Review

Cellular and Molecular Immunopathogenesis of Ulcerative Colitis

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Ulcerative colitis (UC) is an inflammatory disease of the rectal and colonic mucosa and seems to result from a complex series of interactions between susceptibility genes, the environment and the immune system. Various components of the mucosal immune system are implicated in the immunopathogenesis of UC. Evidence from animal models also suggests that an altered immune response to the commensal microflora of the host plays a central role in the development of UC. So in this review, we elucidate the cells and molecules which are implicated in the immunopathogenesis of the disease from four aspects: antigens in the intestine, dendritic cells, toll like receptors and NF-κB in the UC. *Cellular & Molecular Immunology*. 2006;3(1):35-40.

Key Words: ulcerative colitis, immunopathogenesis, LPS, TLR, dendritic cell, NF-κB

Introduction

UC is an inflammatory disease of the rectal and colonic mucosa and seems to result from a complex series of interactions between susceptibility genes, the environment and the immune system. The aetiology of the diseases remains unknown, but the clinical features of the disease, histopathological findings and the therapeutic efficacy of immunosuppressive drugs indicate an involvement of the immune system in the pathogenesis of the disease (1). Various components of the mucosal immune system are implicated in the pathogenesis of UC. These components - luminal antigens, intestinal epithelial cells (IECs), lymphocytes, and cells of the innate and adaptive immune system and their secreted mediators (cytokines and chemokines) - contribute to the cascade of events that end in intestinal damage in a genetically predisposed host. Some molecules and receptors are also implicated in the immunopathogenesis of UC, such as TLR and NF-κB pathway. Evidence from animal models also suggests that an altered immune response to the commensal microflora of the host plays a central role in the development of UC (2-4). So in this review it will be introduced the effects of these cells and molecules which are implicated in the immunopathogenesis of the disease.

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Antigens in the intestine

Bacteria in the intestine are required for the normal maturation of the mucosal immune system and induction of genes in IECs that are required for electrolyte transport, nutrition, and microbial protection. The presence of luminal bacteria can also have a detrimental effect on genetically susceptible hosts, leading to chronic intestinal inflammation (5, 6). Evidence of a relationship between colonic microflora and the pathogenesis of UC comes from studies on genetically engineered animals that develop colitis when exposed to nonpathogenic colonic bacterial microflora, in an environment free from specific pathogens, but not when they are in a sterile germ-free environment. Furthermore, experimental colitis is attenuated when animals are treated with broad spectrum antibiotics (7). The term PAMPs (Pathogen-Associated Molecular Patterns) is an operational designation to describe biochemical motifs that are restricted to, and definitive of, microbial organisms. Structurally, PAMPs are complex macromolecules such as lipopo- lysaccharide (LPS), peptidoglycan (PGN), and lipoproteins, though unmodified polypeptides (flagellin) and nucleic acids (CpG rich DNA, dsRNA) may also be perceived as PAMPs. Specific PAMPs may be characteristic of specific classes of microbes. For example, LPS is a component of Gram-negative cell walls, while PGN is part of the Gram-positive cell walls, and dsRNA is typical of certain viral genomes or replication intermediates. It has also been pointed out that our definition of PAMPs comprises the signature of all microbial life, not necessarily recognized pathogens. Most or all of the PAMPs are fully represented in commensal intestinal organisms, not surprising given that normal flora can be proinflammatory under abnormal host conditions (8). There are receptors of PAMPs known as pattern recognition receptors (PRR). PRR

