Role of toll-like receptors in inflammatory bowel disease

By: Kordjazy, N (Kordjazy, Nastaran)[1,2]; Haj-Mirzaian, A (Haj-Mirzaian, Arvin)[1,2,3]; Haj-Mirzaian, A (Haj-Mirzaian, Arya)[1,2]; Rohani, MM (Rohani, Mohammad Mojtaba)[1,2]; Gelfand, EW (Gelfand, Erwin W.)[4]; Rezaei, N (Rezaei, Nima)[5,6,7]; Abdolghaffari, AH (Abdolghaffari, Amir Hossein)[8,9,10,11]

PHARMACOLOGICAL RESEARCH
Volume: 129 **Pages:** 204-215

PHARMACOLOGICAL RESEARCH

Impact Factor

4.48	4.497
2016	*5 year*

JCR ® Category	*Rank in Category*	*Quartile in Category*
PHARMACOLOGY & PHARMACY	31 of 257	Q1

Data from the 2016 edition of Journal Citation Reports

Publisher
ACADEMIC PRESS LTD- ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND

ISSN: 1043-6618

Research Domain
Pharmacology & Pharmacy

Close Window

KeyWords Plus: INTESTINAL EPITHELIAL-CELLS; PATTERN-RECOGNITION RECEPTORS; MURINE EXPERIMENTAL COLITIS; MESSENGER-RNA EXPRESSION; DEXTRAN SULFATE SODIUM; ULCERATIVE-COLITIS; CROHNS-DISEASE; NEGATIVE REGULATION; IMMUNE-RESPONSES; INNATE IMMUNITY

Author Information

Reprint Address: Abdolghaffari, AH (reprint author)

+ ACECR, Inst Med Plants, Jahade Daneshgahi Res Soc, Karaj Qazvin Freeway,Supa Blvd,POB 141554364, Alborz, Karaj, Iran.

Reprint Address: Rezaei, N (reprint author)

Childrens Med Ctr Hosp, Dr Qarib St,Keshavarz Blvd, Tehran, Iran.

Addresses:

+ [1] Univ Tehran Med Sci, Expt Med Res Ctr, Tehran, Iran

+ [2] Univ Tehran Med Sci, Sch Med, Dept Pharmacol, Tehran, Iran

[3] Shahid Beheshti Univ Med Sci, Tehran, Iran

[4] Natl Jewish Hlth, Div Cell Biol, Dept Pediat, Denver, CO USA

[5] Univ Tehran Med Sci, Res Ctr Immunodeficiencies, Childrens Med Ctr, Tehran, Iran

[6] Univ Tehran Med Sci, Sch Med, Dept Immunol, Tehran, Iran

[7] USERN, NIIMA, Boston, MA USA

[8] ACECR, Inst Med Plants, Med Plants Res Ctr, Tehran, Iran

[9] Islamic Azad Univ, Pharmaceut Sci Branch, Dept Pharmacol, Tehran, Iran

[10] Univ Tehran Med Sci, Fac Pharm & Pharmaceut Sci, Dept Toxicol & Pharmacol, Res Ctr, Tehran, Iran

[11] USERN, GPIG, Tehran, Iran

E-mail Addresses: rezaei_nima@tums.ac.ir; amirhosein172@hotmail.com

Publisher

ACADEMIC PRESS LTD- ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND

Journal Information

Impact Factor: Journal Citation Reports

Categories / Classification

Research Areas: Pharmacology & Pharmacy

Web of Science Categories: Pharmacology & Pharmacy

See more data fields

9 of 820

Cited References: 129

Showing 30 of 129 **View All in Cited References page** *(from Web of Science Core Collection)*

1. **Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function** **Times Cited: 510**
By: Abreu, Maria T.
NATURE REVIEWS IMMUNOLOGY Volume: 10 Issue: 2 Pages: 131-143 Published: FEB 2010

2. **Pathogen recognition and innate immunity** **Times Cited: 5,626**
By: Akira, S; Uematsu, S; Takeuchi, O
CELL Volume: 124 Issue: 4 Pages: 783-801 Published: FEB 24 2006

3. **Toll-like receptors: critical proteins linking innate and acquired immunity** **Times Cited: 3,047**
By: Akira, S; Takeda, K; Kaisho, T
NATURE IMMUNOLOGY Volume: 2 Issue: 8 Pages: 675-680 Published: AUG 2001

4. **Toll-like receptor signalling** **Times Cited: 4,819**
By: Akira, S; Takeda, K
NATURE REVIEWS IMMUNOLOGY Volume: 4 Issue: 7 Pages: 499-511 Published: JUL 2004

5. **The effect of atorvastatin and its role on systemic cytokine network in treatment of acute experimental colitis** **Times Cited: 12**
By: Aktunc, Erol; Kayhan, Basak; Arasli, Mehmet; et al.
IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY Volume: 33 Issue: 4 Pages: 667-675 Published: DEC 2011

6. **NOD2/CARD15, TLR4 and CD14 mutations in Scottish and Irish Crohn's disease patients: evidence for genetic heterogeneity within Europe?** **Times Cited: 166**
By: Arnott, IDR; Nimmo, ER; Drummond, HE; et al.
GENES AND IMMUNITY Volume: 5 Issue: 5 Pages: 417-425 Published: JUL 2004

7. **Innate and adaptive immune responses related to IBD pathogenesis.** (View record in MEDLINE) **Times Cited: 51**
By: Arseneau, Kristen O; Tamagawa, Hiroshi; Pizarro, Theresa T; et al.
Current gastroenterology reports Volume: 9 Issue: 6 Pages: 508-12 Published: 2007-Dec

8. **Polymorphisms in the Toll-Like Receptor and the IL-23/IL-17 Pathways Were Associated with Susceptibility to Inflammatory Bowel Disease in a Danish Cohort** **Times Cited: 13**
By: Bank, Steffen; Andersen, Paal Skytt; Burisch, Johan; et al.
PLOS ONE Volume: 10 Issue: 12 Article Number: e0145302 Published: DEC 23 2015

9. **CARD15 and IL23R influences Crohn's disease susceptibility but not disease phenotype in a Brazilian population** **Times Cited: 39**
By: Baptista, Marcia Luiza; Amarante, Heda; Picheth, Geraldo; et al.
INFLAMMATORY BOWEL DISEASES Volume: 14 Issue: 5 Pages: 674-679 Published: MAY 2008

10. **The c.1-260C > T promoter variant of CD14 but not the c.896A > G (p.D299G) variant of toll-like receptor 4 (TLR4) genes is associated with inflammatory bowel disease** **Times Cited: 23**
By: Baumgart, Daniel C.; Buening, Carsten; Geerdts, Lars; et al.
DIGESTION Volume: 76 Issue: 3-4 Pages: 196-202 Published: 2007

11. **Ubiquitylation in innate and adaptive immunity** **Times Cited: 333**
By: Bhoj, Vijay G.; Chen, Zhijian J.
NATURE Volume: 458 Issue: 7237 Pages: 430-437 Published: MAR 26 2009

12. **The Structural Biology of Toll-like Receptors** **Times Cited: 193**
By: Botos, Istvan; Segal, David M.; Davies, David R.
STRUCTURE Volume: 19 Issue: 4 Pages: 447-459 Published: APR 13 2011

13. **Consequence of functional Nod2 and T1r4 mutations on gene transcription in Crohn's disease patients** **Times Cited: 54**
By: Braat, H; Stokkers, P; Hommes, T; et al.
JOURNAL OF MOLECULAR MEDICINE-JMM Volume: 83 Issue: 8 Pages: 601-609 Published: AUG 2005

14. **The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease** **Times Cited: 133**
By: Brand, S; Staudinger, T; Schnitzler, F; et al.
INFLAMMATORY BOWEL DISEASES Volume: 11 Issue: 7 Pages: 645-652 Published: JUL 2005

15. Title: [not available] **Times Cited: 1**
By: BRIKOS C
TOLL LIK REC TLRS Volume: 183 Pages: 21 Published: 2008

16. **Has toll-like receptor 4 been prematurely dismissed as an inflammatory bowel disease gene? Association study combined with meta-analysis shows strong evidence for association** **Times Cited: 73**
By: Browning, Brian L.; Huebner, Claudia; Petermann, Ivonne; et al.
AMERICAN JOURNAL OF GASTROENTEROLOGY Volume: 102 Issue: 11 Pages: 2504-2512 Published: NOV 2007

17. **Innate Immune Pattern Recognition: A Cell Biological Perspective** **Times Cited: 208**
By: Brubaker, Sky W.; Bonham, Kevin S.; Zanoni, Ivan; et al.

ANNUAL REVIEW OF IMMUNOLOGY VOL 33 Book Series: Annual Review of Immunology Volume: 33 Pages: 257-290 Published: 2015

18. **TNF alpha production to TLR2 ligands in active IBD patients** **Times Cited: 47**
By: Canto, E; Ricart, E; Monfort, D; et al.
CLINICAL IMMUNOLOGY Volume: 119 Issue: 2 Pages: 156-165 Published: MAY 2006

19. **Commensal-associated molecular patterns induce selective toll-like receptor-trafficking from apical membrane to cytoplasmic compartments in polarized intestinal epithelium** **Times Cited: 220**
By: Cario, E; Brown, D; McKee, M; et al.
AMERICAN JOURNAL OF PATHOLOGY Volume: 160 Issue: 1 Pages: 165-173 Published: JAN 2002

20. **Differential alteration in intestinal epithelial cell expression of Toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease** **Times Cited: 849**
By: Cario, E; Podolsky, DK
INFECTION AND IMMUNITY Volume: 68 Issue: 12 Pages: 7010-7017 Published: DEC 2000

21. **Toll-like Receptors in Inflammatory Bowel Diseases: A Decade Later** **Times Cited: 177**
By: Cario, Elke
INFLAMMATORY BOWEL DISEASES Volume: 16 Issue: 9 Pages: 1583-1597 Published: SEP 2010

22. **Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins** **Times Cited: 106**
By: Carpenter, Susan; O'Neill, Luke A. J.
BIOCHEMICAL JOURNAL Volume: 422 Pages: 1-10 Published: AUG 15 2009

23. **Toll-like receptors in inflammation, infection and cancer** **Times Cited: 211**
By: Chen, Keqiang; Huang, Jian; Gong, Wanghua; et al.
INTERNATIONAL IMMUNOPHARMACOLOGY Volume: 7 Issue: 10 Pages: 1271-1285 Published: OCT 2007

24. **The genetics and immunopathogenesis of inflammatory bowel disease** **Times Cited: 539**
By: Cho, Judy H.
NATURE REVIEWS IMMUNOLOGY Volume: 8 Issue: 6 Pages: 458-466 Published: JUN 2008

25. **Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction** **Times Cited: 1,314**
By: Chow, JC; Young, DW; Golenbock, DT; et al.
JOURNAL OF BIOLOGICAL CHEMISTRY Volume: 274 Issue: 16 Pages: 10689-10692 Published: APR 16 1999

26. **Lipopolysaccharide is in close proximity to each of the proteins in its membrane receptor complex - Transfer from CD14 to TLR4 and MD-2** **Times Cited: 328**
By: Correia, JD; Soldau, K; Christen, U; et al.
JOURNAL OF BIOLOGICAL CHEMISTRY Volume: 276 Issue: 24 Pages: 21129-21135 Published: JUN 15 2001

27. **The anti-inflammation effect of baicalin on experimental colitis through inhibiting TLR4/NF-kappa B pathway activation** **Times Cited: 44**
By: Cui, Li; Feng, Liang; Zhang, Zhen Hai; et al.
INTERNATIONAL IMMUNOPHARMACOLOGY Volume: 23 Issue: 1 Pages: 294-303 Published: NOV 2014

28. **Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD)** **Times Cited: 716**
By: Duchmann, R; Kaiser, I; Hermann, E; et al.
CLINICAL AND EXPERIMENTAL IMMUNOLOGY Volume: 102 Issue: 3 Pages: 448-455 Published: DEC 1995

29. **Regulation of the Antimicrobial Response by NLR Proteins** **Times Cited: 171**
By: Elinav, Eran; Strowig, Till; Henao-Mejia, Jorge; et al.

IMMUNITY Volume: 34 Issue: 5 Pages: 665-679 Published: MAY 27 2011

30. **Surface expression of toll-like receptor 9 is upregulated on intestinal epithelial cells in response to pathogenic bacterial DNA** **Times Cited: 90**

By: Ewaschuk, Julia B.; Backer, Jody L.; Churchill, Thomas A.; et al.

