Drugs and microbes: Why drugs affect people differently

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Summary

Why do drugs work well for one patient while failing to have an effect or inducing severe side effects on the other? One factor that could be at the root of this variability are the micro-organisms inhabiting our gastrointestinal tract, in other words, the gut microbiome. This microbiome is opening a new dimension in adjuvant treatment possibilities in the near future. We shed light on recent breakthrough studies that demonstrate how the gut microbiome influences drug response and the perspectives arising for patients using two examples: cancer immunotherapy and biologicals in inflammatory bowel disease.

Samenvatting

Waarom werken geneesmiddelen goed bij de ene patiënt en bij de ander niet of met ernstige bijwerkingen? Een factor die aan de basis van deze variabiliteit kan liggen, zijn de micro-organismen in ons maagdarmkanaal, ofwel het darmmicrobioom. Dit geeft in de nabije toekomst een nieuwe dimensie aan mogelijke complementaire behandelingen. We belichten recente baanbrekende studies die laten zien hoe het darmmicrobioom het effect van geneesmiddelen kan beïnvloeden, en bespreken de mogelijke vooruitzichten voor patiënten aan de hand van twee voorbeelden: kankerimmuuntherapie en biologicals bij inflammatoire darmziekten.

Background: the gut microbiome is shaped by environmental factors

The gut microbiome, a term used to describe all micro-organisms that collectively inhabit the gastrointestinal tract, is a major player in health and disease. The gut microbiome is involved in critical functions of the host, such as digesting the food we eat, participating in the immune response and metabolizing drugs. Advances in high-throughput sequencing have led to greater sample sizes to elucidate the role of the gut microbiome for cancer, inflammatory bowel disease (IBD) and a broad range of other diseases. Besides the composition of the microbiome, the functions of the gut microbiome such as metabolism of nutrients, drugs or xenobiotics, are increasingly being investigated through metabolomic profiling of stool samples. The Dutch Microbiome Project, that included questionnaires and stool samples from over 8000 participants, showed that environmental factors such as diet, cohousing, drug use and early life all influence the gut microbiome composition and function [1]. It follows that the gut microbiome is an interesting modifiable target that is expected to play a crucial role in the development of new treatments and diagnostics.

In recent years, there has been growing recognition of the interactions between drugs and the gut microbiome. There are three main mechanisms of this interaction which we will illustrate in the following:

- Direct effect of the drug on the gut microbiome composition.
- Direct effect of the gut microbiome on the drug through microbial metabolism.
- Indirect effect of the gut microbiome on drug response by modulating the immune system.

Commonly-prescribed drugs have a substantial effect on the gut ecosystem

Besides antibiotics, commonly used drugs including proton pump inhibitors (PPIs), metformin and statins influence the gut microbiome composition substantially.

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Several of the disease-associated bacteria reported in early studies were actually a result of the prescribed medications rather than the underlying disease itself. A drug can affect the gut microbiome composition by promoting translocation of microbiota from other body sites to the gut. An example of this phenomenon has been shown by our research group for PPIs [2]. PPIs are prescribed for acid-related disorders such as gastro-esophageal reflux disease since they increase the pH of gastric acid. Reduction of gastric acidity enables bacteria that usually reside in the oral cavity, to colonize the intestine. As a result, PPIs alter up to 20 per cent of bacterial taxa, with an increase of bacteria predominantly found in the oral cavity and a decrease in intestinal commensal bacteria. Another mechanism through which drugs can influence the microbiome composition is by changing the intestinal micro-environment which directly affects bacterial growth. For example, metformin induces an increased growth of bacteria capable of producing short chain fatty acids (SCFA) which have been shown to contribute to the therapeutic effect of metformin by increasing insulin sensitivity [3]. In contrast, a number of antineoplastic agents and antirheumatic drugs have been shown to decrease bacterial growth, which may contribute to the intestinal side effects of these drugs.

