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Innate immunity in the small intestine

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Abstract

Purpose of review—This manuscript reviews the most recent publications on innate immunity in the small intestine. We will go over the innate immune receptors that act as sensors of microbial presence or cell injury, Paneth cells as the main epithelial cell type that secrete antimicrobial peptides, and mucosal production of IgA. In addition, we will give an update on examples of imbalance of the innate immune response resulting in clinical disease with the most relevant example being Crohn's disease.

Recent findings—Toll-like receptors (TLRs) are involved in B-cell homing to the intestine, rejection of small intestinal allografts and recruitment of mast cells. The TLR adaptor TRIF is necessary to activate innate immunity after *Yersinia enterocolitica* infection. Moreover, MyD88 is required to keep the intestinal microbiota under control and physically separated from the epithelium and RegIIIγ is responsible for the bacterial segregation from the lining epithelial cells. In Crohn's disease, ATG16L1 T300A variant promotes a pro-inflammatory response; and miR-196 downregulates a protective IRGM polymorphism leading to impaired clearance of adherent *Escherichia coli* in the intestine.

Summary—The intestine is continuously exposed to dietary and microbial antigens. The host has to maintain intestinal homeostasis to keep the commensal and pathogenic bacteria under control. Some of the mechanisms to do so are by expression of innate immune receptors, production of antimicrobial peptides, secretion of IgA or autophagy of intracellular bacteria. Unfortunately, in some cases the innate immune response fails to protect the host and chronic inflammation, transplant rejection, or other pathologies may occur.

Keywords

TLR; NOD; IgA; Paneth cell; microbiota; Crohn's disease

Introduction

The small intestine is the longest organ in our body and is critically important for the absorption of nutrients. The small intestine is most commonly affected by diseases such as Crohn's disease or chronic infection as a result of defects in the innate immune response. Because of the dependence of the host on adequate nutrient absorption, the small intestine must be able to protect against pathogenic infection but not interfere with this important process. Even bacterial colonization can be dangerous since commensal flora would de-conjugate bile salts and metabolize nutrients before the host has an opportunity to digest these nutrients. The bacterial load in the small intestine is low and it increases distally. Among the factors purported to keep the bacterial count low in the small intestine is:

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motility which prevents stasis of nutrients and bacteria, mucus which creates a barrier, and antibacterial molecules secreted by epithelial cells. The intestinal epithelium is composed of four cell lineages that come from a common stem cell progenitor: absorptive enterocytes, mucus-producing goblet cells, hormone-producing enteroendocrine cells, and Paneth cells which produce antimicrobial peptides. Beneath the epithelium is the lamina propria, where the macrophages and dendritic cells are largely responsible for the innate immune response in the mucosa. The aim of this manuscript is to review the latest publications on innate immunity of the small intestine, focusing special attention on the innate immune receptors and antimicrobial factors that keep bacteria under control preventing mucosal damage.

Microbial sensors of the intestinal innate immunity

Initiation of the innate immune response in the intestine is triggered by pathogen-recognition receptors (PRRs). These PRRs serve as sensors of pathogen-associated molecular patterns (PAMPs) from the intestinal lumen and damage-associated molecular patterns (DAMPs), which are intracellular molecules produced by the cell in response to an injury or a stress stimulus. The most studied PRRs are the toll-like receptors (TLRs). TLRs are transmembrane proteins that are typically expressed by intestinal epithelial cells either on the cell surface or in endosomes. PRRs are also expressed by other immune cells in the lamina propria, and they activate an inflammatory response characterized by NF-κB activation, cytokine production, and chemokine-medicated recruitment of acute inflammatory cells. TLR signaling in the intestine has been shown to be involved in epithelial cell proliferation [1, 2], IgA production [3], maintenance of tight junctions [4] and antimicrobial peptide expression – functions that are crucial for keeping a healthy epithelial barrier [5]. Because of the close proximity and high density of PAMPs in the intestinal lumen, a variety of mechanisms have evolved to protect against deregulated TLR-mediated inflammation in the absence of pathogens. The NLRs (nucleotide-binding domain leucine-rich repeat-containing receptors) are another class of innate immune receptors, which include nucleotide-binding oligomerization domain protein-1 (NOD1) and NOD2. Several NLRs can assemble multimolecular complexes in response to different stimuli, leading to the activation of inflammatory caspases, such as caspase-1. By analogy to the apoptosome, which activates apoptosis-inducing caspases, the NLR multimolecular complexes are called inflammasomes and they activate caspases necessary for propagating inflammatory signals [6, 7, 8].

