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Review

Bone lysis and inflammation

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Abstract. Over the past decade there have been major advances in our understanding of the factors that regulate osteoclast formation and activity. It is now apparent that receptor activator NFκB (RANK), its ligand, RANKL (also known as TRANCE, osteoclast differentiation factor and osteoprotegerin (OPG) ligand) and the natural RANKL inhibitor, OPG, are the key factors regulating osteoclast formation in normal bone physiology. The molecular interactions of these molecules regulate osteoclast formation and subsequent bone loss in disease and there is now strong evidence that the bone loss associated with inflammatory diseases, such as rheumatoid arthritis, periodontal disease and peri-implant loosening, is regulated by the action of RANK, RANKL, and OPG. These molecules are targets for the pharmacological regulation of severe bone loss in several common inflammatory diseases.

Introduction

Inflammation and bone erosion have been generally considered distinctly different process. Inflammation is considered to be mainly a localised disorder that can affect a variety of tissues where as most previous studies of bone erosion have been concerned with endocrine effects acting systemically. However, destructive erosion of bone is a serious complication of several chronic inflammatory diseases and there appears to be an intimate relationship between inflammation and bone lysis. Three examples of diseases where inflammation and bone lysis are seen closely associated are, rheumatoid arthritis, periodontal disease and peri-implant osteolysis.

In all three diseases bone loss is closely associated with a local chronic inflammatory reaction.

Inflammatory diseases with bone loss

Progressive joint destruction is a hallmark of rheumatoid arthritis, a disease affecting approximately 2% of the world's population. In this disease the inflammatory changes that occur in the joint appear to be related to the breakdown of both soft tissue and bone. The bone erosion seen in rheumatoid arthritis can be localised to the inflamed joint [1, 2], as well as being generalised, with secondary osteoporosis often being associated with rheumatoid arthritis [3]. Despite the widespread prevalence of rheumatoid arthritis, we still have an incomplete understanding of the processes of this chronic systemic disease. Until recently most studies have been concerned with investigating the inflammation that occurs in the soft tissues, however, our recent advances in the understanding of bone metabolism allow us now to better investigate the mechanisms of the bone and cartilage loss in this disease.

Periodontal disease is the most common bone loss pathology in humans and is widely seen in both developing and developed countries. Despite its prevalence little is known about the mechanism by which periodontal bone erosion occurs. As a result there are few treatments that effectively stop the aggressive bone erosion other than surgical removal of the inflamed soft tissues. While this disease appears to be triggered by the body's inflammatory response to bacteria present in the mouth [4] the initiation process remains controversial. Unfortunately, surgical treatment is often unsuccessful and ultimately this disease results in the loss of teeth.

Despite the impressive success of joint replacement surgery, the premature failure of total hip and other arthroplasties is of significant concern. While there have been ongoing improvements in materials and surgical techniques, the need for surgical revision remains a significant problem with up to 10–15% of joints needing to be replaced before 15–20 years [5]. Revision of joint implants is often difficult due to the loss of bone stock around the prosthesis. It is important that we understand the cause of implant failure to develop treatments that will otherwise it will assume epidemic proportions. Many studies over the past two decades have strongly implicated osteoclasts as the major cause of the bone lysis leading to implant failure.

Rheumatoid arthritis, periodontal disease and prosthetic joint loosening are different diseases initiated by distinct causes, however, it is likely that similar pathological process

are involved in the destructive localised bone loss associated with these diseases. An important common factor is the excessive destruction of bone by osteoclasts near the site of inflammation. Osteoclasts are multinucleated, terminally differentiated cells derived from haemopoietic progenitor cells of the monocyte/macrophage lineage that degrade mineralised bone matrix. Normal bone metabolism is maintained by a balance between the bone forming cells, osteoblasts, and osteoclasts. This is regulated by a complex signalling network mediated through cell surface receptors and various cytokines [6]. In normal bone metabolism osteoblasts regulate the differentiation and function of osteoclasts [7] and many researchers have described the complicated signalling between these two cell types. However, in the types of diseases discussed above it is likely that other cells and factors are involved in causing elevated osteoclast activity.

Regulation of osteoclast formation and activity

Rodan and Martin [7] were the first to recognise that osteoblasts played a significant role in the regulation of bone resorption. The early work of Martin et al. [6] proposed the mechanism by which cells of the osteoblast lineage controlled osteoclast formation and activity and it was established that precursors of osteoclasts require co-culture with osteoblasts for osteoclast differentiation to occur.

