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Therapeutic implications of the gastrointestinal microbiome

Purna C Kayshap[1] and Eamonn MM Quigley[2]

Gut microbiome is an integral part of the metabolic machinery that contributes to normal host function. The advent of next generation sequencing technologies has allowed an in-depth investigation of the microbiome at various body sites including microbes which are challenging to culture. The same technologies have revealed the metabolic capacity of the microbiome, identified novel microbial products and suggested possible implications for human health. The gut microbiome has previously not been considered in aspects of human health such as response to medications, which may be metabolized to a varying extent by the microbiome, thereby, altering their efficacy and the incidence of adverse events. Recent data suggest that the gut microbiome is an important factor to consider while evaluating inter-individual responses to medications. The gut microbiome is also a rich source of novel therapeutics — pharmabiotics, which can be harnessed to modify host function or alter the gut microbial ecosystem. We will highlight these aspects of the microbiome in this review.

Addresses
[1] Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
[2] Gastroenterology and Hepatology, Lynda K and David M Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, Houston, TX, USA

Corresponding author: Kayshap, Purna C (Kashyap.purna@mayo.edu)

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Introduction

Not since the human genome project has a new area of biomedical science so enthused the scientific and medical communities for its diagnostic and therapeutic possibilities and captivated the lay public as has the microbiome in all its manifestations. As the myriad functions of the unique microbial communities that inhabit the various surfaces and internal organs of the human body are revealed and the complexities of their interactions with us, their host, identified there has been a rush, at times premature, to link changes in the microbiome and its activities to various disease states. Not surprisingly, many laboratories and clinical research programs now strive to identify microbial signals that may prove diagnostic or prognostic in a given disease state. This review will focus on another, equally promising, aspect of the microbiome — its therapeutic potential, and will concentrate on two aspects: the impact of the microbiome on various therapeutic agents, and attempts to mine the microbiome for novel therapeutics.

Optimizing therapeutics via the microbiome

The gut microbiome has largely been overlooked when considering inter-personal differences in therapeutic responses and adverse events. An early indication of the potential role of the gut microbiome was seen with the description of gut microbiota-mediated inactivation of hepatic dihydropyrimidine dehydrogenase [1], resulting in an adverse event when combining the drug sorivudine with the chemotherapeutic agent 5-fluorouracil (5-FU). It is now apparent that gut microbiota encoded genes significantly enhance the metabolic capabilities of the host [2], including the biotransformation of luminal compounds [3]. In fact, more than 60 drug–microbiome interactions are already listed in the PharmacoMicrobiomics database, and this likely represents just the tip of the iceberg [4]. Interactions between the gut microbiome and therapeutic agents are likely to be significant given that the number of microbial metabolic transformations outnumber human gene encoded drug transformations; thus, the use of microbial markers in addition to human genetic (pharmacogenomics) markers will enhance the prediction of drug efficacy. Importantly, the plasticity of the microbiome makes it a viable target for optimizing drug therapy.

The utility of the microbiome in determining the therapeutic efficacy of drugs is multifold. Microbial fingerprints can serve as diagnostic or therapeutic biomarkers in determining responses to drugs; the microbiome itself can act, in part, as a mediator of the therapeutic effect of the drug; the metabolism of drugs by the microbiome can lead to inactivation of a drug and the ability of the microbiome to metabolize prodrugs to pharmacologically active components can improve or impair efficacy [5]. A few examples demonstrated below highlight these effects but represent just a small window into the broad range of ongoing studies in this area.

Statins are a widely used medication to lower plasma low-density lipoprotein cholesterol (LDL-C) levels, but the

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response to statins can vary among individuals. Interestingly, biomarkers associated with gut microbiome metabolism have been shown to be predictive of the clinical response to statins. In comparing good and poor responders (top and bottom 10% of the LDL-C response distribution matched for body mass index, race, and gender) among a subset of patients from the Cholesterol and Pharmacogenetics (CAP) study, secondary bile acids resulting from microbial action were found to be predictive of a favorable response to statins. This is particularly interesting as statins and bile acids share transporters in the intestine and liver. There was also a correlation between pretreatment coprostanol levels and the response to statins. The ratio of cholesterol to coprostanol is indicative of the ability to remove cholesterol from the circulation; hence, coprostanol-producing bacteria may, in fact, predict the efficacy of statin therapy [6].

