Cell Transplantation, Vol. 23, pp. 631–639, 2014

0963-6897/14 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096368914X678319
E-ISSN 1555-3892
www.cognizantcommunication.com

Review

The Therapeutic Potential of Anti-Interleukin-20 Monoclonal Antibody

Yu-Hsiang Hsu and Ming-Shi Chang

Department of Biochemistry and Molecular Biology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Interleukin (IL)-20, a member of the IL-10 family of cytokines, was discovered in 2001. IL-20 acts on multiple cell types by activating on a heterodimer receptor complex of either IL-20R1–IL-20R2 or IL-22R1–IL-20R2. Recent evidence indicates that IL-20's interaction with its receptors might have proinflammatory effects on chronic inflammatory diseases, particularly rheumatoid arthritis (RA), osteoporosis, and breast cancer. Updated information about IL-20, such as its identification, expression, receptors, signaling, and biological activities, is illustrated in this review based on our research and the data available in the literature. IL-20 is a pleiotropic cytokine, which promotes inflammation, angiogenesis, and chemotaxis. IL-20 also regulates osteoclast differentiation by altering the receptor activator of NF-κB (RANK) and RANK ligand (RANKL) axis. Inflammation, angiogenesis, and osteoclastogenesis are critical for the pathogenesis of RA, osteoporosis, and breast cancer-induced osteolysis. Based on the in vitro and in vivo data and clinical samples, we demonstrated that IL-20 plays pivotal roles in these three diseases. In experimental models, anti-IL-20 monoclonal antibody ameliorates arthritis severity, protects against ovariectomized-induced bone loss, and inhibits breast tumor-induced osteolysis. This review presents the clinical implications of IL-20, which will lead to a better understanding of the biological functions of IL-20 in these diseases and provide new therapeutic options in the future.

Key words: Interleukin (IL)-20; Rheumatoid arthritis (RA); Osteoporosis; Breast cancer

INTRODUCTION

Cytokines are critical modulators of immune responses and therefore will be ideal targets for new therapeutic strategies. Selecting candidates to target and, in particular, identifying cytokines that regulate the critical steps of disease pathways is important to the success of such strategies. Over 100 cytokines and cytokine receptors have been identified, some of which are applied as the basis for the therapeutics on the market (4).

The interleukin (IL)-10 family of cytokines and the closely related interferon (IFN) family of cytokines form the larger class II cytokine family (46,56). IL-10, the first member of the IL-10 family discovered, was identified by Mosmann and colleagues in 1989 (46). The IL-10 family includes IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29 (2,3,11,13,40,79). IL-10, IL-22, and IL-26 are preferentially produced by immune cells (79,80). In contrast, IL-19, IL-20, and IL-24 can be secreted by both tissue cells and immune cells (18,40,49). Using various techniques, such as transgenic mice, gene-deficient mice, or treatment with neutralizing antibodies, scientists have studied the role of IL-10 family cytokines in various inflammatory conditions during the past decade (1,3,5,14,42,55,75). In contrast to IL-10, which is generally considered to be an anti-inflammatory cytokine, IL-20 acts as a proinflammatory cytokine. Recent studies (17,20,22) have implicated IL-20 in angiogenesis, chemotaxis, and osteoclastogenesis, processes that are critical in various inflammatory diseases. This review focuses on new findings on the expression and the pathological roles of IL-20 in rheumatoid arthritis (RA), osteoporosis, and breast cancer-induced osteolysis. We also discuss the therapeutic potential of an anti-IL-20 monoclonal antibody (mAb) in these three diseases.

IL-20

IL-20 was initially identified from the expressed sequence tag (EST) databases using an algorithm designed to identify translated sequences containing both a signal sequence and one or more amphipathic helices commonly found in helical cytokines (3). The IL-20 gene was

Received October 30, 2013; final acceptance January 30, 2014.
Address correspondence to Ming-Shi Chang, Professor, Department of Biochemistry and Molecular Biology, National Cheng Kung University, College of Medicine, Tainan 70428, Taiwan, ROC. Tel: +886-6-235-3535, ext. 5677; Fax: +886-6-274-1694; E-mail: mschang@mail.ncku.edu.tw

mapped to a 195-kb region on chromosome 1q32, which also includes IL-10, IL-19, and IL-24 (3). The other two IL-10-related cytokines, IL-22 and IL-26, are on chromosome 12q15 (11). Clustering of family members may be the result of gene duplication with subsequent divergence of function and regulation. There are two potential nuclear factor of κ light polypeptide gene enhancer in B-cell (NF-κB) binding sites; one is upstream from the start codon in the IL-20 gene, and the other one is in the 3′-untranslated region of the IL-20 gene (53,62). The latter suggests that IL-20 mRNA is rare and short-lived; therefore, IL-20 acts as a quickly regulated protein that may have a short but basic role in initiating inflammation (70).

Reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, and immunohistochemistry (IHC) analysis confirmed that IL-20 was expressed in a variety of tissues. IL-20 was expressed primarily in activated monocytes and in skin, kidney, lung, and reproductive glands. Several cell lines derived from prostate, pancreas, skin, lung, kidney, colon, and breast tissue also expressed IL-20 at different levels (49). Recent studies (17,21–23,39) indicate that other sources for IL-20 are endothelial cells, rheumatoid synovial fibroblasts, proximal tubular epithelial cells, breast cancer cells, and oral cancer cells.

Within the IL-10 family, IL-19, IL-20, and IL-24 exhibit substantial sharing of receptor complexes. IL-19, IL-20, and IL-24 signal through the IL-20R1–IL-20R2 heterodimer (11). In addition, IL-20 and IL-24, but not IL-19, bind to another receptor complex composed of IL-22R1 and IL-20R2 (11,55). Moreover, IL-22 signals through IL-22R1–IL-10R2, and IL-26 binds to IL-20R1–IL-10R2 (68). The interaction of individual IL-10 family cytokines with their receptor complexes is ligand specific.

Little is known about signal transduction mechanisms coupled to the IL-20 receptor complexes except that they all function partly through Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathways. Several studies have reported that IL-20 signaled through different pathways in different cell types: STAT3 in a male human immortalized keratinocyte cell line (HaCaT) (3); extracellular signal-regulated kinase 1 (ERK1/2) in mouse and human RA synovial fibroblasts and mesangial cells (22,38); p38 mitogen-activated protein kinase (MAPK), C-Jun-N-terminal kinase (JNK), JAK2/STAT5, AKT, and ERK1/2 in human and porcine endothelial cells (17,74); JNK and ERK1/2 in rat and human epithelial cells (39); JNK, ERK1/2, AKT, and p38 in mouse osteoblastic cell lines (MC3T3-E1) (20); JNK, ERK1/2, STAT3, and B-cell CLL/lymphoma-extra large (Bcl-X_L) in human and mouse breast cancer cells (21); STAT3, AKT, JNK, and ERK1/2 in human oral cancer cells (23); and ERK1/2, JNK, p38, and JAK–STAT in human bladder cancer cells (33).

