Researchers Reveal New Mechanism for Bone Formation

Citrate exists universally in vertebrate bone as an integral part of apatite nanocomposite, which is important for bone structure and its stability. However, the source of the citrate in the bone is not clear, and in particular, how the intracellular citrate metabolism and its deposition is governed during apatite formation is not well defined.

A recent study led by GUAN Min from the Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences and WANG Junfeng from the Hefei Institutes of Physical Sciences, CAS revealed that during the osteoblast genesis of mesenchymal stem cells (MSC), the citrate is produced as a key intermediate in mitochondrial tricarboxylic acid cycle, and further deposited in bone apatite.

By tracing stable isotopically labeled carbon, researchers found that the citrate of bone apatite was produced by mineralized MSC. They demonstrated that zinc-Runx2/Osterix-ZIP1 regulation axis promotes osteoblast differentiation and apatite formation. They also revealed mitochondrial citrate metabolism and its relationship with zinc homeostasis during bone remodeling. These findings indicated that the mitochondrial and the metabolic changes not only meet higher energy demand during osteogenic differentiation of MSC, but also provide metabolic intermediates directly participating in bone formation.

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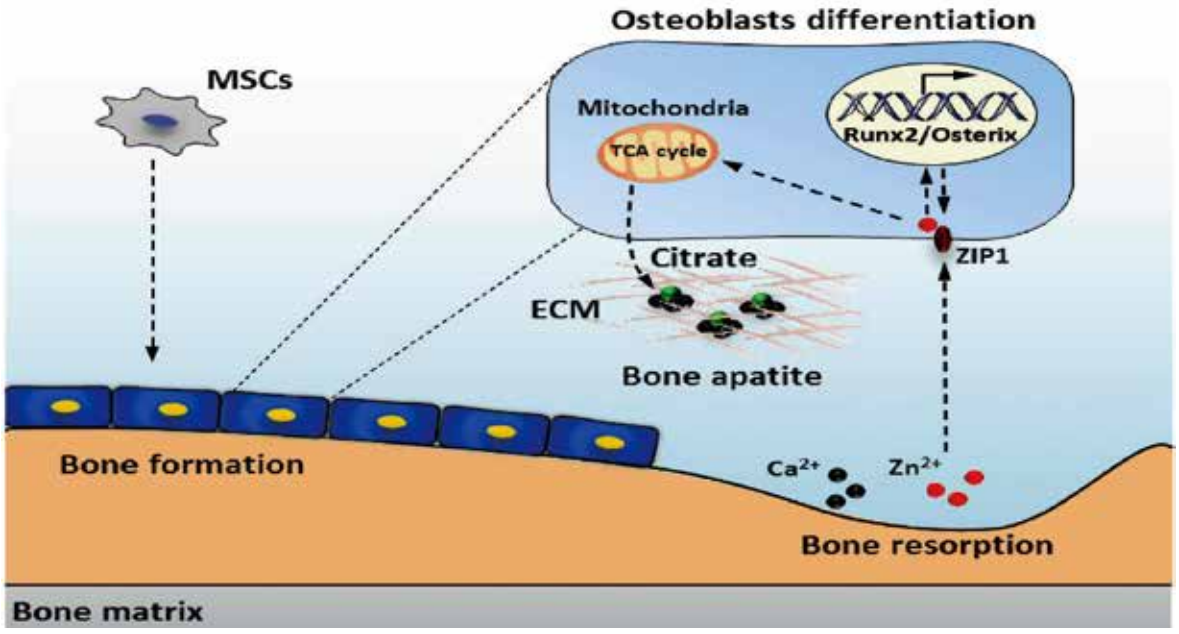

Diagram of Zn^{2+} induced osteoblast differentiation of MSCs and citrate deposition during bone remodeling. During bone remodeling, mineral elements/ions released from the bone matrix comprising the osteogenic microenvironment for differentiation of MSCs. The researchers proposed that zinc (Zn^{2+}) has dual functions: (i) Zn^{2+} influx is influenced by ZIP1 which is transcriptionally mediated by Runx2 and Osterix to form a zinc-Runx2/Osterix-ZIP1 regulation axis promoting osteoblast differentiation at an early differentiation stage; (ii) Zn^{2+} enhances citrate accumulation and deposition in ECM at mineralization stage. This process is more likely to be associated with calcium (Ca^{2+}) deposition for bone apatite formation.