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Shh signaling, negatively regulated by BMP signaling, inhibits the osteo/dentinogenic differentiation potentials of mesenchymal stem cells from apical papilla

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Abstract Mesenchymal stem cells (MSCs) derived from dental tissues show promise for use in tooth-related tissue regeneration, but the molecular mechanisms underlying their directed differentiation remain unclear, limiting their usefulness. Sonic Hedgehog (Shh) signaling is a major signaling pathway that regulates cell differentiation and osteogenesis. We found that when Shh signaling was activated by human recombinant SHH-N protein or by overexpression of active mutant M2-Smoothened (SMO) in stem cells from apical papilla (SCAPs), *GLI1,* a key downstream transcription factor and a marker of Shh signaling, was upregulated. Subsequently, in vitro osteo/dentinogenic differentiation and in vivo osteogenesis were inhibited in SCAPs. Moreover, the expression of *GLI1* and *SMO* were downregulated by BMP signaling while osteo/dentinogenic differentiation in SCAPs was upregulated. These results provide insights into the role of Shh signaling in the directed differentiation of MSCs derived from dental tissues and suggest possible target genes for optimizing the use of stem cells of dental origin for tissue regeneration applications.

Keywords Smoothened (SMO) · Shh signaling · BMP signaling · Mesenchymal stem cells · Osteo/dentinogenic differentiation

Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic, plastic, adherent progenitor cells that were first isolated from bone marrow. Notably, MSCs can differentiate into osteogenic, chondrogenic, and adipogenic lineages both in vitro and in vivo [1]. There is increasing evidence that MSCs are also present in non-bone marrow tissues [2]. Recently, a new population of MSCs was isolated from dental and craniofacial tissues on the

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