Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Microbiome, metabolites and host immunity

Maayan Levy[1], Eran Blacher[1] and Eran Elinav

In the intestine, the microbial genomes and repertoire of biochemical reactions outnumber those of the host and significantly contribute to many aspects of the host's health, including metabolism, immunity, development and behavior, while microbial community imbalance is associated with disease.The crosstalk between the host and its microbiome occurs in part through the secretion of metabolites, which have a profound effect on host physiology. The immune system constantly scans the intestinal microenvironment for information regarding the metabolic state of the microbiota as well as the colonization status. Recent studies have uncovered a major role for microbial metabolites in the regulation of the immune system. In this review, we summarize the central findings of how microbiota-modulated metabolites control immune development and activity.

Address
Immunology Department, Weizmann Institute of Science, Rehovot, Israel

Corresponding author: Elinav, Eran (eran.elinav@weizmann.ac.il)
[1] These authors contributed equally.

Current Opinion in Microbiology 2017, **35**:8–15

This review comes from a themed issue on **Host-microbe interactions: bacteria**

Edited by **Samuel Miller** and **Renée Tsolis**

http://dx.doi.org/10.1016/j.mib.2016.10.003

Introduction

The intestine is a complex ecosystem that is composed of mammalian and prokaryotic components, the latter of which are collectively termed the microbiota. These two elements have coevolved and are in constant interaction through diverse mechanisms.

The intestinal microbiota contributes to multiple physiological processes of the host, including metabolic and nutritional homeostasis, energy expenditure and immunity. A growing number of studies in recent years suggested that the microbiome is playing a crucial role in immune development and function of the host as well as the host metabolic state. This function is to a large part achieved through the exchange of small molecules between the intestinal lumen and the host's mucosal surfaces, as well as the systemic circulation [1].

The mammalian intestine harbors a diverse array of metabolites that have the potential to modulate immunity. The microbiome can synthesize, modulate and degrade a large repertoire of small molecules, thereby providing a functional complementation to the metabolic capacities of the host. In particular, the microbiota can metabolize dietary components that cannot be metabolized by the host such as complex carbohydrates [2]. Moreover, the bacterial metagenome contributes to the production of primary metabolites and the modulation of secondary metabolites that affect host physiology in multiple ways. Several such microbial metabolic pathways have been associated with host physiology, including the production of fatty acids, vitamins, neuroactive metabolites and amino acids, with beneficial effects ranging from epithelial homeostasis, immune cell development and neuronal regulation to nutrient digestion [3].

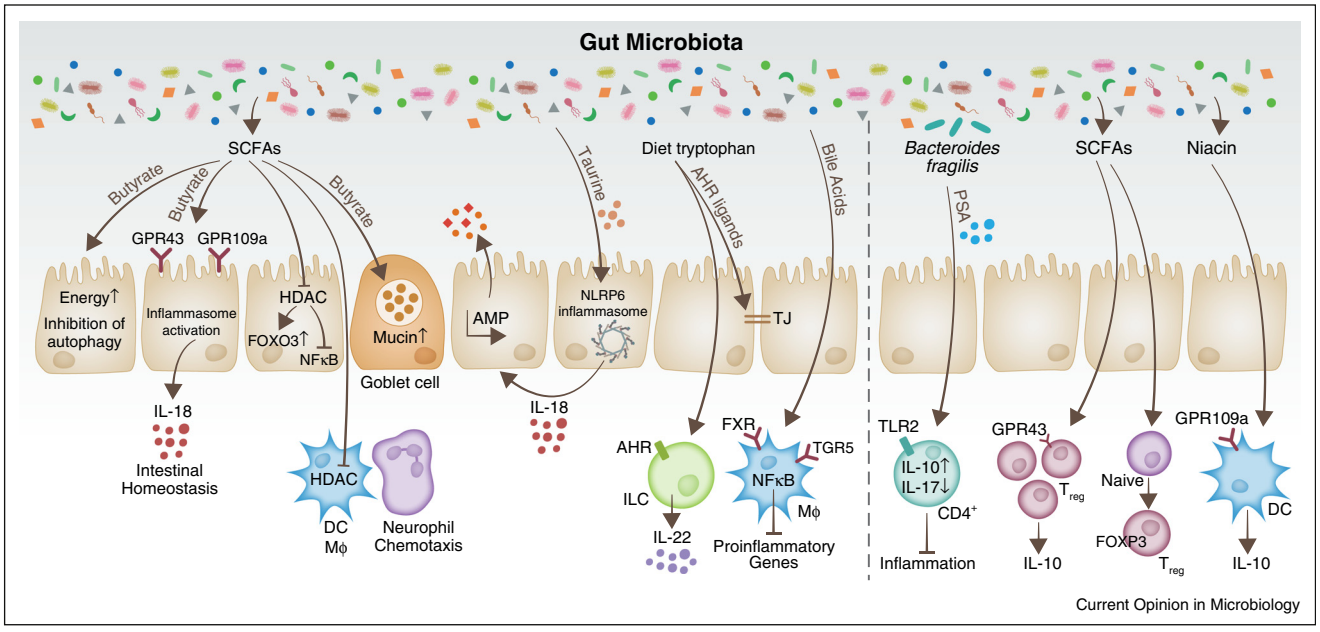
Elucidating the function of microbial metabolites that modulate the host physiology requires identification of metabolites that differ between healthy and disease states. When the balanced interaction between the host and the microbiota is disrupted, intestinal and extra-intestinal diseases may develop. Multiple studies have identified such metabolites that are differentially abundant in health versus disease. Some of these identified metabolites, including short-chain fatty acids (SCFAs) and indoles, were shown to have a protective effect from the development of disease [4], while others, such as trimethylamine N-oxide (TMAO) and 4-ethylphenylsulfate (4-EPS), were shown to directly drive the susceptibility to disease [5,6].

