REVIEWS

Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut

David Artis

Abstract | Mucosal surfaces such as the intestinal tract are continuously exposed to both potential pathogens and beneficial commensal microorganisms. This creates a requirement for a homeostatic balance between tolerance and immunity that represents a unique regulatory challenge to the mucosal immune system. Recent findings suggest that intestinal epithelial cells, although once considered a simple physical barrier, are a crucial cell lineage for maintaining intestinal immune homeostasis. This Review discusses recent findings that identify a cardinal role for epithelial cells in sampling the intestinal microenvironment, discriminating pathogenic and commensal microorganisms and influencing the function of antigen-presenting cells and lymphocytes.

Gut-associated lymphoid tissues
(GALTs). Lymphoid structures and aggregates associated with the intestinal mucosa, specifically the tonsils, Peyer's patches, lymphoid follicles, appendix or coecal patch and mesenteric lymph nodes. They are enriched in conventional and unconventional lymphocytes and specialized dendritic-cell and macrophage subsets.

Immunological hyporesponsiveness
A diminished degree of responsiveness to antigen or other stimulation. It is an active process, not simply a passive lack of response.

Department of Pathobiology, University of Pennsylvania, Philadelphia, Philadelphia 19104-4539, USA.
e-mail: dartis@vet.upenn.edu
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The mucosal surfaces of the mammalian skin, airways, reproductive tract and intestine are in direct contact with the external environment and therefore are susceptible to colonization and invasion by viruses, bacteria, fungi and parasites. To combat these potentially lethal pathogens, mammals have evolved elaborate mucosa-associated lymphoid tissues that are rich in cells of the innate and adaptive immune system. However, mucosal surfaces are continuously exposed to innocuous environmental antigens and 'commensal' microorganisms that live in a symbiotic or mutually beneficial relationship with their mammalian hosts.

In the face of constant immunological stimulation, the requirement for a homeostatic balance between tolerance and immunity represents a unique regulatory challenge for the mucosal immune system. This challenge is arguably most acute in the intestinal tract, the largest mucosal surface of the human body. The intestinal surface covers an area of approximately 100 m^2 and is lined by a single layer of columnar intestinal epithelial cells (IECs) that forms a barrier between the intestinal lumen and host connective tissue. In addition to the constant exposure to dietary and environmental antigens, the adult human intestine is home to an estimated 10^{14} commensal bacteria[1]. In fact, communities of bacteria in the intestine form one of the most densely populated microbial habitats known in biology[2]. In the face of this massive antigenic challenge, immune cells distributed throughout the gut-associated lymphoid tissues (GALTs), although they frequently exhibit hallmarks of recent activation, must remain immunologically hyporesponsive to commensal bacteria while retaining their capacity to respond to a pathogenic challenge.

The necessity to regulate immune responses to commensal bacteria is exemplified by evidence that dysregulation of the balance between tolerance and immunity can contribute to the pathogenesis of numerous inflammatory conditions, including food allergies, inflammatory bowel disease (IBD) and intestinal cancer[3–5]. Paradoxically, experimental manipulation of the commensal bacteria in multiple species has revealed an essential role for microbial communities in the normal physiological functions of the intestine and in the development of the GALTs. Therefore, under steady-state conditions, the mammalian immune system recognizes commensal bacteria and elicits basal or tonic signals in the absence of full activation of the innate and adaptive immune responses[6].

Defining the molecular and cellular mechanisms that regulate immunological hyporesponsiveness is an area of intense research. Recent studies in which various functional capacities of IECs have been targeted, either by the generation of bone-marrow chimaeras or by cell-lineage-specific deletion, have demonstrated that IECs, which were once considered a simple physical barrier to the external environment, are integral to both the discrimination of pathogenic and commensal bacteria and the subsequent regulation of immune responses in the intestinal microenvironment. The anatomical features of the intestinal immune system and functions of dendritic

Tight junctions
Specialized intercellular junctions that seal the apical epithelium. They are formed by several proteins including occludin and claudin, in which two plasma membranes form a sealing gasket around a cell (also known as zonula occludens). Tight junctions prevent fluid moving through the intercellular gaps and prevent lateral diffusion of membrane proteins between the apical and basolateral membranes.

Brush border
The microvilli-covered surface found on the apical surface of epithelial cells that is coated in a rich glycocalyx of mucus and other glycoproteins. The microvilli contain many of the digestive enzymes and transporter systems that are involved in the metabolism and uptake of dietary materials, and provides a large surface area for absorption. Early anatomists noted that this structure appeared very much like the bristles of a paintbrush, hence the name brush borders.

cells (DCs) and regulatory T cells in the intestine have been discussed elsewhere recently[7–10], therefore the central themes discussed in this Review are current concepts of how microorganisms are sampled in the intestine, how IECs discriminate between commensal and pathogenic bacteria, and how epithelial-cell-derived factors, through effects on antigen-presenting cells and lymphocytes, regulate intestinal immune homeostasis.

The intestinal epithelial-cell barrier

The intestinal epithelium exhibits numerous physical adaptations to separate the host connective tissue from the external environment. Intercellular tight junctions that prevent paracellular traffic are coupled with actin-rich microvillar extensions that create a brush border on the apical surface of the epithelium that impedes microbial attachment and invasion (FIG. 1)[11]. This physical barrier is reinforced by numerous biochemical adaptations such as a glycocalyx formed by the secretion and apical attachment of a heavily glycosylated mucin-rich layer by goblet cells. Together, these form a viscous and relatively impermeable sheet on the apical surface of the epithelium[12,13] (reviewed in REF. 14). IECs also secrete a broad range of antimicrobial peptides, including defensins, cathelicidins and calprotectins. Most molecules in this diverse group of peptides are rich in hydrophobic and basic residues that confer broad-spectrum antimicrobial properties through the formation of pores in the bacterial cell wall[15–18]. These adaptations are consistent with the view that IECs, in addition to promoting digestion and absorption of nutrients, perform essential barrier functions that obstruct the entry of commensal and pathogenic bacteria into the underlying lamina propria (FIG. 1).