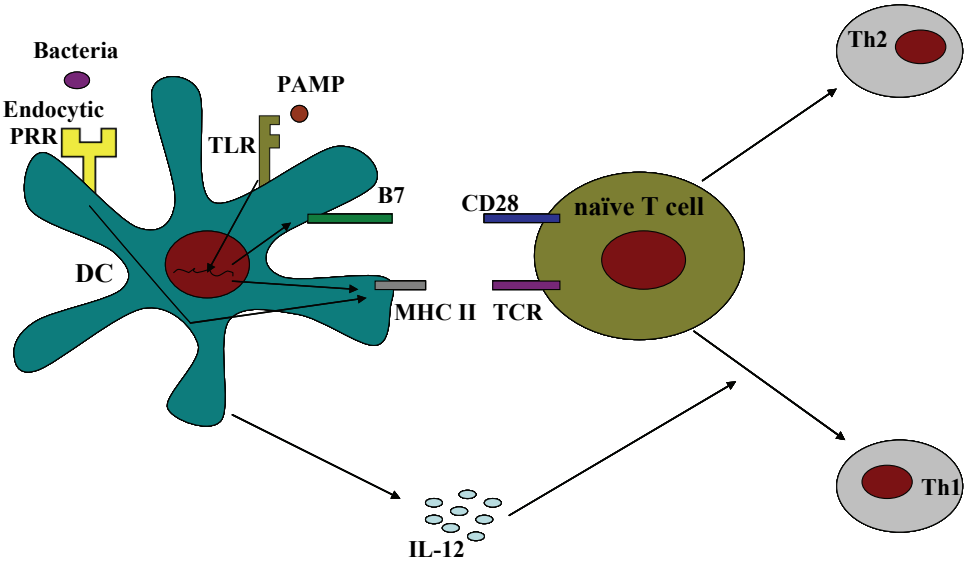

Figure 1. The effects of DCs on UC. When the intact of the intestinal mucosa is destroyed, many intestinal antigens will enter the lamina propria where they meet many DCs and activate them, then the activated DCs induce the innate and adaptive immunity. 1) Endocytic PRR was associated with the bacterial cell wall, then activated the DCs to deal with antigen; 2) TLR upregulated the expression of B7 and MHC II; 3) TLR activated the NF-κB pathway pathway; 4) TLR activated DCs to secrete IL-12, then induce Th0 to convert to Th1.

is another operational term to describe a eukaryotic receptor that specifically interacts with one (or perhaps several) PAMP(s). The most well-known pattern recognition receptors in mammals now are the famous TLRs.

Bacteroides and *E.coli* are the prominent Gram negative bacteria of rectal and colonic mucosa. They are the intestinal normal bacteria, so in normal condition they have no bad effects. But Matsuda H et al. demonstrated that the total bacterial count was significantly higher in the patients with UC compared with the control subjects. When classified according to species, the isolation frequency for bacteroides vulgatus, bacteroides ovatus and bacteroides fragilis was higher in the patients with UC than that in the control subjects. Moreover, the counts for *B.vulgatus* and *B.ovatus* were increased in the UC group (9). Although there are no specific pathogen, but Gram negative bacteria may have their important effect on the occurance and development of UC.

Dendritic cells in the UC

Dendritic cells (DCs) are antigen presenting cells that act as sentinels, acquiring antigen and transporting it to lymphoid tissue where they have the unique ability to activate naïve T cells. From this pivotal position at the intersection of innate and adaptive immunity, DCs shape many aspects of the developing immune response. They can determine whether non-responsiveness or an active immune response occurs, whether a Th1 or Th2 response predominates, and they may control tissue specific homing of antigen specific effector cells. Microbial products play a central role in modulating DC function and influencing these different immune outcomes. Using molecules including TLRs, DCs recognise and respond to microbe specific molecular structures, that's PAMPs. DCs can distinguish between and initiate different responses to even closely related organisms. Emerging evidence suggests that intestinal DCs are critical for regulation of immunity in the gut. They are likely to be pivotal in the balance between tolerance and active immunity to commensal microorganisms that are fundamental to UC (Figure 1).

