



Review

Microbiota at the crossroads of autoimmunity

Oded Shamriz^a, Hila Mizrahi^b, Michal Werbner^b, Yehuda Shoenfeld^c, Orly Avni^{b,*}, Omry Koren^{b,*}^a Pediatric Division, Hadassah-Hebrew University Medical Center, Ein Kerem, POB 12000 Kiryat Hadassah, 91120 Jerusalem, Israel^b Faculty of Medicine, Bar-Ilan University, Henrietta Szold 8, Safed 1311502, Israel^c Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to the Sackler Faculty of Medicine Tel-Aviv University, Tel-Aviv, Israel

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ABSTRACT

Autoimmune diseases have a multifactorial etiology including genetic and environmental factors. Recently, there has been increased appreciation of the critical involvement of the microbiota in the pathogenesis of autoimmunity, although in many cases, the cause and the consequence are not easy to distinguish. Here, we suggest that many of the known cues affecting the function of the immune system, such as genetics, gender, pregnancy and diet, which are consequently involved in autoimmunity, exert their effects by influencing, at least in part, the microbiota composition and activity. This, in turn, modulates the immune response in a way that increases the risk for autoimmunity in predisposed individuals. We further discuss current microbiota-based therapies.

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1. Introduction

The incidence of autoimmune diseases is estimated at 3–5% worldwide [1]. Autoimmunity is known to have a genetic component [2,3];

* Corresponding authors at: Faculty of Medicine, Bar-Ilan University, Safed, Israel.
E-mail addresses: Orly.Avni@biu.ac.il (O. Avni), Omry.Koren@biu.ac.il (O. Koren).

however, concordance rates of autoimmune diseases in monozygotic twins are incomplete, ranging between 12 and 67% [2], indicating a multifactorial etiology. In addition, the differences in autoimmunity incidence rates in different ethnic groups and geographical locations suggest the involvement of environmental factors. Lifestyle, exposure to infection, and nutrition, were all previously implicated [4]. Recently, the critical involvement of microbiota in health, as well as in many diseases including autoimmunity, is gaining attention [4]. Accumulating evidence suggests that the microbiota can be affected by both the environment and genetics, while subsequently influencing the human body with critical implications to our wellbeing [4].

The human microbiome is the genomic collection of the entire repertoire of human-associated microorganisms, the microbiota. Our microbiota account for 1–2 kg of our body weight, and is estimated to outnumber our own cells by an order of magnitude, and our genetic content by two orders of magnitude [4]. The largest microbial community is found in the gut, especially in the large colon where 100 trillion microbes reside [4]. On a day-to-day basis, this symbiosis is beneficial in activities including digestion of nutrients, xenobiotic degradation, vitamin production, and protection from pathogens [4].

At times, homeostasis is disturbed, and changes in microbial composition and diversity occur; these shifts are termed dysbiosis. Dysbiosis, especially in the gut, has been linked in recent years with disease states, but a direct causal relationship cannot be determined in every case. One of the first examples linking microbiome composition and disease occurs in obesity, in which an increased ratio of members of the Firmicutes phylum versus members of the Bacteroidetes was observed in both humans and mice. Moreover, in fecal microbiota transplantation (FMT) to germ free (GF) mice (raised under sterile conditions), the mice receiving the “obese” gut microbiota gained more body fat than mice administered microbiota derived from lean gut [5,6]. Besides obesity, changes in microbiota profiles have also been linked to a growing list of diseases such as metabolic syndrome [7], diabetes [8] and malignancy [9]. This connection was also demonstrated in autoimmune diseases, including systemic lupus erythematosus (SLE) [10], rheumatoid arthritis (RA) [11], inflammatory bowel disease (IBD) [12], psoriasis [13], multiple sclerosis (MS) [14], celiac disease [15], and Bechet’s disease [16].

In this review, we describe evidence connecting microbiome dysbiosis with autoimmunity; we discuss the potential indirect effects of genetic and environmental factors on autoimmune pathogenesis through their effects on microbiota composition and activity.

2. Methodology of microbiome analysis

Our understanding of the microbiome has increased tremendously due to a series of technical advances. Culture-based methods support growth of less than 1% of the entire microbial communities under laboratory conditions, whereas next generation sequencing (NGS) techniques allow characterization of entire bacterial communities without requiring any growth in culture. This process classifies bacterial members based on sequencing of conserved regions of the versatile bacterial 16S rRNA gene, amplifying them using universal bacterial primers (Fig. 1), followed by sequencing and bioinformatic analysis to identify the species present and their relative abundance. Whole genome shotgun sequence analysis further facilitates the identification of microbial genes, and metatranscriptomics provides an understanding of some of the functions carried out by these communities [17]. These techniques are complemented by two relatively new methods, metabolomics and metaproteomics, which identify the metabolites and proteins of the microbiome, respectively (Fig. 1).

These advances in technology have enabled the characterization of the composition of the healthy microbiome, and identification of alterations in disease states. The two major sequencing efforts are concentrated at the National Institutes of Health (NIH) Human microbiome project [18], and The Metahit project [19]. However, with the increased recognition of the numerous factors influencing microbial composition

including geography, diet, and age, recent years have witnessed more defined sequencing projects dissecting distinct populations; these include The American Gut, The British Gut, and Eldermet (the elderly microbiota) [20]. Although the microbiome also contains viruses, Archaea, and Eukaryotes, we focus here specifically on the bacterial component.

3. Microbiota composition and autoimmune diseases

The immune system, which co-evolved with the microbiota, has a complex challenge, on one hand inducing and maintaining tolerance to indigenous bacteria, while on the other hand, being able to initiate an effective immune response against potential insults from commensals, pathobionts (normally symbiotic, but pathogenic in the context of dysbiosis), and external pathogens when crossing the epithelial barriers [21,22].

