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Inflammatory Periprosthetic Bone Loss

Sang-Soo Lee[1], P. Edward Purdue[2] and Ju-Suk Nam[1]
[1]*Institute for Skeletal Aging & Orthopedic Surgery,*
Infectious Disease Medical Research Center,
Hallym University College of Medicine, Chuncheon,
[2]*Osteolysis Research Laboratory,*
Hospital for Special Surgery, New York,
[1]*Korea,*
[2]*US*

1. Introduction

Total hip arthroplasty [THA] is one of the most successful and effective procedures developed for the treatment of pain and lack of mobility associated with end-stage arthritis such as osteoarthritis and rheumatoid arthritis. Approximately 1.5 million joint arthroplastic operations are performed annually worldwide. THA, although considered an excellent surgical procedure, can be complicated by periprosthetic osteolysis. Periprosthetic osteolysis (also called 'Particle disease') is initiated by wear debris derived from the implant. In most long-term studies on hip arthroplasty, osteolysis related loosening, bone loss or periprosthetic fractures are the most frequent causes for revision surgeries (Talmo et al., 2006).

Osteolysis is a particle-induced biologic process at the metal–bone or cement–bone interface of prosthetic implants, manifesting radiographically as scalloped focal or linear endosteal radiolucencies due to bone loss and resulting in the loosening of implants. In the early days of hip arthroplasty, radiolucencies around implants were noticed and were thought to be related to curing of acrylic cement, infection or neoplastic process. These were first described by Charnley in association with Teflon cups, though later were also observed in patients with stable implants (Charnley, 1966). In 1977, Willert and Semlitsch demonstrated the presence of macrophages in response to wear debris and concluded that the particles accumulate macrophages in pericapsular lymph drainage, leading to a foreign body response and eventual loosening of the implant (Willert, 1977).

Goldring *et al.* described the synovial-like character of the interfacial membrane found and demonstrated the presence of prostaglandin E_2 [PGE_2] and collagenase secretion from the associated cells (Goldring et al., 1983). The early observations of osteolysis in cemented implants led to a general belief that osteolysis was related to the acrylic cement and the term 'Cement disease' was introduced. However, after the demonstration of lytic lesions in cementless implants, osteolysis is now considered to be a 'Particle disease', suggesting that wear-generated particulate debris is the main cause of periprosthetic osteolysis (Harris, 1995).

Biologic responses to implant debris, the basis of periprosthetic tissue destruction, are due to a wide variety of complex events. Aseptic failure occurs later as a secondary issue to the chronic granulomatous and inflammatory response, which is stimulated and maintained by

wear particles. This process is progressive and time dependant, ultimately leading to prosthetic loosening and failure (Keener et al., 2003). Wear debris can be generated from the articulating surfaces and bone cement. In general, higher wear rates are observed in patients with osteolysis (Dumbleton et al., 2002). However, the osteolytic process is a result of multiple factors, including physical and biologic components (Clohisy et al., 2004a).
Once macrophages are activated by particulate debris, they secrete various kinds of mediators to incite a complex cascade of events culminating in recruitment and maturation of osteoclasts, the bone resorbing cells directly responsible for the pathogenic bone loss in osteolysis (Glant et al., 1993). Other cell types also seem to be involved in production cytokines and inflammatory mediators during this process, such as osteoblasts and fibroblasts (Jacobs et al., 2001; Dorr et al., 1990). Matrix degradative enzymes and chemokines are also released from several types of cells (Jacobs et al., 2001; Takagi et al., 1998). The core of the biologic response that leads to osteolysis involves receptor activator of NF-κB ligand [RANKL]-RANK axis for osteoclast precursors, resulting in their differentiation and maturation (Abu-Amer, 2005; Khosla, 2001).

Category	Clinical manifestations
Soft tissue lesions	• Acute synovitis (Engler et al., 2001) • Particle-induced synovitis (Niki et al., 2007) • Heterotopic polyethylene granuloma (Walsh et al., 2011)
Osseous impairment	• Periprosthetic osteolysis (Lee et al., 2007) • Impaired osteogenesis (Wang et al., 2004) • Aseptic loosening (Harris, 1995) • Failure of implant (Clohisy et al., 2004)
Systemic reactions	• Metal hypersensitivity (Hallab et al., 2005)

Table 1. Clinical conditions related with wear debris-induced inflammation following total joint arthroplasty

Moreover, recent researches have uncovered the possibility that biological mechanism of osteolysis has to be extended to bone forming activity as well as resorption or dissolution of bone tissue. Recent datas suggest that bone-forming cells - osteoblasts, osteoprogenitors, and adult mesenchymal stem cells - may also contribute to osteolysis. As to date, there is no approved drug therapy to prevent or inhibit periprosthetic osteolysis, this concept will open up possibilities for the development of therapeutic agents that can enhance bone formation. This review presents novel insights into the current knowledge regarding how wear debris interact as an inflammatory process leading to periprosthetic osteolysis. The authors hope to outline potential perspectives for the future therapeutic strategies for this devastating complication.

