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The Cellular and Molecular Biology of Periprosthetic Osteolysis

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The generation of prosthetic implant wear after total joint arthroplasty is recognized as the major initiating event in development of periprosthetic osteolysis and aseptic loosening, the leading complication of this otherwise successful surgical procedure. We review current concepts of how wear debris causes osteolysis, and report ideas for prevention and treatment. Wear debris primarily targets macrophages and osteoclast precursor cells, although osteoblasts, fibroblasts, and lymphocytes also may be involved. Molecular responses include activation of MAP kinase pathways, transcription factors (including NFκB), and suppressors of cytokine signaling. This results in up-regulation of proinflammatory signaling and inhibition of the protective actions of antiosteoclastogenic cytokines such as interferon gamma. Strategies to reduce osteolysis by choosing bearing surface materials with reduced wear properties should be balanced by awareness that reducing particle size may increase biologic activity. There are no approved treatments for osteolysis despite the promise of therapeutic agents against proinflammatory mediators (such as tumor necrosis factor) and osteoclasts (bisphosphonates and molecules blocking receptor activator of NFkappaB ligand [RANKL] signaling) shown in animal models. Considerable efforts are underway to develop such therapies, to identify novel targets for therapeutic intervention, and to develop effective outcome measures.

Periprosthetic osteolysis is the leading complication of a total joint arthroplasty, a surgical procedure so successful that more than 1 million are performed each year.[46] However, periprosthetic osteolysis and subsequent aseptic loosening ultimately develop in approximately 20% of patients,[2] and in younger patients failure rates of 13% for the femoral component and 34% for the acetabular component have been reported.[59] Prosthetic wear is thought to play a central role in the initiation and development of osteolysis. Higher wear rates are seen in patients with osteolysis compared with control subjects who show no osteolysis.[28,142] An enormous amount of wear particles are associated with the periprosthetic interfacial membrane removed during revision surgery.[51,73,105] Particulate debris induced osteolysis in various animal models[76,77,106,111,137,146,152] and inflammatory responses in cultured macrophages.[9,55,70,76,82,145] These findings suggest wear debris is one of the most important underlying causes of periprosthetic osteolysis. Involvement of other potential contributors to osteolysis and aseptic loosening, such as fluid pressure,[4,5,122] are beyond the scope of this review, and are not discussed.

Wear debris may be generated from various prosthesis components (eg, polyethylene, metal, and ceramic) and bone cement.[102] The choice of prosthesis and bearing surface profoundly affects the composition, size, and shape of generated particles. Each influences cellular responses, therefore implant design may have a substantial impact on the potential for development of osteolysis. Because osteolysis is a progressive disease, clinical results with newer implant designs and bearing surfaces have not been fully determined. This is of special interest for younger patients in whom prostheses ideally would function for 50 years or more.

We summarize the current knowledge regarding how wear debris participates in the development of osteolysis. We consider the various possible cellular targets of particulate wear debris, and the molecular consequences of these cell-particle interactions. We emphasize two novel features, namely the critical importance of reevaluating the proposed role of proinflammatory cytokine signaling in osteolysis and the unparalleled value of magnetic resonance imaging (MRI) in the detection and characterization

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of osteolysis. We also consider how research in the cellular and molecular pathogenesis of osteolysis is used to identify molecular candidates for treating patients.

MATERIALS AND METHODS

We performed Medline searches for the terms "periprosthetic osteolysis" and "wear debris" to identify relevant literature. These searches identified 317 and 416 references, respectively. Articles addressing wear debris in osteolysis of the hip, animal models of osteolysis, and in vitro models of particle action were selected for further review. We then manually reviewed the references listed in selected articles.

The Cell Biology of Osteolysis

Multiple cell types have been implicated in the development of periprosthetic osteolysis in response to wear debris, suggestive of a complex network of cellular pathogenesis (Fig 1). We consider these various cell types individually, but interplay between them ultimately determines the cell biologic response to wear debris.