CLINICAL IMPLICATIONS OF IL-20

An increasing number of the biological activities of IL-20 have recently been reported. Although much remains to be explained about the physiological and pathogenic mechanisms of action of IL-20, current data support their association with several diseases and their being potential targets in therapeutics. An overview of the functional properties of IL-20 and their association with bone diseases discovered in our lab is illustrated in the following sections.

IL-20 and Rheumatoid Arthritis

RA is characterized by chronic inflammation of synovial joints with proliferating synovial fibroblasts and infiltrating activated leucocytes (in particular by memory T-cells, macrophages, and plasma cells) (9,25). Angiogenesis in the local synovial tissue of patients with RA is considered to be an early step in the pathogenesis of RA (29,76). Inflammatory cytokines such as IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α are overexpressed in the affected tissue, in the synovial fluid of affected joints, and in the circulation of patients with RA. The effects of TNF-α and IL-1β on synovial fibroblasts, osteoblasts, osteoclasts, and chondrocytes are important in the pathogenesis of RA. These inflammatory cytokines are secreted through activation of T-cells, which then interact with monocytes and macrophages in RA (54).

Synovial fibroblasts are significantly involved in the pathogenesis of RA by synthesizing various proteases, superoxide, chemokines, and cytokines such as TNF-α, IL-1, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-6. Cytokines derived from macrophages and synovial fibroblasts are abundant in the rheumatoid synovium (43). Many of these factors are important in regulating inflammatory cell migration and activation (43). TNF-α is expressed in endothelial cells, synovial fibroblasts, osteoclasts, and cartilage from patients with RA. The elevated level of TNF-α promotes inflammation and bone destruction (12). In addition, molecules such as macrophage-specific colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), which are expressed in the inflamed synovium, stimulate osteoclastogenesis and bone resorption (43). Patients with RA manifest irreversible bone destruction and poor functional outcomes (43). Therefore, preventing bone destruction is important for antiarthritis therapy.

The intracellular signaling involved in regulating IL-20 expression has been investigated in only a few studies. Jones et al. (27) identified a 40-kb conserved region between IL-10 and IL-19 that might be involved in the transcriptional regulation of IL-10-type cytokines. IL-20 expression is induced by lipopolysaccharide/toll-like receptor 4 (LPS/TLR-4) or IL-1β through p38-mitogen-

activated protein kinase (16,53). Hypoxia induces synovial angiogenesis in patients with RA through vascular endothelial growth actor (VEGF). This process further enhances infiltration of immune cells, the production of inflammatory mediators, and causes more severe inflammation (30). We identified a hypoxia-responsive element upstream of the promoter of IL-20 (6) and reported that in cultured monocytes, HaCaT cells, chondrocytes, and human embryonic kidney (HEK293) cells, IL-20 expression was upregulated by $CoCl_2$-mimicked hypoxia. This finding suggested that the regulation of IL-20 by hypoxia is a general phenomenon in various cells. The NF-κB and hypoxia-inducible factor-1 pathways are critical for the induction of several genes in the cells in response to hypoxia and inflammatory stimuli. It is therefore worthwhile to further investigate the role of NF-κB in hypoxia-inducible factor-1-regulated IL-20 expression.

Elevated IL-20 protein and all three IL-20 receptor subunits (IL-20R1, IL-20R2, and IL-22R1) were detected in samples derived from the synovial membranes of patients with RA, but not in those of healthy controls (22). This finding was confirmed in a collagen-induced arthritis (CIA) rat model. IL-20 was produced primarily by macrophages and synovial fibroblasts. IL-20 in turn induces chemokines such as monocyte chemoattractant protein 1 (MCP-1) and IL-8, which recruit neutrophils and T-cells into inflamed tissues. In addition to acting as a proinflammatory factor, IL-20 may also contribute to RA through its effect on angiogenesis and lymphangiogenesis (17,74). Antibodies of IL-20 have been confirmed to reduce the severity of arthritis in CIA rats (19).

Synovial fibroblasts express both types of IL-20 receptors and could be the target of IL-19, IL-20, and IL-24 (19,22,66). IL-20 expression is upregulated in inflamed synovial membranes. IL-20 induces the activation of ERK1/2 and p38 in RA synovial fibroblasts (RASFs); induces RASFs to secrete MCP-1, IL-6, and IL-8; and promotes neutrophil chemotaxis, RASF migration, and endothelial cell proliferation. Both IL-20 and IL-20R1, but not IL-20R2 or IL-22R1, were upregulated in the CIA rat model (22). IL-20 also induces the expression of TNF-α and RANKL in primary cultured synovial fibroblasts derived from CIA rats (19). Interestingly, IL-20 induced RANKL only in the synovial fibroblasts isolated from CIA rats, but not from healthy rats (19).

Inflammation in RA is most likely sustained by an IL-20-dependent autocrine loop: macrophages and synovial fibroblasts produce IL-20, which in turn induces chemoattractants such as MCP-1 and IL-8. The subsequent recruitment of neutrophils and T-cells aggravates the inflammation. The alteration of RANKL expression in synovial fibroblasts by IL-20 also implies that IL-20 is involved in regulating bone metabolism.

Bone erosion is another symptom of RA and is associated with the severity of disease. Erosion of periarticular cortical bone is caused by excessive local bone resorption and inadequate bone formation (67). Low bone mass is associated with an increase in the number of osteoclasts and with excessive osteoclast activity. IL-20 induced TNF-α, RANKL, and IL-17 expression in mouse osteoblastic MC3T3-E1 cells (19,20). In addition, IL-20 is pivotal for the differentiation of osteoclasts from hematopoietic stem cells (20). Osteoclasts express both types of IL-20 receptors and, therefore, could be the target of IL-20. RANK is the specific signaling receptor of RANKL, which regulates osteoclast activation. In CIA rats, anti-IL-20 mAb ameliorated the severity of arthritis by decreasing hind-paw thickness and swelling, preventing bone destruction, and reducing proinflammatory cytokine production in synovial tissue (19). These findings suggest that blocking IL-20 significantly inhibited the symptoms of arthritis and the progression of the disease in CIA rats.

IL-20 and Osteoporosis

Osteoporosis is a serious public health concern with an estimated worldwide incidence of over 200 million (31). It is characterized by low bone density, reduced bone strength, and increased risk of fracture (50). Osteoporosis is caused by an imbalance between bone formation and resorption. The major cell types responsible for these two processes are osteoblasts and osteoclasts, respectively. Both estrogen deficiency in women and androgen deficiency in men cause an imbalance in bone turnover in which bone resorption exceeds bone formation. Rapid bone loss occurs and is accompanied by the destruction of bone microarchitecture (45,69).

