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REVIEW

TLR5 Signaling in the Regulation of Intestinal Mucosal Immunity

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Abstract: Toll-like receptor 5 (TLR5) is a pattern recognition receptor that specifically recognizes flagellin and consequently plays a crucial role in the control of intestinal homeostasis by activating innate and adaptive immune responses. TLR5 overexpression, on the other hand, might disrupt the intestinal mucosal barrier, which serves as the first line of defense against harmful microbes. The intestine symbiotic bacteria, mucous layer, intestinal epithelial cells (IECs), adherens junctions (such as tight junctions and peripheral membrane proteins), the intestinal mucosal immune system, and cytokines make up the intestinal mucosal barrier. Impaired barrier function has been linked to intestinal illnesses such as inflammatory bowel disease (IBD). IBD is a persistent non-specific inflammatory illness of the digestive system with an unknown cause. It is now thought to be linked to infection, environment, genes, immune system, and the gut microbiota. The significance of immunological dysfunction in IBD has received more attention in recent years. The purpose of this paper is to explore TLR5's position in the intestinal mucosal barrier and its relevance to IBD.

Keywords: toll-like receptor 5, intestinal mucosal barrier, microbes, intestinal immune, inflammatory bowel disease

Introduction

The primary function of the immune system, comprised of interconnected innate and adaptive arms, is to launch a robust immune response towards pathogens while maintaining tolerance to self-antigens. The intestinal mucosal immune system is very complex, consisting of the mucus layer, intestinal epithelial cells (IECs), gut-associated lymphoid tissue (GALT), which includes lamina propria dendritic cells (LPDCs), and the enteric nervous system (ENS). Toll-like receptors (TLRs) are a class of transmembrane protein receptors and belong to pattern recognition receptors (PRRs). TLRs can recognize the microbe-associated molecular patterns (MAMPs) and play a central role in the immune response. TLR5, one of the most significant extracellular receptors interacting with the human gastrointestinal microbiome[1] as well as a flagellin-specific receptor, plays a vital part in intestinal immunity.

The intestinal mucosal barrier is regarded as one of the most significant protective barriers in the human body, which can keep the gut microbiota in balance, and protect against bacterial translocation, endotoxemia, and its secondary damage. Intestinal disorders, such as IBD, are closely linked to impaired barrier function. IBD is a chronic nonspecific inflammatory illness of the digestive system that mainly encompasses Crohn's disease (CD) and Ulcerative Colitis (UC). It is characterized by the accumulation of immune cells and pro-inflammatory cytokines in the intestinal mucosa. In recent years, the incidence of IBD has been on the rise in Asia[2,3]. However, the pathophysiology of IBD, which may be associated with barrier disorder, intestinal microecological disorder, and genetic susceptibility to the host autoimmunity, has not been comprehensively understood.

In this review, we provided an overview of TLR5 about its role and potential mechanisms under the circumstances of intestinal homeostasis or inflammation to further explain the occurrence and development of IBD.

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Crosstalk Between IECs and LPDCs

The intestinal mucosa is exposed to a large number of microorganisms and foreign food source antigens. Symbiotic bacteria not only defend against infection by activating mucosal innate immune defenses but also induce regulatory cells to inhibit detrimental inflammatory responses. At the same time, immune cells in the gut identify and resist bacteria and foreign antigens between bacteria and immune cells.[4] Therefore, a tightly regulated barrier is crucial to maintain intestinal homeostasis. IECs, including absorptive cells, goblet cells (GCs), M cells, Paneth cells, and intestine endocrine cells, are differentiated from intestinal epithelial stem cells.[5]

GCs, as secretory intestinal epithelial cells, can synthesize and secrete mucin. Mucin is a high molecular weight glycoprotein that serves as the first line of defense against physical and chemical damage and prevents the intestinal epithelium from the invasion by pathogens. The predominant component of the intestine mucin is Muc2.[6,7] As the factory of mucins, GCs play an important role in maintaining intestinal immunological homeostasis by transmitting luminal antigens to LPDCs. Previous in vitro investigations have revealed that LPDCs can extend beyond the intestinal epithelium to the intestinal lumen via trans-epithelial dendrites (Ted) to detect microorganisms.[8] However, this phenomenon was not found in vivo experiments in mice, because LPDCs could hardly pass through the intestinal mucous layer via Ted. Studies have shown that goblet cell-associated antigen passages (GAPs) is one of the ways for CD103 + LPDCs to obtain intraluminal antigens.[9–11] Recently, some GCs have been identified as sentinel goblet cells (senGCs) with nonspecific endocytosis at the entrance of the colonic crypt. They can activate the downstream NOD-like receptor protein (NLRP) 6 inflammasome of the TLR/MyD88-dependent Nox/Duox reactive oxygen species synthesis, nonspecifically endocytose, and react to the TLR2/1, TLR4, and TLR5 ligands to increase Muc2 secretion, hence expelling bacteria.[12]