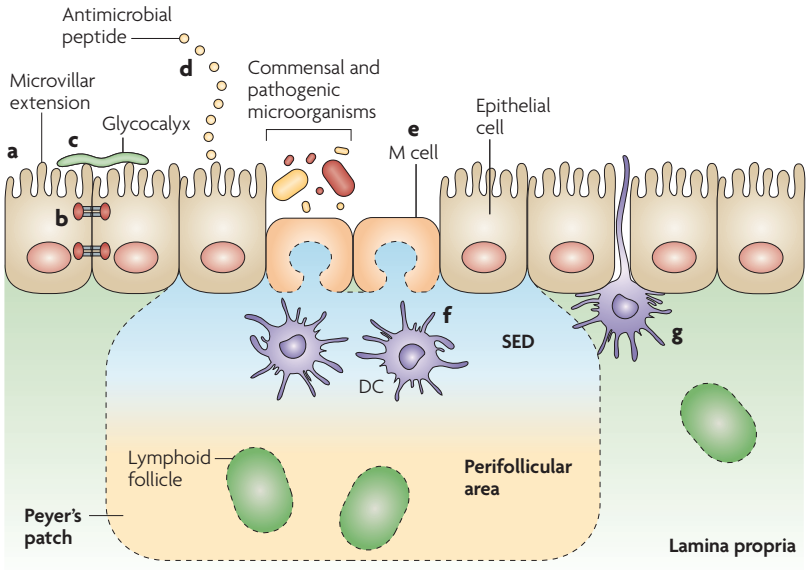

Figure 1 | **The intestinal epithelial-cell barrier.** Simple columnar epithelial cells exhibit physical and biochemical adaptations to maintain barrier integrity including actin-rich microvillar extensions (**a**), epithelial-cell tight junctions (**b**), apically attached and secreted mucins that form a glycocalyx (**c**) and the production of various antimicrobial peptides (**d**). Specialized intestinal epithelial cells known as M (microfold) cells overlie Peyer's patches and lymphoid follicles to facilitate luminal sampling. M cells exhibit reduced mucin secretion and have modified apical and basolateral surfaces (**e**) to promote uptake and transport of luminal contents to professional antigen-presenting cells that inhabit the subepithelial dome (SED) of the Peyer's patches and lymphoid follicles (**f**). Specialized dendritic cell (DC) subsets can also extend dendrites between the tight junctions of intestinal epithelial cells to sample luminal contents (**g**).

Adaptations of the GALT for microbial sampling in the intestine. The basal influence of commensal bacteria on intestinal homeostasis, coupled with rapid recognition of pathogens, suggests that the contents of the intestinal lumen are constantly sampled. The physical constraints that the epithelial-cell barrier imparts on sampling the luminal space are overcome by specialized lymphoid structures, including the Peyer's patches in the small intestine, and isolated lymphoid follicles that are embedded in the lamina propria throughout the length of the intestinal tract (FIG. 1). These inductive sites of the GALT contribute to maintaining the balance of immunity and tolerance at the mucosal surface. The follicle-associated epithelium that overlies Peyer's patches and lymphoid follicles contains specialized M (microfold) cells that can sample antigens and microorganisms and deliver them by transcytosis to the subepithelial dome, an area that is populated by professional antigen-presenting cells, including a number of DC subsets[7,10,19,20].

In addition to these structures, specialized intestinal DCs located in the lamina propria of the small intestine express tight-junction proteins and can extend their dendrites between epithelial-cell tight junctions to directly sample the luminal microenvironment (FIG. 1). Rescigno *et al.* showed that myeloid DCs in the intestine can extend their dendrites into the intestinal lumen and directly acquire luminal bacteria[21], a process that is dependent on CX_3C-chemokine receptor 1 (CX_3CR1)[22,23] and is influenced by the composition of the commensal bacteria[24]. Accordingly *Cx3cr1*$^{-/-}$ mice exhibit defective luminal sampling by DCs and impaired resistance to *Salmonella typhimurium* infection, implicating a crucial role for luminal sampling in the development of protective immune responses in the gut[22].

DCs are known to efficiently acquire antigens from the intestinal lumen[25–29] and express a wide range of pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs) that recognize microbial components[30,31]. IECs also express TLRs as well as intracellular nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)[32,33]. In general, ligation of TLRs and NLRs results in the activation of innate immune responses, inducing the expression of pro-inflammatory cytokines, chemokines and antimicrobial peptides[30,31,34]. The expression of PRRs by IECs coupled with their proximity to commensal and pathogenic bacteria suggest that IECs, beyond their function as a physical barrier, could influence the initiation and regulation of antimicrobial immune responses. The collective capacity of IECs and specialized DC subsets to directly sample the luminal space and recognize bacteria through PRRs provokes the fundamental question as to why these cells do not elicit innate and adaptive immune responses to commensal bacteria.

Box 1 | **Acquisition and composition of commensal communities**

Immediately after birth, mammals begin to acquire commensal microorganisms from their surroundings. The intestine is transformed from a sterile environment to a diverse microbial ecosystem that is densely populated by members of all three domains of life — eukarya, archaea and bacteria. Commensal bacteria are the dominant and best-studied type of microorganism present. The density of bacteria is relatively low in the stomach and proximal small intestine (approximately 10^3–10^5 organisms per ml of luminal contents) but rises to approximately 10^9–10^{12} per ml of luminal contents in the distal small intestine and colon. The greatest diversity of bacteria is in the colon, where anaerobic species, including *Bacteroides* spp., *Eubacterium* spp., *Bifidobacterium* spp., *Fusobacterium* spp. and *Peptostreptococcus* spp. predominate, whereas aerobic bacterial species including *Escherichia coli*, *Lactobacillus* spp. *and Enterobacter* spp. are less abundant[1,40,155,156].