Osteoclasts are derived from the monocyte–macrophage cell lineage and strongly express tartrate-resistent acid phosphatase (TRAP) type 5 and cathepsin K. The phenotype of terminally differentiated mature osteoclasts is characterized by the expression of markers such as TRAP and the calcitonin receptor (31). The activity of osteoclasts is regulated by the parathyroid, calcitonin, and IL-6; soluble factors such as MCSF (60); transcription factors such as cFos, nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 (NFATc1), and NF-κB; and the protein RANKL (73). Bone resorption also involves the synthesis of cysteine proteinases such as cathepsin K and matrix metalloproteinases (MMPs). The principal regulators of osteoclast differentiation, activity, and survival are RANKL and M-CSF (67). RANKL is expressed by osteoblasts and other cells: osteocytes, bone marrow stromal cells, T-cells, and B-cells. When RANKL activates its receptor, RANK, located on the cell surface of preosteoclasts and mature osteoclasts, the induction of

transcription factors and enzymes promotes osteoclastic bone resorption (28).

Our recent study (20) showed that serum IL-20 was highly expressed in patients with osteoporosis and in an ovariectomized (OVX)-induced bone loss mouse model of osteoporosis. This is the first evidence that IL-20 was upregulated in the pathogenesis of osteoporosis. Both M-CSF and RANKL are believed to be essential and sufficient for the differentiation of osteoclast. However, we found that IL-20 is also critical for osteoclast differentiation; our evidence is that anti-IL-20 mAb completely inhibited osteoclast differentiation at the presence of M-CSF and RANKL.

IL-20 and all three IL-20 receptor subunits (IL-20R1, IL-20R2, and IL-22R1) were detected in osteoclast precursor cells and osteoblasts, which indicated that IL-20 targeted both osteoclasts and osteoblasts. We demonstrated that IL-20 upregulates RANK expression in osteoclasts and RANKL expression in osteoblasts. In addition, IL-20 also enhanced osteoclast differentiation by inducing cathepsin G and modulating soluble RANKL production by osteoblasts (20). Therefore, IL-20 is an upstream activator of RANKL–RANK signaling.

RANKL–RANK signaling-mediated NFATc1 activation is pivotal for osteoclast differentiation. IL-20 promoted the activation of NF-κB, TNF receptor-associated factor 6 (TRAF6), STAT3, NFATc1, and c-Fos; anti-IL-20 mAb inhibited these activations, which indicated that IL-20 regulates osteoclastogenic signals and acts as a stimulating factor for osteoclastogenesis.

In an OVX-induced bone loss mouse model (20), anti-IL-20 mAb protected mice against osteoporotic bone loss and increased their bone mineral density (BMD) in vivo. Furthermore, we generated IL-20R1-deficient mice (the deficiency blocks IL-20 signaling) to confirm the critical involvement of IL-20 in osteoclastogenesis. IL-20R1-deficient mice had a higher BMD than did wild-type mice (20). These findings suggest that IL-20 is pivotal for osteoclast differentiation and that the signaling elicited by IL-20R1 is critical for modulating BMD during metabolic bone disease.

IL-20 and Cancer-Induced Osteolysis

Breast cancer is the second leading cause of cancer-related death in women, with metastasis representing a serious cause of morbidity and mortality (48). Breast cancer usually metastasizes to the skeleton. About 85% of women with advanced-stage breast cancer have bone metastases (41). While ductal carcinoma in situ detected early is 98% curable, bone metastases are basically incurable (26). Metastatic cancer cells tend to colonize the heavily vascularized areas of the skeleton, such as the red marrow of the long bones, ribs, and vertebrae, where they disrupt not only bone physiology, but also hematopoiesis and the immune system (7).

In a recent study, we reported that IL-20 may be involved in breast cancer and bone metastasis (21). Immunohistochemistry (IHC) staining and real-time PCR analysis demonstrated the expression of IL-20 and its three receptors in primary breast tumor tissue and bone-metastasis tissue of patients with breast cancer. Higher IL-20 expression was associated with advanced tumor stages, greater tumor metastasis, and poor survival. Therefore, the expression of IL-20 in breast cancer tissue is not only associated with a higher mitotic rate but also correlated with advanced tumor stages and bone metastasis. Therefore, IL-20 might be used as a biomarker for diagnosing breast cancer.

Metastasis is a process characterized by local invasion, intravasation, transportation of tumor cells to the parenchyma of other organs, extravasation, and the establishment of secondary lesions (15). As breast cancer cells establish secondary colonies in the bone microenvironment, tumor cells secrete cytokines, which stimulate RANKL expression in osteoblasts and subsequently interact with its receptor RANK on osteoclast, which leads to osteoclast differentiation and activation (47). Activated osteoclasts then mediate bone degradation by releasing proteases, including MMPs and cathepsins. As bone is degraded, many growth factors and chemoattractants for tumor cells are released and promote bone metastasis (10,47,64). While there is evidence that the MMPs secreted from breast cancer cells can resorb bone in vitro and contribute to bone degradation in vivo (32), it is now well accepted that osteoclasts are largely responsible for osteolytic metastatic lesions (8). In addition, the local cytokine/MMP/protease milieu generated by the tumor microenvironment is important for the growth, metastasis, and immune evasion of breast tumors.

All three IL-20 receptors were expressed in clinical specimens and breast cancer cell lines, which suggested that IL-20 acts in an autocrine manner in breast cancer. We found that IL-20 induced breast cancer cell proliferation and migration and promoted tumor progression by increasing the expression of MMP-9, MMP-12, cathepsin K, and cathepsin G (21). Therefore, IL-20 might provide a good microenvironment for tumor growth and metastasis.

Breast cancer that metastasizes to bone also leads to pathological bone destruction, which causes osteolysis and fractures. Continuation of the vicious cycle depends on a continuous supply of osteoclast precursors and mature osteoclasts that can be activated by RANKL (26). IL-20 stimulated osteoclast differentiation by modulating RANK–RANKL expression (20). Therefore, IL-20 may be involved in breast cancer-mediated bone osteolysis by regulating osteoclastogenesis.

In summary, IL-20 participates in breast cancer-mediated bone metastasis and induces osteolysis through

four possible mechanisms: (i) IL-20 enhances tumor progression by promoting tumor cell proliferation and migration; (ii) IL-20 supplies a microenvironment for tumor colonization in bone by increasing the expression of MMP-9, MMP-12, cathepsin K, and cathepsin G; (iii) IL-20 increased osteoclastogenic activity by upregulating cathepsin G expression in osteoclasts and tumor cells; and (iv) IL-20 also controls osteoclastogenesis by upregulating RANK–RANKL signals, which provides a link between inflammation and tumor-induced osteolysis.

In a murine model of breast cancer, we found that IL-20 was highly expressed in the tumor mass, which is consistent with our clinical findings. IL-20 is a hypoxia-inducible gene, and the hypoxia response element has been identified on the IL-20 promoter (6). Therefore, one possible mechanism upregulating IL-20 in the tumor may be the response of cancer cells to hypoxia in the solid tumor mass. Taken together, these data suggest that IL-20 may be a novel target for breast cancer therapy.

