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Innate Immunity Sensors Participating in Pathophysiology of Joint Diseases: A Brief Overview

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Abstract

The innate immune system consists of functionally specialized “modules” that are activated in response to a particular set of stimuli via sensors located on the surface or inside the tissue cells. These cells screen tissues for a wide range of exogenous and endogenous danger/damage-induced signals with the aim to reject or tolerate them and maintain tissue integrity. In this line of thinking, inflammation evolved as an adaptive tool for restoring tissue homeostasis. A number of diseases are mediated by a maladaptation of the innate immune response, perpetuating chronic inflammation and tissue damage. Here, we review recent evidence on the cross talk between innate immune sensors and development of rheumatoid arthritis, osteoarthritis, and aseptic loosening of total joint replacements. In relation to the latter topic, there is a growing body of evidence that aseptic loosening and periprosthetic osteolysis results from long-term maladaptation of periprosthetic tissues to the presence of by-products continuously released from an artificial joint.

Keywords

innate immunity sensors; PRRs; TLRs; NLRs; RAGE; CLRs; inflammasomes; rheumatoid arthritis; osteoarthritis; aseptic loosening

I. INTRODUCTION

Innate immunity is a pivotal player in controlling host resistance, integrity, and tissue homeostasis. It protects us from microbial invaders, participates in wound healing, and contributes to many other physiological functions.¹ The key step of the innate immune response is the recognition of danger signals or tissue damage by sensors (receptors) located on the surface of sensor cells.² These cells continuously monitor and patrol the host tissues for microbes, damage, and stress, searching for signals of danger and damage. In this sense, receptors on sensor cells are key structures for both the health and survival of an organism.

Innate immunity receptors trigger an inflammatory response that was evolved as a fundamental adaptation to the loss of cellular and tissue homeostasis.^{2–4} The inflammatory responses are highly heterogeneous at least in terms of the cell types and molecular mediators involved. Despite the huge complexity, during the course of the inflammatory response, particular contributors could be ascribed to specific functional categories, such as *inflammatory inducers, sensors, mediators, and target tissues*.² Inducers are signals that initiate distinct types of inflammatory responses via activation of particular defense modules.^{4,5} Sensor cells and their receptors play an essential role in the activation of innate immunity when they—in response to a contact with inducers—produce a unique mediator signature for the inducer acting then on a particular target tissue. Typically, different classes of receptors screen for a particular inducer to guarantee both the sensitivity and robustness of a response.^{6,7} The basic aim of activation of the innate immune system is to eliminate the inducers and restore tissue homeostasis. If elimination of an inducer is not possible, then the goal is to adapt tissue to the noxious state.⁸ In this line, the problem is the inability to resolve the inflammation that is behind a growing number of pathological entities.⁹

Immune-mediated joint diseases are a highly heterogeneous group of conditions affecting almost any joint in the body in adults and children. Upregulation/dysregulation of innate immunity participates in the pathology of a particular joint disease with a different clinical impact. As a result, great clinical variability is observed between chronic diseases such as rheumatoid arthritis and ankylosing spondylitis on one hand, and osteoarthritis and implant-induced complications on the other hand. Joint damage in some of the mentioned conditions can be accompanied by severe disability with increasing dependency on the family and society. As a result, direct and indirect costs associated with these diseases are enormous.^{10–12} Therefore, an understanding of the molecular mechanisms that govern immune-mediated joint diseases is crucial. The aim of this review is to describe innate immune sensors that initiate these diseases.

II. CLASSIFICATION OF SENSING RECEPTORS

The innate immune system uses a broad range of pattern recognition receptors (PRRs) to detect invariant structural motifs on invading pathogens. Traditionally they are called pathogen-associated molecular patterns (PAMPs) or more recently the acronym MAMPs (microbe-associated molecular patterns) has been introduced.¹³ The other major source of stimuli are endogenous danger signals indicating host tissue damage or stress (damage-associated molecular patterns; DAMPs).¹⁴

A large group of receptors is located on the cell membranes (membrane-bound receptors scanning continuously the extracellular milieu) as well as endosomal compartments. In contrast, cytoplasmic receptors monitor the intracellular space (Table 1).

III. MEMBRANE-BOUND RECEPTORS

A. Toll-Like Receptors

Toll-like receptors (TLRs) were first described in humans in 1997.¹⁵ They are expressed on the cell surface and on endolysosomal membranes, and detect a wide range of inducers including microbial patterns, environmental signals, and also tissue damage motifs (e.g., nucleic acids, stress proteins). Following ligation with their ligands, activated TLRs recruit specific combinations of TIR-containing proteins with MyD88 activating canonical pathway and TRIF activating alternative pathway (Fig. 1). specific kinase complexes such as IRAKs or IKK ϵ /TANK-binding kinase-1 (TBK1) play an important role during signal transduction, which leads to the expression of specific genes via the transcription factors NF- κ B, AP1, and IFN regulatory factors IRF3 and IRF7.¹⁶ The final products of the above-mentioned pathways are innate immunity cytokines directing acute inflammatory responses (especially IL-1 β , IL-18, IL-33, IFNs, TNF- α). Importantly, there are a large number of other factors and interactions that co-regulate the expression of inflammatory genes including long noncoding RNA, micro-RNA, chemokines, or other PRRs.^{17–19}

