The Biology of Aseptic Loosening

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Introduction

Total joint replacement is an effective surgical intervention for those patients with end stage of joint diseases. The major factor limiting the survival of joint implants is wear debris which is primarily generated from the bearing articular surface of the artificial joint. Aseptic loosening is a disabling condition affecting patients 10–20 years after joint replacement surgery, leading to the failure of the artificial joint. It appears as a subtle progression of bone tissue destruction (osteolysis, periprosthetic bone loss). It is a major challenge for orthopedic surgeons due to the fact that signs and symptoms may not be clinically apparent until the late stages of destruction and failure [1].

There are several theories related to the appearance of the biological phenomenon of aseptic loosing (wear particle disease, high fluid pressure, micromotion, stress shielding, endotoxin, genetic susceptibility). Particle disease (cement, polyethylene, metal, ceramic) is currently the dominant theory. In order to understand osteolysis and aseptic loosening, we have first to consider that following the implantation of an either cemented or cementless prosthesis, the bone-implant interface passes from an initial face of trauma and inflammation to an early (3–4 months) static stage of healing and mechanical stability (early stability). The interface remains in a biological and mechanical steady state condition for a varying period of time. Later it becomes unstable due to inadequate initial fixation (rarely seen today because of improved surgical techniques and implants), mechanical loss of fixation over time, and biological loss of fixation due to particle-induced osteolysis. This phenomenon is really a complex network of mechanical, cellular, and inflammatory responses [1]. It first appeared in the literature as "the cement disease" (Fig. 11.1), and as a result a boost in the development of cementless implants took place. Later, it became obvious that osteolysis and aseptic loosening are also seen with the use of cementless implants (Fig. 11.2), and thus the multifactorial nature of this biological process was uncovered.

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Comments on Causative Theories

Micromotion

Micromotion, as measured by radiostereometric analysis (RSA) on the clinical setting, if it exceeds a certain threshold, does not lead to

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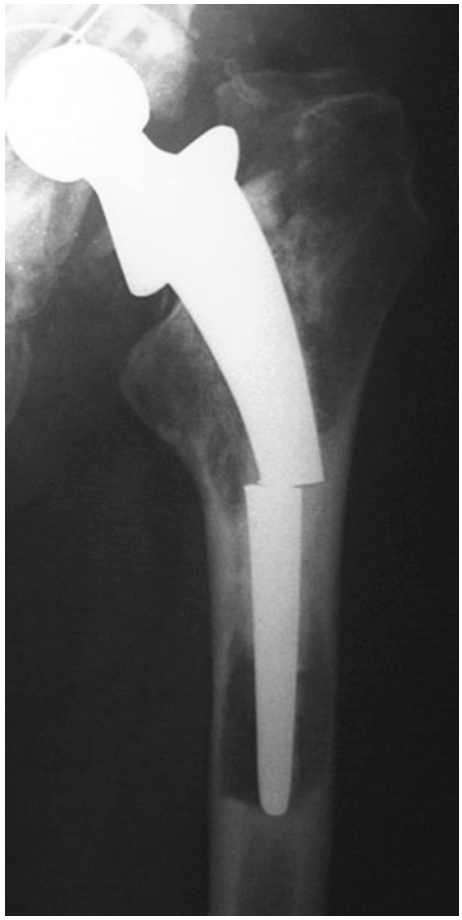

Fig. 11.1 Radiographs of a failed cemented early THA design. This radiological appearance was initially named "cement disease"

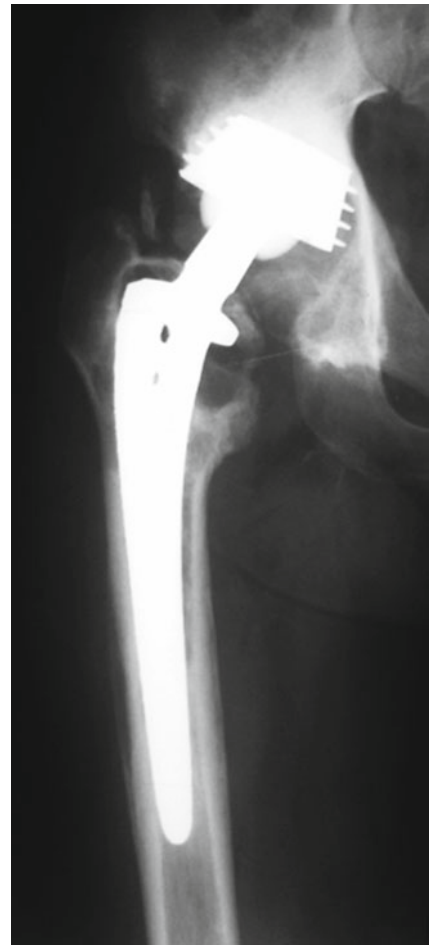

Fig. 11.2 Radiographs of a failed cementless early THA design. This kind of radiological appearance made orthopedic surgeons start thinking that osteolysis is not just a "cement disease"

osteointegration of the implant. Just like the stabilization of a fracture which is essential for porous formation, the lack of initial stabilization of the implant inhibits bone formation and osteointegration. The threshold of micromotion that enables the formation of bone and not of weak fibrous tissue is between 20 and 40 μstrains. The clinical relevance of abnormal micromotion is the existence of weak areas in the bone-implant interface where fiber develops instead of a closed apposition of bone from where joint fluid and wear particles can reach the interface, accumulate, and initiate the biological process of osteolysis. Even in mechanically and biologically stable interfaces, cycling dynamic loading and micromotion causes a time-dependent bone structural adaptation and, eventually, fatigue bone tissue damage, microfractures, microcracks propagation, and interface separation. The latter creates weak areas through which wear particles can reach the interface (Fig. 11.3).