THERAPEUTIC POTENTIAL OF ANTI-IL-20 mAb

Rheumatoid Arthritis

CIA is an experimental model of human RA that is widely used for studying disease processes as well as for evaluating potential therapeutic agents. Two drugs that target TNF-α, namely, etanercept and infliximab, ameliorate inflammation and joint destruction of RA. However, therapy against TNF-α is clinically effective in only 40–70% of patients (43,58,65), which indicates that some novel targets for drug development should be explored.

We showed that anti-IL-20 mAb treatment reduced the severity of arthritis in CIA rats by inhibiting inflammation and bone destruction (19). In addition, treatment with anti-IL-20 mAb combined with etanercept significantly ameliorated arthritis by decreasing hind-paw swelling, preventing cartilage damage and bone loss, and reducing the expression of IL-20, TNF-α, IL-6, IL-1β, RANKL, and MMPs in synovial tissue. Treatment with anti-IL-20 mAb combined with etanercept protected rats from CIA better than did treatment with etanercept alone. In addition, treatment with anti-IL-20 mAb not only neutralized IL-20, but also reduced TNF-α, IL-1β, and IL-6 simultaneously in a CIA model, which suggested that anti-IL-20 mAb may have advantages over current drugs on the market. These observations provide evidence that IL-20 is a novel target and that anti-IL-20 mAb may be a potential therapeutic for RA.

Osteoporosis

Choices of established palliative and disease-modifying therapies are available for osteoporosis. None of them are curative; however, they are only partially effective for slowing down or stopping disease progression. Pharmacological agents for treating osteoporosis may be classified as antiresorptive or osteoanabolic, depending on whether the principal means of improving bone strength is inhibiting osteoclastic bone resorption or stimulating osteoblastic bone formation. RANKL inhibitors such as osteoprotegerin and anti-RANKL antibody are inhibitors of bone resorption, presumably because of their effects on osteoclasts. Denosumab (Prolia and Xgeva; Amgen Inc., Thousand Oaks, CA, USA) is a fully human monoclonal antibody with high specificity for RANKL. By binding to RANKL, denosumab prevents its interaction with RANK, thereby inhibiting bone resorption by reducing osteoclast formation, activity, and survival (35). Denosumab is approved for the treatment of postmenopausal women with osteoporosis at high risk of fracture and for treatment to increase bone mass in women at high risk of fracture who are taking adjuvant aromatase inhibitor therapy for breast cancer. Denosumab at a different dose is approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors (35). The sclerostin inhibitor AMG 785 (anti-sclerostin mAb) (Amgen Inc.) stimulated bone formation and improved the strength of the fracture callus in a primate fibular osteotomy model (37). AMG 785 is in the process of phase II/III clinical trials in postmenopausal women with osteoporosis. Bone formation is linked to resorption through coupling factors (36,44), so treatment with antiresorption agents may result in the simultaneous suppression of bone formation, which may compromise the efficacy of the drug (37,51,59,61). Therefore, it will be more beneficial to identify an agent that synchronously regulates bone resorption and formation.

In an OVX-induced bone loss model (20), anti-IL-20 mAb protected OVX mice against bone loss and increased their bone density. In the in vitro assay, we showed that anti-IL-20 mAb reduced not only the number of $TRAP^+$ osteoclasts, but also the activity of RANK–RANKL signals. In addition, anti-IL-20 mAb almost totally prevented the RANKL-induced activation of TRAF6, c-Fos, NFATc1, and STAT3. Thus, anti-IL-20 mAb not only blocks the production of IL-20 but also of the protein RANKL. It affects not only osteoclast formation but also osteoblast function; hence, it may have advantages over denosumab. Therefore, we conclude that anti-IL-20 mAb is a potential therapeutic for protecting against osteoporotic bone loss.

Cancer-Induced Osteolysis

Most metastasis of breast cancer to bone causes osteolytic lesions. The induction of aberrant osteoclastogenesis is only part of the equation. Breast cancer cells also inhibit osteoblast differentiation and adhesion, downregulate collagen synthesis, and increase osteoblast apoptosis. Thus, bone loss is the result of excessive bone degradation and insufficient bone replacement. In the final stages of

breast cancer-induced osteolysis, the cancer cells, fueled by growth factors released from the degraded matrix, expand unchecked (7).

Since the discovery of RANKL and its role in bone remodeling, the field of bone metastasis has moved rapidly. It is now generally accepted that the bone microenvironment is critical to the colonization and growth or dormancy of metastasized tumors. Our recent data showed that IL-20 provides a microenvironment for tumor colonization in bone by increasing the expression of MMP-9, MMP-12, cathepsin K, and cathepsin G (21). IL-20 modulates osteoclastogenesis by upregulating RANK–RANKL, which provides evidence that IL-20 is critical for tumor-induced osteolysis. Furthermore, anti-IL-20 mAb inhibited tumor proliferation, increased tumor cell apoptosis, and reduced bone colonization in a mouse cancer model. Anti-IL-20 mAb also protected against bone loss in intratibial breast cancer-injected osteolytic mice. Therefore, in vivo data demonstrated that anti-IL-20 mAb modulates bone turnover and provides an unfavorable microenvironment for tumor cells to colonize and grow. Thus, anti-IL-20 mAb is a potential therapeutic agent for inhibiting breast tumor growth and bone colonization and eventually protecting against cancer-induced osteolytic bone loss.

CONCLUDING REMARKS

The involvement of IL-20 in skin inflammation has been reported in many studies (3,34,63,70,77,78). Our recent studies indicate that IL-20 is a pleiotropic cytokine with potent inflammatory, angiogenic, chemoattractive, and osteoclastogenic effects, all of which are characteristics of RA, osteoporosis, and cancer-induced osteolysis. This review addresses the associations between IL-20 and these three diseases. We propose a working model showing how IL-20 is involved in disease progression (Fig. 1).

Blocking the activities of cytokines constitutes a successful therapeutic for inflammation-associated diseases (52,57,71,72) because they are key players in the physiological and pathological processes of multicellular organisms. There is an increasing interest in finding specific