While the function of the immune system impacts microbial inhabitation and activity, as indicated by models in which the activity of the immune system is compromised (see below) [23–26], the microbiota, in turn, modulates the development and tunes the function of innate and adaptive immunity, as demonstrated in models including germ free (GF) mice [27–29]. For example, presence of the microbiota is required for the expression of nucleotide-binding oligomerization domain 2 (NOD2) [30] and activity of NLRP6 [31], both associated with the innate arm of the immune system, necessary for bacterial recognition. The presence of microbiota also affects adaptive immunity, including peripheral differentiation of T helper (Th) cells, especially of T regulatory (Treg) and T helper 17 (Th17) cells [32]; certain *Clostridia* species are associated with increased numbers of Treg cells in the mouse colon [33], while segmented filamentous bacteria (SFB) promote the development of Th17 cells in mice [34]. Some of the mechanisms by which the bacteria shape the functions of the immune system are starting to be revealed, and include the following findings [35]: (i) metabolic products generated from dietary substrates such as short chain fatty acids (SCFAs), continuously regulate the innate and adaptive immune function; for example, butyrate regulates macrophage function, and induces differentiation of Treg cells [36,37]. (ii) Some bacterial metabolites have an immunomodulatory effect; the product of several strains of *Bacteroides fragilis* (*B. fragilis*), the zwitterionic polysaccharide A (PSA), has anti-inflammatory activities, acting through the Toll-like receptor (TLR) 2. (iii) Microbiota-modulated host metabolites can impact the activity of immune proteins; for example, the microbial-modulated bile acid component activates the NLR6 [31]. When the homeostasis-maintaining dialog between the microbiota and the immune system is harmed, as a consequence of external or internal cue-induced dysbiosis or immune dysfunction, uncontrolled inflammatory conditions or breakage of the delicate tolerance towards microbiota can initiate or promote autoimmunity. There is increasing evidence for the key role of the gut, oral and skin microbiota in the pathogenesis of systemic and organ-specific autoimmune diseases, as we will describe below.

3.1. Gut microbiota

The adult gut is home to more than 1000 bacterial species [38] belonging to the four major phyla, Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria, and additional phyla such as Cyanobacteria, Fusobacteria and Verrucomicrobia [39]. Despite the fact that the fecal microbiome is often chosen as a representative sample of the gastrointestinal microbiome, we know today that the microbiome varies quite dramatically along the gastrointestinal (GI) tract (stomach, small intestine and large intestine). The stomach, which is the most acidic part of the GI tract, was believed for a long time to be germ free, until the discovery of *Helicobacter pylori* changed this paradigm [40]. Today, we are aware of the existence of a stomach microbiota (with the lowest microbial biomass in the GI tract) including members of all four major phyla, with *Streptococcus* being the predominant genus, and the other characteristic genera including

