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Commentary

Intercellular mitochondrial transfer in disease: Therapeutic opportunity or driver of tumor progression?

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Intercellular mitochondrial transfer has emerged as a key mode of metabolic communication across tissues. Its outcomes are context dependent, spanning from therapeutic benefits to pathological risks.

Mitochondria have long been discussed primarily from a cell-intrinsic perspective. That framing is starting to feel incomplete. Across the nervous, vascular, and immune systems, and in the tumor microenvironment, there is now consistent evidence that mitochondria can move between cells. Importantly, this is not always a passive spillover from damage. In several settings mitochondrial transfer appears regulated: donor cells package or release mitochondria, recipient cells internalize them, and the exchange can shift metabolism and signaling in ways that matter for tissue function.[1–5]

Although direct evidence in human subjects remains limited, mitochondrial transfer has been repeatedly demonstrated in both animal and cellular models. A major complexity, however, is that the same phenomenon can drive starkly different biological outcomes. It is now established that mitochondrial transfer serves a homeostatic, host-supportive role in injury and degeneration, functioning as metabolic rescue, while in cancer it is pathologically co-opted as an adaptive shortcut that fuels immune escape or dissemination.[1–3,6,7] Rather than representing fundamentally distinct phenomena, these opposing outcomes likely reflect a single conserved stress-response mechanism operating in different cellular contexts: the tumor microenvironment exploits the same biology that sustains injured tissue. Given these context-dependent outcomes, the translational focus, in our view, shifts from whether mitochondrial transfer occurs to when it helps or harms, and whether its directionality and consequences can be meaningfully modulated and controlled (Figure 1).

METABOLIC RESCUE, BUT HOW DURABLE?

In models of ischemia, neural injury, and mitochondrial disease, mitochondrial transfer is repeatedly associated with improved bioenergetics and survival of compromised recipient cells.[4,8,9] Glial-to-neuronal transfer alleviates peripheral neuropathy,[4] and astrocyte-to-endothelial transfer has been linked to blood-brain barrier support.[5] These findings provide compelling evidence that intercellular mitochondrial support can operate *in vivo*. At the same time, in individuals with mitochondrial disorders where mitochondria are intrinsically dysfunctional, mitochondrial transfer could in principle propagate damaged organelles, although this possibility remains largely unexplored.

These risks underscore that the biological outcome of mitochondrial transfer is not determined by the transfer event alone, but by a constellation of variables that remain incompletely understood. Among these, donor cell identity is arguably the most critical determinant, particularly from a therapeutic standpoint.[8] In the context of neuronal injury, for example, it is not yet known whether the source of donated mitochondria matters: would neurons, skeletal muscle cells, or mesenchymal stromal cells (MSCs) differ meaningfully in the functional benefit conferred upon recipient cells? MSC-derived mitochondrial transfer has received the most preclinical attention, but whether donor-specific mitochondrial properties—membrane potential, mtDNA copy number, and metabolic specialization—translate into distinct recipient outcomes remains an open question that must be resolved before therapeutic donor selection can be rationalized. Beyond donor identity, the metabolic state of recipient cells likely gates the functional consequence of transfer: a severely depleted recipient may integrate incoming mitochondria differently than a mildly stressed one. These variables are not independent; the interaction between donor mitochondrial quality and recipient cell context may ultimately determine whether transfer is reparative or inconsequential.

The route of mitochondrial delivery adds another layer of complexity. Mitochondrial transfer can occur through tunneling nanotube (TNT), extracellular vesicle (EV), and experimentally induced uptake methods such as mitoception.[8] Whether these distinct delivery mechanisms produce different biological outcomes in recipient cells—by virtue of differential cargo, membrane interaction, or intracellular routing—remains largely unexplored. No comparative study has directly addressed this question, leaving open the possibility that the delivery route shapes not only transfer efficiency but also downstream signaling in the recipient.

Beyond the risk of dysfunction, another unresolved question is whether mitochondrial transfer occurs durably across diverse physiological contexts within biological systems. In cerebellar degeneration and vascular repair, mitochondrial transfer

