The injured axon: intrinsic mechanisms driving axonal regeneration

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Axonal injury in the adult central nervous system (CNS) often results in irreversible deficits due to the intrinsic inability of mature neurons to regenerate. In contrast, peripheral nervous system (PNS) neurons can activate a robust regenerative program. This review explores the intrinsic mechanisms that underlie axon regeneration, highlighting advances in axon-to-soma signaling, transcriptional and epigenetic reprogramming, local protein synthesis, and mitochondrial remodeling.

Following axonal injury, a rapid influx of calcium initiates a cascade of signaling events that travel retrogradely to the soma. These signals activate transcription factors such as STAT3, ATF3, and members of the KLF family, which together promote a growth-permissive gene expression profile. Epigenetic modifications, including histone acetylation and DNA demethylation mediated by HDAC5, PCAF, and TET3, are essential to unlock transcriptional programs required for regeneration.

Local translation within axons supports the synthesis of critical proteins near the injury site, such as importin-β, vimentin, and mTOR, which are vital for retrograde signaling and cytoskeletal dynamics. Ribosomes and mRNAs stored in stress granules are mobilized through mTOR-dependent mechanisms. Schwann cell-derived ribosomes may also contribute to this local translation machinery.

Mitochondrial transport and turnover are central to meeting the energy demands of regenerating axons. Proteins such as syntaphilin, MIRO1, ARMCX1, GRP75, and PAK5 facilitate the redistribution and tethering of mitochondria, restoring ATP production and calcium homeostasis. In CNS neurons, intrinsic inhibitors including PTEN, SOCS3, REST, and VGCC-associated synaptic proteins restrict regeneration by repressing pro-growth signaling and translation.

The article underscores the therapeutic potential of targeting multiple intrinsic pathways simultaneously to reprogram adult CNS neurons into a regenerative state and overcome current clinical limitations in neural repair.

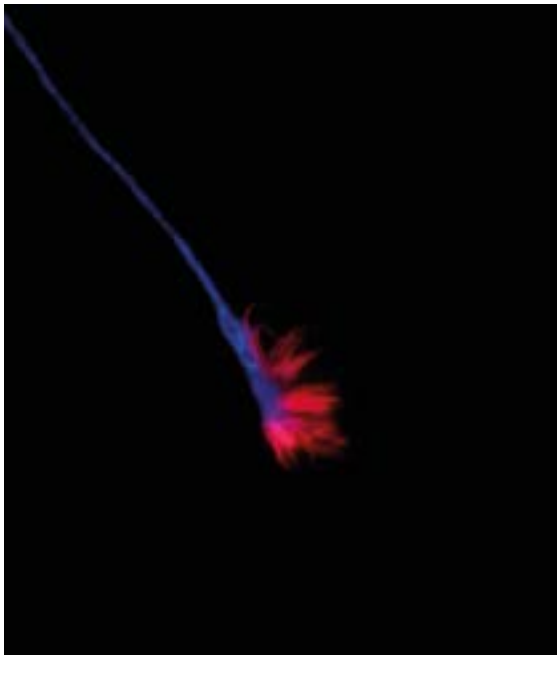

FIGURE 1
Growth cone (red), the precursor of axon regeneration, located at the tip of a rat hippocampal axon (blue).