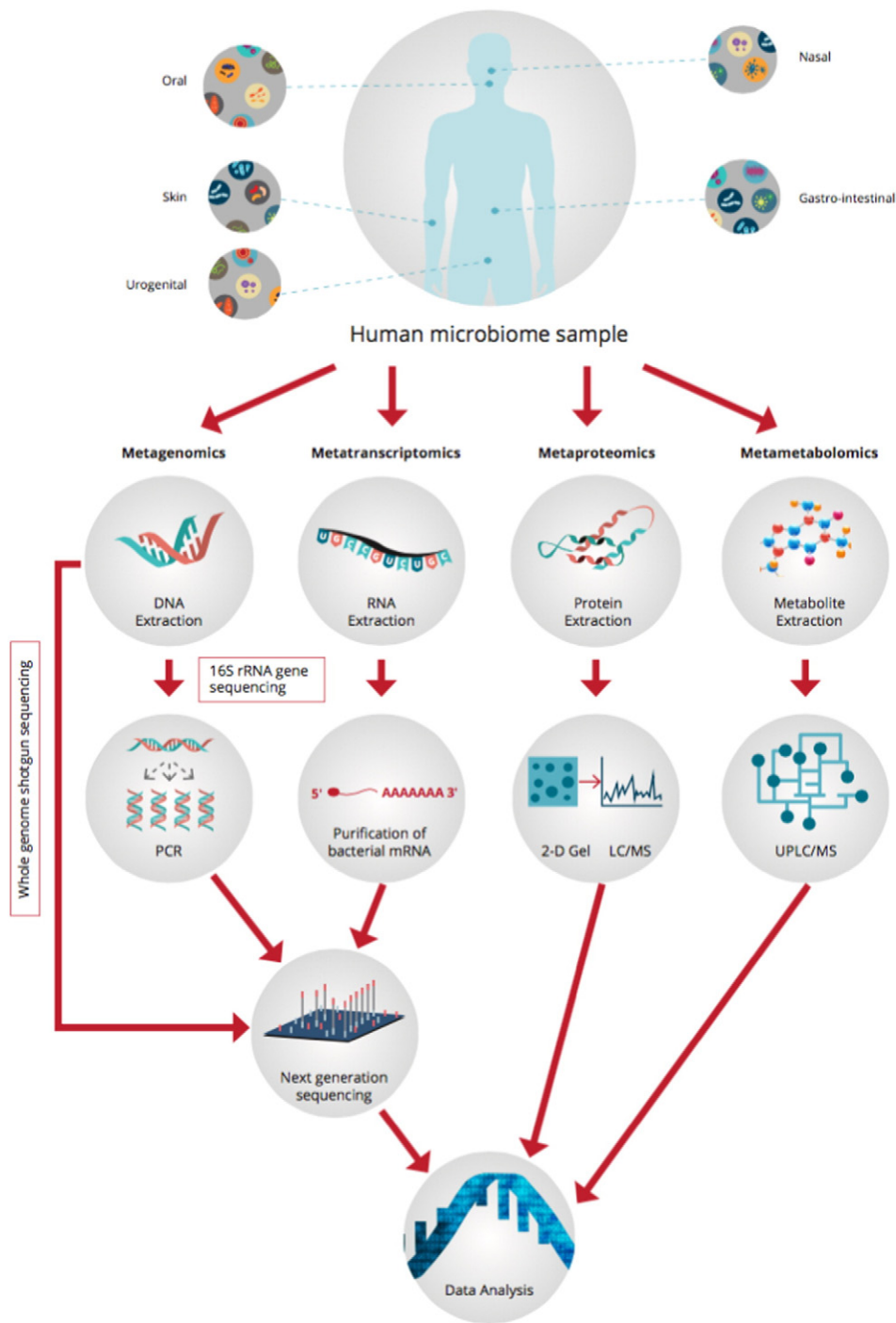


Fig. 1. Methods facilitating analysis of the microbiome composition and activities. See text for more details.

Lactobacillus and *Propionibacterium* [40,41]. The small intestine, where most nutrients are absorbed, is the most poorly characterized section of the GI tract due to difficulty of sampling. Studies have reported a quite variable small intestine microbiota even within individuals over time, but *Streptococcus* and *Veillonella* were consistently detected [42]. The large intestine is home to the densest bacterial community in the GI tract, and is the site at which undigested dietary compounds are fermented to SCFA by the microbiota [43]. The large intestine microbiome is composed of five major phyla, Firmicutes, Bacteroidetes, Verrucomicrobia (mainly the genus *Akkermansia*), Proteobacteria and Actinobacteria [44]. Dysbiosis of the gut microbiota is associated with several disease

states including inflammatory bowel disease – characterized by inflammation at the first barrier line of defense, as well as with many illnesses at more distal sites, including other systemic and organ-specific autoimmune disorders.

IBD, a chronic relapsing inflammation of the GI, comprises ulcerative colitis (UC) and Crohn's disease (CD). While UC is confined to the colorectal region and to the mucosal layer of the GI tract, and is thought to result from dysregulation of the intestinal immunity involving Th2 cytokines, CD is usually transmural and can occur in any region of the GI tract, from the oral cavity to the rectum, and can be related to the over-expression of Th1 cytokines. Other distinctive histological and clinical

characteristics can be found in each disease, although some overlap between the two exists [45–49].

The association of gut microbial dysbiosis with IBD pathogenesis is well established, and is reflected by reduced bacterial diversity, especially of bacteria with anti-inflammatory functions such as *Faecalibacterium*, and in increased levels of *Enterobacteriaceae*, as *Escherichia coli* (Fig. 2) [50]. More than 160 gene variants that confer susceptibility to IBD were identified in genome-wide association studies (GWAS), including variants affecting the innate and adaptive immune system [51–54], indicating that the activity of both arms of immunity is important for maintaining gut homeostasis.

Several murine models with deficiencies in innate and adaptive immune receptor signaling are characterized by altered microbial composition [26]. For example, T-bet $-/-$ Rag2 $-/-$ mice have altered microbial communities, which cause UC when transferred into genetically intact mice in cross-fostering experiments [35,55]. Deficiency in inflammasome components also increases the susceptibility to intestinal inflammation by induction of ‘colitogenic’ (tending to induce colitis) dysbiosis [26,56,57]. In this case, similarly to the above example and other murine models of disease-promoting dysbiosis, transfer of the dysbiotic microbiota into a wild type host harboring a normal microbiome, transfers susceptibility to the disease [31]. These examples suggest that lack of a competent immune response results in impaired regulation of microbial proliferation and/or virulence. This, in turn, reshapes the microbial communities and their functions, with harmful consequences for the host. Therefore a constant, evolutionary-shaped

interactive dialog between the host and its microbiota is necessary for their long-term partnership.

3.2. Oral microbiota

Over 700 bacterial species were identified within the oral cavity [58]; hence, the oral cavity ranks second in total microbial diversity of sites in the human body [59]. Within the oral cavity, the microbiota is found on the tongue, buccal folds, buccal mucosa, hard palate, soft palate, gingiva, tonsils, saliva and tooth surface [60]. The human microbiome project reported that despite the differences in abundances, the majority of sites sampled in the oral cavity contained *Streptococcus*, *Veillonella*, *Prevotella* and *Haemophilus* [18]. In addition to these genera, the gingival plaque samples predominated with the genus *Corynebacterium* [18]. Changes in the oral microbiome were found to be associated with several diseases including oral squamous cell carcinoma, atherosclerosis, bacteremia and RA [58]. RA is one of the most common forms of inflammatory arthritis affecting tens of millions of people worldwide [61,62] and is associated with progressive disability, systemic complications and early death [63].

