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Fecal microbiota transplantation in autoimmune diseases – an extensive paper on a pathogenetic therapy

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Abstract:

The role of infections in the pathogenesis of autoimmune diseases has long been recognized and reported. In addition to infectious agents, the internal composition of the "friendly" living bacteria, (microbiome) and its correlation to immune balance and dysregulation have drawn the attention of researchers for decades. Nevertheless, only recently, scientific papers regarding the potential role of transferring microbiome from healthy donor subjects to patients with autoimmune diseases has been proposed. Fecal microbiota transplantation or FMT, carries the logic of transferring microorganisms responsible for immune balance from healthy donors to individuals with immune dysregulation or more accurately for our paper, autoimmune diseases. Viewing the microbiome as a pathogenetic player allows us to consider FMT as a pathogenetic-based treatment. Promising results alongside improved outcomes have been demonstrated in patients with different autoimmune diseases following FMT. Therefore, in our current extensive review, we aimed to highlight the implication of FMT in various autoimmune diseases, such as inflammatory bowel disease, autoimmune thyroid and liver diseases, systemic lupus erythematosus, and type 1 diabetes mellitus, among others. Presenting all the aspects of FMT in more than 12 autoimmune diseases in one paper, to the best of our knowledge, is the first time presented in medical literature. Viewing FMT as such could contribute to better understanding and newer application of the model in the therapy of autoimmune diseases, indeed.

Keywords – Autoimmunity, microbiome, infection and autoimmunity, fecal microbiota transplantation

Introduction:

Fecal microbiota transplantation (FMT) is a procedure referring to the transplantation of fecal microbial material collected from a healthy host and transferred into the gastrointestinal system of the recipient. The procedure is performed therapeutically to restructure and repopulate the microbiome of the host with beneficial microbes in an aim to combating certain illnesses [1]. Practically, the fecal transplant of the donor is transferred to the host via nasogastric tube, colonoscopy, or capsule [2]. The earliest reports of the utilization of FMT track back to the 4th century where "yellow soup" was used therapeutically in China to treat food poisoning and diarrhea [3]. The so-called "yellow soup" typically consisted of fermented fecal solution, fresh fecal suspension, and dry feces or infant feces. Subsequently, in the 16th century in China, feces-based preparations were consumed to treat systemic symptoms such as fever and pain alongside other gastrointestinal-related ones [4]. In contemporary science, a fecal enema was used as a therapy for *Clostridium difficile* pseudomembranous enterocolitis in 4 patients who failed to respond to other therapies [5].

Meanwhile, the microbiome, which resides all over the human body, consists of a convoluted network of trillions of microorganisms including viruses, bacteria, and fungi [6]. The microbiome is considered essential for maintaining physiological homeostasis and interplays with various metabolic processes. Some of the benefits of the microbiome include the digestion

of dietary compounds, production of vitamins, and protection against the colonization of harmful pathogens [7, 8]. The process of microbiome formation starts from the moment of birth while its development is influenced by numerous factors including environmental exposures and infections [6].

In terms of the gastrointestinal system, the gut microbiome has been studied the most and linked to various autoimmune diseases [9, 10]. Many of the studies focused on gut microbiota and its association with intestinal autoimmune disorders such as Crohn's disease and ulcerative colitis [11]. However, disturbances to the gut microbiota and its composition have been correlated to extraintestinal disorders such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), type 1 diabetes mellitus, and Sjogren syndrome, among others [12-15]. All of the different autoimmune conditions mentioned share the concept of "dysbiosis", which refers to alterations in the symbiotic composition of the microbiome that can result in negative outcomes for the host [16]. In fact, the intricacies of the interplay between dysbiosis and autoimmune diseases are not fully understood nevertheless; one suggested theory illustrates the ability of the gut microbiome to contribute to the formation of short chain fatty acids necessary for the upkeep of the gut barrier protection and the regulation of immune response [17]. The modulation of the immune response by short chain fatty acids (SCFAs) is achieved via utilizing G-protein coupled receptors to inhibit histone deacetylases in regulatory T-cells [18]. Another way with which the gut microbiome is thought to impact immune functions is through the ability to synthesize certain small molecules that behave as inhibitors of cathepsins. Cathepsins are known to be vital in the processes involved in antigen production and presentation [19, 20]. Moreover, studies have linked the restoration of the gut microbiome stability to positive outcomes in a variety of autoimmune diseases. The restoration can be achieved by various

methods including the utilization of bioactive agents such as probiotics, prebiotics and synbiotics, or via the utilization of FMT.

The proposed mechanisms linking the gut microbiome to autoimmunity are illustrated in **Fig. 1**.

FMT protocols, safety and regulation:

A point of contention regarding the utility of FMT as a therapeutic option is the standardization of FMT preparations. Currently there is no uniform protocol in preparing FMT. Multiple routes have been devised for delivering FMT to a patient. Such routes include colonoscopies, enemas, duodenal tubes, or orally ingested capsules [21-24].

The rates of success seem to be similar among the different routes of administration; therefore, the choice of administration method depends on other external factors such as the ability of the patients to tolerate a colonoscopy or if they possess risk factors for aspiration or another possible complications [25].

Generally, FMT is considered safe to use in most patients; however, the possibility of introducing certain pathogens that may be harmful to the recipient must be considered [26]. This has been reflected in reports describing fever, bacteremia and increased C-reactive-protein levels in certain patients following FMT application [27, 28].

Autoimmune diseases, the microbiome, and the utilization of FMT:

1. Inflammatory Bowel Disease:

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder characterized by repetitive episodes of inflammation of the gastrointestinal tract and is subdivided into ulcerative colitis (UC) and Crohn's disease (CD). UC is a chronic, idiopathic inflammatory disease that affects the colon, particularly the rectum, resulting in superficial erosions of the colonic wall associated with bleeding [29, 30]. In turn, CD is a chronic inflammatory bowel disease as well; however, it is characterized by skip inflammatory lesions and transmural mucosal inflammation that can affect any part of the gastrointestinal tract. Both diseases have relapsing and remitting course and show various extraintestinal manifestations [31].

