Emerging Concepts

Weak Microbial Metabolites: a Treasure Trove for Using Biomimicry to Discover and Optimize Drugs

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ABSTRACT

For decades, traditional drug discovery has used natural product and synthetic chemistry approaches to generate libraries of compounds, with some ending as promising drug candidates. A complementary approach has been to adopt the concept of biomimicry of natural products and metabolites so as to improve multiple drug-like features of the parent molecule. In this effort, promiscuous and weak interactions between ligands and receptors are often ignored in a drug discovery process. In this Emerging Concepts article, we highlight microbial metabolite mimicry, whereby parent metabolites have weak interactions with their receptors that then have led to discrete examples of more potent and effective drug-like molecules. We show specific examples of parent-metabolite mimics with potent effects in vitro and in vivo. Furthermore, we show examples of emerging microbial ligand-receptor interactions and provide a context in which these ligands could be improved as potential drugs. A balanced conceptual advance is provided in which we also acknowledge potential pitfalls—hyperstimulation of finely balanced receptor-ligand interactions could also be detrimental. However, with balance, we provide examples of where this emerging concept needs to be tested.

SIGNIFICANCE STATEMENT

Microbial metabolite mimicry is a novel way to expand on the chemical repertoire of future drugs. The emerging concept is now explained using specific examples of the discovery of therapeutic leads from microbial metabolites.

Biomimicry as an Innovation Concept

Biomimicry is derived from the words, *bios* (Greek), or life or nature, and *mimesis* (Greek), or imitation (http://static.biomimicry.org/wp-content/uploads/2012/02/Biomimicry_Resource_Handbook_Excerpt.pdf; Hargroves and Smith, 2006). Various industries have adopted biomimicry-based approaches for innovative solutions (https://www.weforum.org/agenda/2018/03/biomimicry-a-new-approach-to-innovation-inspired-by-nature; Hu et al., 2019; Wood, 2019; Falanga et al., 2020). In medicine, biomimicry involves developing analogs of host

ABBREVIATIONS: AhR, aryl hydrocarbon receptor; DAT, desaminotyrosine; FXR, farnesol X receptor; GPCR (GPR), G-protein–coupled receptor; IA, indoleacrylate; IDO1, indoleamine 2,3-dioxygenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; OCA, obeticholic acid; PXR, pregnane X receptor; SCFA, short-chain fatty acid; UroA, urolithin A.

endogenous molecules that have evolutionarily adapted to target a given receptor and induce a favorable outcome. For instance, the soil bacterium *Sorangium cellulosum* (Gerth et al., 1994; Molnar et al., 2000) has likely evolved in its capacity for epothilone biosynthesis to ensure optimal fitness in its environment (Tang et al., 2000; Gerth et al., 2003; Rachid et al., 2007; Altmann et al., 2009). Epothilones have diverse therapeutic activity in host organisms as anti-inflammatory agents and antibiotics as well as antiviral, anticancer, and other types of therapies (Gerth et al., 1996). Modifying the oxidation states of a parental epothilone compound could give rise to a class of epothilone analogs with improved cytotoxic potential for cancer therapy (Tang et al., 2003). Indeed, a synthetic analog of microbial epothilones, Bristol Myers Squibb 247550 (ixabepilone), targets microtubules in mammalian cells and is approved for the treatment of breast cancer (Li et al., 2017). Beyond cancer indications, obeticholic acid (OCA), or Ocaliva, an analog of the endogenous farnesol X receptor (FXR) ligand chenodeoxycholic acid, has exhibited clinical benefit for primary biliary cholangitis (Pellicciari et al., 2002; Markham and Keam, 2016). Much effort has been allocated toward deriving therapeutics from potent metabolites produced by soil and marine bacteria. Here we will make the case that isolation of weak metabolites from the human commensal microbiome may increase the library of candidate metabolite analogs with therapeutic potential.

