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SnapShot: Bone Metastasis

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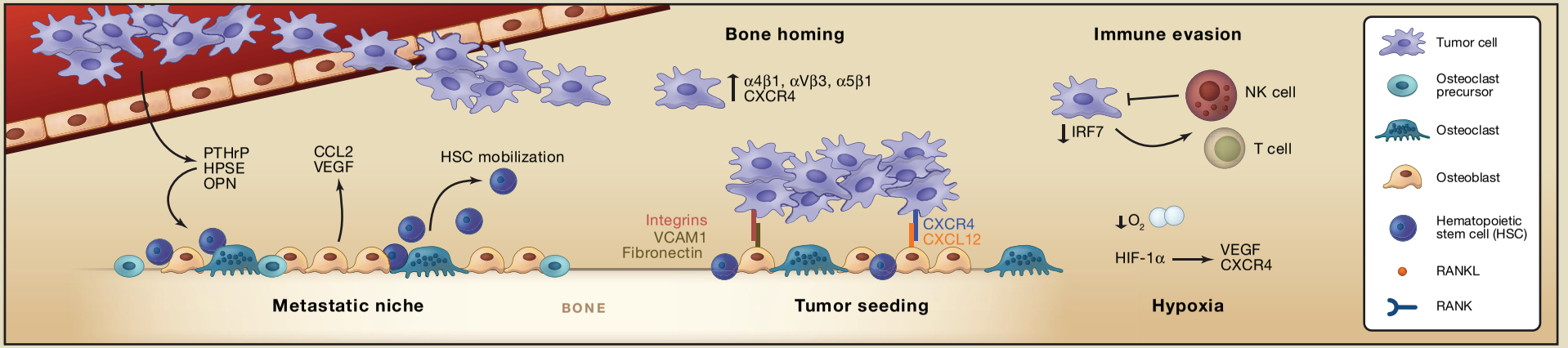
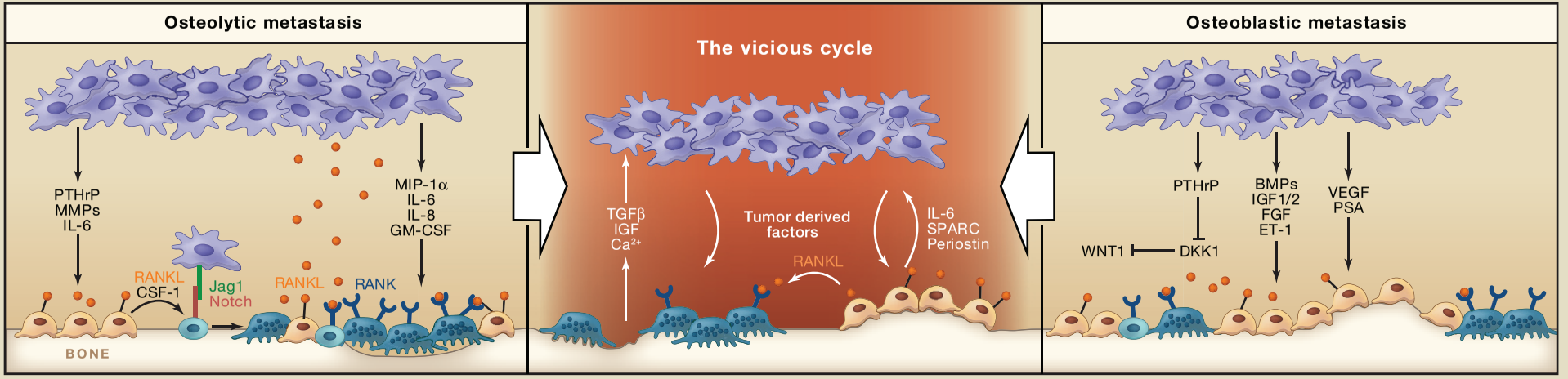
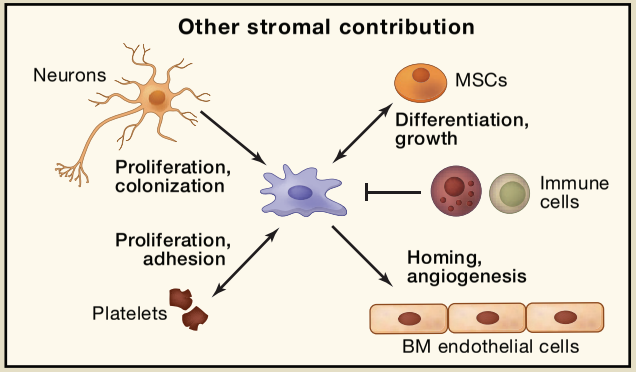
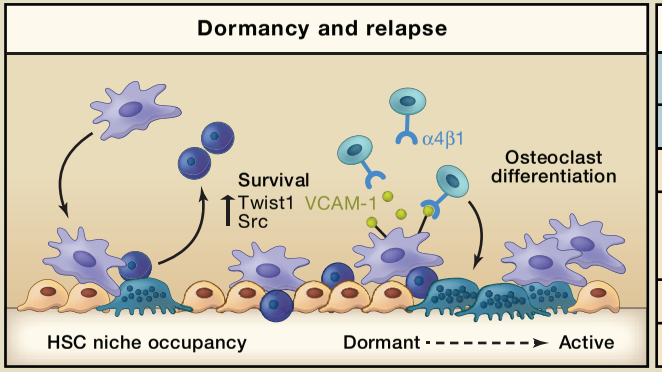
Cell









