Review Article
Autoimmunity and the Gut

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Autoimmune diseases have increased dramatically worldwide since World War II. This is coincidental with the increased production and use of chemicals both in industrial countries and agriculture, as well as the ease of travel from region to region and continent to continent, making the transfer of a pathogen or pathogens from one part of the world to another much easier than ever before. In this review, triggers of autoimmunity are examined, principally environmental. The number of possible environmental triggers is vast and includes chemicals, bacteria, viruses, and molds. Examples of these triggers are given and include the mechanism of action and method by which they bring about autoimmunity.

1. Introduction
Autoimmune diseases have registered an alarming increase worldwide since the end of the Second World War. This pandemic includes more than 80 autoimmune disorders and increases in both the incidence and prevalence of autoimmune disorders such as Crohn's disease, rheumatoid arthritis, multiple sclerosis, and type I diabetes [1, 2]. In the United States, it is far more commonly found in women and is one of the top 10 leading causes of death in female children and women of all age groups. The National Institutes of Health (NIH) estimates that 23.5 million Americans have an autoimmune disease. In contrast, cancer affects 13 million Americans. Symptoms involve many medical specialties and can affect all body organs (http://www.aarda.org/autoimmune-information-statistics/).

Genetic predisposition, environmental factors (including infections), and gut dysbiosis play major roles in the development of autoimmune diseases (Figure 1). Autoimmunity develops over time, and preclinical autoimmunity precedes clinical disease by many years and can be detected in the peripheral blood in the form of circulating autoantibodies [3]. Initially, symptoms of autoimmune disorders are vague and include fatigue, low-grade fever, muscle and joint aches, and malaise. They usually progress and become debilitating with significant morbidity. Patients are often seen by physicians only after their disease process has become symptomatic, clouding the understanding of the early events leading to disease. The clinician familiar with triggers for autoimmunity can order the right combination of laboratory analyses necessary to elucidate the type and stage of the patient's autoimmune reaction. This in some cases may help the clinician initiate preventive therapies aimed at removing the offending triggers and thereby reverse the progression of the autoimmune disorder with the possibility of eliminating the autoimmune disease.

2. Genetics
There are genetic variants that predispose humans to multiple autoimmune diseases and, secondly, multiple genes predispose humans to each disease. The major histocompatibility complex (MHC) is central in mediating inflammatory responses to pathogens. The unique coding or noncoding genetic variations of HLA alleles determine the antigenic responses to self- or non-self-antigens [4]. One of the most common genetic associations with autoimmune disorders is the protein tyrosine phosphatase gene PTPN22 expressed in lymphocytes. The tryptophan allele within PTPN22 has been found in patients with many autoimmune disorders, including type I diabetes mellitus, rheumatoid arthritis (RA),
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3. Environmental Factors

There are a host of environmental factors that trigger autoimmune disorders, including chemical toxicants, heavy metals, viruses, bacteria, emotional stress, and drugs. For example, adjuvants, such as aluminum hydroxide used in vaccines and medical silicones used in breast implants, can cause an autoimmune disorder known as Shoenfeld's syndrome [13]. A recent study published in the journal Apoptosis demonstrates that hepatitis B vaccine causes liver cell destruction in Hepal-6 cells. This cell death is attributed to the use of the adjuvant aluminum hydroxide, increasingly identified as a contributing cause of autoimmune disease in immunized patients [14]. Studies show that hepatitis C is almost indistinguishable from autoimmune hepatitis based on biochemical and clinical features. Autoantibodies detected in patients with autoimmune hepatitis are also frequently found in patients with hepatitis C, and both groups of patients suffer from the same immune-mediated symptoms and diseases with chronic hepatitis C [15]. Indeed, 40–70% of patients suffering from hepatitis C also develop at least one extrahepatic inflammatory disorder, including arthritis, vasculitis, and sicca syndrome [16].

Women with silicone breast implants frequently fulfill the diagnostic criteria for autoimmune syndrome induced by adjuvants, known as autoimmune syndrome induced by adjuvants (ASIA). Although the exact mechanism is not known, medical silicones in breast implants are associated with systemic lupus erythematosus, rheumatoid arthritis, vasculitis, and progressive systemic sclerosis [17, 18].

Smoking is a known risk for RA and recent studies have demonstrated that cigarette smoking may induce citrullination of proteins in pulmonary alveolar cells. This is an important finding because antibodies to citrullinated peptides are highly specific for RA as are the HLA associations that are related to the development of these autoantibodies [19, 20].

Infectious agents, including bacteria, viruses, fungi, and parasites, are also known to trigger autoimmune disorders through several mechanisms: molecular mimicry, epitope spreading, standard activation, viral persistence, polyclonal activation, dysregulation of immune homeostasis, and autoinflammatory activation of innate immunity. It is important to note that an infection may not necessarily be the inducer but rather the total burden of infections from childhood on that trigger autoimmunity [21]. Moreover, an infection can amplify an autoimmune disease by either exacerbating an ongoing disorder, including a relapse, or by leading to chronic progressive disease [22].