Recent evidence indicates that the human microbiome of a 70-kg reference male contains approximately 3.8×10^{13} cells, which is roughly equivalent to the number of human cells in the body (Sender et al., 2016). Although these figures remain best estimates, the massive numbers of microbes present in our bodies underscore their ability to expand the metabolic capabilities of the human organism. For example, in the gut, there are over 3–9 million unique bacterial genes (Yang et al., 2009; Qin et al., 2010). We may speculate that bacterial metabolic pathways are equally as diverse, and that their chemical compounds are highly varied in structure and function. Some metabolites derived from the commensal human microbiome exhibit therapeutic properties (Dobson et al., 2009; Saha et al., 2016; Descamps et al., 2019; Skelly et al., 2019). Metabolites with known therapeutic potential are likely to be only a fraction of the total therapeutic repertoire of microbial metabolites, as suggested in metabolomic studies (Folberth et al., 2020).

Microbial Metabolite Mimicry as a Drug Discovery Concept

We recently described microbial metabolite mimicry as an emerging concept for drug discovery (Dvořák et al., 2020). Based on the potential for improving the potency, selectivity, or pharmacokinetics of weak to moderate natural ligands, microbial metabolite mimics may simultaneously minimize off-target liabilities as a means to expand chemical and drug repertoires (Fig. 1). The feasibility of this approach has been demonstrated through the recent preclinical development of several mimics with promising results.

Examples of Microbial Metabolite Mimicry in Drug Discovery

Indole Mimics and Inflammation. Microbial metabolism of dietary L-tryptophan yields a number of indole-containing
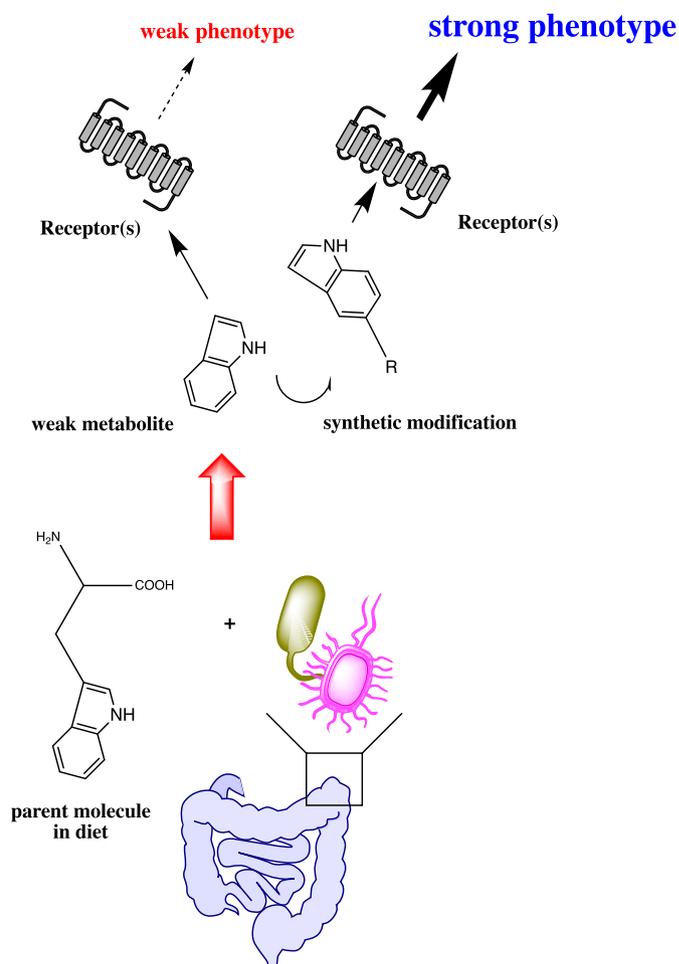

Fig. 1. Conceptual schematic of microbial metabolite mimicry. The intestine (blue) harbors many bacteria (multicolored). Some of these bacteria produce metabolites from a parent molecule in the diet (e.g., L-tryptophan) with weak receptor modulation, represented by an indole structure (weak metabolite). In applying a biomimicry-focused approach, modulating the chemical structure of a weak metabolite (synthetic modification) may produce a more potent modulator of a given receptor, thereby altering host phenotypes. These biomimics are chemically similar to the parent metabolite, and their off-target liabilities are likely to be less than that of xenobiotic structures, as demonstrated for indole mimics (Venkatesh et al., 2014).