Paneth cells are granular secretory cells only found at the base of the small intestinal crypt. They can produce various kinds of antimicrobial peptides (AMPs), such asα-defensins, lysozyme, lipopolysaccharide (LPS)-binding protein, RegIII, and several pro-inflammatory mediators including interleukin-17A (IL-17A), tumor necrosis factor α (TNF-α), and IL-1b,[13] which can stimulate intestinal innate immunity and regulate intestinal microorganism. Hence, Paneth cells are regarded as the fundamental regulator of intestinal homeostasis and intestinal microorganism.[14] Many CD-related genes are expressed by Paneth cells, including ATG16-like 1 (Atg16L1), transcription factor 4 (Tcf4), NOD2, and immune-associated GTPase family M protein (IRGM).[14] Mutations in Atg16L1 and another CD risky gene X-box-binding protein-1 (Xbp1) can lead to abnormal particle morphology and reduce particle number in Paneth cells of genetically deficient mice and CD patients.[15] Xbp1 deletion in intestinal epithelial cells (IECs) results in spontaneous enteritis that will induce endoplasmic reticulum stress and then contribute to spontaneous colitis.[16] Moreover, Paneth cell dysfunction and decreased antimicrobial peptide release have been shown to enhance the formation and development of IBD.[17–19]

GALT is the main site to initiate the gut-adaptive immune response. Over the surface of the GALT is a layer of follicle-associated epithelium (FAE) containing M cells. M cells absorb and transport granular antigens from the lumen to dendritic cells (DCs) and promote T cell activation and secretory immunoglobulin A (SIgA) synthesis.[20,21] SIgA can effectively restrain pathogenic bacteria from adhering to the intestinal mucosa by stimulating immune responses specific to pathogens, increasing intestinal mucus secretion, and enhancing mucus layer flow. Mice that lack intestinal M-cell gene have a delayed IgA secretion response,[21] lower IL-17A production, and are more susceptible to colitis.[22]

In addition to intestinal epithelial cells, tight junction (TJ) plays a critical role in maintaining the epithelial barrier of the intestinal mucosa. Being at the top of IECs, TJs consist of transmembrane protein Occludin, Claudins, junctional adhesion molecule (JAM), cytoplasmic protein ZO-1, ZO-2, ZO-3, and cingulin.[23] TJs are the most significant defense in the paracellular metastatic route and serve a critical function in preserving the paracellular permeability of IECs. Generally, TJs may selectively allow the flow of ions and small molecules and prevent harmful bacteria and antigen macromolecules in the intestinal cavity from passing through the intestinal mucosal barrier. However, changes in TJ protein expression and structure are associated with the occurrence of IBD.[24] Furthermore, some pro-inflammatory cytokines, such as TNF-α,[25] IL-8,[26] and interferon -γ[27] have been shown to increase the permeability of TJs and induce apoptosis in IECs. As a result, this impairs the barrier function and induces epithelial mucosal inflammation. Among

patients with CD and UC, a strong relationship has also been established between intestinal permeability and mucosal inflammation while the permeability is directly proportional to the severity of diarrhea.[28]

LPDCs are a class of antigen-presenting cells (APCs) that play an important role in both innate and adaptive immunity. However, the way that intraluminal antigen transport to LPDCs is controversial. It is generally accepted that soluble antigens may be transported to LPDCs through intercellular or paracellular pathways,[29,30] while the insoluble granular antigens are taken up by M cells on follicle-associated epithelium.[31] As mentioned above, LPDCs can acquire soluble and granular antigens through GAPs formed by GCs. LPDCs can also obtain antigens from apoptotic epithelial cells.[32] Studies have shown that LPDCs can upregulate the chemokine receptor CCR7 and migrate to enteric-draining mesenteric lymph nodes (MLNs) after being activated, where they provide antigens to naive T cells[33,34] to guide their differentiation into T-helper type 1 (Th1), type 2 (Th2), type 17 (Th17)[35,36] or regulatory T cells (Treg)[37] (Figure 1).

