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Decoding the Hidden Cross-Talk Between the Microbiome and the Immune System

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Abstract

The interactions between the development of autoimmune diseases involve complex genetics predisposition, environmental trigger, and immune dysregulation. Microbiota is shown to play a major role in shaping immune responses and recent research has consistently demonstrated the significant interplay between microbiota in gut, skin, and oral microbiomes and disease progression in rheumatoid arthritis, multiple sclerosis, type 1 diabetes as well as inflammatory bowel disease. Both mechanisms of molecular mimicry as well as dysbiosis induced inflammation and microbial metabolites that affect immune signaling are explored here. It also discusses novel therapies aimed at targeting the autoimmunity through microbiota targeted therapies, probiotics and fecal microbiota transplantation, among others, in dealing with autoimmune disease. The possibility to learn something from host versus microbe interaction may provide new precision medicine approaches for treating and preventing autoimmune disease.

Keywords: Microbiome Dysbiosis, Autoimmune Disease Pathogenesis, Host-Microbe Interactions, Immune System Modulation, Microbial Metabolites and Immunity

Introduction

Autoimmune diseases are a leading global health problem with an occurrence of about 5–10% of the population, which is increasing in the last decade (Gallucci et al., 2021). These are disorders in which the immune system fails to become tolerant towards self tissues and ends up attacking them with continual inflammation, tissue destruction and multi organ failure. Rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes (T1D), systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD) are all common immune disease conditions each with different but overlapping immune pathways (Cho & Gregersen, 2021). Genetic predisposition to these conditions is important, but now acknowledged as it is only a critical modulator of immune function and disease progression (Nielsen et al., 2022). Of these factors that influence the environment, host-microbe interaction has received a lot of attention as research suggests that the microbiome is not a mere passenger but part of a host immunomodulation network.

The Microbiome as a Key Immune Modulator

Trillions of different types of bacteria, viruses, fungi and archaea make up the human microbiome, mainly in the gut, skin, and other areas with mucosal surfaces. These microbial communities colonize and immune homeostasis through the regulation of innate and adaptive immune response, tolerance of autoantigens, and the prevention of excessive inflammation (Belkaid & Hand, 2022). Regulatory T cell (Treg) development is aided by beneficial microbes like Bifidobacterium ad Lactobacillus, therefore suppressing autoimmune reaction (Kuczma et al., 2021). On the other hand, pathogenic microbes or dysbiosis can cause immune dysregulation that aborts self tolerance and initiates the autoimmune pathology (Zhang et al., 2023).

Gut microbiota composition is shown to be correlated to autoimmune diseases. The altered gut microbiota is correlated with the increased severity of RA in patients, as well as with inflammatory responses (Maeda & Takeda, 2022). Similarly, people with MS have decreased levels of beneficial Firmicutes and raised

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proinflammatory bacteria, such as Akkermansia muciniphila (Cekanaviciute et al., 2021). These data point to a role of the microbiome in the development and progression of autoimmune diseases as it affects immune cell activation, cytokine production.

Dysbiosis and Autoimmune Pathogenesis

A major hallmark of multiple autoimmune diseases is dysbiosis, the disruption of microbial homeostasis that fundamentally disrupts immune regulation and drives inflammation in a chronic manner (Lee & Kim, 2023). This microbial imbalance represents a mixture of effects on both innate and adaptive immunity, as well as effects on disease pathogenesis itself. Dysbiosis is one of the most important consequences of dysbiosis, including the loss of beneficial microflora, including bacteria that produce short chain fatty acids (SCFA) such as Faecalibacterium prausnitzii. These commensal bacteria have important immune tolerant, dampen proinflammatory cytokine and augment Treg (regulatory T cells) activity actions. Increased Th17 mediated inflammation, an important mechanism of autoimmune disorders has been associated with their depletion (Silva et al., 2022).

On the contrary, dysbiosis may also lead to the overgrowth of proinflammatory microbes with the concomitant release of lipopolysaccharides (LPS) into circulation by gram negative bacteria. LPS is a potent immune stimulant and causes systemic inflammation together with autoimmune activation. Furthermore, this mechanism has been strongly implicated in systemic lupus erythematosus (SLE) and type 1 diabetes (T1D) where LPS levels are elevated and are correlated with disease severity in those diseases (Hufnagl et al., 2021). Another major repercussion related to microbial imbalance is its role in increasing intestinal permeability, also known as ‘leaky gut’. In this condition, the intestinal epithelial barrier becomes permeable, and therefore microbial components such as peptidoglycan and LPS are able to translocate into the blood. It then kicks off autoreactive immune cell activation, chronic inflammation and autoantibody production (Zhang et al., 2023).

Longitudinal studies in T1D also indicate a causative role of gut dysbiosis in autoimmunity since microbial alterations were found prior to disease onset, which means the dysbiotic state may be a trigger rather than a consequence of immune dysfunction (Davis-Richardson et al., 2021). Consistent with this, intestinal microbial dysbiosis has also been implicated to be associated with elevated colonic and systemic inflammation, as well as increased autoantibody generation in the context of SLE (Azzouz et al., 2022).

