REVIEW

Metabolites: messengers between the microbiota and the immune system

Maayan Levy,[1] Christoph A. Thaiss,[1] and Eran Elinav

Immunology Department, Weizmann Institute of Science, Rehovot 76100, Israel

The mammalian intestine harbors one of the largest microbial densities on Earth, necessitating the implementation of control mechanisms by which the host evaluates the state of microbial colonization and reacts to deviations from homeostasis. While microbial recognition by the innate immune system has been firmly established as an efficient means by which the host evaluates microbial presence, recent work has uncovered a central role for bacterial metabolites in the orchestration of the host immune response. In this review, we highlight examples of how microbiota-modulated metabolites control the development, differentiation, and activity of the immune system and classify them into functional categories that illustrate the spectrum of ways by which microbial metabolites influence host physiology. A comprehensive understanding of how microbiota-derived metabolites shape the human immune system is critical for the rational design of therapies for microbiota-driven diseases.

The mammalian intestine harbors a dense and complex microbial community, termed the microbiota. The commensal microbiome and, in particular, the dense and diverse microbial community inhabiting the gastrointestinal tract play a pivotal role in the maintenance of organismal homeostasis and stable physiology. Research over the last decade has highlighted the concept that the eukaryotic host and its microbiota, rather than existing in isolation, compose a complex meta-organism termed the "holobiont," jointly regulating multiple aspects of mammalian physiology, including immune system development, metabolism, and nervous system function (Sommer and Backhed 2013). The interaction between the microbiota and the host is most prominent at mucosal surfaces, which provide an interface between the mostly microbe-free host, the microbiota, and the environment. At the same time, the presence of the microbial community within the eukaryotic host necessitates the development of a sophisticated immune system that controls and maintains a beneficial symbiosis of the holobiont through the continuous communication between the microbiome and the host.

The recognition of microbial patterns by the innate immune system initiates a signaling cascade downstream from pattern recognition receptors, which triggers an anti-microbial immune response. At the same time, signals downstream from microbial pattern recognition can also result in the induction of mechanisms involved in the maintenance of tolerance.

Deficiency of innate immune pathways leads to alterations of the microbial community, termed dysbiosis, which in some cases result in disease pathogenesis (Rakoff-Nahoum et al. 2004; Petnicki-Ocwieja et al. 2009; Elinav et al. 2011; Thaiss et al. 2014). Different microbiome configurations produce, modulate, and degrade a large array of small molecules (referred to here as "metabolites"), thereby providing a functional complementation to the metabolic capacities of the host; e.g., complex proteins and carbohydrates that cannot be degraded by the host can be metabolized by the microbial community (Fischbach and Sonnenburg 2011; Nicholson et al. 2012). One additional important and recently recognized function of this complex network of microbially produced, modulated, and degraded metabolites relates to the intimate communication of the microbiota with its eukaryotic host, mediated by metabolite signaling through a series of innate immune receptors. In addition, metabolites can be a form of bacterial signaling such as quorum sensing and can drive changes in the composition and function of the microbiota (Bassler and Losick 2006).

It has thus become increasingly apparent that the microbiota and its metabolites are important orchestrators of host physiology and pathophysiology through the control of a large range of metabolic, inflammatory, and even behavioral processes (Hsiao et al. 2013; Tang et al. 2013). Here, we provide an overview of the molecular relationship between microbiota, metabolites, and the host immune system and highlight prominent examples of how metabolites contribute to health and disease of the holobiont (Fig. 1). Rather than categorizing metabolites