An example of infectious agents associated with autoimmune disorders is the link between dysregulation of Epstein-Barr virus (EBV) with the occurrence of systemic autoimmune diseases (SADS), a group of connective tissue diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), and mixed connective tissue disease (MCTD), with overlapping symptoms and antibody development. EBV is an omnipresent infectious virus, affecting approximately 95% of the world's population [23]. It is a DNA virus of the herpes family transmitted in saliva and initially infects epithelial cells in the oro- and nasopharynx. Afterwards, EBV enters the underlying tissues and infects B-cells [24]. In childhood, EBV causes a mild asymptomatic infection; in adolescents, it causes infectious mononucleosis (IM) in 30–70% of cases, and up to 20% of B-cells are infected with EBV [25]. After the first lytic infection, EBV persists in resting memory B-cells for the rest of the patient's life and can switch between an active lytic cycle and a latent state from which it occasionally reactivates, making it a continuous challenge to the patient's immune system [26].
Patients with SLE have an elevated viral load in the peripheral blood mononuclear cells (PBMCs) compared to healthy controls, anywhere from 10 to 40 times higher. The viral load is coupled with disease activity and unrelated to any immunosuppressive medication. A study found an elevated EBV DNA in the serum in 42% of patients compared with 3% of healthy controls [27–29]. Lastly, elevated levels of IgA antibodies to early antigen diffuse (EA/D) were found in 58% of SLE patients versus healthy controls and unrelated to immunosuppressive medication, demonstrating that the antibodies were not due to reactivation of EBV due to a suppressed immune system from medications [30].

In patients with RA, EBV DNA/RNA has been found in PBMCs in saliva, synovial fluid, and synovial membranes, as well as a 10-fold higher frequency of EBC-infected B-cells than in healthy controls [31–33]. This demonstrates widespread lytic EBV infection in RA patients that is also localized in the joints, signifying EBV-infected cells in the synovial inflammation that is characteristic of RA patients [34].

EBV infection has also been demonstrated in SS patients, with EBV-directed antibodies and increased viral load [35, 36]. Patients with SS also have a higher risk for EBV-associated lymphomas [37]. Elevated levels of antibodies to EBNA, VCA, and EA have been found in the serum of SS patients [38, 39]. One study showed IgG antibodies to EA/D in 36% of SS patients compared to 4.5% of healthy controls; these antibodies were not associated with immunosuppressive medication [40].

In conclusion, EBV infection is an example of one of the causal environmental factors in autoimmune disorders. As discussed above, EBV infection can lead to SADS as it can persist in the patient as a latent infection that can occasionally reactivate and cause flares as seen in chronic SADS and other autoimmune disorders.

### 4. Mucosal Immunity

The diet of humans has changed dramatically since the Second World War, especially in industrialized countries and in urban areas. For thousands of generations, humans ate food shortly after harvesting and when it was in season. Meat was occasionally consumed and much of it was caught in the wild. In the past 50 or so years, our foods have undergone a considerable transformation. We have developed new strains of grains, especially in wheat, rice, soy, and corn. In the United States, we use more genetically modified crops than the rest of the world combined. We use chemicals such as pesticides, fungicides, and insecticides for other crops such as fruits and vegetables; we inject dairy cows with hormones passing them on into dairy products; antibiotics, heavy metals, such as arsenic, and hormones are used in concentrated animal feeding operations (CAFO’s) which include cattle, hogs, turkey, and chicken; we have chemical ingredients in our foods such as artificial preservatives, colorings, and flavorings; we use artificial sweeteners abundantly, especially in soft drinks; we consume more than twice the amount of salt that we should, leading to cardiovascular disorders and contributing to immune reactions leading to autoimmune disorders [41–44]. Our abundant use of plasticizers such as bisphenol A in food and beverage containers contributes to this overreaching environmental exposure to xenobiotics as well. The widespread use of antibiotics, antacids, proton pump inhibitors, histamine 2 blockers, and other drugs, many of which are available over the counter, adds to what we consume.

Parallel to these dietary changes, there has been a considerable increase in autoimmune diseases such as type 1 diabetes, Crohn’s disease, and multiple sclerosis (MS), especially in developed industrialized countries, suggesting a link between diet and autoimmune problems. For example, it has been established that ingestion of gluten leads to gluten enteropathies and vitamin D deficiency has been epidemiologically correlated with a higher risk for autoimmune diseases [45]. Indeed, type 1 diabetes and MS are also linked to low vitamin D levels as are other autoimmune diseases [46].

There are a large number of bacteria in the oral cavity, approximately $10^{12}$, which include the tongue, teeth, and periodontal tissues. In contrast, the stomach has only $10^2-10^5$ bacteria and there are $10^6-10^9$ in the terminal ileum. The greatest number of bacteria is in the large intestine. The majority of these bacteria, approximately 70%, cannot be cultivated by current laboratory microbiological methods [47]. The gut, with a surface area of approximately 200 square meters, is where we come into greatest contact with the outside world and it follows that the gut also has the largest collection of immune cells, consisting of 70% of all lymphoid tissues in the body [48, 49]. It serves to prevent the outgrowth of pathogenic organisms. Recent studies have discussed the human microbiome and its composition in the healthy gut [50, 51]. We carry approximately $1 \times 10^{13}$ microorganisms in our gut, more than 10 times the total number of cells in our bodies [52]. The two predominant bacterial phylotypes are *Bacteroidetes* and *Firmicutes* [53]. Interestingly, the number of genes of our intestinal microbiota is 150 times greater than the number of genes in the human genome (Figure 2) [54]. Diet can substantially effect the microbiota. For example, in a diet that is high in fat and protein, *Bacteroides spp.* enterotype predominate, whereas in a diet that is high in carbohydrates, *Prevotella spp.* enterotypes predominate [55].

