

Microbiome and Autoimmune Diseases

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1. Introduction to the Microbiome and Autoimmunity

The discovery of human microbiome has revolutionized our understanding of health and disease. These microbes, which live in various parts of the body; play different roles and as well as essential for the body's overall health. Recent innovations in genomics, especially the Human Microbiome Project (HMP), have shown that microbiota intertwines with the host in a complex process (Wang et al., 2017). The gut microbiota, which harbors the highest density of microbes that impact digestion, synthesis vitamins (Bengmark, 2013). Microbiomes present in other body sites such as skin, oral and respiratory microbiota are understood to have a considerable influence on site-specific and overall health.

The human body has a complex mechanism known as the immune system, which is primarily designed to safeguard the body (Parkin & Cohen, 2001). However, a snag may happen that may result in the immune system attacking a part of the body, leading to Autoimmune Diseases. These diseases are numerous and polygenic and many are known to be influenced by both genetic and environmental responses (Migliore & Coppedè, 2009). Recent literature supports that the microbiome-autoimmune connection has a significant role in the development of autoimmune diseases. Under this interaction, it is evident that the two, that is the microbiome and the immune system are interrelated as they respond to each other. Dysbiosis, characterized by abnormal microbiota, and is linked to various autoimmune diseases that encompass inflammatory bowel disease (IBD), according to research (de Oliveira et al., 2017).

Further explanations reveal how the microbiome affects autoimmune diseases: SCFAs are related to the microbial activities and have the ability to exert immunomodulatory effects, influence the regulatory T cell balance (Ratajczak et al., 2019). The autoimmune reactions can also be attributed to the molecular mimicry, where microbial antigens are similar to host antigens. Secondly, if the gut barrier is compromised, it allows luminal microbial components to directly enter the blood stream and potentially worsen systemic inflammation and autoimmune processes (Wells et al., 2017).

This shift in the concept of microbiome, particularly with reference to autoimmune diseases has, significant implication for both fields of study. It offers the chance for a clinical focus in Phillipsburg, to emerge and establish pharmacological strategies based on the disruption of microbiota to correct immunological disorders (Duarte-Chavez et al., 2018). Possible solutions may include use of probiotics as well as prebiotics, diet change and a process called fecal microbiota transplantation (FMT). Subsequently, targeting of biomarkers with links to specific autoimmune diseases would mean early identification and diagnosis of the disease, and elevating the management of autoimmune diseases to the next level: the potential of biomarkers in autoimmune diseases (Giacomelli et al., 2019).

2. The Human Microbiome: A Diverse Ecosystem

The human microbiome is an extensive and multifaceted system comprising trillions of microbes that reside within and on the human bodies, encompassing microbes, viruses, fungi, and archaea (Hoffmann et al., 2016). These microbes inhabit characteristic body locations, introducing

themselves as specific communities that functions to fulfill a range of critical roles for the human body. A more substantial and diverse compartment is the gut microbiome which is inhabited by approximately 100 trillion microbes of Firmicutes and Bacteroidetes phyla (Rinninella et al., 2019). These microbes are essential for digestion processes, the biosynthesis of vitamins and the body's defense mechanisms.

