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Gut Reactions: Breaking Down Xenobiotic–Microbiome Interactions

Gerard Clarke, Kiran V. Sandhu, Brendan T. Griffin, Timothy G. Dinan, John F. Cryan, and Niall P. Hyland

APC Microbiome Ireland (G.C., K.V.S., B.T.G., T.G.D., J.F.C., N.P.H.), INFANT Research Centre (G.C.), Department of Psychiatry and Neurobehavioural Science (G.C., T.G.D.), School of Pharmacy (B.T.G.), and Departments of Anatomy and Neuroscience (J.F.C.), Pharmacology and Therapeutics (N.P.H.), and Physiology (N.P.H.), University College Cork, Cork, Ireland

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***Abstract*——The microbiome plays a key role in health and disease, and there has been considerable interest in therapeutic targeting of the microbiome as well as mining this rich resource in drug discovery efforts. However, a growing body of evidence suggests that the gut microbiota can itself influence the actions of a range of xenobiotics, in both beneficial and potentially harmful ways. Traditionally, clinical studies evaluating the pharmacokinetics of new drugs have mostly ignored the important direct and indirect effects of the gut microbiome on drug metabolism and efficacy. Despite some important observations from xenobiotic metabolism in general, there is only an incomplete understanding of the scope of influence of the microbiome specifically on drug metabolism and absorption, and how this might influence systemic concentrations of parent compounds and toxic metabolites. The significance of both microbial metabolism of xenobiotics and the impact of the gut microbiome on host hepatic enzyme systems is nonetheless gaining traction and presents a further challenge in drug discovery efforts, with implications for improving treatment outcomes or counteracting adverse drug reactions. Microbial factors must now be considered when determining drug pharmacokinetics and the impact that an evolving and dynamic microbiome could have in this regard. In this review, we aim to integrate the contribution of the gut microbiome in health and disease to xenobiotic metabolism focusing on therapeutic interventions, pharmacological drug action, and chemical biotransformations that collectively will have implications for the future practice of precision medicine.**

Address correspondence to: Dr. Gerard Clarke, Department of Psychiatry and Neurobehavioural Science and APC Microbiome Ireland, 1.15 Biosciences Building, University College Cork, Cork, Ireland. E-mail: g.clarke@ucc.ie

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I. Introduction

The principles of xenobiotic metabolism, which is defined as the metabolism of ingested exogenous molecules, emphasize the role of the liver as the predominant site of biotransformation after ingestion by the host. Within this convention, the liver is anatomically, morphologically, and physiologically specialized as a metabolic organ and unrivalled in metabolic capacity in comparison with extrahepatic host sites of chemical transformation (Michalopoulos, 2007). This viewpoint overlooks the fact that before orally delivered compounds reach the liver, an increasing number are first exposed to the gut microbiota and their associated collection of metabolic enzymes (which exceeds the repertoire of the liver) (Li et al., 2014). Indirectly, metabolites produced by the gut microbiome can also tune the expression and function of key liver enzymes such as those in the pivotal cytochrome P450 (CYP) superfamily. Thus, the metabolism of many clinically used drugs is likely to be influenced by either direct or indirect effects of the gut microbiome.

In this review, we first outline the current knowledge of the gut microbiome in health and disease before focusing on the metabolic activities associated with this community of microbes residing in the gastrointestinal tract and their aggregate genomes. The collective direct and indirect metabolic influence of these microbes in the gastrointestinal tract is evaluated with regard to the chemical modification of pharmaceutical compounds, dietary components, and environmental agents, and the implications for host health. This is considered within the context of our expanding knowledge of the role played by the gut microbiota in health and disease, host–microbial interactions, and the reciprocal relationship between xenobiotics and the gut bacteria involved in their metabolism. We also discuss the potential therapeutic implications arising from these observations before providing recommendations to guide a currently neglected but growing area of research toward therapeutic dividends and the improvement of human health.

II. The Gut Microbiome

The gastrointestinal tract is inhabited by a vast array of microbes—bacteria, fungi, yeasts, archaea, and viruses—termed the gut microbiota (Grenham et al., 2011). The bacterial division of this consortium is best studied and reaches the highest density in the large intestine, with recent estimates of 10^{13} bacterial cells in the human colon (Sender et al., 2016a,b). This abundance reflects the optimal bacterial growth conditions in the large intestine, with a mean pH of 6.4 to 7, and the high density of bacteria residing there in turn confers this region with a lower redox potential (Sousa et al., 2008). The large intestine is thus an important host site for microbial metabolism, a convenient truth that fortunately aligns with our reliance on the analysis of stool samples to gain insights into our microbial inhabitants (Fraher et al., 2012; Claesson et al., 2017). However, these samples are not representative of the microbiome of more proximal regions of the large intestine, and the nonuniform localization and spatial organization of the gut microbiota along the gastrointestinal tract require further evaluation in terms of the functional implications for microbial xenobiotic metabolism (Tropini et al., 2017). This overreliance on fecal samples, due in part to ease of collection and availability, means we still have an incomplete understanding of the impact of microbial activity in different regions of the gastrointestinal tract and the implications of region-specific microbial metabolism for health and disease. For example, metabolism of dietary methylamines also occurs in the small intestine with differential profiles of caecal and fecal metabolism (Hoyles et al., 2018b). Moreover, microbes in the small intestine may be an important site for lipid metabolism (Martinez-Guryn et al., 2018) and are enriched in functions specific for the metabolism of simple carbohydrates (Zoetendal et al., 2012; Stremmel et al., 2017). Neither is the gut microbiota homogenous moving from the lumen to the mucosa, instead existing as a type of gradient with colonic mucosa-associated and luminal microbial communities potentially giving rise to niche metabolic capabilities even at seemingly geographically identical gastrointestinal sites (Galley et al., 2014; Donaldson et al., 2016). One recent example of this pertains to the mucin utilizer, *Peptostreptococcus russellii*, which produces indoleacrylic acid from tryptophan, important for the promotion of enhanced intestinal epithelial barrier function and the suppression of host inflammation (Wlodarska et al., 2017). Microbial enzymes residing in the gut lumen can in turn, for example, deconjugate conjugated cathecholamines with ensuing physiologic implications for colonic function such as water transport (Asano et al., 2012).

Focusing on actual numbers and relative abundances of bacterial cells frequently obscures the importance of their collective genome in the gut ecosystem—the gut microbiome. With an aggregate gene catalog exceeding the human genome by more than a factor of 100 (Qin et al., 2010), the gut microbiome exhibits a diverse functional repertoire, and the encoded metabolic activities of these microbial genes equate to a large metabolic capacity far in excess of its counterpart host genome (Lynch and Pedersen, 2016). According to both 16S rRNA gene sequencing and metagenomic shotgun

ABBREVIATIONS: 5-ASA, 5-aminosalicylate; 5-FU, 5-fluorouracil; CYP, cytochrome P450; IBD, inflammatory bowel disease; miRNA, microRNA; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUFA, polyunsaturated fatty acid; TMA, trimethylamine; TMAO, TMA-N-oxide.

sequencing of stool samples, the composition of the adult gut microbiota is dominated by the phyla *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* with lower relative abundances of *Verrucomicrobia* and *Proteobacteria* (Zhernakova et al., 2016). Although the interindividual variation in microbiota composition is considerable such that an accurate definition of the precise composition of a healthy human microbiota remains elusive, recent evidence supports a shared global core microbiota consisting of 14 different genera with medication use making an important contribution to microbiota compositional variation (Falony et al., 2016). It should be noted that there remains to be a consensus on actual membership of the core taxa present in the gut microbiome, and different sequencing and analysis approaches will give different results. The study by Falony et al. (2016) also looked at different populations than earlier studies by Turnbaugh et al. (2009) and Qin et al. (2010).

In contrast to this interindividual variation, a typical healthy adult gut microbiota is characterized by both high compositional diversity and stability (Clarke et al., 2014b). Unlike the host genome, the gut microbiome is readily modifiable (e.g., by diet or antibiotic usage), and this can have important implications for expansion or contraction of its metabolic functions. Prebiotics such as short chain fructooligosaccharides can promote the production of equol, an isoflavandiol nonsteroidal estrogen of importance in cardiovascular, bone, and menopausal health, and whose production varies depending on microbiota composition (Setchell et al., 2002). A more extreme example of the modifiable nature of the gut microbiome lies in the transfer of bacterial genes encoding porphyranases, agarases, and associated proteins from marine red algae to bacteria residing in the gastrointestinal tract of Japanese individuals as a consequence of their seaweed consumption (Hehemann et al., 2010). Unfortunately, the flip side of this coin—loss of function—is most likely the more common scenario, and the low-fiber Western diet is held partially responsible for the lower diversity and the possible extinction of important taxa from the gut microbiota of Western populations (Sonnenburg et al., 2016). Reduced microbial gene richness is common in a range of metabolic and hepatic diseases, with inflammation (Cotillard et al., 2013; Le Chatelier et al., 2013; Qin et al., 2014; Hoyles et al., 2018a) and oxygen availability/gradients playing an important role (Albenberg et al., 2014; Schmidt and Kao, 2014; Friedman et al., 2018). The collateral damage inflicted by excessive or inappropriate antibiotic usage on gut microbiota composition is another example currently being debated (Blaser, 2016).

Despite these concerns over under-represented microbes and/or reduced microbial gene richness, the importance of the dictum that structure begets function for the role of gut microbiota composition in xenobiotic metabolism is difficult to gauge given that members of this bacterial ecosystem may exhibit both functional redundancy and pleiotropy (Clarke et al., 2014b; Moya and Ferrer, 2016). As indicated above, colonization of bacteria increases to highest levels in the large intestine such that sites with a higher exposure to xenobiotics in fact may have a lower potential for microbial metabolism, such as the small intestine. However, this needs to be considered in context of the less well studied small-intestinal microbiota, due in part to the difficulty in obtaining relevant samples.

Consideration of the gut microbiome and xenobiotic metabolism also needs to take account of the variation of the gut microbiome at the extremes of life in comparison with the reported stability during adulthood in healthy individuals. Data indicate a narrowing of diversity and distinctive microbiota configurations associated with ageing in long-stay care individuals compared with that of community dwellers (Claesson et al., 2012; Jeffery et al., 2016). This is a time of life with high parallel medication and dietary supplement consumption, although adverse health events are rarely considered with regard to this narrowing microbiota diversity (O'Dwyer et al., 2016; Walsh et al., 2016; Locquet et al., 2017). Conversely, but equally important, the infant gut is largely thought to be sterile in utero and colonized during birth and postnatally with a trajectory toward an adult-like complexity taking approximately 3 years (Clarke et al., 2014a; Perez-Munoz et al., 2017). There is also a divergence in intestinal microbiome assembly between different birth modes (Bokulich et al., 2016), between breast- and formula-fed infants (Clarke et al., 2014a), and between preterm and full-term infants, with implications for the associated microbial metabolite profile (Hill et al., 2017). Other important factors include the antibiotic usage in early life (Bokulich et al., 2016; Korpela et al., 2018) and malnutrition (Million et al., 2017). Of course, during adulthood there are also a number of factors that shape or distort the gut microbiome in the colonic metabolic niche, reviewed in detail elsewhere, such as diet (Portune et al., 2017; Sandhu et al., 2017; Shanahan et al., 2017), exercise (Campbell and Wisniewski, 2017; Barton et al., 2018), geographical location (Dikongue and Segurel, 2017; Quigley, 2017), host genetics (Kurilshikov et al., 2017), and the experience of stress (Moloney et al., 2014; Martin and Mayer, 2017). The ability of the gut microbiome to remodel and persist in the face of insults such as antibiotic use is probably only matched in the host by the regenerative capacity of the liver (Michalopoulos, 2007) (Fig. 1, A and B).