Mucins are highly glycosylated macromolecules, forming the first barrier between the contents of the gut and epithelial cells. This barrier provides protection for the epithelial cells from direct contact with commensal bacteria and their elements (Figure 3). Changes in either the composition or amount of mucus may lead to inflammatory responses [56]. Secretory IgA is one of the main humoral defense mechanisms ensuring the proper functioning of the mucosal surface barrier. It prevents the adherence of bacteria to mucosal surfaces and the penetration of antigens into the internal environment of the host by specific and nonspecific mechanisms [57, 58]. However, in persons with selective IgA deficiency, the mucosal barrier is deficient and more permeable to immunogens and allergens. Dendritic cells are the main cells that present antigens to the adaptive arm of the mucosal immune system [59]. A mucosal immune
response, either one of tolerance or stimulation, depends on the partaking of different populations of dendritic cells responsible for the activation of regulatory T-cells subpopulations [60]. Activation of regulatory T-cells that inhibit the immune response and induce mucosal tolerance is dependent on the production of IL-10 and transforming growth factor-beta [61]. The maturation of dendritic cells is dependent on inducement by pathogenic organisms and this then brings about the activation of effector T cells crucial for clearing infections and the prevention of subsequent infections with the same or related bacteria.

The epithelial cells of the gut have secretory, digestive, and absorptive functions and have receptors to facilitate their participation in immunological processes. The signaling pathways of these cells are highly regulated by pathways and molecules to provide a negative feedback system to avert uncontrolled inflammatory responses [62, 63]. Epithelial cells are the first point of contact for gut bacteria [64]. The epithelial layer of the gut is a major barrier between the host and the environment and is composed of a single layer of interconnected epithelial cells. This layer is reinforced by tight junctions in the paracellular spaces between the epithelial cells. These tight junctions of the epithelial layer of the gut act as a highly regulated entry that open and close depending on signals, such as cytokines and bacterial components from the lumen, lamina propria, and epithelium. Tight junctions are essential to the intestinal diffusion mechanisms [65]. The epithelial cells also make contact with the immune system of the gut and line the lamina propria of the small and large intestines and Peyer’s patches which are organized lymphoid tissues. The Peyer’s patches are critical for the direct antigen sampling from the gut and are where immune responses are induced and regulated. This is essential for gut health as too little or no bacterial exposure, as in germ-free conditions, can impair immune response, whereas excessive contact with bacteria may cause an increase in proinflammatory immune response. IgA and IgM derived from T-cell dependent and T-cell independent activation of B-cells and their differentiation into immunoglobulin secreting plasma cells are fundamental for the regulation of antigen penetration across the gut [66]. Immune regulation assists the gut to support microbiota and to ensure that effector immune responses are activated as a response to invading pathogens. Studies have shown the importance of Tregs in maintaining tolerance to the microbiota in the gut [67].

5. The Gut Microbiota

The gut microbiota can be influenced by several factors: the motility of the gastrointestinal tract (GIT); the intake of...
pharmaceutical medications, including antacids, antibiotics, and nonsteroidal anti-inflammatory drugs; smoking; the use of alcohol; the GIT transit time; mucosal blood flow; and renal clearance [68, 69]. These factors can lead to the uptake of antigens from the lumen, which play an important role in the pathogenesis of gastrointestinal disorders (Figure 6). The disproportionate uptake of these antigens, coupled with the suppression of immune responsiveness or the failure in immunological tolerance, can lead to immunological reactions both within the gut and in other organs and follow one of two pathways: physiologic transport and pathological transport. Physiologic transport consists of ligand-receptor uptake, antibody uptake, and lastly microfold or M cell transport. Pathological transport is either antigen-specific or nonspecific. Antigen specific transport via the transcellular of paracellular pathways has the ability to bring about a specific disease.

Examples include celiac disease (CD), gliadin, and allergic gastroenteropathies with casein and beta-lactoglobulin. The antigen nonspecific transport occurs when the tight junction becomes more permeable due to environmental factors which activate inflammatory cascade via transcellular or paracellular pathways [70, 71]. Vojdani in his recent study concluded that “increased antigen uptake in the intestine precedes the onset of many immunologically mediated gastrointestinal diseases” [72]. CD is frequently associated with other autoimmune disorders, in particular type 1 diabetes (T1D) and thyroiditis. This suggests that CD shares some common pathogenic mechanisms with other autoimmune diseases [73]. Genetic studies in patients with CD and T1D have shown gut mucosal barrier dysfunction [74–76]. In CD, we now know that disease-specific autoantibodies are directed against the enzyme transglutaminase 2 (TG2) brought about by gluten-reactive T cells within the celiac lesions, giving rise to glutamic acid (deaminated glutamine) [77–79].

One of the easiest ways to affect human health is through nutrition and diet. This, in turn, is influenced to a significant degree by the gut microbiota. Going from a low fat, plant polysaccharide rich diet to a high fat, high sugar Western diet changed the microbiota in one day in GF mice. There were more members of the Firmicute classes Erysipelotrichi...
and Bacilli (Enterococcus) and less Bacteroidetes associated with the Western diet. Another notable finding was that there was a significant increase in adiposity in humanized mice fed the Western diet as compared to those fed the low fat plant polysaccharide diet. These are important findings as they demonstrate that the gut microbiome can change over a very short period of time [80].

