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Review

Complex Interaction between Gut Microbiome and Autoimmunity: Focus on Antiphospholipid Syndrome

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Abstract: Antiphospholipid syndrome (APS), also known as Hughes syndrome, is a systemic autoimmune disorder characterized by recurrent thrombosis and pregnancy complications, accompanied by the presence of antiphospholipid antibodies (aPLs). These antibodies target anionic phospholipids or protein–phospholipid complexes within cell membranes, contributing to the underlying mechanisms of the disease. Although anticoagulation therapy remains the cornerstone of APS management, it often fails to prevent complications, particularly in obstetric and thrombotic cases. As autoimmune diseases become increasingly linked to alterations in the gut microbiome, this study investigates the complex interaction between gut bacteria and immune modulation in APS. We explore how disruptions in the gut microbiome may influence the development of autoimmune conditions, with a specific focus on APS. By identifying key microorganisms potentially involved in this gut–immune axis, we aim to provide insights into novel preventive and control approaches. Future research should focus on harnessing the gut microbiome to develop more effective treatments that target both the immune system and microbial populations in APS patients.

Keywords: gut microbiome; antiphospholipid syndrome; antiphospholipid antibodies; autoimmunity; gut health

1. Introduction

APS is an autoimmune disease characterized by the presence of persistent antiphospholipid antibodies, leading to vascular thrombosis and/or pregnancy-related complications [1]. Typical features of this syndrome are venous or arterial thrombosis, miscarriage, and thrombocytopenia [2]. In addition, APS is considered a thrombo-inflammatory disease that occurs in approximately a third of systemic lupus erythematosus (SLE) cases and is often associated with increasing organ damage over time [3].

Other clinical manifestations of this disease include neurological symptoms such as chorea, livedo reticularis, autoimmune hemolytic anemia, transverse myelitis, migraine, epilepsy, Raynaud's phenomenon, and heart valve lesions [4]. The classification of APS is based on specific clinical criteria and circumstances; the first criterion includes three clinical aspects: arterial or venous thrombosis, obstetric loss, or thrombocytopenia [5] with other diagnostic parameters including lupus anticoagulant and anticardiolipin antibodies [6].

The recent 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria introduces a more detailed classification system. This includes an entry criterion of at least one positive aPL test within three years of identifying an aPL-associated clinical criterion, followed by additive weighted criteria clustered into six clinical domains. Patients must accumulate at least three points each from clinical and laboratory domains to be classified as having APS [7]. Further classification identifies APS as primary when not accompanied by other autoimmune diseases and secondary when associated with autoimmune diseases, infections, drug-related factors, or cancer, with the strongest correlation observed in systemic lupus erythematosus [8]. Other non-criteria manifestations such as thrombocytopenia, APS-associated nephropathy, valvular heart disease, livedo reticularis, and cognitive impairment have also been reported [8]. Another form of APS, known as catastrophic APS, is characterized by the formation of thrombi in multiple small vascular beds, resulting in organ failure and a high mortality rate in this specific group of APS patients [9,10].

Antiphospholipid antibodies are a diverse group of autoantibodies that play a crucial role in the pathogenesis of APS by interacting with various plasma proteins, including beta-2 glycoprotein 1, prothrombin, thrombomodulin, plasminogen, antithrombin III, protein C, protein S, Annexin II, and Annexin V [11,12]. These antibodies trigger prothrombotic mechanisms by activating endothelial cells, monocytes, platelets, coagulation factors, and complement proteins, leading to disrupted fibrinolysis, coagulation pathways, inflammation, and placental injury [13–17]. aPL targets either anionic phospholipids directly or protein–phospholipid complexes within the cell membrane. Categorically, they can be subdivided into three main types: anti-β2-glycoprotein-1 (anti-β2GPI), anticardiolipin, and lupus anticoagulant [18–22]. Notably, the specificity of antiphospholipid antibodies for APS is limited because they may also be present in healthy individuals with a history of thrombosis, pregnancy-related morbidity, or individuals with autoimmune disorders [23].

In this study, we provide a general overview of APS and its clinical manifestations, followed by laboratory findings that reinforce the gut bacteria–immune axis in autoimmunity. We emphasize the potential link between gut microbiota and APS, identify implicated microorganisms, and propose future directions for therapeutic development.

