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Interaction of Materials and Biology in Total Joint Replacement – Successes, Challenges and Future Directions

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A. Abstract

Total joint replacement (TJR) has revolutionized the treatment of end-stage arthritic disorders. This success is due, in large part, to a clear understanding of the important interaction between the artificial implant and the biology of the host. All surgical procedures in which implants are placed in the body evoke an initial inflammatory reaction, which generally subsides over several weeks. Thereafter, a series of homeostatic events occur leading to progressive integration of the implant within bone and the surrounding musculoskeletal tissues. The eventual outcome of the operation is dependent on the characteristics of the implant, the precision of the surgical technique and operative environment, and the biological milieu of the host. If these factors and events are not optimal, adverse events can occur such as the development of chronic inflammation, progressive bone loss due to increased production of degradation products from the implant (periprosthetic osteolysis), implant loosening or infection. These complications can lead to chronic pain and poor function of the joint reconstruction, and may necessitate revision surgery or removal of the prosthesis entirely. Recent advances in engineering, materials science, and the immunological aspects associated with orthopaedic implants have fostered intense research with the hope that joint replacements will last a lifetime, and facilitate pain-free, normal function.

B. Introduction

End-stage arthritic disorders of the hip, knee, shoulder and other large joints in the upper and lower extremities continue to be treated successfully by total joint replacement. These operations significantly reduce pain and restore more normal function for millions of patients worldwide. According to the 10th Annual Report of the National Joint Registry for England, Wales and Northern Ireland, there were 76,448 primary (first time) total hip replacements and 84,833 primary total knee replacements performed in 2012. In the same year, there were 10,040 revision (redo) total hip replacements and 6,009 revision total knee replacements [1]. The revision procedures were performed mostly for aseptic (non-infected) loosening of implants, wear particle-associated bone loss (periprosthetic osteolysis), instability, infection, and fracture around the prosthesis. In the United States, according to the Center for Disease Control and Prevention, there were 332,000 total hip and 719,000 total knee replacements performed in 2010 [2]. Between 10-15% of these cases were revision procedures. Kurtz et al projected that in the USA between the years 2005 and 2030, the numbers of primary total hip and total knee replacements will increase by 174% and 673% respectively[3]. Whereas the number of hip revision surgeries is expected to double by 2026, the number of knee revisions will double by 2015! These impressive statistics point

to the need for more resources to maintain patients with end-stage arthritis in a comfortable, pain-free, fully ambulatory and functional state; furthermore, more durable implants are needed, that will allow more normal activities (including impact loading), and hopefully last the patient's lifetime. This latter point is particularly germane to this discussion, because joint replacement is currently being offered to younger patients with congenital/developmental, traumatic, inflammatory and degenerative arthritis who want to participate in physical and social activities to the fullest extent. Indeed, greater than half of all primary hip and knee replacements are currently being performed in active patients less than 70 years of age [1]. Moreover, with the increasing incidence of obesity in the general population, greater loads are being placed on the joints of the lower extremity (whether natural or artificial), increasing the potential for late complications associated with wear of joint replacements.

In this review, we will discuss the historical aspects, current technological challenges and future directions of total joint replacement of the lower extremity from the point of view of interactions of materials and biology. Although the mechanical characteristics of joint replacement are equally important, many of these issues have already been resolved with the use of super alloys, CAD/CAM design, and exhaustive preclinical mechanical testing. Today, bulk metallic implants for joint replacement rarely encounter fatigue failure. Thus, this article will emphasize the important considerations and interactions of materials and biology in the determination of clinical outcome of joint replacements. Although the topic of infection of total joint replacements is a major determinant of outcome, the enormous complexity of this subject is beyond the scope of the current review.

C. The development of joint replacements

C.1 Historical Perspective

Joint replacement has been a goal that surgeons have pursued for over 150 years. Prior to the introduction of antibiotics, debridement, and if necessary, resection (excision) of the hip joint were the main surgical procedures performed for diseases such as infection of the hip. This latter operation (resection) was sometimes performed for severe painful end-stage degenerative arthritis in order to make the patient's hip less painful and more functional by increasing range of motion. However, this operation resulted in a shortened limb, which was generally painful and weak. Fusion (arthrodesis) of the hip or knee joint relieved pain but sacrificed motion and function. Arthrodesis was associated with late back pain and degeneration of adjacent joints due to chronic overload; in some cases, the operation failed, and resulted in a nonunion. Osteotomy of the hip or knee attempted to redirect forces from degenerated cartilage associated with mechanical overload and anatomical misalignment, to more normal cartilage by cutting and re-aligning the bone(s) adjacent to the joint. However, these operations often did not last the patient's lifetime, as the newly overloaded cartilage degenerated with time. Resurfacing of the hip and knee with biological materials (skin, fascia etc.) also had very limited success.

Arthroplasty of the hip with artificial materials was first attempted by replacing one side of the joint only. This was first accomplished with primitive materials such as ivory, wood, acrylic and other substances. Not only was the infection rate very high in these early cases, but issues related to implant materials and fixation within bone, prosthesis design, and replacement of both sides of the joint (rather than one side only) were not carefully considered.

Successful total joint replacement really began with the pioneering work of Sir John Charnley of Great Britain. Charnley's original ideas were less than successful. His first designs for hip replacement incorporated large femoral heads over 40 mm in diameter articulating with materials such as polytetrafluorethylene, which had suboptimal wear characteristics. Charnley eventually used engineering principles for the design of his "Low Friction Arthroplasty" of the hip [4]. In this operation, after several iterations, a one-piece stainless steel femoral stem with a small femoral head of 22 mm diameter articulated with a high density polyethylene socket. In conjunction with Dennis Smith, a dental researcher, the implants were fixed to bone with polymethylmethacrylate, so called "bone cement" which is still in use today.

Charnley's ideas were modified by many, often with disappointing results due to stem fracture (because of the use of casted metallic implants with imperfections), cement fractures due to suboptimal stem designs and surgical technique, the re-emergence of large femoral heads with high frictional torque and subsequent loosening of the cup, and excessive polyethylene wear with development of a foreign body response and periprosthetic bone loss (osteolysis). Subsequently, the use of super alloys made of cobalt chrome alloy and titanium-6 aluminum-4 vanadium and others, and design changes to optimize load transfer in a precisely prepared cement mantle with more uniform thickness improved femoral implant longevity. The femoral head was kept small (usually 22-32 mm in diameter) to maximize polyethylene thickness and optimize both linear and volumetric plastic wear. However, periprosthetic bone loss and implant loosening due to the chronic inflammatory and foreign body reaction to polyethylene wear particles limited implant durability [5, 6]. The pathogenesis of this reaction will be discussed in detail below. This biological response to wear particles was more prevalent in younger, heavier more active males who might cycle the hip or knee replacement several million times per year [7]. More recently, innovations such as packaging the plastic acetabular cups in an inert oxygen free environment to limit chain scission and oxidation, cross-linking of the polyethylene, the limiting of polyethylene oxidation by the addition of free radical scavengers such as Vitamin E, and repetitive cycles of heating and annealing the polyethylene have shown dramatic preclinical and intermediate term clinical results, with significantly reduced polyethylene wear [8].

