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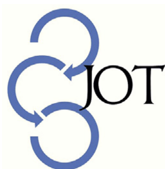

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REVIEW ARTICLE

Danger of frustrated sensors: Role of Toll-like receptors and NOD-like receptors in aseptic and septic inflammations around total hip replacements

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Summary The innate immune sensors, Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), can recognize not only exogenous pathogen-associated molecular patterns (PAMPs), but also endogenous molecules created upon tissue injury, sterile inflammation, and degeneration. Endogenous ligands are called damage-associated molecular patterns (DAMPs), and include endogenous molecules released from activated and necrotic cells as well as damaged extracellular matrix. TLRs and NLRs can interact with various ligands derived from PAMPs and DAMPs, leading to activation and/or modulation of intracellular signalling pathways. Intensive research on the innate immune sensors, TLRs and NLRs, has brought new insights into the pathogenesis of not only various infectious and rheumatic diseases, but also aseptic foreign body granuloma and septic inflammation of failed total hip replacements (THRs). In this review, recent knowledge is summarized on the innate immune system, including TLRs and NLRs and their danger signals, with special reference to their possible role in the adverse local host response to THRs.

Translational potential of this article: A clear understanding of the roles of Toll-like receptors and NOD-like receptors in aseptic and septic loosening of joint replacements will facilitate

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potential strategies to mitigate these events, thereby extending the longevity of implants in humans.
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Introduction

Aseptic loosening and deep infection are two major reasons for reoperation after primary total hip replacement (THR) [1]. Both "aseptic" and "septic" loosening are conditions in which a loose THR implant is accompanied by unfavourable inflammatory immune reactions in periprosthetic connective tissue. Aseptic loosening is considered to be a local foreign body reaction to implant wear debris, in which monocytes/macrophages recognize and phagocytose debris derived from the implant. The septic condition around THRs is attributed to interplay of the host and microbial attacks, and is referred to as a periprosthetic joint infection, in which monocytes/macrophages and neutrophils both play an important role in combating the bacterial infection. Monocytes/macrophages and neutrophils are the major cell types responsible for the innate host defence. These two immune responses drive and define the pathologic state. Various mediators have been identified and linked to the physiologic and pathologic roles of aseptic and/or septic inflammation around THR implants. However, the precise mechanisms of aseptic loosening and the septic condition have not been elucidated yet. In addition, despite "aseptic" and "septic" inflammatory conditions being defined in THRs, the mechanisms, similarities, and differences of these two conditions are still poorly understood. Continued research on the molecular and cellular mechanisms underlying these complex inflammatory processes will undoubtedly contribute to better longevity of patients with THRs.

The human immune system consists of both innate and adaptive immunity. Innate immunity is found in both animals and plants, and serves to protect the host from foreign intruders. The adaptive immune system is found only in vertebrates, and developed at a later evolutionary stage than innate immunity. In vertebrates, the innate and adaptive immunities work together in the host defence against pathogens. The innate immune response is induced not only by microbial attack, but also by sterile tissue injury and degeneration with no invading pathogen present. This paradox was first explained by Matzinger [2] in 1994 (the Matzinger hypothesis). She proposed that the immune system was activated by both external and internal molecules signalling dangers, rather than by recognition of self versus nonself. Sensing receptors, termed "pattern recognition receptors" (PRRs), have since been identified as important components of this theory. Mammalian cells can sense danger signals from both pathogens and damaged tissues *via* PRRs of the innate immune system, which evolved earlier than the highly diverse receptors of the adaptive immune system in vertebrates. Subsequent analyses of innate immune receptors have led to the identification and classification of PRRs into five families: Toll-like receptors (TLRs), retinoid acid inducible gene-I like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectins (CTLs) and absent-in-melanoma-like receptors. These receptor families can respond to exogenous molecules and endogenous danger signals [3,4]. (Abbreviations of the molecules and related structures used in this review are summarized alphabetically in Appendix 1.)

TLRs are located on the cell-surface and on endosomes within the cell. They can sense exogenous "pathogen-associated molecular patterns" (PAMPs) [5] and endogenous "damage-associated molecular patterns" (DAMPs), also known as alarmins [6,7]. RLRs are cytosolic sensors for nucleic acids and are largely responsible for the recognition of cytosolic, virus-derived RNA, subsequently inducing the production of interferons. RLRs can sense RNA species. CTLs, located on the cell membrane, recognize carbohydrate-based ligands and are important receptors in the detection and response to different infections, *e.g.*, fungi and tubercle bacillus. CTLs can function, like TLRs located on the cell membrane, to scan the extracellular milieu for PAMPs. Human immunodeficiency virus exploits CTLs for cell entry. NLRs are cytoplasmic sensors and can promote the inflammatory response *via* signal transduction and/or inflammasome formation. NLRs also function in the process of autophagy [4,8–14]. Moreover, possible mechanisms of collaboration and/or cross-talk among these different innate immune sensors have been suggested [15].

Recent research on TLRs and NLRs has brought new insights into not only the pathogenesis of infectious and rheumatic diseases, but also the adverse local host response around THRs, especially aseptic and septic conditions. TLRs and NLRs are particularly known to be involved in the local host response around THRs [16–19]. This review summarizes recent knowledge and examines the innate immune response of TLRs and NLRs, with special reference to aseptic loosening due to foreign body granuloma and septic condition by microbial attack in THRs.

Toll-like receptors

Toll receptor was originally identified in *Drosophila melanogaster* as a receptor essential for the establishment of the dorso-ventral pattern in developing embryos [20]. In 1996, Lemaitre *et al*. [21] demonstrated that Toll-mutant flies were highly susceptible to fungal infections. A mammalian toll homologue was first reported in 1997 and named TLR [22]. TLRs belong to the PRR family, and are the main innate immune sensors, together with RLRs and NLRs. Thus far, 13 distinct mammalian TLRs have been identified, 10 of which

are functional in humans (TLR1—10), and 12 in mice (TLR1—9 and TLR11—13) [23—25]. TLR1, TLR2, TLR5, TLR6, TLR10, and TLR11 are located on the cell surface. TLR3, TLR7, TLR8, and TLR9 are located in the endosome. TLR4 is located both on the cell surface and in the endosome. The high levels and broadest spectra of TLR expression have been observed in a variety of cell types in the immune system, including monocytes/macrophages [16,26—30] and neutrophils [17,31].

