Scientific Paper Entitled: A Review Of Drug Metabolism And Gut Microbia

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Abstract

The human gastrointestinal (GI) tract hosts a diverse community of microorganisms that plays a crucial role in various processes, such as the synthesis of vital nutrients and vitamins, the digestion of complex carbohydrates, and resistance against foreign microbiota. Recent studies have shown that the gut microbiota is the first to interact with and metabolize foreign compounds, including environmental pollutants, dietary components, and therapeutic drugs. The gut microbiota contributes to approximately 3.3 million unique genes, which is approximately 150 times more than the human gene content. This large repository of enzymes in the gut outnumbers that in the liver and is capable of metabolizing numerous drugs and foreign

compounds, thereby influencing their pharmacological effects either directly or indirectly. While our understanding of the specific gut bacteria strains, their genes, and enzymes involved in the metabolism of foreign substances (xenobiotics) is still in its early stages, it is crucial to recognize that modifying these processes can have significant implications for health and treatment results. By comprehending how xenobiotic metabolism occurs in relation to the gut microbiota and the resulting intra-individual variations, we can improve the planning of therapeutic regimens and enhance treatment outcomes. The identification of microbial functions associated with xenobiotic metabolism can serve as targets for adjusting drug effectiveness and serve as diagnostic indicators in clinical settings. Furthermore, these microbial genetic patterns can contribute to the advancement of precision medicine. The gut microbiome encompasses the genetic material of all microorganisms residing in the mammalian gastrointestinal tract, comprising over 1000 species of bacteria and outnumbering host body cells by about tenfold. Recognized as an essential "metabolic organ," the gut microbiota is pivotal in maintaining human health and influencing various diseases. Additionally, it plays a crucial role in drug metabolism, affecting the pharmacological properties of drugs by either activating or deactivating them. While certain bacterial phyla like Firmicutes, Bacteroidetes, and Actinobacteria dominate the human gastrointestinal tract, the overall composition of the gut microbiota varies significantly among individuals. This variability contributes to differences in responses to drug therapy, alongside genetic polymorphism impacts. Despite extensive focus on the host genetic background in understanding drug responses over recent decades, the role of the gut microbiota has been underestimated due to its complexity and the challenges associated with culturing most gut bacteria in laboratory settings. In recent years, there has been a shift in microbial genomics from reliance on culture-dependent methods to culture-independent approaches like metagenomics. This advancement has greatly facilitated the understanding of the roles of the gut microbiota in diseases and drug metabolism. A new term, "pharmacomicrobiomics," has been coined to describe how variations in the gut microbiota affect both pharmacokinetics and pharmacodynamics. Extensive efforts have been directed towards investigating the influence of the gut

microbiota on pharmacokinetics. It is proposed that the gut microbiota can affect drug metabolism in several ways, including the production of microbial metabolites that interfere with drug metabolism, the production of microbial enzymes that alter drug molecules, and the modification of drug-metabolizing genes or enzymes in the liver or intestines of the host. Despite the complexity of the interaction between the gut microbiota and the host, recognition of the microbial impacts on drug metabolism is still evolving. This evolution is being accelerated by innovative systemic approaches such as metagenomics and metabolomics. Furthermore, there is increasing attention on the impact of the gut microbiota on pharmacodynamics, driven by exciting progress in understanding how gut microbial changes can influence drug efficacy.

Keywords: Gut Microbiota, Xenobiotics, Drug Metabolism, Drug Response.

Introduction

The diverse community of microorganisms residing in the human gastrointestinal (GI) tract is intimately connected with human biology and plays a crucial role in various processes such as the synthesis of vital nutrients and vitamins, the digestion of complex carbohydrates, resistance against the colonization of foreign microbiota, and the maturation of the immune system(1). Although the liver is generally considered the primary organ for metabolism after food intake(2), recent studies have shown that the gut microbiota is the first to interact with and metabolize the chemical structure of numerous orally administered foreign compounds, which include a wide range of substances such as environmental pollutants, dietary components, and therapeutic drugs. The dominant bacterial phyla in the human gut are mainly represented by Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia(3). However, the proportions of these phyla are sensitive to dietary habits, age, and disease conditions(4). The gut microbiota contributes to approximately 3.3 million unique genes, which is approximately 150 times more than the human gene content. This large repository of enzymes in the gut outnumbers that in the liver and is capable of metabolizing numerous drugs and foreign compounds, thereby influencing their

pharmacological effects either directly or indirectly, thereby expanding the range of metabolic reactions taking place within the human body(5).