2. Wear particle debris - the main cause of periprosthetic osteolysis

Wear-generated particulate debris is the main cause of periprosthetic osteolysis. Various kinds of cells have been implicated in the mechanisms leading to periprosthetic osteolysis in response to wear debris. They are indicative of a complex network of cellular pathogenesis (Drees et al., 2007). Several studies with retrieved implants, animal and *in-vitro* model suggest that wear-mediated periprosthetic osteolysis is unlikely to be caused solely by one particular cell type or particulate species, but is rather the cumulative consequence of a number of biological reactions (Wang et al., 2004).

Wear debris is formed at prosthetic joint articulations, modular interfaces, and nonarticulating interfaces (Goldring et al., 1993). The majority of particles are less than 5 um in diameter and exist in a range of shapes and sizes. Within a clinical context, polyethylene wear represents the dominant type of debris that leads to loss of prostheses. With regard to particle size, large particles are recognized as nondigestible foreign bodies. Particles within the broad size range of 0.2 – 10.0 μm are phagocytosed by macrophages leading to cellular activation. Although smaller particles are generally more pro-inflammatory, it is possible that extremely small submicron particles are less biologically active (Green et al., 1998). Particles beyond the size range of 0.2 – 10.0 μm can escape active phagocytosis, and fail to stimulate macrophages to produce high levels of proinflammatory and osteolytic cytokines. *In-vitro* studies of macrophage cultures clearly indicated that smaller [< 20 μm] polymethylmethacrylate [PMMA] and polyethylene particles [PE] elicited a significantly greater inflammatory cytokine response, as indicated by increased release of tumor necrosis factor [TNF-α], IL-1, IL-6, PGE_2, matrix metalloproteinases [MMPs], and other factors (Abbas et al., 2003; Gonzalez et al., 1996; Lee et al., 2003; O'Keefe et al., 1998; Shanbhag et al., 1994).

In addition to size of particles, the cellular response to wear debris depends on numerous other parameters of particles such as the composition (Haynes et al., 1998; Sethi et al., 2003), shape (Yang et al., 2002b), charge, number (Gonzalez et al., 1996; Sabokbar et al., 2003b), volume, and surface area (Shanbhag et al., 1994). Especially the amount of particle around implants exhibits a fair correlation with the severity of aseptic loosening, although certain cases shows an exaggerated biologic response to particulate debris (Abu-Amer et al., 2007). The relative numbers of particles and macrophages are also critical to the intensity of reaction. The extent of the reaction by macrophages was also affected by the particle: target cell ratio. Therefore, the association between particles and osteolysis represents a dose–response relationship (Wilkinson et al., 2005)

Interestingly, osteoblasts also can phagocyte small particles, causing potential adverse effects on viability, proliferation and function of osteoblast as well as on osteoclasts (Goodman et al., 2006; Lohmann et al., 2000). PE, PMMA or metallic particles reduce osteoblasts differentiation of bone marrow osteoprogenitor cells (Chiu et al., 2006), expression of collagens by osteoblasts (Vermes et al., 2001; Vermes et al., 2000), osteoblast viability by inducing apoptosis (Pioletti et al., 2002) characterized with decreased production of matrix, alkaline phosphatase and TGF-β by these cells (Dean et al., 1999). As for macrophages, such suppressive effects are also likely dependent on particle size, composition and dosage: different particle types can differentially affect osteoblast function (Lohmann et al., 2002).

The size and degree of clumping of particles are also important variables determining the biological response, especially in osteoblast. Smaller particles of nano-size have less detrimental effect on the functions of osteoblasts, compared to conventional particles (Granchi et al., 2005; Gutwein & Webster, 2004). The nano-sized particles were associated with increased cell viability, more normal cellular morphology and spreading compared to conventional particles, indicating nano-sized particles are less active (Gutwein & Webster, 2004). Therefore, roles of nano-sized wear debris in periprosthetic osteolysis deserve further testing.

3. Periprosthetic membrane in osteolysis around the implant

The tissue around osteolysis contains a synovial-like interface membrane between the prosthesis and the adjacent bone, called the periprosthetic membrane. Periprosthetic

membranes retrieved from patients contain macrophages, fibroblasts and multi nuclear giant cells such as osteoclasts. T lymphocytes and B lymphocytes are also seen.. The development of osteolysis is triggered by cellular and enzymatic processes within this membrane. The periprosthetic membrane is a histopathological hallmark of aseptic prosthesis loosening and shares some similarities with the hyperplastic synovium in patients with rheumatoid arthritis [RA] (Drees et al., 2007; Goldring et al., 1983; Harris, 1995). At a molecular level, RA synovial fibroblasts and prosthesis-loosening fibroblasts share several common features.