TLRs can recognize a wide variety of PAMPs derived from bacteria, fungi, parasites, and viruses. They act as homo- or heterodimers of type I transmembrane glycoproteins, each comprising a ligand-binding ectodomain containing 19—25 tandem leucine-rich repeat (LRR) motifs, a single transmembrane helix, and a cytoplasmic Toll/interleukin (IL)-1 receptor (TIR) domain, which is required for downstream signalling. Combinations of TLRs and corresponding PAMP ligands include the TLR1—2 heterodimer with triacyl lipopeptides, the TLR2—6 heterodimer with diacyl lipopeptides, the TLR3 homodimer and dsRNA, the TLR4 homodimer and lipopolysaccharide (LPS), the TLR5 homodimer and flagellin, the TLR7 and TLR8 homodimers and ssRNA, the TLR9 homodimer and CpGDNA and the TLR11 homodimer and protozoan profilin-like protein. These receptor/ligand pairs are summarized in Tables 1 and 2 and Figure 1 [23,24,32—65]. TLR10 has an inhibitory effect and is predominantly involved in the modulation of the TLR2-driven activation of immune cells [66].

TLRs can sense not only exogenous PAMPs, but also DAMPs of endogenous origin. Intracellular molecules become DAMPs as they are released into the extracellular milieu by activated and necrotic cells. Similarly, molecules released from the damaged extracellular matrix due to tissue injury, sterile inflammation, or degradation can function as DAMPs. Definite, probable, or possible endogenous TLR DAMP ligands have been reported and can be categorized as proteins/peptides, fatty acids/lipoproteins, proteoglycans/glycosaminoglycans, and nucleic acids/protein-nucleic acids complex [3,10] (Table 2). Proteins and peptides that activate the TLRs include: β-defensin-3

Table 1 Exogenous TLR ligands derived from organisms.

Location/receptor	Major ligands	Origin of the ligand	Refs
Plasma membrane			
TLR 1	triacyl lipopeptide	bacteria & mycobacteria	[32]
	soluble factors	*Neisseria meningiditis*	[33]
TLR 2	lipoprotein/lipopeptides	various pathogens	[34]
	peptidoglycan	gram-positive bacteria	[35]
			[36]
	lipoteichoic acid	gram-positive bacteria	[36]
	lipoarabinomannan	mycobacteria	[37]
	phenol-soluble modulin	*Staphylococcus epidermis*	[38]
	glycoinositolphospholipid	*Trypanosoma cruzi*	[39]
	glycolipid	*Treponema maltophilum*	[40]
	porins	*Neisseria*	[41]
	atypical LPS	*Leptospira interrogans*	[42]
	atypical LPS	*Porphyromonas gingivalis*	[43]
	zymosan	Fungi	[44]
TLR 5	flagellin	bacteria	[52]
TLR 6	diacylpolypeptide	mycoplasma	[53]
	lipoteichoic acid	gram-positive bacteria	[46]
TLR 10	Profilin-like molecule	ND	[57,66]
Plasma membrane/endosomal membrane			
TLR 4	LPS	gram-negative bacteria	[46]
	Taxol	plants	[47]
	fusion protein	respiratory syncytial virus	[48]
	envelope protein	mouse mammary-tumour virus	[49]
	Hsp70 (exogenous)	*Chlamydia pneumoniae*	[50,51]
Endosomal membrane			
TLR 3	dsRNA	viruses	[45]
TLR 7	ssRNA	viruses	[54,55]
TLR 8	ssRNA	viruses	[54]
TLR 9	CpG DNA	bacteria & viruses	[56]
TLR 11	ND	uropathogenic bacteria	[58]
	Profilin like molecule	*Toxoplasma Gondi*	[59,63]
TLR 12	Profilin like molecule	ND	[63]
TLR 13	bacteria 23S rRNA	ND	[63]

ND = not determined. see Appendix 1 for list of all other abbreviations. Note. Adapted and modified with permission from copyright holder [3,63].

Table 2 Endogenous TLR ligands of host origin and synthetic analogues.

Location	TLRs	Ligands		Signal adaptor
		Major DAMPs	Synthetic analogue	
Plasma membrane				
	TLR1—2	ND	triacyl lipopeptides	MAL/MyD88
	TLR2—6	heat-shock proteins	diacyl lipopetides HMGB1, versican, hyaluronic acid	MAL/MyD88
	TLR5	ND	discontinuous 13-amino acid peptide CBLC502	MyD88
	TLR10	ND	ND	MyD88
Plasma membrane/Endosomal membrane				
	TLR4	heat-shock proteins, HMGB1, β-defensin-3, extra domain A of a fibronectin, hyaluronic acid, heparin sulfate, fibrinogen, surfactant-protein A, oxidized phospholipids	lipid A mimetics (monophosphoryl lipid A minoalkyl glucosamine 4-phosphate), E620, E5531, E5564	MAL/ MyD88 TRAM/ TRIF
Endosomal membrane				
	TLR3	mRNA	poly(I:C). poly(I; C_{12}U)	TRIF
	TLR7	ssRNA (immune complex)	oligonucleotides, imidazoquinoline, guanosine nucleotides, bropirimine	MyD88
	TLR8	ssRNA (immune complex)	imidazoquinolines (resiquimod)	MyD88
	TLR9	chromatin IgG complex	CpG oligo-deoxynucleotide	MyD88
	TLR11	ND	ND	MyD88
	TLR12 ND	ND		MyD88
	TLR13	ND	ND	MyD88

ND = not determined; see Appendix 1 for list of all other abbreviations.
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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 and antiphospholipid antibodies for TLR7 and TLR8. Fatty acids and lipoproteins that activate the TLRs include: serum amyloid A for TLR2, and serum amyloid A, oxidized LDL and saturated fatty acid for TLR4. Proteoglycans and glycosaminoglycans that activate the TLRs include: biglycan, versican and hyaluronic acid fragments for TLR2, and biglycan, heparan sulfate fragments, and hyaluronic acid fragments for TLR4. Nucleic acid and protein-nucleic acid ligands of the TLRs include dsRNA for TLR3, ssRNA for TLR7 and TLR8, and IgG-chromatin complexes for TLR9. Thus, TLRs can interact with both PAMPs and DAMPs, and represent a key molecular link among microbial infection, tissue injury, sterile inflammation, and degeneration. Crystal structure analyses 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 coreceptors and accessory molecules [65—72] (Table 2).

Coreceptors and accessory molecules are known to assist PAMP and/or DAMP recognition by some TLRs [69,71], e.g., MD-2, CD14, Mrp8, RP105, and PAR-2 for the TLR4 homodimer, and CD14, CD36, and dectin for the TLR1—TLR2 and TLR2—TLR6 [72—74]. MD-2 and CD14 can work to assist DAMP recognition, either independently or together [10]. In addition, P2X4/P2X7 have been shown to activate TLR2 and TLR4 by biglycan ligand stimulation in macrophages [75]. HMGB1 mediates activation of plasmacytoid dendritic cells and B cells through TLR9 by DNA-containing immune complexes with immunoglobulin superfamily member receptor for advanced glycation end products (RAGE) [76]. CD44, together with MD-2, can assist in the recognition of hyaluronic acid by TLR4 [77].