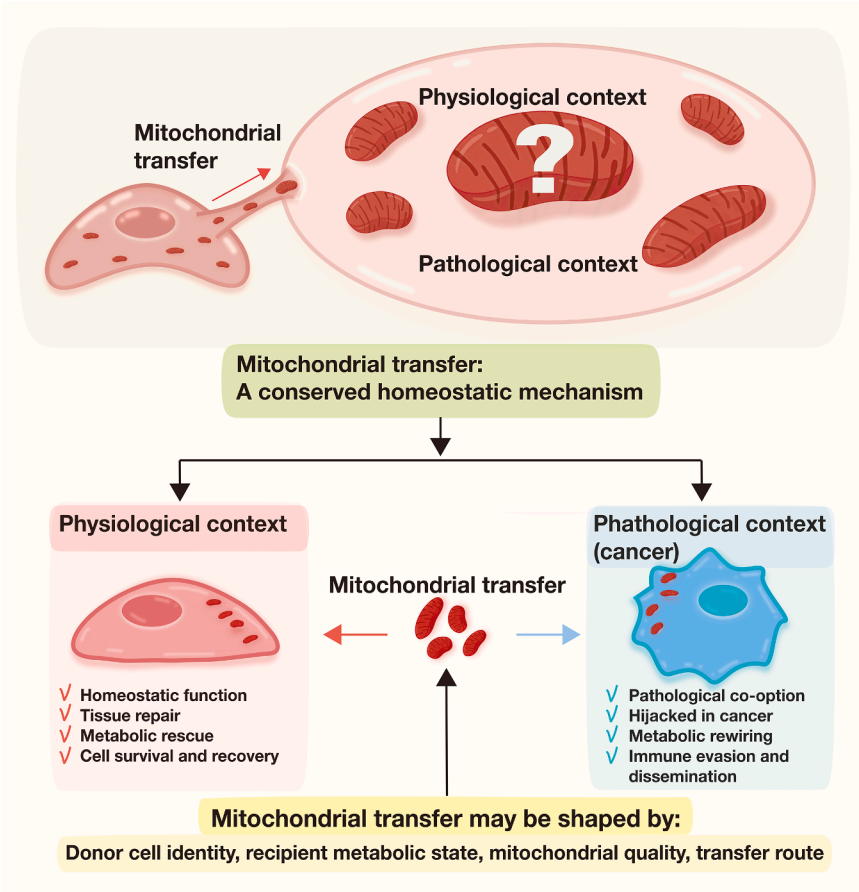

Figure 1. Mitochondrial transfer represents a single conserved stress-response mechanism whose outcomes are determined by cellular context rather than by the process itself
In injured tissues it operates as a homeostatic, host-supportive response, while in the tumor microenvironment the same biology is pathologically co-opted to support cancer cell metabolism, immune evasion, and dissemination.

can restore function in the affected tissue, but the mitochondrial effects occasionally seem transient.[9,10] Whether transferred mitochondria are durably integrated into the recipient network—or instead provide only temporary metabolic support before clearance—remains unclear. Once internalized, mitochondria still face the recipient's quality-control machinery. If mitophagy is engaged early after transfer as part of recipient quality-control mechanisms, mitochondrial delivery may not translate into sustained functional benefit.[10,11] Critically, the functional consequences of this quality-control response are not straightforwardly negative: mitochondrial turnover mediated by mitophagy could also stimulate mitochondrial biogenesis,[10] potentially triggering a broader remodeling of the recipient's mitochondrial network. Whether this remodeling is transient or durable, and whether it translates into meaningful long-term bioenergetic recovery, remains a key unresolved question for the field. These uncertainties directly affect how therapeutic benefit should be defined and measured.

This uncertainty spills into clinical readouts. As mitochondrial transfer-based interventions—including cell and EV approaches—advance through preclinical development,[11] it is not obvious what constitutes meaningful evidence of benefit. Changes in mtDNA copy number or heteroplasmy can provide a rough readout of mitochondrial transfer, but they may not be adequate on their own to support claims of durable functional recovery. Clinically, what may ultimately matter is whether tissues regain durable bioenergetic capacity. That likely requires pairing molecular measurements with functional endpoints that reflect physiology, not only mitochondrial abundance. Defining those benchmarks will be essential if mitochondrial transfer is to move beyond descriptive observations toward validated clinical applications.

TUMOR METABOLIC REWIRING AND IMMUNE SUBVERSION

The same variables that govern mitochondrial transfer (donor identity, recipient metabolic state, and delivery route) may be skewed in the tumor microenvironment compared to physiological contexts. As currently understood, the consequences of mitochondrial transfer itself can resolve toward ends that favor tumor survival and progression. Cancer cells can acquire mitochondria from stromal, immune, or neural neighbors to bolster oxidative phosphorylation under stress.[1,3,6] This is not a tumor-specific invention—it is the same homeostatic transfer mechanism that supports stressed cells in injury contexts, redirected toward malignant ends. This could help bypass hypoxia-related constraints and support the energetic demands of dissemination.[2,3]

