HHS Public Access

Author manuscript

J Long Term Eff Med Implants. Author manuscript; available in PMC 2015 March 20.

Published in final edited form as:

J Long Term Eff Med Implants. 2014 ; 24(4): 259–265.

The role of macrophages in the biological reaction to wear debris from joint replacements

Christophe Nich, MD PhD[1,*] and **Stuart B. Goodman, MD PhD**[2]

[1]Laboratoire de Biomécanique et Biomatériaux Ostéo-Articulaires - UMR CNRS 7052, Faculté de Médecine - Université Paris 7, Paris, France, Department of Orthopaedic Surgery, European Teaching Hospital, Assistance Publique – Hôpitaux de Paris - Université Paris 5, Paris, France

[2]Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, Stanford University School of Medicine, Stanford, CA, USA

Abstract

Normal usage of total joint replacements results in the production of wear debris and other byproducts. In particular, polyethylene (PE) particles are heavily involved in the stimulation of local and systemic biological reactions resulting in chronic inflammation, periprosthetic bone resorption (osteolysis), and, eventually, implant loosening. As sentinels of the innate immune system, cells of the monocyte/macrophage lineage initiate the inflammatory cascade that lead to osteolysis. The biological processes involved are complex, based on the unique properties of the monocytes/macrophages, including sensing, chemotaxis, phagocytosis, and adaptive stimulation. The interaction with wear debris triggers the release of pro-inflammatory factors, such as TNF-α, IL-1, and others, pro-osteoclastic factors such as RANKL, and chemokines, such as MCP-1 and MIP-1, all being crucial to the recruitment, migration, differentiation and ultimately activation of bone resorbing osteoclasts. In parallel, other distinct macrophage populations inhibit inflammation and mitigate its consequences on the bone-implant interface. Here, the role of the monocyte/macrophage cell lineage in the initiation and maintenance of the host inflammatory response to wear debris and subsequent periprosthetic osteolysis is presented.

Keywords

total joint replacement; aseptic loosening; osteolysis; monocyte/macrophage; wear debris; inflammation

I. INTRODUCTION

Aseptic loosening (AL) is one of the leading causes of total joint replacement (TJR) revision procedures, especially in patients with a total hip (THA) or knee arthroplasty (TKA). In most cases, AL is secondary to periprosthetic osteolysis. The latter refers to periprosthetic bone destruction as seen on radiographs and corresponds to bone defects. Recently, it was reported that osteolysis was present in up to 24% of cases in the decade after a THA

[*]**Address all correspondence to**: Christophe Nich, MD, PhD; Department of Orthopaedic Surgery, European Teaching Hospital, 20-40 rue Leblanc, 75015, Paris, France ; Tel.: 0033156093266; Fax: 0033156092396; chrnich@gmail.com.

procedure, with more active patients at increased risk for developing osteolytic lesions.[1] As a result, up to 15% patients are likely to be revised for aseptic loosening in the decade following a total joint arthroplasty.

The development of periprosthetic osteolysis is highly related to wear debris generated continuously from an articulating surface of a TJR. In a metal-on-polyethylene bearing, the periprosthetic tissues are exposed to a large amount of wear debris, specifically polyethylene (PE) particles. The relationship between PE wear and the degree of osteolysis has been well supported by clinical data.[2,3] Analyses of periprosthetic tissues retrieved during revision of failed TJRs showed that ultra-high molecular weight polyethylene (UHMWPE) wear debris is the most frequent type of debris around failed hip, knee and shoulder TJRs.[4]

While there is strong evidence that the process of osteolysis involves different cell types, including osteoblasts, fibroblasts, lymphocytes etc., cells of the monocyte/macrophage lineage predominantly drive the inflammatory response to prosthetic wear debris.[5,6]

In this paper, the basic facts of the cellular reaction and biologic response to debris generated by an artificial joint will be presented, with special focus on the central role of macrophages in this context.

II. THE MONOCYTE-MACROPHAGE LINEAGE

Macrophages are multifunctional cells of the innate immune system. Their primary role is maintaining tissue homeostasis. Hence, they may be viewed as the scavenger cells of the immune system. Macrophages are considered as innate effector cells, since they do not require previous exposure to a given antigen to initiate a response. They phagocytose microbes and debris, and protect the host from adverse noxious stimuli. A major role for the innate immunity is the ‘‘front-line’’ protection of organisms from invasion by pathogenic microbes.

