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Innate Immunity: A Potent Target for Management of Inflammatory Bowel Disease

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1. Introduction

The gastrointestinal tract is a unique organ that cooperates with commensal flora to maintain physiological homeostasis. A layer of mucosa forms the interface between the host and the luminal contents where an elaborate immune system allows co-existence of diverse microorganisms and dietary antigens. The mucosal immunity regulates tolerance to commensal microorganisms while inducing effector immunity to pathogens through a fine interplay between innate and adaptive immune responses. In this process, innate immunity is responsible for recognition of microorganisms and initiation of effector and/or regulatory adaptive immune responses. Therefore, innate immunity is crucial for regulation of luminal microorganisms to maintain mucosal homeostasis.

Within the gastrointestinal mucosa, the effector and regulatory immune responses to commensal microorganisms are normally induced simultaneously, and constantly maintain mucosal immune homeostasis. Loss of this balance may cause uncontrolled mucosal inflammation, the state often seen in inflammatory bowel disease (IBD). IBD is a group of chronic inflammatory disorders in the gastrointestinal tract mainly classified into two types: ulcerative colitis and Crohn's disease. Although the etiology of IBD remains obscure and thus a curative therapy has not been established, genetic and immunological studies have provided cues for therapeutic targets of IBD based on the molecular pathogenesis of the disease. Because the central pathogenesis of IBD lies in abnormal mucosal immune responses to commensal flora, elucidation of immune regulation in gastrointestinal mucosa will help establish more effective strategies for treatment of IBD.

The initial step of the innate immunity is sensing pathogen-associated molecular patterns (PAMP)s through pathogen recognition receptors (PRRs), which induces a variety of gene expression via distinct intracellular signaling pathways. Different types of PRRs induce distinct sets of signaling pathways in response to the pathogens. Because different PRRs within a host cell can simultaneously recognize several molecular patterns of a pathogen, each pathogen triggers a unique combination of signaling pathways. In addition, different cell types may induce different responses to a pathogen, which increases host capacity to establish organized immune responses to a variety of pathogens. Diverse pathogen patterns are precisely recognized by TLRs, nucleotide-binding oligomerization domain (NOD)s and other PRRs including RIG-like helicases and C-type lectins (Table. 1). TLRs are expressed on

the plasma membrane or endosomes, and NODs are expressed within the cytosol of the most cell types in intestinal mucosa (Abreu *et al.*, 2005; Inohara *et al.*, 2005; Kawai and Akira, 2006). Interestingly, several reports have demonstrated up-regulation or down-regulation of certain TLR expression in intestinal epithelial cells and mucosal antigen-presenting cells in patients with IBD (Cario and Podolsky, 2000; Hausmann *et al.*, 2002). Genome-wide association studies have also linked mutations within the genes encoding NODs and TLRs with development of IBD (Franchimont *et al.*, 2004; Hugot *et al.*, 2001; Ogura *et al.*, 2001; Pierik *et al.*, 2006). These findings suggest that signaling of NODs and TLRs may be potent targets for the treatment of IBD.

| PRRs		Ligands	Sauces
TLRs	TLR1	Triacyl Lipoproteins	Mycobacteria
	TLR2	Peptidoglycan, Lipoteichoic acid	Gram-positive bacteria
	TLR3	Double Stranded RNA, poly I:C	Viruses
	TLR4	Lipopolysaccharide	Gram-negative bacteria
	TLR5	Flagellin	Bacteria
	TLR6	Diacyl LipopeptidesZymosan	MycobacteriaFungi
	TLR7	Single Stranded RNA	Viruses
	TLR8	Single Stranded RNA	Viruses
	TLR9	CpG-ODN	Bacteria and viruses
	TLR10	Unknown	Bacteria and Fungi
	TLR11	Uropathogenic bacteria	Uropathogenic Escherichia coli
	TLR12	Unknown	Unknown
	TLR13	Unknown	Unknown
NLRs	NOD1	meso-lanthionine, meso-DAP	Bacteria
	NOD2	Muramyldipeptide	Bacteria
	NLRCs	Flagellin. etc.	Bacteria
	NALPs	Muramyldipeptide, Bacterial RNA, crystals	Bacteria, Viruses, Uric acid crystals Maitotoxin
RNA helicases	RIG-1	Cytoplasmic dsRNA	Viruses
	MDR5	Cytoplasmic dsRNA	Viruses
Other	C-type lectins	Various	Bacteria, Viruses, and Fungi

