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The Gut Microbiota Impact Cancer Etiology through "Phase IV Metabolism" of Xenobiotics and Endobiotics

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ABSTRACT

The human gut microbiome intimately complements the human genome and gut microbial factors directly influence health and disease. Here we outline how the gut microbiota uniquely contributes to cancer etiology by processing products of human drug and endobiotic metabolism. We formally propose that the reactions performed by the gut microbiota should be classified as "Phase IV xenobiotic and endobiotic metabolism." Finally, we discuss new data on the control of cancer by the inhibition of gut microbial phase IV enzymes responsible for tumor initiation and progression.

Introduction

The gut microbiota is comprised of trillions of microorganisms that physically interact with host intestinal cells and functionally impact numerous host physiologic systems. Here we focus on the interplay between gut microbiota and human xenobiotic and endobiotic metabolic processes. Host cytochrome P450s (CYP) are primary drug-converting enzymes, as they add functional groups to a wide range of xeno- and endobiotics as part of phase I drug metabolism. Phase II enzymes append polar moieties to drugs/endobiotics to mark these compounds for excretion by drug metabolism's phase III efflux transporters into the urine or gastrointestinal (GI) tract.

Beyond these three well-characterized phases, the gut microbiome encodes a vast arsenal of metabolic enzymes that we believe should be formally defined as "phase IV" of xeno- and endobiotic metabolism. Phase IV metabolism within the gut typically follows human phase I–III processes, further alters the products of host metabolism, and directly and substantially impacts intestinal and systemic drug and endobiotic metabolism. Indeed, it has been known since the early days of drug discovery that the intestinal microbiota process drugs, including the first antibiotic sulfa compounds in the 1940s (1), as well as the heart medication digoxin (2) and the Parkinson's drug levodopa (3) in the 1970s. Thus, the modification of intact and metabolized drugs and endobiotics by the GI microbes impacts the local and systemic actions of these compounds.

The gut microbiota performs reductions, decarboxylation, demethylation, deamination, and deacylation reactions, as well as hydrolysis and ring-opening reactions as part of phase IV metabolism. This list will certainly grow as we discover and map the full catalytic capacity of the gut microbiome. It is already evident, though, that gut microbial enzymes can extend human drug metabolism, and understanding these reactions is key to treating and preventing disease. Given current and rapidly expanding data, phase IV metabolism should grow into a richly appreciated and physiologically crucial process on par with phase I–III metabolism in its importance to human health outcomes.

Here we detail how the gut microbiota acts on host phase II metabolites of drugs and endobiotics important to cancer progression. In addition, we discuss potential mechanisms to disrupt cancer etiology related to the intestinal microbiome, including lifestyle choices and the novel paradigm of inhibiting gut microbial enzymes.

Drugs and the Gut Microbiota

Metagenomic and metabolomic studies have firmly linked the gastrointestinal microbiome to cancer development. There is accumulating evidence that the gut microbiota is involved in formation and progression of cancers including esophageal, gastric, and colorectal cancers. For example, several strong correlations have been established between the gut microbiota and colorectal cancer. Reddy and colleagues treated germ-free and conventional rats with the carcinogen 1,2-dimethylhydrazine and found that 93% of conventional rats developed colonic tumors compared to only 21% of the germ-free animals (4). Gut *Escherichia, Enterococcus, Bacteroides*, and *Clostridium* species have also been shown to promote colorectal carcinogenesis by increasing aberrant crypt foci (5). Mice transplanted with stool from patients with colorectal cancer showed enhanced intestinal cell

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proliferation and greater tumor formation (6). Beyond these seminal contributions, many others have linked specific bacteria to colorectal cancer development and progression (7–11). Inspired by these data, here we focus on the specific gut microbial xenobiotic and endobiotic metabolism reactions that are known to, or can be reasonably expected to, directly influence cancer etiology.

Following a cancer diagnosis, the gut microbiota also impacts the treatment of colorectal cancer with chemotherapeutics. For example, fluorouracil (5-FU) has remained a standard therapy for the treatment of advanced colorectal cancer for over 40 years, but it is known to cause severe toxicity in some patients. Two independent studies have suggested that enzymes within the gut microbiota responsible for the deamination of 5-fluorocytosine to 5-fluorouracil drive this toxicity and reduce drug efficacy (12, 13).

