The Central Role of Wear Debris in Periprosthetic Osteolysis

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Abstract Periprosthetic osteolysis remains the leading complication of total hip arthroplasty, often resulting in aseptic loosening of the implant, and a requirement for revision surgery. Wear-generated particulate debris is the main cause of initiating this destructive process. The purpose of this article is to review recent advances in our understanding of how wear debris causes osteolysis, and emergent strategies for the avoidance and treatment of this disease. The most important cellular target for wear debris is the macrophage, which responds to particle challenge in two distinct ways, both of which contribute to increased bone resorption. First, it is well known that wear debris activates proinflammatory signaling, which leads to increased osteoclast recruitment and activation. More recently, it has been established that wear also inhibits the protective actions of antiosteoclastogenic cytokines such as interferon gamma, thus promoting differentiation of macrophages to bone-resorbing osteoclasts. Osteoblasts, fibroblasts, and possibly lymphocytes may also be involved in responses to wear. At a molecular level, wear particles activate MAP kinase cascades, NF κ B and other transcription factors, and induce expression of suppressors of cytokine signaling. Strategies to reduce osteolysis by choosing bearing surface materials with reduced wear properties (such as metal-on-metal) should be balanced by awareness that reducing particle size may increase biological activity. Finally, although therapeutic agents against proinflammatory mediators [such as tumor necrosis factor (TNF)] and osteoclasts (bisphosphonates and molecules blocking RANKL signaling) have shown promise in animal models, no approved treatments are yet available to osteolysis

patients. Considerable efforts are underway to develop such therapies, and to identify novel targets for therapeutic intervention.

Key words aseptic loosening · periprosthetic osteolysis · wear debris

Introduction

The generation of prosthetic implant wear in total joint arthroplasty patients is widely recognized as the major initiating event in development of periprosthetic osteolysis and aseptic loosening, which is the leading complication of this otherwise remarkably successful surgical procedure [1]. Evidence in support of this includes the observations that osteolysis is correlated with higher wear rates [2] and that vast numbers of wear particles are found associated with the periprosthetic interfacial membrane removed during revision surgery [3–5]. Furthermore, experimental systems have demonstrated that particulate debris can induce osteolysis in a variety of animal models [6–12], and inflammatory responses in cultured macrophages [8, 13–17]. Taken together, and notwithstanding evidence for some involvement of other factors—such as fluid pressure [18] and adherent endotoxin [19], which lie beyond the scope of this review—these findings clearly demonstrate that wear debris represents the single most important underlying cause of periprosthetic osteolysis.

Wear debris can be generated in a variety of ways, and may include particles from all the various components of the prosthesis (such as polyethylene, metal, and ceramic) as well as bone cement [20]. Since, as discussed below, cellular responses are highly dependent upon the composition, size, and shape of particles, the type of prosthesis and bearing surface used may have a significant impact on the potential for development of osteolysis. In this review, we discuss the current state of knowledge regarding how wear debris participates in the development of osteolysis, paying particular attention to the various possible cellular

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targets of particles and the molecular consequences of these cell–particle interactions. In addition, we identify unanswered questions, and possibly fruitful areas for future research into the molecular pathogenesis of osteolysis that may lead to the identification of candidates for therapeutic intervention.

Cellular targets of wear debris particles

Several different cell types have been implicated in the development of periprosthetic osteolysis in response to wear debris, indicative of a complex network of cellular pathogenesis (see Fig. 1).

Fig. 1. Cellular and molecular regulation of osteoclastogenesis and the influence of wear debris. Osteoclast precursor cells (OCP) are recruited to the periprosthetic tissues and 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 is mediated by interaction of RANKL (which can also exist as a cell surface signaling molecule; not shown for clarity) with the OCP receptor RANK. Osteoprotegerin (OPG), a soluble decoy receptor for RANKL, inhibits this pathway, as does the T lymphocyte cytokine, interferon (IFN) gamma. Various other cell types, including macrophages, fibroblasts, and osteoblasts, can modulate this pathway via production of chemokines and proinflammatory cytokines, and can also contribute directly to tissue destruction and/or formation through expression of proteases and collagens. 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 has yet to be established (?)

