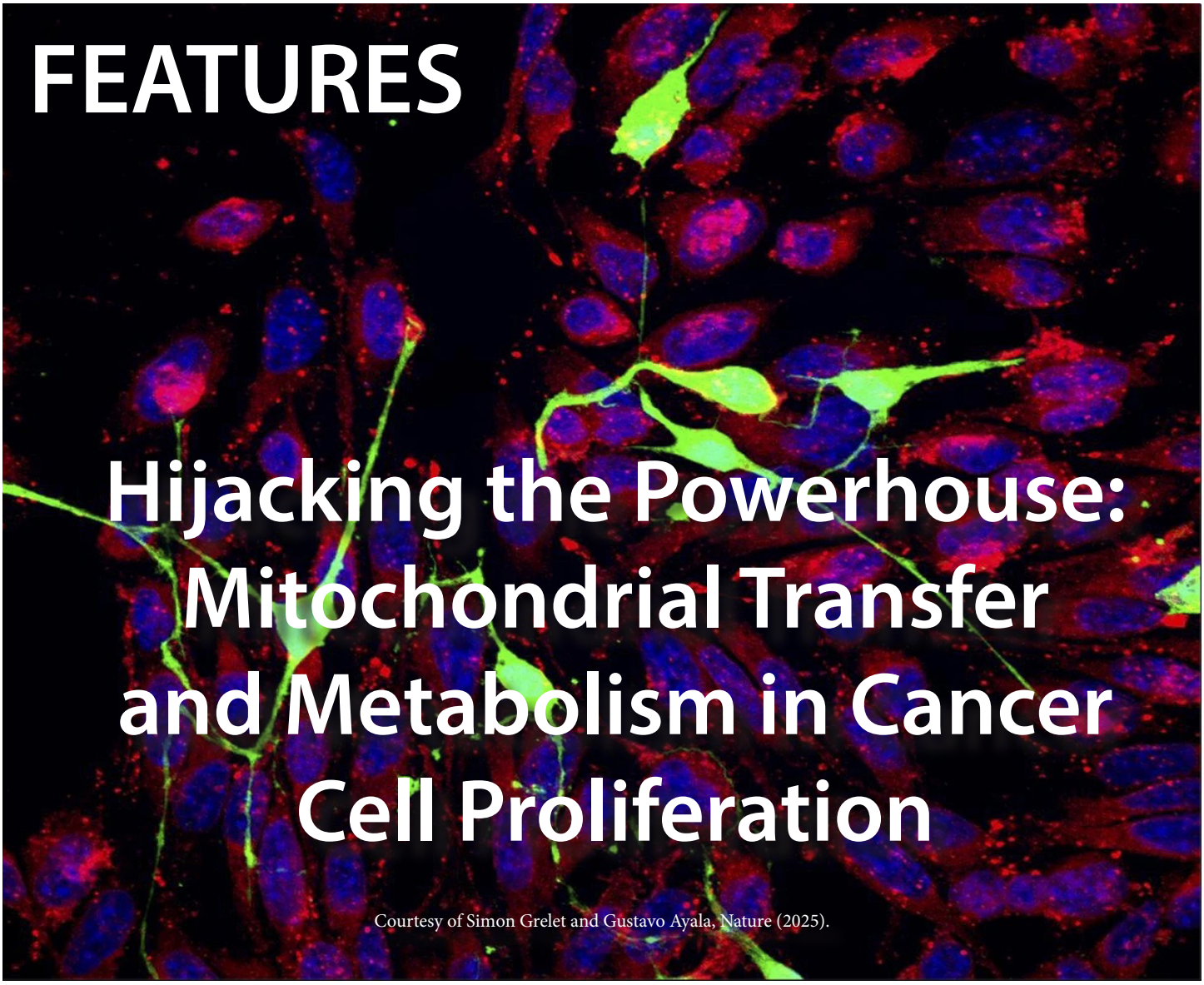

Hijacking the Powerhouse: Mitochondrial Transfer and Metabolism in Cancer Cell Proliferation

Courtesy of Simon Grelet and Gustavo Ayala, Nature (2025).