The ligand for NOD2, also called CARD15 (C-terminal caspase recruitment domain 15), is muramyl dipeptide (MDP) derived from peptidoglycan common to both Gram-positive and Gram-negative bacteria. NOD2 is highly expressed in monocytes and Paneth cells [9]. Rehman et al. recently described that NOD2 is crucial for proper colonization of the intestinal microbiota. NOD2-deficient mice have an altered microbial population and an increased bacterial load in their stool and terminal ileum compared to wild type littermates [10].

NOD1 is expressed by intestinal epithelial cells and is required for recognition of invasive Gram-negative bacteria [11, 12]. The specific ligand recognized by NOD1 is found only in Gram-negative bacterial peptidoglycan. In addition to TLRs, invasive organisms may elicit an innate immune response from intestinal epithelial cells through intracellular NOD1. Gut-associated lymphoid tissue (GALT) (tonsils, lymphoid aggregates in colon, stomach, esophagus and appendix, Peyer's patches) is activated by the presence of Gram-negative commensal bacteria through NOD1 signaling [13]. Recently, NOD1 has been implicated as providing protection against the Gram-positive bacteria *Clostridium difficile* [14]. NOD1-deficient mice show higher lethality, lower neutrophil recruitment and an impaired clearance of *Clostridium difficile* compared to wild-type mice.

Homeostatic control of the intestinal microbiota

Paneth cells are the antimicrobial masters

Paneth cells are present at the base of crypts throughout the small intestine, with a gradient increase in their number at distal locations, reaching their highest concentration in the terminal ileum. These specialized secretory cells are located in the base of the crypts of Lieberkühn and are the major producers of antimicrobial proteins in the small intestine. Paneth cells secrete mainly lysozyme as well as α-defensins (also called cryptidins in mice), as well as secretory phospholipase A2 and the lectin RegIIIγ. In contrast to α-defensins which are expressed only by Paneth cells, β-defensins are secreted by most intestinal epithelial cells.

It has been shown that Paneth cells have an autonomous mechanism to detect potentially invasive bacteria. Paneth cells express PRRs, specifically NOD2 and TLR2, 4, 5 and 9 [9, 15, 16, 17] and signaling through these can induce the secretion of antimicrobial proteins and lectins [18, 19]. It has been shown that orally administered TLR ligands induce Paneth cell degranulation. While the treatment with TLR9 and TLR3 agonists induced a rapid Paneth cell degranulation, TLR4 and TLR5 agonists induce late degranulation, mediated by the action of TNFα [20].

The most frequent area of the intestine that is affected in Crohn's disease is the terminal ileum. One of the characteristics of patients with this disease is an inability to clear intestinal pathogens. Wehkamp and Stange recently coined the term "Paneth's disease" to describe a complex disease of the Paneth cell that might explain the poor antimicrobial capability of the small intestinal Crohn's disease [21]. Defective antimicrobial function in Paneth cells has been described by a variety of mechanisms: mutations in the innate immune receptor NOD2, the autophagy protein ATG16L1, TLR9, α-defensin 5, and also mutations in XBP1, a transcription factor involved in endoplasmic reticulum (ER) stress response.

Paneth cells are susceptible to ER stress due to their highly secretory activity. Under ER stress proteins are misfolded or unfolded leading to activation of the unfolded protein response (UPR). The UPR activates signaling pathways to restore proper protein folding but if this response it is sustained for too long the cell undergoes apoptosis. Grootjans and colleagues have recently published that ischemia/reperfusion of the small intestine activates UPR and correlates with Paneth cell apoptosis. This significantly decreases their antimicrobial function leading to bacterial translocation and finally systemic inflammation [22].

Paneth cells are key regulators of the intestinal microbiota and defective differentiation leads to absence or decrease in number in the small intestine, and/or decrease in antimicrobial production. Several genes described below have been associated with defects in differentiation and quantity of Paneth cells. Defects in autophagy have been linked to Paneth cell hypofunctionality. GATA transcription factors regulate proliferation and differentiation in multiple organs. Specifically, Gata4 is important in intestinal gene regulation and function, where it is specifically expressed in epithelial cells. Recently, Beuling and colleagues have demonstrated that conditional deletion of the transcription factors Gata4 and Gata6 in the epithelium of the small intestine decrease the number of Paneth cells in mice, and increase the number of mucin-producing Goblet cells [23].