The concept of pharmacomicrobiomics

Importantly, the gut microbiome itself also impacts the efficacy and toxicity of a drug by metabolizing it. Microbial metabolism of drugs can produce bioactive, inactive or toxic metabolites, which directly influences an individual's response to a drug. This concept is referred to as pharmacomicrobiomics and is a natural expansion of pharmacogenomics. An example is illustrated by the oral antiviral drug brivudine. Brivudine can be enzymatically transformed to bromovinyluracil by both host and the gut microbiota, with the latter exerting hepatic toxicity. 70 per cent of brivudine toxicity is attributable to the gut microbiota, particularly to certain *Bacteroides* species [4] . In contrast to the long-standing field of pharmaco-genomics, which studies how human genomic variations affect drug metabolism, pharmaco-microbiomics considers how variability in the gut microbiome affects drug metabolism. The gut microbiome, as opposed to human genetics, is modifiable, making it an attractive target for complementary strategies to improve drug responses.

The gut microbiome has an important role in the immune homeostasis and cancer immune response

Finally, the gut microbiome can indirectly impact a patient's response to cancer immunotherapy through its effects on the immune system. The postulated mechanism lies in the role of the gut microbiome in fine-tuning the general host immune status, subsequently promoting the anti-tumor immune response. As an example, a low abundance of specific gut commensals such as Bifidobacteria has been shown to result in decreased priming of dendritic cells through immune checkpoint inhibition and hence a decreased anti-tumor T-cell activation.

The gut microbiome may dictate interindividual variation in drug efficacy

There is increasing evidence that the gut microbiome could be of help in predicting which patients will respond to the prescribed therapy. We will illustrate this concept by using the example of cancer immuno-therapy and biologicals in IBD.

Recent evidence shows that the gut microbiome may predict response to biologic therapy in IBD and immune checkpoint inhibitors (ICIs) in cancer patients. These studies have identified differences in the composition and function of the gut microbiome between patients for whom treatment was effective and those who did not respond or developed drug-induced side effects. Biologicals and ICIs are affecting the immune system in contrasting ways. While the former acts immuno-suppressive, the latter causes a heightened immune response, targeted at the tumor.

The gut microbiome in IBD management

IBD, with the two main forms Crohn's disease and ulcerative colitis, is a chronic disorder of the gastrointestinal (GI) tract in which patients experience periods of inflammation alternating with periods of remission. Collectively, drugs used for IBD management are aimed at 1) reducing inflammation during a disease exacerbation and 2) maintaining remission after induction therapy. In recent years, biologicals have tremendously improved the management of IBD. Biologicals are monoclonal antibodies that may block the function of pro-inflamma-

tory cytokines such as TNF-α (infliximab) or affect T-cell migration (vedolizumab) to reduce intestinal inflammation. On average, around 30 per cent of patients treated with biologicals show long term remission, indicating that there is still room for improvement for a large remainder of patients. In an attempt to improve remission rates of biologicals in IBD, the gut microbiota has received a lot of attention for predicting therapy response and as a (complementary) therapeutic option. For example, the gut microbiome has been shown to be of use in predicting therapy response in IBD patients treated with vedolizumab, response to therapy was associated with wider microbiological diversity and higher abundance of the bytyrate producer *Roseburia inulinivorans* [5]. Our group has demonstrated an increase in α-diversity after 14 weeks in IBD patients responding to vedolizumab [6]. This has also been observed in studies investigating other biologicals, indicating that microbial richness increases in responders over the treatment course.

The gut microbiome and efficacy of cancer immunotherapy

Immunotherapy has revolutionized the treatment of advanced cancer. The most widely used form of cancer immunotherapy are ICIs. Immune checkpoints are proteins expressed on T-cells and important gatekeepers of the immune system. In order to prevent an immune response from being so strong that it damages healthy cells, negative immune checkpoints such as CTLA-4 can act as a 'brake' to shut off T-cell activity. While immune checkpoint activity consist of an important self-tolerance mechanism, the immune system relies on T-cells to eliminate intracellularly infected or cancerous cells.

