



Toll Like Receptors Signaling in Inflammatory Bowel Disease-Are They New Targets of the Future?

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Abstract

Inflammatory bowel disorder is related to situations ulcerative colitis and Crohn's disorder; however, its motive is unknown and the infection may be because of changing of intestine homeostasis with innate immunity performs a crucial position in spotting pathogens, hence keeping intestinal homeostasis. In 1985, Christiane Nüsslein-Volhard and Eric Wieschaus named it toll-like receptors because of the toll gene recognized in *Drosophila*. Toll-like receptors are known for their homeostasis of the immune system. The toll-like receptors from one to thirteen are expressed in humans and mice. Toll-like receptors signalling pathways are the myeloid differentiation factor 88-dependent pathway and TIR-domain-containing adapter-inducing interferon- β -dependent pathway, ends in the induction or suppression of inflammatory response. It is important to keep homeostasis in the intestine and targeting toll-like receptor signalling has been a challenge, in treating many diseases. With new emerging nano-inhibitors, small molecule inhibitors, oligonucleotide, lipid- analogs, microRNAs that inhibits TLR signalling, to control excessive inflammation can we expect a new ray of hope emerging in the future?

Keywords: Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis

Introduction

Inflammatory bowel diseases (IBDs) are associated with two conditions ulcerative colitis (UC) and Crohn's disease (CD). Over the years, Crohn's disease (CD) and ulcerative colitis (UC) has increased, but its cause is unknown and could be due to altering of gut homeostasis [1-5] with innate immunity playing an important role in recognizing pathogens thus maintaining intestinal homeostasis, but there exists a close relationship between IBD and immunity (Figure 1) and with diet [6]. With the increasing incidence and prevalence of inflammatory bowel disease (IBD),

including Crohn's disease (CD) and ulcerative colitis (UC), it has become a global health burden [7]. Some toll-like receptor (TLR) mutations have been identified and directly linked to IBD. The reason for IBD could be an improper response to microbiota and harmful agents. Any breach of the immune system will lead to a confrontation between the TLR and pathogen in the cellular membrane and wall of the gut [8,9] and there are, soluble forms of the TLRs also [10,11].

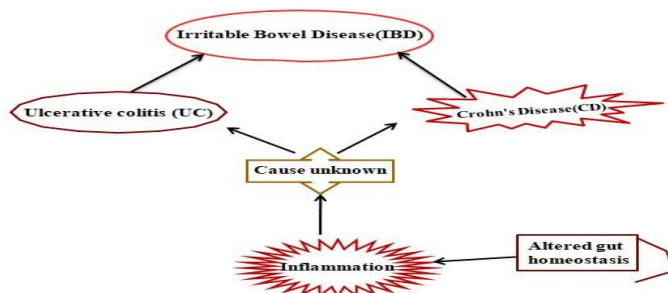


Figure 1: Inflammation and IBD correlation.

Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs) and C-type lectin receptors (CLRs) are the different pattern recognition receptors (PRRs) [12,13]. In 1985, Christiane Nüsslein-Volhard and Eric Wieschaus named it toll-like receptors (TLRs) due to the toll gene identified in *Drosophila* [14]. Toll-like receptors (TLRs) are a class of pattern recognition receptors that guards and recognizes pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPS) that play a key role in the innate immune system [12,15]. They are expressed on macrophages and other cells. TLRs

activate the immune response, once the microbes breach the skin or intestinal tract mucosa as, they are recognized by TLRs, and its expression elevated in the tissues exposed to lung and GIT [16] with unique patterns for specific cell types [17]. There are 13 different TLRs that have been identified in mammals, of which TLR1-11 in humans, TLR1-9, 11-13 in mice [18]. Damage-associated molecular pattern molecules (DAMPs) are endogenous molecules derived by tissue damage and the release of endogenous ligands regulating the inflammatory response by interaction with TLR2 and TLR4 (Figure 2) [19].

