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Review

Beneficial modulation of the gut microbiota

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ABSTRACT

The human gut microbiota comprises approximately 100 trillion microbial cells and has a significant effect on many aspects of human physiology including metabolism, nutrient absorption and immune function. Disruption of this population has been implicated in many conditions and diseases, including examples such as obesity, inflammatory bowel disease and colorectal cancer that are highlighted in this review. A logical extension of these observations suggests that the manipulation of the gut microbiota can be employed to prevent or treat these conditions. Thus, here we highlight a variety of options, including the use of changes in diet (including the use of prebiotics), antimicrobial-based intervention, probiotics and faecal microbiota transplantation, and discuss their relative merits with respect to modulating the intestinal community in a beneficial way.

1. Introduction

Humans are now thought of as "superorganisms" on the basis of the genetic potential encoded within our resident microbial populations in addition to our own genome. It has been suggested that our microbiota develops with us and alters its own composition and gene expression in response to changing environmental conditions [1]. The largest and most varied of the human-associated microbial communities exists in the gastrointestinal (GI) tract.

The gut microbial population is made up of approximately 1000 species from relatively few phyla. The most abundant species are members of the phyla Firmicutes and Bacteroidetes, with smaller numbers being representatives of the Proteobacteria, Fusobacteria, Cyanobacteria, Verrucomicrobia and Actinobacteria, amongst others [2]. The gut microbiota is composed mainly of anaerobes, which outnumber facultative anaerobes and aerobic bacteria by approximately 2–3 orders of magnitude [3]. It has been noted that, although there is great inter-individual variation in the composition of the gut microbiota, there are a conserved set of encoded functions shared between individuals referred to as the core gut microbiome [4], suggesting that it is the functionality of the microbiota rather than its composition that is of greatest importance to the host. The functions and pathways encoded in the core microbiome are thought to confer the greatest benefit to the host and are probably essential for the correct functioning of the gut. Some well-studied benefits include protection against potential pathogens, digestion of polysaccharides, production of essential vitamins, stimulation of angiogenesis, regulation of fat storage and modulation of the host's immune system [5]. Recent studies have also shown that the gut microbiota influences the gut-brain axis and shapes stress-related symptoms such as anxiety and pain tolerance [6].

Advances in high throughput sequencing technologies (HTS) and tools enabling comparative analysis of the large amount of data that are generated by these technologies have led to a better understanding of what constitutes a 'healthy" gut microbiota. One of the most interesting observations drawn from the data generated is that the resident microbiota encodes >100-fold more genes than the human genome [7]. The genes present in the microbiome are responsible for many functions essential to host survival but which are not encoded within the human genome. Due to the range and importance of the metabolic and biochemical processes carried out by the microbiome it has been referred to as "our hidden organ" [8].

While the "healthy" gut microbiota is seen to be a stable community, there are stages within the life cycle of humans during which there can be dramatic alterations in the structure and function of this population. These "natural" changes begin with initial

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colonisation immediately following birth and subsequent development of the microbiota over the first 2 years of life. The earliest colonizers are usually members of the enterococci and enterobacteria followed by strict anaerobes such as *Bifidobacterium*, *Clostridium* and *Bacteroides* spp. once the initial oxygen supply present has been depleted [9]. Despite this general pattern, it is important to appreciate that the method of delivery and subsequent feeding type have a profound effect on the initial populations [10]. Once the infant reaches 2 years of age the microbiota has already begun to transform into its adult form, which is thought to be relatively stable before it undergoes a final "shift" when entering old age [11]. Indeed, with respect to the latter phenomenon, a study by Claesson and colleagues that compared the gut microbiota of individuals ages 65 or older to 9 younger control subjects has highlighted significant changes in community structure associated with ageing, specifically an increase in the abundance of *Bacteroides* spp. and distinct shifts within the *Clostridium* genus [12]. It has been hypothesised that alterations in the elderly microbiota are due to physiological changes in the elderly gastrointestinal tract such as chronic low-grade inflammation, in addition to dietary habits [13].

It has been well established that the human gut microbiota is integral to human health, and, as will be discussed below, it also plays an important role in gastrointestinal disease. It is therefore reasonable to assume that modulation of the gut microbiota can be used as a therapeutic approach to treating chronic gastrointestinal diseases. Thus, this review is focussed primarily on the methods that can be employed to modulate the gut microbiota while highlighting the benefit of guiding community structure towards a more desirable state.

