Review Article

The Role of TLR and Chemokine in Wear Particle-Induced Aseptic Loosening

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Wear particle-induced periprosthetic osteolysis remains the principal cause of aseptic loosening of orthopaedic implants. Monocytes/macrophages phagocytose wear particles and release cytokines that induce inflammatory response. This response promotes osteoclast differentiation and osteolysis. The precise mechanisms by which wear particles are recognized and induce the accumulation of inflammatory cells in the periprosthetic tissue have not been fully elucidated. Recent studies have shown that toll-like receptors (TLRs) contribute to the cellular interaction with wear particles. Wear particles are recognized by monocytes/macrophages through TLRs coupled with the adaptor protein MyD88. After the initial interaction, wear particles induce both local and systemic migration of monocytes/macrophages to the periprosthetic region. The cellular migration is mediated through chemokines including interleukin-8, macrophage chemotactic protein-1, and macrophage inhibitory protein-1 in the periprosthetic tissues. Interfering with chemokine-receptor axis can inhibit cellular migration and inflammatory response. This paper highlights recent advances in TLR, and chemokine participated in the pathogenesis of aseptic loosening. A comprehensive understanding of the recognition and migration mechanism is critical to the development of measures that prevent wear particle-induced aseptic loosening of orthopaedic implants.

1. Introduction

Total joint replacement (TJR) by the implantation of in-dwelling prostheses is an effective operation in terms of relieving pain and restoring function. The common long-term complication of TJR is loosening of an artificial joint that requires revision surgery [1–3]. Kurtz et al. have shown that total hip and total knee revisions will increase by 137% and 601%, respectively, from 2005 to 2030 in the United States [4]. In most cases, aseptic loosening is responsible for revision total joint replacement. It has been reported that aseptic loosening accounts for 70% of hip revisions and 44% of knee revisions [5, 6].

The dominant theory about the causes of aseptic loosening is the particle disease theory [7–9]. Particles can be generated as a result of wear. The concentration of wear particles is directly related to the amount of osteolysis. There are a great number of wear particles in the periprosthetic membrane between bone and prosthesis. These wear particles which are biologically active and indigestible can initiate an innate inflammatory reaction [10–12]. Actually, wear particles alter the function of numerous cells including monocytes, macrophages, fibroblasts, osteoblasts, osteoclasts, and mesenchymal stem cells (MSCs). Macrophages have been accepted to be the key target of wear particles. Wear particles can induce the proliferation, differentiation, and activation of macrophages [13, 14]. Upon activation, macrophages secrete a series of inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), IL-1β, IL-6, and IL-8. These inflammatory mediators can induce osteoclast differentiation or inhibit osteoblast differentiation, leading to periprosthetic bone resorption [15, 16]. Moreover, some cytokines can attract and recruit large numbers of cells including macrophages, osteoclasts, and lymphocytes to the local site. These recruited cells then produce more cytokines, and a process perpetuates a cycle of inflammatory response [17–19]. Apart from macrophages, osteoblasts and fibroblasts can also phagocytose particles, which significantly
increase the expression of TNF-α, IL-6, and RANKL [20, 21]. It has recently been shown that MSCs participate in wear particle-induced aseptic loosening. MSCs are identified around the joint replacement and contribute to maintaining osseous tissue integrity [22]. Wear particles can induce the production of inflammatory cytokine of MSCs on the one hand, while inhibit osteogenic activity on the other hand, resulting in osteolysis in periprosthetic region [23, 24].

Although numerous studies have demonstrated the events underlying periprosthetic inflammation and osteolysis, there are still more questions. First, the mechanisms of the initial cellular interaction with wear particles and the subsequent inflammatory mediator production remain unknown. Second, wear particles induce not only a local response but also a systemic reaction. The mechanism of cellular migration induced by wear particles needs further clarification. In 2007, Takagi et al. first reported that toll-like receptors (TLRs) were detected in the tissues around aseptically loosened implants [25]. 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 [26, 27]. Lassus et al. reported that chemokines participated in the cellular migration in response to wear particles [28, 29]. On the basis of these findings, this paper will discuss the role of TLRs in the recognition of wear particles and the role of chemokines in the cellular migration induced by wear particles, respectively. We believe that this could provide valuable insight into the design of preventive and therapeutic strategies in the future.

