. *J. Physiol.* **2015**, *593*, 3943–3957. [[CrossRef](#)] [[PubMed](#)]
314. Parato, J.; Bartolini, F. The microtubule cytoskeleton at the synapse. *Neurosci. Lett.* **2021**, *753*, 135850. [[CrossRef](#)] [[PubMed](#)]

315. Groschwitz, K.R.; Hogan, S.P. Intestinal barrier function: Molecular regulation and disease pathogenesis. *J. Allergy Clin. Immunol.* **2009**, *124*, 3–20. [[CrossRef](#)]
316. Luissint, A.C.; Parkos, C.A.; Nusrat, A. Inflammation and the Intestinal Barrier: Leukocyte-Epithelial Cell Interactions, Cell Junction Remodeling, and Mucosal Repair. *Gastroenterology* **2016**, *151*, 616–632. [[CrossRef](#)]
317. Ivanov, A.I.; Parkos, C.A.; Nusrat, A. Cytoskeletal regulation of epithelial barrier function during inflammation. *Am. J. Pathol.* **2010**, *177*, 512–524. [[CrossRef](#)]
318. Lamprecht, R. Actin Cytoskeleton Role in the Maintenance of Neuronal Morphology and Long-Term Memory. *Cells* **2021**, *10*, 1795. [[CrossRef](#)]
319. Konietzny, A.; Bar, J.; Mikhaylova, M. Dendritic Actin Cytoskeleton: Structure, Functions, and Regulations. *Front. Cell. Neurosci.* **2017**, *11*, 147. [[CrossRef](#)]
320. Rajan, S.; Kudryashov, D.S.; Reisler, E. Actin Bundles Dynamics and Architecture. *Biomolecules* **2023**, *13*, 450. [[CrossRef](#)]
321. Carlsson, A.E. Membrane bending by actin polymerization. *Curr. Opin. Cell Biol.* **2018**, *50*, 1–7. [[CrossRef](#)] [[PubMed](#)]
322. Firat-Karalar, E.N.; Welch, M.D. New mechanisms and functions of actin nucleation. *Curr. Opin. Cell Biol.* **2011**, *23*, 4–13. [[CrossRef](#)] [[PubMed](#)]
323. Isogai, T.; Danuser, G. Discovery of functional interactions among actin regulators by analysis of image fluctuations in an unperturbed motile cell system. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2018**, *373*, 20170110. [[CrossRef](#)] [[PubMed](#)]
324. Huang, D.; Chen, S.; Xiong, D.; Wang, H.; Zhu, L.; Wei, Y.; Li, Y.; Zou, S. Mitochondrial Dynamics: Working with the Cytoskeleton and Intracellular Organelles to Mediate Mechanotransduction. *Aging Dis.* **2023**, *14*, 1511–1532. [[CrossRef](#)]
325. Svitkina, T. The Actin Cytoskeleton and Actin-Based Motility. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, a018267. [[CrossRef](#)]
326. Yang, C.; Svitkina, T.M. Ultrastructure and dynamics of the actin-myosin II cytoskeleton during mitochondrial fission. *Nat. Cell Biol.* **2019**, *21*, 603–613. [[CrossRef](#)]
327. Shen, J.; Zhang, J.H.; Xiao, H.; Wu, J.M.; He, K.M.; Lv, Z.Z.; Li, Z.J.; Xu, M.; Zhang, Y.Y. Mitochondria are transported along microtubules in membrane nanotubes to rescue distressed cardiomyocytes from apoptosis. *Cell Death Dis.* **2018**, *9*, 81. [[CrossRef](#)]
328. Mehta, K.; Chacko, L.A.; Chug, M.K.; Jhunjunwala, S.; Ananthanarayanan, V. Association of mitochondria with microtubules inhibits mitochondrial fission by precluding assembly of the fission protein Dnm1. *J. Biol. Chem.* **2019**, *294*, 3385–3396. [[CrossRef](#)]