metabolites (Roager and Licht, 2018) that are present and biologically active in rodents and humans (Vyhlídalová et al., 2020). These metabolites are diverse, and many have effects on multiple host receptors (Kim, 2018). For instance, the combination of indole (traditionally an aryl hydrocarbon receptor ligand) and its metabolite indole propionic acid was shown to activate the human pregnane X receptor (PXR). PXR agonism then regulates intestinal inflammation via the toll-like receptor 4–nuclear factor-κB pathway (Venkatesh et al., 2014). Subsequently, the same group developed indole–indole propionic acid pharmacophore analogs like Felix Kopp Kortagere 6 that exhibited potent PXR-dependent anti-inflammatory activity in mice (Nuzzo and Brown, 2020).

Indole can act upon other receptors important to hosting physiology, including the aryl hydrocarbon receptor (AhR). Activation of AhR by indole or other tryptophan metabolites has been shown to protect against colitis in mice (Rogala et al., 2020). There are several microbial-derived tryptophan metabolites that act as AhR agonists and can modulate the gastrointestinal

immune cells, enhance barrier function, and inhibit intestinal inflammation (Zelante et al., 2013; Rothhammer et al., 2016; Aoki et al., 2018; Natividad et al., 2018; Roager and Licht, 2018; Vyhlidalova et al., 2020). In this context, rationally designed indole analogs have been shown to act as potent AhR ligands that abrogate intestinal inflammation (Kawai et al., 2017; Chen et al., 2020). Since these are derived from parent molecules for which the host is likely tolerized, their toxicity is likely to be less than xenobiotics (Chen et al., 2020; Dvořák et al., 2020). More recently, *N*-acetylserotonin, a tryptophan metabolite produced along the serotonin pathway, acts as a positive allosteric modulator of indoleamine 2,3-dioxygenase 1 (IDO1) (Sonowal et al., 2017). IDO1 is an immunoregulatory enzyme involved in converting tryptophan to kynurenine, an endogenous AhR agonist (Mondanelli et al., 2020). The allosteric agonism of IDO1 by *N*-acetylserotonin protected mice from neuroinflammation and restored physiologic IDO1 activity in peripheral blood mononuclear cells from patients with relapsing-remitting multiple sclerosis (Mondanelli et al., 2020). Stable analogs of kynurenine may represent a feasible modality for AhR-targeted anti-inflammatory drug indications for autoimmunity. New classes of microbial-derived AhR ligands have been described (e.g., 1,4-dihydroxy-2-naphthoic acid) (Fukumoto et al., 2014). 1,4-Dihydroxy-2-naphthoic acid inhibits dextran sulfate sodium colitis in mice, and these ligands would appear to be a scaffold for a new class of AhR-active drugs (Fukumoto et al., 2014).

Apart from autoimmunity, pathogens also exploit the role of indole metabolism in maintaining homeostasis in the host. The pathobiont *Klebsiella oxytoca* secretes the indole analog tilivalline to induce antibiotic-associated hemorrhagic colitis (Stampfer et al., 2017). Substantially simplified tilivalline mimics block the production of tilivalline (von Tesmar et al., 2018). As these molecules mimic endogenous indoles produced by gut bacteria, they are likely to be nontoxic and improve health span (Sonowal et al., 2017).

