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What are the local and systemic biological reactions and mediators to wear debris and what host factors determine or modulate the biological response to wear particles?

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Introduction

Orthopaedic implants are subjected to mechanical loads and must integrate with host bone. However, long term clinical success is limited by implant loosening which is often associated with the loss of surrounding bone. Implant loosening is characterized by the formation of a fibrous membrane (instead of osseous integration), production of inflammatory cytokines, and periprosthetic bone resorption. Implant loosening and periprosthetic bone loss is secondary to particulate wear debris.^{1, 2} Wear debris is continuously generated by articulating motion at the bearing surfaces. Periprosthetic bone is often subject to a very unique micro-environment where bone marrow cells and osteoblasts are in direct contact with orthopaedic biomaterials.³ Although cells of the monocyte/macrophage lineage play the primary role in wear-induced osteolysis, many other immigrant and resident cells are also active participants in the bioreactive process.⁴ The biological response to wear debris at the periprosthetic interface is universal with respect to orthopaedic biomaterials.^{5, 6} An increasing volume of literature exists on the cellular and molecular mechanisms by which wear particles stimulate the host inflammatory response, predominantly through macrophage activation.⁷ Particle/macrophage interactions initiate signaling events by cell membrane contact alone or with phagocytosis, and intracellular kinase and transcription factor activation is a critical component of the inflammatory process.

Resident cells

Monocyte/macrophages, as well as lymphocytes, polymorphonuclear leukocytes (neutrophils), and mast cells are hematogenous cells. They or their precursors are formed in the bone marrow, and are mobilized from the marrow compartment to the vascular compartment. When in circulation, these cells first start to tether and roll along the endothelium of the post-capillary venules, then adhere, and finally migrate across the blood vessel wall to tissues. Accordingly, various vascular endothelial cell adhesion molecules have been found in the blood vessels of the synovium-like interface membrane surrounding loosening implants.⁸ Thus, endothelial cells form an important and active participant in the process as a route of transport for the leukocytes to the interface membrane.

Vascular endothelial cells are involved through release and perivascular binding of von Willebrand factor.⁹ Von Willbrand factor is synthesized and stored in the Weibel-Pallade bodies of the vascular endothelial cells and exists in two different molecular forms: (1) the oligomeric von Willebrand factor, also known as factor VIII-related antigen, which acts to bind and stabilize the factor VIII or hemophilia factor VIII; and (2) a polymeric form of von Willebrand factor, which is released as a result of endothelial cell activation and/or damage. Von Willebrand factor has collagen binding domains, allowing it to bind tightly to perivascular collagenous tissue, e.g., as a perivascular cotton wool-like cuff surrounding weakly staining vascular endothelial cells in the synovium-like interface membrane. This injury around

loosening implants is likely due to pathological micro- and macromotion, leading to ischemia-reperfusion injury of the vascular endothelial cells.

Two other well-recognized resident cell types, fibroblasts and osteoblasts, are responsible for the production of the interstitial fibrous collagenous matrix in connective tissue which provides structural support and strength, and the formation of the bony matrix, respectively. The compromised local renewal of these cells will impair peri-implant tissue strength which is why recruitment of these cells, for example from bone marrow or from circulation, must be maintained for the development of a functional implant interface.

Another important function of osteoblastic cells is the production of cell membrane associated receptor activator of nuclear factor kappa B ligand L (RANKL), formerly also known as an osteoclastogenic factor, and macrophage colony stimulating factor (M-CSF). RANKL can bind either to its macrophage receptor RANK or to its decoy receptor osteoprotegerin (OPG). Interaction of osteoblast-derived RANKL with macrophage RANK stimulates the mononuclear cells of the monocyte/macrophage lineage to undergo cell fusion to polykaryons. Connective tissue fibroblasts are likely stimulate formation of the foreign body giant cells^{10, 11} and cytokines released from osteoblasts in bone in turn enhance formation of osteoclasts.^{12, 13} These events are the hallmarks of implant loosening by mediating chronic foreign body reaction and peri-implant osteolysis.

Lately, some attention has been paid to other mesenchymally derived cells, including adipocytes. These cells have been recognized as important inflammatory cells producing adipocytes, however their involvement in implant loosening has not been thoroughly studied.

