

Gut commensal flora: tolerance and homeostasis

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Abstract

Commensal microorganisms are not ignored by the intestinal immune system. Recent evidence shows that commensals actively participate in maintaining intestinal immune homeostasis by interacting with intestinal epithelial cells and delivering tolerogenic signals that are transmitted to the underlying cells of the immune system.

Introduction and context

If we consider that our body is composed of ten times more microbial cells than mammalian cells, it becomes clear that microbes are required for the body to function properly [1]. Microbial genomes encode metabolic functions that humans have not fully evolved, including the ability to extract energy and nutrients from food. Microbes are also required for the correct development of the mucosal immune system. Germ-free rodents have smaller Peyer's patches (the organized lymphoid tissue of the intestine), negligible numbers of isolated lymphoid follicles and intraepithelial lymphocytes, and produce little secretory immunoglobulin A (sIgA) [2,3]. Furthermore, the induction and maintenance of oral tolerance (immunological tolerance of potential antigens that enter the body via the gastrointestinal tract) also requires microbial colonization of the gut early in life [2]. All this shows that the presence of microbes in the gut is not ignored; rather, 'sensing' of bacteria is important for the development and maintenance of intestinal immune homeostasis.

How bacteria interact with their host at mucosal surfaces is still an open question. The first cell types that encounter bacteria are probably the epithelial cells. It is not clear, however, whether this is a direct interaction, as epithelial cells are covered by a mucus layer that imposes a physical and electrically charged barrier to bacteria. Bacteria in the gut can also be bound by secretory IgA, which impedes their direct binding to epithelial cells.

Commensal microorganisms could also interact directly with immune-system cells, in particular with dendritic cells, which have been shown to cross the epithelial layer and interact directly with the contents of the gut lumen [4]. So we are left with several questions. What are the outcomes of bacteria-epithelium or bacteria-dendritic cell interactions? Do bacteria act directly on immune cells or indirectly via epithelial cells? How is immunological tolerance induced by commensals?

Major recent advances

It was initially believed that epithelial cells and commensals would not interact with each other because the commensals would not be able to access pattern-recognition receptors (PRR) on the epithelial cells that recognize common microbial molecules. Indeed, PRRs (such as the Toll-like receptors (TLRs)) were thought to be expressed either intracellularly or exclusively on the basolateral membrane (that is, not exposed to the lumen) in epithelial cells - and would thus be inaccessible to non-invasive commensal bacteria. In the absence of this initial recognition, intestinal bacteria would simply be ignored by the mucosal immune system. Accumulating evidence is challenging this view, in part at least.

It has recently been found that TLRs are not restricted to the interior or the basolateral surface of epithelial cells. TLR-9 for instance, which is only expressed intracellularly in hematopoietic cells, is expressed on both apical and

basolateral surfaces of epithelial cells [5]. And the outcome of its engagement on these two surfaces is different [6]. Engagement of TLR-9 on the apical surface leads to only partial activation of the transcription factor NF- κ B, a master regulator of inflammatory responses. In contrast, basolateral engagement of TLR-9 leads to nuclear translocation of NF- κ B and activation of the signaling cascade that leads to the production of inflammatory cytokines. Interestingly, binding of apical TLR-9 inhibits the activation cascade induced by engagement of basolateral TLR-9. This indicates that as long as bacteria can bind to TLR-9 only from 'outside' of the body, the net response is inhibition of the inflammatory cascade. In agreement with this, engagement of TLRs in mice protects against experimental colitis [7–9] whereas mice lacking TLR-5 develop spontaneous colitis [10]. A final piece of evidence is that intestinal epithelial cells become tolerant to bacterial lipopolysaccharide (LPS) very early in an animal's life [11], indicating that bacteria-derived products are not ignored. Epigenetic mechanisms could be responsible for inducing and maintaining this tolerance by selectively inhibiting the expression of inflammatory genes and sparing those involved in the antimicrobial response [12]. Together, these findings indicate that epithelial cells do not ignore commensals, but rather that their 'sensing' of them actively protects against an inflammatory response.

What are the mechanisms underlying this protection? Incubation of human epithelial cells with non-invasive strains of *Salmonella enteritidis* leads to a reduction of NF- κ B activation and translocation to the nucleus [13,14], and interaction with an abundant commensal bacterium, *Bacteroides thetaiotaomicron*, leads to premature egress of the RelA subunit of NF- κ B from the nucleus [15]. Interestingly, inhibition of epithelial cell activation could also be indirect and depend on the concentrations of reactive oxygen species (ROS) induced by commensals [16]. ROS are responsible for inactivation of the catalytic cysteine residue of the protein Ubc12, resulting in impaired ubiquitination of the NF- κ B inhibitor I κ B and thus in impaired NF- κ B activation [16]. Finally, it has been demonstrated that lipid A isolated from Gram-negative members of the phylum Bacteroidetes that abundantly populate the gut display either non-agonistic or antagonistic properties on TLR-4 [17].