While our understanding of the specific gut bacteria strains, their genes, and enzymes involved in the metabolism of foreign substances (xenobiotics) is still in its early stages, it is crucial to recognize that modifying these processes can have significant implications for health and treatment results. By comprehending how xenobiotic metabolism occurs in relation to the gut microbiota and the resulting intra-individual variations, we can improve the planning of therapeutic regimens and enhance treatment outcomes. The identification of microbial functions associated with xenobiotic metabolism can serve as targets for adjusting drug effectiveness and serve as diagnostic indicators in clinical settings. Furthermore, these microbial genetic patterns can contribute to the advancement of precision medicine(6).

Here, we provide an extensive overview of our comprehension of the direct and indirect ways in which gut microbial consortia impact therapeutics and play a crucial role in both health and disease. Our focus is on the current state of knowledge regarding the intricate interactions between gut microbiota-derived functions and xenobiotics. We evaluated the overall genomic content and metabolic activities of the microbial community inhabiting the human gut. Additionally, we reviewed the current understanding of the chemical modifications of xenobiotic conjugates, drugs, and prodrugs that are carried out by gut microbial consortia(7).

The gut microbiome encompasses the genetic material of all microorganisms residing in the mammalian gastrointestinal tract, comprising over 1000 species of bacteria and outnumbering host body cells by about tenfold(8). Recognized as an essential "metabolic organ," the gut microbiota is pivotal in maintaining human health and influencing various diseases. Additionally, it plays a crucial role in drug metabolism, affecting the pharmacological properties of drugs by either activating or deactivating them(9). While certain bacterial phyla like Firmicutes, Bacteroidetes, and Actinobacteria dominate the human gastrointestinal tract, the overall composition of the gut microbiota varies significantly among individuals(10). This variability contributes to differences in responses to drug therapy, alongside

genetic polymorphism impacts. Despite extensive focus on the host genetic background in understanding drug responses over recent decades, the role of the gut microbiota has been underestimated due to its complexity and the challenges associated with culturing most gut bacteria in laboratory settings(11).

In recent years, there has been a shift in microbial genomics from reliance on culture-dependent methods to culture-independent approaches like metagenomics(12). This advancement has greatly facilitated the understanding of the roles of the gut microbiota in diseases and drug metabolism. A new term, "pharmacomicrobiomics," has been coined to describe how variations in the gut microbiota affect both pharmacokinetics and pharmacodynamics(13).

Extensive efforts have been directed towards investigating the influence of the gut microbiota on pharmacokinetics. It is proposed that the gut microbiota can affect drug metabolism in several ways, including the production of microbial metabolites that interfere with drug metabolism, the production of microbial enzymes that alter drug molecules, and the modification of drug-metabolizing genes or enzymes in the liver or intestines of the host(14).

Despite the complexity of the interaction between the gut microbiota and the host, recognition of the microbial impacts on drug metabolism is still evolving. This evolution is being accelerated by innovative systemic approaches such as metagenomics and metabolomics. Furthermore, there is increasing attention on the impact of the gut microbiota on pharmacodynamics, driven by exciting progress in understanding how gut microbial changes can influence drug efficacy(15).

Overview of Xenobiotics

Xenobiotics refer to substances that are foreign to the human body and can be classified as exogenous or endogenous(16). Exogenous xenobiotics enter the body through sources such as diet, therapeutic drugs, or environmental pollutants, while endogenous xenobiotics are synthesized within the body or produced as metabolites. These xenobiotics can have harmful effects on the body, including toxicity, accumulation, and the potential to cause chronic health problems such as stunted growth, birth defects, and neurological disorders.