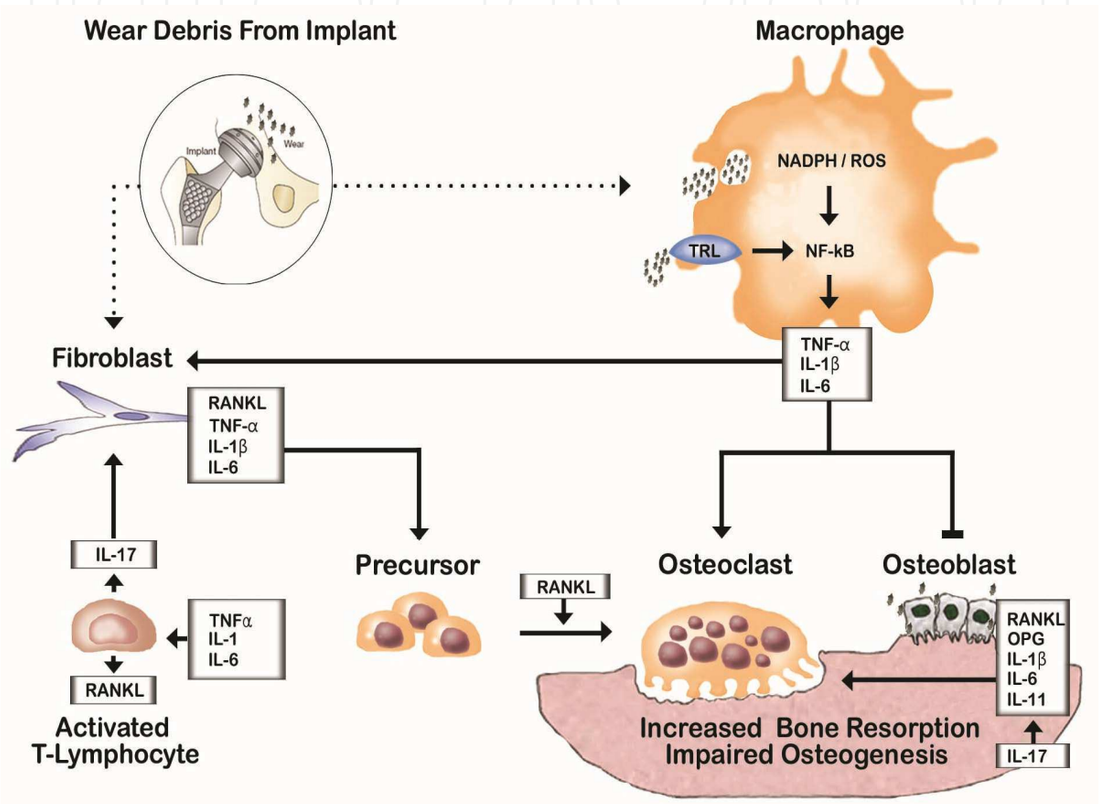

Fig. 1. Possible model of interplay between macrophages, fibroblasts, lymphocyte, osteoclasts and osteoblast in periprosthetic osteolysis. Osteoclasts develop from precursors under the influence of RANKL. The source of RANKL can be fibroblasts, osteoblasts, macrophages, or T cells. Particles may stimulate macrophage, fibroblasts and osteoblasts directly to induce RANKL and pro-inflammatory cytokines that can induce RANKL. It has been hypothesized that T cells stimulated by the pro-inflammatory microenvironment may also promote osteoclast formation, synergized with TNF-α, by secreting IL-17.Thus, RANKL, TNF-α, IL-1, IL-6, IL-17, and M-CSF may mediate the differentiation of myeloid precursor cells into multinucleated osteoclasts and development of impaired osteogenecity (Abu-Amer et al., 2007; Drees et al., 2007; Kotake et al., 1999; Tokuda et al., 2004)

Periprosthetic membranes, retrieved during revision surgery, produce a variety of factors including TNF-α, IL-1, IL-6, and PGs that are involved in mediating osteoclast biology (Chiba et al., 1994; Hirakawa et al., 1996; Jiranek et al., 1993; Margevicius et al., 1994; Shanbhag et al., 1995). These factors induce the final effector molecule, RANKL. It is generally accepted that

macrophage lineage cells do not express RANKL under normal conditions. In RA and periodontal disease, T cells have been known as the major source of RANKL. However, the relatively low numbers of T cells present near periprosthetic osteolysis make it unlikely that T cells are the major source of RANKL in periprosthetic osteolysis.
Studies of periprosthetic membranes of osteolysis patients revealed that fibroblast are the major source of RANKL (Haynes et al., 2004; Sakai et al., 2002), with possible involvement of macrophages and giant cells (Haynes et al., 2004; Sakai et al., 2002). Expression and secretion of MMPs are also elevated in macrophages exposed to wear debris in vitro. Elevated levels of degradation enzymes in periprosthetic osteolysis tissues were also observed (Kido et al., 2004). This array of chemokines, growth factors, pro-inflammatory and anti-inflammatory cytokines, and mediators demonstrate a potent ability of periprosthetic tissues to recruit and stimulate cells capable of inducing osteoclastic bone resorption and fibrous tissue formation (Talmo et al., 2006).

