J Clin Exp Hematopathol
Vol. 51, No. 2, Nov. 2011

Review Article

Toll-like Receptor —A Potent Driving Force behind Rheumatoid Arthritis—

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Toll like receptor (TLR), one of the key functions of innate immune system, can recognize not only exogenous pathogen-associated molecular patterns, namely PAMPs, but also endogenous molecules created upon tissue injury, sterile inflammation and degeneration. Endogenous TLR ligands are called as damage-associated molecular patters (DAMPs), including endogenous molecules released by activated and necrotic cells, and extracellular matrix molecules. DAMPs are also known as *alarmins*. TLR research has brought about new insights in the rheumatic diseases. Previous reports suggest that TLRs and the signal pathways intensively contribute to the pathogenesis of rheumatoid arthritis (RA) and other arthritic conditions with interaction of various TLR ligands. Accumulated knowledge of TLR system is summarized to overlook TLRs and the signaling pathway in arthritis conditions, with special reference to RA. 〔*J Clin Exp Hematopathol 51(2) : 77-92, 2011*〕

Keywords: Toll-like receptor, rheumatoid arthritis, pathogen-associated molecular pattern, damage-associated molecular pattern, innate immunity

INTRODUCTION

Rheumatoid arthritis (RA) is one of the terrible disasters of musculoskeletal system, like repeated tsunami attacking joints by conscious or unconscious manner. If timely therapy fails to calm disease activity down, persistent inflammation leads to severe bone and joint destruction, often combined with serious extraarticular manifestations. Inflammation has been recognized as one of the host immune responses to both internal and external threats. Various mediators have been identified and linked to the physiologic and pathologic roles of inflammation. Complicated inflammatory reactions found in RA are not merely incidental, but rather, drive and define the pathologic state. Better understanding of molecular and cellular mechanisms responsible for inflammation would provide patients with RA relief from pain and disability. The pathogenesis of RA is probably attributed to interplay of genetic and environmental factors, in which immune response plays a central role. However, in spite of intensive research, the precise mechanism is not elucidated yet, and the studies often have been apt to focus on the system of adaptive immunity rather than innate one.

Immune response is induced by not only microbial infection, but also sterile tissue damage and degeneration. This paradox was first explained by Matzieger in 1994, who proposed that immune system is designed to fight with both external and internal dangers, rather than mediate recognition of non-self over self.[1] The following question was how organisms recognized and efficiently responded to the dangers. Three main families of sensing molecules, termed "pattern recognition receptors (PRRs)", have been identified to give the answer. Mammalian cells can sense danger signals from both pathogens and damaged tissues *via* PRRs of innate immune system, which evolved earlier than the highly diverse receptors of adaptive immune system equipped in vertebrate. The innate sensors include Toll-like receptors (TLRs), retinoid acid inducible gene (RIG)-I like receptors (RLRs), and nucleotide-binding oligomelization domain (NOD)-like receptors (NLRs) (Table 1). All the abbreviations of the molecules and related structures used in this review were summarized alphabetically in the Appendix. TLRs are located on the cell-surface and endosome. They can sense exogenous "pathogen-associated molecular patterns (PAMPs)"[2] and endogenous "damage-associated molecular patterns (DAMPs)". They are also known as *alarmins*.[3,4] RLRs are cytosolic sensors for nucleic acids. RIG-1 and MAD5 can sense RNA species. DAI recognize DNAs. NLRs include NOD-1, NOD-2, NLRP and AIM2. The evoked signaling by these

Received : April 24, 2011
Accepted : April 27, 2011
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Support : the Grant-in-Aid for Scientific Research, the Ministry of Science and Culture (C 2-17591546, C-21591929), Yamagata Health Support Society for the Promotion of Science 2006-2009, Japan

Table 1. Three main families of innate immune sensors

Family	Location	Representatives	Ligands
TLRs	Cell surface	TLR1, 2, 4, 5, 6, 10	PAMPs/DAMPs
	Endosome	TLR3, 7-9	PAMPs/DAMPs
RLRs	Cytosol	RIG-1 (RNA helicase)	ssRNA
		MD5 (RNA helicase)	dsRNA
		DAI	microbial/mammalian DNA
NLRs	Cytosol	NOD1 (NLRC1/CARD4)	γ-D-gmda of GNB
		NOD2 (NLRC2/CARD15)	MDP both of GPB/GNB
	Cytosol/Inflammasome	NLRP3 (NALP3)	PAMPs/DAMPs, changes in ionic and redox milieu
		AIM2	DNA

Representative innate sensors are summarized with representatives identified in human.
GPB, gram-positive bacteria; GNB, gram-negative bacteria; other abbreviations; see Appendix.
Type of families, location of the receptor and the signal pathways are illustrated in the Fig. 1.

sensors can promote either the activation and nuclear translocation of transcription factors (IRF, NF-κB and AP-1) that derive expression of cytokines, such as IFNα/β, TNF and proIL-1β, or the assembly of the caspase-1 inflammasome and subsequent maturation of IL-1β from proIL-1β[5-8] (Fig. 1).