All cells from the monocyte-macrophage lineage appear to derive from a same progenitor multipotent cell, the hematopoietic stem cell (HSC).[7] The HSC, located in the bone marrow, may differentiate either into a myeloid or a lymphoid precursor, giving rise to the divergence between the myeloid and plasmacytoid lineage. The myeloid precursor is then able to migrate into the blood stream and to differentiate into a monocyte. Monocyte migration to specific tissues and their differentiation occur upon stimulation by different cytokines, chemokines and other pro-inflammatory factors. Depending on the location, the monocytes become either Kuppfer cells (liver), alveolar macrophages (lung), interstitial dendritic cells, osteoclasts, macrophages etc. Lymphoid precursors develop in a parallel way, but can directly differentiate into another type of dendritic cell, the plasmacytoid dendritic cell. Migration to tissues and differentiation occur with the help of a survival signal, the macrophage-colony stimulating factor (M-CSF), and the presence of adverse stimuli from the local microenvironment such as acute infection, injury etc.

The hallmarks of resident macrophage function include effective phagocytosis of apoptotic cells and cellular debris, host response to infectious/tumor diseases, induction/regulation of

inflammation and subsequent tissue healing. Macrophages perform these roles via four basic innate functions: phagocytosis, sensing, chemotaxis, and adaptive stimulation.

III. THE RECOGNITION OF WEAR DEBRIS BY MACROPHAGES

Macrophages play a pivotal role in wear particle recognition and in the cascade of biological events leading to implant failure. The biologic response to wear debris is complex. At the heart of this concept is that very small prosthetic particles stimulate periprosthetic monocyte/macrophages to express pro-inflammatory/pro-osteoclastic cytokines, surface receptors and other substances that orchestrate increased formation, accumulation, activity, and survival of osteoclasts, and inhibit the osteogenic activity of osteoblasts. As a result, bone resorption predominates over osteogenesis at the bone-implant interface.[8,9] In addition, it has been recently suggested that the macrophage response in particle-induced osteolysis could be polarized, with M1 pro-inflammatory macrophages activated in response to wear particulate debris dominating the M2 anti-inflammatory response that normally promote wound healing and debris scavenging.[10–12]

Wear particle recognition by macrophages involves scavenger receptors. Their most commonly described function is to act as phagocytic receptors mediating direct non-opsonic phagocytosis of pathogenic microbes by macrophages. Scavenger Receptors (SRs) have been shown to act as pattern recognition receptors (PRRs), which are required for the host response to pathogens.

Tissue resident macrophages are equipped with a broad-range of pattern recognition receptors (PRRs). Pattern recognition receptors are important in innate immunity as a first-line defense for recognition of microbial patterns (pathogen-associated molecular patterns or PAMPs). Globally, the PRRs promote the production and release of pro-inflammatory signals including cytokines such as IL-6, TNF-α, and IL-12. Pattern recognition receptors are described as trans-membrane receptors or cytoplasmic receptors (Table).

Toll-like receptors (TLRs) were the first PRRs to be identified. Toll-like receptors recognize a wide spectrum of exogenous danger signals (PAMPs) and endogenous (alarmins) danger signals (also called danger-associated molecular patterns or DAMPS). In 2007, Takagi et al.[13] reported that toll-like receptors were detected in the tissues around aseptically loosened implants. TLR-deficient mice displayed decreased osteolysis. There is increasing evidence that TLRs play a critical role in initiating cellular interaction with particles and the subsequent inflammatory cascade.[14,15]

A. Wear Particle Phagocytosis

Prosthetic particles can influence processes leading to periprosthetic bone resorption via two basic macrophage functions. First, wear particles may be phagocytosed by monocyte/macrophages with or without endogenous proteins. It is of note that particles with attached proteins such as PAMPs, specifically lipopolysaccharides (LPS), stimulate inflammatory foreign body reactions to wear debris more effectively than uncoated particles. This observation supports the hypothesis that subclinical bacterial film on the prosthetic surfaces

can contribute to osteolysis.[16] Subsequently, macrophages produce pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IFN-gamma, and others.