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[1]**These authors contributed equally to this work.**
Corresponding author: eran.elinav@weizmann.ac.il
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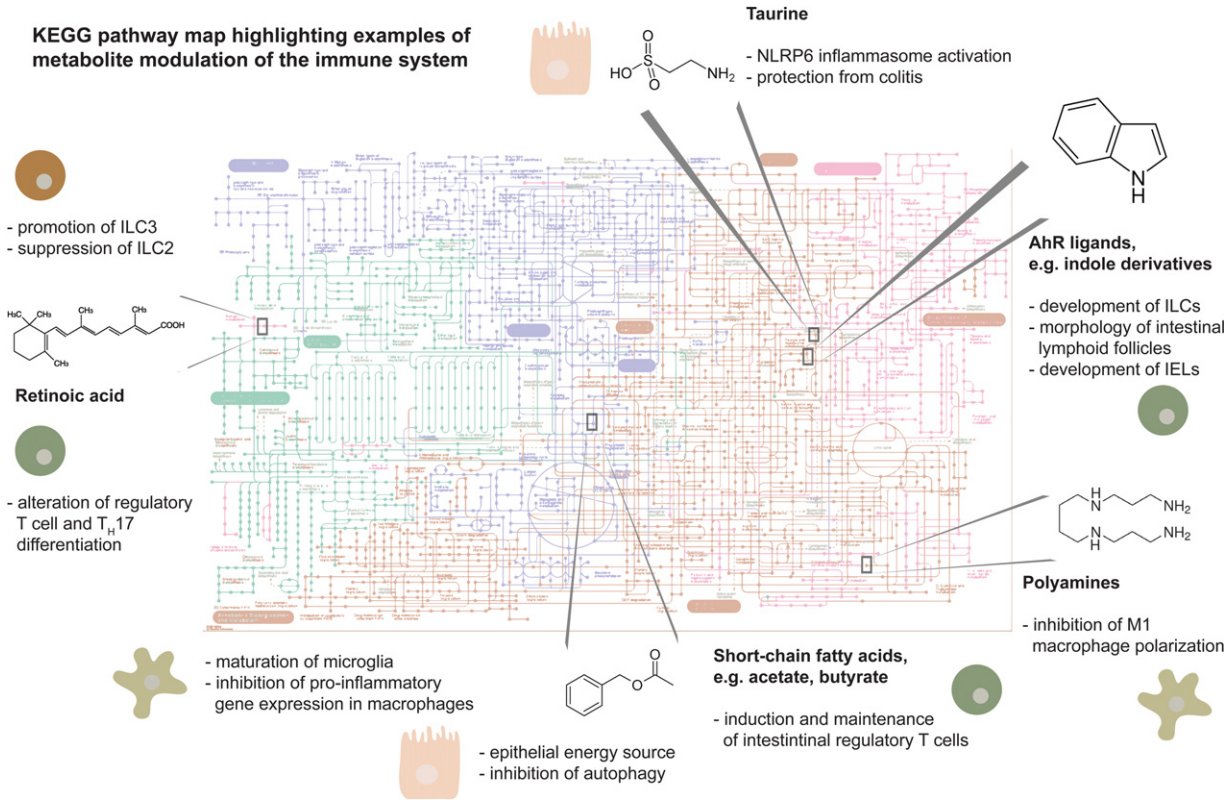

Figure 1. Chart of metabolic pathways with highlighted examples of microbiome-derived or -modulated pathways involved in modulation of the immune response. (ILCs) Innate lymphoid cells; (IELs) intraepithelial lymphocytes. The pathway map was obtained from the Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.kegg.jp/pathway/map01100) (Kanehisa and Goto 2000; Kanehisa et al. 2016).

by chemical groups, we focus on commonalities with respect to their functional impact on the immune system with the goal of illustrating common themes unifying the currently known microbiota–metabolite–immune cell interactions.

Metabolites as drivers of immune system development and differentiation

One of the most striking examples of the importance of the microbiota for the immune system is the observation that germ-free mice, which are raised in the absence of any microbial colonization, feature a profoundly underdeveloped immune system (Smith et al. 2007), which can be largely reversed by adult conventionalization with a species-specific microbiota (Chung et al. 2012). While the molecular mechanisms by which the microbiome controls immune system ontogeny are still largely unknown, several examples have been found that highlight the involvement of specific bacterial-derived metabolites in the regulation of immune cell development and differentiation (Fig. 1).

Short chain fatty acids (SCFAs)

Among the most abundant molecules produced by gut bacteria are SCFAs, which have been found recently to control multiple aspects of human immunity and metabolism (Morrison and Preston 2016). Soluble dietary fibers and nondigestible carbohydrates such as cellulose are an integral component of the human diet. While humans lack the enzymes to degrade such polysaccharides, anaerobic commensal bacteria in the cecum and large intestine can ferment these fibers. Dietary fiber fermentation results in the generation of SCFAs—namely, acetate, propionate, and butyrate, which can be detected by the host through the intracellular receptor PPARγ; the surface proteins GPR41 and GPR43; and the butyrate receptor GPR109a (Brown et al. 2003; Alex et al. 2013). Acetate and propionate are produced mainly by Bacteroidetes, while butyrate is primarily produced by the Firmicutes phylum (Hoverstad and Midtvedt 1986; Macfarlane and Macfarlane 2003).