TLR5 Signal

TLR5 is one of the main extracellular receptors interacting with the human gastrointestinal microbiota, and it is involved in the innate and adaptive immune responses to flagellin.[3] TLR5 gene is located on chromosome 1 and can be expressed in monocytes, immature DCs, and epithelial cells. In IECs, TLR5 is mainly expressed in the basal part of cells.[38,39] CD103+ CD11b+ LPDCs are the main cells expressing TLR5 in the small intestine.[40,41] TLR5 consists of a Leucine-rich repeat (LRR) domain that mediates pathogen-associated molecular patterns (PAMPs) recognition, a transmembrane domain, and a cytoplasmic Toll/IL-1 receptor (TIR) domain that initiates downstream signaling.[42] TLR5, as a specific receptor for flagellin of intestinal symbiotes and pathogenic bacteria, can recognize the conserved domain of different types of G+ and G- flagellin.[43] The flagellin arginine residues in the D1 domain (BS flagellin R89) and the adjacent residues (BS flagellin E114 and L93) form complementary structural and chemical interactions with LRR which activates TLR5 and maximize the flagellin-mediated cellular activity with the assistance of the D0 domain.[44]

Flagellin binds directly to the lateral surfaces of TLR5 in a symmetrical arrangement, leading to the formation of a 2/2 complex.[45] After activated by flagellin, a conformational change in the TIR domain of TLR5 on IECs recruits MyD88,

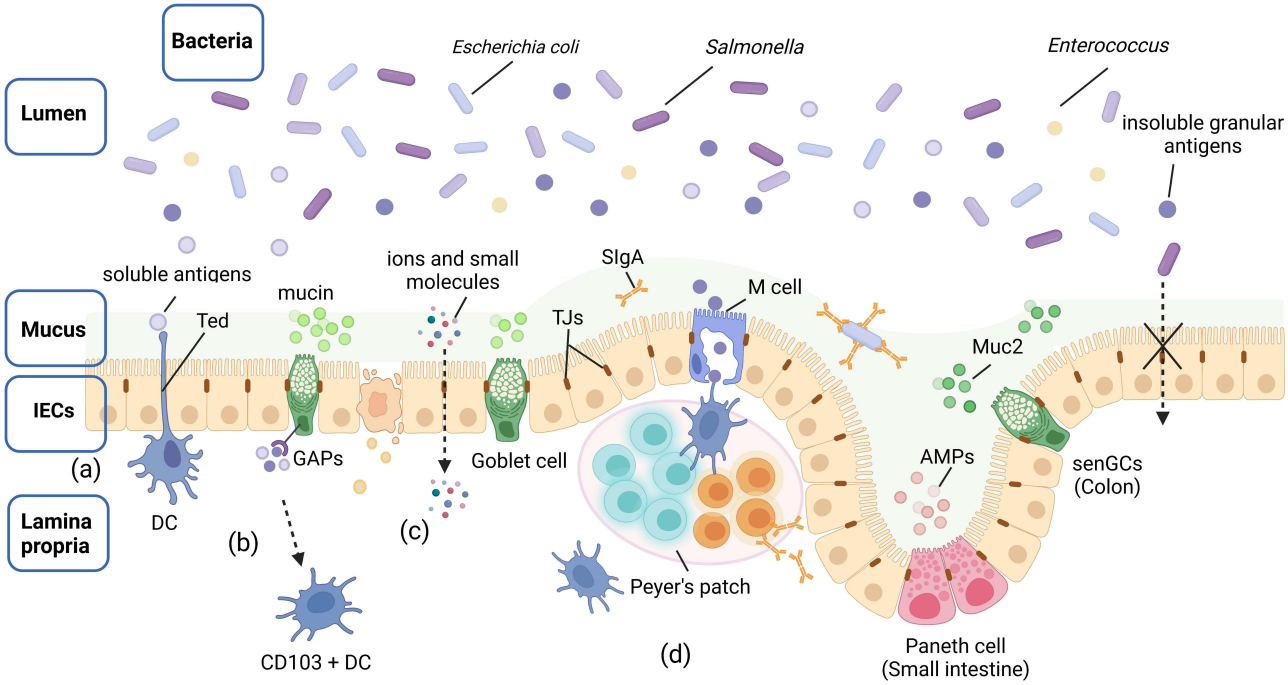

Figure 1 The various roles of different kinds of intestinal epithelial cells (IECs) and the crosstalk between IECs and LPDCs. IECs can secret various components to form a mucus layer and chemical barrier to resist the invasion of pathogenic microorganisms in the gut. LPDCs can obtain antigens by interacting with IECs in four ways: (a) trans-epithelial dendrites (Teds) from dendritic cells (DCs). (b) goblet cell-associated antigen passages (GAPs) from goblet cells. (c) auto-antigens from apoptotic epithelial cells. (d) antigens acquired by M cells. (Created with BioRender.com).