Drug toxicity and reduced efficacy are also driven by the gut microbiota for the colorectal cancer and pancreas cancer drug, irinotecan. The active metabolite of irinotecan, SN-38, is glucuronidated to inactive SN-38-G by host phase II UDP-glucuronosyltransferase enzymes (UGT) in the liver to facilitate intestinal excretion. In the gut, SN-38-G encounters microbial β-glucuronidase (GUS) enzymes that remove the glucuronic acid sugar, effectively reversing host phase II metabolism and reactivating SN-38 in the GI lumen (**Fig. 1A**). This reactivation causes severe, dose-limiting gut toxicity in a significant fraction of patients. However, by inhibiting the GUS enzymes responsible for this reactivation, the associated toxicity can be significantly alleviated in animal models (14, 15). Identifying patients with greater levels of relevant SN-38–reactivating GUS enzymes may serve as a diagnostic tool to improve patient outcomes, as discussed in more detail below.

Somewhere between 40% and 70% of drugs are subject to glucuronidation by UGTs (16). The exact number is not well defined because, unlike CYPs, the actions of UGTs on each drug are not always specified. Gut microbial GUS enzymes are, in principle, capable of reactivating some fraction of all these metabolites, and thus can potentially impact the efficacy and toxicity of dozens of drugs. Indeed, we have shown that specific human gut microbial GUS enzymes are responsible for the toxicity of NSAIDs (17) as well as the colorectal cancer drug, regorafenib (18). Thus, gut microbiome-encoded GUS enzymes are major route of phase IV drug metabolism and they drive poor therapeutic responses by causing intestinal toxicities.

Preventing GUS-mediated drug reactivation may improve patient outcomes for many diseases. However, there are multiple phase II conjugation reactions beyond glucuronidation, including sulfation, methylation, and acetylation. It is critical to define how phase II drug metabolites are processed by gut microbial sulfatases, methyltransferases, and deacetylases to fully unravel the impact of phase IV drug metabolism on disease progression and therapeutic efficacy.

Endobiotics and the Gut Microbiota

The gut microbiota has also been hypothesized to influence the formation and progression of tumors distant from the GI tract. In particular, GUS enzymes have been implicated in a number of hormonal disorders including breast, endometrial, and ovarian cancers by reactivating inactivate estrogen-glucuronides to estrogen, similar to the reactivation of SN-38 from SN-38-G (19). Our group has recently demonstrated that gut microbial GUS enzymes contribute to estrogen-glucuronide reactivation *in vitro* and *ex vivo* but have limited effect in *in vivo* mouse models (20). Thus, our findings suggest that the gut-estrogen metabolism is highly complex and likely involves a wide range of factors, including microbial sulfatases and catechol-O-methyltransferases (COMT).

Like GUS enzymes, gut microbial sulfatases are capable of reactivating compounds inactivated by human phase II metabolism. For example, estrone and dehydroepiandrosterone, key hormonal biomarkers of cancer progression, are sulfated in the liver and other metabolic tissues like the GI tract and sent to the gut for excretion. Given the prevalence of sulfate groups on dietary, endobiotic, and xenobiotic compounds, the gut lumen is expected to contain a diverse array of microbial sulfatases capable of removing sulfate moieties, thus reactivating hormones for potential reabsorption and systemic recirculation (**Fig. 1B**). The impact of microbial sulfatases on estrogen metabolism may be significant and akin to the established roles human sulfatases play in the etiology of hormone receptor–positive cancers (21).

Gut microbial COMTs are also poised to impact hormone bioavailability and disease etiology. After phase I metabolism, it is reasonable to expect that hydroxylated estrogens will serve as substrates for gut microbial COMTs, which are abundant and, like host COMTs, methylate catecholamines and catechol-estrogens (22). We speculate that interindividual differences in gut microbial COMTs may influence the circulating levels of drugs and endobiotics and, in the case of estrogens, would contribute to an individual's total level of hormone. However, in contrast to gut microbial GUS and sulfatase enzymes that generate active estrogens implicated in disease progression, gut microbial COMTs would be protective by producing inactivated methylated hormone derivatives. For example, it has been demonstrated that methylation of 4-hydroxyestrone lowers the potential for DNA damage and increases the concentration of antiproliferative metabolites (**Fig. 1C**; ref. 23). Thus, gut microbial phase IV metabolism is capable of converting the products of human phase I and II metabolism into chemicals that may fuel distal malignancies, like hormone-positive breast and ovarian cancers, or may facilitate the safe elimination of potentially harmful compounds.