In North America during the late 1970's and 1980's, surgeons became somewhat disenchanted with bone cement for hip replacement, because of the increasing

incidence of cement fracture, the generation of cement particle associated chronic inflammation and bone loss, termed “cement disease” [9]. A new generation of implants was developed for hip replacement in which fixation was achieved by “machining” the bone to obtain a “line-to-line” fit or subsequently a “press fit” (a slightly oversized implant literally jammed into the prepared bone bed) to obtain initial implant stability. In addition, porous coatings (small balls or wires) were sintered or plasma sprayed onto portions of the implant surface to facilitate the ingrowth of bone and fibrous/fibro-cartilaginous tissue into the interstices for more long-term stabilization (**Figure 1**). Some manufacturers also implemented coatings with osteoconductive materials such as calcium phosphates on portions of the implant. Although many of these innovations have been adopted for total hip replacement, total knee replacement has largely continued to use cemented implants and conventional (non-highly cross-linked) polyethylene.

C.2 Alternative Bearings

Alternative, so called “hard-on-hard” bearings such as ceramic-on-ceramic (COC) and metal-on-metal (MOM) emerged due to the suboptimal wear properties and presence of periprosthetic osteolysis of metal-on-conventional polyethylene implants, especially in younger, more active hip replacement patients [10]. COC and MOM bearings have significantly less wear compared to metal-on-polyethylene (MOP) articulations. COC hip replacement was popularized by the French; these implant materials and designs have undergone many changes over more than 3 decades. Current COC hip implants demand exacting surgical technique to avoid improper seating of the ceramic liner within the metallic shell of the acetabular component, impingement of portions of the femoral component with the ceramic acetabular insert, chipping of the ceramic cup insert, and striped wear and squeaking due to edge loading and stress concentration [11]. Although catastrophic fracture of the femoral head is rare due to the use of modern composite ceramics containing alumina-zirconia-chromium oxide-strontium with smaller grain sizes, fracture still does occur. In general, ceramic bearings are more expensive than metal-on-highly cross-linked polyethylene (MOXLPE).

MOM bearings for hip replacement were embraced by some surgeons in response to two specific needs. First, with the re-emergence of surface replacement of the hip (a large proportion of which failed quite miserably in the late 1970’s to 1980’s due to excessive wear of metal-on-conventional polyethylene articulations due to loosening and osteolysis), a substitute for polyethylene was needed for the resurfacing concept to be viable. A MOM bearing couple was thus adopted for surface replacements. Second, with the use of smaller femoral heads of 22-32 mm in diameter for total hip replacement, dislocation of the head from the socket was still a major issue. If a MOM articulation were used for total hip replacement, the femoral head size could be increased thus improving stability and decreasing the dislocation rate. A related issue pertains to modularity of femoral stems for hip replacement, in which two

new articulations have emerged, namely modularity between the femoral neck and head (to adjust femoral length and offset), and more recently, modularity between the femoral stem and neck (to adjust femoral prosthesis offset and neck ante- or retro-version).

MOM bearings have generated a great deal of controversy, and their use for surface and conventional hip total replacement has decreased dramatically over the last 5 years. The theoretical, extremely low friction associated with fluid film lubrication has not always been realized, and instead, wear particles and ions of cobalt, chromium and other byproducts have been generated. A number of suboptimal MOM prosthesis designs have been removed from the marketplace altogether. Metallic wear byproducts have been shown to stimulate both the innate and adaptive immune system leading, in some cases, to a chronic inflammatory response, cell death involving soft tissue and bone, and large solid or cystic pseudotumors [12, 13]. These cases are extremely challenging surgical revisions with high complication rates. More recently, similar adverse events have been noted (rarely) with larger modular heads (32, 36, 40 mm in diameter or larger) articulating with polyethylene, and with modular neck-body junctions. These events have been linked with mechanically associated crevice corrosion of modular junctions. Excessive metallic wear particles and ions have been shown to be cytotoxic and can lead to hypersensitivity reactions (a T cell mediated Type IV immune reaction) [13, 14].

C.3 Successful Joint Replacements

The success of total joint replacement depends on choosing the right operation for the right patient, and performing the operation meticulously with state-of-the-art materials. Avoidance of complications such as infection, dislocation and peri-operative medical difficulties together with proper rehabilitation help ensure the expected outcome and the patient's return to society.

The majority of the clinical issues outlined above have been pursued with good success. Infection is still a problem, given the increasing numbers of joint replacements currently being performed on more elderly infirm patients, and those with immunological compromise (diabetes, inflammatory arthritis, cancer, etc.). Pre-operative optimization of medical issues, the use of prophylactic antibiotics and other measures should improve this complication.

Perhaps a greater challenge is to more clearly understand the host reaction to different biomaterials and their byproducts used for joint replacement. Charnley's operation was highly successful, yielding pain free functional results usually for several decades. His operation was recently improved with the use of highly cross-linked polyethylene as a bearing surface. However, recent developments in implant materials and design, as well as an increased understanding of the interaction between implant and biology in joint replacement have presented new challenges. This is especially true given the fact that younger more active

patients now expect their joint replacements to last their lifetime without physical limitations.

D. Challenges

D.1 Biological Reactions to Joint Replacements and their Byproducts

Two biological events simultaneously occur during initial implantation of a total joint replacement. First, all surgical procedures stimulate an acute inflammatory reaction due to surgical trauma. This is not only a local phenomenon, but depending on the extent of the surgical procedure, is associated with a systemic host response that generally lasts for several days to several weeks. Second, joint replacement is associated with implantation of a foreign body. The local host response to this foreign body is an important component of the eventual fate of the implant. Thus, the final outcome is dependent on host factors (i.e. the patient), the technique of surgical implantation (i.e. the surgeon), and implant factors.

Components for joint replacement must obtain initial stability within bone, or there will be motion at the bone-implant interface during loading of the joint, and subsequent bone resorption. This series of events will lead to painful migration of the component(s) and poor function. Revision surgery is then inevitable.

During implantation of the joint replacement, there is always some degree of bone cell death from the mechanical reaming and rasping that occurs to prepare the bone bed. If cement is used to anchor the prosthesis, the trauma of mechanical reaming/rasping is followed by chemical and thermal trauma from the exothermic curing of the polymethylmethacrylate. This leaves an area of necrosis of usually several under micrometers around the prosthesis. With cementless implants, initial “macro” mechanical stability in addition to impaction of reamed/rasped spicules of bone will facilitate osseointegration of the prosthesis, i.e. bone will form immediately adjacent to the prosthesis such that the prosthesis will not migrate under physiological loading [15]. For cemented implants, cement is pressurized into the cleaned and dried interstices of cancellous bone. This yields immediate stability. Two potential locations for loss of fixation of cemented implants may occur: that between the implant and the cement mantle, and that between the cement mantle and surrounding bone.

Metal-on-polyethylene bearings undergo an initial “bedding in” period of about 6-12 months in which the wear rate is higher than in the later steady state, and creep of the polyethylene occurs. The wear rate then becomes more linear over time. This generates polyethylene wear particles usually 1 μm or less in size [16]. Knee replacements tend to have slightly larger sized particles than hip replacements. Wear of modern highly cross-linked polyethylene is significantly reduced compared to conventional polyethylene.

Particles of bone cement, polyethylene, and metals less than 10 μm are phagocytosed by macrophages and other cells which become activated. This

results in a cascade of events leading to the production of pro-inflammatory cytokines, chemotactic cytokines (chemokines), reactive oxygen species, prostanoids and other factors that lead to the degradation of bone (see below) [5, 17-19]. Clinically, this manifests as a particle-induced persistent swelling of the joint (chronic synovitis) with/without pain; if bone loss continues, the prosthesis loses its mechanical support (**Figure 2)** [20, 21]. Micromotion of the implant leads to further pressure-induced bone loss with macromotion and prosthetic loosening [22-24]. Fracture through thinned bone may occur (**Figure 3)**. It is important to diagnose wear particle-associated bone loss early so that corrective steps can be taken to mitigate the ongoing bone destruction.

