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Improving bone formation and tissue engineering of large bone defects through stem cells

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Tissue engineering of large bone defects is approached through implantation of autologous osteogenic cells, named multipotent stromal cells or mesenchymal stem cells (MSCs). The ability of human MSCs to differentiate into adipogenic, chondrogenic, osteogenic, and myogenic lineages has generated a great deal of potential clinical use in regenerative medicine and tissue engineering in the past decade. Although animal-derived MSCs successfully bridge large bone defects, models for ectopic bone formation as well as recent clinical trials demonstrate that bone formation by human MSCs is inadequate. Predifferentiation of human MSCs into the osteogenic lineage in vitro during the expansion phase before implantation offers an opportunity to improve their in vivo performance.

In a recent report [1], it is shown that activation of cyclic AMP-dependent protein kinase (protein kinase A, PKA) in human MSCs in vitro elicits an immediate response through induction of genes such as ID2 and FosB, followed by sustained secretion of bone-related cytokines such as BMP-2, IGF-1, and IL-11. Cyclic AMP-dependent gene induction is therefore followed by stimulation of osteogenesis and osteoblast differentiation. As a consequence, PKA activation results in robust in vivo bone formation by human MSCs derived from orthopedic patients.

These procedures are promising maneuvers to improve tissue engineering of large bone defects in humans.

1. Siddappa R et al. *Proc Natl Acad Sci USA*. 2008;105:7281-7286.

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Mesenchymal stem cells are the precursors of osteoblasts and can be differentiated into the osteogenic lineage. This can be achieved through activation of the cyclic AMP signaling pathway. Cyclic AMP generation from ATP or addition of exogenous cyclic AMP induces protein kinase A activation and, subsequently, phosphorylation of the cyclic AMP responsive element binding protein CRE. CREB moves to the nucleus, binds to DNA, and triggers gene transcription. Some of these genes, such as ID2, ID4, or Fos, stimulate osteogenesis. Other genes such as IL-11, growth factors, or BMP2 act as paracrine mediators and induce osteoblast differentiation.

Activation of this pathway in mesenchymal stem cells in vitro is a promising way to promote bone formation in vivo after implantation of these cells in bone defects.