III. Biochemistry of Gut Microbiome Xenobiotic Metabolism

Although the collective metabolic activity of the gut microbiome is just beginning to be appreciated with the emergence and growth of the pharmacomicrobiomic concept (Saad et al., 2012; ElRakaiby et al., 2014), the

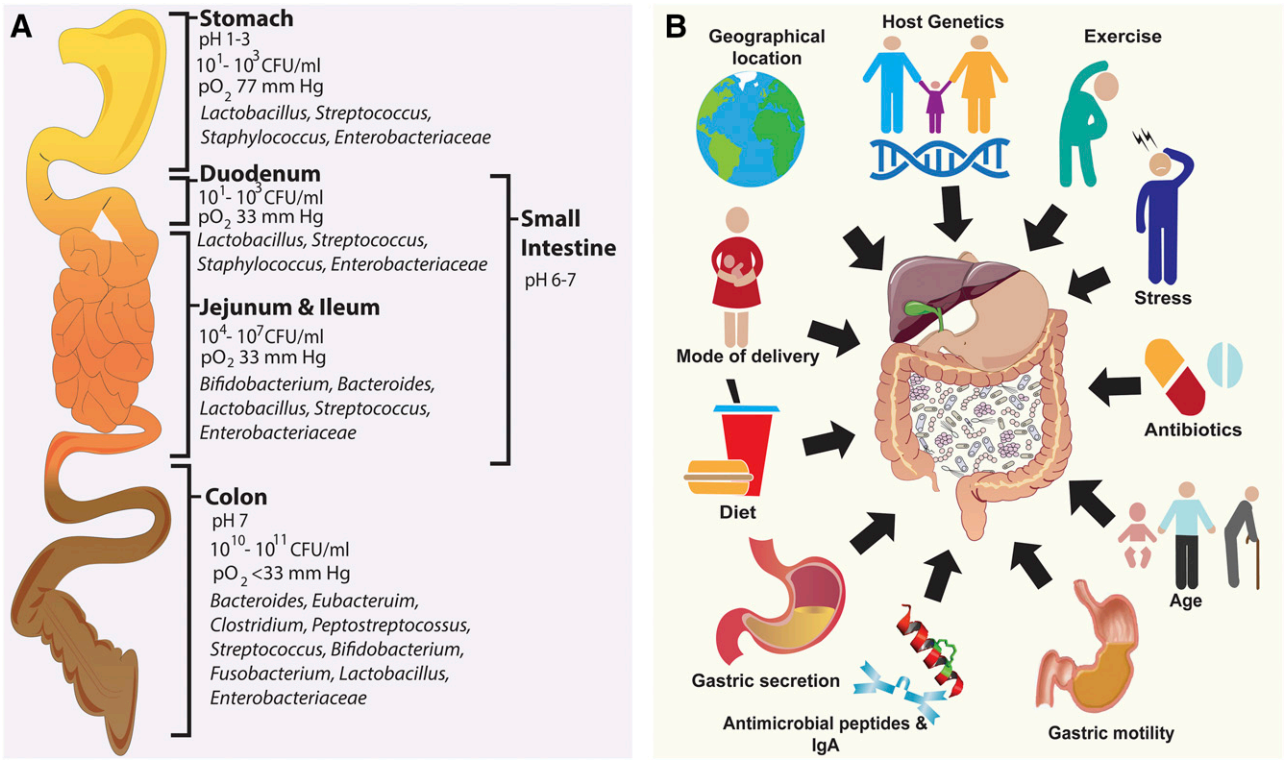


Fig. 1. (A) Metabolic niches in the gut microbiome. The localization and spatial organization of the gut microbiota are not uniform along the gastrointestinal tract. This dynamic gut ecosystem consists of many unique features, such as microniches, pH gradients, and dynamic microbe–tissue interactions of relevance for microbial biotransformations. The highest density of bacteria is present in the large intestine, with recent estimates of 10^{13} bacterial cells in the large intestine associated with microbial genes encoding a broad range of enzymes necessary for xenobiotic biotransformation. These bacteria are likely most important for pharmacomicrobiomics and reside in a reaction chamber with a mean pH of 6.4–7 and a lower redox potential than other gastrointestinal niches. Oxygen partial pressures along the gastrointestinal tract also contribute to these metabolic niches. (B) Factors affecting the composition and function of the large intestine metabolic niche. The compositional characteristics of the gut microbiome are influenced by a number of factors, with the initial seeding and trajectory toward an healthy adult-like diversity and stability determined by mode of delivery (C-section vs. par vaginum) and early feeding patterns (breast feeding vs. formula feeding). Host genetics also plays a role as does geographical location, whereas stress across the life span may be viewed as a threat to the diversity of the gut microbiome. A Westernized diet is also thought to compromise the integrity of the gut microbiome, whereas increased fiber intake is associated with increased diversity. Exercise might also promote the stability of a health microbiome, although the ageing process is associated with a narrowing diversity, as are many disease states and excessive/inappropriate antibiotic use. A number of intrinsic factors, reviewed in details elsewhere by Simren et al. (2013) and partially depicted here, also determine the composition of the gut microbiome, including gastric acid secretion, anticommensal sIgA and antimicrobial peptide production, and gastrointestinal motility.

role of individual microorganisms in drug metabolism has long been studied (de la HUERGA and Popper, 1951; Smith and Rosazza, 1974). This was largely in the context of using microbial models to understand mammalian drug metabolism and with the ambition of using microorganisms for the scalable production of drug metabolites (Murphy, 2015). In contrast to mammalian CYPs, which are usually membrane-bound and heme-containing enzymes, many bacterial CYPs are soluble (Jezequel, 1998). Genome sequencing of *Streptomyces* and *Bacillus* spp. highlighted multiple CYP genes with subsequent culture-based investigations indicating, for example, the production of hydroxylated and amidated metabolites from the nonsteroidal anti-inflammatory drug (NSAID) flurbiprofen that both overlapped with, and were distinct from, the mammalian metabolites (Bright et al., 2011). Enzyme induction was also a noted feature in individual bacterial strains with a CYP-dependent fatty acid monooxygenase from *Bacillus megaterium* strongly inducible by phenobarbital (Narhi and Fulco, 1986). Biotransformation of warfarin by *Streptomyces rimosus* has also been reported (Cannell et al., 1997), whereas the reduction of warfarin to its corresponding alcohol by *Nocardia coralline* is a stereoselective reaction (Davis and Rizzo, 1982). Of course not all of these bacteria are found in the human gastrointestinal tract, and it has been noted that even in cases where they are, we cannot assume equivalent metabolizing activities achieved under specific laboratory culture conditions will be recapitulated in the more dynamic ecological conditions of the gastrointestinal tract (Jezequel, 1998). They do, however, offer a window into the metabolic potential that resides in the gut microbiome as well as hinting at the implications for drug metabolism and host response. Traditionally, consideration of these clinical implications in terms of pharmacokinetics and therapeutic response was largely confined to drugs undergoing enterohepatic circulation (Roberts et al., 2002; Spanogiannopoulos et al., 2016). The principle of microbiota-mediated drug-conjugate

metabolism was also well recognized for many drugs such as oral contraceptives. However, it was rarely considered to have a significant impact clinically except in cases of interactions where broad-spectrum antibiotics resulted in transiently reduced bioavailability of the drugs (Masters and Carr, 2009). In contrast, it is really only as our knowledge of the increasing role that a diverse microbiota can have on health, and the enormous metabolic potential, that interest has turned to the more direct effects of the gut microbiome on metabolizing drugs.

A. Direct Microbial Metabolism of Xenobiotics

Direct microbial biotransformation of xenobiotics occurs following their ingestion, and the nature of these interactions depends on whether the compounds encountered by the gut microbiome are poorly absorbed or are first conjugated by the liver and subsequently reach the intestine via biliary excretion. Once present in the intestinal lumen, an array of bacterial enzymes is capable of a diverse set of chemical reactions. Glucuronides are abundant in the gut and are subject to processing by microbial β-glucuronidase enzymes, which act to liberate glucuronic acid sugars from conjugated compounds (Pellock and Redinbo, 2017). A recent analysis of the Human Microbiome Project gastrointestinal database is instructive on the complexity of this metabolic function, revealing a total of 3013 microbiome-encoded β-glucuronidases, which clustered into structural categories with differing functional capacities for various glucuronide substrates (Pollet et al., 2017). Although the extent of this variation is somewhat bewildering, an earlier study neatly demonstrated the important implications arising from these observations in that the propensity for enzyme inhibition varied according to the bacterial provenance of the orthologous enzymes (Wallace et al., 2015). Endogenous glucuronides such as serotonin glucuronide as well as glucuronidated catecholamines are processed in this way (Asano et al., 2012; Hata et al., 2017). Examples of exogenous glucuronides subject to microbial deconjugation include both therapeutic agents such as the colorectal cancer drug irinotecan and the NSAID diclofenac (Roberts et al., 2013), diet-derived carcinogenic compounds such as 2-amino-3-methyl-3H-imidazo [4,5f]quinoline (Humblot et al., 2007), and likely many representatives from the broad polyphenol family of compounds (Piwowarski et al., 2017; Williamson and Clifford, 2017), including dietary flavonoids (Murota et al., 2018).

In addition to the hydrolysis of these glucuronide conjugates, there are also gut microbial polysaccharide lysases, lipases, reductases (azoreductases and nitroreducases), endoglycosidases, transferases, mono- and dioxygenases, sulfatases, and glycyl radical enzymes (Claus et al., 2016; Koppel et al., 2017). As for the β-glucuronidases, some of these enzyme families, such as the glycyl radical enzymes and S-adenosylmethionine enzymes, have multiple family members and likely different substrate specificities and functions (Lehtio and Goldman, 2004; Haft and Basu, 2011; Murphy et al., 2011). This confers a spectrum of functional metabolic properties on the gut microbiome ranging from proteolysis and deconjugation to amine formation and acetylation (Tralau et al., 2015; Wilson and Nicholson, 2017). Taken together, this functional metabolic repertoire includes the capacity for clinically relevant activation (e.g., sulfasalazine) (Peppercorn and Goldman, 1972b), reactivation (e.g., irinotecan/SN-38) (Wallace et al., 2010), and detoxification (e.g., digoxin) (Haiser et al., 2013) of xenobiotics with broad implications for drug action and toxicity (see Table 1). The administration of probiotics such as *Lactobacillus reuteri* K8 and *Lactobacillus rhamnosus* K9 in mice has also been shown to alter the fecal activity of microbial enzymes such as sulfatase, arylsulfate sulfotransferase, and β-glucuronidase, with implications for the pharmacokinetics of acetaminophen in the case of the former (K8) probiotic (Kim et al., 2018).

In many cases, as for dietary compounds such as the artificial sweeteners xylitol and stevioside, the precise enzymes carrying out their metabolism or their origin microbial species are unknown (Koppel et al., 2017). For others, the enzymatic pathways and the associated implications are becoming clearer. A chalcone isomerase has been isolated from *Eubacterium ramulus*, a human fecal anaerobe capable of degrading various flavonoids (Herles et al., 2004). Experimentally, Western-style high-fat diets have been associated with a diminished microbial capacity to metabolize flavonoids through bacterial chalcone synthase, and microbiome-derived flavonoids can ameliorate the rate of postdieting weight gain (Thaiss et al., 2016a; Chilloux and Dumas, 2017). Daidzin and genistin, glycoside isoflavones, are converted to daidzein and genistein by bacterial β-glucosidases, with the important estrogen equol being the end product following further biotransformation of daidzein (Setchell et al., 2002). Human gut bacteria *Adlercreutzia equolifaciens* and various *Slackia* spp. (all related to *Eggerthella lenta*) have been shown to produce these metabolites (Maruo et al., 2008; Tsuji et al., 2010; Matthies et al., 2012), and the daidzein-induced gene cluster has been described (Tsuji et al., 2010).

B. Microbial Regulation of Host Hepatic Drug Metabolism

The range of metabolic activity of the gut microbiome outlined above is supplemented via microbial regulation of host enzyme expression and activity in both the liver and large intestine, effectively regulating aspects of host drug absorption and metabolism (see Table 2). The use of germ-free animals has revealed that important metabolic enzymes are either up- or downregulated

TABLE 1
Microbial enzymes and associated biotransformations

Microbial Enzyme/Pathway	Substrate Class	Examples	Biotransformation	Comment	Reference
β-Glucuronidase	Pharmaceutical	Irinotecan (colorectal cancer drug), Diclofenac, Indomethacin (NSAIDs)	Glucuronide hydrolysis	Irinotecan is converted to SN-38-G by the host and converted back into cytotoxic SN-38 in intestine with associated gastrointestinal side effects; example of enterohepatic cycling	Wallace et al., 2010; Saitta et al., 2014
	Endogenous	Serotonin dopamine			Asano et al., 2012; Hata et al., 2017
	Environmental pollutant	Nitrotoluene			Claus et al., 2016
	Dietary	IQ		Genotoxic/Carcinogenic compound formed in meat and fish during cooking	Humblot et al., 2007
Azoreductase	Pharmaceutical	Sulfasalazine (IBD medication)	Azo bond reduction	Sulfasalazine is prodrug converted to the active agent 5-ASA by gut microbes	Peppercorn and Goldman, 1972b
Nitroreductase	Pharmaceutical	Bromazepam, Clonazepam, Nitrazepam (Benzodiazepines)	Nitro reduction	Antibiotic pretreatment can abolish enzyme activity; Nitrazepam is metabolized into 7-aminonitrazepam, which undergoes host hepatic metabolism into a teratogen	Elmer and Remmel, 1984; Fujii et al., 1987; Takeno and Sakai, 1991
Cardiac glycoside reductase	Pharmaceutical	Digoxin (Cardiovascular)	Reduction	Reaction contingent on the correct strain of *E. lentum* and inhibited by dietary arginine	Haiser et al., 2013
Tryptophanase	Dietary	Tryptophan	Deamination	Production of indole, which may have a role as an interspecies and interkingdom signaling molecule	Lee et al., 2015
Glycyl radical enzymes (choline TMA-lyase)	Dietary	Choline	C-N bond cleavage elimination/ oxidation	Production of TMA, associated with atherosclerosis and cardiovascular disease following host production of TMAO	Wang et al., 2011; Koeth et al., 2013; Craciun et al., 2014
Carnitine oxygenase (Rieske-type oxygenase/reductase)	Dietary	Carnitine	Oxidation/Reduction	Production of TMA, associated with atherosclerosis and cardiovascular disease following host production of TMAO	Koeth et al., 2013; Zhu et al., 2014
Saccharolytic pathways; butyryl-CoA:acetate CoA transferase	Dietary	Indigestible polysaccharides	Fermentation	Production of short chain fatty acids	Morrison and Preston, 2016
Unknown	Pharmaceutical	Lovastatin	Hydroxylation	Metabolite formation reduced following antibiotic treatment	Yoo et al., 2014
Decarboxylase	Dietary	L-tyrosine	Removal of carboxyl group	Bacterial production of p-cresol, which is sulfated by the host. P-cresol competes with acetaminophen for sulfation.	Smith and Macfarlane, 1997; Clayton et al., 2009; Dawson et al., 2011
Linoleate isomerase	Dietary	Linoleic acid	Conjugation	Production of conjugated linoleic acid from food-derived lactobacilli	Yang et al., 2014
Unknown	Pharmaceutical	L-Dopa	p-Dehydroxulation/ Decarboxylation	L-Dopa can also bind to *H. pylori*; food-associated strain of *L. brevis* expresses tyrosine decarboxylase	Bergmark et al., 1972; Goldin et al., 1973; Niehues and Hensel, 2009; Zhang and Ni, 2014