Stress Shielding

Stress shielding theory refers to bone loss around the implant due to bone adaptive mechanical remodeling and not due to osteolysis. The radiographic marks are quite different from osteolysis (normal architecture with trabecular bone but

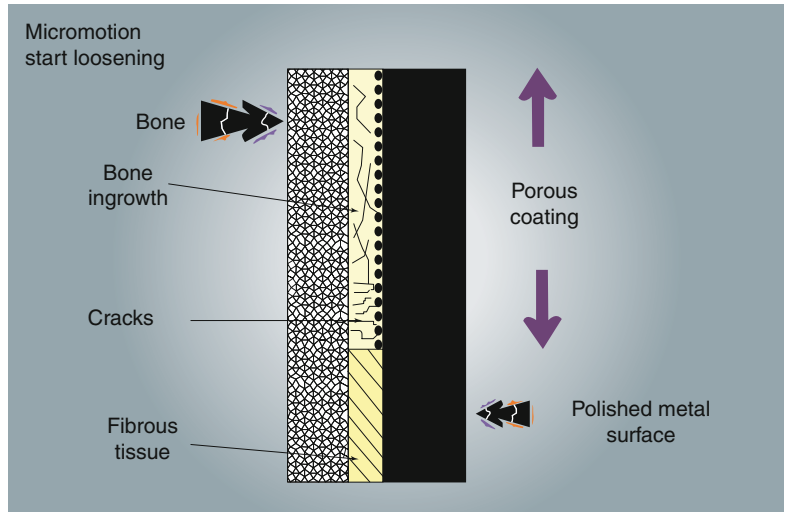

Fig. 11.3 Line drawing showing the pathway with which wear particles can reach the interface

osteopenia). Stress shielding may contribute to wear debris osteolysis by opening of pathways to the bone-implant interface.

High Fluid Pressure

High fluid pressure is related to the effective joint space theory (a closed space around the artificial joint, which contains fluid loaded with wear particle debris) and to the dynamic loading of the artificial joint during walking, accelerating the transfer of wear particles through weak areas to the interface (pumping-hydraulic phenomena) [2, 3]. We now know that hydraulic phenomena facilitate and maintain the osteolytic process. This theory also highlights the fact that high pressure causes osteocyte and chondrocyte death [2], especially in the presence of a loose implant. The death of osteocytes eventually leads to osteolysis and loosening. Higher intracapsular pressure has been measured in loose implants compared with stable implants [3]. Fluid pressure can reach up to 198 mmHg and it has been shown that oscillating pressure between 70 and 150 mmHg induces osteocyte apoptosis and osteolysis [4, 5]. In addition, cyclic loading (in cases of impaired implant fixation) and polyethylene wear debris act synergistically to activate macrophages and induce osteolysis [6]. Another important issue related to aseptic loosening is the presence of endotoxins in a loose interface.

Endotoxins

Endotoxins are found in wear particles and it is assumed that they derive from the transient presence of bacteria in the joint [6, 7], from contaminated implants, or from systemic endotoxins derived from intestinal flora and dental procedures. Recent AAOS guidelines, however, point out that there is limited evidence for the utilization of antibiotics in preventing implant loosening [8]. It is accepted that even dead bacteria with parts of their cell membrane containing endotoxin (lipopolysaccharide, lipoteichoic acid) are capable of macrophage activation and osteolysis [9]. The formation of biofilms on the implants has been proposed as a source of LPS and the continuing activation of macrophages in "aseptic" loosening [10]. In the early period of osteointegration, transient bacteremia may activate macrophages to initiate bone resorption. Osteointegrated implants are more resistant to aseptic loosening [11]. It is thought that early research on wear debris was done with particles covered with endotoxin. Ti particles preparation to remove endotoxin resulted in a reduction of osteolysis by 50–70 % in experiments [12]. The addition of antibiotics to cement has been associated with 50 % reduction in revision arthroplasties [13]. However, the exact role of endotoxins in aseptic loosening has not been clarified yet. *The genetic predisposition* for aseptic loosening has also been investigated. It is believed that some patients are

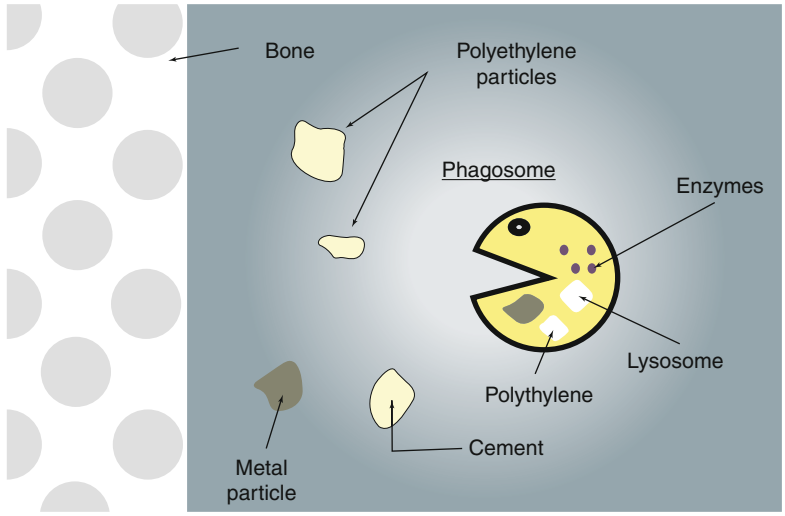

Fig. 11.4 Line drawing showing phagocytosis of wear particles by macrophages

"implant looseners" [14, 15]. Variable activation of macrophages and cytokines production has been shown in different patients in the presence of the same amount of PE particles [13]. Wilkinson et al. found that the allele 238A in the promoter region of TNF is associated with increased incidence (odds ratio 1.7) of aseptic loosening [16]. Another study found an inverse relationship between single nucleotide polymorphism (SNP) rs419598 in IL-1Ra and osteolysis [17]. Conflicting evidence exists for polymorphisms in IL-6 gene and aseptic loosening [15]. Furthermore, the C allele in metalloproteinase MMP-1 is associated with aseptic failure [18]. Genetic variation of the FRZB gene (which encodes Frizzled-related protein 3, a molecule in the Wnt pathway) correlates with reduced osteolysis [17].

