The microbiome: a gut feeling about drug metabolism

MARK GREENER

The human gut microbiome has a crucial role in both health and disease, including drug metabolism. Recent research indicates that boosting the microbiome (for example, by using probiotics) is a promising therapeutic strategy that could enhance the efficacy and reduce the toxicity of many medicines.

Healthcare professionals’ attitudes towards the trillions of bacteria and other micro-organisms on and inside our bodies – our microbiota – traditionally “oscillated between benign neglect and suspicious distrust”. Commensal bacteria, after all, include antibiotic-resistant pathogens. But the ‘microbiome’ also protects our health, contributing to digestion, immune responses and metabolism of potentially harmful chemicals, for example.

A staggering number of bacteria reside in the human gastrointestinal tract: genetic analysis has identified more than 2000 species, in addition to fungi, viruses and other organisms. The total population may reach 100 trillion bacteria. Indeed, we host 10 times more bacterial cells in our intestines than all the human cells in the rest of our bodies. Our microbiome weighs two to three pounds and, collected together, would be a similar size to our brains. Indeed, as we’ll see, the microbiome, in many ways, is effectively another organ.

Now increasing evidence suggests that the microbiome contributes to the efficacy and tolerability of numerous medicines. “The human microbiome is a complex and dynamic system with incredible genomic and functional diversity,” says Libusha Kelly, Assistant Professor, from the Departments of Systems and Computational Biology, and Microbiology and Immunology at Albert Einstein College of Medicine, New York. “There are many microbial enzymes that have the potential to interact with drugs and we are just beginning to understand how these interactions might influence human health and clinical outcomes.”

One study, for example, analysed the genetic composition of gastrointestinal bacteria from 397 people of various ages and nationalities. The researchers identified 850 bacterial genera that could potentially metabolise at least one xenobiotic (a foreign or exogenous substance). Some xenobiotics are drugs. But microbial enzymes also metabolise environmental pollutants, such as carcinogenic polyaromatic hydrocarbons...
released by, for example, burning fossil fuels.6

“The microbiome can play an important role in our ability to metabolise medicines, thereby impacting the efficacy and toxicity of a select group of widely used drugs, including cardiac glycosides and sulfasalazine,” adds Hollie Swanson, Professor in the Department of Pharmacology and Nutritional Sciences in the College of Medicine at the University of Kentucky. “It is quite likely that this list of select drugs will grow larger.”

Common drugs

Indeed, the gut microbiota seems to contribute to the metabolism of numerous widely used drugs (see Table 1).2,5,7 For example, irinotecan – used to treat colorectal cancer – is administered intravenously as an inactive form. Irinotecan undergoes liver metabolism to produce the active metabolite, called SN-38. In turn, SN-38 inhibits topoisomerase I, an enzyme that cuts DNA – an essential step in the normal cell cycle. Liver enzymes produce an inactive glucuronidated form (SN-38G) that enters the intestine by biliary excretion. However, microbial enzymes, called beta-glucuronidases, in the gut can reactivate SN-38G, a process known as ‘deconjugation’.8

In a pilot study, Dr Kelly and colleagues used genetic analysis to examine the gut microbiome of 20 healthy people. Of these, 16 were low metabolisers of SN-38G in the gut and the remainder high metabolisers.8 “People’s microbiomes have different abilities to deconjugate the inactive form of irinotecan,” Dr Kelly says. “High metabolisers are very good at deconjugating and produce more active drug. Low metabolisers produce less of the active form.” The analysis also revealed numerous microbial genes, including enzymes and transporters, that might offer biomarkers for adverse events in patients who received irinotecan.