A variety of cells of the monocyte/macrophage lineage, including terminally differentiated macrophage, have been shown to develop into active osteoclasts [6, 8–14]. These types of cells are abundant at sites of chronic inflammation where osteoclast precursors are likely to be monocytes recruited from the peripheral blood as well as mature tissue macrophages present in the granulomatous, chronic inflammatory tissue. This concept is strongly supported by the fact that mature osteoclasts, capable of resorbing bone, form from cells present in rheumatoid and periprosthetic tissues [15–21]. In addition, the rapid appearance of resorption pits in cultured cells isolated from the RA and peri-prosthetic tissues suggests that mature functional osteoclasts may already have been present in several of these tissues [22, 23].

It is only in the last 5–10 years that the cell surface molecules involved in mediating osteoclast differentiation have been discovered. RANKL (RANK ligand, osteoclast differentiation factor, osteoprotegerin ligand), and its receptor, RANK, have been identified as the key factors, present on osteoblasts and precursor osteoclasts respectively, that stimulate osteoclast formation [24, 25]. It is now clear that RANKL, together with macrophage-colony stimulating factor (M-CSF), is required for osteoclast formation from their precursor monocyte/macrophages[26].

The natural inhibitor of RANK-RANKL interactions is a soluble TNF ‘receptor-like’ molecule, osteoprotegerin (OPG) [24, 25, 27]. OPG binds to RANKL and prevents its ligation to RANK, thus preventing osteoclast differentiation and activation. The importance of these three molecules in regulating bone metabolism is demonstrated by transgenic and gene knock-out studies in mice [28–30]. In vivo the relative levels of RANKL and OPG are likely to be important in determining where and when osteoclasts will form. Considering the importance of RANK, RANKL and OPG in physiologic osteoclast formation it is reasonable to propose that they may also be key regulators of pathological bone resorption.

Osteoclasts in inflammatory tissues

RANKL and OPG have opposing effects on osteoclast formation and it is not surprising that there is a significant correlation between osteoclast formation ex vivo and the ratio of RANKL to OPG mRNA levels in cells isolated from the RA tissues [23]. Furthermore, the ratio of RANKL to OPG mRNA was higher in cells isolated from peri-prosthetic tissues from which osteoclasts readily formed [22]. These results provide strong evidence that a high ratio of RANKL to OPG in tissue adjacent to bone may stimulate macrophages to become mature osteoclasts without the need for them to be in contact with osteoblast cells. It is important to note that in many cases active osteoclasts formed without adding additional osteoblast-like/stromal cells to the ex vivo culture indicating cells other than osteoblasts are supporting osteoclast formation.

Researchers have used antibodies directed against RANKL and OPG to study a variety of healthy and inflamed tissues [31–35]. These studies show that several cell types may be important in the ectopic production of RANKL in the tissues adjacent to bone. RANKL protein was predominant within inflammatory cells in the inflamed tissues adjacent to pathological bone loss in rheumatoid arthritis, periodontal disease and peri-prosthetic loosening. It is important to note that the expression of RANKL in the tissues adjacent to bone loss was significantly greater than in the relevant controls in all diseases [31–33, 36].

In rheumatoid and periodontal diseased tissues lymphocytes expressing CD3 were the predominant cell type that expressed RANKL protein [33, 36]. This is consistent with reports that isolated lymphocytes produce RANKL in inflammatory arthritis [37, 38] and that activated T cells may regulate osteoclast activity by producing RANKL [39]. RANKL was also associated with monocyte/macrophages and multinucleated cells expressing CD68 in tissue from patients with rheumatoid arthritis, periodontal disease and peri-implant loosening. This finding is consistent with a recent report demonstrating RANKL mRNA expression in macrophages and multinucleated cells in periodontal diseased tissues in an animal model of periodontitis [40]. Since these cells also express RANK it is possible that by producing both RANKL and RANK macrophages and multinucleated cells can independently ‘auto-stimulate’ themselves to become osteoclasts.

RANKL is also reported to be expressed by synovial fibroblasts [41] and isolated microvascular endothelial cells [42]. Fibroblasts may contribute to the formation of osteoclasts in inflammation. However, the absence of RANKL protein in endothelial cells residing in a variety of inflamed tissues suggest endothelial cells may not have a role in directly stimulating osteoclasts formation in inflammatory diseases [32, 34, 35]. These studies show that most of the RANKL present in inflamed tissues near bone lysis is produced by activated leucocytes that are recruited to sites of inflammation.