329. Cai, Q.; Sheng, Z.H. Mitochondrial transport and docking in axons. *Exp. Neurol.* **2009**, *218*, 257–267. [[CrossRef](#)]
330. Doussau, F.; Augustine, G.J. The actin cytoskeleton and neurotransmitter release: An overview. *Biochimie* **2000**, *82*, 353–363. [[CrossRef](#)]
331. Gentile, J.E.; Carrizales, M.G.; Koleske, A.J. Control of Synapse Structure and Function by Actin and Its Regulators. *Cells* **2022**, *11*, 603. [[CrossRef](#)] [[PubMed](#)]
332. Moore, A.S.; Holzbaur, E.L.F. Mitochondrial-cytoskeletal interactions: Dynamic associations that facilitate network function and remodeling. *Curr. Opin. Physiol.* **2018**, *3*, 94–100. [[CrossRef](#)] [[PubMed](#)]
333. Sasso, J.M.; Ammar, R.M.; Tenchov, R.; Lemmel, S.; Kelber, O.; Grieswelle, M.; Zhou, Q.A. Gut Microbiome-Brain Alliance: A Landscape View into Mental and Gastrointestinal Health and Disorders. *ACS Chem. Neurosci.* **2023**, *14*, 1717–1763. [[CrossRef](#)] [[PubMed](#)]
334. Wang, R.X.; Lee, J.S.; Campbell, E.L.; Colgan, S.P. Microbiota-derived butyrate dynamically regulates intestinal homeostasis through regulation of actin-associated protein synaptopodin. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 11648–11657. [[CrossRef](#)]
335. Hoyles, L.; Snelling, T.; Umlai, U.K.; Nicholson, J.K.; Carding, S.R.; Glen, R.C.; McArthur, S. Microbiome-host systems interactions: Protective effects of propionate upon the blood-brain barrier. *Microbiome* **2018**, *6*, 55. [[CrossRef](#)]
336. Li, H.; Sun, J.; Wang, F.; Ding, G.; Chen, W.; Fang, R.; Yao, Y.; Pang, M.; Lu, Z.Q.; Liu, J. Sodium butyrate exerts neuroprotective effects by restoring the blood-brain barrier in traumatic brain injury mice. *Brain Res.* **2016**, *1642*, 70–78. [[CrossRef](#)]
337. Knox, E.G.; Aburto, M.R.; Tessier, C.; Nagpal, J.; Clarke, G.; O'Driscoll, C.M.; Cryan, J.F. Microbial-derived metabolites induce actin cytoskeletal rearrangement and protect blood-brain barrier function. *iScience* **2022**, *25*, 105648. [[CrossRef](#)]
338. Ulluwishewa, D.; Anderson, R.C.; McNabb, W.C.; Moughan, P.J.; Wells, J.M.; Roy, N.C. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J. Nutr.* **2011**, *141*, 769–776. [[CrossRef](#)]
339. Horowitz, A.; Chanez-Paredes, S.D.; Haest, X.; Turner, J.R. Paracellular permeability and tight junction regulation in gut health and disease. *Nat. Rev. Gastroenterol. Hepatol.* **2023**, *20*, 417–432. [[CrossRef](#)]
340. Paradis, T.; Begue, H.; Basmaciyan, L.; Dalle, F.; Bon, F. Tight Junctions as a Key for Pathogens Invasion in Intestinal Epithelial Cells. *Int. J. Mol. Sci.* **2021**, *22*, 2506. [[CrossRef](#)]
341. Schroeder, B.O. Fight them or feed them: How the intestinal mucus layer manages the gut microbiota. *Gastroenterol. Rep.* **2019**, *7*, 3–12. [[CrossRef](#)] [[PubMed](#)]
342. Wang, F.; Graham, W.V.; Wang, Y.; Witkowski, E.D.; Schwarz, B.T.; Turner, J.R. Interferon-gamma and tumor necrosis factor-alpha synergize to induce intestinal epithelial barrier dysfunction by up-regulating myosin light chain kinase expression. *Am. J. Pathol.* **2005**, *166*, 409–419. [[CrossRef](#)] [[PubMed](#)]
