gastrointestinal disorders

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Review

Neutrophils in the Focus: Impact on Neuroimmune Dynamics and the Gut–Brain Axis

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Abstract: The growing field of gut–brain axis research offers significant potential to revolutionize medical practices and improve human well-being. Neutrophils have emerged as key players in gut–brain inflammation, contributing to the relocation of inflammatory cells from the gut to the brain and exacerbating neuroinflammation in conditions, such as inflammatory bowel disease and neurodegenerative diseases. The intricate network of molecular and functional connections that interlinks the brain with the gastrointestinal system is characterized by complex signaling pathways. Understanding the complex interplay among the microbiota, gut, and brain offers unparalleled opportunities to develop novel therapeutic interventions for neurological disorders and improve overall health outcomes. The aim of this review was to comprehensively summarize current knowledge and future perspectives regarding the multifaceted role of neutrophils and their impact on the neuroimmune dynamics in the context of the gut–brain axis.

Keywords: gut–brain axis; neuroinflammation; neuroimmune dynamics; neutrophils

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1. Introduction

Neutrophils are vital to the human immune system as they are the first responders to infection or injury sites, playing a key role in defending the body against bacterial and fungal infections [1]. When pathogens invade the body, neutrophils are recruited to the site of infection where they surround and destroy the invading microorganisms through phagocytosis. Additionally, they release inflammatory molecules and enzymes to help contain and eliminate the infection. Recent research has unveiled a fascinating dimension of neutrophil functions—their role in neuroinflammation, inflammatory processes within the central nervous system (CNS) [2–4].

Given the brain's pivotal role as the central controller of all physiological processes, its engagement in and bidirectional communication with the gastrointestinal tract is essential. The bidirectional complex network between the gastrointestinal tract and the CNS is known as the gut–brain axis [5,6].

The intricate network of molecular and functional connections that interlinks the brain with the gastrointestinal system is characterized by complex signaling pathways. Among the well-documented features of this network are the signaling links among the CNS, the enteric nervous system (ENS), and the hypothalamic–pituitary—adrenal axis (HPA) [7]. The axis is anatomically structured with a complex network involving neural, hormonal, and immune pathways, as well as neurons, neurotransmitters, and hormones that play a significant role in the regulation of various physiological functions and facilitate communication between the brain and the gut. Neurons extend from the brain throughout the body, forming a complex neural network. The ENS situated in the intestinal wall, communicates with the CNS through neuroimmune and neuroendocrine signaling pathways mediated by the vagus nerve (VN) [8]. However, the CNS also must maintain tissue homeostasis and nutrient exchange while protecting itself from infectious agents, toxins, and inflammation,

necessitating rapid detection of changes in the bloodstream milieu. This challenges the traditional view of the CNS as an "immune-privileged" site, as emerging evidence emphasizes the dynamic interplay between immune sentinels within the CNS and the periphery [9]. This communication transpires via a cascade of chemical messengers, and in recent years, research has increasingly focused on understanding the complex interactions between the gut and the brain and their impact on health and disease [10].

The gut–brain axis encompasses a multitude of factors, including the gut microbiota, as presented on Figure 1. Neutrophils are crucial elements of innate immunity, defending against pathogens through phagocytosis, the release of antimicrobial peptides (AMPs) and reactive oxygen species (ROS), the secretion of inflammatory cytokines, and the formation of neutrophil extracellular traps (NETs). This arsenal effectively eliminates invading pathogens but can also cause tissue damage in inflammatory diseases. Microbial components are also known to modulate the intensity of inflammatory responses. The interaction between neutrophils and the microbiota fine-tunes the extent of neutrophil-mediated inflammation [11].

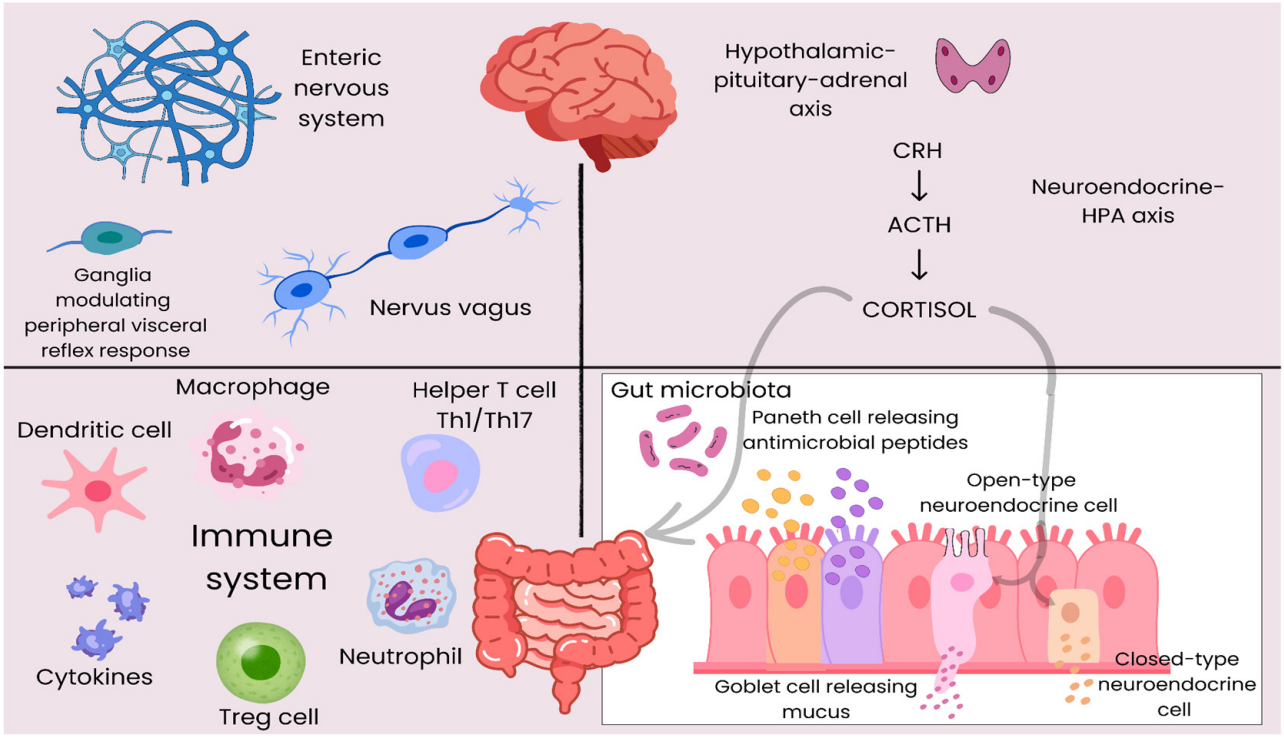

Figure 1. The bidirectional complex network of the gut–brain axis.

Understanding the mechanisms of gut–brain communication, particularly in the context of immune cell functions, is essential for developing targeted interventions that can alleviate neuroinflammation and improve patient outcomes. By unraveling the complexities of the gut–brain axis and the role of neutrophils within this framework, researchers and clinicians can explore innovative therapeutic strategies for addressing gut–brain inflammatory diseases and neurodegenerative disorders [11–15].

2. Role of Neutrophils in Gut–Brain Inflammation

Neutrophils play a crucial role in gut–brain inflammation, as they are involved in the immune response and can migrate from the gut to the brain [16]. Their migration is facilitated by the dysregulation of pathways during dysbiosis, leading to altered permeability of the blood–brain barrier (BBB). This migration of neutrophils contributes to the neuroinflammation observed in conditions, such as inflammatory bowel disease and neurodegenerative diseases. Therefore, understanding the role of neutrophils in gut–brain

inflammation is essential for developing effective interventions and treatments to alleviate neuroinflammation and its associated neurological symptoms [17].

Furthermore, targeting neutrophils as a therapeutic strategy may help mitigate the detrimental effects of neuroinflammation and improve patient outcomes in gut–brain inflammatory diseases and neurodegenerative disorders [18]. By targeting and modulating the activity of neutrophils, it may be possible to reduce their migration to the brain and the release of inflammatory mediators, thus attenuating neuroinflammation and potentially preventing or slowing the progression of related neurological conditions [19]. This understanding also opens up new avenues for research into potential interventions that specifically target neutrophil-mediated inflammation in the gut–brain axis, potentially leading to novel treatment approaches and therapies for gut–brain inflammatory diseases and neurodegenerative disorders [20]. Therefore, studying the role of neutrophils in gut-brain inflammation is crucial for a comprehensive understanding of the underlying mechanisms and for developing effective strategies to alleviate neuroinflammation and improve patient outcomes in these conditions [21].

Neutrophils have emerged as key players in gut–brain inflammation, contributing to the migration of inflammatory cells from the gut to the brain and exacerbating neuroinflammation in conditions, such as inflammatory bowel disease and neurodegenerative diseases [22]. Their activation and the release of inflammatory mediators not only contribute to the development and progression of neuroinflammatory diseases and neurodegenerative diseases but also play a role in exacerbating neurological symptoms [21,23]. Therefore, targeting neutrophils and their inflammatory pathways could offer promising therapeutic strategies for mitigating neuroinflammation, improving patient outcomes, and potentially slowing the progression of gut–brain inflammatory diseases and neurodegenerative disorders [24–26].

2.1. Exploring Reactive Oxygen Species (ROS): Cellular Dynamics and Neurological Health

2.1.1. Localization of ROS Generation in Neutrophils

Neutrophils harbor antimicrobial elements organized within subcellular organelles or granules. Although a portion of neutrophil cytb558 resides in the plasma membrane, the bulk is ensconced in granule membranes, particularly specific granules [27]. The active NADPH oxidase, engendering superoxide, may operate either extracellularly via plasma membrane activation or intracellularly within membrane-enclosed compartments, potentially prompted by specific granule-associated NADPH oxidase. Intracellular ROS generation typically occurs at the phagolysosome, formed post-particle engulfment and granule–phagosomal membrane fusion. Neutrophils unleash copious ROS amounts during microorganism phagocytosis, inaccessible to large ROS scavengers, like superoxide dismutase, hence suggesting intracellular ROS formation.

Historically, intracellular ROS generation was presumed to be linked solely to phagocytosis. Yet, evidence shows that ROS can emerge without phagosome formation, as seen with stimuli like the phorbol ester PMA or lectins (e.g., galectins or wheat germ agglutinin) [28]. The precise organelle for such ROS remains obscure, although a fused granule structure has been proposed [29,30]. NADPH oxidase activation in intracellular membranes relies on distinct signaling pathways compared to plasma membrane activation, suggesting diverse regulatory cues [31]. Given the vital role of phagocyte ROS production, localization likely dictates functionality, notably influencing cell signaling and function.

2.1.2. Exploring ROS Production Triggers in Different Cellular Locations

Various stimuli can activate neutrophil NADPH oxidase, yielding ROS at different locales. Neutrophil chemoattractants, like formylated peptides, are known to activate plasma membrane NADPH oxidase, resulting in extracellular ROS release [32]. Soluble stimuli, including PMA, activate protein kinase C, inducing both extracellular and intracellular ROS generation [28]. Galectins, a group of endogenous lectins, stimulate intracellular NADPH oxidase activation, contingent upon prior cell priming, such as in vivo transmigration.

Intracellular ROS during phagocytosis likely emanate predominantly from the phagolysosomal compartment, though other ROS-producing compartments exist in response to particulate stimuli [31]. Methodological limitations hinder a precise analysis of ROS production localization during phagocytosis, indicating further inquiry is needed.

Human cells host over 50 ROS-generating enzymes, including NOX (NADPH oxidase) family members, NOX1-5, and DUOX1-2, which reduce oxygen to superoxide or synthesize hydrogen peroxide (H_2O_2) [32,33]. NOX enzymes, notably NOX2, generate superoxide as a defense mechanism against pathogens, while DUOX1-2 produce H_2O_2, a key second messenger in cellular signaling pathways [33–35]. H_2O_2 participates in various cellular processes, modulating insulin signaling, MAP kinase activation, and ion channel regulation [36,37].

In neuronal contexts, ROS, prominently NOX enzymes, influence neuronal development and function [38]. ROS exhibit dual roles in neurons, depending on their concentration, site of action, and organismal age. These intricate dynamics of ROS underscore their nuanced impact on neuronal physiology and pathophysiology.