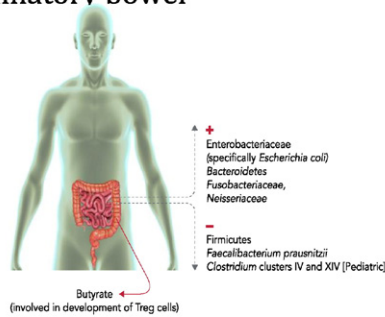
The etiology of RA remains elusive, and includes both genetic and environmental features [64]. Dysbiotic intestinal microbiota is associated with RA (Fig. 2), and is found in genetically RA-susceptible murine models [65]. The notion that oral commensals are also involved in initiation or driving of RA progression is supported by the high occurrence of periodontal inflammatory disorders in RA patients [66]. Patients with new-onset of RA exhibit a high prevalence of periodontal disease at disease onset, despite their young age [67]. The microbiota of the subgingival biofilm from these patients was found to be similar to that of patients with chronic RA. About half of untreated new-onset RA patients, carry *Porphyromonas gingivalis* (*P. gingivalis*), twice the prevalence in healthy individuals [68]. Moreover, an association between RA-related auto-antibodies and serum antibody titers against *P. gingivalis* was demonstrated in healthy first degree relatives of patients with RA, suggesting that an immune response to *P. gingivalis* may play a role in early onset of RA-related autoimmunity [67,69]. The mechanism underlying this association may involve post-translational modifications of human antigens, for example, citrullination by inflammation-induced host and/or *P. gingivalis* peptidylarginine deiminases [70]. This citrullination of new epitopes may lead to loss of tolerance to self-proteins in genetically susceptible individuals [71,72]. Interestingly, dysbiosis was partially resolved following treatment with disease-modifying anti-rheumatic drugs [62], further stressing the bidirectional crosstalk between the microbiota and their hosts.

3.3. Skin microbiota

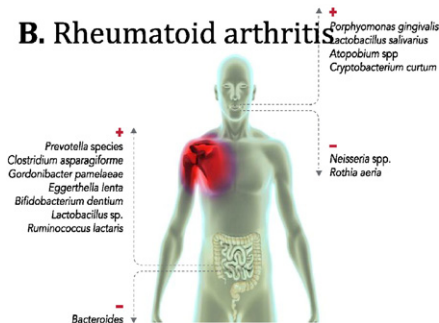
The skin is the largest organ of the human body and one of its main physical defense barriers. It contains a complex and dynamic ecosystem, hosting a multitude of microorganisms. Technically, the skin microbiome is the most challenging microbial milieu to study due to the difficulty of DNA extraction from a low bacterial biomass [73]. As opposed to the gastrointestinal tract, in which the fecal microbiome is representative of a combination of its segments, the sampled skin at each location is uniquely affected by its environment. The skin can be divided into sebaceous, moist and dry sites, each dominated by different bacteria [74]. Members of the β -Proteobacteria, Flavobacteriales and a *Corynebacterium* spp. dominate the microbiota at dry sites. The moist skin sites, such as the Nares and Axilla, are dominated by the β -Proteobacteria, Flavobacteriales and *Corynebacterium* spp. as well, but also contain increased levels of *Staphylococcus* spp. The sebaceous sites differ from the dry and moist sites, and are dominated by *Propionibacterium* [75]. Although most of these bacteria inhabit the upper part of the epidermis, the stratum corneum, bacteria may also reside within deeper layers of the skin [76,77].

Psoriasis, a common skin disorder, is characterized by keratinocyte hyper-proliferation resulting from chronic inflammation promoted by

A. Inflammatory bowel



B. Rheumatoid arthritis



C. Psoriasis

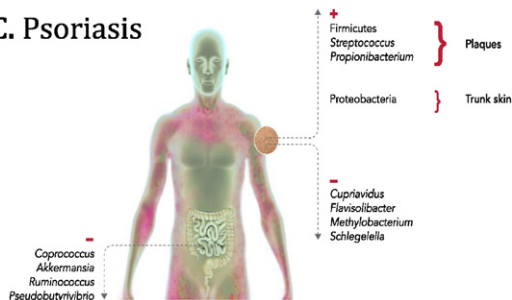


Fig. 2. Autoimmune diseases are associated with alterations in microbial composition. Examples of species that are present at increased (+) or decreased (–) levels at various anatomic sites in several autoimmune diseases.

Th1, Th17 and Th22 cells [78–80]. The initial presentation and periodic exacerbations of psoriasis are induced by unidentified environmental exposures in individuals with genetic predisposition [13]. In a recent genome-wide association study (GWAS) for psoriasis, the majority of the associated loci involved genes of the innate immune system [81], but genes affecting adaptive immune response and epidermal barrier function were also identified [82]. GWAS indicated variations including those associated with the Th17 axis, the pro-inflammatory transcription factor NF- κ B, and specific allele of the HLA-C of the Major Histocompatibility Complex (MHC) class I [83–86]. There are two current theories of the nature of the eliciting antigen in psoriasis. One is that the antigen is a self protein [87,88], and the second suggests that psoriasis is triggered by dysbiotic microbiota [78] (discussed in [89]). The concept that psoriasis is caused by an abnormal tolerance to skin commensal bacteria is strengthened by the high incidence of CD [90] and periodontitis [91] in psoriatic patients – both, as mentioned above, hypothesized to result from abnormal tolerance to oral and gut microbiota, respectively [78]. Studies characterizing the microbiota of the psoriatic plaques, two employing swabs [13,92] and one using biopsies [93], describe modest shifts in microbial compositions, with differences between studies. The inconsistency may reflect differences in sampling techniques, patient demographics, or initial variability between individuals that masks more substantial changes [75,78]. The clinical significance of these differences between bacteria profiles in normal and psoriatic skin is yet to be elucidated, whether it serves as a driving force, perpetrating a vicious cycle, or whether it constitutes a secondary response to changes in the psoriatic skin.