2. TLRs and Wear Particle-Induced Aseptic Loosening

2.1. TLRs and Ligands. TLRs belong to a class of pattern recognition receptors that enable the innate immune system to distinguish self- from nonself-structure. Thirteen TLRs have been identified in mammals since 1997. TLR1, TLR2, TLR4, TLR5, TLR6, TLR10, and TLR11 are expressed on the cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are expressed intracellularly on endosomal membranes [30]. They are type I transmembrane proteins composed of an intracellular toll/interleukin-1 receptor (TIR) domain and leucine-rich repeat motifs in the extracellular domain. Leucine-rich repeats recognize danger signals, while TIRs recruit adaptor proteins and mediate downstream signaling [31, 32]. TLRs can recognize a myriad of stimuli including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs are exogenous molecules derived from bacteria, virus, and fungi. DAMPs include endogenous intracellular molecules and extracellular matrix. The intracellular molecules, such as heat-shock protein (HSP) and high mobility group protein 1 (HMGB1), are released into the extracellular milieu by necrotic cells and activated leukocytes. The extracellular matrix includes biglycan, tenascin-C, and hyaluronic acid which are released upon injury and noninfectious inflammatory response. The PAMPs and DAMPs identified for each TLR member are listed in Table 1 [30, 33].

2.2. TLR Signaling and Negative Regulators. Ligand-TLR interactions trigger the recruitment of adaptor proteins through the cytoplasmic TIR domain. So far, five TIR-containing adaptors have been identified: myeloid differentiation primary response gene 88 (MyD88), TIR domain-containing adaptor protein (TIRAP)/Mal, TIR domain-containing adaptor protein-inducing IFN-β (TRIF)/TICAM1, TRIF-related adaptor molecule (TRAM)/TICAM2, and Sterile-α and HEAT-armadillo motifs containing protein (SARM) [34, 35]. Depending on the usage of adaptor molecules, the signaling pathways activated by TLR are divided into MyD88-dependent and MyD88-independent pathways. MyD88 is the main adaptor shared by TLR1, TLR2, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR11. TIRAP/Mal is involved in the MyD88-dependent pathway via TLR2 and TLR4. The MyD88-dependent pathways lead to the activation of nuclear factor (NF)-κB and activating protein-1 (AP-1), which is responsible for the production of proinflammatory cytokines such as TNF-α, IL-1, and IL-12. MyD88-independent pathways are mediated by TRIF or TRAM. TRIF is an important adaptor which is used by TLR3. TRAM can link the TIR domain of TLR4 with TRIF. The MyD88-independent pathways lead to the activation of NF-κB, AP-1, and interferon-regulatory factors (IRFs). The activation of transcription factors finally triggers the production of cytokines including TNF-α, IL-1β, IL-6, and IFN-α/β/γ.

TLR signaling mediates inflammatory responses which are important for host defense. However, inappropriate TLR signaling may be responsible for the pathogenesis of autoimmune diseases, chronic inflammatory diseases, and aseptic inflammatory diseases [36]. To avoid harmful and excessive inflammatory responses, the immune system has developed multiple mechanisms to control TLR signaling. Many negative regulators have been reported. According to the regulatory mechanisms, these negative regulators can be classified into three groups [37]: (1) negative regulators for degradation of signal proteins: TAG, SARM, IRF4, TIE2, NLRX1, NLRRC5, TANK, MSK1, MSK2, TAK1, SHP1, SHP-2, A20, CYLD, USP4, and DUBA; (2) negative regulators for degradation of signal proteins: PDLIM2, Trim30α, and TRIM38; (3) negative regulators for transcriptional control: ATF3, IκBNS, Bcl-3, Nurr1, Ah receptor, Zc3h12a, TTP, miR-155, miR-146a, and miR-21.

