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Invited Review Article

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AS THERAPEUTIC ALLIES OF THE GUT MICROBIOME ON CHRONIC INFLAMMATION

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Abstract. *Our gut harbours around 10^{14} bacteria of more than 1000 species, accounting for approximately 2 kg of biomass. The gut microbiome plays several vital functions in processes such as the development of the immune system, food digestion and protection against pathogens. For these functions to be beneficial for both host and microbiome, interactions are tightly regulated. Gut and immune cells continuously interact to distinguish among commensal microbiota, harmless foodstuff, and pathogens. A fine balance between inflammatory and anti-inflammatory state is fundamental to protect intestinal homeostasis. Nonsteroidal anti-inflammatories (NSAIDs) are a class of drugs used for management of pain and inflammation. These compounds have heterologous structures but similar therapeutic activities. The target of all NSAIDs are the isoforms of cyclooxygenase enzymes (COX): the primarily constitutive form COX-1, and the inducible from COX-2. Both isoforms catalyse the conversion of arachidonic acid to PGH2, the immediate substrate for specific prostaglandin and thromboxane synthesis. The gut microbiota plays a role in drug metabolism, resulting in altered bioavailability of these compounds. Additionally, complex host-microbiome interactions lead to modified xenobiotic metabolism and altered expression of genes involved in drug metabolism. These effects can be at gut tissue-level, or distant, including in the liver. Besides the gut microbiome influencing drug metabolism, drugs also impact the microbial communities in the gut. As different drugs exert selective pressures on the gut microbiome, understanding this bidirectional relationship is crucial for developing effective therapies for managing chronic inflammation.*

Key words: *gut microbiome, non-steroidal anti-inflammatories, inflammation, dysbiosis.*

Introduction

The gut microbiota includes more than 100 trillion bacterial cells [1], which can be divided into six dominant phyla: Firmicutes, Bacteroidetes and Actinobacteria, and the less abundant Proteobacteria, Fusobacteria and Verrucomicrobia [2]. The human microbiome is not only composed of collective genomes from bacteria, but also from those of archaea, viruses, and eukaryotes colonizing the gut [3]. The composition of the microbiota will depend on environmental factors, diet, age and host genetics [4]. Inter- and intra-individual differences are significantly prevalent, although several species such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Bacteriodes uniformis* have been consistently identified in large scale screenings. The gut microbiome transforms indigestible substrates from food, such as xyloglucans, into short chain fatty acids, which can be used as energy source for the colonocytes [5]. These metabolic activities may directly or indirectly impact health and disease in the host. The commensal microbiota can train the immune system to induce regulatory T cells, which then prompt tolerance to these bacteria [6]. In this way, commensal-induced immunity contributes to maintain mucosal tolerance and protect the host from disease [7]. Such exchanges are tightly regulated: gut and immune cells continuously interact to distinguish between commensal microbiota, harmless foodstuff, and pathogens. A fine balance between inflammatory and anti-inflammatory status is needed to preserve intestinal homeostasis [8].

Interest in developing colon-targeted drug delivery systems has increased in recent years [9]. These formulations are intended for gastrointestinal-related diseases, such as colorectal cancer (CRC) and inflammatory bowel disease (IBD). Despite the numerous research in this field, there are still questions that need to be answered, as differences in microbiome composition may ultimately impact drug metabolism between subjects [10]. For example, which characteristics of the microbiome contribute to the pharmacokinetic differences between individuals? Does the region in the colon reflect a specific colonization pattern, which will later trigger metabolic differences? Do long-term alterations in the gut microbiome generate metabolic dysbiosis? If so, to what extent? Gaining insight into the gut metabolic potency is essential, because characterization of the players involved in drug disposition in the gut will contribute to ensure optimal drug efficacy and safety profile.

Existing colon-specific drug delivery systems hold some limitations. Besides the microbial influence on

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drug bioavailability and pharmacokinetics, low solubility in presence of bile acids and the small aqueous volume in the colon may hinder drug efficacy [11]. Moreover, understanding drug transporter activity is fundamental to improve drug passive permeability. Current models to predict drug efficacy consider plasma concentrations to describe the pharmacokinetics and pharmacodynamics. However, drugs designed for targeting the gut undergo an extensive first pass metabolic clearance. This implies that the relation between plasma concentrations and efficacy has a low predictive value. For this reason, investigating microbiome-drug-host interactions towards improving ADME and safety responses of intestinal targets is fundamental [12].