We have used two different antibodies to OPG that detect different forms of OPG. Mab 8051 detects dimeric and monomeric OPG while Mab 805 detected only dimeric OPG when it is not bound to either of its ligands, TRAIL or RANKL [32]. Dimeric OPG was only detected in blood vessels (on Factor VIII positive endothelial cells), whereas monomeric OPG was predominantly detected in the synovium (on CD68 positive type A synoviocytes) in RA and periprosthetic tissues, as well as the epithelium in periodontal tissues. Whether OPG produced by endothelial cells or the type A synoviocytes is able to block RANKL and inhibit the formation of osteoclasts in these tissues is yet to be determined. However, it may be significant that the expression OPG was markedly reduced in the blood vessels and synovium of the inflamed tissues compared to that of the appropriate control tissues. The role of OPG production by endothelial cells is yet to be understood, however, endothelial OPG and endogenous RANKL may be important in enhancing endothelial cell survival[43, 44] and may have a role in regulating angiogenesis in inflammation.

Other cytokines, such as TNF-α, that stimulate osteoclast formation in vitro are also present in high levels in RA, peri-prosthetic and periodontitis tissues [45–50] [18, 51–53]. Importantly TNF-α, like other inflammatory cytokines stimulates both OPG and RANKL expression [54–57]. Recently it has been shown that TNF-α stimulates osteoclast formation directly in the absence of RANKL in vitro [58]. However, in vivo it is more likely to work in synergy with RANKL by making cells far more sensitive to low levels of RANKL [59]. TNF-α -antagonists and antibodies are now an accepted treatment regime for active rheumatoid arthritis. Inhibition of TNF-α activity not only reduces the inflammatory response [60] but it may also inhibit osteoclast bone resorption by reducing the activity of RANKL present in the tissues.

Arachidonate metabolites are also important inflammatory mediators produced during inflammation and these molecules are reported to regulate osteoclast formation and activity. The role of prostaglandin (PG) E2 has been studied extensively and its effects can vary, possibly depending on the stage of osteoclast differentiation [61]. Leukotriens are reported to stimulate osteolysis and their inhibition is reported to suppress peri-implant osteolysis in an animal model [62].

Treating bone loss in inflammation

While we now have an extensive range of anti-inflammatory drugs to control inflammation there are very few treatments available for inhibiting the debilitating bone loss seen in a variety of inflammatory diseases. The recent discoveries of the key factors involved in regulating osteoclast bone lysis allow us to develop new therapies to treat this problem. Although RA, peri-implant loosening, and periodontitis appear to be quite different diseases, the key mediators involved in pathological bone loss, as a complication of these diseases, are common. Similar approaches can be used to inhibit osteolysis in a variety of bone loss diseases. The RANK-RANKL interaction in the formation of osteoclasts is an ideal target of therapy because it is a point at which numerous pathways for

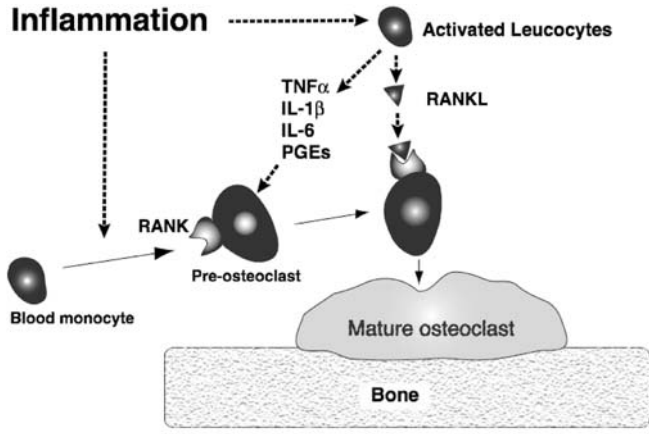

Fig. 1. Simplified diagrammatic representation of how inflammation stimulates osteoclast formation and bone loss in inflammatory disease. Activated leucocytes release inflammatory cytokines as well as expressing RANKL. These mediators stimulate macrophages that express RANK (pre-osteoclasts) to mature to become mature osteoclasts.