(*continued*)

TABLE 1—*Continued*

Microbial Enzyme/Pathway	Substrate Class	Examples	Biotransformation	Comment	Reference
Unknown	Dietary	Caffeic acid	Reduction and dehydoxylation	Present in high levels in herbs such as thyme	Peppercorn and Goldman, 1972a
Phosphorylysases	Pharmaceutical	Sorivudine	Hydrolysis	Bromovinyluracil produced is metablized by the host to an inhibitor of host dihydropyrimidine dehydrogenase, leading to increased concentrations of 5-FU (anticancer drug)	Nakayama et al., 1997
Unknown	Dietary	Melamine	Hydrolysis	Conversion to cyanuric acid, which cocrystallizes with melamine in kidneys	Zheng et al., 2013
N-acyl synthase	Dietary	Oleic acid	Acylation	Products are able to modulate GPCRs	Cohen et al., 2017
Peptide synthetase	Dietary	Amino acids	Peptide bond formation	Dipeiptide aldehyde produced can inhibit human cathepsins L	Guo et al., 2017
Uracil phosphoribosyltransferase	Pharmaceutical	5-FU	Phosphorylation	5-fluorouridine monophospate produced is RNA damaging	Garcia-Gonzalez et al., 2017; Scott et al., 2017
Bile salt hydrolyase	Dietary	Bile acids	Deconjugation	Further metabolism by 7 α dehydroxylase important	Joyce et al., 2014

GPCRs, G protein–coupled receptors.

in the absence of a gut microbiome. This includes glutathione transferases (detoxification enzymes), gastrointestinal glutathione peroxidase (reduction of lipid hydroperoxides), epoxide hydrolases (detoxification of genotoxic compounds), N-acetyltransferases (phase II conjugation reactions), and sulfotransferases (detoxification and hormone regulation) (Meinl et al., 2009). Both mRNA and protein expression of CYP3a11 is markedly reduced in the livers of adult germ-free mice (Selwyn et al., 2015b). CYP3a11 is the mouse homolog of human CYP3A4, and this enzyme metabolizes more than 60% of all drugs. Conversely, the same study showed that gene expression levels of Cyp1a2 (metabolic activation of procarcinogens and deactivation of certain anticancer drugs) and Cyp4a14 (metabolism of fatty acids and eicosanoids) were both substantially increased in germ-free mice. Studies also indicate that the impact of the gut microbiota on hepatic drug-processing genes is enzyme-specific and depends on both age and sex, with expression patterns varying across the life span according to developmental periods, and the most marked effects observed in male mice at 90 days of age (Selwyn et al., 2015a).

Microbial colonization of germ-free animals normalized the expression of Cyp3a and Cyp4a gene clusters to those observed in conventional animals (Selwyn et al., 2016). Administration of VSL3, a probiotic formulation containing eight live strains of bacteria, did not impact on the expression of these genes in germ-free animals but did modulate their expression in conventional animals, suggesting that the composition of the host microbiota can influence the effects of other microbes on expression of host drug–metabolizing enzymes. Moreover, this intervention confirms that less extreme microbiome manipulations, outside of proof-of-principle studies in microbiota-deficient animals, can influence the expression of hepatic drug–processing genes during adulthood. Colonization effects are likely strain specific because monoassociation of germ-free mice with both *Lactobacillus plantarum* Nizo2877 and *Escherichia coli* Nissle 1917 decreased the expression of Cyp1a2 mRNA to conventional levels but did not act to restore the decreased expression of Cyp3a11 mRNA. Differential effects for these strains were also noted with increased expression of hepatic Cyp2e1 following monoassociation with *L. plantarum* Nizo2877 but decreased expression following colonization of *E. coli* Nissle 1917 (Jourova et al., 2017).

This transcriptional regulation of such a range of important host drug–processing genes by the gut microbiome may have important implications in terms of microbiome–drug interactions that are not currently routinely considered. This is especially salient in the context of antibiotic usage and the transient depletion of important members of the

TABLE 2
Microbial regulation of host hepatic cytochrome P450 drug-processing enzymes

Host Enzyme	Impact of Germ-free Status	Comment	Reference
Cyp3a (mice)	Decreased mRNA and protein	Upregulated following colonization, but VSL3 probiotic cocktail was not able to normalize their expression; VSL3 moderately decreased mRNAs of Cyp3a44 and Cyp3a11 in conventional mice; similar to the human CYP3A gene cluster	Selwyn et al., 2016
	Decreased mRNA and protein	Evidence of developmental regulation with largest effects seen at 90 days	Selwyn et al., 2015a
	Decreased mRNA	Monoassociation with *L. plantarum* Nizo2877 or *E. coli* Nissle 1917 had no effect on mRNA expression	Jourova et al., 2017
Cyp1a2 (mice)	Increased mRNA	Largest effects seen at 90 days	Selwyn et al., 2015a
	Increased mRNA	Monoassociation with *L. plantarum* Nizo2877 or *E. coli* Nissle 1917 decreased mRNA expression	Jourova et al., 2017
Cyp2c (mice)	Increased mRNA	Largest effects seen at 90 days in male animals only	Selwyn et al., 2015a
Cyp2e1(mice)	Increased mRNA	Largest effects seen at 90 days	Selwyn et al., 2015a
	Increased mRNA	Monoassociation with *E. coli* Nissle 1917 but not *L. plantarum* Nizo2877 decreased mRNA expression	
Cyp4a (mice)	Increased mRNA and protein	Downregulated following colonization, but VSL3 probiotic cocktail was not able to normalize their expression; similar to the human CYP4A cluster	Selwyn et al., 2016
	Increased mRNA	Evidence of developmental regulation and sex-specific effects with largest effects seen at 90 days in male animals only; increased mRNA between neonatal and adolescent ages	Selwyn et al., 2015a

bacterial consortium in the gut microbiota. It has been shown, for example, that ciprofloxacin (a broad-spectrum fluoroquinolone antibiotic) reduces hepatic Cyp3a expression and metabolism of the benzodiazepine triazolam (Toda et al., 2009a). This was associated with a reduction in lithocholic acid–producing bacteria, consistent with the suggestion that lithocholic acid influences hepatic CYP expression (Toda et al., 2009b). It should be noted that ciprofloxacin is metabolized in the liver and can directly inhibit CYP1A2, CYP2D6, and CYP3A4 (Bolhuis et al., 2011). Whether poorly absorbed antibiotics that avoid significant hepatic metabolism, such as vancomycin and rifaximin, also indirectly modulate hepatic CYP gene expression via depletion of the gut bacteria is currently unknown. An improved understanding of the consequences of indirect host–microbiome drug interactions during these exposures, which are associated with concurrent and relevant drug use, consumption of dietary supplements, or environmental toxins (which might also alter the gut microbiome), is urgently required and should be considered in drug development, safety pharmacology, and pharmacokinetic profiling (Fig. 2).

IV. Factors Influencing the Rate and Extent of Gut Microbiome Xenobiotic Metabolism

Xenobiotics can become a candidate substrate for direct processing if they are poorly absorbed, appropriately formulated, or indirectly reach the colonic lumen following biliary excretion, which is also a route through which i.v. administered drugs can become subject to chemical transformation by gut microbes. In considering the rate and extent to which drugs will be exposed to direct microbiome metabolism, there are a myriad of additional factors that need to be considered (Hall et al., 1999). The majority of orally administered drugs are normally absorbed in the upper small intestine, the prime absorptive region of the intestine, assuming that the drug is highly soluble and highly permeable in this region. However, many drugs display poor solubility, which can lead to slow and incomplete absorption with the drug being absorbed from distal regions of the small intestine and/or the colon. Drugs with low permeability through the intestinal membrane, or drugs that are subject to efflux by apically bound efflux proteins (e.g., P glycoprotein), can prolong drug residence within the intestine, with greater amounts of those drugs reaching distal regions of the intestine (Hall et al., 1999). Finally, it should also be recognized that although microbial abundance is lower in the small intestine, this should not lead to the implicit assumption that it will have a limited impact on the drugs that are predominantly absorbed in this region. On the contrary, in the case in intestinal CYP enzymes, which are present in the intestine, but expressed in vastly lower amounts than the liver, intestinally mediated CYP metabolism can still be the major site of drug metabolism (Hall et al., 1999). For example, in the case of cyclosporine, it is estimated that up to half of the drug is metabolized by intestinal CYP enzymes (Benet and Cummins, 2001), illustrating that relatively low amounts of enzymes in the small intestine could still potentially have a significant impact for orally administered drugs. This needs to be considered in the context that due to our reliance of fecal microbiota assessments, comparatively little is known about the microbiota of the less accessible small intestine (El Aidy et al., 2015).

Oral delivery of advanced drug formulations designed for extended release (e.g., sustained release tablets) is on the increase, circumventing absorption profiles that would usually limit exposure of many drugs to the

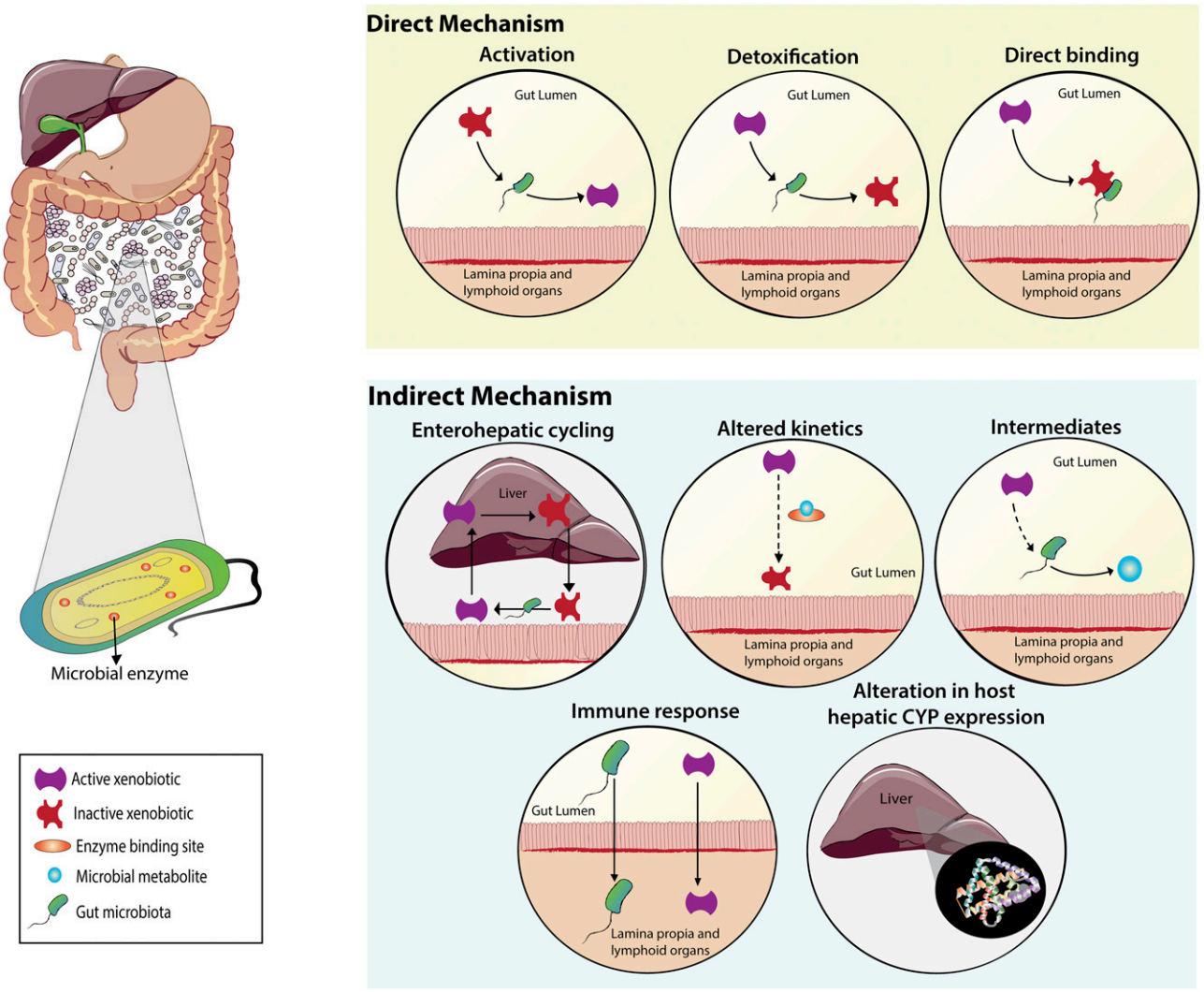


Fig. 2. Metabolic activity of the gut microbiome. There are both direct and indirect mechanisms through which the gut microbiome can influence xenobiotic metabolism to modulate efficacy, absorption, and bioavailability. Direct mechanisms include activation (conversion of prodrugs into active drugs) and deactivation (detoxification). Direct binding of xenobiotics to bacterial cells is also possible (e.g., precursor binding). Indirect mechanisms include enterohepatic cycling, as microbial biotransformation of compounds conjugated in the liver releases the conjugated group, reactivating the compound. The expression of host hepatic CYP genes involved in xenobiotic metabolism is also influenced by the gut microbiome. Microbial metabolites and/or production of pathway intermediates are also important from a pharmacokinetic perspective, as is the impact of bacterial translocation on immune responses in the context of therapeutic efficacy.

colonic gut microbiota (Sousa et al., 2008). This approach has become popular, particularly for the more effective treatment of neuropsychiatric disorders, but, in addition to extending the economic life cycle of drugs (Andrade, 2015), these modified release formulations also increase the scope for drug–microbiome interactions (Enright et al., 2016), and this is a feature rarely appraised for its contribution to bioavailability.