Bone metastasis therapeutics and their targets

Bisphosphonates	Farnesyl Pyrophosphate Synthase
Denosumab	RANKL
Src Inhibitors	Src (KX2–391), SFKs (Dasatinib, others)
LY2157299, Fresolimumab Other TGFβ inhibitors	TGFβ ligand or receptors
Odanacatib	Cathepsin K
Atrasentan/Zibotentan	Endothelin 1 (ET-1)

See online version for legend and references.

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Bone metastasis occurs in the majority of patients with late-stage breast and prostate cancers and is often diagnosed in lung, thyroid, bladder, and kidney cancers. Bone metastasis is associated with characteristic modulation of the bone microenvironment, resulting in the formation of a "metastatic niche" that can form before or upon the arrival of disseminated tumor cells to facilitate seeding and expansion of tumor colonies in bone. Tumor cells condition the metastatic niche through the secretion of soluble factors, such as PTHrP, HPSE, and OPN. Circulating PTHrP induces CCL2 production from osteoblasts and other bone stromal cells, which in turn stimulates VEGF expression in the tumor cells and enhances angiogenesis, while tumor-supplied HPSE increases osteoclast activity and bone resorption. OPN facilitates $\alpha V\beta 3$-mediated adhesion and migration of tumor cells and recruits bone marrow cells, promoting the growth of indolent tumors. Bone-tropic carcinomas express factors that aid in recruitment and seeding to the bone. Tumor cells preferentially adhere to bone marrow endothelial cells and are further localized to the bone through interactions between tumor-expressed integrins and their ligands. Specifically, $\alpha V\beta 3$ binding to vitronectin and OPN and $\alpha 4\beta 1$ integrin binding to VCAM-1 and fibronectin are essential for tumor colonization. Similarly, tumor-expressed CXCR4 binds to osteoblast-produced CXCL12, resulting in tumor cell occupancy of the hematopoietic stem cell (HSC) niche and a decrease in HSC self-renewal. Other factors are commonly upregulated during cancer cells seeding in the bone, including IL-11, CTGF, MMP1, and HIF-1α. HIF-1α is elevated in tumor cells due to the hypoxic conditions found in the bone, resulting in increased expression of VEGF and CXCR4. Decreased expression of IRF7 in metastatic tumor cells helps to accelerate bone metastasis seeding and growth through the suppression of NK and T cell immune responses.