The initial role of TLRs is to function as sensors for danger signals of PAMPs, and to bind DAMPs to initiate innate host responses [21,22]. The binding of a TLR ligand to the receptor triggers conformational rearrangement 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) [78,79]. MyD88 and TRIF are the main adaptors of TLRs. Most TLRs use MyD88. TLR4 uses both MyD88 and TRIF, and TLR3 uses only TRIF. In spite of direct interaction of the intracellular portion of TLRs with MyD88 or TRIF, TLR1, TLR2, TLR4, and TLR6, which are located in the plasma membrane, require additional adaptors for downstream signalling, *e.g.*, TIRAP for MyD88 and TRAM for TRIF. The interaction of adaptor molecules is followed by the recruitment of kinases and ubiquitin ligases, leading to activation and nuclear translocation of several

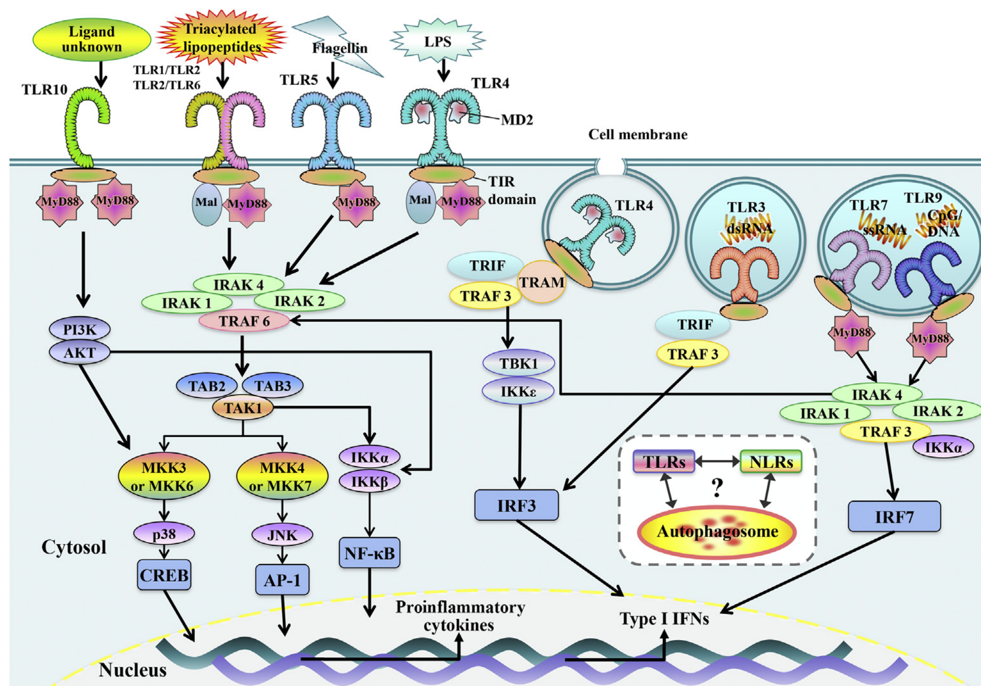

Figure 1 Representative signalling pathway of human TLRs in the cell membrane (TLR1/2, TLR2/6, TLR4, TLR5, and TLR10) and endosome (TLR3, TLR4, TLR7, and TLR9). TLRs signal through two major adaptors, MyD88 and TRIF, which bind directly or indirectly to TLRs through TIR-domain interactions. MyD88 and Mal promote the recruitment of TRAF6 (ubiquitin ligase) and several kinase complexes, such as IRAKs, TAB/TAK, IKKαβ, MAKKs, and/or PI3K/Akt. Subsequent phosphorylation and ubiquitination promote the translocation of the transcription factors CREB, AP-1, and NF-κB, which can induce transcription of certain messenger RNAs, such as TNFs, pro-IL-1β, and other inflammatory molecules. By contrast, TRIF interacts with TRAF3 and TBK1/IKKε in endosomal TLR4 signalling, and with TRAF3 in TLR3 signaling, followed by IRF3 activation. In TLR7 and TLR9 signaling, TRIF interacts with IRAKs and TRAF3, followed by IRF7 activation. Activated and phosphorylated IRF3 and IRF7 in the cytoplasm are translocated into the nucleus, which induces subsequent induction of type I IFNs [63—65]. See Appendix 1 for list of abbreviations.
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transcription factors, such as NF-κB, AP1, CREB, and IRF3/7, which differ between cell types in the innate immune system [8,69,80] (Figure 1).

Activation of these transcription factors *via* TLR signalling leads to upregulation of proinflammatory cytokines, chemokines, and chemokine receptors, such as TNF-α [81], IL-1β [82], IL-6 [81—83], IFN-α/β/γ [81,83—85], CC (or CCβ) chemokines [83,85,86], and CXC (or CXCα) chemokines [83,85]. TLR-ligand interactions also upregulate costimulatory molecules, such as intercellular adhesion molecule-1 [82] and lymphocyte function-associated antigen-1 and -3 [84]. Costimulatory molecules are essential for the induction of pathogen-specific adaptive immune responses [87]. Thus, TLRs link innate host responses to adaptive immunity [88,89]. Synthetic analogues can also stimulate TLR signalling (Table 2).

TLRs are important not only for the identification of infectious agents, but also for various other types of diseases. In inflammatory rheumatoid synovium, increased expression of TLR2, TLR3—5, TLR7, and TLR9 was demonstrated [90,91]. In systemic lupus erythematosus, the possible involvement of TLRs at onset was proposed [92,93]. Pathologic involvement of TLR signalling has been suggested in asthma [94], psoriasis [95], inflammatory bowel disease [96], Alzheimer's disease [97], multiple sclerosis [98], and atherosclerosis [99]. Thus, TLRs have emerged as attractive therapeutic targets, and several biologic and synthetic antagonists to modulate their function have been developed, *e.g.*, for TLR2, OPN-305 (humanized antibody) for delayed graft function; for TLR4, SPA4 (peptide) for lung inflammation, E5564 (small molecules) for sepsis, TAK-242 (small molecule) for septic shock and NI-0101 (antibody) for rheumatoid arthritis; for TLR7-9, IMO-3100 (DNA-based small molecule) for psoriasis; and for TLR7-9: ODN antagonist (oligonucleotides) for inflammation, IMO-880 (DNA-based small molecules) for dermatomyositis and psoriasis and CpG-ODN c41 (oligonucleotide) for inflammation [65,100—102].