Analysis of the temporal and spatial kinetics of the acquisition of commensal bacteria, the factors that regulate this, and the degree of variation within and between individuals is only beginning to be understood. For example, longitudinal analysis of the diversity of commensal bacteria in newborns suggests that there is no deterministic or stereotyped pattern of acquisition. Instead, commensal bacteria appear to be acquired as a result of opportunistic colonization by particular species as a result of random environmental encounters[156]. Therefore, although there appears to be a remarkable degree of inter-individual variation, the composition of the microbiota within adults appears to be relatively stable over time[40,155,156]. Environmental and genetic factors have a major influence of the composition of commensal bacterial communities, whereas the influence of factors including mode of infant delivery and neonatal diet remain controversial[157–162]. The consequences of alterations in the acquisition and/or composition of commensal bacterial communities on mammalian development, normal physiology and susceptibility to disease are an active area of investigation.

Goblet cell
A differentiated epithelial cell that secretes mucus.

Lamina propria
Connective tissue that is found directly under the mucosal epithelial-cell surface of the gastrointestinal tract. It is traversed by blood and lymphoid vessels, physically supports epithelial cells through the basal membrane and is enriched in innate and adaptive immune cells.

Peyer's patches
Groups of lymphoid nodules identified by Peyer in 1677 that are present in the small intestine (usually the ileum). They occur massed together on the intestinal wall, opposite the line of attachment of the mesentery. Peyer's patches consist of a subepithelial dome area, B-cell follicles and interfollicular T-cell areas.

Pattern-recognition receptor
(PRR). A receptor that recognizes unique structures that are present at the surface of microorganisms. Signalling through PRRs leads to the production of pro-inflammatory cytokines and chemokines and to the expression of co-stimulatory molecules by antigen-presenting cells. The expression of co-stimulatory molecules, together with the presentation of antigenic peptides, by antigen-presenting cells couples innate immune recognition of pathogens with the activation of adaptive immune responses.

Angiogenesis
The development of new blood vessels from existing blood vessels.

Commensal bacteria

Acquisition and composition of commensal communities. All metazoan organisms have evolved a strategic alliance with commensal microorganisms. An estimated 10^{14} microorganisms composed of members of all three domains of life — the eukarya, archaea and bacteria — inhabit the intestinal lumen. Commensal bacteria are acquired shortly after birth and are reported to reach a density of 10^{12} per ml of luminal contents in the adult human large intestine[35] (BOX 1). Therefore, the numbers of commensal bacteria are 10 times greater than the combined number of somatic and stem cells in the human body[36–38]. In addition, the collective genetic material of commensal communities, termed the microbiome and which encompasses at least 500–1000 species, is thought to encode as much as 100 times the number of genes in the human genome[1,39,40].

The relationship between mammalian hosts and commensal bacteria is the product of millions of years of co-evolution and is a fundamentally symbiotic one. The mammalian intestine provides a hospitable microenvironment for bacteria, stable in temperature and rich in nutrients, and bacteria-derived signals are essential for normal intestinal physiology. For example, acquisition of commensal bacteria promotes angiogenesis, development of the intestinal epithelium and protection against tissue injury[36,41]. Commensal bacteria also facilitate digestion, absorption and storage of nutrients, such as plant material, that would otherwise be inaccessible to their mammalian hosts[1,41–46]. In addition, colonization of the intestine by beneficial bacterial communities, through occupation of this environmental niche, competition for nutrients and secretion of antimicrobial peptides, probably provides a degree of protection for the host against rapid colonization by pathogenic microorganisms[38,47,48].

Development and function of the immune system. The beneficial properties endowed by commensal bacteria on host physiology underlie the requirement for immune hyporesponsiveness to these microbial communities. Paradoxically, some degree of innate immune recognition of commensal bacteria is essential for normal development and function of the mucosal and peripheral immune system[6]. For example, mice reared under gnotobiotic or germ-free conditions exhibit numerous immunological defects. In the intestinal microenvironment of germ-free mice, the Peyer's patches are poorly formed and the composition of $CD4^+$ T cells and IgA-producing B cells in the lamina propria is altered compared with conventionally housed animals[6,49–52]. In addition, unconventional populations of T cells, including those that express the canonical Vα7.2–Jα33 or Vα19–Jα33 T-cell receptor (TCR) rearrangement are preferentially located in the gut lamina propria of humans and mice, respectively, and are absent in germ-free mice, suggesting that acquisition of commensal bacteria promotes the differentiation, recruitment and/or selective maintenance of these mucosa-associated invariant T cells[53]. In the periphery, the development of the defined follicular T- and B-cell areas of the spleen and peripheral lymph nodes is also impaired in germ-free mice (reviewed in REF. 52). The introduction of a single bacterial product isolated from *Bacteroides fragilis* — one of the dominant commensal bacterial species in mice — corrected the defects in the peripheral lymphoid compartment of germ-free mice[54], which demonstrates that signals from commensal bacteria have an essential role in the development of the peripheral and mucosal immune system. These observations indicate that molecular mechanisms must exist to facilitate the recognition of commensal bacteria and allow for a basal level of immune activation in order to programme gene-expression patterns that are required for the normal development and function of immune cells.

Commensal bacteria and disease. In addition to regulating the development of the intestinal and systemic immune system, recent studies suggest that alterations in the acquisition or composition of commensal bacteria may trigger or influence the course of various metabolic and inflammatory disease states. For example,

the relative proportion of commensals of the order Bacteroidales is reduced in obese individuals and in inbred mouse strains that are genetically predisposed to obesity[1,55,56]. The commensal bacteria isolated from obese mice were more effective at releasing calories from food, and these bacteria transmitted this trait to germ-free mice, resulting in greater deposition of adipose tissue.

Alterations in the composition of intestinal commensal communities may also influence susceptibility to, or progression of, immune-mediated diseases. For example, chronic inflammation is linked to alterations in commensal bacteria in patient groups and murine models of airway inflammation, arthritis, IBD and necrotizing enterocolitis[43,57–64]. Whether alterations in microbial communities that exist during these disease states are the cause or consequence of inflammation remains unclear. Nevertheless, these correlations highlight the complexity of host–commensal interactions in both health and disease.

