Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Review

Symbiotic and antibiotic interactions between gut commensal microbiota and host immune system

Mantas Kazimieras Malys [a,*], *Laura Campbell* [b], *Naglis Malys* [b,*]

[a] *St Catherine's College, University of Oxford, Oxford OX1 3UJ, UK*
[b] *School of Life Sciences, Gibbet Hill Campus, University of Warwick, Coventry CV4 7AL, UK*

ARTICLE INFO

Article history:
Available online 24 March 2015

Keywords:
Immune system
Commensal microbiota
T-cells
B-cells
Dysbiosis

ABSTRACT

The human gut commensal microbiota forms a complex population of microorganisms that survive by maintaining a symbiotic relationship with the host. Amongst the metabolic benefits it brings, formation of adaptive immune system and maintenance of its homeostasis are functions that play an important role. This review discusses the integral elements of commensal microbiota that stimulate responses of different parts of the immune system and lead to health or disease. It aims to establish conditions and factors that contribute to gut commensal microbiota's transformation from symbiotic to antibiotic relationship with human. We suggest that the host-microbiota relationship has been evolved to benefit both parties and any changes that may lead to disease, are not due to unfriendly properties of the gut microbiota but due to host genetics or environmental changes such as diet or infection.

1. Introduction

It is now become evident that microbiota plays an essential role in the function, induction, and training of the host immune system. As a consequence, the immune system has evolved strategies to maintain this symbiotic relationship with a large number of diverse microbes. An average human gut contains approximately 10^{14} bacteria, most of which cannot be cultured. The vast majority of these commensals fall into one of two phyla: gram-negative *Bacteroides* and gram-positive *Firmicutes*. It has been approximated that these bacteria contain over 100 times more genes than a whole human genome [1]. Many of these genes directly influence host metabolic pathways and provide the host with nutrients that otherwise it would not receive [2]. Therefore, the gut commensals differ from pathogens in that they are allowed to co-exist due to the benefits they provide to the host; therefore the host does not try to eradicate them from the mucosa, but still maintains the ability to actively fight pathogens.

* *Corresponding authors.*
E-mail addresses: mantasmalys@yahoo.co.uk (M.K. Malys), n.malys@gmail.com (N. Malys).
Peer review under the responsibility of the Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2015.03.001

Germ free (GF) mice are a tool often used to see the effects of ablated microbiota on host metabolic and immune function [3]. These mice also enable one to re-colonize the gut with a specific species of commensal bacteria to isolate its effects. This review will discuss the gut commensal microbiota interactions with the host immune system, focusing on the responses each part of innate and adaptive immune system elicits. These responses may be beneficial for the immune system, since they enhance immune system's ability to fight pathogens and maintaining the composition of gut microbiota. However, the responses can be unwanted since they may lead to local inflammatory disorders, such as inflammatory bowel disease (IBD) or autoimmune disease away from the gut [4]. This review will also attempt to juxtapose recent evidence on gut commensal interaction with the host to establish what contributes to switching from symbiosis to antibiosis.

2. Commensal microbiota affects infection

Composition of gut commensal organisms is greatly affected when one is subjected to antibiotic treatment [5–7]. This change in composition has been associated with pathogenic infections of the gut [8,9]. Closely related species of pathogenic bacteria that are commensal in the gut seem to tolerate their related pathogenic bacteria colonization [10]. Therefore, it is safe to say that specific microbial species dictate pathogenic microbial colonization.

Even though, certain microbiota permits colonization of pathogens, some can limit pathogenic bacterial growth. *Salmonella typhimurium* induces inflammation which changes microbial composition and suppresses their growth [11]. Avirulent *S. typhimurium* does not cause colitis and fails to outcompete the microbiota unless inflammation is induced. IL-10 knockout mice, a model of IBD, allow the pathogen to overcome colonization resistance. However, transferring normal gut flora to *S. typhimurium* infected gut allows the mice to recover and eliminate the pathogen [12]. The process occurs in the absence of antibody response that clear the pathogen in the secondary infection, thus clearance results as a direct commensal microbiota pressure.

3. Innate responses

Intestinal epithelial cells (IECs) form a barrier that protects the host from bacterial invasion. In addition to acting as a physical barrier, they perform a role in the immune cell regulation via expressing receptors for microbial-associated molecular pattern (MAMPs). Activation of these receptors leads to downstream cascades, which affect the inflammatory status of IECs. Apical expression of toll-like receptor 9 (TLR9) is involved in immune homeostasis [7]. Activation of TLR9 on the apical membrane of IECs leads to partial activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) without stimulating the release of pro-inflammatory cytokines. Apical introduction of CpG sites (where cytosine nucleotide occurs next to a guanine nucleotide) of gut commensals reduces the pro-inflammatory cytokine release when basolateral TLR9 receptors are activated in IECs [13]. Protective effects of microbiota can also be evidenced by *Lactobacillus casei*, a common probiotic, inducing anti-inflammatory effects through inhibition of NFkB pathway via stabilization of IkBα during *Shigella flexneri* infection, which ameliorates the disease symptoms [14].

Short chain fatty acids (SCFA) are produced by fiber carbohydrate fermentation in the gut by *Bacteroides* and *Clostridium* species within the human gut [15]. Butyrate, one of the products of fiber fermentation, provides a signal for inhibition of pro-inflammatory cytokine expression in the IECs that involve inhibition of NFkB pathway [16]. Moreover, butyrate induces other protective mechanisms, such as production of mucin and antimicrobial peptides, as well as increases expression of tight junction proteins strengthening the epithelial barrier [17]. Lower butyrate levels have been associated with inflammatory bowel disease (IBD) such as Crohn's disease [16]. This shows that specific gut microbiota is important in keeping the unwanted organisms in check as well as preventing development of autoimmune disease, such as IBD.

It is important to point out that the host immune mediators play a significant role in controlling the microbiota. Changing part of the immune control system alters the gut flora composition. The effects of dysbiosis have been illustrated by the mice lacking Toll-like receptor 5 (TLR5) [18]. These mice are highly predisposed to type 2 diabetes and cardiovascular disease due to developed obesity. This metabolic syndrome is caused by the altered balance of *Firmicutes* and *Bacteroidetes*, which has been shown by transplanting the gut flora from the knockout mice into the wild-type, leading to development of the metabolic syndrome [18]. Altered host mechanisms of immune regulation have an impact on gut commensal composition and in this way cause the disease. However, under normal conditions the dysbiosis would be unlikely to occur and would not lead to disease.

A new population of innate cells that are of lymphoid origin has been identified recently. Not much is known about the interactions of these cells with the gut commensals. However, it seems that they can respond to direct and indirect actions of gut commensals to elicit inflammatory and barrier strengthening responses [19]. These cells produce a great variety of proinflammatory cytokines in response to activation through TLR and other receptors limited to innate lymphoid cells [20]. Therefore, it is possible to speculate that responses of these cells to gut microbiota affect immune homeostasis.

4. Adaptive responses

4.1. *Th17 cells*

T-cell responses have been shown to be dependent on the gut commensal composition. Germ-free mice tend to have diminished T helper 1 and 17 cells (Th1 and Th17) responses but maintained or increased CD4(+) T regulatory cells (T(regs)) frequency [21]. It has been found that segmented filamentous bacteria (SFB) play an important role in inducing intestinal Th17 cells. These bacteria adhere to the surface of the intestine, possibly contributing to their active sampling by the dendritic cells and the strong induction of Th17 cells [22]. This has been confirmed by increased expression of interleukin 17 and 22