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When Pharmacology Meets the Microbiome: New Targets for Therapeutics?

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Intuitively if one were to consider therapeutics targeted towards microbes, antibiotics may be the first class to come to mind. Indeed, microbial medicine in the 20th century exclusively focused on antibiotic-based therapies as an essential tool in the arsenal used in the fight against pathogenic bacteria and in the management of infectious disease. However, in the 21st century the importance of maintaining an appropriate and diverse microbiome to support optimum health across the lifespan has emerged (Dinan & Cryan, 2017). Indeed, the microbiome is one of the most exiting areas in modern biomedicine with no discipline untouched by its influence including Pharmacology. Thus, this Themed Issue is focused on the relationship between the microbiome and therapeutics opportunities beyond antibiotics.

The collateral damage exerted on commensal organisms by antibiotics may have far reaching consequences for the host as we gain better insights into the metabolic capacity of the gut microbiome. This is not least, in part, because of the microbial transformations which are a key function of the gut microbiota, many of which are established in infanthood and later provide a source of essential nutrients, amino acids and minerals (Bik, Ugalde, Cousins, Goddard, Richman & Apte, 2018). Therefore, disruption of this dynamic microbial ecosystem may have wide-ranging consequences on the host. As part of this issue Bik et al., (2018) elegantly summarizes how dietary and host-derived molecules are utilized by the gut microbiota to yield physiologically significant pre cursors and products which may enter the circulation where they can subsequently influence the function of organs and systems distant from the gastrointestinal tract.

Such microbial biotransformations are also critical in xenobiotic metabolism, and in the context of therapeutics, for example, in the activation and inactivation of drugs (Bik, Ugalde, Cousins, Goddard, Richman & Apte, 2018). These drug-bacteria interactions are, of course, subject to variations in the genetic makeup of the microbiome and this in combination with the metabolic potential of the gut microbiome is now encompassed by the term, *Pharmacomicrobiomics* (Rizkallah, Saad & Aziz, 2010). In contrast to the oxidation and conjugation reactions which are characteristic of hepatic drug metabolism, reduction and hydrolysis reactions dominate gut microbiota-mediated metabolic reactions (Haiser & Turnbaugh, 2013; Walsh, Griffin, Clarke & Hyland, 2018). The complexity and bi-directional nature of drug-microbe interactions is elaborated upon by Walsh et al., (2018) who review not only the direct effects microbes can have on drugs, but who also detail the effects microbiota-derived metabolites can have on host drug metabolism. Therefore, natural variations in the microbiome may underlie variability in drug response or toxicity.

Whilst microbes may have traditionally been viewed as the exclusive target of antibiotics, it is now becoming increasingly clear that the microbiota is impacted by non-antibiotic drugs (Cussotto et al., 2018; Maier et al., 2018). Indeed in a recent *in vitro* study where in excess of 1,000 non-antibiotic drugs representative of all main therapeutic classes, the majority of which were human-targeted, were screened against a panel of ubiquitous gut bacterial species, 24% displayed anti-commensal activity (Maier et al., 2018). The clinical significance of such findings is exemplified by the similarity between antimicrobial-associated side effects and those associated with these human-targeted drugs. These effects on gut microbial populations are intriguing in that they may provide insight into heretofore unexplored mechanisms of action beyond what has been accepted to date. Of note in this regard, is the similarity in anti-commensal activity between classes of chemically diverse drugs, such as antipsychotics which have molecular targets not normally associated with gut microbes. Whether these microbial effects underpin drug-associated side effects or contribute to their mechanism of action now warrants further investigation. For example, subjects treated with atypical antipsychotics not only display a characteristic increase in body mass index, but also significant changes in their gut microbiome (Flowers, Evans, Ward, McInnis & Ellingrod, 2017). In rodents, at least, this clinically significant side-effect could be negated by antibiotic-induced disruption of the gut microbiota (Davey et al., 2013). In this Themed Issue the review article by Walsh et al., (2018) concludes by exploring the implications of drug-gut interactions for neuropharmacology, whilst Bambury and colleagues propose a pathway for discovery of microbial-targeted therapies in psychiatric illness.