343. Schulzke, J.D.; Bojarski, C.; Zeissig, S.; Heller, F.; Gitter, A.H.; Fromm, M. Disrupted barrier function through epithelial cell apoptosis. *Ann. N. Y. Acad. Sci.* **2006**, *1072*, 288–299. [[CrossRef](#)]
344. McElroy, S.J.; Prince, L.S.; Weitkamp, J.H.; Reese, J.; Slaughter, J.C.; Polk, D.B. Tumor necrosis factor receptor 1-dependent depletion of mucus in immature small intestine: A potential role in neonatal necrotizing enterocolitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2011**, *301*, G656–G666. [[CrossRef](#)]

345. McLean, M.H.; Neurath, M.F.; Durum, S.K. Targeting interleukins for the treatment of inflammatory bowel disease—what lies beyond anti-TNF therapy? *Inflamm. Bowel Dis.* **2014**, *20*, 389–397. [[CrossRef](#)]
346. Ordas, I.; Mould, D.R.; Feagan, B.G.; Sandborn, W.J. Anti-TNF monoclonal antibodies in inflammatory bowel disease: Pharmacokinetics-based dosing paradigms. *Clin. Pharmacol. Ther.* **2012**, *91*, 635–646. [[CrossRef](#)]
347. Johansson, M.E.; Gustafsson, J.K.; Holmen-Larsson, J.; Jabbar, K.S.; Xia, L.; Xu, H.; Ghishan, F.K.; Carvalho, F.A.; Gewirtz, A.T.; Sjovall, H.; et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut* **2014**, *63*, 281–291. [[CrossRef](#)]
348. Gassler, N.; Rohr, C.; Schneider, A.; Kartenbeck, J.; Bach, A.; Obermuller, N.; Otto, H.F.; Autschbach, F. Inflammatory bowel disease is associated with changes of enterocytic junctions. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2001**, *281*, G216–G228. [[CrossRef](#)]
349. Zeissig, S.; Burgel, N.; Gunzel, D.; Richter, J.; Mankertz, J.; Wahnschaffe, U.; Kroesen, A.J.; Zeitz, M.; Fromm, M.; Schulzke, J.D. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* **2007**, *56*, 61–72. [[CrossRef](#)]
350. Moriggi, M.; Pastorelli, L.; Torretta, E.; Tontini, G.E.; Capitano, D.; Bogetto, S.F.; Vecchi, M.; Gelfi, C. Contribution of Extracellular Matrix and Signal Mechanotransduction to Epithelial Cell Damage in Inflammatory Bowel Disease Patients: A Proteomic Study. *Proteomics* **2017**, *17*, 1700164. [[CrossRef](#)]
351. Lechuga, S.; Naydenov, N.G.; Feygin, A.; Cruise, M.; Ervasti, J.M.; Ivanov, A.I. Loss of beta-Cytoplasmic Actin in the Intestinal Epithelium Increases Gut Barrier Permeability in vivo and Exaggerates the Severity of Experimental Colitis. *Front. Cell Dev. Biol.* **2020**, *8*, 588836. [[CrossRef](#)] [[PubMed](#)]
352. Gehren, A.S.; Rocha, M.R.; de Souza, W.F.; Morgado-Diaz, J.A. Alterations of the apical junctional complex and actin cytoskeleton and their role in colorectal cancer progression. *Tissue Barriers* **2015**, *3*, e1017688. [[CrossRef](#)] [[PubMed](#)]
353. Ivanov, A.I.; McCall, I.C.; Parkos, C.A.; Nusrat, A. Role for actin filament turnover and a myosin II motor in cytoskeleton-driven disassembly of the epithelial apical junctional complex. *Mol. Biol. Cell* **2004**, *15*, 2639–2651. [[CrossRef](#)] [[PubMed](#)]