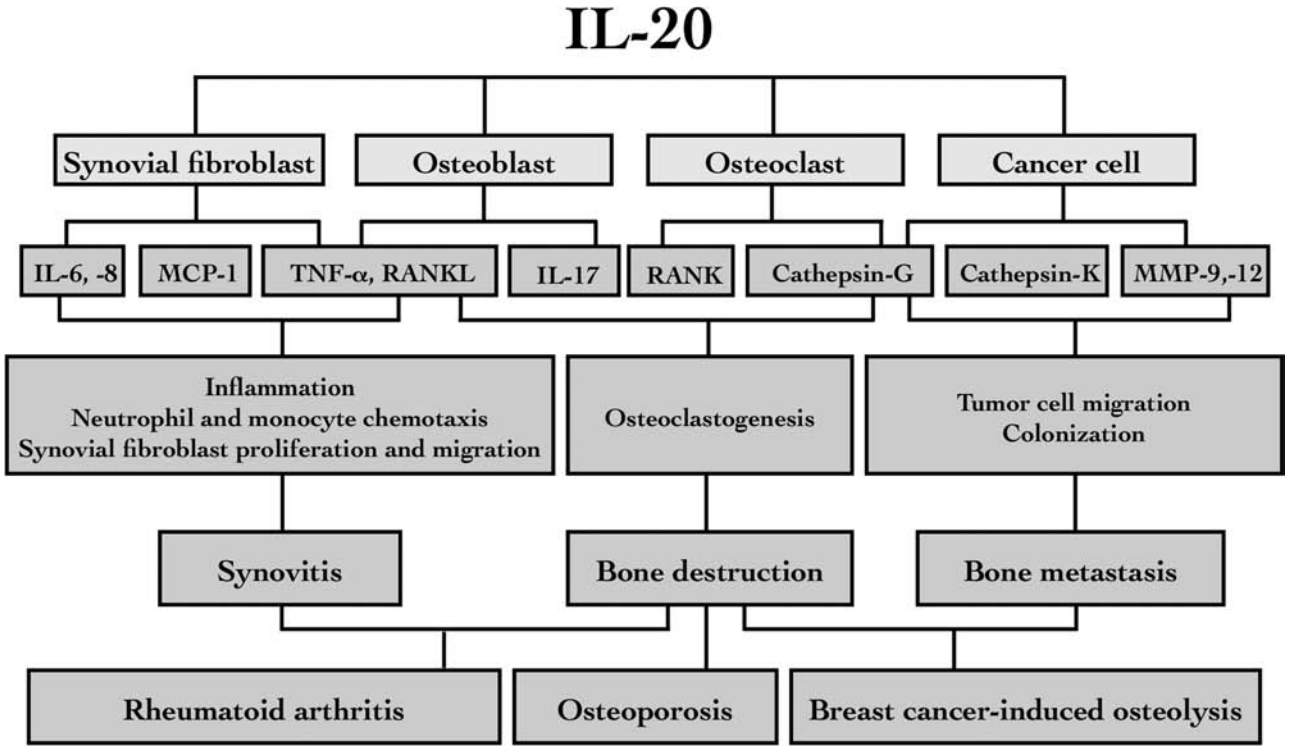

Figure 1. Biological functions of interleukin-2- (IL-20) in the pathogenesis of RA, osteoporosis, and cancer-induced osteolysis. IL-20 may contribute to the pathogenesis of rheumatoid arthritis (RA), osteoporosis, and cancer-induced osteolysis through five possible pathways: by promoting [i] synovial fibroblasts to secrete proinflammatory cytokines, which amplify the inflammatory response in synovial tissue; [ii] immune-cell infiltration and chemotaxis by inducing chemokines; [iii] osteoclast differentiation by inducing cathepsin G and modulating soluble (s) receptor activator of nuclear factor of κ light polypeptide gene enhancer in B-cells (NF-κB) ligand (RANKL) production by osteoblasts; [iv] osteoclastogenesis by altering RANK–RANKL signaling, which provides a link between synovial inflammation and bone destruction; and [v] nurturing a microenvironment for tumor colonization in bone by upregulating matrix metalloproteinases (MMPs) and cathepsins. Therefore, IL-20 is pivotal in many phases of the disease progression of RA, osteoporosis, and cancer-induced osteolysis. MCP-1, monocyte chemoattractant protein 1; TNF-α, tumor necrosis factor-α.

cytokines that play a dominant role in distal portions of the pathogenesis of inflammatory processes and disorders. We preferably want to regulate only the functions of local tissue that are pivotal in the pathogenesis of a specific disease. IL-20 was upregulated only in local synovial fluid, but not in the serum of patients with RA. Both IL-20 and IL-20R1 were detected specifically in the synovial fibroblasts derived from CIA rats, but not from healthy rats. On the other hand, higher expression of IL-20 in breast tumors was correlated with clinical outcome. Clinical tumorous breast tissue also expressed higher levels of IL-20 and its receptors than did nontumorous breast tissue. These data confirm that IL-20 was upregulated in specific local tissue during the pathological conditions of RA, osteoporosis, and breast cancer. Therefore, blocking the activities of IL-20 in these three diseases will be a novel strategy. Anti-IL-20 mAb is currently under development for treating RA. Information from clinical trials will help us to better understand the role of IL-20. A fully human recombinant monoclonal antibody of anti-IL-20 developed by Novo Nordisk (Copenhagen, Denmark) has been tested in a clinical trial that yielded no safety issues (24). Novo Nordisk has finished their phase IIA trial for anti-IL-20 mAb and started a phase IIB clinical trial for RA.

In summary, available data suggest that IL-20 has a broad spectrum of biological effects in many phases of disease progression in RA, osteoporosis, and cancer-induced osteolysis. These observations suggest that anti-IL-20 mAb may be a feasible treatment option for these three diseases in the future.

ACKNOWLEDGMENTS: The authors declare no conflicts of interest.