INFECTION AND IMMUNITY Volume: 75 Issue: 5 Pages: 2572-2579 Published: MAY 2007

Showing 30 of 129 **View All in Cited References page**

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com

Review

Role of toll-like receptors in inflammatory bowel disease

Nastaran Kordjazy[a, b], Arvin Haj-Mirzaian[a, b, c], Arya Haj-Mirzaian[a, b], Mohammad Mojtaba Rohani[a, b], Erwin W. Gelfand[d], Nima Rezaei[e, f, g, **], Amir Hossein Abdolghaffari[h, i, j, k, *]

[a] *Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Shahid Beheshti Universtity of Medical Sciences, Tehran, Iran*
[d] *Division of Cell Biology, Department of Pediatrics, National Jewish Health, Denver, CO, USA*
[e] *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
[f] *Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[g] *Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Boston, MA, USA*
[h] *Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Tehran, Iran*
[i] *Department of Pharmacology, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran*
[j] *Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[k] *Gastrointestinal Pharmacology Interest Group (GPIG), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 5 October 2017
Accepted 14 November 2017
Available online xxx

Keywords:
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Toll-like receptors
Dysregulation

ABSTRACT

Inflammatory bowel disease (IBD) is the chronic inflammation of the gastrointestinal tract. Recently, studies of the interplay between the adaptive and innate immune responses have provided a better understanding of the immunopathogenesis of inflammatory disorders such as IBD, as well as identification of novel targets for more potent interventions. Toll-like receptors (TLRs) are a class of proteins that play a significant role in the innate immune system and are involved in inflammatory processes. Activation of TLR signal transduction pathways lead to the induction of numerous genes that function in host defense, including those for inflammatory cytokines, chemokines, and antigen presenting molecules. It was proposed that TLR mutations and dysregulation are major contributing factors to the predisposition and susceptibility to IBD. Thus, modulating TLRs represent an innovative immunotherapeutic approach in IBD therapy. This article outlines the role of TLRs in IBD, focusing on both animal and human studies; the role of TLR-targeted agonists or antagonists as potential therapeutic agents in the different stages of the disease is discussed.

1. Introduction

Crohn's disease (CD) and Ulcerative Colitis (UC), collectively entitled inflammatory bowel diseases (IBD), are chronic inflammatory disorders of the gastrointestinal (GI) tract. These diseases are characterized by fatigue, bloody diarrhea, abdominal pain, weight loss, and increased risk of GI tumors. CD and UC can be distinguished by the tissues affected; CD might affect any region of the GI tract in a discontinuous and transmural manner, while UC is restricted to the surface mucosa of the colon and particularly the rectum [1,2].

The etiology of IBD remains unclear and the pathogenesis seems to be multidimensional and multifactorial, involving interactions among immune, environmental, and genetic factors. Dysregulation of the intestinal immune response, for example by breakdown of tolerance to normal bacterial flora or environmental antigens is suggested to play an important role in the pathogenic mechanism of IBD; it is plausible that initiation and perpetuation of the inflammatory responses in IBD may be a result of upregulated host defense reactions of the intestinal epithelium to commensal bacteria [3,4]. The immune system balance can be disturbed by either an overactive effector cell response of the immune system or a lack of regulatory mechanisms [5]. Genetic predisposition, such as polymorphisms of a number of contributory genes, are likely involved in the pathogenesis of IBD [6,7].

Toll-like receptors (TLRs) are a class of proteins that play a significant role in the innate immune system. They are type 1 transmembrane receptors that recognize molecules derived from pathogens. TLRs are a type of pathogen pattern recognition molecules (PRRs) [8] and recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [9]. Together with contributions of the secreted proteins MD-2 and CD14 [10], they stimulate downstream signal transduction molecules and lead to the activation of nuclear factor (NF)-κB and activator protein-1. This induces the expression of inflammatory mediators from effector cells,

* Corresponding author at: Institute of Medicinal Plants, ACECR, Karaj-Qazvin Freeway, Supa Boulevard, Jahade-Daneshgahi Research Society, P.O Box: 141554364, Alborz, Karaj, Iran.
** Corresponding author at: Children's Medical Centre Hospital, Dr Qarib St, Keshavarz Blvd, Tehran, Iran.
Email addresses: rezaei_nima@tums.ac.ir (N. Rezaei); amirhosein172@hotmail.com (A.H. Abdolghaffari)

https://doi.org/10.1016/j.phrs.2017.11.017
1043-6618/

directly influencing the immune response and bridging between innate and acquired immunity [11]. Expression of the innate immune receptors plays a key role in the process of abnormal and enhanced inflammatory responses. TLR mutations and dysregulation are major contributing factors in the predisposition and susceptibility to IBD. Previous cellular and animal studies indicated that activation of TLR responses in intestinal epithelium by commensal bacteria play a major role in colonic homeostasis and tolerance induction in the gut [12–14]. It is well-known that TLRs are essential components of innate immunity that recognize microbial components from bacteria, fungi and viruses. TLR activation can lead to secretion of proinflammatory mediators. Despite the fact that TLR activation results in the transcription of inflammatory and immunoregulatory genes, some studies have shown that TLR signaling in the intestine might also limit inflammatory responses and maintain colonic homeostasis [15].

TLRs are expressed in immune cells, fibroblasts and epithelial cells. In healthy and disease conditions, TLR1 to 9 have been detected in human intestine at least at the mRNA levels. Different cell types in the GI tract appear to express TLRs either constitutively or inducibly, including primary intestinal epithelial cells (IECs), monocytes or macrophages, dendritic cells of the lamina propria, and myofibroblasts, endothelial cells and adipocytes of the gut submucosa [16]. IECs of normal mucosa constitutively express TLR2, TLR3, TLR4 and TLR5 and their expression is altered in patients with IBD. For instance, TLR4 and TLR2 are extensively upregulated in IBD and other inflammatory conditions of the gut [17]. TLR8 and TLR9 were also upregulated in intestinal cells of patients with CD and UC [18,19]. On the other hand, in some studies the expression of TLR3 and TLR5 in the intestinal epithelium appeared downregulated in CD and UC patients [20–22]. These data suggest that IBD might be associated with specific alterations in selective TLR expression in the intestinal epithelium. Concerning previous descriptions, TLRs activation can lead to induction of inflammatory processes in the gut, on the other hand, sustained inflammation can lead to increased tissue injury, epithelial cell necrosis, and the subsequent release of DAMPs [23,24], which activate PRRs such as TLR2, and in turn, induce further inflammation in a repeating cycle that eventually results in chronic inflammation [25]. Taken together, the immune imbalance and inflammation in IBD might be either the cause or the effect of TLR dysregulation in IECs (Figs. 1 and 2).

Discovering the underlying molecular events in IBD is essential for developing new therapies. The primary approach for treating IBD is suppression of inflammation in the bowel during the active disease state and to restrain inflammation during remission [26]. Current treatments, including anti-inflammatory and immunosuppressive regimens, are not curative and merely lessen the degree of intestinal inflammation [27]. As a result, the limited outcomes with current treatment strategies accompanied by substantial side effects highlights the need for novel and complementary interventions. Data now defining the involvement of innate immunity and the significant role of the TLRs in IBD [28] suggest that more advantageous immunotherapeutic interventions could be through specific TLR-targeting strategies, some of which have been successfully introduced in other inflammatory conditions. In order to acknowledge this potential consequence, first, we will have to discuss the alterations of TLRs specifically in IBD by reviewing all conducted research. Finally, thorough consideration of all the information from this review, can lead us to an assumption toward the benefit of TLRs as therapeutic target for IBD.

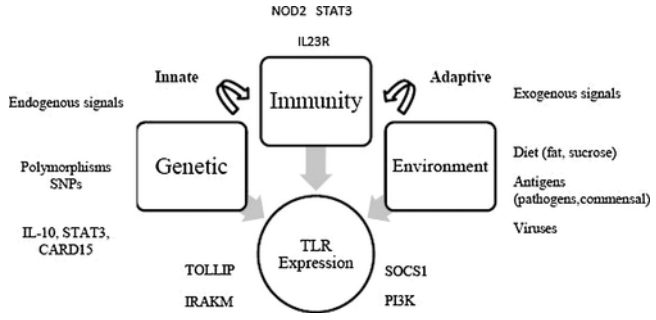

Fig. 1. Multidimensional regulatory triad controlling TLR function in the intestinal mucosa.

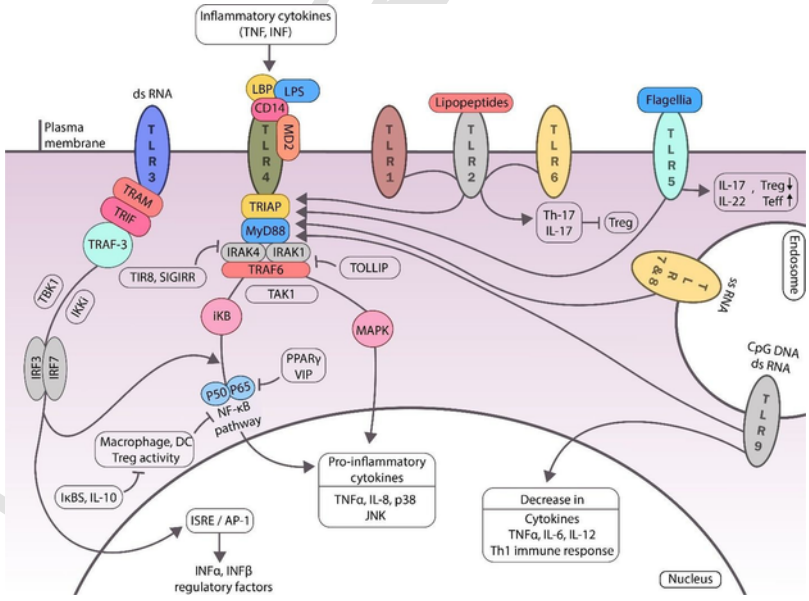

Fig. 2. Crosstalk between TLRs and related adaptor molecules and activated signaling cascade. TLRs play a significant role in the innate immune system. Except TLR3, which signals through TRIF, signaling of all TLRs is MyD88-dependent. TLRs recognize PAMPs and DAMPs and with contribution of regulatory proteins lead to stimulation of downstream signal transduction molecules, finally inducing/inhibiting secretion of inflammatory mediators and initiating biological response.

2. TLR structure, function, and signaling

Recognition of PAMPs involves the contribution of innate immune receptors, including TLRs, membrane-bound C-type lectin receptors, nucleotide binding oligomerization domain-like receptors, and retinoic-acid inducible gene-I-like receptors. Together they play a critical and integrated role in host defense against pathogens. In addition, these receptors recognize DAMPs to initiate controlled innate immune responses which are normally well-regulated to avoid autoimmune destruction [29–32]. TLRs share significant homology with type 1 integral membrane glycoprotein receptors since they are composed of an extracellular N-terminal ligand recognition domain, typically containing 16–28 leucine-rich repeats, and an intracellular C-terminal cytoplasmic signaling region, known as the Toll IL-1 receptor (TIR) domain owing to homology with the signaling domains of IL-1 receptor family members. The TIR domain mediates interactions between TLRs and TIR-domain-containing adaptor proteins, leading to the biological specificity of the TLR response [33–36]. The TIR domain also consists of locales fundamental for association between homo-or heterodimeric TLR subunits and additionally incorporating cytoplasmic adapter proteins to activate downstream cascades. The TIR domain is not particular to TLRs and is also involved in the action of receptors of the IL-1, IL-18, and IL-33 families, identifying possible convergence with common immune responses to different inflammatory stimuli [37]. To date, 10 human and 13 murine TLRs have been characterized (Tables 1–3). Human TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are generally localized in intracellular compartments [32,38,39]. TLRs possess the ability to recognize a wide spectrum of exogenous and endogenous stimuli including lipids and lipopeptides (TLR2/1, TLR2/6, and TLR4), proteins (TLR5 and TLR11), and nucleic acids (TLR3, TLR7, TLR8, and TLR9) [16,40]. Several endogenous TLR ligands have been identified, including intracellular proteins, nucleic acids, and extracellular matrix components. These ligands, often released from necrotic, stressed, or damaged cells, contribute to activation of the innate immune response, acting as endogenous danger signals to induce and promote defensive inflammatory responses [32,41].

