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SEGMENTED FILAMENTOUS BACTERIUM: FROM MUTUALISM TO PATHOLOGY?

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INTRODUCTION

The mammalian intestine is colonized by a considerable and complex community of bacteria which develop with their host mutualistic interactions (*Backhed* et al., 2005). To cope with this massive bacterial load, eukaryotic host have evolved a finely tuned intestinal immune barrier that maintains intestinal homeostasis. Studies comparing germfree and gnotobiotic animals have highlighted how the post-natal maturation of this immune barrier is driven and tuned by the microbiota (reviewed in: *Hooper* and *Macpherson*, 2010; *Lee* and *Mazmanian*, 2010). These studies have also shown that individual bacteria may differentially affect the balance between pro- and anti-inflammatory responses in the intestine and beyond (reviewed in: *Cerf-Bensussan* and *Gaboriau-Routhiau*, 2010; *Round* and *Mazmanian*, 2009). Yet, it is now obvious that the impact of the microbiota will depend on the immune status of the host.

INFLUENCE OF SFB ON THE PRO-INFLAMMATORY/REGULATORY BALANCE IN THE GUT

Colonization of germfree mice by complex mouse microbiota results in the simultaneous induction of pro-inflammatory and regulatory responses (*Gaboriau-Routhiau* et al., 2009; *Geuking* et al., 2011). Recent works have stressed the important regulatory function of Foxp3+ regulatory T (Treg) cells in the colonic mucosa to limit the expansion of inflammatory T cell subsets, possibly via the production of IL-10 (*Atarashi* et al., 2011; *Geuking* et al., 2011). Some strains of bacteria, notably *Bacteroides fragilis*, emerged as prominent inducers of intestinal Treg cells and IL-10 secretion. Accordingly, colonisation by the latter bacteria could prevent the development of inflammation in mouse models of colitis (*Mazmanian* et al., 2008; *Round* et al., 2011; *Round* and *Mazmanian*, 2010). In contrast, other strains, the prototype of which is Segmented Filamentous Bacteria (SFB) can exert a much broader impact on the gut immune system.

SFB are Clostridia-related bacteria which settle in the rodent intestine at the time of weaning and tightly adhere to ileal epithelial cells (and to Peyer's patches) during the first weeks of colonization. As a possible consequence of their adherence to the ileal mucosa and Peyer's patches, SFB can

strongly stimulate postnatal maturation of mouse intestinal immune responses. SFB efficiently activate the expansion of intestinal IgA-producing plasma cells and the recruitment of intra-epithelial lymphocytes (*Klaasen* et al., 1993; *Talham* et al., 1999; *Umesaki* et al., 1995). SFB also induce the differentiation of a broad spectrum of innate and of pro- and anti-inflammatory T cell responses (*Gaboriau-Routhiau* et al., 2009). Notably, mice colonized by a microbiota that does not contain SFB, lack intestinal Th17 cells (*Gaboriau-Routhiau* et al., 2009; *Ivanov* et al., 2009) and cannot control infection by *Citrobacter rodentium* (*Ivanov* et al., 2009). As highlighted by J. Snel in this issue, colonization by SFB can thus benefit to the host by stimulating an efficient intestinal barrier which opposes invasion by enteropathogens. Yet, the beneficial pro-inflammatory effect of SFB observed in immune-competent hosts is possible only when counterbalanced by a regulatory response that maintains "physiological inflammation" (or controlled inflammation) critical for intestinal homeostasis. Such benefit is lost in hosts with impaired immunoregulation. Thus, in severe combined immunodeficient (SCID) mice transferred with naive CD4+ T cells (a model where regulatory T cells are absent), colonization by SFB promoted the onset of colitis (*Stepankova* et al., 2007). The deleterious role of SFB was however only observed when mice were simultaneously colonized by a specific pathogen free (SPF) microbiota, underscoring the fact that SFB is not *per se* a pathogen and that additional signals from the microbiota are necessary to trigger deleterious intestinal inflammation in this model.