The human body has natural mechanisms to detoxify xenobiotics and reduce their toxicity. The gut and liver play significant roles in metabolizing xenobiotics through a process known as the "first pass effect." This involves chemical modifications in two phases: phase I and phase II metabolism. Phase I involves introducing reactive functional groups to xenobiotics through various chemical transformations, making them more polar. Phase II metabolism enhances hydrophilicity by conjugating the phase I metabolites with endogenous polar molecules(17).

The acidic environment of the stomach also contributes to the chemical transformation of pH-sensitive xenobiotics. Additionally, gut microbes and host enzymes play a role in metabolizing xenobiotics, especially in the gastrointestinal tract(18). The gut microbiota, which varies in different regions of the gastrointestinal tract, can metabolize a wide range of xenobiotics, including dietary compounds. The modified metabolites can have implications for health and disease susceptibility.

After being absorbed, xenobiotics and their metabolites are processed by liver enzymes and enter the circulatory system, affecting different tissues and organs. They can be further metabolized or excreted through bile or urine. In the large intestine, poorly absorbed substances can be transformed by the gut microbiota. The metabolites can be reabsorbed or interact with the gastrointestinal tract before being excreted(19).

Gut microbial metabolites have the potential to alter bioavailability, bioactivity, and toxicity of xenobiotics. They can also influence the expression and function of liver enzymes and interact with human xenobiotic-metabolizing enzymes, affecting the resulting metabolites. The gut microbiota, with its anaerobic bacterial colonization, plays a role in metabolizing indigestible substances and producing short-chain fatty acids, which can regulate host metabolism and aid digestion(20,21).

Drug metabolism by host tissues and intestinal microbiota

Xenobiotic metabolism in the small and large intestines differs significantly from metabolism in host tissues. For instance, the intestinal environment, characterized by low oxygen tension, favors reduction reactions, while oxidation is favored in tissues like the liver. Furthermore, the ability of the intestinal microbiota to

metabolize xenobiotics varies widely among individuals due to differences in the resident microbiota(22).

Throughout their lives, humans coexist with essential microbes that play a crucial role in detoxifying xenobiotics, including drugs and dietary compounds, through microbiota-host co-metabolism. The host's detoxification systems involve phase I and phase II reactions. Phase I metabolism, which encompasses oxidation, reduction, and hydroxylation, is primarily mediated by cytochrome P450 (CYP) enzymes found in the liver, gut, and other tissues. These enzymes facilitate the excretion of xenobiotics in urine by increasing their polarity. Phase II metabolism involves conjugation reactions such as glucuronidation and sulfonation, where foreign compounds are conjugated with endogenous molecules by host enzyme transfer systems to enhance their urinary excretion. Phase II enzymes include sulfotransferase (SULT), uridine 5’-diphospho-glucuronosyltransferase (UGT), N-acetyltransferase (NAT), and glutathione S-transferase (GST)(23).

The intestinal microbiota is involved in a variety of metabolic reactions, including reduction, dehydroxylation, acetylation, ring opening, dealkylation, and hydrolysis of glycosides, glucuronides, and sulfates. These reactions occur in response to xenobiotics ingested orally or excreted into the intestine through Phase I and Phase II reactions in host tissues. The consequences of intestinal microbial metabolism of xenobiotics can alter the enterohepatic circulation of metabolites excreted from host tissues, thereby modulating the efficacy and/or toxicity of xenobiotics that rely on metabolism for their actions. Thus, understanding the metabolism of xenobiotics by the intestinal microbiota could serve as an additional factor influencing the biological effects of xenobiotics(24).

It is noteworthy that over 70% of the top 200 prescribed drugs are metabolized in the liver, while approximately 25% are eliminated through the kidneys. About half of all drugs undergo metabolism through the P450 enzyme system, underscoring the pivotal role of P450 enzyme systems in drug metabolism(11).

Currently, there is an urgent need for intensive studies in this area, as only a limited number of therapeutic drugs have been investigated for their metabolism by the intestinal microbiota. Additionally, the specific microbes responsible for xenobiotic metabolism remain largely unidentified.

Several approaches have been used to investigate xenobiotic metabolism by the intestinal microbiota. One common technique involves using intestinal contents or fecal suspensions from animals, including humans, though maintaining strict anaerobic conditions is essential for accurate results. Analytical techniques such as liquid chromatography coupled with mass spectrometry (LC/MS) can be employed to identify metabolites produced by various intestinal microbial enzyme sources under anaerobic conditions(12).