osteolysis converge. Treatments based on the inhibition of RANKL inhibition by its natural inhibitor OPG in peri-implant osteolysis [63] and rheumatoid arthritis [37, 64] have been successful. Soluble RANK has also been used [65]. Suppression of TNF-α has been used to successfully treat peri-implant osteolysis [66]. Suppression of osteoclast formation by various combinations of TNF-α, IL-1β and RANKL inhibitors have also been used in an animal model of RA [67] and may be more successful than individual therapies**.** In addition, selective blockade of potassium channels may also reduce osteoclast formation in T cell driven osteolysis in inflammatory diseases. These animal studies are promising and preliminary studies based on blocking RANK-RANKL interaction in humans are currently underway [68]. Similar therapies based on bisphosphonates, a group of drugs currently used to inhibit osteoclast activity in lytic bone tumours and osteoporosis, have also been used in models of peri-implant osteolysis animal studies [69].

Conclusions

Osteolysis in the joints of RA patients, in the alveolar bone of patients suffering periodontal disease and in the tissues adjacent to loose orthopaedic implants occurs through similar mechanisms (summarized in Fig. 1). The RANKL/RANK pathway of osteoclast differentiation is a key pathway to the formation of osteoclasts at these sites of inflammation and is, therefore, an important target for the pharmaceutical regulation of bone loss in several common inflammatory diseases.

References

[1] Gravallese EM, Harada Y, Wang J-T, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. Am J Pathol 1998; 152: 943–51.