B. C-Type Lectin Receptors

C-type lectin receptors (CLRs) are a diverse family of proteins that possess one or more C-type lectin-like domains that recognize carbohydrate moieties.²⁰ The field of CLRs is still not completely understood but it is clear that all CLRs are not PRRs. On the other hand, a critical role in the activation of innate immunity is played by those acting as PRRs (e.g., Dectin-1, DC-SIGN). Ligand binding of CLRs triggers phosphorylation of intracellular immunoreceptor tyrosine-based activation motif (ITAM) and recruitment and activation of spleen tyrosine kinase (SYK). These molecules orchestrate critical antimicrobial responses in myeloid cells and participate also in the response to endogenous signals of tissue damage.^{20–22} Their occurrence and function in dendritic cells is well described.²³ They can also sense for cell death signals influencing the proportion of the necrosis and apoptosis in damaged tissues.²⁴

C. RAGE

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily of cell surface receptors. It consists of an extracellular domain comprised of an N-terminal sequence and three Ig-like regions. RAGE is a multiligand receptor that has a single transmembrane domain and a short cytoplasmic domain responsible for signal transduction.⁶ Ligation of RAGE and TLRs results in activation of the inflammatory response in a wide range of diseases including immune-mediated joint damage.²⁵ The most influential inducers for RAGE are several advanced glycation end products (AGEs), high-mobility group box 1 protein (HMGB1), S100A4, S100A8/A9, S100A12, S100B (structurally defined family of multifunctional proteins that also participate in activation of innate and adaptive immune responses), nucleic acids, and

lipopolysaccharide.^{26–28} For instance, HMGB1 is a highly conserved nonhistone nuclear protein. It is either released passively during cell damage (“homeostatic danger signals”) or secreted actively on inflammatory stimuli.²⁹ On release from necrotic or pyroptotic cells, HMGB1 passes through three different redox states, being first chemotactic, then a danger signal, and finally inactive. From apoptotic cells, it is released in all oxidized forms and does not stimulate CXCR4 or TLR4.³⁰ That is why HMGB1 and some other ligands are probably overexpressed in inflammatory and osteoarthritic joints, and periprosthetic tissues. As a result, these ligands might contribute—after their interaction with RAGE/other PRRs (e.g., TLR-4)—to the inflammatory response via expression of TNF- α , IL-6, and other cytokines in diverse groups of cells (Fig. 1).

IV. CYTOPLASMIC RECEPTORS

A. Cytoplasmic Nucleic Acid-Sensing Receptors

The endolysosome-restricted nucleic acid (NA)-sensing subset of TLRs (NA-TLRs), e.g., double-stranded RNA-sensing (dsRNA) TLR-3, single-stranded RNA (ssRNA)-sensing TLR-7/8, unmethylated cytosine-phosphate-guanosine motifs (CpG)-sensing TLR-9 and cytosolic ssRNA and dsRNA-sensing cytosolic helicases, utilize IRAKs and the IKK ϵ /TBK1 pathways (Fig. 1). Other cytosolic receptors such as RIG-I (also known as DDX58) and MDA5 both transduce the mitochondrial adaptor IPS-1 (also known as MAVS, VISA, and Cardif) and TBK1 to induce transcription factors AP-1, NF- κ B, and IRF3 or IRF7. The third group of cytosolic receptors represents helicase designated Laboratory of genetics and physiology 2 (Lgp2), exhibiting suppressive function on RIG-I and MDA5 because it lacks caspase-activating and recruitment domains (CARDs) involved in interaction with IPS-1.^{31,32} Furthermore, DNA is detected by DDX41 and IFN γ -inducible protein 16 (IFI16) both signaling through the endoplasmic reticulum-resident stimulator of IFN genes (STING), which merge with the above RNA-sensing pathway by activating TBK1.³³ Cytosolic DNA induces the Apoptotic speck protein containing a caspase recruitment domain (ASC)/caspase-1-mediated secretion of IL-1 β by AIM2 inflammasome.³⁴ The above receptors trigger type I interferons, proinflammatory cytokines, and chemokines. In the case of DNA sensing, they also induce inflammasome activation.¹³

B. NOD-Like Receptors

Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are a family of cytoplasmic PRRs. In humans, there are 22 known NLRs even though the molecular functions of some NLRs remain poorly described. Of those characterized, NOD1, NOD2, NLRP10, NLRX1, and some others stimulate innate immunity via NF- κ B, MAPK, and IRFs, whereas NLRP1, NLRP3, NLRP6, NLRP7, NLRC4, and some others form inflammasomes (“inflammasome-forming NLRs”).^{14,35} inflammasomes are the danger-sensing protein complexes that consist of inflammasome sensor molecule, adaptor protein ASC, and inflammatory caspases 1 and 5. Little is known concerning the inducers of the NLRP1 inflammasome while a wide range of stimuli (including MAMPs and DAMPs) activates NLRP3 inflammasome.^{35,36} NLRs have been implicated in a plethora of diseases including gout, rheumatoid arthritis, obesity, insulin resistance, or atherosclerosis.³⁵