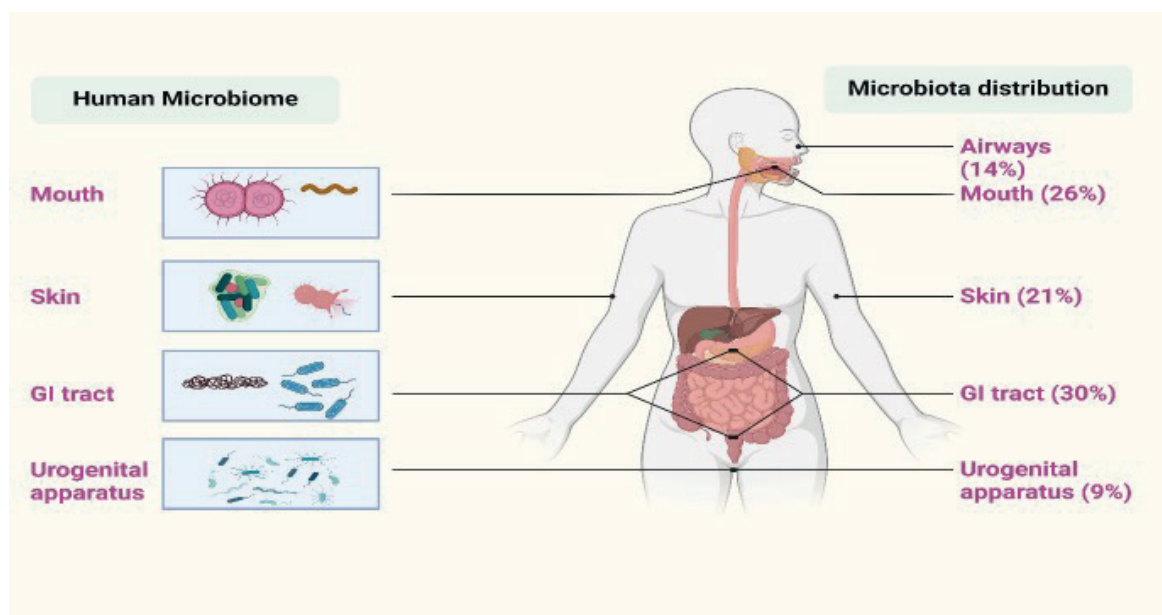


Figure 1. Microbiome and Autoimmunity

The skin microbial communities can differ among various different parts of the body; wet body regions have a different microbial population compared to the dry ones (Rosenthal et al., 2011). Cutaneous commensal flora include *Staphylococcus*, *Corynebacterium* and *Propionibacterium* species; These bacteria has a significance role in maintaining skin homeostasis to prevent colonization of skin by bad pathogens (Percival et al., 2012). The oral biofilm, a diverse ecosystem involving bacteria, fungi and viruses, also contains specific bacterial genera that are involved in the initial breakdown processes and the antagonism of pathogens: *Streptococcus*, *Actinomyces* and *Fusobacterium*. Subtypes of bacteria, including *Streptococcus*, *Haemophiles*, and *Neisseria*, contribute to the lung microbiome's function in patency and protecting against microbial invasion (García et al., 2016).

The microbiome has been credited with indispensable metabolic, protective, and immune-regulatory functions (Samuelson et al., 2015). The colonic microbiota metabolizes non- digestible carbohydrates into SCFAs, which are necessary for colon function and exert an array of general anti- inflammatory functions. They also manufacture important vitamins that are integral part of the body such as vitamin K and the B vitamin group (Shearer & Newman, 2008). By outcompeting for space and nutrients, the microbiome inhibits pathogens through their action of occupying the valuable niche, directly killing pathogens, and inducing host antimicrobial peptides. Additionally, the microbiome modulation of immune systems, including the ability to determine the difference between objects that can have a negative impact and those that are safe, immune tolerance, as well as efficient responses to pathogens (Tamburini et al., 2016).

As we know that human microbiome is a intricate system that is 'constructed' immediately after birth and modified by different factors throughout the lifespan. It explicitly exhibits how the mode of delivery affects the determining initial microbial colonization, directly from the mothers' microbiota for infants delivered through the vaginal route and skin and environmental microbes for those delivered through the cesarean section (Nuriel-Ohayon et al., 2016). Diet has a significant impact on microbiota, with microbial counts increasing in individuals taking the habitual Diet of breastfeeding supporting the growth of *Bifidobacteria* in the gut and high-fiber diet supporting the growth of diverse microbiota in adults (Francino, 2016). Lifestyle factors and the environment

also affect the population of microorganisms within the body, suggesting that there may be fewer microbial species in non-rural contexts due to hygienic practices of modernity.

The concept of microbiome is still comparatively new to the discussion of specific disease manifestation, but recent studies do suggest that the microbiome is connected to autoimmune diseases in some way (De Luca & Shoenfeld, 2019). The human body microbiota is unbalanced, which is popularly known as dysbiosis, in most autoimmune diseases. It has been reported that there are changes in the composition of gut microbiota of RA patients and diabetic, multiple sclerosis (MS) and healthy control indicating that altered microbiome may be related to the development and severity of autoimmune diseases (Chen et al., 2016).

3. Autoimmune Diseases: When the Immune System Goes Awry

Autoimmune diseases can be described as illnesses that occur when the immune system which is supposed to safeguard the body, starts threatening it instead (Condeelis, 1992). This immune system disorganization makes the body experience constant inflammation, tissue necrosis, and impaired organ functions. Genetic factors, environmental contaminants, and microbial infections can be found to be associated with these diseases (Ashbolt, 2004).