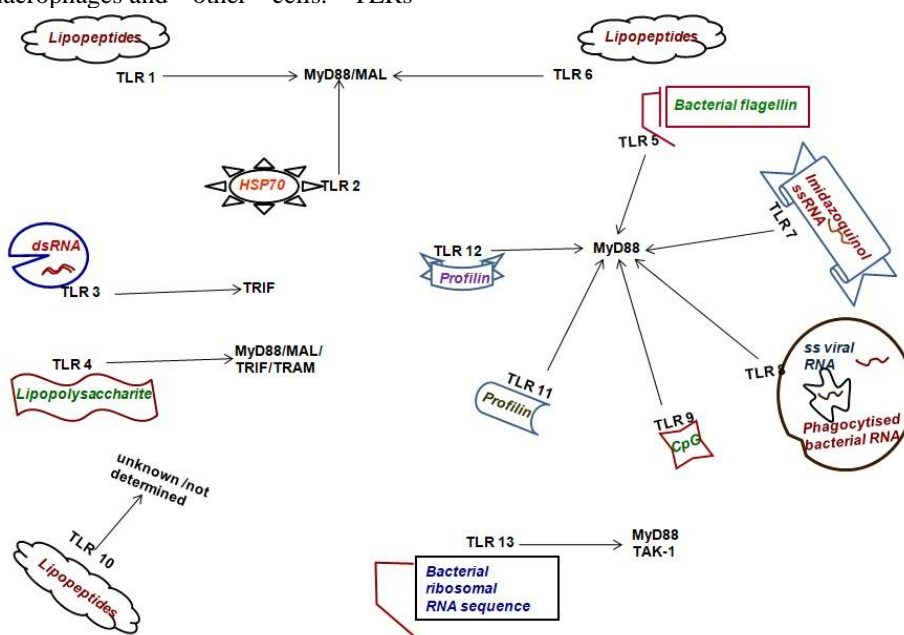


Figure 2: TLR 1-13, Adaptor and ligands.

The pattern recognition receptors (PRRs) family consists of toll-like receptors (TLR), that have the capability to balance the gut microorganisms in the gastrointestinal tract (GIT) which recognize whether friendly or unfriendly, for maintaining homeostasis of the immune system [20]. Nucleotide-binding oligomerization domain-containing protein-2 (Nod2) plays a role in TLR for the revival of the intestinal epithelium, in a recent study [21]. TLRs consisting of a double-strand DNA which is unmethylated, a single-stranded RNA, lipoproteins on activation become dimmers, triggering signaling pathways by inducing inflammatory

cytokines and by mediating the phosphorylation to activate NF- κ B. TLR activation also regulates the maturation of dendritic cells (DCs) inducing T cells (Th1 and Th2) proliferation and differentiation with myeloid differentiation primary response 88 (MyD88) being one of the most essential adaptors of the TLR pathway [22-24]. (Pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPS) recognize the invading pathogens, and activate the immune system (Figure 3).

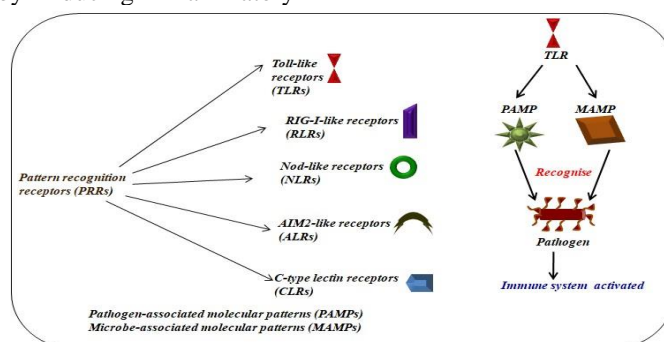


Figure 3: Pattern recognition receptors and activation of immune system.

TLR and its importance

The dendritic cells (DCs) that recognize pathogens and are killed by phagocytosis are expressed on toll-like receptors (TLRs) [25]. Pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPS) recognize the invading pathogens, thereby triggering a self-healing and tissue repair mechanism [26]. TLR1, 2, and 6 recognize the bacterial lipoproteins and glycolipids. The viral dsRNA is recognized by TLR3 while the bacterial and viral nucleic acids recognize TLR7, 8, and 9 [27]. TLR4 recognizes fibronectin and *lipopolysaccharide* (LPS) [28]; TLR5 recognises the bacterial flagellin, TLR11 and 12 recognize profilin, and the role of TLR10 unknown. When there is an infection, interferon type1 and cytokines activate TLR, since both TNF- α and IL-1 β activates the host defense mechanisms.