Table 1. **PRRs and their respective ligands.**

Several TLR agonists and antagonists have been developed. Some TLR and NOD2 agonists have been shown to ameliorate murine IBD (Cario *et al.*, 2007; Fort *et al.*, 2005; Krieg *et al.*, 1995; Vijay-Kumar *et al.*, 2007a; Watanabe *et al.*, 2008). Defective immune responses to the NOD2 ligand have been reported in individuals homozygous for the major Crohn's disease-associated NOD2 mutation (Girardin *et al.*, 2003; Inohara *et al.*, 2003). Decreased mucosal expression of TLR3 has been observed in patients with Crohn's disease (Cario and Podolsky, 2000). Restoring the respective innate immune pathways may be a therapeutic strategy for

patients carrying these innate immune defects. By contrast, blocking certain TLR signaling may be another possibility for treating IBD since some TLRs are up-regulated in IBD mucosa. Therefore, combination strategies of agonists and antagonists that target individual innate immune signaling may need to be considered for future treatment to obtain more effective therapeutic strategies.

2. Role of innate immunity in the pathogenesis of IBD – clinical findings.

The innate and adaptive immunities are the two major immune systems of our body. Innate immunity confers an immediate response to microbial pathogens, which is antigen non-specific and normally completed within several hours (Mahida and Rolfe, 2004). In this process, PRRs play a crucial role in recognition of pathogens and initiation of respective signaling pathways (Figure. 1).
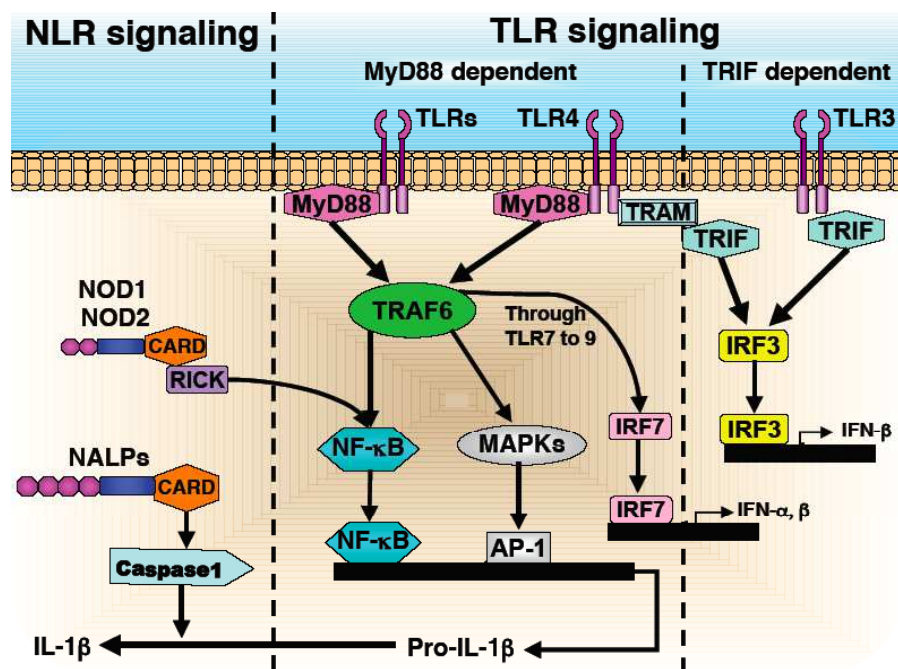
TLR signaling is initiated through the interaction of Toll/Interleukin-1 receptor (TIR) domains of the TLRs and recruited adaptor molecules. Depending on the adaptor molecule, TLR signaling may induce one of the two major downstream pathways, i.e., the MyD88-dependent and TRIF-dependent pathways. Most TLRs induce the MyD88-dependent pathway except for TLR3. In the MyD88-dependent pathway, tumour-necrosis-factor-receptor-associated factor 6 (TRAF6) is recruited and activated by phosphorylation and ubiquitylation to induce sequential phosphorylations of MAP kinases and IκB. These cascades lead to the activation of the transcriptional factors AP-1 and NF-κB, respectively. Activated AP-1 and NF-κB translocate to the nucleus and induce the expression of multiple pro-inflammatory genes including pro-IL-1β. The MyD88-dependent pathway may also induce Type I interferons (IFNs) through transcriptional factor IRF7 activation, when it is induced by TLR7, TLR8 or TLR9. The TRIF-dependent pathway can be induced directly by TLR3 and indirectly by TLR4 via recruitment of an adapter molecule TRAM (TRIF-related adaptor molecule), which results in the expression of the type I IFNs through activation of IRF3. NLRs induce signaling pathways through interaction of their Caspase recruitment domains (CARD)s with other CARD-containing molecules in the cytoplasm. NOD1 and NOD2 recruit a CARD-containing RICK resulting in NF-κB activation. NALPs form a complex of CARD-containing molecules called inflammasome, which activates Caspase-1. Activated Caspase-1 processes pro-IL-1β into mature IL-1β.