Among various surface receptors involved in wear particle phagocytosis, the macrophage receptor with collagenous structure (MARCO) is of interest.[17] It is not normally found in human monocytes, and is only expressed in a very restricted manner such as in chronic foreign body inflammation.[18] It is a distinct member of the class A surface receptor family and is implicated as a PRR. Its expression is strongly upregulated in macrophages by various microbial stimuli in a TLR-dependent manner. MARCO binds soluble LPS and intact Gram + and Gram– bacteria.[19] MARCO expression is induced by wear debris in vitro and in vivo.[20,21] MARCO enhances the expression of IL-12 and nitric oxide (NO) production. Implant-derived wear particles may lead to harmful over-expression of MARCO.[22] This could play an important role in the first line of host defense against unopsonized and opsonized particles in macrophages in periprosthetic tissues.[20]

B. PRR-Mediated Sensing

The response to wear particles is not only due to their phagocytosis by monocyte/macrophages, but also due to PRR-mediated sensing. Hence, implanted biomaterials are coated with proteins from blood and interstitial fluids, and through this adsorbed layer of proteins, cells sense and respond to foreign surfaces. As seen formerly, PAMPs could also contribute to peri-prosthetic particle-induced osteolysis via this mechanism.[23]

Therefore, TLRs are thought to play an important role. TLRs -1 to -9 were detected in synovial-like membranes surrounding loose implants in monocyte/macrophages and some fibroblast-like cells by immunohistochemistry, immunofluorescence and reverse transcription polymerase chain reaction.[13,24–27] Toll-like receptors, among various PRRs, such as C-type lectin receptors (CLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) have been shown to activate the production of pro-inflammatory cytokines. Of note, wear particles activate the NALP3 inflammasome pathway so that the pro-inflammatory cytokine precursors pro-IL-1-β and pro-IL-18 are proteolytically activated by caspase-1.

As a receptor for LPS, TLR4 has received the most attention in aseptic loosening, supported by the observations that TLR4 deficient mice displayed decreased particle-associated osteolysis. There was noted to be a significant increase of TLR4 in the tissues around loosened replacement implants.[13,26] There are two options for signal-transduction, the MyD88 one resulting in the production of pro-inflammatory proteins.[28] Interestingly, disruption of MyD88 signaling diminished particle-induced production of TNF-α.[15] These findings support the hypothesis that TLR4 plays a key role in the pathogenesis of aseptic loosening.

IV. THE BIOLOGICAL FACTORS INVOLVED IN WEAR DEBRIS–INDUCED OSTEOLYSIS

A. Pro-inflammatory Factors

In response to wear debris, bone resorption is mediated via cytokines such as TNF-α, which induce expression of receptor activator of NF-κB (RANK) ligand (RANKL) by osteoblasts and stromal cells.[29] RANKL is the key factor regulating the differentiation and activation of osteoclasts.[30] Macrophages exposed to prosthetic particles of different origin (PMMA, UHMWPE, metal) increase the expression of TNF-α predominantly via the NF-κB pathway. TNF-α expression can be suppressed in macrophages by TNF-α inhibiting factor (TIF) and also by several cytokines (IL-4, IL-10, TGF-β).[31]

IL-1 possesses multiple and diverse properties mediating especially the acute phase response to endogenous and exogenous stimuli acting on macrophages. As previously mentioned, before release from the cell in a biologically active form, precursors of IL-1β and IL-18 (pro-IL-1β and pro-IL-18) must be cleaved by caspase-1 activated by the inflammasome.[25,32]

IL-6 is a multifunctional cytokine strongly involved in the regulation of inflammation and bone metabolism. Several studies demonstrated increased expression of IL-6 after stimulation of monocyte/macrophage populations with prosthetic particles [33] and also in periprosthetic tissues from failed THAs.[34] Shanbhag et al.[35] found that IL-6 and IL-8 could be the primary drivers of end-stage osteolysis, as opposed to TNF-α and IL-1β.