There exist various pathways that are involved in the erosion of immune tolerance, a prominent feature observed in autoimmune diseases. Autoimmune disease has a highly genetic, with some genes making one vulnerable to the bacteria or other infections. The concept of molecular mimicry is whereby the foreign antigens share some similarities with host antigens and this is what leads to the cross immune attack on both pathogens and tissues (Segal & Shoenfeld, 2018). Autoimmune disease develops when a pathological process excites immune cells, which react with a high level of pathogenicity against self-antigens. This leads to epitope spreading, where the initial response increases in scale to attack other unrelated self-antigens, increasing the severity of the particular disease in question. Environmental factors such as infections, drugs and toxins also act as an environmental cause that can lead to the onset or exacerbation of autoimmune diseases (Molina & Shoenfeld, 2005).

There are more than eighty sorts of autoimmune diseases; all these diseases conduct an impact on different tissues and organs. Rheumatoid arthritis is a long-term disease characterized by inflammation affecting the joints resulting in pain, stiffness and swelling (Grassi et al., 1998). Systemic lupus erythematosus (SLE) is a chronic or relapsing systemic disease and disturbs several organs, in which autoantibodies can be produced against different cellular components. (Johnston Jr & Joy, 2001).

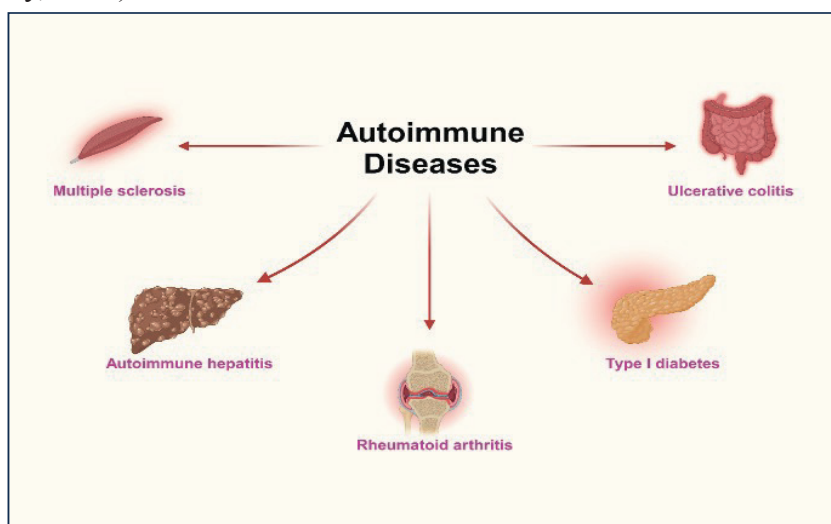


Figure 2. Autoimmune Diseases

It may prove a difficult proposition to diagnose autoimmune diseases especially bearing in mind that their manifestations are numerous and diverse (Touitou & Koné-Paut, 2008). It may involve a general physical examination and or assessments, serologic tests (autoantibodies), and imaging tests (like radiography, MIR, USG). Sometimes, histological samples obtained by biopsy may be required to affirm the diagnosis.

Autoimmune diseases' treatment is accomplished by moderating the immune system's activity, diminishing inflammation, and decreasing disease manifestations (Goodnow, 2001). The interventions include NSAIDs, corticosteroids, synthetic disease-modifying antirheumatic drugs DMARDs, and biologic agents (Smolen et al., 2017). Lifestyle changes which involve dietary changes, exercise regimes, and stress management can also be of immense assistance. Lifestyle changes in chronic illness patients, such as physical therapy and occupational therapy, can show remarkable enhancements in movement and function (Pedersen & Saltin, 2006).

Recent studies have brought the concept of microbiome involvement in autoimmune diseases to the spotlight. An inequity in the microbial makeup of the body, known as dysbiosis and has been positively associated with autoimmune diseases. With emerging evidences for the role of the gut microbiome in diseases such as RA, T1D, and MS, the variations in the gut microbiome composition have been an issue of interest (Vijay & Valdes, 2022). Such pathways of the microbial communication with the immune regulations are microbial metabolite and pattern recognition receptors. MIMS If the balance of the microbiota is shifted dysbiosis-interactions between the bacterial strains, the interaction of the bacteria with the epithelium, epithelium with the underlying tissue, the tight junctions and the permeability of the epithelial layer can be altered and promote further inflammation to the system and can stimulate autoimmune reactions (Yu et al., 2012).