Fig. 1. Pathogen recognition receptors and their signaling pathways.

2.1 Innate immune function in the intestine

The rapid response of innate immunity to pathogens induces the production of antimicrobial peptides, phagocytic microbial killing and expression of cytokines, chemokines, and reactive oxygen species, leading to the recruitment of acute inflammatory cells to establish localized inflammation. Therefore, a defect in innate immunity may result in increased susceptibility of the host to pathogenic invasion even to commensals. In addition, proper induction of innate immunity is important to initiate an adaptive immune response that is antigen-specific and has an ability to temper ongoing inflammation through induction of regulatory immune properties. Abnormal innate immune signaling thus leads to inadequate induction of adaptive immunity that may result in disorganized immune responses to luminal pathogens.

2.2 Innate immune abnormalities in the pathogenesis of IBD

Clinical and basic science studies have indicated that etiology of IBD is associated with a disregulated adaptive immune response characterized by an aggressive T cell response to commensal flora, which is triggered by environmental factors particularly in genetically susceptible individuals (Packey and Sartor, 2008). Both environmental factors and the genetic alterations seen in patients with IBD vary, further making identification of exact etiology of IBD difficult. What is interesting in the pathogenesis of IBD is that any combination of environmental triggers and genetic alterations still result in aggressive T cell response to commensal flora forming chronic inflammation in gastrointestinal mucosa. On the other hand, several reports have demonstrated abnormal innate immune functions as an important pathogenesis of IBD (Latella *et al.*, 2010). The expression of mucosal TLRs, especially in epithelial cells and lamina propria antigen-presenting cells, is normally down-regulated, presumably to avoid inducing an excessive immune response to commensals (Melmed *et al.*, 2003; Otte *et al.*, 2004; Smythies *et al.*, 2005). However, several reports have shown increased expression of TLR4 and TLR2 in intestinal epithelial cells as well as lamina propria antigen-presenting cells in patients with both Crohn's disease and ulcerative colitis (Cario and Podolsky, 2000; Frolova *et al.*, 2008; Hausmann *et al.*, 2002; Szebeni *et al.*, 2008). Increased expression and *in vitro* cytokine responses of TLR2, TLR4, and TLR9 in peripheral blood mononuclear cells or dendritic cells have also been reported in IBD patients (Baumgart *et al.*, 2005; Baumgart *et al.*, 2009; Canto *et al.*, 2006; Jyonouchi *et al.*, 2010). Although increased TLR expression in peripheral blood cells has been found even in IBD patients in remission, up-regulation of these TLRs might not be a primary event in the pathogenesis of IBD, because expression of TLR4 and TLR2 is transcriptionally induced by inflammatory cytokines such as IFN-γ (Abreu *et al.*, 2002; Lin *et al.*, 2000; Rehli *et al.*, 2000). Similarly, NOD2 expression in intestinal epithelial cells is induced by inflammatory cytokines and increased in patients with IBD (Hisamatsu *et al.*, 2003; Rosenstiel *et al.*, 2003). Nevertheless, these findings strongly suggest a substantial involvement of innate immune abnormalities in the pathogenesis of IBD.

2.3 Genetic links between innate immunity and IBD pathogenesis.

Genome-wide association studies have demonstrated that most genetic alterations associated with IBD susceptibility relate to host mucosal barrier or anti-microbial functions, especially those involved in innate immune responses (Abraham and Medzhitov, 2011;

Vermeire *et al.*, 2011). For example, variants of the genes involving mucosal permeation and clearance of bacterial toxins such as mucin gene 19 (MUC19), organic cation transporter (OCTN) 1/2, multidrug resistance-1 (MDR1), have been reported to be associated with IBD (Barrett *et al.*, 2008; Ho *et al.*, 2005; Russell *et al.*, 2006; Waller *et al.*, 2006). Crohn's disease susceptibility genes NOD2, autophagy related protein 16-like 1 (ATG16), and immunity-related GTPase family M (IRGM) are involved in production of anti-microbial peptides and intracellular bactericidal functions (Hampe *et al.*, 2007; Hisamatsu *et al.*, 2003; McCarroll *et al.*, 2008; Rioux *et al.*, 2007; Wehkamp *et al.*, 2005). Moreover, TLR4 gene variants have been associated with both Crohn's disease and ulcerative colitis (Browning *et al.*, 2007; Franchimont *et al.*, 2004; Ouburg *et al.*, 2005; Torok *et al.*, 2004b). Polymorphisms in TLR1, 2, and 6 (TLR2 forms heteromeric receptor complexes with TLR1 or TLR6 to induce signal transduction) have been associated with greater disease extension in both ulcerative colitis and Crohn's disease (Pierik *et al.*, 2006). Polymorphisms in regulatory gene elements of TLR5 (stop codon) and TLR9 (promoter region) have also been associated with Crohn's disease (Hawn *et al.*, 2003; Torok *et al.*, 2004a).