Macrophages

There is considerable evidence the most important cellular target of wear debris is the macrophage. The interfacial membrane of patients with osteolysis shows extensive macrophage infiltration,[143] and the presence of particles in these cells suggests active phagocytosis.[105] In vitro, cultured macrophage lineage cells and cell lines can recapitulate this phagocytosis of wear particles,[9,82,147,149] which is accompanied by the induction of proinflammatory mediators such as prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and the pleitropic cytokine, IL-6.[9,55,70,76,82,145] The specific nature of this response depends on numerous parameters including the composition,[47,109,113] size,[43,149] shape,[151] volume, and surface area[113] of the particulate debris. Expression and secretion of matrix metalloproteinases also are elevated in macrophages exposed to wear debris in vitro.[80] Elevated levels of these and other proteases have been detected in periprosthetic tissues from patients with osteolysis,[60,125] suggesting elevated extracellular matrix levels of proteases could contribute to tissue destruction.

Animal models of osteolysis support a role for macrophages in response to particulate wear debris. For example, implantation of polyethylene in rabbit tibiae induced a foreign-body giant-cell reaction,[39] and tissue surrounding loose rabbit tibial prostheses generated elevated levels of PGE2 compared with the tissue around stable prostheses.[38] Likewise, periprosthetic cells from a canine osteolysis model produced elevated levels of proinflammatory mediators, including PGE2 and IL-1.[118] Rat models of osteolysis using particulate polymethylmethacrylate (PMMA) or ceramic powder introduced into an air pouch,[35,79] or polyethylene particles together with a tibial polyethylene implant,[77] also resulted in inflammatory reactions. In mice, implantation of metal, polyethylene, and PMMA bone cement particulate debris

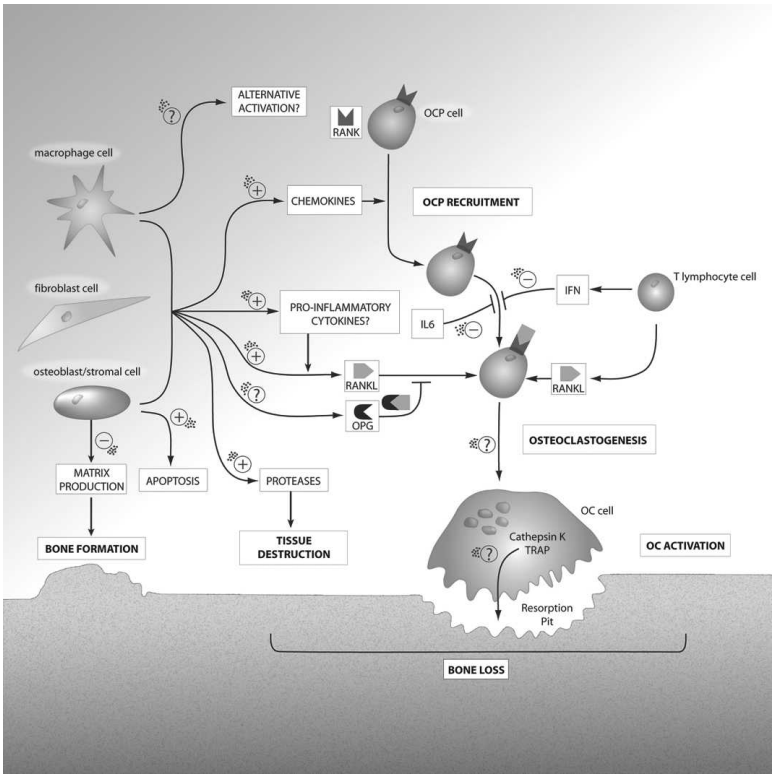

Fig 1. Osteoclast precursor cells (OCP) recruited to the periprosthetic tissues differentiate into functional osteoclasts (OC), which resorb bone by generation of a resorption pit into which enzymes such as Cathepsin K, tartrate-resistant acid phosphatase (TRAP) and carbonic anhydrase II (CAII) are secreted. Osteoclast maturation and activation are mediated by interaction of RANKL with the OCP receptor RANK. Osteoprotegerin (OPG), a soluble decoy receptor for RANKL, inhibits this pathway, as does the T lymphocyte cytokine, interferon gamma (IFN). Positive (+) and negative (–) effects of wear particles on key aspects of this complex regulatory system are shown, as are important steps where possible particles involvement have yet to be established (?).