In contrast to the usual objective of host metabolism, biochemical modification of exogenous compounds by our gut microbes is not always geared toward elimination of these foreign compounds. Once a substrate is available for microbial metabolism, there are a number of considerations that may determine its fate and the extent to which it undergoes biotransformation. Much like the host, these can be considered in terms of interindividual and intraindividual variables (Kramer and Testa, 2008, 2009). Individual-specific genetic makeup of the host genome explains some differences in drug metabolism, and host-genetic influences on gut microbiome composition (Goodrich et al., 2016; Rothschild et al., 2018) are also likely to play a role in influencing the rate and extent of microbial xenobiotic metabolism. Microbial enzymes, such as β-glucuronidases, can differ in substrate selectivity and activity depending on the bacteria from which they arise (Pollet et al., 2017). Of note, interindividual differences in the abundance of a cytochrome-encoding operon, responsible for the deactivation of the cardiac drug digoxin, have recently been reported, and this operon was specific to drug-metabolizing strains of *E. lenta* and was inducible by the drug it metabolizes (Haiser et al., 2013). Other examples of inducible bacterial enzymes include the lac operon of *E. coli*, which contains genes involved in lactose metabolism (Wilson et al., 2007) that is expressed

only when lactose is present and glucose is absent. It is currently unclear the extent to which this feature of inducibility, or indeed repression, generalizes to other microbial enzymes important for xenobiotic metabolism or whether constitutive expression is the more common guiding rule in the gastrointestinal tract.

Factors that are known to influence the composition of the gut microbiome, such as age and geography, also overlap with variable drug pharmacokinetics and impact on the relative abundances of genes coding for xenobiotic-metabolizing enzymes (Das et al., 2016; Quigley, 2017). However, our knowledge of interindividual variation of the gut microbiome during health and disease at the taxonomic level is more advanced than our grasp of the functional implications, if any, of these compositional differences. Although studies suggest that we share a stable set of core functions despite these variable gut microbiota profiles (Human Microbiome Project Consortium, 2012), actual metabolic activity of the gut microbiome may diverge from its functional potential (Tanca et al., 2017). Because the activity of the gut microbiota may exhibit resilience despite fluctuating community membership and structure (Song et al., 2015), it is thus not yet clear how many of the variables associated with alterations in the composition and stability of the gut microbiome, including diet (Shanahan et al., 2017), leave their mark on the capacity for xenobiotic metabolism. It is, however, notable that there are examples of disease-associated gut microbiomes, such as depression, that do result in altered behavioral phenotypes and host physiologic characteristics when transferred into animal models (Kelly et al., 2016a). The microbiome-associated metabolite phenylacetic acid has also been shown to influence disease phenotype in nonalcoholic fatty liver disease, contributing to hepatic lipid accumulation (Hoyles et al., 2018a).

Host xenobiotic metabolism is influenced by circadian rhythms (Ozturk et al., 2017), and this may also be true of microbial enzymatic activity because gut microbiota community structure and metabolic activity also feature biologic rhythms, regulated by diet and time of feeding rather than environmental 24-hour light–dark cycles (Voigt et al., 2016; Johnson et al., 2017). Jet lag can disrupt this diurnal microbiota biology, a feature driven by alterations in feeding patterns (Thaiss et al., 2014). Diurnal microbial behavior in turn is thought to influence the programming of the colonic and hepatic circadian transcriptome via fluctuating microbial metabolites with implications, for example, for the hepatic detoxification of acetaminophen that was dependent on the timing of administration (Thaiss et al., 2016b). This was linked to variation in the number of mucosa-associated bacteria in the mouse gut across the circadian period, which was 10 times higher during the dark phase than during the light phase. Circadian rhythm disruption and appetite fluctuations, including carbohydrate craving, are prominent in stress-related psychiatric disorders such as major depression (Otte et al., 2016), which is also associated with gut microbiome alterations (Dinan and Cryan, 2017) (Fig. 3).

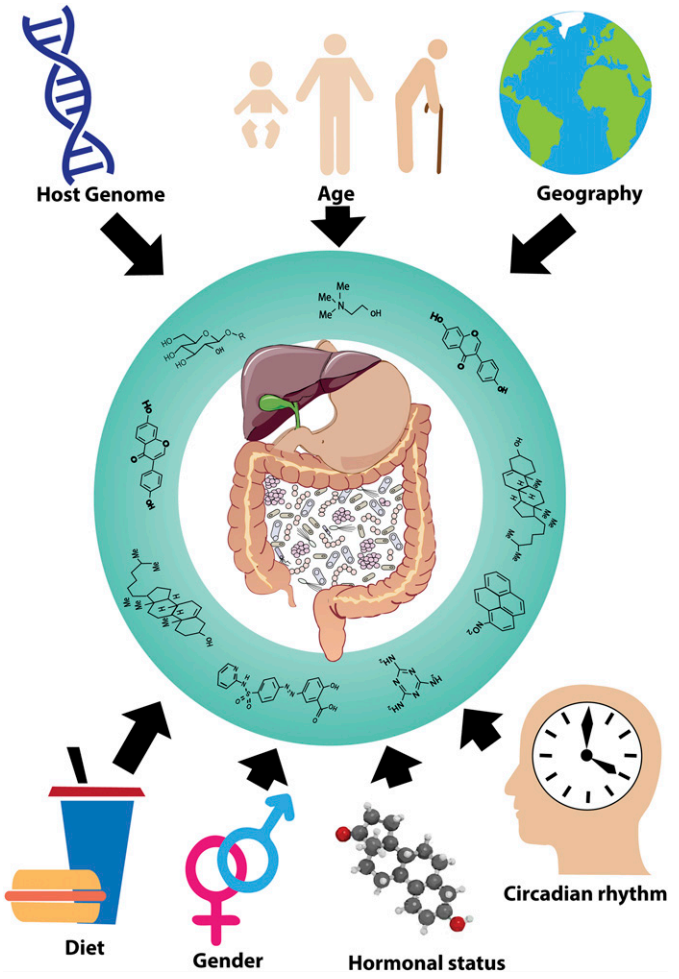


Fig. 3. Factors influencing gut microbiome xenobiotic metabolism. There are a number of considerations that may determine the rate and the extent to which accessible substrates undergo microbial biotransformation. Although compositional differences may not necessarily equate to functional alterations, individual-specific genetic makeup of the host genome explains some differences in gut microbiome characteristics and may affect metabolic outputs. For example, microbial enzymes, such as β-glucuronidases, can differ in substrate selectivity and activity, depending on the bacteria from which they arise. Other factors known to influence the composition of the gut microbiome, such as age, hormone status, and sex, also overlap with variable drug pharmacokinetics and impact on the relative abundances of genes coding for xenobiotic-metabolizing enzymes. Host xenobiotic metabolism is also influenced by circadian rhythms, and this may also be true of microbial enzymatic activity because gut microbiota community structure and metabolic activity also feature biologic rhythms. It is also not yet clear how many of the variables associated with alterations in the composition and stability of the gut microbiome, including diet and geography, leave their mark on the capacity for xenobiotic metabolism. An extreme example of the modifiable nature of the gut microbiome in the context of diet and geography lies in the transfer of bacterial genes encoding porphyranases, agarases, and associated proteins from marine red algae to bacteria residing in the gastrointestinal tract of Japanese individuals as a consequence of their seaweed consumption.

V. The Evolution of Microbial Enzymes for Xenobiotic Metabolism

Host–microbe interactions are frequently viewed from an evolutionary perspective (Davenport et al., 2017). This informs the hologenome theory of evolution with the holobiont encompassing a network of biomolecules derived from both the host plus its associated microbes (Bordenstein and Theis, 2015). Both the host and the microbiome have evolved an extensive metabolic capacity to deal with exogenous molecules with the combined scope impressive in its breadth. Moreover, host–microbe interactions appear critical to both normal and perturbed regulation of metabolic activity, although not all aspects of these actions are mutually beneficial, and the rationale for either the host or the microbiome to have this capability is not always immediately obvious (Patterson and Turnbaugh, 2014). For example, it has been noted that the most common biotransformations carried out by the gut microbiome (hydrolysis and reduction) often serve to undo the oxidative and conjugative chemistry and indeed the intended eliminative purpose of host hepatic drug metabolism (Koppel et al., 2017). As detailed in Table 1, this can have consequences in terms of deactivating or activating drugs in the case of digoxin (Haiser et al., 2013) and sulfasalazine (Peppercorn and Goldman, 1972b), respectively. Toxic or adverse consequences can also ensue, as is the case for irinotecan (Wallace et al., 2010) or the production of trimethylamine (TMA) from dietary carnitine and choline (Wang et al., 2011; Koeth et al., 2013). In many cases, as in the latter example, host–microbe interactions drive the adverse metabolic consequences with the host responsible for processing of the intermediate TMA to the cardiotoxic TMA-N-oxide (TMAO; see section on *VII. A. The Microbiome and Therapeutic Mechanism of Action, Efficacy, and Adverse Effects*). In mice, however, TMA is also a chemosignal involved in species-specific social communication, acting to attract mice but repel rats (Li et al., 2013).

An overarching question relates to why either the host or the associated microbiome would evolve enzymes to metabolize substances that they could not expect to come in contact with on a consistent basis. Or, in other words, has microbial biochemistry evolved to counter the vast increase in xenobiotics they encounter both in the body and in environment as consequence of industrialization and the subsequent expansion of the chemical universe? It has been proposed that the answer lies in the functional redundancy of the enzymes, with a broad substrate specificity being a common feature of reactions catalyzed by both host and microbial enzyme (Patterson and Turnbaugh, 2014). The reactions carried out by the gut microbiome frequently result in the release of small molecules or carbon sources that can be used for microbial growth (Koppel et al., 2017). Exposure of the host, in contrast, to a wide array of bacterial metabolites via the hepatic portal circulation demanded the emergence of enzymatic flexibility primarily in the liver. The most expansive enzyme families, such as the β-glucuronidases, for example, reflect the wide availability of host-derived glucuronide substrates in the gastrointestinal tract. Indeed, these enzymes have an important role in the enterohepatic cycling of endogenous substances such as bile acids (Long et al., 2017). Because much of this chemistry involves the modification of common functional groups, it is perhaps not that surprising that modern pharmaceuticals, dietary components, and environmental pollutants (see Table 1) have become suitable substrates for the expansive range of metabolic functions noted in this review.

VI. Stress-Related Disorders and the Gut Microbiome

Stress is known to impact on host xenobiotic metabolism, particularly via induction of hepatic drug–metabolizing enzymes possibly mediated by glucocorticoids or noradrenaline (Konstandi, 2013; Pantelidou et al., 2017). Gut microbiome alterations are frequently reported in stress-related disorders such as depression, anxiety, and irritable bowel syndrome (Rajilic-Stojanovic et al., 2015; Foster et al., 2017). The impact of stress on the already compromised ageing microbiome is currently under consideration and aligns with studies on the impact of stress on the ageing brain at a time of life when chronic stressors are common and in the context of shifting worldwide population demographics (Prenderville et al., 2015; Allen et al., 2017). Understanding the implications of stress–microbiome interactions, and their functional metabolic consequences and the implications for drug action, is surely now an important research objective (Fig. 4).