Exposure to environmental stressors, like pathogens, chemicals, UV radiation, and heavy metals, can stimulate ROS production, potentially leading to cellular damage and death, which is related to numerous pathologies [39–43]. To counteract oxidative damage, cells deploy antioxidant mechanisms, encompassing enzymatic and non-enzymatic (e.g., flavonoids, ascorbic acid, tocopherols) agents. Despite their damaging potential, ROS also serve as vital signaling molecules at controlled physiological levels. Evolutionarily conserved enzymes, such as phagocytic NADPH oxidase (Phox), are dedicated to ROS synthesis [37].

2.1.3. ROS: Unveiling the Darker Side of Oxidative Biology

The accumulation of ROS in the aging nervous system can yield harmful effects, with ROS management contingent upon factors, such as the timing of production, cellular localization, and concentration [36]. Despite comprising only 2% of the body weight, the brain demands over 20% of total metabolic energy expenditure, primarily to sustain processes like maintaining ionic balance, neurotransmission, and protein trafficking [37,44]. Intriguingly, while mitochondrial ROS are often implicated in neuronal aging, recent research suggests that neuronal mitochondria are also subject to ROS generated by NADPH oxidase (NOX), particularly NOX4. This in vitro study revealed NOX4 expression in neuronal mitochondria, yielding superoxide and inhibiting ETC complex 1, potentially amplifying ROS production during ATP synthesis [45].

A further exploration of the ROS-concentration-dependent effects and mechanisms regulating cellular ROS levels is crucial [36]. This includes investigating molecular regulators balancing ROS, pathways maintaining ROS thresholds, and mechanisms dictating ROS actions across physiological contexts. Insights into neuronal redox biology may foster targeted therapies via cell signaling modulation. For instance, dietary coenzyme Q reduced brain protein carbonyl levels in an Alzheimer's mouse model [46]. Biomolecular screens for neuroprotective strategies against ROS have shown promise, like Baicalin's neuroprotective effects in a traumatic brain injury model [47].

Recent single-cell transcriptomics studies revealed genetic factors contributing to cellular susceptibility to oxidative damage [48–51]. Endogenous contrast MRI detects brain ROS levels pre- and post-therapeutic interventions targeting oxidative damage [52]. Biosensors detecting neuronal glutamate and gamma-aminobutyric acid (GABA) release offer the real-time monitoring of brain neurotransmitters [53]. Advancements in biotechnology and nanomedicine may soon enable the effective delivery of ROS scavengers for oxidative damage alleviation in the human brain [54].

3. Cellular Guidance via Chemotaxis and Transendothelial Migration

As the number of neutrophils rise, so do their patterns of movement, as shown by several mobility-related metrics. When compared to the control group, the LPS-treated group's migratory neutrophils in the brain parenchyma showed much longer track lengths and greater velocities, indicating that they were responding more forcefully to LPS stimulation. Furthermore, the steady movement of infiltrating neutrophils within a 20 μm radius during a 30 min period suggested significant motility during neuroinflammation. Furthermore, mice given an LPS injection had a reduced meandering score, suggesting more directed locomotion in comparison to the control group [55].

Prior studies have indicated that neutrophils interact actively with adjacent cells, including astrocytes, microglia, and adaptive immune cells, during episodes of neuroinflammation [56,57]. Imaging evidence from our investigation, which shows contact between infiltrating neutrophils and native brain microglia, supports this idea. Microglia seemed to devour the neutrophils upon contact, suggesting that these cell types may be communicating molecularly. Furthermore, over the course of neutrophil–microglial interactions, adjacent microglial processes expanded in the direction of the site of contact. This suggests that communication occurs in both directions and affects both the participating cells and the surrounding milieu [55].

3.1. Unraveling the Mystery of Neutrophil Reverse Migration

The reverse transendothelial migration (rTEM) of neutrophils is another fascinating occurrence that has been previously documented in the literature. In this scenario, neutrophils extravasate from blood vessels and then re-enter the circulation [58–60]. Although rTEM has been shown in a variety of tissues, imaging findings by Kim et al. are the first to show that it occurs in brain blood arteries. When neutrophils participate in rTEM, they first approach the blood artery, move through the perivascular area, and then return to the circulation [55].

The movement of neutrophils has garnered significant attention, particularly during inflammation. Chemokines released at the injury site recruit neutrophils via a chemotactic gradient, while departing neutrophils may follow an inverse gradient. Some suggest that neutrophil desensitization to chemotactic signals, rather than signal rejection, drives reverse migration [61,62]. In vitro studies using a U-shaped microfluidic model provide direct evidence, showing that neutrophils move away from chemoattractants, with over 90% exhibiting retrograde movement [63].

Neutrophil drifting and diffusion have been observed in various injury models, including zebrafish fin injury and mouse ischemia–reperfusion injury [64]. Reverse migration may also be influenced by distant chemotactic signals due to increased vascular permeability during inflammation [65]. Neutrophils display diverse patterns of reverse migration, such as reverse transendothelial migration, metastasis from adjacent tissues, or lymphatic dissemination [66,67].

Post-reverse migration, neutrophils exhibit distinct phenotypes, with increased ICAM-1 levels and decreased CXCR1 expression. Increased ICAM-1 mRNA expression in septic mouse lungs and thymus suggests reverse-migrating neutrophils' presence in these tissues. While research on neutrophil reverse migration has proliferated, more evidence is needed to fully understand this phenomenon, along with insights into its mechanisms, influencing factors, and potential drug targets [68].

3.1.1. Potential Mechanisms for Neutrophil Reverse Migration

The intricate process of neutrophil reverse migration remains an area of active investigation, with various mechanisms proposed to elucidate this phenomenon [69–71]. Here, we delve into several potential pathways and factors involved.

One such mechanism revolves around junctional adhesion molecule C (JAM-C) at endothelial cell junctions. Real-time imaging in transgenic zebrafish models has revealed neutrophils breaking through the endothelium, facilitated by reduced JAM-C expression

post-injury, suggesting a pivotal role for JAM-C in regulating reverse migration [69]. Moreover, the leukotriene B4–neutrophil elastase (LTB4–NE) axis has emerged as a key player in promoting reverse transendothelial migration. LTB4 induces neutrophil elastase (NE) production, leading to JAM-C protein hydrolysis and subsequent loss, facilitating neutrophil reverse migration [72].

Additionally, extracellular cold-inducible RNA-binding protein (CIRP) has been implicated in septic neutrophil reverse migration. CIRP induces NE upregulation and JAM-C downregulation in mouse lungs, suggesting a potential therapeutic target for acute lung injury in sepsis [73].

The hypoxia-inducible factor (HIF) signaling pathway has also been linked to neutrophil reverse migration. HIF-1α activation inhibits neutrophil apoptosis and reduces reverse migration in zebrafish experiments, underscoring its role in inflammation resolution [68].

Lipid mediators, such as prostaglandin E2 (PGE2), have been implicated in promoting neutrophil reverse migration. PGE2 signaling through the EP4 receptor increases lipoxin A4 (LXA4) production, aiding in inflammation resolution [70]. The CXCL12/CXCR4 signaling axis and macrophages also play roles in modulating neutrophil reverse migration. The inhibition of CXCL12/CXCR4 signaling accelerates inflammation resolution [62], while macrophages promote reverse migration through redox and Src family kinase signals, either via direct contact or indirectly through secreted substances [55,74]. While these mechanisms shed light on neutrophil reverse migration, further research is needed to fully elucidate this complex phenomenon, including its precise molecular mechanisms and potential therapeutic implications.

3.1.2. Impact of Pharmaceuticals on Neutrophil Reverse Migration

The impact of certain anti-inflammatory medications on regulating neutrophil reverse migration holds promise for improving patient outcomes. Here, we highlight several drugs associated with this process, offering a novel avenue for inflammation treatment. Tanshinone IIA, a Chinese herbal medicine known for its anti-inflammatory properties, has been implicated in modulating neutrophil behavior. Research indicates that tanshinone IIA can induce apoptosis in human neutrophils. Moreover, tanshinone IIA has been shown to inhibit HIF-1α activity and enhance tissue repair, further contributing to its anti-inflammatory effects [75]. In a cystic fibrosis (CF) zebrafish model, tanshinone IIA reversed neutrophil accumulation at inflammatory sites, reducing inflammatory injury [76].

Kuding tea, abundant in chlorogenic acid, has gained attention for its anti-inflammatory and anticancer properties. Scientific studies indicate that chlorogenic acid-enriched kuding tea extract promotes neutrophil reverse migration [68,77]. Lipid mediators also play a role in inflammation resolution and may influence neutrophil reverse migration. The transition from pro-inflammatory lipid mediators, like LTB4, to pro-regressive mediators can impede new neutrophil influx and promote the resolution of existing inflammation. Notably, LXA4 has been shown to enhance human neutrophil reverse migration in vitro, suggesting its potential as a mediator in inflammation resolution [68].

4. Insights into Gut Immunology: Understanding Immune System Dynamics

From an immunological perspective, the intestinal tract harbors a rich population of immune cells, constituting more than 70–80% of the entire body's immune system, which includes macrophages, neutrophils, dendritic cells (DCs), natural killer (NK) cells, and different subsets of innate lymphoid cells (ILCs), such as types 1 through 3, as the first line of defense in the gastrointestinal tract [78,79]. Researchers have been intrigued by the multifaceted roles of gut microbes, including their involvement in brain development regulation, immune modulation, antagonistic activities, anticancer properties, and nutritional functions [80,81]. In the context of the gut–brain axis, investigations have delved into various mechanisms, encompassing the immune system, gut microbiota metabolism pathways, intestinal mucosal barrier and BBB integrity, neuroanatomical pathways, and the

HPA axis neuroendocrine pathway [82]. Importantly, these pathways exhibit interconnectedness and often operate through an immunological lens. According to some older sources, some T and B cells can go to the brain via DC-mediated antigen presentation, even though adaptive immune cells rely on this route for their repertoire. When an ischemic stroke occurs, cerebral inflammatory signals are what trigger these immune cells' activation and functionality. The gut microbiota significantly influences the development of gut-associated lymphoid tissue and innate lymphoid cells. This interaction is crucial for the immunological maturation of the intestinal mucosal immune system [83].

Neutrophil Activity during the Acute Phase of Inflammation

Neutrophils play a pivotal role in the initial defense, employing enzymatic and chemical weapons to combat invaders and aid in tissue repair by secreting inflammatory cytokines [84–86]. They also produce ROS, activate the complement system, and cause direct or indirect damage to neural structures [87]. This entire process is intricately intertwined with the influence of the gut microbiome. Firstly, they alter circulating cytokines, inciting brain inflammatory responses. Numerous studies indicate that both intestinal microbiota and mucosal cells can modulate the activation of immune molecules that impact the CNS [88–90]. Additionally, they influence the development and balance of microglia, which are vital for regulating CNS development processes, like myelination and neurogenesis, in mature brains. Moreover, microglia play a role in maintaining CNS health by acting as immune sentinels, aiding in information transmission, and removing cellular waste [91]. When microglia functions are impaired, their ability to phagocytose accumulated amyloid and tau proteins post-ischemia is compromised [92]. Thirdly, as a significant component of Gram-negative microbes, lipopolysaccharide (LPS) binds with Toll-like receptors (TLRs), one of the pattern recognition receptors in the intestinal mucosa, or other microbial-related molecules. This process activates immune cells, such as dendritic cells (DCs), neutrophils, and macrophages, resulting in the production of proinflammatory cytokines, such as IL-1b, TNF-a, and IL-6, which traverse the BBB to influence brain function [93,94].

These conditions can further impact brain outcomes following an ischemic attack. Researchers have discovered that the gut–brain axis plays a critical role in linking cerebral ischemia to the gut [95,96]. Previous studies have demonstrated that the brain, which is composed of neuronal circuits, neurotransmitters, and receptors, has the ability to regulate the digestive tract's motility, secretion, and immunological response. Moreover, there is frequently a marked dysbiosis of the gut microbiota in individuals with stroke or temporary cerebral ischemia. Remarkably, gastrointestinal issues following a stroke, such as constipation, gastrointestinal bleeding, fecal incontinence, and dysphagia, affect up to 50% of patients and are strongly linked to a poor prognosis for stroke survivors [97].

