Osteogenic Differentiation Determines Bone Regeneration Efficiency in Vascularized Defects: Comparative Evaluation of Umbilical Cord MSCs and Their Osteoblastic Derivatives in Rodent and Goat Models

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Background:

Coordinated osteogenesis and angiogenesis are essential for bone regeneration, yet the relative contribution of each process remains incompletely understood. Human umbilical cord–derived mesenchymal stromal cells (UC-MSCs) possess strong angiogenic and anti-inflammatory activity but limited intrinsic osteogenicity. Here, we compared undifferentiated UC-MSCs with fully differentiated osteoblastic cells derived from UC-MSCs to clarify the mechanistic determinants of bone repair.

Methods:

UC-MSCs were differentiated in a 3D-thermoresponsive hydrogel to obtain osteoblastic cells characterized by elevated alkaline phosphatase activity and expression of osteopontin and osteocalcin. We assessed osteogenic, angiogenic, and anti-inflammatory profiles in vitro, followed by in-vivo evaluation in rat tibial partial-defect, rat calvarial critical-size, and goat femoral diaphyseal defect models. Lentiviral RFP-labeled cells were tracked for persistence and localization up to 28 days.

Results:

Differentiated osteoblastic cells showed enhanced matrix mineralization and loss of angiogenic capacity relative to UC-MSCs. In vivo, osteoblastic cells persisted longer within defect sites and promoted rapid mineralized bridging and lamellar bone formation. UC-MSCs exhibited transient persistence and primarily contributed through angiogenic and immunomodulatory signaling. In the goat diaphyseal model, implants containing osteogenic cells achieved cortical bridging and scaffold resorption, validating translational feasibility.

Conclusions:

Bone regeneration is predominantly governed by the osteogenic differentiation state of transplanted cells, while angiogenic and anti-inflammatory functions play supportive roles in the repair microenvironment. These findings provide

mechanistic insight into how lineage commitment directs MSC-based bone regeneration and establish a foundation for rational design of osteogenic cell therapies for vascularized bone repair.

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Keywords

osteogenic differentiation · umbilical cord MSCs · vascularized bone regeneration · angiogenesis · 3D hydrogel · osteoblastic cells · goat diaphyseal defect · regenerative mechanism