Microbial Short-Chain Fatty Acids and Host G-Protein–Coupled Receptors in Health. Short-chain fatty acids (SCFAs) are produced by intestinal bacterial fermentation of nonabsorbed dietary carbohydrates. They have profound and generally homeostatic effects in the intestine (Kaiko et al., 2016; Chen et al., 2019). There are several SCFA receptors (e.g., GPR43, FFA2, FFA3, GPR109a) involved in the process of regulating colonic epithelial physiology and mucosal immune responses (Smith et al., 2013; Priyadarshini et al., 2018; Bolognini et al., 2019). SCFAs bind to their canonical receptors with weak affinity (micromolar range) (Husted et al., 2017). Homology and crystal structure models, along with mutagenesis and structure-function studies, have paved a clear road for the discovery of potent small-molecule SCFA analogs (Tikhonova, 2017). Alternatively, glycoengineering SCFAs onto a drug candidate improved pharmacologic properties with therapeutic potential for glycan-mediated pathologies (Saeui et al., 2018). SCFA-induced adipocyte differentiation can be enhanced using SCFA analogs (Jiang et al., 2013). SCFAs also exhibit weak inhibition of histone deacetylases. Specific zinc-chelating and motif-tethered SCFA analogs display nanomolar potency as histone deacetylase inhibitors (Lu et al., 2004), which suggests a feasible alternative source of chromatin-modifying drugs. Tributyrin, a prodrug of the SCFA butyrate, has more favorable pharmacokinetic properties than butyrate itself (Egorin et al., 1999) and, furthermore, was shown to have protective effects in ethanol-induced mouse models of intestinal

barrier dysfunction and liver injury (Cresci et al., 2014, 2017). Similarly, tributyrin can decrease the fitness advantage of pathogens like *Salmonella* that depend on lactate metabolism (Gillis et al., 2018). SCFAs may be important as a novel type of "co-drug" that enhances AhR-mediated effects in the gut (Korecka et al., 2016; Jin et al., 2017). Moreover, there is evidence that some high-fiber diets can be metabolized to enhance SCFA production, and these can be used in human studies (Baxter et al., 2019).

Dietary Nutrients, Microbial Metabolites, and Infection. Desaminotyrosine (DAT) is a microbial degradation product of polyphenolic flavonoids (Lambert and Moss, 1980; Schoefer et al., 2003). Recent data suggest that DAT protects against influenza virus infection by inducing type I interferons (Steed et al., 2017). Diets rich in polyphenols could exert a positive influence on DAT production. Identification of the exact molecular targets of DAT is a vital first step toward realizing DAT mimics with improved potency. Although the deployment of better intestinal models of humans is needed for the evaluation of polyphenol bacterial metabolites on preclinical models (van Duynhoven et al., 2011), a few studies have emerged that associate polyphenol metabolites with host health, including one implicating the metabolism of phenolic acids in blueberries (Russell et al., 2007). In these models, defining the targets of phenolic acids would be essential prior to embarking on drug discovery through microbial metabolite mimicry.

Microbial Enzyme Inhibitors, Diabetes, and Obesity. As a proof of concept, acarbose (α-glucosidase inhibitor) is frequently used in diabetic patients to control glycemia and postload insulin levels (van de Laar et al., 2005). Acarbose is made by *Actinoplanes* sp. SE 50/110. It is a pseudotetrasaccharide and contains an aminocyclitol moiety, valienamine, which inactivates intestinal α-glucosidase and sucrase. This combined effect decreases intestinal starch hydrolysis. Similarly, a host of inhibitors are derived from marine microbes, most with weak enzyme-inhibitor properties but with core pharmacophores that could be chemically modified (e.g., indole) (Gomez-Betancur et al., 2019). Amylase inhibitors are also positioned as drugs for weight loss (Mahmood, 2016). Despite the use of such inhibitors in diabetes (Jayaraj et al., 2013), long-term use warrants safe agents. To expand the drug repertoire by improving weak inhibitors, such as those obtained from microbial products (metabolites), mimicry would be applicable. For example, a few microbial α-amylase inhibitors include paim (obtained from culture filtrates of *Streptomyces corchorushii)* and Taisho amylase inhibitor-A and Taisho amylase inhibitor-B (oligosaccharide compounds from *Streptomyces calvus* TM-521) (Demain and Sanchez, 2009). Lipstatin, a pancreatic lipase inhibitor produced by *Streptomyces toxytricini,* is used to treat obesity and diabetes (Híreš et al., 2018). A stable analog of lipstatin, tetrahydrolipstatin (orlistat), is Food and Drug Administration–approved for the treatment of obesity (Filippatos et al., 2008). The side effects of orlistat are minimal and manageable but do include nausea, vomiting, and diarrhea (Khalil et al., 2020). In rats, orlistat may increase aberrant crypt formation during chemically induced inflammation (Garcia et al., 2006).