The remarkable cross-regulation that operates between the intestinal commensals and the host immune system is highlighted by a recent study showing that the immune status of the host can influence the composition of commensal communities. Dysregulation of nuclear factor-κB (NF-κB)-dependent expression of antimicrobial peptides in the intestinal epithelium of *Drosophila melanogaster* resulted in the outgrowth of one 'pathogenic' commensal community, which led to the death of the host[65]. The ability of host immune responses to influence the structure of commensal communities is conserved across species. For example, mice that are deficient in IgA or activation-induced cytidine deaminase (AID), and that therefore lack hypermutated IgA, exhibit aberrant expansion of defined commensal species[66,67]. Garret *et al.* also identified an unexpected role for T-bet — a member of the T-box transcription factor family that regulates the development and function of cells of the immune system — in influencing the composition of commensal populations[64]. In mice lacking an adaptive immune system, deletion of T-bet created a colonic microenvironment that appeared to promote the outgrowth of 'colitogenic' bacteria and the development of severe intestinal inflammation that shared characteristics with ulcerative colitis in humans. Importantly, following transfer to immunosufficient hosts, this population of bacteria could drive intestinal inflammation[64].

Taken together, these studies suggest that the mammalian immune system exerts a significant environmental pressure on commensal bacteria. Immune pressure could act either directly on defined taxonomic groups of bacteria or indirectly by influencing the selection and maintenance of dominant commensal species through the creation of favourable microenvironments for specific microbial communities. As a consequence, selective immune pressure can result in the outgrowth of potentially pathogenic commensal species with detrimental consequences for the host.

Microbial recognition by IECs: a declared truce

The fundamental influence of commensal bacteria on the development and function of the immune system, coupled with evidence that alterations in the acquisition or composition of the microbial community can influence disease susceptibility, supports a model in which components of the mammalian innate immune system are constantly sampling the dynamic composition of commensal communities. As discussed above, host IECs and DCs express a comprehensive array of PRRs and are in direct contact with luminal bacteria[27–29,68]. However, delineating the molecular mechanisms that orchestrate the recognition of commensal bacteria while preventing the generation of innate and adaptive immune responses against them remains an area of intense research.

A traditional explanation for the differential immune recognition of pathogenic versus commensal bacteria is that only pathogenic bacteria that have evolved mechanisms to invade the epithelial-cell barrier and survive within host tissues would be recognized by cells of the innate immune system located in the Peyer's patches, lymphoid follicles or lamina propria. For example, pathogenic bacteria such as *Listeria monocytogenes*, *S. typhimurium* or *Shigella* spp. maintain genes organized within so-called 'pathogenicity islands' that encode virulence factors that allow pathogen adherence, invasion and subsequent subjugation of the host cell machinery thereby enabling efficient entry and dissemination in the host[69–73]. By contrast, commensal bacteria, which lack virulence or pathogenicity genes, would not survive in host cells or disseminate throughout tissues and therefore fail to elicit innate and adaptive immune responses. However, it is clear that IECs — in addition to providing a physical and biochemical barrier to invading pathogens — express a wide range of PRRs that can recognize bacterial factors, such as lipopolysaccharide (LPS), lipoproteins, flagellin and unmethylated CpG-containing DNA[30,31,34] (FIG. 2). Therefore, even in the absence of pathogenicity-island genes, IECs have the capacity to recognize and respond to commensal bacteria.

Recent *in vivo* studies using IEC-specific deletion of genes or the generation of bone-marrow chimeric mice in which the non-haematopoietic-cell compartment, which includes epithelial cells, are specifically targeted, suggest a crucial role for IECs in innate immune recognition of commensal bacteria and in the regulation of the intestinal immune system. For example, IECs deficient in SIGIRR (single-immunoglobulin-domain-containing interleukin-1 receptor (IL-1R)-related protein), which is a negative regulator of TLR and IL-1R signalling[74], exhibited elevated expression of pro-inflammatory genes, and *Sigirr*$^{-/-}$ mice were more susceptible to commensal-dependent intestinal inflammation dependent on bacteria. Moreover, IEC-specific expression of a *Sigirr* transgene in SIGIRR-deficient mice reduced susceptibility to intestinal inflammation[75–77], indicating that the intrinsic expression of SIGIRR by IECs regulates the communication between commensal bacteria and the mammalian immune system.

In addition, deletion of TLR4, NOD1 or myeloid differentiation primary-response gene 88 (MyD88) in non-haematopoietic cells resulted in impaired immunity to bacterial infections, implicating IEC-mediated recognition of bacteria as a key component in the development of protective immunity in the gastrointestinal

Adipose tissue
A type of connective tissue that is specialized for the storage of neutral lipids.

Activation-induced cytidine deaminase
(AID). An RNA-editing enzyme that is necessary for somatic hypermutation and class-switch recombination.