DCs can be divided into subsets that differ in phenotype, function, and anatomical location (10, 11). These subsets may have predetermined functions or display plasticity, depending on their local environment. Two major DC populations are present in human peripheral blood. $CD11c^+$ DCs are termed DC1 or myeloid DCs. They express high level of the granulocyte macrophage-colony stimulating factor (GM-CSF) receptor but low level of the IL-3 receptor (CD123). In contrast, $CD11c^-$ DCs are called plasmacytoid or lymphoid DCs. They express high level of CD123 but few GM-CSF receptors and require activation before displaying characteristic stimulatory activity *in vitro*. They are sometimes called precursors of DC2 (pDC2) because of their relative immaturity. It was well known that monocytes are the precursors of the myeloid DCs. Of the 11 described human TLRs, monocyte-derived DCs predominantly express TLR2 and 4 (12, 13). It was also demonstrated that monocytes preferentially express TLR1, 2, 4, 5 and 8, whereas plasmacytoid pre-DCs strongly express TLR7 and 9. In accordance with these TLR expression profiles, monocytes respond to the known microbial ligands for TLR2 (PGN, lipoteichoic acid) and TLR4 (LPS), by producing tumor necrosis factor (TNF)-α and interleukin (IL)-6. In contrast, plasmacytoid pre-DCs only respond to the microbial TLR9-