Except for TLR3, all TLRs signal through the adaptor protein myeloid differentiation factor 88 (MyD88) [16]. The TLR3 pathway requires TIR-domain-containing adapter-inducing interferon (TRIF), while TLR4 signals through both MyD88-dependent and TRIF-dependent signaling pathways [42,43]. Following ligand binding, TLRs stimulate signaling components to initiate several immune responses. For example, TLR1/2, TLR2/6, and TLR5 induce inflammatory cytokines, while TLR3 and TLR4 induce both type I interferon and inflammatory cytokine responses [44] These differences are likely the result of different signaling cascades involving different TIR-domain-containing adaptor molecules.

The signal transduction pathways initiated and propagated via complex intracellular signaling pathways results in the activation of the transcription factor NF-κB and activating protein 1 following the cascades of mitogen-activated protein kinases. This leads to induction of gene transcription of many proinflammatory cytokines, such as IL-1, IL-6, IL-12, and TNF- α, chemokines, adhesion molecules, acute phase proteins, costimulatory molecules, and other transcription factors [45]. The final result depends on the crosstalk between TLRs and adaptors and the activated signaling pathways [32,46]. Regardless of the differences, each of the downstream effects is involved in conservation of host homeostasis through control of the surrounding milieu.

Throughout the GI tract, both epithelial and non-epithelial cells express TLRs. The ability of the host to recognize commensal non-pathogenic and pathogenic organisms resides in the particular tissue expression of TLRs in GI tract. It was reported that the expression of a functional TLR such as TLR2, TLR3, TLR4, TLR6 or TLR7 was increased after intestinal myofibroblasts were stimulated by LPS. In this manner it could be shown that the expansion of TLRs is a reaction against pathogens in the subepithelial compartment [47]. Likewise, it has been found that TLR2 and TLR4 are expressed in crypt epithelial cells, while mature IECs express TLR3. Expression of TLR2 and TLR4 in crypt epithelial cells does not always appear advantageous to the host in light of the fact that these cells don't specifically contact commensal organisms. Additionally, expression of TLR3 in the intestinal lumen may have a limited role in that the TLR3 ligand, viral dsRNA, is not normally present in the gut microflora [48]. So, it seems that mechanisms involved in regulation of TLRs expression and activity in the gut is crucial for the balanced gut immunity. Studies in humans as well as animal models have demonstrated some of the underlying mechanisms which regulate TLR expression and activation in the GI tract; these mechanisms provide the GI mucosa with the ability to avoid immune reactions against dietary antigens and commensal flora [49]. Regulation of TLRs in the GI tract may exhibit unique features due to the particular environment with continuous exposure to commensual microflora and invading pathogens. Expression and activation of TLRs could be regulated through different mechanisms including downregulation of surface expression of TLRs on the gut epithelium, the specific movement and compartmentalization of TLR-communicating cells in the stomach, and moreover the existence of TLR-foes or tightening factors that

Table 1
Toll-like receptors (TLRs) characteristics.

TLR	Adaptors	Accessory Molecules	Ligands	Cell Types
TLR1	MyD88/TRIAP	PRAT4A, gp96	Triacyl lipopeptides	Monocytes/Macrophages, Dendritic cells, B lymphocytes
TLR2	MyD88/TRIAP	CD14, CD36, RP105/ MD-1, gp96	Lipoproteins/lipopeptides, peptidoglycan, lipoteichoic acid, others.	Monocytes/Macrophages, Neutrophils, Myeloid dendritic cells, Mast cells
TLR3	TRIF	CD14, Unc93B, gp96	dsRNA (virus)	
TLR4	MyD88/TRIAP, TRIF/TRAM		Lipopolysaccharide (LPS), HSP, Fibrinogen, Heparin sulfate, others.	Monocytes/Macrophages, Neutrophils, Myeloid dendritic cells, Mast cells, B lymphocytes/intestinal epithelium
TLR5	MyD88	gp96	Flagellin	Monocytes/Macrophages, Dendritic cells, Intestinal epithelium
TLR6	MyD88/TRIAP	CD14, CD36	D-acyl-Lipopeptides	Monocytes/Macrophages, Mast cells, B lymphocytes
TLR7	MyD88	Unc93B, gp96, PRAT4A	ssRNA	
TLR8	MyD88		ssRNA	
TLR9	MyD88	HMGB1, LL37, Unc93B, gp96	Unmyelinated CpG DNA, oligodeoxynucleotide DNA	Monocytes/Macrophages, Plasmacytoid dendritic cells, B lymphocytes
TLR10	MyD88			
TLR11	MyD88		Uropathogenic bacteria	

Table 2
Association of primary genetic defects in TLR function with IBD susceptibility/progression.

TLR1-R80T	UC pancolitis
TLR2-R753Q	UC pancolitis, impairs IEC restitution and communication
TLR4-D299G and T399I	Increased susceptibility to IBD, interrupts LPS signaling
TLR5-stop	decreased susceptibility to IBD, reduces adaptive immune responses to flagellin
TLR6-S249P	decreased susceptibility to IBD proctitis
TLR9-(-1237T/C), −(2848A/G) (SNP)	CD variants CARD15, IL23R, DLG5

Table 3
Association of dysregulation of TLRs expression with CD and UC.

TLRs	Expression in CD	Expression in UC
TLR1	Not changed	Not changed
TLR2	Not changed	Controversial: not changed/upregulated
TLR3	Controversial:not changed/ downregulated	Controversial: not changed/upregulated
TLR4	Increased	Increased
TLR5	Increased	Increased
TLR6	Not changed significantly	Not changed significantly
TLR8	Not changed	Controversial: not changed/upregulated/ downregulated
TLR9	Not changed	Controversial: not changed/increased expression

could reduce the expression of TLRs [21,50]. These components can recognize and rapidly initiate effective host defense reactions against invading pathogens. Expression of TLR antagonists is another process in the regulation of TLR activities in the GI mucosa as they inhibit the activation of TLRs at the cell surface. Toll-interacting protein (TOLLIP) inhibits TLR signaling through interaction with IL-1 receptor-associated kinase (IRAK), a major component of the TLR signaling cascade [51]. TOLLIP mRNA was significantly expressed in healthy colonic mucosa, and after delayed presentation of TLR ligands to TLR-hyporesponsive primary and immortalized IEC, TOLLIP was upregulated [52,53]. TLR-attenuating factors are known to suppress TLR signaling. The deficiency of some of these TLR-attenuating factors has been demonstrated in cases of intestinal inflammation [54].

3. The role of TLRs in human IBD

Recent studies suggest that dysfunction or dysregulation of TLR expression and activation in IEC as well as polymorphism in TLR genes are contributors to the development and progression of IBD [55]. The high expression of certain TLRs in IBD may be a secondary event, the consequence of inflammatory mediators. On the other hand, the increased expression of TLRs may result from hyperreactivity to the commensal flora [56]. Some of IBD patients may be characterized by dysregulated, constitutively active TLR signaling. Notwithstanding the increased TLR signaling as a propagating or contributing factor to gut inflammation, decreased TLR signaling might also play a deleterious role in IBD. Additionally, several studies have assessed the functional contribution of TLR polymorphisms to IBD susceptibility [57]. Although TLR polymorphisms may not predict the overall disease risk, they may influence phenotype and severity of patients with IBD. It remains to be determined whether the TLR dysregulation in IBD dictates the pathological impact or is a direct cause of the chronic inflammatory response. Adding to the complexity of trying to associate specific clinical phenotypes with TLR findings are inconsistencies among the IBD patients. This is not surprising given the complexities between patients and even in the same patient at different stages of their disease.

3.1. TLR1

Studying the polymorphisms of the TLR1 gene in a Danish population, Bank et al. concluded that the homozygous variant genotype of TLR1 T743C is associated with increased risk of IBD development, both CD and UC. The effect might be due to activation of inflammatory pathways such as NF-kB and various cytokines [58].

On the other hand, the expression of TLR1 mRNA was studied in an IBD cohort in which no changes in receptor expression was observed [59].

3.2. TLR2

TLR2 is ligated by bacterial lipoproteins, lipoteichoic acids, peptidoglycan, and zymosan. Human TLR2 interacts with CD14 to form a LPS receptor complex. In biopsy samples from patients with IBD, a significant increase in TLR2 expression was detected in the non-impaired (by inflammation) parts of the gut, in the terminal ileum of UC patients. In this study, TLR2 expression was significantly increased, regardless of the activity of disease in UC patients. In addition, CD14 expression was highly upregulated in the areas affected by IBD, specifically in the terminal ileum of CD patients and also in the cecum and rectum of UC patients compared to controls [60]. On the other hand, TLR2 mRNA expression was determined to be considerably higher in active UC versus quiescent UC disease. Further, TLR2 mRNA levels correlated with the mRNA levels of inflammatory cytokines including IL-6 and TNF [61]; the mRNA profiles were positively correlated with inflammatory activity, especially for IL-6, suggesting an activity marker of IBD [62]. Similarly, marked TLR2 mRNA expression and protein levels were detected in the cytoplasm of IEC from UC patients compared to normal controls [63,64]. It was shown that a noticeable increase of TNF-α response to TLR2 ligands correlated with higher TLR2 expression in IBD, leading to the suggestion that an abnormal mechanism may provide excessive inflammatory mediators during the active phases of UC and CD [65]. This receptor upregulation is assumed to increase the stimulation of immune and inflammatory pathways activated through ligand binding. Increased TLR2 expression may enhance the recognition and presentation of antigens by inflammatory cells, leading to responses to normal bacterial flora, breaking immune tolerance and resulting in intestinal injury. It is assumed that IBD patients may lose tolerance to intestinal flora. It was reported that TLR2 correlated with colonoscopy and histopathology scores, disease activity, and also the fecal microbial score [63]. Thus, disease severity may be related to TLR2 expression. Hence, activation of gut mucosal immunity may be triggered by the imbalance of intestinal microbial flora. In contrast to these findings, no changes were detected in the expression levels of theTLR2 receptor in UC and CD patients [59].

Although the results of Wang et al. showed that polymorphisms in the TLR2 gene in UC patients in a Japanese population were related to increased risk of intensity of disease, including steroid-dependence, no association was observed between the genetic polymorphisms in TLR2 and the risk of developing UC. TLR2–196 to 174 del/del was related to cases that develop UC at 20 years of age or earlier [66]. One explanation is that such patients may become hyper-responsive to bacterial or food antigens, thus showing clinical manifestations later in life [67].

3.3. TLR3

TLR3 is on chromosome 4 (q35), at the border of a linkage region of an IBD susceptibility gene, suggesting a potential pathogenic association of the TLR3 gene with IBD. Deliberately assessing the mutant polymorphisms in the TLR3 gene may help provide precise insight into IEC-specific dysregulation of this receptor in the disease [68,69].

Primary IEC of normal mucosa constitutively express TLR3. Few studies were conducted on the characterization of TLR3 expression in IBD. No significant changes in TLR3 expression were detected in active UC patients [61,64]. However, in another report, TLR3 expression was mostly observed on the basolateral surface of IECs in colon specimens from UC patients. In addition, inflammatory cell infiltrates in the lamina propria expressed TLR3 on cell surfaces. In active CD patients, expression of TLR3 was significantly down-regulated in active CD specimens compared with specimens from UC patients and normal controls, and this down-regulation was regardless of location and inflammatory activity [21].

3.4. TLR4

TLR4 combined with CD14, LBP, and MD-2, acts as PRR, especially for LPS of gram negative bacteria. The signaling pathway of TLR4 is well characterized; LPS is opsonized by LPS-binding protein (LBP) and subsequently detected by CD14. The formed LPS-LBP-CD14 complex activates TLR4, signaling through adaptor protein MyD88 and serine kinase IL-1R-associated kinase 4 (IRAF4) and the adaptor protein TNF receptor-associated factor 6 (TRAF6). This pathway results in the activation of NF-κB and mitogen-activated protein kinases and triggers cytokine production [70,71]. TLR4 mutations alone or in conjunction with other defects in this LPS-signaling complex might affect the innate immune response in IBD patients.