4. Inflammatory response in particle disease

The cellular response is dominated by macrophages (Archibeck et al., 2001; Lee et al., 2007; Neale & Athanasou, 1999; Quinn et al., 1992). Once macrophages are activated by particulate debris, they secrete various kinds of mediators to incite a complex cascade of events culminating in osteoclast maturation (Glant et al., 1993). This osteolytic response involves various cell types such as osteoclasts, fibroblasts, and osteoblasts/stromal cells, secreting a wide range of factors including cytokines, growth factors, and prostanoids (Dorr et al., 1990; Jacobs et al., 2001; Perry et al., 1995; Shanbhag et al., 1995). Matrix degradative enzymes and chemokines are also released from various cell types (Jacobs et al., 2001; Takagi et al., 1998).
Particle phagocytosis is the important component of the cellular response: the size of these particles is significant. Particles ranging from 0.2 to 10 μm in diameter undergo phagocytosis by macrophages (Gelb et al., 1994). The initial response of macrophage by particle is formation of fibrous tissue to encapsulate the implant. Often, synovial fluid and lining membranes are also formed, and granulomatous tissue is established. Such peripsrosthetic tissues have revealed an abundance of macrophages, fibroblasts and giant cells (Clohisy et al., 2004b; Ulrich-Vinther et al., 2002).
In addition, apart from massive recruitment of macrophages to the site of injury, some studies identified recruitment of lymphocytes (Abu-Amer, 2005; Arora et al., 2003; Gallo et al., 2002; Hallab et al., 2005; Lam et al., 2002; Purdue et al., 2007). Subsequently, pro-inflammatory response begins with secretion of factors, gelatinases, and proteases contributing to periprosthetic osteolysis, and thus causing failure of the implant (Abu-Amer et al., 2007). This inflammatory response is not restricted to the initial process, but rather it continues to appear in middle till late osteolytic stages of periprosthetic osteolysis (Abu-Amer et al., 2007).
Besides suppressing osteogenic activity, wear debris challenge can also affect the production of RANKL and OPG by osteoblasts. Osteoblast lineage cells can express RANKL, OPG, IL-1, TNF-α, IL-6, IL-11 and TGF-β (Hofbauer et al., 2000). Ultra high density molecular weight polyethylene [UHMWPE] increased the release of RANKL from human osteoblasts, while OPG was significantly inhibited. There was inductive also effects on the osteoclastogenesis with UHMWPE-human osteoblast-conditioned medium.
A study of the literature suggests that analysis of the involvement of osteoblasts in periprosthetic osteolysis has generally been limited to direct suppressive effect of particles on osteoblasts rather than through consideration of the possible effects of a pro-

inflammatory environment on osteoblast biology. Considering that TNF-α is also a potent inhibitor of osteoblast differentiation (Ghali et al., 2010; Yamazaki et al., 2009; Zhou et al., 2006; Karmakar et al. 2010), additional investigations into possible involvement of particle-activated macrophages in the impaired osteogencity mediated by proinflammatory cytokines including TNF-α would appear to be warranted. Although insufficient attention has been paid to the involvement of osteoblast, the cell type responsible for bone formation, more research should be conducted to delineate the potentially critical role of osteoblasts in periprosthetic osteolysis.

5. Roles of macrophages in particle disease

Since macrophages are the chief phagocytic cell in periprosthetic membranes, much attention has been focused on their role in cytokine production and osteoclast activation (Blaine et al., 1996; Nakashima et al., 1999b; Shanbhag et al., 1994). Macrophages are abundant in the periprosthetic tissues obtained from osteolysis patients, and are engaged in phagocytosis of wear particles as evidenced by the presence of such nondegradable particles within these cells. However, recent advances in osteoclast biology indicated that bone marrow-derived macrophages may play a dual role in periprosthetic osteolysis. First, as the major cell in host defense, they respond to particles through cytokine production. Second, macrophages have a role as precursors for the osteoclasts (Ingham & Fisher, 2005). Macrophages can phagocytose a variety of types of wear particles. Most notably, pro-inflammatory mediators such as PGE_2, TNF-α and IL-6 are generated in abundance by particle challenged macrophages.

Activation of macrophages by wear debris is a critical event in this process. It is believed that recognition of particles relies on phagocytosis of particles by macrophages and unidentified cell surface interactions. However, a little is known about the molecular mechanisms involved in particle recognition concerning the cell surface receptors that response to particles (Purdue, 2008). Although particle phagocytosis has been identified as a critical component of this biological response, recent studies in human macrophages indicate that direct interactions between particle and cell surface are sufficient to activate osteoclastogenic signaling pathways (Abu-Amer et al., 2007; Gallo et al., 2002; Gonzalez et al., 1996; Nakashima et al., 1999b). The latter interactions may include nonspecific physical induction of transmembrane proteins or recognition of cell surface molecules by particles. Recently this phenomenon was explained with the role of toll-like receptor (Takagi et al., 2007). However, the precise nature of stimulation of cells by particles remains unknown (Abu-Amer et al., 2007).