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Introduction

Mitochondria are cellular organelles that play a vital role in sustaining life: They influence the fate of stem cells, release signaling molecules, regulate cell death, and modulate energy metabolism through the production of adenosine triphosphate (ATP), which cells metabolize for energy, among other functions (Wang et al., 2024). Due to their utility in maintaining cellular health, mitochondria can drive disease when such processes are disrupted, as can be the case in cancer cells, where the breakdown of cell cycle regulators causes uncontrolled cell division (National Cancer Institute, 2021). As a result, mitochondria may be valuable therapeutic targets to increase cancer cells’ vulnerability to treatment (Mukherjee et al., 2023), given that cell division has a high energy cost, driving the need for increased ATP production in mitochondria. Cancer cells also face low oxygen, low blood supply, and acidic conditions in the tumor microenvironment (TME), the network of immune cells and blood vessels surrounding tumors, forcing cancer cells to reprogram their biology to survive (Fadaka et al., 2017). Uncovering how cancer cells achieve this reprogramming may generate more targeted therapies (Liu et al., 2023).

One way cancer cells compensate for increased energy demands is by taking mitochondria from healthy cells in a process called horizontal mitochondrial transfer (Artusa et al., 2025). Among a population of healthy cells, horizontal mitochondrial transfer can be essential in helping boost metabolism in energy-deficient cells to support their survival, as has been observed in certain neurons and heart muscle cells (Borcherding & Brestoff, 2023). Cancer cells can exploit this process to enhance their own survival. There are several mechanisms by

which cancer cells accomplish horizontal mitochondrial transfer, including through the formation of structures called tunneling nanotubes (TNTs), transport sacs called extracellular vesicles, and cell fusion (Marabitti et al., 2024).

Cancer cells can also promote their own survival using mitochondria through metabolic alterations. Reprogramming of the pathway used for energy generation has been observed in cancer cells alongside changes in other biochemical pathways (Wang et al., 2023). Therefore, whether by physically transferring mitochondria to cancer cells or reprogramming mitochondrial function in cancer cells, mitochondria can effectively be hijacked by cancer cells to sustain their proliferation. These mechanisms demonstrate the adaptability of cancer cells, though further study will be needed to exploit them therapeutically. Targeting mitochondria may help increase the effectiveness of existing drugs or prevent cancer cell survival.

Mitochondrial Transfer to Cancer Cells

Cancer cells must increase their supply of energy in order to meet the demands of rapid cell division and survive in the acidic, low-oxygen TME (Fadaka et al., 2017). The idea that mitochondrial transfer can help recipient cells meet their energy demands has been demonstrated experimentally. Growing cells with nonfunctional mitochondria with cells that had sufficient mitochondria restored respiration in mitochondria-deficient cells (Spees et al., 2006). Additionally, studies have shown that breast cancer cells can become significantly more resistant to chemotherapy upon receiving transferred mitochondria. These data suggest that mitochondria transfer may also help cancer cells become more resistant to treatment and aid the recovery of cancer cells with damaged mitochondria, allowing for their continued survival (Pasquier et al., 2013).

"Mitochondria can effectively be hijacked by cancer cells to sustain their proliferation."

Mitochondrial transfer from healthy cells to cancer cells has been observed in various cell types and cancers. In an experiment where lung cancer cells from mice were grown with immune cells that are normally responsible for eliminating tumors, researchers found that mitochondria from the immune cells moved into the cytoplasm of the cancer cells (Zhang et al., 2023). Cancer cells may also be dependent on mitochondria from nerves. When grown with neurons, cancer cells can acquire mitochondria from neurons, and experimentally cutting off the nerve supply in breast cancer cells can cause slowed tumor growth. Accordingly, in human prostate cancer, cells that are closer to a nerve supply have more mitochondria than those that are without a nerve supply (Hoover et al., 2025). Mitochondria can also be transferred in blood cancers; leukemia cells can transfer mitochondria from cells in the connective tissue and cells that line blood vessels (Moschoi et al., 2016; Pasquier et al., 2013). Mitochondrial transfer may be a significant survival strategy for cancer cells. Thus, preventing the process may weaken their survival and have therapeutic effects (Artusa et al., 2025).