Emerging Opportunities

Microbial Metabolites and G-Protein–Coupled Receptor Families. In addition to SCFAs, other human microbiome–specific metabolites (e.g., phenylpropanoic acid, cadaverine, 9,10-methylenehexadecanoic acid, and

12-methyltetradecanoic acid) modulate host G-protein–coupled receptors (GPCRs) (Offermanns, 2017; Colosimo et al., 2019). The authors screened multiple fermentation fractions of bacterial culture broths from a simplified human microbiota simplified human microbiota consortium (Eun et al., 2014) and, after reverse-phase chromatography, applied the fractions to a multiwell 241 GPCR-specific engineered cell-line screen (β-arrestin recruitment screen). Although some metabolites (e.g., nicotinic acid EC_{50} ~2.2 μM for GPR109A) were inherently potent activators of GPCRs, there were several new metabolites with weak agonist activity (e.g., 3-hydroxyoctanoic acid EC_{50} ~304 μM; phenylpropanoic acid, a bacterial ligand, EC_{50} ~208 μM for GPR109B). Homology models, based on prior knowledge of GPR109A (Tunaru et al., 2005), and mutagenesis studies could be leveraged to define the ligand-binding pocket interactions for GPR109B with weak ligands; this could be useful for deriving phenylpropanoic acid mimics. Similar examples are shown by Cohen et al. (2017), whereby a microbiome-synthetic gene-therapy approach is applied toward GPR119-targeted therapy, given that human microbiota produce N-acyl amides that mimic human GPR119 ligands. Furthermore, defining GPCRs with dominant roles for a given ligand would be important to assess so that the correct receptor or set of receptors can be chosen to perform a library screen of mimics (Bolognini et al., 2019).

Bile Acids, Microbial Metabolites, and FXR. The FXR is a major target for liver disease prevention (Hoofnagle, 2020), with the primary bile acid chenodeoxycholic acid as the endogenous ligand. FXR agonists now in clinical use include OCA (Pellicciari *et al.*, 2002, 2018) and cilofexor (a non–bile acid synthetic FXR agonist), which have inspired drug development for a variety of hepatic diseases (Gioiello et al., 2014). The results of this study by Pellicciari and colleagues identified a key small pocket in the receptor ligand-binding domain that accommodates small hydrophobic groups at the C6α-position of chenodeoxycholic acid. In particular, the ethyl moiety perfectly fits the 10-Å cavity, leading to a 100-fold increase in FXR activity, and has become a key structural motif of a novel, potent bile acid–based modulator (findings made by Fraydoon Rastinejad). In 2016, OCA reached patients affected by primary biliary cholangitis and is currently being evaluated in patients with nonalcoholic steatohepatitis (Pellicciari et al., 2018). More recently, microbial amino-acid conjugations of the host bile acids, phenylalanocholic, tyrosocholic, and leucocholic acid, have been identified as FXR agonists (Quinn et al., 2020). Complementing these are other secondary microbial metabolites of bile acids like isodeoxycholate (Campbell et al., 2020). Using these templates, mimics could improve potency while limiting side effects (Quinn et al., 2020).

Dummy Analogs. The underlying rationale for the design of dummy analogs is to mimic a given bioactive molecule to promote competitive inhibition of a given target. Imidazole propionate, a human and rodent microbiome–specific metabolite, blunts insulin-induced mammalian target of rapamycin complex 1 activation, impairing glycolysis (Koh et al., 2018). The authors defined the alternative p38 pathway as a target of imidazole propionate. Thus, dummy imidazole analogs could blunt the effects of imidazole propionate on p38 via competitive binding. Importantly, the design of an imidazole analog library is reasonable given the simplicity of the biosynthesis of imidazole propionate from histidine (Koh et al., 2018).