A series of recent papers highlight the role of the gut microbiome in mediating the therapeutic effect of drugs. *Bacteroides* species were found to be associated with the success of CTLA-4 antibodies used in cancer immunotherapy both in patients with melanoma and in murine models of cancer. Interestingly, tumors failed to respond to CTLA-4 antibodies in germ free mice, but this was overcome by colonization with *Bacteroides fragilis*. A similar effect was also seen with immunization with *B. fragilis* polysaccharides or adoptive transfer of *B. fragilis*-specific T cells, suggesting a role for *B. fragilis* in mediating the immunostimulatory response to CTLA-4 antibodies [7•]. Similarly, another recent study found that gut microbiota composition was associated with augmented T-cell mediated antitumor immunity in melanoma. The tumor specific immune responses were noted to be markedly different in C57BL/6 mice obtained from two different vendors harboring different gut microbiota populations. The differences in immune response were lost by co-housing which permitted the exchange of gut microbiota between animals. Interestingly, the oral administration of *Bifidobacterium* was found to augment dendritic cell function and augment the response to programmed cell death protein 1 ligand 1 (PD-L1)–antibody in the mouse model [8•].

The gut microbiota has also been reported to mediate the anti-diabetic effects of metformin. A double blind placebo controlled crossover trial in patients with type 2 diabetes showed changes in the gut microbiome with metformin treatment. The transfer of metformin treatment-associated gut microbiota from patients to germ free mice led to better glucose control in mice [9•].

A role for the gut microbiota in the inactivation of drugs such as digoxin (a cardiac glycoside with a narrow therapeutic index used to treat arrhythmias) has been recognized for some time. Lindenbaum *et al.* described the conversion of digoxin to reduced products which lacked efficacy in about 10% patients receiving the drug [10]. A similar effect was seen with stool cultures from these patients, and, interestingly, the effect was overcome by the administration of a short course of antibiotics. More recently, Haiser *et al.* demonstrated that *Eggerthella lenta* carried the cardiac glycoside reductase (*cgr*) operon that is stimulated by digoxin in low arginine conditions [11]. They further showed that digoxin reduction by *E. lenta* could be overcome by a high protein diet in gnotobiotic mice.

Another medication which exhibits marked inter-individual differences in response is acetaminophen, which is commonly prescribed for its analgesic effect [12]. The gut microbiome has been implicated in the variability of response to acetaminophen, given the production of p-cresol by certain bacteria (e.g. *Clostridium*), which can compete with acetaminophen as a substrate for Sulfotransferase Family 1A Member 1; a human liver enzyme (SULT1A1) [12] resulting in acetaminophen glucuronidation. This, in turn, can lead to a build-up of N-acetyl-p-benzoquinone imine (NAPQI), which leads to hepatotoxicity. Thus, the inactivation of certain drugs and competition for metabolic transformations between drug and bacteria can significantly impact the therapeutic effects of drugs.

Another example of bacterial transformation of a drug relates to the chemotherapeutic agent irinotecan (CPT-11) which is glucuronidated into an inactive form in the liver. However, these metabolites can be transformed into active drug by bacterial beta-glucuronidases resulting in the development of diarrhea as a side effect of the chemotherapeutic regimen [13]. A targeted inhibition of such bacterial enzymes can significantly improve compliance with chemotherapeutic regimens without affecting efficacy. Microbial beta-glucuronidases have also been shown to enhance the toxicity from use of non steroidal anti-inflammatory drugs (NSAIDS) in an animal model providing yet another example where inhibition of bacterial enzymes can potentially potential ameliorate side effects [14]. These few examples likely represent the tip of the iceberg given the immense metabolic potential of the gut microbiome [15] and future studies will help elucidate the clinical implications of different microbial biotransformations of therapeutic agents.

In summary, the microbiome plays an important role in drug modification (Figure 1), and we need to incorporate these effects when developing precision approaches to the optimization of treatment responses while minimizing adverse events. These are crucial for ensuring patient compliance and, in the long run, will be critical to curbing health care costs. In the future drug development strategies will need to account for the unique effects of the gut microbiota when considering bioavailability and efficacy. In addition to their role in drug modification, the gut

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