Recently, macrophages in periprosthetic space started to be defined as osteoclast precursors. *In-vitro* they have been shown to differentiate into osteoclasts in response to M-CSF and stromal cell-derived factors (Sabokbar et al., 1997): RANK ligand alone; or TNF-α and IL-1 in the absence of RANK ligand (Sabokbar et al., 2003a). Human arthroplasty–derived macrophages are capable of osteoclastic differentiation *in-vitro* in the presence of M-CSF and TNF-α (Ingham & Fisher, 2005; Sabokbar et al., 1997). Although recruitment of osteoclast precursor cells from the blood are more important as their source, the role of macrophages as osteoclast precusors in the periprosthetic space of osteolysis needs to be more clarified.

6. Involvement of lymphocyte in inflammatory osteolysis

The roles of lymphocytes in periprosthetic osteolysis remain to be delineated. Lymphocytes are generally absent or present in low numbers in the periprosthetic membranes. Mice

deficient in T cells, B cells, and natural killer cells develop osteolysis in response to wear particles as readily as wild type mice (Taki et al., 2005). However, the strongest evidence for the involvement of lymphocytes in aseptic loosening are a series of recent reports correlating a metal-specific lymphocyte response to poor implant performance and characterizing lymphocytic infiltration around metal-on-metal arthroplasties (Davies et al., 2005; Hallab et al., 2005). To promote osteoclastogenesis, activated T-cells positively regulate RANKL] and also negatively interferon-γ.

T-cell derived RANKL has been well known to play central role in inflammatory bone loss. In RA, the role of T cells has also been debated and unresolved as well as in periprosthetic osteolysis. An interesting new development has been the recognition of IL- 17 (Kolls & Linden, 2004). IL-17, produced predominantly by T-memory cells, acts synergistically with TNF-α to activate synovial fibroblast-like cells. T-helper cells producing IL-17 show a distinctive cytokine profile, which is consisted of IL-17, TNF-α and RANKL, but only low levels of IFN-γ and no IL-4 (Looney et al., 2006). Therfore, future work on the role of T cells in periprosthetic loosening should include evaluation of T cell signaling, related with the fact that inflammatory osteolysis do not produce much IFN-γ. It may be of special significance since IFN-γ has a potent inhibitory effect on osteoclast development and thus osteolysis (Looney et al., 2006; Takayanagi et al., 2000).

Cytokine	Effects on osteoblasts [OB]	Effects on osteoclasts [OC]
TNF	• Induces RANKL & M-CSF (Wei et al., 2005) • Inhibits OB differentiation & apoptosis (Gilbert et al., 2000; Jilka et al., 1998)	• Increases OC precursor numbers (Li et al., 2004; Yao et al., 2006) • Acts synergistically with RANKL (Lam et al., 2000)
IL-1	• IL-1α: Inhibits differentiation & matrix formation *in- vitro* (Tanabe et al., 2004) • IL-1β: Inhibits collagen synthesis *in-vitro* (Stashenko et al., 1987)	• Increases OC-genesis along with TNF-α (Wei et al., 2005) • Decreases apoptotic rate of OCs (Jimi et al., 1995)
IL-17	• Enhances TNF-α-stimulated IL-6 synthesis (Tokuda et al., 2004) • Increases RANKL/OPG in cells *in-vitro* (Kotake et al., 1999)	• Induces RANKL and RANK (Kotake et al., 1999; Lubberts et al., 2003) • Stimulate OC-genesis in RA (Kotake et al., 1999)

Table 2. Main effects of pro-inflammatory cytokines on osteoblast and osteoclast

7. Biological understandings of osteolytic response

The final cellular consequence of particle action is an excess of osteoclast activity, which results in progressive bone erosion. Osteoclasts are multinucleated cells derived from circulating osteoclast precursor cell of the monocyte/macrophage lineage, and represent the only cell type capable of bone resorption (Boyle et al., 2003). Osteoclast precursors are supplied from the periprosthetic space or recruited from the blood itself (Sabokbar et al., 1997). Wear debris probably increases osteoclast recruitment to periprosthetic tissues via the activation of chemokine [macrophage chemoattractant protein-1 ; IL-8] expression by macrophages and fibroblasts (Fritz et al., 2005; Nakashima et al., 1999a; Yaszay et al., 2001). In addition, macrophage lineage cells isolated from these tissues display a greatly increased propensity to differentiate into osteoclasts (Sabokbar et al., 1997; Sabokbar et al., 2003a). Osteoclasts can be differentiated by two critical cytokines, RANKL and M-CSF.

The molecular balance between RANK−RANKL and OPG has a key role in periprosthetic osteolysis. RANKL is the key cytokine regulator of osteoclast generation and activation. Interaction between RANK and RANKL constitutes a pivotal signaling pathway in the formation of osteoclasts. RANKL is expressed on the surface of activated T cells, marrow stoma cells, and osteoblasts as a 45-kDa transmembrane protein. It binds to RANK expressed on the surface of osteoclasts and also their precursors. This is necessary for the differentiation and maturation of osteoclasts in the presence of the survival factor M-CSF. By the binding of RANKL to RANK, the receptor recruits TNFR [TNF receptor]-associated cytoplasmic factor 6 [TRAF6]. This acts as a key adaptor for the assembling of signaling proteins, which directs osteoclast-specific gene expression and finally leads to their differentiation and activation.

