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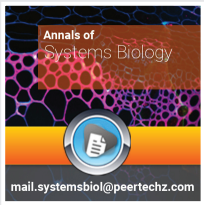

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Review Article

The role of toll like receptor 9 in maintaining gut homeostasis

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Abstract

Toll-Like Receptor 9 (TLR9) is a unique pattern recognition receptor due to its ability to induce either pro- or anti-inflammatory cascades. However, much remains to be elucidated regarding this receptor, such as its localization in different cell and tissue types, the potential epitopes that induce signaling, and how activation of the receptor may result in diverging pathways. Despite these unknowns, the integral role of TLR9 in maintaining gut homeostasis remains clear. In addition to maintaining homeostasis, TLR9 may also have significant potential in treating gut-associated inflammatory diseases such as ulcerative colitis, Crohn's and inflammatory bowel disease via its anti-inflammatory effects. This review will outline some of the key remaining questions regarding the role TLR9 in the gut and highlight its potential utility as a therapeutic target for gastrointestinal disease.

Introduction

The mucosal surfaces of the alimentary tract are perpetually challenged by antigens from environmental, dietary, microbial, and host-cell origins; any number of which have the capability of disrupting the relationship of the host with the delicate homeostatic environment of the gut. Yet, despite this perpetual bombardment, the immune response remains tightly controlled and poised to respond only to potential threats while remaining tolerant to the continuous presentation of foreign substances within the gut lumen.

Intestinal Epithelial Cells (IECs) line the lumen of the small intestine and colon in a single layer, separating the gut luminal contents from the sterile environment of the lamina propria. While the epithelium primarily acts as a physical barrier, it also plays an integral response in mediating innate immune responses to the luminal microbiota. Toll-Like Receptors (TLRs) are critical components of the IEC innate immune response through their detection of highly specific pathogen associated molecular patterns (PAMPs) [1]. Toll-Like Receptor 9 (TLR9) is one such receptor whose cognate ligand is hypomethylated CpG DNA motifs (microbial cytosine-guanine dinucleotide (CpG)-DNA) [2], commonly found in bacterial and viral genomes. CpG/TLR9 refers then to the activation of TLR9 signaling by its cognate ligand. IECs are polarized, columnar cells with the apical surface facing the gut lumen and the basolateral surface facing the lamina propria. Both compartments of the IEC are highly specialized and serve distinct functions in maintaining gut homeostasis [3]. TLR9 is expressed in both compartments and serves dichotomous roles depending on the localization of its activation, whereby apical stimulation induces anti-inflammatory responses and basolateral stimulation induces pro-inflammatory responses [3]. The apical, anti-inflammatory responses can overcome pro-inflammatory signals transduced by other TLRs, highlighting the importance of TLR9 in maintaining gut homeostasis [3].

The microbiome in the large intestine is intimately associated with the IEC monolayer and thus regularly interacts with innate immune pattern recognition receptors without eliciting overt pro-inflammatory responses. This level of immune restraint, or tolerization, is due in large part to TLR9-mediated responses [4]. Thus, in this review, we seek to summarize the role of TLR9 in maintaining gut homeostasis in the face of the microbiome and how the utilization of this

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pathway may contribute to therapeutic interventions for certain inflammatory conditions of the gut.

TLR9 localization and signaling in the gut

TLR9 is usually considered an endosomal receptor expressed in a myriad of cell types, ranging from immunocytes to the mucosal epithelium [5]. However, consideration should be taken when comparing murine and human studies, as TLR9 detects different DNA epitopes between species and cell-specific expression is also different. Human TLR9 is limited to plasmacytoid Dendritic Cells (pDCs), neutrophils, B cells and the epithelium whilst mice share the same cellular expression pattern with the addition of macrophages and myeloid Dendritic Cells (mDCs) [2,6]. Within non-polarized cells such as dendritic cells, the endosomal trafficking system dictates the localization of TLR9 and its resultant signaling cascade [7]. Within these cell types, TLR9 engagement can result in one of two outcomes: either Interferon-Regulatory Factor (IRF)-mediated type 1 interferon or NF κB-mediated pro-inflammatory signaling [7]. Current studies are still examining the mechanisms by which this bifurcated pathway is regulated and the chaperone proteins involved in localizing TLR9 to specific endosomal subtypes [8].

