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Interleukin-6 in Bone Metastasis and Cancer Progression

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Abstract

The bone and bone marrow are among the most frequent sites of cancer metastasis. It is estimated that 350,000 patients die with bone metastases annually in the US. The ability of tumor cells to colonize the bone marrow and invade the bone is the result of close interactions between tumor cells and the bone marrow microenvironment. In this article, we review the contribution of interleukin-6 (IL-6) produced in the bone marrow microenvironment to bone metastasis. This cytokine has a strong pro-tumorigenic activity due to its multiple effects on bone metabolism, tumor cell proliferation and survival, angiogenesis, and inflammation. These effects are mediated by several signaling pathways, in particular the Janus kinase/signal transducer and transcription activator (JAK/STAT-3), Ras/mitogen activated protein kinase (MAPK), and phosphoinositol-3 kinase (PI3K)–protein kinase B/Akt (PkB/Akt), which are activated by IL-6 and amplified in the presence of soluble IL-6 receptor (sIL-6R). Supporting the role of IL-6 in human cancer is the observation of elevated serum levels of IL-6 and sIL-6R in patients with bone metastasis and their association with a poor clinical outcome. Over the last decade several large (monoclonal antibodies) and small (inhibitors of IL-6 mediated signaling) molecules that inhibit IL-6 activity in preclinical models have been developed. Several of these inhibitors are now undergoing phase I and II clinical trials, which will determine their inclusion in the list of effective targeted agents in the fight against cancer.

Keywords

Interleukin-6; tumor microenvironment; bone metastasis

1. Bone marrow microenvironment and bone metastasis

It is estimated that 350,000 patients die with bone metastases annually in the US.[1] Considering its stiff structure and composition, it is surprising that the bone is among the most common sites for the establishment of cancer metastasis.[2,3] However, it is in part explained by the unique microenvironment provided by the bone marrow. The bone marrow is the site of niches where hematopoietic stem cells (HSCs) reside. These niches consist of osteoblasts that line the endosteal surface of the bone and are in close interaction with HSCs, with whom they maintain contact via cell–cell adhesion molecules like osteopontin and

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integrins, and which they attract via soluble factors like stromal-derived factor (SDF)-1, the ligand for the chemokine receptor CXCR4 present at the surface of HSCs.[4–6] Like HSCs, many circulating tumor cells express CXCR4 and home in on the SDF-1 rich environment of the bone marrow and the osteoblastic niche.[7–9] However, the homing of tumor cells into the bone marrow does not necessarily indicate that these cells will be able to proliferate and form bone metastases. The formation of bone metastases requires a significant alteration of the bone metabolism that affects the balance between bone formation and bone degradation in favor of one (osteoblastic metastasis) or the other (osteolytic metastasis). In many cancers, like breast and prostate cancers, this process is the result of the direct production by tumor cells of hormones and growth factors like parathyroid hormone-related peptides (PTHrP), receptor activator of nuclear factor kappa B (NFκB) ligand (RANKL), granulocyte macrophage colony stimulatory factor (GMCSF), IL-1, IL-6, and macrophage inflammatory protein (MIP)-1α, which activate osteoblasts and osteoclasts and disrupt the homeostatic balance that controls bone formation and degradation. However, in other cancers like multiple myeloma and neuroblastoma, it is the interaction between tumor cells and bone marrow mesenchymal cells (BMMCs) that plays a critical role.[10,11] These cells are a source of growth factors, chemokines, and cytokines, which affect tumor cells and whose production is controlled by tumor cells via adhesion-dependent and -independent mechanisms. The interaction and cross talk between tumor cells and BMMCs play a critical role in tumor cell proliferation and survival, and in the progression toward bone metastasis.[12,13] In this review article, we will focus on IL-6, one of the soluble factors that is expressed by BMMCs in the presence of tumor cells. This cytokine plays multiple roles in cancer progression and metastasis. We will primarily focus here on its contributory role in the establishment of bone metastasis.