OPG is a naturally occurring decoy receptor for RANKL secreted by stromal cells including osteoblasts as a soluble 110 kDa disulfide-linked homodimer. It down-regulates osteoclastogenesis by binding RANKL. Osteoclasts formation can be determined principally by the relative ratio of RANKL/OPG in the bone marrow microenvironment, and alterations in this ratio have been correlated with various bone disorders (Hofbauer & Schoppet, 2004).

Another important fact for regulation of osteoclastogenesis is that many pro-inflammatory and anti-inflammatory cytokines act directly to enhance or inhibit the RANKL/RANK axis (Abu-Amer et al., 2007). TNF-α also promotes osteoclastogenesis, particularly in the state of inflammatory osteolysis such as RA and periprosthetic osteolysis. Overexpression of TNF-α is sufficient to induce calvarial osteolysis even in the absence of added particles, emphasizing its pro-resorptive characteristics in mice (Schwarz et al., 2000). The molecular basis of increased RANKL in osteolysis is likely downstream of pro-inflammatory cytokines such as TNF-α and IL-1β, which are known to increase RANKL expression in several cell types (Purdue et al., 2007). RANKL and TNF-α seems to work in collaboration to induce osteoclast activation. Therefore, TNF-α and IL-1β, acting in concert with RANKL, can powerfully promote osteoclast recruitment, activation, and osteolysis (Romas et al., 2002).

During the past decade, the identification of several molecular pathways involved in bone loss raised hope for the development of therapeutic targets for periprosthetic osteolysis. TNF family members, especially RANKL, are prerequisites for osteoclast formation. The downstream signaling by wear particles, unsurprisingly, overlaps with that of TNF and RANKL. Notably, particle-induced pathways lead to the activation of kinases and transcription factors which are essential for osteoclastogenesis, such as activation of the tyrosine kinase c-src, mitogen-activated protein kinases [MAPK], and the NF-κB cascade (Abbas et al., 2003; Abu-Amer, 2005; Lam et al., 2002). Although activation of these pathways might be a secondary pathway, selective blockade of these downstream pathways reduces particle transmitted effects. The molecular targets described above need to be focused for selecting anti-resorptive therapeutic targets (Looney et al., 2006).

8. Impaired osteogenesis as an inflammatory reaction in periprosthetic osteolysis

The role of osteoblasts in periprosthetic osteolysis has received less attention than that of osteoclasts. Osteoblasts play important regulatory roles in bone remodeling. They produce and mineralize bone matrix, in addition to modulating differentiation and function of osteoclast by producing RANKL and OPG (Lorenzo et al., 2008). Osteoblasts are originated from MSCs and differentiated to matured cells. After maturation, osteoblasts diminish their

expression of RANKL and increase their expression of OPG, thereby creating a microenvironment that favors bone formation over bone loss (Atkins et al., 2003). Although osteoblasts have not been intensively investigated within the the field of periprosthetic osteolysis, more intensive research needs to be conducted to delineate the potentially critical role of osteoblasts based on their bone forming activity.

Most researches have limited their focus on *in-vitro* models for the study of direct interaction between osteoblast and particle (Dean et al., 1999; Gutwein & Webster, 2004; Lohmann et al., 2002; Pioletti et al., 2002; Yao et al., 1997). It has been postulated as a main mechanism of impaired osteogenesis that wear particles directly inhibit bone forming activity of osteoblast by altering typical osteogenic characters. For example, particles directly inhibit cell viability and proliferation, in addition to down-regulating the mRNA and protein level of bone formation markers. Particles less than 5 μm can also undergo phagocytosis by mature osteoblasts (Goodman et al., 2006), leading to potential adverse effects on cellular viability, proliferation and function. Along with particle size, composition and dosage can also effect these parameters (Lohmann et al., 2002). Moreover, it was reported that osteoblast challenged with particles can induce the expression of RANKL, OPG, IL-1, TNF-α, IL-6, IL-11, and TGF-β (Hofbauer et al., 2000).

MSCs and osteoprogenitors are also profoundly affected by wear particles (Drees et al., 2007; Goodman et al., 2006). Differentiation of osteoblasts from MSCs is also down-regulated by titanium particles (Wang et al., 2002). PMMA particles reduce osteoblast differentiation of bone marrow osteoprogenitor cells (Chiu et al., 2006). Titanium and zirconium oxide induce MSC apoptosis (Wang et al., 2003). Since MSCs and osteoprogenitors from the bone marrow are the precursors of osteoblasts, the reaction of these cells to wear particles is critical to both initial osseo-integration of implants and ongoing regeneration of the periprosthetic bed (Goodman et al., 2006). Future studies need to delineate the molecular mechanisms by which particles adversely affect bone cell lineage including MSCs and provide strategies to modulate these effects.