4. Factors affecting both the immune system and the microbiome

While associations between dysbiosis and autoimmunity are established, little is known about the mechanism underlying this connection, nor its causes or consequences. Bystander activation, epitope spreading and molecular mimicry were all proposed as mechanisms through which the microbiota promotes autoimmunity [35]. In the next section, we will review evidence suggesting that some of the factors that are known to directly affect the immune system, and consequently, the risk of autoimmunity, such as genetics, gender, pregnancy, and diet may also exert their effect, at least partially, by modulating microbiota profiles and functions (Fig. 3).

4.1. Genetics

Genome-wide association studies identified risk loci conferring susceptibility or resistance to autoimmune disorders [65,94–96]. The most prominent locus is the MHC, which contains genes encoding class I and class II molecules as well as other genes, many of them are related to the function of the immune system [97]. Some other risk loci such as *IL23R* and *STAT4*, affecting the activity of the adaptive immune response, are shared among different autoimmune diseases [98]. In addition, single nucleotide polymorphisms (SNPs) in loci encoding genes that are involved in tuning the strength of antigen receptor signaling in B and T cells, and also involved in differentiation of Th1, Th17 and Treg cells, were found in association to autoimmunity.

SNPs in genes governing innate immunity are also associated with the pathogenesis of various autoimmune diseases, such as polymorphism in TLR genes in type 1 diabetes (T1D), RA and SLE [3], and in the NOD2 gene in CD [49]. The TLR and (NOD)-like receptor (NLR), are pattern recognition receptors (PRRs) that play a key role in sensing pathogens and promoting the function of the innate, and consequently, of the adaptive immune response [26,56].

Studies in human twins have demonstrated the role that genetics plays in regulating human microbiota profiles [99,100]. For example, gut microbiota composition of pairs of monozygotic twins are more similar than that of pairs of dizygotic twins [101]. Genetic variations were found to be associated with microbiome composition in most body sites of humans characterized by the Human Microbiome Project [102]. Several of the immune pathways linked to the genetic variation associated with microbiome composition are pathways which were reported to be involved in IBD [102]. IBD, psoriasis and periodontal diseases, as mentioned above, are probably induced by inappropriate response to normal microbiota, and these diseases seem to be associated with similar genetic variations [103].

Studies in mice have also shown an association between host genetic background and gut microbiota profiles [23,25,104,105], and indicated that some of the genes affecting microbial composition are involved in susceptibility to autoimmunity. Deficiency in pattern recognition receptors (PRRs) such as TLR5 and NOD2 alter the gut communities [26,56]. TLR-5 is the cell surface receptor for bacterial flagellin, and is expressed on intestinal epithelial and dendritic cells. TLR5-dependent induction of anti-flagellin antibodies prevents commensal interaction with the intestinal mucosa by limiting bacterial motility, and therefore reduces

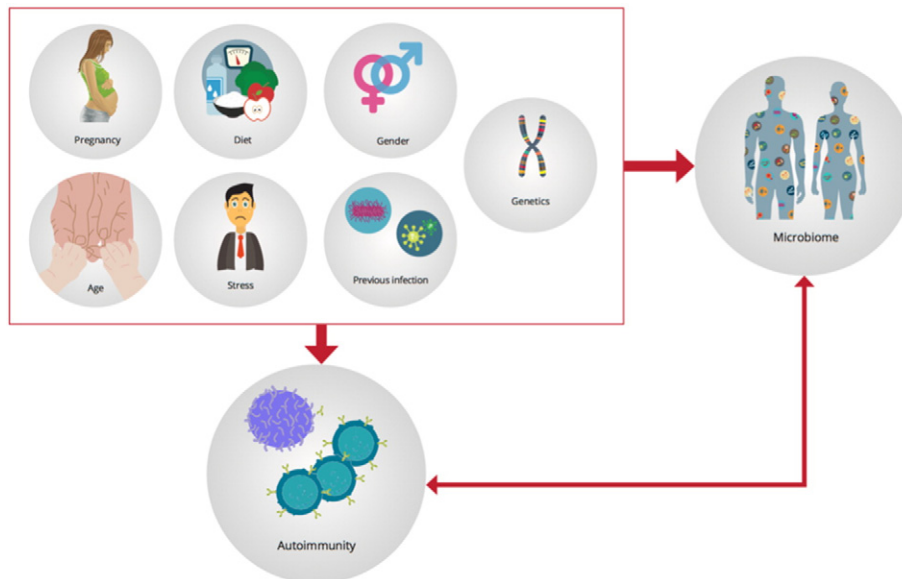


Fig. 3. Genetic and environmental factors that may influence autoimmunity, both by directly affecting immune function, and indirectly, through the microbiota.

crossing of the gut epithelial barrier [106,107]. *Tlr5*-deficient mice have increased susceptibility to colitis in a microbiota-dependent manner and the phenotype can be transferred to germ free mice by fecal transplantation from these mice [106–108]. NOD2, which is expressed mainly in Paneth cells of the small intestine, negatively regulates the proliferation of commensal microbiota, for example by regulation of the expression of anti-microbial β -defensins, which are known to be involved in shaping the microbial milieu [26,30,109,110]. Mutations and SNPs in the human gene encoding NOD2 have been linked to a multitude of inflammatory diseases including CD [111–113]. Several NLR proteins form the inflammasome, a cytoplasmic complex, whose activation leads to maturation of the pro-inflammatory cytokines, IL-1B and IL-18 [114]. Deficiency of the NLRP6 inflammasome subset in mouse colonic epithelial cells results in dysbiosis, predisposing the mice to IBD [57].