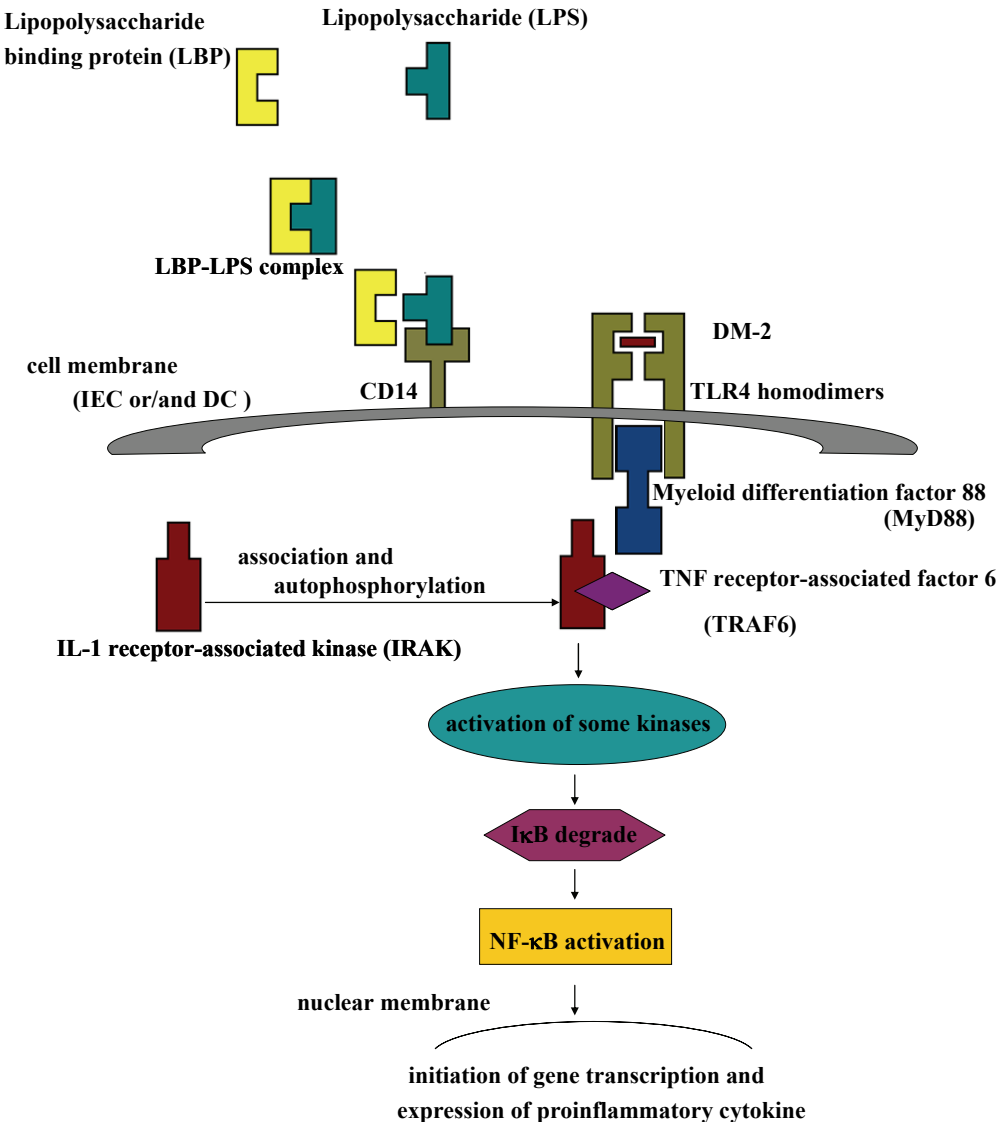

Figure 2. The LPS-TLR4 mediated NF-κB pathway. For the first TLR described in humans was TLR4, the expression and function of TLR4 in the intestine have been best characterized. LPS must first be associated with LBP, then the complex of LPS is sent to CD14, and CD14 gives the LPS to TLR4. Upon activated by LPS, TLR4 most likely forms homodimers, resulting in a conformational change in the cytoplasmic TIR domain and subsequent recruitment of an adapter named MyD88. MyD88 associates with the TLR *via* a homophilic interaction using the TIR domains. The death domain of MyD88 then recruits downstream IL-1 receptor-associated kinase (IRAK) to the receptor complex. IRAK is then autophosphorylated and dissociated from the receptor complex and recruits TNF receptor-associated factor 6 (TRAF6) that in turn activates downstream kinases. Subsequently, IκB is phosphorylated and degraded, leading to nuclear translocation of NF-κB and initiation of gene transcription.

ligand, CpG-ODNs [oligodeoxynucleotides (ODNs) containing unmethylated CpG motifs], by producing IFN-α. The expression of distinct sets of TLRs and the corresponding difference in reactivity to microbial molecules among subsets of pre-DCs and immatured DCs support the concept that they have developed through distinct evolutionary pathways to recognize different microbial antigens (14).

Baumgart DC et al. demonstrate that UC patients in remission have slightly smaller numbers of circulating PBDCs (peripheral blood dendritic cells) (mDC < pDC) compared with healthy controls. In acute flare ups, UC patients experience a significant drop of both pDCs (plasmacytoid dendritic cells) and mDCs (myeloid dendritic cells). The fraction of pDCs in UC patients in remission was calculated to be on average 0.39% of vital PBMCs (peripheral blood mononuclear cells) and dropped to 0.04% in acute flare ups. The mDC-1 fraction in UC patients in remission was calculated to be 0.23% of vital PBMCs and dropped to 0.11% in acute flare ups. A nearly perfect correlation between disease activity and the fraction of

circulating PBDCs was found for pDCs in UC patients at linear regression analysis expressed as quality of fit (r^2) and correlation coefficient - pDC and modified Truelove Witts severity index (r^2, 0.86; CC, 0.93). Preliminary evidence suggests a different response of UC patient DCs to microbial surrogate stimuli. Taken together, these data suggest a migratory process of blood DCs in UC patients to secondary lymphatic organs such as the intestine, where they potentially mature, become activated, and contribute to gut inflammation and tissue damage (15). This process may be the interaction between PAMPs of commensal intestinal organisms and TLRs on the DCs.

Toll like receptors in the UC

TLRs are emerging as key mediators of innate host defence in the intestinal mucosa, crucially involved in maintaining mucosal as well as commensal homeostasis. They comprise a class of transmembrane pattern recognition receptors, and play a key role in microbial recognition, induction of antimicrobial genes, and the control of adaptive immune responses. Recent observations suggest new (patho-) physiological mechanisms of how functional versus dysfunctional TLRs pathways may oppose or favour UC. In health, TLR signaling protects the intestinal epithelial barrier and confers commensal tolerance. In disease, aberrant TLR signaling may stimulate diverse inflammatory responses leading to acute and chronic intestinal inflammation with many different clinical phenotypes including UC.