Most of the IBD associated gene variants are loss-of-function type alterations. Therefore, in the pathogenesis of IBD, chronic inflammation due to aggressive T cell responses to commensal flora may be a result from the host's defective ability to maintain burdens of commensals and/or elimination of invading microbes and microbial toxins, rather than T cell function itself.

3. Role of innate immunity in the pathogenesis of colitis – animal studies

Mouse models of colitis are invaluable tools to determine the involvement of individual molecules in the pathogenesis of colitis. Gene recombination technology has provided ways to investigate the roles of individual PRRs in the pathogenesis of IBD by applying targeted gene knockout mice to animal models of IBD. Although none of the current murine models of IBD perfectly reproduce the human disease, each model has distinctive advantages to investigate a particular aspect of IBD pathogenesis. Most murine models of IBD require commensal flora to develop colitis, indicating that host response to commensal flora may play an important role in initiation of intestinal inflammation. However, the dextran sulfate sodium (DSS)-induced colitis, which is one of the well-established murine models of IBD, demonstrates more severe manifestations of colitis when depleted with the commensal flora (Kitajima *et al.*, 2001; Rakoff-Nahoum *et al.*, 2004). Since the underlying mechanism of DSS-induced colitis is associated with chemical damage of mucosal epithelium, this finding suggests a possible contribution of commensal flora to the protection of mucosa from damages induced by the noxious stimuli. This section details the roles played by the individual PRRs in induction and/or resolution of colitis based on knowledge obtained through studies in murine models of IBD.

3.1 Spontaneous colitis observed in PRR-deficient mice

Many knockout mice have been generated by targeting individual PRRs. Among them, only TLR5 and retinoid acid-inducible gene-I (RIG-I: a RNA helicase that recognizes intracellular RNA viruses) deficient mice develop spontaneous colitis, suggesting their regulatory roles in mucosal inflammation in the context of host-microbial interactions. Despite their importance in host defense against pathogens, most other PRR knockout mice do not

develop spontaneous colitis in the presence of commensal flora. Therefore, some compensatory mechanisms may exist involving both host and microbial factors. For instances, many pathogens carry multiple PAMPs. Host antigen-presenting cells can recognize surface PAMPs of a bacterial pathogen by TLR2 (and TLR1 or TLR6), TLR4, or TLR5, and the same pathogen can be recognized by TLR9 or Nod-like receptors after being digested in the cytoplasm. Importantly, these PRRs share several key innate immune signaling pathways including NF-κB and MAP-kinases. This redundancy of the pathogen recognition system may be reasonable to reduce the risks of outbreaks of pathogens that acquire evolutional changes to evade host immune responses. Cross regulations between PRRs exist as TLR4 deficiency protects TLR5-/- mice from developing spontaneous colitis (Vijay-Kumar *et al.*, 2007a). What we need to take into account is that the roles of PRRs during mucosal damage or inflammation may differ from their roles in homeostatic maintenance of mucosal integrity. Therefore, the lack of intestinal spontaneous phenotypes in the PRR knockout animals does not simply negate their contribution to the pathogenesis of IBD.

3.2 Role of PRRs in acute murine colitis

Consistent with the finding in germ-free mice, most TLR knockout mice demonstrate increased susceptibility to DSS-induced acute colitis. For example, deficiency in TLR2, TLR4, TLR5, and TLR9 has been individually associated with the increased susceptibility to DSS-induced colitis (Fukata *et al.*, 2005; Ivison *et al.*, 2010; Lee *et al.*, 2006; Rakoff-Nahoum *et al.*, 2004). Mice deficient in MyD88, a major downstream molecule of most TLRs except for TLR3, also demonstrated more severe disease than WT mice in this colitis model suggesting the importance of MyD88-dependent TLR signaling in protection against chemically induced mucosal damage (Fukata *et al.*, 2005; Rakoff-Nahoum *et al.*, 2004).

3.3 Role of PRRs in chronic murine colitis

TLR signaling may act differently during chronic colitis where sustained inflammation exists. Unlike their increased susceptibility to the acute DSS model, most TLR-deficient mice are protected in the chronic models of colitis. For example, TLR9-deficient mice demonstrate less severe manifestations of chronic colitis induced by four cycles of DSS treatments compared to WT mice (Obermeier *et al.*, 2005). As I mentioned earlier, TLR9-deficient mice should be more susceptible to each cycle of DSS treatment than WT mice, while mechanism inducing chronic inflammation may differ from acute mucosal damage in this model. MyD88 deficiency protects mice from development of chronic colitis in several IBD models including the IL-10-/- model (Rakoff-Nahoum *et al.*, 2006). IL-10-/- mice are known to develop spontaneous colitis due to uncontrolled pro-inflammatory cytokine production in the presence of commnesal flora (Berg *et al.*, 1996; Kuhn *et al.*, 1993).