354. Chanez-Paredes, S.; Montoya-Garcia, A.; Castro-Ochoa, K.F.; Garcia-Cordero, J.; Cedillo-Barron, L.; Shibayama, M.; Nava, P.; Flemming, S.; Schlegel, N.; Gautreau, A.M.; et al. The Arp2/3 Inhibitory Protein Arpin Is Required for Intestinal Epithelial Barrier Integrity. *Front. Cell Dev. Biol.* **2021**, *9*, 625719. [[CrossRef](#)]
355. Smani, T.; Dionisio, N.; Lopez, J.J.; Berna-Erro, A.; Rosado, J.A. Cytoskeletal and scaffolding proteins as structural and functional determinants of TRP channels. *Biochim. Biophys. Acta* **2014**, *1838*, 658–664. [[CrossRef](#)]
356. Clark, K.; Middelbeek, J.; van Leeuwen, F.N. Interplay between TRP channels and the cytoskeleton in health and disease. *Eur. J. Cell Biol.* **2008**, *87*, 631–640. [[CrossRef](#)]
357. Sama, D.M.; Norris, C.M. Calcium dysregulation and neuroinflammation: Discrete and integrated mechanisms for age-related synaptic dysfunction. *Ageing Res. Rev.* **2013**, *12*, 982–995. [[CrossRef](#)]
358. Marchiando, A.M.; Shen, L.; Graham, W.V.; Edelblum, K.L.; Duckworth, C.A.; Guan, Y.; Montrose, M.H.; Turner, J.R.; Watson, A.J. The epithelial barrier is maintained by in vivo tight junction expansion during pathologic intestinal epithelial shedding. *Gastroenterology* **2011**, *140*, 1208–1218.e2. [[CrossRef](#)]
359. Su, L.; Nalle, S.C.; Shen, L.; Turner, E.S.; Singh, G.; Breskin, L.A.; Khramtsova, E.A.; Khramtsova, G.; Tsai, P.Y.; Fu, Y.X.; et al. TNFR2 activates MLCK-dependent tight junction dysregulation to cause apoptosis-mediated barrier loss and experimental colitis. *Gastroenterology* **2013**, *145*, 407–415. [[CrossRef](#)]
360. Watari, A.; Sakamoto, Y.; Hisaie, K.; Iwamoto, K.; Fueta, M.; Yagi, K.; Kondoh, M. Rebecamycin Attenuates TNF-alpha-Induced Intestinal Epithelial Barrier Dysfunction by Inhibiting Myosin Light Chain Kinase Production. *Cell. Physiol. Biochem.* **2017**, *41*, 1924–1934. [[CrossRef](#)]
361. Ye, X.; Sun, M. AGR2 ameliorates tumor necrosis factor-alpha-induced epithelial barrier dysfunction via suppression of NF-kappaB p65-mediated MLCK/p-MLC pathway activation. *Int. J. Mol. Med.* **2017**, *39*, 1206–1214. [[CrossRef](#)] [[PubMed](#)]
362. Buhner, S.; Buning, C.; Genschel, J.; Kling, K.; Herrmann, D.; Dignass, A.; Kuechler, I.; Krueger, S.; Schmidt, H.H.; Lochs, H. Genetic basis for increased intestinal permeability in families with Crohn's disease: Role of CARD15 3020insC mutation? *Gut* **2006**, *55*, 342–347. [[CrossRef](#)] [[PubMed](#)]
363. Fries, W.; Renda, M.C.; Lo Presti, M.A.; Raso, A.; Orlando, A.; Oliva, L.; Giofre, M.R.; Maggio, A.; Mattaliano, A.; Macaluso, A.; et al. Intestinal permeability and genetic determinants in patients, first-degree relatives, and controls in a high-incidence area of Crohn's disease in Southern Italy. *Am. J. Gastroenterol.* **2005**, *100*, 2730–2736. [[CrossRef](#)] [[PubMed](#)]