Carcinogens and the Gut Microbiota

Gut microbial phase IV metabolism also drives carcinogenesis by producing carcinogenic chemicals in the lumen of

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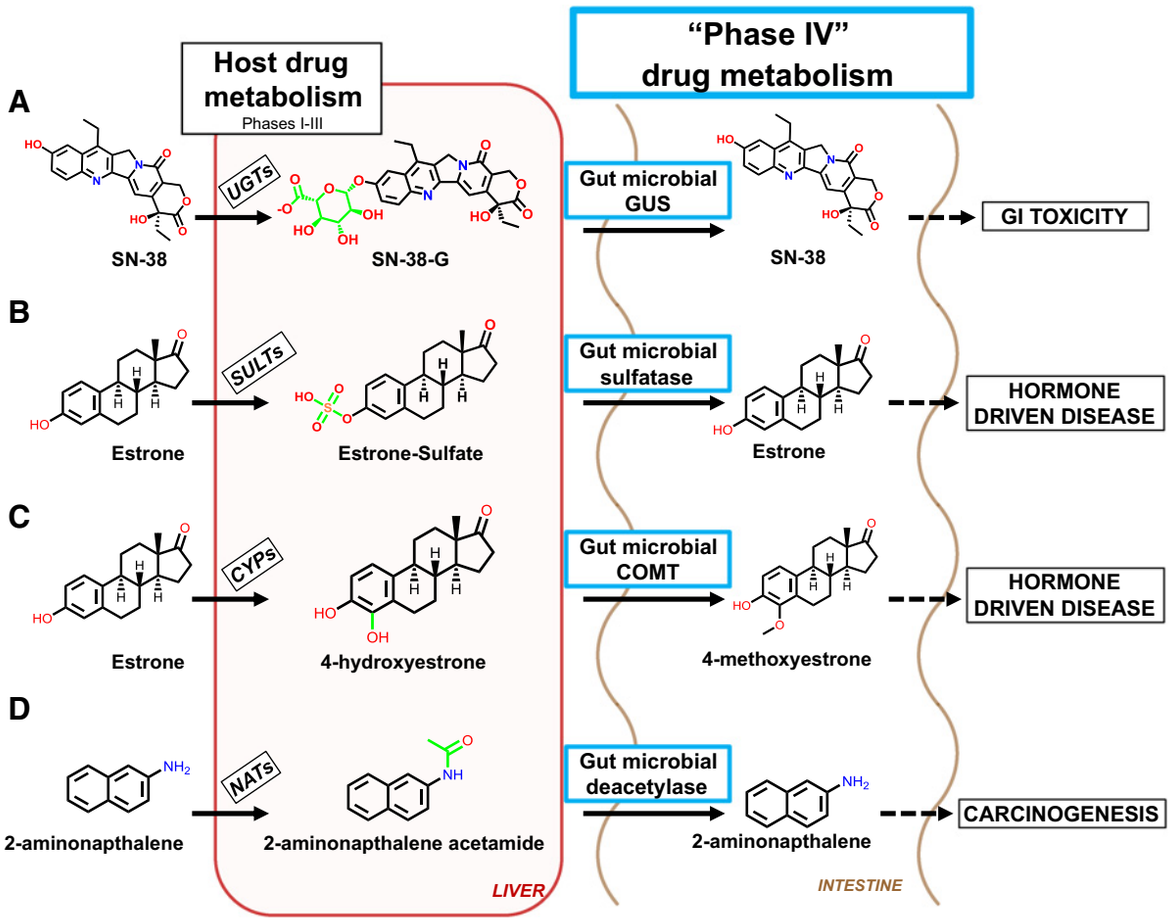

Figure 1.

Host and gut microbiota metabolic interactions. **A,** The active metabolite of irinotecan, SN-38, is glucuronidated to inactive SN-38-G by host Phase II UDP-glucuronosyltransferase enzymes (UGTs) in the liver. In the gut, SN-38-G encounters microbial β-glucuronidase (GUS) enzymes that remove the glucuronic acid sugar, reactivating SN-38 in the GI lumen and causing local GI toxicity. **B,** Estrone is sulfated in the liver via the action of sulfotransferases (SULTs) sent to the gut for excretion. The gut lumen contains microbial sulfatases capable of removing the inactivating sulfate moiety, reactivating hormones for reabsorption and systemic recirculation, contributing to systemic diseases, including hormone driven cancers. **C,** After Phase I metabolism, hydroxylated estrogens may serve as substrates for gut microbial COMTs, which, methylate catechol-estrogens, contributing to total estrogenic burden and thus may also contribute to systemic diseases, including hormone driven cancers. **D,** 2-Naphthalene is acetylated by human N-acetyltransferases (NATs); these acetylated compounds may encounter gut microbial small molecule deacetylases that reactivate the mutagen and facilitate gut epithelial tumorigenesis, exerting systemic effects and potentially contributing to carcinogenesis.