NOD-like receptors

The concept of pathogen recognition and the host defence system in plants was intensively studied in the early 2000s [103,104]. In plants, resistance to pathogens is mediated by a group of disease resistance genes that elicit the hypersensitivity response. This response includes physical isolation of infected lesions through remodelling of the cell wall structure, production of reactive oxygen species (ROS), cell death, and production of antipathogen molecules at the site of infection. Some resistance gene products are transmembrane proteins with ectodomains containing LRRs, such as mammalian TLRs [104]. Another major class of resistance gene products is cytosolic NOD proteins, which

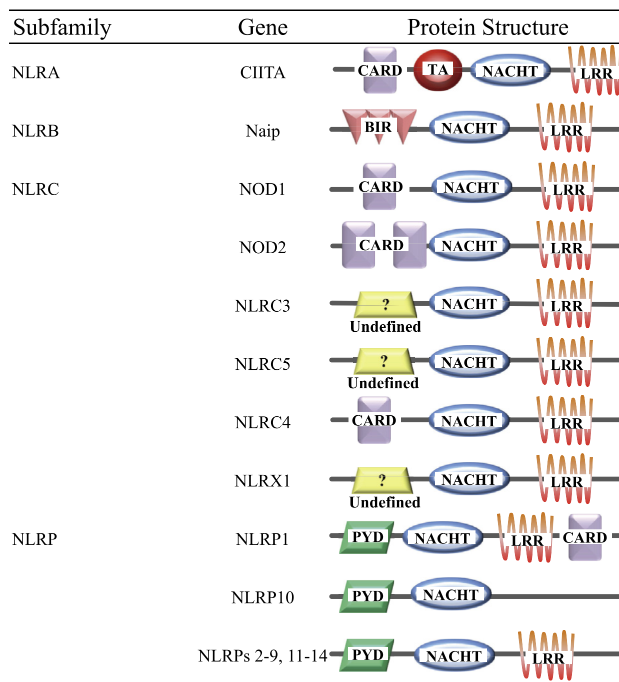

Figure 2 The NLR subfamily. There are four NLR: NLRA, NLRB, NLRC, and NLRP. In their protein structures, the NACHT, CARD, LRR, BIR, TAD, PYD, and undefined regions are major components [4,12,107]. See Appendix 1 for list of abbreviations. Adapted and modified with permission of copyright holder [4].

typically contain amino-terminal α-helix-rich or TIR domains, a central NOD, and carboxyl-terminal LRRs [104]. These receptors were also identified in mammalian cells, and their role in host-microbial interactions and inflammatory diseases have been comprehensively summarized [105,106].

NLRs are cytoplasmic receptors and can recognize PAMPs and DAMPs. Evolutionary and domain structure analyses of the NLRs have clarified four subfamilies: NLRA, NLRB, NLRC, and NLRP [12,107]. Recent findings regarding each subfamily of gene, function and activator is summarized in Figure 2 and Table 3 [108–160]. NLRs share a common domain, a central NOD domain, and carboxyl-terminal LRRs. The NOD domain in NLRs is also known as the NACHT domain, which has been named after the NAIP, CIITA, HET-E, and TP1 proteins. The NACHT domain consists of seven distinct conserved motifs, including the ATP/GTPase specific loop, the Mg2+-binding site, and five more specific motifs, including a transactivation domain (TAD), caspase recruitment and activation domain (CARD), baculovirus IAP repeat (BIR), pyrin domain (PYD) and an undefined region (Figure 2) [4,107,161,162].

Motta *et al.* [4] put forward a functional concept of the NLR family, in which the roles of NLRs were divided into "Signalsome" (signal transduction), "Enhansosome" (transcriptional activation), "Autophagosome" (autophagy), and "Inflammasome" (inflammasome assembly). For example, in signal transduction, NOD1 and NOD2 are known to activate the NF-κB pathway *via* Rip2 [163]. Nuclear translocation of NF-κB induces cytokine production. The peptidoglycans diaminopimelic acid and muramyl dipeptide (MDP) are activators for NOD1 [111,112] and NOD2 [113], respectively. This pathway is different from TLR signalling mediated by MyD88 and TRAF6 [164]. To the contrary, the NALP subfamily members NLRC3 (NLR family CARD domain containing 3) [116], NLRP2 (NLR family pyrin domain containing 2) [134], and NLRP4 [147] negatively regulate this pathway by the suppression of TRAF6 (Figure 3). In response to IFN-γ stimulation, nuclear translocation of CIITA (class II, major histocompatibility complex, transactivator) [108] and NLRC5 [117,118,165] induces MHC class II and MHC class I upregulations, respectively. Nuclear translocation of NLRC5 is followed by dimer formation. IFN-β stimulation can upregulate the inflammatory response *via* NLRC5. Autophagy, a bulk cytoplasmic degradation system, aids in xenography, which plays an important role of bacterial clearance. NOD2 can recognize bacteria at the cell entry site and recruit autophagy-related protein 16L1 (ATG 16L1) to the plasma membrane. Autophagosome formation around intracellular bacteria is initiated and followed by the exclusion of bacteria [114,166–168]. Inflammasomes can be assembled by NLRP3, NLRP1, and NLRC4 and are triggered by various cell stressors: NLPP3 by ATP, K^+ efflux, aluminium, asbestos, silica, ROS, potassium efflux, fungus, uric acid, hyaluronic acid, amyloid, and nanoparticles; NLRP1 by anthrax lethal toxin and MDP and NLRC4 by flagellin and rod proteins (T3SS and T4SS; injectisome, found in several gram negative bacteria). These are summarized in Figures 2 and 3. Upon activation, NLRs form multimeric protein complexes including ASC and procaspase. Procaspase is maturated into caspase-1, which induces activation of pro-IL-1β into IL-1β and of proIL-18 into IL-18 (Figure 3). Thus, inflammasome assembly leads to an inflammatory response, and abnormalities of the genes involved are related to specific diseases [169,170]. Mutation in CIITA is responsible for bare lymphocyte syndrome, in which the immune system is severely compromised and cannot effectively fight infection [171]. Gene deletion in Naip was found in spinal muscular atrophy [172]. Asthma [173] and inflammatory bowel disease [174] have been related to NOD1 mutations, and Crohn's disease [175] and Blau syndrome [176] to NOD2 mutations. NALP1 mutations have been associated with vitiligo [128], Addison's disease [177] and type-1 diabetes mellitus [177]. NLRP12 mutations were also found in one type of hereditary periodic fever syndrome [178]. In addition, many genetic mutations encoding NLRPs have been reported, including Beckwith-Wiedemann Syndrome [179], neonatal-onset multisystem inflammatory disease (also called CINCA syndrome) [180,181], familial cold autoinflammatory syndrome [182], and Muckle-Wells syndrome [182]. Genetic mutations in NLRP3 and inflammasome-related molecules have also been found in human autoinflammatory diseases, hereditary periodic fever syndromes, familial Mediterranean fever, hyperimmunoglobulinaemia D and periodic fever syndrome and necrosis factor receptor superfamily 1A-associated periodic syndrome [183,184]. Gene mutations in the NLRs and their related molecules can affect the onset of diseases and syndromes more distinctly compared to the TLRs. In addition, NLRs are involved in the process of ontogeny in mammals [185,186]. The NLR family of intracellular sensors has emerged not only as a crucial component of the innate

Table 3 Gene, function and the activators of NLRs.