364. Barreau, F.; Madre, C.; Meinzer, U.; Berrebi, D.; Dussaillant, M.; Merlin, F.; Eckmann, L.; Karin, M.; Sterkers, G.; Bonacorsi, S.; et al. Nod2 regulates the host response towards microflora by modulating T cell function and epithelial permeability in mouse Peyer's patches. *Gut* **2010**, *59*, 207–217. [[CrossRef](#)]
365. Arrieta, M.C.; Madsen, K.; Doyle, J.; Meddings, J. Reducing small intestinal permeability attenuates colitis in the IL10 gene-deficient mouse. *Gut* **2009**, *58*, 41–48. [[CrossRef](#)]
366. Morozova, M.V.; Borisova, M.A.; Snytnikova, O.A.; Achasova, K.M.; Litvinova, E.A.; Tsentlovich, Y.P.; Kozhevnikova, E.N. Colitis-associated intestinal microbiota regulates brain glycine and host behavior in mice. *Sci. Rep.* **2022**, *12*, 16345. [[CrossRef](#)]
367. Adolph, T.E.; Meyer, M.; Jukic, A.; Tilg, H. Heavy arch: From inflammatory bowel diseases to metabolic disorders. *Gut* **2024**, *73*, 1376–1387. [[CrossRef](#)]

368. Wang, J.; Sun, Q.; Gao, Y.; Xiang, H.; Zhang, C.; Ding, P.; Wu, T.; Ji, G. Metabolomics window into the diagnosis and treatment of inflammatory bowel disease in recent 5 years. *Int. Immunopharmacol.* **2022**, *113*, 109472. [[CrossRef](#)]
369. Torres, M.; Rossello, C.A.; Fernandez-Garcia, P.; Llado, V.; Kakhlon, O.; Escriba, P.V. The Implications for Cells of the Lipid Switches Driven by Protein-Membrane Interactions and the Development of Membrane Lipid Therapy. *Int. J. Mol. Sci.* **2020**, *21*, 2322. [[CrossRef](#)]
370. Casares, D.; Escriba, P.V.; Rossello, C.A. Membrane Lipid Composition: Effect on Membrane and Organelle Structure, Function and Compartmentalization and Therapeutic Avenues. *Int. J. Mol. Sci.* **2019**, *20*, 2167. [[CrossRef](#)]
371. Yan, M.; Man, S.; Sun, B.; Ma, L.; Guo, L.; Huang, L.; Gao, W. Gut liver brain axis in diseases: The implications for therapeutic interventions. *Signal Transduct. Target. Ther.* **2023**, *8*, 443. [[CrossRef](#)] [[PubMed](#)]
372. Gnewuch, C.; Liebisch, G.; Langmann, T.; Dieplinger, B.; Mueller, T.; Haltmayer, M.; Dieplinger, H.; Zahn, A.; Stremmel, W.; Rogler, G.; et al. Serum bile acid profiling reflects enterohepatic detoxification state and intestinal barrier function in inflammatory bowel disease. *World J. Gastroenterol.* **2009**, *15*, 3134–3141. [[CrossRef](#)] [[PubMed](#)]
373. Chen, L.; Zhernakova, D.V.; Kurilshikov, A.; Andreu-Sanchez, S.; Wang, D.; Augustijn, H.E.; Vich Vila, A.; Lifelines Cohort, S.; Weersma, R.K.; Medema, M.H.; et al. Influence of the microbiome, diet and genetics on inter-individual variation in the human plasma metabolome. *Nat. Med.* **2022**, *28*, 2333–2343. [[CrossRef](#)] [[PubMed](#)]
374. Visconti, A.; Le Roy, C.I.; Rosa, F.; Rossi, N.; Martin, T.C.; Mohny, R.P.; Li, W.; de Rinaldis, E.; Bell, J.T.; Venter, J.C.; et al. Interplay between the human gut microbiome and host metabolism. *Nat. Commun.* **2019**, *10*, 4505. [[CrossRef](#)] [[PubMed](#)]