TLR signaling in host-microbial control

As mentioned above, TLRs act as sensors that recognize PAMPs or DAMPs, and can initiate the innate immune response, activating downstream signaling pathways that lead to production of cytokines, chemokines or antimicrobial peptides. In addition, TLR signaling is

also required to activate immune cells in the intestinal mucosa such as dendritic cells and macrophages. Moreover, it has been reported that γδ intraepithelial T-lymphocytes (IELs) are activated by epithelial MyD88 signaling, and can produce antimicrobial peptides such as RegIIIγ in response to resident microbiota [24].

Similarly, commensal bacteria promote the recruitment of mast cells in the small intestine in a MyD88-dependent manner. Germ-free wild type mice and conventionally-housed MyD88 deficient mice have a decreased number of intestinal mast cells. Kunii et al. showed that intestinal microbiota induces production of CXCR2 ligands in the intestinal epithelium. This recruits mast cells expressing the chemokine receptor CXCR2 recruit to the intestinal mucosa from the blood stream [25].

TLR-3 and TLR-4 can also signal through a MyD88-independent pathway that involves TIR-domain-containing adapter inducing interferon-β (TRIF). It has been recently shown that TRIF signaling is needed to activate innate responses against the intestinal pathogen *Yersinia enterocolitica*. TRIF-deficient mice had an increased mortality and bacterial dissemination after oral infection with *Y.enterocolitica*. In addition, TRIF-deficient macrophages have impaired phagocytosis of gram-negative pathogens such as *Y. enterocolitica*, *Salmonella typhimurium* and *Escherichia coli* [26].

Another mechanism to keep the intestinal microbiota under control is by regulating the physical location of the microorganisms in the lumen. Vaishnava et al. recently described how MyD88-deficient mice have an increase of mucosa-associated bacteria compared to wild-type mice which physically separate the microbiota from the host by a thick mucus layer. In addition, they demonstrated that epithelial MyD88 is sufficient and necessary to limit bacterial association with the small intestinal surface. Moreover, the authors showed that the antibacterial lectin RegIIIγ is responsible for this spatial segregation of the intestinal microbiota and the host [27].

Protective IgA responses

IgA is produced in the intestinal epithelium and secreted to the lumen providing protection against microbes, neutralizing pathogenic bacteria and controlling commensals. Not only is IgA secreted to control the bacterial load in the intestinal lumen, but it has also been shown that these IgA pools are antigen-specific [28].

The secreted IgA found in the intestinal lumen is produced by plasma cells that migrate from Peyer's patches or other mucosal-associated lymphoid tissues, in response to epithelial signals. The chemokine receptor CCR10 is expressed in the majority of IgA+ plasma cells. CCR10 expressing IgA-producing B-cells are recruited to the intestinal lamina propria by epithelial secreted CCL28 (CCR10-ligand). It has been recently reported that CCR10−/− mice do not show a decrease in IgA production however, diversity of IgA was decreased [29]. Thus IgA memory responses in these mice are impaired when reinfected with the same pathogen. This demonstrates the importance of CCR10 in IgA memory acquisition in the intestine. In addition, Liang and colleagues have shown that TLR2 also acts as a B-cell homing receptor in the intestine and induces the expression of IgA [30]. Activation of TLR-2 signaling induces CCR9, CCR10 and IgA expression on circulating B-cells from healthy subjects.

Shulzhenko et al. recently described that B-cell deficient mice or IgA-deficient mice have higher levels of serum LPS than wild-type despite no significant changes in the numbers of intestinal bacteria [31]. In the absence of B-cells or IgA, the epithelium contains the microbiota by upregulating IFN-mediated responses and repressing metabolic functions involving Gata4. This change in the intestinal function leads to an impaired lipid

metabolism, including lipid malabsorption. Intestinal epithelial cells have two interacting gene networks which are inversely correlated; one involving lipid metabolism regulated by Gata4, and the other related to IFN-dependent innate immunity. This study is especially relevant, as the authors confirmed their *in vivo* studies in mice with intestinal biopsies from patients with common variable immunodeficiency or with HIV.

When the intestinal innate immunity fails

Innate immune responses are meant to protect the host from commensal and pathogenic bacteria in the intestinal lumen. However, in some circumstances the innate mechanisms of defense might have adverse effects for the host.