V. EVIDENCE FOR A ROLE OF INNATE IMMUNITY SENSORS IN OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis typically affecting knees, hips, hands, and spine.³⁷ Importantly, it is not a disease of only cartilage, as the disease affects all tissues in and around the joint. The pathogenesis of OA is closely associated with a genetic defect in the structure of a particular joint tissue, intra-articular trauma, and mechanical overload. Most investigators now agree that OA is a highly heterogeneous condition and that the pathogenesis of OA is complex and not yet fully understood.^{38–40} It may be that OA is a final result of a set of tissue responses to a wide range of pathologic events/processes ongoing in affected joints.⁴¹ In this line, it is logical that interactions between tissue damage and innate immunity recognizing DAMPs are an inevitable part of the disease. Surgeons, rheumatologists, and pathologists have investigated the role of inflammation in the early and late stages of OA.^{42–45}

A potential set of stimuli activating membrane and/or intracellular PRRs include intact, post-translationally modified and/or degraded matrix proteins (e.g., collagen), apoptotic and necrotic cell debris (source of nucleic acids), alarmins, calcium containing crystals, and cytokines.^{46,47} In fact, there is some evidence that these inducers can activate several PRRs as a part of the pathogenesis of OA (Table 2). One recent study associates soluble CD14 with promotion and progression of OA as a part of the TLR-2 and TLR-4 pathways.⁴⁸ The others demonstrate *in vivo* and *in human* active involvement of alarmins S100A8, S100A9, or S100A12 in the regulation of synovial activation and cartilage destruction.^{49–51} Other inflammatory inducers might be associated with the activation of the complement pathway with the membrane attack complex (MAC) C5b-9 that has been also associated with progression of OA.⁵² Moreover, it was shown that double-stranded RNA (dsRNA) signaling in OA chondrocytes requires activation of several classes of PRRs (TLR-3, RIG-1, MDA-5) for dysregulation of matrix metalloproteinase (e.g., MMP-13) expression in human cartilage sampled before total joint replacement.⁵³

Taken together, there is moderate to strong evidence for participation of innate immunity mediated inflammation in the pathogenesis of OA.^{41,46,54–56} There is growing agreement that the innate immune regulation network plays an important role in the onset and progression of OA.^{57,58} However, this hypothesis is still controversial because of recent *in vivo* studies in which, for example, the administration of exogenous AGEs failed to demonstrate a significant effect on joint degeneration.⁵⁹ Therefore, further studies are required to obtain direct evidence for participation of innate immunity receptors in OA processes and the potential benefit of therapeutic inhibition.

VI. CONTRIBUTION OF INNATE IMMUNE SENSORS SIGNALING TO RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) has an annual incidence of approximately 0.4 per 1000 in females and 0.2 per 1000 in males. The prevalence is estimated between 0.4 and 1%, therefore much lower than in OA.⁶⁰ On the other hand, the clinical course, morbidity, and mortality

associated with RA are much more serious than in OA. The hallmark of RA is symmetric synovial proliferation and tenderness of multiple joints, particularly small joints of the hands and feet.⁶¹ Key laboratory features of RA are anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF), with the former being more specific for RA than the latter.^{62,63} With regard to the pathogenesis of RA, there is considerable agreement that genetic factors are important in the predisposition to RA and also that they can influence the clinical presentation of the disease.⁶⁴ Similarly, there is general agreement regarding the central role of the immune system in the pathogenesis of RA.⁶⁵

TNF- α and IL-1 are major mediators in the early stages of joint inflammation.⁶⁶ However, a critical step in the pathogenesis of RA is chronic activation of synovial T cells and therefore the most important question is what activates these cells (Fig. 2). Within the T-cell population, Th-17 cells and memory T cells predominate in inflamed tissues.^{65,67} The former drive cartilage and bone damage via pro-inflammatory cytokines while the latter participates in maintaining the pool of synovial T cells in a highly differentiating state.⁶⁵ It was recently revealed that cells of the innate immune system such as mast cells and neutrophils are important sources of IL-17A and other IL-17 family members.⁶⁸ The synovial macrophages express cytokines such as TNF, IL-1, and IL-6, contributing directly to perpetuation of joint inflammation, and also cytokines like IL-15, IL-18, and IL-23 that stimulate accumulation, maturation, and activation of T cells.^{62,69}

A set of potential inducers of immune response in RA ranges from the joint-related ligands (e.g., type II collagen, proteoglycans, alarmins) across extra-articular autoantigens (e.g., citrullinated proteins, heat-shock proteins, fibrinogen, fibronectin) to exogenous agents like bacteria and viruses.^{47,65,70} On the other hand, no auto-antigen has been shown to be central to the pathogenesis of RA; in addition, an infectious etiology of RA has not been proven.⁶⁵ Distinct classes of RA inducers are recognized by particular PRRs localized on immune/nonimmune cells leading to activation of a specific module of innate immune response characterized by the generation of a pathogenic set of T cells in the synovium of patients with RA.^{62,71,72} With respect to innate immunity, a number of studies support the concept of a central role of TLRs in the pathogenesis of RA.⁷³ There is also growing evidence that alarmins (e.g., HMGB1) interact with receptors that include RAGE as well as TLR-2 and TLR-4 in a synergistic fashion contributing together to induction and perpetuation of persistent inflammation in rheumatic diseases.^{74–76} In terms of effector cell populations of innate immunity in RA, it seems that the most important are fibroblast-like synoviocytes, and macrophages.^{77–79} Both cell groups secrete a broad array of mediators contributing to the growth and transformation of the synovium into the hyperplastic synovial pannus tissue, which mediates cartilage, tendon, and bone damage.^{79,80}

Taken together, there is compelling evidence for the pathogenically important contribution of receptors of the innate immune system to the development of RA. However, further research is needed with regard to identification of critical DAMPs and their interactions with specific innate immunity module(s). Additionally, detailed understanding of the mechanisms devoted to signal transduction and amplification is warranted.