2.3. TLRs and Aseptic Loosening. TLRs have been observed on variety of cells including monocytes/macrophages, lymphocytes, fibroblasts, osteoblasts, and osteoclasts. It has recently been reported that TLRs were found in periprosthetic tissues of patients with aseptic loosening. The TLR-positive cells are predominantly monocyte/macrophages [25, 38, 39]. Moreover, both PAMPs and DAMPs have been indicated in the activation of TLRs in aseptic loosening [40, 41]. These findings suggested that TLRs may play an important role in the pathogenesis of aseptic loosening. We will now mainly discuss TLR1/2 and TLR4 which have attracted more attention than other TLRs.

TLR1 and TLR2 are expressed on the cell surface and can form heterodimer [33]. They participate in the recognition of extracellular microbial pathogenic components including
lipoprotein/lipoproteins, peptidoglycan, and atypical LPS [34]. When mouse femur was inserted with stainless steel rod and titanium particles, the expressions of TLR1 and TLR2 were found in peri-implant and bone tissues. RAW 264.7 cells expressed both TLR1 and TLR2. However, only TLR1 was increased when cultured with titanium particles [42]. TLR2 was detected on monocytes/macrophages in asptic synovial-like membranes from loose implants [41]. Hirayama et al. found that the expression of TLR2 was markedly increased after stimulation with LPS-coated titanium particles. On the contrary, other TLRs such as TLR4, TLR5, and TLR9 were decreased, suggesting a self-protective mechanism after stimulation with LPS-coated titanium particles. These findings indicated that TLR4 played a key role in the pathogenesis of aseptic loosening. This phenomenon resulted from the engagement of TLR4 and wear particles with adherent LPS. [48]. LPS can be detected in the tissues around aseptically loosened implants, which contributed to the inflammatory responses induced by wear particles [49]. However, it is still unclear whether endotoxin is required for the biological response to wear particles. People found wear particles with LPS decreased the mRNA expression of TLR4 compared to wear particles without LPS. This can be explained by a self-protective mechanism. LPS-coated wear particles can be easily identified by macrophages via TLR4. After the initiation of response, TLR4 was downregulated to prevent excessive harmful host response [26]. The reduced expression of TLR4 mRNA was also found in RAW 264.7 cells or rat macrophages stimulated with titanium particles in vitro [25, 42]. It seemed that auto- or paracrine inflammatory cytokine downregulated the expression of TLR to avoid damage caused by excessive inflammatory responses [42]. Interestingly, TLR4−/− macrophages showed similar levels of TNF-α compared to wild-type macrophages when challenged with wear particles. The unexpected results may be caused by the cells used in the experiments because a variety of cells expressed TLR4. Beidelschies et al. found that, in macrophages that lack TLR4 and TLR2, the section of TNF-α was completely neutralized when stimulated.