The exact cause of IBD remains a mystery. Generally, the triggers of IBD are multifactorial involving genetic predisposition, an inappropriate immune response to the intestinal flora such as disturbances in the gastrointestinal microbiota, mucosal barrier dysfunction, environmental, and lifestyle factors [32]. Normally, the integrity of the intestinal epithelium prevents bacteria or antigen to gain entry into the circulation nevertheless, in IBD the intercellular junctions are defective either due to severe inflammation or a primary barrier function failure [33]. This is best explained by the gut dysbiosis that causes inappropriate immune activation and loss of immune homeostasis mainly due to reduction in biodiversity (mostly Firmicutes) and decreased stability [34]. Besides, an expansion of Proteobacteria such as Enterobacteriaceae, Bilophila, and certain members of Bacteroidetes are seen [35, 36]. In contrast, the commensal microbiomes are reduced in IBD which further affects the intestinal homeostasis and specific host-microbe interactions that are important for pathogen limitation, generation of antimicrobial peptides, mucus, and repair [37].

Several clinical data have supported the efficacy of targeting the microbiome in IBD patients with treatment strategies like FMT. The exact methodology with which FMT should be prepared for treatment in this particular disease remains unclear however, some studies suggested that certain aspects of FMT preparation might be associated with beneficial outcomes [38]. For instance, some studies reported that FMT samples can be frozen in – 80C for up to two years as frozen samples were linked with better outcomes compared to fresh feces [39], due to an increase in the Firmicutes/Bacteroidetes ratio [40]. Another example is the washed microbiota transplantation (WMT) protocol developed by Zhang and colleagues and characterized by maintaining intact bacteria and washing off smaller molecules [41]. When contrasted with regular FMT preparations, WMT does not result in any improvements in efficacy; nevertheless, WMT is thought to have a better safety profile [42]. In a systematic review and meta-analysis investigating FMT as a protentional treatment for IBD, 53 studies were included (41 in UC, 11 in CD, 4 in pouchitis) [43]. While patients with CD and pouchitis showed no significant improvement, FMT was effective in inducing remission of UC remission. Moreover, a randomized control trial enrolled 81 patients with active UC who received FMT by initial colonoscopic infusion and then unrelated multidonor or open-label FMT enemas 5 days a week for 8 weeks [44]. The study demonstrated that FMT increased microbial diversity and altered composition in addition to the association of specific bacteria and metabolic pathways with induction of remission in UC compared to donors' stool samples. Likewise, an open-label randomized controlled trial of 113 patients demonstrated that multidonor FMT induced deep remission in mild to moderate UC alongside a sustained anti-inflammatory diet over 1 year [45]. Furthermore, a recent systematic review of sixty studies, investigating the efficacy and safety of FMT in IBD, demonstrated a higher rate of clinical remission especially in Crohn's disease when

frozen fecal material from universal donors was used [46]. Another systematic review and meta-analysis of randomized controlled trials involving 6 types of autoimmune diseases illustrated effective and safe results following the application of FMT especially in patients with UC. The positive results were reflected by an increased rate of clinical remission, clinical response, as well as endoscopic remission [47].

If viewed by possible mechanisms, mice treated with FMT were shown to display lesser rates of Erysipelatoclostridium [48]. The latter was linked to higher potentials of inducing TH1 cells, which are thought to be associated with intestinal inflammation [49]. Meanwhile, FMT therapy in IBD is suggested to tip the ratio of helper T cells towards an increase in regulatory T cells [50]. Furthermore, FMT resulted in an increase in IL-10 production and a decrease in blood IL-17 [51]. In an open-label study of 20 patients with UC, FMT, delivered via colonoscopy, led to a decrease in colonic Th1 and Treg cells [52].

2. Autoimmune Thyroid Diseases:

Both extremes of thyroid function can be caused by autoimmune disorders. For instance, Hashimoto disease (HD), the leading cause of hypothyroidism, is the most common autoimmune thyroid disease damaging thyroid cells by antibody-mediated immune mechanisms [53, 54]. In turn, Graves' disease (GD), the most common cause of hyperthyroidism, is an autoimmune disease characterized by the production of thyroid stimulating antibodies mimicking thyroid-stimulating hormone (TSH) action causing thyrotoxicosis [55, 56]. It primarily affects the thyroid gland but commonly affects multiple other organs like the skin and eyes.

Many studies have pointed to a direct relationship between the pathogenesis of autoimmune thyroid disorders like Hashimoto and Graves' disease and the gut microbiome as an active trigger [57]. Indeed, the use of FMT as a treatment method of Hashimoto and Graves' disease, and as an important tool to understand how the gut microbiota is a potential modulator in the pathogenesis of these diseases, is of growing interest [58-60]. Several mechanisms have been proposed in the pathogenesis of Hashimoto disease including the modification of micronutrients metabolism, iodine, and iron, that decrease intestinal pH leading to increased gut permeability and gut dysbiosis [61]. Besides, differences in bacterial richness and diversity were detected among autoimmune diseases and are thought to play a major role in affecting certain clinical parameters [62]. For example, a recent study sequencing and analyzing fecal samples of 27 HD patients and 16 healthy people suggested that HD patients had the highest content of *Proteobacteria* and *Actinomycetes*, followed by the GD group and the healthy control group [63]. Another sequencing analysis proposed group variances and suggested that *Firmicutes*/*Bacteroidetes* ratio was significantly elevated in HD patients, whereas phyla *Bacteroidetes* and *Proteobacteria* were decreased [64]. In contrast, a cross-sectional study to examine the makeup and metabolic function of microbiota in GD patients showcased a significantly lower proportion of *Firmicutes*, α-diversity and reduced *Firmicutes*/*Bacteroidetes* ratio [65, 66].

In terms of FMT as a therapeutic mean, an experimental study of HD analyzing 20 disease-free BALB/c male mice after being exposed to FMT from both healthy individuals and primary hyperthyroidism patients, showed that FMT introduced from primary hypothyroidism patients resulted in a decrease mRNA expression of occludin, junctional adhesion molecule-A and zonula occludens-3211 [60]. The modifications listed alongside the fact that the SCFA producing

capacity of primary hypothyroidism mice was lowered resulted in increased LPS levels in the serum and ultimately lesser total thyroxine levels [61]. Similarly, several studies about the therapeutic use of FMT for GD showcased promising results [60, 67, 68]. Moreover, a transplantation from animal donor into animal model recipient led to an alternation in gut microbiota post-FMT in addition to a greater decrease in T3 and T4 hormone concentrations, increased liver expression of type 2 deiodinase, and better recovery of hypothyroid-induced resting metabolic rate back to normal [67]. Furthermore, a transplantation from human donor into animal model recipient suggested alteration of gut microbiota such as the reduction in *Bacteroides* and increased richness indices [68].