375. Diener, C.; Dai, C.L.; Wilmanski, T.; Baloni, P.; Smith, B.; Rappaport, N.; Hood, L.; Magis, A.T.; Gibbons, S.M. Genome-microbiome interplay provides insight into the determinants of the human blood metabolome. *Nat. Metab.* **2022**, *4*, 1560–1572. [[CrossRef](#)]
376. El-Ansary, A.; Bacha, A.B.; Bjorklund, G.; Al-Orf, N.; Bhat, R.S.; Moubayed, N.; Abed, K. Probiotic treatment reduces the autistic-like excitation/inhibition imbalance in juvenile hamsters induced by orally administered propionic acid and clindamycin. *Metab. Brain Dis.* **2018**, *33*, 1155–1164. [[CrossRef](#)]
377. Ashique, S.; Mohanto, S.; Ahmed, M.G.; Mishra, N.; Garg, A.; Chellappan, D.K.; Omara, T.; Iqbal, S.; Kahwa, I. Gut-brain axis: A cutting-edge approach to target neurological disorders and potential synbiotic application. *Heliyon* **2024**, *10*, e34092. [[CrossRef](#)]
378. Messaoudi, M.; Lalonde, R.; Violle, N.; Javelot, H.; Desor, D.; Nejd, A.; Bisson, J.F.; Rougeot, C.; Pichelin, M.; Cazaubiel, M.; et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *Br. J. Nutr.* **2011**, *105*, 755–764. [[CrossRef](#)]
379. Sorg, J.A.; Sonenshein, A.L. Bile salts and glycine as cogerminants for Clostridium difficile spores. *J. Bacteriol.* **2008**, *190*, 2505–2512. [[CrossRef](#)]
380. Thanissery, R.; Winston, J.A.; Theriot, C.M. Inhibition of spore germination, growth, and toxin activity of clinically relevant C. difficile strains by gut microbiota derived secondary bile acids. *Anaerobe* **2017**, *45*, 86–100. [[CrossRef](#)]
381. Chen, L.A.; Oliva-Hemker, M.; Radin, A.; Weidner, M.; O’Laughlin, B.D.; Sears, C.L.; Javitt, N.B.; Hourigan, S.K. Longitudinal Bile Acid Composition Changes Following Faecal Microbiota Transplantation for Clostridioides difficile Infection in Children With and Without Underlying Inflammatory Bowel Disease. *J. Crohns Colitis* **2023**, *17*, 1364–1368. [[CrossRef](#)] [[PubMed](#)]
382. Seekatz, A.M.; Theriot, C.M.; Rao, K.; Chang, Y.M.; Freeman, A.E.; Kao, J.Y.; Young, V.B. Restoration of short chain fatty acid and bile acid metabolism following fecal microbiota transplantation in patients with recurrent Clostridium difficile infection. *Anaerobe* **2018**, *53*, 64–73. [[CrossRef](#)]
383. Vang, S.; Longley, K.; Steer, C.J.; Low, W.C. The Unexpected Uses of Urso- and Tauroursodeoxycholic Acid in the Treatment of Non-liver Diseases. *Glob. Adv. Health Med.* **2014**, *3*, 58–69. [[CrossRef](#)] [[PubMed](#)]
384. Keely, S.J.; Steer, C.J.; Lajczak-McGinley, N.K. Ursodeoxycholic acid: A promising therapeutic target for inflammatory bowel diseases? *Am. J. Physiol. Gastrointest. Liver Physiol.* **2019**, *317*, G872–G881. [[CrossRef](#)] [[PubMed](#)]
385. Van den Bossche, L.; Hindryckx, P.; Devisscher, L.; Devriese, S.; Van Welden, S.; Holvoet, T.; Vilchez-Vargas, R.; Vital, M.; Pieper, D.H.; Vanden Bussche, J.; et al. Ursodeoxycholic Acid and Its Taurine- or Glycine-Conjugated Species Reduce Colitogenic Dysbiosis and Equally Suppress Experimental Colitis in Mice. *Appl. Environ. Microbiol.* **2017**, *83*, e02766-16. [[CrossRef](#)]