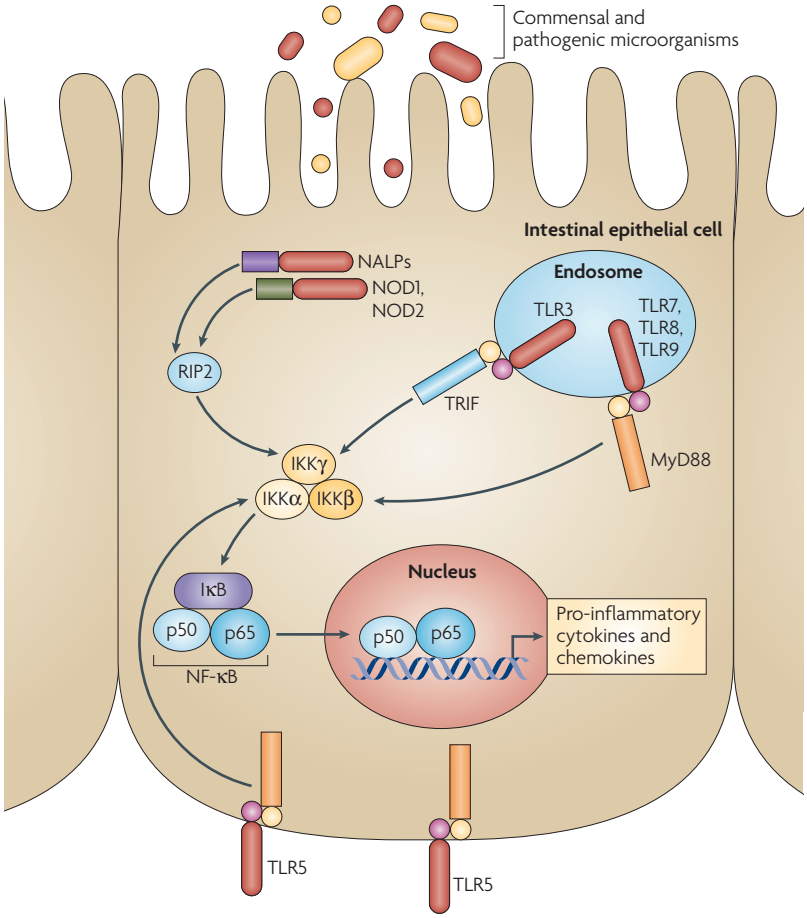

Figure 2 | **Microbial recognition by intestinal epithelial cells.** Pattern-recognition receptors, including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), are expressed by most intestinal epithelial cells. TLRs recognize conserved microbial-associated molecular motifs including bacterial-derived lipopolysaccharide (LPS), lipoproteins, flagellin and unmethylated CpG-containing DNA. TLR ligation results in the recruitment of adaptor proteins such as MyD88 (myeloid differentiation primary-response gene 88), and TRIF (TIR-domain-containing adaptor protein inducing interferon-β) and subsequent activation of several signalling modules including the nuclear factor-κB (NF-κB) and mitogen-activated protein (MAP) kinase pathways. NLRs, including NOD1 and NOD2, recognize bacterial-derived peptidoglycan, a main component of the bacterial cell wall, and activate NF-κB and MAP kinases through the recruitment of receptor-interacting protein 2 (RIP2). Activation of PRRs promotes a cascade of signalling events that result in expression of pro-inflammatory cytokines and chemokines. Basolateral and intracellular localization of most PRRs in or on intestinal epithelial cells is proposed as one mechanism to limit the recognition of commensal bacteria and initiation of innate immune responses. IκB, inhibitor of NF-κB; IKK, IκB kinase; NALPs, NACHT-, LRR- and pyrin-domain-containing proteins.

microenvironment[78–80]. IEC-specific deletion of components of the IKK (inhibitor of NF-κB (IκB) kinase) complex, an upstream kinase required for NF-κB activation[81], also resulted in enhanced expression of pro-inflammatory cytokines and susceptibility to intestinal inflammation in multiple disease models[82–86], suggesting that recognition of commensal bacteria influences gene expression in IECs and susceptibility to intestinal inflammation. Supporting these findings in mice, polymorphisms in the human *NOD2* gene are associated with reduced expression of antimicrobial peptides and severe intestinal inflammation in patients with Crohn's disease[87–90].

Polymorphisms
Single-nucleotide differences in the sequence of genes that represent allelic variants. These differences might lead to altered structure and/or altered expression of gene products, ultimately leading to pathology.

Distribution of PRRs on IECs. Several mechanisms have been proposed to explain IEC-mediated discrimination between commensal and pathogenic bacteria, including the selective distribution of TLRs and NLRs, and the active modulation of IEC function by commensal bacteria. Regulated expression and location of TLRs and NLRs in IECs has been proposed to allow innate immune recognition of commensal bacteria and tonic signalling in IECs but restrain innate immune responses. For example, under steady-state conditions, IECs are reported to express little or no TLR2, TLR4 and CD14, minimizing the recognition of bacterial LPS[91–93]. In addition, the subcellular localization of other TLRs and NLRs in IECs may facilitate the discrimination of commensal versus pathogenic bacteria. For example, TLR5, which recognizes bacterial flagellin, has been reported to be expressed exclusively on the basolateral surfaces of IECs[94], and TLR3, TLR7, TLR8 and TLR9 are expressed in intracellular endosomal organelles[31]. In addition, NLRs are found in the cytoplasm of IECs, similar to their localization in other cell types (FIG. 2)[18,33]. These intracellular PRRs would not encounter luminal commensal bacteria or those attached to the apical surface of IECs but would only recognize pathogenic bacteria that actively invade the epithelial-cell barrier. However, as outlined above, recognition of commensal bacteria probably by both IECs[41,82–86] and haematopoietic cells[95,96] does occur and is essential for normal intestinal homeostasis. In IECs, recognition of commensal bacteria must occur without initiating a cascade of innate immune responses, which suggests that the regulated expression and basolateral distribution of PRRs cannot be the only mechanism that controls the discrimination of commensal and pathogenic bacteria.

Commensal bacteria modulate IEC function. Commensal bacteria can actively modulate signalling in mammalian IECs, providing another mechanism through which they are recognized by IECs in the absence of innate immune responses. For example, although pathogenic bacteria induce TLR- and NLR-mediated NF-κB activation, *in vitro* studies have demonstrated that commensal bacteria such as *Lactobacillus* spp., *Bacteroides* spp. and *Escherichia coli* (as well as attenuated strains of bacteria that are normally pathogenic, such as *Salmonella* spp.) can actively inhibit this pathway. In resting cells, NF-κB is sequestered in the cytoplasm by IκB, which masks the nuclear localization sequences of NF-κB. Following receptor stimulation, classical NF-κB activation results from the phosphorylation of IκB, which targets it for ubiquitylation and subsequent proteasomal degradation[97]. Commensal bacteria can inhibit the degradation of IκB following phosphorylation by disrupting the host-cell machinery that controls the processes of ubiquitylation and degradation[98–100] (FIG. 3).

