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Advances in understanding the interaction between the gut microbiota and adaptive mucosal immune responses

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Abstract

Commensal gut bacteria are necessary for the complete development of mucosal innate and adaptive immunity and thus may influence intestinal and systemic immune disorders. Recent work has advanced our understanding of this association by identification of a single taxon of the murine microbiota which can stimulate T-cell development and differentiation. It is hoped that further characterization of the mechanisms involved will enable targeted manipulation of the microbiota-immune system relationship.

Introduction and context

Eukaryotes have been living in intimate contact with prokaryotes throughout the course of evolution. Especially in the context of the gut, the host has developed highly conserved interrelated systems to protect itself from pathogenic attack whilst allowing beneficial microbes – symbionts – to thrive. Past study of primordial immune mechanisms conserved in non-vertebrates has richly informed our understanding of the activation (and suppression) of innate immune networks. As adaptive immunity is restricted to vertebrates, our appreciation of how gut commensal communities interact with mucosal and systemic adaptive immunity is less understood.

The gut/mucosal arm of the adaptive immune system provides humoral and cell-mediated immunity against ingested antigens and luminal organisms and is localized predominantly in the small bowel. Effector lymphocytes are diffusely distributed in the lamina propria (LP) or in isolated lymphoid follicles or are organized into discrete structures termed Peyer's patches, which are essentially mucosal lymph nodes overlaid with a specialized epithelial cell type, the M cell, which possesses the endocytic machinery for uptake of particulate antigens

from the gut lumen. Members of the normal flora, along with non-viable particulate antigens and all-too-viable pathogens, are continually being sampled by the M cells and perhaps other portals for processing by local dendritic cells or macrophages and subsequent education and activation of effector B and T cells [1].

The microbiota is clearly involved in the anatomic and functional development of mucosal immunity [2]. Peyer's patches are grossly hypoplastic and IgA responses are reduced in germ-free animals. It is also known that germ-free animals have reduced total CD4⁺ T-cell populations and an inappropriate balance of T_H-cell subsets [3], which can be moderated within weeks upon colonization with a representative member of the normal flora (*Bacteroides fragilis*) [4] via dendritic cell recognition of a specific polysaccharide (polysaccharide A) component of *B. fragilis* [5]. Interestingly, the intestinal LP in healthy animals was shown to be a major location of a unique population of interleukin-17-producing CD4⁺ T cells (T_H17 cells) distinct from T_H1- or T_H2-cell lineages [6,7]. This work has spawned an explosion of interest in the development and functions of T_H17 cells in health and disease, especially in the gastrointestinal tract. While T_H17 cells are increased in

inflamed intestinal tissue, it remains unclear whether these cells are pathogenic or protective during intestinal inflammation; additionally, the mechanisms driving their development and differentiation are now only beginning to emerge [8].

Major recent advances

Analyses in germ-free mice as well as antibiotic-treated conventional mice have shown that the intestinal microbiota can drive the development of T_H17 cells in the murine intestine [9,10]. The mechanism by which the intestinal microbiota induces T_H17 cells is not via the classical Toll-like receptor adaptor molecules MyD88 or Trif, but potentially via ATP generation. To begin to probe which components of the diverse microbiota may preferentially induce T_H17 cells, Ivanov *et al.* [11] performed an immunophenotypic comparison of the same mouse strain (B6) obtained from two commercial vendors (Taconic, Tarrytown, NY, USA, and The Jackson Laboratory, Bar Harbor, ME, USA) and found that the mice from The Jackson Laboratory showed a remarkable lack of T_H17 cells in the LP. Interestingly, transfer of Taconic flora (by direct gavage of fecal flora or by cohousing) to the mice from The Jackson Laboratory resulted in the induction of LP T_H17 cells, indicating a stark difference in the immunostimulatory potential of the distinct microbiota. This observation has been further developed in two recent papers by Ivanov *et al.* [11] and Gaboriau-Routhiau *et al.* [12], both reaching the surprising conclusion that T-cell development in general and T_H17 differentiation in particular are largely induced by the action of a single (or at least limited) number of bacterial taxa.