Mechanisms Linking Microbiota and Autoimmune Diseases

Several underlying molecular mechanisms governing host microbe interactions in influencing immune activation and tolerance drive the relationship between host microbe interation and auto immune disease development. Molecular mimicry is one of the most well documented mechanism and involves microbial antigens that actually resemble self proteins and provoke immune crossreactivity. Multiple sclerosis (MS), for instance, is a disease that has been particularly implicated as a result of this phenomenon where Epstein Barr virus (EBV) antigens have structural homologies with the myelin proteins and may lead to an autoimmune attack on the central nervous system (Lassmann et al., 2022).

Bystander activation is another type of mechanism which occurs as result of chronic infections or persistent immune activation. In this case, the immune system takes offense to the first pathogen, and expands its assault to its own tissues. There has been such observation in autoimmune diseases like rheumatoid arthritis (RA) and T1D, infections seem to trigger a cascade of autoimmunity (Kumar et al., 2022).

Along with these bacteria themselves, microbial metabolites also help in fine tuning immune responses, especially those generated by resident gut bacteria. T cells are also influenced by SCFAs, tryptophan

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metabolites, other bacterial by products, and hence T cell differentiation and cytokine production as well as immune homeostasis. In general, these microbial metabolites promote immune tolerance under normal conditions, but the dysregulation of their production can provoke proinflammatory immune responses and breakdown of self tolerance (Mielcarz & Kasper, 2022).

In neuroimmunological autoimmune diseases like MS, there is increasing research on the role of the gut–brain axis in the autoimmune disease. The gut microbiota has been shown to be able to send signals to the central nervous system (CNS) via immune signaling or metabolites with influence on neuroinflammation and immune profile of the brain (Erny et al., 2021). The presence of disruptions in this axis may be involved in the occurrence and evolution of MS and, as a consequence, in the systemic effect of gut microbiota on autoimmune diseases.

Microbiome-Based Therapeutic Approaches

Because a strong relationship has been established between dysbiosis and autoimmunity, microbiome targeted interventions are becoming a focus of research as therapeutic strategies. Probiotics and prebiotics have emerged as promising tools to modulate gut microbiota and immune responses. Certain bacterial strains like Lactobacillus and Bifidobacterium have anti-inflammatory properties and have been successful in improving the disease outcome in RA and in MS (Santoru et al., 2022). Furthermore, dietary fiber, which is part of the prebiotic dietary component, promotes immune homeostasis and decreases autoimmune inflammation by increasing SCFA formation.

Fecal microbiota transplantation (FMT), also emerging as one therapy, is the transfer of healthy donor's gut microbiota to a patient for repairing microbial balance. For inflammatory bowel disease (IBD) and MS, FMT may improve partial disease remission, which suggests the alleviation of autoimmune symptoms is related to correcting gut dysbiosis (Zuo et al., 2021). Challenges still exist with standardization, of donors, and long safety.

Also, dietary modulation is also a major factor in the multinomial therapy. Thus, diets rich in fiber, which enables the production of SCFAs, increase Treg function and lower inflammation, reducing the risk of autoimmunity (Brown et al. 2023). In addition, synthetic biology is subduing advances towards the engineering of the microbiome with genetic modifications to bacteria that secrete immunomodulatory molecules; what has been termed microbiome engineering (Jiang et al., 2023).

Microbial Influence on Specific Autoimmune Diseases

There is a positive role of gut microbiome and other microbial communities in the development and progression of autoimmune diseases. Specific bacteria, viruses, and fungi assist in the same disease mechanisms by immune modulation either directly, or indirectly by disseminating epitope spreading or inflammation. Knowing the alterations to the microbial in individuals with rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes (T1D), and systemic lupus erythematosus (SLE) might reveal the course of pathogenisis and offer germ free animals for targeted therapies of the microbiome.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a phlogistic prolonged autoimmune disease which is manifested by destruction of synovial joint cartilage and joint deformities as the result of autoimmunity directed against synovial joint. More and more evidence has been accumulating to indicate that periodontal bacteria, gut microbiota, and mucosal dysbiosis are linked to pathogenesis of RA.

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Porphyromonas gingivalis (Pg), a periodontitis associated oral pathogen, is one of the microbial key contributors to RA. It was linked to the citrullination of proteins, a hall mark of RA autoimmunity. The most prominent marker of RA that P. gingivalis expresses is an enzyme called peptidylarginine deiminase (PAD), which catalyzes the conversion of arginine in to citrulline, to produce anti citrullinated protein antibodies (ACPAs) (Konig et al., 2021).

More importantly, gut microbiota changes have been observed in RA patients including decrease of beneficial bacteria such as Bifidobacterium and increase of Prevotella spp.. Therefore, Prevotella copri is linked to the increased Th17 cell activity associated with joint inflammation and autoimmunity in human subjects. The gut microbial imbalance plays a role in immune system dysregulation and further RA progression (Maeda & Takeda, 2022).