Indeed, the proportion of high metabolisers in the pilot study is broadly consistent with the incidence of severe diarrhoea associated with irinotecan. Between 30% and 40% of patients receiving irinotecan monotherapy experience grade 3–4 diarrhoea. Even combined with other chemotherapeutics, 11–37% of patients experience grade 3–5 diarrhoea, which can require hospitalisation, result in dose reductions and be life-threatening, or even cause death.9

Dr Kelly’s team aims to examine whether faecal samples before patients start irinotecan predict whether or not they will suffer an adverse event. “More broadly, we hope that pretherapy microbiome analysis will help patients and their treatment teams make more informed decisions and improve clinical outcomes,” she says. The findings may also offer pathogenic insights: the activity of microbial beta-glucuronidases is elevated in people with colorectal cancer and rises with meat consumption. The enzymes may produce reactive metabolites from, for example, the diet, which damage colonic mucosal cells.8

Many other drugs undergo glucuronidation – which adds a carbohydrate group to the drug backbone – including paracetamol, diclofenac, codeine, chloramphenicol, some vitamins and tamoxifen.8 “Microbes have a tremendous number of enzymes devoted to carbohydrate metabolism and the genes are often swapped by horizontal gene transfer between members of the microbiome,” Dr Kelly explains. “The mobility of these carbohydrate-active genes is important not just for drug metabolism, but also for how we metabolise foods and compounds endogenous to the human body. Deconjugation of glucuronidated substrates probably has a broader impact on human health than we currently understand.”

Antibiotics and microbiome metabolism

Antibiotic-associated diarrhoea often arises following a disruption to the bacteria residing in the gut. So, it’s not surprising that antibiotics can alter drug metabolism by changing the microbiota. For example, generations of pharmacology lecturers used digoxin as an example of a drug with a narrow therapeutic window. About 20% of people excrete a substantial proportion of a dose of digoxin as a dihydrolactone metabolite. Antibiotics, such as erythromycin and tetracycline, markedly reduce formation of the metabolite. As a result, serum concentrations of digoxin can rise as much as twofold,1 which increases the risk of adverse events.

Against this background, a recent review concluded that “the effect of antibiotic treatment on in vivo xenobiotic metabolism may be more extensive and potent than previously recognised”. In the meantime, the review suggests “carefully monitoring the pharmacological effects of oral drugs administered with antibiotics.”

In addition, other drugs – including metformin and proton-pump inhibitors (PPIs) – can alter the microbiome. For example, in addition to their effects on Helicobacter pylori, prolonged PPI treatment seems to be associated with an increased incidence of Clostridium difficile infection.9 “These studies reveal how an ‘unhealthy’ microbiome impacts drug therapy in our most vulnerable populations: the very young, the very old, patients with chronic conditions like diabetes and chronic inflammatory conditions, and those suffering from infections, including H. pylori or C. difficile,” Professor Swanson says. “A very important theme is a note of caution regarding our current use of antibiotics, especially in these vulnerable populations, which should be more judicious.”

Boosting the microbiome

On the other hand, probiotics (formulations containing live bacteria) and prebiotics (nutrients that stimulate the growth or

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**Table 1. Examples of drugs subject to gut microbial metabolism**

<table>
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<th>Drug</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Metabolism by Gut Microbiota</strong></td>
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<tr>
<td>Benzylpenicillin</td>
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<td>Clonazepam</td>
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<td>Digoxin</td>
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<td>Fluorouracil</td>
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<td>Glycerol trinitrate</td>
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<td>Insulin</td>
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<td>Irinotecan</td>
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<td>Levodopa</td>
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<td>Mesalazine</td>
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<td>Methotrexate</td>
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Indeed, the gut microbiota can produce a strategy that uses ‘psychobiotics’ containing live micro-organisms to improve mental health. The findings that probiotics improve mental health indicate that patients may be able to take lower doses of these drugs and hence avoid their side-effects,” Professor Swanson comments. “As we learn more about the benefits of pre- and probiotics, we should be able to improve patient outcomes by playing close attention to specific combinations of dietary modifications and drug therapies.”

“There are many microbial enzymes that have the potential to interact with drugs and we are just beginning to understand how these interactions might influence human health and clinical outcomes.”

