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Scientists discover key factor in controlling the breakdown of bone

A new study demonstrates that a chemical mediator in the blood that influences immune cell migration also plays a key role in maintaining the balance between the build-up and breakdown of bones in the body. This mediator, which acts on cells that degrade bone, may provide a new target for scientists developing therapies and preventions for bone-degenerating diseases such as osteoporosis and rheumatoid arthritis.

The study comes from the laboratory of immunologist Ronald Germain, M.D., Ph.D., at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. A report describing the project, conceived by Masaru Ishii, M.D., Ph.D., a visiting fellow from Osaka University in Japan, appears online in *Nature*.

Bone is a dynamic tissue, constantly undergoing growth and degradation. Bone degeneration, also known as bone resorption, is caused by specialized cells called osteoclasts. Immature osteoclasts circulate within the blood and migrate to the surface of the bones, where they mature and start to degrade the bone matrix. Osteoclasts are the only cells known to degrade bone.

Normally bone resorption is balanced by the activity of bone-forming cells, called osteoblasts. In people with bone-destructive disorders such as osteoporosis, however, osteoclast activity outpaces osteoblast activity, leading to a loss of bone density.

"Most current therapies for bone-degrading diseases target mature osteoclasts," says NIAID Director Anthony S. Fauci, M.D. "Understanding how immature osteoclasts are recruited to the bone in the first place and targeting the signals that control that migration represents a potential new approach to treating and preventing debilitating joint and bone diseases." In the United States, approximately 1.5 million fractures per year are attributed to the bone-weakening effects of osteoporosis.

As a rheumatologist who treats people with bone diseases, Dr. Ishii became interested in understanding what signals control immature osteoclast recruitment. He knew that cells can migrate to specific sites in the body in response to chemical mediators in the blood known as chemokines or chemoattractants. These molecules act like homing signals, telling cells that have certain receptors to move toward or away from certain tissues in the body.

Previously, Dr. Ishii had discovered that the chemoattractant sphingosine-1-phosphate (S1P), which is associated with the trafficking of immune cells into and out of the lymph nodes, also caused immature osteoclasts to mobilize.

"Because immature osteoclasts come from the same parent stem cell that gives rise to specific white blood cells already shown to respond to S1P," comments Dr. Ishii, "it seemed plausible that S1P could play a role in osteoclast migration."

Once at NIAID, Dr. Ishii worked with Dr. Germain's group to determine if S1P controlled immature osteoclast migration in live mice. Using a unique imaging technique, the researchers could see immature osteoclasts migrating away from the bones of the mice in response to S1P in the blood.

To confirm that S1P plays a direct role in bone metabolism, the research team compared the bone density in mice having the S1P receptor on their cells' surfaces with that of mice lacking the S1P receptor. They found that mice with functional S1P receptors had denser bones than mice lacking functional S1P receptors.

The researchers also tested a mouse model of postmenopausal osteoporosis to see if adding a synthetic S1P activator, known as FTY720, could help preserve bone. Postmenopausal mice given FTY720 had fewer immature osteoclasts on their bones and greater bone density when compared with untreated postmenopausal mice.

According to Dr. Ishii, these findings, combined with previous data, indicate that it may be possible to use combined therapies that target immature osteoclast migration and mature osteoclast function to treat and prevent bone-resorptive disorders.

"Observing that the S1P pathway plays a role in osteoclast migration is a good demonstration of 'osteoimmunology,' where the research disciplines of immunology and bone metabolism intersect," notes Dr. Germain.

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Reference: M. Ishii et al. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. *Nature*. DOI: 10.1038/nature07713.3d (2009).

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