Subfamily	Gene	Function	Activator	Refs
NLRA	CIITA	MHC class II expression	IFNγ	[108]
NLRB	Naip	control of *legionella pneumophila* infection	flagellin	[109]
NLRC	NOD1	NF-κB	DAP	[110–112]
	NOD2	NF-κB, autophagy, type 1 IFN production	MDP	[113,114]
	NLRC3	negative regulator of T cell activation, response to LPS & TRAF6	unknown	[115,116]
	NLRC5	inflammatory response & MHC class I upregulation	IFNγ, IFNβ	[117–119]
	NLRC4	caspase 1 activation, cell death, phagosome maturation	rod proteins, flagellin	[120–123]
	NLRX1	ROS production & antiviral response	unknown	[124–127]
NLRP	NLRP1	response to anthrax bacteria	lethal toxin, MDP	[128,129]
	NLRP10	dendritic cell migration	unknown	[130,131]
	NLRPs 2–9, 11–14			
	NLRP2	embryonic development, caspase 1 activation, TRAF6 suppression	unknown	[132–134]
	NLRP3	caspase 1 activation	ATP, K^+ efflux, alum, asbestos, silica, ROS, fungi, MSU, HA, amyloid, nanoparticle	[135–140,142–146]
	NLRP4	embryogenesis, suppression of type 1 IFN, autophagy, & TRAF6	unknown	[147–150]
	NLRP5	embryogenesis	unknown	[151]
	NLRP6	NF-κB inhibition & caspase 1 activation	unknown	[152,153]
	NLRP7	embryonic development, caspase 1 activation	lipopetides	[154–156]
	NLRP12	inhibition of noncanonical NF-κB, ERK, & AKT pathway, activation caspase 1	Yersinia	[157–159]
	NLRP14	spermatogenesis		[160]

See Appendix 1 for list of abbreviations.

immune response, but also a key regulator of life phenomena.

As previously described for TLRs, the molecular mechanisms responsible for innate immunity have become possible therapeutic targets in various diseases. However, when compared to clinical trials examining the therapeutic use of several TLR-related molecules [65,100–102], those related to NLRs have not yet progressed at the clinical trial level. This is probably due to more complicated interactions of various ligands with NLRs, as well as at least four different roles of the intracellular receptors (signal transduction, transcriptional activation, autophagy, and inflammasome assembly) which potentially interact with each other in a complicated fashion. In addition, TLR and NLR interaction has become a great concern [4,15,187]. TLRs can promote the induction of autophagy and promote the delivery of infecting pathogens to the lysosome. Induction of autophagy and interplay between autophagy and NOD1/NOD2, which are associated with ATG 16L1, has been demonstrated [168]. Several NLRs, including NLRP3 and NLRC4, have been shown to mediate caspase-1-dependent cell death of infected cells, which is termed pyroptosis. TLRs and NLRs coordinately influence the outcome of infections by controlling the fate of host cells [187]. However, the precise mechanism of the interactions between the two innate sensors remains unclear.

Frustrated TLRs and NLRs in the local host response to THR implants

Expression of TLRs in aseptic periprosthetic connective tissue was first reported in 2007. CD68-positive monocytes/macrophages in the synovial membrane showed marked immunoreactivity of TLR4 and TLR9, which was more intense than that found in osteoarthritic synovial tissue [16]. Enhanced immunoreactivity of TLR1, TLR2, TLR5, and TLR6 in CD68-positive monocytes/macrophages was also observed [17–19]. Upregulation of various TLRs, including TLR1, TLR2, TLR6, and TLR9, in aseptic interface tissue was also demonstrated using quantitative reverse transcription polymerization reaction [188]. Subsequently, the

