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REVIEW ARTICLE

Current research in the pathogenesis of aseptic implant loosening associated with particulate wear debris

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Periprosthetic osteolysis is the most common long-term complication of a total joint arthroplasty, often resulting in aseptic loosening of the implant, which occurs in up to 34% of younger implant recipients and usually requires surgical revision. Particulate wear debris, continuously generated by articulating motion at the bearing surfaces, has been implicated as one of the primary causes of periprosthetic bone loss and implant loosening. With developing implants and bearing surfaces designs, various types of wear particles with specific chemical nature, dimension and shape are formed, which may initiate different immune or inflammatory responses. Wear debris induces down-regulation or up-regulation of various pro-inflammatory cytokines and chemokines in a range of cell types at the interface between implants and the surrounding bone, such as macrophages, osteoclast precursor cells, osteoblasts, lymphocytes, fibroblasts etc. Concomitantly, these mediators further affect functions of cells through distinct signaling mechanisms in either an autocrine or a paracrine manner. This review summarizes current concepts of how wear debris causes osteolysis, and describes the interaction and effects of wear debris on functions of primary cell types involved in osteolysis.

Keywords : wear debris ; aseptic loosening ; osteoclastogenesis ; arthroplasty failure ; biological reaction.

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INTRODUCTION

Total joint replacement is one of the most successful treatment modalities for terminal stages of arthritis. While failure due to infection, fracture and dislocation becomes relatively rare with improved surgical techniques and advanced technology, osteolysis-associated aseptic prosthetic loosening has become the most common cause for total joint replacement failure (*29,44*). Aseptic loosening (AL) is characterized by migration of the prosthetic

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component or areas of osteolysis found at the bone-implant interface that can be identified radiographically as radiolucent zones (*29*). It was previously believed to be a simple mechanical complication resulting from the instability of the implant. However, periprosthetic osteolysis as a biological mechanism of aseptic loosening occurring at the bone-implant interface has recently been proposed (*11,44,50*). A number of investigators have examined the periprosthetic tissues from patients with aseptic loosening who experienced revision surgery, for periprosthetic osteolysis (*11,17,50*). Kadoya *et al* have reported that the production of wear debris in the bone-implant interface resulted in adverse reactions in the human body, especially if the exposure to particulate debris became repetitive (*17*). One of the major reasons for arthroplasty failure is the continuous generation of debris particles from the articulating interface, which leads to the development of a foreign-body reaction. Particulate debris consisting of metals, polyethylene, ceramics, and bone cement have all been shown to provoke a biological response in joint tissues (*42*).

Various types of cells including fibroblasts, osteocytes, bone marrow cells, osteoblasts and haematogenous cells such as phagocytes, monocytes, lymphocytes are often present in periprosthetic tissue retrieved at the bone-implant interface during revision surgery for aseptic loosening (*11,20,31*).

Particle phagocytosis is a central event in the pathogenesis of periprosthetic osteolysis (*20,37,40*). Monocyte/macrophage cell lineage, generally considered as the main phagocyte, is thought to play the primary role in wear-induced osteolysis (*32*). In the literature, macrophage activation is predominantly considered as the frontline of osteolysis (*23,51*). Signaling events, which include intracellular kinase and transcription factor activation for the local inflammatory and osteolytic process, are initiated by interactions of wear debris particles at the cell surface or after phagocytosis (*28,45,48*).

Many other immigrant and resident cells also actively participate in the bioreactive process (*20*). The biological response to wear debris at the periprosthetic interface is universal with orthopaedic biomaterials. Fibroblasts and osteoblasts are two other well-recognized resident cell types that stimulate the cells of monocyte/macrophage lineage to form polykaryons, such as generation of foreign body giant cells and osteoclasts (fibroblasts of adjacent tissues are likely to stimulate formation of foreign body giant cells , and cytokines released from osteoblasts in turn enhance formation of osteoclasts (*21*). These interactions are the characteristics of peri-implant osteolysis and aseptic loosening by mediating chronic inflammatory foreign body reaction.