TLRs activate dendrite cells (DC), during sepsis, that stimulate apoptosis of infected cells, by inhibiting protein synthesis, thus limiting the infection, while TLR3, 7, and 8 have shown to play significant roles in allergen recognition and allergic rhinitis [29,30]. Cytokines secreted by the immune response activate peptides in antigen- presenting cells (ACP) resulting in chronic inflammation and tissue damage [31]. In the innate immune system, TLRs play a critical role in the host defense against microbes, which disrupts immune homeostasis that leads to a severe increase in the production of the pro-inflammatory cytokines. Hence by inhibition of TLR signal pathways an effective therapeutic method to predict suppression of inflammatory responses [25].

TLRs control innate immunity and regulate adaptive immunity, like T cell activation regulatory cells (T_{regs}) inhibit other T cells from functioning effectively to maintain immune tolerance thus having a key role to play and imbalance between T_{regs} and effector T cells is seen in patients with IBD [32]. When the progression of IBD goes out of control, the function of T_{regs} is suppressed and Th1, Th2, Th17, and NKT cells are activated, that release inflammatory cytokines [33]. With age gut flora composition and its quantity change. It gets specialized as the gut flora stabilizes. The gut flora in children is less diverse than in adults. The intestinal microbiota is important for maintaining the homeostasis of the gut. Conditions like UC and CD are likely to result with drugs like antibiotics that are known to affect the flora; the intestine becomes more susceptible to pathogens [34], due to defects in the innate immune system. In several metabolic disorders [35], TLR

inhibition can be achieved by stopping the signal transduction, as it interferes with signaling pathways.

TLR signaling

The TLR signaling pathway is characterized by Toll-IL 1 receptor (TIR) domain-containing adaptor protein (TIRAP), protein kinase, and a transcriptional factor to transfer the signal like the interleukin (IL)-1R family. NF- κ B and mitogen-activated protein kinase (MAPK) require MyD88 to activate it and to control the inflammatory response in the TLR signaling pathway. TIR domain-containing adaptor inducing IFN β (TRIF) is involved in TLR3 and TLR4 signaling pathway. The TLR signaling pathways activates NF- κ B and interferon regulatory factor (IRF) to produce inflammatory cytokines and IFNs, which promotes inflammation [36,37]. T cells are known to be associated with the TLRs and their signal pathway, so when there is loss of signals by T cells, the results are significant changes in the gut's microbial composition and in addition, also regulates B-cell responses for non-specific IgM, IgG, and IgA antibodies, involved in adaptive immunity that can mediate intestinal homeostasis and regulate microbiota. MyD88-dependent and TRIF-dependent pathway are the two pathways by which TLR signaling occurs.

Pathways involved in signaling

The IECs and Paneth cells are promoted by toll-like receptors to provide antimicrobial nondefensin family proteins Reg III β / γ which can kill Gram-negative bacteria. On the mucosal surface, the expression of Reg III β / γ activate causing an increased level of Reg proteins expression in IBD and the activated TLR signaling pathways protect intestines, against the invasion of pathogens [34].

Myeloid differentiation factor 88(MyD88)-Dependent Pathway

In response to MyD88-dependent pathway, dimerization of the TLR receptors occurs that utilizes all the TLRs except TLR3. NF κ B and Mitogen-activated protein kinase is activated mainly. MyD88 then recruits interleukin-1 receptor-associated kinase (IRAK) i.e. IRAK4, IRAK1 and IRAK2. IRAK kinase then phosphorylates and activates the protein TRAF6 activating TAK1 protein, facilitating binding to IKK- β TAK1 then phosphorylates IKK- β , allowing NF κ B to activate the inflammatory cytokines (Figure 4) [37].