Many studies have evaluated the association between the polymorphisms of TLR4 and IBD in different populations; however, the results from these reports are inconsistent and inconclusive [72–81]. This controversy might be explained by the diverse methodologies and the small sample sizes used in most of these studies. Two co-segregating polymorphisms in the TLR4 gene have been characterized in humans, Asp299Gly and Thr399Ile. Most of the studies have reported an increased frequency of the Asp299Gly allele in CD and UC patients compared to controls [67,73–75,79]. In a study in a Belgian population with IBD, variant alleles of Asp299Gly were associated with both CD and UC; the allele was transmitted from carriers to affected subjects in a transmission disequilibrium test [82]. In an Australian population, TLR4 ASP299 was associated with CD limited to the colon [81]. TLR4 D299G and T399I were shown to be associated with both UC and CD in a Caucasian population by meta-analysis, but no genotype-phenotype association was observed between CD phenotypes and D299G carriage [83]. A high distribution of TLR4 A299G and CD14 C159T SNPs and a high expression of TLR4 and CD14 mRNAs in monocytes were detected in an Indian group of UC patients in comparison to healthy people, concluding that these genes polymorphisms leads to increased risk of UC [84].

In contrast, in a smaller German IBD population, an association was identified between Thr399Ile and UC, but not CD, yet there was no association between Asp299Gly and UC, nor CD [75]. In another study, no association was found between the Asp299Gly polymorphism with IBD, either CD or UC, in Scottish patients [79]. No significant differences regarding the T399I and D299G SNPs were observed between CD and UC patients and healthy controls in Southeastern Brazilians, suggesting a lack of TLR4 variant involvement in IBD susceptibility [85]. The distribution of polymorphic genotypes of TLR4 was similar among CD and UC patients and controls. Studies in Japanese and Chinese population did not detect any UC patient with TLR4 allele mutations and no association was reported between TLR4 polymorphisms and IBD [86]. These controversies may be explained by ethnic differences.

The initiation and progression of IBD may be associated with abnormal expression of TLR4 in intestinal epithelium. IEC and lamina propria of the non-IBD control group mucosa do not express or weakly express TLR4 [23]. The normal or low expression of TLR4 in normal intestine controls inflammation while the prolonged rise in TLR4 expression in intestinal mucosa of IBD patients may lead to abnormal LPS-mediated signal transmission in the intestine, resulting in sustained secretion of inflammatory cytokines, ultimately causing development or progression of intestinal inflammation. Impaired host tolerance toward luminal LPS antigens might underlie increased TLR4 expression in IBD patients [87,88]. In the inflamed and injured intestinal mucosa of UC patients, TLR4-positive macrophages were also localized to sites of inflammatory intestinal mucosa, further elevating hyperreactivity to LPS [63]. Upregulated TLR4 mRNA expression in UC patients was positively correlated with disease activity and histopathology scores and fecal microbial score [64]. Increased expression of TLR4 was observed in both active vs. quiescent UC; higher expression was detected in quiescent UC compared to control and also active compared to quiescent UC. TLR4 was extensively distributed on the surface of the enteric cavity, and deep afferents in the lower part and the base of the crypt. TLR4 expression was highly upregulated in the terminal ileum and rectum of UC patients and in the terminal ileum of CD patients compared to healthy controls [60]. In another cohort study, TLR4 expression was shown to be strongly unregulated in active UC patients compared to healthy controls, while this increase was negligible in inactive UC and active or inactive CD [59].

MD-2 and CD14 upregulation in the IEC and lamina propria was detected in IBD; CD14 expression was also upregulated in the terminal ileum of CD patients and in the cecum and rectum of UC patients [60]. It is possible that the expression of TLR2, TLR4, and CD14 was the result of the interaction of IECs with intestinal microbiota and might play a role in the pathobiology of UC [60].

TLR4 expression in IBD was correlated with TNF and IL6 mRNA levels [61]. The expression of TNF-α and macrophage migration inhibitory factor was elevated in the intestinal mucosa of UC patients, both of which can increase the expression of TLR4 [61]. In this regard, high expression of TLR4, CD14, and NF-kB in Chinese UC patients was positively correlated with disease development, degree of inflammation, disease activity, and pathologic grade. This might suggest that TLR4 and CD14 interact with antigen and activate NF-kB, augmenting the release of inflammatory mediators. The excessive activation of TLR4/CD14/NF-kB pathway can lead to enhanced inflammation [23].

TLR4 was shown to regulate COX-2 expression and lead to chronic inflammation of intestinal mucosa, especially in UC patients [89]. Epithelial cells in TLR4 or MyD88-deficient mice proliferated to a lesser extent during colitis presumably through COX2/PEG inhibition. TLR4 appears to be required for healing of the injured intestinal epithelium and induction of COX-2 in IECs in response to injury. The COX2/PGE2 pathway is important for proliferation of the injured intestine. Defects in TLR signaling may predispose the intestinal epithelium to impairements in ability to heal [90].

3.5. TLR5

The bacterial flagellum is comprised with a protein called flagellin which is a ligand for TLR5 [91,92]. Bacterial flagellin is known as a dominant antigen in CD [93]. Ligation of flagellin by TLR5 leads to proinflammatory cytokine release from cultured IECs [94]. Flagellin triggers inflammatory responses only in contact with the TLR5 in the basolateral membrane. This may clarify why only the flagellin of pathogenic bacteria causes inflammatory responses by intestinal epithelia. When commensal microorganisms penetrate the epithelial barrier as in injury, inflammatory responses may be activated. In this manner, inflammation activated by invasive pathogens or commensal bacteria are implicated in the pathogenesis of IBD [94].

In a cohort study in Denmark, TLR5 T936T SNP was shown to be significantly associated with the risk of IBD and particularly CD, relative to other TLRs and ILs polymorphisms and activation [95].

Some studies showed no changes in TLR5 expression in IBD [21,59]. However, in UC patients, TLR5 expression was strongly correlated with IL-6 and TNF mRNA levels, and with endoscopic and histological activity of disease [61]. TLR5 mRNA levels were significantly higher in active UC versus quiescent disease; however, lower TLR5 expression was detected in the quiescent stage compared to controls [61]. Conflicting results have also been published. In mucosal biopsies of UC patients, TLR5 gene expression was decreased significantly; TLR5 protein immunoreactivity was diminished or absent in the cytoplasm of epithelial cells, possibly due to their downregulation caused by flagellin abundance in inflamed and injured epithelium. A negative correlation was also shown between TLR5 expression and degree of inflammation [22].

3.6. TLR6

TLR6, which forms a heterodimer with TLR2, is known to contribute to the development of Th17 cells that are related to many pro-inflammatory molecules including TNF and ILs. TLR6-positive cells are detected in intestinal biopsies from IBD patients [96]. Although TLR6 mRNA and protein levels were slightly higher in inflamed tissue, they did not differ significantly from healthy controls. Likewise, in a cohort study, TLR6 mRNA expression was not significantly different in UC and CD patients compared to controls [59]. However, TLR6 mRNA levels were correlated with expression of the Th17 transcription factor in the intestine, which is itself involved in IBD and disease activity [96].

3.7. TLR8

TLR8 mRNA levels were shown to be increased in active versus quiescent UC and correlated with increases in IL-6 and TNF levels, the extent of inflammation, and histological and endoscopic activity [61]. In another study, TLR8 mRNA expression was significantly upregulated in colonic epithelial cells from patients with IBD compared to controls; substantially higher levels were detected in inflamed mucosa of UC and CD patients. Specimens from inflamed IBD tissue and especially CD patients demonstrated significant positive staining for TLR8 protein in surface epithelium, cytoplasm, and intracellular organelles [19]. The suggestion was that TLR8 mediated increased IL-8 secretion from colonic epithelial cells and inhibited the function of T regulatory cells, resulting in reduced immunosuppressive activity and increased proinflammatory activity in the gut [19,97]. In another IBD cohort, TLR8 expression in active and inactive UC and CD did not differ significantly from expression levels in healthy subjects [59].

3.8. TLR9

TLR9 is activated by unmethylated CpG DNA, triggering innate immune responses [98,99]. In vitro experiments showed that TLR9 recognizes pathogenic bacteria, leading to intestinal damage through its signaling pathway [100]. TLR9 contributes to dendritic cell signaling in response to commensal bacteria DNA, inhibiting the differentiation of regulatory T cells [101,102]. This pathway results in the release of Th1 cytokines, such as IL-6, IL-10, IL-12 and TNF-α [101,103]. Previous studies showed that polymorphic sequences in the TLR9 promoter of IBD patients may upregulate gene expression of TLR9. On the other hand, it was suggested that gut inflammation along with neutrophil infiltration and dysbiosis contribute to the increased expression of TLR9 in the colon mucosa of UC patients [63]. Genetic variations in TLR9 were shown to be associated with CD in a German population [104]. An association between TLR9 polymorphisms and UC in Japanese patients was also identified [105]. Previous findings associated the importance of TLR9 with the genetic control of reactions to intestinal microbes in UC [106].

Increased TLR9 mRNA expression was observed in submucosa inflammatory cells in the lamina propria and cryptic epithelia of UC patients, and was correlated with disease activity, endoscopic and histopathological scores, and fecal bacterial flora scores [63]. In rectal biopsies from patients, mRNA levels were significantly higher in active UC versus healthy controls and patients in remission; TLR9 and IL-6 levels were also positively correlated [18]. Expression of TLR9 protein and mRNA were significantly higher in the cytoplasm of epithelial cells of patients with UC [64]. On the other hand, TLR9 mRNA levels were shown to be increased in active UC versus quiescent UC and it was correlated with IL-6 and TNF levels, and also with degree of inflammation, cytokines level, and histological and endoscopic activity. In contrast, Pedersen et al. did not observe significant differences between TLR9 mRNA expression in colonic mucosa of control and IBD groups [107]. Similarly, in an IBD cohort TLR9 expression in either active or inactive UC and CD did not differ significantly from that in healthy controls [59].

3.9. TLR modulators

Many TLR inhibitory proteins which are expressed in the GI mucosa have been recognized which regulate TLR-related responses and inflammation. In a cohort of IBD patients, expression of some of these inhibitory proteins was measured. A20 and SOCS1 expression was significantly increased in active UC, while IRAK-M expression was upregulated in both active UC and CD patients. On the other hand, expression level of Bcl-3 was shown to be higher in inflamed UC and also active and inactive CD. The high expression of TLR inhibitory factors might be due to a positive feedback mechanism following induction of the inflammatory processes in the GI tract such as the NF-kB pathway, committed to suppress the inflammatory response in IBD. However, TOLLIP and PPAR-g mRNA and protein expression were decreased in CD and UC, suggesting that down-regulation of these inhibitory proteins contributed to the inflammatory responses and increased the susceptibility to IBD and colitis [59].

Nur77 is a nuclear receptor and acts as a transcription factor along with its physiologic and pathologic extra-nuclear effects. Nur77 is known to interact with TRAF6 and also inhibit the TLR-IL-1R-dependent inflammatory processes, preventing activation of NF-kB and AP-1. Genetic variants leading to decreased NUR77 expression in-

creased susceptibility to IBD. Nur77 expression was significantly reduced in CD and UC patients. In light of the inhibition of TLR-IL-1R agonist-induced TRAF6 auto-ubiquitination by Nur77 and its effect on TLR-related inflammatory responses and inflammatory cytokines production, Nur77 might serve as a protective factor against development of IBD and be considered as a potential strategy for TLR-IL-1R modulation in IBD management [108].

3.10. Comparing TLR gene expression and polymorphisms in CD and UC

The observations regarding TLR expression in different studies were somehow distinct between UC and CD patients. Some TLRs show similar pattern of expression in both diseases. According to the reviewed studies, TLR1 and TLR6 expressions were not changed in either UC or CD. TLR8 was shown to be upregulated or sometimes no changes were detected in its expression in both UC and CD. Thus, TLR1, TLR6, and TLR8 are so far expressed with a similar pattern in CD and UC. Focusing on TLR2 and TLR9, we can assume both TLRs remained unchanged and in some studies upregulated in UC, but in CD patients no changes in their expression was observed. However, comparatively, some TLRs seem to be differently regulated in these two diseases. For example, TLR3 tends to downregulate in CD, while data presented that it might not change in UC or we might even face a higher expression of this receptor in UC patients. Taking together the studies on TLR5 expression in humans, although controversial results were obtained in UC (either increase or decrease) no data considering its expression in CD was found.

Analyzing the role of TLR polymorphisms separately in UC and CD, we observed that in sum, data concerning the role of TLR gene polymorphisms appear to be virtually similar in these two diseases; TLR polymorphisms to mention are TLR1 T743C (increased susceptibility to UC and CD), TLR4 A299G (increased susceptibility to UC and CD or no significant changes), TLR4 T399I (increased susceptibility or no changes in UC versus no observed changes in CD), and TLR9 (increased susceptibility to both UC and CD). TLR 2 and TLR5 polymorphisms were only assessed in UC and CD patients, respectively.