WEAR DEBRIS

Orthopaedic implants are subjected to mechanical loads and must integrate with host bone. The continuous generation of wear particles by articulating motion at the bearing surfaces is believed to be a major component of loosening during the lifetime of an implant. Numerous wear particles are found in the periprosthetic interfacial membrane removed during revision surgery. Furthermore, macrophages cultured *in vitro* showed inflammatory response to wear particulates (*32*), and multifarious animal models established in the field have demonstrated that particulate debris evidently resulted in osteolysis (*28,49,51*). Although there is evidence of involvement of other factors such as fluid pressure and adherent endotoxin (*35*) that lie beyond the scope of this review, studies have clearly demonstrated that wear debris represents the single most important underlying cause for periprosthetic osteolysis.

GENERATION OF WEAR DEBRIS

Various types of wear debris (polymer, metal, and bone cement) from total joint arthroplasty can be generated in repetitive motions (Fig. 1). The choice of prosthesis and bearing surface dramatically influences the chemical nature, dimension, and shape of the wear debris particles which may initiate different immune or inflammatory responses (*17,42,47*). When wear particles are retrieved from periprosthetic tissue, characterization is usually accomplished through light microscopy and scanning electron microscopy. Such studies often revealed information on morphologies, prevalence, and size distribution of wear debris.

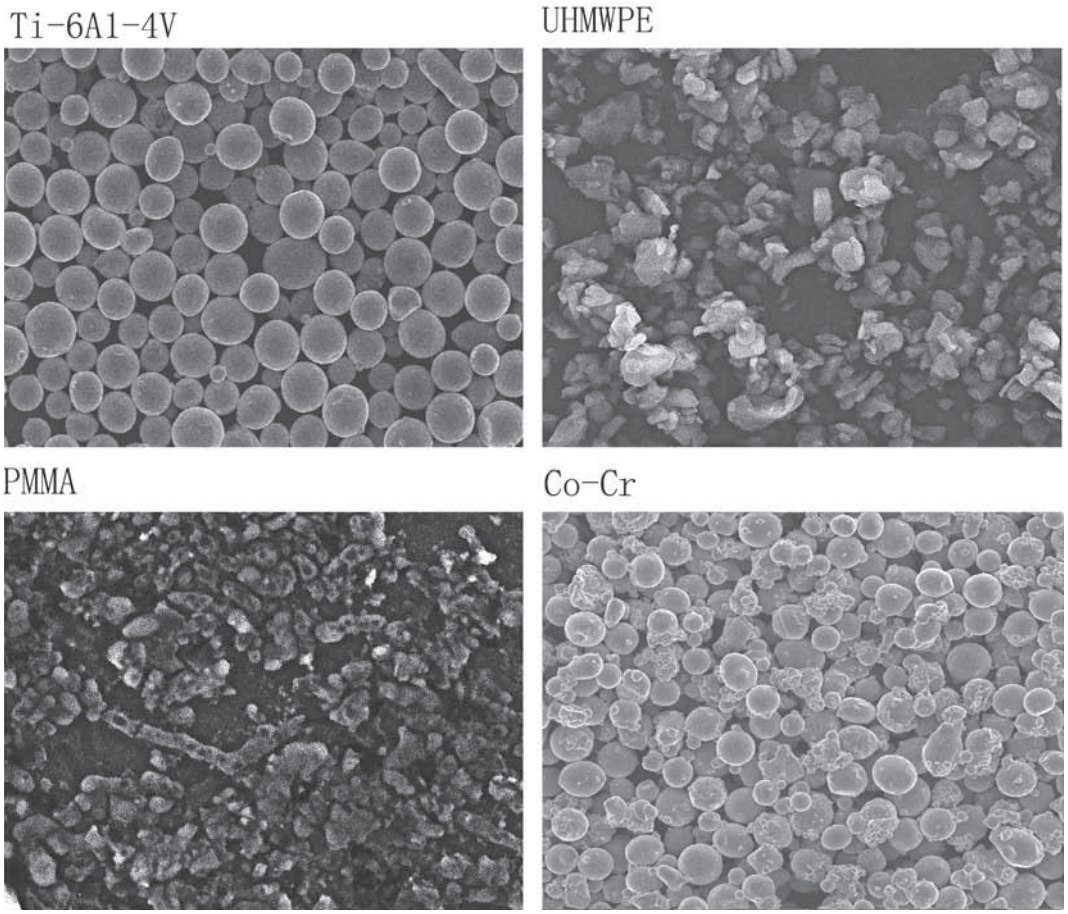

Fig. 1. — Scanning electron microscopy (SEM) appearance of common types of orthopaedic wear debris : Titanium alloy particles (Ti–6Al–4V), Ultra high molecular weight polyethylene (UHMWPE) particles, polymethylmethacrylate (PMMA) particles, and Cobalt–Chromium alloy (Co-Cr) particles.