Since microbiome is the mainly involved in the development of autoimmune diseases, it is quite logical to consider the manipulation of the microbiome as a viable strategy for the treatment of autoimmune diseases. Interpositions such as probiotics, prebiotics, nutrition modification, and fecal microbiota transplantation (FMT) are under trials for the restoration of PAH symbiosis and the dampening down of autoimmune responses (Flandroy et al., 2018). Future studies can potentially give better understanding of the effects of microbiome and immune system, which gives hope that people with autoimmune diseases can be alive better through innovative therapeutic strategies.

4. Microbiome-Immune Crosstalk: A Delicate Balance

Both the immune system and microbiota are constantly actively interacting through bidirectional communication necessary for optimal health (Zheng et al., 2020). This interplay is termed microbiome-immune crosstalk, and understanding these interactions is critical to deciphering how dysbiosis, perturbations in microbial communities, can contribute to immune system disorders such as autoimmunity.

The immune system is a coordinated group of defenses in the body, comprising of various cells, tissues, and organs. It consists of two main components: non-specialized immunity also known as the natural immunity, which is the first line of defense, and specialized immunity also known as the acquired immunity which forms the second line of defense (Spoel & Dong, 2012). There is also the innate system which comprises of barriers such as skin, and immune cells like the macrophages and neutrophils while the second is the adaptive immunity consist of lymphocytes comprised of the B and T cells that are selective to the antigens in question.

The interactions between microbiome and immune system are not well understood but can happen in several ways (Maynard et al., 2012). Some of the metabolites include short-chain fatty acids (SCFAs) that have immunosuppressive characteristics and stimulate Treg cells which are involved in immune tolerance. Cells involved in innate immunity contain molecules called pattern recognition receptors (PRRs) that bind to microbial molecules and affect the immune response. We found that mucosal immunity especially in the GALT site has important function in taking samples

of microbial antigens and immune cell education (Kawai & Akira, 2010). The Intestinal epithelial barrier is involved in preventing the microbes from crossing into the systemic circulation while the microbiome supports the epithelium. Microbes also modulate cytokine production which are chemical mediators involved in immune system communication (Thomas & Versalovic, 2010).

Imbalance in the two complexes, microbiome, and immunity, can cause disruption in the system, dysbiosis and immune dysregulation, autoimmune diseases. These are infection, antibiotics, diet, and stress among them though there may be other causes, as well. The pathogenesis of Visceral leishmaniasis begins from increased permeability of the intestine (“leaky gut”) and additionally increases the blood circulation of microbial products that cause inflammation (Slyepchenko et al., 2016). Dysbiosis can also change immunological biases for inflammation, IMDs reducing T regs, and activating PRRs. Also, molecular mimicry, through which microbial antigens resemble self-antigens and initiate the autoimmune response in the susceptible host.

Some examples of microbiome-immune communication in autoimmune disorders include Rheumatoid arthritis (RA), Type 1 diabetes (T1D) and Multiple sclerosis (MS) (Zheng et al., 2020). For example, in RA, a more significant number of *Prevotella copri* have been linked to the development of the disease. In T1D, research has shown a connection of dysbiosis with both less bacterial richness and variations in certain bacterial populations. Literature on MS reports changes in the gut microbiota in the following ways: reduced ratio of anti-inflammatory bacterial strains and increased ratio of pro-inflammatory bacteria (Cristofori et al., 2021).

Knowledge regarding this crosstalk unveils novel pharmacological possibilities. There are various ways of altering the microbiome balance including probiotics, prebiotics, diet modification, and fecal microbiota transplant (FMT) (Cammarota et al., 2014). Other antimicrobial strategies that are under development are targeted therapies for individual microbial Immune interactions. Thus, studying these mechanisms and their consequences would help generate new ideas and solutions to eliminate autoimmune diseases.

5. Gut Microbiome and Autoimmunity: The Gut-Immune Axis

The gut microbiome states to the microbial community that resides in the human gastrointestinal tract and it has been earlier established that the microbiome plays a critical role in determining overall health and disease, especially in relation to autoimmunity (Thursby & Juge, 2017). The interactions between the gut and the immune system form a bidirectional communication system with the microbiota and are effective in maintaining the immune system and preventing autoimmune diseases. This crosstalk is complex and includes the GALT (gut-associated lymphoid tissue), the mucosal barrier, microbial metabolites, or immunocytes (Laissue et al., 1993). Role of Gut Microbiota in autoimmune disease is shown in below figure.