Macrophages and the inflammatory response

There is compelling evidence that the most important cellular target of wear debris is the macrophage. Abundant numbers of macrophages can be identified in the interfacial membrane of patients undergoing revision surgery, and the presence of particles within these cells suggests that they are actively phagocytosing these particles [3]. Phagocytosis of wear particles can be reproduced with cultured macrophage lineage cells and cell lines [13, 14, 21, 22], and this is accompanied by the induction of proinflammatory mediators such as tumor necrosis factor (TNF) alpha, IL-1 β , PGE2, and the pleiotropic cytokine IL-6 [8, 13–17]. This suggests that the interfacial membrane macrophages are probably mounting an inflammatory response, and indeed elevated levels of proinflammatory cytokines have been reported in periprosthetic tissues and joint synovial fluid of osteolysis patients [23–26]. However, there is no clear evidence in favor of elevated levels of proinflammatory markers in serum of patients [27–29]. Expression and secretion of matrix metalloproteinases is also elevated in macrophages exposed to wear debris *in vitro* [30], and elevated levels of these and other proteases have been detected in periprosthetic tissues from osteolysis patients [31, 32], suggesting that elevated extracellular matrix levels of proteases could contribute to tissue destruction in osteolysis patients. Although a variety of different types of wear debris have been shown to induce proinflammatory responses, the specific nature of this response is dependent upon numerous parameters, including composition [33, 34], size [21, 35], shape [36], and volume [37]. In addition, responses to wear particles can be modulated by the presence of adherent endotoxin [19, 38, 39], and also by a variety of physical insults such as application of pressure [40, 41] and stretching [42]. This complexity is further compounded by observations that cells from different donors can respond very differently to particles [21, 33]. Taken together, the extensive body of research on *in vitro* cellular responses to wear debris suggests that while an inflammatory response by macrophages is central to the development of periprosthetic osteolysis, the detailed nature of this response will vary based upon several parameters, including prosthetic type, patterns of wear, and host factors.

Animal models of osteolysis support a role for an inflammatory response to a variety of types of particulate wear debris. For example, implantation of particulate debris into rabbit tibia induces a foreign body giant cell reaction [43], and tissue surrounding loose rabbit tibial prostheses generates elevated levels of PGE2 compared to the tissue around well-fixed prostheses [44]. Likewise, periprosthetic cells from a canine osteolysis model produce elevated levels of proinflammatory mediators, including PGE2 and IL-1 [45]. Rat models of osteolysis using particulate matter introduced into an air pouch [46, 47] or together with a tibial polyethylene implant [7] have similarly resulted in inflammatory reactions. These early canine, rabbit, and rat *in vivo* models have, by and large, confirmed the results of *in vitro* cell culture studies, dem-

onstrating that various particle compositions can induce an inflammatory response (and osteolysis).

More recently, three murine models of wear debris-induced osteolysis have been developed, allowing the power of murine knockout and transgenic technologies to be applied to the study of osteolysis *in vivo*. In the first of these three murine models, implantation of metal, polyethylene, and PMMA bone cement particulate debris into subcutaneously generated air pouches all induce macrophage infiltration and production of proinflammatory cytokines [10]. Gene therapy with the anti-inflammatory cytokines IL-1Ra or viral IL-10 protects mice from the inflammatory response to particles [48] and, importantly, also ameliorates wear debris-induced osteolysis of bone fragments introduced into the air pouch [12], suggesting that the inflammatory response to particles contributes to the eventual bone loss characteristic of osteolysis. The second mouse model to gain prominence involves direct application of particulate matter to the exposed calvarium [6, 8]. This calvarial model was extensively used to study the involvement of the key proinflammatory cytokine, TNF-alpha, in particle-induced inflammation and osteolysis. Interestingly, inhibiting TNF alpha action by deletion of the genes encoding TNF receptors [8, 49], or by treatment with Etanercept, a TNF antagonist consisting of the extracellular region of human p75 TNF-alpha receptor fused to the Fc portion of human IgG1 [50], diminishes particle-induced inflammation and osteolysis, providing more evidence for inflammation/TNF-alpha production as essential precursors of bone erosion in osteolysis. The calvarial model was also used to show that the anti-inflammatory cytokine viral IL10 can suppress wear debris-induced osteolysis [51], and to identify a role for COX2 in osteolysis. COX2-deficient mice were significantly protected from calvarial osteolysis induced by titanium particles, whereas Celecoxib, a selective COX2 inhibitor, inhibited PGE2 production, inflammation, and osteolysis in response to particles in wild-type mice [52]. No involvement of COX1 was identified.

