Journal of Autoimmunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex

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ARTICLE INFO

Keywords:
Autoimmunity
Gut microbiota
Bile acids
SCFA
Microbial metabolism

ABSTRACT

Unresolved low grade systemic inflammation represents the underlying pathological mechanism driving immune and metabolic pathways involved in autoimmune diseases (AID). Mechanistic studies in animal models of AID and observational studies in patients have found alterations in gut microbiota communities and their metabolites, suggesting a microbial contribution to the onset or progression of AID. The gut microbiota and its metabolites have been shown to influence immune functions and immune homeostasis both within the gut and systematically. Microbial derived-short chain fatty acid (SCFA) and bio-transformed bile acid (BA) have been shown to influence the immune system acting as ligands specific cell signaling receptors like GPRCs, TGR5 and FXR, or via epigenetic processes. Similarly, intestinal permeability (leaky gut) and bacterial translocation are important contributors to chronic systemic inflammation and, without repair of the intestinal barrier, might represent a continuous inflammatory stimulus capable of triggering autoimmune processes. Recent studies indicate gender-specific differences in immunity, with the gut microbiota shaping and being concomitantly shaped by the hormonal milieu governing differences between the sexes. A bi-directional cross-talk between microbiota and the endocrine system is emerging with bacteria being able to produce hormones (e.g. serotonin, dopamine and somatostatine), respond to host hormones (e.g. estrogens) and regulate host hormones' homeostasis (e.g by inhibiting gene prolactin transcription or converting glucocorticoids to androgens). We review herein how gut microbiota and its metabolites regulate immune function, intestinal permeability and possibly AID pathological processes. Further, we describe the dysbiosis within the gut microbiota observed in different AID and speculate how restoring gut microbiota composition and its regulatory metabolites by dietary intervention including prebiotics and probiotics could help in preventing or ameliorating AID. Finally, we suggest that, given consistent observations of microbiota dysbiosis associated with AID and the ability of SCFA and BA to regulate intestinal permeability and inflammation, further mechanistic studies, examining how dietary microbiota modulation can protect against AID, hold considerable potential to tackle increased incidence of AID at the population level.

1. Introduction

The incidence of autoimmune diseases (AID) has increased significantly in Westernized countries over the past decades, with a higher prevalence in women (~80% of overall incidence). The prevailing hypothesis suggests unresolved systemic inflammation as a key factor in disease emergence and progression. In genetically predisposed subjects unchecked systemic inflammation leads to the formation of autoantibodies, physiological dysregulation and tissue damage which can eventually manifest as specific AID.

While AID has a strong genetic basis, increasing evidence indicates an important contribution from environmental factors. A number of recent studies have highlighted the influence of genetics and environmental factors [1], such as antibiotics [2], dietary habits [3,4] and sex hormones [5] in AID. The host immune system plays an important role in shaping the gut microbiota and reciprocally, host-associated microorganisms significantly influence the development and function of innate and adaptive immunity [6,7], by establishing a "tolerant" phenotype and therefore facilitating the continuation of host-microbe coexistence [8]. Similarly, the gastrointestinal microbiota has recently been highlighted as one of the major contributors to the regulation of immune effector cell maturation and activity, and its dysbiosis has been

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https://doi.org/10.1016/j.jaut.2018.05.008
Received 3 April 2018; Received in revised form 18 May 2018; Accepted 21 May 2018

shown to contribute to intestinal mucosa permeability, induction of innate defenses, and thus a candidate environmental risk factor capable of triggering AID [3,9–11]. In addition, mucosal immune function and susceptibility to chronic inflammation differs between sexes [12,13].

Aberrant microbiota community structure has been reported in different AID including asthma [14], inflammatory bowel disease (IBD) [15], type 1 diabetes (T1D) [16], rheumatoid arthritis [17], food allergies [18], systemic lupus erythematosus (SLE) [11] and multiple sclerosis (MS) [19]. The human microbiome provides key immune and metabolic regulatory services to the host, which are set early in life and contribute to life-long immune function. However, environmental factors like nutrition, medicines, hormonal changes and psychological stress can disrupt the gut microbiota and determine its influence on immune homeostasis. The contribution of diet and the relevance of microbially-derived dietary metabolites are only just starting to be appreciated [8,20].

This review will present evidence supporting a role for diet:microbe interactions in the emergence of AID, with a special focus on extra-intestinal AID, such as T1D, SLE and MS. We will highlight connections with the gut microbiota and its cell signaling metabolites which influence inflammation systemically or provide a pathological pressure for the onset and maintenance of AID via continuous exposure to inflammatory triggers by compromising the intestinal barrier. The contribution of the estrogen-gut microbiota axis, the bi-directional modulation existing between gut microbiota and sex hormones, and the gender bias in autoimmunity will be also discussed.

2. Impact of gut microbiota on gender-specific differences in immunity and onset of autoimmunity

Males and females present some differences in the immune system [12] and sex bias is an important aspect of many AID [12,21,22]. The increasing number of microbiome studies is revealing a bi-directional cross-talk between microbiota and the endocrine system is emerging with bacteria being able to produce hormones (e.g. serotonin, dopamine and somatostatine), respond to host hormones (e.g. estrogens) and regulate host hormones' homeostasis by inhibiting gene transcription (e.g prolactin) or converting them (e.g. glucocorticoids to androgens) [23,24].

