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Macrophages as A Mechano-Transducer to Direct the Osteogenic Differentiation of Mesenchymal Stem Cells

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Abstract: It has been widely recognized that stem cells possess the potential of osteogenic differentiation, which greatly contribute to bone repair. Recently, accumulating evidences have indicated that mechanical cues are required for bone repair [1,2]. However, how local and recruited stem cells in the bone architecture receive the mechanical signals is poorly understood [3,4]. The purpose of this study is to demonstrate that macrophages potentially transduce the mechanical signals for stem cell osteogenic lineage. This demonstration has been carried out through a co-culture system to investigate the effect of macrophages which subjected to cyclic stretch on the osteogenic potential of bone marrow mesenchymal stem cells (BMSCs). Concretely, Macrophages were subjected to cyclic stretch at the magnitude of 5% strain to verify the mechanical sensibility. Additionally, a co-culture experiment was conducted to prove that macrophage is able to transduce the mechanical signals for osteogenesis of BMSCs. Furthermore, YAP, mechanosensing-related transcription factor, was silenced in macrophages to investigate the underlying mechanisms involved in the mechanotransduction ability of macrophages for BMSCs osteogenic differentiation. Our results showed that macrophages are mechano-sensitive, which respond to mechanical stimulation with alterations in cytoskeleton and gene expression profiles, especially the mechanosensing-related genes, such as YAP, TAZ1, ERK2, FAK, MAPK3, Rac1, and BMPs. BMSCs, co-cultured with mechanically loaded-macrophages, displayed significant osteogenic differentiation, as evidenced by increased ALP activity, enhanced calcium deposition, and upregulated expression of osteogenesis markers (Col 1, and sp7). However, when YAP was silenced in macrophages, the levels of Wnt5a and BMP2 were both decreased after mechanical stretch. Meanwhile, BMSCs, co-cultured with siYAP-and stretched-macrophages, showed no observable osteogenesis. This study strongly reveals maximum mechanical transduction from macrophages to MSCs, which can occur to efficaciously direct stem cell osteogenesis during bone repair.

Keywords: Macrophage; mechanotransduction; MSC; osteogenesis

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