Recent studies have shown that the colonization of the small intestine in mice with a single commensal microbe, segmented filamentous bacterium (SFB), induced Th17 cells in the lamina propria. SFB are spore-forming Gram-positive bacteria related to the genus Clostridium and are found in many species as well as in humans. They are associated with reduced colonization and growth of pathogenic bacteria in the ileum where they are most abundant and adhere tightly to the epithelium. This colonization with SFB resulted in augmented resistance to Citrobacter rodentium, an intestinal pathogen, and with increased expression of genes linked with inflammation and antimicrobial defenses [81]. TGF-β differentiate Th17 and Treg cells and are defined by the expression of lineage-specific transcription factors RORyt and Foxp3 [82–86]. Th17 cells are essential mediators of autoimmune diseases, as they have potent inflammatory effects; they have important roles in protection from bacterial and fungal infections, especially at mucosal surfaces, and secrete IL-17, IL-17F, and IL-22. The increased production of Th17 cell effector cytokines, for example, IL-17 and IL-22, and the consecutive increase in antimicrobial peptide production from epithelial cells augment the ability of the host to fight off intestinal infections. At the same time, however, this increase in proinflammatory cytokines may render the host more susceptible to chronic autoimmune inflammation [87].

6. The Gut and Rheumatic Disease

Rheumatoid arthritis (RA) is one of the most prevalent systemic autoimmune diseases targeting principally the joints. RA leads to joint deformity, disability, and increased mortality without treatment. It is a multifactorial and complex disease caused by genetic and environmental factors with increased production of self-reactive antibodies and proinflammatory T lymphocytes [88]. In RA there is a prolonged period of autoimmunity with circulating autoantibodies such as rheumatoid factor and anticitrullinated peptide antibodies. This preclinical state may last many years without any clinical signs or symptoms of inflammatory arthritis. However, there is an increase in antibody titers and epitope spreading with elevation in circulating proinflammatory cytokines before the onset of clinical disease. In these situations, environmental factors may be the triggering event for systemic joint inflammation. Microbes from the periodontal tissue, the airways, and the gut microbiota have been implicated [89, 90].

RA has pathogenic disease-specific autoimmunity to citrullinated proteins. Citrullination, a modification of arginine catalyzed by peptidylarginine deiminase enzymes, has the ability to change the structure, antigenicity, and function of proteins. Porphyromonas gingivalis, a major pathogenic bacterium related to gingivitis, is linked to RA in epidemiological studies and is the only bacterium that expresses endogenous citrullinated proteins [91].

The gut microbiota composition can be changed by antibiotics. Studies have shown that antibiotic use reduced Bacteroides and Bifidobacterium and led to the growth of Campylobacter, Streptococcus, Leuconostoc, or yeasts like Candida Albicans in the gut [92]. An alteration causing an imbalance in the gut microbiota can change T-cell responses and modulate systemic inflammation. Germ-free mice lack Th17 cells; when the gastrointestinal tract of these mice is colonized with segmented filamentous bacteria (SFB), Th17 cells are induced to accumulate in the lamina propria [81] (Figure 4). Mice raised in germ-free environments are persistently healthy. By introducing specific gut bacterial species, joint inflammation ensues. Treatment with antibiotics in these mice will prevent and negate a rheumatoid arthritis-like phenotype. When the gut of arthritis-prone K/BxN mice gut is colonized with SFB, the inflammatory disease is potentiated by Th17 cells [82]. An imbalance in gut microbiota with predominance of SFB may result in the reduction of functions of Treg cells and a predisposition to autoimmunity. This may affect systemic inflammatory processes and may partially be why
there is reduced Treg function in patients with RA. This demonstrates that T cells whose functions are under the control of the gut commensal microbiota can also be the effectors of pathogenesis in autoimmune disorders [83].

A recent study showed that 75% of patients with new onset RA (NORA) carried Prevotella copri in their intestinal microbiota. Furthermore, 37.5% of psoriatic arthritis patients also had Prevotella copri in their gut compared to 21.4% of healthy controls [93]. This again demonstrates the effects of the environment from the gut microbiota aspect on autoimmune disorders.

Patients with juvenile idiopathic arthritis have been shown to have increased intestinal permeability along with gastrointestinal symptoms, suggesting a role for intestinal changes in the pathogenesis of rheumatic diseases [94]. Arthritis is frequently found in patients with IBD, again suggesting the participation of the gut in immune-mediated rheumatic disorders [95]. IBD is an autoimmune disorder affecting the GI tract in two main forms: Crohn’s disease and ulcerative colitis. The phyla of gut microbiota in patients with IBD greatly differ when compared with normal patients [96]. Studies have shown that antibiotics treatment benefits patients as well as animal models of IBD, indicating that bacteria play an important role in the pathogenesis [97]. A recent study has identified the specific microbiota in the dysbiosis of IBD patients. These patients have an overgrowth of proteobacteria and a reduction in Firmicutes and Bacteroides species [98].

Reactive arthritis and autoimmune reactions in joints may be triggered by infections with intestinal microbial pathogens, including Salmonella, Shigella and Yersinia [99]. Antibodies against antigens of certain species of gut bacteria, for example, Proteus, suggest that these bacteria and rheumatoid arthritis have a pathogenic relationship [100]. This parallels the findings in patients with ankylosing spondylitis having increased titers of anti-Klebsiella antibodies suggesting again a bacterial triggering factor [101].

7. The Gut and Neuroautoimmunity

The gut-brain axis acts as a bidirectional communication between the brain and the gut (Figure 5). The brain modulates gastrointestinal function and the gastrointestinal system is monitored by the brain via neural, immunological, and endocrine mechanisms. The development and function of the enteric nervous system are influenced by the intestinal microbiota [102]. The gastrointestinal system is directly controlled by the enteric nervous systems, the “second brain”. This system consists of more neurons than the spinal cord, mainly in the myenteric and submucosal plexuses. Neuropeptides are able to increase the permeability of tight junctions to macromolecules and thereby modify the function of the mucosal barrier [103,104].

