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The gut microbiome: an unexpected player in cancer immunity

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Abstract

Numerous independent studies link gut microbiota composition and disease and imply a causal role of select commensal microbes in disease etiology. In the gut, commensal microbiota or pathobionts secrete metabolites that underlie pathological conditions, often impacting proximal tissues and gaining access to the bloodstream. Here we focus on extrinsic and intrinsic factors affecting composition of gut microbiota and their impact on the immune system, as a key driver of anti-tumor immunity. In discussing exciting advances relevant to microbiome-tumor interaction, we note existing knowledge gaps that need to be filled to advance basic and clinical research initiatives.

Introduction

One of the surprising discoveries in medical research in the past decade is the crucial role played by gut microbiota in numerous fundamental physiological and developmental processes [1–3]. Accordingly, it is not unanticipated that perturbation of normal gut microbiota contributes to diverse pathological conditions, including neurodegenerative diseases (Alzheimer's and Parkinson's diseases), immune and inflammatory diseases (inflammatory bowel disease [IBD], multiple sclerosis), behavioral disorders (autism), obesity [4], cardiovascular disease [5], and cancer [6,7]. Among these relationships, the interplay of gut microbiota with the immune system has received the most attention, probably due to the myriad of pathophysiological processes affected, including even cognitive function and behavior [8,9]. A growing number of studies report identification of specific bacterial populations within the gut microbiota potentially linked to host cellular pathways and processes. Yet, our mechanistic understanding of gut microbiota-dependent physiological changes remains limited, and large gaps are yet to be filled to enable advanced basic and clinical evaluations.

In this arena we can now pose three important but unanswered questions. They include: to what extent and how do environmental and genetic factors [10] influence the composition and function of gut microbiota? How does gut microbiota composition influence the host? Which host proximal and distal tissues are most impacted by gut microbiota and how? Given current knowledge that gut microbiota modulates immune responses, and also our

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appreciation of the effectiveness of immune checkpoint therapies [11,12], we address these questions in the context of this gut microbiota - immune response axis.

Factors shaping the composition of microbiota

Immune homeostasis is maintained *via* interactions of commensal gut bacteria [13]. Intrinsic and extrinsic factors influence microbiota composition and hence impact physiological and pathological processes. Intrinsic factors include genetic events, such as mutations, gene rearrangements, gene amplification, and chromosomal changes, each affecting cellular homeostasis in the gut and its underlying immune cell populations. Environmental factors, such as diet [14], stress [15], jet-lag [16], sleep quality [17], exercise [18], and chronic disease (e.g., obesity, viral infections, IBD, multiple sclerosis, and type 1 and 2 diabetes) also influence gut microbiota composition.

While diet and life style impact gut microbiota composition, antibiotics, chemotherapies, and gastrointestinal infections are factors with an immediate and significant effect on gut microbiota composition. Immediate modulation of gut microbiota community structure differentially effects the degree of their perturbation, resulting in dysbiosis with concomitant effects on local and systemic inflammation. However, we have not yet defined molecular mediators that underlie immediate response-associated changes. Correspondingly, host-derived factors (such as cytokines and chemokines) and bacterial factors (among them, short chain fatty acids (SCFAs), peptidoglycan components, LPS, flagellin and lipid metabolites) that mediate inflammatory responses likely directly drive changes in both the gut microenvironment and in distant tissues and organ systems.

Diet has the most stable and long-lasting effect in shaping gut microbiota composition [14]. Several studies report that dietary changes alter not only gut microbiota but the composition of gut-associated immune cells, which then can lead either to suppression of inflammation and amelioration of autoimmune disease (e.g. type 1 diabetes, multiple sclerosis, IBD), or to enhanced anti-tumor immunity and improved outcomes of cancer immunotherapy [19,20]. Yet, the precise changes in gut commensals over time, and their impact nearby tissues, (from intestinal epithelial cells to stem cells and immune cell components), remains to be defined.