2. Pathophysiology of APS

Infections, especially those caused by bacterial or viral pathogens, are believed to be the primary triggers for developing antiphospholipid antibodies; this is evident in the case of anti-β2GPI [23]. This process, known as molecular mimicry, involves similarities between the amino acid sequences of infectious agents (bacteria or viruses) and that of amino acid sequences from beta-2 glycoprotein-1 (β2GPI), which contributes to the formation of autoantibodies [24]. While the pathophysiology of APS depends on the diverse action of antibodies on their myriad antigenic target sites in various patients [25], the etiology of these pathogenic autoantibodies is likely a result of an intertwined intricacy of different environmental factors in individuals who carry genetic markers further increasing disease susceptibility [26,27], Although the mechanism is not fully understood, the APS has been reported to disrupt the homeostatic regulation of blood coagulation [28]. The precise mechanism of thrombosis is not yet defined. Still, a hypothesis is that there is a deficiency in cellular apoptosis, exposing membrane phospholipids and instigating antiphospholipid antibody formation [29]. In the APS, pathogenic antiphospholipid autoantibodies have been shown to cause various thrombotic events that encourage coagulation while preventing fibrinolysis [28]. This is achieved by autoantibodies that target phospholipid-binding

proteins that cause blood clots in veins and arteries and bolster thrombosis through a diverse array of means by disrupting the function of vital phospholipid-binding proteins crucial to blood clot regulation and activate platelets, pivotal for clot formation [30].

Additionally, they activate endothelial cells, which in turn causes the expression of coagulation-related molecules hindering the activity of naturally occurring anticoagulants like protein C and protein S, which usually prevent the formation of clots, further interfering with the fibrinolytic system and preventing the clot from dissolving [30]. Overall, APS represents a complex interplay between autoantibodies and physiological processes that predispose people to thrombotic events and pregnancy complications. In the context of APS, these antibodies play a diverse role in pregnancy loss by inducing thrombosis in the placenta, which leads to placental insufficiency and fetal death [31]. Also, the triggering of the activation of endothelial cells, monocytes, and platelets leads to the overproduction of tissue factor and thromboxane A2, ultimately leading to placental damage and fetal loss [32].

3. Clinical Features of APS

APS affects various tissues and organs in the body, including blood vessels, the kidneys, the brain, the heart, the lungs, the skin, the liver, and the gastrointestinal tract, resulting in various clinical symptoms and complications. These clinical features include venous, arterial, or small vessel thrombosis; fetal loss; and thrombocytopenia. Deep vein thrombosis is the most common manifestation, while cerebrovascular accidents represent the predominant form of arterial thrombosis. Early fetal loss, preterm birth, and pre-eclampsia are the most common fetal and obstetric manifestations [33]. Additional clinical features such as cognitive dysfunction or demyelination may be associated with interactions between phospholipid antibodies and cells, possibly due to a disrupted blood–brain barrier or increased intrathecal synthesis of phospholipid antibodies [34]. This disease has various clinical manifestations, which differ in their respective frequencies. In over 20% of cases, patients may experience venous thromboembolism, thrombocytopenia, miscarriage or fetal loss, stroke or a transient ischemic attack, migraine, and livedo reticularis. Less commonly occurring in 10–20% of cases, the APS may manifest as heart valve disease, pre-eclampsia or eclampsia, premature birth, hemolytic anemia, and coronary artery disease. Rare manifestations, occurring in less than 10% of cases, include vascular dementia, retinal artery or venous thrombosis, amaurosis fugax, pulmonary hypertension, leg ulcers, digital gangrene, osteonecrosis, antiphospholipid nephropathy, and mesenteric ischemia. Occurring in less than 1% of cases, APS may lead to adrenal hemorrhage and Budd-Chiari Syndrome [35]. This spectrum of clinical manifestations underscores the complexity and heterogeneity of APS, necessitating thorough evaluation and tailored management approaches for affected individuals.

4. Current Treatments of APS

Despite the volume of knowledge so far, there are still uncertainties in treating APS, with some aspects requiring further evidence [36]. The primary goals of treatment for individuals with APS include preventing thrombosis in individuals without prior incidents (i.e., primary thromboprophylaxis), effectively treating acute thrombosis if it occurs, and averting the recurrence of thrombosis in individuals with established APS (secondary thromboprophylaxis) [37]. Treatment strategies for APS include a variety of anticoagulant approaches. For instance, vitamin K antagonists such as warfarin have historically been the cornerstone of treatment for thrombotic APS [11]. In addition, low-dose aspirin is recommended for people who have abnormal antiphospholipid antibodies without a history of blood clots [38,39]. Also, heparin and direct oral anticoagulants (DOACs) such as rivaroxaban are considered in cases of warfarin intolerance, allergy, or inadequate anticoagulant control [11]. Lastly, emerging evidence suggests possible adjunctive therapies such as hydroxychloroquine, rituximab, and statins, although further research is needed [38,40]. Long-term management goals in APS revolve around preventing recurrent thrombosis while minimizing anticoagulation-related side effects,

especially for catastrophic APS, where early intervention is crucial and typically involves a combination of anticoagulants to address severe manifestations [41,42].