There are conflicting data in IL-10 x TLR4 double knockout mice demonstrating either increased or reduced colitis compared to IL-10-/- mice depending on the facilities (Biswas *et al.*, 2011; Gonzalez-Navajas *et al.*, 2010). In the presence of *Helicobacter hepaticus*, IL-10 x TLR4 double knockout mice generate atypical regulatory T cells which possess pro-inflammatory properties (Matharu *et al.*, 2009). Therefore, TLR4 deficiency may be colitogenic or protective in the IL-10-/- model depending on the presence or absence of *H. hepaticus*. Regulatory T cells are indispensable for termination of ongoing inflammation, and TLR4 has been

suggested to foster the recruitment and/or proliferation of regulatory T cells in the intestine during colitis (Heimesaat *et al.*, 2007).

3.4 Compartmental specificities of the role of PRRs in intestinal inflammation

Since TLRs are expressed by most cell types in intestinal mucosa, the complexity of their function during chronic colitis may be due to the distinct roles played by TLR signaling in different cell types in the pathogenesis of chronic colitis. Compartmental differences of the role of TLR signaling in chronic colitis have been examined mainly in the MyD88 pathway (Asquith *et al.*, 2010; Fukata *et al.*, 2008; Gong *et al.*, 2010). Intestinal inflammation induced by *H. hepaticus* infection has been shown to be myeloid cell MyD88 dependent. In this infectious model, RAG2 x MyD88 double knockout mice as well as RAG2-/- chimeric mice that carry MyD88-deficient bone marrow demonstrate no intestinal inflammation but succumb to the infection, while MyD88 sufficient RAG2-/- counterparts show chronic colitis with splenomegaly but are protected from mortality (Asquith *et al.*, 2010). On the other hand, epithelial specific deletion of MyD88 results in spontaneous chronic inflammation in the small intestine (Gong *et al.*, 2010). These findings indicate that the MyD88 pathway in the myeloid compartment is necessary to induce intestinal inflammation against luminal pathogens and sufficient to block invasion of *H. hepaticus* at the mucosal interface.

Although there is a conflicting report, we and others have shown a defective colitogenic function of MyD88-/- T cells in an adoptive T cell transfer model of colitis, in which MyD88-/- naïve T cells have less ability to induce chronic colitis compared to MyD88 sufficient T cells after transfer to RAG-/- mice (Fukata *et al.*, 2008; Tomita *et al.*, 2008). In addition, we have shown that MyD88-/- regulatory T cells are unable to sufficiently suppress T cell mediated colitis, indicating that TLR signaling in T cells is important to elicit the full suppressive activities of regulatory T cells (Fukata *et al.*, 2008).

Ligation with TLR2 in combination with T cell receptor stimulation has also been reported to expand regulatory T cells in a MyD88-dependent manner, while it induces transient loss of their suppressive function (Sutmuller *et al.*, 2006). Therefore, TLR signaling in T cells seems to act as a co-stimulatory factor. Although antigen-presenting cells are thought to be a major cell type expressing TLRs, their TLR signaling is normally down regulated in the intestine (Rescigno and Matteoli, 2008; Smith *et al.*, 2005). Nevertheless, There unique roles for TLRs in individual cell types in intestinal inflammation may be revealed with future exploration.

3.5 Animal studies of phenotypic testing of disease susceptibility genes in human IBD

Testing the phenotype of individual susceptibility genes in IBD using mouse models is one of the priorities in the field of IBD research. Most IBD susceptible genes carry loss-of-function mutation, but by now we have not seen spontaneous intestinal inflammation in any mouse models that carry a functional deletion of the disease candidate gene. NOD2 deficient mice and those with an insertion of the human disease-associated mutation 3020insC do not demonstrate spontaneous intestinal inflammation but are more susceptible to DSS-induced colitis (Kobayashi *et al.*, 2005; Maeda *et al.*, 2005). ATG16L1 hypomorphic mice have abnormal Paneth cell granules and defective cryptdin production similar to Crohn's disease patients with ATG16L1 mutation, but these mice do not develop spontaneous colitis

(Cadwell *et al.*, 2008). The phenotypic discrepancies in these IBD susceptibility genes between human and mouse may be due to differences of species, but these results remind us the fact that the pathogenesis of IBD is complex of abnormalities of genetic, immunological, and environmental factors.