VII. EVIDENCE FOR CONTRIBUTION OF INNATE SENSOR SIGNALING IN ASEPTIC LOOSENING AND PERIPROSTHETIC OSTEOLYSIS

Aseptic loosening and periprosthetic osteolysis are the most frequent late complications of total joint arthroplasty (TJA). The most prominent inducers of innate immunity response in these complications are prosthetic particles liberated from the surface of the biomaterial during its life in service. Particles are non-homogeneously distributed around an artificial joint coming in continuous contact with diverse cell groups and their receptors.^{81,82} Even distant extra-articular distribution of prosthetic particles has been reported.⁸³ In addition, metallic ions (corrosion by-products) can be cytotoxic, carcinogenic, and genotoxic.^{84–86} Another very important source of periprosthetic inflammatory inducers is tissue ischemia and cell necrosis resulting from chronic particle and ion load, non-resolved inflammation, unfavorable mechanical conditions, and repetitive joint fluid waves.^{87–89}

Currently, a number of studies give strong experimental evidence that prosthetic particles can activate surface/intracellular innate immune receptors of macrophages, fibroblasts, and osteoblasts. Accordingly, polyethylene, metallic, and polymethylmethacrylate particles released from an implant are able to stimulate receptors in macrophages and other cell groups to express proinflammatory molecules like PGE₂, TNF- α , IL-1 β , IL-6, and others contributing to inflammation.^{90–102} Particles coated by diverse host proteins including complement are endocytosed or stimulate innate immunity cells via surface receptors (Fig. 1).^{103–106} The prosthetic particles can simultaneously influence both the expression of osteoclastogenic molecules and suppression of osteoblastic cell line.^{107–110} As a result, the bone-multicellular units around an implant are imbalanced (Fig. 3), leading eventually to osteolysis.^{111,112} In this line, it can be deduced that the high-volume producers of prosthetic particles are at higher risk for development of osteolysis and aseptic loosening in comparison to low-volume producers regardless of the origin of particles (concept of “particles as a fuel of particle disease”).^{113,114} Additionally, inorganic particles are indigestible per se; hence, they can destabilize the phagolysosomal membrane leading to the leakage of their content and stimulation of cytosolic PRRs.

With regard to the biomaterial origin, polyethylene and metallic particles appear to be biologically more active than titanium and ceramic particles.^{115–117} Particles of highly cross-linked polyethylene have been shown to induce higher *in vitro* inflammatory responses than conventional polyethylene even though there are far fewer particles generated from the former compared to the latter material.^{118,119} In addition, the size and shape of the polyethylene particles are critical parameters influencing the robustness of inflammation around an implant.^{120,121} Moreover, the particles of different biomaterial origin can stimulate the innate immune cells in a synergistic fashion.¹²² Some investigators also noticed that the expression of proinflammatory cytokines and chemokines was increased when particles were contaminated with endotoxin in comparison to experiments with endotoxin-free samples.^{123–128} Finally, the synergistic effect between chronic inflammation and intermittent joint fluid waves could contribute to induction and expansion of bone defects around an implant.^{129,130}

Recently, researchers investigated the mechanisms of cross talk between innate immune receptors and prosthesis induced danger/damage signaling. It was suggested that hydrophobic molecules are likely to be strong stimulators of innate host response through PRRs.¹³¹ In this line, it is not surprising that polyethylene is a rather hydrophobic material. In addition, it has been shown that polymeric alkane structures released during ultrahigh molecular weight polyethylene (UHMWPE) breakdown can directly activate the TLR-1, -2 signaling pathway while UHMWPE particles phagocytosed by periprosthetic cells could induce endosomal destabilization and inflammasome activation.¹³² To date, a number of studies have demonstrated expression of TLRs in tissues retrieved from *in vitro* and *in vivo* models and during revision surgeries in humans, giving strong evidence for participation of TLRs in the activation of innate immunity by prosthetic by-products.^{133–138} In addition, there is growing evidence that particle-driven inflammation and bone resorption around an implant could be at least in part regulated via stimulation of inflammasomes.^{139–141}

In addition, a number of signal transduction pathways related to TLRs activation are involved in the mechanisms of aseptic loosening and osteolysis development. Of them, the most important seem to be MyD88, IRAK-1, MAPK such as c-Jun N-terminal kinase (JNK), and the phosphoinositol-3-kinase (PI3K)/Akt pathways that mediate the *in vitro* and *in vivo* activation of macrophages by orthopedic wear particles.^{138,142–145} In addition, cold inducible RNA binding protein (CIRP) responds to a wide spectrum of cellular stresses including hypoxia and inflammation. It was shown that CIRP could regulate NF- κ B transcription factor and expression of IL-1 β .¹⁴⁶ Similarly, HMGB1 was released with the potential to enhance the expression of RANKL, TNF- α , IL-1 β , and IL-6.¹⁴⁷