2. IL-6 and its signaling mechanism

2.1. IL-6 signaling and transsignaling

Interleukin-6 is a pleiotropic cytokine overexpressed in response to injury, inflammation, and infection.[14] It was originally cloned as a B cell stimulatory factor and designated Interferon β2. It was later found to stimulate cytotoxic T cells and to induce the differentiation of osteoclast precursor cells into mature and active osteoclasts.[15,16] IL-6 is produced by many cells including osteoblasts, monocytes and macrophages, and BMMCs. Serum levels of IL-6 are low or undetectable under normal physiological conditions. However, the production of IL-6 is regulated by several physiological factors like diet, exercise, and stress. IL-6 production by skeletal muscle increases 100-fold during physical activity [17] and adipose tissues are another main source of IL-6. In muscles IL-6 sensitizes myotubes to insulin and enhances glycogen synthesis and glucose uptake, whereas in adipose tissues it reduces insulin-dependent hepatic glycogen synthesis, decreases glucose uptake, increases triglyceride release, and down-regulates lipoprotein lipase, thus promoting obesity and insulin-resistant type 2 diabetes.[18] Elevated levels of serum IL-6 concomitantly with elevated levels of acute phase C reactive protein, are reported to be associated with depression, chronic inflammation, and cardiac diseases.[19] IL-6 interacts with a heterotrimeric membrane-associated receptor, member of the class I cytokine receptor family (Figure 1). This receptor is composed of an α subunit (IL-6Rα/gp80), which binds the soluble ligand IL-6 and β2 subunits (gp130), which, through their cytoplasmic domain, function as the signal-transducing component of the complex.20 Whereas gp130 is ubiquitously expressed by cells, IL-6Rα/gp80 is expressed in selected cells like B cells, macrophages, and osteoclasts that respond to IL-6.21 IL-6Rα/gp80 also exists in a soluble form designated sIL-6R, produced either by alternate splicing or by shedding via proteolytic cleavage mediated by metalloproteinases such as a disintegrin and metalloproteinase (ADAM) 10 and 17 (TACE).[22,23] In contrast to most soluble receptors that trap the ligand and act as antagonists, sIL-6R stabilizes IL-6, promotes the formation of a functional

multimolecular complex with gp130, and enhances signaling.24 This mechanism known as transsignaling allows cells that do not express the specific IL-6R/gp80 receptor protein to respond to IL-6.25 The source of sIL-6R in cancer patients is not entirely known, but it is shed by inflammatory cells like neutrophils, monocytes/macrophages, and T cells.26,27 Gp130 can also be solubilized, but in contrast to sIL-6R, soluble gp130 prevents the binding of IL-6 to the receptor and has an antagonistic activity on IL-6 signaling.28,29 IL-6 activates several intracellular signaling pathways. Binding of IL-6 to its receptor activates the Janus family of kinases (JAK1, JAK2, and TYK2) bound to the cytoplasmic domain of gp130.30 These kinases phosphorylate signal transduction and activator of transcription (STAT)-3 at Tyr705, promoting its nuclear transfer and transcriptional function.31 IL-6 also activates Ras and promotes its translocation to the plasma membrane where it activates Raf, mitogen-activated protein kinase kinase (MEK), and MAP (Erk1/2).32 A third pathway activated by IL-6 is the phosphoinositol 3 kinase (PI3K)–protein kinase B (PkB/Akt) pathway as JAK can phosphorylate PI3K.33,34 Binding of STAT-3 to a specific DNA domain promotes the expression of a large variety of genes (Figure 1). Among those are survival proteins like survivin, X-linked inhibitor of apoptosis (XIAP), Bcl-2, Bcl-XL, and Mcl-1; proteins involved in cell proliferation like cyclins and MYC and proangiogenic factors like hypoxia-inducible factor (HIF)-1α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinase (MMP)-2 and -9.