the GI tract. PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) is a heterocyclic aromatic amine found in cooked meats. Dietary exposure to PhIP has been implicated in the etiology of cancer in humans (24). During phase I metabolism PhIP is oxidized via cytochrome P4501A2 (CYP1A2) enzymes to a hydroxylated intermediate, N-OH-PhIP (22). N-OH-PhIP, which is itself mutagenic, can be converted to a more biologically reactive form via phase II metabolizing enzymes, primarily the acetyltransferases or sulfotransferases (22). The esterification generates electrophilic O-sulfonyl and O-acetyl esters, which bind DNA and cellular proteins (25).

In contrast, human phase II glucuronidation of N-OH-PhIP inactivates this compound. However, gut microbial phase IV GUS enzymes may reactivate N-OH-PhIP and result in intestinal carcinogenesis (24). Thus, like SN-38-G and other therapeutics, gut microbial GUS enzymes reverse phase II drug metabolic reactions to drive poor outcomes or transitions to disease.

Numerous heterocyclic aromatic amines, including 2-aminonapthalene (**Fig. 1D**), are also carcinogens. These compounds are known to be glucuronidated and, like PhIP-G, their gut reactivation produces mutagenic DNA adducts that promote carcinogenesis (26). When heterocyclic aromatic amines are acetylated by human N-acetyltransferases, the products are inactivated as mutagens and sent to the GI tract for elimination. Therefore, it is reasonable to expect that such acetylated compounds will encounter known microbial deacetylases (27) capable of reactivating mutagens toward increased gut epithelial tumorigenesis (**Fig. 1D**).

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Although the interplay between host and agent is often very complex, we find that conjugation is regularly employed to inactivate and eliminate carcinogens via the GI tract. The American Cancer Society lists more than 100 compounds as carcinogenic (28). We have outlined the phase II metabolic reactions for the most common carcinogens, including some chemotherapeutics (**Table 1**). Thus, such compounds may encounter gut microbial enzymes that metabolize and reactivate these carcinogens within the intestinal lumen and reverse the action of host enzymes. It is also likely that some compounds are first metabolized by the gut microbes and then absorbed via the vasculature for further processing by host metabolic enzymes. Thus, a more complete understanding the relationship between host and microbe is key to understanding carcinogenesis and its prevention.

Table 1. List of known carcinogens and their host phase II metabolic conversions.

		Host phase II metabolic conversions					
Carcinogen	**Source**	**Acetylation**	**Glucuronidation**	**Methylation**	**Sulfation**	**Glutathione conjugation**	**References**
1,3-Butadiene	1,3-Butadiene is a chemical made from the processing of petroleum. About 75% of the manufactured 1,3-butadiene is used to make synthetic rubber for tires on cars and trucks.					√	33
1,4-Butanediol dimethylsulfonate (Busulfan)	Chemotherapeutic					√	34
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD); "dioxin"	Meat and dairy products		√		√		35
2-Naphthylamine	Cigarette smoke	√	√		√		26
Aflatoxins	Produced by certain molds which grow in soil, decaying vegetation, hay, and grains					√	36
Analgesic mixtures containing phenacetin	Pain-relieving and fever-reducing drug	√	√	√	√		37
Azathioprine	Immunosuppressant drug			√			38
Benzene	Used to make plastics, resins, synthetic fibers, rubber lubricants, dyes, detergents, drugs and pesticides	√	√	√	√	√	39
Chlorambucil	Chemotherapeutic	√					40
Cyclophosphamide	Chemotherapeutic	√					41
Estrogen-progestogen (combined)	Menopausal therapy or contraceptives		√	√	√		42
Ethanol	Alcoholic beverages		√				43
Formaldehyde	Particleboard, plywood, and fiberboard; glues and adhesives; permanent-press fabrics; paper product coatings; and certain insulation materials					√	44
PhIP	Dietary grilled meat	√	√		√		45
Polychlorinated biphenyls (PCBs)	PCBs were once widely deployed as dielectric and coolant fluids in electrical apparatus, carbonless copy paper and in heat transfer fluids		√	√	√		46
Tamoxifen	Chemotherapeutic		√	√	√		47
Thiotepa	Chemotherapeutic	√				√	48
Trichloroethylene	Stains and varnishes, adhesives, typewriter correction fluids, paint removers, and cleaners. Contaminated air and water are the most important sources of exposure to trichloroethylene.	√	√	√			49