The relative amounts or size of debris from different kinds of articulating bearings, such as hard-on-hard material couples (i.e., metal-on-metal or ceramic-on-ceramic) and hard-on-soft material (i.e., metal-on-polymer), are important to discover the pathogenesis of the joint prosthesis failure (*33*). There has been a revived interest in metal-on-metal total hip replacements because of their potential for improved wear performance compared with conventional metal-polyethylene implants, and studies indicated that the clinical and radiological results following metal-on-metal THA are satisfactory with low revision rates. Cobalt and chromium ion levels peaked at four and five years, respectively, and gradually decreased thereafter (*1,10*). However, recent studies show that almost 6 percent of individuals with metal-on-metal implants needed surgical revision after five years, compared with just 1.7 to 2.3 percent of those who had other friction pairings. Additionally, metal wear debris from metal-on-metal hip implants develop pseudo-tumours growing in the tissue surrounding the metal and may lead to more serious long term health issues (*4,7,8*).

Polymeric particles retrieved from AL prosthesis generally fall into the range of 0.23 to 1 μm, with a mean size of approximately 0.5 μm. Metal and ceramic particles (approximately 0.05 μm diameter) are generally an order of magnitude smaller than polymer particles, and the metallic-wear debris may

disseminate to systemic organs of the body through the bloodstream. The released soluble metal ions [aluminum (Al), chromium (Cr), vanadium (V), cobalt (Co), and titanium (Ti)] may bind to proteins and increase the levels of circulating metals in blood (*15,24,25*). The traditional particle-sizing techniques such as scanning electron microscopy (SEM) or transmission electron microscopy (TEM) may have limitations in detection and quantification of nano- to submicron particles, The development of new methodologies facilitates a better understanding of particle properties both in quantity and size, such as low-angle laser light scattering (LALLS), substantially detects millions to billions of particles as they flow in front of a laser beam (*15*).

There have been assertions that newer implants or bearing surfaces designs may significantly improve their anti-wear properties (*35,44*). However, the potential impact of the generation of much smaller sized wear debris is yet to be fully determined, owing to the slow progressive nature of the osteolysis-associated prosthesis failure.

BIOLOGICAL REACTIVITY OF WEAR DEBRIS

The major factors that influence osteolysis are the amount, appearance, rate of production, time of exposure, and antigenicity of the wear particulates (*17,33*). The release of wear debris may be followed by opsonization of different types of antigenic substances, including carbohydrates, lipids, proteins, and nucleic acids (*34*). Once coated, the particles may then influence the host immune system either through the acquired immune pathway or the innate immune pathway.

It is generally accepted that small particles, nanometer-sized particles (less than 150 nm) can be ingested by cells through endocytosis or pinocytosis , while the ingestion of larger particles (more than 150 nm to 10 μm) occurs by phagocytosis in a series of cells types, including endothelial cells, fibroblasts, osteoblasts, and macrophages (*21,23,37,40*). Generally, local inflammatory response is positively related to the particle load which is dependent on both the average size and the amount per tissue volume of phagocytosable particles. It has been reported that the size of the particles should be less than 10 μm, i.e. within a phagocytosable range, to generate an *in vitro* inflammatory response (*14*). Purportedly, the most proinflammatory particles need a mean size of 0.24 to 7.2 μm. Within this range, there is no consensus as to what specific size and dose of particles (particles and cell, particles and tissue volume) are maximally inflammatory (*12*). Elongated particles are more proinflammatory than round particles, which has been well demonstrated as early as over three decades ago for asbestos fibers (*14,47*). Cumulative evidence has indicated that more chemically reactive particles are more proinflammatory, i.e, metal particles are more proinflammatory or toxic, or both, when compared to polymers (*7,8*). This conclusion is however not unanimous, since others have reported that polymers are more proinflammatory than metals (*34,42*). Implant loosening associated with the loss of surrounding bone is characterized by the formation of granulomatous tissue with a pseudo-synovial appearance, instead of osseous integration. This tissue exhibits a varied cellular composition that includes macrophages, foreign body giant cells, lymphocytes, plasma cells and fibrocytes (*11,31*). This is accompanied by elevated levels of proinflammatory cytokines, such as tumor necrosis factor (TNF-α), IL-1β, PGE2 (*43*). Many immigrant and resident cells indeed participate in the bio-reactive process of periprosthetic osteolysis, such as macrophages, osteoclast precursor cells, osteoblasts, lymphocytes, and fibroblast (*20,21,40*). These cells produce a number of cytokines, chemokines, and prostaglandins, which may further affect the function of cells in either an autocrine or a paracrine manner with distinct signaling mechanisms. This may break the homeostasis of bone metabolism, ultimately increase osteoclast activity or decrease osteoblast function, either mechanism or both mechanisms may result in a net bone loss (*26,42,46,48*).

