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Regenerative medicine based on muscle stem cells

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Members of the Stem Cell Research Center (SCRC) have isolated various populations of myogenic cells from the postnatal skeletal muscle of normal mice by means of the cells' adhesion characteristics, proliferation behavior, and myogenic and stem cell marker expression profiles. Although most of these cell populations have displayed characteristics similar to those of skeletal muscle satellite cells, we also have identified a unique population of muscle-derived stem cells (MDSCs). The MDSCs exhibit long-term proliferation abilities, elevated self-renewal rates, increased resistance to stress, and they are multipotent and can differentiate toward a variety of tissue types including: muscle (skeletal and cardiac), neural, endothelial, osteogenic, and chondrogenic lineages, both *in vitro* and *in vivo*. In contrast to other myogenic cell types, MDSCs show very efficient engraftment and regeneration of skeletal and cardiac muscle upon their transplantation into these tissues, as well as other tissues of the musculoskeletal system. MDSCs have also been utilized in gene therapy and tissue engineering applications designed to improve bone and cartilage healing through the genetic modification of MDSCs to express osteogenic proteins (BMP-2 and -4) as well as the angiogenic and anti-angiogenic factors (VEGF and sFLT-1). Interestingly, it has been observed that female MDSCs (F-MDSCs) can more efficiently regenerate the dystrophic skeletal muscle of mdx mice (a mouse model of Duchenne muscular dystrophy) than their male MDSCs (M-MDSCs) counterparts. Moreover, M-MDSCs when compared to F-MDSCs have been shown to be superior at bone and cartilage repair. MDSCs are influenced by environmental cues released within dystrophic or injured skeletal muscle, which have been shown to negatively impact MDSCs and cause the cells to differentiate toward a fibrotic cell lineage and hence produce scar tissue rather than healthy skeletal muscle fibers. Potential strategies are being explored to prevent the formation of scar tissue within injured skeletal muscle by blocking the action of TGF-β1. Finally, blood vessels contain several cell types, including myo-endothelial cells and pericytes, and are likely the place of origin of the murine MDSCs discussed above. The results outlined above open new avenues by which researchers could use muscle stem cell-based gene therapy and tissue engineering to improve tissue regeneration.

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