Studies suggested that imbalances in Th17/Treg ratios can contribute to the development of GD and FMT could pose as an option to correcting these imbalances and treating the disease [65]. This dysfunction is characterized by an increase Th17 cells and a decrease in Tregs [69].

3. Autoimmune Liver Diseases:

Autoimmune liver diseases comprise a spectrum of inflammatory diseases with three distinct entities of idiopathic progressive disorders including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) [70, 71]. AIH is a chronic inflammatory liver disease of unknown cause, characterized by elevation of aminotransferases and immunoglobulin G (IgG) that may progress to liver cirrhosis and end stage liver disease [72-74]. PBC, formerly known as primary biliary cirrhosis, is an autoimmune cholestatic liver disorder with variable progressive course of destruction of the intrahepatic bile ducts leading to periorbital inflammation, cirrhosis, and hepatic failure if left untreated [75, 76]. PBC shows a

strong female predominance and is characterized by circulating antimitochondrial antibodies (AMAs). Primary sclerosing cholangitis (PSC) is a rare chronic progressive liver disorder of unknown cause, characterized by diffuse inflammatory destruction and fibrosis of the bile ducts, resulting in bile stasis, cirrhosis, and ultimately requiring liver transplantation [77-79]. The disorder is known to accompany IBD, particularly UC.

In addition to the genetic and environmental factors which play an important role in breaking self-tolerance, there is a strong association between the alteration of the commensal microbiome configuration and the initiation and progression of autoimmune liver diseases [80]. Emerging studies suggest several mechanisms contributing to this association. For instance, the inflammation of the intestinal mucosa affects its integrity, allowing translocation of enteric pathogens, mainly via the gut-liver axis [81, 82]. Subsequently, a cholangiocytic response will be initiated and PSC, for example, will be seen. Besides, an immune mediated damage will precede an activated T-cells from the intestines [83, 84]. Since the etiology of the autoimmune liver diseases remains unknown, understanding the microbiota hypothesis would contribute to a better treatment approach through methods like FMT.

In a study evaluating gut microbial profiles of treatment-naive PBC patients in comparison with healthy controls, Yi-Jun Zhou and colleagues found significant disturbances in the composition of the gut microbiome of PBC patients when compared to healthy controls [85]. Based on that, the authors concluded a connection between PBC and the gut microbiome. In regard to immune dysregulation, several studies illustrated that FMT therapy can repair the dysregulation between T follicular helper cells (TFH) and Follicular T regulatory cells (TFR). This is largely thought to be achieved through the TLR4/11-MyD88 signaling pathway [86]. In a mouse model study

representing AIH, FMT therapy at 28 days contributed to correcting TFH/TFR ratio, as well as a decreased liver levels of IL-21 [87], which is a critical player in the pathogenesis of AIH [88]. Furthermore, gut dysbiosis was linked to increased levels of Th17. The latter is associated with IL-17 secretion accompanied with the development of PBC. Actually, FMT is a potential avenue to balance gut dysbiosis and regulate Th17 levels [89]. Moreover, receptor pathways such TLR4 and G protein coupled receptors like GRP41/GPR43, GPR109a were found to play an impactful role in the development of AIH which further emphasizes the potential of FMT in the treatment of autoimmune liver diseases [90]. Recently, a study was established to test the efficacy of controlling the progression of AIH by therapeutic FMT administration on follicular regulatory T (TFR), helper T (TFH) cell imbalances, and intestinal microbiota (IM) composition in vivo. The study was conducted in a murine model of experimental AIH (EAH) harboring dysbiosis similar to that of AIH patients [87]. Therapeutic FMT was capable of controlling hepatitis progression in EAH mice by attenuating liver injury and bacterial translocation, according to the paper. Besides, FMT improved the imbalance between splenic TFR cells and TFH cells in ABx EAH mice and reversed the increasing levels of serum liver enzymes (ALT and AST) of CXCR5−/−EAH mice only after almost a month. Another study evaluating FMT in EAH mice models found that EAH mice displayed significant liver inflammation and T follicular helper/follicular T regulatory (TFH/TFR) cell dysregulation [86]. The TFH/TFR dysregulation improved following the administration of FMT to the EAH mice. In PSC, several studies reported that FMT therapy improved intestinal flora, and resulted in lower ALP levels. Patients with PSC had 70% lower ALP levels as well as a 30% reduction in ALT and AST after treatment with FMT [91]. Microbial diversity improved in the first week and continued to improve for 24 weeks.

Additionally, in a case report of a PSC patient with recurrent cholangitis, FMT decreased the rate of recurrence, improved liver function tests, and intestinal microbial diversity [92].

4. Multiple Sclerosis:

Multiple Sclerosis (MS) manifests as a consequence of autoimmune progressive demyelination and worsening of neurological function [93, 94]. MS patients present in one of four clinical types: primary progressive MS (PPMS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS) [95-97]. RRMS is the most common form of the disease and consists of attacks and remissions preceding recoveries of varying levels.

In terms of gut microbiota, recent studies have shown that SCFAs are lower in MS patients [98, 99]. Moreover, the microbiomes of MS patients were observed to possess lower quantities of *Butyricimonas*, an anaerobic Gram-negative bacteria from the family of Odoribacteraceae. Alongside the drop in SCFAs, the alterations in the gut microbiome result in an upregulation of the pro-inflammatory autoreactive T cells, i.e., Th17 and Th1 cells in peripheral blood. Th17 is thought to be increased in the presence of short filamentous bacteria (SBF) [100]. The role of SBFs is manifested through their ability to produce certain metabolites that in turn activate macrophages. The activated macrophages participate in the production IL-23 which influences T cells to differentiate into Th17 [101]. The bacteria *Bacteroides fragilis*, which is a gram-negative anaerobic microorganism, part of the gut microbiome, is considered to be another player in the regulation of Th17 response [102]. This is achieved via the ability to facilitate transforming of CD4+ T cells into IL-10-producing Foxp3+ Tregs through Toll-like receptor 2 (TLR2) [34, 103-

105]. The increase in Th17 levels is notable because studies showcased higher levels of Th17 mRNA in peripheral blood of MS patients when compared to healthy controls [106, 107].