Microscopically, the bone-implant interface of particle-associated osteolytic tissue demonstrates a chronic inflammatory and foreign body reaction to wear particles containing macrophages and giant cells in a fibrous stroma [25]. Scattered lymphocytes may also be seen but are not a prominent finding. The presence of polymorphonuclear leukocytes suggests infection. The histological characteristics of the harvested tissues have some variability based on the location of the biopsy.

D.2 Cellular and Molecular Biology of inflammation

Leukocytes are white blood cells that initiate and regulate the acute inflammatory reaction to adverse stimuli and function as sentinels of the innate immune system. When local cells and tissues encounter perturbations that jeopardize the homeostatic state (such as with mechanical, thermal or chemical trauma, infection, surgery etc.), the result is local tissue damage and cell necrosis. Cellular proteins and DNA fragments are released, and stimulate leukocytes in the local area and circulating surveillance leukocytes through the recognition of specific molecular sequences via Pattern Recognition Receptors (PRRs) on cell membranes or within cells. The initiating chemical sequences can be derived from microbial pathogens (Pathogen Associated Molecular Patterns or PAMPS) or fragments of cells (Damage Associated Molecular Patterns or DAMPS). The PRRs can be membrane bound and include the Toll-like receptors (TLRs) and C-type lectin Receptors (CLRs). Intracytoplasmic receptors include the NOD-like receptors (NLRs) (including NODs and NALPs), and RIG-I-like receptors (RLR). Other Scavenger Receptors can be intracellular or extracellular.

Toll-like receptors

DAMPs and PAMPs can be generated from the surgical procedure and also during the progression of wear particle mediated disease. These molecular patterns adhere to the surface of implanted devices or the generated wear particles, and can be recognized by immune cells mainly through TLRs [26-32]. TLRs are a family of proteins that regulate the innate immune response through multiple signaling pathways. Thirteen different TLRs have been reported, and each of these receptors can recognize their specific ligands on the cell surface or inside the cells. For example, TLR2 can recognize peptidoglycan and lipoproteins, and TLR4 can recognize lipopolysaccharide (LPS) on the cell surface.

Alternatively, TLRs located on endosomes such as TLR3 can recognize double stranded RNA (from viruses), and TLR9 can recognize DNA containing specific CpG motifs.

Among all the proteins in the TLR family, TLR2, TLR4, TLR5, and TLR9 have been reported as being relevant to wear particle induced inflammation and osteolysis [33]. A study of clinical tissue samples showed that monocyte/macrophages from aseptically loose periprosthetic tissues and septic synovial membranes around total hip implants showed increased TLR2, 4, 5, and 9 expressions [34]; TLR2 and TLR5 expression were found to be significantly higher than the others. In experimental mouse models, exposure of UHMWPE increased TLR2 expression in the synovial membranes of knee joints [35], while TLR2 and TLR4 expression were both increased in a calvarial model [36]. However, when the mouse femur was exposed to titanium particles, the number of TLR positive cells was reduced [37]. In TLR2 and TLR4 deficient transgenic mice, titanium particle induced TNF-α expression in macrophages was significantly reduced using a mouse calvarial model [38]. However, the resultant osteolysis induced by particle exposure was only partially reduced, suggesting that titanium particles may also induce osteolysis in a TLR2 and TLR4 independent pathway. *In vitro* stimulation of rat bone marrow derived macrophages by titanium particles coated with LPS increased TLR2 expression but decreased TLR4, 5, and 9, suggesting a self-protective regulation may exist to restrict an excessive response [39].

Wear particles may be recognized by TLRs and activate downstream signaling pathways in the absence of PAMP. TNF-α secretion was reduced in MyD88 deficient mice, or with the use of MyD88 inhibitors, when macrophages were stimulated by polymethylmethacrylate (PMMA). Osteolysis was also reduced in MyD88 deficient mice when exposed to PMMA particles using the murine calvarial model [40]. These results suggest that PMMA particles activate macrophages and induce osteolysis via TLR pathway in the absence of PAMP. However, Greenfield et al. showed that bacterial derived PAMP is required for titanium particle induced inflammatory responses and osteolysis [38], suggesting that wear particle induced TLR activation may depend on the particle characteristics and the experimental model used.

Byproducts

Implanted biomaterials can generate different byproducts including large particles from micro-fracture (tens of microns), moderate to small wear particles (0.1-10μm) due to wear, and metal ions from corrosion at articulating and non-articulating sites such as with metal-on-metal bearings or mechanically assisted crevice corrosion of modular metallic implants [41]. Phagocytosable wear particles at the sub-micron to micron size can elicit an aggressive inflammatory response; the wear rate and particle type, size, and physical and chemical characteristics are different for various biomaterials used in orthopaedic surgery including plastics, ceramics, metals and others [42]. The biological effects of metallic

byproducts including wear particles and metal ions are summarized separately in **D.4**, due to their unique biological behavior.

The biological response of immune cells to wear particles is dependent on the particle composition [43], dose [44, 45], size [44, 46-48], shape, and surface chemistry, energy and topography [49]. In one study, periprosthetic tissues from patients with aseptic loosening of implants were transplanted into the muscles of immunodeficient mice. Peripheral blood macrophages from these patients were stimulated in vitro with Ti-6Al-4V, polymethylmethacrylate (PMMA), ultra high molecular weight polyethylene (UHMWPE), or Co-Cr alloy particles for 3 days before the cells were injected into the peritoneal cavity of the mice. At harvest 2 weeks later, IL-1β and TNF expression was higher in the xenografts in macrophages previously exposed to Ti-6Al-4V and PMMA particles; MCP-1 and IL-6 expression was higher in the group with previous UHMWPE particle exposure [43]. In vitro studies using mouse primary bone marrow derived osteoprogenitor cells and the MC3T3-E1 cell line suggested that UHMWPE particles reduce bone mineralization in a dose dependent manner [50]. Green et al. demonstrated that particle size and ratio are both critical factors that affect bone resorption and inflammation [44, 46]. By using mouse peritoneal macrophages exposed to UHMWPE particle, small particles (0.21-0.24μm) induced higher bone resorption rates and pro-inflammatory cytokine production at a particle volume to macrophage ratio of 10:1, whereas moderate size particles (0.45-4.3μm) showed significant effects at a ratio of 100:1. Larger particles (>7μm) were shown to have no effect on bone resorption and cytokine production. In another study using mouse RAW264.7 macrophages, corundum particles in the nanometer size induced higher pro-inflammatory cytokine production and more giant cell formation than micrometer sized particles [48]. Human THP1 macrophage cells exposed to conventional or highly cross-linked UHMWPE particles induced significant pro-inflammatory cytokine production when the particles were of a larger size (>10μm); cells exposed to conventional UHMWPE particles showed higher cytotoxicity with small particles (0.7μm) [47]. The shape and surface texture of wear particles can also affect the tissue response. In a murine air-pouch model of inflammation, UHMWPE particles with a fibrillar shape and rough surface induced significantly higher TNF-α and IL-1β expression, compared to particles with a globular shape and smooth surface [49].

Macrophage polarization

Macrophages also play significant roles in the response to injurious stimuli and tissue repair. Macrophages can be polarized by stimuli from the micro-environment, and exhibit distinct phenotypes and functions. Classical polarization of macrophages by LPS or IFN-γ triggers the pro-inflammatory cytokine response (M1 type). Alternatively, macrophage polarization by IL-4 or IL-13 induces the secretion of cytokines with immune modulation or tissue repair functions (M2 type) [51]. The number of infiltrated macrophages and the ratio of M1 to M2 macrophages in the interface between an implanted device and the surrounding tissue can therefore determine the tissue response induced by wear particles.