While the exact signaling pathway of TLR9 in dendritic cells remains to be elucidated, even less is known regarding TLR9 in the polarized epithelium. Traditionally TLR9 was believed to be localized only within the endosome due to selective evolutionary pressure to hide TLR9 from identifying self- DNAs [9]. This hypothesis was tested in a murine model where the membrane localization domain of TLR9 was swapped with that of TLR4 to induce surface expression of TLR9. These transmembrane mutant mice died within 4 weeks due to systemic inflammation and anemia [10]. Furthermore, in an elegant study by Price, et al. the authors created novel, fluorescently tagged TLR reporter mice that were used to visualize the expression of individual TLRs in IECs. They found unique temporal and spatial expression of TLRs in the murine gut, notably that in the small intestine and colon, TLR9 is not expressed (or undetectably low) in the epithelium but abundantly expressed in the lamina propria [5]. The authors reasoned that expression may change during inflammation, and thus challenged the reporter mice with Dextran Sodium Sulfate (DSS) to induce colitis, or alternatively challenged mice with *Salmonella* Typhimurium. Neither challenge altered TLR9 expression from basal homeostatic conditions [5]. These results are mirrored in a cohort of Irritable Bowel Syndrome (IBS) patients who showed no significant changes in TLR9 mRNA expression in the jejunum or sigmoid colon compared to healthy controls [11]. In contrast, other *in vitro* and *in vivo* studies have shown that TLR9 could indeed be abundantly expressed on the surface of IECs and not limited to localization in endosomes [2,3,12,13]. Lee et al. demonstrated that TLR9 is expressed and also activated on both the apical and basolateral membrane surfaces of IECs and that the addition of chloroquine, an endosomal inhibitor, had no effect on TLR9 signaling, suggesting that TLR9 was in an active state when expressed on the cell surface in an endosome-independent fashion [3]. Their study utilized polarized HCA7 and $CaCo_2$ cell lines challenged with specific TLR9 agonists, and further demonstrated the unique pro- versus anti-inflammatory signaling cascade resultant from stimulation in the basolateral versus apical compartment, respectively and that the anti-inflammatory effects of apical TLR9 stimulation could overcome pro-inflammatory responses induced by TLRs 2, 3 or 5 [3]. The possibility that TLR9 expression is inducible and its variable expression may contribute to differences in the reported findings was suggested when TLR9 expression was reported to increase by DSS treatment. Transcriptional modulation of pattern recognition receptors in chronic colitis in mice is accompanied by Th1 and TH17 responses [14]. Site-specific expression of TLR9 is also more distinct in the small intestine than colon. Specifically, while small intestinal ordinary villi are immune-negative for TLR9, the roof of M-cells of follicle-associated epithelium are immune-positive for TLR9 [15]. Taken together, these data suggest that cell-specific TLR9 expression may be constitutive or inducible and its function may be pro- or anti-inflammatory depending on whether the TLR9 examined is located on the surface or within the endosome. Thus, much remains to be elucidated regarding the expression, localization and localization-specific signaling cascades of this immunoregulatory receptor.

TLR9 signaling in response to the gut microbiome

While IECs present a physical barrier between the luminal microflora and the host, it also provides a platform that enables elaborate crosstalk between the microbiome and the immune response. TLRs have been shown to directly mediate the IEC response to the luminal microbiome via promoting the production of antimicrobial peptides and mucins which, in turn, promote gut barrier integrity [16]. Most TLRs are sequestered to the basolateral compartment of the epithelium or within the immune cells of the lamina propria [16,17]. This localization-specific pattern of expression protects the host from aberrant immune activation and thus only mediates a response when the barrier has been penetrated. However, TLR9 represents an exception to the basolateral localization pattern, as some studies have shown that it is expressed at the apical surface of IECs and can promote anti-inflammatory signaling [3]. As such, TLR9 may act as a unique molecular rheostat which controls the appropriate level of inflammation to commensal microbes in the intestinal lumen (apical TLR9, anti-inflammatory) vs. those that translocate across the intestinal barrier (basolateral TLR9, pro-inflammatory). Such site-specific activation of differential TLR9 responses could potentially be useful in distinguishing between commensals and pathogens. In this regard, TLR9 can specifically determine the origin of DNA fragments to identify microbes as commensals versus pathogen and mount the appropriate response. Multiple studies have demonstrated the ability of probiotic bacterial DNAs to dampen the inflammatory response in both humans and mice [12,13,18-26]. Ewaschuk, et al. demonstrated that apical surface expression of TLR9 in IECs is up-regulated in response to pathogenic *Salmonella* DNA, while Katakura, et al. have proposed that probiotic DNA absorption in the small intestine and subsequent priming of $TLR9^+$ immune cells may have systemic anti-inflammatory implications, such as amelioration of colitis [24]. This anti-

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inflammatory effect is mediated mostly by the production of type I IFNs from pDCs [24]. As the administration of CpG oligodeoxynucleotides before the induction of experimental colitis reduces the severity of inflammation [25], the anti-inflammatory role of TLR9 was further confirmed by showing that a lack of CpG/TLR9 interaction can significantly reduce the efficacy of immune-suppressive Helper $CD4^+$ T cells in the lamina propria of mice. Furthermore, that transplantation of $CD4^+$ T cells from those *Tlr9*$^{-/-}$ mice induced severe colitis in wild-type recipient mice [27].