Osteopontin (OPN) is a pleiotropic cytokine expressed by activated T cells, dendritic cells, and macrophages. Osteopontin is involved in chronic inflammation and osteolysis.[36] Increased expression of OPN has been found in macrophages, regardless of their site, in interfacial membranes retrieved from patients with aseptically loosened implants. In the absence of OPN, wear debris induced osteolysis was found to be diminished.[37]

B. THE RANK/RANKL/OPG Pathway

The essential signaling for osteoclastogenesis is the interaction of RANKL and RANK. RANK (receptor activator of NF-κB) is a membrane-bound receptor expressed on osteoclast precursors and mature osteoclasts. RANK activates NF-κB, a transcription factor that regulates numerous pro-inflammatory and anti-inflammatory pathways, including TNF-α and IL-1β. RANK signaling was shown to be essential for PE particle-induced osteoclastogenesis in the murine calvarial model, although its disruption in knockout mice did not seem to alter particle-induced inflammation. The expression of RANK is upregulated in tissues around failed total joint replacements.[38–40]

RANKL (receptor activator of nuclear factor κB ligand) is a receptor ligand expressed on the cell surface of osteoblasts, bone marrow stromal cells, and other activated cells, including T cells, in the inflammatory process. RANKL is also active as a soluble factor.[9] Following RANK-RANKL interaction, numerous signaling molecules are activated, regulating osteoclast activity. RANKL, together with Macrophage Colony-Stimulating

Factor (M-CSF), is essential for the differentiation, maturation and survival of bone-resorbing osteoclasts. RANKL is inhibited by the soluble decoy protein receptor antagonist osteoprotegerin (OPG). Disruption of RANK signaling prevented experimental particle-induced osteolysis.[41] Therefore, the molecular ratio of RANK/RANKL/OPG expression appears to be a key indicator for assessing bone remodeling.[42]

C. Chemokines

Chemokines are a group of small proteins with a central role in leukocyte migration and activation. The chemokines are classified into four groups (CXC, CC, CX3C and XC). About 50 chemokines and 25 chemokine receptors have been identified in humans.

The role of chemokines in particle-induced osteolysis is supported by the observation that they are upregulated in periprosthetic tissues retrieved from patients with failed total joint arthroplasties, and that wear particles can induce chemokine expression in macrophages.

MCP-1, also known as CCL2, can attract macrophages to the sites of inflammation through the activation of CCR2 or CCR4. In a recent work, Gibon et al.[43] injected MCP-1 into the femur in a murine femoral implant model. They found that MCP-1 recruited exogenous genetically marked reporter macrophages (RAW 264.7 cells) to the femur; infusion of UHMWPE particles into the femur via a diffusion pump and tubing also lead to the recruitment of reporter macrophages and osteolysis. Blocking the interaction of MCP-1 with its receptor, CCR2 resulted in decreased migration of the reporter macrophages and diminished the particle-induced osteolysis.

MIP-1 includes MIP-1α (CCL3) and MIP-1β (CCL4). Neutralizing antibody to MIP-1α also mitigated wear particle induced migration.[44]

Production of inflammatory chemokines, such as CCL2 and CCL3, among others, is characteristic of “M1” macrophage phenotype, promoting the inflammatory response.[45,46] Taken together, these findings strongly suggest that macrophage migration mediated by chemokines is important in wear particle-induced inflammatory reaction.

V. CONCLUSIONS

Wear particles stimulate chronic inflammation and bone destruction, that may ultimately result in implant loosening. Macrophages, as sentinels of the innate immunity system, are central to the initiation of this inflammatory cascade via the release of pro-inflammatory and pro-osteoclastic factors. The current scheme includes numerous biological steps that have been clarified in part, such as sensing by pattern recognition receptors. Recent developments indicate that wear particles initiate systemic migration of monocyte/macrophage precursors to the local site of particle generation. With a better understanding of the biologic response to wear debris, new concepts have emerged, such as the role of individual biological and genetic factors in the modulation of particle-induced osteolysis. Taken together, these new insights should result in potential strategies to mitigate the adverse events related to wear particles.