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in subcutaneously generated air pouches induced macrophage infiltration and production of proinflammatory cytokines,[146] as did direct application of PMMA or titanium particles to the exposed calvarium[76,106] or around tibial implants.[137]

Results from tissue-retrieval in vitro and animal model studies forged a model for wear debris osteolysis in which the critical initiating event is a proinflammatory response of macrophages to particulate debris, which then leads to excessive recruitment, generation, and activation of osteoclasts. Powerful supportive evidence for involvement of proinflammatory cytokine signaling in mouse models of osteolysis includes the observations that gene therapy with the antiinflammatory cytokines IL-1Ra or viral IL-10 protects mice from the inflammatory response to polyethylene particles[150] and ameliorates wear debris-induced osteolysis of bone fragments introduced into the air pouch.[152] In addition, inhibiting TNF-α action by deletion of the genes encoding TNF receptors,[76,108] or by treatment with etanercept, a TNF antagonist consisting of the extracellular region of human p75 TNF-α receptor fused to the Fc portion of human immunoglobulin G1 (IgG1),[19] reduces PMMA and titanium particle-induced inflammation and osteolysis. The calvarial model also has been used to show that the antiinflammatory cytokine viral interleukin-(IL)10 can suppress titanium wear debris-induced osteolysis,[15] and to identify a role for COX2.[158]

However, direct evidence for similar involvement of proinflammatory cytokines in humans is far from conclusive. For example, although some reported elevated levels of TNF-α in periprosthetic tissues and joint synovial fluid of patients with osteolysis,[17,84,120] others found these as lower than in control subjects or as undetectable.[101,112] There is no evidence in favor of elevated levels of TNF-α in the serum of patients with osteolysis.[32,41,50] Measurements of TNF-α mRNA levels also are inconclusive.[48,57,121] Messenger ribonucleic acid (mRNA) has been detected in periprosthetic tissues of patients with osteolysis, but the suggestion that it is elevated in these tissues is compromised by the use of nonquantitative methods for detection which are poorly suited to the quantitative measurement of transcript levels.[48,57,121] Immunohistochemistry and in situ hybridization approaches tend to support the presence of elevated levels of TNF-α-expressing cells in periprosthetic tissues from patients with osteolysis.[40,120,148] These techniques are semiquantitative at best and cannot be reliably be translated into quantitative measurements of the levels of TNF-α protein and mRNA in tissues. The data for TNF-α expression in patients with osteolysis are inconclusive. One possibility consistent with the importance of TNF in the murine model of osteolysis is that human TNF is involved in the early stages of pathogenesis, but not in the end stages of disease progression. Careful resolution of this issue is important to better understand osteolysis and loosening and for the rational design and choice of treatments. A pilot study failed to detect any beneficial effects of TNF blockade with etanercept on progression of osteolysis in patients with established disease, although this study was not powered to meaningfully evaluate drug efficacy.[107] Approximately 166 patients were required for a suitably powered trial.[107] It might be prudent to carefully revisit the measurement of TNF levels in such patients before starting such a trial.

Osteoclasts

Osteoclasts (OCs) are multinucleated cells derived from circulating osteoclast precursor cells (OCPs) of the monocyte/macrophage lineage, and represent the only cell type capable of bone resorption.[13] When considering the causes of excessive bone resorption in patients with osteolysis, it is important to consider recruitment of OCPs from the blood and generation of functional OCs from these OCPs in the periprosthetic space. Increased recruitment of OCPs to the periprosthetic tissues of patients with osteolysis is implied by the observation that pseudomembrane macrophage lineage cells isolated from these patients display a greatly increased propensity to differentiate to OCs (relative to analogous cell populations from patients with osteoarthritis).[99] Chemokines (the principal mediators of hematopoietic cell recruitment to tissues) such as MCP-1 and MIP-1-α are expressed in the periprosthetic tissues of patients with osteolysis.[49,81] CCR1, a receptor for MIP-1-α is expressed in OCs and their precursors,[155] and MIP-1-α increases OC motility. Another chemokine, IL-8, has also been implicated in aseptic loosening.[57,65,112,127] Expression of chemokines in cultured macrophages and fibroblasts (which are also abundant in periprosthetic tissues) is increased by exposure to PMMA and titanium wear particles.[81,154] Thus, wear debris probably increases OCP recruitment to periprosthetic tissues via activation of chemokine expression by macrophages and fibroblasts.