Administration of SCFAs leads to alterations in hematopoiesis, resulting in an enhanced myeloid output due to elevated numbers of myeloid precursors (Balmer et al. 2014; Khosravi et al. 2014). This myeloid skew promotes clearance of systemic infection (Balmer et al. 2014; Khosravi et al. 2014) and ameliorates allergic reactions (Trompette et al. 2014). SFCAs also influence myeloid cells post-hematopoiesis, as has been described for microglia in the brain. The cells feature abnormalities in morphology and function in the absence of the microbiota, which can be partially restored by SCFA supplementation (Erny et al. 2015). These examples illustrate that part of the impact

that the microbiota exerts on host immune system development is mediated through microbiota-modulated metabolites.

Apart from these examples of the systemic effects of microbiota-derived metabolites that influence molecular and cellular processes far from the intestinal tract, the microbiota also modulates tissue-level immune system maturation through its profound impact on local metabolite levels.

Tryptophan metabolites

One prominent example of how the microbiota impacts tissue-level immune maturation is the microbial metabolism of tryptophan. It was shown that commensal *Lactobacilli* use tryptophan as an energy source to produce ligands of the aryl hydrocarbon receptor (AhR), such as the metabolite indole-3-aldehyde (Zelante et al. 2013). AhR is a ligand-activated transcription factor critically important for the organogenesis of intestinal lymphoid follicles (ILFs). Immune cells expressing AhR include RORγt$^+$ group 3 innate lymphoid cells (ILC3s) that are involved in ILF genesis, and AhR expression on ILC3s is functionally required for their expansion (Kiss et al. 2011). In addition, AhR-induced IL-22 production by ILCs drives the secretion of the anti-microbial peptides lipocalin-2, S100A8, and S100A9, which protect from pathogenic infection by *Candida albicans* (Zelante et al. 2013). Similarly, mice lacking AhR are more susceptible to infection with *Citrobacter rodentium* and *Listeria monocytogenes* (Shi et al. 2007; Qiu et al. 2012).

In addition to its role in the function of ILCs, AhR was also found to be necessary for the maintenance of the epithelial barrier and the homeostasis of intraepithelial lymphocytes (IELs) (Li et al. 2011; Lee et al. 2012). When AhR-deficient mice were subjected to DSS-induced colitis, they featured enhanced disease susceptibility compared with wild-type mice, which was not apparent when mice were fed a synthetic diet depleted of dietary AhR ligands. The transfer of functional IELs to AhR-deficient mice resulted in ameliorated disease and enhanced recovery (Li et al. 2011; Lee et al. 2012).

Retinoic acid (RA)

In addition to the orchestration of immune system maturation, metabolites fine-tune immune responses at the level of post-developmental differentiation. The vitamin A lipid metabolite RA was shown to regulate the balance between proinflammatory and anti-inflammatory immune responses. RA deficiency affects both the composition of the microbiota and immune system function. Mice deficient in RA harbor reduced numbers of segmented filamentous bacteria (SFB), which might contribute to the decreased number of T helper 17 (T_H17) cells present in vitamin A-deficient mice (Gaboriau-Routhiau et al. 2009; Cha et al. 2010).

In the steady state, RA has an important role in the maintenance of immune homeostasis in the intestine, as it can promote both regulatory T (Treg) cell development through TGF-β and the production of IgA by B cells (Mora et al. 2006; Coombes et al. 2007; Mucida et al. 2007; Sun et al. 2007). RA mediates the expansion of Treg cells and the suppression of T_H17 lineage (Bergstrom et al. 2010; Hall et al. 2011b) through induction of histone acetylation at the FoxP3 promoter, the master regulator of Treg cell identity (Kang et al. 2007). DCs from the lamina propria of the small intestine can promote CD4$^+$ T cell conversion to Tregs in a manner dependent on TGF-β and RA (Sun et al. 2007). This capability of DCs is influenced by the microbiota, as feeding of mice with *Bifidobacterium infantis* results in elevated number of DCs capable of synthesizing RA as well as FoxP3$^+$ cells in the lamina propria (Konieczna et al. 2013).