We now know that the biological process of osteolysis and aseptic loosening is complex, a mechanical and biological phenomenon (at least in the late stages) with particle disease being a key element. An in-depth understanding of this process is necessary in order to prevent it and to develop therapeutic strategies.

Particle Disease

The pathogenesis of implant-associated osteolysis includes wear particle generation, an inflammatory process, and an osteolytic process. Wear debris is produced mainly from the prosthetic articulation, modular implant interfaces, nonarticulating interfaces, and impingement areas. It is estimated that during each gait cycle tens of thousands particles (<5 μm in size) are produced. Other sources of particle accumulation are implant surface wear, corrosion in response to micromotion, oxidative reactions, and pathogen contamination. The initial response is a nonspecific foreign body reaction with the characteristics of a localized pro-inflammatory reaction, increased circulation, elevated fluid levels, formation of fibrous tissue around the implant (poorly vascularized granulomatous tissue), and synovial lining membranes. Pro-inflammatory factors are secreted (gelatinases, proteases) which leads to the initiation of interface degradation. Particle phagocytosis is an important component of the local cellular response and depends mainly on the size of the particle (particles from 2 to 10 undergo phagocytosis by macrophages and removal from the interface area) (Fig. 11.4). It seems that there is a certain threshold after which an activation of a cellular and biochemical signaling mechanism starts (Fig. 11.5). A local chronic inflammatory response follows with the recruitment of a variety of cell populations which express osteoclastic and osteolytic activity (Fig. 11.6). Locally, a secretion of osteoclastogenic and inflammatory cytokines, an exacerbated osteoclastic activity and enhanced osteolysis and a vicious circle of tissue reaction leads to the formation of the aseptic loosening

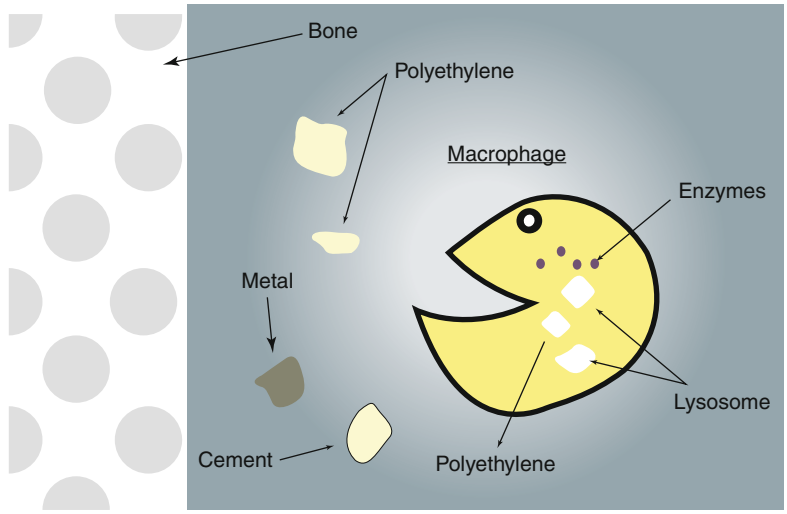

Fig. 11.5 Line drawing showing that macrophages, within limits, have the ability to "digest" and remove particles

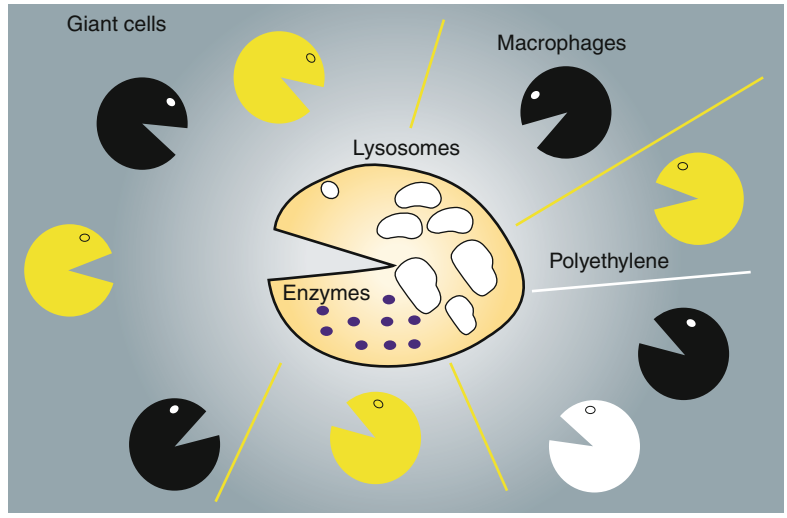

Fig. 11.6 Line drawing showing that above a threshold an activation of a cellular and biochemical signaling mechanism takes place

membrane. Particles which can be removed by macrophage undergo a lymphatic transport to local lymph nodes, to the spleen, to the liver, and possibly to other organs causing granulomatoid lesions. The biological response varies related to the number, charge, composition, surface, size, and surface of the particles.