The effects of wear debris on generation of functional OCs from these OCPs in the periprosthetic space are more complicated, involving direct actions of particles on OCPs and effects secondary to perturbations in the cytokine milieu by particles action on macrophages and other cell types in the periprosthetic region.[96,108] Direct effects include antiosteoclastogenic interferon gamma signaling in OCPs being potently inhibited by titanium wear debris.[96] Signaling by IL6, which also can suppress differentiation of OCPs, is suppressed by titanium and PMMA bone cement.[96]

Investigations of indirect effects of wear debris on osteoclastogenesis have focused mainly on the well-known bone proresorptive actions of cytokines such as TNF-α and IL1, which have been identified as key mediators in mouse models of osteolysis.[19,30,152] Overexpression of TNF-α is sufficient to induce calvarial osteolysis even in the absence of added particles, emphasizing its proresorptive characteristics in mice.[108] However, it is unclear whether these inflammatory cytokines are elevated in end-stage osteolysis, suggesting other mechanisms may be at work. The most important candidates are RANKL, receptor activator of NFkB (RANK), and osteoprotegerin (OPG). Receptor activator of NFkB ligand is the key cytokine regulator of osteoclast generation and activation. Receptor activator of NFkB ligand binds to RANK expressed on the surface of OCs and OCPs,[54] and is necessary for the differentiation of OCPs to mature, functional OCs in the presence of the survival factor MCSF.[83,93] Osteoprotegerin is a naturally occurring decoy receptor for RANKL functions to down-regulate osteoclastogenesis by binding RANKL, thus preventing its interaction with RANK.[115] The RANKL/OPG ratio is a critical parameter in the regulation of bone resorption, and has been correlated with various bone disorders.[52] Although RANKL/OPG ratios have yet to

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be correlated with osteolysis, there are reasons to suspect bone loss may be mediated by elevated RANKL/OPG. First, some reports have identified elevated RANKL expression in the interfacial membranes from patients with osteolysis, with expression localized to the abundant macrophages, giant cells, and fibroblasts in these tissues.[34,48,53,72,94] Because macrophage lineage cells generally are thought not to express RANKL under normal conditions, expression of RANKL in such cells presumably reflects up-regulation by wear debris. Second, RANKL blockade with OPG[36,128] or RANK:Fc (a RANKL antagonist consisting of the extracellular region of RANK fused to the Fc portion of human IgG1),[20] or by using mice genetically deficient in RANK[20] prevented wear debris-induced osteolysis in the murine calvarial model. Third, metallic and polyethylene wear debris can increase the RANKL/OPG ratio in murine calvarial tissues,[74] and expression of RANKL by cultured osteoblasts[88] and fibroblasts.[138] Titanium-treated fibroblasts, and also fibroblasts isolated from arthroplasty membranes of patients with osteolysis (which presumably had been exposed to wear debris in vivo), can support differentiation of OCPs to OCs.[100,138]

These observations suggest particulate debris may induce osteoclast generation and activation by modulation of the RANKL/OPG ratio. This most likely involves direct effects of particles on cells in the periprosthetic tissue and indirect effects mediated by particle-mediated perturbations of cytokines, which can modulate RANKL/OPG ratios.[52]

Osteoblasts

Under normal conditions, resorption and formation balance each other to allow bone remodeling and homeostasis. It is important to consider whether, in addition to promoting osteoclast activity, wear debris might also contribute to osteolysis through inhibiting bone formation. Insufficient attention has been paid to the possible involvement in osteolysis of osteoblasts (OBs), the cell type responsible for bone formation. Research has been limited to in vitro models of cell-particle interactions. Polyethylene and metal particles can be phagocytosed by OBs.[68] Metallic and polymeric particles decrease expression of collagen Types I and III by OBs,[129,130,153] and polyethylene also decreases osteoblast matrix production.[25,26] In addition, titanium has been reported to reduce OB viability by inducing apoptosis,[89] and PMMA bone cement reduces OB proliferation.[156] Different particle types can differentially affect OB proliferation and activity.[67] There is also evidence that differentiation of OBs from mesenchymal stem cells is down-regulated by titanium particles,[135] and that titanium and zirconium oxide induce mesenchymal stem cell apoptosis;[136] suggesting wear debris might inhibit OB formation and function. These in vitro findings require in vivo testing to delineate the potentially critical role of osteoblasts in disease development.