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It is important to stress how little we know about gut microbiome and the functions it encodes. As a result, we have an incomplete understanding of the types of biotransformations that these carcinogens, as well as drugs and endobiotics undergo in the gut. We can certainly imagine that such compounds encounter microbial enzymes catalyzing hydrolysis, dehydrogenation, and elimination reactions, as well as a wealth of other transformations performed by the most talented chemists on earth — the microbes. It is also likely that some compounds are first metabolized by the gut and then absorbed via the vasculature for further processing by host metabolic enzymes. Thus, a detailed understanding of the enzymatic processes performed within the gut and their relationship to the host is fundamental to fuel new discoveries related to cancer etiology.

Treating Cancer through the GI Microbiome

Diet and other environmental factors impact health by modulating the composition and metabolic activity of the human gut microbiota. Smoking, stress, and obesity have all been associated with dysbiosis, while an active, nonsedentary lifestyle promotes a diverse and healthy gut microbiome (29). In addition, western-style diets rich in fats and proteins have been shown to exert negative effects on the gut microbial composition and may contribute to chronic cardiovascular diseases, colorectal cancer, and other conditions. However, while changes in diet, lifestyle, and antibiotics may induce microbial shifts, their impact may not be sufficient alone improve health (30).

Thus, in addition to dietary and lifestyle changes, pre- and probiotics have been explored to disrupt cancer etiology. Prebiotics are dietary substrates that selectively promote proliferation and/or activity of beneficial indigenous gut bacteria, while probiotics are live bacteria administered to achieve the same goals. Both have been shown to increase gut levels of select bacteria. The most commonly consumed probiotics are *Lactobacillus* and *Bifidobacterium* taxa. Pre- and probiotics may improve host health through several mechanisms including modulating the mucosal transfer of luminal organisms and metabolites, increasing mucosal antibody production, strengthening epithelia integrity, and direct antagonism of pathogenic microorganisms (30). Although outcomes vary, in general, changes in human gut microbiota composition are relatively small and only persist for the period of intervention. Thus, definitive proof of the benefits of pre- and probiotics in combatting the complex etiology of cancer remains to be established.

The direct and selective modulation of gut microbial enzymes to address cancer etiology has shown promise in animal models and human *ex vivo* studies. As pioneered in Wallace and colleagues, potent bacterial GUS inhibitors alleviated the GI toxicity caused by the gut reactivation of SN-38 from SN-38-G (14). Inhibitors were highly specific for bacterial GUS enzymes and not mammalian orthologs; this is critical because mutations inactivating human GUS cause a lethal lysosomal storage disease. Selectivity was achieved based on active site features unique to bacterial GUSs to the human ortholog.

Exploiting such differences between human and microbial enzymes may accelerate the development of other inhibitors that specifically target gut microbial enzymes. Furthermore, pinpointing specific microbial enzymes in human fecal samples may lead to precision biomarkers and individualized treatment regimens that realize the promise of personalized medicine for cancer and beyond. In addition, those at risk for colorectal cancer development or its return may employ GUS inhibitors to prevent the gut reactivation of carcinogens, perhaps lowering the chances of disease initiation or progression.

Finally, studies like those conducted by Zimmermann and colleagues and Maier and colleagues provide crucial pathways to fully map gut microbial drug metabolic processes. Both used human gut microbiota and specific gut microbial strains to systematically identify microbial gene products that metabolize drugs and/or are influenced by the presence of drugs (31, 32). Ultimately, optimized cancer treatment and prevention will never be a tangible reality until proteomic, metagenomic, and metabolomic, biochemical and structural biology studies completely define phase IV drug metabolism conducted by the human gut microbiota. Only then can we fully appreciate how these systems interface with human phase I–III metabolism to drive the therapeutic outcomes and variabilities associated with cancer etiology.

Disclosure of Potential Conflicts of Interest

S.M. Ervin reports grants from NIH and grants from NSF GRFP during the conduct of the study. M.R. Redinbo reports grants from NIH (CA207416, GM135218) during the conduct of the study and personal fees from Symberix, Inc. (a pharmaceutical company that is targeting the gut microbiota) outside the submitted work. No other potential conflicts of interest were disclosed.

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Cancer Prevention Research

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