REFERENCES

1. Lübbeke A, Garavaglia G, Barea C, Stern R, Peter R, Hoffmeyer P. Influence of patient activity on femoral osteolysis at five and ten years following hybrid total hip replacement. J Bone Joint Surg Br. 2011 Apr; 93(4):456–463. [PubMed: 21464482]
2. Devane PA, Bourne RB, Rorabeck CH, MacDonald S, Robinson EJ. Measurement of polyethylene wear in metal-backed acetabular cups. II. Clinical application. Clin Orthop Relat Res. 1995 Oct. 319:317–326. [PubMed: 7554645]
3. Berger RA, Jacobs JJ, Quigley LR, Rosenberg AG, Galante JO. Primary cementless acetabular reconstruction in patients younger than 50 years old. 7- to 11-year results. Clin Orthop Relat Res. 1997 Nov.344:216–226. [PubMed: 9372773]
4. Willert HG, Semlitsch M. Reactions of the articular capsule to wear products of artificial joint prostheses. J Biomed Mater Res. 1977 Mar; 11(2):157–164. [PubMed: 140168]
5. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg Am. 1992 Jul; 74(6):849–863. [PubMed: 1634575]
6. Howie DW, Manthey B, Hay S, Vernon-Roberts B. The synovial response to intra-articular injection in rats of polyethylene wear particles. Clin Orthop Relat Res. 1993 Jul.292:352–357. [PubMed: 8519131]
7. Le Douce V, Herbein G, Rohr O, Schwartz C. Molecular mechanisms of HIV-1 persistence in the monocyte-macrophage lineage. Retrovirology. 2010 Apr.7:32. [PubMed: 20380694]
8. Nich C, Takakubo Y, Pajarinen J, Ainola M, Salem A, Sillat T, Rao AJ, Raska M, Tamaki Y, Takagi M, Konttinen YT, Goodman SB, Gallo J. Macrophages-Key cells in the response to wear debris from joint replacements. J Biomed Mater Res A. 2013 Oct; 101(10):3033–3045. [PubMed: 23568608]
9. Ingham E, Fisher J. The role of macrophages in osteolysis of total joint replacement. Biomaterials. 2005 Apr; 26(11):1271–1286. [PubMed: 15475057]
10. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008 Dec; 8(12):958–969. [PubMed: 19029990]
11. Purdue PE. Alternative macrophage activation in periprosthetic osteolysis. Autoimmunity. 2008 Apr; 41(3):212–217. [PubMed: 18365834]
12. Rao AJ, Gibon E, Ma T, Yao Z, Lane SR, Goodman SB. Revision joint replacement, wear particles, and macrophage polarization. Acta Biomater. 2012 Jul; 8(7):2815–2823. [PubMed: 22484696]
13. Takagi M, Tamaki Y, Hasegawa H, Takakubo Y, Konttinen L, Tiainen V-M, Lappalainen R, Konttinen YT, Salo J. Toll-like receptors in the interface membrane around loosening total hip replacement implants. J Biomed Mater Res B Appl Biomater. 2007 Jun; 81(4):1017–1026.
14. Hirayama T, Tamaki Y, Takakubo Y, Iwazaki K, Sasaki K, Ogino T, Goodman SB, Konttinen YT, Takagi M. Toll-like receptors and their adaptors are regulated in macrophages after phagocytosis of lipopolysaccharide-coated titanium particles. J Orthop Res. 2011 Jul; 29(7):984–992. [PubMed: 21308757]
15. Pearl JI, Ma T, Irani AR, Huang Z, Robinson WH, Smith RL, Goodman SB. Role of the Toll-like receptor pathway in the recognition of orthopedic implant wear-debris particles. Biomaterials. 2011 Aug; 32(24):5535–5542. [PubMed: 21592562]
16. Greenfield EM, Bi Y, Ragab AA, Goldberg VM, Nalepka JL, Seabold JM. Does endotoxin contribute to aseptic loosening of orthopedic implants? J Biomed Mater Res B Appl Biomater. 2005 Jan; 72(1):179–185. [PubMed: 15449253]
17. Areschoug T, Gordon S. Scavenger receptors: role in innate immunity and microbial pathogenesis. Cell Microbiol. 2009 Aug; 11(8):1160–1169. [PubMed: 19388903]
18. van der Laan LJ, Döpp EA, Haworth R, Pikkarainen T, Kangas M, Elomaa O, Dijkstra CD, Gordon S, Tryggvason K, Kraal G. Regulation and functional involvement of macrophage scavenger receptor MARCO in clearance of bacteria in vivo. J Immunol. 1999 Jan; 162(2):939–947. [PubMed: 9916718]

