REVIEW ARTICLE

Autoimmune Diseases and Gut Symbionts: The Unpopular Liaison

S Zulkafli Nor Effa1, Shou Jin Phang1,2, Hajar Fauzan Ahmad3

1 Regenerative Medicine Cluster, Advanced Medical And Dental Institute, Universiti Sains Malaysia, Bertam, 13200, Kepala Batas, Penang.
2 Inflammation, Immunology And Immunotherapy Division, Institute Of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, Ne2 4hh.
3 Faculty of Industrial Sciences And Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak, 26300 Gambang Kuantan Pahang Darul Makmur

ABSTRACT

In the past few years, compelling data have shown the potential crosstalk between dysbiosis of gut microbiota (GM) and impairment of systemic immune system. Since then, ideas on how GM partake in autoimmune conditions was put forward. Although genetic variability have been proven to contribute towards the pathogenesis of autoimmune conditions, epigenetics control have gained interest among researchers. Current review highlights the crosstalk between autoimmune conditions and GM and its potential regulatory mechanisms. Convincing data from existing literature help in paving ways for more well-defined species in the future studies. The studies should focus on identifying the distinct species involve in different types of autoimmune diseases and their definitive role in autoimmunity. Ultimately, these data can be used for the advancement of therapeutic approach in personalized medicine.

Keywords: Autoimmune disease, Immunity, Gut microbiota, Probiotics, Microbiome.

Corresponding Author:
Nor Effa S. Zulkafli, PhD
Email: effa@usm.my
Tel: +604-5622041

INTRODUCTION

The immune system of vertebrae provides systematic approach to combat insults from the inside and outside the body. When immune system go awry, deregulated immune response may result in autoimmunity, a condition where the immune cells destruct body own cells. The pathogenesis of autoimmune condition is multifactorial where genetic predisposition and epigenetics regulation herald changes into uncontrolled immune responses, giving rise to the formation of autoantibodies damaging one’s own cell. The presence of pathogenic autoantibodies are highly specific in organ-specific autoimmune diseases such as thyroiditis, type 1 diabetes and primary biliary cirrhosis. Whereas in systemic autoimmune diseases like systemic lupus, the production of autoantibodies is less specific and directed against multiple organs (1).

Interestingly in recent years, it has becoming a common notion that host immunity has co-evolved with the GM due to their long co-existence mutualistic relationship; and this justified the homeostasis between these components are fundamental to both the gut integrity and healthy immune system. The first step towards understanding the symbiotic relationships of the GM with their hosts is to characterize these community at baseline healthy and disease states (2). Mounting evidences suggested that dysbiosis - an imbalance or maladaptation of gut microbiome communities would affect the host bodily functions. Perturbations in gut microbiome have now been linked with disease states such as cardiovascular disease (3, 4) obesity (5, 6) several type of cancers (7, 8) and inflammatory bowel disease (9).

ESSENTIAL MICROBES IN HUMAN HEALTH MAINTENANCE

Overall temporal stability of the core microbial community within healthy individuals conferred health benefits relating to pathogen protection, host metabolism, immune modulation, and food digestion and nutrient absorption (2, 10) However, a number of factors including decline in the physiology of the gastrointestinal tract due to ageing, antibiotic exposure, diet, and environmental factors can cause changes in composition as well as function (11, 12). Furthermore, dysbiosis observed in autoimmune diseases is associated with inflammation during infection, reduced bacteria function and diversity, bacterial translocation, impaired epithelial barrier, and declined regulatory T cells in the gut mucosa (13). Hence, gut microbiota and their
metabolites could regulate immune cells and cytokine release via epigenetic modifications, suggesting their possible role in autoimmune disease development (14). Understanding how the GM affect health and disease requires a shift in focus from individual pathogens, towards an ecological approach considering the community as a whole. Mounting studies showed that manipulating GM via probiotics and prebiotics interventions could be useful to improve immunity in humans and animal models. To this end, is therefore logical that modulating the gut microbiome should be considered as a therapeutic strategy to treat the diseases via supplementation with probiotics (14, 15, 16, 17), the diet or the use of prebiotics (18). Remarkably, polyphenol-enriched diet modulates mucosal immune responses (19) and dietary cinnamaldehyde enhances acquisition of specific antibodies in animal studies (20). Moreover, reconstitution of bacterial populations by fecal transplantation or by employing antimicrobials to eliminate pathogens or manipulate the GM in a way that will benefit host health (21).