In adults, chronic stress affects the composition of the gut microbiota with increase of Bacteroides spp. and Clostridium spp. Coupled with this are increasing levels of IL-6 indicating immune activation [105]. Chronic stress also makes the gut leaky, increasing circulating levels of LPS. Findings of altered intestinal permeability (leaky gut) may play a pathogenic role in patients with depression and their first-degree relatives [106,107].

Multiple sclerosis (MS) is one of the most frequent and severe demyelinating neurological diseases, mainly affecting young people, eventually leading to their becoming disabled. Increased intestinal permeability in these patients and in their relatives has been reported. MS has also been related to infections with bacteria and viruses [108]. Experimental autoimmune encephalomyelitis (EAE) is the animal model widely used for MS. A study in germ-free mice showed attenuated induction of EAE by myelin oligodendrocyte glycoprotein (MOG) peptide in complete Freund’s adjuvant [109]. Another study with mice genetically predisposed to develop EAE showed that when they were housed in germ-free or pathogen-free conditions, they were protected from developing EAE. Once they reached adulthood and had normal gut colonization, the protection was lost [110].

There are increasing numbers of studies demonstrating the importance of the permeability of the gastrointestinal tract to large molecules and how this is linked to the development of various neurodegenerative disorders, including Parkinson’s disease (PD). Lewy bodies, the pathological hallmark of Parkinson’s disease, were found in intestinal biopsies of patients with PD [108–110].

8. The Other Side of the Same Coin

The gut microbiome can also help the host. There are commensal gut bacteria that can ameliorate disease. For example, in immunocompromised mice, B. fragilis can lessen the colitis induced by Helicobacter hepaticus via its production of PSA,
which stimulates the anti-inflammatory IL-10 production from CD4+ T cells and the downregulating of proinflammatory IL-10 production in the colonic tissues. This, in turn, suppresses disease [111]. In another example, short-chain fatty acids (SCFAs) produced by the gut microbiota interact with G-protein-coupled receptors expressed on immune cells and reduce inflammation in the dextran sulfate sodium (DSS-) induced colitis model [112].

9. When Did It All Start?

Bacterial colonization during and shortly after birth plays a major role in the formation of gut microbiota. Factors affecting the communities in this microbiota include premature birth, Caesarean section versus vaginal birth, breast milk versus commercial formula, and many more. For example, premature infants were colonized principally by *C. difficile*. Infants born vaginally were colonized mostly by bacterial communities similar to their mother’s vaginal microbiota, including *Lactobacillus*, *Prevotella*, or *Sneathia* spp, whereas Caesarean section born infants were colonized by bacteria found on the skin surface, including *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species. Formula fed infants had colonization predominantly by *Staphylococci*, *E. coli*, *C. difficile*, *Bacteroides*, *Atopobium*, and *Lactobacilli* [113–117]. Infants delivered via Caesarean section have an increased risk of developing asthma, allergies, and autoimmune disease in later childhood [118, 119]. These are clear demonstrations of the importance of the gut microbiota starting at birth and affecting the patient years later.

10. Conclusion

Factors such as genetics, the environment, infections, and the gut microbiota all play a role in the mediation of autoimmune disorders. There have been tremendous recent advances in
our understanding of the interplay of these factors. It is clear that the gut microbiota has a profound and long-term effect starting at birth on the host immune system. It is also evident that it plays a significant role in autoimmune diseases both inside and outside the gut. There are still questions that remain to be answered: does the immune system shape the gut microbiota or vice-versa? This complex and dynamic symbiosis needs further elucidation and may help in determining the outcome of autoimmune diseases in patients. The clinician can assist the patient by being aware of the triggers of autoimmune disorders and monitoring immune and autoimmune markers in the peripheral blood, thereby being able to take preventive measures to hopefully avert the progression towards an autoimmune disease.

**Conflict of Interests**

The author declares that there is no conflict of interests regarding the publication of this paper.

**References**

[1] J.-F. Bach, “The effect of infections on susceptibility to autoimmune and allergic diseases,” *The New England Journal of Medicine*, vol. 347, no. 12, pp. 911–920, 2002.

[2] G. A. W. Rook and L. R. Brunet, “Microbes, immunoregulation, and the gut,” *Gut*, vol. 54, no. 3, pp. 317–320, 2005.

[3] A. Vojdani, “Antibodies as predictors of complex autoimmune diseases and cancer,” *International Journal of Immunopathology and Pharmacology*, vol. 21, no. 3, pp. 553–566, 2008.

[4] L. A. Zeneewicz, C. Abraham, R. A. Flavell, and J. H. Cho, “Unraveling the genetics of autoimmunity,” *Cell*, vol. 140, no. 6, pp. 791–797, 2010.

[5] J. C. Barrett, D. G. Clayton, P. Concannon et al., “Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes,” *Nature Genetics*, vol. 41, no. 6, pp. 703–707, 2009.

[6] L. A. Criswell, K. A. Pfeiffer, R. F. Lum et al., “Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes,” *American Journal of Human Genetics*, vol. 76, no. 4, pp. 561–571, 2005.

[7] R. P. Nair, K. C. Duffin, C. Helms et al., “Genome-wide scan reveals association of psoriasis with IL-23 and NF-kB pathways,” *Nature Genetics*, vol. 41, no. 2, pp. 199–204, 2009.