Lymphocytes

Renewed interest in metal-on-metal prostheses has reinvigorated the debate surrounding the involvement of metal hypersensitivity in osteolysis. Despite the reduced wear of these second-generation devices, implant failure is associated with lymphocytic infiltrations indicative of hypersensitivity reactions.[24,144] Metal-specific lymphocyte responses can be correlated with poor implant performance.[44] T lymphocytes are key regulators of bone homeostasis because of their ability to generate proosteoclastogenic (ie, RANKL) and antiosteoclastogenic (ie, interferon gamma) cytokines during activation, and are critically involved in the RANKL-dependent bone loss observed in inflammatory bone erosion diseases such as rheumatoid arthritis.[42,61,62] However, involvement of T cells in periprosthetic osteolysis has been controversial. Although some earlier studies of the cellularity of periprosthetic tissues retrieved from patients with osteolysis during revision surgery suggest the presence of a substantial amount of activated T cells,[3,31] others discount this possibility, finding only unactivated or low amounts of T cells.[6,66] The presence of Th1 and Th2 cytokines in the periprosthetic tissues has been reported,[3] and others report no involvement.[6,66] In animal studies, mice with lymphocyte deficiencies retain the ability to form granulomas[37,58] and develop osteolysis[126] in response to wear debris, suggesting lymphocytes are not causally involved in these processes. However, mice with lymphocyte deficiencies fail to mount an inflammatory response to polyethylene particles injected into the knee,[103] and titanium particles induce larger sutures in athymic mice than wild type controls when applied to exposed calvaria.[18] More studies are needed to definitively define the role of lymphocytic reactions in periprosthetic osteolysis.

The Molecular Biology of Osteolysis

Little is known about the molecular signaling pathways that underpin the perturbations in expression of factors such as cytokines, chemokines, and proteases seen in the interfacial membranes of patients with osteolysis. However, in vitro experiments have started to unravel the nature of these wear debris-activated signaling pathways, setting the stage for focused in vivo experiments to identify potential novel drug targets.

The most notable transcription factor implicated in wear debris action is NFkB. Mice lacking NFkB are osteopetrotic, resulting from an inability to generate functional osteoclasts.[33,56] Titanium and PMMA wear debris can activate NFkB in cultured macrophages,[82] OCPs,[22] and the J774 murine macrophage cell line,[108] and inhibition of NFkB blocks PMMA induction of osteoclastogenesis in vitro[22] and polyethylene induction of osteolysis in mice.[97] Supporting in vivo evidence for a role of NFkB in osteolysis comes from observations that deficiency of NFkB1 in mice protects against titanium-induced calvarial osteolysis.[108] Other transcription factors, such as NF-IL6[82] and AP-1,[78] become activated after titanium treatment of macrophages. However, the relevance of these factors in osteolysis remains unclear.

The three major MAP kinase subgroups (p38, ERK, and JNK) also are involved in macrophage responses to wear debris in vitro.[1,82,96] Titanium and PMMA can induce rapid activation of these MAP kinase family members, and inhibition of MAP kinase activation reduces the ability of these particles to induce proinflammatory cytokine induction in cultured OCPs,[96] suggesting MAP kinases are critical transducers of the signals emanating from particle-cell interaction to the nucleus. p38 MAP kinase (but neither ERK nor JNK MAP kinases) activity is also essential for PMMA-mediated down-regulation of IL-6 signaling.[96] p38 inhibition protects against inflammatory bone destruc-

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tion in vivo, suggesting this might represent a valid target for therapies.[75] In addition, MAP kinases mediate the ability of PMMA and titanium wear debris to induce expression of SOCS3, a suppressor of antiosteoclastogenic cytokine signaling.[96]

Little is known about the molecular basis of wear debris interaction with the surfaces of cells. There is evidence polyethylene activates complement,[27] which argues in favor of a role for macrophage complement receptors (eg, CR3) in particle uptake. CR3 expressing phagocytes have been detected in granulomatous lesions associated with total hip arthroplasty.[104] Involvement of CR3 in particle action also is supported by the observation that antibodies against CR3 reduce macrophage uptake of titanium[82] and PMMA particles, and that CR3 expression in nonphagocytic cells enhances interactions with PMMA particles.[95] Scavenger receptors, such as MARCO, are involved in opsonin-independent uptake of titanium particles by alveolar macrophages,[86] suggesting different particles may use different surface receptors. Opsonization is not essential (although it may be involved) in responses of human monocytes and macrophage cell lines to titanium.[71,87] In addition, the scavenger receptor antagonist polyinosinic acid reduces phagocytosis of titanium particles by macrophages, and heterologous expression of scavenger receptor enhances the ability of cells to bind titanium particles.[95]