Paradoxically, during inflammation, RA is also involved in eliciting proinflammatory CD4$^+$ T-cell responses to infection (Hall et al. 2011a). Accordingly, mice fed a diet deficient in vitamin A were reported to feature inhibited T_H17 cell differentiation in the lamina propria of the small intestine (Cha et al. 2010). RA was also shown to be important for the expression of gut-homing molecules on immune cells. In the absence of TLR signaling in MyD88-deficient mice, intestinal DCs express low levels of retinal dehydrogenases, a critical enzyme for RA biosynthesis, and are impaired in their ability to induce gut-homing lymphocytes (Iwata et al. 2004; Mora et al. 2006; Wang et al. 2011; Bakdash et al. 2015).

The impact of vitamin A even reaches beyond T-cell immunity. In the absence of vitamin A, the numbers of ILC3s are strongly diminished, while ILC2 cells and their immune program became more dominant (Spencer et al. 2014). A similar phenomenon can be observed in adaptive lymphocytes, where T_H2 cells expand under vitamin A-deficient conditions on the expense of T_H1 and T_H17 immunity (Pino-Lagos et al. 2011). Together, these studies highlight the power of a diet-derived and microbiota-modulated metabolite in directing a specific type of immune response.

Other vitamins can likewise participate in the post-developmental fate decisions of leukocytes. For instance, vitamin D profoundly affects T-cell activation (von Essen et al. 2010). Several studies have linked vitamin D deficiency to inflammatory bowel disease susceptibility (Sun 2010), and vitamin D receptor expression is significantly lower in IBD- and colitis-associated colon cancer patients (Abreu et al. 2004; Wada et al. 2009).

The link between the gut microbiota and vitamins is particularly apparent in the case of vitamins belonging to B and K groups, as, in their case, the host is unable to perform the biosynthetic reactions and depends on members of the commensal microbiota (Roth et al. 1996; Hill 1997; Martens et al. 2002). For instance, the gut commensals *Bifidobacterium* and *Lactobacillus* can synthesize the B9 vitamin folate (Noda et al. 1994; Pompei et al. 2007; Strozzi and Mogna 2008; Kleerebezem and Vaughan 2009), which was shown to have a critical role in the maintenance of Treg cells in the small intestine (Kunisawa et al. 2012). Vitamin B12 deficiency results in a decreased number of lymphocytes and suppressed NK cell activity (Tamura et al. 1999). The recent discovery of vitamin metabolite presentation to mucosa-associated invariant T

(MAIT) cells by the MHC class I-like molecule MR1 (Kjer-Nielsen et al. 2012; Le Bourhis et al. 2013) suggested a direct link between microbial vitamin metabolism and immune cell priming.

Metabolites as regulators of symbiosis

The quintessential task of mutualistic host–microbiota interactions at mucosal surfaces is the preservation of tissue homeostasis. Over the last decade, several microbial molecules have been identified that aid in the orchestration of the tightrope walk between immunity and tolerance at the mucosal–bacterial interface (Fig. 1). A common strategy by several such molecules is the promotion of an anti-inflammatory response. The commensal *Bacteroides fragilis* produces surface polysaccharide A (PSA) that suppresses the production of the proinflammatory IL-17 and promotes expression of IL-10 by $CD4^+$ T cells through binding to TLR2 (Mazmanian et al. 2008; Round and Mazmanian 2010). It was first demonstrated that monocolonization of germ-free mice with *B. fragilis* modulates $CD4^+$ T-cell homeostasis and cytokine production in a PSA-dependent manner. PSA presented by DCs activates cognate $CD4^+$ T cells (Mazmanian et al. 2005). Later, it was shown that PSA of *B. fragilis* dampens *Helicobacter hepaticus*-driven intestinal inflammation and likewise prevents colitis induced by the chemical compound TNBS and that a mutant of *B. fragilis* lacking PSA could not prevent inflammation (Mazmanian et al. 2008). The recognition of PSA by TLR2 specifically expressed on Treg cells induces their activation, which in turn leads to suppression of the inflammatory response. This circuit is required for the colonization of *B. fragilis* (Round et al. 2011), potentially providing an example for active niche construction by a commensal bacterium through modulating the host immune response.