19. Doyle SE, O'Connell RM, Miranda GA, Vaidya SA, Chow EK, Liu PT, Suzuki S, Suzuki N, Modlin RL, Yeh W-C, Lane TF, Cheng G. Toll-like receptors induce a phagocytic gene program through p38. J Exp Med. 2004 Jan; 199(1):81–90. [PubMed: 14699082]
20. Chen Y, Pikkarainen T, Elomaa O, Soininen R, Kodama T, Kraal G, Tryggvason K. Defective microarchitecture of the spleen marginal zone and impaired response to a thymus-independent type 2 antigen in mice lacking scavenger receptors MARCO and SR-A. J Immunol. 2005 Dec; 175(12):8173–8180. [PubMed: 16339556]
21. Józefowski S, Arredouani M, Sulahian T, Kobzik L. Disparate regulation and function of the class A scavenger receptors SR-AI/II and MARCO. J Immunol. 2005 Dec; 175(12):8032–8041. [PubMed: 16339540]
22. Zhao D-S, Ma G-F, Selenius M, Salo J, Pikkarainen T, Konttinen YT. Ectopic expression of macrophage scavenger receptor MARCO in synovial membrane-like interface tissue in aseptic loosening of total hip replacement implants. J Biomed Mater Res B Appl Biomater. 2010 Feb; 92(2):641–649.
23. Greenfield EM, Beidelschies MA, Tatro JM, Goldberg VM, Hise AG. Bacterial pathogen-associated molecular patterns stimulate biological activity of orthopaedic wear particles by activating cognate Toll-like receptors. J Biol Chem. 2010 Oct; 285(42):32378–32384. [PubMed: 20729214]
24. Lähdeoja T, Pajarinen J, Kouri V-P, Sillat T, Salo J, Konttinen YT. Toll-like receptors and aseptic loosening of hip endoprosthesis-a potential to respond against danger signals? J Orthop Res. 2010 Feb; 28(2):184–190. [PubMed: 19725103]
25. Maitra R, Clement CC, Scharf B, Crisi GM, Chitta S, Paget D, Purdue PE, Cobelli N, Santambrogio L. Endosomal damage and TLR2 mediated inflammasome activation by alkane particles in the generation of aseptic osteolysis. Mol Immunol. 2009 Dec; 47(2–3):175–184. [PubMed: 19804908]
26. Tamaki Y, Takakubo Y, Goto K, Hirayama T, Sasaki K, Konttinen YT, Goodman SB, Takagi M. Increased expression of Toll-like receptors in aseptic loose periprosthetic tissues and septic synovial membranes around total hip implants. J Rheumatol. 2009 Mar; 36(3):598–608. [PubMed: 19208601]
27. Pajarinen J, Cenni E, Savarino L, Gomez-Barrena E, Tamaki Y, Takagi M, Salo J, Konttinen YT. Profile of toll-like receptor-positive cells in septic and aseptic loosening of total hip arthroplasty implants. J Biomed Mater Res A. 2010 Jul; 94(1):84–92. [PubMed: 20127718]
28. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2004 Jul; 4(7):499–511. [PubMed: 15229469]
29. Kobayashi K, Takahashi N, Jimi E, Udagawa N, Takami M, Kotake S, Nakagawa N, Kinosaki M, Yamaguchi K, Shima N, Yasuda H, Morinaga T, Higashio K, Martin TJ, Suda T. Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. J Exp Med. 2000 Jan; 191(2):275–286. [PubMed: 10637272]
30. Jimi E, Nakamura I, Duong LT, Ikebe T, Takahashi N, Rodan GA, Suda T. Interleukin 1 induces multinucleation and bone-resorbing activity of osteoclasts in the absence of osteoblasts/stromal cells. Exp Cell Res. 1999 Feb; 247(1):84–93. [PubMed: 10047450]
31. Baer M, Dillner A, Schwartz RC, Sedon C, Nedospasov S, Johnson PF. Tumor necrosis factor alpha transcription in macrophages is attenuated by an autocrine factor that preferentially induces NF-kappa B p50. Molecular and Cellular Biology. 1998 Oct; 18(10):5678–5689. [PubMed: 9742085]
32. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: A novel mechanism for implant debris reactivity. J Orthop Res. 2009 Jul; 27(7): 847–854. [PubMed: 19105226]
33. Green TR, Fisher J, Matthews JB, Stone MH, Ingham E. Effect of size and dose on bone resorption activity of macrophages by in vitro clinically relevant ultra high molecular weight polyethylene particles. J Biomed Mater Res. 2000 Sep; 53(5):490–497. [PubMed: 10984696]
34. Goodman SB, Huie P, Song Y, Schurman D, Maloney W, Woolson S, Sibley R. Cellular profile and cytokine production at prosthetic interfaces. Study of tissues retrieved from revised hip and knee replacements. J Bone Joint Surg Br. 1998 May; 80(3):531–539. [PubMed: 9619952]