In a broader sense, all cell types of the periprosthetic tissue (macrophages, fibroblasts, osteoclasts, and osteoblasts) are able to phagocytose particulate wear debris, and virtually all cells can reach an activated state (Fig. 2). However, the most important cellular target for wear debris appears to be the macrophage, which responds to the particle

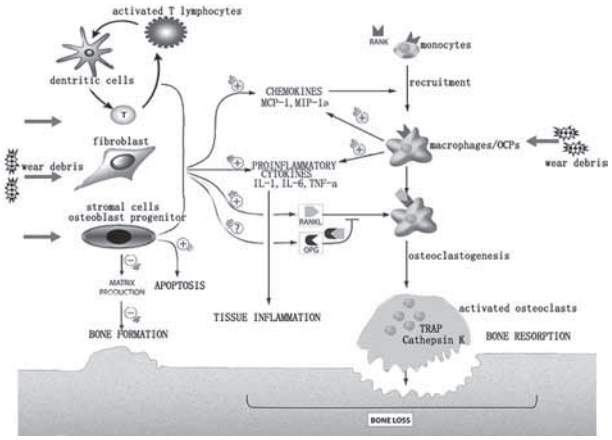

Fig. 2. — Schematic views of cellular and molecular response initiated by wear particles. A series of cytokines and mediators can be produced by a range of cell types in responding to the particulate wear debris challenges. Monocytes/OCPs are recruited to the periprosthetic tissue and differentiated into functional osteoclasts. Wear debris also contribute to osteolysis through inhibiting bone formation from osteoblast progenitor cells.

challenges in two distinct ways to increase bone resorption (*23*). It is well known that wear debris activates proinflammatory signaling, which leads to increased osteoclast recruitment and activation (*23,32*). More recently, it has been established that wear debris particles also inhibit the protective actions of anti-osteoclastogenic cytokines such as interferon gamma, thus promoting the differentiation of macrophages to bone-resorbing osteoclasts. Osteoblasts, fibroblasts, and possibly lymphocytes may also be involved in responses to wear (*8,21,37,40*).

PARTICLE-MEDIATED OSTEOLYSIS

Monocyte/Macrophage

Studies have shown that the circulating monocytes are among the first cells to colonize the inflammatory site (*50,51*). Histologically, numerous macrophages with presence of phagocytosed particulates can be identified in pseudo-synovial tissue of patients undergoing revision surgery (*11*). Phagocytosis, a nonspecific defense mechanism for the elimination of wear debris, can be recapitulated in cultured macrophage lineage cells with particles *in vitro* (*27,32,33*).

The phagocytic process requires the opsonization of particles and a protein coat on the surface of particles that bind to phagocytosis receptors (such as Fcγ receptors, Toll-like receptor family members or TLRs, Macrophage mannose receptor or MMR, and β1 integrins, CD11b, CD14) (*34*). TLRs are characterized by an amino-terminal extracellular domain composed of repeated motifs high in leucine and known as leucine-rich repeats (LRRs), followed by a single transmembrane domain and a globular cytoplasmic domain called the Toll/interleukin 1 receptor (TIR) domain, or TIR domain that is also found in IL-1 receptors (*22*). The mannose receptor is a C-type lectin carbohydrate binding protein primarily present on the surface of macrophages and dendritic cells. It helps recognizing pathogens that have mannose on their surface, and triggers one pathway of the complement syste. Multiple intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK) cascade, are activated through the interactions between particles and macrophages, which may result in cytoskeletal reorganization, pseudopod formation, and the ingestion of the particles. Simultaneously, this phagocytosis-induced signaling pathway up-regulates or down-regulates various genes expression through the action of corresponding nuclear transcription factors, especially genes of proinflammatory cytokines and chemokines (*27*).