A net result of epithelial cell-bacteria interaction is the inhibition of inflammatory signaling cascades via blockade of NF- κ B activation. However, to avoid inflammation, it is not sufficient just to inhibit epithelial cell activation. As mentioned above, dendritic cells can also interact with luminal bacteria. Dendritic cells express

tight junction proteins and establish tight-junction-like structures with adjacent epithelial cells for direct bacterial uptake [4]. Dendritic cells could thus sense bacteria and be activated by commensals. Activated dendritic cells would then be able to get into draining lymph nodes, where they might activate T cells. Systemic immunity to commensal bacteria does not occur, however [18], which means that intraepithelial gut dendritic cells are somehow unable to initiate immunity. This is due to the specialized properties of resident gut dendritic cells, which differ from those of dendritic cells isolated from other lymphoid organs such as the spleen (reviewed in [19,20]). Dendritic cells isolated from the lamina propria (LP) of the gut wall express very few Toll-like receptors, or are unresponsive to their ligands [21,22]. After inflammatory stimuli or bacterial infection, LP dendritic cells release the cytokine interleukin-10 (IL-10), but fail to induce the Th1 type of effector T cells [20–25]; also, a population of LP dendritic cells can drive the differentiation of Th17 T cells [26] and support IgA production [22]. This subpopulation expresses CD70 and several receptors for ATP, which is involved in conferring the ability of DCs to promote Th17 differentiation [27]. Interestingly, ATP is released by commensal bacteria, indicated by the fact that gut cavities of germ-free mice are devoid of ATP and consequently Th17 cells are reduced in numbers in the lamina propria. Along similar lines, cytophaga-flavobacter-bacteroidetes (CFB) have been shown to favour the development of Th17 cells [28], while a major member of the Firmicutes family, *Faecalibacterium prausnitzii*, offers its host protection against Crohn's disease, as it has been shown that a reduction in the number of this bacteria is associated with a higher risk of postoperative recurrence of ileal disease [29].

It would be interesting to understand the capacity of *F. prausnitzii* to produce ATP. A subtype of CD103-positive mesenteric lymph node (MLN) or LP dendritic cells is involved in T-cell-mediated regulation of experimental colitis [30], the differentiation of CD25⁺ Foxp3⁺ T regulatory cells (T_{reg}) [31,32], and in imparting gut-homing properties to T cells in both mice [33] and humans [34]. Interestingly, CD103⁺ and CD103⁻ intestinal dendritic cells seem to colonize different areas of the intestinal mucosa - the LP of the villi and the solitary intestinal lymphoid tissues, respectively [34]. Peyer's patch DCs release IL-6 [35] and retinoic acid and drive the development of gut-homing IgA-secreting B cells [36] and T cells [37–39]. Together, these findings suggest that gut dendritic cells are more prone to drive non-inflammatory or tolerogenic responses. These could be the 'default' responses in the gut, aimed at sparing the induction of immune responses to commensal bacteria.

