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Dental pulp stem cells alleviate Schwann cell pyroptosis via mitochondrial transfer to enhance facial nerve regeneration

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ABSTRACT

Dental pulp stem cells (DPSCs) have demonstrated remarkable potential in enhancing peripheral nerve regeneration, though the precise mechanisms remain largely unknown. This study investigates how DPSCs alleviate Schwann cell pyroptosis and restore mitochondrial homeostasis through intercellular mitochondrial transfer. In a crab-eating macaque model, we first observed that DPSC-loaded nerve conduits significantly promoted long-term nerve regeneration, facilitating tissue proliferation and myelin recovery. We further established a rat facial nerve injury (FNI) model and found that DPSC treatment reduced pyroptosis and mitochondrial ROS production in Schwann cells. A pivotal mitochondrial protective mechanism, resembling the effects of a ROS-targeted inhibitor, involved the transfer of mitochondria from DPSCs to pyroptosis-induced Schwann cells via tunneling nanotubes, while blocking intercellular junctions or mitochondrial function diminished the therapeutic effects. TNFα secreted by pyroptosis-induced Schwann cells activated the NF-κB pathway in DPSCs, enhancing mitochondrial transfer and adaptive stress responses, thereby promoting mitochondrial protection against pyroptosis in Schwann cells, as reflected in the improved therapeutic efficacy of TNFα-preconditioned DPSCs in the FNI model. These findings unveil a mechanism through which DPSCs foster nerve regeneration via mitochondrial transfer, presenting a promising strategy for enhancing stem cell-based therapies for nerve injuries.

1. Introduction

Peripheral nerve injuries (PNIs), unlike central nervous system lesions, exhibit a remarkable capacity for repair, a process that is primarily supported by the activity of Schwann cells [1]. Schwann cells, integral to the peripheral nervous system, not only form the myelin sheath around axons but also guide the regrowth of damaged axons by establishing regeneration pathways after injury [1,2]. In addition, Schwann cells rapidly clear debris from the injury site, such as degenerated myelin, and create a pro-regenerative environment by secreting neurotrophic factors. This regenerative capacity, particularly evident in smaller nerve injuries, highlights the indispensable role of Schwann cells in the regenerative process. The survival and functional restoration of Schwann cells are, therefore, critical to successful nerve regeneration

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