In addition, members of the genus *Bacteroides* can also inhibit the NF-κB pathway by hijacking the peroxisome-proliferation-activated receptor-γ (PPARγ) pathway. PPARγ is a member of the nuclear hormone receptor family that can inhibit the transcriptional activity of NF-κB by associating with RelA, a transcriptionally active subunit of NF-κB, and promoting the export of the complex from the host nucleus to the cytoplasm.

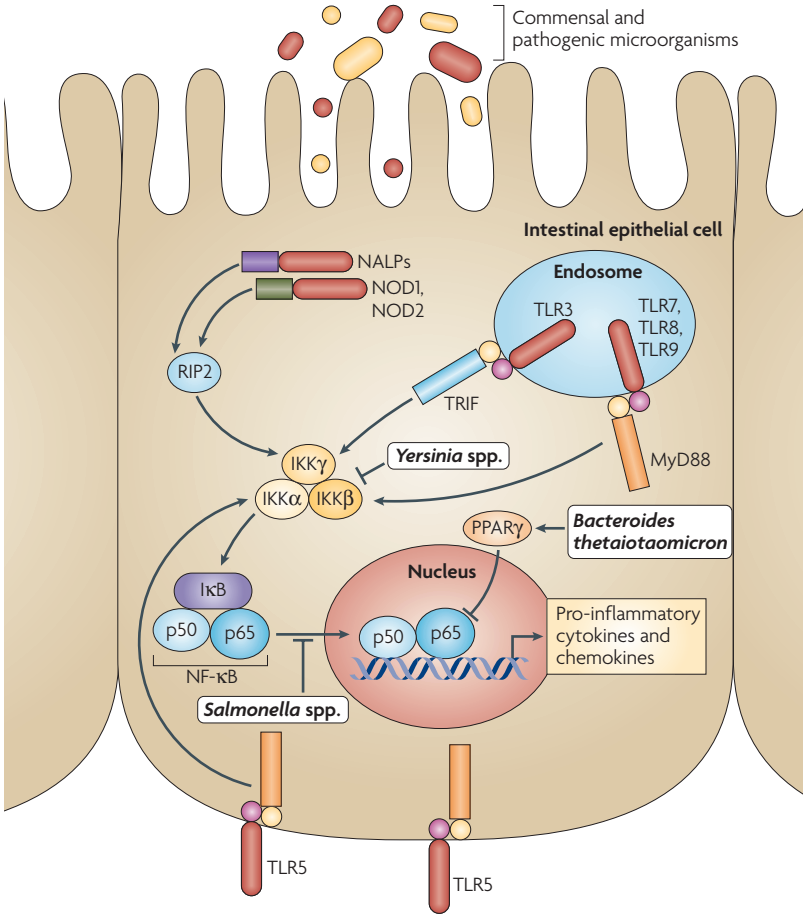

Figure 3 | **Commensal bacteria regulate intestinal epithelial-cell gene expression.** In resting cells, nuclear factor-κB (NF-κB) is sequestered in the cytoplasm by inhibitor of NF-κB (IκB), which masks nuclear localization sequences. Following stimulation through Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), classical NF-κB activation is the result of IκB kinase (IKK)-mediated phosphorylation of IκB, which targets the inhibitor for ubiquitylation and subsequent proteasomal degradation. Commensal and attenuated pathogenic bacteria have been shown to inhibit innate signalling pathways in intestinal epithelial cells. For example, *Yersinia* spp. inhibit the NF-κB pathway at the levels of IκB phosphorylation, whereas attenuated *Salmonella* spp. block the polyubiquitylation and degradation of IκB that is required for efficient nuclear translocation of NF-κB. By contrast, *Bacteroides thetaiotaomicron* can also inhibit the NF-κB pathway by hijacking the peroxisome-proliferation-activated receptor-γ (PPARγ) pathway. MyD88, myeloid differentiation primary-response gene 88; NALP, NACHT-, LRR- and pyrin-domain-containing protein; RIP2, receptor-interacting protein 2; TRIF, TIR-domain-containing adaptor protein inducing interferon-β.

Bacteroides thetaiotaomicron induces PPARγ expression and promotes PPARγ-dependent cytoplasmic shuttling of NF-κB[101] (FIG. 3). It is important to note that most of these analyses were carried out using *in vitro* systems and future *in vivo* studies will be required to determine the functional significance of commensal-dependent regulation of IEC-intrinsic innate signalling pathways in the maintenance of homeostasis.

As mentioned above, commensal bacteria contribute to mammalian metabolism by digesting complex polysaccharides that would otherwise be inaccessible to mammals. In addition to contributing to nutrient extraction, commensal-derived metabolites can also impair innate immune responses and so aid in the maintenance of the commensal–host relationship. For example, digestion of starch by commensal bacteria creates short-chain fatty acids such as butyrate that can inhibit the expression of pro-inflammatory cytokines that are induced by commensal bacteria and augment the production of regulatory cytokines, such as IL-10 (REF. 102).

Collectively, these studies identify multiple adaptations that have evolved in both host IECs and commensal bacteria to facilitate the recognition of bacteria and basal activation of IECs while simultaneously limiting innate immune responses. This homeostatic balance in the epithelial-cell response is essential to preserve the symbiotic relationship between mammals and their commensal communities. Indeed, it is tempting to speculate that the dominant evolutionary pressure to evolve and retain PRRs in the mammalian genome was their role in the establishment of mutualism between mammals and their commensals, whereas the capacity of PRRs to promote innate immunity to pathogens is a secondary function that is only required in the presence of bacterial-derived virulence factors that promote systemic dissemination of pathogens.