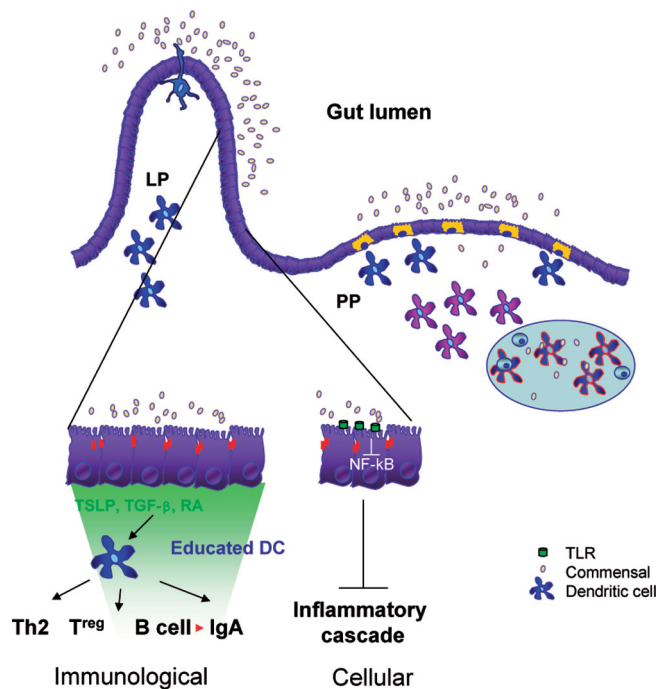
These specialized functions of intestinal dendritic cells are in part imprinted by the local microenvironment. In particular, epithelial-cell-derived factors are important in the differentiation of non-inflammatory dendritic cells [40]. Intestinal epithelial cells release the cytokine thymic stromal lymphopoietin (TSLP), which inhibits IL-12 production by dendritic cells in response to bacteria and polarizes the T-cell response towards Th2 cells [27]. Similarly, impairment of NF- κ B signaling in intestinal epithelial cells in mice by deletion of the protein kinase IKK β results in decreased expression of TSLP and the upregulation of dendritic cell-derived subunit p40 of IL-12 [41]. This is associated with an inability to drive Th2 cells and to control whipworm (*Trichuris*) infection [41]. TSLP is also involved in driving the production of tolerogenic dendritic cells in humans (I.D. Iliev and M.R., unpublished work), while TSLP-conditioned dendritic cells drive the production of T_{reg} in the mouse [42]. Intestinal epithelial cells can also release transforming growth factor- β (TGF β) and retinoic acid, which are responsible for promoting the development of CD103⁺ tolerogenic dendritic cells from CD103⁻ cells (I.D. Iliev and M.R., unpublished work). In addition, TSLP favors the release of the cytokines BAFF and APRIL by epithelial cell-conditioned dendritic cells and supports IgA class switching directly in the lamina propria [43,44] in humans. Notably, incubation of bacteria with epithelial cells *in vitro* results in differing levels of TSLP and TGF β 1 upregulation, depending on the nature of the bacteria, with Gram-negative species being the most effective [45]. This suggests that bacteria can indirectly control dendritic cell activation via their interaction with epithelial cells through the release of 'educating' factors.

Hence, the interaction between commensals and epithelial cells has two important consequences. First, it inhibits the generation of inflammatory responses that would normally occur when 'virgin' epithelial cells meet bacteria. Second, it induces the release of educating factors that drive the differentiation of tolerogenic dendritic cells whose function is to promote the differentiation of T regulatory cells and IgA-producing B cells (Figure 1).

Future directions

It is becoming clear that the interaction of commensals with epithelial cells and dendritic cells is fundamental to keep peace at mucosal surfaces. However, this symbiosis has risks as well as benefits. Indeed, the homeostatic balance is based on very fragile interactions. Sudden variations in the microbiota or in the immune response could lead to the development of a colitogenic flora. This has recently been demonstrated in mice lacking the gene

Figure 1. Commensals participate in intestinal homeostasis.



On the left-hand side of the figure, the interaction of commensals with intestinal epithelial cells results in inhibition of NF- κ B activation and blockade of the inflammatory cascade (cellular events) and the release of 'educating' factors (TGF- β and TSLP, immunological events). Binding of commensals or their components to Toll-like receptors (TLRs) on the apical faces of epithelial cells can result in inhibition of NF- κ B activation by blocking κ B degradation or favoring the egress of RelA from the nucleus. TSLP, TGF β and retinoic acid (RA) released by activated epithelial cells educate non-inflammatory and tolerogenic resident dendritic cells (dark blue cells), which can extend their processes into the intestinal lumen. These cells enable sampling of non-harmful commensal bacteria and presentation of their antigens and may be involved in tolerance induction under homeostatic conditions. The educated dendritic cells are shown driving the development of Th2 or T_{reg} cells (pale blue cells) in intestinal lymphoid tissues such as mesenteric lymph nodes (not shown) and Peyer's patches (right hand side). They also drive B-cell class switch recombination to IgA both in the lamina propria and in Peyer's Patches. Immunity to pathogenic bacteria is initiated by non-educated dendritic cells (purple cells). LP, lamina propria; PP, Peyer's patch.

for the transcription factor T-bet (*T-bet*^{-/-}) [46], in which the inability to control production of the inflammatory cytokine tumor necrosis factor (TNF) results in infectious colitis. It is still not clear how bacteria interact with epithelial cells - whether they are able to hydrolyze mucus and reach the apical surface - or whether bacterial products are sufficient to induce tolerance. Furthermore, commensals are also likely to be coated with secretory immunoglobulins and might interact with epithelial cells only via IgA receptors whose nature is still unknown.

Thus we are still far from having dissected out the mechanisms responsible for the fine balance between inflammation and tolerance. *In vivo* studies dissecting out the role of mucins, antimicrobial peptides and cell-cell interactions are required for a better understanding of bacteria-host interactions.

Competing interests

The author declares that she has no competing interests.

Abbreviations

IgA, immunoglobulin A; PRR, pattern recognition receptor; TLR, Toll-like receptor; ROS, reactive oxygen species; dendritic cells; LP, lamina propria; MLN, mesenteric lymph node; TSLP, thymic stromal lymphopoietin.

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