[8] D. M. Waid, R. J. Wagner, A. Putnam et al., “A unique T cell subset described as CD4<sup>+</sup>CD40<sup>−</sup> T cells (TCD40) in human type 1 diabetes,” *Clinical Immunology*, vol. 124, no. 2, pp. 138–148, 2007.

[9] A. L. Peters, R. M. Plenge, R. R. Graham et al., “A novel polymorphism of the human CD40 receptor with enhanced function,” *Blood*, vol. 112, no. 5, pp. 1863–1871, 2008.

[10] J.-P. Lin, J. M. Cash, S. Z. Doyle et al., “Familial clustering of rheumatoid arthritis with other autoimmune diseases,” *Human Genetics*, vol. 103, no. 4, pp. 475–482, 1998.

[11] S. A. Broadley, J. Deans, S. J. Sawcer, D. Clayton, and D. A. S. Compston, “Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey,” *Brain*, vol. 123, no. 6, pp. 1102–1111, 2000.

[12] M. Salvetti, G. Ristori, R. Bomprezzi, P. Pozzilli, and R. D. G. Leslie, “Twins: mirrors of the immune system,” *Immunology Today*, vol. 21, no. 7, pp. 342–347, 2000.

[13] O. Vera-Lastra, G. Medina, M. D. P. Cruz-Dominguez et al., “Human adjuvant disease induced by foreign substances: a new model of ASIA (Shoenfeld’s syndrome),” *Lupus*, vol. 21, no. 2, pp. 128–135, 2012.

[14] H. Hamza, J. Cao, X. Li, C. Li, M. Zhu, and S. Zhao, “Hepatitis B vaccine induces apoptotic death in Hepa-6 cells,” *Apoptosis*, vol. 17, pp. 516–527, 2012.

[15] C. P. Strassburg, A. Vogel, and M. P. Manns, “Autoimmunity and hepatitis C,” *Autoimmunity Reviews*, vol. 2, no. 6, pp. 322–331, 2003.

[16] C. Palazzi, D. Buskila, S. D’Angelo, E. D’Amico, and I. Olivieri, “Autoantibodies in patients with chronic hepatitis C virus infection: pitfalls for the diagnosis of rheumatic diseases,” *Autoimmunity Reviews*, vol. 11, no. 9, pp. 659–663, 2012.

[17] J. W. Cohen-Tervaert and R. M. Kappel, “Siliconeimplant-compatibilitysyndrome (SIS): afrequentcauseofASIA(Shoenfeld’ssyndrome),” *Immunologic Research*, vol. 56, pp. 293–298, 2013.

[18] N. Agmon-Levin, G. R. V. Hughes, and Y. Shoenfeld, “The spectrum of ASIA: autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants,” *Lupus*, vol. 21, no. 2, pp. 118–120, 2012.

[19] L. Klareskog, P. Stolt, K. Lundberg et al., “A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination,” *Arthritis and Rheumatism*, vol. 54, no. 1, pp. 38–46, 2006.

[20] G. A. Schellekens, H. Visser, and B. A. de Jong, “The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide,” *Arthritis & Rheumatology*, vol. 43, no. 1, pp. 155–163, 2000.

[21] S. Kivity, N. Agmon-Levin, M. Blank, and Y. Shoenfeld, “Infections and autoimmunity: friends or foes?” *Trends in Immunology*, vol. 30, no. 8, pp. 409–414, 2009.

[22] T. F. Davies, “Infection and autoimmune thyroid disease,” *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 3, pp. 674–676, 2008.

[23] J. A. James, B. R. Neas, K. L. Moser et al., “Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure,” *Arthritis and Rheumatism*, vol. 44, pp. 1122–1126, 2001.

[24] H. H. Niller, H. Wolf, and J. Minarović, “Regulation and dysregulation of Epstein-Barr virus latency: implications for the development of autoimmune diseases,” *Autoimmunity*, vol. 41, no. 4, pp. 298–328, 2008.

[25] P. Tattevin, Y. Le Tulzo, S. Minjollet al., “Increasing incidence of severe Epstein-Barr virus-related infectious mononucleosis: surveillance study,” *Journal of Clinical Microbiology*, vol. 44, no. 5, pp. 1873–1874, 2006.

[26] D. A. Thorlakson, “Epstein-Barr virus: exploiting the immune system,” *Nature Reviews Immunology*, vol. 1, no. 1, pp. 75–82, 2001.

[27] U. Y. Moon, S. J. Park, S. T. Oh et al., “Patients with systemic lupus erythematosus have abnormally elevated Epstein-Barr virus load in blood,” *Arthritis Research & Therapy*, vol. 6, no. 4, pp. R295–R302, 2004.

[28] I. Kang, T. Quan, H. Nolasco et al., “Defective control of latent Epstein-Barr virus infection in systemic lupus erythematosus,” *Journal of Immunology*, vol. 172, no. 2, pp. 1287–1294, 2004.
[65] A. Fasano, “Physiological, pathological, and therapeutic implications of zonulin-mediated intestinal barrier modulation: living life on the edge of the wall,” *American Journal of Pathology*, vol. 173, no. 5, pp. 1243–1252, 2008.

[66] P. Brandtzaeg, “Homeostatic impact of indigenous microbiota and secretory immunity,” *Beneficial microbes*, vol. 1, no. 3, pp. 211–227, 2010.

[67] F. Powrie, “Immune regulation in the intestine: a balancing act between effector and regulatory T cell responses,” *Annals of the New York Academy of Sciences*, vol. 1029, pp. 132–141, 2004.