### Table 1: Toll-like receptors and their corresponding ligands.

| TLR   | Exogenous ligands (PAMPs)                                                                 | Endogenous ligands (DAMPs)                                                                 |
|-------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| TLR1  | Triacyl lipopeptide                                                                      | β-defensin 3                                                                            |
|       | Soluble factors                                                                          |                                                                                         |
| TLR2  | Lipoglycans (mycobacterium)                                                               | HSP 60, HSP70, gp96, β-defensin 3, HMGB1, surfactant proteins, HMGBl-nucleosome complexes, serum amyloid A, cosinophil-derived neurotoxin, antiphospholipid antibodies, cardiac myosin, PAUF, CEP, monosodium urate crystals, Biglycan, versican, hyaluronic acid fragments |
|       | Lipoteichoic acids (gram-positive bacteria)                                               |                                                                                         |
|       | Peptidoglycan (gram-positive bacteria)                                                    |                                                                                         |
|       | Zymosan (yeast)                                                                          |                                                                                         |
| TLR3  | dsRNA                                                                                    | mRNA                                                                                    |
|       | LPS (gram-negative bacteria)                                                             |                                                                                         |
|       | Mannan (Candida)                                                                         |                                                                                         |
|       | Envelope protein (virus)                                                                 |                                                                                         |
|       | Hsp70 (exogenous)                                                                       |                                                                                         |
| TLR5  | Flagellin (gram-negative bacteria)                                                        |                                                                                         |
| TLR6  | Diacylpolypeptide                                                                        |                                                                                         |
|       | Lipoteichoic acid (gram-positive bacteria)                                               |                                                                                         |
| TLR7/8| ss RNA (virus)                                                                           | Antiphospholipid antibodies, cardiac myosin, ss RNA,                                    |
| TLR9  | Cpg motif (bacteria, virus)                                                               | IgG-chromatin complexes, mitochondrial DNA                                              |
| TLR10 | Diacylated peptide?                                                                      | Immunostimulatory CpG motifs                                                            |
| TLR11 | Profilin-like molecule                                                                   |                                                                                         |

TLR4 is the membrane receptor that can recognize LPS, mannan, glycoinositolphospholipids, envelope proteins, or some self-proteins including HSP60 and HSP70 [44, 45]. As a receptor for LPS, TLR4 has received the most attention in asptic loosening. There was a significant increase of TLR4 in the tissue around loosened replacement implants [25, 43, 46, 47]. The mutation of TLR4 resulted in inhibited inflammatory response and osteolysis when exposed to wear particles [48]. TLR4−/− mice displayed decreased osteolysis. These findings indicated that TLR4 played a key role in the pathogenesis of asptic loosening. Monocytes/macrophages are equipped with TLRs and HSPs. Hao et al. found that UHMWPE particle upregulated the expressions of TLR4 and HSP60 on monocytes. HSP60 can bind to TLR4, leading to the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α [40]. In this scenario, TLR4 played a critical role because interfering with TLR4 resulted in reduced cytokine production [40]. Like UHMWPE particle, titanium particle exposure can also elicit cytokine production and osteolysis. This phenomenon resulted from the engagement of TLR4 and wear particles with adherent LPS. [48]. LPS can be detected in the tissues around aseptically loosened implants, which contributed to the inflammatory responses induced by wear particles [49]. However, it is still unclear whether endotoxin is required for the biological response to wear particles. People found wear particles with LPS decreased the mRNA expression of TLR4 compared to wear particles without LPS. This can be explained by a self-protective mechanism. LPS-coated wear particles can be easily identified by macrophages via TLR4. After the initiation of response, TLR4 was downregulated to prevent excessive harmful host response [26]. The reduced expression of TLR4 mRNA was also found in RAW 264.7 cells or rat macrophages stimulated with titanium particles in vitro [25, 42]. It seemed that auto- or paracrine inflammatory cytokine downregulated the expression of TLR to avoid damage caused by excessive inflammatory responses [42]. Interestingly, TLR4−/− macrophages showed similar levels of TNF-α compared to wild-type macrophages when challenged with wear particles. The unexpected results may be caused by the cells used in the experiments because a variety of cells expressed TLR4. Beidelschies et al. found that, in macrophages that lack TLR4 and TLR2, the section of TNF-α was completely neutralized when stimulated.
with wear particles. However, osteolysis in vivo was only partly inhibited. They supposed that early inflammatory response induced by particles was TLR dependent, while later osteolysis was just partially TLR dependent.

