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Intestinal microbiota in inflammatory bowel disease and carcinogenesis: Implication for therapeutics

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Introduction

Trillions of bacteria inhabit our intestine, forming a community called the microbiota, whose contributions are essential to maintain host homeostasis. Disruption of this normal microbial-host communication network has deleterious consequences for the host and is associated with intestinal pathologies such as inflammatory bowel diseases and colorectal cancer. Here, we present key concepts and mechanisms by which bacteria may participate in intestinal pathology, and discuss possible means to therapeutically target the microbiome.

The field of microbiome medical research has evolved at a rapid pace in the past decade, moving from early descriptive ecological and geographical microbial studies to groundbreaking functional and potentially therapeutic investigations. This research progress is particularly witnessed in organs harboring a complex microbiota such as the intestine. This organ is host to diseases such as inflammatory bowel diseases (IBD) and colorectal cancer (CRC), two pathologies where microorganisms may be implicated. The gastrointestinal microbiota is a diverse and rich ecosystem encompassing Archea, Eukarya and Bacteria. The latter domain of life is the dominating group of the intestine and is composed of the high hierarchy phyla Firmicutes and Bacteroidetes representing 90% of the bacterial community. The ecosystem is completed by the phyla Proteobacteria, Actinobacteria and Fusobacteria representing ~10% of the community. These phyla and their respective lower hierarchical representatives forms a complex ecosystem interacting in a symbiotic fashion with the host. Microbial community associated with host homeostasis form a state designated as eubiosis. In contrast, in intestinal pathologies such as IBD, CRC and enteric infection, a state of microbial imbalance or dysbiosis characterizes the community, where relative abundance of various members and their associated genes are disproportionate compared to healthy individuals. This dysbiosis state may cause harm to the host in different ways such as loss of bacteria responsible for the production of protective molecules and/or overrepresentation of microorganisms capable of generating deleterious compounds (toxins, inflammatory products, genotoxins, etc). However, the functional

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impact of this microbial imbalance in disease initiation and progression remains unclear. There is a real challenge in addressing this question because, as opposed to infectious diseases where causative microorganisms could be ascertained through Koch's postulates, pathologies such as CRC or IBD derived from an ensemble of activities derived from diverse organisms, making cause-effect studies challenging. Nevertheless, deleterious activities derived from various members of the dysbiotic microbial community are likely responsible for the development of intestinal pathologies such as IBD and CRC.

Carcinogenic pro-inflammatory microbiota

To establish a functional impact of carcinogenic microbiota, investigators have studied the effect of over-abundance or depletion of specific candidate microorganisms identified in microbiome studies^{1,2}. For example, relative abundance of *Fusobacterium nucleatum* increased in mucosal tissues of IBD and CRC patients and daily oral introduction of the bacterium increased tumor development in *Apc^{min/+}* mice³. Subsequent studies identified various genes such as *Fap2* and *FadA* from *F. nucleatum* that directly influence host responses including immune cells cytotoxic activities and epithelial cell proliferation respectively². Thus, *F. nucleatum* represents a double threat where the bacterium subverts the immune response to diminish anti-tumor activities while activating intestinal epithelial cell proliferation to promote tumor growth. Another bacteria linked to the development of intestinal pathologies, including CRC, is enterotoxigenic *Bacteroides fragilis*. This bacterium promotes development of CRC through the action of the *B. fragilis* toxin (BFT), responsible for intestinal inflammation and augmented secretion of IL-17A³. These findings indicate that some cancer-associated microorganisms utilize a number of strategies (secreted toxins, metabolites, cell surface proteins) to promote carcinogenesis and that targeting these activities may represent a novel mean to alleviate tumorigenesis¹. However, the effects of human-derived dysbiotic community on development of IBD or CRC using pre-clinical models are still poorly documented. Nevertheless, these investigations suggest that certain members present in a dysbiotic bacterial community possess carcinogenic activities that could promote tumor development in pre-clinical models.

Microbiota as therapeutic target?