Particle Production

Wear particle disease is the main biological phenomenon causing osteolysis and aseptic loosening. Bone cement (PMMA) has been initially investigated as a source of wear particles [19]. Bone cement, which has been popularized by Charnley, is responsible for the production of particles that cause osteolysis. The rate of production is thought to be correlated to cement porosity, time (as bone cement ages, more microcracks are generated) [20, 21], the pattern of forces acting on cement (compressive forces on knees and acetabulum or shearing forces in femoral stem), and the debonding of the cement-implant interface (polished, pre-coated, or blasted) [22, 23]. Several implant modifications and techniques have been introduced in order to reduce the production of bone cement particles. Vacuum mixing of the

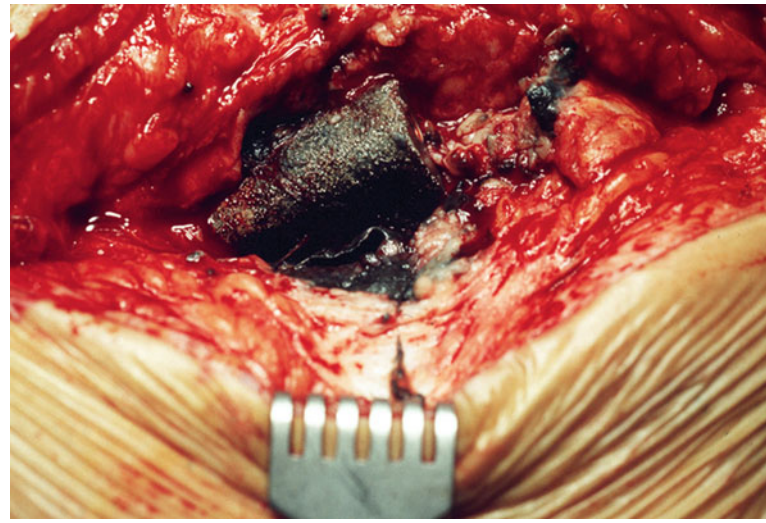

Fig. 11.7 "Black tissue staining" caused by metallic wear debris

cement and pressurization with a cement gun and distal plug reduce porosity, microfracture imitation, and wear production. Pre-coated or blasted stem implants were developed in order to increase the bond between cement and implant and to decrease the effective joint space where wear particles can accumulate. Investigating periprosthetic membranes from loose implants, Willert et al. found that cement particles are generated first and polyethylene particles follow as a result of third-body wear [18]. Both cement and polyethylene particles can cause osteolysis. Polyethylene particles (<5 μmon average of random shape) are also capable of the activation of osteolysis. Factors affecting polyethylene wear and the production of particles are the type of resin, the manufacturing method (ram extrusion or compression molding), the sterilization method, the presence of cross-links which increase wear resistance, and the shelf life of the product (oxidative degradation occurs when storing the implants). Polyethylene wear and particles are produced mostly through abrasion in the hip joint and through abrasion and delamination in the knee joint. An important issue is the rate of wear. Studies have shown that the rate of 0.1 mm/year is not associated with aseptic loosening, while a rate 0.2 mm/year or more is [24]. Additionally, there are differences between the knee and hip artificial joints [25]. Particles from the hip joint are smaller in size. This means that high fluid pressures can be produced, and a smaller amount of debris is required to start the phenomenon of aseptic loosening. As far as the knee is concerned, the introduction of modularity has had, as a result, the production of backside PE wear. The development of high cross-linked PE through radiation and melting or annealing increased wear resistance [26, 27]. The addition of Vit E and sequential annealing was introduced in an attempt to reduce the free radicals of radiation [28, 29]. Metal-on-metal bearing coupling is characterized by low wear particle production (2.5–5 μm/year) [30]. Biological reaction around metal particles depends on particle size (nanoparticles), corrosion products, and metal ions (Fig. 11.7). The size of the metal particles is small (average size 50 nm) [31], so they are easily phagocytosed and easily corroded and excreted from the kidneys. Round nanoparticles are more easily phagocytosed than rod-shaped ones. The mechanism of entrance into the cells includes diffusion, pinocytosis, or receptor-mediated endocytosis (clathrin). Cellular uptake is facilitated by positively charged metal nanoparticles [32]. Despite increased wear resistance, both cobalt chrome and titanium particles are capable of macrophage activation, osteolytic cytokine production, and aseptic loosening [33–35]. Concerns about metal-on-metal bearings include the possibility of renal impairment and carcinogenesis by metal ions released by bio-corrosion. Metal ions are released from the surface of the implant because of corrosion and failure of the

oxidized layer covering the implant. Metal ions (especially Co) are cytotoxic in a dose- and time-dependent manner. Ti ions, especially, bind to phosphorous-containing molecules in cells like euchromatin in the nucleus, ribosomes in the cytoplasm, and phospholipids in the membrane, interfering with cellular pathways and functions. Neither kidney failure nor carcinogenesis has been proved except for hematopoietic cancer [36, 37]. On the contrary, there is concern about the hypersensitivity reaction of type IV (ALVAL) and the creation of pseudotumors [38, 39]. These represent variations in the spectrum of metal sensitivity. Metal sensitivity is characterized by lymphocyte reaction and relative low wear, while reaction to PE particles or PMMA is characterized by high wear and predominantly macrophage activation. Metal ions (Ti) are nonantigenic but when bound with serum proteins like albumin can induce the formation of specific T lymphocytes [40]. These cells can induce hypersensitivity reactions [41]. So the type of immune reaction to metal particles is different from the immune reaction to PMMA. PMMA and metal particles induce different pro-inflammatory cytokines (TNF-a, IL-1, IL-6 for the former and IL-2, INF-γ, IL-22 for the latter) and different chemokines (increased production of IL-8 in Ti particles only), resulting in different tissue reactions independent of the number and quantity of produced wear debris [42]. Ceramic-on-ceramic prostheses have even more wear resistance (0.5–2.5 μm/year) [43]. With normal loading conditions the wear rate is 0.1 mm^3/one million cycles, but it can increase to 1.24–1.74 mm^3/one million cycles when there is micro-separation of the prosthesis components [44]. Ceramics are also capable of activating macrophages and inducing osteolysis [45, 46]. Alumina wear debris has a bimodal distribution with larger particles (0.05–3.2 μm) coming from micro-separation and rim loading and acting like UHMWP particles. Smaller particles (5–90 nm) come from physiologic contact and act more like metal particles [45] but are less toxic than metal particles. Fewer macrophages and no giant cells have been observed around all ceramic arthroplasties [47]. This is due to the fact that all ceramic arthroplasties produce a lesser amount of particles to stimulate macrophages and are not big enough to induce macrophage fusion as giant cells. However, the production of smaller particles when exceeding a certain threshold can be toxic to cells. Smaller ceramic particles have a reduced oxidation state and release more toxic ions. This is supported by the fact that more necrosis is identified around all ceramic arthroplasties compared with metal on PE arthroplasties. The size and the morphology of the particles have played a major role in inflammation, induced by wear debris. Most particles are smaller than 0.5 μm [48], and it has been shown that macrophage activation is greater with smaller (<20 μm) particles [49]. Polyethylene particles of 0.24 μm are most biologically reactive [49].

