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Prg4+ fibroadipogenic progenitors in muscle are crucial for bone fracture repair

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Bone regeneration depends on several local and systemic factors. Bone injury activates the quiescent periosteal mesenchymal progenitors, driving their expansion and differentiation into chondrocytes and osteoblasts for callus formation. Periosteal damage or removal often leads to fracture nonunion. Similarly, less muscle coverage and muscle swelling are observed to adversely affect bone fracture healing. In this context, muscle fibroadipogenic progenitors (FAPs), mesenchymal progenitors residing in muscle interstitium differentiate into fibrous and adipose tissue, or under special conditions into periosteal cells for bone regeneration. Proteoglycan 4 (*Prg4*) marks a specific subpopulation of FAPs that localizes in the muscle tissue but not periosteum, cortical bone or intact bone marrow. This study demonstrates that muscle-resident *Prg4*$^{+}$ FAPs, rather than tendon-derived FAPs, contribute to closed, transverse fracture healing. Upon acute injury, *Prg4*$^{+}$ FAPs expand and show potential for differentiation into periosteal cells. Furthermore, the descendants of *Prg4*$^{+}$ FAPS in the periosteum serve as mesenchymal progenitors that assist in second injury healing of closed tibial fractures. Ablation experiments confirm that *Prg4*$^{+}$ FAPs are essential for fracture callus formation and functional repair. In contrast, *Prg4*$^{+}$ FAPs show limited contribution in intramembranous cortical drill-hole injury.

Overall, this research reveals the cross-talk between muscle and bone tissues, and expands the concept of cross-tissue cellular transdifferentiation and fibroblast plasticity. It brings forth possible therapeutic applications and highlights how muscle injury status, muscle health, or the integrity of muscle tissues at fracture sites might be more important than previously thought for bone healing.

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