Xenobiotic Metabolism of the Gut Microbiome

Chemotherapeutic outcomes are mainly linked to human genetic polymorphisms [13], but the impact of the human gut microbiome has been overlooked, as it has been even called the "forgotten organ". Although microbiome research has flourished in recent years, the association between the microbiota and xenobiotics metabolism remains underexplored. The host cytochrome CYP2C9 predominantly eliminates lipophilic drugs through the liver, whereas orally administered drugs encounter the gut microbiota before reaching host tissues [10]. This first-pass metabolism by the colonic microbiota must be considered, as the metabolites generated from this process can impact drug activity, resulting in toxicity for the host and further inflammation, or altering gut microbiota and producing dysbiosis [14].

The anaerobic environment of the human gut prevents the microbial use of oxygen as terminal electron acceptor for oxidation [10, 14]. Thus, anaerobic respiration and increase in microbial growth are facilitated by the two main metabolic transformations: reduction provides alternative electron acceptors, while hydrolysis ensures substrates that can be used by microorganisms [15]. Since these two reaction types are commonly observed, core microbial species or core gene families performing such functions are hypothesized to participate [16].

Links between gut bacteria and drug metabolism are via direct and indirect mechanisms. Direct mechanisms involve the transformation of the drug into metabolites with a different effect. Conversely, indirect mechanisms are those influencing drug transport or metabolism [14]. Knowledge of these metabolic pathways is fundamental to predict whether drug metabolism and disposal will be impacted.

Additionally, biliary excretion is essential for drug recirculation and ultimate metabolism. In this respect, β-glucuronidases can play a key role, because they are important for host drug detoxification [17]. Glucuronic acid is coupled to several substrates in the liver, thereby increasing molecular weight and solubility. Consequently, elimination through urine or faeces is enhanced, and gut bacteria can reactivate these products, generating higher toxicity. Likewise, non-steroidal anti-inflammatory drugs (NSAIDs) have side-effects [18]. Microbial β-glucuronidases can separate the aglycone from the glucuronide, so the aglycone is absorbed into the enterocytes and transformed into reactive metabolites, harming the mitochondria and the endoplasmic reticulum. In this way, not only the host detoxification pathway is diminished, but also inflammation is evoked as a result of decreased mucosal integrity [19]. The impact of the gut microbiota on hepatic drug-processing genes is enzyme-specific and age and sex-dependent, with patterns varying throughout life span and developmental periods, and xenobiotic pathways significantly downregulated in male mice at 90 days of age [20].

Moreover, probiotic interventions have confirmed that microbiome manipulations not involving antibiotics can influence the expression of hepatic drug–processing genes during adulthood [21]. Poorly absorbed antibiotics such as vancomycin and rifaximin, may indirectly modulate hepatic CYP gene expression, as they bypass hepatic metabolism and impact gut bacteria [22]. Understanding the outcomes of indirect host–microbiome-drug interactions occurring because of drug use, consumption of dietary supplements, or environmental toxins should be considered in drug development, safety pharmacology, and pharmacokinetic profiling [20].

The Gut Microbiome and Xenobiotic Metabolism during Chronic Inflammation

Although research efforts are ongoing to more precisely define a healthy gut microbiome [23], one of the most frequently reported findings across an array of disorders is a narrowing of gut microbiome diversity often accompanied by more specific but less consistent compositional alterations at various taxonomic levels. Dysbiosis refers to the state where the composition of the microbiome is disrupted [24, 25], providing continuous immunological stimulation and leading to anomalies in the immune response. The polarized induction of immune cells and the subsequent increased amounts of pro-inflammatory T cells may fuel the development and severity of the disease. Excessive inflammation results in loss of epithelial integrity, which in turn leads to further bacterial translocation and thus further induction of inflammation [8, 24]. This condition is observed in a number of gastrointestinal diseases such as inflammatory bowel disease (IBD) and colorectal cancer (CRC) [26], central nervous system disorders such as depression and schizophrenia [27], obesity [28], diabetes mellitus [29], cardiovascular disorders [30], rheumatoid arthritis [31] and multiple sclerosis [24], and asthma and atopy in children [32]. Research found that *Faecalibacterium prausnitzii* is reduced in patients with ulcerative colitis, another chronic inflammatory condition of the colon [33]. This bacterium has been reported to promote the accumulation of regulatory T cells (T_{reg}), which contribute to anti-inflammatory responses [34]. On the

contrary, Enterobacteriaceae, Bacteroides, *Clostridium ramosum* and *Akkermansia muciniphila* are increasingly present in patients with IBD. These organisms have also been linked with increased inflammation [35]. Although the importance of the gut microbiome in chronic inflammatory conditions has been reported [36], it is still unclear whether dysbiosis is a consequence or a cause of associated diseases [8, 24].