In vitro studies using bacterial or mammalian cell cultures can also be conducted to examine the role of intestinal microbial metabolism in the pharmacological actions or toxicity of xenobiotics. Additionally, in vivo models, such as antibiotic-pretreated animals or germ-free animals, can provide valuable insights into the role of the intestinal microbiota in xenobiotic metabolism(25).

Further research is needed to fully understand the impact of intestinal microbial metabolism on xenobiotic-induced pharmacological actions, particularly regarding natural products and synthetic drugs. Emphasizing specific investigations in this area will contribute to a better understanding of xenobiotic metabolism by the intestinal microbiota(26).

In addition to the host's own drug metabolism system, the gut microbiota also plays a significant role in drug metabolism through the secretion of microbial drug-metabolizing enzymes or through microbiota-host co-metabolism. Despite decades of research, only around 40 drugs or natural products have been thoroughly studied in this regard. The gut microbiota typically influences the oral drug bioavailability or half-life by altering the capacity of drug-metabolizing enzymes or by affecting the expression of genes involved in drug metabolism in host tissues. Furthermore, the composition or function of the gut microbiota is often influenced by environmental factors such as diet and antibiotic use, as well as the physiological status of the host, given the association between many diseases and gut dysbiosis or vice versa(27). The interindividual variation in response to drug therapy is often linked to variations in the gut microbiota. Below, we specifically discuss two widely used drugs:

1- Microbiota variation influences acetaminophen metabolism and acetaminophen-induced hepatotoxicity

Acetaminophen, a widely used analgesic and antipyretic medication, is associated with the most common cases of hepatotoxicity in the USA and UK(28). The deactivation of acetaminophen primarily occurs through glucuronidation and sulfation, leading to the formation of conjugated metabolites. A small portion of acetaminophen is metabolized by P450 enzymes to N-acetyl-p-benzoquinone imine, considered the toxic metabolite of acetaminophen(29).

Studies using metabolomics approaches have shown that individuals with elevated levels of predose urinary p-cresol, a microbial metabolite, exhibit lower postdose urinary ratios of acetaminophen sulfate to acetaminophen glucuronide. This suggests a microbial contribution to acetaminophen metabolism. Additionally, experiments in antibiotic-treated rats have demonstrated higher levels of acetaminophen glutathione conjugates in blood compared to untreated rats, further supporting the influence of gut microbiota on acetaminophen metabolism(30).

The competition between p-cresol and acetaminophen for binding with cytosolic sulfotransferase may alter the bioavailability of acetaminophen and its metabolites, leading to individual variations in acetaminophen metabolism and hepatotoxicity(31).

However, recent findings in mice suggest that while germ-free mice exhibit milder acute liver failure and differential acetaminophen metabolism compared to conventionally housed mice, there are no significant differences in the extent of hepatocellular injury induced by acetaminophen between the two groups. This indicates that variations in gut microbiota may not fully explain differential susceptibility to acetaminophen-induced liver injury, at least in mice(32).

Given the physiological differences between animals and humans, further investigation is needed to understand the influence of gut microbial metabolism on acetaminophen-induced hepatotoxicity.

2- Microbial metabolism on digoxin

Digoxin, a cardiac glycoside used to treat chronic heart failure, undergoes significant alteration in its cardiac activity due to gut microbial metabolism. The gut microbiota metabolizes digoxin into an inactive metabolite, dihydrodigoxin, by reducing the lactone ring of digoxin. This metabolic process is further evidenced by observations that antibiotic treatment decreases the secretion of dihydrodigoxin in urine while increasing the concentration of digoxin in blood, and by the identification of gut bacteria capable of metabolizing digoxin(33,34).

Recent research has identified a cytochrome-encoding operon in a common gut bacteria that is activated by digoxin. This operon, named the cardiac glycoside reductase (cgr) operon, is believed to predict digoxin inactivation, as demonstrated by a significant correlation between the "cgr ratio" (cgr abundance normalized by E. lenta 16S rDNA level) and ex vivo digoxin inactivation in healthy volunteers. Understanding the mechanisms underlying gut microbial metabolism of digoxin enhances our knowledge of gut microbial impacts on pharmacokinetics and opens avenues for clinical interventions aimed at reducing drug toxicity by manipulating gut microbiota(35,36).

