

Microbiota of the Gut: Antibiotic-Induced Dysbiosis and the Adverse Effects on Human Health

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Abstract

A healthy gut microbial community is essential for homeostasis in mammals. A symbiotic relationship between host and microbe is essential in developing the immune system, providing biomolecules and generating energy through utilisation of indigestible compounds. The diversity of the gut microbiota is altered following antibiotic treatments, the effect this has on the health and wellbeing of the host has long been underestimated and is now the subject of intense debate. Antibiotics facilitate the selection of energy harvesting microbes within the gut and hence heavily influence the gaining of weight and may be contributing more than we anticipated to the modern obesity epidemic. These changes to the bacterial composition of the gut, dysbiosis are caused by elevated oxygen levels within the gut that promotes the propagation of facultative anaerobic *Proteobacteria*, a condition associated with inflammation and cancer. Additionally, the altered oxygenated intestinal climate allows the growth of aerobic pathogens, conveying clinically relevant resistance genes on highly transmissible mobile elements between communities or acquiring them from commensal bacteria, in turn aiding the spread of antibiotic resistance. Here we discuss the indirect pleiotropic effects antibiotics have on the microbial community and environment of the gut leading to hidden adverse implications to human health.

Keywords: Gut microbiota; Anaerobes; Antibiotic treatment; Dysbiosis; Obesity; Inflammation

Introduction

The intestinal microbiota, one of the densest bacterial communities in mammals, plays an important role in health and wellbeing of the host. The gut microbiota provides the host with essential biomolecules, energy metabolism [1] and has recently been found to be the unexplored epicentre of antibiotic resistance genes [2]. The balanced bacterial community is mainly dominated by obligate anaerobes, *Firmicutes* and *Bacteroidetes* due to the strict hypoxic nature of the gut. Obligate anaerobes of the intestine break down indigestible polysaccharides into short-chain fatty acids (SCFA), which are important for the development of the immune system and hence, vital in maintaining homeostasis. Changes in the gut bacterial composition due to e.g. antibiotic (AB) treatments have been shown to lead to both selection of microbes with high energy harvesting capacity that may contribute to obesity and an imbalanced microbiota, termed dysbiosis. This is associated with an expansion of facultative anaerobes, *Proteobacteria* in response to an increase in epithelial oxygenation [3-5]. A shift of the luminal bacterial

composition from obligate to facultative anaerobes is associated with inflammation and propagates expansion of pathogens via aerobic respiration [6] as well as commensal *Escherichia coli* [7]. Potentially, *E. coli* may carry clinically relevant AB resistance genes on highly transmissible mobile elements and hence increases the risk of spreading AB resistance genes [Lamaudiere and Morozov personal communication]. These independent studies suggest a pleiotropic effect of AB on the composition of the human gut with respect to obesity, dysbiosis, infection and the immune system. A more tailored approach to the use of AB in a clinical setting should be considered, a view that could pave the way to the development of novel preventative initiatives for human gut associated disease.

Discussion

Anaerobic environment of the healthy mammalian gut governs the bacterial composition and promotes a dominance of obligate anaerobes which constitute around 95% of the total community

[8]. They deplete intestinal oxygen via β -oxidation of microbiota-originated butyrate to CO_2 , the main pathway of energy production, which is vital for the hosts immune system. A disruption of anaerobiosis due to AB treatment leads to an increased oxygenation of the colon and therefore dysbiosis, an expansion of facultative anaerobic *Proteobacteria* via aerobic respiration [4,5]. Dysbiosis allows energy to be obtained through anaerobic glycolysis, glucose to lactate [9], that does not require oxygen, leading to increased epithelial oxygenation [10]. This in turn enables an expansion of facultative anaerobes, including commensal and pathogenic *E. coli*. This can result in a number of consequences as it increases the risk of aerobic pathogens colonizing the gut [6] and predisposes individuals to a number of diseases, including cancer via the activation of pro-inflammatory responses of the immune system [11,12]. *E. coli* constantly produce ethanol, enhancing permeability of the colon. This decreases the defence mechanisms of the host against bacteria-driven toxins such as dimethyl arsine, which is metabolized by *E. coli* to produce micro metabolites, potential carcinogens of the gut [13]. Furthermore, an expansion of *E. coli* in healthy livestock in response to AB pressure has recently been found to carry mobile elements with highly transmissible resistance determinants. For example, *mrc-1* and *mcr-2* alleles confer resistance to last resort AB, i.e. colistin and multi-drug efflux pumps, e.g. *oqxAB* confers resistance to quinolones, AB of the first choice [14,15]. This significantly reduces the choice of treatment of infections as well as increasing the risk of spreading resistance within the gut microbiome and beyond. Therefore, AB treatment of infection-free individuals must be considered as high risk, facilitating the emergence and transfer of mobile resistance to human pathogens.