Immigrant cells

Apart from monocytes, other leukocytes are recruited from the circulation to the interface membrane, the site of the foreign body reaction. Lymphocytes have been found in the membrane, recent studies using high-throughput protein chips have identified several T-cell chemotactic factors (IP-10, MIG) present in peri-implant tissues which highlight the existence of adaptive immune processes.¹⁴ In a small number of patients, lymphocytes are actively engaged in delayed, type IV hypersensitivity reactions or other responses and proliferate as a result of antigen-driven clonal expansion. This has been documented in metal hypersensitivity, in which metal ions derived from electrochemical corrosion of metallic implants or metallic wear debris bind to proteins and modify them such that they are recognized by lymphocytes. This response involves a predominantly Th1-type of lymphocyte engagement, which has also been reported in culture positive septic loosening. Patients with well functioning implants demonstrate a shift in the CD4/CD8 circulating lymphocytic ratio, however the clinical implications of this finding remains uncertain.¹⁵

Neutrophils only occur to any significant degree in septic loosening. Locally proliferating bacteria produce antigens that attract neutrophils to the site. Mast cells are mediators of immediate type I hypersensitivity where cell surface IgE has sensitized mast cells, which, upon contact with IgE cross-linking allergy causing antigen (allergen) are activated and release preformed mediators such as histamine. Mast cells also produce lipid and cytokine mediators; their presence, mastocytosis, and activation in the interface membrane have been observed.¹⁶

Host Inflammatory Response to Particulate Biomaterials

The compelling factors that contribute to osteolysis are related to the number, size, shape, rate of generation, time of exposure, and antigenic properties of the wear debris particles.^{14, 17-20} The antigenic properties may be related to the biolayer (10 to 100 nm thickness) that forms when the implant is placed in the body. The release of wear debris may be followed by

opsonization of different types of antigenic substances, including carbohydrates, lipids, proteins, and nucleic acids.²¹ Once coated, the particles may then influence the host immune system either through the acquired immune pathway or the innate immune pathway. The acquired immune response depends on T- and B-lymphocyte interactions with specific epitopes. T cells recognize antigens presented by antigen presenting cells such as macrophage/dendritic cells and then prime B cells to produce antibodies for a specific immune reaction. Conversely, the innate immune system is non-epitope-specific but functions via the action of phagocytic cells, primarily the monocytes/macrophages, including leukocytes (neutrophils & eosinophils), to remove foreign materials. The macrophage is the predominant cell type with respect to biomaterial particles in inciting periprosthetic inflammatory bone loss. Other cells recognized as integral to progression of osteolysis are fibroblasts, osteoblasts, osteoprogenitor cells (adult mesenchymal stem cells, or MSCs), synovial cells, and osteoclasts. There are similarities in the activation process in which wear debris activates macrophages and other cells within the interfacial membrane.

Macrophage Activation

Macrophage activation requires surface interaction and can occur with or without phagocytosis. In the case of interactions between particles and macrophages in the outer membrane, single or multiple receptors may be involved (CD11b, CD14, Toll-like receptor family members or TLRs). The TLR functions in the innate immune response as a transmembrane protein with an outer leucine-rich motif and an inner IL-1 receptor homologous kinase domain. Signal transduction occurs through the mitogen-activated protein kinase (MAPK) cascade, targeting transcription factor activation and nuclear translocation. Transcription factor activation results in a decrease in the inhibitor of kappaB (IKB) and activation of the nuclear factor of kappaB (NFkB) which transactivates the cluster of genes for proinflammatory cytokines and chemokines. The consequence of proinflammatory cytokine production, including TNF- α , interleukins (ILs), vascular endothelial growth factor, and interferons, is the subsequent activation of cells in the interfacial membrane.²²⁻²⁵ Immunohistochemical and RT-PCR studies on human tissues obtained at the time of revision surgeries confirmed the presence of TNF- α , IL-1, IL-6, PGE-2, M-CSF, and RANKL.²⁶⁻²⁹ Likewise, the synovial-like membrane collected at the host bone-loosened implant interface produces a large amount of prostaglandin E2, TNF- α , IL-1, IL-6, IL-8, and matrix metalloproteinases, including collagenases, under organ/tissue culture conditions.^{2, 30} In addition to proinflammatory cytokines, a class of *chemoattractive cytokines*, the *chemokines*, are also produced by macrophages, osteoblasts, fibroblasts, and synovial cells.³¹⁻³⁴ The most abundant chemokines include monocyte chemoattractant protein-1 (MCP-1), monocyte inflammatory protein-1 alpha (MIP-1 α), and IL-8. Chemokines recruit circulating monocytes and osteoclast precursors into the interfacial membrane, and these monocytic infiltrates eventually form osteoclasts in response to RANKL and macrophage-colony stimulating factor (M-CSF) with NFkB activation.³⁵ The osteoclast progenitors express RANK that interacts with RANKL produced by fibroblasts, osteoblasts, and adult MSCs. Recently, nuclear factor of activated t cells (NFAT) was also reported to be involved with cytokine induction in macrophages, where inhibition of NFAT suppressed TNF-alpha and MIP-1 α production.³⁶