Microbial syntrophy and metabolite production.

The stability and metabolic output of gut microbiota are primarily controlled by different community members producing numerous bioactive molecules, including vitamins B and K, anti-inflammatory lipids and amino acid metabolites (such as serotonin [8]). Among examples of bacterial cooperativity are production and metabolism of oligosaccharides, disaccharides, and monosaccharides from complex sugar polymers *via* activities of extracellular glycosyl hydrolases. Once generated, smaller sugar units cross-feed fermentative microbes that produce SCFAs such as lactate, butyrate, propionate, and acetate, each of which alters host physiology locally and systemically [21,22]. SCFAs contribute to intestinal homeostasis by modulating functions of intestinal epithelial cells and immune cells including T cells, macrophages, dendritic cells (DCs), and neutrophils [23]. Butyrate in particular, stimulates expansion of IL-10 producing Treg cells. While the mechanism through which SCFAs alter host cell transcriptional profiles via HDAC inhibition, is

reasonably well characterized, we lack such information for most of the presumptive bioactive molecules generated by gut microbiota. One conclusion emerging from recent publications is that changes enacted by gut microbiota result from a community effort, rather than from a single bacterial strain. Along these lines, a screen to identify species capable of stimulating T regulatory (Treg) cell expansion defined a consortium of 17 *Clostridia* species. However, individual members of this consortium were unable to induce the same effect [24]. The contribution of the 17 consortium members to the Treg phenotype, remains an intriguing question to address, along with the mechanism of their actual effect on Tregs. This important observation raises additional questions, namely what mechanisms underlie generation of a given bacterial equilibrium that impacts cellular process (given the dynamics of bacterial commensal interactions), what is the nature of material secreted from this bacterial community that impacts nearby cellular targets, and what is the impact of that secreted material on host target cells. Furthermore, do targeted cells initiate distinct antigen presentation programs to modulate the immune response, and would enhancing secretion of those factors regulate proximal and distal organ function?

Analysis of stool and blood metabolites in man indicated that approximately half of the 901 metabolites found in blood were also present in stool, suggesting that microbial metabolism contributes substantially to the levels of circulating metabolites [25]. After entering the circulation, microbial products can affect numerous distal tissues. For example, absorption of lipopolysaccharide (LPS) stimulates neuroinflammation in disorders such as Parkinson's and Alzheimer's diseases [26,27]. Likewise, microglial cells are reportedly chronically activated by LPS produced by *Enterobacteriaceae* [28]. Future studies are needed to elucidate which microbiota-produced metabolites and products are functionally dysregulated in human diseases as a way of devising therapeutic interventions. Devising strategies designed to improve the integrity of the gut barrier, in part by altering resident communities of microbiota, is also important, and could offer a new modality to attenuate inflammation induced by bacterially-secreted factors.

Studies with gnotobiotic mice have contributed to our knowledge of host immune–microbe interactions and the immunomodulatory effects of secreted microbial metabolites. Systematic mining of this information to develop immunotherapies has recently been reviewed [29] and is briefly discussed here. In mice, *Bacteroides fragilis* polysaccharide A secreted *via* outer membrane vesicles (OMVs) bind to Toll-like receptor 2 (TLR2) on Treg cells, resulting in Treg expansion and concomitant suppression of the proinflammatory Th17 response [30,31]. Similarly, feeding *Bifidobacterium infantis* to mice stimulated retinoic acid production by DCs, increasing TGF-β production and Treg expansion [32]. *Akkermansia muciniphila*, an abundant mucin-adherent species, produces multiple metabolites that affect the host. The relative abundance of this bacterial species correlates with host mucin production [33] and increased gut barrier integrity, possibly *via* OMV secretion and activation of enteroendocrine signaling pathways [34]. Would specific bacterial strains identified in different gnotobiotic mice elicit comparable effects in wildlings mice [35] or in heterogeneous mouse populations that better model the human microbiome are questions we must address before advancing related therapies to the clinic.