To make an abstract, the expression and polymorphism of TLR genes are almost identical in CD and UC, insomuch as among the seven compared TLRs (TLR5 was only evaluated in UC patients) six TLRs exerted at least nearly similar patterns of expression (TLR1, TLR2, TLR4, TLR6, TLR8, TLR9) and four of them were exactly equally regulated in the two diseases (TLR1, TLR4, TLR6, TLR8) and only TLR3 demonstrated totally contrary expressions in UC and CD.

4. Role of TLRs in IBD (animal studies)

4.1. TLR2

Duodenal biopsies from dogs with IBD contained higher TLR2 mRNA levels compared with control dogs and these mRNA increase was weakly correlated with disease severity. However, mRNA content was not correlated with histopathology grades of the dogs [109].

4.2. TLR4

In a study of different SNPs of the TLR4 gene, two, the A1571T and G1807A were associated with increased risk of IBD in German shepherds [110].

No significant alterations were observed between the IBD and control dogs regarding TLR4 mRNA levels or the pathology scores. Likewise, the mean relative expression of TLR4 mRNA in rectal biopsies from IBD and healthy horses did not differ significantly. However, the expression of TLR4 was higher in histopathologically active disease compared to control [109].

4.3. TLR5

In order to investigate the role of TLR5 gene polymorphisms in IBD, three different SNPs of TLR5 gene were studied in various breeds of dogs. The G22A SNP was shown to be associated with IBD risk, while C100T and T1844C SNPs established a protective effect against IBD and dogs carrying the risk-associated haplotype were five times more likely to be affected by IBD compared to those carrying the risk-protective haplotypes [111]. On the other hand, the TLR5 risk-associated haplotype was shown to cause and even increase NF-kB production, along with a higher TNF development in response to flagellin, compared with the risk-protective haplotype [112].

4.4. TLR6

TLR6 mRNA and protein levels were significantly upregulated in inflamed distal colon tissue of mice exposed to experimental colitis. During the colitis phase, TLR6 was upregulated in immune cells of the colon. On the other hand, gut stimulation with TLR6 ligand caused a higher production of various inflammatory cytokines in T cells either after 48 h or following long-term investigation. Progressing with the experiments, Morgan et al. also detected that introducing mice to TLR6 ligand worsened the severity of colitis and activated Th17 responses. Interestingly, they also realized that in comparison with wild type mice, TLR6-deficient mice were protected against induced experimental colitis, and correlated with the lower T helper-mediated inflammatory responses [96].

4.5. TLR modulators

Nur77 expression was significantly reduced in mice subjected to DSS-induced colitis. Interestingly, administration of a Nur77 agonist, cytosporone B, suppressed the colitis-associated colon inflammation and damage in mice [108].

5. TLR agonist/antagonists in IBD therapy

Advanced understanding of the underlying pathogenesis of IBD diseases has led to the development of new biological therapeutic agents. A few are currently attributed to regulation of TLRs since TLRs play an important role in host defense against exogenous stimuli such as microbes, in tissue repair and regeneration and also in inflammatory processes. TLR specific involvement in the pathogenesis of inflammatory conditions provides opportunities to block disease progression through activating and/or inhibiting TLR signaling by using specific TLR agonists or antagonists or even through inhibition of downstream proteins involved in the signaling pathways. Many TLR agonist and antagonist compounds have been designed recently which are able to target specific innate immune receptors (Tables 4 and 5). On the other hand, targeting the endogenous regulators might also serve a therapeutic purpose. Unfortunately, to date few clinical trials have been conducted targeting IBD pathobiology by TLR modulators. This raises the significance of further experiments and clinical trials focusing on IBD therapy through TLR-modulating agents.

Table 4
Drugs targeting TLRs currently in clinical trials.

Drug	Indications
Rintatolimod (TLR3 agonist)	Chronic fatigue syndrome (phase 3)
Polyinosinic-polycytidilic acid (TLR3 agonist)	Healthy volunteers (phase 1)
Polymixin-B (TLR4 antagonist)	Sepsis (phase 4)
GNbAC1 (TLR4 mAB)	MS-associated retrovirus (phase 1)
Eritoran tetrasodium (MD2-TLR4 antagonist)	Severe sepsis (phase 3)
TLR9/8/7 antagonist	Healthy volunteers (phase 1)
TLR9/8/7 antagonist	Falciparum Malaria
HCQ (TLR9/8/7 antagonist)	Autoimmune diseases, Sjogren's syndrome, dry eye (phase 3)
DIMS0150 (TLR9 agonist)	UC (phase 2)

6. Current TLR modulators as candidates for IBD therapy

The potential benefits of DNA-based immunomodulatory sequences (DIMS0150) in steroid-refractory UC patients was reported in the study by Musch et al. [113]. The synthetic DIMS0150 is the first compound of this class under clinical study for severe, chronic active, treatment-refractory UC. Administered locally to the colon of steroid-refractory UC subjects, DIMS0150 directly contacted with target cells harboring the TLR9 receptor. This drug possesses immunomodulatory properties and activates the TLR9 signaling pathway in effector cells including T and B lymphocytes, dendritic cells, and macrophages [114]. It is postulated that DIMS0150 is effective in restoring sensitivity to glucocorticoids through activation of the TLR9 receptor, which in turn, results in the release of steroid-sensitizing cytokines such as IL-10 and interferons [115], inducing local as well as systemic sensitizing benefits [113]. The clinical benefits were determined in a phase III clinical study and showed higher symptomatic remission, mucosal healing, and clinical remission rate compared to placebo-treated patients. Furthermore, the safety and tolerability of this therapeutic agent was confirmed during the study [116].

Extracts from feijoa, a South American fruit cultivated in New Zealand, was efficient in reducing inflammation induced by TLR2 signaling. The study determined that feijoa was capable of activating autophagy along with inhibiting TLR2 signaling, and thus had the potential to inhibit NF-κB activation in mouse embryonic fibroblasts, regulating inflammation in the models tested [117]. Feijoa possibly interacts directly with the TLR2 receptor and its machinery to augment the response to pathogens. This study offers some hope for potential benefit using dietary interventions to manage IBD in patients with a personalized nutrition based on an individual's genetic profile. In fact, more animal studies followed by human experiments are required for further evaluation of this consequence.

Chloroquine, the antimalarial drug is known to exert immunomodulatory effects and is used in the treatment of many autoimmune diseases such as rheumatoid arthritis and systematic lupus erythematous. It interferes with the innate immune response via TLR1/2 and TLR9 signaling as well as interfering with T cell responses. Chloroquine treatment lessened the degree of weight loss and colon shortening in mice subjected to a DSS model of IBD. It also ameliorated inflammatory cells infiltration and tissue damage. The results of this study suggests that chloroquine administration seems to be beneficial/curative in mice subjected to IBD due to its effect on innate and adaptive immunity, tissue pathology, and blocking TLR2 and TLR9 signaling [116].

The in vitro and in vivo effects of the synthetic TLR4 antagonist, CRX-526 have been studied. Pre-incubation of human monocyte-derived macrophages and murine macrophages with CRX-526 blocked LPS-stimulated TNF and IL-6 production, and this LPS signaling inhibition was TLR4-dependent. CRX-526 administration to mice partially protected them from IBD development both in an acute and a chronic model of murine IBD, lessening either the histopathological score or disease activity. CRX-526 treatment significantly decreased disease activity index in TLR4 wild-type mice compared with mutant mice, suggesting a TLR4-mediated mechanism for this effect [118].

Table 5
Targeting TLRs in rodents for treatment of IBD.

Drug	Animal	Colitis Induction Model	Target	Result
Chloroquine	Mice	DSS	TLR 2 and TLR 9 antagonist	Decreased weight loss Decreased colon shortening Decreased inflammation
CRX-526	Mice	DSS	TLR 4 antagonist	Decreased histological score Decreased disease activity index
1A6	Mice	DSS/CD45Rbhi T cells transfer	TLR 4 antagonist	Improved stool inconsistency Improved signs of colon inflammation
Curcumin	Rats	TNBS	Decreased TLR4/MyD88 proteins expression	Decreased histological score Decreased disease activity index
Baishaoqiwu	Rats	TNBS	Decreased TLR4/MyD88 gene expression	Decreased histological damage Decreased macroscopic damage
Baicalin	Mice	DSS	Decreased TLR4 expression	Reduced pro-inflammatory cytokines level Decreased disease-activity index
recombinant TFF3 (trefoil factor peptide)	Mice	TNBS	Decreased TLR4 expression and production	Decreased histological damage Decreased macroscopic damage Decreased inflammation
Penta-*O*-galloyl-$_{\beta}$-D-glucose	Mice	TNBS	Interaction with MyD88 adaptor protein/decreased expression of MyD88	Decreased weight loss Decreased colon shortening Decreased inflammation Decreased histological score
Atorvastatin	Rats	TNBS	Inhibition of TLR4 signaling pathway	Decreased histological damage Decreased ulcer index

Administration of a TLR4/MD-2 monoclonal antibody, 1A6, during colitis induction by DSS in mice ameliorated rectal bleeding, improved stool consistency and signs of colon inflammation, and also reduced TNF, IL-6 and chemokine production. Blocking TLR4 during induction of colitis resulted in recruitment of dendritic cells and macrophages and pro-inflammatory cytokines and chemokines to the lamina propria, protecting against acute murine colitis [119].

Curcmin, the active ingredient of Curcuma Longa was known to exert anti-inflammatory effect in colitis. Administration of curcumin to rats subjected to TNBS-induced colitis resulted in a significant improvement in DAI, colonic mucosa damage index, and histological findings. The mechanism was attributed to a decrease in TLR4 and MyD88 proteins. Curcmin seems to affect the TLR4/MyD88/NF-kB pathway and might be considered as a treatment in IBD [120,121].

Baishaoqiwu is a Chinese herb traditionally used as anti-inflammatory remedy in colitis. It abrogated the macroscopic and histological damage consequent to UC induction in rats. Following baishaoqiwu administration, TLR4 and MyD88 genes expression levels were lowered compared to control animals [84]. The therapeutic effects of baishaoqiwu in IBD may be partly mediated through TLR4/MyD88/Nf-kB pathway suppression [122].

The anti-inflammatory mechanism of the flavonoid extract from Scrutellaria Baicalensis was studied in DSS colitis model of mice. Intragastric administration of baicalin suppressed the signs and symptoms of experimental UC and reduced pro-inflammatory cytokines level through inhibition of the TLR4/NF-kB pathway and down-regulation of TLR4 expression (and MyD88 expression, to some extent) in the gut mucosa. Expression of TLR2 and TLR9 did not differ compared with the control group, concluding that this signaling pathway was not involved in the anti-inflammatory response by baicalin [123,124]. The dramatic anti-inflammatory effect of baicalin and the contribution of TLR4/NF-kB signaling pathway together support such pharmacological interventions for treating UC.

Mice treated with rectal instillation of trinitrobenzene sulphonic acid (TNBS) were administered recombinant human trefoil factor (TFF3) peptide which is a secretory product of the GI mucosal cells. As a result of a reduced TLR4 expression and production in colonic tissue, microscopic and macroscopic indices and inflammation severity were significantly ameliorated in colon. Thus TFF3 is assumed to exert potent anti-inflammatory effects in IBD [125].

Penta-*O*-galloyl-$_{\beta}$-D-glucose (PGG) abrogated the weight loss, shortening of colon, macroscopic disease features, and expression of pro-inflammatory molecules. PGG did not affect the expression of TLR4 in TNBS-induced colitis in mice. It inhibited binding of an anti-MyD88 antibody to macrophages but did not inhibit binding of IRAK-1 and IRAK-4 antibodies. The underlying mechanism of the protective effects of PGG in mouse IBD is presumed to be through the interaction with MyD88 adapter protein, finally inhibiting the TLR signaling [126].

Statins have ameliorated inflammation in different models of colitis [127–129]. Atorvastatin administration dramatically lessened the ulcer index and the histologic damage to the intestines of rats treated with TNBS. Furthermore, atorvastatin treatment decreased TLR4 and MyD88 protein expression. Atorvastatin exerted anti-inflammatory effects likely through TLR4/NF-kB pathway inhibition [130].