Microbial-derived activities that impair intestinal epithelial cell integrity could have a deleterious effect on barrier function. Identifying these activities could have significant potential for therapeutic intervention for pathologies such as IBD and CRC. Strategic targeting of the microbiome could provide anti-cancer, anti-inflammatory, therapeutic adjuvants and pro-inflammatory resolution compounds. However, therapeutic targeting of the human microbiome represents a significant challenge and would likely represent an unconventional/novel approach that deviates significantly from classical pharmaceutical methods. The mechanism responsible for the maintenance of eubiotic microbiota in a specific host is not well understood, nor is specific molecular targets or even general goals for therapeutic approaches. Evidence suggests that restoring the balance of the symbiotic relationship between host and microbiome will reduce dysbiosis and likewise pathogenicity. However, it is likely that a full restoration of a eubiosis state is not necessary, and that the elimination of causative deleterious microbial activities may be sufficient to obtain a

therapeutic effect. Investigated and implemented therapeutic approaches that have been developed in the past few years are largely global in nature and range from diet intervention, delivery of microbial populations and the administration of general antibiotics (Fig.1). For example, microbial fecal transplantation for treatment of ulcerative colitis has shown promise in humans, but it is too early to make firm conclusion about wide clinical application. In general, a molecular approach is favored in the industry with a single, characterized molecular entity targeting a single macromolecular target. An attractive approach toward small molecules is the exploitation of secondary metabolites produced by components of the microbiome. It has been established that these natural products can disrupt microbial composition and host homeostasis, and targeting biosynthetic gene clusters should alter the microbial balance leading to a therapeutic advantage. Targeting a pathobiont species, or more specifically a virulence gene island, could selectively remove virulence factors from the population. For example, certain strains of *E. coli* are able to induce a megalocytosis phenotype in infected mammalian cells including intestinal epithelial cells, a phenomenon caused by the presence of the polyketide synthase (*pks*) genotoxic island responsible for the production of the natural product colibactin⁴. Although numerous pathogenic *E. coli* strains possess various toxins such as cytolethal distending toxin and cytotoxic necrotizing factor I, the megalocytosis mammalian response is directly due to *pks*-derived colibactin. With mucosal adherent *E. coli pks+* strains highly prevalent in patients with IBD and CRC, deleterious activities from this pathobiont could be important in the pathophysiology of these diseases. For example, *E. coli pks+* strains are able to induce development of CRC in various animal models including *III10*^{-/-} and *Apc*^{min/+} mice⁵. The cancer promoting activity of these *E. coli* strains depend on the presence of the *pks* island since genetic deletion of the island prevents carcinogenesis¹. Mechanistically, *pks*-derived colibactin causes double strand DNA damage in human and murine cells, an event that could lead to genetic instability and ultimately carcinogenesis. At the genetic level, the *pks* island encodes for polyketide synthases (PKS; *clbC,I,O*), nonribosomal peptide synthetases (NRPS; *clbH,J,N*), hybrid NRPS-PKSs (*clbB,K*), a transporter (*clbM*), a prodrug processing peptidase (*clbP*) a self-defense protein encoded by *clbS* and additional genes with proposed or unknown functions (*clbA,D-G,L*). Crystal structures for some of these proteins have been elucidated (*clbM*, *clbP*) and selective small inhibitors could be generated based on this information. The specificity of these structures and associated microbial functions represents a clear advantage for therapeutic intervention as inhibitors are unlikely to trigger host toxicity.

In addition to targeting the production of specific, virulent products, the administration of natural products or natural product-derived entities that affect microbe/host and microbe/microbe interactions and thus population is an attractive possibility. A recent example, linaclotide, a drug targeting irritable bowel syndrome and constipation disorders, is a derivative of the *E. coli* produced heat stable enterotoxin. To successfully implement any approach, knowledge of the molecular basis of host/microbe interactions and a thorough understanding of the metabolome is necessary.

Conclusion

Growing evidence indicates that the microbiota is implicated in intestinal pathologies, especially IBD and CRC. Emerging bacterial candidates among the dysbiotic community have been identified and their pro-carcinogenic activities validated in preclinical models. Although mechanisms by which these microorganisms promote intestinal pathologies are slow to emerge, it has become clear that the microbiota and associated microbiome could represent a potential therapeutic target. Harnessing the therapeutic potential of the microbiome represents an exciting and promising area of research for IBD and CRC.

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Figure 1. Modulation of the gut microbiota could alleviate disease states

Genetic and environmental factors could disrupt (red arrow) the healthy state of the intestinal microbiota (eubiosis) implicated in the maintenance of host homeostasis and promote microbial dysbiosis, a state associated with development of IBD and CRC. Strategies to attenuate microbial-derived deleterious activities are diverse and include diet, targeting specific bacteria (antibiotics) or virulence factors, introduction of bacteria or communities and manipulation of host-microbe/microbe-microbe interactions (blue arrow). These interventions may not lead to a complete reestablishment of a eubiosis state, but rather remove deleterious activities responsible for disease state.