Unlike other TLRs whose cognate ligands are unique to microbes, TLR9 detects DNA which is ubiquitous among all life. As such, TLR9 must be able to discriminate not only self from non-self DNA, but also between DNAs from commensal and potentially pathogenic bacteria or viruses. The mechanism by which TLR9 differentiates the origin of these molecules still remains to be elucidated. Multiple hypotheses have been proposed, including the detection of hypomethylated CpG motifs [28], (as DNA methylation occurs only on cytosine in eukaryotes [29], but primarily, on adenine in prokaryotes [30], the specificity of cellular uptake of select DNA molecules which are not degraded by host DNases [31], the structure of the DNA backbone [32-34], the sequence of the DNA fragment (immunoregulatory versus immunostimulatory sequences, IRS:ISS ratio) [23,35] and the localization of TLR9 during DNA uptake [3]. Recently Ohto, et al. demonstrated that TLR9 has two DNA binding sites, a CpG motif binding site and a 5'-xCx motif, and that when both sites are bound they cooperatively activate signaling to a greater extent than CpG DNA alone [36].

As the cognate ligand of TLR9 is DNA, this suggests that its response need not be limited to bacterial members of the microbiome. In most microbial communities, including the gut, the number of bacteriophage (phage) vastly outnumber the bacterial populations by an order of magnitude [37]. While most phage are sequestered within the bacterial host, studies have demonstrated that free phage can reside within the mucus layer and protect the gut barrier from invasive bacteria [38]. Intriguingly, a recent study by Gogokhia *et al.* has demonstrated that phage may also directly improve gut health via TLR9 signaling [39]. Although bacteriophage cannot directly infect eukaryotic hosts, studies have shown that they can be transcytosed through epithelial cell lines, leaving the open possibility that they may engage immune cells, such as DCs, of the lamina propria *in vivo*. Gogokhia, et al. demonstrated that phage could directly stimulate IFNγ production, and that this response was specifically due to phage DNA engagement of TLR9 [39].

Clinical implications of TLR9 signaling in the gut

As a unique regulator of both pro- and anti-inflammatory responses and its presence within a variety of cell types, TLR9 has gained traction as a possible receptor for therapeutic intervention of inflammatory diseases as well as adjuvant therapy in vaccine development.

The exact mechanism by which TLR9 detects DNAs remains to be elucidated, whether it is sequence or methylation dependent motifs, or tertiary structures/confirmations that confer the epitopes required for TLR9 binding and activation. Nonetheless, different types of DNAs (commensal origin, pathogenic, or self) confer unique signaling that can be exploited for therapeutic functions. Multiple studies have shown that administration of cell-free, probiotic DNAs can ameliorate the inflammation from DSS-induced colitis in mouse models [18,21-24,40]. This response is likely due to engagement of pDCs in the colon and the induction of type I IFNs. This anti-inflammatory response has also been obtained from the administration of synthetically derived Oligodeoxynucleotide (ODN) sequences as well as from pathogenic strains of *H. pylori* DNA [23,35,41]. The results of these studies were consistent despite different modes of administration, ranging from gavage and i.p. injections in mice to topical administration during endoscopy in humans [22,24,42].

As research into phage therapy, particularly within the context of the microbiome, continues to grow, recent advances have shown the utility of TLR9 in promoting phage-based vaccine development. Bacteriophage have been used to present small fragments of pathogen epitopes without infecting eukaryotic cells to cultivate an immune response [43,44]. Once the antigen-displaying phage is endocytosed by pDCs, the phage DNA then activates TLR9 to induce strong cytokine production, DC maturation, and ultimately a protective immune response to the displayed antigen [43]. This method has proven successful in using filamentous *fd* phage to develop a vaccine against *T. cruzii* in murine models [44]. However, TLR9 signaling may not always provide an adjuvant effect, as work with M13 phage has shown that TLR9 signaling dampens immune response, particularly in IgG1, IgG2b and IgG3 mediated responses [45]. These dichotomous results from different phage highlight both the exciting potential and highly nuanced applicability of phage therapy for vaccine design.

Conclusions

Despite the many unknowns surrounding TLR9, ranging from questions of its expression and localization, how it detects and discriminates between DNA ligands, to how it regulates unique and bifurcated signal transduction pathways in various cell types to be either pro- or anti-inflammatory- its critical role in establishing and maintaining gut homeostasis remains abundantly clear. Further research into this unique molecular rheostat will only prove to be fertile ground for potential therapeutics both within the gut and systemically.

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