5. Involvement of Microorganisms in APS

It is well known that persistent pathogenic autoantibodies targeted at membrane phospholipids and/or their linked plasma proteins play a role in establishing APS [29]. This is the major characteristic of APS, where two mechanisms are forwarded to cause the presence of aPLs [43]. One reason explains the occurrence of clinical events such as vascular thrombosis and/or pregnancy morbidity with the persistence of aPLs such as lupus anticoagulant (LA), anticardiolipin antibodies(aCL), and anti-β2 glycoprotein 1 antibody (anti-β2GP1) [1]. However, a thrombosis event in the pathogenesis of APS rarely occurs, indicating the involvement of other determinants that modulate the thrombotic milieu. This brought about the conception of a second hit that focuses on exploring innate immunity like inflammation, infection, or surgery essential to precipitate the thrombotic event in aPL carriers, with a line of thought of infective agents being one of the mechanisms increasing the aPL exposure [44–46]. Research has shown that microbial pathogens can provoke the production of aPLs in an antigen-dependent manner, such as the previously mentioned molecular mimicry or through an antigen-independent manner, which includes the breakdown of immune tolerance due to an inflammatory response [44]. Molecular mimicry is one of the most relevant mechanisms to explain the association between infections and clinical manifestations linked with aPLs in APS because it justifies the generation of cross-reactive T and B lymphocyte cells that recognize antigens from pathogens but cross-react to autoantigens [47,48].

An example is rheumatic fever, a human autoimmune disease believed to have originated from cross-reactivity with protein or carbohydrate structures from pathogens. Further research shows several similarities between rheumatic fever and APS due to the bond and cross-reactivity of streptococcal proteins with β2GP1 [49], with homologies between proteins of microorganisms and peptides generated from β2GP1 that contribute to T and B cell activation [50]. Various animal models are used to understand the potential pathogenic effect of infections exhibiting surface components analogous to the major immunogenic epitopes targeted by anti-β_2GP1 antibodies. From this research, it is seen that upon immunization, high titers of antipeptide anti-β_2GP1 antibodies were detected in murine immunized with *Haemophilus influenza*, *Neisseria gonorrhea*, *Candida albicans*, and *tetanus toxoid* and showed APS features like thrombocytopenia with an increased risk of fetal loss. A succinct link between gut microbiome and APS highlights the intestine as a potential chronic trigger in patients with APS. *Roseburia intestinalis* (bacteria abundant in the human gut) contains amino acid sequences homologous to those found in the B cell and T cell epitopes within [51–54]. Significantly, when *R. intestinalis* is administered orally using a mouse model of APS, it leads to the development of anti-human-β2GP1 antibodies with the occurrence of morbidity and mortality associated with APS [55]. Some studies demonstrate that fermented milk contains a probiotic bacterial strain that can modify aPLs in non-autoimmune animals which further suggests that gut microbes may be able to regulate the development of pathogenic autoantibodies and APS.

Furthermore, an association between APS and other infectious agents, including hepatitis C virus (HCV) and HIV, cytomegalovirus, Epstein–Barr virus, and herpes simplex virus have been reported (Table 1). Other reports have also shown the induction of APS by parvovirus unique region (VP1u) [55]. During the COVID-19 pandemic, APS severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) with eight types of aPL antibodies was discovered in the plasma of over 50% of hospitalized COVID-19 patients [56]. Similarly, aPLs have been associated with some bacterial infections, caused by *Coxiella burnetii*, *Helicobacter pylori*, *Mycoplasma pneumonia*, *Streptococci*, *Borrelia burgdorferi*, and *Mycobacterium tuberculosis* (Table 1). For instance, syphilis patients show aCL antibodies that could have been provoked by the cross-reactivity of syphilis antibodies with treponemal cardiolipins [57]. Likewise, patients with leprosy also present aPL and β2GP1-dependent

binding [44]. However, there is a paucity of data on the ability of parasitic or fungal infections to trigger aPLs [44].