2.2. Interaction between IL-6 and other regulatory pathways

Interleukin-6 interacts with several pathways that also contribute to its pro-tumorigenic activity, in particular cyclooxygenase (Cox)-2, Wnt, transforming growth factor-β (TGF-β), and NFκB. IL-6 stimulates the expression of Cox-2 in osteoblasts, osteoclasts, and tumor cells, and the production of prostaglandin E2 (PGE2). PGE2 acts as a mediator of osteoclast activation by increasing the expression of RANKL in osteoblasts and the expression of RANK in osteoclasts. In addition, IL-6 induces the expression of PGE2 receptors, EP2, and EP4 in osteoblasts, triggering a positive feedback loop where more IL-6 results in production of PGE2 via Cox-2 and at the same time enhances PGE2 response by increasing the number of PGE2 receptors at the cell surface. PGE2 then stimulates the expression of IL-6, creating a cascade of signals that increases osteolysis.35,36 IL-6 also interacts with the Wnt signaling pathway. Wnt plays a regulatory role in osteogenesis by promoting the differentiation of BMMCs into osteoblasts and the synthesis of collagen by these cells. Wnt signaling itself is controlled by several inhibitors, in particular Dickkopf-1 (DKK-1), a soluble protein that, when bound to Wnt, prevents its interaction with Frizzled and the lipoprotein co-receptor protein LRP5/6, and thus inhibits Wnt signaling.37 DKK-1 is expressed by many metastatic cancer cells like breast cancer cells and myeloma, and is responsible for the inhibition of osteogenesis associated with osteolytic bone metastasis. By stimulating the production of DKK-1 in myeloma cells, IL-6 prevents the differentiation of osteoblast progenitor cells into mature osteoblasts and prevents bone-promoting osteolysis. 38 The bone matrix is also a reservoir of growth factors and in particular transforming growth factor-β (TGF-β), with which IL-6 interacts. TGF-β is released in a soluble and active form upon proteolytic degradation of the bone by osteoclasts.39,40 TGF-β upregulates IL-6 expression in several cell types like fibroblasts and osteoblasts, and prostate cancer cells, and stimulates the production of PTHrP in tumor cells. TGF-β and IL-6 thus act synergistically to potentiate bone degradation.41 IL-6/STAT-3 interacts with NFκB as STAT-3 prolongs NFκB retention through acetyltransferase p300-mediated p65 NFκB acetylation, which inhibits the nuclear export of NFκB. STAT-3 is therefore necessary to maintain NFκB activity not only in cancer cells, but also in tumor-associated hematopoietic cells.42 STAT-3 also binds to p53 and represses its function as a regulator of apoptosis.[43]

3. IL-6 and cancer metastasis

3.1. Autocrine and paracrine mechanisms of IL-6 activity

The role of IL-6 in cancer is complex and includes autocrine and paracrine mechanisms. Many tumor cells from prostate, breast, and colon cancer produce large amounts of IL-6 and express the IL-6R/gp80 and gp130 receptor subunits, which allows them to respond to IL-6 stimulation in an autocrine manner. STAT-3 is also persistently activated in tumor cells.[44,45] However, in other cancers, in particular myeloma and neuroblastoma, most tumor cells do not produce IL-6, but express a functional IL-6 receptor complex and thus respond to IL-6 produced in the tumor microenvironment in a paracrine manner (Figure 2). In myeloma, adhesion contact between myeloma cells and stromal cells induces the expression of IL-6 by stromal cells.[46] We have shown that in neuroblastoma, the production of IL-6 is induced in BMMCs in the presence of neuroblastoma cells, but in contrast to myeloma this induction does not require cell–cell contact and is mediated by soluble factors including galectin-3 binding protein (Gal-3BP)/Mac2.[11,47] IL-6 has multiple effects on tumor progression. Some are the result of its direct action on tumor cells; others are the result of its activity on normal cells in the tumor microenvironment, in particular osteoblasts, osteoclasts, endothelial cells, and immune cells.

3.2. Effect of IL-6 on tumor cell proliferation and survival

Interleukin-6 has a direct growth stimulatory effect on many tumor cells through the activation of several signaling pathways. By activating Ras/Raf/MEK/Erk1/2, IL-6 stimulates tumor cell proliferation.[36,48,49] Activation of STAT-3 by IL-6 upregulates the expression of cyclins D1, D2, and B1, and MYC, and downregulates the expression of cdk inhibitor $p21^{Cip1}$, thus promoting entry into the cell cycle.[50–52] IL-6 is also an important regulator of cell survival, providing tumor cells with a mechanism to escape cell death induced by stress and cytotoxic drugs. IL-6 increases the expression of several survival proteins, including Bcl-2, Bcl-XL, Mcl-1, survivin, and XIAP.[53] Overexpression of these proteins is commonly associated with increased chemoresistance and constitutive activation of STAT-3 are resistant to chemotherapeutic agents.[54] IL-6 thus contributes to a sanctuary effect in the bone marrow, where tumor cells acquire resistance to cytotoxic chemotherapy.[55]