In vitro studies have shown that the phagocytosis of particulate wear debris stimulates macrophages/monocytes in producing a large number of prostaglandin E2, TNF-α, IL-1, IL-6, IL-8, and matrix metalloproteinases including collagenases (*14*). Elevated levels of these factors or proteases have also been detected in periprosthetic tissues of osteolysis models (*46,50,51*). Besides proinflammatory cytokines, activated macrophages also produce a range of chemokines, including monocyte chemoattractant protein-1 (MCP-1), monocyte inflammatory protein-1α (MIP-1α), and IL-8 (*18*). By the action of chemokines, circulating monocytes and osteoclast precursors (OCPs) migrate across the blood vessel wall to periprosthetic tissues, and these monocyte infiltrates eventually form osteoclasts in

response to RANKL and macrophage-colony stimulating factor (M-CSF) with NF-κB activation (*6,26*).

Osteoclast

Osteoclasts (OCs), generally accepted as the principal cell type capable of bone resorption, are derived from OCPs of the monocyte/macrophage cell line (*3*). Recruitment of OCPs from blood and generation of functional OCs at interface between implant component and the surrounding bone play a critical role in periprosthetic osteolysis and bone resorption (*40*). With the stimulation of wear debris, various proinflammatory factors, such as TNF-α, IL-1, *et al* can be produced by a range of cell types (*12,18,37,42*). These proinflammatory cytokines have also been demonstrated as critical mediators in animal models (*28,46,48,49*) in which generation and activation of osteoclasts may be involved. In the past decade, receptor activator of NF-κB ligand (RANKL), the key cytokine regulator of osteoclastogenesis was found.

RANKL has been shown to play a fundamental role in regulating osteoclast generation and activation. It has been reported that elevated RANKL was expressed in the pseudo-synovial tissue between implant and surrounding bone with osteolysis (*26*). *In vitro*, osteoblasts or fibroblasts stimulated by metallic and polyethylene wear debris expressed higher level of RANKL (*5,13*). Targeted disruption of the related genes in mice led to severe osteopetrosis and a lack of osteoclasts (*9*). In addition, several cell types including osteoblasts, fibroblasts, and T-lymphocytes in the periprosthetic tissue overexpressed RANKL expression (*2,13,19,41*). RANKL binds to receptor activator of NF-κB (RANK) on the surface of OCs and OCPs and arouses the cascade of intracellular NF-κB signal pathways, which appears essential to complete the osteoclast differentiation and activation (*6,26*).

Osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor (OCIF), is a decoy receptor for the receptor activator of NF-κB ligand (RANKL) (*3,6*). By competent binding to RANKL, OPG prevent its physiological interaction with RANK, which suppresses the differentiation of osteoclasts, inhibits their activation and induces apoptosis (*3,26*). RANKL blockade by OPG have prevented the wear debris-induced osteolysis in murine models (*45,52,53*). Therefore, the OPG/RANKL balance is essential to regulate bone metabolism, by controlling the activation state of RANK on osteoclasts.

During the different phases of the osteoclastogenesis, specific genes or proteins may play a critical role. Macrophage-colony stimulating factor (M-CSF) receptor, c-fms, promotes the proliferation and survival of the hematopoietic-committed progenitors ; RANK and c-fos mediate the ability of OCPs to undergo differentiation ; c-src, tartrate-resistant acid phosphatase (TRAP), cathepsin k (CATK) contribute to the adherence lytic function of the mature osteoclast ; calcitonin receptor (CTR) is hormonal control of the osteoclastogenesis (*3,13*).

Lymphocyte

Growing evidence has suggested the involvement of lymphocytes in the periprosthetic osteolysis process (*8,16,39*). It has been reported that a number of activated T cells were present in the interface membrane retrieved from patients with osteolysis, while other studies suggested the presence of T cells that were inactivated or in small quantity (*16,36,39*). Several T-cell chemotactic factors (IP-10, MIG) have been identified in peri-implant tissues which may contribute to the infiltration of T-cells (*16*). Activated T-cells may be involved in the regulation of bone homeostasis through their capability to generate RANKL, which influences the differentiation of OCs as previously demonstrated (*2,19*). In animal studies, many mice models with lymphocytic deficiencies were established to investigate the effect of lymphocyte in wear debris associated osteolysis, which showed inconsistent results (*36*).