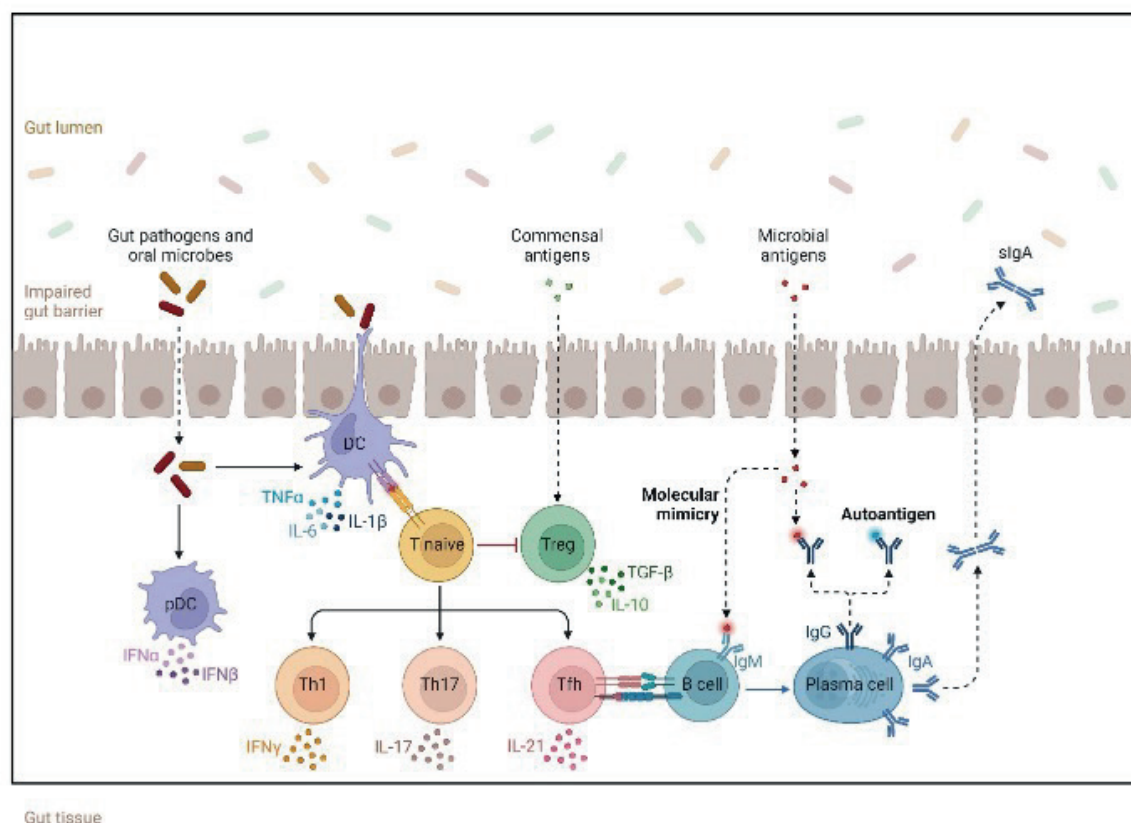


Figure 3. Role of the Gut Microbiota in Autoimmune Diseases

GALT makes up a major proportion of the immune cells, and it plays a crucial role in analyzing antigens from the gut and make the right responses. The intestinal epithelium also serves as a barrier whose primary function is to deny pathogenic organisms and their products entry into the systemic circulation (Powell, 1981). Saturated fatty acids can also influence immune function via preserving gut integrity and regulating inflammation and Tregs. The GI tract mucosa contains immune cells which, interacting with microbial antigens, get differentiated into Tregs or effector T cells that modulate immune response (Acheson & Luccioli, 2004).

An anomalous distribution of the microbiota, termed dysbiosis and it is the key contributor to the expansion of autoimmune diseases. This can alter the permeability of the gut, allowing toxins to penetrate the intestinal lining and enter the systemic circulation resulting in autoimmune type inflammation. Additionally, dysbiosis causes chronic inflammation, which enhances pro-inflammatory cytokines and shortages anti-inflammatory cytokines to aggravate autoimmune diseases. Furthermore, such shifts in microbiota composition affect the development and the functionality of immune cells and lead to immune intolerance and autoimmunity.