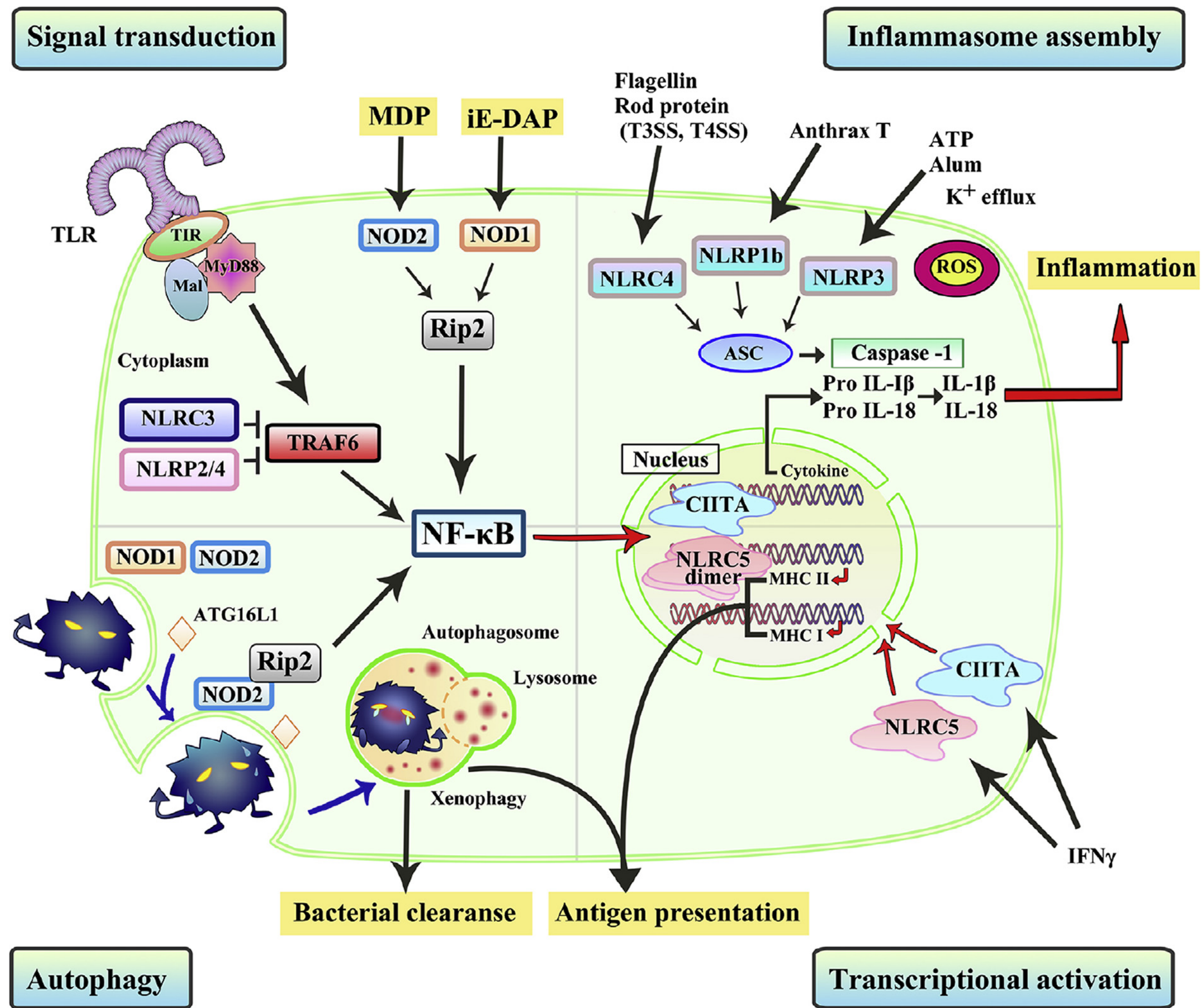

Figure 3 NLRs play four major roles as intracellular sensors: signal transduction via NF-κB, enhancement of immune and inflammatory cytokine induction, autophagosome-related antigen presentation and/or bacterial clearance and inflammasome formation leading to inflammatory reactions induced by activated IL-1β and IL-18, mediated by caspase-1 [4]. See Appendix 1 for list of all other abbreviations.
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expression of TLR4 was found to correlate with several proinflammatory and chemotactic mediators in peri-implant tissue, suggesting a role of TLR4 in the peri-implant inflammatory process [189]. Similarly, increased expression of TLRs was observed in an animal model of wear particle disease [190]. In the septic synovial tissue of THR patients, enhanced immunoreactivity of TLR1, TLR2, TLR4, TLR5, and TLR9, was seen in CD15-positive polymorphonuclear neutrophils and CD68-positive monocytes/macrophages [17,191] (Figure 4). These findings indicate that both aseptic and septic periprosthetic tissues around THRs are well equipped with TLRs, which can respond promptly to microbial stimuli (PAMPs) and DAMPs induced in the process of tissue damage, degradation, and remodelling. The cell types responsible for TLR signalling are mainly monocytes/macrophages in aseptic periprosthetic tissue and neutrophils and monocytes/macrophages in septic inflammation. Increased expression of NLRs and related molecules was also observed both in aseptic and septic periprosthetic tissues around THRs. NLRP3, caspase-1, ASC, and IL-1β, were found both in aseptic and septic inflammatory periprosthetic tissues [19,191] (Figure 4). Prior to immunohistochemical analysis of the retrieved tissue samples, secretion of IL-1β from macrophages after titanium particle exposure was demonstrated. IL-1β secretion was dependent on inflammasome activation, namely, NALP3, ASC, and caspase-1 [192]. In addition, involvement of NLRP3 in polymethylmethacrylate particle-induced inflammation and osteolysis was demonstrated in both *in vitro* macrophage culture and an *in vivo* mouse calvarial model [193]. This suggests the potential role of the inflammasome in the pathogenesis of periprosthetic osteolysis.

Taken together, these studies indicate that the innate immune sensors, TLRs and NLRP3, are possibly involved in the pathogenesis of "aseptic" and "septic" inflammation around THR implants. In the "septic" condition, monocytes/macrophages and neutrophils utilize TLRs, and at least NLRP3, to combat microbes. Microbial components, PAMPs, can stimulate these sensors; thus, the inflammatory reaction is evoked and enhanced. In the process of