Recent research has uncovered the possibility that periprosthetic osteolysis likely involves multiple mechanisms including bone forming activity as well as bone resorption. It was reported that biologic effects on bone-forming cells - osteoblasts, osteoprogenitors, and adult MSCs - may also contribute to osteolysis (Chiu et al., 2009; Wang et al., 2002). These findings suggest that the following mechanisms of particle bioreactivity may contribute to osteolysis by means of exacerbated inflammation by reactive oxygen species [ROS] (Chiu et al., 2009) released from activated macrophages and osteoclasts, resulting to impaired periprosthetic bone formation with cytotoxic response and suppressed osteogenic differentiation of mesenchymal stem cells (Wang et al., 2004).

So far, most researches in terms of involvement of osteoblast in periprosthetic osteolyis have been limited to determine the direct suppressive effect of particle to osteoblast. However, the possibility that osteoblast can indirectly communicate with immune cells through many sectreted molecules such as TNF-α, IL-1, ROS requires further exploration (Ghali et al., 2010; Yamazaki et al., 2009; Zhou et al., 2006). Following phagocytosis of particles and the resultant pro-inflammatory reaction, the released cytokines from macrophages can be regarded as a potent inhibitor of osteoblast differentiation. Although insufficient attention has been paid to the involvement of osteoblasts, more extensive research should be conducted to delineate the potentially critical role of osteoblast in periprosthetic osteolysis. Modulation of bone forming activity in addition to existing anti-osteoclastic therapies, such as bisphosphonates and TNF-α blockade that inhibit bone destruction, represent a potential new therapeutic approach to this destructive disorder.

9. Molecular basis of inflammatory osteolysis

Inflammatory osteolysis is a major complication of conditions such as RA, periodontal disease, and orthopedic implant loosening. The persistence of these responses is often associated with skeletal pathology ranging from localized focal bone erosion and peri-articular osteolysis in the vicinity of inflamed area, to generalized osteopenia. This inflammatory osteolysis reflects increased osteoclast activity with enhanced osteoclast recruitment prompted by higher circulating levels of inflammatory mediators. Therefore, pathogenesis of inflammatory osteolysis is composed of distinct two primary components, inflammatory factors and regulation of osteoclasts. These are thought to operate through an ultimate common pathway of accelerated osteoclast recruitment and activation under the control of cytokines produced in the inflammatory environment.

As the only cell type capable of bone resorption, osteoclasts play a central to the pathogenesis of inflammatory osteolysis. Differentiation and activation of osteoclast are under the aegis of a variety of cytokines. Receptor activator of RANKL and M-CSF are the essential osteoclastogenic cytokines and are increased in inflammatory skeletal disease. The hyperplastic inflamed synovium also contains inflammatory cells such as lymphocytes, plasma cells, activated macrophages, and neutrophils. These cells can secrete a multitude of cytokines and growth factors including RANKL, TNF-α, IL-1, IL-6, PGE2, and IL-17 (Abu-Amer, 2009). This microenvironment is the evidence for recruitment and differentiation of osteoclasts that contribute to bone erosion.

The interaction of RANK and its ligand, RANKL is central to osteolytic responses on account of its critical role in osteoclast differentiation and survival. Interstingly, mouse models for the overexpression of OPG or administration of OPG-Fc are resistant to focal and systemic bone loss despite existence of the inflammatory response (Kong et al., 1999; Wong et al., 1999). These findings suggest that the osteoclast differentiation pathway, the RANKL/RANK signaling cascade, play a role as a target for other modulators for preventing bone resorption.

In addition, produced proinflammatory cytokines also play a vital role in the inflammatory osteolysis in RA, periprosthetic osteolysis, and periodontitis. Factors including TNF-α, IL-1, IL-17 and bacterial endotoxins also seem to impact osteoclastogenesis and bone resorption directly and indirectly (Abu-Amer, 2009). The dominant cytokine in the inflammatory osteolysis condition is TNF-α, primarily produced by activated T cells, macrophages and synoviocytes.

TNF-α is the most notable cytokine that can modulate both inflammatory and osteolytic process in the inflammatory osteolysis (Abu-Amer et al., 2008). Therefore, TNF-α can be regarded as the rate-limiting factor and it can be a target to eliminates both the inflammatory and osteoclastogenic components of these diseases (Wei & Siegal, 2008). However, in the most of researches, the role of TNF-α as the inflammatory mediator more than the osteolytic effector has been highlighted. This point is supported by studies in which inhibition of RANK signaling halted osteolysis whereas inflammation persisted. Nevertheless, TNF-α augments RANK/RANKL signaling tremendously leading to exacerbated osteoclastogenesis of RANKL-treated precursor cells. Therefore it appears that osteolytic activity of TNF-α requires RANKL/ RANK system in inflammatory disease (Abu-Amer, 2009). IL-1 also plays an essential role in the pathophysiology of inflammatory bone loss. Other prominent pro-inflammatory and pro-osteolytic factors include IL-17 and IL-6.