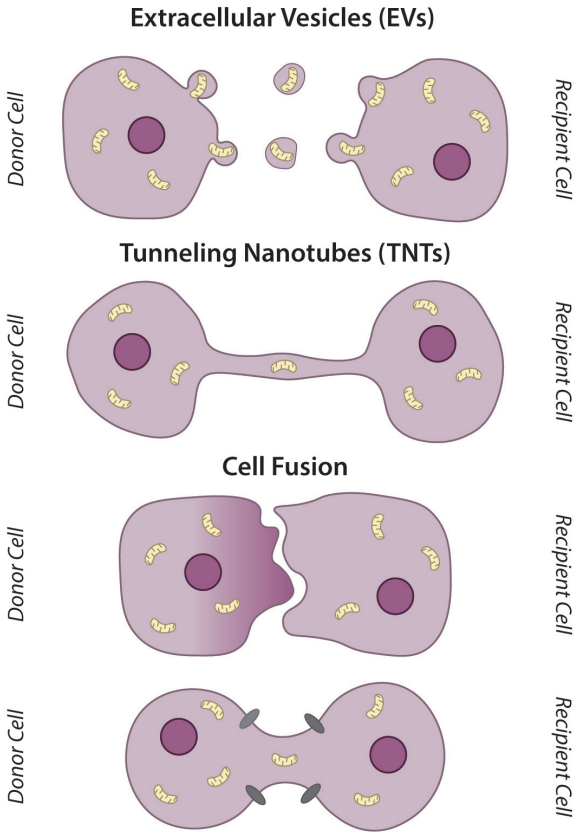

Figure 1. Routes of mitochondrial transfer. (Adapt to include TNTs, EVs, and cell fusion and display the physical elements) (Marabitti et al., 2024b).

Mechanisms of Acquisition

Cancer cells can acquire mitochondria from healthy cells in various ways. For instance, cancer cells are able to make distant, physical connections with nearby

cells by forming a bridge-like protrusion linking them with healthy cells. Through such protrusions, called tunneling nanotubes, organelles like mitochondria can be transferred (Pasquier et al., 2013). Another way cancer cells can obtain mitochondria is via extracellular vesicles, which package bioactive molecules and deliver them between cells. Through different signaling pathways, cancer cells can traffic mitochondria towards them (Marabitti et al., 2024). Finally, mitochondria are also able to move directly between cancer and healthy cells by cell fusion, where part of the membranes of the cells combine (Spees et al., 2006).

The TME promotes the mechanisms by which cancer cells acquire mitochondria from healthy cells. Stressors like low oxygen cause healthy cells to package their mitochondria, and in the low-oxygen TME, cancer cells may exploit this tendency to acquire mitochondria (Zhang et al., 2021). It has also been seen that ovarian cancer cells that are resistant to chemotherapy form more TNTs in low-oxygen environments like the TME. Thus, low oxygen appears to induce signaling of TNT-forming pathways (Desir et al., 2016). The TME also supports tumor proliferation by suppressing the mitochondrial function of immune cells responsible for attacking tumors, allowing tumor cells to survive and contribute to this immunosuppression by taking mitochondria from the immune cells (Scharping et al., 2016). Because cancer cells rely significantly on TNTS for mitochondrial transfer, devising effective ways to inhibit TNT formation could potentially advance cancer therapies. Several drugs that block structural elements necessary for the process have been identified (Marabitti et al., 2024a).