In summary, ‘Genetic dysbiosis’ [103], the effect of genetics on the microbial composition, is probably the result of the impact of the genetic variation on the recognition and responsiveness of the immune system to the microbiota. Misrecognition and inappropriate response to these bacteria can lead to dysbiosis, which in turn, may play a role as an initiator or perpetuator of autoimmune disease in a genetically susceptible individual, in the presence of predisposing environmental factors [103]. Therefore, distinct genetic profiles can impose autoimmunity-prone or autoimmunity-protective microbial compositions, which may dictate host susceptibility to autoimmunity.

4.2. Gender

Female gender is known to be a risk factor for several autoimmune diseases, as in the cases of RA (female:male ratio 3:1–4:1), systemic sclerosis (SSc, 3:1–4:1) and SLE (9:1) [115–118]. The explanation is possibly derived from the differences between men and women with respect to sociologic characteristics (discussed elsewhere) [119], as well as sex chromosomes [120] and sex hormones [118,121]. Observations in humans demonstrated an increased risk for autoimmunity endowed by the presence of an extra X chromosome [122], independent of gonadal hormone production [120]. The expression of several X-linked genes involved in the immune response [123,124] can theoretically affect the development of autoimmunity [116]. Sex hormones themselves play a key role in the function of both the innate and adaptive immune response [65,118,121,125]. Estrogens can enhance the immune response, while androgens and progesterone may downregulate it. Therefore, although the effects of these hormones as immunomodulators are more complex than presented here, the general increased immunocompetence in females may render them more susceptible to autoimmunity [118,125].

The association of increased rates of gingival inflammation with periodical elevation in female hormonal levels, suggested the notion that sex steroids play an etiological role by altering the subgingival bacterial community [126]. Early investigations suggested that increase in female sex hormones led to preferential colonization by black-pigmented *Bacteroides* (a classification term used to signify a genetically heterogeneous group of microorganisms that was based on phenotypic characterization). Since sex hormones exert a predominantly pro-inflammatory effect on the gingiva, it was difficult to dissect the direct effects of female sex steroids on bacteria from indirect effects on the immune response [126]. More recent human data demonstrated that life cycle stages associated with rapidly changing female hormonal levels, such as puberty [127] and pregnancy (see below) [128] are followed by alterations in intestinal microbiota profiles. In infancy, the microbiotas of opposite-sex dizygotic twin pairs are as similar to one another as the microbiota of same-sex dizygotic twin pairs [127]. After puberty, the microbiotas of opposite-sex twins are more diverse in comparison to the same-sex twins [127]. Thus, the hormonal changes during puberty mold sex-specific microbiome profiles. However, studies reporting specific gender associations of the gut [129–132] or skin [75] microbiome compositions in healthy humans in the general

population are inconsistent, and it is difficult to interpret causality versus consequence [129–132].

The term “microgenderome” has recently been used to describe the gender-related microbial differences leading to the development of autoimmunity in the non-obese diabetic (NOD) mouse model of T1D [133]. Although the microbial communities of weanling NOD males and females are indistinguishable from each other, sex-specific differences in microbiome composition become evident at puberty, and are most apparent in adult mice. Germ free NOD mice do not exhibit a gender bias in development of diabetes [134,135]. However, gender bias under SPF conditions occurs more often in females, and can be reversed via transfer of gut microbiota from males. Transfer of gut microbiota from adult males to immature females altered the microbiota of the recipient female, resulting in elevated testosterone and protection from T1D. These effects were dependent on androgen receptor activity [125,134]. There are several examples of steroid biosynthesis by bacteria, but not by gut commensal species [136]; therefore it is possible that the effect of male gut microbiota on testosterone level is indirect [125]. Based on the lack of a strict correlation between the amount of inducible testosterone and protection from T1D, it was suggested that once a testosterone threshold is achieved, the sex-restricted signals from the microbiota can determine whether disease will occur [135]. Thus, androgen enhancement by microbiota is not sufficient to explain the gender bias in T1D development, and the microbiota could contribute in an additive fashion to other effector mechanisms, for example by increasing the production of IFN γ in the pancreatic lymph nodes, a cytokine with suggested inflammatory-limiting function under this biological context.

All together, the data so far suggest that the gut microbiome may interact with sex hormones to modulate sex-biased disease onset and progression [65,137]. The feedback loop between sex hormones and gut microbes shapes a microbial community that can affect autoimmunity by triggering an inflammatory or tolerogenic input. It is not yet known whether sex-associated characteristics can directly affect the microbiota composition, and consequently, the risk for autoimmunity, or whether these factors affect the microbiota indirectly through initial instruction of the function of the immune system.

4.3. Pregnancy

During pregnancy the immune response is modulated in a systemic manner, and more effectively, at the maternal–fetal interface [138]. The dynamic of immunological changes during pregnancy probably follows the pattern of hormonal expression. i.e., as mentioned above, placenta-derived hormones, estrogens, and progesterone can directly affect the activity of immune cells [139,140]. The estrogens have dual effects; they promote an immune response at normal levels, but have anti-inflammatory functions at elevated concentrations, as in pregnancy [141]. Progesterone, in general, possesses immunosuppressive effect as in the induction of the differentiation of cord blood fetal T cells into Treg cells, and promotion of the dominant Th2 response during pregnancy [138]. This Th2 skewing may explain why some Th1-associated autoimmune diseases, such as MS and RA, are ameliorated during pregnancy. The onset of MS typically takes place during the childbearing years, and hence commonly during pregnancy. Pregnant women with MS typically have reduced relapse rate in the latter half of pregnancy, whereas soon after the delivery, disease activity returns, often at greater severity than in pregnancy [142]. The reasons for this increased activity are not entirely clear, but the decrease in estrogen levels and the loss of the immunosuppressive state of pregnancy are likely to be involved [140]. In the case of RA, two-thirds of pregnant patients also experience an improvement in their RA disease activity [143]. For SLE, which is a more heterogeneous disease, the changes in the disease state during pregnancy appear to be more varied [144–147].