REFERENCES

1. Azuma, Y. T.; Matsuo, Y.; Kuwamura, M.; Yancopoulos, G. D.; Valenzuela, D. M.; Murphy, A. J.; Nakajima, H.; Karow, M.; Takeuchi, T. Interleukin-19 protects mice from innate-mediated colonic inflammation. Inflamm. Bowel Dis. 16(6):1017–1028; 2010.
2. Bartlett, N. W.; Dumoutier, L.; Renauld, J. C.; Kotenko, S. V.; McVey, C. E.; Lee, H. J.; Smith, G. L. A new member of the interleukin 10-related cytokine family encoded by a poxvirus. J. Gen. Virol. 85(Pt 6):1401–1412; 2004.
3. Blumberg, H.; Conklin, D.; Xu, W. F.; Grossmann, A.; Brender, T.; Carollo, S.; Eagan, M.; Foster, D.; Haldeman, B. A.; Hammond, A.; Haugen, H.; Jelinek, L.; Kelly, J. D.; Madden, K.; Maurer, M. F.; Parrish-Novak, J.; Prunkard, D.; Sexson, S.; Sprecher, C.; Waggie, K.; West, J.; Whitmore, T. E.; Yao, L.; Kuechle, M. K.; Dale, B. A.; Chandrasekher, Y. A. Interleukin 20: Discovery, receptor identification, and role in epidermal function. Cell 104(1):9–19; 2001.
4. Chan, A. C.; Carter, P. J. Therapeutic antibodies for autoimmunity and inflammation. Nat. Rev. Immunol. 10(5):301–316; 2010.
5. Chan, J. R.; Blumenschein, W.; Murphy, E.; Diveu, C.; Wiekowski, M.; Abbondanzo, S.; Lucian, L.; Geissler, R.; Brodie, S.; Kimball, A. B.; Gorman, D. M.; Smith, K.; de Waal Malefyt, R.; Kastelein, R. A.; McClanahan, T. K.; Bowman, E. P. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. J. Exp. Med. 203(12):2577–2587; 2006.
6. Chen, W. Y.; Chang, M. S. IL-20 is regulated by hypoxia-inducible factor and up-regulated after experimental ischemic stroke. J. Immunol. 182(8):5003–5012; 2009.
7. Chen, Y. C.; Sosnoski, D. M.; Mastro, A. M. Breast cancer metastasis to the bone: Mechanisms of bone loss. Breast Cancer Res. 12(6):215; 2010.
8. Clohisy, D. R.; Perkins, S. L.; Ramnaraine, M. L. Review of cellular mechanisms of tumor osteolysis. Cli. Orthop. Relat.Res. 373:104–114; 2000.
9. Cush, J. J.; Lipsky, P. E. Phenotypic analysis of synovial tissue and peripheral blood lymphocytes isolated from patients with rheumatoid arthritis. Arthritis Rheum. 31(10): 1230–1238; 1988.
10. Delaisse, J. M.; Engsig, M. T.; Everts, V.; del Carmen Ovejero, M.; Ferreras, M.; Lund, L.; Vu, T. H.; Werb, Z.; Winding, B.; Lochter, A.; Karsdal, M. A.; Troen, T.; Kirkegaard, T.; Lenhard, T.; Heegaard, A. M.; Neff, L.; Baron, R.; Foged, N. T. Proteinases in bone resorption: Obvious and less obvious roles. Clin. Chim. Acta 291(2): 223–234; 2000.
11. Dumoutier, L.; Leemans, C.; Lejeune, D.; Kotenko, S. V.; Renauld, J. C. Cutting edge: STAT activation by IL-19, IL-20 and mda-7 through IL-20 receptor complexes of two types. J. Immunol. 167(7):3545–3549; 2001.
12. Feldmann, M.; Brennan, F. M.; Foxwell, B. M.; Maini, R. N. The role of TNF alpha and IL-1 in rheumatoid arthritis. Curr. Dir. Autoimmun. 3:188–199; 2001.
13. Gallagher, G.; Dickensheets, H.; Eskdale, J.; Izotova, L. S.; Mirochnitchenko, O. V.; Peat, J. D.; Vazquez, N.; Pestka, S.; Donnelly, R. P.; Kotenko, S. V. Cloning, expression and initial characterization of interleukin-19 (IL-19), a novel homologue of human interleukin-10 (IL-10). Genes Immun. 1(7):442–450; 2000.
14. Geboes, L.; Dumoutier, L.; Kelchtermans, H.; Schurgers, E.; Mitera, T.; Renauld, J. C.; Matthys, P. Proinflammatory role of the Th17 cytokine interleukin-22 in collagen-induced arthritis in C57BL/6 mice. Arthritis Rheum. 60(2):390–395; 2009.
15. Gupta, G. P.; Massague, J. Cancer metastasis: Building a framework. Cell 127(4):679–695; 2006.
16. Hosoi, T.; Wada, S.; Suzuki, S.; Okuma, Y.; Akira, S.; Matsuda, T.; Nomura, Y. Bacterial endotoxin induces IL-20 expression in the glial cells. Brain Res. 130(1–2):23–29; 2004.
17. Hsieh, M. Y.; Chen, W. Y.; Jiang, M. J.; Cheng, B. C.; Huang, T. Y.; Chang, M. S. Interleukin-20 promotes angiogenesis in a direct and indirect manner. Genes Immun. 7(3):234–242; 2006.
18. Hsing, C. H.; Ho, C. L.; Chang, L. Y.; Lee, Y. L.; Chuang, S. S.; Chang, M. S. Tissue microarray analysis of interleukin-20 expression. Cytokine 35(1–2):44–52; 2006.
19. Hsu, Y. H.; Chang, M. S. Interleukin-20 antibody is a potential therapeutic agent for experimental arthritis. Arthritis Rheum. 62(11):3311–3321; 2010.
20. Hsu, Y. H.; Chen, W. Y.; Chan, C. H.; Wu, C. H.; Sun, Z. J.; Chang, M. S. Anti-IL-20 monoclonal antibody inhibits the differentiation of osteoclasts and protects against osteoporotic bone loss. J. Exp. Med. 208(9):1849–1861; 2011.

