RANK Ligand and Bone Metastases Fact Sheet

Amgen Research Extends to Bone Biology

Since its founding in 1980, Amgen has been committed to helping patients through innovative research and revolutionary therapeutics. This commitment has led to the discovery of numerous important therapies that have enhanced the lives of millions of people with cancer, kidney disease, and rheumatoid arthritis.

Driven by this commitment to innovation, Amgen scientists also are working to advance the scientific understanding of bone biology and find ways to treat bone loss associated with a broad range of conditions.

Recently, this effort led to a better understanding of the role of RANK Ligand, a protein that is the primary mediator of osteoclast activity, the cells associated with bone resorption or break down.

Understanding Bone Biology

The human skeleton is essential for mobility, as well as for support and protection of the body's internal organs. It consists of more than 200 bones, which are composed of two distinct types of bone tissue: cortical bone, the dense outer shell that comprises approximately three-quarters of the total skeletal mass; and trabecular bone, the spongy matrix inside. Cortical bone is essential because it provides strength. Trabecular bone also contributes strength but is less dense; it contains the bone marrow that generates blood cells.

To maintain its strength and integrity, bone is continuously removed and formed through a natural process of remodeling. Balanced remodeling is essential to maintaining the structural integrity of the skeleton. Abnormalities in remodeling are among the primary causes of bone loss.

Remodeling involves the work of osteoclasts (cells that resorb, or break down, bone) and osteoblasts (cells that form bone). Most adult bone loss conditions are due to excess osteoclastic activity, leading to an imbalance in bone remodeling which favors resorption.

RANK Ligand's Role in Bone Loss & Destruction

RANK Ligand drives the activity of osteoclasts in both cortical and trabecular bone throughout the body and is essential for bone resorption.

Scientists have revealed that RANK Ligand, which is produced by osteoblasts and other cells, binds to its receptor, RANK, causing them to form and differentiate into active osteoclasts, which begin resorbing bone. RANK Ligand is also critical for the ongoing activity of mature osteoclasts. Without RANK Ligand, osteoclasts can't form, function, or survive.

The human body has complex biological processes that carefully regulate RANK Ligand activity, keeping the bone loss process in check and maintaining skeletal integrity. To help neutralize the effects of RANK Ligand, osteoblasts and stromal cells naturally produce another protein called osteoprotegerin, or OPG. OPG inhibits RANK Ligand, preventing it from reaching its receptor on osteoclasts, thus helping to maintain a natural balance between the actions of osteoclasts and osteoblasts.

In bone-loss conditions, however, RANK Ligand overwhelms the effects of OPG, causing an imbalance in the remodeling process favoring resorption. Too much resorption causes progressive bone loss and weakens cortical and trabecular bone throughout the skeleton.

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RANK Ligand is Implicated in a Broad Range of Conditions

It is now understood that RANK Ligand is responsible for osteoclast-mediated bone loss and destruction in a broad range of conditions, including: osteoporosis, rheumatoid arthritis, bone metastases, multiple myeloma, and treatment-induced bone loss resulting from androgen deprivation therapy, aromatase inhibitor therapy, chronic exposure to glucocorticoids, and immunosuppressive treatment.

About Bone Metastases

More than 10 million people worldwide have bone metastases. Approximately 50-80 percent of all those diagnosed with carcinoma are predicted to have metastases to bone at the time of their death.

Bone metastases are cancer cells that separate from tumors, enter the bloodstream or the lymph system, and migrate to bone tissue where they settle and grow. Once they have settled in bone, they secrete growth factors that stimulate RANK Ligand production, promoting increased bone resorption. This stimulation may lead to the release of other factors that further promote tumor growth, creating a vicious cycle of bone destruction and cancer cell proliferation. Inhibiting RANK Ligand may interrupt this vicious cycle.

Certain cancers, like breast, prostate, thyroid, and lung are more likely to spread to the bone than others.

Tumor Type	Worldwide Incidence of Bone Metastases
Myeloma	95-100 percent
Breast	65-75 percent
Prostate	65-75 percent
Thyroid	60 percent
Lung	30-40 percent
Renal	20-25 percent

Source: Coleman RE. Skeletal Complications of Malignancy. *Cancer* 1997;80(suppl 8):1588-94.

Bone metastases are one of the most frequent cause of pain in people with cancer and may lead to skeletal-related events (SREs), such as fractures; the need for bone surgery and radiation; and may lead to high levels of calcium in blood (known as hypercalcemia which may lead to nausea and loss of appetite).

Symptoms of bone metastases include:

- **Bone pain:** Bone pain results from the pressure on the bone caused by tumor growth. It often begins as intermittent and then becomes chronic.
- **Broken bones:** The bones most likely to break are the long bones of the arms and legs and the bones of the spine.
- **Pressure on the spinal cord:** Pressure can be painful and damage the spinal cord so that the legs become numb or even paralyzed.
- **Hypercalcemia:** High levels of calcium are caused by release of calcium from broken bones. This can cause loss of appetite, nausea, thirst and tiredness, and can even lead to a coma if left untreated.

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