Aseptic Loosening Pathways

A large number of cells and molecules are implicated in the biological process of aseptic loosening. The precise mechanism is not fully understood and probably is complicated, but the initial cell that starts the reaction is the macrophage. The cell that is responsible afterwards for the osteolysis is the osteoclast through the RANKL-RANK-OPG-NF-κB axis. Other cells that contribute to loosening are the osteoblasts and the lymphocytes (Th1, Th2, Th17). The molecules that are critical in interactions between cells are the TNF-a, IL1, IL18, IL17, IL6, IL10, and INF-γ. The main cascade of reactions includes the PMMA, polyethylene, titanium, metallic, or ceramic particles being phagocytosed by macrophages. Macrophages produce TNF-a, IL1, and metalloproteinases which activate the bone-resorbing osteoclasts through the RANKL-RANK axis. Metalloproteinases, on the other hand, cause destruction of the extracellular matrix. This main interaction is enhanced by other cells (osteoblasts, lymphocytes), cytokines (IL6, IL10, IL17, IL18), and pathways (Wnt, ADP/ATP pathways, complement).

The first evidence that wear debris causes osteolysis was the correlation between the production of wear debris and the rate of aseptic loosening [50–53].

Macrophages have been shown to be activated by wear debris. The activation includes

either phagocytosis [54] of particle debris or direct interaction with the particles of critical size [55, 56] and shape [57]. Direct interaction involves the complement receptor CR3 (in case of PMMA, PE, titanium particle) [58, 59] and the scavenger receptor MARCO (in case of titanium particles) [60]. Metal particles/ions are capable of activating the inflammasome pathway in which metal ions induce inflammasome proteins activation (NADPH/ROS, nalp3) and activate caspase to produce IL-1 from inactive form [61]. In turn, IL-1 feeds back in a paracrine manner to produce TNF-a through the NFκB pathway in macrophages. Another possible mechanism of activation and production of pro-inflammatory cytokines is through activation of protein tyrosine kinases (PTKs). Macrophage PTKs are activated by titanium particle wear and are necessary for phagocytosis and mediator release [62]. Activation of macrophages results in the production of inflammatory mediators like TNF-a, IL-1β, IL-6, and PGE2. This activation has been shown experimentally in vitro, in the calvarium modeland in mice [63]. Specifically, PE wear or titanium and ceramic particles are capable of inflammation induction in rat models [64]. Studies in humans are less clear [65–67] but also show the macrophage activation in the periprosthetic membrane. Joint fluid and periprosthetic membrane analyses in conjunction with in situ hybridization reveal increased TNF-a in patients with osteolysis [67]. Lastly, macrophages are capable of RANKL production which promotes osteoclastogenesis. The activation of macrophages to pro-inflammatory subtype requires two signal steps. Apart from phagocytosis, a second danger signal is essential for activation (either pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide or endogenous danger molecules (DAMPs)). In the case of metal particles, it was thought that endotoxin (LPS) is the second signal, but recently, it has been shown that metal ions can stimulate toll-like receptor 4 (TLR4), a receptor of PAMPs [68]. The next main step in the cascade of osteolysis is the production of pro-inflammatory cytokines (TNF-a, IL-1, IL-6). As mentioned above TNF is an osteoclastogenic cytokine found in periprosthetic membranes and increases with the presence of particle wear. It facilitates the production of other cytokines like IL-1, IL-6, IL-8, and GM-CSF (the latter is necessary for the maturation of progenitor cells to osteoclasts) [66, 68]. It acts on stromal cells and osteoblasts to produce RANKL. Subsequently, it acts synergistically with RANKL on osteoclasts to promote maturation. The activation of the TNF receptor results in NK-κB pathway activation [63]. TNF-a acts directly on osteoclasts precursors, while IL-1 acts indirectly by increasing the production of RANKL and M-CSF from osteoblasts and stromal cells. IL-1 is a cytokine with osteoclastogenic actions. First of all it acts on stromal cells and osteoblasts to produce RANKL, induces the production of TNF-a [69], helps TNF-a-depended RANKL production in stromal cells (through expression of IL-1RI), and finally acts as a costimulatory in osteoclast formation. Again, the activation of IL-1 results in NK-κB pathway activation [70]. The transfer of interleukin-1 receptor antagonist (IL-1Ra) gene in a model of UHMWPE osteolysis resulted in reduction of IL-1 and TNF-a [71]. It is important to mention that different metals produce different kind of cytokines. Cobalt-chromium particles produce predominantly TNF-a, while Ti particles mediate an IL-6 response [72, 73]. This may have implications in therapy. IL-6 (as well as IL-11) has the additional property of activating osteoclasts in a RANKL-independent way which under physiologic conditions is not apparent but, in case of inflammatory conditions with cytokine production, like aseptic loosening, may play a vital role. IL-6 in the presence of M-CSF, acts through IL-6R in macrophages activating the gp130 pathway and inducing osteoclastogenesis. This is not inhibited by OPG or RANK antibodies [74]. The exact role of IL-6 is not yet clear as it has been shown that it has an anti-osteoclastogenic effect on precursor cells in a metal wear particle model through a negative feedback loop of TNF-a production [75]. Probably the indirect (through osteoblasts) pro-osteoclastogenic effect of IL-6 is more robust than the direct anti-osteoclastogenic effect on osteoclasts. TNF-a and IL-1 polymorphisms have an impact on the risk of aseptic loosening [16, 76]. PGE2, an inflammation

mediator, is produced by macrophages activated by wear particles. Cox-2, which produces PGE2, is essential for osteoclastogenesis and the production of prostaglandins [76, 77].