IMPACT OF THE MICROBIOTA AND OF SFB OUTSIDE THE GUT

There is ample evidence that the intestinal microbiota can influence the peripheral immune system. Thus, comparison between conventional and germfree mice have shown that spleens of germfree animals contain fewer and smaller germinal centres (*Macpherson* and *Harris*, 2004) and a decreased number of CD4+ T cells with a skewed Th2-type profile (*Dobber* et al., 1992; *Mazmanian* et al., 2005). Yet, specific responses to bacterial antigens, as reflected by specific serum IgG or specific proliferative responses of spleen CD4+ T cells against bacterial antigens, were only observed in hosts with defective intestinal immune barrier and were associated with increased bacterial translocation into the spleen (*Konrad* et al., 2006; *Macpherson* and *Uhr*, 2004; *Slack* et al., 2009). Altogether, these results suggest that, in immunocompetent hosts, bacterial products (but not bacteria) may cross the intestinal barrier and exert an adjuvant effect on peripheral responses. Accordingly, peptidoglycan was shown to reach the bloodstream and bone marrow, and activate bactericidal activity of neutrophils through stimulation of their innate immune receptors (*Clarke* et al., 2010). Translocation of lipopolysaccharide, favoured by lipid-rich diet, has been associated with inflammation in adipose tissue and onset of metabolic disorders (*Cani* et al., 2008). Along the same line, oral administration of the capsular polysaccharide A of *Bacteroides fragilis* could recapitulate the effect of colonization of germfree mice by this bacterium, i.e. increase the number of T cells in the spleen and correct the Th1/Th2 imbalance (*Mazmanian* et al., 2005).

The role of the microbiota on systemic immunity has also been recently addressed in various experimental disease models in either competent or immunocompromised hosts. This role varies according to models (reviewed in: *Cerf-Bensussan* and *Gaboriau-Routhiau*, 2010). Several severe models of autoimmunity affecting central tolerance developed independently of the microbiota. In contrast, a protective effect of the microbiota was observed in the models of collagen-induced arthritis (*Breban* et al., 1993) and of non-obese diabetic (NOD) mice-associated type 1 diabetes (*Wen* et al., 2008). Interestingly, reduced sensitivity to type 1 diabetes was observed in female NOD mice only when SFB was present in their faecal microbiota, and protection was ascribed to the induction of IL-17-producing T cells in the small intestinal lamina propria of SFB-positive females (*Kriegel* et al., 2011). Yet, the reduced sensitivity to diabetes observed in males was neither associated with SFB detection nor with lamina propria Th17 response, suggesting that complex host-microbiota interactions control the onset of diabetes in NOD mice.

Contrasting with these data, the microbiota promoted the onset of autoimmunity in other mouse models. Thus, inflammatory arthritis in transgenic K/BxN mice and experimental autoimmune encephalomyelitis (EAE) induced by myelin-derived proteins were attenuated in germfree mice compared to mice colonized with SPF microbiota (*Lee* et al., 2010; *Wu* et al., 2010). In both models, mono-colonization with SFB could largely recapitulate the impact of the SPF microbiota. In EAE, the deleterious impact of SFB was associated with a strong adjuvant effect on the immune system, as illustrated by a simultaneous increase in pro-inflammatory (IL-17, IFNγ) and regulatory T cell responses, notably in the spinal cord (*Lee* et al., 2010). In K/BxN mice, the arthritis results from an uncontrolled pro-inflammatory Th17 response in the periphery, that drives the production of auto-antibodies and deposition of immune complexes in the joints (*Wu* et al., 2010). SFB, alike an SPF microbiota, stimulated a strong increase in the number of spleen Th17 cells, which may partly derived from the intestinal compartment (*Wu* et al., 2010). This model however precludes the efficient induction of regulatory T cells. Altogether, these data indicate that the microbiota, and notably SFB, can influence the onset of autoimmune diseases outside the gut. The impact of the microbiota and of SFB, however, largely depends on the host immune status and/or on the mechanisms of the diseases.

CONCLUSION

In the complex cross-talk between the host and its microbiota some bacteria, such as SFB, have emerged as key drivers of the physiological inflammation that maintains intestinal homeostasis. However, the equilibrium between the host and the microbiota is fragile and SFB can become a risk factor for disease development when host immunoregulatory mechanisms are impaired. It will be interesting to identify an SFB-like bacterium in the human microbiota and examine how this bacterium might contribute to human health and disease.

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