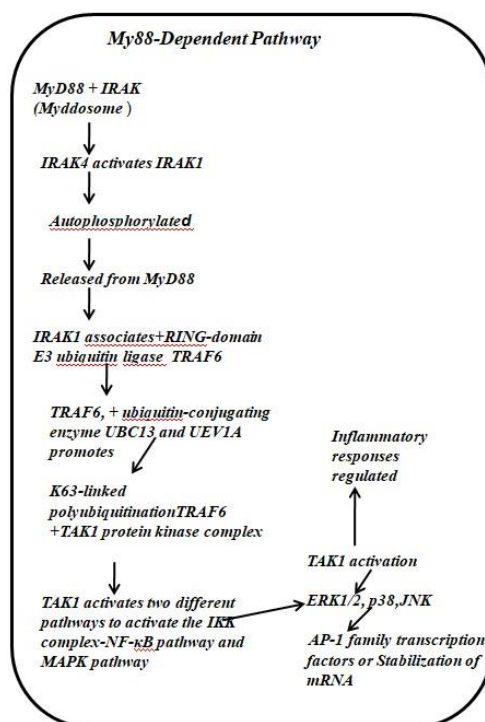


Figure 4: MyD88-dependent pathway.

TIR-domain-containing adapter-inducing interferon- β (TRIF)-Dependent Pathway Pattern recognition receptors, TLR3 and TLR4 utilize the TRIF-dependent pathway, are activated by dsRNA and LPS. For, dsRNA leads to activation of TLR3, leading to, recruitment of the adaptor TRIF.

TRAF6 recruits the kinase RIP-1, interacts with the TAK1 complex, activating NF- κ B and MAPKs and inflammatory cytokines.

TRIF activates the kinase TBK1 and RIPK1, activating the signaling pathway. IRF3 phosphorylates TRIF/TBK1 signaling complex allowing its translocation into the nucleus and production of interferon type I. The activation of RIPK1

causes activation of TAK1 and NF κ B like MyD88-dependent pathway (Figure 5) [37].

Activation of both the MyD88-dependent and TRIF-dependent pathways by TLR 4 induces a balanced production of inflammatory cytokines and type I IFN in controlling tumour cell growth and autoimmune diseases. TRAF3 as well as the TRIF complex in TLR4 signaling was shown to be incorporated into the MyD88 complex. TAK1 gets activated when the MyD88 complex is degraded. MyD88-dependent pathway is inhibited by TRAF3. NRDP-1, binds to induce the degradation of MyD88 and activate TBK1, reducing inflammatory cytokine and type I IFN [38].

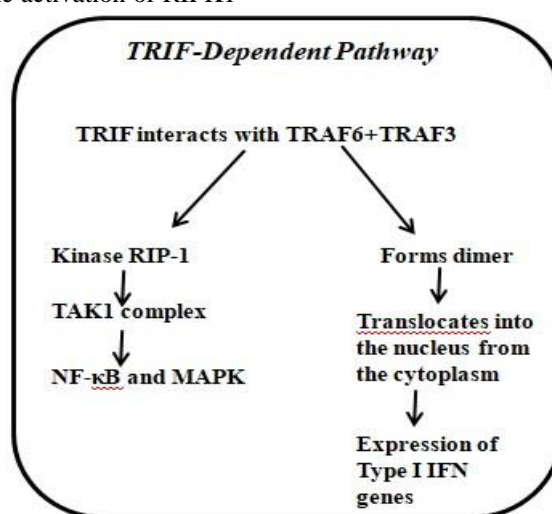


Figure 5. TRIF-dependent pathway.

Epithelial restitution mechanism

In mucosal healing of IBD, intestinal epithelial cells (IECs), goblet cells, and paneth cells play an important role.

Epithelial restitution occurs, when the IEC moves to the injured area and starts the process of healing, in which there is an increase in cell proliferation and differentiation that starts once injury occurs. The signals to induce nuclear factor- κ B (NF- κ B), signal transducer and activator of transcription 3 (STAT3), proliferation, survival of the cell are received by the IECs, leading to the closure of erosions and ulcerations. In intestinal homeostasis defensins and regenerating protein families (REG proteins) play a role [39-42].