Table 1. List of key organisms involved in aPL generation and thrombosis. aCL means anticardiolipin antibodies, anti-β2GP1 means anti-β2 glycoprotein, and LA means lupus anticoagulants.

Infection	Organism	aCL	Anti-β2GP1	LA	Thrombosis
Viral	CMV	+	+	+	+
	EBV	+	+	+	+
	HIV	+	+	+	+
	SARS-Cov-2	+	+	+	+
	Varicella zoster virus	+	+	+	+
	Parvovirus B19	+	+	+	+
	Hepatitis A Virus	+	-	-	+
	Hepatitis B Virus	+	+	+	-
	Hepatitis CVirus	+	+	+	+
	Hepatitis D Virus	+	+	+	-
	mumps virus (MuV)	+	-	-	-
	Rubella	+	-	-	-
	Adenovirus	+	+	-	-
	Human T-lymphotropic virus	+	+	-	-
	Influenza A	+	-	-	+
Bacterial	*Mycobacterium leprae*	+	+	+	+
	Borrelia burgdorferi	+	+	+	+
	Salmonella sp.	+	+	+	+
	Streptococcus spp.	+	+	+	+
	M. tuberculosis	+	+	-	+
	Escherichia coli	+	+	-	+
	Coxiella burnetiid	+	-	+	-
	Helicobacter pylori	+	+	-	-
	Klebsiella sp.	+	-	-	-
	Chlamydia	+	+	-	-
	Mycoplasma pneumonia	+	+	-	+
	Treponema pallidum	+	+	-	-
Parasitic	*Plasmodium malariae*	+	+	-	+
	Leishmania sp.	+	+	+	-
	Leptospira sp.	+	+	-	-
	Plasmodium falciparum	+	-	-	-
	Toxoplasma sp.	+	-	-	-

6. Gut Microbiome

6.1. Overview

The development of the human gut microbiota begins early, even before birth, because it is essential in maintaining the host organism's normal physiological processes [58]. This microbiota can synthesize diverse metabolic compounds that can exert beneficial and detrimental effects on human health through interactions with the host due to its ability to proliferate along the intestinal surfaces, establishing a resilient system that serves as a barrier against the intrusion of pathogenic microorganisms [58].

6.2. Gut Microbiome—Metabolic and Protective Role

The gut microbiota plays a pivotal role in metabolizing dietary components, transforming indigestible carbohydrates like cellulose, hemicelluloses, resistant starch, pectin, oligosaccharides, and lignin into short-chain fatty acids (SCFAs), including acetic, propionic, and butyric acids produced by *Firmicutes*, *Bacteroidetes*, and certain anaerobic gut microorganisms. The gut microbiota also contributes to the host's well-being by facilitating the synthesis of essential vitamins such as biotin, thiamine, cobalamin, riboflavin, nicotine, pantothenic acids, as well as vitamins B and K. It is worth noting that the gut microbiota can also produce neurochemicals, including gamma-aminobutyric acid (GABA), an im-

portant inhibitory neurotransmitter in the brain; dysregulation of GABA has been linked to various neuropsychiatric disorders. Additionally, the microbiota generates various compounds such as carbohydrates, branched-chain amino acids, amines, phenols, indoles, and phenylacetic acid. Moreover, it plays a role in synthesizing bile acids, cholesterol, and conjugated fatty acids. In summary, the microbiota's metabolic activities are multifaceted and encompass transforming dietary components, vitamin synthesis, neurochemical production, and generating various bioactive compounds [59]. The protective role of the microbiota is to occupy intestinal surfaces and create stability in the system that prevents the invasion of pathogenic microorganisms. The production of SCFAs serves as a significant energy source for intestinal epithelial cells. It strengthens the mucosal barrier, which is regarded as a tumor suppressor due to its promising anti-inflammatory and chemopreventive properties [60]. The microbiota plays a protective role by colonizing intestinal surfaces and establishing a stable environment that acts as a barrier against the intrusion of pathogenic microorganisms. Moreover, producing short-chain fatty acids (SCFAs) is a crucial energy source for intestinal epithelial cells, reinforcing the mucosal barrier. SCFAs are also recognized as tumor suppressors, owing to their notable anti-inflammatory and chemo-preventive properties [61].