[2] Goldring SR, Gravallese EM. Pathogenesis of bone lesions in rheumaotid arthritis. Curr Rheum Rep 2002; 4: 226–31.
[3] Gough A, Sambrook P, Devlin J, Huissoon A, Njeh C, Robbins S, et al. Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis. J Rheumatol 1998; 25: 1282–9.
[4] Schwartz Z, Goultschin J, Dean DD, Boyam BD. Mechanisms of alveolar bone destruction in periodontitis. Periodontol 2000; 14: 158–72.
[5] Johnsson R, Franzen H, Nilsson LT. Combined survivorship and multivariate analysis of revisions in 799 hip prostheses: a 10- to 20-year review of mechanical loosening. J Bone Joint Surg [Br] 1994; 76-B: 439–43.
[6] Martin TJ, Ng KW. Mechanisms by which cells of the osteoblast lineage control osteoclast formation and activity. J Cell Biochem 1994; 56: 357–66.
[7] Rodan GA, Martin TJ. Role of osteoblasts in hormonal control of bone resorption – a hypothesis. Calcif Tissue Int 1982; 34: 311.
[8] Takahashi N, Akatsu T, Udagawa N, Sasaki T, Yamaguchi A, Moseley JM et al. Osteoblastic cells are involved in osteoclast formation. Endocrinology 1988; 123: 2600–2.
[9] Udagawa N, Takahashi N, Akatsu T, Tanaka H, Sasaki T, Nishihara T. Origin of osteoclasts: mature monocytes and macrophages are capable of differentiating into osteoclasts under a suitable microenvironment prepared by bone marrow-derived stromal cells. Proc Natl Acad Sci USA 1990; 87: 7260–4.
[10] Kodama H, Nose M, Niida S, Yamasaki A. Essential role of macrophage colony-stimulting factor in the osteoclast differentiation supported by stromal cells. J Exp Med 1991; 173: 1291–4.
[11] Suda T, Udagawa N, Nakamura I, Miyaura C, Takahashi N. Modulation of osteoclast differentiation by local factors. Bone 1995; 17: 87S–91S.
[12] Fujikawa Y, Quinn JMW, Sabokbar A, McGee JOD, Athanasou NA. The human osteoclast precursor circulates in the monocyte fraction. Endocrinology 1996; 137: 4058–60.
[13] Tsurakai T, Takahashi N, Jimi E, Nakamura I, Udagawa N, Nogimori K et al. Isolation and characterization of osteoclast precursors that differentiate into osteoclasts on calvarial cells within a short period of time. J Cell Physiol 1998; 177: 26–35.
[14] Quinn JMW, Neale SD, Fujikawa Y, McGee JOD, Athanasou NA. Human osteoclast formation from blood monocytes, peritoneal macrophages, and bone marrow cells. Calcif Tissue Int 1998; 62: 527–31.
[15] Fujikawa Y, Shingu M, Torisu T, Itonaga I, Masumi S. Bone resorption by tartrate-resistant acid phosphatase-positive multinuclear cells isolated from rheumatoid synovium. Br J Rheumatol 1996; 192: 97–104.
[16] Fujikawa Y, Sabokbar A, Neale SD, Athanasou NA. Human osteoclast formation and bone resorption by monoytes and synovial macrophages in rheumatoid arthritis. Ann Rheum Dis 1996; 55: 816–22.
[17] Sabokbar A, Fujukawa Y, Neale S, Murray DW, Athanasou NA. Human arthroplasty derived macrophages differentiate into osteoclastic bone resorbing cells. Ann Rheum Dis 1997; 56: 414–20.
[18] Neale S, Sabokbar A, Howie DW, Murray DW, Athanasou NA. Macrophage colony-stimulating factor and interleukin-6 release by periprosthetic cells stimulates osteoclast formation and bone resorption. J Orthop Res 1999; 17: 686–94.
[19] Itonaga I, Sabokbar A, Murray DW, Athanasou NA. Effect of osteoprotegerin and osteoprotegerin ligand on osteoclast formation by arthroplasty membrane derived macrophages. Ann Rheum Dis 2000; 59: 26–31.
[20] Itonaga Y, Fujikawa Y, Sabokbar A, Murray DW, Athanasou NA. Rheumatoid arthritis synovial macrophage osteoclast differentiation is osteoprotegerin ligand-dependent. J Pathol 2000; 192: 97–104.
[21] Suzuki Y, Tsutsumi Y, Nakagawa M, Suzuki H, Matsushita K, Beppu M et al. Osteoclast-like cells in an in vitro model of bone destruction by rheumatoid synovium. Rheumatology 2001; 40: 673–82.