Furthermore, due to the impact of the gut microbiota, specific immune cells originally located in the intestinal tract migrate towards the brain, showcasing contrasting functions that worsen inflammatory consequences [98].

5. Insights into the Complexities of the Human Microbiota

The gut microbiota is a broad category of microorganisms, comprising trillions of microorganisms, mainly bacteria, that are mainly found in the intestines and on the oral mucosa. The host organism and this microbiome continue to coexist symbiotically, which is essential for regulating a number of physiological and pathological processes [99,100]. Remarkably, the total genome size of these microorganisms is thought to be larger than that of humans [101]. According to recent studies, the human body is thought to contain about 3.8×10^{12} bacterial cells, with the digestive tract housing a large proportion of these cells [102]. But the microbiota is not only made up of bacteria—it also consists of more than 250 different species of viruses, fungi, archaea, and protozoa. The microbiome influences blood pressure control, immunological dynamics, brain development, and metabolic processes via the microbiome–gut–brain axis [103]. Bacteria predominate among these species, outnumbering fungi and archaea by many orders of magnitude [104].

The potential health advantages of the microbiota have come to light more and more recently [105]. In contrast to 3.0×10^{13} human cells in a 70 kg individual, Sender et al. found an astounding amount of 3.8×10^{13} bacterial cells in the gut microbiome (GMB) [102]. Even while healthy people have a diverse range of bacteria in them, the microbial community tends to be dominated by particular bacterial phyla, including Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes [106], and one archaeal phylum (Euryarchaeota), which is essential for the digestion of polysaccharides, the synthesis of short-chain fatty acids, the synthesis of vitamins and amino acids, preservation of the intestinal barrier, immune system maturation, and the metabolism of xenobiotics [107,108] Nevertheless, from infancy until old age, the makeup of these bacteria differs greatly throughout people due to variables, such as body habitats, lifestyle, and illness states. There are several common kinds of bacteria that have been discovered, including Bifidobacterium, Streptococcus mutans, Lactobacillus bulgaricus, Helicobacter pylori, Cladosporium spp., and Lactococcus lactis subspp. Cremoris [109]. Numerous variables, including genetics, immunological interactions throughout early development, lifestyle, nutrition, and antibiotic administration, affect the diversity and specific makeup of the microbiome [110].

The gut microbiota also has emerged as a key regulator of host pathophysiology. Its involvement has been linked to the development of numerous disorders, such as cancer, celiac disease, various neurological conditions, inflammatory bowel disease, and major depressive disorder [111–116]. Furthermore, the immune system can be modulated by the microbiome, which might lead to the pathophysiology of autoimmune disorders [117–120].

Evidence across various animal taxa highlights the role of the gut microbiota in shaping host behavior, including in humans. Research has revealed behavioral changes associated with gut bacteria, often manifesting as food preferences or orientations. For instance, studies on the nematode worm Caenorhabditis elegans have demonstrated that while infection leads to aversive behavior, the consumption of nutritive bacteria can induce attraction and exploitation of the bacterial food supply [121]. Additionally, restoring the gut microbiota in antibiotic-treated mice can reverse the overconsumption of high-sucrose pellets. Gut dysbiosis has been observed in mouse models and patients with anorexia nervosa, suggesting a link between the gut microbiota and the disorder's development [122–126]. Nonetheless, the mechanisms through which the gut microbiota affects neuronal changes and behavioral adjustments remain incompletely understood.

5.1. Microbial Influence on Neutrophil Generation

The microbiota has a significant influence over neutrophil production, impacting both the generation of neutrophil progenitors in the bone marrow (BM) and the supportive niche for hematopoiesis. Antibiotic use and germ-free conditions have long been associated with diminished myelopoiesis in the BM, resulting in reduced neutrophil numbers and increased susceptibility to infections [127–129]. Components derived from the microbiota, such as heat-killed E. coli or LPS, can rescue neutrophil reductions in microbiota-depleted models, indicating their pivotal role in this process [129].

Microbial molecules, including LPS and peptidoglycan, trigger interleukin-17 (IL-17) production and subsequently granulocyte colony-stimulating factor (G-CSF) secretion via the TLR4/Myd88 pathway [130,131]. This orchestrated response regulates neutrophil differentiation according to microbial cues. Additionally, microbiota-mediated signals, such as NOD1 ligands, influence stromal cells in the BM, prompting the expression of hematopoietic cytokines that are crucial for hematopoiesis. For instance, the administration of NOD1 ligands in germ-free mice restores cytokine expression and promotes hematopoiesis [132].

Moreover, dietary factors, like high-fat diets, can perturb the BM niche, favoring a myeloid bias and altering the expression of hematopoietic cytokines [133]. Interestingly, high-fat-diet-induced changes in the microbiome mirror niche deregulation and myeloid bias, underscoring the microbiota's role in this process [133,134]. Microbiota-derived signals also impact macrophages, key components of the BM niche, particularly during

viral infections [135]. A further exploration of the microbiota-mediated regulation of niche constituents promises deeper insights into hematopoiesis and neutrophil production.

5.2. Neutrophil Priming: Impact of the Microbiome

Microbial components derived from the microbiota wield considerable influence over neutrophil functions, shaping inflammatory responses and impacting both local and distal organs. For instance, contact between segmented filamentous bacteria (SFB) and the gut epithelium prompts the release of serum amyloid A, driving Th17 differentiation in the intestine and activating NF-κB signaling in circulating neutrophils, thereby enhancing their migration and the inflammatory response [129,136]. Neutrophils from germ-free mice exhibit diminished activity and impaired chemotaxis, particularly via Myd88-mediated pathways, underscoring the role of microbiota signaling in neutrophil functions. Furthermore, microbial depletion reduces the phagocytic killing capacity of BM-derived neutrophils, predominantly mediated by NOD1 signaling [129,130].

5.3. Impact of Microbial Metabolites on Neutrophil Activities

The microbiota generates a diverse array of metabolites from fermenting dietary compounds or converting host-secreted endogenous compounds. These metabolites, primarily short-chain fatty acids (SCFAs), secondary bile acids, tryptophan metabolites, and amines, significantly influence host physiology and disease processes [137,138]. While microbial products, like formyl peptides, can activate neutrophils, they may also signal through specific receptors to induce anti-inflammatory effects, as evidenced in certain infection models [129]. SCFAs, for instance, inhibit NF-κB signaling and promote the apoptosis of neutrophils, contributing to the resolution of inflammation [129,136–138].

5.4. Neutrophil Behavior in Response to the Microbiota

In homeostasis, signals from commensals foster a regulatory environment that dampens immune activation and leukocyte recruitment, safeguarding against unnecessary responses to harmless microbes [139]. However, when encountering unfamiliar microorganisms, both innate and adaptive immune mechanisms swiftly mobilize to eliminate potential threats. Within this dynamic interplay, neutrophils emerge as pivotal effector cells tasked with eliminating unwanted microbial species.

Neutrophils act as guardians of microbiota containment, ensuring that their activation does not inadvertently harm commensals or healthy host tissues. In the intestine, mononuclear phagocytes produce precursor proteins of the proinflammatory cytokine IL-1β, which remain inert unless activated by pathogenic species, like Salmonella or Pseudomonas, through the NLRC4 inflammasome. This activation triggers robust neutrophil recruitment to the epithelium, where they form protective "luminal casts", limiting microbial translocation and overgrowth during infection [140,141]. Neutrophil recruitment relies on chemotaxis receptor CXCR2 and cytokine IL-17, with recruited neutrophils contributing to IL-22 production, a cytokine crucial for antimicrobial peptide (AMP) and IgA production [131,142,143]. Ultimately, this orchestrated response serves to precisely regulate commensal species and prevent overgrowth.

Furthermore, neutrophil-derived AMPs play a crucial role in fine-tuning the microbiota. By releasing these small molecules upon encountering pathogens, neutrophils contribute to the maintenance of a healthy microbial community. The microbiota, in turn, evolves strategies to resist AMPs, fostering stability and resilience within the microbial ecosystem [144]. Notably, a deficiency in neutrophil-derived cathelicidins leads to dysbiosis and increased susceptibility to colitis, highlighting the importance of these molecules in preserving mucosal integrity [145]. Neutrophils, through the secretion of AMPs, thus actively participate in shaping the composition of the microbiota, underscoring their indispensable role in host–microbe interactions [144].

5.5. Neutrophil-Microbiota Dynamics in Chronic Conditions

Neutrophils play dual roles in immunity, combating pathogens while also contributing to chronic inflammatory diseases and cancer [129]. The microbiota significantly influences these processes [139].

Inflammatory diseases affecting barrier sites, like IBDs and airway disorders, arise from a complex interplay of genetic factors, the immune system, and the microbiota [129]. Dysbiosis triggers robust neutrophil responses, exacerbating inflammation [129,146]. Similarly, in cystic fibrosis and other airway disorders, dysbiosis fuels neutrophil-driven inflammation, worsening disease severity [147,148].

Beyond barrier sites, neutrophils contribute to autoimmune and vascular diseases. The microbiota influences these diseases by regulating systemic neutrophil activity. In cancer, neutrophils modulate tumor progression, influenced by the microbiota [129,144]. The microbiota also impacts cancer therapy responses, affecting neutrophil activation [129].

6. Brain–Gut–Microbiota (BGM) Axis

The common sensations of a "gut feeling" or "butterflies" in the stomach illustrate how signals from the brain are perceived in the gut. However, the interactions within the microbiota–gut–brain axis are much more complex, as evidenced by extensive research efforts aiming to uncover connections with brain development, physiology, function, and health [149]. The brain–gut–microbiota axis is the key player in shaping brain development and maintaining its health. Research efforts have shown the strong link between the gut and the brain [150–152]. Recently, attention has shifted towards investigating the role of the gut microbiota [151,153–155], with discoveries suggesting that specific gut microorganisms may impact memory [156], learning [156], stress [157], mood [155,158,159], and neurodevelopmental [160,161] and neurodegenerative disorders [151].

6.1. Neural Pathway: Vagus Nerve and the Brain–Gut Connection

The VN regulates internal organ functions, like digestion, heart rate, and respiratory rate. Consisting of efferent and afferent neurons, it transmits motor signals between the brain and organs, including intestinal cells, influenced by the gut microbiota. This allows the brain to perceive the gut environment [162]. Most of these communication-mediated metabolites, peptides, hormones, and endotoxins are locally detected by receptors on the afferent VN [163]. Activation of VN receptors by signaling molecules, such as serotonin, gut hormones, and cytokines, initiates signal transmission to the brainstem [164,165]. Additionally, a portion of these bioactive molecules may traverse the intestinal barrier and enter the bloodstream, potentially reaching the brain and crossing the blood–brain barrier (BBB) [166].

The VN acts as a vital communication highway in brain–gut interactions [166,167]. Microbiota metabolites, such as long-chain fatty acids, trigger VN receptors via CCK-mediated pathways, while short-chain fatty acids (SCFAs) directly influence VN terminals [168]. Furthermore, VN receptors interact with secretions from metabolite-activated gut sensory cells, such as enteroendocrine cells (EECs), further facilitating communication between the gastrointestinal tract (GIT) and CNS [166,169].

EECs, comprising <1% of resident mucosal cells, are dispersed throughout the GIT mucosa and serve as a significant population of endocrine cells [170–172]. These cells sense luminal contents, including metabolites and endotoxins, and produce over twenty hormones that regulate food consumption, GI motility, and secretion via the enteric ENS [165,173,174]. Microbial metabolites stimulate the release of EEC hormones, initiating signals that act on afferent vagal fiber receptors, transmitting stimuli to the brainstem, showing their important roles in different pathologies [173,175–177].

6.2. Immune System Anchored in the Gut: Unveiling the Link

From a perspective focused on brain health, the interactions between the microbiota and the immune system are intriguing because of the systemic low-grade inflammation commonly observed in different pathological conditions [177–179]. Furthermore, the gut microbiome engages in intricate interactions with mucosal immune cells, shaping immune–neural interactions from an early stage of life [180]. This interaction educates the host defense system, promoting a balanced function between tolerance and immunity for host homeostasis [165,181]. Approximately 70% of the immune system, known as the gut-associated lymphoid tissue (GALT), is located in the gut, where around 80% of immunoglobulin A (IgA) plasma cells reside. These cells play a significant role in maintaining the immune system balance and physiological functions by interacting with the gut microbiome [181–183].