Such metabolite-induced feedback loops might emerge as a common theme in the regulation of a stable microbial colonization by the immune system. This is best illustrated by the epithelial innate immune sensor NLRP6, a member of the NOD-like receptor family, which is involved in viral recognition as well as inflammasome formation (Levy et al. 2015a; Wang et al. 2015a). The inflammasome pathway is influenced by the microbiota-modulated metabolites taurine, histamine, and spermine, thereby regulating the level of epithelial IL-18 production, anti-microbial peptide secretion, and intestinal community composition (Levy et al. 2015b). Thus, the metabolic activity of the microbiome is sensed by the immune system, and this sensing is translated into an anti-microbial response aimed at maintaining a stable colonization. If this pathway is disturbed in genetically modified mice, dysbiosis arises, leading to the manifestation of intestinal autoinflammation (Elinav et al. 2011), enhanced susceptibility to enteric infection (Wlodarska et al. 2014), intestinal tumorigenesis (Hu et al. 2013), and liver inflammation (Henao-Mejia et al. 2012).

In addition to the amino acids that modulate NLRP6 signaling, other amino acids are involved in the maintenance of intestinal homeostasis. It was shown that protein malnutrition (and specifically tryptophan depletion) alters the severity of intestinal inflammation (Hashimoto et al. 2012). Angiotensin-converting enzyme 2 (ACE2) controls the expression of the neutral amino acid transporter in the intestine. $Ace2^{-/-}$ mice feature altered gut microbial composition, and these mice develop severe colitis after induction of epithelial damage by DSS. Transplantation of the gut microbiota to germ-free mice transfers the inflammatory phenotype and susceptibility to colitis, while a tryptophan-rich diet reverses microbial composition in this model (Hashimoto et al. 2012).

Similar to $Ace2^{-/-}$ mice, mice lacking indoleamine 2,3-dioxygenase (IDO1) display altered microbial composition as well as aberrations in metabolic pathways of both the microbiota and the host (Puccetti and Grohmann 2007; Zelante et al. 2013). IDO1 activity was shown to inhibit IL-10, which, in a model of atherosclerosis, leads to ameliorated disease (Metghalchi et al. 2015). $Ido1^{-/-}$ mice showed blooming of *Lactobacilli* similar to mice on a tryptophan-rich diet, which resulted in an accumulation of the AhR ligand indole-3-aledhyde. Moreover, tryptophan catabolism through IDO1 affects the differentiation of $CD4^+$ T cells that secrete IL-17, which is modulated by the microbiota (Huengsberg et al. 1998; Romani et al. 2008; Favre et al. 2010).

In addition to tryptophan, the microbiota is pivotal for the regulation of intestinal levels of the amino acid arginine, which in turn exerts a modulatory effect on the immune system. Germ-free mice feature elevated levels of arginine, indicating that commensal bacteria are involved in the metabolism of arginine to downstream derivatives, including polyamines (Matsumoto et al. 2012; Mardinoglu et al. 2015). Correspondingly, polyamine levels are strongly diminished in the absence of the microbiome (Matsumoto et al. 2012). Polyamines in turn exert their immunomodulatory effect on various cell types, including macrophages and epithelial cells, where they contribute to suppressed inflammation (Kibe et al. 2014; Levy et al. 2015b).

Although arginine is primarily metabolized in the liver, immune cells can also serve as an extrahepatic source for arginase-1 (Arg1) activity during infection and inflammation (Raber et al. 2012; Wynn et al. 2013; Thomas and Mattila 2014; Murray 2015). Myeloid cell Arg1 has immunosuppressive capacities (Rodriguez et al. 2004; Munder et al. 2006), and, recently, Arg1 was shown to perform a cell-intrinsic role in the regulation of ILC2 metabolism and type 2 inflammation in the lung (Monticelli et al. 2016).