386. Chen, W.; Zhao, H.; Li, Y. Mitochondrial dynamics in health and disease: Mechanisms and potential targets. *Signal Transduct. Target. Ther.* **2023**, *8*, 333. [[CrossRef](#)]
387. Vetrano, S.; Rescigno, M.; Cera, M.R.; Correale, C.; Rumio, C.; Doni, A.; Fantini, M.; Sturm, A.; Borroni, E.; Repici, A.; et al. Unique role of junctional adhesion molecule-a in maintaining mucosal homeostasis in inflammatory bowel disease. *Gastroenterology* **2008**, *135*, 173–184. [[CrossRef](#)]
388. Vermeire, S.; Pierik, M.; Hlavaty, T.; Claessens, G.; van Schuerbeeck, N.; Joossens, S.; Ferrante, M.; Henckaerts, L.; Bueno de Mesquita, M.; Vlietinck, R.; et al. Association of organic cation transporter risk haplotype with perianal penetrating Crohn’s disease but not with susceptibility to IBD. *Gastroenterology* **2005**, *129*, 1845–1853. [[CrossRef](#)]
389. Perez-Torras, S.; Iglesias, I.; Llopis, M.; Lozano, J.J.; Antolin, M.; Guarner, F.; Pastor-Anglada, M. Transportome Profiling Identifies Profound Alterations in Crohn’s Disease Partially Restored by Commensal Bacteria. *J. Crohns Colitis* **2016**, *10*, 850–859. [[CrossRef](#)]
390. Alaimo, A.; Rubert, J. The Pivotal Role of TRP Channels in Homeostasis and Diseases throughout the Gastrointestinal Tract. *Int. J. Mol. Sci.* **2019**, *20*, 5277. [[CrossRef](#)]
391. Guo, R.; Chen, L.H.; Xing, C.; Liu, T. Pain regulation by gut microbiota: Molecular mechanisms and therapeutic potential. *Br. J. Anaesth.* **2019**, *123*, 637–654. [[CrossRef](#)] [[PubMed](#)]

392. Fernandes, E.S.; Fernandes, M.A.; Keeble, J.E. The functions of TRPA1 and TRPV1: Moving away from sensory nerves. *Br. J. Pharmacol.* **2012**, *166*, 510–521. [[CrossRef](#)] [[PubMed](#)]
393. Puthumana, E.A.; Muhamad, L.; Young, L.A.; Chu, X.P. TRPA1, TRPV1, and Caffeine: Pain and Analgesia. *Int. J. Mol. Sci.* **2024**, *25*, 7903. [[CrossRef](#)] [[PubMed](#)]
394. Balemans, D.; Boeckxstaens, G.E.; Talavera, K.; Wouters, M.M. Transient receptor potential ion channel function in sensory transduction and cellular signaling cascades underlying visceral hypersensitivity. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2017**, *312*, G635–G648. [[CrossRef](#)]
395. Akbar, A.; Yiangou, Y.; Facer, P.; Brydon, W.G.; Walters, J.R.; Anand, P.; Ghosh, S. Expression of the TRPV1 receptor differs in quiescent inflammatory bowel disease with or without abdominal pain. *Gut* **2010**, *59*, 767–774. [[CrossRef](#)]
396. Meseguer, V.; Alpizar, Y.A.; Luis, E.; Tajada, S.; Denlinger, B.; Fajardo, O.; Manenschijn, J.-A.; Fernandez-Pena, C.; Talavera, A.; Kichko, T.; et al. TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins. *Nat. Commun.* **2014**, *5*, 3125. [[CrossRef](#)]
397. Scuto, M.; Rampulla, F.; Reali, G.M.; Spano, S.M.; Trovato Salinaro, A.; Calabrese, V. Hormetic Nutrition and Redox Regulation in Gut-Brain Axis Disorders. *Antioxidants* **2024**, *13*, 484. [[CrossRef](#)]

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