VII. The Gut Microbiome and Xenobiotics in Health and Disease: a Reciprocal Relationship

Although research efforts are ongoing to more precisely define a healthy gut microbiome (Falony et al., 2016; Zhernakova et al., 2016), one of the most frequently reported findings across an array of disorders is a narrowing of gut microbiome diversity often accompanied by more specific but less consistent compositional alterations at various taxonomic levels. This includes central nervous system disorders such as depression (Kelly et al., 2016a) and schizophrenia (Schwarz et al., 2018), metabolic disorders such as obesity (Torres-Fuentes et al., 2017) and diabetes mellitus (Sohail et al., 2017), cardiovascular disorders (Ryan et al., 2015; Winek et al., 2016), inflammatory disorders such as inflammatory bowel disease (IBD) (Sheehan and Shanahan, 2017), rheumatoid arthritis and multiple sclerosis (Forbes et al., 2016), and cancer (Aviles-Jimenez et al., 2017). Many of the therapeutic interventions for such disorders are subject to

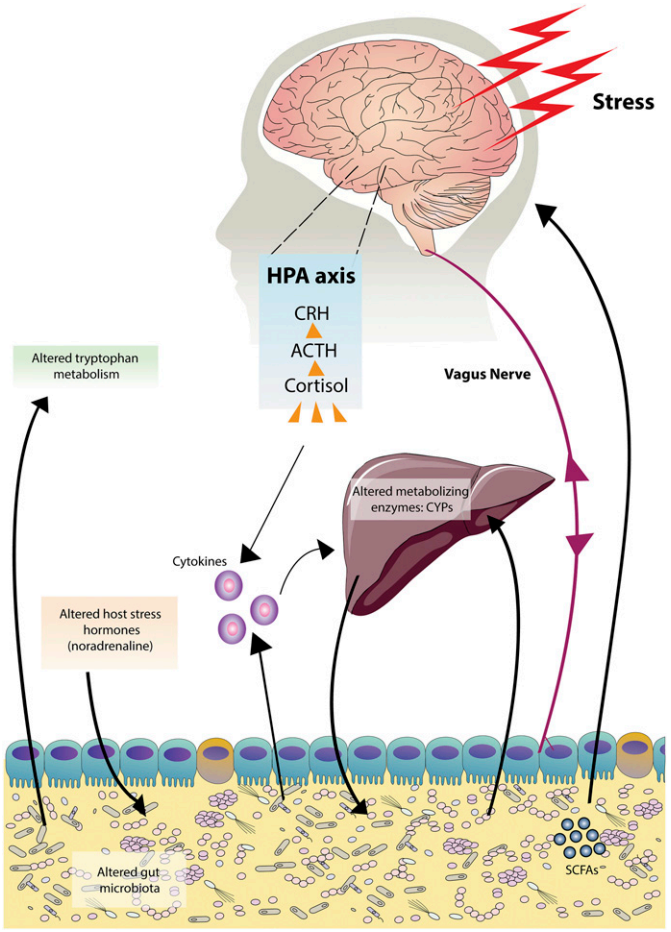


Fig. 4. Stress and the gut microbiome. The gut microbiome recruits the gut–brain axis to signal to the central nervous system. Signaling pathways include the vagus nerve, neuroendocrine and neuroimmune routes, as well as the impact on tryptophan metabolism. Communication along this axis is bidirectional. Although the host response to stress is coordinated by the brain with the central nervous system responding to stressors by structural remodelling of neural architecture (McEwen, 2017), the gut microbiome appears to be equally vulnerable and plastic in its response to homeostatic threats directed at either terminus of the gut–brain axis (Dinan and Cryan, 2017). Hypothalamic–pituitary–adrenal axis programming and responses show a dependency on an intact gut microbiome (Clarke et al., 2014b). Preclinical studies indicate that stress exposure across the life span can impact on gut microbiome composition. This includes early-life prenatal (Golubeva et al., 2015) or postnatal stressors (O'Mahony et al., 2009) as well as stress experienced during adulthood (Bharwani et al., 2016; Burokas et al., 2017; Galley et al., 2017).

biotransformation by our gut microbiome (see Table 3), and the functional implications of these gut microbiome alterations are not currently clear for microbial xenobiotic metabolism. This gap in knowledge surrounding how these disease-associated gut microbiome alterations feed into variations in drug response and toxicity is further compounded by the realization that many of the interventions themselves may also change the composition and function of the gut microbiome.

A. The Microbiome and Therapeutic Mechanism of Action, Efficacy, and Adverse Effects

Perhaps the best example in the literature that ties the compositional characteristics of the gut microbiome to drug action explicitly via microbial metabolism relates to digoxin, a cardiac glycoside used in the management of cardiovascular disorders. Haiser et al. (2013) elegantly demonstrated that digoxin inactivation was significantly influenced by the presence or absence of metabolizing *E. lenta* strains in the gut microbiota of patients, a feature offered as an explanation for variable digoxin metabolite levels. Digoxin can be used for the treatment of heart failure and atrial fibrillation, common disorders in the elderly who are noted to have reduced elimination of digoxin (Haiser et al., 2013). Despite the important conceptual advance provided by this study and the template offered for the design of future studies in this area, it is also worth noting that digoxin use is on the decline amid the emergence of alternative therapies with preferable safety profiles (Haynes et al., 2008; Eade et al., 2013). Other examples of microbiota–drug interactions of relevance to cardiovascular pharmacology include the hydroxylation of lovastatin, albeit less well-characterized in terms of specific enzyme involvement, in an animal model following coadministration of an antibiotic that resulted in a more extreme depletion of the microbiota that is known to be present in cardiovascular disorders (Yoo et al., 2014).

Choline TMA-lyase, a glycyl radical enzyme, is also widely distributed among gut bacteria and exhibits selectivity for choline cleavage. Choline is an essential nutrient found in a wide variety of foods, but excess conversion to TMA can lead to artherosclerosis as a consequence of further metabolism by host hepatic processing to TMAO (Zeisel and da Costa, 2009; Wang et al., 2011; Koeth et al., 2013; Craciun et al., 2014). TMAO can be produced from dietary TMA via metabolic retroconversion (Hoyles et al., 2018b) and is predicted to be produced from betaine (Jameson et al., 2016). TMA is also produced by carnitine oxygenase, a Rieske-type protein, using carnitine found in red meat as a substrate (Zhu et al., 2014). Choline TMA-lyase may be more vulnerable to compositional variations in the gut microbiome, and a recent study indicated that it was only present in 26% of individuals, while also noting that further studies were required to characterize the TMA-producing capacity of bacterial communities in at-risk groups (Rath et al., 2017) and consequential effects on cardiovascular health. Interestingly, although red meat has been negatively implicated as a substrate source, commentators have pointed out that fish and other seafood presumed to be beneficial to health also contain significant amounts of TMA precursors as well as free TMAO (Landfald et al., 2017). As TMAO is excreted into urine via the kidney, and circulating levels of TMAO increase significantly in patients suffering from chronic kidney disease, there is a line of thought suggesting plasma TMAO concentrations may be a better marker of impaired renal function associated with atherosclerosis of the renal vasculature rather than a direct cause of

TABLE 3
Clinical specialties, therapeutic interventions, and pharmacomicrobiomics

Specialty	Drug Class	Example	Reference
Oncology	Immune checkpoint inhibitor	Anti-programmed cell death 1 protein	Gopalakrishnan et al., 2018; Routy et al., 2018
		Anti–CTLA-4 antibodies	Alexander et al., 2017
	Antineoplastic enzyme inhibitor	Irinotecan	Wallace et al., 2010
	Anthracycline	Doxorubicin	Yan et al., 2017
	Alkylating agent	Cyclophosphamide	Alexander et al., 2017
Cardiology	Statin	Lovastatin	Yoo et al., 2014
	Cardiac glycoside	Digoxin	Haiser et al., 2013
Diabetes	Biguanide	Metformin	Wu et al., 2017
Gastroenterology	Sulfa drug	Sulfasalazine	Peppercorn and Goldman, 1972b
Psychiatry	Antipsychotic	Olanzapine	Davey et al., 2012
		Risperidone	Bahr et al., 2015
	Benzodiazepine	Bromazepam	Fujii et al., 1987
		Clonazepam	Elmer and Remmel, 1984
		Nitrazepam	Takeno and Sakai, 1991
Neurology	Precursor	L-Dopa	Bergmark et al., 1972

atherosclerosis in humans (Miller et al., 2014). There are still open questions as to what exactly constitutes a toxic level of TMAO, as even in the absence of dietary sources of methylamines, baseline levels of TMA and TMAO are found in the circulation (De La Huerga et al., 1953; Hoyles et al., 2018b). It is important to acknowledge that circulating TMAO may play a role in the protection from hyperammonemia (Kloiber et al., 1988) and from glutamate neurotoxicity (Minana et al., 1996). Chronic exposure of mice to TMAO attenuates diet-associated glucose tolerance, reducing endoplasmic stress and adipogenesis in adipocytes (Dumas et al., 2017). Flavin monooxygenase 3, associated with the conversion of TMA to TMAO, is downregulated by testosterone (Bennett et al., 2013), suggesting possible differential processing of TMA in men and women.

In the context of inflammatory disease, the microbiota is responsible for the conversion of the prodrug sulfasalazine into 5-aminosalicylate (5-ASA), the active agent with anti-inflammatory properties used in the treatment of IBD (Peppercorn and Goldman, 1972b). This is a reaction carried out by microbial azoreductases, enzymes noted to be present in a wide variety of anaerobic bacteria from the human microbiota (Chung et al., 1992), making it difficult to envisage a loss of this function being associated with the gut microbiome alterations noted in IBD and resonating with the concept of functional resilience mentioned earlier. It is, however, notable that 5-ASA can be converted to N-acetyl 5-ASA by intestinal bacteria, a reaction that does show variability in human fecal samples (van Hogezand et al., 1992). The metabolism of azo dyes to aromatic amines is also carried out by azoreductases, and fibers, antibiotics, or supplementation with live cultures of lactobacilli were able to affect azoreductase enzyme activity (Chung et al., 1992), an interesting observation in light of their potential application in IBD.

Drugs used in the treatment of cancer also represent examples of microbially-processed therapies and may be associated with adverse and toxic side effects, as is the case with irinotecan (Wallace et al., 2010). This reaction involves β-glucuronidases, bacterial enzymes noted to have a wide distribution in the gut microbiome (Cole et al., 1985). It has also been demonstrated more generally that of a panel of 30 chemotherapeutic drugs examined in vitro against various bacteria, 10 were found to be inhibited and six exhibited improved efficacy in a way that could be linked to modification of the chemical structure of the drug in the case of gemcitabine, fludarabine, cladribine, and CB1954 (Lehouritis et al., 2015).

Drug–drug interactions can also arise as a consequence of microbial biotransformations. The hydrolysis of the antiviral drug sorivudine to bromovinyluracil, which is then subsequently metabolized by the host to an inhibitor of host dihydropyrimidine dehydrogenase, may lead to toxicity due to inhibited degradation and increased concentrations of coadministered 5-fluorouracil (5-FU) (Nakayama et al., 1997). Specifically, conversion of bromovinyluracil by host dihydropyrimidine dehydrogenase produces a reactive intermediate that irreversibly inhibits the enzyme (Nishiyama et al., 2000). The production of bromovinyluracil is carried out by bacterial phosphorolytic enzymes with high enzymatic activity observed in *Bacteroides* species (Alexander et al., 2017).

More recently it has been demonstrated that the widely present bacterial uracil phosphoribosyltransferase (Martinussen and Hammer, 1994) can convert 5-FU to the RNA-damaging 5-fluorouridine monophosphate using the nematode *Caenorhabditis elegans* as a model system (Garcia-Gonzalez et al., 2017; Scott et al., 2017). Also using this model, it has been demonstrated that the deglycosylation of doxorubicin by *Raoultella planticola* is associated with reduced toxicity (Yan et al., 2018). Other gut-microbiota–mediated mechanisms through which the pharmacological effects of chemotherapeutics and immune therapeutics can be modulated include translocation and immunomodulation following interventions such as cyclophosphamide, doxorubicin, and

anti–CLTA-4 therapies (Alexander et al., 2017). Understanding how alterations in gut microbiota profiles can dictate the host response to chemotherapeutic drugs may have important implications in clinical practice. Indeed, recent studies confirm the potential importance of patient stratification on the basis of gut microbiome composition to identify responders and nonresponders to immunotherapy for the treatment of epithelial tumors and melanomas (Gopalakrishnan et al., 2018; Jobin, 2018; Routy et al., 2018) (Fig. 5).

B. Impact of Current and Putative Therapeutic Interventions on Microbial Community Structure and Function

Many xenobiotics also impact on the composition of the gut microbiome, often in a clinically meaningful way. The possible extent of these occurrences was revealed recently following a screen of the interactions between over 1000 marketed and individual gut bacteria (Maier et al., 2018). The authors reported that 24% of the drugs with human targets across therapeutic classes inhibited the growth of at least one bacterial strain in vitro. Commonly used drugs, such as antipsychotics, proton-pump inhibitors (PPIs), hormones, and anticancer drugs, were included in the screen. Although the study largely focused on the in vitro antibacterial activity of each drug screened against one representative bacterial strain per species, the implications for more complex bacterial communities need to be considered. The results are also consistent with reported interactions between these drugs (antipsychotics, PPIs, and anticancer drugs) and the gut microbiome documented in previous preclinical and clinical studies (Davey et al., 2012, 2013; Imhann et al., 2016; Gopalakrishnan et al., 2018).