Neglected microbiota.

Most studies of gut microbiota have assessed the bacterial composition of feces as a surrogate for communities present in the distal colon. However, it is likely that microbes and host immune cells interact in multiple distinct regions of the gastrointestinal tract, including the small intestine [36]. For example, segmented filamentous bacteria (SFB) in the terminal ileum are well studied and known to stimulate host production of serum amyloid A, which stimulates Th17 cell expansion [37]. Moreover, spatially segregated microbiota along the length of the gastrointestinal tract likely carry out distinct metabolic processes, and metabolites uniquely produced in the small intestine also likely influence the host immune system. Further development of technologies capable of assessing dynamic changes in bacterial populations in different intestinal domains should enable better assessment of their impact on physiological processes.

Microbe–host communication.

Cross-talk between the immune system and intestinal microbiota alters immune cell function at local and distal sites. SCFAs, in particular, modulate production of retinoic acid by DCs [23], with subsequent effects on Tregs and Th17 cells [38]. Changes in the microbiota can disturb immune cell composition and function due to altered production of bacterial products (metabolites), or by impacting proximal epithelial cells, with concomitant effect on immune cell function. Once activated, epithelial cells can activate DCs and macrophages increase their capacity to present antigens to gut-associated intra-epithelial and lamina propria T cells and promote DC migration to Peyer's patches, mesenteric lymph nodes, and peripheral lymph nodes, where they activate naive T cells and trigger immune responses to microbial antigens at distant sites [39]. Activated T cells entering circulation from the gastrointestinal tract also localize at peripheral sites of inflammation/infection and in tumors, where they engage in either anti-inflammatory or anti-tumor immune responses. It is noteworthy that the dynamics and changes over time of gut microbiota-dependent activation of immune cell components through diverse mechanisms is largely unexplored, owing in part to technical limitations.

The impact of the gut microbiome on anti-tumor immunity.

The impact of gut microbiota on anti-tumor immunity and the effectiveness of immune checkpoint therapy (ICT) represent physiological changes along this novel regulatory axis [11,12,40–43]. We now appreciate how gut microbiota modulates the immune system, although most immunomodulatory gut microbiota products characterized to date are limited to a rather small number of metabolites or cell wall components. The absence of microbial antigens from this pool either presents a knowledge gap or indicates a lack of superantigens, aspects deserving experimental clarification. Future studies could identify cell-associated or secreted antigens that trigger immune responses *via* proximal and distal cells and tissues. Incorporation of bioactive molecules into OMVs also represents one mechanism underlying the gut microbiota's effect on organ function [44].

We recently documented a causative role for gut microbiota in anti-tumor immunity. Specifically, we mapped 11 bacterial strains that could induce anti-tumor immunity in gnotobiotic mice, resulting in melanoma growth inhibition. Changes that prompted

microbiota-dependent activation of the immune system were associated with altered unfolded protein response (UPR) signaling, which affected both intestinal epithelial cells and DCs within proximal lymph nodes. [45]. Deregulated UPR signaling coincided with patient responsiveness to immune checkpoint therapy, further illustrating the importance of this signaling pathway in defining anti-tumor immunity that is gut-microbiota dependent. These observations also raise a number of questions, among them the need to identify bacterial products that induce immune cell activities directly or indirectly (through their effect on intestinal epithelial cells). We also do not fully understand the role of the UPR in this process and the primary cell type(s) responsive to perturbed UPR signaling to trigger effective antitumor immunity phenotypes. While earlier studies note the importance of UPR component sXBP1 in DC activation along the anti-tumor immunity axes [46], the importance of the UPR in global physiological changes remains to be addressed. Cross talk between gut microbiota and surrounding cells is one possible mechanism that deserves careful examination. Anti-microbial peptides expressed by paneth cells or altered IgA, may alter bacterial abundance. Independent studies demonstrate that the composition of gut microbiota influences effectiveness of immune checkpoint therapy [41,42] [12]. Initial characterization of patients for changes in gut microbiota following immune checkpoint therapy identified overexpression of *A. muciniphila* in the gut of those responsive to ICI therapy. Accordingly, gnotobiotic mice transplanted with feces from ICI-responsive or -nonresponsive patients phenocopied patient responses: feces from patients that responded also caused comparably-treated mice to respond, whereas feces obtained from non-responsive patients did not elicit responses in transplanted mice. Likewise, *A. muciniphila* colonization was sufficient to prevent tumor growth in gnotobiotic mice transplanted with feces from an ICI-nonresponsive patient [12], confirming that gut microbiota plays a pivotal role in the success of ICI therapy.