With regard to innate immunity effector cells, a murine osteolysis model was used to attempt to demonstrate the key role for macrophages as well as osteoclastogenic pathways in the pathology of aseptic peri-implant osteolysis.^{148,149} In relation to the former, macrophages were depleted pharmacologically, while with regard to the latter, RANK knockout mice were examined.^{150,151} As well, dendritic cells, fibroblasts, and nerves could influence the periprosthetic inflammation and fibrosis significantly. However, the evidence for their contribution is still low.^{152–158}

Taken together, key receptors of innate immunity contribute strongly to inducement and perpetuation of the periprosthetic inflammation and also to alteration of the balance between bone resorption and formation around an implant. In this line, the research on the molecular mechanisms underlying aseptic loosening and periprosthetic osteolysis induced a number of preventative strategies including those targeting innate immunity receptors and their transduction pathways.^{159–162} On the other hand, an *in vivo* situation is much more complex than an experimental one, especially in terms of complex signaling networks containing also powerful regulatory and anti-inflammatory pathways controlling for the tissue integrity and status postoperatively.^{163–165} As a result, the concept of aseptic loosening as an example of pure immune-mediated disease is somewhat questionable and other cofactors such as mechanical stresses have to be included into the theory to explain realistically the development of osteolysis and aseptic loosening.¹⁶⁶ In addition, there is some evidence for genetic susceptibility to an osteolytic response due to prosthetic by-products.^{167,168} The

difference is probably also between patients with rheumatoid arthritis and non-arthritic patients.¹⁶⁹

Further research should be focused on the detection of “non-TLR sensors” of innate immunity located on specific cell groups of interest in experimental and clinical settings. For example, there is no evidence for participation of RAGE receptors (or CLRs and nucleic acid sensors) and their signaling pathways in the pathogenesis of aseptic loosening and periprosthetic osteolysis despite the fact that theoretically there is no reason why they could not be implicated in the activation and perpetuation of immune-mediated peri-implant bone resorption.¹⁷⁰ As well, there is currently little direct evidence for participation of other alarmins including heat shock proteins and nucleic acid fragments in the mechanisms of aseptic loosening and osteolysis.^{133,171} However, the activation of the innate immunity pathway should be investigated in a network fashion and together with their regulatory counterparts.¹⁷² The experiments have to simulate more realistically the peri-implant situation, especially in terms of time parameters and synergy between prosthetic particles and mechanical factors. Models with continual delivery of prosthetic particles are now available.^{173–176}

VIII. CONCLUSION

There is growing evidence that sensors of innate immunity play an essential role in the pathogenesis of immune-mediated joint diseases. In this review, we summarize the evidence for the role of activation of innate immunity in the pathogenesis of osteoarthritis, rheumatoid arthritis, and aseptic loosening. The key question is how to protect the joint tissues against irreversible damage in the consequence of nonresolved inflammation. Increasing understanding of how innate immunity sensors participate in the pathogenesis of joint diseases can provide a road map to translate new biological insights into clinical practice.

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ABBREVIATIONS

ACPAs	anti-citrullinated protein antibodies
AF	activation of fibroblasts
AGEs	advanced glycation end products
AIM2	absent in melanoma 2
AP 1	activator protein 1
ASC	apoptotic speck protein containing a caspase recruitment domain

CARD	caspase-recruitment domain
CarP	carbamylated proteins
catK	cathepsin K
CCPs	cyclic citrullinated peptides
CD14	cluster of differentiation 14
CIRP	cold inducible RNA binding protein
CLRs	C-type lectin receptors
CpG	cytosine-phosphate-guanosine
DAMPs	damage-associated molecular patterns
DC-SIGN	dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
DNA	deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acids
HMGB1	high-mobility group box 1 protein
HSP	heat shock proteins
IFI16	gamma interferon-inducible protein 16
IFN	interferon
IKK	I κ B kinase
IL	interleukin
IPS-1	interferon-beta promoter stimulator 1
IRAKs	interleukin-1 receptor associated kinases
IRF3,7	interferon regulatory factor 3,7
ITAMs	immunoreceptor tyrosine-based activation motifs
JNK	c-Jun N-terminal kinase
lgp2	Laboratory of genetics and physiology 2
LPS	lipopolysaccharide
LRR	leucine-rich repeat
MAC	membrane attack complex
MAMPs	microbe-associated molecular patterns
MAPK	mitogen-activated protein kinase
MAVS	mitochondrial antiviral signaling protein
MDA5	melanoma differentiation-associated protein 5