The calvarial and air-pouch murine models have proved extremely valuable in the search for key molecules implicated in osteolysis. However, they suffer from a number of features that distinguish them from the analogous situation experienced by osteolysis patients, the most significant being the absence of a loaded implant, and the use of implanted bone slices (air-pouch model) or flat bones (calvarial model) as opposed to long bones with the periosteum removed. In response to these concerns about the appropriateness of these models for some aspects of the human disease, work in the Goodman laboratory [11, 53] and in our own laboratory, has begun on the development of a third class of mouse osteolysis model, in which load-bearing implant are introduced to the long bones, and the effects of particles around the prosthesis are studied. Early results from these models are promising and have confirmed that particles around the implants induce a proinflammatory response in the periprosthetic tissue [11], and that the proinflammatory cytokine IL-1 [53] and the pleiotropic cytokine IL6 (our unpublished data) are involved in this response.

Osteoclast lineage cells

The final cellular consequence of particle action is an excess of osteoclast activity, which results in unchecked bone erosion. How do particles cause this? Osteoclasts (OCs), the only cell type capable of bone resorption, are derived from circulating hematopoietic cells of the monocyte/macrophage lineage. We shall thus consider two ways in which particles might increase OC activity: generation of functional OCs from osteoclast precursor cells (OCPs) within the periprosthetic space and recruitment of OCPs from the blood.

OC generation and activation

As mentioned above, inhibition of the inflammatory response to wear debris alleviates osteolysis in mouse models, suggesting that one important bone loss pathway is secondary to the inflammatory response. This is consistent with known bone proresorptive actions of cytokines such as TNF alpha and IL1, which act—at least in part—directly on osteoclast precursors (OCPs). In addition to their direct actions on osteoclasts and their precursors, proinflammatory cytokines may indirectly promote OC activity, through induction of expression of receptor activator of NFκB ligand (RANKL), the key cytokine regulator of osteoclast generation and activation. RANKL binds to receptor activator of NFκB (RANK) expressed on the surface of OCs and OCPs [54], and is necessary and sufficient for the differentiation of OCPs to mature, functional OCs in the presence of the survival factor MCSF [55, 56]. Osteoprotegerin (OPG), a naturally occurring decoy receptor for RANKL functions to down-regulate osteoclastogenesis by binding RANKL and thus preventing its interaction with RANK [57]. Thus, the RANKL/OPG ratio has emerged as a critical parameter in the regulation of bone resorption, and has been correlated with a variety of bone disorders [58]. Although RANKL/OPG ratios have yet to be correlated with osteolysis, there are compelling reasons to suspect that bone loss in these individuals is mediated by elevated RANKL/OPG. First, RANKL blockade with OPG [59, 60] or RANK:Fc (a RANKL antagonist consisting of the extracellular region of RANK fused to the Fc portion of human IgG1) [61], or by using mice genetically deficient in RANK [61] prevents wear debris-induced osteolysis in the murine calvarial model. Second, wear debris can increase the RANKL/OPG ratio in murine calvarial tissues [62]. Third, several reports have identified elevated RANKL expression in the interfacial membranes from osteolysis patients [63–66]. Our own data also indicate that very low levels of OPG in osteolysis patients may underlie dramatic increases in periprosthetic RANKL/OPG ratios (Koulouvaris and Purdue, unpublished observations). The cellular basis for elevated RANKL expression is complicated by the fact that several different cell types within the periprosthetic tissue are capable of RANKL expression, including osteoblasts, fibroblasts, and T lymphocytes, each of which are considered in the following sections. Remarkably, macrophages and giant cells in the interfacial membranes of osteolysis patients have also been

reported to express RANKL [63–66], despite the fact that macrophage lineage cells are generally thought not to express RANKL under normal conditions. The molecular basis of increased RANKL in osteolysis is likely downstream of proinflammatory cytokines such as TNF alpha and IL1, which are known to increase RANKL expression in several cell types [58].