The antimicrobial activity of human-targeted drugs also raises further concerns, with the suggestion that human-targeted drugs may lead to the acquisition of antibiotic resistance (Maier et al., 2018). Though an important and underappreciated effect of such drugs, more generally antibiotic resistance has fuelled the drive, or refocused efforts in the development of novel antimicrobial strategies. In an associated review aligned to this Themed Issue, 'Phages of life – the path to pharma', Forde and Hill (2018) examine the therapeutic potential and limitations of developing phage in the context of the challenges posed by the World Health Organization's list of 'drug-resistant' priority pathogens. The step-wise progression to 'pharma' proposed encompasses an integrated approach between physiology, genetics, and pharmacology along with commercial and regulatory considerations (Forde & Hill, 2018). Although challenges apply to the therapeutic development of phage, such as the development of resistance and delivery, with the application of metagenomic approaches their therapeutic potential, beyond the most urgent need, can now be realized as we better understand the role of the microbiome in health and disease.

The concept that manipulation of the gut microbiota, by drugs or otherwise, unlocks new avenues for the management of clinically significant disorders. For instance the concept that psychobiotics, defined as live organisms that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness, as a novel class of psychotropic is gaining traction (Dinan, Stanton & Cryan, 2013). Any such microbial intervention is likely, however, to need to exert pleotropic effects on the host across inflammatory and endocrine pathways (Dinan, Stanton & Cryan, 2013). Bambury and colleagues (2018) discuss the application of inter-omic methods, integrating metagenomic, proteomic and metabolomic approaches, in hastening the discovery of novel microbial therapeutics and present a rational and systematic approach to be adopted in order to realize the identification of novel psychobiotics (Bambury, Sandhu, Cryan & Dinan, 2017).

However, such approaches are not limited to psychiatric illness given that the microbiome, the metabolites it can produce and its effects on host homeostasis are of equal relevance to other body systems. For example, bacterial derived trimethylamine is a substrate for host flavin monooxygenases which gives rise to trimethylamine N-oxide which has been implicated in cardiovascular disease (Kiouptsi & Reinhardt, 2018). As in psychiatric illness, the underlying pathophysiology of cardiovascular disease is unlikely to involve a single microbial-associated mechanism and in this regard microbial associated molecular patterns and their recognition systems have also been implicated in the development of atherosclerosis (Kiouptsi & Reinhardt, 2018). Kiouptsi & Reinhardt (2018) therefore propose that pattern recognition receptors, such as toll-like receptors, may not be the only prospective microbial-associated therapeutic targets, but also suggest that targeting bacterial enzymatic pathways implicated in the pathophysiology of cardiovascular disease and atherosclerosis may be equally valid with proof-of-concept studies demonstrating that non-lethal inhibition of trimethylamine may be therapeutically relevant (Wang et al., 2015).

We are only beginning to fully appreciate the relationship between the microbiome, pharmacology and therapeutics. It is clear that the gut microbiota is a rich reservoir for metabolites that act on pharmacological targets (Cohen et al., 2017; Cryan, Clarke, Dinan & Schellekens, 2018; Stilling, van de Wouw, Clarke, Stanton, Dinan & Cryan, 2016). The editors hope that the articles contained in this themed section will prove useful in providing an introduction to the biologically significant biotransformations carried out by the gut microbiota, and, how, as we better understand these processes through the application of new technologies, may yield novel drug targets. This is exemplified in the context of cardiovascular disease and atherosclerosis. The significance of drug-gut microbiota interactions are highlighted, which may skew our traditional understanding of pharmacokinetics and pharmacodynamics, and will undoubtedly have to be considered as a significant factor in the development of new drugs, either microbial- or host-targeted. And finally, we introduce rational approaches which can be applied to the discovery, and application of, therapeutic phage and novel psychotropics.

Conflict of Interest

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