MDP	muramyl dipeptide
MMP	matrix metalloproteinase
MyD88	myeloid differentiation primary response gene 88
NA	nucleic acid
NACHT	NAIP, CIITA, HET-E, and TP1
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP	NALP, NACHT-LRR-PYD-containing protein
NLR	NOD-like receptor
NO	nitrogen oxide
NOD	nucleotide-binding oligomerization domain-containing protein
OA	osteoarthritis
OPG	osteoprotegerin
PAD	peptidyl arginine deiminase
PAMP	pathogen-associated molecular pattern
PRRs	pattern recognition receptors
PYD	pyrin domain
RA	rheumatoid arthritis
RAGE	receptor of advanced glycation end products
RANKL	receptor activator of NF- κ B ligand
RF	rheumatoid factor
RIG-I	retinoic acid-inducible gene 1
RNA	ribonucleic acid
Ror	receptor tyrosine kinase-like orphan receptor
ROS	reactive oxygen species
S100 proteins	family of proteins inducing a range of intracellular and extracellular function including stimulation of innate and adaptive immune response (alarmins)
SFRP	secreted frizzled-related proteins
ssRNA	single-stranded RNA
SYK	spleen tyrosine kinase
TAK1	transforming growth factor β activated kinase 1
TANK	TRAF family member-associated NF- κ B activator
TBK1	TANK-binding kinase 1

TGF-β	transforming growth factor β
TIR	toll/IL-1 receptor
TJA	total joint arthroplasty
TLRs	toll-like receptors
TNFR	TNF receptors
TNF-α	tumor necrosis factor α
TRAF	tumor necrosis factor receptor associated factor
TRAM	TRIF-related adaptor molecule
TRAP	tartarate-resistant acid phosphatase
TRIF	TIR-domain-containing adaptor inducing interferon- β
UHMWPE	ultrahigh molecular weight polyethylene
VEGF	vascular endothelial growth factor
VISA	virus-induced signaling adapter
WP	wear particles

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FIG. 1.

Intracellular signaling proposed to be involved in the inflammatory response during immune-mediated joint diseases such as aseptic loosening. Extracellular and intracellular PRR sense various bacterial and endogenous stimuli including opsonized wear particles (WPs), such as polyethylene, CoCrMo, and Cr₂O₃, released from the surface of biomaterial that could trigger the production of inflammatory signals represented mostly by cytokines. Extracellular PRR receptors such as TLR-1, -2, -5, -6, and -11 are stimulated by bacterial lipoprotein, flagellin, profilin, and WPs such as opsonized Cr₂O₃ and opsonized CoCrMo triggering the activation and translocation of transcription factors nuclear factor κ -chain-enhancer of activated B cells (NF- κ B) and activator protein 1 (AP-1) to the nucleus. NF- κ B

is activated by a cascade initiated here by cytoplasmic toll/IL-1 receptor (TIR) domain that associates with a TIR domain-containing adaptor myeloid differentiation primary response gene 88 (MyD88), which recruits IL-1 receptor-associated kinase (IRAK)4 and IRAK2. This complex associates with tumor necrosis factor receptor-associated factor (TRAF) 6 and subsequently activates transforming growth factor β -activated kinase 1 (TAK1), followed by activation of I κ B kinase (IKK) complex for NF- κ B and mitogen-activated protein kinases (MAPK) including JNK and p38 for AP-1. The above-described pathways involved in the activation of NF- κ B and AP-1 are also stimulated by lipopolysaccharide (LPS), calcium- and zinc-binding proteins S100 [predominantly found as calprotectin (S100A8/A9)], and high-mobility group box 1 protein (HMGB1), all sensed by the receptor for advanced glycation end products (RAGE), and on ligation of TNF- α to its receptor (TNF-R). LPS also activates its primary extracellular receptor TLR-4. In the case of TJA, TLR-4 could be activated also by Co²⁺ ions, which induces dimerization of TLR-4 subunits leading to MyD88 activation through TIR domain-containing adaptor protein (TIRAP). TLR-4 activates also interferon regulatory factor (IRF) 3, a transcription factor involved in the regulation of expression of several proinflammatory cytokines through a pathway initiated by TIR-domain-containing adaptor inducing interferon- β (TRIF)-related adaptor molecule (TRAM). This interaction recruits TRAF 3 leading to activation of TRAF family member-associated NF- κ B activator (TANK)-binding kinase-1 (TBK1) and IKK ϵ for activation of IRF3. After endocytosis of opsonized WP, its components get to the lumen of the endolysosomal network organelles, stimulating here membrane-anchored TLR-3, -7, -8, and -9, or WP components could be released to cytosol, for example, after endosomal rupture, and could interact with a nucleotide binding oligomerization domain (NOD) receptors or with inflammasome. inflammasomes represent a heterogenous group of protein complexes forming either NLRP or NALP (used as an example in the figure) or NLRC. NLRP abbreviates for NAIP, CIITA, HET-E and TP1 (NACHT)-, leucine-rich repeat (LRR)- and pyrin domains (PYD)-containing protein. NLRC abbreviates for NACHT- LRR- and caspase-recruitment domain (CARD)-containing protein (NLRC). inflammasomes contain further the apoptosis-associated speck-like protein containing PYD and CARD, which are in the NLRP involved in the binding of effector protein—pro-caspase1—through its CARD subdomain. NLRC bind pro-caspase 1 directly. Selected PAMP and DAMP interaction with LRR domain induces conformational changes leading to caspase-1 activation allowing cleavage of cytokine precursors pro-IL-1 β and pro-IL-18 to active IL-1 β and IL-18, which are subsequently released from the cell. NODs are activated by bacterial flagellin, RNA, and muramyl dipeptide (MDP), but also by CoCrMo or Co²⁺ released from WP during endosome disruption. NLRP and NLRC are activated by biphasic manner consisting of (a) their transcription initiated with contribution of transcription factors NF- κ B and probably AP-1 and IRF3, and (b) their subsequent activation, in TJA through CoCrMo or Co²⁺ wear. Bacterial and viral nucleic acids could stimulate inflammation through TLR-3, -7, -8, -9, which signal through IRAK4 and IRAK1 to activate TRAF 6 but also IRF7, transcription factor involved in the regulation of transcription of several members of IFN α family. Nucleic acids could also stimulate inflammation through cytosolic helicases: retinoid acid-inducible gene I (RIG-I) and MELANOMA differentiation-associated protein 5 (MDA5) signaling through mitochondrial membrane-associated adaptor IPS-1 involved in activation of TBK1/IKK ϵ , NF- κ B, and MAPK-dependent AP-1. Double-stranded cytosol-