6.3. Short-Chain Fatty Acids (SCFAs): Building Blocks of Gut Health

Moreover, the gut microbiome's contact with innate and adaptive immune cells across the intestinal mucosa impacts immune-related homeostasis, including GALT and CNS-immune cells [180,184]. As the gut microbiota undergoes manipulation, gut microbiota metabolize indigestible fiber-rich carbohydrates and primary bile acids to produce SCFAs and secondary bile acids (2BAs), respectively, which significantly impacts the neuroimmune system, particularly influencing microglia development and maturation [180,185–189].

This intricate relationship is underscored by the role of short-chain fatty acids (SCFAs), such as propionate, butyrate, and acetate [187]. SCFAs, acting on receptors of enterochromaffin cells (ECCs), regulate the secretion of hormones, such as glucagon-like peptide (GLP-1) and peptide YY (PYY), influencing food intake and blood sugar homeostasis [190–193]. Additionally, SCFAs increase the biosynthesis of serotonin in colon ECCs, further impacting gut–brain communication [191,194].

In GF mouse studies, microglial immaturity and malformation were observed, which could be restored by short-chain fatty acids (SCFAs) [195–197]. Conversely, moderate levels of short-chain fatty acids (SCFAs), particularly those abundant in butyrate, enhance the protection and repair of a compromised intestinal barrier when exposed to inflammatory factors, like LPS or tumor necrosis factor-α (TNF-α) [198]. SCFAs induce regulatory T cell (Treg) differentiation and increase interleukin-10 (IL-10) production by Tregs, influencing inflammation and immune regulation [199–201].

6.4. Role of Toll-Like Receptors, Lipopolysaccharide, and Gut Peptides

The bacterial outer membrane contains LPS, which has pro-inflammatory characteristics and is known to play a crucial role in the development and course of low-grade systemic inflammation. While commensal bacteria live on many body surfaces, most of them—mainly Gram-negative bacteria with LPS in their cell walls—are found in the gut. Increased LPS levels frequently signify the movement of gut-dwelling Gram-negative bacteria into the blood and internal body cavities.

Through the stimulation of intestinal inflammation and the disruption of tight junction (TJ) organization via certain signaling pathways, LPS directly impairs gut function. These mechanisms cause oxidative stress, mitochondrial malfunction, and mitophagy in epithelial cells, and they cause enterocyte loss without compensatory TJ release [202].

TLRs contribute to maintaining balance in the intestines by detecting microbial signals and are present in the ENS [203,204]. Pathways are dependent on the Toll-like receptor 4 (TLR4) and the cluster of differentiation 14 (CD14), and when TLR4 recognizes substances, like LPS, it indirectly induces a pro-inflammatory response through the NF-κB pathway [203]. The pattern recognition receptor (PRR) TLR4 is expressed in hepatocytes, adipocytes, endothelial cells, and different immune cells. LPS-binding protein (LBP) and CD14 aid in TLR4's recognition of LPS, with MD-2 protein being essential. Two signaling pathways are triggered by TLR4 activation: one involves the adaptor proteins TIRAP and MyD88 at the plasma membrane, while the other depends on TRAM and TRIF after

CD14-mediated receptor endocytosis. The degree of systemic inflammation caused by LPS is determined by the pace at which TLR4 is endocytosed and trafficked through the endo-lysosomal compartment. The inflammatory response usually ends with the lysosomal degradation of LPS-activated TLR4 and the subsequent activation of MyD88- and TRIF-dependent signaling pathways [205,206]. Moreover, TLR2 plays a role in preserving ENS integrity by regulating inflammation within the intestines [207]. Often likened to a "second brain", the ENS interacts with enteroendocrine cells (EECs) and the gut microbiome, possibly via sensory nerves, like the VN [175,180]. When Toll-like receptor (TLR) signaling is altered, it results in the promotion of regulatory T (Treg) cells and T helper 17 (TH17) cell proliferation, while also dampening the responses of intestinal epithelial cells (IECs) [208–210]. The microbiome's proposed role in regulating inflammatory cytokine levels highlights its importance in shaping the immune response dynamics.

A high-fat diet may also contribute to systemic inflammation because it has been shown that SFA may activate Toll-like receptor 4 (TLR4). Lipid A from LPS and dietary SFA shares structural similarities that might be the cause of this activation. Chain lengths affect the pro-inflammatory efficacy of SFA; lauric acid has the highest activity, while myristic and stearic acids have the lowest [206].

The endocannabinoid system (EC) plays a crucial role in regulating food intake and is implicated in glucose and energy metabolism regulation in mammals. Research indicates that specific gut microbes, such as Akkermansia muciniphila, can modulate the EC system, altering its activity levels. Dysbiosis, particularly associated with obesity or high-fat diets, can elevate EC activity, leading to increased gut permeability and the subsequent translocation of LPS. Muccioli et al. demonstrated that inhibiting cannabinoid receptor-1 (CB1) with CB1 antagonists in obese mice reduced gut permeability and adipogenesis by normalizing the expression of Occludin and ZO-1, whereas CB1 stimulation increased permeability markers both in vivo and in vitro [211].

6.5. The Neuroendocrine Pathway: Gut Hormones and the Path to Well-Being

As previously discussed, the gut microbiota plays a significant role in regulating the activity of the host immune system, affecting the production of pro-inflammatory cytokines and subsequently influencing and activating the release of corresponding hormones by the HPA axis, involved in regulating many different psychological segments, including mood and emotions and furthermore the immune system [212–222].

Additionally, the interaction among stress, the gut microbiome, and inflammatory factors can compromise the integrity of two crucial barriers within the BGM axis: the intestinal barrier and the BBB [166,182]. Under normal circumstances, the gut epithelial layer acts as a protective barrier, preventing the unregulated movement of gut microbiota into the gut lamina propria [223,224]. However, various environmental factors can impact the intestinal barrier and compromise its integrity [182].

6.6. Microbiota–Serotonin Axis: An Important Link in Brain-Gut Communication

Numerous studies have established a strong connection between the microbiota and serotonin regulation within the gut, emphasizing its pivotal role in brain–gut communication [191,225]. Serotonin, a vital neurotransmitter, originates from the metabolism of tryptophan, further highlighting its significance in facilitating communication between the brain and the gut [224]. Serotonin is involved in mood, cognition, sleep, and appetite control [225–229].

Inflammation in the gut and disruptions in the brain–gut-microbiota (BGM) axis, such as gut dysbiosis, have been linked to various metabolic and neurological disorders [230]. Thus, targeting essential elements of the GMB network, including short-chain fatty acids (SCFAs), serotonergic pathways, the VN, and CNS macrophages, holds significant therapeutic and investigative promise for alleviating the repercussions of gut dysbiosis.

7. Regulating Inflammation through the Microbiome

7.1. Navigating Inflammation: Striking the Balance between Protection and Overreaction

Distinguishing between protective and uncontrolled inflammation is crucial in understanding the dynamics of immune responses. The acute inflammatory response, essential for defense against pathogens, is typically self-limiting. Neutrophils, the predominant leukocytes in the blood, play a pivotal role in the initial defense, employing enzymatic and chemical weapons to combat invaders and aid in tissue repair [150–152,231]. However, dysregulated neutrophil recruitment and activation can exacerbate tissue damage, perpetuating inflammation and potentially leading to chronic conditions [152,154,158,232–234].

Evidence suggests that the impaired removal of neutrophils from inflamed tissues exacerbates inflammation [154]. This persistent inflammation is implicated in various diseases, spanning cardiovascular, respiratory, neurodegenerative, metabolic, and autoimmune disorders, along with conditions like rheumatoid arthritis (RA), multiple sclerosis, inflammatory bowel disease, periodontitis, and sepsis [156,233]. The resolution of inflammation is an intricate process, orchestrated by specialized lipid mediators, proteins, and gaseous molecules that promote tissue restoration. These mediators, such as lipoxins, resolvins, protectins, and maresins, facilitate repair by acting on immune cells, particularly phagocytes [189,235,236]. However, ongoing low-grade inflammation can impede the activation of resolution mechanisms [154,202], contributing to acute exacerbations of chronic inflammatory conditions [205,206,237,238].

Furthermore, evolving evidence suggests that neutrophils contribute to wound healing and tissue repair [221,226,231]. Their involvement in providing extracellular matrix components and facilitating the clearance of apoptotic cells underscores their role beyond the initial inflammatory response [187,221,224,226,229,231]. However, defects in phagocytosis or neutrophil-induced genomic instability may impede resolution and hinder wound healing [161].

7.2. Microbiome and Inflammation: Deciphering the Interactions

According to the updated definition, the microbiome includes not only microorganisms but also their activities, collectively forming unique ecological niches.

The human microbiome is increasingly acknowledged as the "final organ", highlighting its crucial significance [239–241]. There are considerable variations in its composition across individuals and bodily sites [109,242–244]. Different factors impact interaction outcomes and disease emergence, including inflammatory bowel disease [245–254], cancer [251,252], and major depressive disorder. Additionally, the microbiome composition undergoes alterations with aging and may vary significantly [253,254]. Understanding their precise roles in the pathogenesis of these disorders can lead to innovative clinical interventions, ranging from diagnostic biomarkers to therapeutic approaches with enhanced specificity and efficacy.

The latest finding showed the microbiome's ability to modulate the immune system, leading to alternative states. Strong correlations have been observed between microbiome alterations and various autoimmune and inflammatory conditions. In certain scenarios, antibodies produced against microbiome-associated antigens may act as autoantibodies, mistakenly targeting "self" tissues and causing damage. This phenomenon has propelled autoimmune disease pathology into the realm of microbiome research, with conditions like RA being a prominent example [255–257]. Studies in rat models have demonstrated that the presence or absence of microbes can influence disease progression [258]. Additionally, recent investigations in transgenic mice have revealed differences in microbial compositions correlating with disease susceptibility, alongside variations in mucosal permeability and the transcriptomic profile of T helper 17 (TH17) cells, which regulate the host response to microbes and inflammation [259]. These findings provide a foundation for further human clinical exploration and investigation.

Another proposed mechanism connecting gut microbes and autoimmunity, particularly concerning RA, suggests that joint inflammation might stem from harmful metabolites resulting from imbalances in the gut microbiota. This theory is based on the observed association between the prevalence of specific microbial species and strains and an elevated susceptibility to particular diseases. For example, gut Prevotella, a specific Gram-negative intestinal commensal anaerobic bacteria, has been associated with various inflammatory and autoimmune disorders [260]. An increase in Prevotella is reported to correlate with enhanced susceptibility to arthritis, and a reduction of Prevotella via dietary modulation leads to reduced pro-IL-1β secretion in distal neutrophils [261,262]. While comprehensive "pan-microbiome" investigations are crucial to gaining deeper insights into the role of the human microbiome in RA pathogenesis, it is apparent that microbial participation significantly influences the autoimmune process.

7.3. Neuroinflammation: Bridging the Gap between the Immune Response and Disease

A wide range of biologically active mediators influence the inflammatory response within the nervous system and associated tissues. These inflammatory agents are generated by resident glial cells in the CNS (including microglia and astrocytes), endothelial cells, and immune cells originating from peripheral sources [263]. While neuroinflammation is commonly linked to the development of various neurological disorders, its primary function is to act as a protective mechanism, demonstrating beneficial and adaptive effects [264].

Neuroinflammation serves as a mode of communication between the CNS and the immune system [265], enabling a coordinated response by producing cytokines and secondary signals that trigger appropriate behavioral and physiological adjustments, such as fever, lethargy, reduced activity, and diminished social interaction [266]. These adaptations help redirect the host's resources to combat infections [267] and contribute to brain development, plasticity [268,269], and processes like long-term potentiation (LTP), which are crucial for learning and memory [270]. Essential elements of neuroinflammation, including IL-1β, IL-6, and TNFα, are involved in maintaining synapses [271,272], with IL-1β supporting the learning process, while IL-6 inhibits it [273]. Additionally, neuroinflammation aids in the healing process following spinal cord or traumatic brain injury by regulating the activation states of microglia [274].

