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Human microbial metabolites as a source of new drugs

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Crosstalk between the microbiome and the human host is mediated by specific ligand–receptor interactions involving microbially generated metabolites that can be either agonists or antagonists of human proteins. The evolved co-compatibility of gut microbiota with human systems points to a potentially rich area for discovering new drug-like molecules that are both highly specific modulators of human pathways and derisked for adverse effects. In this review, we discuss the rapidly growing research into the role of microbial metabolites in human health and suggest potential strategies for developing these molecules into therapeutic agents.

Introduction

The discovery of safe and effective drugs is the cornerstone of the pharmaceutical industry. It is estimated that compound toxicity and/or lack of efficacy accounts for up to 90% of early-stage discovery terminations and withdrawals [1]. To address these challenges, drug discovery scientists are looking for innovative approaches to find new candidate compounds. The human body requires the functional interactions between thousands of naturally occurring metabolites and many cellular receptor proteins. Human transporters have evolved to preferentially interact with specific metabolites and, in fact, many successful drugs resemble such metabolites [2]. Moreover, metabolite-mimic drugs are more likely to be well tolerated because they naturally occur in our bodies. Thus, the human gut itself could be a potential apothecary for new safe and efficacy drugs [3].

Emerging science increasingly suggests that the collective genome of intestinal microbial communities, the so-called 'gut microbiome', has a crucial role in supporting the normal functioning of human metabolic and immune systems [4]. Dysbiosis, the state of imbalance among bacterial species or the microbiota, has been associated with many immunity-related diseases, including Type 1 diabetes, Type 2 diabetes mellitus (T2DM), inflammatory bowel diseases, and asthma [5,6]. However, determining circumstances in which changes in bacterial species or microbiota composition can influence disease severity versus occasions where differences in the microbiome between the healthy and diseases state are merely secondary adaptations to a shifting host environment is essential for translating microbe – disease associations into therapeutic opportunities.

Understanding the specific functional relationships between microbes and humans is a rapidly growing area of research. Recent studies of human gut microbiota are increasingly revealing bacterial metabolites, peptides, and cellular components that can modulate human gene expression and pathways. For example, bacterial lipopolysaccharide (LPS), the outer membrane component of Gram-negative bacteria, such as Proteobacteria, is well known for its damaging, proinflammatory effects [7]. Other molecules have more specific and beneficial actions. A naturally cleaved peptide fragment secreted by the bacterium *Lactobacillus plantarum* has been shown to stimulate the production of the cytokine interleukin 10 (IL10) by human intestinal dendritic cells [8]. A customized probiotic mixture of *Clostridium* type IV and XIVa symbiont strains that promoted the accumulation of specific regulatory T cells (T_{regs}) expressing transcription factor Forkhead box P3 (FOXP3) were found to protect mice from colitis [9] and, more recently, to modulate type 2 immunity and allergic inflammation [10]. The peptide polysaccharide A or PSA produced from another human symbiont, *Bacteriodes fragilis*, has been shown to suppress the production of the proinflammatory cytokine interleukin 17 (IL17) from

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intestinal immune cells [11]. Sphingolipids, also produced by *B. fragilis*, inhibit host invariant natural killer T (iNKT) cells and confer protection in mice against oxalone-induced colitis [12].

The spectrum of microbiota-produced molecules and their potential interactions with the host have been extensively reviewed elsewhere [13]. The examples of bacterial modulators listed above are arguably very different structurally from the conventional small molecules developed for decades by the pharmaceutical industry. However, metabolite by-products of biotransformation reactions driven by gut bacterium better embody the drug-like properties desired by medicinal chemists [2]. In addition, there are several recent and exciting developments in defining those specific metabolite ligand–human receptor interactions and their linkages to human disease. In this review, we focus on the role of endogenous bacterial metabolites in facilitating microbe–human host crosstalk and their potential as new therapeutics.