Gut microbiota are known to play a role in the metabolism of drugs, hereby having an effect on the host health . Many of the therapeutic interventions for chronic disorders are subject to biotransformation by the gut microbiome, and the functional implications of changes in gut bacterial communities for xenobiotic metabolism are yet to be described. The gut microbiome can affect drug therapy via direct or indirect mechanisms. The direct mechanisms compromise metabolization of the drugs by the microbiota, resulting in altered bioavailability of these compounds. Indirect mechanisms include complex host-microbiome interactions, resulting in a modified xenobiotic metabolism of the host [10]. In the latter case, one of the routes is that microbiota affect host gene expression involved in drug metabolism. These effects can be either local, meaning in the gut tissue [37], or distant, including in the liver [38].

Understanding how alterations in gut microbiota profiles influence host response to chemotherapeutic drugs may have important clinical implications. Stratifying patients based on their gut microbiome composition may assist in identifying responders and non-responders to immunotherapy [39] for the treatment of epithelial tumours and melanomas [20, 40]. Other mechanisms modulated by the gut microbiome include the translocation and immunomodulation following interventions with cyclophosphamide, doxorubicin, and anti–CLTA-4 therapies [41].

Dynamics of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) towards the Gut Microbiome

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used for inflammation management. The compounds in this group are heterologous in structure but show similar therapeutic activity [42]. The target of all NSAIDs are cyclooxygenase enzymes (COX). There are two isoforms of COX, the primarily constitutive form COX-1, and the inducible from COX-2 [42]. COX-1 and COX-2 both catalyse the conversion of arachidonic acid to PGH_2 [43]. PGH_2 is the immediate substrate for some cell specific prostaglandin and thromboxane synthases [42].

COX-1 is expressed in different tissues such as the kidneys, lungs, stomach, ileum and colon [44]. It is considered to be a “housekeeping” enzyme, playing an important role in the production of prostaglandins that serve homeostatic functions [45]. These prostaglandins, among others, maintain the integrity of the gastric mucosa, mediate normal platelet function and regulate renal blood flow [46]. COX-2 on the other hand, is normally not expressed in tissues with the exception of the macula densa of the brain and kidney, the placenta, the vessel walls and the heart, where it is believed to play a role in homeostatic functions [47]. This isoform of the enzyme is upregulated in response to tissue damage or the presence of pro-inflammatory cytokines [43]. In turn, COX-2 is responsible for the generation of pro-inflammatory prostaglandins, thus contributing to inflammation [45]. One of these prostaglandins is PGE_2, which is implicated in carcinogenesis. COX-2 expression is found to be increased in colorectal cancer causing proliferation, enhanced angiogenesis and suppression [48] of apoptosis (Pugh & Thomas, 1994; Surh et al., 2001).Thus, COX-2 is the main target of chronic inflammation therapy using non-steroidal anti-inflammatory drugs (Fig. 1).

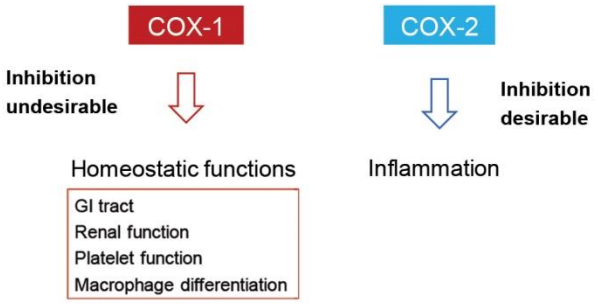

Fig. 1 Isoforms of COX enzymes and their functions

Orally administered drugs are subject to the so called “first-pass metabolism”, where the gut microbiome plays a crucial part. Prior to reaching the target tissue, microbiota and liver metabolize the drugs, altering their bioactivity [10]. The bacterial metabolism results in three scenarios, namely activation, inactivation, and increased toxicity of the drug. In the first situation, the pharmaceutical compound is activated into its therapeutic window, resulting in increased drug efficacy. An example is the described transformation of sulindac to its bioactive sulphide metabolite. In the case of inactivation, the availability of the active drug is lowered resulting in decrease or loss of therapeutic effect. For instance, microbial arylamine N-acetyltransferases inactivate the bioactive component of the anti-inflammatory drug sulfasalazine [14], while the NSAID diclofenac can exert toxic effects after being glucuronidated in the liver by the host and then being exposed to microbial β-glucoronidases in the gut [10, 18]. In these scenarios, activity of the gut microbiome results in increased toxicity and adverse effects for the host. In addition, simultaneous use of probiotics significantly increased the microbiota-mediated enzymatic degradation of the antipyretic and analgesic paracetamol [20, 39]. Similarly, short-term administration of a probiotic cocktail of *L. acidophilus*, *B. lactis* and *Streptococcus salivarius* to rats significantly increased azoreductase activity in *ex vivo* incubation of sulfasalazine with colon contents, ultimately impacting the metabolism of this drug [49].