[22] Haynes DR, Crotti TN, Potter AE, Loric M, Atkins GJ, Howie DW et al. The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. J Bone Joint Surg Br 2001; 83 B: 902–11.
[23] Haynes DR, Crotti TN, Loric M, Bain GI, Atkins GJ, Findlay DM. Osteoprotegerin and receptor activator of nuclear factor kappa B ligand (RANKL) regulate osteoclast formation by cells in the human rheumatoid arthritic joint. J Rheumatol 2001; 40: 623–30.
[24] Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S-I et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclast inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci USA 1998; 95: 3597–602.
[25] Lacey DL, Timms E, Tan H-L, Kelley MJ, Dunstan CR, Burgess T et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998; 93: 165–76.
[26] Haynes DR, Atkins GJ, Loric M, Crotti TN, Geary SM, Findlay DM. Bidirectional signaling between stromal and hemopoietic cells regulates interleukin-1 expression during human osteoclast formation. Bone 1999; 25: 269–78.
[27] Yasuda H, Shima N, Nakagawa N, Mochizuki S-I, Yano K, Fujise N et al. Identity of osteoclastogenesis inhibitory factor (OCIF) and osteoprotegerin (OPG): A mechanism by which OPG/OCIF inhibits osteoclastogenesis in vitro. Endocrinology 1998; 139: 1329–37.
[28] Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 1998; 12: 1260–8.
[29] Mizuno A, Amizuka N, Irie K, Murakami A, Fujise N, Kanno T et al. Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. Biochem Biophys Res Commun 1998; 247: 610–5.
[30] Kong Y-Y, Yoshida H, Sarosi I, Tan H-L, Timms E, Capparelli C et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 1999; 397: 315–23.
[31] Haynes DR, Barg E, Crotti TN, Holding C, Weedon H, Atkins GJ et al. Osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathies and osteoarthritis and normal controls. Rheumatology (Oxford) 2003; 42: 123–34.
[32] Haynes DR, Barg E, Crotti TN, Weedon H, Atkins GJ, Zannettino A et al. Osteoprotegerin (OPG) Expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathies, osteoarthritis and normal controls. Rheumatol 2003; 43: 1–12.
[33] Crotti TN, Smith MD, Weedon H, Ahern MJ, Findlay DM, Kraan M et al. Receptor activator NF-kappaB ligand (RANKL) expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathy, osteoarthritis, and from normal patients: semiquantitative and quantitative analysis. Ann Rheum Dis 2002; 61: 1047–54.
[34] Crotti T, Smith MD, Hirsch R, Soukoulis S, Weedon H, Capone M et al. Receptor activator NF kappaB ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. J Periodontal Res 2003; 38: 380–7.
[35] Crotti TN, Smith MD, Findlay DM, Zreiqat H, Ahern MJ, Weedon H et al. Factors regulating osteoclast formation in human tissues adjacent to peri-implant bone loss: expression of receptor activator NFkappaB, RANK ligand and osteoprotegerin. Biomaterials 2004; 25: 565–73.
[36] Crotti TN, Smith MD, Hirsch RS, Soukoulis S, Weedon H, Capone M et al. Receptor activator NF k B ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. J Perio Res In press.
[37] Kong Y-Y, Feige U, Sarosi I, Bolon B, Tafuri A, Morony S et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. Nature 1999; 402: 304–9.
[38] Romas E, Bakharevski O, Hards DK, Kartsogiannis V, Quinn JMW, Ryan PFJ et al. Expression of osteoclast differentiation factor at sites of bone resorption in collagen-induced arthritis. Arthritis Rheum 2000; 43: 821–6.
[39] Udagawa N. The mechanism of osteoclast differentiation from macrophages: possible roles of T lymphocytes in osteoclastogenesis. J Bone Miner Metab 2003; 21: 337–43.