Among bacterial species that directly modulate anti-tumor immunity in germ-free mice are *Bifidobacterium longum, A. muciniphila, B. fragilis, B. thetaiotaomicron*, and *B. rodentium* [11,12,40–43,45]. Most recently, studies with humanized gnotobiotic mice treated with selective antibiotics found that ampicillin-treated mice showed a more potent anti-tumor phenotype than did untreated mice [43]. Analysis of fecal isolates from these mice identified 11 strains that strongly increased the frequency of $CD8^+$ interferon-γ-producing cells in the gut and potentiated the effects of anti-PD-1 and anti-CTLA-4 antibodies on tumor growth. The 11 strains included multiple, phylogenetically unrelated species, among them *Bacteroides, Parabacteroides, Alistipes*, and uncharacterized *Ruminococcaceae* [42].

Microbiota-based therapy?

Microbiota-based therapeutics will likely rely on two strategies: remediation of pathogenic dysbiosis and targeted alteration of host signaling *via* modulation of gut microbiota. Pathogenic dysbiosis, exemplified by colorectal cancer, involves activities of a small number of taxa that contribute to disease initiation, progression, or treatment outcome. Bacteriophage therapy promoting elimination of pathobionts associated with disease may prove highly efficacious but remain largely untested. Targeted alteration of host signaling *via* modulation of gut microbiota through diet, prebiotics, probiotics, and fecal microbiome transplantation (FMT) may represent achievable strategies to promote select beneficial host–

microbe interactions. Yet, as we acquire greater understanding, we recognize the complexity and variability in human microbiota, an observation that hinders immediate effective translation of currently available knowledge. As such, potential use of an individual's data to tailor personalized gut-based therapies is appealing [47,48] but requires that we gain better understanding of the dynamics underlying gut microbiota commensals abundance and location in response to external cues. Also essential for clinical translation of current knowledge is an understanding of bacterial byproducts that impact the immune system as well as proximal and distal tissues. Additional advances in the engraftment efficiency of fecal microbiome transplants will be required to enable this potentially powerful strategy to provide maximal therapeutic benefits [49].

Conclusions

In the Introduction we posed three questions that – once addressed – would advance our understanding and ability to translate studies of gut microbiota; in discussing these questions we recognize that many gaps remain to be filled in the years to come. Nonetheless, important tools are being developed to help us address these questions, including powerful computer simulations that predict the dynamics of complex taxa [50–52] and imaging tools for real time monitoring of population abundance [53]. Future studies will define factors that control the microbiota population in terms of population dynamics and abundance in distinct intestinal locations and how diet and/or factors secreted or presented on intestinal epithelial cells alter gut microbiota. It is now essential that we understand precisely how gut microbiota impacts cellular physiology and affects the immune system in proximal and distal organs and possibly impacts neurophysiology. The years ahead should prove exciting as we advance these studies to therapies benefitting patients.

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Highlights

- Changes in gut microbiota composition are implicated in disease
- Gut microbiota composition impacts immune system function
- Extrinsic and intrinsic factors govern relative abundance of gut microbiota commensals
- Manipulation of gut microbiota could impact anti-tumor immunity