A recent genome-wide microarray study confirmed that the response of human macrophages to titanium particles is determined by the polarization status [52]. Compared to non-polarized macrophages, M1 macrophages expressed significantly higher pro-inflammatory cytokines and chemokines when exposed to titanium particles, while the expression in M2 macrophages was restricted. MCP1 and TNF-α may be most important cytokines secreted by M1 macrophages in wear particle induced osteolysis. MCP-1 secretion by polarized M1 macrophages recruits more macrophages to the injury site and enhances the inflammatory tissue reaction [53]. TNF-α can induce osteoclast maturation via NF-κB signaling, and may either suppress or enhance osteoblastogenesis depending on the TNF-α concentration and exposure time (see the comprehensive review by Osta B et al. [54]). The direct effects of LPS on bone homeostasis are still in debate. Mouse mesenchymal stem cells exposed to conditioned media from mouse macrophages polarized by LPS exhibited increased osteogenic ability [55]. When a titanium disc was implanted in the femoral diaphysis of pigs, the osteolytic response was increased in the presence of LPS at an earlier stage but not at a later stage [56]. The balance between polarized macrophages and mesenchymal stem cells may determine the overall effect of LPS on bone homeostasis, but may lead to an osteolytic process with excessive chronic inflammation clinically

Polarization of M2 macrophages could be an effective strategy to restrict adverse wear particle-induced tissue responses. The pro-inflammatory cytokines induced by PMMA [57] or titanium particles was effectively suppressed when M2 type macrophages were polarized by IL-4. TGF-β is an immune-suppressive cytokine secreted by M2 macrophages that may mediate the inhibition of cytokine expression. The direct effect of M2 macrophages on osteogenic differentiation remains unclear. An in vitro study showed that conditioned medium from IL-4 polarized M2 macrophages had no significant effect on osteogenic differentiation of human mesenchymal stem cells [55]. In an in vivo study using the murine calvarial model, local delivery of IL-4 reduced UHMWPE induced osteolysis [58].

In summary, macrophages recognize wear particles and molecular patterns via TLRs to elicit an inflammatory response often leading to osteolysis. The ratio of M1/M2 polarized macrophages may also determine the extent and progression of this inflammatory response and the results on bone (**Figure 4**).

D.3 Cellular and Molecular Biology of the Implant Interface

Many types of cells are involved in the processes of peri-prosthetic osteolysis including macrophages, osteoprogenitor cells/osteoblasts, fibroblasts, osteoclasts and others.[59] Wear particles activate inflammatory cells and promote osteoclastogenesis. NF-κB is a transcriptional factor that plays a central role in the inflammatory response. Titanium alloy, PMMA, UHMWPE and other wear particles activate NF-κB in macrophages and enhance pro-inflammatory cytokine expression.[60] Titanium wear particle-induced calvarial osteolysis was reduced in mice treated with NF-κB inhibitors[61] or in NF-κB deficient mice.[62] Mitogen

Activated Protein (MAP) kinase is also activated in macrophages and osteoclast precursor cells exposed to wear particles. Human osteoclast precursor cells exposed to titanium or PMMA particles in vitro induced MAP kinase activation; inhibition of MAP kinase activity suppressed pro-inflammatory cytokine expression.[63] In this section, the biological roles of the cells in response to wear particles and disease progression are summarized.

Macrophages and other immune cells

Several lines of evidence indicate that macrophages and macrophage-derived pro-inflammatory cytokines are the main mediators of wear debris induced osteolysis.[64, 65] Histopathological samples from the peri-implant tissue typically show macrophage infiltrates and foreign body giant cells, with occasional scattered T lymphocytes.[18, 66-68] Neutrophils and lymphocyte subsets other than T cells are typically absent from lesions caused by polyethylene or PMMA particles, and are usually associated with implant infection or adverse reactions to metals.[69-71] Retrieval studies have shown increased production of pro-inflammatory factors such as TNF-α, IL-1β IL-6, PGE-2, IL-8, as well as chemokines CCL2 and CCL3 from peri-implant tissues derived from implants with osteolytic lesions.[72-77]

Human and mouse macrophages stimulated with implant derived wear debris in vitro secrete pro-inflammatory chemokines and cytokines, although this effect is likely dependent on the various danger signal molecules adhering to the particle surfaces as well as on the macrophage phenotype.[52, 78-80] It is assumed that the macrophage-derived chemokines are responsible for the continued recruitment of monocyte-macrophages and osteoclast precursors to the peri-implant tissues.[81] Macrophage-derived pro-inflammatory cytokines support osteoclast formation and function both directly and indirectly by regulating the production of osteoprotegerin (OPG) and Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL) from local osteoblasts and fibroblasts.[64, 65] Detailed information of RANKL/OPG with peri-prosthetic osteolysis is described below.

Further evidence to this sequence of events has been provided by in vivo studies utilizing various different model systems of wear debris-induced osteolysis. For example, PMMA wear debris induced an acute inflammatory reaction with production of prostaglandin E2 (PGE2), TNF-α and neutral metalloprotease in a rat air pouch model.[82] In a similar mouse model system, titanium alloy, UHMWPE and PMMA particles induced local macrophage infiltration and production of IL-1β and IL-6.[83] In a mouse calvarial model titanium particles induced the production of TNF-α, IL-6, CCL2 and M-CSF.[84] Particle-induced inflammation and osteolysis were also observed in a mouse intramedullary model.[85] Implantation of polyethylene particles in the rabbit tibia induced a foreign body reaction[86], and tissue surrounding loose rabbit tibia prostheses generated elevated levels of PGE2.[87] More recently it has been shown that ex vivo labeled reporter macrophages systemically migrate to the peri-implant tissue in a murine continuous femoral intramedullary particle infusion model, and that blockade of

CCL2 signaling inhibits systemic macrophage migration and local osteolysis.[88] Of note are observations that inflammatory and osteolytic reactions develop similarly in mice with or without a functioning adaptive immune system indicating that these reactions are mainly driven by cells of innate immunity.[89, 90] TNF-α levels were elevated in periprosthetic tissues and synovial fluid samples from patients with periprosthetic osteolysis,[91, 92] but not in patients' serum samples in other independent studies.[93-95]

Interferon-γ (IFN-gamma), produced by T-cells and natural killer cells, polarizes monocytes/macrophages to an M1 phenotype and they express IL-1β, granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF).[96] Cellular ingrowth into a biomaterial was delayed by inhibition of IFN-gamma.[97] In vitro co-culture of primary mouse natural killer T lymphocytes and dendritic cells exposed to UHMWPE but not PMMA particles enhanced IFN-γ expression, and induced macrophage M1 polarization.[98]

The inflammatory nature of wear debris-induced osteolysis is also highlighted by the fact that blockade of inflammatory pathways or local application of anti-inflammatory factors prevents particle-induced reactions. For example, virus mediated gene transfer of the anti-inflammatory cytokines IL-1Ra or IL-10 mitigated polyethylene debris-induced inflammatory response and osteolysis in a mouse air pouch model.[99, 100] A similar effect was observed in the calvarial model in which IL-10 gene transfer mitigated titanium particle inflammation and osteolysis.[101] Particle-induced osteolysis was also reduced by deletion of the gene encoding the TNF-α receptor[62, 84] or by treatment a TNF-α receptor antagonist in the mouse calvarial model.[102]

IL-6 can also regulate both pro- and anti-inflammatory processes. IL-6 works as an anti-inflammatory cytokine which down-regulates pro-inflammatory cytokines such as TNF-α, CXCL-2, GM-CSF, and INF-γ[103] and enhances the production of IL-10, IL-1Ra, and soluble TNF-α receptor.[104, 105] IL-6 also binds to the soluble IL-6 receptor; this complex can bind to and activate cells via binding to the receptor glycoprotein 130.[106]