Taken together, these observations indicate that one likely mechanism whereby particulate debris may induce osteoclast generation and activation is an indirect one, mediated through the actions of proinflammatory mediators that can act on osteoclast precursors and, most importantly, modulate the RANKL/OPG ratio through actions on cells within the periprosthetic tissue. But is this the only way in which wear debris may act upon OCPs? Recent studies in our laboratory question whether, in addition to stimulating inflammatory RANKL expression within periprosthetic tissues, wear debris might also act *directly* upon OCPs, to modulate signaling pathways and responses to cytokines within these cells, and hence impact their differentiation and/or activation [68].

For example, several cytokines have demonstrated antiosteoclastogenic activities, which inhibit the differentiation of OCPs to fully fledged, active osteoclasts. Perhaps the best characterized of these is interferon gamma, which potentially down-regulates RANKL-induced osteoclastogenesis [67]. We have shown that antiosteoclastogenic interferon gamma signaling in OCPs (as characterized by activation of the STAT1 signaling molecule) is potentially inhibited by titanium wear debris [68]. Similar findings show that signaling by IL6, which can also suppress differentiation of OCPs, is also suppressed by titanium and by PMMA bone cement (which has no effect on interferon gamma signaling) [68]. Thus, wear debris may simultaneously act in two ways to promote bone loss: activation of proinflammatory signaling in macrophages, and inhibition of the protective effects of antiosteoclastogenic cytokines in OCPs.

Osteoclast precursor recruitment

Excess osteoclast activity in osteolysis may involve not just generation and activation of OCs in the periprosthetic vicinity, but also recruitment of increased numbers of OCPs to these sites. The existence of increased levels of OCPs in the pseudomembrane of osteolysis patients is implied by the observation that macrophage lineage cells isolated from these tissues display a greatly increased propensity to differentiate to OCs (relative to analogous cell populations from osteoarthritis patients) [69]. The principal mediators of hematopoietic cell recruitment to tissues are chemokines, a large family of chemotactic cytokines, which interact with specific chemokine receptors expressed upon the cell surface of target cells. Expression of the chemokines including MCP-1 and MIP-1-alpha in cultured macrophages is increased by exposure to wear particles [70], and these same proteins are expressed in the periprosthetic tissues of osteolysis patients [70, 71]. MIP-1-alpha is of particular interest here, because

it is reported to increase OC motility, and its receptor, CCR1, is expressed in OCs and their precursors [72]. Another chemokine, IL8, has also been implicated in aseptic loosening [73–75].

Bone formation cells

While most effort has been concentrated on understanding excessive bone resorption in osteolysis patients, less attention has been paid to the possible involvement of defective bone formation. Under normal conditions, resorption and formation balance each other to allow bone remodeling and homeostasis. It is therefore important to consider whether, in addition to promoting osteoclast activity, wear debris might also contribute to osteolysis by inhibiting bone formation. Wear debris particles have been shown to decrease expression of collagen types I and III by osteoblasts (OBs), the cell type responsible for bone formation [76–78]. In addition, titanium has been reported to reduce OB viability by inducing apoptosis [79], and PMMA bone cement reduces OB proliferation [80]. There is also evidence that differentiation of OBs from mesenchymal stem cells is down-regulated by titanium particles [81], and that titanium and zirconium oxide induce mesenchymal stem cell apoptosis [82], suggesting that wear debris might inhibit both OB formation and function.

In addition to modulating bone formation by OBs, particles may also disrupt the contribution of OBs to OC generation and/or recruitment. For instance, expression of RANKL and MCSF by cultured OBs can be induced by low concentrations of wear debris [83], as can expression of proinflammatory mediators such as TNF- α , IL6 and PGE2 [76, 80], which—as discussed above—can subsequently lead to osteoclast activation. In addition, OBs can produce chemokines involved in OCP recruitment, such as MIP-1- α , and this is elevated by proinflammatory cytokines such as TNF- α and IL-1- α [72].