21. Hsu, Y. H.; Hsing, C. H.; Li, C. F.; Chan, C. H.; Chang, M. C.; Yan, J. J.; Chang, M. S. Anti-IL-20 monoclonal antibody suppresses breast cancer progression and bone osteolysis in murine models. J. Immunol. 188(4):1981–1991; 2012.
22. Hsu, Y. H.; Li, H. H.; Hsieh, M. Y.; Liu, M. F.; Huang, K. Y.; Chin, L. S.; Chen, P. C.; Cheng, H. H.; Chang, M. S. Function of interleukin-20 as a proinflammatory molecule in rheumatoid and experimental arthritis. Arthritis Rheum. 54(9):2722–2733; 2006.
23. Hsu, Y. H.; Wei, C. C.; Shieh, D. B.; Chan, C. H.; Chang, M. S. Anti-IL-20 monoclonal antibody alleviates inflammation in oral cancer and suppresses tumor growth. Mol. Cancer Res. 10(11):1430–1439; 2012.
24. http://clinicaltrials.gov/ct2/show/NCT01261767.
25. Janossy, G.; Panayi, G.; Duke, O.; Bofill, M.; Poulter, L. W.; Goldstein, G. Rheumatoid arthritis: A disease of T-lymphocyte/macrophage immunoregulation. Lancet 2(8251):839–842; 1981.
26. Jemal, A.; Siegel, R.; Ward, E.; Murray, T.; Xu, J.; Thun, M. J. Cancer statistics, 2007. CA Cancer J. Clin. 57(1):43–66; 2007.
27. Jones, E. A.; Flavell, R. A. Distal enhancer elements transcribe intergenic RNA in the IL-10 family gene cluster. J. Immunol. 175(11):7437–7446; 2005.
28. Kearns, A. E.; Khosla, S.; Kostenuik, P. J. Receptor activator of nuclear factor kappa B ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocr. Rev. 29(2):155–192; 2008.
29. Koch, A. E. Review: Angiogenesis: Implications for rheumatoid arthritis. Arthritis Rheum. 41(6):951–962; 1998.
30. Konisti, S.; Kiriakidis, S.; Paleolog, E. M. Hypoxia—A key regulator of angiogenesis and inflammation in rheumatoid arthritis. Nat. Rev. Rheumatol. 8(3):153–162; 2012.
31. Lampropoulos, C. E.; Papaioannou, I.; D'Cruz, D. P. Osteoporosis—A risk factor for cardiovascular disease? Nat. Rev. Rheumatol. 8(10):587–598; 2012.
32. Lee, J.; Weber, M.; Mejia, S.; Bone, E.; Watson, P.; Orr, W. A matrix metalloproteinase inhibitor, batimastat, retards the development of osteolytic bone metastases by MDA-MB-231 human breast cancer cells in Balb C nu/nu mice. Eur. J. Cancer 37(1):106–113; 2001.
33. Lee, S. J.; Cho, S. C.; Lee, E. J.; Kim, S.; Lee, S. B.; Lim, J. H.; Choi, Y. H.; Kim, W. J.; Moon, S. K. Interleukin-20 promotes migration of bladder cancer cells through extracellular signal-regulated kinase (ERK)-mediated MMP-9 protein expression leading to nuclear factor (NF-kappaB) activation by inducing the up-regulation of p21(WAF1) protein expression. J. Biol. Chem. 288(8):5539–5552; 2013.
34. Leng, R. X.; Pan, H. F.; Tao, J. H.; Ye, D. Q. IL-19, IL-20 and IL-24: Potential therapeutic targets for autoimmune diseases. Expert Opin. Ther. Targets 15(2):119–126; 2011.
35. Lewiecki, E. M. Monoclonal antibodies for the treatment of osteoporosis. Expert Opin. Biol. Ther. 13(2):183–196; 2013.
36. Lewiecki, E. M. New targets for intervention in the treatment of postmenopausal osteoporosis. Nat. Rev. Rheumatol. 7(11):631–638; 2011.
37. Lewiecki, E. M. Sclerostin monoclonal antibody therapy with AMG 785: A potential treatment for osteoporosis. Expert Opin. Biol. Ther. 11(1):117–127; 2011.
38. Li, H. H.; Cheng, H. H.; Sun, K. H.; Wei, C. C.; Li, C. F.; Chen, W. C.; Wu, W. M.; Chang, M. S. Interleukin-20 targets renal mesangial cells and is associated with lupus nephritis. Clin. Immunol. 129(2):277–285; 2008.
39. Li, H. H.; Hsu, Y. H.; Wei, C. C.; Lee, P. T.; Chen, W. C.; Chang, M. S. Interleukin-20 induced cell death in renal epithelial cells and was associated with acute renal failure. Genes Immun. 9(5):395–404; 2008.
40. Liao, Y. C.; Liang, W. G.; Chen, F. W.; Hsu, J. H.; Yang, J. J.; Chang, M. S. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J. Immunol. 169(8):4288–4297; 2002.
41. Lipton, A.; Uzzo, R.; Amato, R. J.; Ellis, G. K.; Hakimian, B.; Roodman, G. D.; Smith, M. R. The science and practice of bone health in oncology: Managing bone loss and metastasis in patients with solid tumors. J. Natl. Compr. Canc. Netw. 7(Suppl 7):S1–S29; quiz S30; 2009.
42. Liu, L.; Ding, C.; Zeng, W.; Heuer, J. G.; Tetreault, J. W.; Noblitt, T. W.; Hangoc, G.; Cooper, S.; Brune, K. A.; Sharma, G.; Fox, N.; Rowlinson, S. W.; Rogers, D. P.; Witcher, D. R.; Lambooy, P. K.; Wroblewski, V. J.; Miller, J. R.; Broxmeyer, H. E. Selective enhancement of multipotential hematopoietic progenitors in vitro and in vivo by IL-20. Blood 102(9):3206–3209; 2003.
43. Maini, R. N.; Taylor, P. C. Anti-cytokine therapy for rheumatoid arthritis. Annu. Rev. Med. 51:207–229; 2000.
44. Martin, T. J.; Sims, N. A. Osteoclast-derived activity in the coupling of bone formation to resorption. Trends Mol. Med. 11(2):76–81; 2005.
45. McClung, M. Role of RANKL inhibition in osteoporosis. Arthritis Res. Ther. 9(Suppl 1):S3; 2007.
46. Moore, K. W.; de Waal Malefyt, R.; Coffman, R. L.; O'Garra, A. Interleukin-10 and the interleukin-10 receptor. Annu. Rev. Immunol. 19:683–765; 2001.
47. Mundy, G. R. Metastasis to bone: Causes, consequences and therapeutic opportunities. Nat. Rev. Cancer 2(8):584–593; 2002.
48. Mundy, G. R.; Bertolini, D. R. Bone destruction and hypercalcemia in plasma cell myeloma. Semin. Oncol. 13(3): 291–299; 1986.
49. Nagalakshmi, M. L.; Murphy, E.; McClanahan, T.; de Waal Malefyt, R. Expression patterns of IL-10 ligand and receptor gene families provide leads for biological characterization. Int. Immunopharmacol. 4(5):577–592; 2004.
50. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 285(6):785–795; 2001.
51. Odvina, C. V.; Zerwekh, J. E.; Rao, D. S.; Maalouf, N.; Gottschalk, F. A.; Pak, C. Y. Severely suppressed bone turnover: A potential complication of alendronate therapy. J. Clin. Endocrinol. Metab. 90(3):1294–1301; 2005.
52. Olsen, N. J.; Stein, C. M. New drugs for rheumatoid arthritis. N. Engl. J. Med. 350(21):2167–2179; 2004.
53. Otkjaer, K.; Kragballe, K.; Johansen, C.; Funding, A. T.; Just, H.; Jensen, U. B.; Sorensen, L. G.; Norby, P. L.; Clausen, J. T.; Iversen, L. IL-20 gene expression is induced by IL-1beta through mitogen-activated protein kinase and NF-kappaB-dependent mechanisms. J. Invest. Dermatol. 127(6):1326–1336; 2007.
54. Panayi, G. S.; Lanchbury, J. S.; Kingsley, G. H. The importance of the T cell in initiating and maintaining the chronic synovitis of rheumatoid arthritis. Arthritis Rheum. 35(7):729–735; 1992.
55. Parrish-Novak, J.; Xu, W.; Brender, T.; Yao, L.; Jones, C.; West, J.; Brandt, C.; Jelinek, L.; Madden, K.; McKernan,