Besides the gut microbiome influencing drug metabolism, drugs also impact the microbial communities in the gut. As discussed earlier, a shift in gut microbiome, and more specifically dysbiosis, is linked to disease. Therefore, understanding the effects of drugs on the gut microbiota is crucial for providing suitable therapies [14]. Obvious examples include the use of antibiotics, resulting in altered gut microbiome [50]. NSAIDs have been reported to impact the gut microbiome and changes in composition have been observed [51] depending on the NSAID administered. Subjects exposed to aspirin showed greater abundance in *Prevotella* spp., *Bacteroides* spp., *Barnesiella* sp. and Ruminococcaceae. Celecoxib and ibuprofen users showed enrichment in Enterobacteriaceae and Acidaminococcaceae. Ibuprofen users were also enriched in Propionibacteriaceae, Pseudomonadaceae, Puniceicoccaceae and Rikenellaceae [52]. In contrast, a different study observed no effects on the microbiome composition after administration of celecoxib [53]. Sulfasalazine induced the expression of thioredoxins and nitrate reductases, while nizatidine, subject to bacterially mediated N-oxide bond cleavage, up-regulated the expression of drug enzymes and transporters acting on nitrogen bonds [54]. This finding supports the earlier hypothesis that drugs may shift the microbiota to favour the abundance of taxa involved in its metabolism. Furthermore, this altered metabolic capacity of the microbiota could consequently affect not only the pharmacokinetics of subsequent doses of the drug itself (a phenomenon referred to as autoinduction) but also the pharmacokinetics of co-administered medication may be act as substrates of the same metabolic pathway or transporter. Production of diet-derived by-products such as like *p*-cresol (from protein digestion) can affect drug metabolism. Research showed that acetaminophen, an analgesic and antipyretic drug, underwent less sulfonation due to competitive O-sulfonation of *p*-cresol [55].

COX-1 plays a role in guaranteeing the mucosal integrity of the gastrointestinal tract and thus, non-specific NSAIDs blocking both isoforms of COX have been linked with intestinal damage [19]. These environmental changes place a selective pressure on the microbiome resulting in fluctuations in microbial composition [56]. Blocking intestinal bacterial enzymatic functions has been proposed to amend intestinal homeostasis, while enhancing efficacy and decreasing toxicity of IBD therapies, as realised for cancer therapies [4, 17]. Precision editing of the gut microbiota by tungstate ameliorates experimental gut inflammation through preventing the dysbiotic expansion of Enterobacteriaceae [57]. This is merely an example of the complex host-microbiome-drug interactions and it is likely that different drugs exert selective pressures on the gut microbiome through different mechanisms [14]. The use of designer lactic acid bacteria as factories for the production of antimicrobial and anti-inflammatory biomolecules may also have potential for the future treatment of infectious diseases, cancer, and metabolic diseases [54, 58].

Conclusion

It is clear that the gut microbiome play an enormous role in patient health, but also in pharmacokinetic and pharmacodynamic drug response. Before official approval, government agencies such as the FDA run three phases of clinical trials, where pharmacokinetics, pharmacodynamics, and safety of a drug are determined. However, gut bacteria is not currently considered within these evaluations, although the microbiome is the first checkpoint following drug intake. *In vitro* studies have shown that some NSAIDs can be metabolized by bacteria, potentially jeopardizing its anti-inflammatory effects. More than 60 interactions between drugs and the microbiome have already been documented. Unfortunately, most of the underlying molecular and genetic mechanisms remain unclear. The PharmacoMicrobiomics online database was launched in 2011 to assemble the literature about those interactions [59]. Future efforts may focus on combining available information about the drug-bug interactions on biochemical pathways with existing genomic, pharmacogenomic and human microbiome sequence databases [52].

Personalized medicine has achieved excellent results in some areas of medicine, such as oncology [4]. Yet, genetic factors can influence up to 50% of therapy responses [13]. It is at this crossroads that recent discoveries on the roles of gut microbiota have become paramount [60]. Stratification of patients based on their gut microbiome may improve treatment accuracy [17] and cost-effectiveness [61]. A combined strategy to restore eubiosis may require synchronised targeting of dominant pathobionts and replacing missing beneficial species or their functions by manipulating the bacterial microbiota with dietary strategies. Thus, homeostatic immune responses, and mucosal barrier function would be reconditioned. This integrated approach may result safer than the current lifelong treatments with immunosuppressive drugs, once remission has been accomplished by traditional therapies.

Understanding how our "second genome" [4] is involved in therapeutic responses could pave the way for approaches using the intestinal microbiome as the target for modulating drug efficacy and enabling tailored treatments. Revealing the specific mechanisms driving defective bacteria–host interactions will enable precision editing of gut microbiota functionality and composition for ameliorating chronic inflammatory diseases.

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