Autoimmune diseases like RA, T1D, MS, and IBD have been linked to dysbiosis. For example, in early RA the levels of *Prevotella copri* are increased, as well as in T1D there is reduced diversity of microbiota and some bacterial shifts in T1D (Miyachi et al., 2023). In MS, it has been revealed that there are reduces the number of anti-inflammatory microbes and the number of pro-inflammatory microbes has been found to be high. IBD contributes to the dilution of effective bacteria, as well as the proliferation of pathogenic bacteria that cause chronic inflammation.

It showed that SCFAs which benefits gut and immune system and Toll like receptors which senses microbial signals to trigger immune response are the two interconnected components of microbiome and Immune system. Immunological tolerance is kept by Tregs which are regulated by the GM but dysbiosis reduces their number and functionality. It is established that some microbial

antigens are capable of inducing autoimmune reactions due to cross-reactivity with self-antigens in susceptible persons (Cooke et al., 1983).

Probiotics, prebiotics, diet modifications, and FMT are therapeutic interventions that may provide an option for tackling autoimmune diseases (Mangalam et al., 2021). Some of the aids include prebiotics which help in the restoration of the friendly bacteria while the probiotics assist in restoring the balance of the immune system. There is evidence that dietary modification to the Mediterranean diet reduces inflammation and has a positive effect on the microbiome. FMT involves the deposition of stool from a healthy individual is termed as FMT and this can assist in reconstructing the impaired functions. Having an understanding of the interaction between the microbes and the immune system will help encourage the use of focused treatments to enhance the synthesis of SCFAs or to nurture the growth of healthy bacteria in the body (Parada Venegas et al., 2019).

6. Beyond the Gut: Other Microbiomes in Autoimmunity

While autoimmunity perturbation is assigned to gut microbiota, the skin, mouth, lung, and urogenital tract microbiota are also significant, and their dysbiosis exists (De Pessemier et al., 2021). All of these microbiomes have various touch points with the immune system and factors that can influence the development and progression of autoimmune diseases. Oral biofilm states to a complex and ever-changing community of microorganisms such as bacteria, fungi, and viruses that make close associations with the teeth, gums, and tongue and plays a critical role in oral diseases and immune system functioning. Disharmony of the microflora of the oral cavity can affect different organs and tissues adversely and is believed to be involved in the development of certain autoimmune diseases such as rheumatoid arthritis due to systemic inflammation and molecular mimicry. Eubacteria lung microbiome is present in less number but diverse and has an essential impact on the respiratory tract and the immune response (Shukla et al., 2017).

The urogenital microbiota is relatively host specific and can be qualitatively and quantitatively altered by many factors, making it crucial to urogenital health. Dysbiosis is supposed to be one of the factors contributing to the shift in the urogenital microbiota which may be the cause of autoimmune urogenital diseases such as interstitial cystitis and autoimmune thyroiditis.

Thus, the regulation of these SITE-OTHERS by use of the concepts of probiotics, prebiotics, and antimicrobial targeting can be considered as therapeutic management strategies for autoimmune diseases (Shihata, 2004). Higher awareness and knowledge of these microbial communities regarding immune modulation may create a path to new therapies if autoimmune diseases impact multiple organs.