Osteoprogenitor cells as targets of particle-mediated osteolysis

A functional tissue-implant interface depends on mineralized tissue ingrowth and effective bone tissue remodeling, a function coordinated by the activities of osteoclasts, osteoblasts, and their respective progenitor cells. MSCs are generally considered the major osteoprogenitor cell type and are thus likely to be critically affected during particle-mediated osteolysis.

Particulate disruption of osteogenic differentiation

Several studies showing particulate suppression of bone formation have been conducted on osteoblasts or osteoblast-like cells. Titanium particles disrupt osteoblast function in MG-63 human osteosarcoma cells,³⁷ trigger apoptosis in calvarial osteoblasts,³⁸ alter osteoblast adhesive behavior,³⁹ and stimulate chemokine production in osteoblasts.⁴⁰ Particulate wear debris also compromises osteogenic differentiation of bone marrow-derived MSCs.⁴¹ Bone marrow stroma represents an abundant source of MSCs.^{42, 43} During the course of implant life, particularly in the case of poor initial implant fixation with excessive micromotion or constant accumulation of wear particles over time, marrow cells are continuously exposed to high concentrations of debris throughout the stage of mesenchymal bone repair when implant fixation is relatively weak. As a result of the prolonged exposure to particles, disruption of the normal osteogenic differentiation process of MSCs may occur and subsequently result in a diminished population of functional osteoblasts, thus compromising osseointegration at the bone-implant interface. During culture under osteogenic conditions, exposure of human MSCs to sub-micron size titanium particles suppresses bone sialoprotein (BSP) gene expression, reduces collagen type I and BSP production, decreases cellular proliferation and viability, and inhibits matrix mineralization.^{41, 44, 45} Prolonged exposure of bone marrow cells *in vivo* to implant-derived wear debris may thus effectively diminish the population of viable MSCs and compromise their differentiation into functional osteoblasts, the long-term quality of periprosthetic bone tissue, and maintenance of osseointegration.

Particle-mediated MSC cytotoxicity

Exposure to titanium particles also adversely affects hMSC viability through the induction of apoptosis, eliciting increased levels of the tumor suppressor proteins, p53 and p73, in a manner dependent on material composition, particle dosage, and exposure time.⁴¹ Interestingly, these effects on MSC proliferation, apoptosis, and differentiation appear to be mediated via particle endocytosis by the MSCs.⁴⁶ Agents that disrupt endocytosis, such as cytochalasin D, protect the MSCs from these particle-mediated effects.

Adult trabecular bone is an abundant source of MSCs

Multipotent, MSC-like progenitor cells are also found in adult human bone.^{47, 48} These bone-derived MSCs can undergo chondrogenic, osteogenic, and adipogenic differentiation *in vitro*, and form a bone-like tissue when seeded into three-dimensional biomaterial scaffolds.⁴⁹ Since the implanted prosthesis surface will be directly juxtaposed to bone, these MSCs are a prime candidate osteoprogenitor cell type affected by wear debris. Although the mechanism in which debris particles exert their effects on MSCs is presently unknown, they may be related to biological effects on the cell membrane such as receptor signaling, matrix-integrin interactions, and physical disruption of cytoskeletal architecture.

Recent studies using murine bone marrow-derived osteoprogenitor cells, and the murine MC3T3 cell line have also noted suppressed proliferation and differentiation of osteoprogenitors, and decreased matrix calcification in the presence of polymethylmethacrylate and polyethylene particles.^{50, 51}

Genetic Contribution to Osteolysis

The clinical variation seen in the osteolytic response to implant wear suggests a possible genetic contribution. In most diseases of multi-factorial origin, both environmental and genetic factors contribute to disease susceptibility. The heritable component arises from the interaction of multiple minor DNA sequence variations that occur with a stable frequency within the population. These variations can result in subtle changes in gene function, giving rise to altered susceptibility or severity for that disease. The most common form of these DNA sequence

variations consists of single letter changes in the genetic code for a gene, termed single nucleotide polymorphism (SNPs). The human genome contains approximately 10 million SNPs. Little is known about the role that this genetic variability may play in the development of periprosthetic osteolysis.

