Microbiota–Immunity–Hormone Interactions on Autoimmune Diseases and Infection

Subjects: Immunology

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The immune system has to develop to defend against pathogens while simultaneously tolerating the beneficial microorganisms that coexist symbiotically with the host. Moreover, the microbiota in the large intestine plays a significant role in preserving mucosal and systemic homeostasis. The interaction between the large intestine microbiota and local immune cells is crucial for directing specific immune responses and, consequently, for performing immunomodulatory functions.

Keywords: autoimmune diseases ; infections ; microbiota ; hormones ; immune system

1. Introduction

The majority of interactions between the immune system and the external environment occur within the gastrointestinal (GI) tract, primarily affecting the community of resident microorganisms known as the intestinal microbiota [1]. These microorganisms present a significant source of antigenic diversity, which the host immune system must carefully manage its responses to. The preservation of tolerance and anti-inflammatory responses requires the engagement of a large range of innate and adaptive immune pathways that work together to control microbiota shaping and reduce systemic inflammation [2].

Additionally, the microbiota plays crucial roles in signaling the correct development, education, and epigenetic capabilities of various immune cells [3][4]. This mutual relationship has evolved over thousands of years. However, the rapid modernization of human communities has led to significant changes in environmental exposures and microbiota composition, leading to an increase in autoimmune diseases [4][5]. Autoimmune diseases require a combination of uncontrolled inflammation and self-antigen-specific T cells. Three essential conditions must be met for T cell-mediated autoimmune disorders to manifest: (a) self-reactive T cells must be present and be activated; (b) these T cells must proliferate; and (d) immune regulation must fail to regulate autoreactive responses. Complementarily, hormones, especially estrogens, not only modulate the reproductive system but also regulate immunity development and function. Innate, adaptive, humoral, and cell-mediated immune responses are impacted by hormones, and dysregulation of these mechanisms can contribute to immune-mediated disorders, including autoimmunity [6][7][8].

2. Microbiota–Immune System Interactions

As previously mentioned, the microbiota is essential for the proper maturation of the host immune system from the earliest stages of life [9]. The immune system has to develop to defend against pathogens while simultaneously tolerating the beneficial microorganisms that coexist symbiotically with the host [10]. Moreover, the microbiota in the large intestine plays a significant role in preserving mucosal and systemic homeostasis. The interaction between the large intestine microbiota and local immune cells is crucial for directing specific immune responses and, consequently, for performing immunomodulatory functions [11]. Notably, the interactions between GM and the immune system established in the first year of life can exert long-term effects on immune responses [12]. This, in turn, may play a role in determining the host's susceptibility to infections and immune-related disorders later in life [13][14]. In addition, throughout life, GM affects immune functions, often with systemic outcomes that can be independent of the GM colonization site. The GM influences multiple aspects of innate and adaptive immunity. Activation of recognition receptors (PRRs), such as nucleotide-binding oligomerization domain-like receptors (NODs) and Toll-like receptors (TLRs), through commensal bacteria, enhances enterocyte regeneration and survival [15]. The commensal bacterium *Bacteroides fragilis* (*B. fragilis*) produces polysaccharide A (PSA) that recognizes the TLR2/TLR1 heterodimer, inducing the expression of anti-inflammatory genes through cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) [16].

In addition, GM can prevent intestinal inflammation by controlling the differentiation of T regulatory (Treg) cells [17]. Metabolites produced by GM, such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), can influence innate and adaptive immune cells in several ways, while the butyrate, through enhancing histone H3 acetylation, induces monocyte-to-macrophage differentiation [18] and TMAO can drive their polarization [19]. Moreover, these molecules reinforce antimicrobial defenses and induce the differentiation of naïve CD4+ into Treg cells [20].

Myeloid differentiation primary response protein (MyD88) serves as an adaptor for various innate immune receptors that detect microbial signals and mediate signaling pathways activated by IL-1 and IL-18 through their respective receptors [3]. Mice lacking MyD88 show a modified microbial composition [21] and MyD88 plays a crucial role in controlling the epithelial expression of several antimicrobial peptides (AMPs), including RegIIIγ. This regulation limits the presence of surface-associated Gram+ bacteria and constrains the activation of adaptive immunity [22]. Additionally, MyD88 influences T cell differentiation, supports microbiota homeostasis by promoting immunoglobulin A (IgA) stimulation, and regulates the differentiation of Th17 cells by inhibiting the growth of segmented filamentous bacteria (SFB) in mice [23].

Of note, GM can also modulate the T helper 17 (Th17) cells; indeed, *Citrobacter* can promote their pro-inflammatory capabilities [24]. Fung et al., show that commensal bacteria residing in lymphoid tissues (LRC) colonized germ-free and antibiotic-treated mice and influenced the cytokines' production of dendritic cells. This colonization led to the induction of various members of the IL-10 cytokine family, such as dendritic cell-derived IL-10 and group 3 innate lymphoid cell (ILC3)-derived IL-22. As previously reported, IL-10 played a crucial role in limiting pro-inflammatory Th17 cell responses, and IL-22 production contributed to enhanced LRC colonization under steady-state conditions. Those results highlight the straight crosstalk between the host and commensal bacteria [25].

GF colonized by human GM exhibited decreased levels of CD4+ and CD8+ T cells, limited proliferation of T cells, low number of dendritic cells, and decreased expression of antimicrobial peptides in the intestinal tract. Conversely, when GF mice were colonized with SFB derived from mice, the Th17 cell number was restored to levels comparable to those observed in conventionally reared mice (CONV-R mice). These data suggest that specific mice GM may be essential for achieving complete immune maturation in these animals [26].

In addition, gut colonization by SFB elicits IL-17A production by RORγt+ Th17. SFB flagellins stimulate the production of more cytokines, such as IL17, IL21, and IL22, and drive immune endothelial cells (IECs) to secrete serum amyloid (SAA3). These cytokines lately can promote Th17 cell production [27]. Th17 lymphocytes have functional plasticity in response to inflammatory signals; indeed, the presence of high amounts of IL-12 enables them to differentiate in Th17/Th1, while IL-1 and IL-6 can stimulate a Treg-Th17 trans-differentiation [28][29]. These lymphocytes are more pathogenic compared to cells that did not undergo these shifts and can assume a pathogenic role, especially in chronic inflammatory conditions, where inflammation is frequently started by unidentified agents and the immune system lacks the ability to suppress the response [30][31]. On the other hand, Treg cells have a suppressive role (mainly secreting the anti-inflammatory cytokine IL-10). Indeed, they recognize commensal-derived antigens [32], maintain tolerance to intestinal microbes [33], and are essential for suppressing the aberrant activation of myeloid cells and Th17 cells [34]. *Clostridium* species are able to restore the Treg cells' colonization in germ-free mice through the SCFAs involvement [20][35][36]. Finally, the *Lactobacillus reuteri*, *Lactobacillus murinus*, *Helicobacter hepaticus*, and *B. fragilis* increase the proportion of IL-10-producing Treg cells in mice [17][37]. In other words, the GM composition plays a relevant role in maintaining the proper balance and regulation of T cell subtypes, which is crucial in determining a person's health status.

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