The microbiota alterations alongside others have allowed the potential for FMT to be considered as a viable treatment for patients with MS [108-111]. In a mouse model study representing MS treated with FMT, FMT therapy resulted in an increased CD4+ FoxP3 T cells and MOG-specific Tregs in the spleen [112]. Bacteriodes fragilis which is promoted by FMT therapy produces polysaccharide A (PSA) and thus lowering neuroinflammation by controlling the migratory potential of CD39+ CD4 T cell subsets. PSA also regulates CNS demyelination by promoting IL-10 producing T-reg cells and resulting in a decrease in proinflammatory IL-17 [113, 114]. Moreover, in a paper presenting 3 MS patients treated by FMT, patients reported significant improvement of the neurological symptoms following treatment [115]. Another study demonstrated gradual neurological improvement in a MS patient treated with FMT for *Clostridium difficile* [115]. Similarly, a 52-year-old woman with 20-year history of PRMS underwent FMT therapy for recurrent *Clostridium difficile* infection. The GI symptoms of the patient were alleviated a week following therapy, whereas the neurological symptoms gradually improved over a year, and the patient eventually displayed better muscle strength and EDSS scores [116]. A case of a 48-year-old RRMS patient with walking difficulties and treated with 10 sessions of FMT, increased level of butyrate-producing bacteria, *Faecalibacterium prausnitzii*, SCFA and improved diversity in the microbiome, were all observed [117]. The patient reported significant improvements in walking after treatment with FMT. Finally, a recent systematic analysis of 5 studies showed that MS patients treated with FMT displayed increased levels of certain intestinal bacteria such as *Blautia*, *Streptococcus*, *Akkermansia*, and others and decrease

levels of *Prevotella*, *Bacteroides*, and *Clostridia* species [118]. The results were associated with amelioration of the neurological symptoms of the patients enrolled in the studies.

5. Systemic Lupus Erythematosus:

SLE is an autoimmune chronic disorder characterized by the production of autoantibodies and immune complexes that target multiple organs and systems in the body. The affected systems include the kidneys, the skin, and the CNS, among others [119]. The pathogenesis of SLE is thought to be a congregation of environmental and genetic factors. Some of the environmental factors are extended exposure to sunlight, certain infections, medications, and hormonal changes [120]. Symptoms of SLE include fatigue, fever, varying skin rashes, headaches, kidney disease, and joint pain among others [121].

Generally, patients with SLE display less microbial diversity in the gut microbiome when compared to healthy controls [122-124]. Moreover, another way with which the gut microbiome is thought to influence the pathogenesis of SLE is throughout the so-called “leaky gut”. This is largely an outcome of impaired gut barrier functionality resulting in toxins, bacteria, and other pathogens to leak into other organ systems [122]. Some of the leaking bacteria share certain structures with the hosts resulting in molecular mimicry and ultimately extenuating immune reactions [125, 126]. Patients with SLE were found to possess a significantly lesser ratio of *Firmicutes*/*Bacteroidetes* (F/B) [127]. This is further compounded by the fact that *Firmicutes* bacteria are linked with lesser SLE disease activity index score.

Interestingly, numerous studies have shown that the utilization of FMT is effective in the treatment of SLE in mice models [128-130]. Subsequently, in a clinical trial enrolling 18 SLE

patients for FMT treatment Huang and colleagues registered SLE responder index scores of 42.12% at week 12 of treatment [131]. Furthermore, significant reductions from baseline were observed in SLEDAI-2k scores alongside serum levels of anti-dsDNA. Based on that, the authors concluded that FMT possesses a potential for being a viable and safe therapy in SLE by achieving positive alterations in the gut microbiome. As studies continued to explore the landmass of FMT therapy in SLE, some authors focused on the utility of individual strains of microbes rather than the entire gut microbiome. As an example, in a trial evaluating renal function of lupus-prone mice, Mu et al. found that therapy with a mixture of 5 different *Lactobacillus* strains improved renal functionality [132]. Moreover, in an analysis of a single arm clinical trial on FMT therapy in SLE [131], Xin and friends found that patients with good response to SLE therapy possessed an increased amount of *Bifidobacterium* species [133].

Lately, Xin et al [133] conducted a single-arm trial evaluating 20 patients with SLE over 12 weeks. The enrollees received 30 capsules of FMT (considered a single dose) once a week for three weeks. From 18 patients showed for the final follow-up; 8 patients had positive response to FMT therapy. The patients had higher levels of *Anaerobutyricum hallii* and lesser abundances of Parabacteroides, unclassified Lachnospiraceae and *Senegalimassilia faecalis*. Based on the results, the authors outlined the following indications for FMT utilization in the treatment of SLE: 1) High disease activity with limited response to first-line therapies; (2) Refractory albuminuria due to lupus nephritis; (3) Serological activity (high anti-dsDNA titers); (4) High abundance of *Anaerobutyricum hallii*, and low abundance of unclassified Lachnospiraceae, unclassified Parabacteroides and *Senegalimassilia faecalis* in fecal microbiota; and (5) The expression levels of IFN-related genes.

In terms of the impact of FMT therapy on the immune system in SLE patients, lymphocytes and myeloid cells are negatively associated with the efficacy of FMT therapy [134]. On the other hand, FMT results in a decrease in the expression of interferon related genes in CD4+ T, CD8+ T, double positive T cells, NK, and B cells of SLE patients [133]. FMT treatment has also been linked to decreased levels of IL-6 in peripheral blood [135]. Studies also showed that the expression of GZMH and NKG7, which are cytotoxic genes, are increased CD8+ T cells of SLE patients following FMT treatment [134]. Additionally, Huang et al. illustrated that FMT therapy caused an increase in CD4+CD45RA+ naïve T cells as well as a decrease in CD4+CD45RO+ memory T cells on the 8^{th} and 12^{th} week of therapy [136].