6.3. Microbiota and the Gut–Brain Axis

The brain–gut–microbiota axis is a bidirectional system enabling gut microorganisms to communicate with the central nervous system (CNS) and the CNS with the gut. The mechanisms of signal transmission are complex and not fully understood but include neural, endocrine, immune, and metabolic pathways which influence the array of factors affecting the microbiome–gut–brain axis such as diet, genetics, drugs, environment, exercise, cognitive behavior, stress, social interactions, and fear [61,62]. Gut microbes can produce most neurotransmitters in the human brain and their precursors. However, some neurotransmitters, like glutamate, GABA, dopamine, and serotonin, cannot cross the blood–brain barrier and must be synthesized in the brain from local pools of precursor neurotransmitters [63]. These precursors mostly comprise amino acids, e.g., food-derived neurotransmitters (tyrosine and tryptophan) that pass through the blood–brain barrier. They are absorbed by the corresponding cells in the brain that produce neurotransmitters [63].

The precursors are subsequently transformed via several intermediate processes utilizing different host enzymes into functional neurotransmitters, such as dopamine, norepinephrine, and serotonin; therefore, by controlling the metabolism of neurotransmitter precursors, the gut microbiota can affect host behavior due to the dietary origin of these precursors. For instance, probiotic bifidobacterial therapy can raise the tryptophan levels necessary for serotonin synthesis. Certain Lactobacilli species change how gamma-aminobutyric acid (GABA) is metabolized and how the GABA receptor expresses itself and behaves in the brain. [64] *Escherichia*, *Bacillus*, and *Saccharomyces* spp. can produce GABA, as Lactobacillus and Bifidobacterium species can produce enterococcus, streptococcus, and Escherichia, and norepinephrine can create dopamine, acetylcholine, and serotonin; Bacillus can produce both [64]. Outside the brain, dopamine production has been detected in *Staphylococcus* in the human intestine, which can take up the precursor l-3,4-dihydroxyphenylalanine (l-DOPA) and convert it into dopamine by staphylococcal aromatic amino acid decarboxylase (SadA) expressed by these bacteria. More than 50% of dopamine in the human body is synthesized in the gut. Dopamine and its receptors are widely distributed in the intestinal tract and affect gastric secretion, motility, and mucosal blood flow [65,66].

6.4. Microbiota and the Gut–Kidney Axis

The gut–kidney axis, a pathological interaction between the gut microbiota and kidney diseases, appears to be associated with a variety of clinical manifestations, including hemodialysis, peritoneal dialysis, immunoglobulin A (IgA) nephropathy, acute kidney injury (AKI), hypertension, nephrolithiasis, and chronic kidney disease (CKD) [67]. The gut–kidney axis is driven by various important processes. Studies show that alterations in the

functions and compositions of gut microbiota can induce inflammation, increase oxidative stress, and cellular and DNA damage [68]. A significant involvement for abnormal gut microbiota has been found in the pathogenesis of chronic kidney disease (CKD) with severe results [69]. Additionally, alterations like decreased α-diversity gut microbiota composition are associated with kidney stone formation [69].

Potential links exist between the gut–kidney axis and APS, notwithstanding the lack of empirical evidence in this regard. Vascular dysfunction and coagulation dysregulation, which are hallmarks of the disease, lead to a wide range of complicated symptoms, including kidney failure in APS. Dissimilar to lupus nephritis, kidney disease associated with aPL is not inflammatory [70]. Novel therapeutics aimed at the gut–kidney axis, like probiotics and dietary adjustments, might exhibit possibility of treating kidney problems associated with APS, albeit further investigation is recommended [71].

6.5. Gut Microbiome in Health and Diseases

The gut microbiome refers to the diverse community of microorganisms inhabiting the human gastrointestinal tract, including bacteria, viruses, fungi, and other microbes. It plays a crucial role in maintaining overall health and is implicated in various diseases when its composition and function are disrupted, as shown in Figure 1. The gut microbiota has the largest quantities of microorganisms and the most species compared to other body parts. They consist of thousands of microorganisms, including bacteria, viruses, and some eukaryotes, that colonize the digestive tract just after birth. The microbial composition of the gut microbiota varies across the digestive tract. In the stomach and small digestive tract, relatively few species of bacteria are present. The intestinal microbiota consist of more than 1500 species distributed in more than 50 different phyla. The colon contains a densely populated microbial ecosystem with up to 10^{12} cells for every gram of intestinal substance [71]. The most dominant bacterial phyla in the human gut are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*, and the most recorded bacterial genera are *Bacteroides*, *Clostridium*, *Peptococcus*, *Bifidobacterium*, *Eubacterium*, *Ruminococcus*, *Faecalibacterium*, and *Peptostreptococcus* [72]. It was reported that *Bacteroidetes* and *Firmicutes*, followed by Proteobacteria, Fusobacteria, Tenericutes, Actinobacteria, and Verrucomicrobia, were the most dominant phyla, making up to 90% of the total microbial population in humans [73]. Among these, Bacteroides are the most abundant, comprising about 30% of bacteria in the gut, suggesting they are particularly significant in the functioning of the host organism. Most gut bacteria (99%) are anaerobes; however, high densities of aerobic microbes are recorded in the cecum. Fungi, protists, archaea, and viruses are also present in the gut flora; however, less is known about their activities [71]. Several factors can change the gut microbiota composition and function. These factors include host genetics, diet, age [74], antibiotics use, and diseases [75]. The gut microbiota has a lot of significant functions in the human body, including supporting protection from pathogens by colonizing mucosal surfaces, creating different antimicrobial substances, enhancing the immune system, playing a vital role in digestion and metabolism, controlling epithelial cell proliferation and differentiation, modifying insulin resistance, and affecting its secretion influencing brain–gut communication and thus affecting the mental and neurological functions of the host; hence, the gut microbiota plays a significant role in maintaining normal gut physiology and health [71].