Current and Future Treatment Possibilities

Classification of osteolysis as an inflammatory bone erosion disease has resulted in two main treatment approaches; antiinflammatory agents and suppressors of bone resorption. Antiinflammatory agents have proved effective for treatment of osteolysis in animal models. Etanercept[19] and pentoxifylline,[106] TNF antagonists that operate as a decoy receptor and an inhibitor of secretion, respectively, diminish particle-induced osteolysis in the murine calvarial model, as does the COX2 inhibitor, celecoxib.[158] However, despite these encouraging animal studies, it is not known how well these antiinflammatory agents may perform in the prevention or treatment of human osteolysis. Orally administered pentoxifylline reduces the inflammatory response of isolated monocytes to wear debris in healthy subjects,[90] but has not been tested in patients with osteolysis. A small trial of etanercept[107] used in patients with osteolysis proved inconclusive. Because it remains uncertain whether TNF-α and other proinflammatory cytokines are elevated in end-stage osteolysis periprosthetic tissues, they may not be useful for treating patients with established disease.

Bisphosphonates induce OC apoptosis by blocking the mevalonate pathway of isoprenoid biosynthesis, and have been widely used as antiresorptive agents (eg, treating osteoporosis).[11] Given that excessive osteoclast activity represents the cellular end point of osteolysis, bisphosphonates have been considered as possible therapeutic agents. Animal model studies have been encouraging. Alendronate inhibited wear debris-induced osteolysis in a rat loaded tibial implant model of osteolysis[77] and in a similar canine model.[111] It was also effective in preventing osteolysis in the murine calvarial model.[106] A single dose of zoledronic acid administered directly after surgery also suppressed particle-induced osteolysis in mouse calvaria.[133] Because statins, as HMGCoA reductase inhibitors, also target the mevalonate pathway, they have been considered as possible drugs for osteolysis. Simvastatin prevents wear debris-induced osteolysis in the murine calvarial model.[132] However, despite promising results in animal models, there is no clinical evidence supporting the effectiveness of bisphosphonates in treating patients with osteolysis. High local levels of TNF may protect OCs from bisphosphonate-induced apoptosis,[157] which may be of relevance to possible use of these drugs in osteolysis. Despite these findings, there is evidence bisphosphonate treatment shortly after total hip arthroplasty may transiently decrease postoperative bone loss, possibly contributing to the prevention or delay of osteolysis. For example, one dose of pamidronate reduced postoperative bone loss at 6 months.[141] However, this effect was lost by 2 years postoperatively. It is not known whether additional doses or oral therapy would maintain the beneficial effects of the initial dose of pamidronate. As summarized in a metaanalysis,[8] additional studies using clinically relevant outcome measures are needed to definitively assess whether short-term decreases in bone loss by bisphosphonates translate into long-term benefits after total hip arthroplasty.

The central role of RANKL in osteoclastogenesis makes this cytokine an attractive target for possible therapies. Osteoprotegerin and RANK-Fc, which reduces RANKL levels, have been used successfully to prevent osteolysis in animal models.[20,36,128] AMGN-0007, a recombinant form of OPG, was well-tolerated and effective in clinical trials in patients with multiple myeloma or breast cancer with bone metastases.[10] In addition, rationally designed of OPG-like peptidomimetics antagonized RANKL signaling and bone loss in a murine model of osteoporosis,[16] and small molecule activators of OPG gene expression also inhibited bone resorption in rodents.[85] However, observations that OPG may bind TNF-related apoptosis-inducing ligand (TRAIL) in addition to RANKL, and thus act as a cancer cell survival factor,[114] have raised questions whether OPG-based drugs may have undesirable side effects. Clinical trials with a monoclonal antibody against RANKL (AMG-162) showed safety and antiresorptive activity,[7,124] but this new agent has yet to be assessed in patients with osteolysis. Such treatments would be expected to decrease bone loss, but not reduce inflammation (as seen in OPG treatment of rat adjuvant arthritis).[61] An alternative approach would be combined therapy with antagonists against RANKL and proinflammatory mediators. Such an approach proved successful in an arthritis model.[160] Because RANK signaling is transduced via NFkB, antagonists against this transcription factor may be effective treatments for osteolysis. Direct inhibition of NFkB with the NEMO-binding domain (NBD) peptide is reported to prevent bone loss in patients with inflammatory bone erosion.[23] In addition, inhibition of NFkB with the macrolide antibiotic erythromycin blocks osteolysis in the murine air pouch model.[98] However, because persistent inhibition of NFkB could result in immune deficiency or cell death, such treatments should be approached with caution.