localized DNA is also sensed by helicases DDX41 and IFN γ -inducible protein 16 (IFI16) both signaling through endoplasmic reticulum (ER)-associated stimulator of interferon genes (STING), which interacts with TBK1/IKK ϵ . All above pathways merge on three transcription factors NF- κ B, AP-1, and IRF3 involved in transcription of proinflammatory cytokines IFN β 1, IL-6, IL-12, TNF- α , GM-CSF, IL-8, IL-10, and IL-33, as well as IL-1 β and IL-18. Fourth depicted transcription factor IRF7 is responsible for transcription of several members of IFN α family.

FIG. 2.

Simplified overview of the RA-associated inflammation-promoting factors. Although the cause of rheumatoid arthritis (RA) is currently unknown, three factors, genetics, environment, and autoimmunity, play predominant role. It is currently accepted that autoimmune reaction is probably initiated at mucosal surfaces mostly of oral cavity, lungs, and gastrointestinal tract by not-well-described triggers involving environmental factors such as smoking and mucosal microbiota leading in predisposed individuals to development of B- and T-cell clones involved in the producing of autoantibodies. They recognize either

Fc portion of normal immunoglobuline molecules and rheumatoid factor (RF) or they recognize citrullinated proteins (anti-citrullinated protein antibodies, ACPAs, or cyclic citrullinated peptides or CCP antibodies) formed by post-translational modification of amino acid arginine to citrulline. Produced autoantibodies could also recognize mutated citrullinated vimentin (MCV), and carbamylated proteins (CarP) formed by post-translational modification of the amino acid lysine to homocitrulline. In this scenario, after long period of preclinical RA, inflammation is relocated from mucosal tissues to joints. This process probably involves immune complexes formation and their joint deposition, sharing antigenic determinants between sites of autoimmunity initiation and the joints, epitope spreading leading to the generation of autoimmunity directed to joint, and memory T and B cells. During relocation from mucosal tissues to joints, changes in autoantibodies isotype, avidity, and glycosylation, and epitope spreading should take place in response to as yet unknown stimuli. Joint synovial membrane-deposition of auto-antibodies and immune complexes trigger local inflammation by several mechanisms including (a) complement activation, (b) probably also direct interaction of autoantibodies with Fc receptors on innate immunity cells (MΦ, DC), (c) stress/inflammation-induced release of endogenous DAMP, (d) successive activation of innate immunity cells (similarly to those described in TJA loosening above), and (e) immigration and activation of T cells (Th1). All those stimuli lead to predominance of osteoclastogenic cytokines involved in the differentiation of bone marrow GM-CFU precursors to fully mature osteoclasts (M-CSF, RANKL, IL-1β, TNF-α) or M1 macrophages (IFN-γ, type 1 IFNs, TNF-α). In RA, activated synovial fibroblasts (AFs) and T cells are the major source of RANKL contributing thus to bone resorption. Th1 cells further support this by inflammatory activation of fibroblasts through TNF-α. On the other hand, osteoclast-suppressive, osteoblastogenic cytokines (IL-4, IL-6, IL-10, TGF-β, IL-1Ra, OPG) released by Th2, M2 macrophages, physiologically activated resident fibroblasts, and Treg cells are suppressed (for simplicity, not shown in the picture). One of prominent regulatory immune cells, Treg, was reported to be deficient in RA synovium. Some negative feedback during inflammation-activated bone resorption represents IFN-γ and type 1 IFNs produced predominantly by MΦ, DC, and fibroblasts. They inhibit the RANKL signaling in osteoclast. One of crucial regulator of bone formation and remodeling represent wingless-type MMTV integration site family (Wnt)/β-catenin signaling pathway. Wnt ligands are soluble intercellular signaling molecules involved in embryogenesis. Wnt ligands enhance osteoblast differentiation and activity and they upregulate OPG. Wnt ligands (here, Wnt5a and Wnt3a) interact either with canonical receptor complex consisting of frizzled-related protein (FRP) and low-density lipoprotein-related receptor LRP5/6 or with non-canonical single transmembrane receptor tyrosine kinase-like orphan receptor (Ror)1/2. On binding to canonical receptor, Wnt3a activates whereas Wnt5a inhibits osteoblasts. Furthermore, binding of Wnt5a to Ror2 upregulates the expression of the receptor for RANKL on osteoclast precursors. Therefore, Wnt5a promotes bone resorption and inhibits the bone remodeling. RA synovial activated fibroblasts (AFs) produce substantial amount of Wnt5a as well as inhibitors of the Wnt pathway: Dickkopf Wnt signaling pathway inhibitor (DKK)-1, DKK-2, DKK-3, secreted frizzled-related proteins (SFRP)2, and SFRP4 impairing osteoblast functions at sites of joint erosions, situation typical for RA.