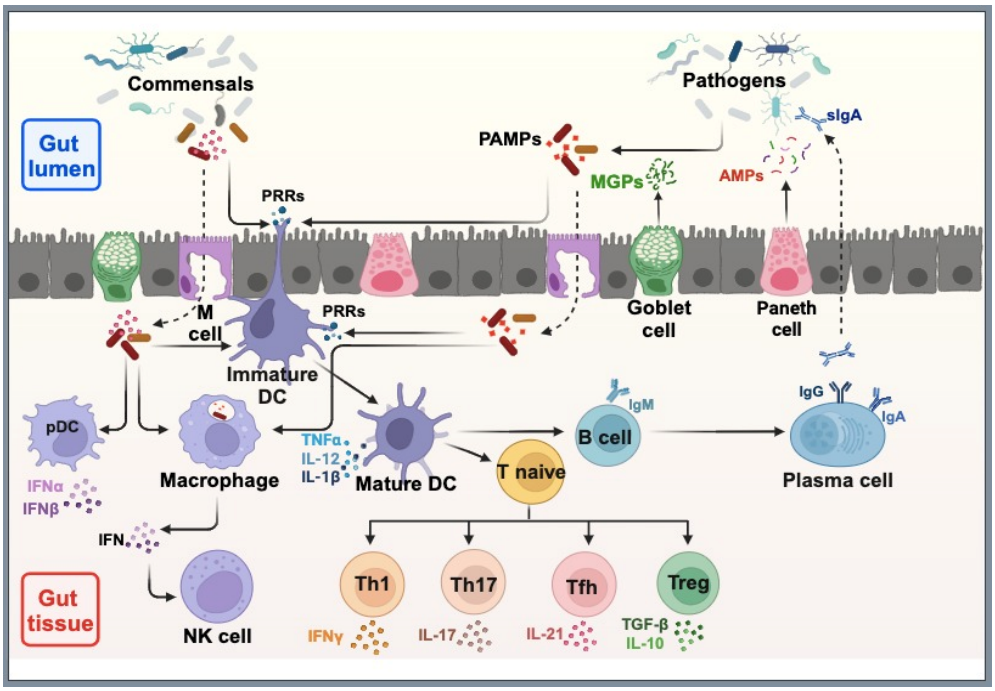

Figure 1. Gut microbiome and immune pathways. The gut microbiota beneficially aids in forming a thick protective layer of mucus made up of mucins glycoproteins (MGPs) secreted from Goblet cells. Microbes and their derived products could cause the Paneth and gut epithelial cells to generate antimicrobial peptides (AMPs). Commensals and their products are recognized by immune cells like dendritic cells (DCs), epithelial cells, and macrophages in the gut lumen or within the gut tissue. Foreign pathogens arriving in the gut and their pathogen-associated molecular patterns (PAMPs) are also recognized by immune cells like DCs, epithelial cells, and macrophages, within the gut lumen and gut tissue with the aid of pattern recognition receptors (PRRs) expressed by these immune cells. Antigens in the gut lumen are detected directly by dendritic extensions of DCs piercing through borders between gut epithelial cells. A specialized endocytic intestinal epithelial cell known as an M cell can also transport microbial antigens across the epithelial surface and present them to DCs and macrophages to process and activate the immune response. Microbial antigens are also recognized by plasmacytoid dendritic cells (pDCs), which secrete high levels of type I interferons that help effect antiviral immunity. DCs and macrophages use the prompts from the normal gut microbiota to train the immune system by secreting inflammatory mediators and contributing to developing specialized cells like B cells and T cells. Macrophages and mature DCs also transfer signals received from invading pathogens to secrete inflammatory mediators and induce the development of naïve T cells into inflammatory T-cell subsets, including T helper 1 (Th1), T helper 17 (Th17), T follicular helper (Tfh), and T regulatory (Treg) cells. Mature DCs also induce the differentiation of B cells into plasma cells, which produces antibodies including protective secreted IgA (SIgA). The various T cell subsets express inflammatory mediators like interferon-gamma (IFNγ), interleukin 17 (IL-17), and interleukin 17 (IL-17), which helps to localize pathogenic infections and prevent their systemic dissemination. However, T regulatory (Treg) cells secrete TGF-b and IL-10, which can limit the functions of many immune cells and create an anti-inflammatory cytokine condition in a regulatory manner.