The host responses *via* the sensors initially can work to eliminate infection and are beneficial in most cases, but the defective regulation may result in autoimmune and/or autoinflammatory responses, many of which present rheumatic manifestations.[6] Essential keys of autoimmune response include the nature and relative contribution of endogenous *versus* exogenous stimuli, the abnormalities that override the normal discrimination between self and foreign antigens, and the interplay between innate and adaptive immune systems. RA and systemic lupus erythematosus (SLE) are representative diseases. Recognition of self nucleic acids by TLRs seems to be the major pathogenetic mechanism in SLE. In RA, recognitions of products from microbes and damaged tissues by the TLRs and other innate sensors are likely to contribute the pathogenesis. By contrast, several genetic mutations, that either provoke or permit uncontrolled activation of the innate immune system, can trigger "autoinflammation", in which IL-1β disorders including NLRP3/ASC/capase-1 (IL-1 convertase) and their related pathway play a major role. They often accompany with rheumatic manifestations with arthritis, *i.e.*, Blau syndrome, cryopyinopathies, familial Mediterranean fever, and pyogenic arthritis with pyoderma gangrenosum. Excessive deposition of crystal also induces the host reaction as a result of autoinflammatory reaction, seen such as gout and pseudogout. Psoriatic arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Schnitzler syndrome and Gaudaloupe variant periodic fever syndrome are categorized as possible candidates of autoinflammatory diseases.[6,8-10]

Recent TLR research has brought about new insights in the pathogenesis of many rheumatic diseases. Moreover, possible mechanism of collaboration and cross-talk among innate immune sensors have been discussed. Increase level of cryopyrin, which is linked to caspase-1 and one of central components of inflammasome, was identified in RA synovium.[11] Biglycan, one of extracellular matrix components in cartilage, also increased[12,13] and activated NLRP3 inflammasome *via* TLR2 and TLR4.[14] RA, psoriatic arthritis, Blau syndrome and gout are the possible candidates, involving interplay of the sensors.[10,15-17] In this review, accumulated knowledge of TLRs and the signaling is summarized with discussions of possible pathogenesis of arthritis, with a special reference to RA.

TLRs AND PAMPs

Toll receptor was originally identified in *Drosophila melanogaster* as a receptor essential for the establishment of the dorso-ventral pattern in developing embryos.[18] In 1996, Hoffmann and Lemaitre demonstrated that Toll-mutant flies were highly susceptible to fungal infections.[19] A mammalian toll homologue was first reported in 1997 and named TLR.[20] TLRs belong to the family of PRRs, and consist of main innate immune sensors, together with RLRs and NLRs. So far, 13 distinct mammalian TLRs have been identified 10 of which are functional in humans (TLR1-10), and 11 in mice (TLR1-7, TLR9, TLR11-13).[20,21] TLR1, 2, 4, 5, 6, 10 and 11 are located on the cell surface, whereas, TLR3, 7, 8 and 9 are located in the endosome. The high levels and broadest spectra of TLR expression have been observed in variety of cell types in the immune system, including monocytes/macrophages,[23-28] dendritic cells (DCs),[23-26,29-31] neutrophils,[29,32] B cells,[26] T cells[26] and NK cells.[26,33,34] Moreover, TLRs have been identified in synoviocytes,[35,36] fibroblasts,[37,38] osteoblasts,[39,40] osteoclasts,[41,42] chondrocytes[43-45] and endothelial cells.[27,46]

TLRs can recognize a wide variety of PAMPs derived from bacteria, fungi, parasites and viruses, which were summarized in Table 2 with references (47-74). They act as homodimers or heterodimers of type I trans-membrane glycoproteins, each comprising a ligand-binding ectodomain con-