Osteoblasts and stromal cells are linked with the formation of osteoclast through the RANKL axis. Activated osteoblasts produce RANKL that promotes the osteoclast formation. In addition, the wear particles have a direct influence on osteoblasts. Firstly, particle wear induces mesenchymal stem cell apoptosis [78], osteoblasts apoptosis [79], and reduced differentiation of MSC to osteoblasts [80]. As a result, bone formation is impaired. On the other hand, wear debris (metal or polyethylene) halts the formation of collagen type I [81, 82] and the production of the matrix by osteoblasts [83]. Osteoblasts enter in a catabolic state. In addition, decreased IGF-I was found in periprosthetic interface tissue of loose implants. IGF-I is a growth factor acting on osteoblasts, so the reduction of this growth factor is associated with bone loss [84]. The activated cells (macrophages, lymphocytes, osteoblasts) produce RANKL as an end result. The RANKL-RANK-OPG-NK-κB axis is the main pathway that drives the osteolysis around the implants. RANKL, a member of TNF superfamily, is produced by mature osteoblasts, stromal cells, macrophages, and lymphocytes. It can be found as membrane-anchored protein and less often as a free molecule after cleavage [85]. It acts on RANK in osteoclasts precursors and stimulates the differentiation to mature osteoclasts mediating wear debris osteolysis. Other conditions where T lymphocyte-produced RANKL causes osteolysis are asthma, autoimmune diseases, chronic viral infections, cancers, and periodontal disease [86]. RANK (receptor activator of NK-κB) is also a member of the TNF superfamily and is found on the surface of precursors of osteoclasts, mature osteoclasts, chondrocytes, and mammary epithelial cells [87]. The absence of RANK in genetic modified mice results in the inhibition of osteoclast formation [88]. The downstream pathway includes activation of NK-κB primarily and recruitment of protein kinase A and protein kinase C. NK-κB exists as dimmers in cytoplasm, and when the RANK is activated NK-κB disengages from inhibitory proteins (IκB) and travels to the nucleus where it acts as a transcription factor, mediating the expression of genes implicated in osteoclastogenesis (rcas). PMMA wear particles induce activation of precursor osteoclasts cells through NK-κB translocation in the nucleus and DNA binding. Inhibition of NK-κB halts this DNA binding and osteoclastogenesis [89]. In addition NK-κB is involved in the stress response cataract of the cell and regulates apoptosis and inflammation [90]. The other molecule that orchestrates the osteoclastogenesis together with the RANKL is osteoprotegerin (OPG). OPG is a competitive inhibitor of the RANKL, causing inhibition of the RANKL-RANK therefore inhibiting osteoclastogenesis [91]. Mice deficient of OPG are osteoporotic while transgenic mice with increased OPG have osteopetrosis [92, 93]. OPG is also increased by estrogens, explaining menopausal osteoporosis [94]. OPG blocks osteoclastogenesis of precursor cells by fluid of aseptic loosened arthroplasties and inhibits wear debris osteolysis [89, 95]. Gene transfer of the OPG gene in an osteolysis animal model caused reduction in calcium production and a decrease in RANK [96]. In general, all factors that affect osteoclastogenesis and osteolysis bottom down to the influence they have in the RANKL/OPG ratio. The osteoclast, the only bone-resorbing cell, mitigates the phenomenon of osteolysis. Osteoclast is a multinucleated cell that comes from the differentiation of precursor cells of monocyte/macrophage lineage [97]. Osteoclasts are found in abundance in the periprosthetic tissues of loose implants [98]. In addition, in these tissues there is an increased expression of chemokines like MCP-1, MIP-1-a, and IL-8. Thus, there is recruitment of precursor cells through the CCR1 receptor in the areas of osteolysis [99–101]. Differentiation of precursor cells by wear debris is done in two ways. Firstly, as described previously, through the production of RANKL by activated stromal cells by phagocytosed wear particles. Secondly by inhibition of interferon gamma and IL-6 signaling in precursor cells by wear debris. Both these molecules suppress preosteoclast differentiation [102]. Osteoclasts have also the ability to directly cor-

rode metal and release metal ions, increasing inflammation. It has been shown that osteoclasts can grow on stainless steel and produce osteolytic pits. The release of the metal ions increased the production of pro-inflammatory cytokines, which further activates osteoclasts and thus enhancing the vicious cycle [103]. Lastly metal ions (Co) have a direct influence in osteoclasts, activating them through chemical hypoxia. Co inhibits HIF prolyl hydroxylases (PHDs), activating hypoxia-inducible factor-alpha (HIF-a), and stimulates osteoclast formation [104]. The bone resorption by osteoclasts is mediated by the raffled border of the osteoclast which contains H-ATPase and lowers the pH. Low pH enhances dissolution of hydroxyapatite. After demineralization, collagen is degraded by cathepsin K. Cathepsin is found in macrophages after activation with particle wear and more interestingly in periprosthetic membranes of loose implants with low pH. Maybe the low pH near loose implants together with the cathepsin which is activated by low pH may contribute to bone loss [105].