Epithelial-cell regulation of immune-cell function

The consequences of altering the composition of the commensal bacterial communities or disrupting coordinate recognition and signalling in IECs for the development of intestinal inflammation provide a clear demonstration of the role that IECs have in the recognition of commensal bacteria and in the maintenance of intestinal immune homeostasis. In particular, disruption of IEC-intrinsic pathways required for innate recognition of commensals results in dysregulated innate and adaptive immune responses in mouse models of oral tolerance, IBD and immunity to infection[84–86,103]. However, subsets of DCs are capable of directly sampling the luminal microenvironment and there is evidence that in the steady state or during intestinal inflammation, bacteria-laden DCs can migrate to the mesenteric lymph nodes that drain the intestine[22,104]. But, why do these DC populations not recognize commensal bacteria as foreign and initiate a cascade of signalling events, resulting in the production of pro-inflammatory cytokines and adaptive immune responses? It is now clear that IECs, in addition to providing a physical barrier and first line of innate defence against pathogenic and commensal bacteria, can influence the function of antigen-presenting cells and lymphocytes in the intestinal microenvironment.

Epithelial regulation of DC and macrophage function. Several DC populations have been reported in mouse Peyer's patches and mesenteric lymph nodes[10,20,27,105–109]. In addition, a subset of myeloid DCs that are distinguished by their expression of CX_3CR1 are resident in the lamina propria of the jejunum and proximal ileum of the small intestine and have the capacity to extend their dendrites between the tight junctions of IECs to take up luminal bacteria[24,25,110–112]. *In vitro* studies have implicated IECs, through their secretion of cytokines, in the tissue-specific conditioning of DCs by limiting the pro-inflammatory cytokine production by these cells and maintaining intestinal immune homeostasis. Supporting these findings,

Ubiquitylation
The attachment of the small protein ubiquitin to lysine residues that are present in other proteins. This tags these proteins for rapid cellular degradation the proteasome.

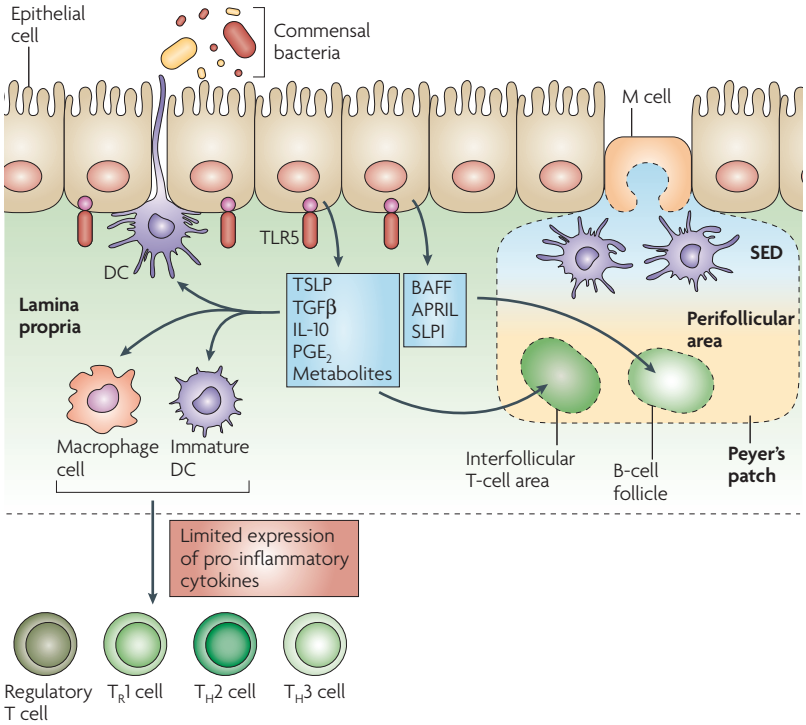

Figure 4 | **Intestinal epithelial cells regulate immune-cell function.** Basal recognition of commensal bacteria by intestinal epithelial cells (IECs) may influence the secretion of cytokines, including thymic stromal lymphopoietin (TSLP), transforming growth factor-β (TGFβ) and interleukin-10 (IL-10), that can directly influence the expression of pro-inflammatory cytokines by dendritic cell (DC) and macrophage populations that resident in the lamina propria and Peyer's patches. Signals derived from commensal bacteria may influence tissue-specific 'licensing' of accessory-cell functions resulting in the expansion and/or survival of T cells with regulatory capacities, including regulatory T cells, T regulatory type 1 (T_R1) cells, T helper 2 (T_H2) cells and T_H3 cells. In addition to TSLP, TGFβ and IL-10, other IEC-derived factors, including APRIL (a proliferation-inducing ligand), B-cell-activating factor (BAFF), secretory leukocyte peptidase inhibitor (SLPI), prostaglandin E_2 (PGE_2) and other metabolites have the capacity to directly regulate the functions of both antigen-presenting cells and lymphocytes in the intestinal microenvironment. TLR5, Toll-like receptor 5; SED, subepithelial dome.

in vivo deletion of NF-κB signalling specifically in IECs resulted in the dysregulated expression of DC-derived pro-inflammatory cytokines and the development of spontaneous and infection-induced intestinal inflammation[85,86], providing the first *in vivo* evidence of a crucial role for IECs in the conditioning of intestinal DC responses.

How do IECs regulate DC function? One mechanism is through the secretion of immunoregulatory molecules including thymic stromal lymphopoietin (TSLP), transforming growth factor-β (TGFβ) and prostaglandin E_2 (FIG. 4). TSLP is expressed by the epithelium of the Hassall's corpuscles of the thymus, where it activates myeloid DCs in the thymic medulla and these are in turn proposed to promote the positive selection of regulatory T cells[113]. Subsequent analysis revealed that epithelial cells expressed high levels of *Tslp* mRNA at most mucosal surfaces including the skin, airways and intestine. *Tslp* mRNA is constitutively expressed by IECs, although its expression by mucosal epithelial cells can be upregulated in response to a range of stimuli, including infection, inflammation and tissue injury[85,111,114–117], in an NF-κB-dependent manner[118]. A role for IEC-derived TSLP in extrathymic regulatory T-cell development was supported by the identification of mucosal-derived plasmacytoid DCs that can promote the differentiation of T cells with regulatory capacity[119].