The effects of microbiome-modulated metabolites on metabolic and other host physiological functions are highlighted elsewhere [7,8]. Here, we highlight key metabolites that are formed or modulated by the gut microbiota and describe their effects on the different arms of the host immune system (Figure 1).

Metabolite interactions with innate mechanisms of defense

The immune system and the microbiota are two components that influence one another to orchestrate host physiology as well as to maintain a stable microbiome community. The mammalian host recognizes microbial presence and activity through a number of germ-line encoded microbial sensors called pattern recognition receptors (PRRs). Such receptors are able to recognize microbial structure and effector molecules [8,9]. Microbial metabolites serve as an additional layer of communication between the host and the microbiota.

Figure 1



Modulation of immune signalling through microbial metabolites. Examples of metabolites that are produced or modulated by the intestinal microbiota, and their impact on the intestinal immune response. Metabolite effects are either direct on immune cells, or relayed by the intestinal epithelium.

The identification of specific microbiota-derived metabolites and their effect on the immune system have provided mechanistic insight into colonization mechanisms and immune cell-microbiota co-regulation (Table 1).

The interaction between the host's innate immune system and the microbiome through metabolites spans multiple cell types. Although not considered a classical immune cell, epithelial cells of the intestine are an integral part of the mucosal immune system as they are equipped with innate PRRs and contribute to intestinal homeostasis through bacterial recognition [10]. As part of the mucosal immune system, epithelial cells provide an innate mechanism through which the host develops and maintains a stable healthy microbiota composition, while preventing pathogen entry. To this end, epithelial cells are equipped with a large anti-microbial arsenal of effector mechanisms and undergo intense communication with the myeloid and lymphoid cells in the local environment [11]. Interestingly, the influence of the microbiota on intestinal epithelial cells strongly couples immunological and metabolic functions, as evidenced in particular by the role of a common bacterial metabolite, short-chain fatty acids (SCFAs).

SCFAs are the result of non-digestible carbohydrates fermentation by anaerobic commensal bacteria. The host recognizes SCFAs, namely acetate, propionate and butyrate, through the G-coupled-receptors GPR41, GPR43 and GPR109a [4,12]. SCFAs have been found to function as energetic substrates for epithelial cells. Butyrate has been reported to regulate energy metabolism in intestinal epithelial cells [13], as colonocytes can utilize bacterially produced butyrate as a primary energy source. Consequently, colonocytes of germ-free mice display an energy-deprived state and enhanced autophagy that can be rescued by butyrate supplementation [13]. Recently, butyrate was identified as an inhibitor of intestinal stem cells [14]. Butyrate suppresses proliferation by acting as a histone deacetylase (HDAC) inhibitor therefore allowing for increased promoter activity of the negative cell-cycle regulator Foxo3 during injury. Butyrate utilization by enterocytes limits the access of butyrate to the intestinal crypts, thereby protecting stem cells from the anti-proliferative effect during homeostasis [14]. This study suggests that SCFAs contribute to the maintenance of the epithelial barrier. Epithelial cells integrity is further achieved through the SCFA acetate, which was shown to enhance the protection against infections [15]. Other studies showed that supplementation with SCFAs contributes to the preservation of mucosal immunity through goblet cells as these cells up-regulate the expression of MUC genes in response to butyrate [16].

An integral part of innate immunity is the immune sensing complex called inflammasome [17]. A recent study suggests that high-fiber diet, which activates GPR43 on intestinal epithelial cells, results in activation of the NLRP3 inflammasome leading to its assembly and