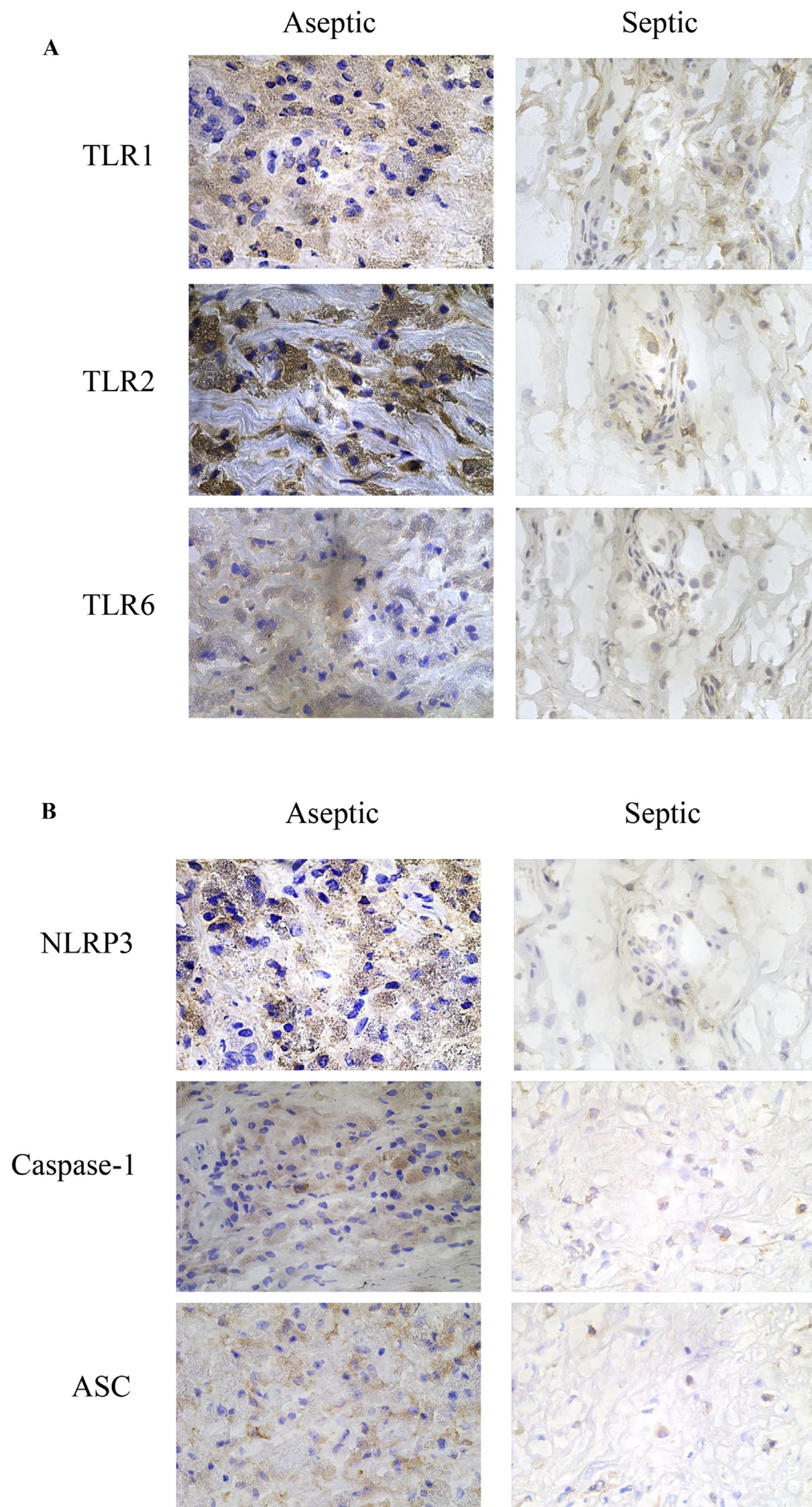

Figure 4 Immunohistochemical localization of (A) TLR1, TLR2, and TLR6 and (B) NLRP3, Caspase-1, and ASC in aseptic foreign body granuloma and septic synovial membrane in failed THRs. The main immune-reactive cells were monocytes/macrophages in aseptic tissues, and monocytes/macrophages and neutrophils in septic tissues. Retrieved tissue samples were embedded in OCT compound, followed by thin-cut and fixation with formaldehyde. Avidin-biotin peroxidase complex method was applied as previously described [19]. See Appendix 1 for list of abbreviations.

inflammation, these sensors can also possibly react with DAMPs from damaged cellular components and the various mediators produced and/or released in the response to pathogen-induced inflammation. For example, proteins/peptides, fatty acids/lipoproteins, proteoglycans/glycosaminoglycans, and nucleic acids/protein-nucleic acids complexes found in infectious sites are candidates for DAMPs as TLR-ligands in septic inflammation around THRs, as described previously [3,17]. Potential ligands that activate NLRP3 include ATP, ROS, and uric acid released from the damaged cells.

The question remains as to how the sensors behave in the "aseptic" condition. Immunohistochemical analyses confirm that monocytes/macrophages involved in foreign body granulomas are equipped with TLRs, NLRP3, and associated molecules. Monocytes/macrophages work as scavengers of the innate immune system to eliminate unknown foreign wear particles. However, except for subclinical infections, there does not appear to be a PAMP ligand to stimulate the sensors *in loco*. One possible explanation for the function of the sensors abundantly found in aseptic foreign body granulomas and osteolysis is the induction and/or enhancement of inflammatory reactions by direct contact and/or phagocytosis of wear debris from implants. Maitra *et al*. [194] demonstrated that polymeric alkaline structures, with side chain oxidation, directly bind and activate the TLR1—TLR2 signalling pathway and initiate phagocytosis of the particle, inducing enlargement, fusion and disruption of endosomal components. This leads to NALP3 inflammasome activation and ROS release by cathepsins [194,195]. Hydroxyapatite and cobalt-alloy particles and/or cobalt ions also enhance proinflammatory cytokine production via TLR4. Several previous studies have suggested that direct contact and/or phagocytosis of the debris itself evokes innate immune responses via the sensors [196—198]. Indeed, it has recently been demonstrated that, in contrast to ions, cobalt particles induce inflammation and osteolysis mainly by activating NLRP3 rather than TLR4 [199]. Similarly, endotoxin-free titanium particles were reported to be insufficient to induce and enhance proinflammatory cytokines *via* TLR signalling pathways. Removal of LPS (a ligand for TLR4) contamination from titanium particles almost completely inhibited the production of TNF-α, IL-1β, and IL-6 at the protein level, and did not affect osteoclastic differentiation *in vitro*. In addition, the removal of endotoxin from the particles reduced wear-driven osteolysis by 50—70% *in vivo* [200]. LPS-free and lipoteichoic acid (LTA) (ligand for TLR2)-free titanium particles were also shown not to elevate TNF-α, IL-1β, and IL-6 mRNA levels in macrophages stimulated by these particles *in vitro* [19,30]. Additional coating of particles by LPS and LTA *in vitro* reversed this phenomenon. Thus, these *in vitro* studies may support the hypothesis that PAMPs, either present on the implant surface [201] or accumulated in the effective joint space *via* circulation [202], can adhere to wear particles and stimulate the innate immune sensors, and induce and/or enhance the osteolytic inflammatory reaction [203]. This hypothesis is further supported by the observations from genetic association studies that polymorphisms in innate immune sensors and relevant signalling molecules can alter the risk for periprosthetic osteolysis [204].

However, the discrepancy in the findings between titanium wear particles and those made of other materials, including polymers, cobalt-alloy, and hydroxyapatite, seems unusual. Rigorous treatment of wear particles to remove residual endotoxins by strong acid (nitric acid) and strong alkali (sodium hydroxide) may alter the surface chemistry of the wear particles, including their hydrophobicity, oxidation, ionization, and/or electric charge, and result in an impaired cellular response. This might account for the fact that removal of endotoxins reduced particle-induced *in vivo* osteolysis by 50—70%, but not completely [200]. The surfaces of the endotoxin-free particles *in vivo* are exposed to cells, extracellular matrix, and fluid after particle implantation. This can allow the adherence of various molecules of host-origin to the particles. These substances may include DAMPs derived from cells, extracellular matrices, and fluid content from exudate of serum and/or extracellular space, which are induced as a result of the stimulus and invasive particle implantation. Adherence of DAMPs to particles potentially evokes TLR-related inflammatory responses, although the reaction is probably weaker compared to PAMP adherence. This phenomenon could be explained an increase in TNF-α and IL-1β mRNA, even in the absence of LPS and LTA coatings [30,190]. Cellular debris, containing DAMPs, produced during cell culture can potentially adhere to particles. The particles and/or cellular DAMPs themselves can stimulate innate immune sensors *in vitro*. Alternatively, particle implantation *in vivo* can evoke foreign body reactions apart from their effects on TLRs or other innate immune sensors. These effects might also be due to misrecognition relating to phagocytosis, such as the interaction between the Fc receptor of immune cells and nonspecific immunoglobulin attached on the particle surfaces, or between scavenger receptors and denatured cholesterol and/or allied substances of serum origin after invasive processes of particle implantation and the ensuing tissue response. Serum amyloid A, complement components, hyaluronic acid, fibronectin, and other endogenous molecules in the serum might act as additional ligands covering the particles.