4. Challenges manipulating innate immunity (stimulate or suppress)

Manipulation of a particular immune pathway especially within a targeted organ is challenging. In this regard, manipulating an innate immune response as a therapeutic target of IBD has some advantages and disadvantages. The major advantage includes the non-specific nature of the innate immune responses, which provides broader effects than targeting adaptive immune responses which are antigen-specific. The rapid responses in both induction and resolution of innate immune signaling imply that exogenous control may be relatively easy. On the other hand, the multiple effects that can be induced by activation of a PRR may be a difficult point to enhance or suppress a specific function of the innate immune responses. In this section, possible targets in the innate immunity that may be utilized to treat or prevent intestinal inflammation and their potential pitfalls will be discussed through reviewing previously reported challenges in murine models of IBD (Table 2).

PRRs	Agonist / Antagonist	Model of IBD used	Major effect
TLR2	Agonist (Pam3CSK4)	Acute DSS colitis Chronic MDR1α-/-	Prevention and treatment. Strengthen epithelial barrier. Increase TFF3.
TLR3	Agonist (poly I:C)	Acute DSS colitis	Prevention. Involvement of Type I IFN?
TLR4	Antagonist (1A6) Antagonist (CRX-526)	Acute DSS colitis Chronic MDR1α-/-T cell transfer colitis	Prevention. Blocking acute inflammatory infiltrate. Blocking cytokine responses.
TLR5	Agonist (flagellin)	Acute DSS colitis	Prevention if it is administered intraperitoneally.
TLR9	Agonist (CpG-ODN) Antagonist (AV-ODN)	Acute DSS colitis TNBS colitis Chronic DSS colitis IL-10-/-, T cell transfer colitis	Prevention. Anti-apoptotic effect. Immuno-modulatory effect. Induction of tolerance. Blocking host response to luminal bacterial CpG.
NOD2	Agonist (MDP)	Acute DSS colitis TNBS colitis	Down-regulation of multiple TLR responses.

Table 2. Therapeutic challenges of PRR manipulation for murine models of IBD.

4.1 TLR2

Oral administration of a TLR2 agonist Pam3CSK4 has been suggested to have therapeutic potential in DSS-induced colitis (Cario *et al.*, 2007). The protective effect of the TLR2 agonist is associated with preservation of epithelial tight junctions and reduced apoptosis, and largely depends on the expression of the gap-junctional protein Connexin 43 in epithelial cells (Cario *et al.*, 2007; Ey *et al.*, 2009; Podolsky *et al.*, 2009). TLR2 stimulation also increases the colonic production of trefoil factor (TFF) 3 that facilitates wound healing and blocks apoptotic signaling (Podolsky *et al.*, 2009). Moreover, oral TLR2 agonist has been shown to delay induction of spontaneous colitis in MDR1α-/- mice (Ey *et al.*, 2009). The central pathogenesis of MDR1α-/- colitis is an impaired epithelial barrier function (Collett *et al.*, 2008). Therefore, the TLR2 agonist can be a cytoprotective rather than immunomodulatory strategy for acute as well as chronic phases of colitis. TLR2 agonists have not yet entered clinical trials for human diseases. Conversely, a TLR2 antagonist (OPN-305) has been developed, but its effects have not been tested on murine colitis (Hennessy *et al.*, 2010).

4.2 TLR3

Interesting data has been reported regarding the preventive effect of a TLR3 agonist on murine models of IBD (Vijay-Kumar *et al.*, 2007b). Pre-treatment of mice with a synthetic TLR3 ligand, polyinosinic:polycytidylic acid (poly I:C) protected mice from development of DSS-induced acute colitis (Vijay-Kumar *et al.*, 2007b). Similar effects of poly I:C treatment were observed in IL-10-/- mice. In this report, poly I:C was subcutaneously injected and the oral application did not show any protective effect on the colitis probably due to degradation of poly I:C by abundant RNAse in the gastrointestinal lumen. Although the exact mechanism underlying poly I:C-mediated preventive effect on colitis has been obscure, type I interferons which are predominantly induced by TLR3 signaling may have an immuno-regulatory capacity. Since intraperitoneal administration of high dose poly I:C (about ten times more than the dose in the former report) has been reported to cause mucosal destruction in the small intestine, we have to adjust the dose and route of poly I:C administration before clinical application (Zhou *et al.*, 2007a; Zhou *et al.*, 2007b). Because TLR3 expression has been shown to be significantly down regulated in the inflamed and non-inflamed mucosa of Crohn's disease as well as the mucosa of ileal pouches in patients with ulcerative colitis, stimulating TLR3 may restore an immunological defect caused by its down regulation (Cario and Podolsky, 2000; Heuschen *et al.*, 2007; Toiyama *et al.*, 2006). The existence of clinically tested poly I:C analogue (poly I:C_{12}U: Ampligen) is advantageous for the development of a TLR3 stimulation strategy (Nicodemus and Berek, 2010). Ampligen has been proven to have less toxicity than poly I:C and completed a phase III clinical trial for chronic fatigue syndrome (Nicodemus and Berek, 2010). Several antagonists for TLR3 signaling has been reported, but have not been developed as a therapeutic strategy for colitis (Bunting *et al.*, 2011; Cheng *et al.*, 2011).