which subsequently forms a complex with IL-1 receptor-associated kinase (IRAK) 4 and IRAK1/2 kinase called Myddosome.[46] Myddosome induces the binding and activation of E3 ubiquitin (Ub) ligase TNF receptor-associated factor 6 (TRAF6).[46] Then, the polyubiquitin chain produced by TRAF6 interacts with the complex formed by TAK1-binding protein 2 (TAB2) and 3 (TAB3) to activate the TGF-β activated kinase 1 (TAK1).[47] After being sensitized, TAK1 activates the MAPK pathway and the IKK complex is composed of catalytic subunits IKKα, IKKβ, and regulatory subunit NEMO (also known as IKKγ). IKK complex phosphorylates nuclear factor-kappa B (NF-κB) inhibitory protein IκBα and leads to proteasome degradation, so that NF-κB can translocate into the nucleus to induce pro-inflammatory gene expression.[48] IECs can also sense the endogenous luminal flagellin through TLR5-mediated signaling pathways to induce the expression of zinc-finger protein A20, which functions as the first-line defense against excessive innate immune responses in the early stage of inflammation.[49] The A20 can inhibit the NOD2 signaling pathway stimulated by MDP, which ultimately activates the NF-κB signaling pathway.[50]

TLR5 signaling can lead to extensive transcriptional activation of at least 500 genes,[51] including Janus kinase (JAK)/signal sensor and transcriptional activator (STAT), mitogen-activated protein kinase (MAPK), extracellular signal-associated kinase (ERK), as well as C-Jun N-terminal kinase (JNK),[52–54] and also activate anti-apoptotic or proliferation pathways.[55] This activation of anti-apoptotic gene expression enables cells to survive when facing deadly damage. Erk1/2, JNK, p38MAPK, and ERK5 are the four confirmed cascades of MAPKs. The ERK cascade preferentially regulates proliferation, differentiation and metastasis. The P38 cascade and the JNK cascade have similar functions in regulating stress response, inflammation, apoptosis, and proliferation. The ERK5 cascade is mainly involved in stress response and proliferation.[56] MEKl and MEK2 are activators of ERKl/2, so as MEK5 to ERK5, MKK4 and MKK7 to JNK, and MKK3 and MKK6 to P38MAPKs.[57] Ap-1, a co-product of P38, JNK, and ERK, activates downstream signaling molecules through kinase, leading to the release of various inflammatory cytokines and immune modulators (Figure 2).

TLR5 Signaling in IECs: The First Responder to Flagellin

IECs are a crucial line of defense against gut bacteria. However, PRRs on IECs do not always lead to inflammatory activation, because it depends on whether the stimulation received by PRRs comes from the apical side or the basolateral side.[58] That is, PRRS can selectively inhibit or initiate inflammation. TLR5 is specifically expressed in the basal side of IECs and forms physical isolation from the lumen contents, which enables it to respond to the flagellin of translocative bacteria, such as *Salmonella*, but not to the non-translocative symbiotic *Escherichia coli*.[59] Hence, inflammation occurs only when microorganisms penetrate the sterile room. This separation of inflammatory signal transduction helps to prevent uncontrolled inflammation caused by symbiotic microorganisms. Studies have found that the tolerance of polarized IECs to flagellin seems to be achieved through the internalization of TLR5, which blocks the activation of NF-κB, MAPK, and phosphoinositol 3-kinase (PI3K) signaling pathway, thereby preventing the secretion of pro-inflammatory cytokine IL-8. After incubation with flagellin for 24 hours, polarized monolayers showed a 10–50% reduction in TLR5 expression on the cell surface, avoiding the threshold of inflammatory activation and inhibiting pro-inflammatory responses.[60] Interleukin-1 receptor-associated kinase (IRAK) is a key factor in the downstream TLR and IL-1R signaling pathways and plays an important role in systemic inflammatory responses.[61] In the flagellin-tolerant state, TLR5 inhibits inflammation through the inhibition of IRAK4 phosphorylation.[60] Thus, flagellin tolerance appears to help protect the host epithelium from uncontrolled immune responses and contribute to the healing process after initial inflammatory damage.

The expression of TLR5 in IECs can regulate the composition and localization of the intestinal microbiome, thus preventing diseases related to intestinal inflammation. The high expression of TLR5 on cells makes TLR5 signaling an important regulatory factor in the host immune response to flagellate microorganisms and maintenance of intestinal homeostasis.[62] The symbiotic microbiome may evade TLR5-mediated intestinal immune surveillance by down-regulating flagellin expression.[63] On the other side, a lack of TLR5 will lead to intestinal microbiome disorder, low-level inflammation, metabolic syndrome, and susceptibility to colitis.[64–66] TLR5 deficient mice were animal models susceptible to the development of spontaneous colitis,[67] suggesting that TLR5 is critical for the regulation of potentially harmful bacterium. As was shown in an experiment by Kinnebrew MA et al, systemic application of flagellin to antibiotic-treated mice significantly reduced vancomycin-resistant *Enterococcus* colonization.[68]