3.3. IL-6 promotes osteolysis

Interleukin-6 enhances bone degradation in many ways. First, it induces the production of RANKL by BMMCs and osteoblasts. Under physiological conditions, these cells express low levels of IL-6R, but in the presence of sIL-6R, STAT-3 is activated and the expression of RANKL is induced.56–59 The binding of RANKL to its receptor RANK activates NFκB, Erk1/2, and p38/MAP kinase signaling, and induces osteoclast maturation and the expression of osteoclast-associated receptors (OSCAR), an Ig-like surface receptor that acts as a co-stimulatory receptor for osteoclast differentiation.60,61 Second, IL-6 induces in tumor cells the expression of several proteins involved in bone resorption such as PTHrP, IL-8, IL-11, RANKL, and Cox-2. IL-6 and sIL-6R stimulate PTHrP production by osteoblastic stromal cells via MEK/Erk1/2 pathways. PTHrP increases the expression of RANKL and downregulates the expression of osteoprotegerin (OPG), the decoy receptor for RANKL by osteoblasts tipping the bone metabolism toward osteolysis.59,62 Third, by stimulating the expression of DKK-1 in tumor cells, IL-6 inhibits Wnt-mediated osteogenesis and further imbalances the bone homeostasis toward excessive degradation.38 IL-6 also increases the activity of estradiol 17 β-hydroxysteroid dehydrogenase, thereby inhibiting the anti-osteoclast activity of estrogens, promoting osteolysis and hypercalcemia in breast cancer patients. Furthermore, IL-6 downregulates the synthesis of genes like type II collagen and aggrecan, contributing to a decrease in new bone formation.56,63

3.4. Role of IL-6 in metastasis to other organs

Interleukin-6 also plays an important role in promoting metastasis to organs other than the bone. Overexpression of IL-6 in specific organs like the lungs, brain or liver will attract circulating tumor cells to these organs and promote their establishment into metastatic tumors. For example, IL-6-dependent STAT-3 activation in human melanoma promotes the growth of metastatic tumors in the brain by inducing the overexpression of bFGF, MMP-2, and VEGF, which contribute to invasion and angiogenesis.[64] NFκB activation in Kupffer cells stimulates their production of IL-6, which promotes the growth of metastatic Lewis lung carcinoma cells in the liver. Interestingly, it has also been recently demonstrated that the production of IL-6 (and IL-8) in a primary tumor promotes the recruitment of circulating tumor cells back into their primary tumor, creating a process called “tumor self-seeding” that accelerates tumor growth, angiogenesis, and stromal cell recruitment.[65]

3.5. IL-6 stimulates angiogenesis and vasculogenesis

Interleukin-6 plays multiple functions in angiogenesis and vascular remodeling. IL-6 enhances *in vitro* the proliferation, migration and matrigel tube formation of endothelial progenitor cells isolated from adult human circulating blood in a dose-dependent manner, suggesting a role in vasculogenesis.[66] IL-6 increases angiogenesis by transcriptional upregulation of VEGF in a JAK/STAT-3- and HIF-1α-dependent manner in tumor cells and the expression of bFGF and MMP-9 in tumor-associated myeloid cells and endothelial cells that contribute to tumor angiogenesis.[67–70]

3.6. Immunomodulatory role of IL-6

Interleukin-6 belongs to the group of inflammatory cytokines and chemokines associated with a Th2 and M2 response of the immune system and to an inflammatory reaction that is pro-tumorigenic. [71] IL-6-mediated activation of STAT-3 in regulatory T cells is responsible for the production of several pro-inflammatory cytokines like IL-10 that help tumor cells escaping immune surveillance. IL-6-induced STAT-3 activation inhibits the expression of MHC class II, CD80, CD86, and IL-12 expression in dendritic cells, preventing their maturation and compromising their ability to trigger cytotoxic CD8+T cells and natural killer (NK) cells. IL-6 downregulates the activity of NK cells and their anti-tumor function. [72] By promoting inflammation and immune escape, IL-6 thus contributes to an immune microenvironment that is favorable to tumor progression.

4. Prognostic significance of IL-6 and IL-6R levels in peripheral blood of cancer patients

Considering the pro-tumorigenic roles of IL-6, it is therefore not surprising that elevated serum levels of IL-6 and sIL-6R have been associated with poor clinical outcome in many human cancers, including in breast and prostate cancer, multiple myeloma, hepatocellular carcinoma, lymphoma, and pediatric solid tumors.[73–76] The levels of IL-6 typically found in the serum of cancer patients is within the picogram range (100–500 pg/ml), at which there is very little evidence *in vitro* that IL-6 activates STAT-3. In contrast, the concentration of sIL-6R found in the serum of patients with cancer is within the ng/ml range. These observations suggest that in the absence of sIL-6R most tumor cells could remain insensitive to IL-6 *in vivo* because of its low concentration and instability. By stabilizing IL-6 and enhancing IL-6-mediated signaling, sIL-6R could be a critical regulator of IL-6 activity in the tumor microenvironment. The source of sIL-6R in cancer is presently unclear. Whereas several tumor cells can shed IL-6R or produce it as a result of alternate splicing,[28] inflammation is likely to play a key role, as monocytes, and in particular neutrophils, can produce sIL-6R.[26,77,78]

