# Potential cellular target for eliminating bone breakdown in osteoporosis found

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New research has discovered a cell type that governs the way bones form and maintain themselves, opening up a potential target for future therapies for bone disorders like osteoporosis. Led by faculty from the Perelman School of Medicine at the University of Pennsylvania, a rodent study showed that bone marrow adipogenic lineage precursors (MALPs) play a distinct role in the way bones remodel themselves. Defects in this process are the key issue at play in osteoporosis, so a therapy using these MALP cells to better regulate bone remodeling could result in better treatments. This research was published in the *Journal of Clinical Investigation*.

"Discovering new cellular and molecular mechanisms to control bone turnover will enable fine-tuning of existing therapies or design of novel therapeutics," said the study's senior author, Ling Qin, Ph.D., an associate professor of Orthopaedic Surgery. "For example, with the advance of gene-editing technology and novel cell-specific delivery approaches, in the future it would be possible to regulate MALP behavior as a therapy for bone disorders like osteoporosis."

Healthy bone maintenance is a balance between osteoblasts, which secrete the materials necessary to form new bone, and osteoclasts, which absorb old bone material to make way for the new. A disruption in this balance one way or the other can result in unhealthy bone. In the case of osteoporosis, overactive osteoclasts eat away at bone faster than it can be reformed, resulting in bones that are less dense and more susceptible to fracture.

The general consensus among scientists was that osteoblasts and osteocytes, the cells within fully-formed bone, were the ones that kicked off the production of osteoclasts to begin the remodeling of bone. On the other hand, the role of adipocyte lineage cells, such as MALPs, in regulating the resorption of bone was not known.

Earlier in 2020, Qin's group discovered the abundant existence of MALPs within bone. MALPs are the precursors for adipocytes that carry fats, called lipids, inside bone marrow. And recent studies by Qin and her fellow researchers better cleared up how MALPs appear to factor in bone turnover. They showed that MALPs, but not osteoblast or osteocytes, have cell-to-cell contact with osteoclasts. Additionally, using advanced sequencing techniques at a single cell level, Qin and her colleagues found that MALPs secrete RANKL, a protein essential for forming osteoclasts, at a high level.

With that information, the researchers for this study, who included lead author Wei Yu, MD, Ph.D., working as a visiting scholar at Penn Medicine, studied mice with RANKL deficiencies in their MALPs. From the point those mice turned a month old, the researchers saw 60 to 100 percent higher density of the spongy components of long bones (like the femur) and vertebrae, something the researchers qualified as "a drastic increase" compared to typical mouse bone mass.

Since the osteoblasts and osteocytes continued to work as they always do, it would seem that MALPs and their RANKL secretions have been pinpointed as the main driver of osteoclast function and the absorption of existing bone.

"By identifying what appears to be the full function of MALP cells, we believe that we have uncovered an extremely promising target that would never have been considered before," Qin said. "If their RANKL secretions can be reliably disabled, it could rebalance bone remodeling in people with osteoporosis and allow for osteoblasts and osteocytes to 'catch up.'"

Qin's co-author, Jaimo Ahn, MD, Ph.D., a former faculty member at Penn Medicine now chief of orthopaedic trauma and associate chair of orthopaedic surgery at the University of Michigan, believes these discoveries could be very useful in more effectively rebuilding bone."An exciting future step, with an eye toward clinical application, would be to target MALPs in a timed and therapeutic fashion to test how well they simultaneously decrease the bone resorption and increase bone formation," Ahn said.

**More information:** Wei Yu et al, Bone marrow adipogenic lineage precursors (MALPs) promote osteoclastogenesis in bone remodeling and pathologic bone loss, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI140214

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