Another subset of intestinal DCs has recently been shown to preferentially promote regulatory T-cell development. $CD103^+$ DCs isolated from the GALT were shown to express retinal dehydrogenase, an enzyme responsible for the metabolism of vitamin A. The vitamin A metabolite retinoic acid has been shown to be crucial for promoting the peripheral conversion of regulatory T cells by these DCs[120,121]. Whether IEC-derived factors such as TSLP influence vitamin A metabolism in DCs is unclear at present. However, a more prominent function for TSLP–TSLPR (TSLP receptor) interactions at mucosal sites appears to be in influencing the expression of pro-inflammatory cytokines and subsequent T helper (T_H)-cell differentiation. In *in vitro* studies, Rescigno and colleagues demonstrated that IEC-derived TSLP could limit the expression of IL-12 by DCs and limit their capacity to promote T_H1-cell differentiation. Moreover, IEC-mediated-conditioning promoted IL-10 production by activated DCs and enhanced their capacity to promote regulatory and T_H2-type cytokine responses[111,122]. Deletion of TSLPR in mice resulted in constitutive overexpression of IL-12p40 by intestinal DCs and in the inability of the host to generate protective T_H2-type cytokine responses following exposure to the nematode parasite *Trichuris muris*[85]. Consistent with these *in vivo* findings, overexpression of TSLP by keratinocytes of the skin or by airway epithelial cells results in T_H2-type cytokine-mediated pathologies at multiple mucosal surfaces[123–128].

IECs and stromal cells also produce abundant amounts of TGFβ in the intestine[129,130], another potent immunoregulatory cytokine that can inhibit NF-κB-dependent gene expression[131] and limit the expression of pro-inflammatory cytokines by macrophages[132] and DCs[133] (FIG. 4). In addition to the expression of immunoregulatory cytokines, IECs express a range of metabolic enzymes and intermediates, including indoleamine 2,3-dioxygenase (IDO) and cyclooxygenase-2 and its arachidonic-acid metabolite prostaglandin E_2, which can regulate multiple innate and adaptive immune-cell functions[134,135]. Metabolic by-products derived from commensal bacteria can also influence the expression of heat-shock proteins in IECs[136] that can have broad effects on IEC survival and on the expression of pro-inflammatory cytokines[137–140]. Although the possibility that IECs can directly regulate the functions of other innate cells such as granulocytes or natural killer (NK) cells remains to be examined, IEC-derived factors such as TSLP can also influence mast-cell activation[114], demonstrating that the ability of IECs to govern the function of innate immune cells is not limited to macrophages and DCs.

Epithelial-cell regulation of intestinal lymphocyte function. The majority of lymphocytes in the GALT exhibit hallmarks of recent activation yet remain hyporesponsive to commensal bacteria, suggesting the immunoregulatory effects of IECs and other tissue-specific signals act on effector cells. In addition to effects on macrophages

and DCs, there is increasing evidence that IEC-derived signals can positively and negatively regulate T- and B-cell functions in the intestine. Deletion of IKKβ exclusively in IECs resulted in dysregulated infection-induced T- and B-cell responses in the GALT[85], although whether these effects were direct or indirect is unclear at present. A role for activated IECs in directly regulating B-cell responses was shown through their secretion of B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL)[141,142] that favoured T-cell-independent IgA responses[143,144] (FIG. 4). Production of TSLP and IL-10 by IECs can also promote B-cell responses[141,142,145], a comprehensive discussion of which is covered in this issue[146].

In addition, IECs are in direct contact with intraepithelial lymphocytes and express all the molecular machinery required for antigen processing and presentation, including proteolytically active cathepsins, the invariant chain and MHC class II molecules[147]. *In vitro* studies showed that rodent IECs, although less potent than professional antigen-presenting cells, can process and present antigen through the MHC class II pathway[148–152]. Supporting a role in promoting T-cell responses, IECs isolated from patients with IBD express MHC class II molecules and can localize exogenous antigens to the late endosome on their basolateral surfaces[153]. However, the lack of co-stimulatory molecule expression by IECs[154] suggests IECs cannot prime naive T cells. Memory T cells exhibit less stringent requirements for co-stimulation, and therefore the influence of IEC-intrinsic antigen processing and presentation on the maintenance and/or functions of memory T cells may be more significant, although this hypothesis has yet to be investigated. Alternatively, antigen presentation by IECs in the absence of co-stimulation may promote local and systemic T-cell tolerance. Delivery of inhibitory or tolerogenic signals directly to T cells is consistent with the negatively regulatory influence of IECs on B-cell responses. For example, following activation IECs secrete the antimicrobial peptide secretory leukocyte peptidase inhibitor (SLPI) that inhibits NF-κB activation and can limit BAFF-induced immunoglobulin class switching in B cells[141].

Taken together, these studies highlight that IEC-mediated recognition of commensals results in remarkable changes in IEC-intrinsic gene expression associated with metabolic and immunological functions. Furthermore, IEC-derived regulatory signals control innate and adaptive immune-cell function in the intestinal microenvironment. Deciphering how commensal bacteria are recognized by IECs and whether IECs exhibit unique mechanisms to translate signals derived from commensal bacteria to regulate the functions of antigen-presenting cells and lymphocytes offers exciting future challenges and therapeutic prospects.

Future perspectives

Although still in it infancy, the experimental studies outlined in this Review, coupled with correlations in patient groups, collectively highlight the complexity of the relationship between commensal bacteria and the mammalian immune system. The emerging recognition of the relationship between commensal communities, the host immune system and susceptibility to inflammatory diseases emphasizes the need for a better understanding of the pathways that initiate and maintain host–bacterial symbiosis. The identification of a cardinal role of IECs as central mediators in these interactions will focus future efforts on delineating the molecular and cellular mechanisms through which IECs recognize commensals and how they coordinate intestinal immune homeostasis in health and disease.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
AID | CX$_3$CR1 | NOD1 | NOD2 | PPARγ | SIGIRR | TGFβ | TLR4 | TLR5 | TSLP

FURTHER INFORMATION

David Artis's homepage: http://www.med.upenn.edu/micro/faculty/artis.html

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