CROSstalk of GM on Immune System

The fact that bacteria in the gut interact with the host immune system is now well accepted and illustrated by in vitro and in vivo experiments. And this has becoming progressively supported by human intervention trials (22). The symbiotic relationship provides beneficial outcomes to the host by metabolizing ingested nutrients, drugs and substances, maintenance of gut mucosal microenvironments and protection against pathobionts. Also, they produce beneficial outcome to the host by fermentation and digestion carbohydrates into absorbable short-chain fatty acids (SCFAs), vitamin synthesis as well as regulating the gut-associated immune cells (14). GM are essential for the complete development of the immune system, representing a binary network in which the microbiota interact with the host, providing important immune and physiologic function and conversely the bacteria protect themselves from host immune defence (23). Thus, GM play an important role in maintaining normal function of systemic immune system by regulating gut immune system as described in Figure 1.

Bassaganya-Riera and colleagues have demonstrated the manipulation of gut probiotics and their metabolites has potentially alleviates IBD in mouse models (24). In a randomized control trial performed among colicky infants, oral supplement of Lactobacillus reuteri for one month have reduced the crying time as opposed to placebo by reducing Th17 cells and promoting Foxp3+ cells thus suppressing inflammatory reactions (25). In fact, previous work has attested that the metabolism of GM modulates serotonin-producing cells which in turn regulates gastrointestinal physiology (26). These metabolites are further appraised as immune regulators shown by induction of tolerance in food-allergy models (27) and improved gut symbionts in children with anti-islet autoantibody (28). Interestingly, supplement of probiotics in addition to breastfeeding has improved the composition of GM in infants treated with antibiotics and caesareaen-birth infants by restoring the microbial metabolic capacity of bifidobacteria (29). This significantly contribute to better immune function in compromised caesareaen-birth infant as they are prone to develop metabolic diseases and autoimmunity (30,31).

Meanwhile, oral tolerance induced by GM controlled the development of food allergy in mice models fed with high-fibre diet (27). It was shown that the levels of CD103+ dendritic cells (DC) is higher in allergy-induced mice fed with high-fibre diet as opposed to zero-fibre diet (27). Modulation of 103+ DC is important as they possess the capacity to induce naïve T cells into iTreg cells in MLN to minimize adverse pro-inflammatory responses (32). Moreover, microbial metabolites repertoire has recently been compiled thus intrigued researchers to further investigate their roles on the immune system. One of the compounds that recently came to limelight are tryptophan-derived metabolites which is known to be the ligand for aryl hydrocarbon receptor (AHR). Activation of AHR leads to the activation of anti-inflammatory responses via IL-22 signalling pathway (33, 34). On more detailed understanding as how GM regulate host immune functions, although not many, a few studies have already revealed molecular mechanisms involved in mediating immune responses in animal models. One of the proposed mechanism is via G-protein coupled receptor 43 (GPR43) on epithelial cells and GPR109a on immune cells which serve as receptors for SFCA. Binding of GPR43 receptors to SCFA produced by GM alleviated colitis and allergy in mouse models, suggesting the metabolite of GM as one of mediators in immune regulation (27, 35). A study revealed the capacity of GM to regulate distant organs

![Figure 1: Gut microbiota modulates the intestinal immune homeostasis by their metabolites. CD103+ DCs resides in the lamina propria interact with CX3CR1+ macrophages which are capable to reach up for antigens in the lumen and presenting them to the DCs for activation. Activated CD103+ DCs will further activate T cells including its subset Foxp3+ T-regulatory (Foxp3+Treg) cells. Interaction between CD103+ DCs and Foxp3+ Treg cells is important to determine the tolerance levels to certain food antigens. Thus, depending on the levels of activation and exposure of particular antigens, the interaction between CD103+/Foxp3 Treg cells will eventually lead to peripheral tolerance via IL-10 mechanism.](image.jpg)
GM INVOLVEMENT IN AUTOIMMUNE CONDITIONS

A healthy immune system is essential for mounting an effective immune response against foreign antigen in order to eliminate any potential pathogenic infection but still remain tolerant against autoreactive immune cells. However, autoimmune diseases are established when immune tolerance is breached by overexuberant and unwanted immune responses, which may contribute to a lower quality of life and raise health concern. In fact, recent epidemiological data have suggested that the incidence and prevalence of autoimmune diseases is increasing worldwide (50), which provide an insight that environmental factors (e.g., dietary changes and overuse of antibiotics that leads to dysbiosis) might be more important than we initially thought in the pathogenesis of autoimmune disease. In this review, we aimed to highlight the effect of the gut microbiota in autoimmune disease pathogenesis by summarising data from both murine models and human case study.