TLR family

Toll-like receptors have been detected in both IECs and stromal tissue cells of the gastrointestinal tract (GIT). TLR1, 2, 3, 4, 5, and 9 are expressed in the small and large intestines of mice and humans [43]. Mucosal protection against oral infection caused by a Gram-negative pathogen is associated with TLR1 signal pathway [44], activation and transmutation in the composition of the gut bacteria [45], indicating that TLR1 and its signaling pathway might prevent chronic inflammation of the colon in IBD. TLR2 has been shown to selectively induce synthesis of trefoil factor TFF3, thereby favouring the survival of IECs and mucosal wound healing [47]. TLR2 is also known as cluster of differentiation 282 (CD282).

TLR3 is reduced in patients with IBD display a mixed TLR3 and TLR7 genetic variations in patients with IBD especially in the severe cases of UC, lead to TLR3 and TLR7 agonists using pDCs thus protecting inflammatory conditions [47,48]. TLR4 is expressed in the IECs [50] although the primary role of TLR4 is beneficial for induction of an inflammatory response protecting from invading bacteria and promoting mucosal integrity, and the role of the lipopolysaccharide (LPS) ligand -TLR4 in wound healing cannot be ruled out [50]. TLR5, in the colon, is expressed on basolateral surfaces of gut epithelial cells, while in the ileum its expressed on both apical and basolateral [52]. In the American and Indian populations associated with UC, the polymorphisms in the TLR5 genes, R392X and N592S, were significant and, the cytokine level was significantly modulated in patients with different genotypes of TLR4 and TLR5 single-nucleotide polymorphisms [52]. TLR5 expressed on IECs, not only regulates the composition and localization of intestinal microbiota but also prevents diseases associated with intestinal inflammation [53]. TLR5 overall is crucial in the development of IBD and may be a good target for developing a promising therapeutic strategy against IBD. IRF7 is phosphorylated, by IRAK1 and/or IKK α . The translocation into the nucleus regulates the expression of type I IFN while on the other hand MyD88-IRAK4-TRAF6 complex activates NF- κ B-dependent inflammatory cytokine induction [54]. TLR9 triggers MyD88-IRAK4-TRAF6-dependent NF- κ B activation after

CpG-DNA stimulation. TLR9 incorporates TRAF3 to activate IRF7 and induce type I IFN followed by AP3 binding to TLR9 that is required for type I IFN induction. Several other IRFs participate in TLR signaling other than IRF3 and IRF7. By interacting with IRF1 MyD88 contributes to TLR9-mediated cytokine production in the presence of IFN γ , whereas IRF5 is involved in the MyD88-dependent signaling pathway for inducing inflammatory cytokine production [55,56]. TLR8 is high in patients with active UC, but the mechanism is less known in disease conditions. Tumor necrosis factor (TNF)- α and IL-1 β , are associated with mucosal inflammation in UC, where TLR8 signaling is enhanced. An X-linked IBD susceptibility gene, is TLR8, suggesting the importance of genetic variation in innate immunity as a crucial factor of UC [57]. The bacterial CpG DNA located on TLR9 is recognized by intracellular endosomes [58]. It is interesting to note that IL-4 and STAT6 down regulates Treg cells resulting in IL-9 production, by inhibiting FOXP3 expression [59]. The severity of endoscopic and histological inflammation in UC patients are seen due to TLR9 expression [60]. Once TLR9 signaling pathway is activated by its agonist, significant improvements in clinical remission of UC were found to be associated with its mucosal healing and reduction of symptoms, clearly displaying the protective function of TLR9, highlighting the potential therapeutic relevance of TLR9 agonist in relation to mucosal injury and inflammation by inducing type I interferons [61]. Moreover, immunostimulatory DNA and probiotics appear to be mediated by their protective effects on barrier function, mucosal healing, and intestinal inflammation by activation of TLR9 signaling [62].