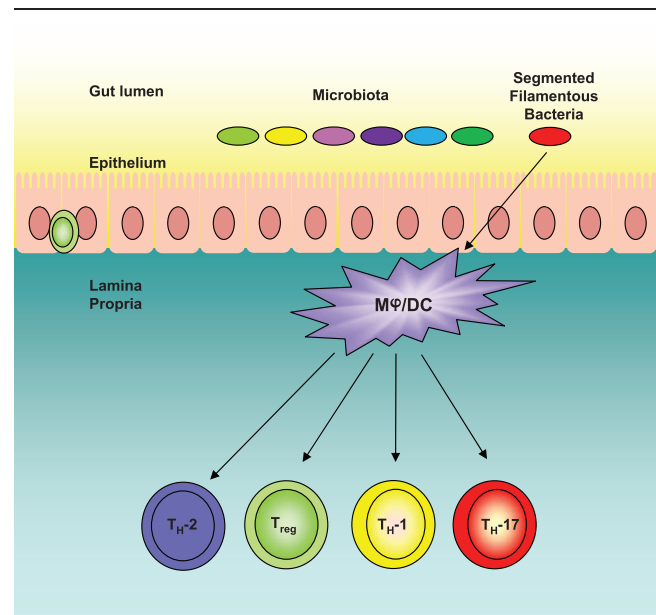
In the paper of Ivanov and colleagues [11], the authors exploited the Phylochip (Affymetrix, Santa Clara, CA, USA) – a 16s ribosomal microarray platform that serves as a massive (300,000 probe) parallel survey of microbial taxa – and identified segmented filamentous bacteria (SFB), a non-culturable spore-forming Gram-positive Clostridia-related species present in B6 mice from Taconic, but not The Jackson Laboratory. With the use of germ-free mice or Jackson Laboratory-sourced mice colonized ('conventionalized') with SFB, this group studied T_H17 differentiation in LP lymphocyte populations and expression profiling to show that SFB could recapitulate the inductive effects of the intact Taconic microbiota [11]. An independent group headed by Gaboriau-Routhiau also used an expression profiling approach to characterize host responses of germ-free mice conventionalized with normal murine microbiota and found distinct patterns of innate (inflammatory) gene expression and adaptive immune stimulation (LP T-cell maturation). This signature of normal immune

development was not induced by candidate mono-associated microbiota representatives or complex normal human microflora [12]; however, the host immune response pattern to normal murine microflora could be recapitulated by SFB as a mono-associated strain, further implicating this taxon as a primary driver of adaptive immune development (Figure 1).

Future directions

Though intriguing, these findings raise many important questions. SFB are not cultivable and must be maintained in monocultured mice [13] and introduced to other mice by cohousing. Thus, further characterization of the SFB is obviously necessary; sequencing of their genome will be eagerly anticipated, as will be culture techniques that may allow them to be more readily introduced into test systems. It will be interesting to see what other taxa can mediate the immune stimulatory phenotype and whether there is a specific ligand (microbial-associated molecular pattern, or MAMP) present on a subset (perhaps a very limited subset) of commensals. Conversely, what are the specific receptors that the host uses to perceive this functional class of

Figure 1. Intestinal microflora modulates mucosal immune responses



Recent reports implicate segmented filamentous bacteria (SFB) as the major component of the commensal microbiota which modulates mucosal T-cell development/responses. SFB, in particular, are potent inducers of T_H17 differentiation. The mechanisms by which these bacteria direct T-cell differentiation are poorly understood at present but may include direct interactions with intestinal epithelial cells, dendritic cells (DC), or macrophages (Mφ) (or all three). T_{reg} , regulatory T cells.

microbe and which cell types in specific regions of the intestine sense SFB in order to direct adaptive immunity? In directing T_H -cell differentiation, do SFB and other commensal bacteria directly interact with LP dendritic cells and macrophages that augment T_H17 and T_{reg} (regulatory T) responses [14-17] or do they induce changes in intestinal epithelial cells that in turn imprint dendritic cells with this capacity [18]? Are SFB invasive to epithelial cells? It is also clearly important to identify the human SFB equivalent(s). As potential targets for modification, SFB may offer a clue to the identification of bacteria that could be added to (or suppressed from) the microflora to accrue benefits such as altered immune regulation relevant to human disorders such as inflammatory bowel disease and systemic autoimmunity.

Abbreviations

LP, lamina propria; SFB, segmented filamentous bacteria; T_H17 , interleukin-17-producing $CD4^+$ T (cell).

Competing interests

The authors declare that they have no competing interests.

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