An appropriate balance between Treg and Th17 cells is also crucial during pregnancy. Treg cells have a critical role in maintaining immune

tolerance to self-antigens and towards the semi-allogenic fetus [148–151]. The percentage of fetal Treg cells correlates closely with the percentage of maternal Treg cells, suggesting that within the context of pregnancy, the Treg cell compartment of the maternal and fetal immune system is tightly interrelated [152,153]. Treg and Th17 cells have some opposing actions; in the context of autoimmunity, Treg cells have a role in suppressing the autoimmune response, while Th17 promotes inflammation and autoimmunity [148]. Several clinical studies suggest that the expansion of Treg cells during pregnancy mediates protection from MS and RA [149]. Indeed, it has been shown in patients with RA that the number of Treg cells during pregnancy, is inversely correlated with disease activity in the third trimester and after delivery [154]. Many other immunoregulatory factors such as cytokines, adipokines, Fas-ligand, indoleamine 2,3-dioxygenase, and pregnancy-specific serum proteins such as HLA-G probably influence the success of pregnancy, but also the pathogenicity of autoimmune disorders [140,149].

Accumulating evidence suggests major changes in the microbiota of pregnant women [128,155,156]. Pregnancy is accompanied by changes in the bacterial load and composition in the GI tract [128,157]. The phylogenetic α -diversity (within an individual) decreases with advancing pregnancy, while the β -diversity (between individual variation) is increased in the third trimester. The third trimester is also characterized by elevated presence of Proteobacteria and Actinobacteria phyla, resembling the dysbiotic profile of inflammatory diseases [128]. Indeed, pro-inflammatory cytokines, such as IFN γ , IL-2, IL-6, and TNF α , are more abundant in the third trimester stool relative to the first trimester [128]. GF mice receiving third trimester microbiota gained more weight, had greater low grade inflammation and insulin resistance in comparison to GF mice receiving the gut microbiota from women in their first trimester, indicating the casual role of the pregnancy-associated microbiota in the pro-inflammatory environment in the last period of pregnancy [128].

The vaginal microbial community also has a unique structure during pregnancy [156]. Pregnancy was found to be associated with an overall decrease in α -diversity accompanied by enrichment of *Lactobacillus* and members of the Clostridiales, Bacteroidales, and Actinomycetales [155]. The richness of some of these species including *Lactobacillus jensenii* may have clinical significance, as these anaerobic bacteria contribute to the acidic vaginal environment [156]. Nevertheless, it is unclear whether changes in the microbial composition in the vagina or GI tract are beneficial to the pregnant mother or to fetal development, or alternatively, reflect a strategy employed by certain bacteria to increase their fitness for vertical transfer to the next generation. It is also unclear whether the changes in the microbial composition in pregnant women are a result of a direct recognition of the pregnancy-associated hormonal milieu by the bacteria, or a consequence of an indirect bacterial reaction to pregnancy-associated alterations in immune function, or both. Nevertheless, the resulting dynamic changes in microbial composition, can affect the function of the maternal immune system, and consequently, her autoimmune response. Deciphering the correlation between specific microbial compositions and specific autoimmune diseases may be of great importance for developing novel diagnostic and therapeutic approaches.

Evidence strongly suggests that the maternal microbiota during pregnancy has long-lasting effects on the offspring's microbial structure, and subsequently on its susceptibility to disease. It was demonstrated that the neonatal microbiome can differ based on the delivery mode [156,158]. Cesarean section deliveries are associated with a 20–30% increase in autoimmune disorders and childhood obesity [158], as shown in meta-analyses of observational studies [159,160]. Higher risk for allergy and celiac disease was also related to Cesarean section [161]. Therefore the altered bacterial colonization after Cesarean section probably causes the critical window of opportunity for optimizing the immune response to indigenous or pathogenic bacteria to be missed [162,163].

While critical for normal development, the exact timing of colonization of the pioneer microbiome in the neonate is unknown. The prevailing dogma of the sterile intrauterine environment during normal term pregnancies has been challenged [153,164–167]. In situ hybridization with specific probes for bacterial DNA have detected bacteria in the fetal membranes of up to 70% of women undergoing elective Cesarean section at term [165,168–170]. Furthermore, sequencing studies have identified a 'placental microbiome' present in normal healthy pregnancies [171]. The placental microbiome profiles were most similar to the oral microbiome, although whether and how the bacteria translocate from the mouth and other parts of the GI tract, or from additional sites harboring microbiota such as the skin and vagina, to the placenta is still poorly understood [166].

Nevertheless, the potential importance for this in utero colonization in modulating disease susceptibility is now more fully appreciated [172–174]; antibiotic treatment during pregnancy is associated with asthma in the offspring [175], and prenatal supplementation seems to be crucial for the preventive effect of probiotics on infant eczema [173, 174]. Recently, it was shown that the maternal microbiota of pregnant female mice shapes the intestinal mucosal lymphoid and mononuclear cells of the innate immune system, and programs the intestinal transcriptional profiles of the offspring to increase expression of genes associated with microbial interactions [176]. Some of these changes were dependent on the presence of maternal antibodies that transfer microbiota-derived compounds to the fetus. Altogether, it seems that the window of opportunity for educating the immune system to respond appropriately to pathogens and commensals after birth, begins within the fetal period [166,177–182].