6. Membranous Nephropathy:

Membranous nephropathy (MN) is considered to be the most prominent cause of idiopathic nephrotic syndrome in adults [137]. MN results in a range of symptoms including severe proteinuria, edema, and hypoalbuminemia, among others. Patients may also display other symptoms such as hypertension, hematuria, and renal insufficiency [138]. The exact pathophysiology of how MN develops is not fully understood however, the disease is associated with the detection of autoantibodies against phospholipase A2 receptor (PLA2R) and the thrombospondin type-1 domain-containing 7A (THSD7A) [139]. The autoantibodies ultimately form complexes that deposit in the glomerular basement member and result in a complement reaction and inflammation.

Studies have linked the gut microbiome and dysbiosis with MN and chronic kidney disease (CKD) and suggested that dysbiosis might be a contributing factor in the development and pathophysiology of CKD [140-142]. Dysbiosis was found to decrease gut barrier integrity that could lead to the dissipation of certain bacterial endotoxins and metabolites contributing eventually to uremic toxicity and progression of the disease [141]. In a study evaluating the alterations in gut microbiome compositions in MN and IgA nephropathy Dong et al. found various alterations in the compositions of the microbiome of MN patients when compared to healthy controls [140]. These alterations included the abundance of *Escherichia-Shigella* and proteinuria which displayed negative correlation to MN as well as *Bacteroides* and *Klebsiella* with similar correlation. Additionally in a study evaluating changes in microbiome and fecal metabolites in MN patients versus healthy controls, Shi and friends found that MN patients had lower microbiota richness and diversity [143]. Fecal metabolomics also highlighted that MN patients had lesser levels of tryptophan metabolism.

In a case presenting a 31-year-old man who had history of MN and chronic diarrhea, Zhou et al described a patient treated with tacrolimus for the nephropathy, which was initially beneficial however, the disease relapsed once the dosage of tacrolimus was tapered down [144]. Rituximab therapy thereafter caused no improvement. Ultimately, the patient was treated with two rounds of FMT resulting in increased serum albumin and total protein. Moreover, the levels of creatine, 24-hour urine protein and PlA2R antibody titers decreased significantly. Despite a lack of current research on FMT in MN, this therapeutic outcome alongside the previously established links with the gut microbiome led the authors to suggest FMT as a viable option in the arsenal of MN therapy and encouraged further research.

The impact of FMT in MN is thought to be via the promotion of Lachnospira species, a Gram-positive anaerobic bacteria, which possess immunomodulatory effects via the foxp3 gene and Treg cells [145].

7. Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is a chronic multifactorial autoimmune disease, primarily causing inflammatory arthritis alongside extra-articular involvement [146, 147]. A combination of genetic and environmental factors contributes to the pathogenesis of RA. Recently, about 100 genes have been described to be associated with RA, whereas factors such as smoking, microbiota, and infection are among critical environmental ones. Importantly, several studies have shown that RA patients have altered microbiota indicating a possible role of FMT in the therapeutic arsenal of RA [15, 148]. The dysbiosis seen in patients with RA was found to have specific bacterial lineages causing changes in the host immune profile and driving inflammatory responses. For example, a study enrolling 108 RA patients and 99 healthy control subjects investigated the correlation among intestinal microbiota diversity, cytokine levels, disease activity, and cluster of differentiation (CD)4+ T cell subpopulations [149]. The study showed that the diversity of intestinal microbiota was decreased in RA and the type of bacteria available affected the CD4+ T cell counts and cytokine levels all contributing to the pathogenesis of RA. Besides, mechanisms like molecular mimicry of autoantigens and the impairment of the intestinal mucosal barrier indicate a critical role of the gut microbiota in RA [150].

In terms of the application of FMT in RA, in a study analyzing the utilization of FMT obtained from healthy mice for the purpose of treating mice afflicted with RA, the authors observed that

FMT therapy positively augmented the composition and diversity of gut microbiome in RA mice. The study also displayed that FMT decreased the severity of arthritis in the affected mice [151]. Moreover, a 20-year-old patient with refractory RA was successfully treated with FMT indicating its potential as a therapeutic target [152]. The role of FMT in RA is suggested to be achieved via adjustments in autoreactive CD4+ T cells [153]. Likewise, mouse model studies linked TH-17 activation to RA development in mice which received Pre-RA feces [154]. Similarly, FMT therapy from mice with high magnesium diet was shown to reduce arthritis severity in mice and promote foxp3+ Treg, and IL-10-producing T cells [155].

8. Graft Versus Host Disease:

Graft versus host disease (GVHD) is an autoimmune reaction that takes place following hematopoietic stem cell transplantation (HSCT). HSCT is usually used as a therapeutic option in hematological malignancies such as leukemia and lymphoma. The concept behind the therapy is to utilize alloreactive donor lymphocytes that neutralize neoplastic cells; however, the alloreactive donor lymphocytes can target host cells causing an inflammatory condition known as GVHD [156]. On this subject, a balanced gut microbiome is paramount to maintaining a homeostatic immune system. This is achieved through various mechanisms including the production of certain metabolites such as SCFAs including propionate, butyrate, and acetate among others, which perform vital immunomodulatory functions [157]. Some of these functions include the ability of SCFAs to promote the synthesis of IL-10 by regulatory T cells which alongside IL-22 promote certain processes that result in enhanced gut barrier functionality [158-160]. Similarly, the gut microbiota plays an important role in the pathogenesis of GVHD. For

instance, during the first phase of GVHD, the conditioning therapy is accountable for tissue damage that results in the release of TNFα, IL-6, and IL-1 triggering the influx of APC [161]. Importantly, the use of antibiotics eliminates SCFA producing bacteria and hence worsening of GVHD is seen due to the lack of SCFA needed for maintaining intestinal integrity and inhibiting apoptosis of intestinal wall cells [159]. Furthermore, the gut microbiota of patients with GVHD is of poor diversity. Therefore, during the second stage, the host APC presents antigens to the donor T cells leading to further aggravation of the disease [162].