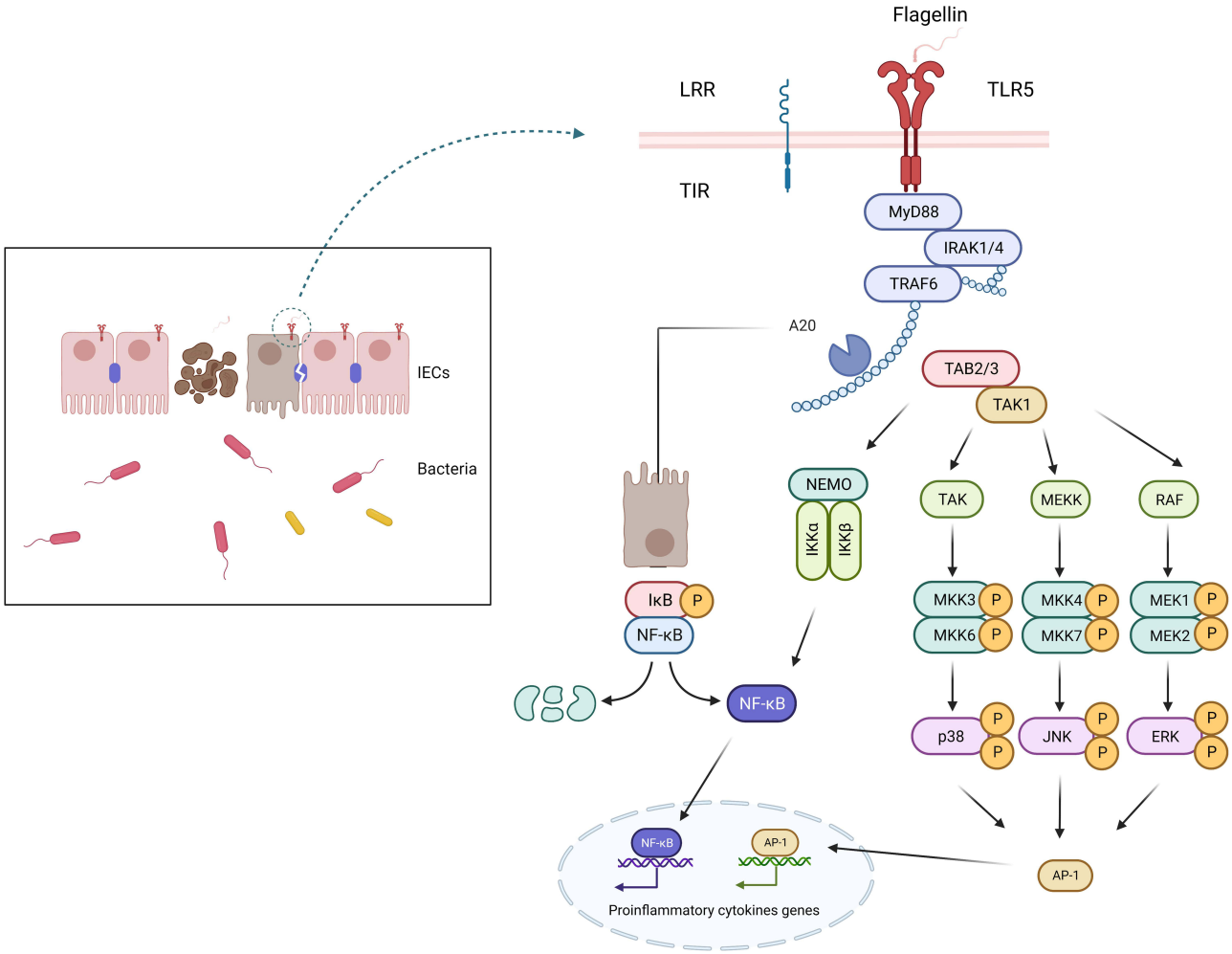

Figure 2 The flagellin-dependent TLR5 signaling pathway. The flagellin activates the TLR5 after the damage of the intestinal mucosal barrier. The activated TLR5 recruits intracellular adaptor protein MyD88 to form a complex with IRAK 4 and IRAK1/2 kinase called Myddosome and then activates TAK1. After being sensitized, TAK1 activates the MAPK pathway and the IKK complex composed of catalytic subunits IKKα, IKKβ, and regulatory subunit NEMO (also known as IKKγ). IKK complex phosphorylates NF-κB inhibitory protein IκBα and leads to proteasome degradation so that NF-κB can translocate into the nucleus to induce pro-inflammatory gene expression. Then the NF-κB and AP-1 translocate into the nucleus, promoting the transcription of pro-inflammatory cytokines genes. (Created with BioRender.com).