7. Conclusions

Environment, genetics, and host immunity set a multidimensional and interactive regulatory complex controlling TLR function in the intestinal mucosa. Any imbalance in these elements may lead to aberrant TLR signaling and acute and chronic intestinal inflammatory processes, such as in IBD and colitis.

Several reports have confirmed the up-regulation or down-regulation of expression of different TLRs in IECs and mucosal antigen-presenting cells or macrophages in patients with IBD. Other studies have also linked the polymorphisms or mutations within the genes encoding TLRs with development of IBD. Taken together, targeting of the TLR signaling pathways hold promise in the management of IBD.

In normal intestine, the overstimulation of TLR is impaired by endogenous regulators, such as a short form of MyD88 (sMyD88), IRAKM, suppressor of cytokine signaling-1 (SOCS1), TOLLIP, PI3K, and A20. Triggering the expression of such regulatory factors could prevent TLR overstimulation as a means of treating autoimmune disease including IBD. On the other hand, blocking certain TLR signaling pathways such as TLR2 and TLR4 is another approach for treating IBD since these TLRs are upregulated in IBD mucosa. Based on the data accumulated in animals and human studies, which were to some extent contradictory, we cannot undoubtedly presume the TLR modulating agents as beneficial targets to control or improve symptoms associated with IBD, however, targeting the individual innate immune signaling pathways using known TLR agonists and antagonists can undergo valid and authentic animal and human investigations in future, and the observations would be utilized to establish therapeutic options for IBD in order to obtain better clinical outcomes.

Funding

There is no funding source to report.

Conflict of interest

All authors including Nastaran kordjazy, Arvin Haj-Mirzaian, Arya Haj-Mirzaian, Mohammd Mojtaba Rohani, Erwin W. Gelfand, Nima Rezaei and Amir Hossein Abdolghaffari declare that there is no conflict of interest.

Author contributions

Nastaran kordjazy has written the most part of the manuscript.

Arvin Haj-Mirzaian has provided the images and has written some part of the manuscript.

Arya Haj-Mirzaian and Mohammad Mojtaba Rohani, and Erwin W. Gelfand have written some part of the manuscript and worked on literature reviewing.

Nima rezaei and Amir Hossein Abdolghaffari have designed the manuscript and all works have been done under their supervision. Also, they have written some part of the manuscript.

Acknowledgement

None.

References

[1] W. Strober, I. Fuss, P. Mannon, The fundamental basis of inflammatory bowel disease, J. Clin. Invest. 117 (3) (2007) 514–521.
[2] J.H. Cho, The genetics and immunopathogenesis of inflammatory bowel disease, Nat. Rev. Immunol. 8 (6) (2008) 458–466.
[3] S.B. Hanauer, Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities, Inflamm. Bowel Dis. 12 (5) (2006) S3–S9.
[4] L.V. Hooper, J.I. Gordon, Commensal host-bacterial relationships in the gut, Science 292 (5519) (2001) 1115–1118.

[5] G.S. Lichtenberger, R.A. Flavell, L. Alexopoulou, Innate immunity and apoptosis in IBD, Inflamm. Bowel Dis. 10 (7) (2004) S58–S62.
[6] R. Xavier, D. Podolsky, Unravelling the pathogenesis of inflammatory bowel disease, Nature 448 (7152) (2007) 427–434.
[7] B. Khor, A. Gardet, R.J. Xavier, Genetics and pathogenesis of inflammatory bowel disease, Nature 474 (7351) (2011) 307–317.
[8] S.W. Brubaker, K.S. Bonham, I. Zanoni, J.C. Kagan, Innate immune pattern recognition: a cell biological perspective, Annu. Rev. Immunol. 33 (2015) 257–290.
[9] E. Meylan, J. Tschopp, M. Karin, Intracellular pattern recognition receptors in the host response, Nature 442 (7098) (2006) 39–44.
[10] J. da Silva Correia, K. Soldau, U. Christen, P.S. Tobias, R.J. Ulevitch, Lipopolysaccharide is in close proximity to each of the proteins in its membrane receptor complex transfer from CD14 to TLR4 and MD-2, J. Biol. Chem. 276 (24) (2001) 21129–21135.
[11] S. Akira, K. Takeda, T. Kaisho, Toll-like receptors: critical proteins linking innate and acquired immunity, Nat. Immunol. 2 (8) (2001) 675–680.
[12] J.M. Wells, L.M. Loonen, J.M. Karczewski, The role of innate signaling in the homeostasis of tolerance and immunity in the intestine, Int. J. Med. Microbiol. 300 (1) (2010) 41–48.
[13] L.W. Peterson, D. Artis, Intestinal epithelial cells: regulators of barrier function and immune homeostasis, Nat. Rev. Immunol. 14 (3) (2014) 141.
[14] S. Frosali, D. Pagliari, G. Gambassi, R. Landolfi, F. Pandolfi, R. Cianci, How the intricate interaction among toll-like receptors, microbiota, and intestinal immunity can influence gastrointestinal pathology, J. Immunol. Res. (2015) 2015.
[15] O. Shibolet, D.K. Podolsky, TLRs in the Gut: IV. Negative regulation of Toll-like receptors and intestinal homeostasis: addition by subtraction, Am. J. Physiol. Gastrointest. Liver Physiol. 292 (6) (2007) G1469–G1473.
[16] S. Akira, K. Takeda, Toll-like receptor signalling, Nat. Rev. Immunol. 4 (7) (2004) 499–511.
[17] B. Szebeni, G. Veres, A. Dezsofi, K. Rusai, A. Vannay, M. Mraz, et al., Increased expression of Toll-like receptor (TLR) 2 and TLR4 in the colonic mucosa of children with inflammatory bowel disease, Clin. Exp. Immunol. 151 (1) (2008) 34–41.
[18] F. Sánchez-Muñoz, G.C. Fonseca-Camarillo, M.A. Villeda-Ramirez, R. Barreto-Zuniga, R. Bojalil, A. Domínguez-Lopez, et al., TLR9 mRNA expression is upregulated in patients with active ulcerative colitis, Inflamm. Bowel Dis. 16 (8) (2010) 1267–1268.
[19] C. Steenholdt, L. Andresen, G. Pedersen, A. Hansen, J. Brynskov, Expression and function of toll-like receptor 8 and Tollip in colonic epithelial cells from patients with inflammatory bowel disease, Scand. J. Gastroenterol. 44 (2) (2009) 195–204.
[20] M. Vijay-Kumar, J.D. Aitken, A.T. Gewirtz (Eds.), Toll Like Receptor-5: Protecting the Gut from Enteric Microbes. Seminars in Immunopathology, Springer, 2008.
[21] E. Cario, D.K. Podolsky, Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease, Infect. Immun. 68 (12) (2000) 7010–7017.
[22] M. Stanislawowski, P. Wierzbicki, A. Golab, K. Adrych, D. Kartanowicz, J. Wypych, et al., Decreased Toll-like receptor-5 (TLR-5) expression in the mucosa of ulcerative colitis patients, J. Physiol. Pharmacol. 60 (Suppl 4) (2009) 71–75.
[23] M. Yu, H. Wang, A. Ding, D.T. Golenbock, E. Latz, C.J. Czura, et al., HMGB1 signals through toll-like receptor (TLR) 4 and TLR2, Shock 26 (2) (2006) 174–179.
[24] Q. Zhang, M. Raoof, Y. Chen, Y. Sumi, T. Sursal, W. Junger, et al., Circulating mitochondrial DAMPs cause inflammatory responses to injury, Nature 464 (7285) (2010) 104–107.
[25] R. Medzhitov, Inflammation 2010: new adventures of an old flame, Cell 140 (6) (2010) 771–776.
[26] A.B. Pithadia, S. Jain, Treatment of inflammatory bowel disease (IBD), Pharmacol. Rep. 63 (3) (2011) 629–642.
[27] S.R. Targan, Current limitations of IBD treatment, Ann. N. Y. Acad. Sci. 1072 (1) (2006) 1–8.
[28] K.O. Arseneau, H. Tamagawa, T.T. Pizarro, F. Cominelli, Innate and adaptive immune responses related to IBD pathogenesis, Curr. Gastroenterol. Rep. 9 (6) (2007) 508–512.
[29] E. Elinav, T. Strowig, J. Henao-Mejia, R.A. Flavell, Regulation of the antimicrobial response by NLR proteins, Immunity 34 (5) (2011) 665–679.
[30] Y.-M. Loo, M. Gale, Immune signaling by RIG-I-like receptors, Immunity 34 (5) (2011) 680–692.
[31] N. Rezaei, Therapeutic targeting of pattern-recognition receptors, Int. Immunopharmacol. 6 (6) (2006) 863–869.
[32] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nat. Immunol. 11 (5) (2010) 373–384.
[33] S.N. Vogel, K.A. Fitzgerald, M.J. Fenton, TLRs differential adapter utilization by toll-like receptors mediates TLR-specific patterns of gene expression, Mol. Interventions 3 (8) (2003) 466.
[34] M.S. Jin, J.-O. Lee, Structures of the toll-like receptor family and its ligand complexes, Immunity 29 (2) (2008) 182–191.
[35] S. Carpenter, L.A. O'Neill, Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins, Biochem. J 422 (1) (2009) 1–10.
[36] I. Botos, D.M. Segal, D.R. Davies, The structural biology of Toll-like receptors, Structure 19 (4) (2011) 447–459.
[37] E. Cario, Toll-like receptors in inflammatory bowel diseases: a decade later, Inflamm. Bowel Dis. 16 (9) (2010) 1583–1597.
[38] K. Chen, J. Huang, W. Gong, P. Iribarren, N.M. Dunlop, J.M. Wang, Toll-like receptors in inflammation, infection and cancer, Int. Immunopharmacol. 7 (10) (2007) 1271–1285.
[39] S. Akira, S. Uematsu, O. Takeuchi, Pathogen recognition and innate immunity, Cell 124 (4) (2006) 783–801.
[40] A. Marshak-Rothstein, Toll-like receptors in systemic autoimmune disease, Nat. Rev. Immunol. (November (11)) (2006) 823–835, PubMed PMID. 17063184. Epub 2006/10/26. Eng..
[41] K. Miyake (Ed.), Innate Immune Sensing of Pathogens and Danger Signals by Cell Surface Toll-Like Receptors. Seminars in Immunology, Elsevier, 2007.
[42] K. Takeda, T. Kaisho, S. Akira, Toll-like receptors, Annu. Rev. Immunol. 21 (1) (2003) 335–376.
[43] T. Kawai, S. Akira, TLR signaling, Cell Death Differ. 13 (5) (2006) 816–825.
[44] C. Brikos, L.A. O'Neill, Signalling of Toll-Like Receptors. Toll-Like Receptors (TLRs) and Innate Immunity, Springer, 200821–50.
[45] V.G. Bhoj, Z.J. Chen, Ubiquitylation in innate and adaptive immunity, Nature 458 (7237) (2009) 430–437.
[46] M.M. Holley, Y. Zhang, E. Lehrmann, W.H. Wood, K.G. Becker, T. Kielian, Toll-like receptor 2 (TLR2)-TLR9 crosstalk dictates IL-12 family cytokine production in microglia, Glia 60 (1) (2012) 29–42.
[47] J.-M. Otte, I.M. Rosenberg, D.K. Podolsky, Intestinal myofibroblasts in innate immune responses of the intestine, Gastroenterology 124 (7) (2003) 1866–1878.
[48] E. Furrie, S. Macfarlane, G. Thomson, G.T. Macfarlane, Toll-like receptors-2, −3 and-4 expression patterns on human colon and their regulation by mucosal-associated bacteria, Immunology 115 (4) (2005) 565–574.
[49] A. Izcue, J.L. Coombes, F. Powrie, T. Regulatory, cells suppress systemic and mucosal immune activation to control intestinal inflammation, Immunol. Rev. 212 (1) (2006) 256–271.
[50] E. Cario, D. Brown, M. McKee, K. Lynch-Devaney, G. Gerken, D.K. Podolsky, Commensal-associated molecular patterns induce selective toll-like receptor-trafficking from apical membrane to cytoplasmic compartments in polarized intestinal epithelium, Am. J. Pathol. 160 (1) (2002) 165–173.
[51] G. Zhang, S. Ghosh, Negative regulation of toll-like receptor-mediated signaling by Tollip, J. Biol. Chem. 277 (9) (2002) 7059–7065.
[52] G. Melmed, L.S. Thomas, N. Lee, S.Y. Tesfay, K. Lukasek, K.S. Michelsen, et al., Human intestinal epithelial cells are broadly unresponsive to Toll-like receptor 2-dependent bacterial ligands: implications for host-microbial interactions in the gut, J. Immunol. 170 (3) (2003) 1406–1415.
[53] J.-M. Otte, E. Cario, D.K. Podolsky, Mechanisms of cross hyporesponsiveness to Toll-like receptor bacterial ligands in intestinal epithelial cells, Gastroenterology 126 (4) (2004) 1054–1070.
[54] F.Y. Liew, D. Xu, E.K. Brint, L.A. O'Neill, Negative regulation of toll-like receptor-mediated immune responses, Nat. Rev. Immunol. 5 (6) (2005) 446–458.
[55] G. Harris, R. KuoLee, W. Chen, Role of Toll-like receptors in health and diseases of gastrointestinal tract, World J. Gastroenterol. 12 (14) (2006) 2149.
[56] M. Fukata, M.T. Abreu, What are toll-like receptors and what role may they have in IBD?, Inflamm. Bowel Dis. 14 (S2) (2008) S90–S92.
[57] B.L. Browning, C. Huebner, I. Petermann, R.B. Gearry, M.L. Barclay, A.N. Shelling, et al., Has toll-Like receptor 4 been prematurely dismissed as an inflammatory bowel disease gene? association study combined with meta-analysis shows strong evidence for association, Am. J. Gastroenterol. 102 (11) (2007) 2504–2512.
[58] S. Bank, P.S. Andersen, J. Burisch, N. Pedersen, S. Roug, J. Galsgaard, et al., Polymorphisms in the toll-like receptor and the IL-23/IL-17 pathways were associated with susceptibility to inflammatory bowel disease in a Danish cohort, PLoS One 10 (12) (2015) e0145302.
[59] P. Fernandes, J. MacSharry, T. Darby, A. Fanning, F. Shanahan, A. Houston, et al., Differential expression of key regulators of Toll-like receptors in ulcerative colitis and Crohn's disease: a role for Tollip and peroxisome proliferator-activated receptor gamma?, Clin. Exp. Immunol. 183 (3) (2016) 358–368.
[60] L. Frolova, P. Drastich, P. Rossmann, K. Klimesova, H. Tlaskalova-Hogenova, Expression of Toll-like receptor 2 (TLR2), TLR4, and CD14 in biopsy samples of patients with inflammatory bowel diseases: upregulated expression of TLR2 in terminal ileum of patients with ulcerative colitis, J. Histochem. Cytochem. 56 (3) (2008) 267–274.
[61] F. Sánchez-Muñoz, G. Fonseca-Camarillo, M.A. Villeda-Ramírez, E. Miranda-Pérez, E.J. Mendivil, R. Barreto-Zúñiga, et al., Transcript levels of toll-like receptors 5, 8 and 9 correlate with inflammatory activity in ulcerative colitis, BMC Gastroenterol. 11 (1) (2011) 1.
[62] R. Matsuda, T. Koide, C. Tokoro, T. Yamamoto, Ti Godai, T. Morohashi, et al., Quantitive cytokine mRNA expression profiles in the colonic mucosa of pa-