The signaling of TLR is mediated through the adapter proteins and kinase are targeted. Signals from TLRs lead to cell activation. MyD88, TIRAP (also called Mal/MAL), TRIF, and TRAM (TRIF-related adaptor molecule) are the four adapter molecules involved in signaling [63]. The cell types of the intestinal epithelium such as paneth cells, express TLR2, TLR4, and TLR5 with other cells of the immune system such as macrophages and dendritic cells (DCs) [64]. TLR2 and TLR4 are expressed on the macrophages. Colonic IECs from patients with inflammatory bowel disease (IBD) have higher expression levels of TLR4 in particular as well as lower levels of TLR2 and TLR5 [65]. The expression levels of the TLR2 and TLR4 are increased especially in the intestinal macrophages during inflammation [66]. In patients with IBD levels of TLR2 and TLR4 are also increased in the DCs displaying no differences between Crohn's diseases and ulcerative colitis. Finally, TLR2 and TLR4 are also increased in the intestinal macrophages with inflamed mucosa (Table 1).

Table 1: Toll like receptors Family 1-13.

TLR receptor	Adaptor	Ligands	Location	What is involved
TLR 1	MyD88/MAL	Lipopeptide, Glycolipids, Proteolipids	Cell surface	Monocytes, Macrophages, Dendritic cells, B lymphocytes
TLR 2	MyD88/MAL	Lipoteichoic acid, heatshock proteins 70 (HSP70)	Cell surface	Monocytes, Macrophages, Mast cells, Neutrophils, Myeloid dendritic cells
TLR 3	TRIF	Double stranded RNA	Cell component	Dendritic cells, B lymphocytes
TLR 4	MyD88/MAL/TRIF/TRAM	Liposaccharide, Fibrinogen	Cell surface	Monocytes, Macrophages, Neutrophils, Myeloid dendritic cells, Mast cells, Intestinal epithelium, Breast cancer cells
TLR 5	MyD88	Bacterial flagellin, Profilin	Cell surface	Monocytes, Macrophages, Neutrophils, Intestinal epithelium, Breast cancer cells, B lymphocytes
TLR 6	MyD88/MAL	Lipopeptides	Cell surface	Monocytes, Macrophages, B lymphocytes, Mast cells
TLR 7	MyD88	Imidazoquinolin, Single stranded RNA	Cell component	Monocytes, Macrophages, B lymphocytes, Plasmacytoid, Dendritic cells
TLR 8	MyD88	Single stranded RNA, Phagocytised bacterial RNA	Cell component	Monocytes, Macrophages, Dendritic cells, Mast cells, Intestinal epithelial cells in Crohns ulcerative colitis
TLR 9	MyD88	Unmethylated CpG, Oligodeoxynucleotide DNA	Cell component	Monocytes, Macrophages, Dendritic cells, B lymphocytes
TLR 10	Unknown/Not determined	Lipopeptides	Cell component	B cells, Monocytes, Macrophages, Intestinal epithelial cells
TLR 11 (mice)	MyD88	Profilin	Cell component	Liver cells, Kidney, Urinary bladder epithelium
TLR 12 (mice)	MyD88	Profilin	Cell component	Neurons, Plasmacytoid dendritic cells, Dendritic cells, Macrophages
TLR 13 (mice)	MyD88 TAK-1	Bacterial ribosomal RNA sequence, not methylated	Cell component	Monocytes, Macrophages, Dendritic cells

Soluble TLRs

TLR2, sTLR2 are known to bind to microbial ligands and, by trapping ligands directly thus prevents infection. The signaling cascade can be diminished, leading to decreased release of pro-inflammatory cytokines [67,68]. The sTLR2 is also produced by the intestinal epithelial cells and around six sTLRs have been identified for TLR1, 2, 4, and 6. The sTLR4 has been described as a marker for poor survival of early-stage non-small cell lung cancer. The role of sTLR4 in tumours is yet to be seen [69,70].

There are some non-bacterial ligands that interact with TLRs with the goal of reducing the risks associated with gut-related diseases, and glucans seen in oat, barley, and wheat, are of interest, that activates TLR4 [71]. TLR2 interacts in

the human immune system that activates NF- κ B cells than TLR4. TLR2 and TLR4 activate pectins (like lemon pectin), thus increasing the function of intestinal epithelial cell barrier and it has been noted that the higher is the activation of the MYD88/NF- κ B pathway could be due to a higher degree of methyl esterification.