A further example of an anti-inflammatory molecule produced by the microbiota is provided by SCFAs, which have been briefly discussed above in the context of their impact on hematopoiesis, indicating that certain metabolites may perform a multitude of functions at several layers of immune regulation. The anti-inflammatory effect of SCFAs has been well characterized in both immune cells and epithelial cells. The intestinal microbiota, through the production of SCFAs, can suppress inflammation through several distinct mechanisms. Germ-free mice as

well as colonized mice treated with acetate show ameliorated severity of DSS-induced colitis, and this beneficial effect is dependent on the receptor GPR43. Consequently, *Gpr43*$^{-/-}$ mice feature elevated severity of inflammation compared with wild-type mice (Maslowski et al. 2009). As in the case of immune system development, SFCAs exert their symbiosis-promoting effects both locally at the tissue level and systemically. Circulating SCFAs can suppress the inflammatory response in the lungs in a GPR41-dependent manner. A low-fiber diet increased the severity of allergic airway inflammation, while propionate administration protected from airway inflammation with reduced amounts of IL-4, IL-5, IL-13, and IL-17 in the lung (Trompette et al. 2014).

Another major function of SCFAs in dampening the inflammatory response is the regulation of colonic Treg homeostasis (Atarashi et al. 2011, 2013; Smith et al. 2013). SCFAs were shown to selectively expand Tregs in the large intestine. Feeding of germ-free mice with SCFAs increased the numbers of FoxP3^{+} Treg cells to a level similar to that observed in conventionalized mice. Propionate administration increased the expression of FoxP3 and IL-10 in colonic Treg cells (Smith et al. 2013). It was further shown that intestinal Tregs express GPR43 and that, in *Gpr43*$^{-/-}$ mice, the expansion of Tregs by SCFAs was abrogated (Smith et al. 2013). Interestingly, a mixture of Clostridia species, which are a prominent source of SCFA production, induced the development of Tregs and the production of the anti-inflammatory cytokine IL-10 (Atarashi et al. 2011, 2013). Mechanistically, Clostridia species cooperatively produce SCFAs that elicit a TGF-β response by epithelial cells. SCFAs also facilitate peripheral extrathymic generation of Tregs through a different mechanism (Furusawa et al. 2013; Smith et al. 2013). Butyrate epigenetically regulates gene expression through inhibition of histone deacetylases (HDACs), resulting in enhanced histone acetylation in the noncoding sequences of the FoxP3 locus (Arpaia et al. 2013; Smith et al. 2013). Consequently, butyrate-treated CD4^{+} T cells depicted increased histone H3 acetylation of the FoxP3 promoter region and at the intragenic enhancer element conserved noncoding DNA sequence 1 (CNS1) (Arpaia et al. 2013; Furusawa et al. 2013; Smith et al. 2013).

The role of butyrate as a HDAC inhibitor was also shown to contribute to the suppression of inflammatory response by intestinal macrophages (Chang et al. 2014). Treatment of bone marrow-derived macrophages with butyrate induced hyporesponsiveness to LPS stimulation and suppressed the proinflammatory cytokines IL-6 and IL-12p40 due to the HDAC inhibitory activity of butyrate and H3K9ac deposition on the *Il6* and *Il12b* loci (Chang et al. 2014). Taken together, these results highlight the central importance of SCFAs in the communication between the microbiome and the host immune system.

Conclusions

The study of metabolites as messengers between the microbiota and the immune system has initiated a paradigm change in our understanding of host–microbial interactions. The increasing mechanistic knowledge about how microbiota metabolism shapes the physiology of its host impacts at least three areas of fundamental importance to both the conceptualization of host–microbiota interactions and its translation to clinical applications.

First, the discoveries made in the field of microbiome research over the last decade have challenged our model of how the immune system recognizes and eliminates micro-organisms upon contact with the host. The notion that microbial recognition by pattern recognition receptors of the innate immune system inevitably leads to the initiation of an immune and inflammatory response that aims at achieving eradication of the microbial trigger cannot possibly apply to the situation of colonization by commensal microbes. As such, the mechanisms of an immune response to pathogenic infection, studied in detail for almost a century, might represent the exception rather than the rule with regard to microbial handling by the immune system. The conceptual difficulty in the distinction between commensal colonization and pathogenic infection by the immune system lies in the fact that the ligands of all known pattern recognition receptors are conserved molecular structures that are essential for microbial existence and therefore shared across the spectrum of pathogenic and nonpathogenic micro-organisms. To reconcile these apparently opposing concepts, microbial viability, localization, and virulence factor expression have been suggested as hallmarks of pathogen-induced immune responses (Sander et al. 2011; Kamada et al. 2013). The discovery of bacterial metabolites as modulators of immune responses adds an important facet to our understanding of the distinction between mutualism and pathogenicity at the host–microbial interface. By sensing microbial metabolites, the immune system may evaluate microbial activity rather than the mere presence or absence of micro-organisms at a given location. The metabolite profile characteristic of a pathogenic invasion likely differs from the one characteristic of homeostasis, and thus this change in metabolite composition and concentrations may be sensed by the immune system as a deviation from homeostatic set points to initiate an appropriate inflammatory response.