Ligand-TLR binding induces rearrangements of TIR domains and recruitment of adaptors (MyD88, TRIF, and TIRAP), triggering the activation of NF-κB. Pearl et al. found that the inflammatory responses induced by PMMA particles can be decreased using a MyD88 inhibitor. Similar results were found in MyD88−/− macrophages stimulated with PMMA [27]. These findings strongly supported that particles can be recognized through TLR, partly dependent on MyD88 signaling pathway. Maitra et al. reported that UHMWPE particles activated TLR1/TLR2, leading to an inflammatory program mediated by NF-κB-signaling pathway [50]. It has been reported that the p38 and JNK signaling pathways can mediate wear particle-induced osteoclast differentiation in vitro. However, the relationship between specific TLRs and downstream p38 and JNK-signaling pathways remains unknown in wear particle-induced aseptic loosening. It is hypothesized that wear particles can be recognized by TLR, triggering downstream signaling pathway including AP-1 and NF-κB, leading to inflammatory responses and osteolysis (Figure 1).

3. Chemokines and Wear Particle-Induced Aseptic Loosening

3.1. Chemokines and Chemokine Receptors. Chemokines are a group of small proteins with a crucial role in leukocyte migration and activation. These molecules can also affect cytokine secretion, apoptosis, phagocytosis, angiogenesis, and collagen production [51, 52]. The chemokine family can be classified into four groups as CXC, CC, CX3C, and XC, based on the number and spacing of conserved cysteines. CXC, CC, and CX3C chemokines contain four conserved cysteines, whereas XC chemokines contain two conserved cysteines. In the CXC and CX3C chemokines, one (CXC) or three (CX3C) amino acids are inserted between the first two of four cysteines. In the CC chemokines, the first two cysteines are adjacent. About 50 chemokines have been identified in humans. Most chemokines are members of CC or CXC groups, while others belong to XC or CX3C groups [53, 54].

The effects of chemokines are mediated by a family of G protein-coupled receptor on the target cell surface [55]. These chemokine receptors are also classified into four groups as CXCr, CCR, CX3CR and XCR, based on the chemokine group they bind. About 25 chemokine receptors have been identified in human. The relationship between chemokines and chemokine receptors is complex because chemokine receptors bind different chemokines and vice versa.

3.2. Chemokines in Particle-Induced Cellular Migration. In the early time, it was assumed that wear particles induced a localized response. In brief, wear particles stimulated resident cells (including macrophages, osteoblast) to produce cytokines such as TNF-α, IL-1α, IL-1β, and IL-6, resulting in local osteolysis. It has recently been shown that wear particles can induce chemokine expression in macrophages, fibroblasts, and osteoblasts, indicating a cellular migration mechanism in aseptic loosening [56–58]. Monocytes/macrophages accumulated in the periprosthetic tissue were mainly polarized M1 macrophages. Rao et al. hypothesized that monocyte/macrophage progenitors may be attracted to the local microenvironment in response to wear particles, and then differentiate into M1 phenotype [10]. More recently, Ren and Gibon both demonstrated that wear particles induced significant chemotaxis of macrophages in vivo [29, 59, 60]. These findings strongly support the mechanism of cellular migration to the site around the implants, which contributed to pathogenesis of aseptic loosening (Figure 2). In the following article we will focus on the specific chemokines involved in the cellular migration in response to wear particles.

IL-8, also known as CXCL8, is a member of the CXC chemokine family [61]. IL-8 is mainly produced by monocytes/macrophages. The coupled receptors for IL-8 are CXCR1 and CXCR2, which are located on the surface of
Figure 2: Wear particles induced chemokine expression and cellular migration.
wear particle-stimulated inflammatory responses. However, in another research, MIP-1α seemed not to play a role in the chemotaxis function of wear particle-challenged RAW 264.7 cells. First, RAW 264.7 cells produced similar levels of MIP-1α when stimulated with or without wear particles. Second, although MIP-1α possessed potent chemotactic ability for macrophages, neutralizing antibody to MIP-1α failed to inhibit the migration of THP-1 cells in the culture stimulated with particles [79]. These results are complicated and have not been explained by now. One possible explanation may be the specific culture condition or neutralizing antibody used in the experiments. Surprisingly, the supernatant from PMMA-challenged RAW 264.7 cells significantly chemoattracted human MSCs, which can be inhibited by neutralizing antibody to MIP-1α. This result indicated that particle-stimulated MIP-1α release was responsible for the migration of MSCs [79]. CCR1 was one of the receptors for MIP-1α. Huang et al. found that neutralizing antibody to CCR1 failed to affect the migration of MSCs in culture with wear particles in vitro. On the contrary, using a murine model, Gibon et al. have recently shown that UHMWPE particles induced increased migration and osteoblast differentiation of MSCs in vivo, which can be neutralized by antagonist to CCR1 [82]. Since CCR1 can bind to a variety of ligands including MIP-1α, MCP-3, and RANTES, these findings were not sufficient to support the chemotaxis ability of MIP-1α. The specific chemokines participated in the migration of MSCs to the site around implants that need further investigation.