Mammalian TLRs comprise a family of (so far) 11 individual type I transmembrane receptors which are characterized by three common structural features: a divergent ligand binding extracellular domain with leucine rich repeats, a short transmembrane region, and a highly homologous cytoplasmic Toll/interleukin 1 receptor (TIR) domain. As their name suggests, TIR motifs of TLRs exhibit significant homology to the intracellular signaling domain of the type I IL-1 receptor (IL-1RI) and therefore, TLRs are thought to belong to the IL-1R superfamily. So it's similar to that of the interleukin 1 receptor family and essential for initiation of downstream signaling cascades.

Different TLRs can recognize different PAMPs: TLR2, for example, recognizes bacterial lipopeptides and lipoteichoic acid which are found abundantly in cell walls of Gram positive bacteria (16). TLR2 may cooperate with TLR6 and TLR1, suggesting an essential mechanism for diversifying the repertoire of TLR mediated responses (17). RNA from double stranded and "sense" single stranded viruses activates TLR3 (18, 19), whereas RNA from "antisense" single stranded viruses activates TLR7 and TLR8 (20, 21). TLR4 is the major receptor for LPS activation (22), which may require the presence of accessory proteins, such as MD-2, CD14 and LPS binding protein (Figure 2). Flagellin and flagellated bacteria have been identified as specific ligands for TLR5 (23). Unmethylated CpG DNA found in prokaryotic genomes and DNA viruses modulates TLR9 (24) and TLR11, and is activated by uropathogenic bacteria (25). Because the first TLR described in humans was TLR4, the expression and function of TLR4 have been best characterized in the intestine. Gram-negative bacteria account for approximately 50% of the bacterial flora in the gut. Thus, LPS is abundantly present in the intestinal lumen. Several studies have described that expression of TLR4 is low in the normal colonic mucosa and upregulated in UC (26-28). Expression of TLR4 on colonic epithelial cells appears to be largely apical (29) but may traffic to the basolateral pole of polarized intestinal epithelial cell lines upon LPS stimulation (8). TLR4 requires expression of a secreted molecule, MD-2, for recognition of LPS and possibly for its transport to the cell surface. We have found that expression of MD-2 is very low in normal human colonic epithelium and increased in UC (27). Inflammatory cytokines, such as interferon γ (IFN-γ) and TNF-α, increase the expressions of TLR4 and MD-2 in intestinal epithelial cell lines and result in increased LPS responsiveness (26, 30) (Figure 2).

Regarding TLR expression in primary IECs, there is field wide consensus that TLR2 and TLR4 are present only in small amounts on IECs *in vivo*, thus minimising recognition of lumenal bacteria in the healthy intestine (26, 27, 31, 32). In contrast, TLR4 is significantly increased in primary IECs throughout the lower gastrointestinal tract in active disease of UC (31). Surprisingly, TLR4 immunostaining revealed a strictly cytoplasmic paranuclear distribution. This paranuclear compartment could be identified as the Golgi apparatus. LPS added to the supernatant was internalized by m-IC_{cl2} cells and colocalized with TLR4 (31, 33). This may explain why so many human IECs are hyposensitive to LPS.

As introduced in the above section myeloid DC can express TLR2 and TLR4. It has been demonstrated *in vitro* and *in vivo*, bacterial LPS and CpG DNA in the immunologic environment enhance Th1 T-cell development through DC producing IL-12 (34). In addition to DCs and antigen presenting cells, studies have demonstrated that regulatory T cells express a limited repertoire of TLRs too (4, 5, 7, 8, 35).

