SciTechnol
International Publisher of Science, Technology and Medicine

Advanced Biomedical Research and Innovation

Depletion of TM9SF4 promotes osteogenic differentiation of mesenchymal stem cells

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Abstract

Cytoskeleton reorganization is a critical factor of mesenchymal stem cell (MSC) differentiation. The change of cytoskeleton is closely related with mechanical stress signals, which participate in MSCs lineage commitment. Usually, spread and flatten MSCs will undergo osteogenesis, while round cells will turn into adipocytes. Trans-membrane 9 superfamily member 4 (TM9SF4) belongs to the trans-membrane 9 superfamily and involves in phagocytosis in Dictyostelium discoideum and Drosophila. The lab has previously found that TM9SF4 can induce actin S-glutathionylation on Cys374, which leads to the de-polymerization of actin fibres and change the cytoskeleton. It is supposed that TM9SF4 may play a role in MSC differentiation through actin fibres reorganization. Primary MSCs isolated from the bone marrow of TM9SF4-/- mice showed longer and more spread actin fibres than MSCs from TM9SF4+/+ mice. After cultured in osteopenia medium, the expression level of osteogenic genes was higher in TM9SF4-/- MSCs than TM9SF4+/+ MSCs. Alizarin Red S staining and ALP assay showed that TM9SF4-/- MSCs had higher potential to differentiate into osteocytes. These results were confirmed in the pre-osteoblast cell line, MC3T3-E1. By contrast, TM9SF4-/- MSCs showed lower expression level of lipogenesis related genes and less lipid accumulation under adipogenic induction. Besides, knockout of TM9SF4 has no significant effect on osteoclast differentiation. To explore the molecular mechanism under this phenotype, the critical modulator during MSC osteogenesis, β-catenin, was detected. A higher level of active β-catenin was found in TM9SF4-/- MSCs, indicating that the superior osteogenic differentiation due to TM9SF4 knockout and cytoskeleton change was regulated by β-catenin in the nucleus. Besides, the upstream mechanical stress signalling cascade of β-catenin was also detected. Several mechanical related genes showed higher expression in TM9SF4-/- MSCs, indicating that cytoskeleton reorganization by TM9SF4 depletion can promote osteogenesis through mechanical stress signalling pathway. Osteoporosis has a wide influence on elderly people. The formation of osteoporosis is due to the imbalance of osteoblast (osteogenesis) and osteoclast (osteolysis). Decreased osteoblast function and increased osteoclast function will reduce bone density and lead to osteoporosis. Hormone therapy has profoundly potential side-effects on patients, especially women. Therefore, an alternative therapy is imperative. By elucidating how TM9SF4 depletion promotes osteogenesis, it is promising to find a new way to delay osteoporosis in elderly people.

Biography

Libo Yu is a PhD student in the School of Biomedical Sciences, The Chinese University of Hong Kong. She has completed her master's studies on exosome mediated tumour metastasis in the Chinese Academy of Sciences in 2017. At present her research interest focuses on the differentiation of mesenchymal stem cell and related cell signalling pathways.

3rd International Conference on Stem Cells and Regenerative Medicine, June 29-30, 2020

Citation: Libo Yu, Depletion of TM9SF4 promotes osteogenic differentiation of mesenchymal stem cells, Stem Cell Congress 2020, 3rd International Conference on Stem Cells and Regenerative Medicine, June 29-30, 2020, 04