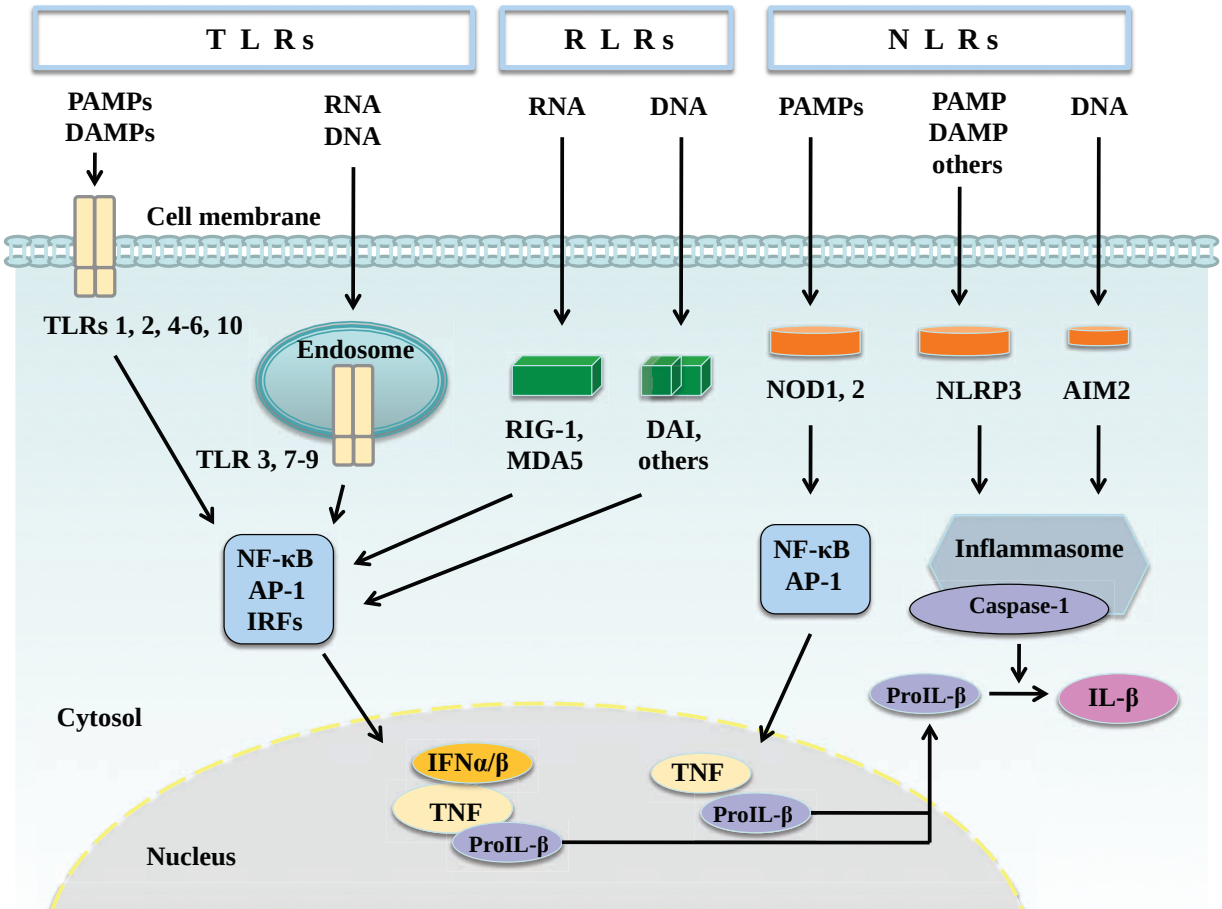

Fig. 1. Representative human innate sensor systems is demonstrated. Signals are generated by exogenous and endogenous ligand stimulation *via* sensors. The innate sensors includes TLRs, RLRs and NLRs. TLRs are located in the cell membrane and endosome, They can sense PAMPs of exogenous origin and DAMPs of endogenous origin. RLRs are cytosolic sensors for nucleic acids. RIG-1 and MAD5 can sense RNA species. DAI recognize DNAs. NLRs include NOD-1, NOD-2, NLRP and AIM2. The signaling induced by sensor-ligand interactions can promote either the activation and nuclear translocation of transcription factors (IRF, NF-κB and AP-1) that derive expression of cytokines, such as IFNα/β, TNF and proIL-1β, or the assembly of the caspase-1 inflammasome and subsequent maturation of IL-1β from proIL-1β.

taining 19-25 tandem leucin-rich repeat (LRR) motifs, a single transmembrane helix, and a cytoplasmic Toll/interleukin (IL)-1 receptor (TIR) domain, which is required for downstream signaling. Combination of TLR and corresponding ligand of PAMP includes TLR1-TLR2 heterodimer/triacyl lipopeptides, TLR2-TLR6 heterodimer/diacyl lipopeptides, TLR3 homodimer/dsDNA, TLR4 homodimer/LPS, TL5 homodimer/flagellin, TLR7 and TLR8 homodimers/ssRNA, TLR9 homodimer/CpGDNA, and TLR11 homodimer/protozoan profiling-like protein (Fig. 2).[21,22,75-77]

TLR extodomain has a typical horseshoe-shaped solenoid structure. The inner surface of concave is mostly formed by parallel β-strands and the outer surface of convex has various secondary structural elements, such as loops of different lengths, α-helices and right-handed helical structures. Crystal structure analyses suggest that TLR agonists can promote TLR dimerization by stabilizing the interaction between the C termini of the horseshoe-shaped modules, followed by trigger of signaling. The cytoplasic TLR domain displays a compact globular confirmation formed by five parallel β-strands and five α helices connected by flexible loops.[78,79] To the contrary, no crystal structures of TLR-DAMP complex have been reported yet.

DAMP RECOGNITION BY TLRs

TLRs can recognize not only exogenous PAMPs, but also DAMPs of endogenous molecules. Intracellular molecules released into the extracellular milieu by activated and necrotic cells, as well as extracellular matrix molecules either up-

Table 2. Exogenous TLR ligands derived from organisms

Receptor	Ligand	Origin of ligand	References
TLR1	Triacyl lipopeptide	Bacteria and mycobacteria	47
	Soluble factors	*Neisseria meningiditis*	48
TLR2	Lipoprotein/ lipopeptides	Various pathoges	49
	Peptideglycan	Gram-positive bacteria	50, 51
	Lipoteichoic acid	Gram-positive bacteria	51
	Lipoarabinomannan	Mycobacteria	52
	Phenol-soluble modulin	*Staphylococcus epidermis*	53
	Glycoinositolphospholipid	*Trypanosoma cruzi*	54
	Glycolipid	*Treponema maltophilum*	55
	Porins	*Neisseria*	56
	Atypical LPS	*Leptospira interrogans*	57
	Atypical LPS	*Porphyromonas gingivalis*	58
	Zymosan	Fungi	59
TLR3	dsRNA	Viruses	60
TLR4	LPS	Gram-negative bacteria	61
	Taxol	Plants	62
	Fusion protein	Respiratory syncytial virus	63
	Envelope protein	Mouse mammary-tumor virus	64
	Hsp70 (exogenous)	*Clamydia pneumoian*	65, 66
TLR5	Flagellin	Bacteria	67
TLR6	Diacylpolypeptide	*Mycoplasma*	68
	Lipoteichoic acid	Gram-positive bacteria	61
TLR7	ssRNA	Viruses	69, 70
TLR8	ssRNA	Viruses	69
TLR9	CpG DNA	Bacteria and viruses	71
TLR10	Di-acylated peptide ?	ND	72
TLR11	ND	Uropathogenic bacteria	73
	Profilin like protein	*Toxoplasma Gondi*	74