Fibroblasts

Fibroblasts are abundant within the interfacial membrane of osteolysis patients, and express RANKL [66, 84]. Expression of RANKL by fibroblasts can be up-regulated by incubation with titanium particles or by the inflammatory mediator PGE2, and these stimulated cells can support differentiation of OCPs to OCs in the presence of MCSF [85]. Likewise, fibroblasts isolated from arthroplasty membranes of osteolysis patients (which had presumably been exposed to wear debris *in vivo*) were able to support generation of OCs from human monocytes [86]. These observations suggest that periprosthetic fibroblasts exposed to wear and/or proinflammatory mediators may be a major source of the RANKL required to drive osteoclastogenesis in osteolysis patients. Particles can also induce production in cultured fibroblasts of proinflammatory mediators, collagenase and stromelysin [87, 88], which could contribute to the development of osteolysis, and chemokines, which could contribute to the recruitment of increased numbers of OCPs to periprosthetic tissues [89].

Lymphocytes

Involvement of lymphocytes in osteolysis is an attractive hypothesis, but remains controversial. T lymphocytes are emerging as key regulators of bone homeostasis because of their ability to generate both proosteoclastogenic (i.e., RANKL) and antiosteoclastogenic (i.e., interferon gamma) cytokines upon activation, and are critically involved in the RANKL-dependent bone loss observed in inflammatory bone erosion diseases such as rheumatoid arthritis [90–92]. However, although some studies of the cellularity of periprosthetic tissues retrieved from osteolysis patients during revision surgery suggest the presence of significant numbers of activated T cells [93, 94], others discount this possibility, finding only unactivated T cells present in significant [95] or low [96] amounts. At a molecular level, some studies report the presence of Th₁ and Th₂ cytokines in the periprosthetic tissues [94], while other researchers find none [95, 96]. In animal studies, mice with deficiencies in lymphocytes retain the ability to form granulomas [97, 98] and develop osteolysis [99] in response to wear debris, suggesting that lymphocytes are not causally involved in these processes. On the other hand, mice with deficiencies in lymphocytes fail to mount an inflammatory response to polyethylene particles injected into the knee [100], and titanium particles induce larger sutures in athymic mice than wild-type controls when applied to exposed calvaria [101]. Perhaps the strongest evidence for the involvement of lymphocytes in aseptic loosening are two recent reports correlating a metal-specific lymphocyte response to poor implant performance [102] and characterizing lymphocytic infiltration around metal-on-metal arthroplasties [103]. More research will be necessary to determine whether lymphocytes are substantially involved in osteolysis or not.

Molecular targets of wear debris

As discussed above, a good deal is known about the eventual modulation of expression of numerous proteins, including cytokines, chemokines, and proteases, by wear debris. In contrast, considerably less is understood about the molecular events upstream of the transcription of the genes encoding these proteins initiated by particles.

Macrophage cell surface receptors

Remarkably little is known about the molecular basis of wear debris interaction with the surfaces of cells. Even for macrophages, the best-characterized cellular target for particle action, the identity of the cell surface receptors responsible for recognition of the particles, and the full repertoire of signaling cascades initiated or modified by particle binding, remain poorly understood. One important consideration in determining the involvement of specific macrophage surface receptors is the extent to which different particles become opsonized with host serum proteins prior to phagocytosis. There is evidence that polyethylene

activates complement [104], and this would argue in favor of a role for complement receptors, such as CR3, in particle uptake. Indeed, CR3 expressing phagocytes have been detected in granulomatous lesions associated with hip replacement [105]. By contrast, research on alveolar macrophage response to environmental particulate matter has implicated scavenger receptors, such as MARCO, in opsonin-independent uptake of titanium particles [106], suggesting that different particles may use different surface receptors. This would provide an intriguing explanation of the abilities of different types of wear debris to elicit particle type-specific responses in cultured macrophages. Consistent with this, opsonization was shown to be not essential (although it may be involved) in responses of human monocytes and macrophage cell lines to titanium [107, 108]. The concept that opsonization may differentially regulate uptake of different compositions of wear debris is also supported by observations that the spectra of adherent human serum proteins demonstrates a level of particle specificity [109]. To further explore this important line of inquiry, our laboratory has developed a flow cytometry assay to monitor particle uptake by macrophages, and confirmed that scavenger receptor inhibition specifically reduces titanium particle phagocytosis. Interestingly, PMMA bone cement uptake was inhibited by blocking the CR3 complement receptor, but not affected by scavenger receptor inhibition (Rakshit et al., unpublished data). An involvement of CR3 in particle action is also supported by observations that antibodies against CR3 reduces particle uptake [14], and that activation of this receptor mimics several aspects of downstream signaling by particles (discussed in more detail below), in that MAP kinases [110] and the transcription factors NF κ B, NF-IL6, and AP-1 are activated [14, 111], and production of proinflammatory cytokines [14] and chemokines [111] are elevated.