CCL17 and CCL22 are the two recognized ligands for the chemokine receptor CCR4. They are known to be mainly produced by cell lineages closely related to osteoclasts such as dendritic cells. CCL22 has been shown to be expressed by activated macrophages and mature dendritic cells, whereas CCL17 has been shown to be secreted by keratinocytes and endothelial cells. Titanium particles increased the expressions of CCL17 and CCL22 in osteoclasts and hFOB cells. Moreover, the expression of CCR4 was upregulated when osteoclast precursors were stimulated with titanium particles. These results implied a role for CCL17 and CCL22 in the chemotaxis of CCR4 expressing osteoclast progenitors to the site around implants [83].

4. Conclusions and Perspective

Aseptic loosening is the common cause of the failure of TJR, and the mechanisms underlying it appear complex and multifaceted. A large number of scholars have focused on the biological activity of wear particles. Macrophages recognize wear particles and release proinflammatory mediators, leading to osteoclast activation and osteolysis. Although it has been accepted that the interaction between wear particles and macrophages is critical, little is known about how wear particles are recognized and activate macrophages in the early inflammatory response. In vivo and in vitro studies have supplied strong evidence that wear particles can activate macrophages through TLRs. TLRs are evolutionarily conserved pattern recognition receptors in sensing exogenous PAMPs and endogenous DAMPs. Both PAMPs and DAMPs are responsible for the activation of TLRs in aseptic loosening. DAMPs/PAMPs-TLR interaction may be a novel mechanism of aseptic loosening. Although the relationship between TLRs and chemokines have not been clarified, it seems possible that the activation of TLR may promote macrophages to express different chemokines. In brief, the pathogenesis of implant-associated aseptic loosening includes a series of events: macrophages response to wear particles acting as PAMPs/DAMPs via various TLRs, especially TLR4 and TLR2. These TLRs then interact with adaptor protein MyD88, finally triggering the activation of NF-κB and production of inflammatory cytokines. The cytokines induced by wear particles include chemokines such as IL-8, MCP-1, and MIP-1. These chemokines bind to specific G-protein-linked transmembrane receptors and activate intracellular signaling pathways, leading to recruit more macrophages, MSCs, neutrophils, and osteoclasts to the site of injury. The accumulation of cells further facilitates propagation of inflammatory and subsequent osteolytic events.

Given the fact that wear particles are recognized via TLRs, effective strategies can be designed to block the event. For example, MyD88 interfering may block TLR downstream signaling pathway and then prevent wear particle-induced periprosthetic osteolysis. Another promising approach involves inhibiting recruitment of macrophages and other cells to the inflammatory site. Pharmacologic intervention targeted at chemokine-receptor axis may provide the means to mitigate the response to wear particles. Indeed, in vivo study has shown disruption of MCP-1 ligand-receptor axis can inhibit wear particle-induced migration of macrophages and osteolysis. In general, understanding the mechanisms of wear particle-induced cellular activation and migration will provide insight into the prevention and treatment of prosthetic aseptic loosening. The future of research needs to focus on some areas: the specific TLRs which are activated by exposure to different types of wear particles, the downstream signaling pathway mediated by TLR, the specific chemokine-receptor axis participating in wear particle-induced cellular migration, the exact role of cell recruited by wear particles in aseptic loosening.

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