4.3 TLR4

TLR4 is one of the most studied PRRs as a therapeutic target of IBD. A TLR4 antagonist (CRX-526; a synthetic lipid A mimetic molecule) has been shown to prevent the

development of acute (DSS-induced) and chronic (MDR1α-/-) colitis (Fort *et al.*, 2005). We have further detailed the effect of a specific TLR4 antagonist monoclonal antibody on induction and resolution of acute DSS-induced colitis (Ungaro *et al.*, 2009). Consistent with the former report, our TLR4 antagonist antibody suppressed induction of acute inflammatory infiltrate by blocking the expression of several chemokines in the large intestine when administered prior to DSS treatment (Ungaro *et al.*, 2009). However, blocking TLR4 signaling after colitis was established delayed mucosal healing from the DSS-induced injury (Ungaro *et al.*, 2009). These results indicate that there are multiple roles of TLR4 signaling in the pathogenesis of DSS-induced colitis; it is responsible for acute inflammatory infiltrate through induction of chemokines during induction of colitis, but also contributes to mucosal repair during resolution of colitis. The mechanism underlying the contribution of TLR4 to mucosal repair is associated with TLR4-dependent induction of cyclooxygenase 2 and following production of prostaglandin E_2 in response to mucosal damage (Fukata *et al.*, 2006). In addition, the therapeutic effect of the TLR4 antagonist antibody was not found in chronic model of T cell transfer colitis (Ungaro *et al.*, 2009). Therefore, blocking TLR4 may be beneficial in interfering with a particular aspect of colitis pathogenesis i.e., acute inflammatory infiltration, and thus combination therapies with cytoprotective agents may be required to proceed to the clinical stage using this strategy to treat colitis patients.

4.4 TLR5

Since deficiency of TLR5 results in spontaneous development of colitis, the targeting strategy of TLR5 has been focused on stimulating TLR5 signaling for treatment of colitis. There are conflicting data on the use of the TLR5 agonist flagellin as a therapeutic agent of acute DSS-induced colitis. Intraperitoneal injection of purified flagellin has been reported to be protective in acute DSS-induced colitis (Vijay-Kumar *et al.*, 2008). By contrast, rectal administration of flagellin has been reported to aggravate DSS-induced colitis (Rhee *et al.*, 2005). The discrepancy of the flagellin effect may be due to administration route (systemic vs. topical), but a recent report has suggested that flagellin-mediated aggravation of colitis is independent of TLR5 signaling as the exacerbation of DSS colitis by flagellin is also observed in TLR5-deficient mice (Ivison *et al.*, 2010). TLR5 agonist has been under pre-clinical stage, but further screening of its efficacy and adverse effects using different mouse models of colitis may be required in addition to clarifying the effector component of flagellin and optimization of their administration route.

4.5 TLR9

Augmentation and suppression of TLR9 signaling have been challenged in multiple mouse models of colitis. Unmethylated cytosin-guanosin dinucleotide (CpG) dinucleotides, the immunostimulatory components of bacterial DNA, are known to be a TLR9 ligand (Bauer and Wagner, 2002; Krieg *et al.*, 1995). Administration of CpG oligodeoxynucleotides (CpG-ODNs) has been shown to prevent the induction of DSS-induced colitis, but this treatment aggravates colitis when CpG-ODNs are administered after the onset of DSS colitis (Obermeier *et al.*, 2002; Obermeier *et al.*, 2003; Rachmilewitz *et al.*, 2002). The mechanism of these opposing effects of CpG-ODNs is associated with an anti-apoptotic effect and

immunostimulatory effect of CpG-ODNs, respectively. Since abundant bacterial ODNs naturally exist in the colorectal lumen that play a part of inflammatory stimuli in the setting of mucosal damage, pretreatment with CpG-ODNs has been suggested to induce host immune tolerance against endogenous bacterial ODNs (Obermeier *et al.*, 2003). Preventive effect of CpG-ODNs on induction of colitis has also been shown in other models such as 2,4,6-trinitrobenzene sulfonic acid (TNBS) colitis and can be achieved by oral administration, making this strategy further relevant (Rachmilewitz *et al.*, 2002). Although CpG-ODNs are generally thought as immunostimulative, CpG-ODN stimulation suppresses TNF-α and IL-1β expression in *ex vivo* colonic mucosa taken from active UC patients (Rachmilewitz *et al.*, 2006). A subset of patients with ulcerative colitis responds to Type I INF therapy through a yet unknown mechanism (Jacobs *et al.*, 2000; Madsen *et al.*, 2001; Nikolaus *et al.*, 2003). Since TLR9 signaling may induce Type I interferons which may act as immunomodulatory property during intestinal inflammation, emphasizing this aspect of TLR9 signaling may be another therapeutic target in the management of IBD (Katakura *et al.*, 2005).