Libusha Kelly, Assistant Professor, Department of Systems and Computational Biology, Albert Einstein College of Medicine, New York

In particular, studies need to explore differences between populations. “Our responses to many drugs can vary significantly from patient to patient,” Professor Swanson adds. “The microbiome is one factor that contributes to this variability.” For example, Indian, Chinese and Japanese people seem to show similar compositions of xenobiotic-metabolising bacteria. These, however, differ from those in American and European individuals. Moreover, several genera of xenobiotic-metabolising bacteria made less of a metabolic contribution in children and older people than in those of other ages, which potentially influences age-related differences in drug metabolism.

“Defining the microbiome in a way that enhances efficacy and prevents toxicity. For example, Dr Kelly’s group is exploring the potential role of probiotics and prebiotics in modulating pharmacokinetics and pharmacodynamics. However, the microbiome’s diversity means that researchers might have to personalise therapy. “If multiple enzymes influence drug metabolism and those enzymes are not always uniformly present in patients, we’d need to personalise this approach,” Dr Kelly says. “We are trying to understand how microbial drug-metabolising enzymes are distributed in human guts and how this changes based on diet or health state.”

To aid this understanding, Dr Kelly’s team is developing a database connecting foods, drugs, microbial enzymes and toxicity information to characterise which drugs the gut microbiome is most likely to metabolise and the potential influence on drug toxicity and nutrient availability. “We are developing new computational approaches to analyse how microbiomes change over time and how microbiome composition is associated with health outcomes,” she explains.

Professor Swanson notes that in animal models, probiotics (containing Lactobacillus) exert anti-inflammatory properties that reduce damage to the small intestine caused by NSAIDs. In addition, dietary modifications may alter the metabolism of, and so enhance the efficacy of, certain drugs, such as amiodarone or digoxin. “In addition, studies indicate that probiotics may enhance the effectiveness of immunotherapies used to treat many cancers,” she says. “Pilot studies in humans also report that probiotics reduce gastrointestinal toxicity and diarrhea associated with chemotherapies such as irinotecan.”

**Effects on the liver and the brain**

In addition, gastrointestinal microbes can release several chemicals that directly interact with and activate specific receptors, and induce or inhibit drug metabolising enzymes and transporters. For example, one study found that levels of mRNA encoding cytochrome P450 3A (CYP3A) in the liver were 87% lower in germ-free mice than in conventional mice. CYP3A contributes to the metabolism of about half of all drugs.3

“We are currently incorporating microbiome-based assays into our pre-clinical pharmacokinetic studies that traditionally focus on hepatic metabolism,” Professor Swanson says. “We will have a better sense of the interplay between the microbiome and the liver as these assays become more established.”

Signalling molecules released by gastrointestinal bacteria may also influence the brain and behaviour through immunological (cytokines), endocrinological (cortisol) and neural mechanisms. Indeed, the gut microbiota can produce several neurotransmitters, including serotonin, dopamine and noradrenaline. Against this background, increasing evidence links the microbiome’s composition with several psychiatric and neurological diseases, including autism, schizophrenia, attention deficit hyperactivity disorder (ADHD), Parkinson’s disease, Alzheimer’s disease and multiple sclerosis.

This growing body of evidence inspired a new therapeutic strategy that uses ‘psychobiotics’ containing live micro-organisms to improve mental health.2
“The most interesting aspect of this work for me is that it provides a scientific rationale for improving how we treat diseases by combining a lifestyle that contributes to a healthy microbiome with appropriate use of medications,” Professor Swanson comments. “This holds the promise of decreasing our current over-reliance on a ‘pill to fix everything’. In a sense, it is refocusing our perspective of how we treat patients, from our current view of patients as a constellation of symptoms to be treated to an approach that is more holistic and aligned with more ‘traditional’ medicine.”

Despite the numerous outstanding issues, it’s clear that microbiome drug metabolism will remain an active area of research and will increasingly influence therapeutic approaches. “The microbiome is an entirely new piece of our understanding of pharmacokinetics and pharmacodynamics,” Dr Kelly concludes. “We know the microbiome can influence drug metabolism, but we don’t know how that impacts clinical outcomes. These are still very early days.”

References
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Declaration of interests
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or financial interests relevant to this article.

Mark Greener is a freelance medical writer