Other Cells, Molecules, and Pathways

Besides the main cataract of osteolysis, there are other cells contributing to osteolysis, molecules interacting with osteoclasts, and alternative pathways in osteolysis. Osteocytes, the end result of osteoblast differentiation, which consist up to 90 % of the cells of the bone may be involved in the initiation of osteolysis. Osteocytes are known to sense microfracture, which results in apoptosis through TNF-a, and recruit osteoclasts. This apoptotic phenomenon can also begin with metal implant debris acting on osteocytes [106]. In particular metal particles can activate calcineurin, leading to the dephosphorylation and nuclear translocation of nuclear factor of activated T-cell (NFAT) proteins in the nucleus. Subsequently NFAT activates the expression of TNF-a [107]. In addition SOST/sclerostin production of osteocytes (which reduces bone formation) has been shown to increase when osteocytes are challenged by particle wear [108]. Mesenchymal stem cells (MSC) are also affected by particle wear. Stem cells endocytose titanium particles resulting in suppression of osteogenic differentiation and apoptosis. So there is an imbalance between osteoblasts formation from stem cells which decreases and osteoclast formation from inflammation which increases. Production of osteogenic molecules like BMP-6, IGF-1, and FGF-2 by MSC is decreased when exposed to Ti debris [109]. Mesenchymal stem cells treated with titanium particles produce IL-8, a potent chemokine, which is associated with implant loosening [110]. Fibroblasts are abundant in tissues retrieved from loose implants. Challenged with particle wear, fibroblasts increase the production of metalloproteinases like gelatinase A, collagenase, stromelysin, and tissue inhibitor of metalloproteinases [111]. All these promote the degradation of extracellular bone matrix contributing to the osteolysis phenomenon [112]. In addition synovial fibroblasts have been shown to produce RANKL in a COX-2-depended manner when stimulated with titanium particles. PGE2 acts on EP4 receptor of fibroblasts which is coupled with Gsa proteins and activates protein kinase C (PKC). This pathway leads to the production of RANKL. All these suggest the contribution of fibroblasts in aseptic loosening [113]. Lymphocytes are implicated in osteolysis caused by particle debris. They play major role in metal sensitivity. They are found in periprosthetic tissue, are capable of producing anti-osteoclastogenic (INF-γ, IL-4, IL-10), or osteoclastogenic (RANKL) cytokines [114–116]. In particular Th2 lymphocytes produce IL-4, and it has been shown that patients with erosive disease have decreased IL-4 mRNA [117]. In addition lymphocytes are involved with late-onset hypersensitivity reactions in metal-on-metal arthroplasties. The formation of pseudotumors (painful effusion or solid or cystic mass) around total hip arthroplasties is characterized histologically by diffuse and perivascular infiltration of B and T lymphocytes. The immunoreaction of lymphocytes in Ti particles can be either positive (activating the lymphocytes) or of no effect, probably, reflecting the individual predisposition for metal sensitivity. Metal ions (nickel, cobalt) linked with proteins are immunogenic and produce T lymphocytes specific for metals. Even if

failed hip arthroplasties have been reported in conjunction with hypersensitivity reactions and there is increased incident of hypersensitivity in failed implants, the causative role of hypersensitivity and osteolysis has not been robustly established [118]. In the case of metal-on-metal arthroplasties, however, excessive osteolysis has raised the possibility of metal ion-induced T-cell-mediated delayed hypersensitivity reaction. Metal ions when bound to self proteins change their structure and are presented by MHC class II on the surface. Therefore, they are recognized as non-self peptides by T-cell receptors (TCR) initiating the hypersensitivity reaction. Moreover, metal ions bound with proteins can reveal immunogenic epitopes of these proteins, can alter MHC molecules so TCRs recognize them as presented by foreign tissue, and can act as superantigens promoting polyclonal T-cell activation [119]. Activation of T-cells needs a second signal, and this comes from metal ion binding in TLR4. Another type of T lymphocyte (Th17) involved in inflammation and autoimmunity may play a role in osteolysis. The production of IL-17 by these cells can stimulate the production of RANKL by osteoblasts or directly produce RANKL [120]. Th17 cells are produced by naive T lymphocytes in the presence of TGF-β and IL-6 [121] and need IL-23 for Th17 stabilization. The source of IL-23 is the macrophage. Neurogenic inflammation also contributes to osteolysis and aseptic loosening. Substance P (SP) axons have been identified in periprosthetic membranes of loose implants. In a mouse model SP-deficient animals treated with UHMWPE particles had reduced osteolysis, smaller numbers of osteoclasts, and increased bone mass. This type of inflammation mediated by the nervous system has a role in aseptic loosening [122]. Besides, IL-18, which is a member of the IL-1 family, blocks particle-induced osteoclastogenesis. IL-18 is committed to the Th1 cells and acts synergistically with IL-12 to expand Th1 cells. Holt et al. have shown that IL-18 can inhibit wear debris-induced osteolysis in vitro [123]. IL-10, an anti-inflammatory cytokine, may also play a role in downregulation of inflammation in aseptic loosening. IL-10 is a cytokine produced by T regulatory lymphocytes. Gene transfer of IL-10 in an animal model of wear debris osteolysis resulted in decreased production of IL-1β and TNF-a [71]. The role of chemokines is also important to osteolysis. As previously mentioned, the CCR1 receptor in precursor osteoclast cells is important in recruitment in areas of osteolysis. Other chemokines like CCL17 and CCL22 have been found to be upregulated in osteoclast and osteoblasts by titanium particles. In addition, metal particles upregulate the CCR4 (whose legend is CCL17 and CCL22) in precursor cells and Th17 cells, thereby enhancing their recruitment in the implant interface. The end result is the activation of precursor osteoclasts and the increased production of RANKL by Th17 cells [124]. The complement system has been also implicated in osteolysis. CR3 receptors are involved in phagocytosis of wear debris [59]. VEGF is a growth factor essential for angiogenesis. It is implicated in osteolysis in many ways and is found in tissues from failed hip arthroplasties [125]. It is produced by wear debris-activated macrophages. Increased osteoclastogenesis, acts as a chemokine for the recruitment of macrophages, increases vascular permeability in periprosthetic tissue so there is increased pressure in joints which enhance osteolysis [126, 127]. Obesity has been investigated as a factor of osteolysis. In mouse models, obese animals with implanted PE particles have lower numbers of osteoclasts and fewer osteolysis. Obesity may be protective for implant loosening as it is for osteoporosis [128].