Microglia, together with perivascular macrophages (pvMFs) and meningeal macrophages (mMFs), represent the surviving macrophages of early primitive hematopoiesis within the CNS [101–103]. Microglia, often referred to as the "policemen of the brain" for their role in coordinating signals between the immune system and the brain, serve as the principal resident macrophages in the brain, constituting the frontline defense against CNS injury and infection and participating in numerous crucial processes for brain function, development, and immune responses [104,275–277]. Throughout their lifespan, microglia exhibit remarkable plasticity, swiftly transitioning between context-dependent activation states characterized by distinct transcriptomic profiles, each associated with varying physiological functions during development and adulthood, ranging from an active to a homeostatic state [105].

Although essential for CNS protection, the chronic or excessive activation of microglia may lead to pathological outcomes, like neuronal injury, death, and neurocognitive disorders [204]. Additionally, due to their close proximity to other CNS cells, microglia play crucial roles in the development and modulation of various neuroinflammatory and neurodegenerative conditions [106,109]. With aging, microglia undergo a transition from quiescence to activation, triggering processes, such as branching, surveillance, and IL-1β release via the two-pore domain K+ channel THIK-1, thereby contributing to the onset of neurodegenerative diseases [110,111]. Additionally, chronic or traumatic stress can lead to a significant neuroinflammatory response, with animal studies suggesting the release of diverse inflammatory signals by macrophages in response to stressors [278–280].

Even subtle imbalances or prolonged inflammatory events may cause behavioral abnormalities and damage to neurons, especially to developing neurons that are crucial for brain function and mood control [162].

Moreover, oxidative stress resulting from inflammation and injury, along with the production of ROS, can exacerbate neurodegeneration [281–283]. Importantly, anomalies in the immune system, combined with genetic and environmental factors, can trigger neuroinflammation, which, in turn, stimulates inflammatory pathways, leading to a positive feedback loop and ongoing neuronal loss [284].

As microglia undergo aging, disruptions in immune communication within the brain arise, accompanied by an imbalance in immune mediators [285]. Aged microglia display distinct morphological characteristics and maintain a pro-inflammatory profile long after injury, contributing to adverse outcomes [286]. Aging-related conditions and the overall health status serve as significant predictors of neuroinflammation, directly influencing the risk and development of brain and nervous system disorders [287]. Inflammation has been implicated in resistance to conventional antidepressant therapies [288], with its mechanisms in depression encompassing oxidative stress, cytokine imbalances, and hyperglutamatergia [289,290]. Furthermore, inflammatory triggers may act as precursors to various neurodegenerative disorders, underscoring the pivotal role of neuroinflammation in disease onset and progression [291].

While neuroinflammation represents a crucial physiological process, prolonged and uncontrolled inflammation can contribute to the onset of nervous system disorders, such as anxiety, depression, memory impairment, and cognitive decline. A comprehensive understanding of neuroinflammation pathways holds promise for deciphering disease mechanisms and developing novel therapeutic agents with enhanced specificity and improved prognostic outcomes for these conditions.

The Gut–Brain Connection: Understanding the Microbial Influence on Neuroinflammation

The human microbiome exerts effects over the immune response, notably shaping inflammatory reactions and playing a pivotal role in regulating neuroinflammation within the brain, thus emerging as a crucial factor in brain physiology, behavior, and cognition regulation [292]. Patients with irritable bowel syndrome (IBS) have shown improvements in both IBS symptoms and associated depression through administration of the probiotic Bifidobacterium longum NCC3001 (BL) [293]. The observed positive effects of the probiotic are linked to alterations in brain activation patterns and reduced limbic activity.

The concept of the "gut-brain axis" has emerged as a significant area of study, focusing on the bidirectional influence between the gut and the brain on their respective functions. This relationship is particularly evident in Alzheimer's disease (AD). Reports have highlighted a potential link between fungal infections and AD-affected brains [294]. Additionally, investigations using the APP/PS1 mouse model of AD have suggested a connection between alterations in the gut flora and disease phenotype [295]. Studies have shown that the exposure of human primary brain cells to LPS can induce neuroinflammatory consequences by activating the NFκB (p50/p65) complex [296]. Moreover, gut bacteria have been implicated in triggering neuroinflammation by producing amyloids. Compelling evidence from various studies has associated the reinforcement of normal or beneficial flora with changes in disease susceptibility or progression. Dietary modifications impacting the microbiome have been shown to influence neuroinflammation, but further investigations are needed [297,298].

Similar observations have been made in conditions like Gulf War Illness (GWI), characterized by neurological abnormalities and gastrointestinal disturbances. Rodent models of GWI have shown that chemical exposure can alter gut bacteria, leading to a leaky gut, which activates TLR4 and induces neuroinflammation [299]. In the context of hepatic encephalopathy (HE), an altered gut–liver–brain axis may serve as a risk factor, and fecal microbial transplant (FMT) following antibiotic administration has shown promise in improving outcomes by restoring the normal microbiota and normalizing gut–brain

communication in inflammation [300]. Strategies aimed at restoring the microbiota balance through butyrate consumption and dietary soluble fiber have demonstrated improvements in neuroinflammation parameters associated with aging [301,302].

The relationship between microbial dysbiosis in the gut and the neuroinflammatory response following stroke is bidirectional [303]. In synucleinopathies like Parkinson's disease (PD), gut microbiota alterations have been linked to motor deficits and αSyn pathology, suggesting a role for postnatal gut–brain signaling in disease modulation [304]. Additionally, neurological symptoms following COVID-19 infections may be related to disruptions in the gut microbiome [305].

7.4. Understanding the Versatile Nature of Neutrophil Extracellular Traps (NETs)

Neutrophil extracellular traps (NETs) are a unique type of inflammatory response that were first identified in 2004 [306]. Extracellular DNA traps were released to characterize NETs. It was discovered that these DNA traps were made of decondensed DNA fibers, histones, and neutrophil granule proteins. While initially the release of NETs was associated with neutrophil death, termed NETosis, recent findings reveal that neutrophils also undergo a process of vital and mitochondrial NET production [307].

Over the last 20 years, there has been a growing body of research on the physiological properties of neural epithelial cells (NETs) and their impact on a wide range of disorders [308–312]. NET formation involves the uncoiling of DNA strands in response to stimuli, facilitated by proteases, such as peptidyl arginine deiminase 4 (PAD4) and neutrophil elastase (NE) [313–318]. Neutrophils extrude their contents through blebbing from the cell membrane while remaining alive and retaining their functional capabilities [307]. The orchestrated activation of various signaling pathways leads to the blebbing process from and extracellular release of NETs from the neutrophil cell membrane aided by gasdermin D, while neutrophils remain alive and retain their functional capabilities [307,319,320]. Interestingly, different stimuli and disease contexts can trigger distinct forms of production and NET release, including suicidal or lytic NETosis, where neutrophils undergo cell death concurrent with NET expulsion triggered by infections, cytokines, and platelet activation. Vital NETosis, which occurs without cell death, is predominantly induced by infections and involves the vesicular trafficking of DNA to facilitate NET release, without membrane rupture, thereby preserving cell integrity [307,321]. Additionally, both infections and autoimmune diseases are associated with mitochondrial NETs [307].

Various signaling pathways regulate NET formation, including JNK, ERK1/2, Akt, and Scr. The PKC activator phorbol 12-myristate-13-acetate (PMA) is commonly used as a NET inducer [322–325]. Interactions between NETs and other immune-related mechanisms, such as the inflammasome and autophagy, are gaining attention [326]. These findings underscore the complexity of NET formation and its role in immune responses, suggesting avenues for further research and potential therapeutic applications.

7.4.1. NETs and Inflammatory Crosstalk: Insights into Immune Regulation

The inflammasome of innate immunity, which is triggered by inflammatory and immunological stimuli, is made up of a number of different proteins that, through their detection of PAMPs or DAMPs, facilitate inflammatory and immune responses. Numerous inflammasomes, such as NLRP1, NLRP2, NLRP3, NLRC4, and AIM2, have been linked to autoimmune, CNS, and cardiovascular illnesses. It has been observed that inflammasomes and NETs interact, for example, in atherosclerosis, where NETs activate macrophages to produce IL-1β. Recent research indicates that NETs may activate the NLRP3 inflammasome in peripheral neuropathy caused by oxaliplatin, notwithstanding the paucity of data. Further research to examine this interaction is needed [309,327].

Autophagy is essential for maintaining cellular homeostasis and has been identified as a major factor in a number of diseases that affect immunity and inflammation. The relationship between NETs and autophagy is becoming more widely understood. Neutrophil autophagy is linked to NET-mediated cell death, and in sepsis, autophagy-driven NET pro-

duction leads to inflammatory responses and immunological failure. Even though studies have linked autophagy to NETs in CNS disorders and aging-related spontaneous NET development, further investigation is required to fully understand this association [328–331].

The fate of NETs is controlled by mechanisms of degradation primarily executed by macrophages and dendritic cells, involving enzymes like DNase 1 and TREX1 [332,333]. Notably, the protein LL-37 aids in NET uptake by macrophages while shielding NETs from degradation by bacterial nucleases [333]. Furthermore, recent findings suggest that certain resolvins enhance the uptake of NETs by macrophages, though the exact receptor remains unidentified [334].

Despite their beneficial role in combating infections, microbial capture, and direct antimicrobial activity, their uncontrolled formation can lead to tissue damage and perpetuate inflammation, contributing to various pathological conditions [321]. Cell-free DNA, histones, MMP-9, and LL-37 contribute to this damage through mechanisms, such as cytotoxicity, thrombosis, and inflammation [335–337]. For instance, NET components, like histones and granular proteins, can induce thrombin generation and endothelial injury, exacerbating inflammatory responses [321]. Moreover, dysregulated NET formation has been implicated in the severity of diseases, such as sepsis and COVID-19-associated acute respiratory distress syndrome [338–341]. In COVID-19, NETs infiltrate pulmonary tissues, causing damage and microthrombi formation, further exacerbating the disease [339,341–343].

7.4.2. Neutrophil Extracellular Traps: Disrupting the Blood–Brain Barrier Dynamics

Brain microvascular endothelial cells (BMECs) contribute to formation of the highly selective BBB. Consequently, neutrophils face barriers in crossing the BBB and are seldom encountered in a healthy brain. Activated astrocytes and microglia cells release pro-inflammatory cytokines, leading to the upregulation of adhesion molecules on BMECs, which aids in neutrophil adhesion [344]. Consequently, interactions between neutrophils and endothelial cells without transmigration contribute to increased BBB permeability [345].

Various mechanisms underlie neutrophil adhesion-dependent disruption of the BBB. Initially, neutrophil adhesion induces blood flow stagnation, resulting in vascular obstruction; the depletion of neutrophils enhances CNS perfusion and reduces brain damage post-stroke [346]. Neutrophil adhesion to BMECs via β2 integrins LFA-1 and MAC-1 triggers neutrophil activation, escalating oxidative stress and NETosis [347]. Activated neutrophils release neutrophil elastase (NE), potentially within NETs, which disrupts adherens junction proteins, like VE-cadherin and β-catenin, elevating BBB permeability [348–351].

7.4.3. Therapeutic Potential of Neutrophil Extracellular Traps in Central Nervous System Treatment: Exploring Opportunities

As discussed previously, NETs play a crucial role in various CNS diseases, including cerebral stroke, Alzheimer's disease, multiple sclerosis, ALS, and neurological cancers. Several therapeutic approaches targeting NETs have been explored for these conditions [352–360]. Following cerebral ischemia, neutrophils infiltrate the CNS and are positively correlated with neuronal loss, the infarct size, and cognitive impairment. Neutrophils from ischemic stroke patients display heightened NET formation compared to healthy controls [344,361]. Additionally, CNS-infiltrating neutrophils in ischemic stroke patients generate NETs [362]. Elevated serum levels of cell-free DNA in acute ischemic stroke patients are associated with worse clinical outcomes based on the modified Rankin scale, while lower serum DNase levels are observed in patients with stroke-associated infections [363]. High-mobility group box-1 (HMGB1), primarily derived from platelets, serves as a major inducer of NET production in ischemic stroke, and its depletion attenuates NET formation post-stroke and improves neurological outcomes [362–366].