ND ; not determined. Abbreviations : see Appendix.

regulated or degraded by tissue injury, sterile inflammation and degeneration. They all have potential to work as DAMPs. Definite, probable or possible endogenous TLR ligands of DAMP have been also reported and can be categorized as proteins/peptides, fatty acid/lipoproteins, proteoglycan/glycosaminoglycans, and nucleic acids/protein-nucleic acids complex, which was summarized by Piccinini and Midwood.[7] Proteins/peptides include ; β-defensin-3 for TLR1, HSP60, HSP70, gp96, HMGB1, HMGB1-nucleosome complex, β-defensin-3, surfactant proteins, eosinophil-derived neurotoxin, and antiphospholipid antibodies for TLR2, HMGB1, fibronectin EDA, fibrinogen, tenascin C, surfactant proteins, β-defensin-3, HSP60, HSP70, HSP72, HSP22 (B8), gp96, S100A8 (Mrp8), S100A9 (Mrp14), neutrophil elastase, antiphospholipid antibodies, and lactoferrin for TLR4, antiphospholipid antibodies for TLR7 and TLR8. Fatty acids/lipoproteins include ; serum amyloid A for TLR2, serum amyloid A, oxidized LDL, and saturated fatty acid for TLR4. Proteoglycans/glycosaminoglycans include ; biglycan, versican, and hyaluronic acid fragments for TLR2, biglycan, heparan sulfate fragments, and hyaluronic acid fragments for TLR4. Nucleic acids/protein-nucleic acid includes dsRNA for TLR3, ssRNA for TLR7 and TLR8, and IgG-chromatin complexes for TLR9. Thus, TLRs can react with both PAMPs and DAMPs, and represent a key molecular link among microbial infection, tissue injury, sterile inflammation and degeneration. Crystal structure analyses have proposed possible diverse modes of exogenous ligand recognition by TLRs, involving TLR homodimerization and heterodimerization, as well as direct TLR-ligand interactions or interactions with co-receptors and accessory molecules.[78-82]

CO-RECEPTORS AND ACCESSORY MOLECULES

Co-receptors and accessory molecules are known to assist PAMP recognition together with some TLRs,[80,82] *e.g.*, MD-2, CD14, Mrp8, RP105 and PAR-2 for TLR4 homodimer, and CD14, CD36 and dectin for heterodimers of TLR1-TLR2 and TLR1-TLR6.[83-85] MD-2 and CD14 can work to assist DAMP recognitions, independently or together.[7] In addition, P2X4/P2X7 was shown to activate TLR2 and TLR4 by ligand stimulation of biglycan in macrophages.[14] HMGB1 mediates activation of plasmacytoid DCs and B cells through TLR9 by DNA-containing immune complexes with immunoglobulin superfamily member RAGE.[86] CD44, together with MD-2, can assist recognition of hyaluronic acid by TLR4.[87]