Gut microbiota influence on interindividual variation in drug efficacy

Variability in drug effectiveness among individuals is frequently observed in clinical practice, highlighting the potential for personalized medicine to optimize therapeutic outcomes while minimizing drug-related adverse effects(37). The factors contributing to this interindividual variation in response to identical therapies are multifaceted, encompassing host genetic variability as well as physiological and environmental factors. While pharmacogenomics has significantly advanced our understanding of how genetic variations influence individual responses to drug therapy(38), emerging evidence suggests that differences in gut microbiota composition among individuals may also contribute to interindividual variability in drug efficacy.

Gut microbiota modulates the effect of antitumor chemotherapeutics

The commensal gut microbiota plays a significant role in regulating mammalian immunity. However, the use of antitumor chemotherapeutics often disrupts the gut microbiota, leading to

adverse intestinal effects and modulation of host immune responses(39). Cyclophosphamide (CTX), an antitumor drug, induces immunogenic cancer cell death, suppresses immunosuppressive T cells, and promotes the control of tumor cell growth by TH1 and TH17 cells. Recent studies have shown that CTX can alter the composition of the gut microbiota, causing the translocation of certain Gram-positive bacteria into secondary lymphoid organs. These bacteria stimulate the generation of a specific subset of "pathogenic" TH17 cells and memory TH1 immune responses. Additionally, germ-free mice or mice treated with antibiotics to deplete Gram-positive bacteria exhibit reduced TH17 responses and resistance to the antitumor effect of CTX(40). Similar observations have been made with the disruption of gut microbiota affecting the therapeutic responses of subcutaneous tumors to immunotherapy and platinum chemotherapy. Germ-free or antibiotic-treated mice show poor responses to therapy. These findings highlight the importance of the gut microbiota in influencing the efficacy of certain antitumor chemotherapeutics, suggesting the potential for microbiota-targeted interventions to enhance the effectiveness of chemotherapy(41).

Irinotecan (CPT-11) is an intravenously administered chemotherapeutic drug used for colorectal cancers. It is converted into its active form, SN-38, by carboxylesterases in host tissues, which acts as an inhibitor of topoisomerase I in tumor cells(42). SN-38 is then conjugated into SN-38-G by hepatic UDP-glucuronosyltransferases before being secreted into the intestine. However, the nontoxic SN-38-G can be converted back to SN-38 by gut bacteria's β-glucuronidase, leading to severe diarrhea as a side effect(43). Antibiotic treatment has been shown to significantly reduce the intestinal side effects of CPT-11 by suppressing the gut microbiota. Furthermore, a potent inhibitor of β-glucuronidase has been identified, which effectively decreases CPT-11-induced diarrhea and protects intestinal tissue by reducing cellular inflammation. These findings demonstrate that the gut microbiota plays a crucial role in modulating the intestinal side effects of CPT-11, highlighting its profound impact on drug metabolism, not only for orally administered drugs but also for intravenously delivered ones(44).

Microbiota variation contributes to therapeutic difference of statin

Statins are commonly prescribed drugs for lowering LDL cholesterol levels and reducing the risk of cardiovascular disease by inhibiting HMG-CoA reductase. However, the effectiveness of statins in reducing LDL cholesterol varies among individuals, and the reasons for this variation are not well understood. In a study by Kaddurah-Daouk et al., the correlation between baseline metabolites and the therapeutic efficacy of simvastatin was investigated using targeted metabolomics. The data showed that the baseline levels of certain secondary bile acids, which are derived from the gut microbiota, could predict the extent to which simvastatin lowers LDL cholesterol(45). Additionally, these microbial-derived secondary bile acids were also found to be associated with the plasma levels of simvastatin, suggesting that the gut microbiota might influence the bioavailability of the drug. Similarly, another study demonstrated that incubating lovastatin with fecal preparations from humans or rats resulted in the production of four metabolites. The co-administration of antibiotics significantly reduced the activity of enzymes responsible for metabolizing lovastatin by over 50% compared to control rats. Furthermore, the plasma concentration of the active metabolite of lovastatin was significantly lower in antibiotic-treated rats, indicating the involvement of gut microbiota in the co-metabolism of lovastatin. Overall, the variation in individual responses to simvastatin or lovastatin therapy may be partly attributed to differences in gut microbiota(46).