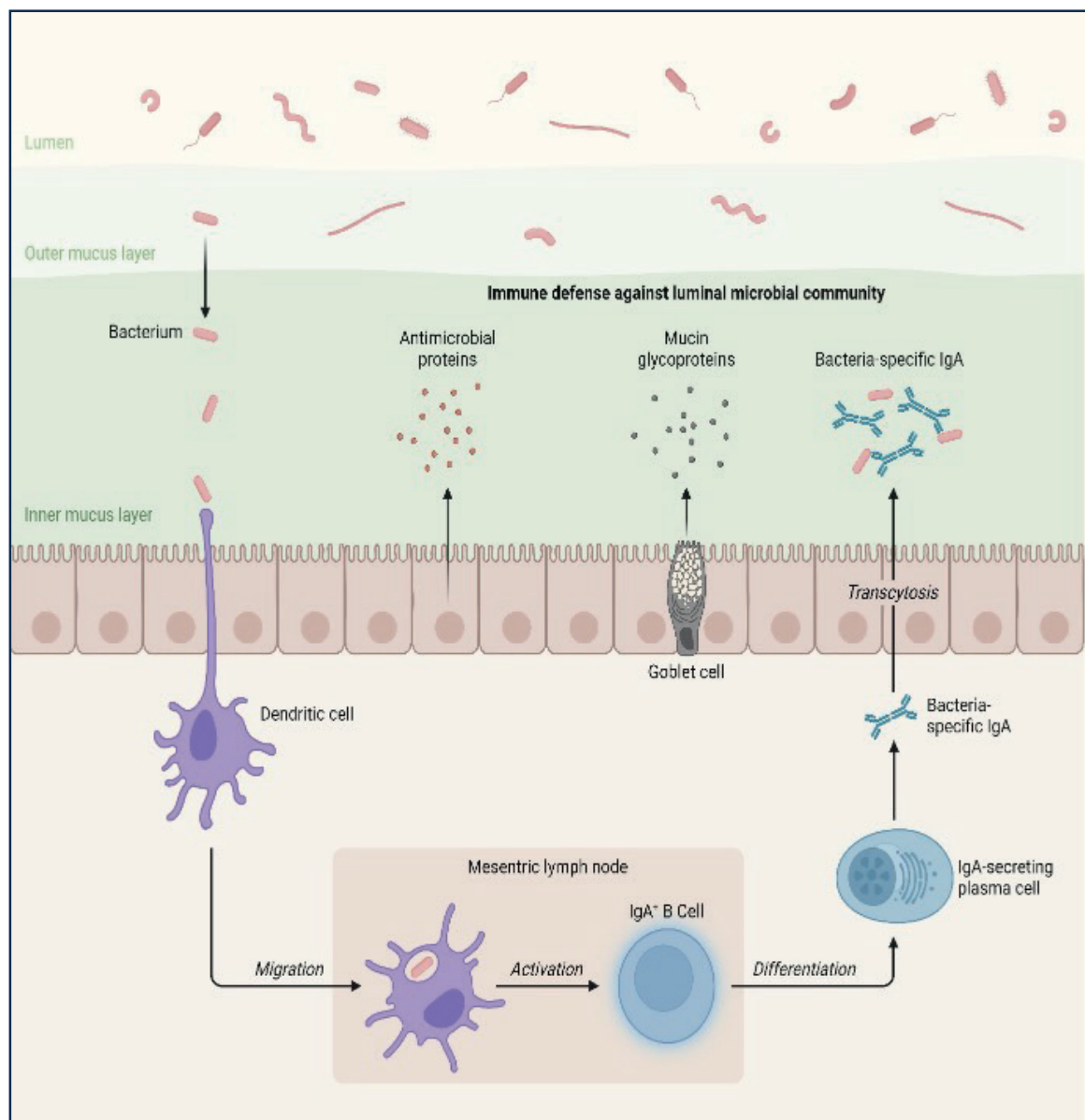


Figure 4. Intestinal Immune Défense Against Luminal Microbes

7. Therapeutic Potential: Harnessing the Microbiome for Treatment

Autoimmune diseases are expected to be influenced by gut microbiota and thus represent an extensive application target in medicine. This includes the introduction of naturally occurring or synthetically produced beneficial microorganisms or substrates, shift in diet, FMT and other novel microbiota modification therapies for disease (Quigley & Gajula, 2020).

The standard definition of probiotics is live bioactive microorganisms that are beneficial to the host, which can be achieved by intake of adequate quantities of such microorganisms. They operate through enhancing the mechanical and chemical barrier of the gut, modulating immune responses and producing antibiotics. However, it is evident from available research, that probiotics could prove beneficial in managing IBD, RA and MS.

Prebiotics are termed as non-hydrolysable agents or non-digestible oligosaccharides that act as factors enhancing the population of the beneficial bacteria in the GI tract. These extend the production of short-chain fatty acids (SCFAs) that contain anti-inflammatory properties and enable the development of favorable bacterial strains. A encouraging evidence regarding the use of Prebiotin was also witnessed in IBD, IBS and autoimmune diabetes (Sanders et al., 2019).