Based on that, FMT provides promising results due to growing evidence about the role of gut microbiota in the disease, as it basically reverses the imbalance in the composition of gut microbiota. Besides, most of the autoimmune diseases that showed improvement after FMT are characterized by a proinflammatory skewed immune response, hence proving its action as an immunoregulatory factor decreasing the vicious circle of the production of proinflammatory cytokines [163, 164]. Spindelboeck and friends reported the results of treating 3 GVHD patients with FMT [165]. All three patients clinically responded to FMT with one patient significantly improved microbe diversity following FMT sessions. In the same patients, the authors observed an improved clinical picture despite decreasing adherence to immunosuppressive medications. Another series reported a total of 4 patients with acute GVHD treated with FMT [166]. Three of the patients were steroid resistant. Nevertheless, 3 patients expressed complete responses while 1 displayed a partial response. Similarly, in a prospective study of 15 GVHD patients (either steroid dependent or steroid refractory) treated with FMT therapy, van Lier and colleagues demonstrated full remission in 10 patients, with 6 out of 10 patients were able to maintain remission [167]. Interestingly, the authors stressed that antibiotics utilization has been associated with FMT failure. Another phase II trial has tested the potential of FMT in preventing acute

GVHD [168]. After the analysis of pre- and post-FMT stool samples and the estimation of donor microbiota engraftment, microbiota network analysis revealed major rewiring as a potential mechanism of FMT effect. Based on the results, FMT, especially in patients with more severe microbiota disruptions, could have protective effects against acute GVHD. Besides, a cohort study reported 21 patient treated with FMT and the add-on of ruxolitinib as a salvage treatment in intestinal steroid-refractory acute GVHD (SR-aGVHD) after hematopoietic stem cell transplantation (HSCT) [169]. A decline in the inflammatory cytokines and T-cell and NK cells activation in addition to improved diversity of intestinal microbiota were demonstrated.

9. Sjogren's Syndrome:

Sjogren's syndrome is an inflammatory autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. Symptoms experienced in Sjogren's syndrome include dry mouth, difficulty swallowing, joint pain, and dry eyes, among others. Sjogren's syndrome occurs either as a primary disease or secondary in the aftermath of pathologies such SLE and rheumatoid arthritis, among others [170, 171].

When compared to healthy controls, both *Bacteroidetes* and *Proteobacteria* levels were found to be increased in Sjogren's syndrome patients while the levels of *Actinobacteria* and *Firmicutes* were shown to be higher in the gut microbiome [172]. Moreover, an entire collection of other microbiome alterations was found in patients with Sjogren's syndrome while these alterations lacked consistency and showcased variance among the different studies observed [61]. Watane et al. [173] conducted a study evaluating the response of 10 patients with immune-mediated dry

eyes for the treatment with FMT. The patients were 30% male, and the mean age of the selected patients was 60.4 years. Despite the fact that the recipients of FMT therapy showcased increased gut microbiome variability when compared to donors, half of the patients recruited for the trial reported alleviated symptoms. This led the authors to acknowledge the potential of FTM as a viable therapeutic option; however, the authors still emphasized that an optimum method for FMT administration has not been established yet.

By mechanisms, FMT in Sjogren's syndrome aims to retore the gut microbial imbalance that is causing an extensive communication with the innate immunity. Specific signaling molecules produced by the host cells and the gut bacteria leads to the activation of monocytes, macrophages, and innate lymphoid cells (ILCs) that lie the gut endothelial barrier [174, 175]. Meanwhile, the immune memory and tolerance are mainly regulated by the microbiome and tissue-resident dendritic cells (DCs). To maintain microbiota homeostasis, mechanism like FMT can promote healthy communication between gut microbiota and B-cells via IgA production facilitating the expansion of Foxp3+ regulatory T cells (Tregs) and the interaction with colonic regulatory CD4+ T cells [176]. In fact, interaction between gut bacteria and follicular helper T (Tfh) cells also contributes to microbiota homeostasis [177].

10. Type 1 Diabetes Mellitus:

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by a deficiency in insulin production as a consequence of antibody-mediated destruction of pancreatic beta cells [178]. The

pathogenesis of T1DM is influenced by a mixture of environmental and genetic factors [179-183].

Multiple studies have demonstrated links between T1DM and gut microbiota [184-186]. Such papers displayed higher and more balanced levels of butyrate-producing microbes in the gut microbiome of healthy individuals compared to patients with T1D. Moreover, T1D patients possessed lower levels of acetate and propionate relative to healthy controls [186, 187]. Unsurprisingly, FMT has showcased potential in treating T1DM in various aspects. FMT is established to restore levels of SCFAs which are crucial in regulating the progress of T1DM. This is especially important since SCFA-producing components of the gut microbiome were found to be decreased in mice afflicted with T1DM [188]. It is also important to know that the gut-brain axis contributes to changes in weight, mood, and insulin sensitivity, and FMT therapy can help in regulating this axis [189]. In a case report of a female patient with 8 year history of diabetes and hypertension compounded with poor glycemic control and diabetic neuropathy, the patient had improved glycemic control and noticeable alleviation of symptoms after FMT applied twice in three months [190]. Another case report of a 24-year-old patient diagnosed recently with T1DM suffering from malnutrition and gastrointestinal symptoms, FMT led to significant relief of the symptoms alongside better glucose control [191].

When viewed from a molecular aspect, recent study has emphasized the importance of gut microbiome dysbiosis and possible therapeutic effect of FMT on type 2 diabetes. The study included 8 control mice as FMT donors for 16 genetically diabetic mice [192]. Results were confirmed using several tests, for example analysis of the gut microbiome and serum metabolome was carried out by 16S ribosomal RNA sequencing and liquid chromatogram-mass

spectrometry, respectively. This in addition to immunohistology and clinical indicators testing which provided valuable data regarding the effects of FMT on the gut barrier and pancreas. Immunostaining was performed to confirm the beneficial effect of FMT on mucosal inflammation and gut barrier dysfunction [192]. Immunostaining of TNF-α and RT-quantitative PCR of interleukin (IL)- 1β, IL-6, IL-10 and TNF-α revealed significantly decreased levels of TNF-α and IL-6 but a significant increase in IL-10 [51]. Furthermore, FMT was shown to regulate peripheral blood immune cells [193]. These cells influence chronic inflammatory-associated insulin resistance which may be an important link between alterations in the gut microbiota and potential effects on the pancreas in diabetes [194]. Correspondingly, flow cytometric analysis, demonstrating the effects of FMT on circulating immune cells, revealed a reverse in the increased number of monocytes (CD45+, CD11b+, Ly6C+) in CD45+ cells of diabetic mice. Following FMT the circulating T lymphocytes in CD45+ cells in diabetic mice have increased but the CD4+/CD8+ was only modestly decreased. As a conclusion FMT ameliorates type 2 diabetes mellitus via metabolic remodeling of the gut microbiota with changes in intestinal epithelial, inflammation, and circulating immune cells [195-197].