Osteoclasts

Osteoclasts are generated from infiltration of monocyte/macrophage lineage cells in the circulation. Activated osteoclasts are capable of bone resorption, and excessive osteoclasts can cause osteolysis. Wear particles can enhance osteoclastogenesis by increasing the infiltration of osteoclast precursor cells, or activating osteoclasts directly. Chemokine receptors including CCR1, CCR2, and CCR3 are expressed in mouse bone marrow derived osteoclasts.[107] Expression of the chemokines MCP-1 (ligand for CCR2) and MIP-1α (ligand for CCR1) was found in cells from periprosthetic tissues of patients with osteolysis.[108, 109] In vitro studies also showed that PMMA, and polyethylene particles induce the

expression of multiple chemokines including MCP-1, MIP-1α, and CCL5.[109, 110] MIP-1α treatment increased mobility of osteoclasts in vitro.[111] Nevertheless, impaired bone formation and increased osteoclastogenesis was observed in mice lacking CCL5,[112] suggesting that CCL5 might be a negative regulator for osteoclast recruitment.

Wear particles can generate the infiltration of osteoclast precursor cells into functional osteoclasts via indirect effects from cytokines secreted from cells in the interface region,[62, 63] or by direct activation the precursor cells. In vitro studies have shown that wear particles can either suppress the cytokines with anti-osteoclastogenesis function (interferon-γ and IL-6),[63] or enhance expression of TNF-α and IL-1β that activate bone resorption.[62] In addition, functional osteoclasts can be activated via the RANK/RANKL pathway. RANKL is the key cytokine regulator of osteoclast generation and activation. Interaction of RANK/RANKL activates NF-κB signaling in osteoclast precursor cells and induces cell differentiation and maturation in the presence of the survival factor MCS-F.[113, 114] Expression of RANK and RANKL was significantly enhanced by UHMWPE in a study using the murine air-pouch model. [115] OPG is a naturally occurring decoy receptor for RANKL, which can suppress the action of RANKL via competitive binding to the receptor.[116] The ratio of RANKL/OPG has been correlated with various bone disorders.[117] The local imbalance in the production of OPG/RANKL from clinical tissue samples and the ability of pseudosynovial fluid to induce osteoclast formation has been demonstrated.[77, 118, 119]

Osteoblasts/osteoprogenitors

Osteoblasts are the cells that form bone via secretion of extracellular matrix and induction of bone mineralization. While most studies on wear particle-induced osteolysis have focused on macrophages and osteoclasts, the response of osteoblasts to particles is also critical. Osteoblasts can be generated from mesenchymal stem cells (MSCs) and osteoprogenitor cells locally or in the circulation. Primary murine macrophages exposed to PMMA particles secreted MIP-1α to recruit mouse bone marrow derived MSC migration.[120] An in vivo study further demonstrated that blocking of MIP-1α by its receptor antagonist reduced the infiltration of MSCs and impaired their protective function in an UHMWPE continuous pump femoral mouse model.[121] These results suggest that wear particles may indirectly enhance infiltration of osteoprogenitor cells and MSCs into inflammatory sites as a mechanism of repair.

However, osteoblasts exposed to the wear particles demonstrate an impairment of their cell viability and osteogenic functions.[122] PMMA, titanium, and cobalt-chromium wear particles induced cell apoptosis in primary human osteoblasts and osteoblast-like cells.[123, 124] Titanium particles reduced proliferation and osteogenic differentiation in primary human MSCs.[125] Secretion of type 1 collagen in osteoblasts is also decreased when exposed to wear particles including titanium, cobalt chromium, polyethylene, and PMMA. In addition, wear particle-induced cytokine expression by osteoblasts including TNF-α, IL-1β, IL-6,

IL-8, prostaglandin E2, and RANKL.[87, 123, 126-128] indirectly enhances wear particle-mediated osteoclastogenesis.

Taken together, wear particle-induced osteolysis is a dynamic process involving immune cells such as macrophages, fibroblasts, osteoclasts, and osteoblasts. An imbalance involving bone destruction (osteoclastogenesis) over new bone formation caused by wear particles eventually leads to peri-prosthetic osteolysis.

D.4 Uniqueness of metallic byproducts from implants

In addition to polyethylene (PE) and polymethylmethacrylate (PMMA) wear particles, metals released from total joint replacement implants can cause adverse host responses with progressive peri-implant inflammation and bone loss. The metal byproducts released from total joint replacements are mainly due to the combined effects of mechanical wear and corrosion and are particularly common for implants with MOM bearing surfaces and/or modular components. Indeed, the high failure rates of MOM implants have been attributed to the release of large amounts of metal byproducts from the implant bearing surfaces. Metal debris can also occur with other types of total joint replacements, for example when a polyethylene liner is extensively worn and the underlying acetabular metal cup is exposed to and ground against the metallic femoral head, or when metal particles are released from porous surfaces of non-cemented implants. The metallic wear particles from MOM or modular implants are typically one order of magnitude smaller than the polyethylene and PMMA wear products i.e. nano-meter sized and, reflecting the materials of total joint replacements, are typically composed of cobalt-chromium or titanium alloy [129, 130]. Likewise, the metal ions released from total joint replacements are typically cobalt, chromium or titanium, with smaller amounts of other metals such as nickel.

The local adverse tissue reaction that is caused by nano-sized metal particles and elevated concentrations of metal ions is distinct from that caused by polyethylene and PMMA wear particles, and is characterized by the formation of large solid or cystic tissue masses, known as pseudotumors, and large areas of necrosis and bone-loss that can be substantial [70, 131-134]. In histopathological analysis, macrophage and various lymphocyte subpopulations (T-, B- and plasma cells) can be seen infiltrating the periprosthetic tissues. Peri-vascular T lymphocyte infiltrates, or aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), have been described as characteristic for the adverse reaction to metal byproducts released from MOM implants. More recent reports have, however, challenged this assumption by describing similar lesions from the aseptic implant loosening associated with polyethylene wear [135, 136]. In any case, macrophages and, possibly T lymphocytes, have been considered as the key mediators of local metal-induced inflammation and peri-prosthetic bone loss.

In addition to local tissue reactions, the potential systemic effects of metal ions from total joint replacements have caused much concern. Indeed, elevated levels

of cobalt and chromium ions have been described not only in periprosthetic tissues, but also in the blood and urine of MOM joint replacement recipients [137-139]. Although sporadic cases of systemic cobalt toxicity have been described [140, 141] the significance and the long-term effects of this systemic metal ion exposure remain to be determined. For example, studies have not found evidence of increased risk of neoplasia in patients with MOM implants, even though various metal ions display genotoxic effects in vitro, but the clinical follow-up times are still relatively short [142, 143].

The exact pathophysiological mechanisms leading to the local adverse host response associated with nano-sized metal particles and metal ions are still under vigorous investigation. In vitro and in vivo studies over the past decade have, however, shed some light on the matter. Various studies have reported that cobalt and chromium ions have a dose-dependent geno- and cytotoxic effect on several types of cells including macrophages, osteoblasts, fibroblasts and lymphocytes [12, 13]. For example, a study by Catelas et al. found that low concentrations of cobalt and chromium ions induced macrophage apoptosis, while larger ion concentrations caused macrophage necrosis [144]. These in vitro observations might directly explain the extensive areas of necrosis that are typical for the adverse host reaction associated with metal byproducts released from MOM implants. Likewise the cell necrosis with continued release of various danger signal molecules might partially explain the chronic inflammatory reaction with continued macrophage recruitment and activation.