FIG. 3.

The factors triggering inflammatory reaction on TJA insertion. For simplification, the picture does not show regulatory anti-inflammatory signals, which parallel inflammatory signals depicted here. After implantation of TJA into the bone, the inflammatory response could be stimulated by several factors including (a) signals of local necrosis, ischemia, and other tissue degradation (together called DAMPs) sensed mostly by macrophages (MΦ), dendritic cells (DCs), fibroblasts, and the complement system; (b) signals related to the presence of bacteria (PAMPs) either from direct contamination or from the blood; (c) signals

related to micromotion at the implant-host interface, joint fluid, and formation of a synovial interface-like membrane around the implant leading to the activation of fibroblasts (AFs) and other mesenchymal cells and to the secretion of osteoclast-activating factors such as receptor activator of NF- κ B ligand (RANKL), macrophage colony-stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF); (d) the inflammation is further stimulated by wear particles (WP), liberated from the articulating and/or non-articulating surfaces, which are opsonized by bacterial proteins or host proteins such as complement, albumin, fibrinogen, proteoglycans, immunoglobulins (shown as a red strings). The above-mentioned factors induce macrophage differentiation toward M1 phenotype mostly through LPS, IL-3, GM-CSF, TNF- α , and IFN- γ signaling. M1 macrophages and subpopulations of DCs secrete Th1- and Th17-stimulating cytokines (e.g., IL-6, IL-12, IL-23, TNF- α , and IL-8), as well as reactive nitrogen and oxygen species (NO, ROS), CYCLOOXYGENASE 2 (COX-2), IL-1 β , and IL-8. Regulatory, inflammation-suppressive response is mediated by M2 macrophages, Th2, Treg lymphocytes, and resident fibroblasts producing several anti-inflammatory and anti-osteoclastogenic cytokines including IL-4, IL-6, IL-10, transforming growth factor β (TGF- β), or soluble receptor for IL-1 (IL-1Ra), and soluble RANKL inhibitor osteoprotegerin (OPG); these are not shown. Both proinflammatory and anti-inflammatory factors act toward cells of the bone multicellular unit as shown in lower half of the blue-green area: RANKL, TNF- α , IL-1 β , and WP induce pre-osteoclast differentiation and osteoclast activation leading to increased bone resorption. Osteoclasts resorb the bone by pumping the protons (H⁺) toward the bone surface, by secreting bone destructing cathepsin K (cat K) and tartrate-resistant acid phosphatase (TRAP). Bone resorption is further supported by the attraction of neutrophils. IL-1 β and TNF- α stimulate osteoblasts to secrete RANKL, thus creating positive feedback for bone resorption. On the other hand, physiologically activated interface tissue fibroblasts/tissue-resident fibroblasts respond to TNF- α by production of OPG and their exposure to WP induces production of IL-6. OPG is produced also after stimulation of fibroblast and osteoblast precursor by TGF- β . OPG blocks RANKL activity by competing for RANKL receptor (RANK). IFN- γ and IL-6 inhibit intracellular signaling stimulated by RANKL in osteoclast and thus both act as osteoclast suppressors. The equilibrium between bone resorption and remodeling is further modified by hormonal and neuronal regulation.

TABLE 1

Pattern recognition receptors (PRRs) classified according to their location in the cell

Type of PRRs	Examples
Membrane bound	TLRs, CLRs, RAGE
Cytoplasmic	Cytoplasmic nucleic acid-sensing receptors (e.g., AIM2, RIG-I, MDA5), NLRs

AIM2 = absent in melanoma 2; CLRs = C-type lectin receptors; MDA5 = melanoma differentiation-associated protein 5; NLRs = intracellular nucleotide-binding oligomerization domain (NOD)-like receptors; RAGE = receptor for advanced glycation end products; RIG-I = retinoic acid-inducible gene I; TLRs = toll-like receptors

TABLE 2

List of potential inducers of PRRs participating in osteoarthritic damage of a joint

Receptor	Potential stimuli	Refs.
TLRs 2, 4 (CD14)	DAMPs ligands robustly expressed by synovium and/or cartilage; ligands present in the joint/tissues during OA progression (hyaluronan, fibronectin, HMGB1, HSP, S100A8/A9/A12 proteins, ...)	41, 45, 48, 51, 177
RIG-1	ssRNA, dsRNA	53, 177, 178
MDA-5	dsRNA	53, 178, 179
RAGE	AGEs, β 2-integrin Mac-1, HMGB1, HSP, S100 proteins	50, 51, 180, 181

AGEs = advanced glycation end products; DAMPs = damage/danger associated molecular patterns; dsRNA = double-stranded RNA; HMGB1 = high-mobility group box 1; HSP = heat shock protein; OA = osteoarthritis; ssRNA = single-stranded RNA.