6.6. Gut Microbiome and Age

Maternal milk, which is the optimal food for infants, meets all their nutrition and physiologic requirements and protects against infections due to the presence of immune effectors, such as immunoglobulin A (IgA); this natural mode of feeding contributes to the maturation of the infant's immune system and modulates the development of its gut microbiota. Human milk, which is not sterile, contains protein, fat, carbohydrates, immunoglobulins, and endocannabinoids. It also contains as many as 600 different species of bacteria, including beneficial *Bifidobacterium breve*, *Bifidobacterium adolescentis*, *Bifidobac-*

terium longum, *Bifidobacterium bifidum*, and *Bifidobacterium dentium* [76]. Moreover, the carbohydrate component of human milk has oligosaccharides, which make up the third largest solid component of the entire food source. Human milk oligosaccharides are indigestible polymers formed by a few monosaccharides that serve as prebiotics by selectively stimulating the growth of members of the genus *Bifidobacterium* [77]. They have been linked with strengthening gut mucosal protection through activities against pathogens, also increasing the production of immunoglobulin A, which is correlated with modulation of the intestinal immune system [78,79]. It is noted that the *Bifidobacterium*-dominated microbiota of the infant changes over time into the *Bacteroidetes* and *Firmicutes*-dominated microbiota of adults. This distribution remains stable throughout adulthood without perturbations, such as long-term dietary changes, repeated antibiotic usage, or disease. Declines in dentition, salivary function, digestion, and intestinal transit time may affect the gut microbiota upon aging. There are notable differences in the microbiota in elderly people compared with young adults, with relative proportions of *Bacteroidetes* predominating in elderly people compared with higher proportions of *Firmicutes* in young adults [80].

6.7. Gut Microbiome and Environmental Influences—Focus on APS

There is a research gap and a lack of a detailed scoping review on the environmental factors influencing the gut microbiome shape, structure, functions, and association with APS. The gut microbiome is extremely dynamic, and its variations are linked to various health outcomes, including neurological diseases, inflammatory bowel disease, respiratory illnesses, obesity, arthritis, depression, cardiovascular diseases, chronic liver diseases, and pancreatic disorders, as stated above. These variations are often influenced by environmental factors such as environmental contaminants and medication use [81,82]. The impact of environmental factors on the gut microbiome can differ based on demography and level of exposure. The interactions between the environment and gut microbiome are complex, with diverse environments playing crucial roles in shaping the gut microbiome [83]. This becomes particularly important during early life stages, as differences in hygiene and diet among households and communities significantly contribute to gut colonization by various bacterial species, predisposing individuals to different health conditions [83]. The gut microbiome changes throughout life, starting from neonatal development. The nurturing surroundings where a child grows up can notably impact the development of specific gut microbiome species. This could affect their vulnerability to APS because various healthy microbiomes support a varied and balanced array of microorganisms and their activities, which is vital for a strong immune system [84].

