

Bones Hold the Key to Blood Renewal

Though we think of them as solid and permanent, our bones are actually constantly being rebuilt throughout our lives. A team of scientists at the Weizmann Institute of Science has now revealed how cells that work at remodeling the bones play a direct part in the ongoing renewal of another system – the blood. Their findings, which may lead to future improvements in bone marrow transplantation and a better understanding of diseases involving bone or blood renewal, were published in the June issue of *Nature Medicine*.

Bones are really two systems in one. The cavities inside bones are filled with spongy bone marrow, in which stem cells divide and their daughter cells differentiate into all kinds of blood cells, including large numbers of immune cells for the body's defense.

The hematopoietic (literally, blood-creating) stem cells, which can give rise to any kind of blood cell, reside in special 'stem cell niches' nestled in the bones' inner walls. Inside these sheltered nurseries, the stem cells remain undifferentiated; with the help of other nearby cells, they hang on to their juvenile qualities. Only when they leave the niches do they morph into specialized blood cells, possibly becoming immune cells for fighting infection or cells for blood clotting and healing after injury. They can even respond to calls for help from organs such as the liver, migrating through the bloodstream to assist in repairing damage.

The inner walls of the bones are also sites of intensive reconstruction. While one type of cell, the osteoblast, is busy building bone, its partner, the osteoclast, breaks it down and reassimilates the material. Osteoclasts are formed when several cells (which themselves originate from hematopoietic stem cells) fuse together at a signal from the osteoblasts, and the two work together in a sort of 'urban renewal' scheme to keep the bones healthy and strong.

The Weizmann Institute team headed by Prof. Tsvee Lapidot of the Immunology Department, which included Dr. Orit Kollet and colleagues, found that the bone-dismantling osteoclasts are instrumental in releasing hematopoietic stem cells into the bloodstream. As they wear away the bone, they allow the stem cells out of the niches and into the bloodstream. Although some hematopoietic stem cells can always be found circulating in the blood, when there is bleeding or inflammation in the body, more stem cells are needed to deal with the situation and restore balance.

The team's study showed that the bone marrow response to the body's call for help involves stepping up production of osteoclasts, putting machinery that normally operates at a leisurely pace into high gear. The osteoclasts not only clear away bone, they also break up 'nurturing' substances in the niche that attract and hold the stem cells to that spot, thus allowing more stem cells into the bloodstream.

The team carried out their research on mice, including some developed in the lab of Prof. Ari Elson of the Molecular Genetics Department, in which the osteoclasts carried a mutation that rendered them only partially functional in the young females. They found abnormally low stem cell levels in the blood of these mice even when they tried to encourage their mobilization, giving them solid evidence of the connection.

In normal mice, using a chemical compound that stimulates osteoclast formation, they were able to boost osteoclast levels and thus manage the release of stem cells into the blood in a variety of stress situations. This finding may have implications for bone marrow transplant techniques: The drugs given today to donors to increase the supply of stem cells in their bloodstream before they are harvested for transplantation cause the release of many other mature cells as well. Injecting the osteoclast-promoting substance into the mice, on the other hand, resulted in an increase mainly in stem cell release. These findings add a new dimension to our understanding of the processes of renewal and breakdown in the body, and the

relationship between blood-forming stem cells, bone, and the immune system. In some forms of osteoporosis, autoimmune arthritis, and cancer that has metastasized to the bone, for instance, the osteoclasts demolish bone faster than it is built up. This study suggests the effects of such an imbalance may reach well beyond the bone.

Prof. Tsvee Lapidot's research is supported by the M.D. Moross Institute for Cancer Research; the Levine Institute of Applied Science; the Belle S. and Irving E. Meller Center for the Biology of Aging; the Gabrielle Rich Center for Transplantation Biology Research; the Crown Endowment Fund for Immunological Research; the Loreen Arbus Foundation; the Concern Foundation; the Charles and David Wolfson Charitable Trust; and Silvia Schnur, Scarsdale, NY.

Source: Weizmann Institute of Science

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