tients with steroid naive ulcerative colitis during active and quiescent disease, Inflamm. Bowel Dis. 15 (3) (2009) 328–334.
[63] Y. Tan, K.F. Zou, W. Qian, S. Chen, X.H. Hou, Expression and implication of toll-like receptors TLR2, TLR4 and TLR9 in colonic mucosa of patients with ulcerative colitis, J. Huazhong Univ. Sci. Technol. (Med. Sci.) 34 (2014) 785–790.
[64] Y. Fan, B. Liu, Expression of Toll-like receptors in the mucosa of patients with ulcerative colitis, Exp. Ther. Med. 9 (4) (2015) 1455–1459.
[65] E. Cantó, E. Ricart, D. Monfort, D. González-Juan, J. Balanzó, J.L. Rodríguez-Sánchez, et al., TNFó production to TLR2 ligands in active IBD patients, Clin. Immunol. 119 (2) (2006) 156–165.
[66] F. Wang, T. Tahara, T. Arisawa, T. Shibata, M. Nakamura, H. Fujita, et al., Genetic polymorphisms of CD14 and Toll-like receptor-2 (TLR2) in patients with ulcerative colitis, J. Gastroenterol. Hepatol. 22 (6) (2007) 925–929.
[67] P.L. Lakatos, S. Fischer, L. Lakatos, I. Gal, J. Papp, Current concept on the pathogenesis of inflammatory bowel disease-crosstalk between genetic and microbial factors: pathogenic bacteria and altered bacterial sensing or changes in mucosal integrity take toll, World J. Gastroenterol. 12 (2006) 1829–1840.
[68] J. Hampe, S. Schreiber, S.H. Shaw, K.F. Lau, S. Bridger, A.J. Macpherson, et al., A genomewide analysis provides evidence for novel linkages in inflammatory bowel disease in a large European cohort, Am. J. Hum. Genet. 64 (3) (1999) 808–816.
[69] F.L. Rock, G. Hardiman, J.C. Timans, R.A. Kastelein, J.F. Bazan, A family of human receptors structurally related to Drosophila Toll, Proc. Natl. Acad. Sci. 95 (2) (1998) 588–593.
[70] J.C. Chow, D.W. Young, D.T. Golenbock, W.J. Christ, F. Gusovsky, Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction, J. Biol. Chem. 274 (16) (1999) 10689–10692.
[71] A. Poltorak, X. He, I. Smirnova, M.-Y. Liu, C. Van Huffel, X. Du, L.P.S. et al. Defective, signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene, Science 282 (5396) (1998) 2085–2088.
[72] C. Figueroa, A. Peralta, L. Herrera, P. Castro, A. Gutiérrez, J. Valenzuela, et al., NOD2/CARD15 and Toll-like 4 receptor gene polymorphism in Chilean patients with inflammatory bowel disease, Eur. Cytokine Netw. 17 (2) (2006) 125–130.
[73] L.E. Oostenbrug, J.P. Drenth, D.J. de Jong, I.M. Nolte, E. Oosterom, H.M. van Dullemen, et al., Association between Toll-like receptor 4 and inflammatory bowel disease, Inflamm. Bowel Dis. 11 (6) (2005) 567–575.
[74] S. Brand, A. Konrad, A. Crispin, B. Göke, P. Lohse, T. Ochsenkühn, The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease, Inflamm. Bowel Dis. 11 (7) (2005) 645–652.
[75] H.-P. Török, J. Glas, L. Tonenchi, T. Mussack, C. Folwaczny, Polymorphisms of the lipopolysaccharide-signaling complex in inflammatory bowel disease: association of a mutation in the Toll-like receptor 4 gene with ulcerative colitis, Clin. Immunol. 112 (1) (2004) 85–91.
[76] M. Gazouli, G. Mantzaris, A. Kotsinas, P. Zacharatos, E. Papalambros, A. Archimandritis, et al., Association between polymorphisms in the Toll-like receptor 4, CD14, and CARD15/NOD2 and inflammatory bowel disease in the Greek population, World J. Gastroenterol. 11 (February (5)) (2005) 681–685, PubMed PMID. 15655821. Pubmed Central PMCID: Pmc4250738. Epub 2005/01/19. Eng..
[77] J. Hong, E. Leung, A.G. Fraser, T.R. Merriman, P. Vishnu, G.W. Krissansen, TLR2, TLR4 and TLR9 polymorphisms and Crohn's disease in a New Zealand caucasian cohort, J. Gastroenterol. Hepatol. 22 (11) (2007) 1760–1766.
[78] H. Braat, P. Stokkers, T. Hommes, D. Cohn, E. Vogels, I. Pronk, et al., Consequence of functional Nod2 and Tlr4 mutations on gene transcription in Crohn's disease patients, J. Mol. Med. 83 (8) (2005) 601–609.
[79] I. Arnott, E. Nimmo, H. Drummond, J. Fennell, B. Smith, E. MacKinlay, et al., NOD2/CARD15, TLR4 and CD14 mutations in Scottish and Irish Crohn's disease patients: evidence for genetic heterogeneity within Europe?, Genes Immun. 5 (5) (2004) 417–425.
[80] D.C. Baumgart, C. Büning, L. Geerdts, H.H. Schmidt, J. Genschel, T. Fiedler, et al., The c. 1-260C> T promoter variant of CD14 but not the c. 896A> G (p. D299G) variant of toll-like receptor 4 (TLR4) genes is associated with inflammatory bowel disease, Digestion 76 (3–4) (2007) 196–202.
[81] G.E. Hume, E.V. Fowler, J. Doecke, L.A. Simms, N. Huang, O. Palmieri, et al., Novel NOD2 haplotype strengthens the association between TLR4 Asp299gly and Crohn's disease in an Australian population, Inflamm. Bowel Dis. 14 (5) (2008) 585–590.
[82] D. Franchimont, S. Vermeire, H. El Housni, M. Pierik, K. Van Steen, T. Gustot, et al., Deficient host-bacteria interactions in inflammatory bowel disease? The toll-like receptor (TLR)-4 Asp299gly polymorphism is associated with Crohn's disease and ulcerative colitis, Gut 53 (7) (2004) 987–992.
[83] X. Shen, R. Shi, H. Zhang, K. Li, Y. Zhao, R. Zhang, The Toll-like receptor 4 D299G and T399I polymorphisms are associated with Crohn's disease and ulcerative colitis: a meta-analysis, Digestion 81 (2) (2010) 69–77.
[84] G. Sivaram, S.K. Tiwari, A. Bardia, F. Anjum, S. Vishnupriya, A. Habeeb, et al., Macrophage migration inhibitory factor, Toll-like receptor 4, and CD14 polymorphisms with altered expression levels in patients with ulcerative colitis, Hum. Immunol. 73 (2) (2012) 201–205.
[85] M.L. Baptista, H. Amarante, G. Picheth, V.L. Sdepanian, N. Peterson, U. Babasukumar, et al., CARD15 and IL23R influences Crohn's disease susceptibility but not disease phenotype in a Brazilian population, Inflamm. Bowel Dis. 14 (5) (2008) 674–679.
[86] Q. Guo, B. Xia, Y. Jiang, S. Morré, L. Cheng, J. Li, et al., Polymorphisms of CD14 gene and TLR4 gene are not associated with ulcerative colitis in Chinese patients, Postgrad. Med. J. 81 (958) (2005) 526–529.
[87] R. Duchmann, I. Kaiser, E. Hermann, W. Mayet, K. Ewe, K.H. BÜSCHENFELDE, Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD), Clin. Exp. Immunol. 102 (3) (1995) 448–455.
[88] S. Lange, D.S. Delbro, E. Jennische, I. Mattsby-Baltzer, The role of the Lps gene in experimental ulcerative colitis in mice, APMIS 104 (7–8) (1996) 823–833.
[89] M. Fukata, M. Abreu, TLR4 signalling in the intestine in health and disease, Biochem. Soc. Trans. 35 (6) (2007) 1473–1478.
[90] M. Fukata, A. Chen, A. Klepper, S. Krishnareddy, A.S. Vamadevan, L.S. Thomas, et al., Cox-2 is regulated by toll-like receptor-4 (TLR4) signaling: role in proliferation and apoptosis in the intestine, Gastroenterology 131 (3) (2006) 862–877.
[91] V. Feuillet, S. Medjane, I. Mondor, O. Demaria, P.P. Pagni, J.E. Galán, et al., Involvement of Toll-like receptor 5 in the recognition of flagellated bacteria, Proc. Natl. Acad. Sci. 103 (33) (2006) 12487–12492.
[92] M. Vijay-Kumar, H. Wu, J. Aitken, V.L. Kolachala, A.S. Neish, S.V. Sitaraman, et al., Activation of toll-like receptor 3 protects against DSS-induced acute colitis, Inflamm. Bowel Dis. 13 (7) (2007) 856–864.
[93] M.J. Lodes, Y. Cong, C.O. Elson, R. Mohamath, C.J. Landers, S.R. Targan, et al., Bacterial flagellin is a dominant antigen in Crohn disease, J. Clin. Invest. 113 (9) (2004) 1296–1306.
[94] A.T. Gewirtz, T.A. Navas, S. Lyons, P.J. Godowski, J.L. Madara, Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression, J. Immunol. 167 (4) (2001) 1882–1885.
[95] S. Bank, P.S. Andersen, J. Burisch, N. Pedersen, S. Roug, J. Galsgaard, et al., Polymorphisms in the toll-like receptor and the IL-23/IL-17 pathways were associated with susceptibility to inflammatory bowel disease in a Danish cohort, PLoS One 10 (12) (2015) e0145302, (PubMed PMID. 26698117. Pubmed Central PMCID: Pmc4689491. Epub 2015/12/25. eng.).
[96] M. Morgan, P. Koelink, B. Zheng, M. den Brok, H.J. van de Kant, H. Verspaget, et al., Toll-like receptor 6 stimulation promotes T-helper 1 and 17 responses in gastrointestinal-associated lymphoid tissue and modulates murine experimental colitis, Mucosal Immunol. 7 (5) (2014) 1266–1277.
[97] G. Peng, Z. Guo, Y. Kiniwa, K. shin Voo, W. Peng, T. Fu, et al., Toll-like receptor 8-mediated reversal of CD4+ regulatory T cell function, Science 309 (5739) (2005) 1380–1384.
[98] A.M. Krieg, CPG motifs in bacterial dna and their immune effects, Annu. Rev. Immunol. 20 (1) (2002) 709–760.
[99] H. Wagner, Toll meets bacterial cpG-DNA, Immunity 14 (5) (2001) 499–502.
[100] J.B. Ewaschuk, J.L. Backer, T.A. Churchill, F. Obermeier, D.O. Krause, K.L. Madsen, Surface expression of Toll-like receptor 9 is upregulated on intestinal epithelial cells in response to pathogenic bacterial DNA, Infect. Immun. 75 (5) (2007) 2572–2579.
[101] J.A. Hall, N. Bouladoux, C.M. Sun, E.A. Wohlfert, R.B. Blank, Q. Zhu, D.N.A. et al. Commensal, limits regulatory T cell conversion and is a natural adjuvant of intestinal immune responses, Immunity 29 (4) (2008) 637–649.
[102] J. Lee, D. Rachmilewitz, E. Raz, Homeostatic effects of TLR9 signaling in experimental colitis, Ann. N. Y. Acad. Sci. 1072 (1) (2006) 351–355.
[103] D. Ghadimi, Vrese Md, K.J. Heller, J. Schrezenmeir, Effect of natural commensal-origin DNA on toll-like receptor 9 (TLR9) signaling cascade, chemokine IL-8 expression, and barrier integritiy of polarized intestinal epithelial cells, Inflamm. Bowel Dis. 16 (3) (2010) 410–427.
[104] H.-P. Török, J. Glas, L. Tonenchi, G. Bruennler, M. Folwaczny, C. Folwaczny, Crohn's disease is associated with a toll-like receptor-9 polymorphism, Gastroenterology 127 (1) (2004) 365–366.
[105] 布施香 Toll-like receptor 9 gene mutation and polymorphisms in Japanese ulcerative colitis patients, (2009).
[106] G. Reid, F. Guarner, G. Gibson, T. Tompkins, H. Gill, I. Rowland, et al., Discussion on toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis, Gastroenterology 127 (July (1)) (2004) 366–367, author reply 7. PubMed PMID. 15236226. Epub 2004/07/06. eng..
[107] G. Pedersen, L. Andresen, M. Matthiessen, J. Rask-Madsen, J. Brynskov, Expression of Toll-like receptor 9 and response to bacterial CpG oligodeoxynucleotides in human intestinal epithelium, Clin. Exp. Immunol. 141 (2) (2005) 298–306.
[108] H. Wu, X.M. Li, J.R. Wang, W.J. Gan, F.Q. Jiang, Y. Liu, et al., NUR77 exerts a protective effect against inflammatory bowel disease by negatively regulating the TRAF6/TLR–IL-1R signalling axis, J. Pathol. 238 (3) (2016) 457–469.

