Paper - Basic Science

Paper Session: Fracture Healing:
Cells and Bone

Atrophic Nonunions Are Associated With Functional Defects in Human Skeletal Stem Cells

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Purpose: Fracture nonunions are a significant source of patient morbidity and societal cost. In the majority of patients who develop nonunions, the underlying cause is unknown. Fracture nonunion remains poorly understood from the perspective of the human skeletal stem cell (hSSC), a cell that gives rise to lineage-restricted bone and cartilage progenitor cells. We isolated hSSCs from nonunions, compared them to hSSCs from normally healing fractures, and hypothesized that hSSCs at nonunion sites demonstrate defects in self-renewal and differentiation capacity.

Methods: We prospectively isolated hSSCs (Podoplanin+, CD146-, CD73+, CD164+) by fluorescence-activated cell sorting from acute fractures and nonunions in patients undergoing surgical treatment. Nonunions were classified as atrophic or hypertrophic based on radiographic features. Purified SSCs were counted, cultured, and then analyzed for clonogenicity by colony-forming unit formation (CFU-F). After in vitro osteogenic differentiation, cell staining for alizarin red was quantified by spectrophotometry.

Results: There were 181 acute fractures, 17 atrophic nonunions, and 11 hypertrophic nonunions. SSC frequency was higher in atrophic nonunions than in acute fractures ($P < 0.001$). SSCs from atrophic nonunions demonstrated significantly less clonogenicity compared to SSCs from acute fractures ($P < 0.05$) as well as diminished osteogenic capacity, compared to acute fractures ($P < 0.005$). There were no significant differences between atrophic and hypertrophic nonunions with respect to osteogenic differentiation and clonogenicity.

Conclusion: Based on this clinical series, hSSCs localize to fracture nonunion sites. hSSCs at atrophic fracture nonunion sites in particular exhibit defects in both self-renewal capacity and osteogenic differentiation capability. hSSCs in nonunions demonstrate functional defects that could represent points of intervention for future clinical translation.

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