Exposure in incubation experiments to a panel of host-targeted drugs, including digoxin and sulfasalazine, induces subtle changes in community structure, but more marked changes in the genes expressed by the gut microbiome, including those genes involved in xenobiotic metabolism (Maurice et al., 2013). Medication use was also confirmed to be an important

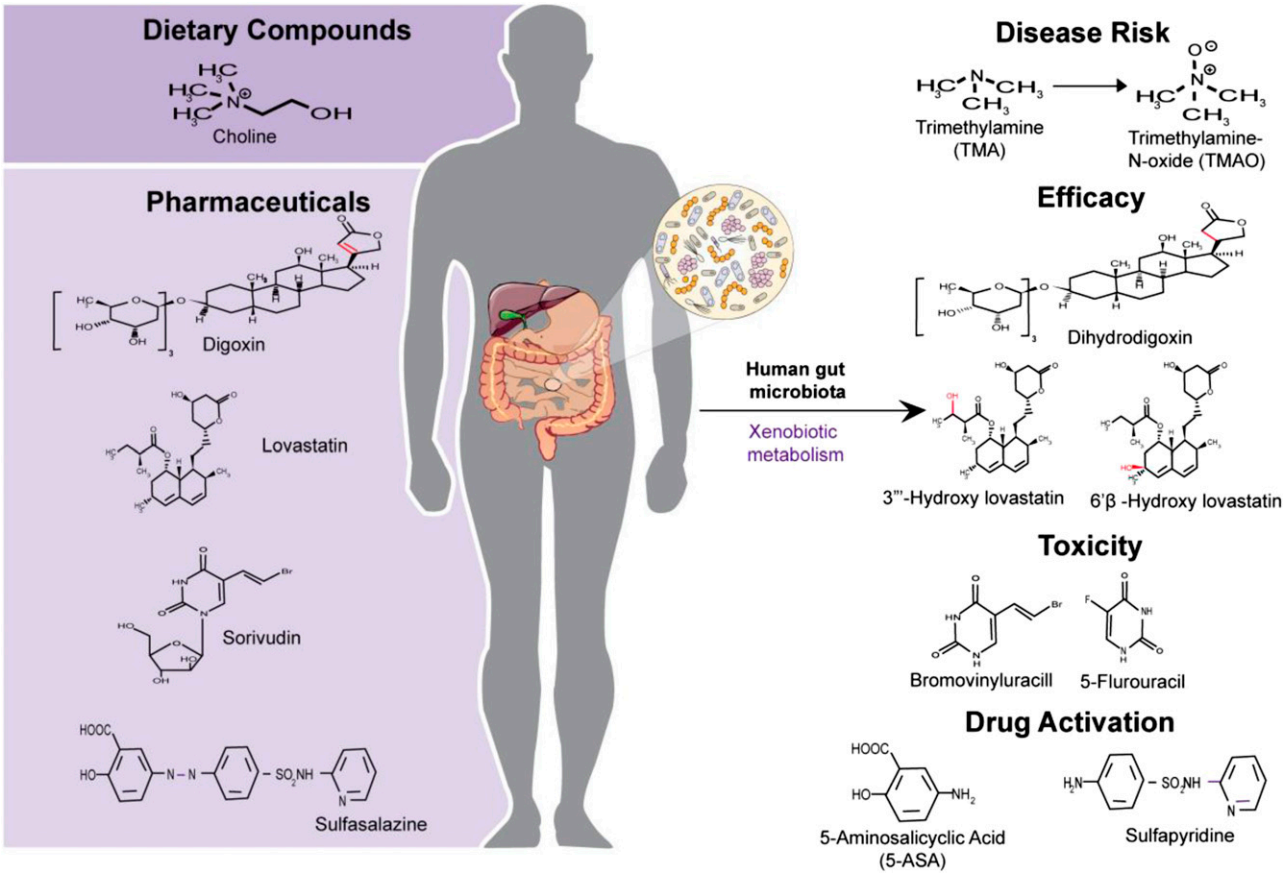


Fig. 5. Examples of clinically relevant microbial biotransformations. Direct microbial biotransformation of xenobiotics occurs following their ingestion, and, once present in the intestinal lumen, an array of bacterial enzymes is capable of modifying a diverse set of chemical structures, including dietary and pharmaceutical compounds. Taken together, this functional metabolic repertoire includes the capacity for clinically relevant activation (e.g., sulfasalazine) or inactivation (digoxin). Microbiota–drug interactions of relevance to cardiovascular pharmacology potentially include the hydroxylation of lovastatin. Drug–drug interactions can also arise as a consequence of microbial biotransformations, such as the hydrolysis of the antiviral drug sorivudine to bromovinyluracil. Bacterial conversion of dietary choline to TMA can lead to artherosclerosis as a consequence of further metabolism by host hepatic processing to TMAO. The consequences of microbial metabolism are thus of broad importance for disease risk, and drug efficacy and toxicity.

covariate associated with human microbiota compositional variation in a recent large-scale study of Belgian and Dutch populations (Falony et al., 2016). A number of studies focused on specific candidates have also shone a light on this important area, as discussed below.

Metformin, used for the treatment of type 2 diabetes, has recently been shown to alter the gut microbiota composition of treatment-naive individuals in a way that improves glucose tolerance. This effect was probably achieved by promoting functional shifts in the gut microbiome with, for example, the enrichment of genes for carbohydrate metabolism, amino acid metabolism, and lipopolysaccharide biosynthesis (Wu et al., 2017). Metformin appears to have a dose-dependent antimicrobial effect with inhibition of specific bacterial strains only apparent once tested at physiologic intestinal concentrations (Maier et al., 2018). Interestingly, metformin can also promote in vivo the growth of specific bacterial species such as *Akkermansia muciniphila* and *Clostridium cocleatum* (Lee and Ko, 2014). This of course makes it difficult to distinguish type 2 diabetes versus metformin treatment signatures when assessing human gut microbiota composition (Forslund et al., 2015). Irinotecan can also alter the composition of the intestinal microbiome in rats, although it is unclear how well this aligns with the toxicity of this treatment (Lin et al., 2012; Alexander et al., 2017).

Methotrexate results in reduced microbiota diversity and compositional shifts in the abundance of Bacteroides associated with the induction of diarrhea in rats (Fijlstra et al., 2015). A recent systematic review indicates that other prescription medications are also associated with alterations in gut microbiome diversity, including PPIs, opioids, and NSAIDs (Le Bastard et al., 2018). The effect of PPIs in particular on gut microbiota diversity has been noted to be characteristic of an unhealthy gut microbiome and may increase the risk for enteric infections (Imhann et al., 2016).

There is mounting interest in the possibility that psychotropic agents might alter the composition of the gut microbiome (Kelly et al., 2016b). Currently, this has best been explored for the atypical antipsychotic drug olanzapine, which induces alterations in gut microbiome composition in rodents linked to the weight gain and other metabolic side effects that are associated with its use (Davey et al., 2012, 2013; Morgan et al., 2014). It has also been demonstrated that olanzapine has antimicrobial properties in vitro against two bacterial strains commonly residing in the human gut (Morgan et al., 2014). It is of note that olanzapine is metabolized by hepatic glucuronidation, and an unusually high percentage (30%) of an oral dose is recoverable in human feces (Kassahun et al., 1997). Prebiotic administration concurrently with olanzapine can reduce the antipsychotic-induced weight gain in rodents (Kao et al., 2018). Another antipsychotic, risperidone, also causes shifts in gut microbiome composition in mice (Bahra et al., 2015), and in children and adolescents (Bahr et al., 2015). More recently, it has been demonstrated that similar bacterial species are affected by different and chemically diverse antipsychotics (Maier et al., 2018). Chronic alcohol abuse also alters gut microbiome composition (Leclercq et al., 2017), and other drugs of abuse possibly do the same, such as methamphetamine (Ning et al., 2017). More generally, substance use disorders are associated with reduced microbiota diversity (Xu et al., 2017).

Although the therapeutic potential of microRNAs (miRNAs) is far from fully realized, these small nucleotide sequences with the ability to regulate gene expression represent molecular effectors of importance in a range of areas, including psychiatric disorders such as depression and anxiety (Scott et al., 2015; Gururajan et al., 2016; O'Connor et al., 2016) as well as cancer (Slaby et al., 2017) and cardiovascular disorders (Mellis and Caporali, 2018). Understanding the role of the gut microbiome–miRNA interactions is a novel departure that has seen evidence emerge from studies in germ-free rodents of microbial regulation of miRNA expression in brain regions of importance for neuropsychiatry such as the amygdala, prefrontal cortex, and hippocampus (Chen et al., 2017; Hoban et al., 2017; Moloney et al., 2017). It also seems that host miRNA production by intestinal epithelial cells has a role in shaping the gut microbiome by affecting bacterial growth (Liu et al., 2016), and fluctuations in microbial composition of the gut microbiome are associated with alterations in fecal miRNAs (Moloney et al., 2018). This will be an important consideration if the miRNA-targeted therapeutics in clinical development make their way to the clinic for the treatment of disorders associated with gut microbiome alterations.

Dietary compounds exert a major impact on the gut microbiome. In mice, a number of nutritional and nutraceutical interventions for cardiovascular disease were compared against a standard pharmaceutical intervention for their impact on the gut microbiome. Plant sterol ester produced the strongest compositional effect with more modest alterations noted following oat β-glucan and bile salt hydrolase-active *L. reuteri* APC 2587, with few effects noted for atorvastatin. Functional alterations following plant sterol ester, oat β-glucan, and atorvastatin were also noted in this study, using microbial and host-derived metabolites in the serum metabolome as a readout (Ryan et al., 2017). Polyunsaturated fatty acids (PUFAs) are thought to exert an antidepressant effect, possible via their anti-inflammatory properties (Burhani and Rasenick, 2017). Omega-3 PUFAs also have important cardioprotective and neurodevelopmental properties and support the function and aging of the central nervous system (Pusceddu et al., 2016). Dietary omega-3 PUFA status impacts on the cecal microbiome and metabolome in

mice (Robertson et al., 2017b) and is also able to impact on gut microbiota development in adolescence and adulthood when varied in the maternal and early-postnatal diet (Robertson et al., 2017a). It has also been reported that the disruptions to the gut microbiota induced by the early-life stressor maternal separation in female rats can be rescued by omega-3 PUFA supplementation (Pusceddu et al., 2015). In clinical populations, and although omega-3 PUFA supplementation did not change gut microbiome diversity or composition at the phyla level, an increase in several short chain fatty acid–producing bacteria such as *Bifidobacterium*, *Roseburia*, and *Lactobacillus* was noted (Watson et al., 2017).

Dietary phytochemicals can induce gut microbiota alterations, exerting prebiotic-like effects to stimulate the growth of beneficial bacteria (Laparra and Sanz, 2010). Recent revisions of the definition of prebiotics have expanded their scope and now include both PUFAs and phytochemicals (Gibson et al., 2017). Polyphenolic phytochemicals in particular are known to exert beneficial health effects beyond their antioxidant capacity (Stevenson and Hurst, 2007). Recent evidence suggests that resveratrol, for example, may act to remodel the gut microbiome to yield cardiovascular benefits, anti-obesity effects, and improvements in glucose homeostasis (Chen et al., 2016; Bird et al., 2017; Sung et al., 2017). Flavonoids also shape gut microbiota membership and function (Oteiza et al., 2018). Other dietary compounds known to alter the composition of the gut microbiome include noncaloric artificial sweeteners such as saccharin, sucralose, and aspartame (Suez et al., 2015), a feature with functional implications associated with the induction of glucose intolerance in mice (Suez et al., 2014). Although probiotics are not thought to substantially change the global compositional characteristics of the gut microbiome (Kristensen et al., 2016), they do impact on functional metabolic outputs such as the production of short chain fatty acids and other pharmabiotics, which may be important in their propensity to influence host health (Patterson et al., 2014).

C. Environmental and Industrial Chemicals

The capacity of the gut microbiome to metabolize environmental chemicals is mediated by enzymes with a wide distribution such as β-glucoronidases, azoreductases, and nitroreductases, which are able to chemically transform a range of agents such as nitrotoluenes, pesticides, polychlorobiphenyls, azo dyes, and metals (Claus et al., 2016). Many of these same chemical agents can also alter the composition and/or function of the gut microbiota. Chronic exposure to low doses of the insecticide, Chlorpyrifos, changed the composition of the gut microbiota in both a simulated human intestinal microbiota preparation and rats, reducing the abundance of *Lactobacillus spp*. and *Bifidobacterium spp*, bacteria presumed to be beneficial (Joly et al., 2013). Glyphosate, the most commonly used herbicide (Cuhra et al., 2016), inhibits microbial enzymes (5-enolpyruvylshikimate-3-phosphate synthase), and some glyphosate formulations do have antibacterial properties (Tarazona et al., 2017). It remains to be seen whether the detrimental impact of glyphosate seen on soil, plant, and farm animal microbiomes will be consistently reflected in the human microbiome where the concentrations reached are usually much lower (Flandroy et al., 2018). Heavy metals such as mercury, lead, cadmium, and arsenic may also have an important impact on the gut microbiota (Lu et al., 2015). Traffic-related air pollution can result in a decreased relative abundance of *Bacteroidaceae* and an increased relative abundance of *Coriobacteriaceae* (Alderete et al., 2018). Exposure to endocrine-disrupting chemicals such as bisphenol A and ethinyl estradiol, by incorporation into the diet from periconception through weaning, induced generational and sex-dependent gut microbiome changes in mice, including increased relative abundances of *Bacteroides*, *Prevotellaceae*, and *Akkermansia* (Javurek et al., 2016). The collective literature in this area requires further elaboration to understand the implications for host health, not least within a framework that places the characteristics of the early-life microbiome as critical to the subsequent emergence of adult pathologies (Clarke et al., 2014a; Claus et al., 2016) (Fig. 6).