2. Role of the gut microbiota in gastrointestinal disease

There are a growing number of gastrointestinal conditions that have been linked with alterations in the gut microbiota. To properly implement strategies to modulate the gut microbiota as a therapeutic tool, it is first necessary to understand the role of the gut microbiome in specific GI, and other, diseases. Given the recent rapid expansion in the number of disease states that have been linked with alterations in the gut microbiota, it is not possible to address the issue in depth in the confines of this review. Instead, some well-studied examples are discussed below and we refer you to some other recent reviews that address this topic in depth [3,14].

2.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a relapsing disorder characterised by chronic inflammation of the GI tract, and of the colon in particular. The two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Evidence suggests that IBD is a complex disease arising from a combination of genetic and environmental factors. From a genetics perspective, genome-wide association studies (GWAS) and subsequent meta-analyses have identified a total of 163 genetic risk loci for IBD [15–17]. A German twin cohort study confirmed the strong genetic element to IBD by observing that monozygotic twins are significantly more likely to be concordant for the disease than dizygotic twins [18]. However, concordance rates between monozygotic twins are nonetheless low (35% for CD and 16% for UC), highlight that environmental triggers do indeed play an important role in both diseases, and in UC in particular.

It is notable that murine studies have revealed that the presence of commensal enteric bacteria is necessary for the development of spontaneous colitis and immune system activation [19] and, indeed, transferring colitogenic gut microbiota into healthy mice can induce spontaneous colitis [20]. Similarly, it has consistently been observed that patients suffering from IBD harbour an altered gut microbiota [21,22], specifically reduced bacterial diversity and changes within the Firmicutes phylum [23]. The changes in microbiota composition appear to be somewhat different between UC and CD. For example, decreased abundance of the butyrate-producing bacteria *Roseburia hominis* and *Faecalibacterium prausnitzii* have been observed in UC patients relative to controls [24], while the opposite has been observed in CD patients who possessed increased *F. prausnitzii* levels in addition to a reduced overall diversity [25]. Although these microbial changes could be a result of increased inflammation, evidence suggests that it is more likely that shifts in the microbiota are involved in the disease's pathogenesis, either due to an intolerance to a specific group of commensals or due to an imbalance between protective and harmful members of the population [21,23,26].

2.2. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic GI disorder that presents with symptoms including abdominal pain, bloating and altered bowel function. IBS is divided into several subtypes based on stool characteristics; diarrhoea, constipated or mixed. It's cause, as of yet, is not fully known and although the aetiology is thought to be a combination of a number of factors, it is hypothesised that perturbations in the normal microbial microbiota play a role in the syndrome's characteristic low-grade inflammation [27]. Indeed, Rajiić-Stojanović et al. used qPCR and phylogenetic microarrays to show that the gut microbiota of IBS patients differed significantly from healthy controls, with IBS sufferers having a 2-fold higher Firmicutes to Bacteroidetes ratio and correlation analysis implicating several groups of Firmicutes and Proteobacteria in IBS pathogenesis [28]. Contrastingly, Jalanka-Tuovinen and colleagues observed that the faeces of diarrhoea-predominant IBS sufferers harboured 12-fold higher levels of several Bacteroidetes members. This group also noted that healthy controls have 35-fold higher numbers of uncultured clostridia [29]. Interestingly, these alterations in the microbiota correlated with changed in expression of host genes involved in amino acid synthesis, cell junction integrity and inflammatory response, suggesting impaired epithelial barrier function in IBS patients. Small intestinal bacterial overgrowth (SIBO), which is characterised by excessive bacteria in the small intestine, has also been put forward as a possible factor in IBS aetiology [30]. Bacterial overgrowth can result in overproduction of gas in the small intestine by degradation of carbohydrates, contributing to the symptoms of IBS [31]. The most commonly isolated bacteria from SIBO patients are *Escherichia coli*, *Streptococcus*, *Lactobacillus*, *Bacteroides* and *Enterococcus* species [32]. However it is not fully understood if any of these microorganisms play a specific role in IBS progression. It should also be recognised that differences between studies may be due to the causative microorganisms or imbalances differing between IBS subtypes. Regardless, a bacterial role in IBS onset would seem to be clear, as further evidenced by the disease's response to antibiotic therapy [33] and differential expression levels of Toll-like receptors in colonic biopsies of patients with IBS [34].

2.3. Obesity

Obesity is a complex disease resulting from a prolonged imbalance of energy input and energy expenditure. Modern dietary and exercise habits are major contributing factors but it is now understood that the composition and function of the gut microbiome plays an important role through a variety of mechanisms [35]. A

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