Recently it was reported that cobalt ions can activate TLR4 signaling by directly binding to and crosslinking the receptor protein [145, 146]. The mechanism of cobalt induced TLR4 activation is analogous to that previously described for nickel ions, and is of significance at least for two reasons [14, 147]. Firstly the observation explains how cobalt ions elicit an inflammatory reaction and activation of macrophages and other cells. Secondly, as TLR signaling is one of the danger signal cues that is required to initiate effective antigen presentation to T helper cells, the observation links the activation of innate and adaptive immunity together (see below). Indeed, the early observations of cobalt ion induced macrophage activation and the accompanied upregulation of co-stimulatory molecules are likely explained by the now discovered cobalt-induced TLR4 signaling [148].

In addition to inducing cell death and macrophage activation, metal ions have an impact on various other cell types. For example, cobalt and chromium ions induce oxidative stress, inhibit osteoblast function and alter the balance of osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B (RANKL) production to favor bone resorption over formation in cultured osteoblasts [149-152]. Together with continued macrophage activation and production of pro-inflammatory cytokines, these observations might explain the sustained osteoclast formation and the development of peri-implant bone-loss. More recently it was reported that cobalt ions induce the activation of vascular

endothelial cells with increased production of chemokines and adhesion molecules that promote the recruitment and endothelial transmigration of lymphocytes [153]. This observation might partially explain the peri-vascular lymphocytic infiltrates commonly observed in the peri-prosthetic tissue surrounding MOM implants.

Finally, in addition to metal ions, various studies have shown that larger (around one micron sized) metal particles of various materials can directly activate macrophages and other cells in a similar manner that has been described for polyethylene and PMMA wear debris, such as direct recognition of protein coated particles by various pattern recognition receptors as well as by particle phagocytosis followed by endosomal damage and activation of intracellular danger signal mechanisms [78, 90, 154-156].

While the adverse host reaction associated with polyethylene and PMMA wear is often considered to be mediated solely by the innate immunity, it has been long speculated that adaptive immune response could play a significant role in the adverse tissue response to total joint replacement derived metal debris. This assumption is based on the well-characterized ability of metal ions to activate adaptive immunity via acting as haptens [157]. Haptens are small substances that do not elicit immune reactions as such but can become immunogenic when bound to a larger carrier molecule; in the case of metal ions these larger molecules are host proteins. The binding of metal ions alters the protein conformation so that immunogenic neo-epitopes are formed. In addition to hapten formation, metal ions can also alter the conformation of MHC molecules causing it to be recognized as foreign by T cells and can also activate T cell receptors directly (**Figure 5**).

The best known example of this metal allergy, or type IV hypersensitivity reaction, is nickel-induced contact dermatitis [158]. Nickel ions released from the metal in jewelry activate TLR4 signaling in dermal dendritic cells. Activation of this danger signaling pathway initiates dendritic cell maturation and migration to local lymphatic tissues. In the lymphatic tissues, mature dendritic cells present nickel haptens to the T lymphocyte population and some of the T cell are activated, assume Th1 polarization and migrate to the area of inflammation where they enhance the inflammatory reaction and regulate the function of macrophages and other cells. In addition to nickel, several other metals, including cobalt and chrome, are commonly known to induce contact dermatitis. However, dermal allergy towards titanium is a rarely encountered phenomenon.

Although the role of adaptive immunity is well established in the context of dermal metal allergy and contact dermatitis, the extent to which it contributes to reactions associated with total joint replacements and metal wear debris is still somewhat controversial. The presence of ALVAL lesions in the peri-implant tissue has been suggested to indicate adaptive immune response against implant derived metal debris [70, 131, 132, 134]. Indeed, two recent studies found that peri-

prosthetic metal content was correlated to the type of cell infiltrates, with low-metal concentrations being associated with macrophage-dominated infiltrates and higher metal content to lymphocyte dominated infiltrates [159, 160]. Other studies, however, have not seen a clear relationship between tissue metal content and the type of inflammatory cell infiltrates and even the specificity of ALVAL lesions to MOM byproducts has been questioned [133, 135, 136]. Furthermore, the activation state of lymphocytes in these lesions is not currently known.

Several studies have investigated the peripheral blood lymphocyte populations derived from total joint replacement recipients. Some of these studies have described Th1-type metal reactive lymphocyte subpopulations from total joint replacement recipients thus suggesting development of type IV hypersensitivity against implant derived metal byproducts [161-163]. A recent systematic review and meta-analysis of clinical studies investigating the relationship between MOM implant survivorship and metal allergy found that the occurrence of metal allergy was higher in patients with MOM implants but the metal allergy did not predict implant failure[164].

Thus the role of adaptive immunity in adverse tissue responses associated with total joint replacement derived metal debris still remains unanswered. One likely explanation for the uncertainty is that the detection of dermal metal allergy does not comprehensively reflect the immunological microeviroment of the deeper peri-implant tissue. Taken together, it seems likely that there exists a subset of particularly metal reactive patients in which adaptive immunity contributes to the adverse tissue reaction to metal debris, while in other individuals adaptive immunity plays a more minor role. This point is reflected by the development of typical ALVAL lesions with relatively minor implant wear and metal ion release in some patients, while in other cases the ALVAL lesions are associated with high implant wear and metal release with cell necrosis and development of pseudotumors.

E. Summary

Despite its long-term successes, TJR still faces many challenges. Indeed, the durability of TJR in elderly patients, and the need for and extension of these surgical procedures to younger, more active patients have highlighted some of the shortcomings of TJR.

Cemented and cementless joint replacements generally function favorably in elderly patients, and demonstrate 90% implant survivorship (without revision for mechanical reasons) for approximately 15-20 years or more. Assuming appropriate patient selection and surgical technique, this fact would usually lead to implant survivorship exceeding the patient's lifespan. The problem of wear of conventional polyethylene and subsequent periprosthetic osteolysis of hip replacements has generally been solved with the use of metal or ceramic femoral heads articulating with highly cross linked polyethylene liners, or COC bearings. Issues related to implant osseointegration in patients with normal bone have

generally been solved with the use of porous coated devices and other surface treatments, numerous implant sizes and meticulous surgical technique. This has lead to increased use of cementless implants for hip replacement worldwide. On the other hand, because of different anatomical and kinematic considerations, knee replacements are generally still cemented.

Hip and knee implants, once integrated with the surrounding tissues, wear at a reasonably slow rate with normal usage (i.e. avoidance of impact loading). The local inflammatory and foreign body reaction to wear byproducts is generally mitigated by biological systems that ensure a state of regional homeostasis. In particular, macrophages and other surveillance cells rid the tissues of wear debris without major local or systemic consequences.

However in some patients, usually younger, heavier, more active individuals with osteoarthritis in a limited number of joints, wear is more profound and thus the biological reaction to wear debris has been a major issue. These events may occur with bearings incorporating conventional (non-highly cross-linked) thinner polyethylene, and suboptimal implant design or surgical technique. In these cases, wear debris stimulates a cascade of events that can lead to chronic synovitis, periprosthetic osteolysis and pathologic fracture. These events are mediated primarily by inflammatory cells of the innate immune system, and bone resorbing osteoclasts. Complexes of wear particles and serum proteins stimulate Toll-like receptors (TLRs) and other surface integrins. Wear debris may be phagocytosed, leading to a cascade of inflammatory and reparative events involving numerous cell types, cytokines, chemokines, growth factors and other substances. If persistent, the acute inflammatory reaction transitions into a chronic phase, leading to continued osteolysis, fibrosis and ineffectual resolution and repair. Pain, implant loosening or failure is the end result. The biological attributes of the host are a major contributory factor to the intensity of these events. Some patients develop extensive osteolysis with minor polyethylene wear, whereas others develop little to no radiographic evidence of osteolysis despite advanced wear. The biological mechanisms that underlie these findings is still elusive. The degree of osteolysis is not always directly correlative with the amount of wear or wear debris generated. Indeed, one hypothesis attempts to define the degree of osteolysis with the presence of single nucleotide polymorphisms in the host [165-169]. Another hypothesis specifies that low-grade infection is more prevalent than previously thought, accounting in part for the degree of subsequent tissue destruction and osteolysis present [29, 170].