VIII. Experimental Approaches in Pharmacomicrobiomics

Understanding the complex and bidirectional interplay between the gut microbiome and xenobiotics requires an array of experimental approaches geared toward extracting the necessary complementary information. Many of the strategies employed, such as the use of microbiota-deficient animals, are commonly applied across cognate areas of microbiome research (Williams, 2014; Luczynski et al., 2016). This includes both germ-free models or those generated via depletion of the gut microbiota with a cocktail of antibiotics, and can provide valuable pharmacokinetic and pharmacodynamic insights. These approaches are not without their limitations, not least because of the intrinsic gastrointestinal and microbial differences between humans and rodents (Nguyen et al., 2015). There are also physiologic and morphologic differences between germ-free animals and conventional controls relevant for xenobiotic metabolism (Sousa et al., 2008). For example, host hepatic enzyme expression and activity are altered in animals reared in a germ-free environment (Selwyn et al., 2016). However, the use of these animal models in mono-association studies or following the transplant of human microbiota profiles is clearly an invaluable option (Haiser et al., 2014). Insights from invertebrate models, such as the nematode *C. elegans*, are

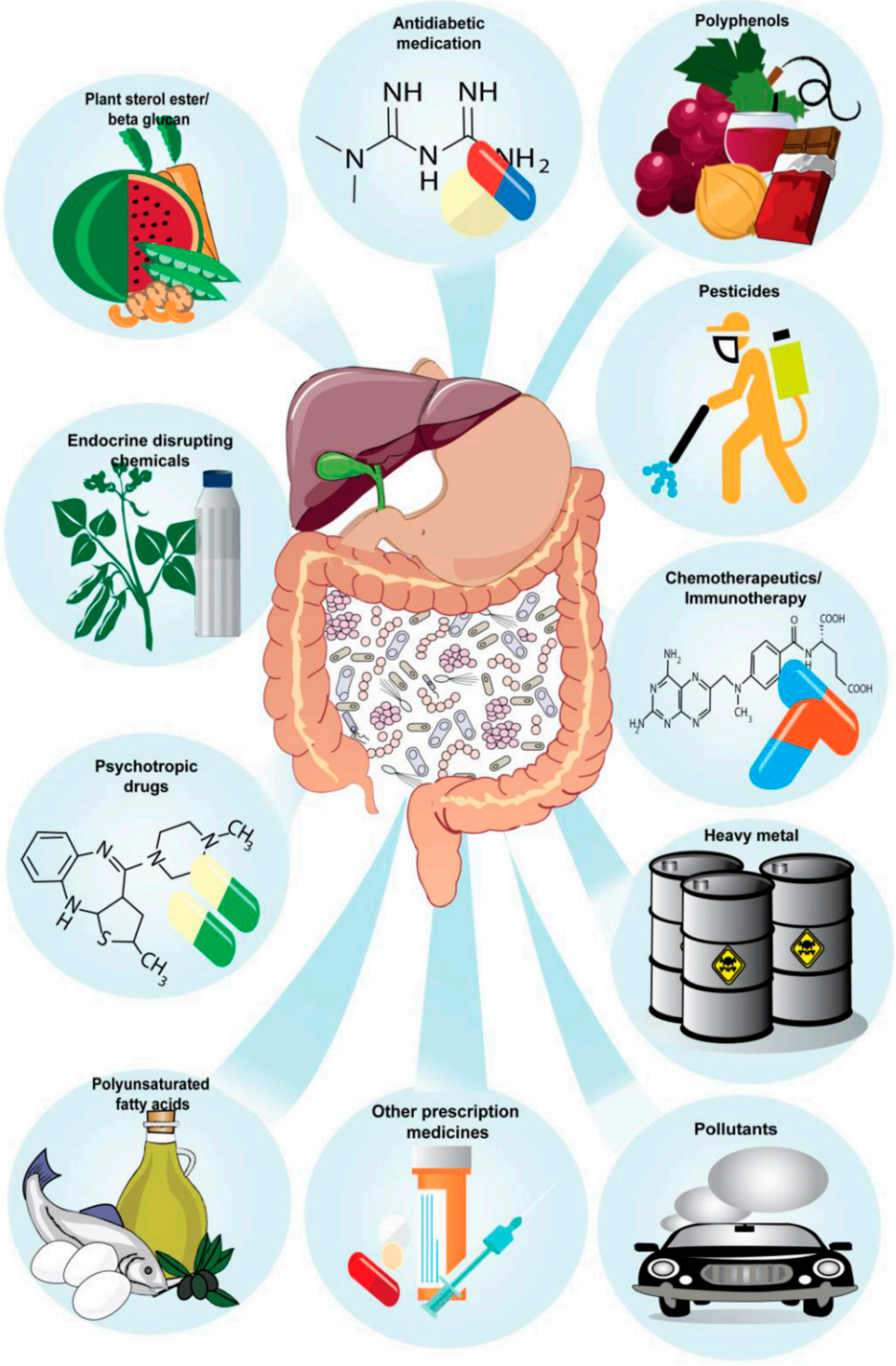


Fig. 6. Xenobiotics that alter the gut microbiome. Many xenobiotics also impact on gut microbiome characteristics. This includes pharmaceutical compounds such as metformin and methotrexate and psychotropic agents such as olanzapine. Other prescription medications are associated with alterations in gut microbiome diversity, including PPIs, opioids, and NSAIDs. Dietary compounds also exert a major impact on the gut microbiome, including polyphenolic phytochemicals (resveratrol, flavonoids), polyunsaturated fatty acids, and plant sterol ester. In addition, environmental and industrial chemicals, including endocrine disrupting chemicals, heavy metals, pesticides, and pollutants, exert an influence on gut microbiome structure, composition, and function.

increasingly used to inform our understanding of host–microbe interactions (Clark and Walker, 2018), and in the current context, a number of examples have been discussed, including studies focused on the chemotherapeutics doxorubicin (Yan et al., 2018) and 5-FU (Garcia-Gonzalez et al., 2017; Scott et al., 2017).

Conceptually, contrasting lower gut metabolites with upper gut metabolites in rodents or comparing extended

release versus immediate release formulations or i.v. drug delivery with oral drug delivery in human in vivo studies can also be informative (Sousa et al., 2008). More routine screening of reciprocal microbiome–xenobiotic interactions can be conducted in various in vitro batch culture or fermentation systems or in the more complex simulator of the human intestinal microbial ecosystem, as was demonstrated for the insecticide Chlorpyrifos (Sousa et al., 2008; Joly et al., 2013; Ou et al., 2015). Large scale in vitro screening of commonly used drugs for antibacterial activity also offers important information (Maier et al., 2018). There are also advantages to the use of in silico models to predict outcome from a variety of inputs, possibly by combining microbiota metabolism rates with host drug absorption and metabolic rates. Specifically adapting many of the emerging physiologically based pharmacokinetic models, which predict drug levels in tissues based on a variety of drug and host parameters (Min and Bae, 2017; Thiele et al., 2017; Donovan et al., 2018), to allow for greater contribution of microbiota-mediated metabolism, may be a useful approach to predict overall clinical impact.

Fecal sample incubations are often used in xenobiotic metabolism studies, as they are easily accessible and provide a reasonably reliable means of assessing the metabolic activity of the colonic microbiota. Fecalase or cecalase, stable and translationally relevant cell-free extracts of feces or cecal matter with bacterial enzymatic activity, are frequently used incubations (Tamura et al., 1980). This has been applied in the study of lovastatin (Yoo et al., 2014) and amlodipine (Yoo et al., 2016) and to look at the effect of probiotics on the pharmacokinetics of acetaminophen (Kim et al., 2018). Concerns about the variability of the assay have seen the development of a fecal microbial enzyme mix (Yeo et al., 2012).

Haiser et al. (2014) have outlined how these approaches might be combined in a framework for studying microbial drug metabolism that includes functional metagenomics to gain mechanistic insights and bioinformatics to guide rational microbiome-targeted therapeutic interventions. The value of such an approach once it leads to well-defined enzyme biochemistry can be seen in an earlier study that demonstrated that it was possible to selectively inhibit bacterial β-glucuronidases to alleviate drug-induced gastrointestinal toxicity arising from irinotecan (Wallace et al., 2010). There is also a variety of predictive and computational tools for the evaluation of microbial effects on drugs during gastrointestinal passage that can be used to streamline the process and provide targets for downstream in vitro and in vivo hypothesis assessments (Pieper and Bertau, 2010; Klunemann et al., 2014; Magnúsdóttir and Thiele, 2018).

Many of the in vitro approaches discussed are perhaps overly simplistic and do not best capitalize on the unique features of the gut ecosystem, such as microniches, pH gradients, and dynamic microbe–tissue interactions (Tralau and Luch, 2013). Organ-on-a-chip microphysiological systems are likely to increase efficiency and contribute in the future to a better understanding of microbial metabolism and host–microbiome crosstalk (Park et al., 2017). Gastrointestinal organoids can be used to more accurately model aspects of epithelial barrier dynamics, including cellular differentiation and proliferation, in specific intestinal segments bring advantages over cell culture models in unraveling the molecular basis of the host–microbe interactions (Hill and Spence, 2016). Meanwhile, recent reports of an ingestible electronic capsule that can provide real-time information on gastrointestinal oxygen, hydrogen, and carbon dioxide may ultimately see use as a chemical biosensor to improve our understanding of the biogeography of gut microbial metabolism (Kalantar-Zadeh et al., 2018). Indeed, this is already partially functional in this regard because the detection of hydrogen signals can be used as a proxy for regional fermentation patterns (Fig. 7).

IX. Toward Microbiome-Based Treatments and Novel Biotherapeutics

The prospect of targeting the microbiome for enhancing drug efficacy and therapeutic benefit is appealing, and the development of innovative, more personalized approaches in the practice of medicine can potentially be expedited with successful incorporation of our knowledge of host–microbe interactions outlined above. A number of other options are also currently under consideration and include drug delivery via designer probiotics or biotherapeutics that take advantage of the modified biochemical prowess of gut bacteria (Maxmen, 2017). For example, a genetically engineered *Lactococcus lactis*–secreting interleukin-10 has been used to deliver a localized therapeutic dose of IL-10 for the amelioration of murine colitis in an animal model of IBD (Steidler et al., 2000). The use of designer lactic acid bacteria as factories for the production of antimicrobial and anti-inflammatory biomolecules may also see utility in the future treatment of infectious diseases, cancer, and metabolic diseases (Cano-Garrido et al., 2015; Singh et al., 2017). Meanwhile, next-generation probiotics may be based on the use of microbes found to be deficient in certain disorders, as is the case of *A. muciniphila* in obesity, diabetes, and cardiometabolic diseases (Cani and de Vos, 2017), or *Faecalibacterium prausnitzii* in IBD if the positive preclinical results in models of colitis successfully translate to the clinic (O'Toole et al., 2017). Pathogen-specific antimicrobials and the development of bacteriocins as alternative therapeutic options is another avenue under exploration (Maxson and Mitchell, 2016; Mathur et al., 2017; Munguia and Nizet, 2017), as is the potential use of bacteriophage (Forde and Hill, 2017). Precision editing of the gut microbiota may also be possible, with an example being the use of tungstate treatment to selectively inhibit microbial respiratory pathways, which are operational specifically

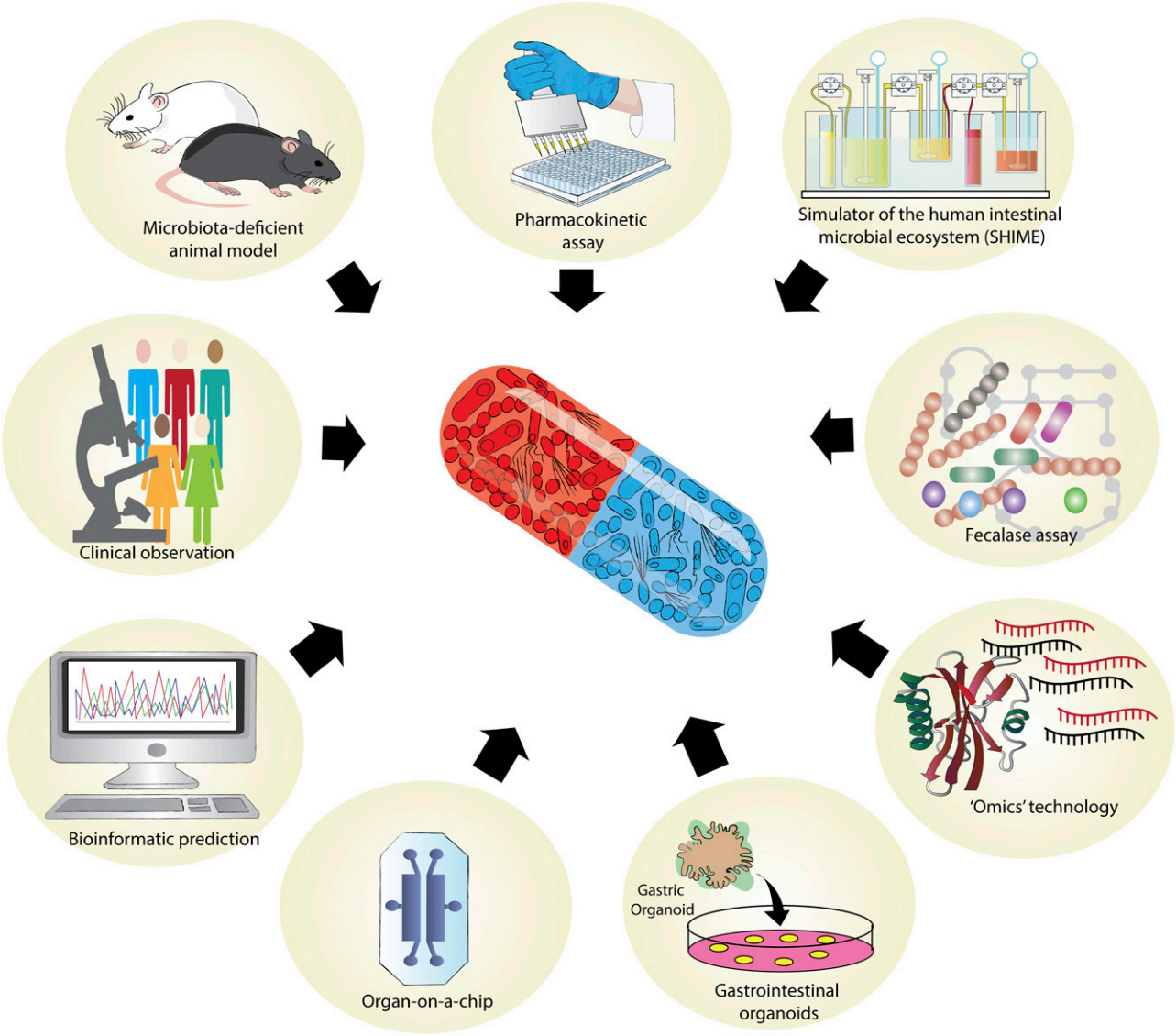


Fig. 7. Experimental approaches. Although we have been aware of isolated, but clinically relevant examples for a number of years, most commentators agree that the current bank of known pharmacomicrobiomic reactions is likely to be expanded greatly in future years. Coupled with clinical observations, a range of experimental approaches may be geared toward extracting complementary information about the complex and bidirectional interplay between the gut microbiome and xenobiotics. Many of the strategies employed, such as the use of germ-free models or those generated via depletion of the gut microbiota with a cocktail of antibiotics, can provide valuable pharmacokinetic and pharmacodynamic insights. Insights from invertebrate germ-free models, such as the nematode *C. elegans*, are increasingly used to inform our understanding of host–microbe interactions. More routine screening of reciprocal microbiome–xenobiotic interactions can be conducted in various in vitro batch culture or fermentation systems or in the more complex simulator of the human intestinal microbial ecosystem. Fecal sample incubations, such as fecalase or cecalase assays, are often used in xenobiotic metabolism studies. Functional metagenomics and bioinformatics can be used to guide rational, mechanistically-oriented microbiome-targeted therapeutic interventions. There is also a variety of predictive and computational tools for the evaluation of microbial effects on drugs during gastrointestinal passage that can be used to streamline the process and provide targets for downstream in vitro and in vivo hypothesis assessments. Organ-on-a-chip microphysiological systems are likely to increase efficiency and contribute in the future to a better understanding of microbial metabolism and host–microbiome crosstalk. Gastrointestinal organoids can be used to more accurately model aspects of epithelial barrier dynamics, including cellular differentiation and proliferation, in specific intestinal segments and bring advantages over cell culture models in unraveling the molecular basis of the host–microbe interactions.

during episodes of localized gut inflammation (Zhu et al., 2018). It remains to be seen whether fecal microbiota transplantation, which has been so effective in the treatment of recurrent *Clostridium difficile* infection, will also see applications in this area (de Groot et al., 2017).