Immune-to-tumor mitochondrial transfer is particularly concerning because it could carry two parallel liabilities. It can weaken donor immune cells—reducing antitumor capacity—while reshaping innate immune signaling in recipient tumor cells. Pathways such as cGAS-STING may be engaged, but the outcome is not uniformly tumor suppressive. In some contexts, signaling can settle into chronic inflammation that is permissive for metastatic seeding and immune evasion.[2]

Here again, key translational questions remain unresolved. To what degree does this phenomenon manifest across human cancers, and at which stages of cancer does it matter most? Which donor cell populations drive cancer progression, and does donor identity matter as much in the tumor microenvironment as it appears to in injury contexts? If we attempt to correct mitochondrial dysfunction in tumor-infiltrating lymphocytes, will this restore antitumor immunity—or merely shift molecular readouts? Beyond these questions, the neuro-tumor interface has added another layer: mitochondrial transfer from neurons to tumor cells has been described in metastatic contexts, but its prevalence and tractability in patients remain largely unmapped.[3] Conversely,

evidence from bone microenvironment suggests that mitochondrial transfer from osteocytes to tumor cells can paradoxically prime antitumor immunity.[7] Similarly, mitochondrial donation from mesenchymal stromal cells to T cells has been reported to enhance T cell metabolic fitness and antitumor efficacy,[6] which reinforces the core point: directionality is context dependent.

CONTROLLING DIRECTIONALITY: CONSERVED NODES AS THERAPEUTIC LEVERS

Across these diverse settings, the same control points recur, and their relationships to one another suggest a coordinated logic with direct therapeutic implications. Mitophagy determines the intracellular fate of incoming mitochondria, controlling whether they persist long enough to engage downstream signaling or are cleared before functional integration can occur.[10,11] This process also gates innate immune sensing: effective mitophagy limits mtDNA release and thereby constrains cGAS-STING activation, whereas failed clearance permits mtDNA accumulation and amplifies inflammatory signaling.[2,7] This relationship is not unidirectional, however; cGAS-STING activation can itself induce autophagy and mitophagy through STING-dependent membrane trafficking, independent of interferon induction, pointing to a potential feedback loop between these two regulatory nodes. The downstream metabolic outcome, reinforcing oxidative phosphorylation versus shifting toward glycolysis, then reflects whether this upstream axis resolves toward repair or pathological exploitation.[1–3,6]

These are not just mechanistic curiosities. Because these nodes are interconnected, modulating one without regard to the others risks shifting the system toward an unintended outcome. Several of them are therefore pharmacologically targetable not as isolated points of intervention but as a coordinated set.[8] That creates an opportunity for rational combination therapies: enhancing mitochondrial support where it is reparative, while constraining the same axis where it could feed tumor evolution. Among the primary challenges, achieving specificity of targeting must be considered a prerequisite step that precedes safety considerations.[12] Before safety can even be meaningfully evaluated, we must first be able to direct mitochondrial transfer to the intended cell type, tissue context, and disease stage—without which any intervention risks being simultaneously ineffective and harmful. The absence of targeting precision means that even a well-tolerated intervention could reinforce pathological transfer in off-target compartments, most notably by inadvertently fueling tumor progression while attempting to support injured tissue. Only once targeting can be controlled in a context-specific manner does the question of safety become tractable.

Realizing this potential will require a translational framework that is more sophisticated than is currently available in humans today. To ensure we can identify and act on these divergent trajectories early enough, this framework could include companion measurements that report mitochondrial flux *in vivo* and longitudinal sampling within trials. Such tools will enable real-time monitoring, allowing investigators to discern beneficial rescue from pathological exploitation at a stage where intervention is still effective. These measures are essential to minimize the risk of adverse effects and unintended tumor progression. Furthermore, it is imperative to investigate in greater detail whether the acceleration of mitochondrial transfer or its inherent directionality might inadvertently trigger secondary pathological sequelae, particularly in individuals with intrinsic mitochondrial disorders. This also underscores the need to clarify when and where mitochondrial transfer occurs in human tissues beyond experimental models.

Taken together, these considerations point to a single overarching challenge: control, in our view. If we can specify the donor cell type, the delivery route, and the intracellular fate of transferred mitochondria and understand how each of these variables interacts with recipient cell context, mitochondrial trafficking might be amplified to sustain tissue repair while remaining restricted when it drives malignant adaptation. Reaching that point will depend on coordinated mechanistic work and clinically informed trials, together with a more explicit understanding of how to define meaningful mitochondrial transfer in preclinical and clinical settings.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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