Inhibitors of mature OC function are another possible class of therapeutic agents yet to be evaluated in patients with osteolysis. As more becomes known of the molecular details of osteoclast biology and particle action, additional targets for drug design

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should become available. For instance, there are inhibitors for cathepsin K (an OC-specific protease),[12,64] the osteoclast ATPase proton pump,[131] vitronectin receptor,[45,63] and src tyrosine kinase,[110] all of which are required for resorption. All sustained, systemic therapies targeting OCs have a common concern—perturbation of normal bone remodeling activity through relentless OC repression may adversely affect the mechanical quality of bone and fracture healing. This concern applies to all the putative osteolysis therapies as none involve local administration to the osteolysis site. However, oral administration of alendronate for osteoporosis in postmenopausal women for more than 10 years has been reported to result in no loss of benefit,[11] suggesting such OC inhibitors remain viable therapies for localized periprosthetic osteolysis.

Perhaps the biggest impediment to the development of treatment strategies for osteolysis is the lack of an accepted outcome measure. Conventional imaging techniques used to localize, quantify, and monitor the progression of particle disease face unique challenges. As bone loss surrounding arthroplasties is often asymptomatic, clinicians frequently recommend routine radiographic imaging. However, joint anatomy may be quite complex (particularly in the pelvis), rendering difficulty in obtaining accurate, reproducible information regarding three-dimensional segments of bone loss from two-dimensional radiographs. Modified oblique views have been reported to increase the recognition of osteolysis.[117,159] Radiographs can fail to detect lesions or grossly underestimate the extent of segmental bone loss.[14,123] There is also poor interobserver reliability in characterizing pelvic bone loss on standardized radiographs.[29] Although CT with protocol modification can more precisely quantify osteolysis,[21,69,92] techniques that result in diminished beam-hardening artifact require increased radiation doses and radiographic exposure.[140] Although more accurate than conventional radiographs, CT presents a cumulative radiation burden to the patient, particularly when serial examinations may be necessary before revision.

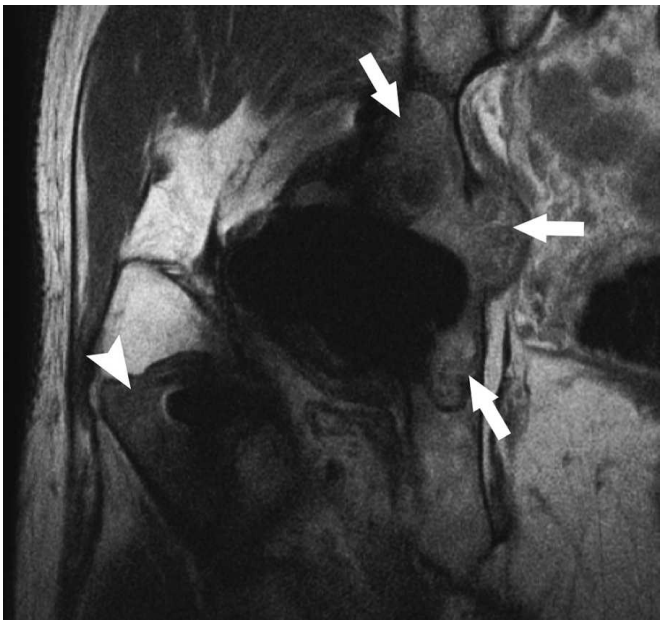

Fig 2. A coronal fast-spin echo MR image through the posterior column of the right hip in a 52-year-old man 17 years after primary arthroplasty shows severe periacetabular osteolysis, manifested as intermediate signal intensity material (arrows) replacing the normally high signal intensity of the fat in the marrow. There also is involvement of the proximal femur (arrowhead).