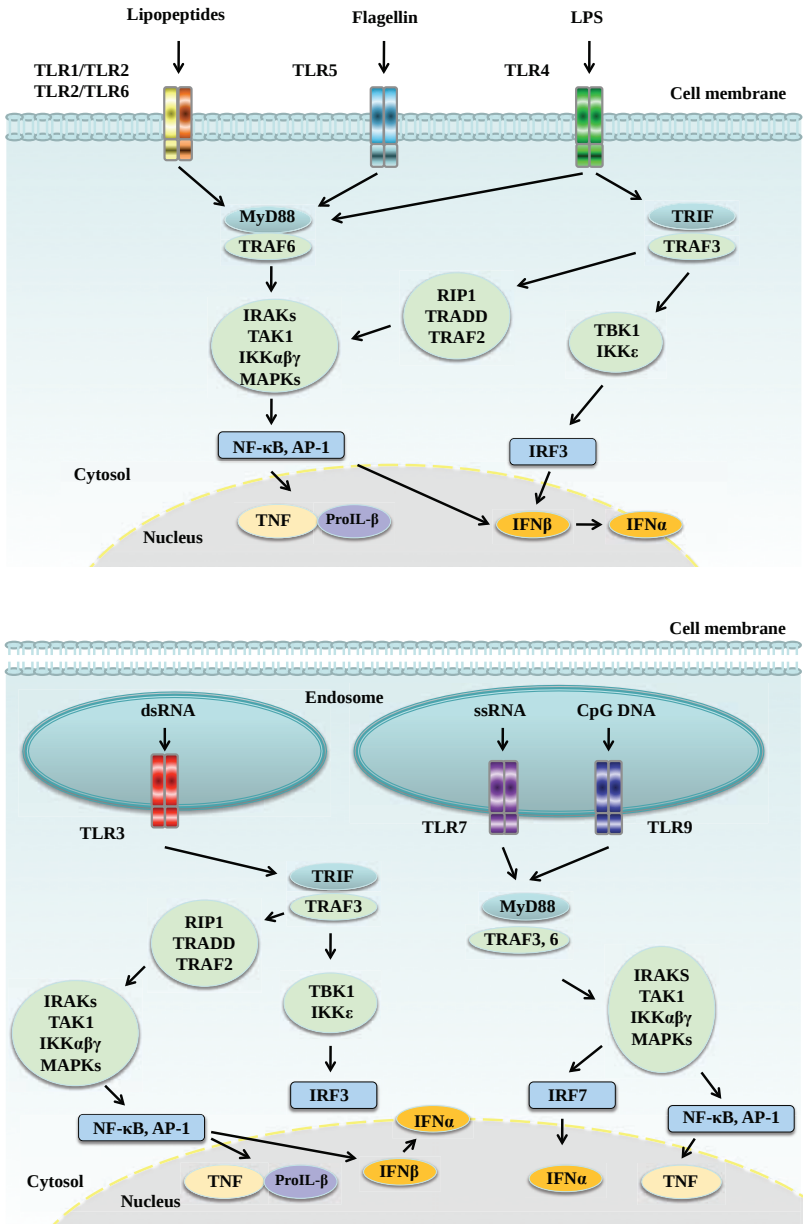

Fig. 2. Representative signal pathway of human TLRs in the cell membrane and endosome are illustrated. TLR signalings take two major routes of adaptors, MyD88 and TRIF, which bind directly or indirectly to TLRs through TIR-domain interactions. (***2a***): MyD88 promotes the recruitment of the TRAF6 (ubiquitin ligase) and several kinase complex as IRAKs, TAK1, IKK$\alpha\beta\gamma$ and MAPKs. Subsequent phosphplilations and ubiquitinations promote translocation of transcription factors, NF-$\varkappa$B and AP-1, which can induce production of messenger RNA, such as TNF, proIL-1β and other inflammatory molecules. On the other hand, TRIF can engage to interact with TRIF3 and kinases of TKB1 and IKKε, followed by IRF3 activation. Expression of IFNβ and subsequent induction of IFNα are induced by activated IRF3, together with NF-$\varkappa$B and AP-1. TRIF also mediates translocation of NF-$\varkappa$B and AP-1 *via* RIP1, TRADD and TRAF2. The pathway of TLR1/2, TLR2/6 and TLR4 is seen in conventional or myeloid dendritic cells (DCs), and also macrophages. The pathway of TLR5 is estimated to use same pathway in macrophages based on the related reports. (***2b***): By contrast, in plasmacytoid DCs, engagement of MyD88 leads to recruitment of ubiquitin kinases of TRAF3 and TRAF6, followed by recruitment of kinases of IRAKs, TAK1, IKK$\alpha\beta\gamma$ and MAPKs. This induces activation transcription factor, IRF7, followed by expression of IFNα, and also NF-$\varkappa$B and AP-1, followed by TNF and other inflammatory molecules.

TLRs AND THE ADAPTORS FOR SIGNALING

The initial role of TLRs is to function as sensors for danger signals of PAMPs and also bind DAMPs to initiate innate host responses.[19,20,67] Binding of TLR ligands to the receptor triggers conformational rearrangements of the cytoplasmic TIR domains and recruitment of specific adaptors *via* homotype TIR-TIR interactions. The main adaptor molecules include MyD88, TRIF (also known as TICAM-1), TIRAP (also known as Mal), and TRAM (also known as TICAM-2).[88,89] MyD88 and TRIF are main adaptors. Most TLRs use MyD88. TLR4 uses both MyD88 and TRIF, and TLR3 uses TRIF. In spite of direct interaction of intracellular portion of TLRs with MyD88 or TRIF, TLR1, 2, 4 and 6, which are located in the plasma membrane, require additional adaptors for the signaling to down-stream; *e.g.*, TIRAP for MyD88, and TRAM for TRIF. Interaction of adaptor molecules are followed by recruitment of kinases and ubiquitn ligases, thus leading to activation and nuclear translocation of several transcription factors, such as NF-κB, AP1 and IRF 3/7, which was dependant on the cell types of innate immune system[5,77,90] (Fig. 2a and 2b).

Ligand-TLR interactions lead to up-regulation of proinflammatory cytokines, chemokines, and chemokine receptors, such as TNF-α,[91] IL-1β,[92] IL-6[91-93] and IFN-$\alpha/\beta/\gamma$,[91,93-95] CC (or β) chemokines[93,95,96] and CXC (or α) chemokines.[93,95] TLR-ligand interactions also up-regulate co-stimulatory molecules, such as intercellular adhesion molecule-1,[92] lymphocyte function-associated antigen-1 and -3.[94] Co-stimulatory molecules are essential for the induction of pathogen-specific adaptive immune responses.[97] Thus, TLRs link innate host responses to adaptive immunity.[98,99]

INHIBITORY REGULATORS AND POSSIBLE MEHANISM FOR TLR SIGNALING

Immune system needs to constantly strike a balance between activation and inhibition to escape from detrimental and inappropriate inflammatory responses as well as inadequate and lower host defense. TLR system must be tightly regulated both in physiologic and pathologic states, otherwise, either insufficient or excessive reactions endanger the host severe or lethal events in microbial infections. Furthermore, immune-mediated aseptic inflammatory diseases are evoked. Negative regulators of TLR signaling have been reported, which may affect the pathway at the levels of extracellular space, cell membrane, cytosol and endosome.[77,87,100-102] Currently known negative regulators and the candidates, together with their corresponding TLRs and posible inhibitory mechanisms, are listed in Table 3 with references (103-136). The possible regulators include EGCG and soluble TLR2/4 in the extracellular space, TMED1, TRAILR and SIGIRR on the cell membrane, and A20, BCAP-$_L$, EGCG, IRAKM, IRF4, MSK1, MSK2, NOD2, PI3K, SHIP-1, SOCS1, symvastatin, TANK, TcpB, TcpC, TOLLIP, Triad3A, TRIB1, TRIB3 and VV protein A46R in the cytoplasm, and chroloquine, citalopram, fluoxetine, and NC-2300 in the endosme.