4.4. Nutrition (diet)

Dietary factors are believed to be among the triggers for autoimmune disease [183]. This is reflected by the differential distribution of autoimmune diseases along the lines of ethnicity and geography, for which culture-based dietary differences are partially responsible [183,184]. The hallmark for the effects of nutrition on autoimmunity is the induction of Celiac disease following ingestion of gluten [185]. A gluten-free diet is known to improve Celiac disease symptoms, even its rheumatic manifestations [186]. Other examples include early exposure to cow's milk, increased iodine consumption in Japanese diets, and our Western diet enriched with fat and sugar, which were previously implicated in the pathogenesis of T1D, autoimmune thyroiditis and IBD, respectively [183]. Diet also has an obvious and strong direct effect on the microbiota composition, and studies investigating microbiomes of subjects from different geographic locations that are each associated with a typical diet (e.g., Burkina Faso vs. Italy, Malawi and Amerindians vs. USA) found highly distinct microbial compositions, attributed to dietary variability [127,187]. The strong effect of diet is evident during the first years of life when different foods are introduced for the first time. An infant time series demonstrated not only how diet influences the establishment of the infant microbiota, but also demonstrated how the bacterial metagenome changes to enable metabolism of the new dietary components [188]. Recent studies demonstrated the immediate effect of Western diet and processed foods on the gut microbiota. The use of dietary emulsifiers was shown to cause the microbiota of GF mice to change in a manner resembling metabolic syndrome [189]. Similar harmful effects were also shown to be caused in mice by artificial sweeteners [190].

In conclusion, diet is the factor with the quickest impact on the microbiome composition and we are recently learning how certain components of a given diet which affect the microbial composition also affect the predisposition to autoimmune disease. Could the microbiome be the link through which a person's diet affects his/hers health remains to be elucidated.

5. Microbiota-based therapies of autoimmune diseases

Since, as described above, accumulating data associates the microbiota with initiation or progression of autoimmune disease, in the following section, we suggest approaches by which modulating the microbiota might change disease outcome.

5.1. Probiotics

Understanding the role of dysbiosis in autoimmunity pathogenesis has led to attempts to manipulate the gut microbiome, hoping to re-equilibrate its homeostasis and to thereby promote disease remission. Such therapeutic modalities include the use of selected strains of live bacteria (probiotics) or fecal microbiota transplantation (FMT). The future holds great promise for the use of probiotics as disease interventions. Currently, research into the role of probiotics in treatment of autoimmune diseases has focused mainly on IBD. The results of these studies to date are not conclusive, and while some studies show extremely promising results others report no effect. For example, VSL#3, a probiotic product with a putative immune regulatory role [191] containing four strains of *Lactobacilli*, three strains of *Bifidobacteria*, and one strain of *Streptococcus salivarius* subsp. *Thermophilus*, promoted remission in mild to moderate UC, with responses as high as 77% [192]. The exact mechanism underlying this remission is not clear but may involve the induction of the anti-inflammatory cytokine IL-10 by *Bifidobacterium* [193]. In CD, however, results of probiotic treatment have been less encouraging. Schultz et al. found no benefit from the use of *Lactobacillus GG* in initiation or maintenance of medically-induced remission in CD [191,194]. Furthermore, no effect on recurrence in children, nor on post-operative recurrence was noted after the use of *L.GG*, and *Lactobacillus acidophilus*, respectively [191].

The use of FMT was described as early as the 4th century by the Chinese in order to cure diarrhea [195]. In modern medicine, the use of FMT was recently approved for the treatment of *Clostridium difficile* infection [195]. The rationale behind this treatment is restoration of the microbiota by transplanting the gut microbiota from a healthy donor. The use of FMT as a therapeutic modality for autoimmune diseases has been suggested, and studied mainly for IBD. A recent meta-analysis of 18 studies evaluated FMT efficacy in IBD patients. Results demonstrated that 45% of IBD patients receiving FMT achieved clinical remission [196]. Still, the field of FMT for IBD is still in its infancy so that the different studies are heterogeneous in the methodologies used.

5.2. Antibiotics

Antibiotics are probably the most obvious way to manipulate the microbiome. Antibiotics have been prescribed as a therapeutic option since the initial association was shown between bacterial infections and several autoimmune diseases [197–199]. The literature reports several studies regarding the use of antibiotics to treat autoimmune diseases, but this should be done cautiously as their anti-bacterial activity is not specific, and in some cases has even been shown to cause disease states to worsen [200,201].

A good example of how antibiotics might improve autoimmune disorders is the eradication of *H. pylori*. In immune thrombocytopenic purpura (ITP), antibiotic-mediated eradication of *H. pylori* was found to increase platelet count recovery [202] and was also reported to be beneficial in RA, as disease activity and markers, such as erythrocyte sedimentation rate, fibrinogen and anti-nuclear antibody titers, were lower in treated RA patients [203]. There are several other examples summarized elsewhere [199] supporting the potential therapeutic effect of antibiotics in autoimmune diseases.

6. Conclusions

The complex interaction between the human body and its microbiome affect our health and disease, as presented here in the context of autoimmunity. Unraveling the exact mechanisms by which dysbiosis participates in the pathogenesis of autoimmune diseases may facilitate the identification of populations at risk, and enable the development of new approaches for patient-tailored early intervention. Therefore, characterization and manipulation of the autoimmunity-associated microbiome may have a great potential as diagnostic and therapeutic tools, respectively.

Take-home messages

- Some of the known cues affecting the function of the immune system, such as genetics, gender, pregnancy and diet, which are consequently involved in autoimmunity, exert their effects by influencing, at least in part, the microbiota composition and activity.
- Characterization and manipulation of the autoimmunity-associated microbiome may have a great potential as diagnostic and therapeutic tools.

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