35. Shanbhag AS, Kaufman AM, Hayata K, Rubash HE. Assessing osteolysis with use of high-throughput protein chips. J Bone Joint Surg Am. 2007 May; 89(5):1081–1089. [PubMed: 17473147]

36. Uede T. Osteopontin, intrinsic tissue regulator of intractable inflammatory diseases. Pathol Int. 2011 May; 61(5):265–280. [PubMed: 21501293]

37. Zreiqat H, Kumar RK, Markovic B, Zicat B, Howlett CR. Macrophages at the skeletal tissue-device interface of loosened prosthetic devices express bone-related genes and their products. J Biomed Mater Res B Appl Biomater. 2003 Apr; 65(1):109–117.

38. Quinn JM, Horwood NJ, Elliott J, Gillespie MT, Martin TJ. Fibroblastic stromal cells express receptor activator of NF-kappa B ligand and support osteoclast differentiation. J Bone Miner Res. 2000 Aug; 15(8):1459–1466. [PubMed: 10934644]

39. Haynes DR, Crotti TN, Potter AE, Loric M, Atkins GJ, Howie DW, Findlay DM. The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. J Bone Joint Surg Br. 2001 Aug; 83(6):902–911. [PubMed: 11521937]

40. Horiki M, Nakase T, Myoui A, Sugano N, Nishii T, Tomita T, Miyaji T, Yoshikawa H. Localization of RANKL in osteolytic tissue around a loosened joint prosthesis. J Bone Miner Metab. 2004; 22(4):346–351. [PubMed: 15221493]

41. Ren W, Wu B, Peng X, Hua J, Hao H-N, Wooley PH. Implant wear induces inflammation, but not osteoclastic bone resorption, in RANK(−/−) mice. J Orthop Res. 2006 Aug; 24(8):1575–1586. [PubMed: 16779834]

42. Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA. 2004 Jul; 292(4):490–495. [PubMed: 15280347]

43. Gibon E, Ma T, Ren P-G, Fritton K, Biswal S, Yao Z, Smith L, Goodman SB. Selective inhibition of the MCP-1-CCR2 ligand-receptor axis decreases systemic trafficking of macrophages in the presence of UHMWPE particles. J Orthop Res. 2012 Apr; 30(4):547–553. [PubMed: 21913218]

44. Nakashima Y, Sun DH, Trindade MC, Chun LE, Song Y, Goodman SB, Schurman DJ, Maloney WJ, Smith RL. Induction of macrophage C-C chemokine expression by titanium alloy and bone cement particles. J Bone Joint Surg Br. 1999 Jan; 81(1):155–162. [PubMed: 10068024]

45. Jiang Y, Beller DI, Frendl G, Graves DT. Monocyte chemoattractant protein-1 regulates adhesion molecule expression and cytokine production in human monocytes. J Immunol. 1992 Apr; 148(8): 2423–2428. [PubMed: 1348518]

46. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004 Dec; 25(12):677–686. [PubMed: 15530839]

Table

Pattern Recognition Receptors are presented according to their localization

Pattern Recognition Receptors	
Membrane-bound PRRs	***Cytoplasmic PRRs***
Toll-like Receptors (TLRs)	NOD-like receptors • NOD • NALPs
C-type lectin Receptors (CLRs) • Mannose receptors • Asialoglycoprotein receptor family	RIG-I-like receptors (RLRs)

Four different classes of pattern recognition receptor (PRR) families have been identified. These PRRs are expressed in macrophages and dendritic cells and also in various immune cells. They include transmembrane proteins such as the Toll-like receptors (TLRs), and C-type lectin receptors (CLRs). Cytoplasmic proteins are the NOD-like receptors (NLRs), and Retinoic acid inducible gene (RIG)-I-like receptors (RLRs).