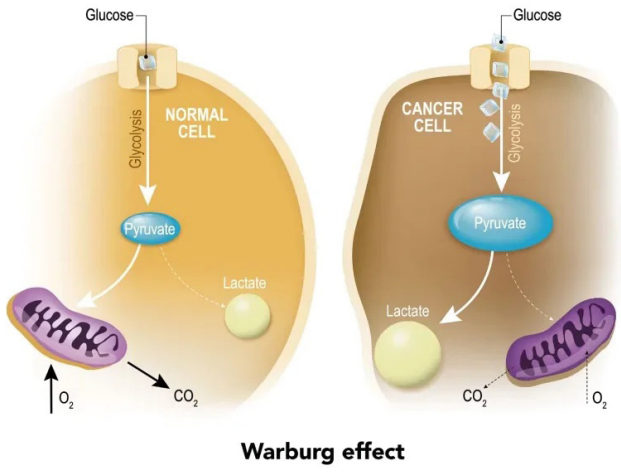

Figure 2. Warburg effect; pyruvate is a product of glycolysis that is normally put through mitochondrial respiration (Oncodaily, 2024).

Alterations in Mitochondrial Metabolism

Inside cancer cells, mitochondria are manipulated in a phenomenon known as the Warburg effect. German physiologist Otto Warburg observed in the 1920s that cancer cells used oxygen-independent glycolysis to generate ATP even in oxygen-sufficient conditions. This shift in metabolism appears to be counterproductive, as the ATP yield from glycolysis is less than that from oxygen-dependent respiration, which takes place in mitochondria (Zhang et al., 2023). Cancer cells tend to favor glycolysis for its faster production of ATP and because it generates intermediate building blocks necessary to support tumor growth. Mitochondria in cancer have been seen to use a different starting material in the energy-generating Krebs cycle, putting intermediates through pathways generating biomolecules needed for cancer proliferation (Wang et al., 2023).

This hallmark metabolic reprogramming in some cancers may separate cancer cells from healthy cells in treatment. By inhibiting altered metabolism in reprogrammed cells, more selective targets may be provided. Cancers like acute myeloid leukemia and glioma have mitochondria that harbor mutant enzymes of the Krebs cycle, which can regulate gene expression to promote cancer growth. These cancers are found in TMEs that are resistant to standard anti-cancer drugs, so targeting such mutations may improve disease outcome (Zhang et al., 2023). Cancer cells are also distinguished from healthy cells in their increased levels of antioxidants, which help them balance the increased stress from reactive molecules generated by processes in the mitochondria. In a mouse model of skin cancer, increasing antioxidants promoted the spread of cancer, demonstrating the need for a balance in reactive molecules and antioxidants. Cancer cells could be targeted by blocking pathways that contribute to antioxidant production, subjecting them to the stress placed upon them by increased biochemical activity in mitochondria (Vyas et al., 2016).

Conclusion

Although they hold great therapeutic potential, the exact biochemical mechanisms for mitochondrial manipulations remain unclear. What genes are involved in the formation of TNTs? What are the deeper molecular mechanisms enabling mitochondrial transfer? How does the Warburg effect influence other metabolic processes in cancer cells? Answering these questions may drive the development of new therapies and further the field of cancer biomedicine.

The hijacking of the cellular powerhouse, both by horizontal mitochondrial transfer and by metabolic manipulation, creates a distinct angle from which cancer proliferation can be studied. Understanding how cancer hijacks mitochondria will allow medicine to combat the numerous side effects brought about by traditional chemotherapy, a consequence of these drugs' inability to distinguish cancer cells from rapidly dividing healthy cells. Identifying areas where cancer cells differ from healthy cells, and what cancer cells rely on for survival, is vital in making therapies more selective and effective, minimizing side effects, and preserving the health of normal cells. The mitochondrial biology of cancer cells is among these hallmarks, and has the potential to advance treatment by reducing cancer's resistance or eradicating its energy supply altogether.

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