11. Celiac Disease:

Celiac disease is an autoimmune disorder that presents with various symptoms including bloating, diarrhea, abdominal pain, weight loss, and ultimately malnutrition [198]. The disease can be controlled only by strict adherence to a gluten free diet [199]. In terms of etiology, celiac disease is caused by an autoimmune reaction to gluten and its metabolites resulting in damage to the small intestine manifesting as atrophy of the villi [77, 198]. Studies have suggested the role

of the gut microbiota in the pathogenesis of celiac disease [200]. Among others, external factors like the cesarean section, which highly affects the microbial composition of the intestine of the newborn, was proposed as well [201]. Moreover, increasing evidence has shown a positive correlation between early antibiotic use and the development of celiac disease [202].

As for gluten, the gut microbiota is known to play an active role in the metabolism of gluten; particularly, *Lactobacilli* and *Bifidobacterium* species are thought to catabolize gluten and its peptide resulting in alterations in its immunogenic potential [203, 204]. *Lactobacilli* are of particular interest due to their ability to neutralize gliadin and counter immunogenic peptides synthesized by *Pseudomonas aeruginosa* proteases. Furthermore, studies have highlighted microbiota dysbiosis in patients with persistent symptomatology despite appropriate adherence to long-term gluten free diet [205, 206]. The same studies underlined the importance of gut microbiota alterations in the active phase of the disease.

Cellularly, T-cells and B-cells are known to have a crucial role in mediating the immune response in celiac disease [207, 208]. Activated CD+4 T-cell stimulates B-cells to produce autoantibodies like anti-gluten, transglutaminase 2 (TG2) and anti-tissue antibodies that could induce changes in the cytoskeleton of enterocyte [209, 210]. Besides, T cells produce high levels of pro-inflammatory cytokines like IL-21 and IFN- γ through Th1 cells leading to exacerbation of intestinal inflammation, epithelial tissue damage, and finally villous atrophy in genetically predisposed hosts [211]. On the other hand, the increased production of IL-15 by stressed intestinal epithelial cells contributes to inflammatory lesions in the intestines by several mechanism including disturbing the integrity of the epithelial barrier and altering intestinal immune regulation. Additionally, IL-15 participates in the production of IL-21, the differentiation of T Reg cells, and stimulation of IFN-γ producing CD8 + IELs (intraepithelial

lymphocytes) [212]. IL-15 has been proposed to have anti-apoptotic effect, and natural killer group 2 member D (NKG2D) ligand expression on intestinal epithelial cells in refractory celiac disease [213]. Therefore, FMT by altering the composition of the microbiota may also alter the immune response by T-cells, B-cells and specific cytokines resulting in improvement of both clinical and histological consequences of celiac disease [214].

Interestingly, a 68-year-old patient with celiac disease who suffered three recurring episodes of *Clostridium difficile* infection despite receiving various treatments, underwent FMT after the third episode [215]. The symptoms of the patient improved dramatically within 2 weeks. Following FMT, intestinal biopsy displayed full recovery 6 months after the initial treatment.

12. Myasthenia Gravis:

Myasthenia Gravis (MG) is an autoimmune disease characterized by muscle weakness and fatigue caused by autoantibodies damaging the neuromuscular junction [216]. Around 70 to 80% of patients with MG were found to possess acetylcholine receptors (AChR) antibody titers that correlate with disease severity. Anti-AchR antibodies are important in the sense that its production is an outcome of the imbalance of Th17 and Treg cells. This allows the restoration of the Th17/Treg balance to serve as a potential avenue for MG therapy.

Studies evaluating the role of the gut microbiome in MG patients found low diversity of the microorganisms [217, 218]. Moreover, the levels of SCFAs were found to be lower in the feces of MG patients. This is both a result of the disturbances of the microbiome and the observation of a lower *Firmicutes*/*Bacteroidetes* ratio which correlates to lower SCFA production [218, 219].

Extensive data indicated the imbalance of T-cell subtypes (Th1, Th17, and Treg cells) are involved in MG though a complex process among these cells and their cytokines [220]. An unwanted increase in Th1 and Th17 in addition to a decrease in the useful Treg cells was detected in the peripheral blood of patients with MG in comparison to healthy individuals [221]. For example, Th1 cells produce pro-inflammatory cytokines like IFN-γ and IL-2 that amplify the immune response and activate antigen-presenting cells. Also, Treg cells increase anti-inflammatory cytokines such as TGF-β and inhibit the function of other activated T cells [222]. Frequency and function of Treg cells were shown to be impaired in MG patients, which was accompanied by down-regulation of Foxp3 expression and showed inverse relationships with clinical symptoms [223].

In a mouse model study, Zheng et al. found significant differences in the gut microbiota compositions and concluded that these differences can be used to distinguish MG mice from healthy controls [224]. The study also found that mice with healthy gut microbiome could walk longer distances than those with dysbiotic microbiota. Another animal study used astragaloside IV (AS-IV) treated mice's feces in MG mice showcased that mice who were transplanted feces from other mice treated with AS-IV significantly alleviated myasthenia symptoms, reduced Th1 and Th17 cells levels in the spleen and thymus, and increased Treg cell levels in the spleen [225]. It was hypothesized that beside alleviating the symptoms of MG, AS-IV might affect the expression of T cells and influence the composition of intestinal flora, therefore affecting the progression of MG disease, which may contribute to the clinical application of AS-IV in the prevention and treatment of MG.

13. Psoriatic Arthritis:

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis with heterogeneous clinical features complicating psoriasis in about 20% of the patients [226, 227]. The role of the gut microbiome in the pathogenesis of the skin, joint, and gastrointestinal involvement of psoriatic arthritis has been investigated for years ending with several theories. Among others, the imbalance of short and medium chain fatty acid-producing bacteria and altered immune homeostasis have been proposed [228]. Targeting dysbiosis of the intestinal microbiota by FMT has been the study of interest recently. While the gut microbiota can mediate both pro- and anti-inflammatory responses, the potential to play a significant role in the pathogenesis and treatment of PsA [229, 230], is not surprising.