The genes encoding many of the cytokines implicated in osteolysis contain SNPs that are associated with other osteolytic diseases including osteoporosis, periodontitis, and inflammatory arthritis. Recent data suggest that some of these SNPs also correlate with osteolysis after joint replacement.

Wilkinson *et al.*⁵² reported an association between the SNP at the -238 position in the TNF gene promoter and osteolysis after THA, based on the comparison of carriage of rare alleles in 481 subjects (214 failed versus 267 radiologically intact implants) following cemented THA. Independent of other known risk factors for osteolysis, the carriage rate of -238A in the osteolysis group was approximately twice that of the THA controls and the local background population (odds ratio 1.7). Carriage was highest in patients with osteolysis affecting both the pelvis and the femur (odds ratio 2.1). A subsequent functional analysis using a luciferase reporter gene assay suggested that the -238A allele resulted in increased TNF gene activation compared to the (more common) -238G allele, in response to stimulation with polyethylene particles. Subsequent studies have also implicated the genetic variability within the IL-1 gene cluster in the development of osteolysis. Interleukin 1 receptor antagonist (IL-1RA) is an anti-inflammatory soluble peptide which blocks the activity of IL-1 α and IL-1 β . Patients carrying the IL-1RA +2018T allele variant are less likely to have osteolysis (odds ratio 0.6).

In vitro evidence suggests that wear debris can alter osteoblast and osteoprogenitor cell function and increase osteoclast activity, resulting in decreased bone matrix production and osteolysis. The gene FRZB encodes Secreted Frizzled-Related Protein 3, which plays a role in Wnt regulation of MSC osteogenic differentiation. A study performed on 268 patients with osteolysis versus 341 non-osteolysis THA controls demonstrated that the carriage of the FRZB200T allele (that results in substitution of the amino acid arginine for tryptophan) was negatively associated with osteolysis (odds ratio 0.62), but positively associated with the development of heterotopic ossification after THA.⁵³ This study suggests that allelic variants of genes associated with bone formation pathways may have a role in modulating the risk of osteolysis and heterotopic ossification after THA.

Future Directions for Research

Continuing research on the biological effects and mechanisms of action of wear particles will provide a rational basis for the development of novel, effective preventative and therapeutic strategies for wear-induced inflammatory bone loss. Specifically, pharmacologic therapies that block the production of cytokines and inhibit the accumulation and activities of inflammatory cells at the interfacial membrane represent attractive targets.⁵⁴ TNF-alpha inhibition has been found to reduce wear debris-induced osteolysis via gene therapy and etanercept, a TNF-alpha receptor fusion protein.^{55, 56} Given the likely involvement of MSCs as an osteoprogenitor cell type capable of new bone formation, future therapeutic developments should also focus on reagents and treatments that will enhance MSC viability, proliferation, and osteogenic activity, as a means of optimizing bone quality.

Genetic variation as well as other patient factors, environmental factors, implant factors, and surgical factors all contribute to a patient's risk of osteolysis. However, candidate gene approaches such as those used above require replication in independent cohorts to be considered robust. With the completion of the human genome sequence and data from the HapMap project, new methods of probing the genetic contribution to osteolysis are available.

Genome wide array analysis will allow a more complete understanding of genetic risk factors and their relevance in osteolysis.

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Biological Reactions to Wear Particles

Figure 1.

Biologic reactions between wear debris and host cells. IL = interleukin, MCP = monocyte chemoattractant protein, M-CSF = macrophage colony-stimulating factor, MIP = macrophage inflammatory protein, NFκB = nuclear factor κB, RANKL = receptor activator of nuclear factor κB ligand, TLR = toll-like receptor, TNF = tumor necrosis factor

Figure 2.

Interaction between antigen-presenting cells (APC) and T cells. CTLA = cytotoxic T-lymphocyte antigen, ICAM = intercellular adhesion molecule, IFN = interferon, IL = interleukin, LFA = lymphocyte function-associated antigen, MHC = major histocompatibility index, TCR = T-cell receptor, TNF = tumor necrosis factor