Letter to Editor

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Mitochondrial Reprogramming of Tumor-Infiltrating T Cells as a Next-Generation Strategy to Overcome Immunotherapy Resistance

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DEAR EDITOR

Despite major advances in immune checkpoint inhibitors (ICIs), resistance in solid tumors remains a persistent challenge. Recent studies highlight mitochondrial dysfunction in tumorinfiltrating lymphocytes (TILs) as a central driver of T cell exhaustion and failed antitumor immunity (1-3). Here, we argue that mitochondrial reprogramming—targeting biogenesis, dynamics, and oxidative fitness—represents a promising nextgeneration approach to enhance immunotherapy responses. Importantly, several mitochondrial and metabolic reprogramming strategies, including metabolic modulators combined with ICIs and ex vivo engineering approaches for adoptive cell therapy, are no longer merely theoretical; they are increasingly being investigated as translational advancements in preclinical, late-stage preclinical, and early clinical settings (4-7). Therefore, the major challenge is shifting from establishing proof-of-concept efficacy toward achieving durable in vivo persistence, functional stability, and therapeutic activity within the hostile tumor microenvironment.

Exhausted T cells in the tumor microenvironment (TME) display impaired mitochondrial mass, reduced membrane potential, excessive reactive oxygen species (ROS) accumulation, and suppressed oxidative phosphorylation (OXPHOS) (8). Hypoxia and nutrient deprivation in the TME further inhibit mitochondrial quality control via hypoxia-inducible factor 1α (HIF1α)–mediated metabolic reprogramming, which diverts cellular metabolism toward glycolysis (9). Collectively, this mitochondrial insufficiency drives the epigenetic stabilization of the exhausted phenotype and critically diminishes responsiveness to PD1 blockade (8).

Recent evidence suggests that restoring

mitochondrial fitness can reinvigorate dysfunctional TILs. Overexpression of PGC1α, the transcriptional coactivator of mitochondrial biogenesis, enhances OXPHOS capacity and restores effector cytokine production in exhausted T cells (10, 11). Similarly, modulating mitochondrial dynamics —specifically via inhibition of the fission-regulating GTPase DRP1— preserves cristae ultrastructure, promotes the acquisition of memorylike phenotypic features, and improves the in vivo persistence of antitumor T cells (12). Additionally, targeting mitochondrial ROS with selective scavengers has also been shown to rescue T cell effector function and synergize with ICIs (13, 14).

Innovative metabolic engineering of adoptive cell therapies, including CART and TIL therapies, has revealed that promoting fatty acid oxidation, enhancing mitochondrial fusion, or supporting NAD^+ metabolism significantly improves antitumor efficacy in solid tumors (15). Recent work suggests that mitochondrial transfer from stromal cells or biomaterialmediated mitochondrial delivery may potentiate Tcell bioenergetics (16,17). Beyond these established approaches, intercellular mitochondrial transfer and artificial mitochondrial transplantation have recently emerged as next-generation strategies to directly restore the bioenergetic fitness of exhausted T cells (18, 19). Intercellular mitochondrial transfer, which may occur through tunneling nanotubes, extracellular vesicles, or other cell-contact-dependent mechanisms, can remodel redox signaling, mitochondrial metabolism, and cellular plasticity. In the context of antitumor immunity, transfer of healthy mitochondria from supportive stromal or engineered donor cells to dysfunctional T cells may rapidly improve oxidative phosphorylation, reduce mitochondrial stress, and enhance effector function. Similarly, artificial mitochondrial transplantation or biomaterial-assisted mitochondrial delivery provides a potential platform for introducing healthy or engineered mitochondria into metabolically exhausted T cells. These approaches hold particular promise for improving CAR-T and TIL-based therapies; however, their clinical translation will require optimization of mitochondrial sourcing, delivery specificity, intracellular stability, safety, and durable in vivo function (16-19).

To advance this promising field, several complementary strategies should be prioritized. First, the development of therapeutics that specifically enhance mitochondrial biogenesis in TILs may restore metabolic competence and effector function, building on evidence that PGC1α activation improves OXPHOS and cytokine production in exhausted T cells (10,11). Second, integrating mitochondrial fitness–related biomarkers into immune checkpoint inhibitor (ICI) response prediction could refine patient stratification and inform therapeutic decisionmaking. Third, rational combinations of metabolic modulators, including PGC1α activators, DRP1 inhibitors, and regulators of mitochondrial ROS, with established immunotherapies may synergistically reinvigorate dysfunctional T cells and enhance antitumor immune responses (12–14). Fourth, incorporating mitochondrial reprogramming strategies into CART and TIL manufacturing pipelines may improve cellular metabolic fitness, persistence, and cytotoxic capacity, thereby strengthening the efficacy of adoptive cell therapies (15). Finally, emerging approaches such as intercellular mitochondrial transfer and artificial mitochondrial transplantation warrant further investigation as innovative strategies to restore mitochondrial function and extend the functional persistence and antitumor activity of exhausted T cells in vivo (16–19). Given the central role of mitochondrial fitness in T cell exhaustion, reprogramming T cell metabolism represents a transformative direction for nextgeneration cancer immunotherapy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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