Intracellular signaling molecules

MAP kinases

Data from our laboratory and others have shown that wear debris of various compositions can induce rapid activation of MAP kinase family members [14, 68, 112]. For instance, PMMA bone cement and titanium can each, within 15–30 min, induce activation by phosphorylation of all three of the major MAP kinase subgroups, namely, p38, ERK, and JNK [68]. These three pathways are involved in numerous cellular activities, and all three are required for osteoclast generation and activation [113]. Inhibition of MAP kinase activation reduces the ability of wear debris to induce proinflammatory cytokine induction in cultured OCPs [68], suggesting that MAP kinases are critical transducers of the signals emanating from particle–cell interaction to the nucleus. There appears to be considerable redundancy among the different MAP kinase families in this respect, because inhibition of multiple MAP kinase subgroups is far more effective in down-regulating particle action than inhibition of any single subgroup alone. Our laboratory has recently reported a second, distinct role for MAP kinases in wear

particle action, relating to the ability of PMMA and titanium to inhibit antiosteoclastogenic IL-6 signaling. Use of inhibitors for specific MAP kinases has revealed that p38 MAP kinase (but neither ERK nor JNK MAP kinases) activity is essential for wear-mediated down-regulation of IL-6 signaling [68]. CR3 engagement also stimulates MAP kinase activation, consistent with a role for this receptor in wear debris recognition [14, 110].

Transcription factors

Perhaps the most notable transcription factor implicated in wear debris action is NF κ B. This protein complex, long known as a key regulator of inflammatory gene expression, is also emerging as an important player during osteoclastogenesis. Mice lacking NF κ B, in addition to having defective macrophages, are also osteopetrotic, resulting from an inability to generate functional osteoclasts [114, 115]. Wear debris can activate NF κ B in cultured macrophages [14], OCPs [116], and the J774 murine macrophage cell line [49]. Supporting evidence for a role of NF κ B in osteolysis comes from observations that deficiency of NF κ B1 in mice protects against titanium-induced calvarial osteolysis [49], and that inhibition of NF κ B blocks wear debris induction of osteoclastogenesis in vitro [116, 117]. Other transcription factors, such as NF-IL6 [14] and AP-1 [118], have also been shown to become activated following wear debris treatment of macrophages. However, the relevance of these factors in osteolysis remains unclear.

Suppressors of cytokine signaling (SOCS) proteins

As discussed above, we have demonstrated that wear debris can inhibit signaling by antiosteoclastogenic cytokines, such as interferon gamma and IL-6. These cytokines signal via the JAK-Stat pathway, with interferon gamma principally activating Stat1, and IL6 chiefly activating Stat3 [119]. How might the wear particles down-regulate JAK-Stat signaling? At least two mechanisms for inhibition of JAK-Stat signaling are known: MAP kinase activation [120, 121] and induction of a family of proteins known as suppressors of cytokine signaling (SOCS) [122]. Specifically, SOCS1 inhibits interferon gamma activation of Stat1 and SOCS3 inhibits IL-6 activation of STAT3. As noted above, p38 MAP kinase mediates inhibition of IL-6 signaling. However, this does not appear to be the only mechanism whereby wear debris inhibits IL6, since results from our laboratory also show that PMMA and titanium strongly induce expression of SOCS3 [68]. Thus particles trigger multiple pathways (MAP kinase activation and SOCS3 induction) that collaborate to effectively shut down IL-6 signaling.

Current options for implant design

Biologic response to wear particles, corrosion products, or both has been shown to be the primary source of morbidity and early implant failure. Wear rates in excess of 0.2 mm/year have been reported to cause 100% failure of total hip

replacement. In the same study, wear rates greater than 0.15 mm/year were shown to put the hip at risk for aseptic loosening [123]. In well functioning THR, wear rate has been measured to be 0.05 mm/year [124]. One of the biggest challenges in implant design research today is to develop better wear-resistant materials to reduce the generation of particles. Bearing surface choices include a metal (cobalt–chrome, CrCo) head and polyethylene (PE) socket, ceramic-on-polyethylene, ceramic-on-ceramic, and metal-on-metal.