P. A.; Foster, D. C.; Jaspers, S.; Chandrasekher, Y. A. Interleukins 19, 20, and 24 signal through two distinct receptor complexes. Differences in receptor-ligand interactions mediate unique biological functions. J. Biol. Chem. 277(49):47517–47523; 2002.
56. Pestka, S.; Krause, C. D.; Sarkar, D.; Walter, M. R.; Shi, Y.; Fisher, P. B. Interleukin-10 and related cytokines and receptors. Annu. Rev. Immunol. 22:929–979; 2004.
57. Philipp, S.; Wolk, K.; Kreutzer, S.; Wallace, E.; Ludwig, N.; Roewert, J.; Hoflich, C.; Volk, H. D.; Sterry, W.; Sabat, R. The evaluation of psoriasis therapy with biologics leads to a revision of the current view of the pathogenesis of this disorder. Expert Opin. Ther. Targets 10(6):817–831; 2006.
58. Pope, R. M. Apoptosis as a therapeutic tool in rheumatoid arthritis. Nat. Rev. Immunol. 2(7):527–535; 2002.
59. Rachner, T. D.; Khosla, S.; Hofbauer, L. C. Osteoporosis: Now and the future. Lancet 377(9773):1276–1287; 2011.
60. Radi, Z. A.; Guzman, R. E.; Bell, R. R. Increased connective tissue extracellular matrix in the op/op model of osteopetrosis. Pathobiology 76(4):199–203; 2009.
61. Reid, I. R.; Miller, P. D.; Brown, J. P.; Kendler, D. L.; Fahrleitner-Pammer, A.; Valter, I.; Maasalu, K.; Bolognese, M. A.; Woodson, G.; Bone, H.; Ding, B.; Wagman, R. B.; San Martin, J.; Ominsky, M. S.; Dempster, D. W.; Denosumab Phase 3 Bone Histology Study Group. Effects of denosumab on bone histomorphometry: The FREEDOM and STAND studies. J. Bone Miner. Res. 25(10):2256–2265; 2010.
62. Rich, B. E.; Kupper, T. S. Cytokines: IL-20 – A new effector in skin inflammation. Curr. Biol. 11(13):R531–534; 2001.
63. Sabat, R.; Wallace, E.; Endesfelder, S.; Wolk, K. IL-19 and IL-20: Two novel cytokines with importance in inflammatory diseases. Expert Opin. Ther. Targets 11(5):601–612; 2007.
64. Saftig, P.; Hunziker, E.; Wehmeyer, O.; Jones, S.; Boyde, A.; Rommerskirch, W.; Moritz, J. D.; Schu, P.; von Figura, K. Impaired osteoclastic bone resorption leads to osteopetrosis in cathepsin-K-deficient mice. Proc. Natl. Acad. Sci. USA 95(23):13453–13458; 1998.
65. Saito, H.; Kojima, T.; Takahashi, M.; Horne, W. C.; Baron, R.; Amagasa, T.; Ohya, K.; Aoki, K. A tumor necrosis factor receptor loop peptide mimic inhibits bone destruction to the same extent as anti-tumor necrosis factor monoclonal antibody in murine collagen-induced arthritis. Arthritis Rheum. 56(4):1164–1174; 2007.
66. Sakurai, N.; Kuroiwa, T.; Ikeuchi, H.; Hiramatsu, N.; Maeshima, A.; Kaneko, Y.; Hiromura, K.; Nojima, Y. Expression of IL-19 and its receptors in RA: Potential role for synovial hyperplasia formation. Rheumatology 47(6):815–820; 2008.
67. Schett, G.; Gravallese, E. Bone erosion in rheumatoid arthritis: Mechanisms, diagnosis and treatment. Nat. Rev. Rheumatol. 8(11):656–664; 2012.
68. Sheikh, F.; Baurin, V. V.; Lewis-Antes, A.; Shah, N. K.; Smirnov, S. V.; Anantha, S.; Dickensheets, H.; Dumoutier, L.; Renauld, J. C.; Zdanov, A.; Donnelly, R. P.; Kotenko, S. V. Cutting edge: IL-26 signals through a novel receptor complex composed of IL-20 receptor 1 and IL-10 receptor 2. J. Immunol. 172(4):2006–2010; 2004.
69. Simonet, W. S.; Lacey, D. L.; Dunstan, C. R.; Kelley, M.; Chang, M. S.; Luthy, R.; Nguyen, H. Q.; Wooden, S.; Bennett, L.; Boone, T.; Shimamoto, G.; DeRose, M.; Elliott, R.; Colombero, A.; Tan, H. L.; Trail, G.; Sullivan, J.; Davy, E.; Bucay, N.; Renshaw-Gegg, L.; Hughes, T. M.; Hill, D.; Pattison, W.; Campbell, P.; Sander, S.; Van, G.; Tarpley, J.; Derby, P.; Lee, R.; Boyle, W. J. Osteoprotegerin: A novel secreted protein involved in the regulation of bone density. Cell 89(2):309–319; 1997.
70. Stenderup, K.; Rosada, C.; Worsaae, A.; Clausen, J. T.; Norman Dam, T. Interleukin-20 as a target in psoriasis treatment. Ann. N. Y. Acad. Sci. 1110:368–381; 2007.
71. Sterry, W.; Stingl, G.; Langley, R. G.; Zacharie, H.; Lahfa, M.; Giannetti, A.; Ferrandiz, C.; Sinclair, R.; Saurat, J. H.; CLEAR Multinational Study Group. Clinical Experience Acquired with Raptiva (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: Results from extended treatment in an international, Phase III, placebo-controlled trial. J. Dtsch. Dermatol. Ges. 4(11):947–956; 2006.
72. Suryaprasad, A. G.; Prindiville, T. The biology of TNF blockade. Autoimmun. Rev. 2(6):346–357; 2003.
73. Teitelbaum, S. L. Osteoclasts: What do they do and how do they do it? The Am. J. Pathol. 170(2):427–435; 2007.
74. Tritsaris, K.; Myren, M.; Ditlev, S. B.; Hubschmann, M. V.; van der Blom, I.; Hansen, A. J.; Olsen, U. B.; Cao, R.; Zhang, J.; Jia, T.; Wahlberg, E.; Dissing, S.; Cao, Y. IL-20 is an arteriogenic cytokine that remodels collateral networks and improves functions of ischemic hind limbs. Proc. Natl. Acad. Sci. USA 104(39):15364–15369; 2007.
75. Wahl, C.; Muller, W.; Leithauser, F.; Adler, G.; Oswald, F.; Reimann, J.; Schirmbeck, R.; Seier, A.; Weiss, J. M.; Prochnow, B.; Wegenka, U. M. IL-20 receptor 2 signaling down-regulates antigen-specific T cell responses. J. Immunol. 182(2):802–810; 2009.
76. Walsh, D. A. Angiogenesis and arthritis. Rheumatology 38(2): 103–112; 1999.
77. Wegenka, U. M. IL-20: Biological functions mediated through two types of receptor complexes. Cytokine Growth Factor Rev. 21(5):353–363; 2010.
78. Wei, C. C.; Hsu, Y. H.; Li, H. H.; Wang, Y. C.; Hsieh, M. Y.; Chen, W. Y.; Hsing, C. H.; Chang, M. S. IL-20: Biological functions and clinical implications. J. Biomed. Sci. 13(5):601–612; 2006.
79. Wolk, K.; Kunz, S.; Asadullah, K.; Sabat, R. Cutting edge: Immune cells as sources and targets of the IL-10 family members? J. Immunol. 168(11):5397–5402; 2002.
80. Wolk, K.; Witte, E.; Warszawska, K.; Schulze-Tanzil, G.; Witte, K.; Philipp, S.; Kunz, S.; Docke, W. D.; Asadullah, K.; Volk, H. D.; Sterry, W.; Sabat, R. The Th17 cytokine IL-22 induces IL-20 production in keratinocytes: A novel immunological cascade with potential relevance in psoriasis. Eur. J. Immunol. 39(12):3570–3581; 2009.