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Discussion: Regeneration of Vascularized Corticocancellous Bone and Diploic Space Using Muscle-Derived Stem Cells: A Translational Biologic Alternative for Healing Critical Bone Defects

Matthew P. Murphy, M.B., B.Ch., B.A.O., Charles K. F. Chan, Ph.D., Michael T. Longaker, M.D., M.B.A.

Hagey Laboratory for Pediatric Regenerative Medicine, Department of Surgery, Plastic and Reconstructive Surgery Division; and the Lorry I. Lokey Stem Cell Research Building, Stanford Stem Cell Biology and Regenerative Medicine Institute, Stanford University.

Since the work of Urist et al. in 1965, our understanding of osteogenesis has advanced significantly.^{1,2} However, the osteogenic potential of the stem cell population residing in muscle is not fully understood. Lough et al. have compared muscle-derived stem cells, adipose-derived stem cells, and bone marrow-derived mesenchymal stem cells in the regeneration of full-thickness defects of the mouse parietal skull.³

In vitro, at 1 week, adipose-derived stem cells and bone marrow–derived mesenchymal stem cells formed microaggregates within culture, whereas muscle-derived stem cells developed a structure resembling cortical bone. In vivo, the muscle-derived stem cells formed three-dimensional corticocancellous bone containing a diploic space at 8 weeks. Grossly, the defects treated with muscle-derived stem cells were smaller, had less fibrosis at the defect/scaffold interface, and the bone that formed within the defect was more planar.

The differences seen highlight the importance of the niche environment and the potential intrinsic differences within each population.^{4,5} Mechanical and material influences include the collagen scaffold and bone morphogenetic protein-2 media in vitro and the insertion of the scaffold into the host environment in vivo. The three-dimensional structure of the scaffold plays an important role, determining the fate of the residing stem cells.⁶

Although there are differences in isolation between the groups transplanted,^{7–9} muscle-derived stem cells showed superior osteogenic capacity in the model reported by Lough et al. The osteogenic potential of muscle-derived stem cells could be used in reconstructive surgery. However, adipose-derived stem cells may be a more attractive option with minimal donor-site morbidity and high yields of adipose-derived stem cells.¹⁰

chazchan@stanford.edu.

Charles K. F. Chan, Ph.D. Lorry I. Lokey Stem Cell Research Building 265 Campus Drive Stanford, Calif. 94305

Michael T. Longaker, M.D., M.B.A. Hagey Laboratory for Pediatric Regenerative Medicine 257 Campus Drive Stanford, Calif. 94305

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The multipotency of muscle-derived stem cells questions the true identify of so-called mesenchymal stem cells. The presence of adult mesenchymal stem cells capable of differentiating into multiple mesenchymal lineages in vivo remains to be confirmed. The relationship of these mesenchymal stem cells to mesenchymal stem/progenitor cell lineages such as skeletal stem cells has yet to be understood.^{11–14} The multipotency may reflect population heterogeneity or the presence of multipotent mesenchymal stem cells, explaining pathologic osteogenesis within muscle in fibrodysplasia ossificans progressiva or injury-induced heterotopic ossification.^{15–18}

The osseous ultrastructure and cellular bridging capacity shown in three dimensions of muscle-derived stem cells demonstrate exciting new prospects with which to potentially address the technical difficulty of applying stem cell populations to defects. Lough et al. have provided us with a well-described, potential solution for challenging clinical scenarios.

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