(a) *Metal (CrCo) head-on-polyethylene* has been in use for 30 years. Although the conventional polyethylene (PE) has shown excellent energy absorption, good wettability, and low coefficient of friction, it has been associated with higher wear characteristics (0.075–0.4 mm/year [123]). Highly cross-linked PE has been introduced in total joint replacement to reduce the wear debris. Hip simulator studies have shown that highly cross-linked PE had better wear resistance, higher resistance to delamination, and less wear against rough femoral balls than conventional PE [125]. Moreover, cross-linking has been correlated with superior wear behavior in vitro with large femoral heads [126]. Clinical studies have shown short term results with superior wear resistance [127–129]. The need for longer follow-up has been recognized. Due to lack of long-term follow-up data of in vivo use of cross-linked PE, some authors have reported the continued use of standard PE sterilized with gamma radiation in an air environment with a shelf life of less than 3 years [130].

(b) *Ceramics (aluminum or zirconium oxide)* have a long history as implant articulating surfaces [131]. The incidence of high fracture rates has been reduced with the third generation of ceramics [132]. Wear rates for ceramic-on-polyethylene bearings ranged from 0 to 150 $\mu\text{m}/\text{year}$ and 10% to 50% less wear than with a standard metal femoral head [133]. Moreover, in hip simulator testing, alumina-on-alumina produced wear rates of 1 $\mu\text{m}/\text{year}$ compared with 200 $\mu\text{m}/\text{year}$ for a standard cobalt chromium-on-polyethylene [132]. However, in a multicenter, prospective, and randomized study an alumina-on-alumina bearing had no significant difference in clinical performance with a CrCo-on-polyethylene bearing [132]. Another alternative with ceramics is *oxinium*, an oxidized zirconium metal, which showed lower wear rates and more resistance to scratching when articulated with cross-linked polyethylene [134]. Although ceramics have demonstrated very good results in both clinical and laboratory experiments, there are some concerns that need to be addressed. Microseparation, a unique pattern of stripe wear during gait, has been described in zirconium femoral heads [131]. The incidence of fracture, although low, continues to be an issue. Revision can be very challenging because of the inability to use a ceramic head for the second time and the loss of head and liner options intraoperatively. Moreover, fracture of the ceramic head produces particles that are retained and may compromise the results of revision. Another issue is chipping of liner that may occur with component impingement. Ceramic liner chipping may also occur during insertion, when the liner is locked in a nonconcentric manner and introduces wear debris from a second modular

interface [131]. Finally, another concern is the cost of ceramics, which is 20% higher than metal-on-polyethylene [130].

(c) *Metal-on-metal THR* has the longest clinical history of any of the currently used articular couples. Retrieval analysis of metal-on-metal THR demonstrated wear between 1 and 5 $\mu\text{m}/\text{year}$ in comparison with 100–200 $\mu\text{m}/\text{year}$ associated with metal–polyethylene wear [135, 136]. Although the metal particles are smaller in size, the numbers are much higher. However, the immune response is mild and no multinucleated giant cells have been found in retrieved metal-on-metal bearings [135], although lymphocytic reactions have been observed [103]. There continues to be an issue concerning elevated serum metal ions that have been documented in several reports [135]. Despite the variabilities in techniques of measuring the metal ions, no evidence of necrosis or pathologic abnormalities has been reported [136]. Another concern is the possibility of carcinogenesis due to the metal ions. This has been reported in animal studies; however, in human studies this was not statistically greater than the conventional metal-on-polyethylene [135]. Currently, there are limited data to show a causal link between the elevated ions and the development of carcinogenesis. The short-term clinical results of metal-on-metal THR are equal or better than those of conventional articular couples. Additional advantages of metal-on-metal are the ability to use larger-diameter femoral heads for enhanced stability and the absence of possible fracture of the articular components.

