

## **CATECHIN STIMULATES OSTEOGENESIS BY ENHANCING PP2A ACTIVITY IN HUMAN MESENCHYMAL STEM CELLS**

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Human mesenchymal stem cells (hMSCs) derived from bone marrow, useful as a species specific cell culture system for studying cell lineage differentiation, were examined as a tool to identify novel herbal ingredients and Chinese traditional compounds for enhancing osteogenesis. Using immortalized hMSCs, we first identified catechin, evodiamin 18 $\beta$ - glycyrrhetic acid, baishao, and danggui with osteogenic properties, which enhanced calcium deposition at the dose without significant cytotoxic effects. Primary hMSCs were then applied for confirming the osteogenic effects of catechin, which increased alkaline phosphatase activity, calcium deposition, and mRNA expression of Runx2 and osteocalcin. We then explored the underlying mechanism and found the ERK pathway was downregulated upon stimulation with catechin. Catechin increased the level and activity of protein phosphatases 2A (PP2A) that dephosphorylates MEK and ERK. Further, inhibition of PP2A by okadaic acid abolished the effect of catechin-mediated inactivation of ERK and stimulation of osteogenesis. The blocking effect of okadaic acid on osteogenesis was further reversed in the presence of PD98059, a specific inhibitor of MEK. Co-immunoprecipitation revealed the association of PP2A to mainly MEK rather than ERK. Based on our study we propose catechin enhanced osteogenesis by increasing the PP2A level that inhibits the ERK signaling pathway in hMSCs. These results prove the concept of using hMSCs as a convenient tool for rapid and consistent screening of the osteogenic herbal ingredients and traditional Chinese compounds.