In each binding process of TLR and ligand, it is interesting and noteworthy that PAMPs and DAMPs may have potential to occupy the same or neighboring biding sites on TLRs to modulate the reaction each other. For example, surfactant protein A was shown to bind extracellular domain of TLR2 and down-regulate induction of NF-κB and TNF-α secretion, competing the same receptor with peptidoglycan and zymosan.[137,138] This suggests possible interaction between the different ligands, which can bind to same receptors, leading to modification of activated signal pathways depending type, amount and distribution of the ligands both in physiological and pathologic conditions. Complex of TLR-like molecule, RP105 and MD-1 can acts as TLR4 decoy receptor. They can inhibit TLR4 activation to compete the receptor with microbial ligands in DCs.[139] Cathepsin K inhibitor, NC-2300 and disease-modifying anti-rheumatic drug, chloroquine, showed inhibitory effect of TLR9-CpG DNA interaction in DCs.[135] Selective serotonin reuptake inhibitors have been known to have anti-inflammatory effect, which was confirmed by systemic administration of fluoxetine and citalopam to suppress the signaling of endosomal TLR3, 7 and 9 in murine collagen-induced arthritis model and cell culture of macrophages and fibroblasts.[136]

EXPERIMENTAL ARTHRITIS INDUCED BY PAMPs AND DAMPs

Experimental models of acute and chronic synovitis indicated the relevant pathogenesis *via* TLRs and their ligands. Systemic injection of streptococcal cell wall could induce arthritis,[140] which has been followed by numerous studies using PAMPs to evoke arthritis in animal models. Microbes-derived TLR ligands, such as peptideglycan for TLR2,[141] dsRNA via TLR3,[142] LPS for TLR4[143] and CpGDNA for TLR9[144] have frequently been used for to provoke or accelerate experimental arthritis. TLR4 was reported to be involved in the chronicity and erosive destruction of streptococcal cell wall-induced arthritis, which was coincident with the antigen-specific IL-17 response.[145]

DAMP can also induce arthritis. Endogenous mitochondrial DNA, containing unmethylated CpG motifs and oxidatively damaged products, could evoke arthritis by monocyte/macrophages, but not B cells or T cells.[146] Intraarticular injection of tenascin-C promoted joint inflammation *in vivo* in mice. Mice that did not express tenascin-C showed rapid resolution of acute joint inflammation and were protected from erosive arthritis. The synthesis and tissue expression were induced in myeloid cells upon tissue injury or infection Thus, tenascin-C acted as TLR4 activator and novel autocrine

Table 3. Possible negative regulations of TLRs and the suggested mechanisms

Molecules	Affected TLR	Suggested mechanism	Reference
Soluble extracelluar regulators			
EGCG	TLR2, 4	Interaction with 67LR or TOLLIP	103, 104
soluble TLR2	TLR2	TLR2 antagonist	105
soluble TLR4	TLR4	Block of interaction of TLR4 and MD-2	106
Transmembrane regulators			
TMED1 (STL2)	TLR2, 4, 9	Sequestration of MyD88 and TIRAP	107
TRAILR	TLR2, 3, 4	Stabilization of IκBα	108
SIGIRR	TLR4, 9	Interaction with TRAF6 and IRAK	109, 110
Intracytosolic regulators			
A20	TLR2, 3, 4, 5, 9	De-ubiquitylation of TRAF6	111, 112
BCAP-L	TLR4	Tyrosine phosphorylation	113
EGCG	TLR2, 4	Interaction with 67LR or TOLLIP	103, 104
IRAKM	TLR4, 9	Inhibition of IRAK1 phosphorylation	114
IRF4	NE	Interaction with MyD88	115
MSK1, 2	TLR4	Regulation of IL-1ra	116
MyD88s	TLR4	MyD88 antagonist	117, 118
NOD2	TLR2	Suppression of NF-κB	119
PI3K	TLR2, 4, 9	Inhibition of p38, JNK and NF-κB	120
SHIP-1	TLR3, 4	Inhibition of TBK-1	121, 122
SOCS1	TLR3, 4, 9	Suppression of IRAK/TRIF	123, 124, 125
Simvastatin	TLR2	Prevention of Rho A activation	126
TANK	NE	Suppression of TRAF6	127
TOLLIP	TLR2, 4	Autophophorylation of IRAK1	128, 129
Traid3A	TLR4, 9	Ubiquitylation of TLRs	130
Tcp	TLR/MyD88	Inhibition of TLR-MyD88	131
TRIB1	NE	Inhibition of NF-IL6	132
TRIB3	TLR2	Inhibition of MAPK	133
VV protein A46R	TLR/ MyD88	Inhibition of MyD88, Mal, TRIF	134
Intraendosomal			
Chroloquine	TLR9	Inhibition of TLR9-CpG DNA	135
Citalopram	TLR3, 7, 8, 9	Possible direct blockade of the receptors or share accessory molecule	136
Fluoxetine	TLR3, 7, 8, 9	Possible direct blockade of the receptors or share accessory molecule	136
NC-2300	TLR9	Inhibition of TLR9-CpG DNA	135