Suppression of TLR9 signaling has also been beneficial for treating chronic murine colitis. Intraperitoneal as well as oral administration of adenoviral-ODN (AV-ODN) known to block the effect of bacterial CpG-ODN effectively suppressed intestinal inflammation during chronic DSS colitis (Obermeier *et al.*, 2005). The protective effect of AV-ODN was also observed in other chronic colitis models such as IL-10-/- and T cell transfer colitis models (Obermeier *et al.*, 2005). The protective effect of blocking TLR9 signaling during chronic colitis is consistent with the fact that TLR9-deficient mice have reduced severity of chronic colitis (Obermeier *et al.*, 2005). These results indicate that bacterial CpG-ODN abundantly existing in colorectal lumen is one of the indispensable factors inducing intestinal inflammation during chronic colitis.

4.6 NOD2

NOD2 signaling is a plausible therapeutic target as NOD2 mutations are associated with susceptibility to Crohn's disease. The mutations are known to be loss-of-function type mutations and thus the backup of this signaling is a reasonable idea. The use of NOD2 knockout models is consistent with the human disease setting. NOD2 transgenic mice are resistant to TNBS colitis (Yang *et al.*, 2007). In addition, intraperitoneal injection of a NOD2 ligand MDP protected mice from induction of acute colitis in DSS and TNBS models (Watanabe *et al.*, 2008). The mechanism underlying MDP-mediated protection is associated with down regulation of multiple TLR responses by NOD2 stimulation, as pretreatment of dendritic cells with MDP has been shown to inhibit cytokine responses induced by TLR stimulation. One concern is that the NOD2-deficient mice introduced NOD2 construct with a CARD15 frame-shift mutation were not protected from colitis by MDP (Watanabe *et al.*, 2008). Nevertheless, development of NOD2-stimulation strategy is advantageous because MDP has already been applied to several clinical trials of cancer treatments (Meyers *et al.*, 2008).

5. Conclusion and future direction

We discussed the unique aspects of innate immunity in the context of intestinal homeostasis and the pathogenesis of colitis. It is important to understand intestinal-specific innate

immune functions as host interactions with commensal flora are a crucial part of intestinal homeostasis. PRRs recognize microorganisms and thus play major roles in the regulation of the intestinal-specific innate immune functions. Since abnormal host immune responses to commensal microorganisms is thought to be a center of the pathogenesis of IBD, PRRs can be potent targets of therapeutic intervention. Despite our high excitement, recent studies in murine models of IBD have demonstrated the complexity of intestinal PRR signaling as therapeutic target of IBD. Much of the complexity lies in the fact that signaling of PRRs is not only involved in the induction of intestinal inflammation but also it is indispensable for maintenance of mucosal homeostasis. For instance, PRR signaling that contributes to the induction of colitis may be required for the mucosal repair process during resolution of inflammation; blocking a particular PRR signaling may suppress intestinal inflammation but may delay mucosal healing. The involvement of individual PRRs may also differ in different phases of colitis. Therefore, we may need to select phases of colitis to manipulate the selective PRRs to achieve more effective strategies. For example, TLR4 antagonists and TLR9 agonists appear to prevent intestinal inflammation if given prior to induction of colitis. By contract, TLR2 agonists and TLR9 antagonists may be more beneficial if they are given after the induction of or during the chronic phase of colitis. Nucleotide sensing PRRs may have a specific application in IBD therapy because of their potential immunomodulatory properties through induction of type I IFNs. Understanding of cell-type specific differences of PRR expression and responses and targeting their individual signaling pathways in intestinal mucosa may provide more practical strategies to utilize PRR signaling for the treatment of IBD.

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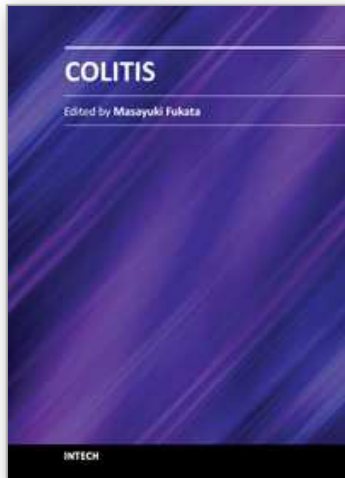
Colitis

Edited by Dr Fukata

Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

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