Microbial Metabolites and Antioxidant Drug Discovery. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a global regulator of the antioxidant response that is evolutionarily conserved. A resident mucin-degrading bacterium *Peptostreptococcus russellii* produces the tryptophan metabolite indoleacrylate (IA), which activates Nrf2 and improves barrier function (Wlodarska et al., 2017). Although it remains unclear whether IA directly binds Nrf2, deeper investigation could reveal methods to mimic IA. Other small-molecule scaffolds, such as oxo fatty acids that activate the Nrf2–antioxidant responsive element pathway, can also be used to enhance the potency of mimics (Sofyana et al., 2020). Urolithin A (UroA) is a major microbial metabolite derived from polyphenolics of berries and pomegranate fruits. UroA displays anti-inflammatory and antioxidative activities yet weak potency. A recent report demonstrates the therapeutic potential of a more potent UroA analog UAS03 that enhanced barrier function and decreased inflammation in mice (Singh et al., 2019). It is to be noted that UroA could also act via the AhR pathway as a ligand, and therefore, its effects on any phenotype could be due to pleiotropic molecular mechanisms (Muku et al., 2018; Pernomian et al., 2020). In this context, vitamin metabolism by gut bacteria could affect the overall health of the host. For example, vitamin E acetate is metabolized by *Lactobacillus acidophilus* NCFM (Roager et al., 2014) similarly to the metabolism of natural forms of vitamin E, α-tocopherol, and γ-tocopherol by the intestinal microbiota of rats (Ran et al., 2019). Understanding the consequences of vitamin E metabolites and mimics on host health requires further study. These investigations should be coupled with defining not only host phenotypes but specific protein targets affected by those vitamins and their bioactive long-chain metabolites (e.g., garcinoic acid) (Bartolini et al., 2020). Along with PXR, these targets appear to include other nuclear receptors (e.g., peroxisome proliferator-activated receptor-γ) recently reviewed elsewhere (Torquato et al., 2020) and the anti-inflammatory protein 5-lipoxygenase (Pein et al., 2018). In another example, microbiome-derived ascorbate inhibits glucose transporter 1 in human CD4^{+} effector T cells, inducing apoptosis (Chang et al., 2019). However, alternative mechanisms of ascorbate delivery to sites of local inflammation cannot be excluded (Wang et al., 1997). Ascorbate mimics that potently inhibit glucose transporter 1, which is upregulated in activated T cells, could be a unique way to develop drugs targeting Crohn disease and other T cell–mediated nonmalignant disorders. In this regard, since multiple transporters are involved in ascorbate transport in different tissues, analogs specific to each transporter may also be feasible and could have reduced systemic, off-target toxicity (Corpe et al., 2005).

Microbial Metabolites and Mimics as Alternatives to Antibiotics. Discovery of new antibiotics is of crucial importance to combat antimicrobial resistance, with a very significant impact on global health and the agriculture industry. Microbial metabolite mimicry can certainly be applied here, wherein most clinically used antibiotics are microbially derived (Lewis, 2020). In the pork industry, early weaning of piglets improves the reproductive cycle in sows (Campbell et al., 2013); however, early weaning often causes stress-induced diarrhea in the piglets that can respond to antibiotics (Lallès et al., 2007), although antibiotic resistance remains a major problem (Allen et al., 2014; Chen et al., 2018). More

recently, it has been shown that fecal transplants from resistant to susceptible early-weaned piglets reduce this stress-induced diarrhea (Hu et al., 2018). Two dominant strains, *Lactobacillus gasseri LA39* and *Lactobacillus frumenti*, were identified from diarrhea-resistant feces that also confer resistance to diarrhea in susceptible piglets. The principal inhibitor that prevents diarrhea is the bacterial circular peptide gassericin A, which mediates its effect via host keratin 19 (Hu et al., 2018). It remains unclear whether this peptide fragment is optimized for keratin 19 binding, and optimizing the peptide sequence for this effect could present new therapeutic modalities.