5. Targeting IL-6

The abundance of evidence supporting a pro-tumorigenic effect of IL-6 in tumor progression and bone metastasis has prompted the initiation of clinical trials testing the safety and therapeutic efficacy of inhibitors of IL-6 and IL-6 signaling in cancer treatment. Currently, the strategies focus on large proteins like humanized monoclonal antibodies (mAb) and small molecules that inhibit IL-6-mediated signaling or the production of IL-6 (Table 1).

5.1. Large molecules: mAb

Several humanized mAb against IL-6 and IL-6R have been developed. A humanized mAb against IL-6 developed by Centocor (CNTO 328) has shown good activity in preclinical models of myeloma when used alone or in combination with bortezomib or dexamethasone.[79–81] It has been FDA-approved for a phase II multicenter trial in multiple myeloma. A similar anti-IL-6 antibody (B-E8) has been developed by Diaclone (Besancon, France) and has been tested in a non-randomized trial in combination with dexamethasone and melphalan in 24 patients with multiple myeloma. It has improved overall survival (68.2% at five years).[82] A humanized anti IL-6Rα/gp80 mAb (Tocilizumab/Actemra®) developed by the Japanese company Chugai and licensed to Genentech and its parent company Roche, has been used in Japan since 2005 to treat patients with Castelman's disease and arthritis. It has recently been tested in three concomitant but independent European and international studies in non-cancer patients (≥18 years of age) with rheumatoid arthritis. All three studies have been recently reported.[83–85] These studies show that this mAb is well tolerated and effective. It is being currently tested in children (aged 2 to 19) with juvenile rheumatoid arthritis and seems to be similarly well tolerated and effective.[86] The reported adverse effects seem relatively mild and reversible, and primarily associated with the anticipated immunosuppressive effect of blocking IL-6. The most frequent side effects reported were respiratory and skin infections, gastrointestinal disorders, psychiatric disorders, and hypertension associated with elevated cholesterol levels. Serious side effects leading to discontinuation of the therapy, like gastrointestinal hemorrhage and perforation, were reported in less than 1.8% of treated patients.[87] Actemra has very recently (January 2010) been approved by the Food and Drug Administration to treat rheumatoid arthritis. Although not yet approved for cancer, the abundant data supporting the pro-tumorigenic role of IL-6 in cancer make the testing of Actemra in cancer patients very attractive.

5.2. Small molecules

Several small molecule inhibitors of IL-6/IL-6R-mediated signaling have been developed. Some have only been tested in preclinical models of cancer, but others are currently being tested in patients.[88] Among these is INCB20 (Incyte Corp., Wilmington, DE, USA), a synthetic compound that inhibits JAK family members.[89] It inhibits IL-6-dependent proliferation of INA-6 myeloma cells *in vitro* at concentrations between 0.1 and 1 μM and when administered in myeloma-bearing mice, it inhibits tumor growth and survival. This inhibitor also inhibits the Ras/Raf/MEK/Erk1/2 and the PI3K–PkB/Akt pathways, all downstream of JAK1/2 activation. 531–201 (NSC 74859) is an inhibitor that was identified by the structure-based high throughput virtual screen of the National Cancer Institute chemical library (and was named 531–201 when resynthesized as a pure compound). It selectively inhibits the DNA binding activity of STAT-3 *in vitro* with an IC50 value of 86 μM. It induces apoptosis in tumor cells that constitutively express active STAT-3.[90] When administered to MDA-MB-231-bearing mice, it significantly inhibits tumor growth and STAT-3 phosphorylation in tumor tissues. It is also active in hepatocellular cancer in mice[91], but has not been tested yet in patients. Sorafenib (Nexavar, Bay 43-9006) is a multikinase inhibitor that was originally developed by Bayer on the basis of its inhibitory effect on Ras-signaling. It has been recently shown to inhibit STAT-3 phosphorylation in