The same theory was reached in 2022, when interventions aimed at suppressing NETs have shown promise. Dhanesha et al. (2022) demonstrated that inhibitors of nuclear pyruvate kinase muscle 2 (PKM2), a modulator of systemic inflammation, could mitigate neutrophil hyperactivation and NET release, thereby improving functional out-

comes post-stroke [367]. Similarly, the combination therapy Edaravone Dexborneol, comprising Edaravone and (+)-Borneol, was found to ameliorate acute ischemic stroke by mitigating NET-induced blood–brain barrier damage and implicating its therapeutical potential [368,369].

In multiple sclerosis (MS), elevated neutrophil levels and NET formation are associated with relapsing-remitting MS (RRMS), suggesting a potential role in its pathogenesis [344]. In glioma, neutrophil-associated inflammation, including NETosis, promotes tumor growth and resistance to therapy, suggesting a complex interplay with tumor progression [370–372]. Similarly, in Alzheimer's disease (AD), neutrophils and NETs contribute to neuroinflammation and disease progression, with potential implications for therapy [373–375]. Intermittent hypoxia–hyperoxia training was shown, by Serebrovska et al., to improve cognitive function and slow disease progression by suppressing NET-mediated blood–brain barrier damage and parenchymal destruction [376]. Additionally, dimethylfumarate, a common food additive, was found to alleviate neutrophil-mediated chronic inflammatory diseases, like multiple sclerosis, by inhibiting neutrophil activation and NET formation [377]. The collective results indicate a significant rise in neutrophil mobility in the cerebral parenchyma during neuroinflammatory reactions, which is indicative of changes in their molecular and metabolic profiles. These studies highlight NETs as potential therapeutic targets for CNS diseases. These findings highlight the importance of understanding neutrophil dynamics in CNS disorders and their potential as therapeutic targets [378].

In traumatic brain damage (TBI), neuroinflammation is frequently observed [379]. In TBI models in mice, neutrophils cling to cerebral arteries, invade hypoxic brain tissue, and produce neural epithelial cells or NETs. These cells are linked to adverse TBI outcomes such cerebral edema, cognitive deficits, and paroxysmal sympathetic hyperactivity [380]. Neutrophil stimulation of the Toll-like receptor-4 (TLR4) causes NET development after traumatic brain injury (TBI), which raises the intracranial pressure (ICP). This suggests that neutrophils have a role in cerebral edema by producing NETs. Reducing NET development in the brain after traumatic brain injury (TBI) and improving neurological and behavioral outcomes have been demonstrated by techniques, such TLR4-knockout, the NET formation inhibitor Cl-amidine, and DNase-1 [381]. According to these results, treatments that target neural edema and hypoxia may be able to reduce these symptoms after traumatic brain injury.

Interestingly, NETs exhibit a dual role in cancer, demonstrating both anti-tumor and pro-tumor activities [382]. While they can inhibit cancer cell proliferation and exert cytotoxic effects on certain tumor types, they may also promote tumor progression by facilitating metastasis, awakening dormant cancer cells, and shielding tumor cells from immune surveillance [382–386]. These diverse functions highlight the complex interplay between NETs and cancer progression, warranting further investigation into their precise role in tumorigenesis.

7.4.4. Modulating Neutrophil Behavior: Implications for Degranulation, NET Release, and Clearance

The excessive or abnormal formation of neutrophil extracellular traps (NETs) has been linked to the development of various diseases, suggesting that inhibiting NET release or enhancing NET clearance could be promising therapeutic strategies. Compounds like ROS scavengers, myeloperoxidase inhibitors, and PAD4 inhibitors have shown efficacy in inhibiting NET release and reducing tissue damage in experimental models [321]. Moreover, reversible PAD4 inhibitors, such as GSK484, have demonstrated the ability to inhibit suicidal NETosis and prevent neutrophil-mediated kidney injury associated with cancer in mice [387]. Certain lipid specialized pro-resolving mediators (SPMs), such as resolvin D4 and T-series resolvins, also exhibit the capacity to restrict NET formation [388–390].

Enhancing the degradation of neutrophil extracellular traps (NETs) through treatment with DNase I reduced tissue damage and improved survival rates in mouse models of severe bacterial pneumonia, transplantation-associated lung injury, tumors, and lu-

pus [338,391]. Ongoing clinical trials are investigating the effectiveness of inhaled dornase-α in reducing ARDS incidence in severe trauma patients [392]. Additionally, metformin enhances NET clearance and efferocytosis, providing a potential therapeutic avenue [321].

7.5. Navigating the Interplay between Neutrophils and Pathogens

The interaction between neutrophils and various types of pathogens, including bacteria, fungi, parasites, and viruses, is critical for host defense. Bacterial pathogens, through surface molecules and toxins, delay neutrophil apoptosis, prolonging their lifespan for ample pathogen clearance [393]. Phagocyte recognition of bacteria is mediated by specific receptors, facilitating efficient phagocytosis. However, some bacterial pathogens alter the neutrophil fate post-phagocytosis, promoting rapid lysis or prolonging apoptosis, impacting inflammation and pathogenesis. Moreover, neutrophil extracellular traps (NETs) play a role in trapping and killing bacteria, but their excessive release can cause tissue damage.

Similarly, fungal pathogens pose unique challenges to neutrophils due to their diverse structures. While neutrophils efficiently kill certain fungi, primary fungal pathogens exhibit resistance [394]. Parasitic protozoans and helminths modulate neutrophil responses, exploiting the neutrophil lifespan to facilitate disease progression [395]. They can also trigger neutrophil extracellular traps (NETs), contributing to host defense or tissue damage.

Viruses, although diverse, can manipulate neutrophil survival pathways, impacting host defense. Neutrophils can transport viruses to other tissues, contributing to dissemination [396]. Moreover, viruses may trigger neutrophil lysis and NET formation, which can either aid in viral clearance or exacerbate tissue damage.

Despite the complexity, neutrophils play a crucial role in host defense against pathogens. Their interactions with various pathogens highlight the intricate balance between pathogen elimination and host tissue damage, emphasizing the importance of further research in understanding these mechanisms.

Certain microbial species have devised cunning strategies to exploit neutrophil-mediated inflammation for their own benefit, often at the expense of the commensal microbiota, such as Salmonella [397]. Similarly, pathogenic strains of Escherichia coli can capitalize on intestinal inflammation for their own growth advantage. Inflammation prompts the upregulation of inducible nitric oxide synthetase by recruited leukocytes and the epithelium, leading to the production of nitrate. While the majority of gut microbiota species cannot utilize nitrate, pathogenic E. coli possess mechanisms to employ it as an electron acceptor for energy generation. This ability grants them a competitive edge over other gut microbes, facilitating their proliferation during episodes of intestinal inflammation [398].

7.6. The Complex Relationship between Gut Dysbiosis and Disease

"Leaky gut" or intestinal permeability syndrome are terms used to describe the disorder of the intestinal barrier. This problem leads to the development of several clinical illnesses and is mostly caused by bacterial infections, oxidative stress, alcohol intake, extended exposure to allergens, and an imbalance in the gut flora. These comprise obesity, liver cirrhosis, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease, celiac disease, irritable bowel syndrome, type 1 diabetes mellitus (T1D), and various autoimmune conditions [108,399].

There are three main types of gut dysbiosis that can lead to an imbalance in the gut flora. The first type occurs when there is an insufficient presence of beneficial bacteria in your gut flora. In this case, you may have lost an excessive amount of "good" bacteria. The second type involves an overabundance of harmful bacteria. These hazardous bacteria overgrow in your intestines, leading to an imbalance in your gut microbiota. The third type entails a significant reduction in the diversity of your gut flora. Both beneficial and harmful bacteria are lost, resulting in a decreased variety of bacterial species in your gut [400]. The goal of microbiota research is to define "Eubiosis", or a condition of a healthy microbiota that is marked by a stable functional core, a diversity of taxa, and high

microbial gene richness. On the other hand, disease promotion results from dysbiosis, which is characterized by altered phylum ratios, decreased microbial diversity, and an overabundance of Gram-negative bacteria, like Proteobacteria [401].

Increased intestinal permeability frequently coexists with dysbiosis, which makes it easier for bacterial products to translocate and trigger immunological reactions that may result in chronic inflammation. While dysbiosis is associated with a number of inflammatory illnesses, it also has the ability to cause inflammation and disturb intestinal homeostasis [402]. Numerous illnesses, such as autoimmune disorders, neurological issues, obesity, metabolic diseases, inflammatory bowel diseases, and particular pathologies, including necrotizing enterocolitis and diarrhea connected to Clostridium difficile, have been linked to dysbiosis [401].

Using high-throughput DNA sequencing methods, like 16S rRNA gene sequencing or whole-metagenome shotgun sequencing, it is possible to determine the pathogenicity of individual gut bacteria, in opposition to the infectious disease microbiology hypothesis of Koch. Because much of the gut microbiota cannot be grown in isolation, these techniques enable the detection of altered bacterial populations or the replication of illnesses [403].

Therapeutic Insights

The integrity of the intestinal barrier and bacterial-derived products play crucial roles in various chronic diseases, though a standard for assessing barrier function and establishing cause–effect relationships remains elusive. Diet, probiotics, and prebiotics emerge as key factors in managing metabolic endotoxemia and compromised intestinal barriers. Certain dietary habits, such as alcohol abuse and high saturated fat intake, contribute to inflammation, while oils rich in n-3 polyunsaturated fatty acids offer protective effects [404]. Probiotics like Lactobacillus plantarum MB452 or Lactobacillus rhamnosus GG enhance intestinal survival, while prebiotics like Enteromorpha prolifera polysaccharides combat gut dysbiosis induced by high-fat diets [405,406].

Supplementation with vitamins D and A, along with zinc, shows promise in preserving intestinal barrier function [407]. Combining prebiotics and probiotics yields better outcomes in improving intestinal function than individual components [408].

Therapeutic strategies focus on preserving intestinal barrier integrity and neutralizing LPS pathways [409,410]. Microbial modulation through fecal microbiota transplantation (FMT) offers significant contributions to managing NAFLD/NASH and hepatic encephalopathy [411,412]. Clinical trials examining FMT's effect on inflammatory bowel disease (IBD) show promising results, though further investigation is needed due to inconsistent donor selection and administration methods [413].

8. The Bidirectional Relationship between the Hypothalamic–Pituitary–Adrenal Axis and the Gut Microbiota

The HPA axis serves as the main response system during periods of stress [414]. The critical role of the gut microbiota in the postnatal maturation of the HPA axis, essential for stress response regulation, is significantly modulated by various factors. These encompass the specific bacterial strains present, the availability of metabolized substrates, and host attributes, like age and gender [415–418]. Considering the direct impact of alterations in the HPA axis on the inflammatory response, the microbiome forms a tripartite stress response system alongside neuroendocrine and neuroinflammatory components [419,420]. The vulnerability of the STAT5 signaling pathway to shifts in the microbiome composition [421,422] indicates that changes in the microbiome can impact the neuroinflammatory process and related disorders.

The quality and quantity of the gut microbiota, along with Toll-like receptor (TLR) expression, may impact neuroendocrine secretion, playing a pivotal role in stress responses. Studies on mice deficient in the stress response have revealed reduced expression of 2A isoforms of brain-derived neurotrophic factor and N-methyl-D-aspartate (NMDA) receptors [423]. NMDA receptors influence the release and expression of corticotropin-

releasing hormone (CRH) in the hypothalamus, leading to alterations in HPA axis functions. The de novo synthesis of corticosteroids in the intestine is directly influenced by the intestinal microbiota [424,425]. Glucocorticoids have been found to modulate the expression of inflammatory mediators, exerting anti-inflammatory effects [426].

