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Interleukin-6 in bone metastasis and cancer progression

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ARTICLE INFO

Article history:
Received 2 February 2010
Accepted 16 February 2010
Available online 23 March 2010

Keywords:
Interleukin-6
Tumor microenvironment
Bone metastasis

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 United States. 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 phases I and II clinical trials, which will determine their inclusion in the list of effective targeted agents in the fight against cancer.

1. Bone marrow microenvironment and bone metastasis

It is estimated that 350,000 patients die with bone metastases annually in the United States (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 integrins, and which they attract via soluble factors like stromal-derived factor (SDF)-1, the ligand for the chemokine receptor CXCR4

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doi:10.1016/j.ejca.2010.02.026

present at the surface of HSCs.[4–6] Like HSCs, many circulating tumor cells express CXCR4 and home in 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 plays 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 (Fig. 1). This receptor is composed of an α subunit (IL-6Rα/gp80), which binds the soluble ligand IL-6 and 2β 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 in soluble form, 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 transducer 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 (Fig. 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.