primary medulloblastoma cells *in vitro* and the growth of human medulloblastoma tumors in nude mice.92 It has been tested in several phase I and II clinical trials in patients with solid tumors and shown to be safe.93,94 Sunitinib (Su11248) is a similar multikinase inhibitor available orally that targets several receptor tyrosine kinases like platelet-derived growth factor receptor (PDGFR), kit, FLT3 or VEGFR, and has been shown to inhibit STAT-3 phosphorylation in renal cell carcinoma cells.95 It has been tested in phase I clinical trials in patients with metastatic renal cell carcinoma in combination with bevacizumab with an objective response rate of 52%.96 Lenalidomide (Revlimid, Celgene, NJ, USA) is an immunomodulatory drug derivative of thalidomide that has been approved by the Food and Drug Administration (FDA), and is currently undergoing clinical trials in multiple myeloma, myelodysplastic syndromes, and melanoma.97 Its mechanism of action is not entirely known, but it has anti-angiogenic, immunosuppressive, and anti-metastatic activities, in part via inhibition of HIF-1α.98 It is a potent inhibitor of IL-6 expression in tumor cells and myeloid cells.

5.3 Combining anti-IL-6 with other strategies to combat bone metastasis

There have been two other main strategies developed over the last decade to combat bone metastasis, inhibition of osteoclast activity and inhibition of RANKL. Nitrogen-containing bisphosphonates are pyrophosphoric acid-based compounds that have a high affinity for the bone, are potent inducers of apoptosis in osteoclasts,99,100 and have been used in clinical practice for patients with osteoporosis and in cancer patients with bone metastasis.101,[102] Denosumab (AMG162), a humanized monoclonal antibody against RANKL, has been used in phase I and II clinical trials in patients with metastatic prostate and breast cancer and multiple myeloma.[103],104 It is safe and effective in reducing bone metastasis. Whether denosumab and zoledronic acid should be used in combination with Actemra or other anti-IL-6-based therapies is an interesting question considering that they have different targets that are part of the same pathway responsible for the formation of osteolytic metastases.

Conclusion

Over the last decade, IL-6 has emerged as an important contributor to the tumor microenvironment and inflammation contributing to pro-tumorigenic activity. IL-6 function involves multiple cell–cell interactions and signaling pathways that together promote osteolytic bone metastasis, tumor cell proliferation and survival, angiogenesis and vasculogenesis, and immune escape. As a result, inhibition of IL-6 and IL-6R-mediated signaling has been the subject of intense investigation. We are at a time when several clinical trials testing the safety and clinical efficacy of inhibitors of IL-6 are ongoing, and will soon determine the validity of targeting IL-6 in cancer treatment.