NE; not examined, Abbreviations; see Appendix.

loop in the arthritis.[147,148] S100A8 is a strong promoter of activating FcγRI and FcγRIV in macrophages through the activation of TLR4 and act as a regulator of FcγR expression in inflamed synovium in chronic experimental arthritis.[149]

TLRs AND THE ADAPTORS IN RA SYNOVIAL TISSUES

Synovial tissues from RA joints expressed TLR2 predominantly at sites of attachment and invasion into cartilage and bone, mostly in synovial fibroblasts, but not in macrophages, which expression was enhanced not only by IL-1β and TNF-α, but also LPS.[150] Immunoractivities of TLR2,[91,150,151] TLR3,[151,152] TLR4[91,151] and TLR7[152] were demonstrated in RA synovial lining and sublining, but the precise cellular identification was not done. In RA synovium of early stage, increased expression of TLR3 and TLR4 were demonstrated as well as that of TLR2, 3 and 4 in long-lasting RA synovitis.[153] Current analyses using double immunofluorescent staining revealed tissue localization of TLR1, 2, 3, 4, 5, 6 and 9, as well as adaptor molecules in inflamed rheumatoid synovium. TLR1, 2, 3, 4, 5, 6, 9, MyD88, TIRAP/Mal and TRIF/TICAM-1 were strongly labeled in DCs both of myeloid and plasmacytoid types, moderately in type A macrophage-like lining cells/ intimal macrophages and weakly-to-moderately in type B fibroblast-like lining cells/intimal fibroblasts. $CD3^+/CD4^+$ and $CD3^+/CD8^+$ T cells and $CD20^+$ B cells in perivenular areas and in lymphoid follicles were moderately TLRs and weakly adaptor positive. In osteoarthritic synovium, TLRs and the adaptors were only very weakly immuno-labeled in vascular, lining and inflammatory cells.[36] Taken together, the data suggested that RA synovium well-equipped with TLRs and adaptors, which implies high and prompt responsiveness to the external and internal stimuli, namely, PAMPs and DAMPs.

In vitro analyses on TLRs of peripheral blood mononuclear cells demonstrated that TLR1 was expressed monocytes, polymorphonuclear leukocytes, B cells, T cells and NK cells.

TLR2, 4 and 5 were expressed in myelomonocytic elements. TLR3 was only expressed in DCs, wherein maturation induced by bacterial products or cytokines was associated with reduced expression.[29] Same type of analyses revealed that TLR1 and TLR6 were expressed in all cell types of monocytes, plasmacytoid DCs, B cells, NK cells and T cells in peripheral blood. Evident expression of TLR2, 4 and 5 in monocytes, and that of TLR7 and 9 with high responsiveness to CpG DNA were observed.[26] In addition, DCs in blood sample expressed TLR1, 2, 3, 4, 5, 6 and 8 in myeloid type, and TLR7 and 9 in plasmacytoid type.[154] Immature monocytic DCs of blood expressed TLR1, 2, 3, 4 and 5, but evidently expressed TLR3 with decrease of TLR1, 2, 4 and 5 after maturation induced by LPS.[24] Monocytes/macrophages derived from bone marrow showed expression of TLR2, 4, 5 and 9.[27,28] Embryonic fibroblasts showed potential to have responsiveness to various type of ligands *via* TLR1, 2, 3, 4, 5, 6, 7, 8 and 9. Thus, when compared with mesenchymal cell types, hematopoietic cell types showed relatively restricted presentation of TLRs. There is discrepancy between immunohistochemical analyses and *in vitro* experiments. In addition to the presence of immunoreactive cells of TLR2 and 4[91] as well as those of TLR 3 and 7[152] in synovial lining and sublining intima, well equipment of TLR1, 2, 3, 4, 5, 6 and 9 in monocytes/macrophages, DCs, B cells and T cells in RA synovium were observed by immunohistochemisty.[36] Marked inflammation in RA synovium can produce a variety of mediators and DAMPs, which may influence expression of TLRs in the diseased tissues, being with various states of maturation and/or activation of each cell type. Thus, it may contribute to different profiles of TLR expressions between inflamed RA tissues and *in vitro* studies with blood samples. It would be studied precisely, with careful further evaluation of the specificity of the antibodies used in immunohistochemistry. Embryonic fibroblasts,[38] cell lines[155] and cancer cells were also known to display various types of TLR.[156] It is important to study how different vital circumstances affect expression of TLRs in cell types and tissues, as well as examination of the difference between *in vivo* and *in vitro*.

PAMPs AND DAMPs IN RA SYNOVIAL TISSUES

Possible infectious causes of RA have been long suggested by potential pathogenetic mechanisms; mycoplasma by direct synovial infections and super antigens, parvovirus B19 and retrovirus by direct synovial infection, enteric bacteria and Epstein-Bar virus by molecular mimicry of QKRAA of HLA-DR β1 region, mycobacterium by molecular mimicry of proteoglycans, QKRAA and immunostimulatory DNA, and bacterial cell wall by macrophage activation.[157] Anaerobic bacterial DNA and high levels of antibodies against these bacteria have been detected in the serum and synovial fluid from patients with early and late stage of RA.[158,159] Oral bacteria, such as prophyromonas gingivalis by molecular mimicry of citrullinated enolase, has been suggested to be involved in triggering of the disease.[160] Apart from such possible combined effect of genetic and environmental factors, there is also increasing awareness that innate immune system could directly contribute to onset and lasting course of RA. High percentage of bacterial DNA was detected in the RA and reactive arthritis patients.[161] In addition, bacterial peptideglycans was demonstrated in the synovial macrophages.[162] Exogenous PAMPs can evoke initial immune response *via* TLRs, which has been implicated to be involved in triggering of joint inflammation and disease flares in RA.