[40] Ogasawara T, Yoshimine Y, Kiyoshima T, Kobayashi I, Matsuo K, Akamine A et al. In situ expression of RANKL, RANK, osteoprotegerin and cytokines in osteoclasts of rat periodontal tissue. J Periodontal Res 2004; 39: 42–9.
[41] Quinn JMW, Horwood NJ, Elliott J, Gillespie MT, Martin TJ. Fibroblastic stromal cells express receptor activator of NF-kappa *B* ligand and support osteoclast differentiation. J Bone Miner Res 2000; 15: 1459–66.
[42] Collin-Osdoby P, Rothe L, Anderson F, Nelson M, Maloney W, Osdoby P. Receptor activator of NF-κB and osteoprotegerin expression by human microvascular endothelial cells, regulation by inflammatory cytokines, and role in human osteoclastogenesis. J Biol Chem 2001; 276: 20659–72.
[43] Malyankar UM, Scatena M, Suchland KL, Yun TJ, Clark EA, Giachelli CM. Osteoprotegerin is an alpha vbeta 3-induced , NF-kappa B-dependent survival factor for endothelial cells. Biol Chem 2000; 275: 20959–62.
[44] Kim HH, Shin HS, Kwak HJ, Ahn KY, Kim JH, Lee HJ et al. RANKL regulates endothelial cell survival through the phosphatidylinositol 3′-kinase/Akt signal transduction pathway. Faseb J 2003; 17: 2163–5.
[45] Chu CQ, Field M, Feldman M, Maini RN. Localization of tumor necrosis factor a in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis Rheum 1991; 34: 1125–32.
[46] Geivelis M, Turner DW, Pederson ED, Lamberts B. Measurements of interleukin-6 in gingival crevicular fluid from adults with destructive periodontal disease. J Periodontol 1993; 64: 980–3.
[47] Yamazaki K, Nakajima T, Gemmell E, Polak B, Seymour GJ, Hara K. IL-4 and IL-6-producing cells in human periodontal disease tissue. J Oral Pathol Med 1994; 23: 347–53.
[48] al-Saffar N, Revell A. Interleukin-1 production by activated macrophages surrounding loosened orthopaedic implants: A potential role in osteolysis. Br J Rheumatol 1994; 33: 309–16.
[49] Arend WP, Dayer J-M. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor-α in rheumatoid arthritis. Arthritis Rheum 1995; 38: 151–60.
[50] Xu JW, Konttinen YT, Lassus J, Natah S, Ceponis A, Solovieva SA et al. Tumour necrosis factor-alpha (TNF-alpha) in loosening of total hip replacement (THR). Clin Exp Rheumatol 1996; 14: 643–8.
[51] Kotake S, Sato K, Kim KJ, Takahashi N, Udagawa N, Nakamura I et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. J Bone Miner Res 1996; 11: 88–95.
[52] Xu JW, Li T-F, Partsch G, Ceponis A, Santavirta S, Konttinen YT. Interleukin-11 (IL-11) in aseptic loosening of total hip replacement (THR). Scand J Rheumatol 1998; 27: 363–7.
[53] Merkel KD, Erdmann JM, Mchugh KP, Abu-Amer Y, Ross FP, Teitelbaum SL. Tumor necrosis factor-α mediates orthopedic implant osteolysis. Am J Pathol 1999; 154: 203–10.
[54]. Brandstrom H, Jonsson K, Vidal O, Ljunghall S, Ohlsson C, Ljunggren O. Tumor necrosis factor-α and -β upregulate the levels of osteoprotegerin mRNA in human osteosarcoma MG-63 cells. Biochem Biophys Res Commun 1998; 248: 454–7.
[55] Horwood NJ, Elliot J, Martin TJ, Gillespie MT. Osteotropic agents regulate the expression of osteoclast differentiation factor and osteoprotegerin in osteoblastic stromal cells. Endocrinology 1998; 139: 4743–6.
[56] Hofbauer LC, Lacey DL, Dunstan CR, Spelsberg TC, Riggs BL, Khosla S. Interleukin-1β and tumor necrosis factor-α, but not interleukin-6, stimulate osteoprotegerin ligand gene expression in human osteoblastic cells. Bone 1999; 25: 255–9.
[57] Nakashima T, Kobayashi Y, Yamasaki S, Kawakami A, Eguchi K, Sasaki H, et al. Protein expression and functional difference of membrane-bound and soluble receptor activator of NF-κ*B* ligand: Modulation of the expression by osteotropic factors and cytokines. Biochem Biophys Res Commun 2000; 275: 768–75.
[58] Kobayashi K, Takahashi N, Jimi E, Udagawa N, Takami M, Kotake S et al. Tumor necrosis factor α stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. J. Exp. Med. 2000; 191: 275–85.
[59] Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-α induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. J Clin Invest 2000; 106: 1481–8.
[60] Assuma R, Oates T, Cochran D, Amar S, Graves DT. IL-1 and TNF antagonists inhibit the inflammation response and bone loss in experimental periodontitis. J Immununol 1998; 160: 403–9.
[61] Quinn JMW, Sabokbar A, Denne M, de Vernejoul MC, McGee JO, Athanasou NA. Inhibitory and stimulatory effects of prostaglandins on osteoclast differentiation. Calcif Tiss Int 1997; 60: 63–70.
[62] Anderson DM, MacQuarrie R, Osinga C, Chen YF, Langman M, Gilbert R. Inhibition of leukotriene function can modulate particulate-induced changes in bone cell differentiation and activity. J Biomed Mater Res 2001; 58: 406–14.
[63] Goater JJ, O'Keefe RJ, Rosier RN, Puzus JE, Schwartz EM. Efficacy of ex vivo OPG gene therapy in preventing wear debris induced osteolysis. J Orthop Res 2002; 20: 169–73.
[64] Romas E, Sims NA, Hards DK, Lindsay M, Quinn JW, Ryan PF et al. Osteoprotegerin reduces osteoclast numbers and prevents bone erosion in collagen-induced arthritis. Am J Pathol 2002; 161: 1419–27.
[65] Childs LM, Paschalis EP, Xing L, Dougall WC, Anderson D, Boskey AL et al. In vivo RANK signaling blockade using the receptor activator of NF-kappaB:Fc effectively prevents and ameliorates wear debris-induced osteolysis via osteoclast depletion without inhibiting osteogenesis. J Bone Miner Res 2002; 17: 192–9.
[66] Childs LM, Goater JJ, O'Keefe RJ, Schwarz EM. Efficacy of etanercept for wear debris-induced osteolysis. J Bone Miner Res 2001; 16: 338–47.
[67] Zwerina J, Hayer S, Tohidast-Akrad M, Bergmeister H, Redlich K, Feige U et al. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: effects on synovial inflammation, bone erosion, and cartilage destruction. Arthritis Rheum 2004; 50: 277–90.
[68] Schwarz EM, Campbell D, Totterman S, Boyd A, O'Keefe RJ, Looney RJ. Use of volumetric computerized tomography as a primary outcome measure to evaluate drug efficacy in the prevention of peri-prosthetic osteolysis: a 1-year clinical pilot of etanercept vs. placebo. J Orthop Res 2003; 21: 1049–55.
[69] Iwase M, Kim KJ, Kobayashi Y, Itoh M, Itoh T. A novel bisphosphonate inhibits inflammatory bone resorption in a rat osteolysis model with continuous infusion of polyethylene particles. J Orthop Res 2002; 20: 499–505.