Spontaneous colitis occurring in STAT3 knockout mice does not develop when these mice are crossed with TLR4 knockout mice, suggesting that aberrant TLR4 signaling in response to the indigenous intestinal flora contributes to the development of intestinal inflammation through the Th1 pathway (36). These studies so far suggest that commensal mediated TLR4 signaling of mucosal T cells can be detrimental, leading to some forms of murine mucosal inflammation associated with excess Th1 responses. Maybe UC is one of them.

NF-κB in the UC

NF-κB is a collective term for members of the Rel family of DNA binding transcription factors that recognize and bind characteristic sequence motifs present in the promoters of many genes involved in immune and inflammatory responses. Structurally each of the NF-κB family proteins shares a highly conserved NH2-terminal region, known as the Rel

homology domain (37). Rel homology domain contains a nuclear location sequence and is involved in dimerization, sequence-specific DNA binding and interaction with the inhibitory IκB protein. In unstimulated cells, NF-κB dimers are bound to IκBs and retain in the cytoplasm in an inactive form. Stimuli such as proinflammatory cytokines and PAMPs can activate the classical NF-κB signaling pathway, mainly acting through the phosphorylation of IκBs (38).

Engagement of TLRs by PAMPs leads to the activation of innate immune responses (39), and a major signaling target of the TLRs is activation of the transcription factor NF-κB, a key regulator of immune and inflammatory responses (40). Upon activation, TLRs most likely form homodimers, resulting in a conformational change in the cytoplasmic TIR domain and subsequent recruitment of an adapter named MyD88 (Myeloid differentiation factor 88) (39, 41). MyD88 associates with the TLR *via* a homophilic interaction using the TIR domains. The death domain of MyD88 then recruits downstream IL-1 receptor-associated kinase (IRAK) to the receptor complex (41). IRAK is then autophosphorylated and dissociated from the receptor complex and recruits TNF receptor-associated factor 6 (TRAF6) that in turn activates downstream kinases. Several such kinases have been found to be involved in TLR/NF-κB signaling pathways including NF-κB-inducing kinase (NIK) and mitogen-activated protein kinase/ERK kinase kinase 1 (MEKK1) (40). Subsequently, IκB is phosphorylated and degraded, leading to nuclear translocation of NF-κB and initiation of gene transcription. It is not known whether all TLRs use the same signaling intermediates to activate NF-κB (Figure 2).

NF-κB regulates the expression of a wide variety of genes that play critical roles in innate immune responses. These NF-κB target genes include those encoding cytokines, such as IL-1, IL-2, IL-6, IL-12, TNF-α and so on (42, 43). Furthermore, some of these cytokine, such as IL-1 and TNF-α, which upregulate intestinal epithelial TLR4 expression *in vitro* have been found to play significant pathophysiological roles in triggering UC (26, 30). IL-1 and TNF-α also share a multitude of proinflammatory properties and appear to be critical to the amplification of mucosal inflammation in UC (44, 45). Both cytokines are primarily secreted by monocytes and macrophages upon activation and induce intestinal macrophages, neutrophils, fibroblasts and smooth-muscle cells to elaborate prostaglandins, proteases and other soluble mediators of inflammation and injury, as well as other inflammatory and chemotactic cytokines. Also an enhanced expression of IL-1 and TNF-α was found in UC.

Conclusions

Through the discussions above we may conclude that the immunopathogenesis of UC in genetic susceptible humans and animal models is the inappropriate immune responses driven by apparently normal intestinal microflora when epithelial barrier function was impaired. Breaks in this mucosal barrier may facilitate ligand permeation. Subsequent contact between luminal antigens and TLRs likely fuels continuing immune stimulation rather than tolerance towards luminal microflora. TLRs may exert their effects through activating the NF-κB pathway or other pathways which are participated in secretion of proinflammatory cytokines and chemokines that link to the adaptive immune system. But how they exert their effects exactly is not well known. Are there other molecules taking part in the process? With the studies going on more evidence will be found, and the immuno-pathogenesis of UC will be more clearly.

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