RESEARCH HIGHLIGHT

Borrowed mitochondria, spared neurons

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Cell Research (2026) 0:1–2; https://doi.org/10.1038/s41422-026-01230-y

Peripheral sensory neurons face extreme metabolic demands and are highly vulnerable to mitochondrial dysfunction in neuropathic pain. A recent *Nature* study by Xu et al. reveals that satellite glial cells actively protect these neurons by transferring mitochondria, uncovering a previously unrecognized mode of neuro–glial metabolic support.

Peripheral sensory neurons in the dorsal root ganglia (DRG) are uniquely susceptible to energetic stress. These neurons extend exceptionally long peripheral axons — reaching up to a meter in humans — while sustaining high levels of electrical activity, placing extraordinary demands on mitochondrial function.[1] Consistent with this vulnerability, mitochondrial dysfunction has emerged as a unifying feature of peripheral neuropathies such as chemotherapy-induced peripheral neuropathy (CIPN) and diabetic peripheral neuropathy (DPN), which are characterized by axonal degeneration, sensory loss, and chronic pain.[2] Satellite glial cells (SGCs), which tightly enwrap neuronal cell bodies in the DRG, are well recognized for roles in ionic, neurotransmitter, and inflammatory regulation.[3] Whether they also provide direct metabolic support to neurons has remained unresolved. Although intercellular mitochondrial transfer has been reported in other settings,[4,5] convincing evidence that this mechanism operates in vivo within peripheral sensory circuits has been lacking.

Using complementary genetic, imaging, and ultrastructural approaches, the authors provide direct evidence that mitochondria move from SGCs into sensory neurons in vitro, ex vivo, and in vivo.[6] By selectively labeling mitochondria in SGCs, glia-derived organelles are detected within neuronal somata and axons in intact DRG, establishing that mitochondrial transfer occurs under physiological conditions rather than being an artifact of culture systems. Electron microscopy reveals tunneling nanotube (TNT)-like structures connecting SGCs and neurons in both mouse and human DRG, containing vesicular cargo consistent with mitochondria. Although TNTs have been described previously between neurons and astrocytes, neurons and microglia, or tumor cells and surrounding glia — often in pathological or in vitro contexts[7] — such ultrastructural evidence within peripheral sensory ganglia has been rare. Importantly, mitochondrial transfer is dynamically regulated: it increases with neuronal activity, is enhanced after nerve injury, and is suppressed when neuronal firing is blocked, directly linking transfer to functional demand. While mitochondria are known to accumulate in injured axons through intrinsic neuronal transport mechanisms,[8] these findings identify an extrinsic source of mitochondrial support. Transfer occurs predominantly from SGCs to neurons, consistent with context-dependent functional unidirectionality observed in other systems.[5]

At the mechanistic level, the study identifies myosin 10 (MYO10) as a central regulator of TNT-dependent mitochondrial transfer between SGCs and neurons (Fig. 1a). TNTs are actin-based structures, and MYO10 — a motor protein previously implicated in filopodial extension and TNT formation in multiple cell types[9] — localizes to these conduits in the DRG. Single-cell transcriptomic and histological analyses show that MYO10 is enriched in SGCs relative to neurons, positioning glia as the primary cellular compartment poised to initiate and maintain TNTs, although MYO10 expression is not exclusive to this lineage. Genetic or siRNA-mediated reduction of *Myo10* markedly decreases TNT abundance, disrupts intercellular connectivity between SGCs and neurons, and sharply reduces mitochondrial transfer both in vitro and in vivo. These defects are accompanied by heightened pain sensitivity, underscoring the functional relevance of this pathway. While endocytosis and connexin 43-containing gap junctions also contribute to mitochondrial exchange, these mechanisms are insufficient in the absence of intact TNTs, which emerge as integral organizers of efficient glial–neuronal contact.

When this MYO10-TNT-dependent support system fails, its breakdown maps directly onto neuropathic disease. In models of CIPN and DPN, the authors observe compromised intercellular connectivity between SGCs and neurons, reduced MYO10 expression, and a marked decline in mitochondrial transfer. These changes coincide with increased neuronal reactive oxygen species, heightened excitability, and progressive axonal degeneration. Notably, mitochondrial delivery is not uniform across sensory neuron subtypes: medium- and large-diameter neurons preferentially receive glial mitochondria, whereas small nociceptive neurons remain largely unsupported. Why these small-diameter neurons receive comparatively little glial mitochondrial support remains unresolved and may reflect differences in energetic demand, access to TNT-mediated contacts, or subtype-specific signaling cues. This selectivity offers a mechanistic explanation for small fiber neuropathy, a defining feature of many chronic pain states,[10] and positions defective metabolic coupling as a driver — rather than a secondary consequence — of peripheral sensory dysfunction.

