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Skeletal Muscle Preservation During Nerve Regeneration

Cell-Based, Extracellular Vesicle, and Biomaterial Approaches

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Academic dissertation

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Abstract

Peripheral nerve injuries often result in prolonged denervation of skeletal muscle, leading to muscle atrophy and impaired functional recovery. Although surgical repair can restore nerve continuity, successful outcomes depend on both axonal regeneration and preservation of the target muscle during the denervation period. This work investigates strategies to support the regenerative environment and maintain skeletal muscle following nerve injury, focusing on secretory mechanisms and biomaterial-based approaches.

Adipose-derived stem cells (ASCs) were studied as a source of regenerative secretome. Human ASCs were isolated and expanded under xeno-free, Good Manufacturing Practice (GMP)-compatible conditions. The influence of culture conditions and a short stimulation protocol on ASC properties and secretory activity was evaluated. Both affected the composition of the secretome, resulting in enhanced angiogenic activity under defined conditions. To examine cell-free signalling, extracellular vesicles (EVs) were isolated from denervated skeletal muscle tissue. Denervation increased EV release and altered their molecular profile. However, muscle-derived EVs did not impair neurite outgrowth in vitro, indicating that EVs from denervated muscle do not negatively affect axonal growth under the conditions tested. Finally, a nerve-derived extracellular matrix hydrogel was evaluated in a rat sciatic nerve repair model. When used as a filler in a synthetic nerve conduit, the hydrogel supported axonal regeneration and contributed to preservation of skeletal muscle structure following reinnervation.

Together, these findings highlight the importance of the regenerative environment in peripheral nerve repair and support the development of strategies that modulate secretory activity to improve muscle preservation and functional recovery.

Keywords: Peripheral Nerve Injury; Skeletal Muscle Denervation; Nerve Regeneration; Regenerative Microenvironment; Adipose-derived Stem Cells; Extracellular Vesicles; Secretome; Extracellular Matrix Hydrogel.

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