[68] I. Bjarnason, G. Zanelli, and T. Smith, “Nonsteroidal anti-inflammatory drug-induced intestinal inflammation in humans,” *Gastroenterology*, vol. 93, no. 3, pp. 480–489, 1987.

[69] I. Bjarnason, K. Ward, and T. J. Peters, “The leaky gut of children. I. Association with virus infections,” *Journal of Allergy and Clinical Immunology*, vol. 63, no. 4, pp. 228–241, 1979.

[70] R. P. Ford, I. S. Menzies, A. D. Phillips, J. A. Walker-Smith, and M. W. Turner, “Intestinal sugar permeability: relationship to diarrhoeal disease and small bowel morphology,” *Journal of Pediatric Gastroenterology and Nutrition*, vol. 4, no. 4, pp. 568–574, 1985.

[71] A. Vojdani, “For the assessment of intestinal permeability, size matters,” *Alternative Therapies in Health and Medicine*, vol. 19, no. 1, pp. 12–24, 2013.

[72] A. Fasano and T. Shea-Donohue, “Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmunity diseases,” *Nature Clinical Practice Gastroenterology and Hepatology*, vol. 2, no. 9, pp. 416–422, 2005.

[73] M. C. Wapenaar, A. J. Monsuur, A. A. van Bodegraven et al., “Associations with tight junction genes PAR3 and MAGI2 in Dutch patients point to a common barrier defect for coeliac disease and ulcerative colitis,” *Gut*, vol. 57, no. 4, pp. 463–467, 2008.

[74] J. Visser, J. Rozing, A. Sapone, K. Lammers, and A. Fasano, “Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes,” *Diabetes/Metabolism Research and Reviews*, vol. 24, pp. 59–63, 2008.

[75] L. M. Solild, “Coeliac disease: dissecting a complex inflammatory disorder,” *Nature Reviews Immunology*, vol. 2, no. 9, pp. 647–655, 2002.

[76] W. Dieterich, T. Ehnis, M. Bauer et al., “Identification of tissue transglutaminase as the autoantigen of celiac disease,” *Nature Medicine*, vol. 3, no. 7, pp. 797–801, 1997.

[77] P. J. Turnbaugh, V. K. Ridaura, J. J. Faith, F. E. Rey, R. Knight, and J. I. Gordon, “The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice,” *Science Translational Medicine*, vol. 1, no. 6, ra14 pages, 2009.

[78] I. I. Ivanov, K. Atarashi, N. Manel et al., “Induction of intestinal Th17 cells by segmented filamentous bacteria,” *Cell*, vol. 139, no. 3, pp. 485–498, 2009.

[79] H.-J. Wu, I. I. Ivanov, J. Darce et al., “Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells,” *Immunity*, vol. 32, no. 6, pp. 815–827, 2010.

[80] S. J. Aujla, P. J. Dubin, and J. K. Kolls, “Th17 cells and mucosal host defense,” *Seminars in Immunology*, vol. 19, no. 6, pp. 377–382, 2007.

[81] E. Bettelli, M. Oukka, and V. K. Kuchroo, “TH-17 cells in the circle of immunity and autoimmunity,” *Nature Immunology*, vol. 8, no. 4, pp. 345–350, 2007.

[82] J. D. Fontenot, M. A. Gavin, and A. Y. Rudensky, “Foxp3 programs the development and function of CD4+ CD25+ regulatory T cells,” *Nature Immunology*, vol. 4, no. 4, pp. 330–336, 2003.

[83] I. I. Ivanov, B. S. McKenzie, L. Zhou et al., “The orphan nuclear receptor RORgammaT directs the differentiation program of proinflammatory IL-17+ T helper cells,” *Cell*, vol. 126, no. 6, pp. 1121–1133, 2006.

[84] P. Mangan, L. Harrington, D. O’Quinn et al., “Transforming growth factor-beta induces development of the T(H)17 lineage,” *Nature*, vol. 441, pp. 231–234, 2006.

[85] I. B. McInnes and G. Schett, “The pathogenesis of rheumatoid arthritis,” *The New England Journal of Medicine*, vol. 365, no. 23, pp. 2205–2219, 2011.

[86] K. D. Deane, J. M. Norris, and V. M. Holers, “Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation,” *Rheumatic Disease Clinics of North America*, vol. 36, no. 2, pp. 213–241, 2010.

[87] J. U. Scher, C. Ubeda, M. Equinda et al., “Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis,” *Arthritis & Rheumatology*, vol. 64, no. 10, pp. 3083–3094, 2012.

[88] N. Wegner, K. Lundberg, A. Kinloch et al., “Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis,” *Immunological Reviews*, vol. 233, no. 1, pp. 34–54, 2010.

[89] D. A. Hill, C. Hoffmann, M. C. Abt et al., “Metagenomic analyses reveal antibiotic-induced temporal and spatial changes in intestinal microbiota with associated alterations in immune cell homeostasis,” *Mucosal Immunology*, vol. 3, no. 2, pp. 148–158, 2010.

[90] J. Scher, A. Szczekan, R. Longman et al., “Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis,” *Elife*, vol. 2, Article ID e01202, 2013.

[91] P. Weber, T. Brune, G. Ganser, and K.-P. Zimmer, “Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis,” *Clinical and Experimental Rheumatology*, vol. 21, no. 5, pp. 657–662, 2003.