Multiple Sclerosis (MS)

Demyelinating autoimmunne neuroinflammatory disease of the CNS is known in pathologic terms as multiple sclerosis (MS). There is increasing evidence that the initiating and propagation of disease is antimicrobial, both due to microbial dysbiosis and viral infection in MS. The study of gut microbiome in MS patients shows lower levels of beneficial Firmicutes and higher levels of pro-inflammatory immune response promoting Akkermansia muciniphila. Such microbial alteration may also lead to the induction of neuroinflammation and the recruitment of immune cells into the CNS (Cekanaviciute et al., 2021). In addition, MS onset has been linked to viral infections, especially Epstein Barr virus (EBV) and human herpes virus 6 (HHV-6). In this way, these viruses may act to trigger an immune response that cross reacts with myelin antigens, causing demyelination and neurodegeneration (Lassmann et al., 2022).

Type 1 Diabetes (T1D)

T cell-mediated destruction of pancreatic β cells destroys insulin of type 1 diabetes (T1D). Recent research shows that the balance of microbes (dysbiosis) and exposures during early life may influence the risk for T1D.

Several longitudinal microbiome studies have demonstrated that children that later develop T1D have lower Bifidobacterium and higher proinflammatory microbes (Bacteroides and Ruminococcus). Our interpretation is that these microbial shifts may contribute to gut barrier dysfunction (leaky gut) that allows activation of the immune system against pancreatic autoimmunity (Davis-Richardson et al., 2021).

T1D onset also has been linked to viral infections especially to enteroviruses. In some cases, some enteroviruses can infect pancreatic β cells and lead to immune mediated destruction by way of epitope spreading, bystander activation etc. (Richardson et al., 2022).

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a systemic autoimmune disease withautoantibody, chronic inflammation, and muplicitaniorgan damage. Increasingly, we appreciate that alterations to gut and oral microbiome are important for the pathogenesis of SLE.

SLE patients carrying studies which show increased gut permeability (leaky gut), known as increased intestinal permeability, show the bacterial endotoxins Lipopolysaccharides (LPS) to enter circulation in order to cause chronic immune activation. Previously, this microbial translocation has been linked with increased exacerbated autoimmunity and inflammation (Azzouz et al., 2022).

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Also, like in SLE, oral microbiome contributes to SLE pathogenesis by generating autoantibodies and systemic inflammation; Porphyromonas gingivalis and Fusobacterium nucleatum are the two contributors. Such bacteria might provoke immune responses that foster autoreactive B cell activation and thus disease progression (Chen et al., 2021).

Therapeutic Interventions Targeting Microbiome-Immune Interactions

As the relationship between the dysbiosis and autoimmune diseases is very strong, microbiome targeted therapies are of interest as potential approaches to restore immune homeostasis and decrease disease activity.

Probiotics and Prebiotics

Both Lactobacillus and Bifidobacterium probiotics have anti-inflammatory properties that include Treg expansion and reduced production of proinflammatory cytokines. The studies reported that probiotic supplementation is beneficial in reducing disease severity in animal models of RA, MS, and T1D (Santoru et al., 2022).

Fiber rich diets prebiotics as they have higher growth of beneficial mucosal microbes that resulted in enhanced production of SCFA and improved immune regulation. With their support, immunity in homeostasis and gut barrier barrier fortify, which may help autoimmune flare-ups.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) is a therapy in which donor microbiota is transferred to a patient to resettle his microbiota. FMT has been shown, in clinical trials, to get rid of autoimmune diseases such as IBD and MS (Zuo et al.) on a partial level.

Nevertheless, standardization of FMT, donor selection, and long term safety are still challenges. However good the early results are, much more research is required to establish how effective it might be with other autoimmune diseases.

Microbiome-Based Precision Medicine

The metagenomics and microbial sequencing rapidly evolves to personlized microbiome based therapeutics according to an individual’s microbial profile. Therefore, a combined systems approach to targeted probiotic supplementation, dietary interventions as well as their derivatives with function as so called 'next generation immunomodulators', initiates this work. (Jiang et al., 2023). Research in development aims at synthetic microbiota engineering, where helpfull bacterial consortia are created to suppress autoimmunity while keeping immune tolerance.

Conclusion

The host microbe relationship is an intricate one which makes it intensely clear how the microbiome can regulate immune system. Recent research has shown that inflammatory autoimmune disorders including rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes (T1D), and systemic lupus erythematosus (SLE) are associated with developing gut dysbiosis, molecular mimicry, microbial metabolites as well as viral infection. The disruption of microbial homeostasis, whether through loss of beneficial bacteria, expansion of pro-inflammatory microbes, or increased intestinal permeability, plays a critical role in immune dysregulation and chronic inflammation. Traditional autoimmune disease treatments have mainly utilized immunosuppression, but as increasing evidence is emerging towards the potential of the microbiome targeted interventions for more precise modulation of immune responses, the novel and more precise approach is

microbiome targeted interventions. Restoring balance of the microbiome through probiotics, prebiotics, fecal microbiota transplantation (FMT) and microbiome based precision medicine is also being tested as therapeutic strategies involving the reduction of disease severity as well as improving immune regulation. Nevertheless, microbiome based treatments must be standardized and the challenge to determine the causality and to consider the individual variability of microbiome will need to be addressed to optimize the clinical outcomes.

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