Interaction in IBD between TLR and Microbiota

When TLRs are triggered, an inflammatory response occurs after the recognition of specific pathogenic molecules [72]. The distributions of TLRs are related to regulating intestinal homeostasis in the GIT, that, part can be achieved by the

detection of ligands belonging to commensal bacteria or factors that induce damaged epithelium [73]. There is already an existing relationship between TLRs and microbiota that is of utmost importance for the onset and microbiota when compared with normal tissue [74]. In chronic inflammation, NF- κ B activation and inflammatory cytokine release is increased due to the expression of TLR2 [75]. Maintaining intestinal homeostasis by TLR2, TLR4, and TLR5 is important as pathological conditions, alter TLR activity and whether these changes initiate the disease, or whether they represent the effect resulting from pro-inflammatory cytokines release, and needs to be studied [76]. TLR2 and TLR 4 in the colonic mucosa of children with IBD displayed higher levels, but their role in IBD is unclear [77]. Diabetes mellitus and rheumatoid arthritis, and those associated with CNS, autistic children and T2DM are other pathological conditions. T2DM patients with high levels of TLR4 were seen in albuminuria, suggesting its possible role in the pathogenesis of diabetic nephropathy, associated with TLRs activity [78].

Small molecule inhibitors (SMIs)

These are either synthetic or natural in origin that inhibits TLR signaling by accumulation in endosomes and lysosomes leading to suppression and, blockade of endosomal TLR7, 8, and 9 signals, thus decreasing cytokine production [79] that consists of SM934, CpG-52364, hydroxychloroquine sulfate (HCQ), and chloroquine (CQ) [80]. HCQ displayed a reduction in blood pressure and aortic endothelial dysfunction [81]. CpG-52364 was found to be therapeutically effective with fewer adverse effects than HCQ in SLE animal studies [82]. CQ has proven effectiveness with HIV, influenza, and dengue, and reduces sepsis-caused acute renal failure [83] and has shown to enhance the effects of cerebral ischemia in a rat model, which can be useful for patients suffering from cardiovascular diseases [84]. Angiotensin II receptor blockers (ARBs) and statins and antimalarials, inhibit TLR2 and TLR4 signaling [85].

New emerging nano-inhibitors

Non-anticoagulant heparin nanoparticles (NAHNP), a nano-inhibitor is a new class of TLR inhibitor that can target either a single pathway or multiple TLR pathways which inhibit cytokine production in mouse macrophages and also suppress LPS-induced MyD88-dependent NF- κ B activation. A TLR4 antagonist was developed using high-density lipoprotein (HDL)-like nanoparticle (HDL-like NP) by sequestering LPS. A new TLR4 antagonist that was developed was the cationic glycolipid-coated GNP system. Except for the peptide-GNP, P12, that displays inhibitory activity on multiple TLRs, the rest of the TLR nano-inhibitors act on TLR4 signaling. The anti-inflammatory activity of P12 in LPS-induced gene expressions, confer the reduction of the pro-inflammatory cytokines like IL-12 and IFN- γ by increasing anti-inflammatory cytokine IL-1RA [86-90].

progression of pathological conditions of the GIT, for which IBD is an example.

IBD is responsible for producing an inflamed intestinal mucosa with a reduced composition in the diversity of the

Conclusion

TLRs are the principal factors within the innate immune machine. The predominant situation must be retaining characteristics of TLRs, and the integrity of the innate immune machine. A new assignment in treating many illnesses is concentrated on TLR signaling. Neither unique genes nor environmental triggers were definitively diagnosed although there may be growing proof for IBD. Understanding the dynamic equilibrium that exists among microorganisms inside the intestine and the interest of the immune machine regulated through Some clinical trials have recommended that manipulation of TLR pathways may also provide a novel approach to reverse chronic liver diseases. TLRs are important for retaining or re-organizing homeostasis in the GIT. Small molecule inhibitors (SMIs), antibodies, oligonucleotide, lipid- analogs, microRNAs, and new emerging nano-inhibitors that inhibit TLR signaling have been developed to control excessive inflammation. TLRs 2 and 4 are two major SMIs and TAK-242 is an anti-sepsis SMI that targets the TLR4 signaling pathway. With new emerging nano-inhibitors, can we expect a new ray of hope emerging in the future?

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Conflict of Interest

No conflict of interest.

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