Foreign body granuloma formation and periprosthetic osteolysis occur gradually over several years, and often over more than 10 years in aseptic loosening of THRs. Pathologic extracellular connective tissue remodelling by proteinases and cell cycling (recruit, proliferation, apoptosis, and/or necrosis) continues, but proceeds slowly in response to the phagocytosis of wear particles. This process can also provide DAMPs *in loco*, which stimulate TLRs and NLRs, but is probably regulated by a self-protection mechanism, as the addition of particles to monocytes/macrophages *in vitro* precipitated downregulation of TLR mRNA [16,30], and, in spite of the upregulation of IL-1β mRNA, the release at protein levels was not high [19]. Eventual downregulation of TLRs after particle stimulation was also observed in a mouse model [205]. This phenomenon seems compatible with the *in loco* status around the aseptic loosening of THRs, where inflammatory markers, *e.g.*, C-reactive protein, are within normal limits, along with the absence of redness and local heat driven by inflammasomes and active IL-1β. Down- and/or upregulation of the TLR- and NLR-mediated response to wear particles probably reflects the proactive behaviour of effector cells *in vitro*, but appears to be more complex

in vivo. Further analyses on the effect of DAMPs from tissue debris, as well as PAMPs *in vitro* and *in vivo*, are required. We have to keep in mind that *in vitro* experiments and *in vivo* animal models only provide short time points when compared to the extended timeline of the aseptic loosening of THRs in humans.

The boundary between "aseptic" and "septic" conditions still seems unclear. For example, clinically unapparent microbial attack, which does not show the expected tissue response with active neutrophil invasion, and the presence of biofilms, probably makes the situation more complex to decipher. Multifactorial interactions among the genetic variations, including deletions and polymorphism in immune cells, types of foreign substances, including PAMPs and biomaterial related-wear, and DAMPs produced in the process of tissue response, need to be precisely taken into account to explain the individually different local tissue and systemic reactions, and require more study [206]. In addition, the problem of adverse local host response to metals and various types of tissue reaction, often overlapping perivascular lymphocytic infiltration and/or lymphocyte-dominant reaction, foreign body granuloma, tissue necrosis, fibrosis, or infection, is now raising additional questions on the role of innate immune sensors [207,208].

In the basic research field of TLRs and NLRs, intensive and broad analyses are ongoing. Although the precise mechanism of TLRs, NLRs, and their interaction is not yet completely elucidated, current knowledge can certainly provide hints to clarify the pathology of unfavourable host reactions around THRs. In addition, the clinical approach of modifying TLR and NLR signalling using synthetic agents and/or by identification of individual differences at genetic and epigenetic levels probably improves the pathologic status of aseptic and septic conditions around THRs, leading to upgrading of therapeutic and prophylactic levels. Further intensive research not only on the frustrated immune sensors, TLRs and NLRs, but also on the global interaction of the innate and adaptive immune system in the local host response are required. These studies provide relevant information on more accurate patient-specific implant selection, and therapeutic and/or prophylactic approaches for unfavourable host responses around THRs in the future.

ND = not determined. see Appendix 1 for list of all other abbreviations. *Note*. From "Toll-like receptor–A potent driving force behind rheumatoid arthritis," by M. Takagi, 2011, *J Clin Exp Hematop*, *51*, p. 77–92. Copyright 201X, Name of Copyright Holder. From "The history of Toll-like receptors — redefining innate immunity," by L.A. O'Neill, D. Golenbock, A.G. Bowie, *Nat Rev Immunol*, 2013, *13*, p. 453–60. Copyright 201X, Name of Copyright Holder. Modified with permission.

Conflict of interest

There is no conflict as for the review article.

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Appendix 1. List of abbreviations for molecules and related structures.

Akt	protein kinase B
AP-1	activating protein-1
ATG16L1	autophagy-related protein 16
BIR	baculovirus inhibitor of apoptosis protein(IAP) repeat
CARD	caspase activation and recruitment domain
CC	C-C motif
CD	cluster of differentiation
CIITA	MHC class II transcription activator
CpG DNA	DNA containing unmethylated CpG motifs
CTL	C-type lectin
CREB	cyclic-AMP response element-binding protein
CXC	CXC-motif
DAI	DNA-dependant activator of IFN-regulatory factor
DAMP	damage-associated molecular pattern
ds	double-stranded
EDA	extradomain A
ERK	extracellular signal-regulated kinase
FcγR	fragment crystallisable gamma receptor
gp96	glycoprotein 96
HET-E	heterocaryon incompatibility locus E protein from *Podspora anserina*
HMGB	high mobility group box
Hsp	heat shock protein
IAP	inhibitor of apoptosis protein
IFN	interferon
IL	interleukin
IL-1ra	IL-1 receptor antagonist
IRAK	IL-1 receptor-associated kinase
IRF	interferon regulatory factor
IKK	inhibitor κB kinase
IκB	inhibitor kappa B
JNK	c-Jun N-terminal kinase
LDL	low-density lipoprotein cholesterol
LPS	lipopolysaccharide
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

(*continued*)

MKK	MAPK kinase
MSK	mitogen- and stress-activated kinase
MSU	monosodium urate
MyD88	myeloid differentiation primary response protein 88
NACHT	NAIP, CIITA, HET-E and TP1
NAIP	neuronal 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 oligomerization domain
NLRC3-5	NLR family CARD domain-containing 3-5
NLRP	NLR with PYD-containing protein
PAMP	Pathogen-associated molecular pattern
PAR-2	proteinase-activated G-protein-coupled receptor -2
PI3K	phosphatidylinositol 3-kinase
PRR	pattern recognition receptor
PYD	pyrin domain
RAGE	receptor for advanced glycation end-products
RIP	receptor-interacting protein
RLR	retinoic acid-inducible gene 1-like receptor
RP105	radioprotective 105
ss	single-stranded
T3SS/T4SS	type III/IV secretion system
TAD	transactivation domain
TANK	TRAF family associated NF-kB activator
TBK	TANK-binding kinase
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 domain-containing protein
TNF	tumour necrosis factor
TP1	telomerase-associated protein 1
TRAF	TNF receptor-associated factor
TRAM	TRIF-related adaptor molecule
TRIF	TIR-domain-containing adapter-inducing IFN

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