In RA synovial tissues and/or fluid, several DAMPs have been suggested to act as stimulators of TLRs; biglycan,[12,13,163] fibrinogen,[164,165] fibronectin EDA (FENDA),[166,167] HMGB1,[168] HSP70,[169,170] HSP B8 (HSP22),[171] low molecular weigh hyarulonic acid,[172,173] S100A8/9[174-176] and tenascin-C.[148,177-179] These molecules have potential to stimulate TLRs, thus evoke and/or enhance innate immune system, and couple with adoptive immune reaction in RA.

CONCLUSION

Extensive research revealed that identification of receptors, ligands and the molecular pathway on TLR system have contributed to better understanding of the pathogenesis of RA and allied arthritic conditions. Further analyses on the interplay between TLRs and other innate sensors, combined with inhibitory mechanisms by negative regulators, would provide more precious information on arthritis responsible for inflammation and joint destruction induced by not only autoimmune and autoinflammatory responses, but also infection and sterile degeneration. This will be beneficial for the diagnostic and therapeutic strategies, and also contribute to prevention or progress of the diseases.

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Appendix. List of abbreviation for molecules and related structures

ASC	apotosis-associated speck-like protein containing a caspase activation and recruitment domain
AIM2	absent in melanoma 2
AP-1	activating protein-1
BCAP-$_L$	full length B cell adaptor for phosphatidylinositol 3-kinase
CARD	caspase activation and recruitment domain
CIIA	MHC class II transcription activator
CD	cluster of differentiation
CpG DNA	DNA containing unmetylated CpG motifs
DAI	DNA-dependant activator of IFN regulatory factor
DAMP	damage-associated molecular pattern
DNA	deoxyribonucleic acid
ds	double-stranded
EDA	extradomain-A
ERK	extracellular signal-regulated kinase
FENDA	fibronectin EDA
FcγR	fragment crystallizable gamma receptor
HET-E	heterocaryon incompatibility locus E protein from *Podspora anserine*
Hsp	heart shock protein
HMGB	high-mobility group box
IFN	interferon
IL	interleukin
IL-1ra	IL-1 receptor antagonist
IRAK	interleukin-1 receptor-associated kinase
IRF	interferon regulatory factor
IKK	inhibitor of kinase
IκB	inhibitor kappa B
JNK	c-Jun N-terminal kinase
gp96	glycoprotein 96
γ-D-gmda	γ-D-glutamyl-*meso*-diaminopimelic acid
LDL	low density lipoprotein cholesterol
LPS	lipopolysaccaride
LR	laminin receptor
LRR	leucine-rich repeat
MAD5	melanoma differentiation-associated gene 5
Mal	MyD88-adapter like
MAPK	mitogen-activated protein kinase
MD-1, 2	myeloid differentiation factor-1, 2
MDP	muramyldipeptide
MHC	major histocompatibility complex
Mrp	myeloid-related protein
MSK1, 2	mitogen- and stress-activated kinase
MyD88	myeloid differentiation primary response protein 88
MyD88s	short form of MyD88
NACHT	NAIP, CIIA, HET-E and TP1
NAIP	neutral apoptosis inhibitor protein
NALP	NACHT, leucine-rich repeat, and pyrin-domain-containing protein
NF-IL6	nuclear factor interleukin 6
NF-κB	nuclear factor-kappa B
NLR	NOD-like receptor
NOD	nucleotide-binding oligomelization domain
NLRP	NLR with a pyrin domain
PAMP	pathogen-associated molecular pattern
PAR-2	proteinase-activated G-protein-coupled receptor-2
PI3K	phosphatidylinositol 3-kinase
PRR	pattern recognition receptor
RAGE	receptor for advanced glycation end products
RIP	receptor interacting protein
RIG-1	retinoid acid inducible gene-1
RLR	RIG-1 like receptors
RNA	ribonucleic acid
RP105	radioprotective 105

SHIP	*src* homology 2 domain-containing inositol-5-phosphatase
SIGIRR	single immunoglobulin and toll-interleukin 1 receptor (TIR) related (identical to TIR-8)
SOCS	suppression of cytokine signaling
ss	single-stranded
ST2L	suppression of tumorigenicity 2L
TANK	TRAF family member-associated NF-*x*B activator
TBK	TANK-binding kinase
TcpB, C	TIR-domain containing protein ; B (*Brucella melitensis*), C (*E. coli*)
TIR	Toll/IL-1 receptor
TICAM-1,2	TIR-containing adaptor molecule-1, 2
TIRAP	Toll/interleukin receptor domain-containing adaptor protein
TLR	Toll-like receptor
TMED	transmembrane emp24 protein transport domain
TNF	tumor necrosis factor
TOLLIP	Toll-interacting protein
TP1	telomerase-associated protein 1
TRADD	TNF receptor 1-associated death domain
TRAF	TNF receptor-associated factor
TRAILR	TNF-related apoptosis-inducing ligand receptor
TRAM	TRIF-related adaptor molecule
TRIB	*tribble*
TRIF	TIR domain-containing adapter inducing IFNß
VV A46R	vaccinia virus protein A46R