Impact of Drugs on the Gut Microbiome

Various drugs, including proton pump inhibitors, statins, and angiotensin-converting enzyme inhibitors, have been found to influence the gut environment, consequently impacting the composition, growth, and functions of gut microbial communities(47). For example, metformin has been shown to alter the composition and function of gut microbiota. When germ-free mice were treated with gut microbiota from individuals who had been treated with metformin, they exhibited lower blood glucose levels compared to those treated with gut microbiota from individuals who had received a placebo. This suggests that metformin-induced changes in gut microbiota can improve glucose metabolism(48).

A comprehensive screening of over 1000 drugs, encompassing a broad spectrum of therapeutic classes, was conducted against 40

isolated gut microbial strains. Approximately 835 of these drugs targeted molecular pathways in human cells, while the remainder were anti-infective agents. Using drug concentrations similar to those expected to be present in the gut for many drugs, the study revealed that 27% of non-antibiotics inhibited the growth of at least one of the tested microbial strains(49). This underscores the intricate and bidirectional interplay between gut microbiota and drugs.

Toxicological Assessment of Drug Metabolites

As previously discussed, microbial activity can lead to drug toxicity, as demonstrated by meticulous studies on the intestinal toxicity caused by gut microbes' action on the anti-cancer drug irinotecan. The active metabolite of irinotecan, SN-38, is glucuronidated in the liver to SN-38G and secreted into the bile. In the intestine, bacterially-derived β-glucuronidases convert SN-38G back to SN-38, which is responsible for the severe diarrhea induced by irinotecan(50). The toxicity of drug metabolites produced by gut microbes is primarily assessed through comparative clinical observations and histologic examination of tissues from germ free/antibiotic-treated and conventionally raised/HFA animals. Additionally, other tools such as toxicity predicting software and omics technology for studying toxico-microbiomics are utilized (51).

The toxicity of short-lived reactive metabolites is analyzed by trapping the electrophilic metabolites with nucleophiles like glutathione and cyanide ions, followed by mass spectrometric analysis of the formed adducts(52). Manipulation of gut microbial composition or metabolic activity can reduce the production of toxic metabolites or improve therapeutic outcomes. Wallace and colleagues demonstrated that administration of a selective bacterial β-glucuronidase inhibitor protected mice from irinotecan-induced toxicity without eliminating the bacteria. This inhibitor selectively inhibits bacterial β-glucuronidase, preventing the formation of SN-38 that is harmful to the microbiota essential for human health, thereby alleviating irinotecan-induced toxicity(53).

Expert opinion

Individuals often exhibit varying responses to the same drug therapy, which has traditionally been attributed to genetic diversity. However, emerging evidence suggests that the gut

microbiota plays a crucial role in drug metabolism and can significantly influence therapeutic outcomes in conjunction with host metabolism. While significant progress has been made in unraveling the complex relationship between the gut microbiota and drug metabolism in recent years, there is still a long way to go before we can effectively leverage this knowledge for rational drug design and personalized medicine, aiming for enhanced drug efficacy and reduced toxicity.

Currently, most efforts are focused on accumulating knowledge regarding the identification of the roles and mechanisms underlying gut microbiota-mediated drug metabolism and toxicity. However, several challenges lie ahead. Firstly, it remains a significant challenge to determine the specific contributions of gut bacteria to drug metabolism. Antibiotic-treated animal models are commonly used to investigate the involvement of the gut microbiota in drug metabolism and toxicity(54). Different antibiotics or combinations with varying antibacterial spectrums can help establish a more specific relationship between certain bacterial species and drug metabolism. While germ-free or gnotobiotic animals are better suited for studying the contributions of specific bacteria to drug metabolism, their use is limited by cost and strict facility requirements. Therefore, antibiotic-treated animal models are expected to continue being the practical choice for most studies. However, distinguishing the impacts on drug metabolism between the antibiotics themselves and the alterations induced by antibiotics on the gut microbiota is crucial. Additionally, it is important to consider potential direct drug-drug interactions in the intestine between unabsorbed antibiotics and the drugs under investigation, as they may influence our understanding of the role of the gut microbiota in drug metabolism.