Osteolytic and Osteoblastic Metastasis

Osteolytic metastases (predominant in breast cancer metastasis) are mediated by interactions of tumor cells with osteoblasts and osteoclasts and involve aberrant bone resorption due to the recruitment and activation of osteoclasts to the tumor-bone interface. In addition to secreting elevated levels of osteoclast differentiation factor RANKL, tumor cells also produce PTHrP and IL-6 to activate RANKL secretion from osteoblasts. Additionally, secreted matrix metalloproteases (MMPs) play an important role in osteolysis; MMP7 cleaves and activates RANKL, whereas MMP1 decreases levels of OPG, the decoy receptor and inhibitor of RANKL. Activated osteoblasts at the metastatic lesion also secrete CSF-1/MCSF, initiating osteoclast differentiation from monocyte precursors, followed by further induction via RANKL. Osteoclast differentiation is enhanced by the binding of tumor-expressed Jagged1 to Notch receptors on pre-osteoclasts, and osteoclast differentiation and activity are amplified by tumor-secreted MIP-1α, IL-6, IL-8, and GM-CSF.

Osteoblastic lesions (predominant in prostate cancer) involve imbalanced bone homeostasis that leads to increased osteoblast differentiation and activity and results in uncontrolled bone formation. Tumor-secreted WNT is central to osteoblast differentiation during bone metastasis, activating multiple downstream genes, including the essential transcription factor RUNX2. DKK1, a secreted inhibitor of WNT, is highly expressed in osteolytic metastasis but is suppressed by PTHrP in late-stage prostate cancers, enforcing the osteoblastic lesions. Bone metastases stimulate osteoblast activity through the secretion of additional factors, including BMPs, IGFs, FGF, and Endothelin-1. Tumor cells also secrete factors that indirectly influence osteoblast activity, including VEGF, which can regulate osteoclasts and induce angiogenesis, and PSA, which can degrade PTHrP and decrease osteolysis. In addition to improper bone formation, osteoblastic lesions often feature aberrant osteolysis due to osteoblast-secreted RANKL.

Vicious Cycle

The dysregulated bone development during bone metastasis results in the release of factors from stromal cells and the bone microenvironment, many of which positively regulate tumor growth, leading to a vicious cycle. TGFβ, IGF, and Ca^{2+} are released from the bone matrix during lysis, enhancing tumor proliferation and survival. TGFβ signaling in tumor cells enhances expression of bone metastasis proteins PTHrP, Jagged1, CTGF, IL-11, and MMPs. Calcium signaling through the calcium-sensing receptor leads to increased proliferation and survival. Osteoblasts also secrete a number of proteins that positively regulate tumor growth, including IL-6, SPARC, and periostin. SPARC induces cancer migration and homing through the $\alpha V\beta 5$ integrin, whereas Periostin and IL-6 promote tumor survival.

Interactions with Other Bone Stromal Cells

Other stromal cells interact with metastatic cells, including neurons, platelets, and bone marrow endothelial cells. Sympathetic neuron activation by bone metastasis results in severe pain, as well as increased tumor proliferation and colonization. Tumor cells preferentially bind to bone marrow endothelial cells and activate platelet aggregation, inducing angiogenesis and increasing tumor survival and proliferation. Tumor cells also influence mesenchymal stem cell differentiation into osteoblast and other mesenchymal lineages.

Dormancy and Outgrowth of Disseminated Tumor Cells in Bone

The presence of disseminated tumor cells (DTCs) in the bone marrow is an indicator of poor prognosis. DTCs occupy the HSC niche, displacing HSCs and maintaining a dormant state. Survival of dormant cells is enhanced through expression of Twist1, as well as Src signaling that enhances tumor response to CXCL12 and decreases TRAIL-mediated apoptosis. Increased VCAM-1 expression in dormant tumor cells can recruit osteoclast precursors expressing $\alpha 4\beta 1$ integrin, leading to the induction of osteolysis.

Treatment Options

Osteoclasts are a prominent therapeutic target. FDA-approved treatments include bisphosphonates, direct inhibitors of osteoclasts, as well as the anti-RANKL antibody denosumab. Other therapeutics in stage II or stage III trials include inhibitors of Cathepsin K (an osteoclast-secreted protease), Src, and TGFβ. In addition, osteoblasts are targeted by inhibitors of Endothelin1 in osteoblastic metastases.

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