Second, despite the rapid progress over the last decade in the identification of bacterial drivers of human diseases, the selective eradication of disease-associated micro-organisms from the intestinal microbial community remains a major challenge. Currently, antibiotics and fecal microbiota transplantation are the only clinically approved approaches to targeting a disease-causing microbiota. The use of antibiotics in the treatment of aberrant host–microbial interactions resembles the use of chemotherapy in cancer treatment in that it removes the causative agent of a disease at the cost of major disruptions in the endogenous cellular organization. Similarly, the effectiveness of fecal microbiota transplantation is based on the replacement of the entire intestinal community—a radical intervention resulting in an often unpredictable outcome. The identification of specific microbiota-derived metabolites and their effect on the host immune

system has provided mechanistic insights that are much more tangible than the association of disease phenotypes with microbial taxa in large data set collections. On the one hand, metabolites are ideally suited as biomarkers for disease development, as their detection is usually affordable and scalable and may precede the onset of clinically manifest disease symptoms. On the other hand, the causal involvement of microbiota-derived metabolites in the molecular etiology of human disease presents direct opportunities for the rational development of new patient-tailored therapies. Beneficial metabolites can be administered with typically easy-to-control pharmacokinetics and without the danger of inadvertent immune responses to the drug. In addition, disease-associated metabolites can be targeted by pharmacological or nutritional intervention, potentially without strong interference from the homeostatic metabolism. The first proof of principal studies have included microbial targeting of the TMAO metabolism in the treatment of atherosclerosis (Wang et al. 2015b), and future research is warranted to further exploit such metabolite-based therapeutic options.

Third, the microbiome harbors a sheer endless reservoir of metabolic capabilities, which has led to the suggestion that, while the cataloging of microbial taxa that colonize mammalian mucosal surfaces may reach saturation within the next decade of microbiome research, the assessment of the entirety of the chemical complexity encoded by the microbiome is still in its infancy. This is interesting with regard to the pharmacologic opportunities mentioned above but may also help to better define a fundamental aspect of host–microbiota interactions; namely, the evolutionary teleology of microbial niche construction through modulation of the host immune system. The initial goal at early stages of the Human Microbiome Project had been to define a core microbiome shared by all individuals, motivated by the assumption that coevolution between the microbiota and its host has yielded an indispensable canon of bacteria characteristic of the intestinal community in the human gut (Turnbaugh et al. 2007). At later states, however, this notion has been replaced by the realization that the immense interindividual variability in the composition of the microbiota does not allow for the definition of a shared "core" on the taxonomic level (The Human Microbiome Project Consortium 2012). With the study of metabolites as common outputs of bacterial metabolic function, the notion of a functional core can be revisited. It is conceivable that different taxonomic groups of bacteria have evolved to perform similar metabolic functions and are thus classifiable by the type of metabolites that they produce and, consequently, the type of physiologic response that they elicit in the host. One may speculate that, despite the vast taxonomic diversity and variability that has been documented in cataloging studies of various human microbiomes to date, the members of the commensal microbiota can be classified into a limited variety of functional subsets with respect to their metabolite profile (Thaiss and Elinav 2014). Therefore, distinct groups of bacteria with niche-specific immunomodulatory activity might have evolved, employing similar metabolic pathways and metabolite signatures for the maintenance of homeostatic colonization. Such a level of understanding regarding the molecular details of colonization mechanisms and immune cell–microbiota cross-talk would open up a new area in this young field of study, resulting in numerous possibilities for the therapeutic exploitation of basic discoveries.

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Maayan Levy, Christoph A. Thaiss and Eran Elinav

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