In 1995 Jim Allison found that by blocking CTLA-4, T-cells continued their work and eliminated cancer in a laboratory setting. This discovery has since led to the development and approval of several immune checkpoint inhibitors including ipilimumab, which blocks the immune checkpoint protein CTLA-4, pembrolizumab and nivolumab, which block the protein PD-1. Durable tumor responses are seen for ~40 per cent of cancer patients treated with ICIs. Yet, a large remainder of patients is resistant to treatment or develops drug-induced toxicity. As immune checkpoints are an important self-tolerance mechanism, patients treated with ICIs also often develop intestinal inflammation of varying degrees.

To elucidate the role of the gut microbiome for cancer immunotherapy, we recently completed a large mult-i cohort study, associating pre-treatment gut microbiome composition to response in melanoma patients treated with ICI's [7]. While there is still variability seen in microbial signatures across different countries, three types of bacteria were consistently associated with response: *Bifidobacterium pseudo-catenulatum*, *Roseburia* spp. and *Akkermansia muciniphila*. The precise mechanisms through which the gut microbiome impacts immunotherapy response still have to be elucidated. It is currently thought that the microbiome is in part responsible for general peripheral immune homeostasis and that microbial antigens induce exaggerated T-cell reactivity which can promote the anti-tumor response. In mice it has been shown that both innate and adaptive immune cells exposed to specific gut microbes can infiltrate the tumor micro-environment and produce chemotactic factors which induce trafficking of immune cells to the tumor site. Another hypothesis is the cross-reactivity between microbial and tumor-associated antigens. Finally, the gut microbiome can produce metabolites such as SCFAs [8]. SCFAs are the end products of gut microbial fermentation of fiber and have been shown to modulate host immunity in various ways. For example, they stimulate regulatory T-cells and have anti-inflammatory roles in the intestine. Moreover, pre-clinical studies have shown that SCFAs can recover an impaired immune response and aid in invigorating a tumor specific T-cell response, raising the efficacy of cancer immunotherapy. For example, butyrate and propionate can affect the gene expression of cytotoxic T-cells and T-helper 17 cells, while butyrate and valerate inhibit histone deacetylases, sub-sequently upregulating PD-1 ligands in cancer cells [8].

Potential for enhancing treatment responses via microbiome-targeted strategies

Since the gut microbiome is modifiable, strategies such as fecal microbiota transplantation (FMT), probiotics, targeted diets or prebiotics can be foreseen to complement the use of immunotherapy and biologicals in the future. Baruch et al. recently published promising results of FMT in a phase 1 clinical trial in 10 patients with immunotherapy refractory melanoma [9].

Recipients underwent oral antibiosis with vancomycine and neomycine for 72 hours, followed by FMT with stool from two responders. Upon reintroduction of immunotherapy, three patients achieved a response, with favourable changes in immune cell infiltrates and gene expression in the gut lamina propria and the tumor microenvironment. In IBD, FMT has been shown to be more beneficial in ulcerative colitis than in Crohn's disease. While there is currently not enough evidence to support FMT in the management of IBD, studies are underway to bring more certainty regarding the selection of the right stool donors and the frequency and (long-term) safety of the procedure.

Another promising strategy to maximize efficacy of ICIs and biologicals could be the diet. A recent observational study in melanoma patients treated with anti-PD-1 immunotherapy indicated that patients with a high-fiber diet could be up to five-times more likely to respond to treatment, while consumption of commercially available probiotics was associated with a lower probability [10]. Other diets or prebiotics currently under investigation to enhance ICI efficacy include ketogenic diet, fasting mimicking diet combined with metformin, Omega-3 fatty acid supplementation and fermented foods. SCFAs have also been linked to treatment responses to biologicals. In IBD patients treated with infliximab or adalimumab, Aden et al. found significantly higher levels of butyrate in fecal samples of responders compared to non-responders, both before and after treatment [11]. Given previously described associations of SCFA-producing bacteria with dietary factors [12], it can be speculated that consumption of a plant-dominated Mediterranean diet increases the abundance of these gut microbiota, further augmenting treatment responses.

Conclusion

Summarized, an increasing body of evidence shows that the variability in efficacy of biologicals and cancer immunotherapy may be related to the patients' gut microbiome. FMT, gut microbiome-targeted diets or prebiotics offer exciting new avenues to extend the reach of these drugs to more patients in the future.

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