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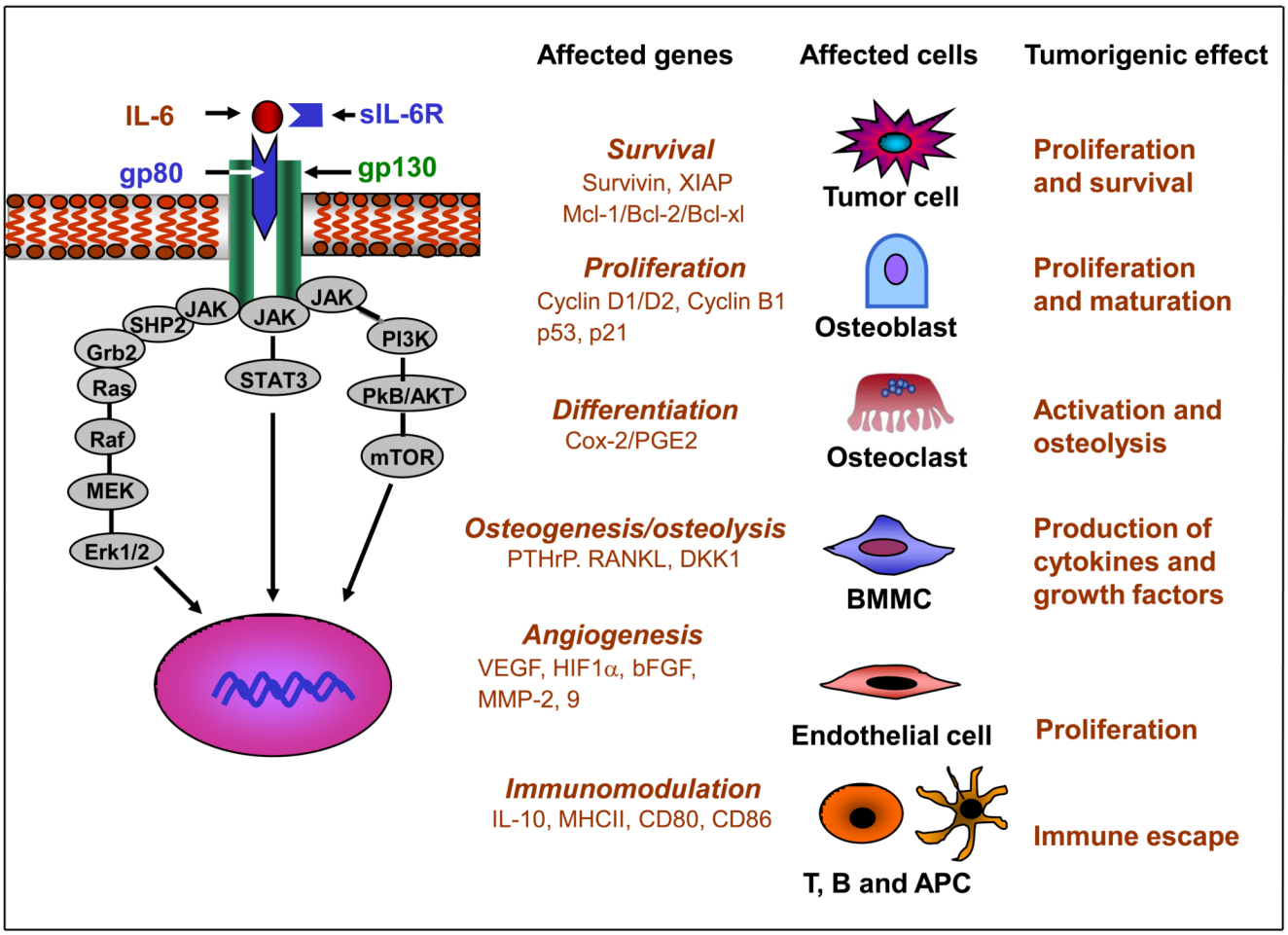

Figure 1. IL-6-mediated signaling, gene expression, and its cellular effects

IL-6 activates three pathways, STAT-3, Erk1/2, and PkB/Akt. This results in the upregulation of a number of genes that affect survival, proliferation, differentiation, osteogenesis/osteolysis, angiogenesis, and immune modulation, in a variety of target cells. The expression of these genes has several pro-tumorigenic effects.