Probably the most puzzling part is how GM controlling intestinal regulation may affect systemic immune response and organ-specific autoimmune diseases. Indeed, with trillions of GM in adult human, it is possible that any changes in the gut composition or function may alter immune responses in host physiology (24). When SCFA production by gut microbiome are altered as a result of dysbiosis, the intestinal barrier may be disrupted and permeabilise the intestinal epithelium, leading to infiltration of bacteria into the mesenteric lymph node (MLN) (27, 36, 51). As a result, the intestinal dendritic cells at the surface mucosa is activated more frequently (due to more bacteria breaches the intestinal barrier) and more T cells are differentiated, which would result in the over reactivity T cells for the establishment of autoimmune conditions (33, 36). Indeed, the leaky gut hypothesis propose that bacterial translocation could be potentially increased, leading to elevation of cross-antigen presentation between self and nonself-antigen recognition and result in the exacerbation of extra-intestinal autoimmune diseases like T1D, SLE and atopic dermatitis (36, 51, 52, 53, 54, 55) (Figure 2).

The existence of gastrointestinal-related autoantibodies in different types of autoimmune diseases may suggest the crosstalk between GM regulation and onset of autoantibodies formation. The most studied GI-related antibodies include anti-gliadin antibodies (AGA) and anti-tissue transglutaminase (TTG) antibodies. These autoantibodies formation. The most studied GI-related antibodies include anti-gliadin antibodies (AGA) and anti-tissue transglutaminase (TTG) antibodies. These
antibodies have been titred in patients with multiple sclerosis (56, 57, 58) and inflammatory myopathies (59). This in fact is shown clinically by celiac disease (51). Furthermore, the putative role of gut microbiome in structuring autoimmunity has been demonstrated by Wu and colleagues (2010) on segmented filamentous bacteria (SFB) as a general immunomodulator in which enhance the establishment of autoimmune arthritis (75) and EAE (76), albeit protecting from T1D pathogenesis (77). Notably, a germ-free, IL-1 receptor antagonist deficient (GF IL-1Rn−/−) mouse model that represent a spontaneous T-cell mediated arthritis failed to develop autoimmune arthritis but subsequent mono-colonisation of Lactobacillus blifidus are able to restore the disease (75, 78). Another reports have shown that three microorganisms, including Dialister invvisus, Gemella sanguinis, and Bifidobacterium longum, are correlated with compromised gut integrity and higher intestinal permeability eventually elevated T1D risk (71,72,79,80). Nonetheless, Tryptophan (Trp) metabolism by GM (e.g. Clostridium sporogenes, Bifidobactera infantis and Lactobacillus reuteri) can also contribute to the homeostasis of intestinal immune activation and also tolerance (81). Similarly, Lactobacillus reuteri modulate inflammation at different body sites (intestinal and extraintestinal) by regulating the microbiota-adenosine-inosine receptor 2A (A2A) axis and alleviating the pro-inflammatory Th1 and Th2 cell differentiation in Scurfy model to resemble SLE in human (82). Altogether, these studies propose that our gut microbiome is one of the dictators in shaping autoimmune diseases outcome and further investigations are required in order to explore the microbiota/immunity crosstalk thoroughly (83).

CONCLUSION

Compelling data have shown that GM are closely liaised with various types of autoimmune diseases in the form of dysbiosis- alteration of individual species and/or global communities of the GM (dysbiosis) which can give rise to different outcomes of autoimmune conditions. Certainly, gut microbiome could possibly be applied as a biomarker for autoimmune diseases prediction. Furthermore, the knowledge can also be manifested into probiotics enhancement as precision editing of GM may be utilized to reverse autoimmune conditions.

Besides, an association between dysbiosis and IBD has also been reported earlier in murine model by Nagalingam and colleagues (73). The interrelationship between RA and celiac disease (CD) suggesting the potential crosstalk between gut-joint pathogenesis (74). GM composition of buccal mucosa from pSS patients are distinctly different with healthy control in such that the microbiome of pSS patients consist of a higher Firmicutes/Proteobacteria ratio when compared to healthy control (54). Similarly, in induced-dysbiosis of pSS mouse models have shown a reduction in the microbiome diversity and accelerate the establishment of autoimmune mucosal inflammation. In specific, the stool samples from antibody-treated mice have shown a reduction in Clostridium genus while a pilot study involving pSS patients also shown a significant loss in Faecalibacterium among the fecal microbiome (54).
modulators during their “transit” stay in the gut. Furthermore, prescription of lactobacillus probiotics in some circumstances may be unfavourable in infants, leading to the progression of D-lactic acidosis (84). These results have shed light into considerations of administrating the same probiotics regimen into human body as “one probiotic will not fit all”. Therefore, further researches are much needed in order to delineate the optimal choice of probiotic composition for each disease entity studies.

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