Obesity and dysbiosis

The common view-point that genetic disposition or dietary habits heavily influence weight gain is contradicted in light of recent data [16]. The enrichment of the microbiome with energy harvesting bacteria elucidates the role of the gut microbiota in the gaining of weight leading to obesity. Recent data has shown that changes in animal gut microbiota in response to AB treatment resemble the microbiota of obese humans/animals without any dietary alterations [3,17]. Equally, weight gain in humans, both adults and children [18] has been observed with some AB however, effects on health have been disregarded until recently. An AB dependent selection of both methanogenic Archaea and Prevotellaceae spp together as a novel biomarker of obesity in humans and animals has been recently reported. During the fermentation process by Prevotellaceae the accumulation of excess H_2 reduces the yield of ATP, which leads to a gradual increase in the fermentation process itself [19]. The methanogenic Archaea are believed to not only have a role in obesity through promoting caloric intake from indigestible polysaccharides [20,21], but in addition an increase in Prevotellaceae, can utilise the excess H_2 generated by acetate production, a highly absorbed SCFA [22]. Additionally, *Escherichia* spp are responsible for increasing intestinal permeability, leading to more efficient absorbance of calories [23]. Furthermore, the animal gut microbiota treated with AB is enriched with *Erysipelotrichaceae*, bacteria that produce butyrate,

another major SCFA source, an excess of which contributes to obesity [24]. Findings strongly argue that the bacterial community of the obese gut is more efficient in extracting calories from food than in a healthier bacterial counterpart and becomes less efficient as the host loses weight, being self-perpetuating through the propagation of bacteria more suited to an obese state. This is consistent with reports that the bacterial gut microbiota of normal mice transplanted into germ-free rodents leads to an increase in the body fat of recipients without any increase in food intake [25]. Hence, AB should be considered as an important contributor to energy consumption and obesity-preventative programmes should be made an integral part of AB treatment protocol.

Immune disorders

The symbiosis between the immune system and the anaerobic-dominant gut microbiota governs the anaerobic intestinal conditions, being a key determinant in preventing pathogen colonization. Hypo responsive CD4^+ T cells ensure a tolerogenic response to the balanced microbiome via interleukin-10 (IL-10), an anti-inflammatory cytokine, aiding the maintenance of the anaerobic intestinal environment [26]. Consequently, a number of gastrointestinal diseases, e.g. inflammatory bowel disease, which encompasses ulcerative colitis and Crohn's Disease are associated with a pro-inflammatory immune response e.g. IL-17 and IL-23 that sustain an inflammation environment in the tumour [27]. Subsequently, this leads to the selection and propagation on facultative anaerobes, elevating oxygen levels within the gut, dysbiosis through depletion of obligate anaerobes such as *Clostridia* (phylum *Firmicutes*), compromising intestinal homeostasis [28-30]. The gut microbiota can both protect against and promote the development of Colorectal cancer. The gut *Bacteroides fragilis* (class *Clostridia*) are known to induce regulatory T cells (T-reg) and anti-inflammatory cytokines. *B. fragilis* produce polysaccharide A which promotes T-reg development and the clostridial species produce butyrate, the SCFA which stimulates extrathymic differentiation of T-reg and IL-10-producing T-cells that protect against intestinal inflammation [26,31,32]. Additionally, dysbiosis is sufficient to induce tumorigenesis and leads to increased colon permeability, therefore facilitating the access of mutagens (H_2S , NO, Reactive Oxygen Species and toxins) to colon epithelial cells this, in turn leads to DNA damage [33,34]. Understanding the mechanisms by which the gut microbiota modulates the immune system and hence promotes cancer will lead to the development of novel preventative and therapeutic approaches in stemming intestinal tumorigenesis [35].

Conclusion

A broad spectrum of human disease, including obesity, intestinal inflammation, infection and cancer appears to be tightly modulated by the composition of microbes dwelling in the gut. A disruption of the hypoxic intestine by environmental cues, e.g. AB or disease, changes the population of the gut microbiota, enabling facultative anaerobes to support and perpetuate luminal dysbiosis. This increases human susceptibility to disease and sustaining a diseased state, hence diminishing effectiveness of treatments. Elucidating the mechanisms by which the gut microbiome modulates human health

and diseases will mark a paradigm shift in our understanding of the importance of developing personalised preventative medicine. This will include development of fundamentally novel and long-term strategies to control the disease (preventing dysbiosis and the spread of AB resistance, facilitating weight loss and coordination of the immune system) via manipulating the composition of the gut microbiota.

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