Simultaneously, the stress–HPA axis interplay influences the gut microbiota composition. The HPA axis and intestinal microorganisms mutually influence each other, jointly participating in the pathophysiological processes following ischemic stroke (IS). Dysregulation of the gut microbiota post-IS results in the over-release of substances like cytokines (e.g., IL-1β, IL-6, and TNF-α), which penetrate the brain via the BBB due to enhanced permeability, activating the HPA axis. Cortisol, a central stress response mediator, regulates its further production by modulating corticotropin in the hypothalamus [427,428]. Thus, the HPA axis, a pivotal regulator of the stress response, also modulates the gut–brain axis. In the hypothalamus, IL-1 and IL-6 can induce cortisol release by activating the HPA axis [429]. Finally, the gut epithelium houses various types of hormone-secreting specialized neuroendocrine cells included in delicate metabolic pathway regulatory mechanisms [430–433]

9. Therapeutic Opportunities

9.1. The Evolving Concept of Neutrophil Heterogeneity

Our understanding of neutrophils is rapidly evolving. Once thought to be a homogeneous cell population with uniform functions, recent insights have revealed their heterogeneity in various physiological and pathological contexts [434–436]. While traditional classification methods relied on morphology, gradient separation, or surface markers, cutting-edge techniques, like single-cell RNA sequencing, have unveiled transcriptomically distinct neutrophil populations, even among mature peripheral neutrophils and those involved in chronic inflammatory states [437–439]. This newfound heterogeneity is conceptualized through a developmental continuum known as the "neutrotime", revealing distinct poles separated by transcriptomic shifts [440]. However, further research is required to elucidate the precise links between neutrophil transcriptomes and their phenotypic or functional properties.

Certain subsets of neutrophils, such as CD177+ and CD117+ neutrophils, have emerged with specific functions or associations with disease states [321]. Moreover, the notion of "low density neutrophils", encompassing both mature and immature neutrophils with both proinflammatory and immunosuppressive properties, challenges the traditional view of neutrophil homogeneity [441]. These subsets have been implicated in a variety of conditions, including systemic lupus erythematosus and sepsis, highlighting their clinical relevance [442,443]. Additionally, distinct subsets of tumor-infiltrating neutrophils, such as the N1 and N2 subsets, exhibit differential effects on tumor growth, suggesting a complex interplay between neutrophil phenotypes and the tumor microenvironment [321].

Neutrophils also demonstrate remarkable transcriptional and translational plasticity in response to inflammatory cues, leading to alterations in functions and heterogeneity [444]. Metabolic reprogramming during the neutrophil life cycle further contributes to their functional diversity, with metabolic pathways influencing key aspects of neutrophil biology, including lifespan and the resolution of inflammation [445,446]. These findings underscore the intricate nature of neutrophil biology and highlight the importance of understanding neutrophil heterogeneity in both health and disease contexts.

9.2. Understanding the Fate of Emigrated Neutrophils

Neutrophils, the foot soldiers of the immune system, are recruited to sites of infection or tissue injury, where they execute a variety of functions critical for mounting an effective immune response and restoring tissue homeostasis. However, the outcomes of their actions are multifaceted, influenced by numerous factors, and can either promote protective inflammation or contribute to uncontrolled, chronic inflammatory states. Neutrophil swarming, a fascinating phenomenon, involves the congregation of neutrophils in tissues following their migration across endothelial barriers [321]. This coordinated clustering

around the site of infection or injury is crucial for containing pathogens and sealing off damaged areas. Swarming is orchestrated by a series of events, including neutrophil contact with necrotic cells, the release of signaling molecules, like LTB4, and the formation of stable gradients that guide further neutrophil migration [447]. While swarming is generally considered protective, excessive neutrophil accumulation and activation during this process can lead to collateral tissue damage and exacerbate inflammation [448].

9.2.1. Beta-2 Integrin as a Target for Therapeutic Innovation

The conformational variations in Mac-1 and its broad ligand-recognition ability influence neutrophil responses and contribute to their functional diversity [449]. Consequently, β2 integrins have emerged as promising therapeutic targets [449,450]. Alternative strategies involve targeting specific Mac-1 conformations or ligand-specific signaling pathways without compromising host defense [321]. Allosteric inhibitors stabilizing β2 integrins in the high-affinity bent conformation effectively hindered neutrophil adherence and restricted neutrophil accumulation in murine models [451]. The targeted inhibition of specific glycan motifs on Mac-1 with plant lectins reduced neutrophil adhesion and transmigration while enhancing phagocytosis and neutrophil apoptosis [452]. Additionally, small molecule agonists, like leukadherins, activated Mac-1, reducing neutrophil trafficking into the kidney while enhancing leukocyte adherence to the endothelium in murine models, leading to arterial narrowing attenuation and improved renal functions [321].

9.2.2. Shifting towards Resolution through FPR2 Stimulation

The activation of the ALX/FPR2 receptor triggers various processes critical for resolution, such as blocking neutrophil trafficking into tissues, promoting neutrophil apoptosis, and enhancing macrophage efferocytosis [453–455]. Moreover, annexin A1-containing microparticles and exosomes released by activated neutrophils mediate anti-inflammatory activity. Neutrophil-derived microvesicles can penetrate cartilage, protecting joints in RA [321]. These findings suggest the potential therapeutic use of annexin A1-loaded microvesicles for reducing neutrophil infiltration and preventing tissue damage [456,457]. For instance, 15-lipoxin A4 expedites inflammation resolution across various experimental models in mice [321,454]. The nanomedicine delivery of SPMs to correct resolution deficits represents a promising avenue for preventing chronic disease progression, evidenced by the decreases in tissue SPMs immediately before plaque rupture [458–461].

The intriguing biology of the ALX/FPR2 receptor has spurred numerous medicinal chemistry programs aimed at developing small-molecule agonists to activate resolution programs [456]. Synthetic lipoxin mimetics and the prototype peptide agonist WKYMVM have demonstrated beneficial effects in various preclinical models [462,463]. Phase I clinical trials have reported promising tissue-protective actions with other small-molecule ALX/FPR2 agonists, such as compound ACT-389949 and compound BMS986235, in heart failure [464].

9.3. Manipulating Neutrophil Survival and Programmed Cell Death

Significant advancements have occurred in understanding neutrophil apoptosis. Early studies by Savill et al. in 1989 showed that aged neutrophils undergo programmed cell death, marked by chromatin condensation, DNA fragmentation, and cytoplasmic vacuolation, remaining intact for at least 24 h without granule enzyme release [465]. This process, termed efferocytosis, involves the macrophage-mediated clearance of apoptotic neutrophils [393]. Further research by Whyte et al. demonstrated that apoptotic neutrophils exhibit reduced antimicrobial and proinflammatory capacities [466].

Neutrophil apoptosis can proceed via intrinsic or extrinsic pathways, involving mitochondrial permeabilization or death receptors, like FAS and TNF receptor [467]. Proinflammatory molecules, both host- and pathogen-derived, can delay neutrophil apoptosis, prolonging their lifespan and priming them for enhanced function [468]. Additionally, the host microenvironment, particularly hypoxia, can inhibit neutrophil apoptosis, regulated

by hypoxia-inducible factor-1 alpha [469]. Despite their prolonged lifespan, neutrophils in hypoxic conditions exhibit reduced ability to kill pathogens, like S. aureus, due to impaired ROS production [470].

Direct interactions with intact microbes also influence neutrophil survival, leading to either delayed apoptosis or rapid lysis post-phagocytosis [393]. However, specific mechanisms for these processes remain incompletely understood, underscoring the need for further research.

Preclinical evidence suggests the therapeutic potential of targeting neutrophil apoptosis to facilitate inflammation resolution. The pharmacologic blockade of cyclin-dependent kinases (CDKs) has shown potent anti-inflammatory effects in neutrophil-dominated inflammation models and the enhanced resolution of severe lung injury. For instance, the CDK inhibitor R-roscovitine increased bacterial clearance, possibly through an unidentified mechanism [471]. The annexin A1 mimetic peptide Ac2-26 also induces neutrophil apoptosis [472]. Moreover, IFN-β, produced by resolution-phase macrophages, promotes neutrophil apoptosis through the IFNαR1–STAT3 signaling pathway and accelerates Mcl-1 degradation [473]. These findings highlight Mcl-1 as a promising target for resolution therapy. Restoring impaired phagocytosis represents another strategy to accelerate neutrophil apoptosis. Bacterial and mitochondrial DNA reduce phagocytosis, bacterial clearance, and phagocytosis-induced death by inducing the cleavage of the complement C5a receptor, crucial for mediating phagocytosis [454,474].

9.4. Microbiota Modulation and Cognitive Function: Insights and Innovations

Research has linked the gut microbiota to various stress- and mood-related conditions [475]. Regarding stress, clinical studies have associated probiotic and prebiotic supplementation with positive outcomes [476]. However, most studies on mood and anxiety have relied on pre-clinical animal models [475]. For instance, healthy mice administered a probiotic formulation containing Lactobacillus rhamnosus showed improved performance in tests designed to induce anxiety, depression, and stress [477]. Clinical trials have yielded conflicting results [477,478]. Reviews of clinical trials have indicated that probiotics may have limited effects on psychological outcomes, partly due to incomplete evidence and heterogeneity in populations, cognitive tests, and interventions [477]. Nevertheless, one study found a positive probiotic effect on mood and anxiety in patients with inflammatory bowel disease (IBD) [479].

9.4.1. Implications for Autism Spectrum Disorder

The microbiota has been implicated in autism spectrum disorder (ASD). Transplanting microbes from individuals with ASD into mice induced ASD-like behavior [480]. Conversely, clinical studies have shown that microbiota modulation through antibiotics, prebiotics, probiotics, and fecal transplantation can improve social behavior in ASD patients [481–483]. These interventions have also led to reductions in anxiety behavior, hyperactivity, and defiance [481]. Children with ASD are four times more likely to experience gastrointestinal (GI) symptoms, such as inflammation and abdominal pain [481]. Fecal transplantation has shown long-term beneficial effects on both intestinal and behavioral symptoms [483].

9.4.2. Learning and Memory

Studies have investigated the link between the gut microbiota and memory during childhood [484]. It is increasingly recognized that sensitive developmental periods occur across the microbiota–gut–brain axis. Animal studies suggest that alterations in the gut microbiota can affect performance in visual-spatial learning and memory tasks [162]. While human data are limited, one study has correlated microbial diversity with cognitive function in infants.

There is a need for a new perspective on cognitive development research, one that recognizes the microbiota–gut–brain axis as a significant player alongside other biological systems shaping behavior. Enhanced comprehension could open avenues for groundbreaking therapies targeting learning and memory disorders [484]. Studies in mice have shown that fecal microbiota transplantation can correct age-related immune defects [485]. Transplanting fecal microbiota from aged to young mice, however, negatively impacts CNS functions [486,487]. These findings underscore the importance of the microbiota–gut–brain axis in aging, suggesting that a "young" microbiota may maintain or improve cognitive functions in later life [488–491].

9.5. Gut Microbiota: A Double-Edged Sword in Cancer Treatment

Empirical evidence has demonstrated a reciprocal relationship between the gut microbiota and therapeutic approaches. Specifically, distinct therapeutic approaches may modify the gut microbiota in distinct ways, and the presence of the gut microbiota may influence distinct therapeutic outcomes. To improve the treatment outcome, altering the gut microbiota to lessen drug-induced toxicity may serve as an adjuvant therapy. With the intricate role that gut microbiota play in cancer treatment, there are alternatives for reducing damage and enhancing the effectiveness of cancer therapy [492].

It has long been a struggle for the research community to develop a cure for cancer, as it is the top cause of mortality globally. The aforementioned anticancer treatments have demonstrated success in offering palliative or curative care for cancer; nevertheless, a number of side effects persist during this process, which compromises both efficacy and prognosis. Preclinical and clinical studies, together with reports on the microbiota's function in cancer, have revealed this subject as a potentially important mediator in the response to cancer treatment [492].

The interaction between the gut microbiota and chemotherapy is complex, with microbiota influencing both the toxicity and efficacy of anticancer drugs [492]. Microbes exert their effect on cancer through contact-dependent and contact-independent mechanisms. Contact-dependent effects occur locally, while contact-independent effects involve microbial metabolites and outer membrane vesicles circulating systematically [493]. Pathogenic microbes, like lipoteichoic acid and deoxycholic acid, can promote cancer development through contact-independent effects [494]. The gut microbiota can enhance drug toxicity by metabolizing certain drugs into compounds that inhibit critical detoxification enzymes, leading to increased side effects. Conversely, microbiota can also enhance the anticancer activity of chemotherapy drugs by inducing the expression of enzymes responsible for ROS production, facilitating tumor cell apoptosis. Additionally, microbiota can modulate the immune response to chemotherapy, influencing its effectiveness [492].