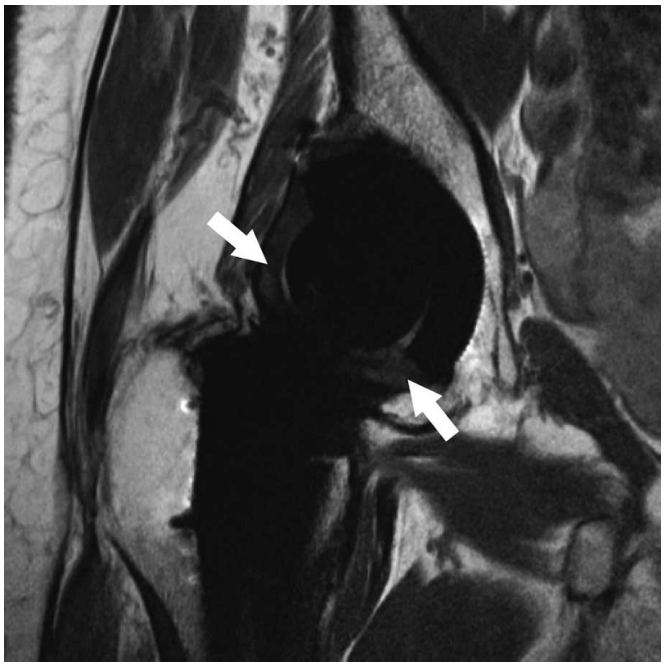

Fig 3. A coronal fast-spin echo MR image of the right hip in an 81-year-old patient 16 years after arthroplasty shows intermediate signal intensity debris (arrows) in the absence of discernible osteolysis, consistent with a moderate intracapsular burden of particle disease.

Given its lack of ionizing radiation, multiplanar capabilities, and superior soft tissue contrast, MRI would intuitively be well suited in assessing this process. Traditional techniques are limited by the presence of the artifact generated by the metallic components. The intensity of the artifact generated by the arthroplasty is a function of several factors, including the degree of relative ferromagnetism of the metallic components, their orientation relative to the static magnetic field, and their geometry. The clinical utility and safety of MRI of an arthroplasty has been shown in clinical series using minor pulse sequence modifications of commercially available software (Fig 2).[116,119] Magnetic resonance imaging is superior in locating and quantifying areas of periacetabular bone loss compared with conventional radiographs.[91] Magnetic resonance imaging may disclose the burden of intracapsular synovial disease that precedes osteoclastic bone resorption (Fig 3).[91] A clinical study showed these techniques are safe with appropriate imaging protocol modifications and consistent observation of the soft tissue envelope (including intracapsular synovial deposits).[91]

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These techniques must be validated before being applicable to a prospective study cohort. Inspecting the joint at the time of revision surgery is often an imperfect standard for judging the accuracy of imaging in determining the location and total volume of bone loss. In a cadaveric pelvic model to compare the ability of optimized radiographs and MRI to locate and quantify simulated osteolytic lesions, MRI was 95% sensitive with a specificity of 98% and an accuracy of 96%, and lesion detection was not dependent on lesion location.[139]

In a comparative nonclinical model of modified MRI, optimized plain radiographs and optimized CT, MRI was the most sensitive technique in detecting osteolytic lesions, with a sensitivity of 95%, compared with 75% for CT and 52% for radiographs.[134] Magnetic resonance imaging was the most effective tool for detecting small periacetabular osteolytic lesions less than 3 cm.[134] These newly available MRI techniques provide an effective means to prospectively assess the synovial and intraosseous burden of particle disease, thus serving as a means by which to noninvasively monitor disease progression. This improved sensitivity in the detection of osteolysis will facilitate preoperative planning for revision arthroplasty, and provide a critical outcome measure for serial evaluation of clinical trials of treatments.

DISCUSSION

Despite the prevalence of periprosthetic osteolysis, which eventually afflicts a sizeable proportion of patients who have total joint replacements, there are no approved medical therapies for this condition. This relates primarily to a lack of full understanding of the molecular and cellular pathogenesis of end-stage osteolysis. Elucidation of the responsible molecular and cellular pathways is critical to the rational identification of treatment strategies for the devastating disease. We have summarized progress on these questions and identified areas where information is lacking.

One of the most important problems is relating the extensive body of literature on wear debris actions in vitro and animal models of osteolysis to the realities of the human disease. For example, despite the prominent involvement of proinflammatory cytokines in models of osteolysis, the evidence that these are similarly pivotal in patients with end-stage osteolysis has not been firmly established. More extensive patient-oriented molecular and cellular pathogenesis studies are essential to resolve such discrepancies. Rapid advances have been seen in the development of therapeutic agents targeting osteoclasts. Meaningful clinical trials of such therapies are needed in patients with osteolysis. Critical to the success of such trials will be additional refinement of outcome measures for evaluation of disease progression. Recent advances in adaptation of imaging techniques such as MRI and CT have shown promise in more accurate monitoring of osteolytic lesions. Equally valuable would be the identification of serum markers for disease progression.

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