2.1. Sex differences in immunity and pathogen sensing

In general, normal healthy women show greater antigen presenting activity and mitogenic responses, higher immunoglobulin levels and more enhanced antibody production than males, being more resistant to infection diseases and much more likely to develop AID, while healthy male are thought to have an immune system that maintain tolerance [25]. Generally, steroid hormones exert an opposite role on the immune response, with estrogens promoting humoral immunity by enhancing B cell survival and androgens and progesterone acting in prevention or suppression of autoimmunity [26,27].

Accumulating evidence has linked Toll like receptor (TLR) function to estrogen and estrogen receptor α (ERα) and β (ERβ), suggesting a possible contribution of different microbial sensing and TLR activation to sex bias in AID, likely linked to gut microbe-associated molecular patterns (MAMPs) recognition [28]. Several immune-related genes including TLR7/8 - involved in nucleic acid recognition - and FOXP3 – the master transcriptional regulator of Treg expansion -, are present on X chromosome [1] and incomplete inactivation of X chromosome in female can potentially lead to increased activation of those genes [21,29]. The balance among TLR7/8 and 9, signaling receptors detecting microbial- and self-nucleic acids, has been shown to be crucial to SLE onset in animal models [30], as discussed below. Moreover, Jiang et al. found that female SLE patients possess more active monocytes with enhanced TLR4 receptiveness than male SLE patients and present increased plasma levels of soluble CD14 upon *in vitro* LPS challenge [31].

Through binding specific receptors in immune cells, sex hormones such as estrogens, can influence immune function, such as enhancing the humoral responses as in the case of 17-β-estradiol and prolactin [5]. It has been suggested that male hormones are protective in SLE or T1D and estrogens may contribute to disease progression by promoting B cell survival [12]. In lupus-prone mice, ERα deficiency leads to autoantibody production ameliorates renal damage and prolongs survival compared to ERα-sufficient controls [32]. Knocking out ERα in both lupus-prone and control mice resulted in impaired TLR4 activation in immune cells, indicating that estrogen and ER signaling can influence TLR4 responsiveness [31]. ERα deficient mice and lupus-prone ERα deficient mice also showed a decreased TLR9-mediated inflammatory cytokine production by DCs [33], particularly interleukin (IL)-6, MCP-1, IL-1β and IL-23, a cytokine milieu modulating the IL-23/IL-17 pathway and the priming of the T helper (Th) 17 response. Furthermore, decreased percentages of IL-17$^+$ RORγt$^+$ cells were isolated from the spleen of ERα$^{-/-}$lupus prone mice [33]. The protective effects of estrogens, particularly 17-β-estradiol, has been described in the onset and progression of experimental autoimmune encephalomyelitis (EAE), the prototypic animal model of MS, by enhancing regulatory B cells and M2 macrophage activities, and prevents the dysbiosis associated to EAE [34]. By contrast, endocrine disrupting chemicals such as bisphenol A, have been shown to be associated with risk of T1D in non-obese diabetic mice, a mouse model of insulitis and leukocytic infiltration of pancreatic islets leading to T1D [35–37] as well as with SLE pathogenesis, as evidenced in MRL/lpr mice, the animal model of lupus nephritis [38,39].

These evidences suggest a link between estrogen setting and its impact in regulating immune function through activation of specific microbial recognizing receptors (Fig. 1).

2.2. Sex hormones and their impact on microbiota

Host hormones can affect bacterial gene expression, bacterial virulence and growth, with consequences on host physiology [24]. The sex hormones estriol and estradiol decrease bacterial virulence by inhibiting quorum sensing signaling [40] while progesterone has been shown to promote growth of oral *Bacteroides* species and *Prevotella intermedius* [41]. Changes in expression of ER-β ERβ affects the composition of gut microbiota of female mice and that microbiota enriched from differential ERβ expression respond differently to changes in diet complexity [42]. By using high-throughput sequencing, sex hormones have been shown to modulate mammalian microbiota composition [22,43–49] (Fig. 1). Healthy male mice have been shown to bear higher abundance of *Ruminococcus*, *Coprococcus* and *Dorea* and lower abundance of Porphyromonaceae and *Rikenella*, while female mice present higher abundance of *Allobaculum*, *Anaeroplasma*, and Lactobacillaceae and Veilonellaceae [22,46,49]. Mueller at al. (2006) showed that healthy male subjects had a higher abundance of Bacteroides-*Prevotella* than female while post-menopausal woman microbiota did not differed from male one [47]. Very recently, Fransen et al. (2017) showed a decreased relative abundance of *Alistipes*, *Rikenella* and Porphyromonadaceae in female mice associated with a concomitant higher cell content in the thymus, a bigger thymus size and an increased IFN-β signaling than in male mice [43]. However, whether sex-dependent immunity differences are a cause or consequence of an alteration of the gut microbiota is still not clear. Gut microbiota analysis on 341 female and 348 male mice from 89 inbred animals demonstrated that under a controlled environment male and female mice show significant differences in gut microbiota composition, although genetic differences obscured sex differences in examination of the entire population [22]. Furthermore, gonadectomy and hormone replacement induced a microbiota shift driven by sex hormones. Those treatments led also to gender-specific differences in bile acid (BA) profiles between sexes [22]. An higher rate of BA synthesis and BA pool sizes in females than in males has been previously reported [50,51]. This is important given the