Flagellin of symbiotic microbiome also played an antibacterial role through the TLR5-regIIIγ pathway. RegIIIγ is an antibacterial peptide of the C-type lectin family expressed in the intestine,[69] which is synthesized by IECs. RegIIIγ can exert direct antibacterial activity by specifically binding to bacterial peptidoglycan.[69] Studies have shown that the RegIIIγ expression requires the activation of the TLR-MyD88-mediated signaling pathway in IECs when in intestinal homeostasis, which is directly activated by microbial products released by the intestinal microbiome. RegIIIγ expression may affect mucosal homeostasis and sensitivity to intestinal G+ pathogens through the composition of a symbiotic microbiome.[70]

Studies have shown that when the steady state is broken, the specific activation of TLR5 can significantly decrease the epithelial barrier resistance and alter the expression of TJ proteins, leading to increased intestinal permeability,[71] translocation of bacteria, and antigens.[72] Flagellin-stimulated endothelial cells rapidly induce proinflammatory mediators, such as the chemokine CXCL1, CXCL2, CXCL5, CXCL8, CCL2, CCL20, or CXCL10, which in turn attract immune cells belonging to the myeloid and lymphoid lineages,[73,74] and pass on the baton (Figure 3).

TLR5 in DCs: The Key to Response to Flagellin

DC activation is a key parameter to determine whether intestinal tolerance or protective immunity is induced. After maturation under the action of danger signals (including MAMPs) or cytokines, cDC matures and up-regulates