Further research is necessary to define the importance of these factors.

Metal-on-metal articulations are currently used sparingly, because of the development of metal debris and ions. These metallic byproducts can complex with serum proteins to form haptens, leading, in some cases, to both innate and adaptive immune responses. Similar debris can be generated from modular parts, such as the head-neck, neck-stem and other modular junctions. As

outlined above, these metallic complexes and ions can result in severe biological consequences termed histologically “adverse tissue reactions”, in some cases a Type IV hypersensitivity reaction to metal byproducts. The resultant macro-destructive findings may include widespread destruction of bone and soft tissue jeopardizing the function of the prosthesis. Unfortunately, in some cases, the outcome of revision surgery is less gratifying than with other causes of implant failure.

The ideal implant materials, design and bearing surfaces for all patients undergoing joint replacement have not been delineated. Obvious essential requirements including safety, efficacy and cost-effectiveness of the device must be considered with other factors including ease of implantation and extrication, and the physical activities enabled by the device. It will be difficult to exceed the successful outcomes afforded by currently used devices. Ongoing pre-clinical studies and well-designed clinical trials will undoubtedly discover novel implant materials and designs that will further improve the utility and durability of joint replacements.

F. Future Directions

Joint replacement still remains one of the most time-honored, cost-effective procedures in all of surgery. However, there is room for improvement and innovation to maximize the outcome for patients suffering from end-stage arthritis.

First, techniques for improved patient selection will identify the optimal patient characteristics to enhance clinical outcome and implant longevity. In this respect, databases and registries may play a key role.

Second, surgical technique, implants and instrumentation can be improved. Although minimally invasive techniques are controversial and have not been shown to increase objective outcome parameters, improved methods to reliably expose the joint with less trauma, implant the prosthesis more accurately, and rehabilitate the patient quickly will certainly improve the clinical result. This is important because in some countries in the Americas and Europe, hip and knee replacements are performed primarily by general orthopaedic surgeons who may do less than 20 arthroplasty cases per year.

Third, coating or modification of implants to obtain quicker, more robust integration with bone will also facilitate rehabilitation and functional outcome. This is especially important in patients with specific medical co-morbidities that inhibit bone ingrowth (certain drugs, smoking, diabetes etc.), poor bone quality, and in revision situations in which the vascularity and robustness of the remaining bone and soft tissue may be compromised.

Fourth, methods to prevent and combat infection of joint replacements are sorely needed. These methods may encompass local or systemic interventions.

Fifth, new materials and bearing surfaces, especially for younger, more active patients are needed. These implants should have a modulus of elasticity that is closer to bone than current more stiff metallic implants, to avoid adverse bone remodeling around the implant. Novel bearing surfaces that provide stable articulations with minimal wear are needed. Understanding the characteristics of the innate and adaptive immune reactions to implants and their byproducts will foster the development of novel materials and processing techniques.

Sixth, novel methods for peri-operative pain control and rehabilitation will speed recovery and facilitate the patient's re-integration into society after joint replacement.

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Figure Captions

Figure 1:
Left: Pre-operative radiograph of a right hip with severe degenerative arthritis associated with hip dysplasia and impingement (arrow).

Right: Post-operative radiograph with a modern, modular, porous coated, cementless metal-on-plastic total hip replacement.

Figure 2:
Left: Pre-operative radiograph of a left total hip replacement with a cementless cup and a loose, cemented stem, which as migrated away from the cement mantle so that it is no longer centralized. The cement mantle has cracked and there is cement particle associated periprosthetic bone loss (osteolysis – arrows). Note the bowing of the femur due to remodeling.

Right: Post-operative radiograph showing revision using a long-stem cementless femoral component. The femur was cut longitudinally to excise all of the cement and subsequently reduced and stabilized with wires (extended trochanteric femoral osteotomy).

Figure 3:
Left: Pre-operative radiograph of a left hip with severe polyethylene wear of the acetabular component. Note that the femoral head is not centralized in the cup, indicating severe polyethylene wear. There is bone destruction in the acetabulum, and greater trochanter of the femur (arrows) due to the wear particle-induced inflammation. The cementless stem is well-fixed.

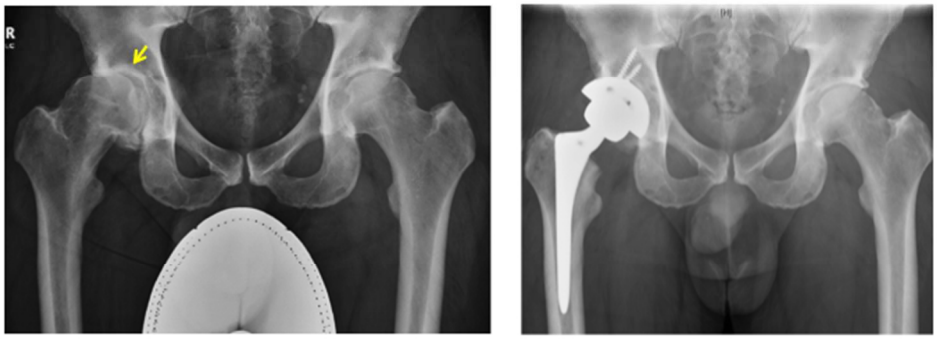
Right: Post-operative radiograph showing revision of the entire acetabular cup and modular femoral head exchange, with bone grafting of the areas of osteolysis.

Figure 4:
The balance between M1/M2 macrophages may influence the results of wear particle induced osteolysis. During wear particle induced chronic inflammation, infiltrated macrophages can recognize DAMP/PAMP/wear particles through TLRs. TLR activation enhances pro-inflammatory cytokine secretion including TNF-α, MCP-1, MIP1-α, IL-6, and IL-1β which leads to peri-prosthetic osteolysis. On the other hand, cytokines including IL-4, IL-10, or IL-13 can polarize macrophages into an M2 phenotype with anti-inflammatory functions. A decreased M1/M2 ratio of macrophages may therefore mitigate the osteolysis.

Figure 5.
Metal-induced activation of innate and adaptive immune systems. (a) Total joint replacement derived metal wear debris can activate the innate immune system via several mechanisms. Protein coated wear particles of approximately micron

size can activate macrophages and dendritic cells via recognition by TLRs and other PRRs. Metal ions activate innate immunity either indirectly by inducing cell necrosis and release of DAMP molecules, or in the case of cobalt ions, activating TLR4 signaling directly. TLR signaling induces dendritic cell maturation with increased expression of MHC-II and co-stimulatory molecules as well as cell migration to the local lymphatic tissue. At the same time macrophages and dendritic cells also phagocytose metal haptens, processing them along the endolysosomal route and finally presenting haptens on MHC-II molecule. (b) In lymphatic tissue, activated dendritic cells present metal haptens to the lymphocyte population. In genetically susceptible individuals, a subset of T lymphocytes recognize the neo-antigen with their T cell receptor and become activated assuming Th1-polarization and migrating back to the peri-implant tissues. (c) In peri-implant tissue immunocompetent Th1 cells recognize the macrophages that are presenting similar metal haptens and regulate their function by secreting such cytokines as IFN-γ. (d) IFN-γ secreted by the Th1 cells further enhances the metal-induced macrophage activation e.g. by increasing the expression of TLRs and the production of such pro-inflammatory factors as TNF-α and CCL2 that eventually lead to further macrophage recruitment and development of peri-implant bone loss.