Therapeutic possibilities, now and in the future

Identification of osteolysis as an inflammatory bone erosion disease has culminated in the consideration of two main approaches to treatment: anti-inflammatory agents and suppressors of bone resorption. Anti-inflammatory agents, such as cox-2 inhibitors and TNF antagonists, have yielded encouraging results in animal models of osteolysis. For instance, Etanercept [50] and pentoxifylline [6], TNF antagonists that operate as a decoy receptor and an inhibitor of secretion, respectively, have been independently shown to diminish particle-induced osteolysis in the murine calvarial model, along with COX2 inhibitor Celecoxib [52]. However, despite these encouraging animal studies, it is not yet known how well these anti-inflammatory 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 [137], but has not been tested in osteolysis patients, and a small trial of Etanercept [138] in osteolysis patients proved inconclusive.

Given that excessive osteoclast activity represents the cellular endpoint of osteolysis, it is not surprising that the bisphosphonate class of osteoclast inhibitors have come in for much discussion as possible therapeutic agents for this disease. Again, however, despite promising results in animal models, there is no clinical evidence supporting the effectiveness of these drugs in the treatment of osteolysis

patients. Alendronate inhibits wear debris-induced osteolysis in the rat loaded tibial implant model of osteolysis [7] and in a similar canine model [9], and is also effective in preventing osteolysis in the murine calvarial model [6]. A single dose of zoledronic acid administered directly after surgery also suppressed particle-induced osteolysis in mouse calvaria [139]. Bisphosphonates inhibit OC formation by blocking the mevalonate pathway of isoprenoid biosynthesis. Because statins, as HMGCoA reductase inhibitors, also target the mevalonate pathway, they have been considered as possible drugs for osteolysis. Indeed, simvastatin has been shown to prevent wear debris-induced osteolysis in the murine calvarial model [140]. The central role of RANKL in osteoclastogenesis makes this cytokine an attractive target for possible therapies. OPG (a naturally occurring RANKL antagonist) and RANK-Fc, which reduce RANKL levels, have been successfully used to prevent osteolysis in animal models [59–61]. It remains to be seen whether these approaches will be effective in the treatment of osteolysis patients. Clinical trials with a monoclonal antibody against RANKL (AMG-162) have demonstrated safety and antiresorptive activity [141, 142], but this new agent has yet to be assessed in osteolysis patients. Such treatments would be expected to decrease bone loss, but not reduce inflammation (as seen in OPG treatment of rat adjuvant arthritis [92]), which may be a concern, as elevated TNF and IL1 levels are capable of promoting osteoclastogenesis in the presence of only very low levels of RANKL, suggesting that without reducing inflammation, blockade of RANKL would have to be essentially complete to be effective. An alternative approach would be combined therapy with antagonists against both RANKL and proinflammatory mediators. Such an approach proved successful in an arthritis model [143]. Because RANK signaling is transduced via NF κ B, antagonists against this transcription factor may represent effective treatments for osteolysis. In this regard, it is intriguing to note that direct inhibition of NF κ B with the NEMO-binding domain (NBD) peptide is reported to prevent bone loss in inflammatory bone erosion patients [144]. However, since persistent inhibition of NF κ B could result in immune deficiency or cell death, such treatments should be approached with caution.

Inhibitors of mature OC function represent another possible class of therapeutic agents yet to be evaluated in osteolysis patients. As more become known of the molecular details of osteoclast biology and particle action, it is hoped that additional targets for drug design will become available. For instance, inhibitors of cathepsin K (an OC-specific protease) [145, 146], the osteoclast ATPase proton pump [147], vitronectin receptor [148], and src tyrosine kinase [149], all of which are required for resorption, have been developed.

Perhaps the biggest impediment to the development of therapeutic strategies for osteolysis is the lack of an accepted outcome measure. In response to this, we are developing modified magnetic resonance imaging approaches toward the evaluation of periprosthetic osteolysis [150]; three-dimensional computed tomography is also being applied to this problem [151, 152].

Conclusion

Much progress has recently been made in understanding how, at the molecular and cellular levels, prosthetic wear debris can ultimately cause osteolysis and aseptic loosening. The established scenario of particle-induced proinflammatory signaling has been embellished with an understanding of how wear can also promote maturation of osteoclasts from macrophages, by inhibiting protective, antiosteoclastogenic cytokines such as interferon gamma. We are starting to unravel the complexities of interactions between wear particles and macrophage cell surface receptors, and to describe the intracellular signaling pathways activated by such interactions. Such progress emphasizes the reality that development of therapeutic approaches to the treatment of osteolysis is long overdue.

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