Secondly, advancements in technology are crucial for elucidating the roles of the gut microbiota in drug metabolism. The hypervariable regions of bacterial 16S rDNA allow for the classification of bacteria through gene sequencing, typically at the family or genus level. However, the bioinformatics analysis of the vast and noisy data generated by metagenomics, which analyzes collective DNA sequences from whole samples, poses a significant challenge(55). This analysis is necessary to extract useful biological information for phylogenetic studies and the identification of bacteria species relevant to diseases or therapeutics. Additionally,

metabolomics and other omics approaches are increasingly being adopted to analyze gut microbiota-related metabolic profiles or specific microbial-associated metabolic pathways. It is estimated that at least 10% of metabolites in plasma are related to the gut microbiota, and evidence linking these metabolites to specific bacterial species is growing(56). Therefore, investigating the role of the gut microbiota in drug metabolism through combined approaches such as metabolomics and metagenomics holds great promise.

Thirdly, the mechanisms by which the gut microbiota modulates drug metabolism are complex and not yet fully understood. Currently, the effects of gut microbiota-mediated drug metabolism have been well-characterized for only about 40 clinical drugs, despite the existence of thousands of clinical drugs. Determining the roles of the gut microbiota in drug metabolism and drug-induced toxicity is an urgent and challenging task. Furthermore, the increasing use of antibiotics, often in combination with other medications, puts patients at risk of unexpected drug-induced toxicity or compromised drug efficacy. Gut microbial modulation of drug metabolism can occur through various means, including the direct secretion of drug-metabolizing enzymes in the intestine, competition for receptors or transporters in host tissues through the production of bacterial metabolites, and microbial modulation of the activity of drug-metabolizing enzymes in host tissues. Consequently, studying the gut microbiota requires efficient collaboration among scientists from various disciplines, including pharmacology, toxicology, microbiology, molecular biology, bioinformatics, and analytical chemistry.

Despite the challenges, with sustained enthusiasm for gut microbiota research and continued technical advancements, it is expected that dozens of drugs co-metabolized by the gut microbiota will be extensively studied in the next five to ten years. Uncovering the role of gut microbiota metabolism in these clinically used drugs will deepen our understanding of the microbiota-related mechanisms underlying interindividual variations in drug activity and toxicity.

Conclusion

Current understanding of the role of gut microbiota in influencing treatment outcomes remains limited. However, the diverse metabolic capabilities and variable composition of gut microbes in

the human gut underscore the need to thoroughly examine their intricate involvement in interindividual variability. Advances in omics technologies, such as metabonomics and metagenomics, offer promising avenues for systematically investigating the roles of gut microbiota in pharmacokinetics and pharmacotherapy. This integration of technologies is expected to enhance our understanding of how gut microbiota influence drug response. Furthermore, novel drug candidates targeting gut bacteria or their enzymes may be developed to modulate efficacy or reduce toxicity, as demonstrated in the case of mitigating irinotecan-induced gastrointestinal toxicity using β-glucuronidase inhibitors (Wallace et al., 2010). Manipulating gut microbiota through interventions like probiotics, prebiotics, antibiotics, and fecal transplant may also be explored (Jia et al., 2008; Holmes et al., 2012; Rohlke and Stollman, 2012). Given the significant impact of gut microbes on pharmacokinetics and treatment outcomes, strategic manipulation and engineering of gut microbiota hold promise in the field of personalized medicine.

Moreover, beyond their primary role in host metabolism, gut microbiota play a crucial role in modulating the efficacy of both oral and systemic drugs commonly used in healthcare. Recent advancements in multi-omics platforms, germ-free animal models, and in vitro mechanistic studies are aiding in the identification of microbial functions and elucidating the molecular mechanisms underlying the microbiome-drug metabolism axis. This knowledge can greatly inform translational research aimed at developing microbiota-targeted interventions, enhancing drug efficacy, preventing drug toxicity, and improving metabolic health.

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