Recent studies have showed that lymphocytes involved in a metal-specific response to poor implant performance, and conspicuous lymphocytic infiltration in tissues around contemporary metal-on-metal joint replacements in patients (*8*). This may be postulated as the hypersensitivity of metal allergy, in which the released ions (soluble debris) from corrosion of metallic implants are chelated with native

proteins and recognized by lymphocytes to activate the immune system (*4,7*).

Osteoblast

Bone is a dynamic tissue with a well-balanced homeostasis preserved by both formation and resorption of bone. It is important to consider whether, in addition to promoting osteoclast activity, wear debris might also contribute to osteolysis through inhibiting bone formation. Osteoblasts also phagocytose particles (*37*). This process leads to the suppression of procollagen α1(I) gene expression followed by reduced type-I collagen synthesis (*37,38*), which may result in decreased bone formation. Simultaneously, particle-stimulated osteoblasts upregulate the produce of IL-6 and prostaglandin E2 (*38*), activating osteoclast which are assumed to already be in an activated state because of phagocytosed particles. Activated macrophages/monocytes express other cytokines such as IL-1β and TNF-α, which in turn activate osteoblasts to secrete IL-6 and suppress type-I collagen synthesis (*37,38*). The suppression of procollagen α1(I) mRNA and upregulation of many other genes including the genes of proinflammatory cytokines such as IL-1, IL-6, and TNF-α in particle-challenged cells may be achieved by the activation of nuclear transcription NF-κB signal pathway (*27,38*). Otherwise, local delivery of certain growth factors (IGF-I or TGF-β1), protein tyrosine kinases, or NF-κB inhibitors can reverse the suppressive effect of either proinflammatory cytokines or wear particles on type-I collagen synthesis in osteoblasts (*37*).

In vitro studies revealed that different kinds of particles behave differently in the OB formation and functions, such as decreased expression of collagen Types I and III, diminished osteoblast matrix production (*5,37,38*), retarded OB differentiation from mesenchymal stem cells, and elevated OB apoptosis (*5*). Another important function of osteoblastic cells is the production of RANKL. As we have previously demonstrated, the altered RANKL/OPG ratio plays a crucial role in the differentiation of OCs from osteoclast precursors (*13*). Thus, wear debris particles challenged osteoblasts may contribute to the periprosthetic osteolysis through both osteoclast activation and impaired osteoblast functions.

Fibroblast

Fibroblasts are ubiquitously found within periprosthetic granulomatous tissue of patients with osteolysis (*11,30,31*). I*n vitro* studies also illustrated that particle-challenged fibroblasts significantly promoted expression of proinflammatory cytokines, collagenase and stromelysin, which contributed to the development of osteolysis (*21*). Wei *et al* reported that titanium particles provoked RANKL expression in fibroblast cultures (*41*). Furthermore, fibroblasts isolated from pseudomembranes of patients with osteolysis also suggested the OC differentiation from human monocytes (*30*). All these findings suggest that fibroblast may be an important source of RANKL and contribute to bone resorption through the generation of OCs.

CONCLUSIONS

Aseptic prosthetic loosening following total arthroplasty may be attributed to many reasons, yet the most important factor appears to be the periprosthetic osteolysis due to unbalanced homeostasis of bone formation and resorption. It is widely believed that particulate implant debris induces local inflammation and osteolysis. The choice of prosthesis and bearing surface significantly affects the ingredients, dimension, and shape of generated particles which may result in different immune or inflammatory responses. A range of cells originated from haematopoietic stem cells and bone marrow stem cells participates in the wear debris associated inflammatory response. Simultaneously, these cells produce a number of cytokines, chemokines, and other mediators, which may further influence the function of cells in either an autocrine or a paracrine manner with distinct signaling mechanisms. Although much progress has been made in the past decade in our understanding of how prosthetic wear debris ultimately cause osteolysis and aseptic loosening, more studies are needed to definitively elucidate the responsible molecular and cellular pathways of

periprosthetic osteolysis which may have the potential to prevent or treat aseptic loosening.

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