Environmental factors such as the dissemination of contaminants, including pesticides, heavy metals, and microplastics, pose significant threats to the human gut microbiome and are highly associated with various diseases resulting from changes in the composition, diversity, and metabolic activity of the gut microbiome community [85]. Most contaminants remain persistent and bioactive in the environment. Upon ingestion, contaminants are metabolized by the gut microbiome, and the bioactive metabolites, i.e., residues, affect the homeostasis balance of the gut microbiome, resulting in severe health complications. Indeed, bioactive metabolites' effects on the gut microbiome were found to interfere with neurotransmitters, leading to cognitive impairments and mental health disorders [86]. The assimilation of glyphosate, a pesticide, has been shown to cause neurological disorders, including autism, through the modification of gene expression, DNA replication, and immunomodulation of gut microbial communities [87]. Heavy metals such as mercury, copper, lead, and cadmium in food, soil, and water have been shown to impose selective pressure on the gut microbiota composition, thereby increasing the vulnerability of the host to different types of cancers, immune response alteration, and inflammatory cytokine increments [88]. The most adverse effects of heavy metals are inhibiting gut microbiome proliferation, interfering with the composition and metabolic prowess of the gut bacterial community, and distorting the oxidative and immune status of the host [85].

Microplastics are reservoirs of organic and inorganic contaminants as well as antibiotics. Such microplastics as virgin polystyrene absorb polyaromatic hydrocarbons. Also, the concentrations of copper and zinc were determined to be highly correlated with the amounts of virgin polystyrene bead and polyvinyl chloride, respectively. These were studied to be widely distributed in the environment [89] and cause several health issues, including intestinal tract infections, mucosa damage, and increasing permeability [90]. Microplastics are home to diverse microbial communities, including pathogens [90,91]. These can displace gut microbiota, leading to the dominance and dissemination of bacterial pathogens in the gut. This impacted cytokine secretion and the proportion of Th17 and Treg cells within CD4+ cells, leading to inflammation of the intestines [92].

Medication use, including antibiotics and their effects on gut microbiota, has been extensively studied. Antibiotics are substances that kill or inhibit bacterial growth but also target commensal bacteria in the gut, causing various collateral damage [93]. Antibiotics can either be bactericidal or bacteriostatic by killing bacteria or inhibiting bacterial proliferation. Antibiotic exposure induces long-term changes in the gut microbiome structure and increases the susceptibility of the host to immunological, inflammatory, metabolic, gastrointestinal, and allergic consequences [94]. Antibiotic exposure during pregnancy results in an imbalanced gut microbiome, which in turn predisposes pregnant women to severe risk of depressive symptoms [95]. After childbirth, antibiotic consumption increases postpartum depression within six months [85]. Different antibiotics target different bacterial cells, but some are broad-spectrum, with activities directly affecting the gut microbiome, leading to dysbiosis and resulting in a dysfunctional immune system, which is a major factor facilitating the predisposition of the host to APS [96].

7. Conclusions

The gut microbiome is a complex environment vital in maintaining host health and controls several physiological mechanisms, such as metabolism and regulation of the immune system, among others. Disturbances in or interruptions of the gut microbiota have been associated with several health problems, such as neuropsychiatric disorders, metabolic conditions, and immune dysregulation. Several studies have highlighted the role of microbiota in protecting against pathogens and regulating immune and metabolic pathways. Moreover, the gut microbiota is influenced by various environmental factors, especially diet and medications. Therefore, investigating these environmental factors, specifically in the context of autoimmune disorders like APS, emphasizes the need for continued research. Investigating the gut microbiome's activities in several disease scenarios has the potential to develop novel therapeutic strategies aimed at controlling and preventing those menaces.

8. Recommendations and Perspectives: A Need for a Holistic Treatment Approach

Understanding the link between infectious disease agents, gut microbiota, and APS is necessary for curating and advancing alternative approaches to treating APS [97]. The complex, intricate relationships between the gut microbiota, the neuronal mechanisms, and the hormonal pathway of the gut need to be further studied to be able to interpret molecular-level interactions useful in animal models, healthy individuals, and patients to yield novel methods for diagnosing, preventing, and managing APS and other associated autoimmune conditions [98]. Rather than the conventional treatment approaches, which aim to eliminate venous thrombosis, there is a need for an evidence-based treatment regimen that manages the syndrome with concise consideration for older adults and pregnant mothers due to the complications of their gut microbiota proliferation, which has been found to influence the production of aPLs [97]. Also, considering all the prospects that may promote the proliferation of the intestinal microbiome leading to the release of various aCL antibodies or their molecular mimicry could hinder the established treatment regimen and cause failure and delayed recovery, further aggravating the autoimmune disease syndrome [98].

Furthermore, beyond anticoagulation, which is regarded as the cornerstone of APS treatment, current studies are progressively focused on a few biologics, largely because

these biologics, such as rituximab and eculizumab, are generally indicated for refractory catastrophic APS [7] with high specificity and sensitivity, albeit with some limitations so far. Ultimately, more studies are needed to design useful, safe, and effective vaccines and therapies for APS.

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