The human gut microbiome and metabolome

The human intestinal tract is home to a diverse and essential ecosystem of microbes. The number of microbial cells in a given individual exceeds the number of human cells by at least tenfold [14], while the collective genome of the microbial community or the microbiome has a gene content exceeding by 100 times that of the human genome [15]. These microbiota are not idle: they are continuously metabolizing ingested substances flowing through the digestive system as well as endogenously secreted peptides, bile acids, and metabolites. Although the main symbiotic function of the microbiome is energy conversion, the intestinal metabolite milieu engages multiple human host receptors to modulate the immune system, both to our benefit and detriment. Many secondary metabolites with beneficial effects can be traced back through bacterial metabolic pathways to specific foodstuffs, such as fiber and plant flavonoids, which are associated with good health (Fig. 1). Thus, it is not coincidental that these metabolites can have positive interactions with the human host immune system and act as suppressors of disease-associated inflammatory pathways [16]. We have only begun to decipher the networks of bacterial metabolite–human receptor interactions and their subsequent downstream effects on cellular response. However, several specific interactions of metabolites are becoming better understood, which are discussed below.

Short-chain fatty acids

Of the hundreds of bacterial metabolites in the gastrointestinal tract (GIT), short-chain fatty acids (SCFAs) are the most well studied to date. SCFAs are saturated aliphatic organic acids comprising one–six carbon atoms that are fermentation products of dietary plant fibers produced by bacterial glucosidases (reviewed in [17,18]). The most common SCFAs in the colon are acetic (C2), propionic (C3), and butyric (C4) acids, which are predominantly produced by bacteria from the phylum Firmicutes, such as species from the genera *Lactobacillus*, *Clostridium*, *Lactococcus*, and others (Table 1). Deficits of SCFA-producing species are associated with increased severity of many metabolic and inflammatory diseases, including T2DM, obesity, colorectal cancer, inflammatory bowel disease, and irritable bowel syndrome [19–22]. SCFAs, as modulators of energy homeostasis and insulin sensitivity, exert positive changes in metabolic diseases associated with insulin resistance and glucose metabolism (reviewed in [23]).

SCFAs modulate cell function and maintain epithelial integrity in the gut by binding to 'metabolite-sensing' G-protein-coupled receptors (GPCRs, now called free fatty acid receptors or FFAR), such as FFAR1 (formerly GPR40), FFAR2 (GPR43), FFAR3 (GPR41),

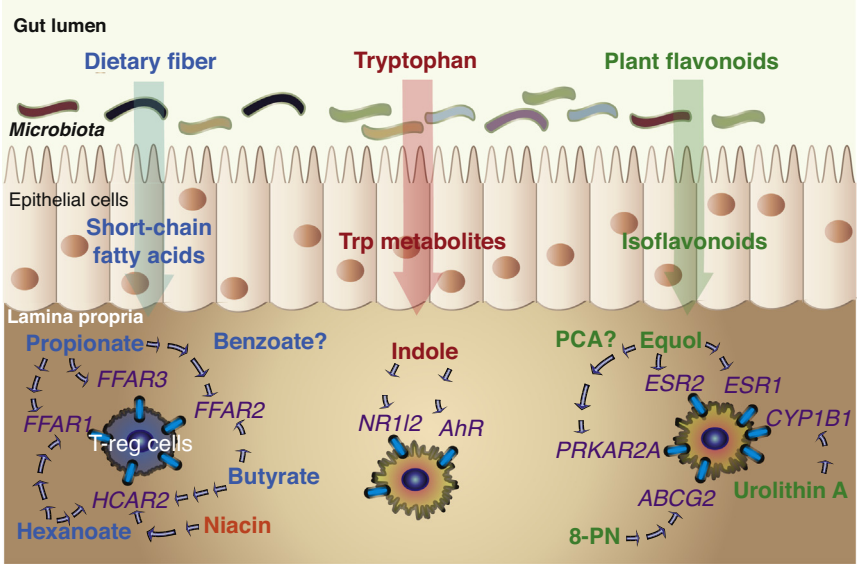

FIGURE 1

Examples of gastrointestinal tract metabolites produced by microbiota and their human receptor interactions. Metabolites with unknown receptors have a question mark (see Table 1 and the main text for further details). HUGO gene names are given for: free fatty acid receptors (FFAR); hydroxycarboxylic acid receptor 2 (HCAR2); nuclear receptor subfamily 1 group | member 2 (NR1|2 or PXR); aryl hydrocarbon receptor (ArH); estrogen receptors (ESR); protein kinase, cAMP-protein kinase A (PRKAR2A); cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1); and ATP binding cassette subfamily G member 2 (ABCG2).