Mucositis is a serious adverse effect of cancer chemotherapy and radiotherapy that can compromise the treatment and the quality of life of patients with cancer. It is caused by epithelial damage induced by chemotherapy. The intestine is especially sensitive to chemotherapeutics due to it's rapid proliferation. Kaczmarek and colleagues described that TLR-2 and TLR-9 signaling worsens doxorubicin-induced intestinal mucositis [32]. Interestingly, GSK-3β activation is inhibited in the absence of TLR2, decreasing doxorubicin-induced intestinal damage. The authors conclude the use of TLR-2 and TLR-9 antagonists may decrease the severity of intestinal mucositis of some cancer-therapies.

In small intestine transplant model the microbiota may play a role in the outcome of the surgery. It has been demonstrated that TLR4 signaling increases the risk of small intestine allograft rejection in mice [33]. TLR2 and TLR4 expression has been shown to be increased in small intestine syngeneic (BALBc to C57BL/6) and allogenic (C57BL/6 to C57BL/6) grafts. TLR4 knock-out mice are less likely to reject a small intestinal transplant than WT mice which may be explained by decreased levels of peripheral inflammatory cytokines. [33]

Another question related intestinal TLRs are their temporal expression during development. This is an important concept as newborns don't have bacteria in their gut; the intestinal mucosa matures and becomes colonized by bacteria in the first few weeks after birth. As such, newborns are susceptible to necrotizing enterocolitis (NEC). NEC is diagnosed mainly in premature newborns. They suffer bowel necrosis most frequently in the ileocecal region. It is postulated to occur as an immature immune response against intestinal bacterial colonization however, NEC pathophysiology is still unclear. Recently, the co-stimulatory molecule CD40, which is required for an adequate innate immune response against microbial pathogens, has been shown to be downregulated in NEC [34]. Using a NEC model with Gravid Sprague-Drawley rats, CD40 and its ligand CD40L were found in the distal ileum of control rats, whereas they were not detectable in NEC pups. NEC newborns presented an increased expression of proinflammatory mediators such as TLR-4, IL-18 and IL-10Rβ, as previously shown.

Crohn's disease

Crohn's disease is known to be a consequence of an uncontrolled inflammatory response to the commensal microbiota and several innate immune susceptibility genes, including NOD2 mutations, have been identified [35].

Autophagy is an evolutionary conserved mechanism by which cells engulf and recycle proteins and organelles. Autophagy also serves as a mechanism to clear intracellular bacteria. IRGM1 and ATG16L1, two autophagy genes, have been linked to a higher susceptibility to Crohn's disease [36, 37, 38]. NOD1 and NOD2 have also been described to regulate autophagy by interacting with ATG16L1 [39, 40]. Recently, Plantinga and

colleagues described how ATG16L1 T300A polymorphism is associated with an increased production of pro-inflammatory cytokines such as IL-1β or IL-6 which could explain the failure to control inflammation in patients with Crohn's disease [41]. A microRNA, miR-196, is overexpressed in the intestinal epithelium of active Crohn's disease patients and downregulates a protective variant of IRGM but not the risk-associated allele [42]. Subsequently, Crohn's disease patients have impaired control of an invasive *Escherichia coli* associated with this disease.

Conclusion

The small intestine has an enormous surface area that is continuously exposed to dietary and microbial antigens. These antigens need to be tolerated by the innate and adaptive immune systems to maintain homeostasis but pathogens must also be prevented from harming the host. Some of the mechanisms to achieve this balance include the expression of innate immune receptors, production of antimicrobial peptides, secretion of IgA or autophagy of intracellular bacteria. Unfortunately, in some cases the innate immune system's attempt to protect the host fails and chronic inflammation, transplant rejection, or other pathologies occur. For this reason a better knowledge of the mechanisms underpinning the intestinal innate immune response are crucial for the pursuit of new therapies and vaccines to protect against pathogens and chronic inflammation.

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Key points

- The intestine maintains control over the intestinal microflora by means of the innate immune response.
- Some of the host mechanisms to regulate intestinal homeostasis include the expression of innate immune receptors, production of antimicrobial peptides, secretion of IgA or autophagy of intracellular bacteria.
- Toll-like receptors (TLRs) are involved in B-cell homing to the intestine, rejection of small intestinal allografts and recruitment of mast cells.
- The TLR adaptor TRIF is necessary to activate the innate immunity after *Yersinia enterocolitica* infection.
- Antibacterial RegIIIγ is responsible for the spatial segregation of host and microbiota in the intestine.
- In Crohn's disease, ATG16L1 T300A variant promotes the production of pro-inflammatory cytokines and miR-196 downregulates a protective IRGM polymorphism leading to impaired clearance of adherent *Escherichia coli* in the intestine.