[92] J. S. Fontenot, M. A. Gavin, and A. Y. Rudensky, “Foxp3+ regulatory T cells,” *Immunity*, vol. 19, no. 6, pp. 345–350, 2007.

[93] I. I. Ivanov, K. Atarashi, N. Mane et al., “Induction of intestinal Th17 cells by segmented filamentous bacteria,” *Cell*, vol. 139, no. 3, pp. 485–498, 2009.

[94] I. I. Ivanov, K. Atarashi, N. Mane et al., “Induction of intestinal Th17 cells by segmented filamentous bacteria,” *Cell*, vol. 139, no. 3, pp. 485–498, 2009.

[95] T. Brune, G. Ganser, and K.-P. Zimmer, “Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis,” *Clinical and Experimental Rheumatology*, vol. 21, no. 5, pp. 657–662, 2003.

[96] T. Brune, G. Ganser, and K.-P. Zimmer, “Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis,” *Clinical and Experimental Rheumatology*, vol. 21, no. 5, pp. 657–662, 2003.
[99] P. Toivanen, “Normal intestinal microbiota in the aetiopathogenesis of rheumatoid arthritis,” Annals of the Rheumatic Diseases, vol. 62, no. 9, pp. 807–811, 2003.

[100] A. Ebringer, T. Rashid, and C. Wilson, “Rheumatoid arthritis, proteus, anti-CCP antibodies and Karl Popper,” Autoimmunity Reviews, vol. 9, no. 4, pp. 216–223, 2010.

[101] T. Rashid and A. Ebringer, “Ankylosing spondylitis is linked to Klebsiella—the evidence,” Clinical Rheumatology, vol. 26, no. 6, pp. 858–864, 2007.

[102] J. Bienenstock and S. Collins, “99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: psycho-neuroimmunology and the intestinal microbiota: clinical observations and basic mechanisms,” Clinical and Experimental Immunology, vol. 160, no. 1, pp. 85–91, 2010.

[103] S. M. Collins and P. Bercik, “The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease,” Gastroenterology, vol. 136, no. 6, pp. 2003–2014, 2009.

[104] M. D. Gershon, “The enteric nervous system: a second brain,” Hospital Practice, vol. 34, no. 7, pp. 31–42, 1999.

[105] M. T. Bailey, S. E. Dowd, J. D. Galley, A. R. Hufnagle, R. G. Allen, and M. Lyte, “Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation,” Brain, Behavior, and Immunity, vol. 25, no. 3, pp. 397–407, 2011.

[106] J. D. Söderholm and M. H. Perdue, “Stress and the gastrointestinal tract II. Stress and intestinal barrier function,” American Journal of Physiology: Gastrointestinal and Liver Physiology, vol. 280, no. 1, pp. G7–G13, 2001.

[107] M. Maes, M. Kubera, and J.-C. Leunis, “The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression,” Neuro Endocrinology Letters, vol. 29, no. 1, pp. 117–124, 2008.

[108] B. Yacyshyn, J. Meddings, D. Sadowski, and M. B. Bowen-Yacyshyn, “Multiple sclerosis patients have peripheral blood CD45RO+ B cells and increased intestinal permeability,” Digestive Diseases and Sciences, vol. 41, no. 12, pp. 2493–2498, 1996.

[109] Y. K. Lee, J. S. Menezes, Y. Umesaki, and S. K. Mazmanian, “Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis,” Proceedings of the National Academy of Sciences of the United States of America, vol. 108, no. 1, pp. 4615–4622, 2011.

[110] K. Berer, M. Mues, M. Koutrolos et al., “Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination,” Nature, vol. 479, no. 7374, pp. 538–541, 2011.

[111] H. Tlaskalova-Hogenova, L. Tuckova, R. Lodinova-Zadnikova et al., “Mucosal immunity: its role in defense and allergy,” International Archives of Allergy and Immunology, vol. 128, pp. 77–89, 2002.

[112] C. B. Forsyth, K. M. Shannon, J. H. Kordower et al., “Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson’s disease,” PLoS ONE, vol. 6, no. 12, Article ID e28032, 2011.

[113] A. Fasano, “Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer,” Physiological Reviews, vol. 91, no. 1, pp. 151–175, 2011.

[114] S. K. Mazmanian, J. L. Round, and D. L. Kasper, “A microbial symbiosis factor prevents intestinal inflammatory disease,” Nature, vol. 453, pp. 620–625, 2008.

[115] K. M. Maslowski, A. T. Vieira, A. Ng et al., “Regulation of inflammatory responses by gut microbiota and chemotaxin receptor GPR43,” Nature, vol. 461, no. 7268, pp. 1282–1286, 2009.

[116] M. G. Domínguez-Bello, E. K. Costello, M. Contreras et al., “Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns,” Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 26, pp. 11971–11975, 2010.

[117] E. Bezirtzoglou, A. Tsiotsias, and G. W. Welling, “Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH),” Anaerobe, vol. 17, no. 6, pp. 478–482, 2011.

[118] J. Penders, C. Vink, C. Driessen, N. London, C. Thijs, and E. E. Stobberingh, “Quantification of Bifidobacterium spp., Escherichia coli and Clostridium difficile in faecal samples of breast-fed and formula-fed infants by real-time PCR,” FEMS Microbiology Letters, vol. 243, no. 1, pp. 141–147, 2005.

[119] P. L. Stark and A. Lee, “The microbial ecology of the large bowel of breast-fed and formula-fed infants during the first year of life,” Journal of Medical Microbiology, vol. 15, no. 2, pp. 189–203, 1982.