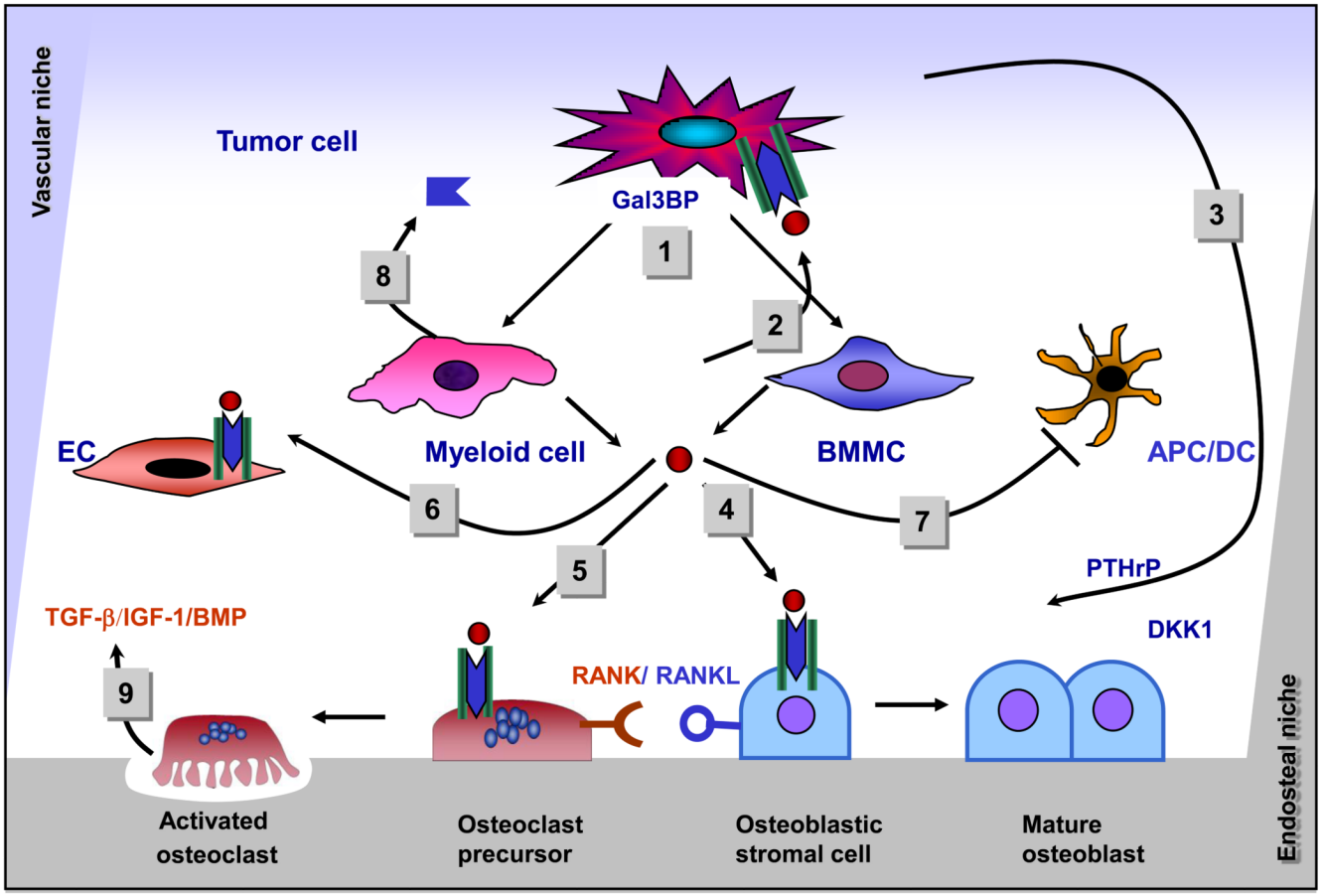

Figure 2. Paracrine effects of IL-6 in the bone marrow microenvironment

(1) Tumor cells induce the production of IL-6 in BMMCs and myeloid cells in the bone marrow microenvironment, (2) IL-6 stimulates the proliferation and enhances the survival of tumor cells, (3) IL-6 increases the production of PTHrP and DKK-1 by tumor cells, (4) IL-6 promotes the degradation of the bone matrix by inducing the expression of RANKL in osteoblasts, (5) IL-6 activates osteoclasts, (6) IL-6 stimulates endothelial cells and endothelial progenitor cells, promoting angiogenesis and vasculogenesis, (7) IL-6 inhibits the maturation of APC and dendritic cells, (8) myeloid cells produce sIL-6R, which potentiates the effect of IL-6, (9) growth factors like TGF-β, IGF-1, and BMP are released from degraded bone, and enhance IL-6 production, contributing to the vicious circle of bone metastasis.

Table 1

Inhibitors of IL-6 and IL-6-mediated signaling: preclinical and clinical trials

Agent	Description	Target	Characteristics	Clinical	Clinical efficacy
CNTO 328	Humanized anti-IL-6 mAb	IL-6	1/2 life of twoweeks	Phase I – III in MM, hematological malignancies and Castleman's disease	65% five-year survival in MM
Tocilizumab/Actemra	Humanized recombinant anti-IL-6R antibody	IL-6R/gp-80	Inhibits IL-6R and sIL-6R	Phases I & II in advanced cancers, Castleman's disease and phase III in rheumatoid arthritis	Well tolerated
INCB20	JAK inhibitor	JAK1/2	Inhibits JAK dependent STAT3 and Akt activation	INCB 018424 tested in Phase I & II in RA	Well tolerated
S31–201 (NSC 74859)	STAT-3 inhibitor	STAT-3	Inhibits STAT-3 dimerization (SH2)	Not tested	NA
Sorafenib	Multikinase inhibitor	Multiple	Inhibits Raf/MEK/ERK and STAT-3	Phases I and II in solid tumors (Renal Cell Ca, Lung Ca, Hepato Ca).	Well tolerated
Lenalidomide	Immunomodulator	Multiple	Inhibits IL-6 production in monocytes	Myeloma and MDS	Well tolerated