Abbreviations: PAMP – Pathogen associated molecular pattern; DAMP – Danger associated molecular pattern; TLRs – Toll-like receptors; PRRs – Patter recognition receptors; MHC-II – Major histocompatibility complex class II: TCR – T cell receptor; CD – Cluster of differentiation; IL – Interleukin; IFN – Interferon; TNF – Tumor necrosis factor



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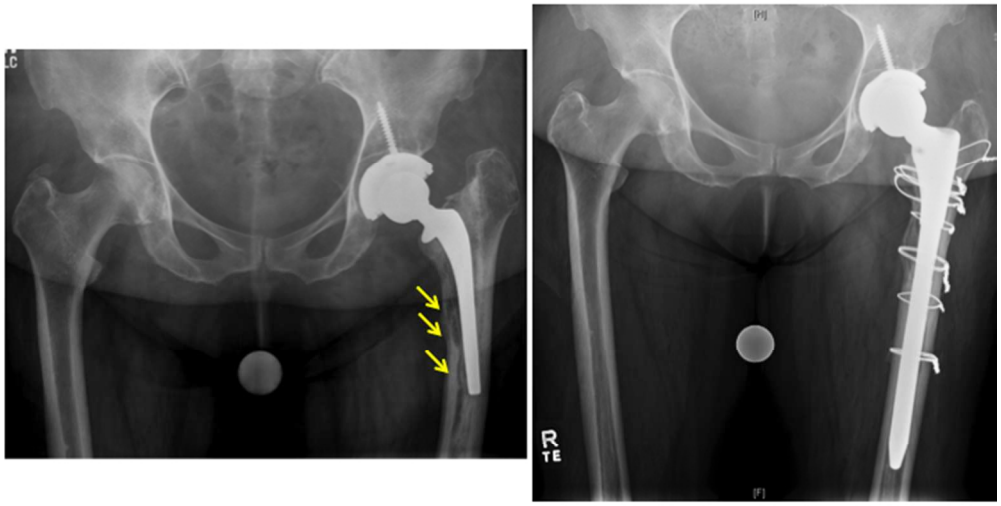
254x142mm (72 x 72 DPI)



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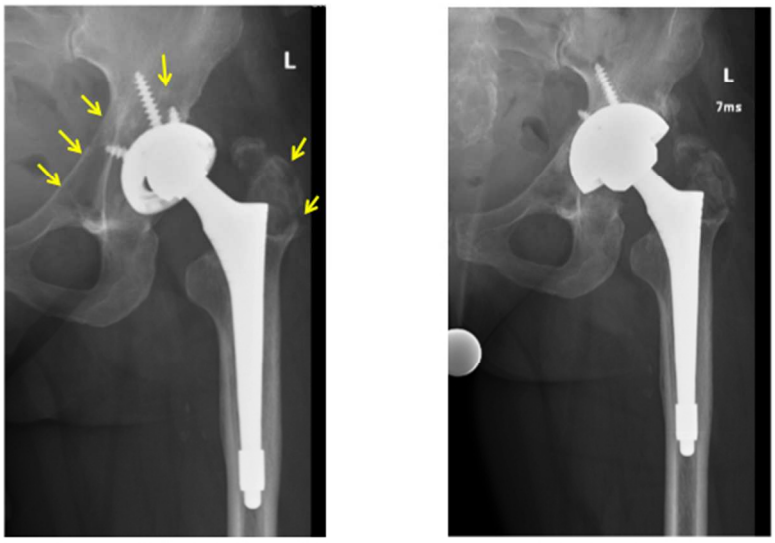

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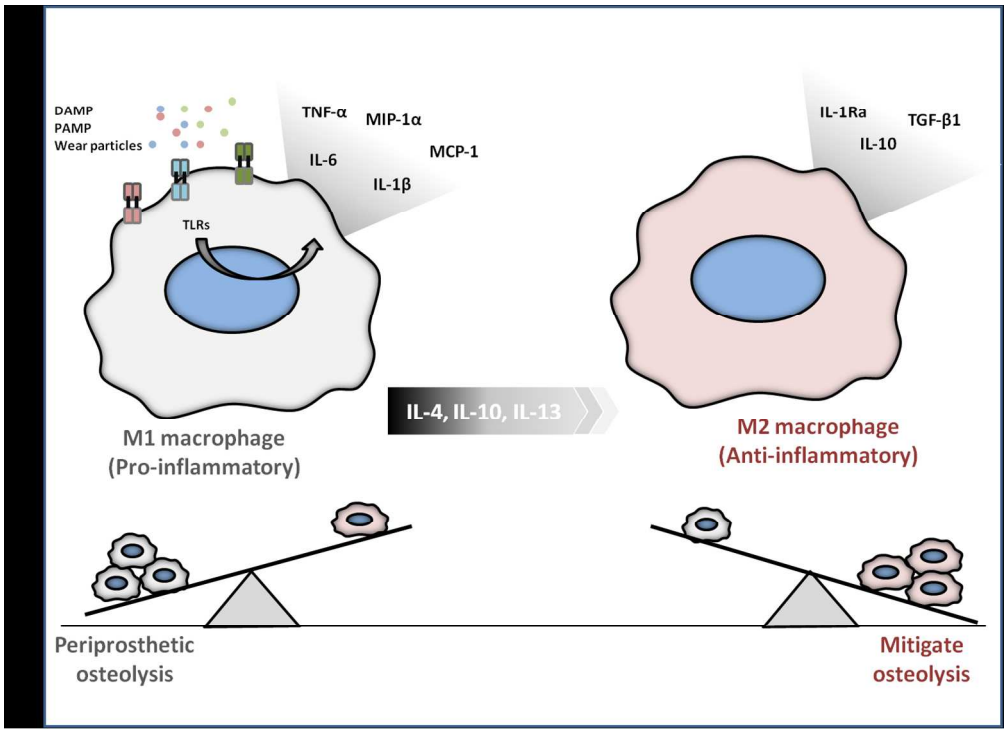

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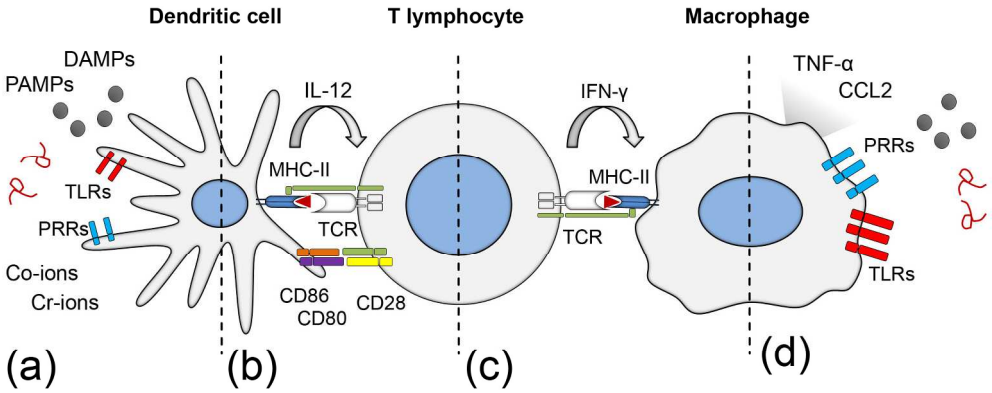

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199x97mm (300 x 300 DPI)