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miR-375-3p negatively regulates osteogenesis by targeting LRP5 and β-catenin

Tianhao Sun, Chen-Tian Li, Frankie Leung and **William W Lu**
The University of Hong Kong, China

Wnt signaling pathways are essential for bone formation. Previous studies showed that Wnt signaling pathways were regulated by miR-375. Thus, we aim to explore whether miR-375 could affect osteogenesis. In the present study, we investigated the roles of miR-375 and its downstream targets. Firstly, we revealed that miR-375-3p negatively modulated osteogenesis by suppressing positive regulators of osteogenesis and promoting negative regulators of osteogenesis. In addition, the results of TUNEL cell apoptosis assay showed that miR-375-3p induced MC3T3-E1 cell apoptosis. Secondly, miR-375-3p targeted low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of the Wnt signaling pathways and β-catenin as determined by luciferase activity assay and it decreased the expression levels of LRP5 and β-catenin. Thirdly, the decline of protein levels of β-catenin was determined by immunocytochemistry and immunofluorescence. Finally, silence of LRP5 in osteoblast precursor cells resulted in diminished cell viability and cell proliferation as detected by WST-1-based colorimetric assay. Additionally, all the parameters including the relative bone volume from μCT measurement suggested that LRP5 knockout in mice resulted in a looser and worse-connected trabecula. The mRNA levels of important negative modulators relating to osteogenesis increased after the functions of LRP5 were blocked in mice. Finally, the expression levels of LRP5 increased during the osteogenesis of MC3T3-E1, while the levels of β-catenin decreased in bone tissues from osteoporotic patients with vertebral compression fractures. In conclusion, we revealed miR-375-3p negatively regulated osteogenesis by targeting LRP5 and β-catenin. In addition, loss of functions of LRP5 damaged bone formation *in vivo*. Clinically, miR-375-3p and its targets might be used as diagnostic biomarkers for osteoporosis and might be also as novel therapeutic agents in osteoporosis treatment. The relevant products of miR-375-3p might be developed into molecular drugs in the future. These molecules could be used in translational medicine.

sunmishu@126.com