Furthermore, it has been shown that altering the gut microbiome through the use of probiotics or FMT can improve the response to cancer treatments. These techniques may also be used in future research to precisely regulate the composition of the microbiota, including the quantity of a given microbiota genus. Clinical trials are necessary to thoroughly assess which makeup of the gut microbiota is most suitable to stimulate the anti-tumor immune response. Additional key elements that need to be determined in order to modify the gut microbiota include modifying the preparation prior to antibiotic administration [492–496].

Moreover, certain gut microbiota species have been linked to chemoresistance, either by activating oncogenic pathways or by inactivating chemotherapy drugs [495]. This highlights the importance of understanding the microbiota composition in cancer patients to address chemoresistance effectively. Furthermore, the microbiota can impact the efficacy of immunotherapy, with specific strains enhancing immune responses against cancer cells [496]. Conversely, immunotherapy can alter the gut microbiota composition, potentially affecting treatment outcomes [497,498].

Regarding the effects on the intestinal mucosal surface, certain luminal microbes pose a threat to the host, increasing the risk of carcinogenesis [499,500]. For instance, H. pylori induces DNA damage in gastric epithelial cells, promoting gastric carcinogenesis [501]. Additionally, bacteria like F. nucleatum trigger inflammation and disrupt the mucosal barrier, contributing to colorectal cancer initiation and progression [502,503].

In the tumor microenvironment (TME), microbes thrive due to factors like angiogenesis and immune suppression, influencing the cancer phenotype and progression [504,505]. Intratumoral bacteria, such as F. nucleatum, enhance metastatic potential and inhibit local antitumor immunity, impacting cancer prognosis [506,507]. Microbial components, like outer membrane vesicles and metabolites, reshape the TME, exacerbating inflammation and promoting tumor growth [508]. Furthermore, fungal species, like Malassezia and Candida, are found in the TME, potentially contributing to tumor progression [509,510]. The relationship between fungal and bacterial communities within the TME remains unclear [511]. Overall, understanding microbial interactions in cancer development and progression is essential for developing targeted therapies and improving patient outcomes.

In the context of surgery, changes in the gut microbiota composition post-operation can influence the recurrence rate and disease-free survival of cancer patients [512,513]. Similarly, radiotherapy can alter the gut microbiota diversity, leading to side effects, such as inflammation, and compromising therapeutic efficacy [492,514]. However, manipulating gut microbiota holds promise for improving therapeutic efficacy, as the microbiota composition can influence the treatment response [492].

10. Future Perspectives on the Neutrophil Role in the Gut–Brain Axis

The intersection of research on the microbiota–gut–brain axis has reached a pivotal juncture [475]. With the ubiquitous presence of the gut microbiota and its multifaceted influence on physiological systems, there is a growing recognition of the need for a holistic, interdisciplinary research approach to unravel the intricate mechanisms and potentials for enhancing human well-being and quality of life, akin to approaches seen in metabolic diseases [512]. Multifaceted interventions that combine dietary modifications with other health-promoting lifestyle strategies have demonstrated efficacy, targeting both endogenous and environmental factors, which modulate the gut microbiota, highlighting substantial variability among individuals [162].

Consequently, while current tools and methodologies have significantly advanced our comprehension of the microbiota–gut–brain axis's role in brain health and disease, most studies thus far have been confined to animal models and primarily observational in clinical settings. Many unanswered questions within the field necessitate clearer elucidation to propel meaningful advancements toward microbiota-targeted strategies for enhancing brain health. Addressing these knowledge gaps demands adept scientific inquiry.

Numerous studies have established causal connections between the gut microbiota and the CNS [513–515]. However, focused studies are needed to identify and validate the mechanisms of action in humans. Significant gaps in existing knowledge include the following: determining the hormonal characteristics of microbiota-regulated neurotransmitters in humans, including the processes by which they stimulate the HPA axis, as well as the immunological effects of particular microbes in the human gut microbiota and their roles in neurodevelopmental, neurodegenerative, and neuropsychiatric disorders; furthermore, studying the roles that particular microbes play in the early development of the brain, as well as the effects that microbial by-products, including methylamines, peptides, SCFAs, and branched-chain fatty acids, have on brain function in conjunction with immunological and neurological signaling molecules.

It is also important to highlight that the characteristics and functions of a "healthy" gut microbiota remain elusive. Although numerous studies have documented reduced functional diversity and compositional alterations associated with various disorders, little is known about how the microbiota evolves over time and may indicate impending disease onset [516]. Unraveling the phenomenon of microbiota diversity could offer in-

sights into defining a "healthy aging microbiota pattern" [517]. Similarly, there is a dearth of knowledge regarding disease biomarkers and their reversibility through treatment or dietary interventions. While some studies reported positive effects on depression and anxiety symptoms [518,519], others found insignificant data to support dietary interventions' role in mood and cognitive functions [520]. Moreover, targeting the gut microbiome to alleviate anxiety and depression symptoms appeared to be more pronounced in clinical patient populations compared to healthy adults [521]. Additional double-blind, randomized, placebo-controlled clinical trials in clinical populations are warranted to further evaluate efficacy.

There are significant prospects in developing methods to track neurotransmitter movement from the gut through the BBB in response to neuroinflammatory processes. Some methodologies are emerging, with human brain imaging offering the possibility to monitor the microbiota's influence on neurotransmission [522]. Metabolomic, metaproteomic, and metagenomic analyses, along with gut biopsies, present additional methodological avenues.

Advancing future research hinges on the innovation of novel models and sophisticated tools to explore bidirectional communication pathways. While animal models have been instrumental in establishing current knowledge, the substantial differences between the rodent and human gut microbiota necessitate the development of robust humanized rodent models [523]. In vitro models offer promising avenues, with three-dimensional brain and gut organoids and advanced co-culture systems incorporating the ENS, VN, and BBB providing alternative means to investigate realistic conditions for unraveling the mysteries of microbiota–gut–brain interactions [524]. When combined with digestion models, these organoids and co-cultures could serve as in vitro workflow models for studying the gut–brain axis comprehensively. Although organ-on-a-chip in vitro models have been developed for this purpose, they still have limitations [525].

The integration of machine learning technology will be pivotal in enhancing study efficiency and accuracy. Bioinformatics holds the key to integrating large, multi-dimensional datasets and gaining a better clinical understanding of their significance. With ongoing technological advancements, there is the potential for such tools to identify high-risk patients early, determine microbial/immunological imbalances contributing to these risks, and suggest interventions to mitigate them [526]. Additionally, incorporating statisticians from the outset of research studies ensures robust study design, while computational and data scientists are indispensable for maximizing research value through comprehensive data analysis. Specialized computer programs can provide advanced precision in generalizing and stratifying results concerning specific population groups, such as those at risk of brain disorders [527].

Moreover, collaboration is paramount for extracting maximum knowledge and building a validated evidence base. Establishing new biobanks to facilitate material sharing from human and animal studies is essential, along with deep phenotyping databases and standardized data formats [528]. In vitro models must also become more accessible across laboratories. While competition for funding has hindered scientific collaboration, initiatives like the Community Research and Development Information Service (CORDIS) within Europe aim to foster collaboration by gathering and disseminating results from EU-funded research projects [529]. Projects like the GEMMA, ONCOBIOME, and MICROB-PREDICT, funded by Horizon 2020, are exploring microbiome-related research across various health domains [530–533]. Organizations like the International Life Science Institute Europe (ILSI Europe) and the International Scientific Association for Probiotics and Prebiotics (ISAPP) promote progress in the field by supporting scientific integrity, harmonizing efforts, and providing guidance for collaborative research [534,535]. ISAPP, in particular, sets an example by focusing on objectives relevant to advancing microbiota–gut–brain axis research and developing dietary strategies targeting the gut microbiota.

Future Perspectives in Cancer Management

Therapeutic resistance and adverse effects continue to pose significant challenges in cancer treatment, despite ongoing efforts to enhance treatment efficacy and minimize toxicity. The gut microbiota emerges as potential predictive biomarkers and treatment targets, although challenges lie ahead [536]. These include gaps in understanding how microbiota modulation affects treatment responses, undefined microbial signatures as biomarkers, and the absence of a consensus on optimal modulation methods. Additionally, while current research primarily focuses on bacteria, commensal viruses, fungi, and archaea also play notable roles in cancer [537,538]. Consequently, the utilization of cancer-associated microbes in clinical settings presents both prospects and challenges that require acknowledgment and resolution.

Currently, the lack of standardized methodology, including variations in sample selection, collection techniques, technology, data quality, and resource analysis, hinders the homogeneity and consistency of understanding the mechanistic effects of microbes on cancer. Heterogeneous results may arise from different sample types collected, such as the digestive tract mucosa and feces, which have similar but not identical microbial compositions [539]. On note, fecal microbiota transplantation (FMT) transfers not only bacteria but also other non-bacterial microbes, raising safety concerns due to unclear effects on recipients [536]. To mitigate bias, research should involve the collection and analysis of multiple sample types.

Moreover, errors during sample collection and handling, particularly in tumor microbiota with low biomasses, can significantly impede microbial research due to contamination risks from various sources, such as long surgeries or laboratory environments. Implementing stringent measures, like wearing protective clothing during sample collection, is crucial to minimize contamination [540]. Technical variables in identifying microbial signatures, including sample handling and DNA extraction methods, further contribute to data heterogeneity and accessibility challenges [541].

Beyond methodological hurdles, individual biological differences, such as genetics, diet, age, sex, and accompanying diseases, as well as regional variations, complicate microbial strategy applications [542,543]. Regional differences, influenced by factors like economic development and ecological environment, significantly impact the human microbiota composition, limiting the generalizability of findings across diverse populations. Addressing these challenges requires the stratification of microbiota and in-depth research into host-specific microbial strains.

In the future, focusing on precise microbiota stratification and leveraging advanced preclinical models, like patient-derived organotypic tumor spheroids, can enhance the mechanistic understanding and validate findings in vitro. Despite accumulating evidence, the clinical translation of microbial interventions in cancer management remains limited due to complex individual sensitivities to microbial agents [544]. Integrating microbial-targeted interventions into existing cancer-management systems necessitates more preclinical research and prospective clinical trials to address challenges effectively.

Addressing these challenges requires intensive efforts and multifaceted research [545–548]. While significant challenges persist, the pivotal role of the gut microbiota in developing new anticancer strategies cannot be overstated. Exploring holistic approaches that incorporate microbial modulation therapy into current cancer management systems is imperative for advancing cancer treatment [536]. Collaborative efforts from scientists and clinicians are expected to unravel more mysteries of the human microbiota, paving the way for next-generation personalized medicine.

11. Conclusions

In both health and disease, neutrophils and the microbiota engage in complex interactions, yet much remains unknown about the underlying mechanisms. Questions persist regarding the impact of various microbiota members, such as protozoa, viruses, and fungi, on neutrophil regulation. Furthermore, while some microbial nutrients and metabolites have been shown to influence neutrophil activity, the coordination of these signals from the microbiome remains unclear. Disruptions in the microbiota can lead to disease, affecting immune regulation, barrier integrity, and brain function.

Understanding the mechanisms governing the microbiome's interaction with the CNS offers insights into neurological disorders like depression and anxiety. Studies suggest that probiotics and microbial transplants may offer therapeutic benefits for these conditions, highlighting the potential for microbiota-based interventions in neurological diseases. Understanding these interactions holds therapeutic promise for conditions like cancer and chronic inflammatory diseases, driving the need for further investigation into their molecular processes and the identification of key commensal species with pro- or anti-inflammatory properties.

It is evident that the expanding field of gut–brain axis research holds immense promise for transforming medicine and enhancing human well-being. Understanding the intricate interplay among the microbiota, gut, and brain offers unparalleled opportunities to develop novel therapeutic interventions for neurological disorders and improve overall health outcomes. The continued investment in research, interdisciplinary collaboration, and the development of advanced methodologies are imperative to unlock the full potential of this field and translate scientific discoveries into tangible clinical benefits for patients worldwide.

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