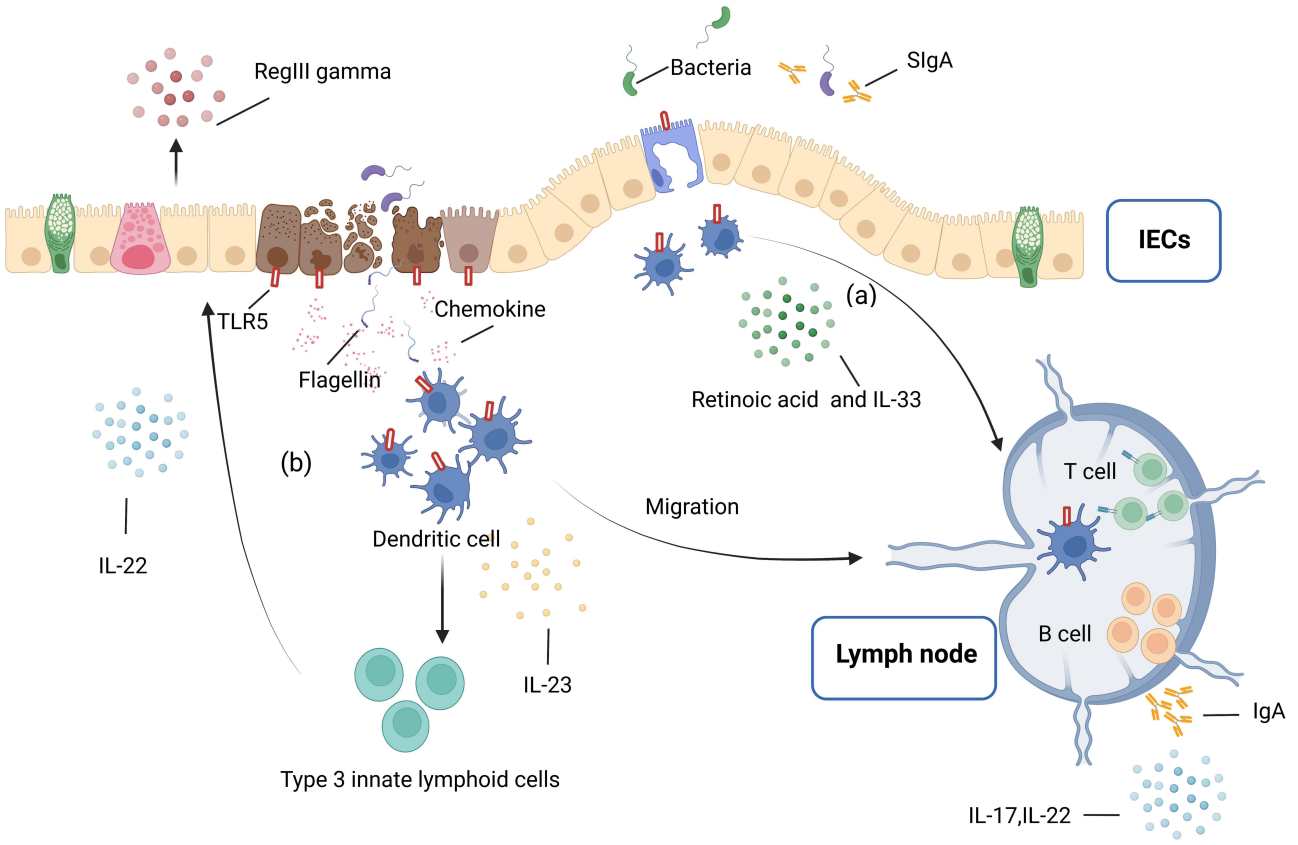

Figure 3 Response to flagellin. (a) Under steady-state flagellin delivery through the IECs to the immature DCs, and LPDC presents flagellin in a tolerant manner, which catalyzes the conversion of vitamin A metabolite retinaldehyde to retinoic acid and secretion of IL-33 by expressing high levels of aldehyde dehydrogenase, thereby inducing immature CD4+T cells to differentiate into Foxp3+Treg. (b) Flagellin-stimulated endothelial cells rapidly induce proinflammatory mediators through the TLR5-related signal pathway and therefore attract LPDCs. After activation, LPDCs migrate into lymphatic vessels and induce the differentiation of naive B cells into plasma cells that produce IgA, IL-17, and IL-22, and positively regulate the differentiation of Th17-producing cells, while the involvement of TLR5 limits the production of Treg cells. Also, LPDCs can rapidly produce IL-23 through the flagellin-TLR5 signal pathway, thereby stimulating group 3 innate lymphoid cells (ILC3) to produce IL-22, promoting IECs recovery and inducing RegIIIγ expression. (Created with BioRender.com).

C chemokine receptor 7 (CCR7), which interacts with ligand CCL21 on lymphatic endothelial cells.[75] This interaction enables cDC to enter the lymphatic vessels in both stable and inflammatory states and migrate directionally to draining lymph nodes to draining lymphoid tissue for antigen presentation,[76,77] providing appropriate signals for the development of CD4 + T helper cells (Th), regulatory T cells (Treg), CD8 + T cells, and B cell responses. As mentioned above, CD103+ CD11b+ LPDCs (cDC2) are the main cells expressing TLR5 in the small intestine, while colonic DCs are concentrated mainly in isolated lymphoid follicles, few of which are present in the lamina propria. Therefore, we will focus on the effects of TLR5 + LPDC on CD4 + T cells. Interestingly, TLR5 exerts a novel MyD88-independent, endocytic receptor function by enhancing the presentation of the flagellar peptide to antigen-specific CD4 + T cells.[78] The enhancement of flagellin processing and/or presentation by TLR5 seems likely to be caused solely as a consequence of increased antigen uptake by specific surface receptors.[79]

Under physiological conditions, the migration of cDC from intestinal LP mainly results in “harmless” antigen presentation to immature T cells in MLN. Intestinal LPDC presents flagellin in a tolerant manner, which catalyzes the conversion of vitamin A metabolite retinaldehyde to retinoic acid and secretion of IL-33 by expressing high levels of aldehyde dehydrogenase, thereby inducing immature CD4+T cells to differentiate into Foxp3+Treg.[80,81]

However, when there are inflammatory stimuli such as flagellin, cDCs will mature and release inflammatory cytokines and initiate protective acquired immunity. After being stimulated, LPDCs migrate into lymphatic vessels and induce the differentiation of naive B cells into plasma cells that produce IgA and interleukins (IL-17 and IL-22), facilitating early defense against pathogen invasion[40,82] and positively regulating the differentiation of Th17-producing

cells.[36,40] Meanwhile, the involvement of TLR5 limits the production of Treg cells.[62] Therefore, the high expression level of TLR5 on LPDCs ensured that TLR5+ LPDCs play an important role in inducing effector T cells to respond to the invasion of flagellated pathogens. CD103+ CD11b+ LPDCs can rapidly activate antibacterial inflammation after flagellin enters lamina propria by producing IL-23 through the flagellin-TLR5 signal pathway, thereby stimulating group 3 innate lymphoid cells (ILC3) to produce IL-22, promoting IEC recovery and inducing RegIIIγ expression.[83] Contrary to the activation of lymphocytes caused by migratory DC in lymphoid tissue, ILC3 activation is immediate and heavily dependent on tissue-resident DC[75] (Figure 3).