Regulation of pro-inflammatory cytokines appears to be a major function of IL-17. IL-17 directly upregulates IL-1 and TNF-α-induced inflammatory responses (Abu-Amer, 2009). IL-17, secreted by a distinct lymphocyte subset cells, plays an important role in

inflammation and bone erosion in a mouse model of CIA. Treatment with anti-IL-17, even after the onset of disease, markedly attenuates damage and inflammation of myocardium (Fan et al., 2011). In addition, IL-17 producing T cells are present in the synovium of RA patients (Page et al., 2004). Moreover IL-17 induces expression of RANKL by osteoblasts and synovial fibroblasts, leading to decreasing expression of OPG by stromal cells. Overall, a cascade from inflammatory cells lead to secretion of IL-17 which in turn up-regulates expression of RANKL, TNF-α and IL-1 and down-regulats expression of OPG, providing an intricate system supporting inflammation and subsequent osteolysis (Abu-Amer, 2009). Due to interdependence of TNF-α or IL-1, blockade of either TNF-α or IL-1 does not completely arrest the periarticular bone loss of inflammatory arthritis, however, inhibition of the two cytokines in combination is substantially more effective (Wei & Siegal, 2008).

The overall mechanism described above also can be applied to periprosthetic osteolysis from wear debris. Studies using animal model involving TNF-α blockade has been shown to significantly reduce wear debris-induced osteolysis (Childs et al., 2001a, b), but residual osteolysis still persists. In contrst, disruption of RANKL signaling via genetic ablation or high dose RANK-Fc treatment completely eliminates osteoclasts and bone resorption in this model (Childs et al., 2002). Similar effects were also achieved via OPG gene therapy (Goater et al., 2002; Ulrich-Vinther et al., 2002; Yang et al., 2002a).

It can be considered that the biological responsive pattern in periprosthetic osteolysis is similar to other modes of inflammatory osteolysis in that it is composed of two primary components, inflammatory factors and regulation of osteoclasts. This is thought to operate through common signaling pathways of cytokines such as TNF-α, IL-1 and RANKL to accelerate osteoclast recruitment and activation under the control of cytokines produced in the inflammatory environment against wear debris.

Understanding the mechanisms by which osteoclasts resorb bone, and the cytokines that regulate their differentiation and activity, provides mechanism-based candidate therapeutic targets to prevent inflammatory bone loss induced by wear debris from orthopedic implants. The success of anti-TNF-α and IL-1 therapy highlights the central role that these specific cytokines play in this disease except periprosthetic bone loss by wear debris. In addition, the interdependence of TNF-α, RANKL and IL-17 in the generation of osteoclasts also allows to explain the observation that combined blockade is more effective in preventing pathological bone loss in the inflammatory conditions including periprosthetic osteolysis (Buckland, 2011).

10. Conclusions

We hereby describe the biological mechanisms that are responsible for inflammatory bone loss in periprosthetic osteolysis, highlighting potential targets for further therapeutic approaches to prevent and minimize this devastating complication. As it is generally accepted that the inflammatory interaction between wear debris and activated macrophages is defined as a key event in periprosthetic osteolysis, much effort has been focused on this process and its role in osteoclast activation.

However, to date, despite extensive and complex research concerning periprosthetic osteolysis, there is no effective medical therapy to prevent or inhibit periprosthetic osteolysis. Therefore, an appreciation of the complex cellular and molecular signal network leading to cellular and inflammatory responses will form a foundation, on which several therapeutic interventions can be developed to overcome inflammatory periprosthetic bone loss. For the future direction, it seems to be reasonable that additional attention should be

equally paid to potentiate osteogenesis to overcome bone loss in the periprosthetic osteolysis.

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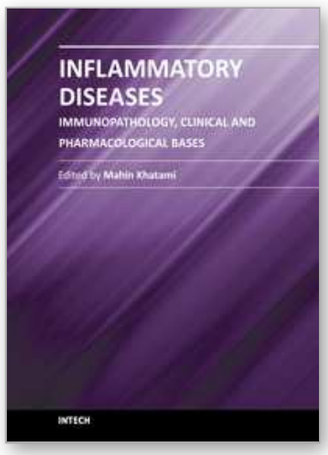

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This book is a collection of comprehensive reviews contributed by experts in the diverse fields of acute and chronic inflammatory diseases, with emphasis on current pharmacological and diagnostic options. Interested professionals are also encouraged to review the contributions made by experts in a second related book entitled "Inflammation, Chronic Diseases and Cancer"; it deals with immunobiology, clinical reviews, and perspectives of the mechanisms of immune inflammatory responses that are involved in alterations of immune dynamics during the genesis, progression and manifestation of a number of inflammatory diseases and cancers, as well as perspectives for diagnosis, and treatment or prevention of these disabling and potentially preventable diseases, particularly for the growing population of older adults around the globe.

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Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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