One aspect that deserves even more attention is that dietary interventions are the only possible approach to the change of the microbiome and immune response. According to research, there is information that shows that certain diets like the Mediterranean diet and low FODMAP diet aid in reducing inflammation and boost immune responses (García-Montero et al., 2021). These trials can be used to deduce some foods to eliminate from one's diet since their consumption is likely to aggravate autoimmune disease symptoms. These includes the farm to fork strategy for food and nutrition or the consumption map to specified microbiome characteristics and moderation for microbiota optimization.

This treatment process involves transferring stool sample from a normal person to a patient who has dysbiosis in order to improve microbial issues. FMT has also been very effective in treating recurrent *C difficile* infection and has been employed to reasonable extent for management of IBD and other autoimmune bowel disease related cases (Borody & Khoruts, 2012).

The future continuous lines of microbiome-based medication include symbiotic that is both probiotics and prebiotics, postbiotic which is the metabolites that the probiotics yield, phage therapy which uses the viral particles to counter specific bacterial types plus the microbiome modulation drugs. They are more beneficial in treating autoimmune diseases because they provide prospects at achieving new balance of the microbial community and immunologic functioning (Tlaskalová-Hogenová et al., 2004).

Table: Microbiome-Based Therapeutic Interventions for Autoimmune Diseases

Microbiome-Based Therapies	Description	Potential Applications
Probiotics	Live microorganisms that confer health benefits to the host.	Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS)
Prebiotics	Non-digestible food ingredients that promote the growth of beneficial bacteria in the gut.	IBD, Irritable Bowel Syndrome (IBS), Autoimmune Diabetes
Dietary interventions	Modification of food intake to alter gut microbiota and immune response.	Inflammatory Bowel Disease, Rheumatoid Arthritis
Fecal Microbiota Transplant (FMT)	Transfer of stool from a healthy donor to restore a healthy gut microbiome in a recipient.	Recurrent <i>Chloridoids</i> difficile infection, IBD
Emerging therapies	Symbiotic (probiotics + prebiotics), postbiotics (metabolites produced by probiotics), phage therapy (use of viruses to target specific bacteria), microbiome-modulating drugs.	Various autoimmune diseases

8. Future Directions and Challenges

The revelation of the functioning of microbiome in autoimmune diseases has helped to expand the paradigm in the field of study and treatment (Kaufmann, 2019). Areas that need further research include the geographical mapping of microbiota to determine the distribution of microbes within designated areas, functional analysis of microbial consortiums, and analysis of the symbiotic relationship between the host and microbiota. Interpreting research to therapeutics entails precision-driven microbiome therapies, new therapeutic approaches such as symbiotic and postbiotics, and conceptualizing the microbiome therapy guidelines and standards.

Major concerns in this field include microbiome heterogeneity, evaluating the risk and potential side effects of all therapies, and patient awareness of the microbiome and its function in the body. There are also more general questions related to the ethical and societal impact, including how to

provide equal and fair access to the pros of microbiome-based treatments, how to protect patients' data privacy, and how to address the public and make people trust those innovations.

Thus, the knowledge of the microbiome, translation of the research findings into useful treatment and management strategies, tackling barriers, and the ethical aspects could help maximize the potential of the microbiome to enhance the quality of life for the autoimmune disease sufferers.

9. Conclusion

It can be stated that the relations of the human microbiome with immunity as a topic that can be highly effective in the development of auto immune diseases. Specifically, the intricate inter- and interrelation between the aforementioned microbes/toxins and the immune system as a whole, not to mention the trillion-shaped microbial orchestra existing inside or on us, may shed light on the multiple faces of autoimmunity and prompt the creation of unprecedented immunotherapies. Furthermore, by comparing what the composition of the microbiome is, and how it can interrupt and speak to the immune system, or if therapeutic-solutions based on microbiome may actually contribute to understanding the extent to which the microbiome seems to manage and transform the immune system to counter autoimmune diseases we have recovered a sense of the ways in which it might work. Therefore, as more have been done to find out how the host microbiota signals the immune system there is no doubt that microbiome holds enormous opportunities in generating new and wider horizons in autoimmune diseases prevention, detection and control. Therefore, there is a hope that through the implementation of the ability to use potential microbiome, it will be possible to show the theoretical and proof-base for the individual and selective methods for treating such diseases that will give people with such ailments a desired and better quality of life. However, some limitations can be circumvented in the future, so it can be concluded that the prospects for the development of the microbiome in autoimmunity are impressive as part of the concept of personalized medicine micro biome in health and disease.

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