A. Psychobiotics

Psychobiotics were originally defined as "a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness" (Dinan et al., 2013). That has since expanded to include prebiotics that enhance the growth of beneficial gut bacteria and also to include healthy individuals (Sarkar et al., 2016). Currently, preclinical behavioral screening platforms are most frequently used to identify candidate psychobiotics for further evaluation in clinical platforms (Bravo et al., 2011; Savignac et al., 2014, 2015; Burokas et al., 2017). This

has met with somewhat mixed results in healthy human subjects with strain-specific positive results (Allen et al., 2016; Papalini et al., 2018) and a failure to translate (Kelly et al., 2017). Refinements of the discovery pipeline may be necessary at various pressure points, and this could include the development of psychobiotics with specific mechanisms of action, tailored toward individual patient requirements (Bambury et al., 2018).

One option in this regard may be the selection of psychobiotics to fine-tune host or microbial tryptophan metabolism, an important source of neuroactives for microbiome–gut–brain axis signaling, including therapeutic targets for stress-related disorders such as serotonin and kynurenine (O'Mahony et al., 2015; Yano et al., 2015; Kennedy et al., 2017). Candidate psychobiotics that beneficially impact on host tryptophan metabolites include *Bifidobacterium longum subsp. longum* 35624 (previously *B. infantis* 35624) (Desbonnet et al., 2008) and *L. reuteri* (Marin et al., 2017). Bacterial metabolism of tryptophan to indole compounds may be equally important because either in their own right or following host processing, these microbial tryptophan metabolites can impact on host physiology and behavior (Lee et al., 2015). Next-generation psychobiotics may be selected to metabolize tryptophan at specific gut locations, as is the case for specific mucin utilizing *Peptostreptococcus* species, which produce indoleacrylic acid close to the intestinal epithelium, where it acts

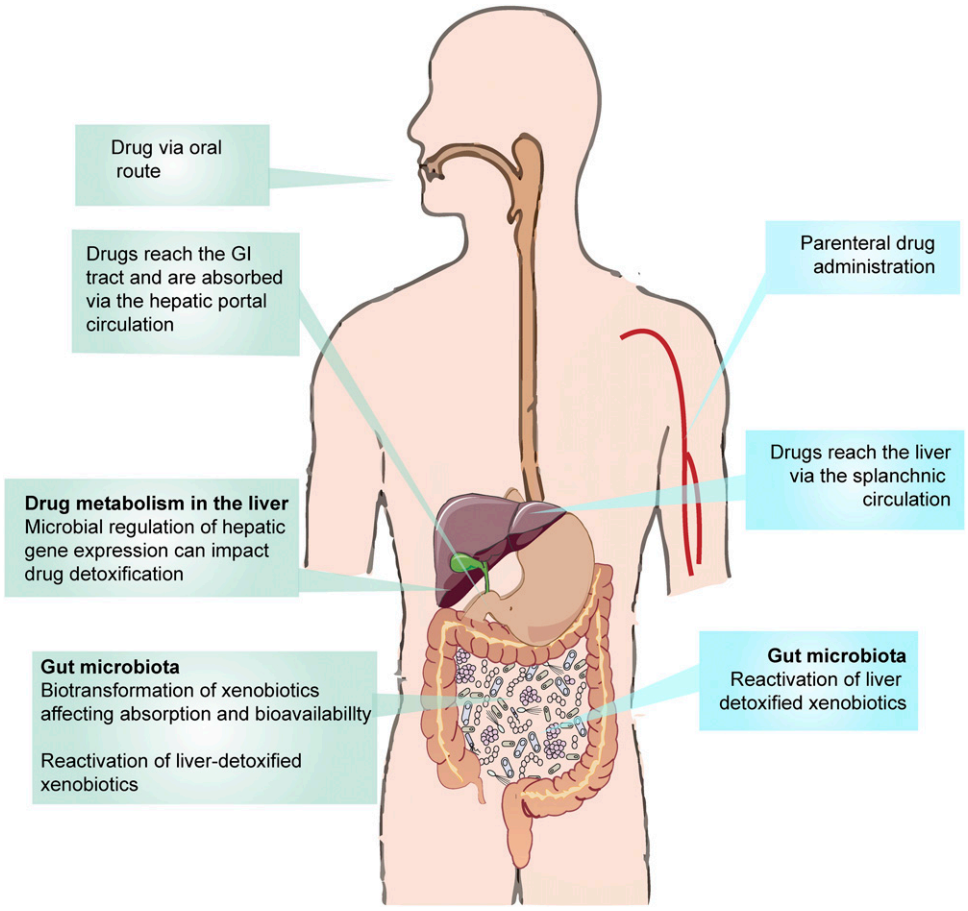


Fig. 8. Microbial contribution to drug metabolism. Following enteral administration, the physiochemical properties or formulation of a drug impacts the region of the gastrointestinal tract where the major exposure to microbial drug metabolism occurs. The nature of these interactions depends on whether the compounds encountered by the gut microbiome are poorly absorbed or are first conjugated by the liver and subsequently reach the intestine via biliary excretion, which is also a route through which i.v. administered drugs can become subject to chemical transformation by gut microbes. The majority of orally administered drugs are normally absorbed in the upper small intestine assuming that the drug is highly soluble and highly permeable in this region. Although there is a lower density of microbes in the small intestine, we have an incomplete understanding of the impact of microbial activity in different regions of the gastrointestinal tract, and there may be important implications of region-specific microbial drug metabolism for health and disease. However, many drugs display poor solubility, which can lead to slow and incomplete absorption with the drug being absorbed from distal regions of the small intestine and/or the colon. Drugs with low permeability through the intestinal membrane can lead to greater amounts of those drugs reaching these distal regions of the intestine. Drugs can also become a candidate substrate for direct microbial processing if they are appropriately formulated. The highest density of bacteria is found in the colon, and the prevalent use of advanced drug formulations designed for extended release (e.g., sustained release tablets) is on the increase, circumventing absorption profiles that would usually limit exposure of many drugs to the colonic gut microbiota. This ensures that an increasing number of pharmaceuticals are first exposed to the gut microbiota and their associated collection of metabolic enzymes with the potential for relevant microbiome–drug interactions highest in this region. The fate of drugs following oral ingestion is most often considered, but parenteral routes can still lead to gut microbiome–drug interactions, for example, via the splanchnic circulation and bilary excretion. Enterohepatic circulation is an important consideration in this regard, as is the potential for an indirect impact via microbial regulation of hepatic drug metabolism.

to improve barrier function (Wlodarska et al., 2017). Gut-derived microbial metabolites such as propionate, whose production could be stimulated by prebiotics, can also exert protective effects on blood-brain barrier integrity (Hoyles et al., 2018c). Given the importance of intestinal and blood-brain barrier permeability for health and disease (Bischoff et al., 2014; Kelly et al., 2015), this strategy could be combined with the selection of at-risk or compromised individuals to improve treatment outcomes.

X. Summary, Conclusions, and Perspectives

The gut microbiome can have a wide variety of direct and indirect effects on the metabolism of pharmaceuticals, dietary compounds, and environmental chemicals. The pharmacomicrobiomic web portal currently lists over 90 examples of such chemicals (http://pharmacomicrobiomics.com/view/chemical/). Although we have been aware of isolated, but clinically relevant examples for a number of years, most commentators agree that the current bank of known reactions is likely to be expanded greatly in future years. For drug metabolism alone, the implications of microbial biotransformation or other indirect actions of gut bacteria are hugely significant because it results in the activation or inactivation of drugs and often generates byproducts that are toxic to the host (Fig. 8).

An increased focus on this important area comes at a time when sequencing studies have identified gut microbiome alterations in many of the disorders treated by these same drugs. The reciprocal nature of these microbe–drug interactions has also been demonstrated with many of these therapeutic agents also modifying the composition and function of the gut microbiome (see Table 3), although increased application of techniques to study both microbial transcriptional activities and metabolic profiles is warranted (Carmody and Turnbaugh, 2014). Taken together, this paints a complex picture, and whereas a research framework is being put in place, cross-disciplinary input and increased attention from the scientific community are required to address the many outstanding questions in this field (see Table 4) and to achieve a more comprehensive view of pharmacology (Saad et al., 2012; Carmody and Turnbaugh, 2014). We can take encouragement in these efforts from recent observations regarding the importance of gut microbiome composition and the response to cancer therapeutic drugs (Jobin, 2018). If this can even be partially replicated across the range of disorders discussed above, the move toward the practice of precision, personalized medicine may well be expedited by incorporation of microbiome research.

Although there are many examples of remediation opportunities, we should not neglect the prophylactic power of diet to help sculpt the diversity that is necessary in a healthy gut microbiome (Shanahan et al., 2017). We have noted above a number of instances in which diet–microbe–host interactions can lead to adverse consequences. Indeed, the prescription of dietary modifications is also now being considered in a number of disease areas, including psychiatry (Jacka, 2017), as are other lifestyle factors such as exercise, which is also known to improve gut microbiota profiles (O'Sullivan et al., 2015). Stress exposure is also an important consideration, particularly during the extremes of life when the gut microbiota is more chaotic and vulnerable. Although there are many reports of elevated or decreased circulating levels of microbiome-associated metabolites in pathologic states, there remains an incomplete understanding of their functional important in the absence of disease. Defining normal physiologic ranges and toxic concentrations is an important objective before interventions designed to remove specific bacteria and/or their associated functions from the human gut microbiome can be effectively implemented. Neither should we ignore the other human microbial ecological niches. For example, although we have focused above on the gut microbiome, microbicide efficacy in African women has been linked to vaginal microbiome characteristics, with tenofovir being depleted by bacterial metabolism (Klatt et al., 2017). Also neglected to date is the gut mycobiome, and there are indications that our intestinal fungi are an important component of host–microbe interactions of relevance to immune homeostasis and inflammatory disorders (Leonardi et al., 2018) and stress-related disorders such as irritable bowel syndrome (Botschuijver et al., 2017).

As our knowledge of the gut microbiome continues to increase and the balance shifts from new discoveries to mechanistic insights, so too does our appreciation that virtually all aspects of host physiology need to be

TABLE 4
Outstanding questions in pharmacomicrobiomics

Key Questions
Do disease-associated microbiomes impact on bacterial enzyme expression and/or activity to dysregulate xenobiotic metabolism?
What is the impact of extreme of life microbiome variation on pharmacokinetics and pharmacodynamics?
Can we unravel disease vs. drug-induced contributions to microbiome alterations?
Can the use of microbiome composition to predict therapeutic response be incorporated into clinical practice?
Can we identify bacteria- and/or enzyme-specific host–microbe interactions for subsequent therapeutic targeting?
Can we compile and systematically evaluate currently unexplained aberrant pharmacokinetic observations?
Can diet be used to beneficially tune microbial xenobiotic metabolism?
Can we differentiate between effects of acute and long-term exposure to xenobiotics on the gut microbiome?
Should we re-evaluate the guidelines for coadministration of antibiotics?

reconsidered in light of reciprocal host–microbiome interactions. It is only now logical to include the broad metabolic capacity of the gut microbiome within fundamental principles of pharmacokinetics and pharmacodynamics, the difficulty in rationally manipulating the chemical biotransformations by unknown enzymes and members of the gut microbiome notwithstanding. The future practice of precision medicine may depend on our ability to successfully navigate the challenges that lie ahead and incorporate a more microbial perspective into clinical guidelines and applications.

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Authorship Contributions

Participated in research design: Clarke, Sandhu, Griffin, Dinan, Cryan, Hyland.

Performed data analysis: Clarke, Sandhu, Griffin, Dinan, Cryan, Hyland.

Wrote or contributed to the writing of the manuscript: Clarke, Sandhu, Griffin, Dinan, Cryan, Hyland.

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