Microbial Metabolites and Mimics to Shape Microbial Diversity. Some microbial metabolites can shape the emergence or loss of microbial diversity (Lilja and Johnson, 2017; Goldschmidt et al., 2018; Douglas, 2020). Microbial metabolite mimics with specific antibacterial effects could be screened against a consortium of intestinal bacteria in in vitro– and in consortia–inoculated germ-free mice to look for diversity control as a means to aide in host disease control. In this way, mimicry allows for expanding the metabolite repertoire to diversify the microbiome and maintain homeostasis of host health (Haag and Siegmund, 2014). This might be particularly relevant to the rapidly increasing Western-predominant inflammatory conditions associated with dysbiosis, such as inflammatory bowel diseases (Crohn disease and ulcerative colitis), metabolic syndrome, obesity, fatty liver disease, and inflammatory arthritis. In this respect, a dietary approach could be taken. A natural flavanol Kaempferol demonstrated significant activity against collagen-induced arthritis in mice when administered orally but not intraperitoneally, and Kaempferol was retained in the gut and diversified the microbiota; these data support the contribution of microbiome diversity toward the therapeutic effect (Aa et al., 2020). Kaempferol mimics with potent microbial reshaping ability could be designed for the treatment of arthritis (Aa et al., 2020).

The examples provided in this section of emerging opportunities demonstrate specific pathways in which microbial metabolites produced by bacteria in the host effectively engage one or more receptors in tissues. There is a clear phenotype observed when the metabolite engages the host tissue receptor. Indeed, modifying the metabolite to either improve its potency or to make the metabolite more stable could provide broad approaches toward improving drug discovery.

Future Efforts

Based on the rationale and examples presented, we recommend exploiting metabolically focused host-microbe relationships for future drug discovery using the microbial metabolite mimicry approach. These efforts should be coupled with medicinal chemistry and medium to high-throughput host phenotype assays. In some cases, multispecific small molecules may be feasible, especially when targeting a protein complex, as has been shown for antibodies (Deshaies, 2020). The chemistry should be simple, possibly automated, and integrated in innovative discovery platforms (Gioiello et al., 2020) to keep the process more efficient and at a low cost. Emphasis should also be on utilizing microbial chemistry pathways and well-designed and well-engineered biocatalysts

to synthesize novel mimics–perhaps using concepts of directed evolution of salient genes involved in the metabolite-synthesis pathway (Chen and Arnold, 1993).

In summary, several microbial metabolites have weak interactions with host receptors and offer the potential to generate mimics with increased binding affinities that will produce little to no toxicity when applied as therapies due to the host's tolerance to the native forms of these metabolites. Microbe-host interactions are critical to host physiology, and these relationships could be exploited chemically to drive favorable interactions. In drug discovery, in comparison with efforts on soil and marine bacterial metabolites, the human microbiome offers many such interactions that warrant chemical mimicry. Although these mimics could suffer the same metabolic fate as other xenobiotics, by keeping the chemistry simple and with a full understanding of its metabolic fate/liabilities, it is possible to design better drugs.

Evolutionarily, it is also possible that these weaker receptor-ligand interactions are advantageous to the host to prevent hyperstimulation of the respective receptors, which may in fact have detrimental consequences. Furthermore, not all microbial metabolites benefit the host because some may drive inflammation and carcinogenesis (Nyangale et al., 2012; Windey et al., 2012; O'Keefe, 2016). As such, in developing this new field of pharmacology, it is essential to understand the balance between binding affinities and physiologic outcomes to fine-tune receptor-ligand interactions for optimal health outcomes.

Authorship Contributions

Participated in research design: Dvorak, Klapholz, Gioiello, Pelliciari, Galli, March, Sartor, Levy, Mani.

Wrote or contributed to the writing of the manuscript: Dvorak, Klapholz, Burris, Willing, Gioiello, Pelliciari, Galli, March, Sartor, O'Keefe, Kim, Levy, Mani.

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