Treatment Options

The potential therapeutic intervention relies on a combination of improvements such as improved implant integration to host bone, improved bearing surfaces, and strategies to target the cellular components [1]. The latter includes strategies to target osteoclast precursor cells which are recruited to inflammatory sites by circulating cytokines to target precursors that are stimulated by the particle-mediated cellular response to differentiate and form bone-resorbing osteoclasts and to target activation mechanisms of mature osteoclasts.

Management of osteolysis and loosening starts with prevention. Prevention has to do firstly with successful osteointegration. Modifications of implants have been introduced to increase osteointegration. These modifications include newer biomaterials with osteoinductive properties, like tantalum, plasma spraying, or grit blasting of implants (to increase the surface and become more osteoinductive), and covering with hydroxyapatite (to facilitate osteointegration). Successful osteointegration reduces the effective joint space. Newer improvements include the incorporation of growth factors like BMPs or peptides of growths factors to stimulate osteoblasts and enhance osteointegration. Lastly there is the incorporation of antibiotics in implants. Besides infections, it may reduce endotoxin osteolysis and low-grade infection which has been implicated in aseptic loosening [129]. Gene therapy has been tried to reverse the osteolysis. Therapy with anti-inflammatory genes (IL-1R and IL-10) in animal models was found to be protective of UHMWPE particle-induced bone resorption [71]. Gene transfer of TNFR (TNF receptor) had antiresorptive results. Gene transfer of OPG had the same results [130]. Erythromycin is an antibiotic with anti-inflammatory properties. It has a tropism for macrophages/monocytes in bone marrow and inflammatory tissues. Oral erythromycin therapy has been shown to reduce osteoclasts and inflammation in tissues from revision arthroplasties when delivered preoperatively [131]. Another antibiotic with anti-resorbing capacities is doxycycline. Doxycycline inhibits metalloproteinases, inhibits osteoclastogenesis, induces apoptosis of osteoclasts, and ameliorates their bone-resorbing actions [132, 133]. In vivo and in vitro, doxycycline has shown that it halts particle-induced osteolysis [134]. Bisphosphonates have been shown to reduce particle wear-induced osteolysis [135, 136]. They induce osteoclast apoptosis. In addition they can halt the migration of the implant postoperatively [138], which has been shown to decrease the risk of osteolysis and revision rates [138]. In the Danish registry it was found that long-term use of the bisphosphonates decreases the risk of revision, but the perioperative use may increase the risk of deep infection. Probably the osteolysis occurring in infections is essential in clearing microbes from the bone, and bisphosphonates counteract this mechanism [139]. Unfortunately, the use of bisphosphonates in loosening implants did not have the desired outcomes [140]. This may be due to the fact that bisphosphonates have to be ingested before acting and the "test bite" of continuously recruited osteoclasts results in bone loss despite treatment with bisphosphonates. Bisphosphonates may have a role in prophylaxis [141]. Indeed treatment with one dose of pamidronate postoperatively in a randomized controlled trial resulted in a reduction of bone loss around the implants as measured with bone mineral density (BMD). Again this positive result was not associated with better clinical outcomes [142]. Anti TNF-a therapy is a valuable option for treatment of implants with aseptic loosening. Because of the similarities between inflamed synovium in rheumatoid arthritis and periprosthetic pseudomembranes in aseptic loosening, etanercept was used as therapy for aseptic loosening. Etanercept is a soluble extracellular TNF-a receptor (p75 hTNF-a) fused with Fc region of immunoglobulin (IgG1) with impressive results in rheumatoid arthritis. Even if in animal models etanercept did show positive results, a randomized trial failed to show a reduction in revision arthroplasties [143]. This study, however, is criticized because it was underpowered. Targeting the RANKL-RANK-OPG axis has been associated with better results in animal models. Blocking RANKL with OPG-Fc tag, which increases the bioavailability of OPG, inhibited the osteolysis around loose implants [141]. RANK blockade with fusion protein (RANK-Fc) in a mouse model of titanium osteolysis resulted in a reduction of osteoclastogenesis and osteolysis without affecting new bone formation [144]. Treatment with COX-2 inhibitors like celecoxib may be useful in the treatment of aseptic loosening. Studies in animals demonstrated positive results (reduction in PGE2 and osteolysis). Other possible therapies regarding osteolysis include the blocking of V-ATPase in osteoclasts. Bafilomycin A_1 (a macrolide antibiotic) has the ability to block V-ATPase in osteoclasts which is located in the ruffled border and is involved in acidification of the

microenvironment and degradation of bone [145]. Purinergic signaling has been described recently in osteoclasts and can be manipulated to decrease osteolysis. The ADP receptor P2RY12 blocking by results in decreased activation of GTPase Ras-related protein (RAP1) and a2b3 integrin. a2b3 is essential for osteoclast formation, adhesion, and bone resorption so clopidogrel therapy can protect from pathologic osteolysis as in aseptic loosening [146]. Statins due to anabolic and anti-catabolic on bone have been shown to protect from particle-induced osteolysis in murine calvaria models [147]. Statins are HMGCoA reductase inhibitors and target the mevalonate pathway like bisphosphonates. In a population study statin users had decreased risk for revision due to aseptic loosening [148]. Lastly, the Wnt signaling on bone cells (osteoblasts) has received attention. Wnt binds to LPR5/6-stabilizing β-catenin and enables its translocation to nucleus to activate gene expression. β-catenin has a critical role in the proliferation and survival of osteoblasts. In addition it acts indirectly on osteoclasts by increasing the production of OPG. Sclerostin is an inhibitor of wints; it is produced by bone cells (especially osteocytes), and inhibition of sclerostin by antibodies results in enhanced bone formation. These pathways may have a role in osteolysis [149, 150].

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