Crucially, the study moves beyond association to establish causality by showing that restoring mitochondrial support is sufficient to alleviate neuropathic pain (Fig. 1b).[6] Adoptive transfer of healthy SGCs into the DRG of neuropathic mice rapidly reduces mechanical hypersensitivity and improves neuronal mitochondrial

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Published online: 04 March 2026

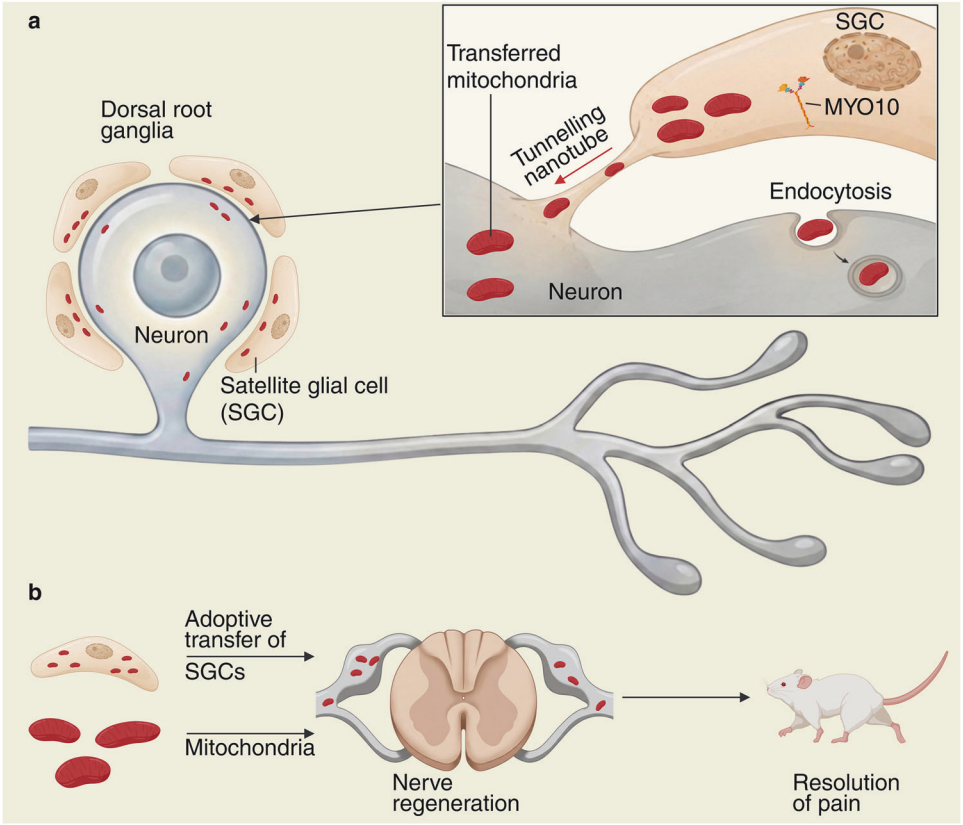

Fig. 1 SGC–neuron mitochondrial transfer supports peripheral sensory neuron integrity. a In the DRG, SGCs ensheath sensory neuron cell bodies and extend TNT-like structures toward neurons. MYO10-dependent TNTs facilitate directional mitochondrial transfer from SGCs to neurons, followed by neuronal internalization via endocytic mechanisms. **b** Functional consequences of restoring mitochondrial support. Adoptive transfer of healthy SGCs or direct delivery of SGC-derived mitochondria into the DRG improves neuronal mitochondrial function and alleviates pain hypersensitivity in vivo, whereas disruption of MYO10-dependent TNT formation or transfer of metabolically compromised mitochondria abrogates these effects.

function, whereas SGCs lacking MYO10 fail to confer protection. Direct delivery of isolated, healthy SGC-derived mitochondria similarly suppresses pain, whereas mitochondria from metabolically compromised or diabetic SGCs provide little benefit. Cross-species transfer of human SGC-derived mitochondria further underscores the conserved bioenergetic nature of the effect. Together, these experiments provide clear proof of principle that neuronal dysfunction in peripheral neuropathy can be driven — and reversed — by the quality and availability of glial mitochondria, without overextending therapeutic claims.

Taken together, this work reframes SGCs as active metabolic guardians of peripheral sensory neurons rather than passive support elements. Mitochondrial transfer now joins ATP buffering, ion homeostasis, cytokine signaling, and gap junction communication as a central component of SGC–neuron interaction. At the same time, important questions remain. The fate of transferred mitochondria within recipient neurons is unclear — whether they are transiently utilized, degraded, or functionally integrated into the host mitochondrial network, and how long any metabolic benefit persists. These uncertainties suggest that mitochondrial transfer may operate as a dynamic, demand-driven process rather than a one-time rescue event. Further resolution will require disentangling cell type-specific contributions of MYO10 to TNT formation and refining strategies to achieve greater SGC specificity. By identifying mitochondrial transfer as a regulated, activity-dependent axis of neuro–glial communication, this study opens a new framework for understanding how metabolic cooperation preserves neuronal integrity — and how its failure may drive neuropathic disease.

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ADDITIONAL INFORMATION

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