[109] L. McMahon, A. House, B. Catchpole, J. Elson-Riggins, A. Riddle, K. Smith, et al., Expression of Toll-like receptor 2 in duodenal biopsies from dogs with inflammatory bowel disease is associated with severity of disease, Vet. Immunol. Immunopathol. 135 (1) (2010) 158–163.
[110] A. Kathrani, A. House, B. Catchpole, A. Murphy, D. Werling, K. Allenspach, Breed-independent toll-like receptor 5 polymorphisms show association with canine inflammatory bowel disease, Tissue Antigens 78 (2) (2011) 94–101.
[111] A. Kathrani, A. Holder, B. Catchpole, L. Alvarez, K. Simpson, D. Werling, et al., TLR5 risk-associated haplotype for canine inflammatory bowel disease confers hyper-responsiveness to flagellin, PLoS One 7 (1) (2012) e30117.
[112] N.V. Kuznetsov, A. Zargari, A.W. Gielen, O.D. von Stein, E. Musch, R. Befrits, et al, Biomarkers can predict potential clinical responders to DIMS0150 a toll-like receptor 9 agonist in ulcerative colitis patients, BMC Gastroenterol. 14 (1) (2014) 1.
[113] E. Musch, T. Lutfi, P. von Stein, A. Zargari, C. Admyre, M. Malek, et al., Topical treatment with the toll-like receptor agonist DIMS 0150 has potential for lasting relief of symptoms in patients with chronic active ulcerative colitis by restoring glucocorticoid sensitivity, Inflamm. Bowel Dis. (2012).
[114] M.T. Abreu, Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function, Nat. Rev. Immunol. 10 (2) (2010) 131–144.
[115] D. Franchimont, H. Martens, M.-T. Hagelstein, E. Louis, W. Dewe, G.P. Chrousos, et al., Tumor necrosis factor α decreases, and interleukin-10 increases, the sensitivity of human monocytes to dexamethasone: potential regulation of the glucocorticoid receptor, J. Clin. Endocrinol. Metab. 84 (8) (1999) 2834–2839.
[116] J. Nagar, S. Ranade, V. Kamath, S. Singh, P. Karunanithi, S. Subramani, et al., Therapeutic potential of chloroquine in a murine model of inflammatory bowel disease, Int. Immunopharmacol. 21 (2) (2014) 328–335.
[117] N.A. Nasef, S. Mehta, P. Powell, G. Marlow, T. Wileman, L.R. Ferguson, Extracts of Feijoa inhibit toll-like receptor 2 signaling and activate autophagy implicating a role in dietary control of IBD, PLoS One 10 (6) (2015) e0130910.
[118] M.M. Fort, A. Mozaffarian, A.G. Stöver, J. da Silva Correia, D.A. Johnson, R.T. Crane, et al., A synthetic TLR4 antagonist has anti-inflammatory effects in two murine models of inflammatory bowel disease, J. Immunol. 174 (10) (2005) 6416–6423.
[119] R. Ungaro, M. Fukata, D. Hsu, Y. Hernandez, K. Breglio, A. Chen, et al., A novel Toll-like receptor 4 antagonist antibody ameliorates inflammation but impairs mucosal healing in murine colitis, Am. J. Physiol. Gastrointest. Liver Physiol. 296 (6) (2009) G1167–G1179.
[120] A. Lubbad, M. Oriowo, I. Khan, Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis, Mol. Cell. Biochem. 322 (1-2) (2009) 127–135.
[121] Z. Zeng, L. Zhan, H. Liao, L. Chen, X. Lv, Curcumin improves TNBS-induced colitis in rats by inhibiting IL-27 expression via the TLR4/NF-κB signaling pathway, Planta Med. 29 (02) (2013) 102–109.
[122] X. Xu, L. Zhang, Z. Liu, Y. Pan, D. Chen, Z. Yang, et al., Therapeutic efficacy of the traditional Chinese Medicine Baishaoqiwu on TNBS-induced colitis is associated with down-regulation of the TLR4/MyD88/NF-κB signaling pathway, In Vivo 30 (3) (2016) 181–186.
[123] J. Feng, C. Guo, Y. Zhu, L. Pang, Z. Yang, Y. Zou, et al., Baicalin down regulates the expression of TLR4 and NFkB-p65 in colon tissue in mice with colitis induced by dextran sulfate sodium, Int. J. Clin. Exp. Med. 7 (11) (2014) 4063.
[124] L. Cui, L. Feng, Z.H. Zhang, X.B. Jia, The anti-inflammation effect of baicalin on experimental colitis through inhibiting TLR4/NF-kB pathway activation, Int. Immunopharmacol. 23 (1) (2014) 294–303.
[125] S.E. Jang, S.R. Hyam, J.J. Jeong, M.J. Han, D.H. Kim, Penta-O-galloyl-β-D-glucose ameliorates inflammation by inhibiting MyD88/NF-κB and MyD88/MAPK signalling pathways, Br. J. Pharmacol. 170 (5) (2013) 1078–1091.
[126] X. Teng, L.-F. Xu, P. Zhou, H.-W. Sun, M. Sun, Effects of trefoil peptide 3 on expression of TNF-α, TLR4, and NF-κB in trinitrobenzene sulphonic acid induced colitis mice, Inflammation 32 (2) (2009) 120–129.
[127] M. Sasaki, S. Bharwani, P. Jordan, T. Joh, K. Manas, A. Warren, et al., The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor pravastatin reduces disease activity and inflammation in dextran-sulfate induced colitis, J. Pharmacol. Exp. Ther. 305 (1) (2003) 78–85.
[128] E. Aktunc, B. Kayhan, M. Arasli, B.D. Gun, F. Barut, The effect of atorvastatin and its role on systemic cytokine network in treatment of acute experimental colitis, Immunopharmacol. Immunotoxicol. 33 (4) (2011) 667–675.
[129] Y. Naito, K. Katada, T. Takagi, H. Tsuboi, Y. Isozaki, O. Handa, et al., Rosuvastatin, a new HMG-CoA reductase inhibitor, reduces the colonic inflammatory response in dextran sulfate sodium-induced colitis in mice, Int. J. Mol. Med. 17 (6) (2006) 997–1004.
[130] A. Rashidian, A. Muhammadnejad, A.R. Dehpour, S.E. Mehr, M.M. Akhavan, R. Shirkoohi, et al., Atorvastatin attenuates TNBS-induced rat colitis: the involvement of the TLR4/NF-kB signaling pathway, Inflammopharmacology 24 (2–3) (2016) 109–118.

Pharmacol Res. 2017 Nov 16. pii: S1043-6618(17)31060-5. doi: 10.1016/j.phrs.2017.11.017. [Epub ahead of print]

Role of toll-like receptors in inflammatory bowel disease.

Kordjazy N[1], Haj-Mirzaian A[2], Haj-Mirzaian A[1], Rohani MM[1], Gelfand EW[3], Rezaei N[4], Abdolghaffari AH[5].

Author information

Abstract

Inflammatory bowel disease (IBD) is the chronic inflammation of the gastrointestinal tract. Recently, studies of the interplay between the adaptive and innate immune responses have provided a better understanding of the immunopathogenesis of inflammatory disorders such as IBD, as well as identification of novel targets for more potent interventions. Toll-like receptors (TLRs) are a class of proteins that play a significant role in the innate immune **system** and are involved in inflammatory processes. Activation of TLR signal transduction pathways lead to the induction of numerous genes that function in host defense, including those for inflammatory cytokines, chemokines, and antigen presenting molecules. It was proposed that TLR mutations and dysregulation are major contributing factors to the predisposition and susceptibility to IBD. Thus, modulating TLRs represent an innovative immunotherapeutic **approach** in IBD therapy. This article outlines the role of TLRs in IBD, focusing on both animal and human studies; the role of TLR-targeted agonists or antagonists as potential therapeutic agents in the different stages of the disease is discussed.

KEYWORDS: Crohn's disease; Dysregulation; Inflammatory bowel disease; Toll-like receptors; Ulcerative colitis

PMID: 29155256 DOI: 10.1016/j.phrs.2017.11.017

Journal Search

Search Terms

Database

Search Type Title Word

Master Journal List

Search

Search Term(s): **1043-6618** · The following title(s) matched your request

First Previous Next Last

Total journals: **1** · Journals 1-1 (of 1)

Format for print

- **PHARMACOLOGICAL RESEARCH**
  Monthly ISSN: 1043-6618
  ACADEMIC PRESS LTD- ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON, ENGLAND, NW1 7DX
  Coverage
  - Science Citation Index
  - Science Citation Index Expanded
  - Current Contents - Life Sciences
  - BIOSIS Previews

Total journals: **1** · Journals 1-1 (of 1)

Format for print

Clarivate

Accelerating innovation

Follow us