Expression of TLR5 in IBD

The onset of IBD is not caused by a single factor but by many factors. Among them, the intestinal barrier damage and immune response deficiency caused by innate genes include T cell differentiation (IL-10, IL-21), Th17 cell maintenance (IL-23R, JAK2, PTPN2), and NF-κB activation (TNF signal gene).[84–86] The imbalance of key host–microbe interactions is an important cause of the pathogenesis of IBD. T-cell infiltration is a key feature of chronic intestinal inflammation,[87] and T-cell-derived cytokines play an important role in the occurrence and development of IBD.[88]

Flagellin has been proven to be the major antigen of the adaptive immune response associated with IBD.[89] Increasing evidence supports the critical role of flagellin/TLR5 in the pathogenesis of IBD, especially CD.[72] Increased intestinal permeability is a common problem in IBD.[90] When the barrier integrity gets impaired, the basolateral receptors of cells will be exposed to potential pathogenic ligands, including flagellin.[3]

Michael and his team[91] used the molecular technique of serum expression cloning (SEC) to identify specific bacterial antigens which lead to IBD. The dominant antigens they identified were related to novel flagellin families, and they could activate the innate immunity through TLR5. Dubinsky and Targan et al came to a similar conclusion to Lodes.[92,93] Gewirtz AT et al also found that the polymorphism of TLR5 termination codon reduced the adaptive immune response of anti-flagellin (CBir1) and played a positive role in protecting CD, which meant that TLR5 regulated the immune response to flagellin.[94]

Some studies indicate that TLR5 expression level is not positively correlated with the incidence of IBD. Abreu et al showed that the expression levels of TLR2 and TLR5 are not high in the colonic IECL of patients with IBD.[89] Stanislawowski M et al have found that the expression of the TLR5 gene and protein was decreased in mucous of patients with moderate and severe active UC, suggesting that the down-regulation of TLR5 may be caused by an increase of ligand molecules near epithelial cells in inflammatory tissues.[95,96]

Therefore, we believe that it may be necessary to dynamically track the expression of intestinal TLR5 in patients with IBD. More research is needed to determine the role of TLR5 in the adaptive immune system in order to promote the development of IBD treatment drugs or diagnostic tools. The most important thing in the next stage is how to carry out clinical transformation targeting TLR5 on an existing basis, that is, how to use diet or drugs to accurately regulate intestinal flora or its metabolites to regulate the expression of TLR5, to achieve the goal of treating diseases through the interaction of innate immunity and adaptive immunity.

Conclusion

Innate and adaptive immunity in humans is significantly influenced by the intestinal mucosal barrier. IECs and LPDCs collaborate to develop the gut immune system. PPRs play an important role in the crosstalk between the two.

TLR5, a particular recognition receptor of flagellin, is an essential component of intestinal immunity. It mediates immune tolerance to symbiotic flagellin under intestinal homeostasis by recognizing bacterial flagellin and mediating dynamic interactions between the microbiota and the host's innate immunity. This is a two-way communication and balance. On the one hand, symbiotic bacteria down-regulate the expression of flagellin by detecting the TLR5 signal on IECs, and on the other hand, Intestinal homeostasis is maintained by the asymmetric distribution of TLR5, the internalization of a fraction of the basolateral TLR5 and the crosstalk between IECs and LPDCs——TLR5 signaling in the FAE promotes antigen transport from the M cells to the immature DC,[97] and then stimulate IgA secretion to inhibit bacterial motility. After the intestinal immune homeostasis is broken, IECs, which receive flagellin stimulation, secrete chemokine through the activation of the TLR5 signal to recruit myeloid and lymphatic immune cells. Then, cDC matured

and up-regulated CCR7, migrated into the draining lymphoid tissue for antigen presentation, and promoted the activation of CD4+T cells and B cells. However, it is still not clear why flagellin can mediate T cell differentiation in different directions, and whether it is related to how to prevent further expansion of the immune cascade at the beginning of inflammation is still worth pondering. Similarly, whether different types of dendritic cells play a synergistic role in the immune process induced by flagellin is also a question worth exploring.

IBD is a disease related to intestinal mucosal barrier damage, intestinal flora disorder, and T cell differentiation, which fits well with the intestinal immune disorder mediated by flagellin-TLR5. Flagellin is indeed the main antigen of adaptive immune response associated with inflammatory bowel disease. It has been proved by a large number of studies that there are differences in the expression of TLR5 in inflammatory bowel disease, but the role of TLR5 in the disease is still unknown. It may be the fuse of the immune cascade, the defender of intestinal homeostasis, or both but have different identities with different stages of the disease.

To summarize, addressing the gut microbiota-TLR5 axis offers enormous potential for clinical prognosis and treatment of IBD, but major efforts are required to expand our understanding of molecular links and integrate them into clinical practice.

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Disclosure

The authors report no conflicts of interest in this work.

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