In an exploratory randomized placebo-controlled trial studying the safety and efficacy of FMT as a novel treatment for active peripheral PsA, 26-week clinical evaluation demonstrated no adverse events [231]. A more recent study on the effect of FMT on 92 inflammation associated plasma proteins in PsA has been conducted. In the study, 31 patients with moderate-to-high peripheral PsA disease activity were included in a 26-week, double-blind, randomized-controlled trial [232]. A significant change among 26 serum proteins between PsA and healthy control was observed. PsA showed an elevation in IL-6, CCL20, CCL19, CDCP1, FGF-21, HGF, interferon-γ (IFN-γ), IL-18R1, monocyte chemotactic protein 3, and IL-2. On the other hand, FMT notably affected 12 proteins (tumor necrosis factor (TNF), CDCP1, IFN-γ, TWEAK, signaling lymphocytic activation molecule (SLAMF1), CD8A, CD5, Flt3L, CCL25, FGF-23, CD6, caspase-8). Mainly IFN-γ, Axin-1 and CCL25 were positively affected by FMT while CCL19 and IL-6 were negatively affected. Altogether, the changes seemed to alter disease severity and might contribute to improve outcomes.

Conclusion:

The implication of FMT in the presented autoimmune diseases, among others, is promising. While the association between infection and autoimmunity, or microbiome and autoimmunity, is based upon the etiology, pathogenesis, and exacerbations of autoimmune diseases, viewing FMT as a pathogenetic-based therapy seems unsurprising and encouraging. As shown, the effects of FMT in autoimmune diseases vary from positive to significantly beneficial depending on the disease it was applied for. Moreover, as the side effects of FMT are minor, the clinical implications of FMT in autoimmune diseases can have favorable outcomes when compared to immunosuppressants with all the profile of adverse events. Nevertheless, and as the case in all diseases when it comes to therapeutic models, particularly new ones, more investigations are needed. Clinical studies, preferably randomized and double-blinded, should be conducted and evaluated appropriately in order to allow for clear indications and firm protocols for treatment to be established.

Declaration:

The authors declare no conflict of interests.

Authors' contributions:

Isa Seida – Writing original draft.

Maisam Al Shawaf - Writing original draft.

Naim Mahroum – Supervision, writing, and editing.

Figures:

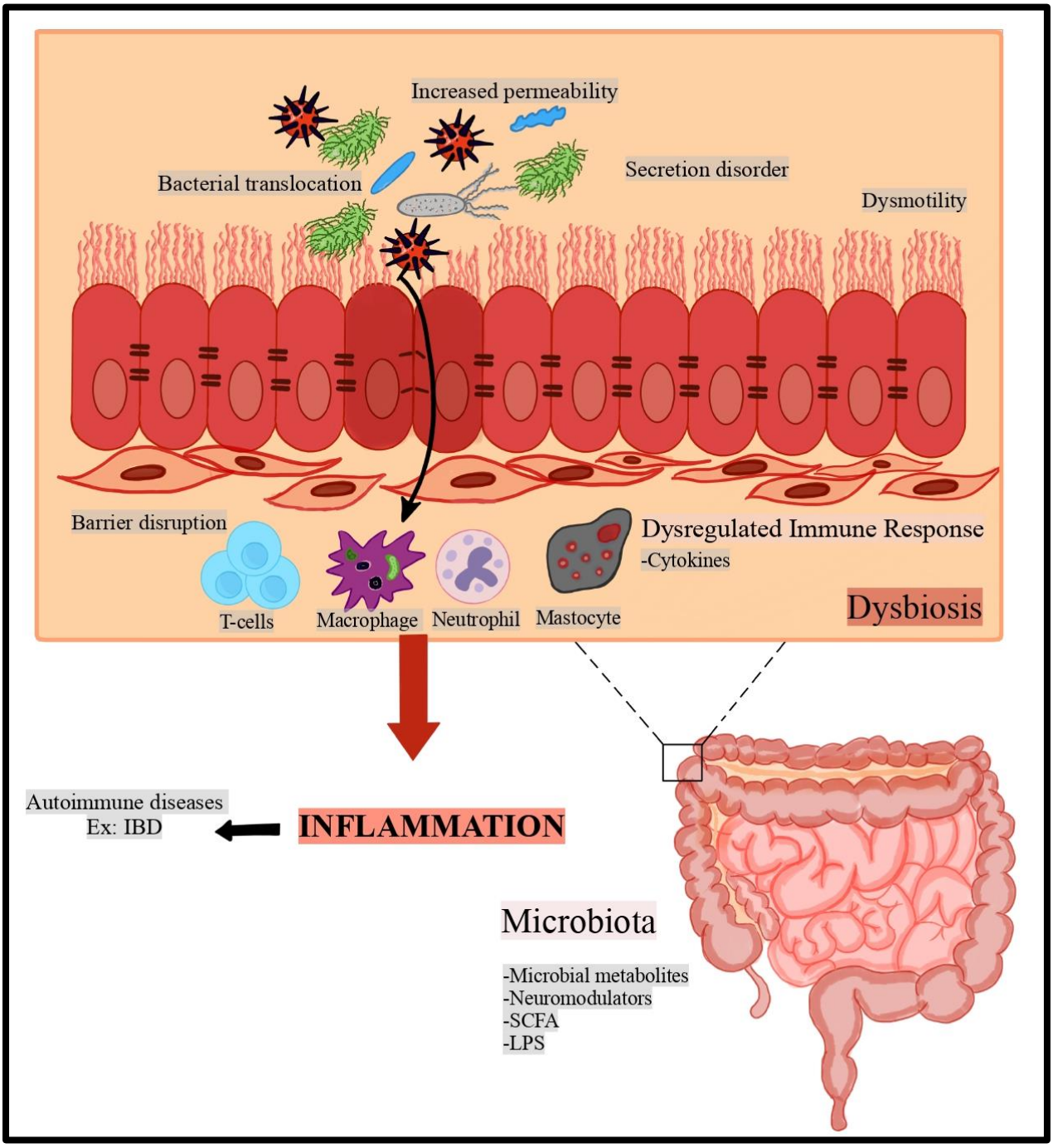

Figure-1: The figure illustrates the pathophysiology behind the connection of microbiome to autoimmunity. Gut dysbiosis and the dysregulated immune response play a major role in autoimmune diseases.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: