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Are Mitochondria the True Origin of Cancer? A Hypothesis-Driven Perspective

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Simple Summary

Cancer is commonly blamed on faulty genes in the cell's nucleus, but new research points to mitochondria—the cell's ancient energy regulators—as a possible root cause. These tiny organelles act almost like independent entities, with their own DNA and survival strategies that can sometimes clash with the cell's needs. This paper reviews the literature to suggest that when mitochondria become damaged, they can disrupt energy regulation, rewire the cell's metabolism, and even disable the immune system's ability to fight tumors. Seeing mitochondria as active players—not just passive power regulators—could change how we understand cancer's origins. If this idea holds, future treatments might focus on repairing mitochondrial defects or blocking their harmful effects, opening new paths for early detection and therapy.

Abstract

Conventional wisdom holds that nuclear oncogenes and tumor suppressors initiate malignant transformation. However, mounting research suggests that mitochondrial dysfunction—rooted in the unique evolutionary history and genetic autonomy of mitochondria—may serve as a more fundamental driver of oncogenesis. This paper proposes a "mitochondria-first" hypothesis of cancer, emphasizing the pivotal role of mitochondrial DNA (mtDNA) mutations, metabolic reprogramming, and immune evasion. By examining the evolutionary conflict between host and mitochondria, evaluating high mtDNA mutation rates, and highlighting the disruptive potential of mitochondrial transfer to immune cells, we outline robust mechanisms through which mitochondria could ignite cancer development. We also discuss emerging diagnostic and therapeutic approaches that target mitochondrial integrity, offering a potential paradigm shift in oncology.

Keywords: mitochondrial dysfunction; mtDNA mutations; cancer initiation; metabolic reprogramming; immune evasion; mitochondrial signaling; oncogenesis; tumor microenvironment; mitochondria-host conflict; mitochondrial medicine

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1. Introduction

For decades, cancer research has centered on the "nuclear-centric" view of oncogenesis, wherein mutations in nuclear genes such as RAS, MYC, and TP53 are believed to underlie tumor initiation and progression [1]. However, evidence increasingly implicates mitochondria—relics of ancient α-proteobacterial symbionts—in the earliest stages of tumorigenesis [2,3]. Mitochondria harbor their own circular DNA (mtDNA), maintain semi-autonomous replication, and play a pivotal role in bioenergetics, redox balance, and

apoptosis [4,5]. These features render them capable of bypassing or co-opting the cell's regulatory networks when mutations arise [6].

This paper presents the hypothesis that mitochondrial dysfunction, driven by the rapid accumulation of mtDNA mutations [7] and the organelle's capacity for metabolic manipulation [8], represents the prime catalyst for malignant transformation. We examine how the evolutionary tug-of-war between mtDNA and nuclear genes may foster tumorigenic processes [5], how these mutations perpetuate clonal expansion within neoplastic cells [9], and how mitochondria, through direct transfer to lymphocytes, sabotage antitumor immunity [10]. A deeper comprehension of this mitochondria-centered model could reshape cancer diagnostics and therapies by shifting the focus toward preserving or restoring mitochondrial health.

Although the idea that mitochondrial dysfunction plays a central role in cancer is well-established, this paper presents a hypothesis-driven synthesis that brings together emerging lines of evidence—ranging from metabolic reprogramming to immune evasion—that collectively reinforce the view of mitochondria as a primary driver of malignant transformation. The phrase "mitochondria-first" is not intended to assert originality but rather to provide a clear framework for interpreting a paradigm that has been shaped by decades of research. The novelty of this work lies not in claiming priority but in offering a cohesive and explicitly hypothesis-based interpretation that positions mitochondrial dysfunction as an initiating force in oncogenesis rather than a downstream consequence. Notably, this perspective incorporates evolutionary insights into host–mitochondrion dynamics, framing cancer as a reemergence of conflict within this ancient symbiotic relationship.

2. Mitochondrial Evolution and Autonomy

2.1. Endosymbiotic Legacy and Genomic Conflict

Mitochondria originated from α-proteobacteria engulfed by early proto-eukaryotes around 1.5 billion years ago [2]. Although most bacterial genes transferred to the nuclear genome, mitochondria retained a specialized subset for oxidative phosphorylation [4]. This arrangement preserves an element of genomic conflict: mitochondria replicate independently under partial nuclear control but can accumulate mutations favoring their own replication rather than the host's welfare [5]. Moreover, fission–fusion dynamics enable damaged mitochondria to mingle their contents with healthier counterparts, potentially diluting defects or propagating deleterious mtDNA [6].

2.2. Selfish mtDNA and Clonal Expansion

Natural selection acts on mtDNA within the cellular environment [7,9]. Mutations that grant a replicative or survival advantage—such as evasion of mitophagy—may expand within a population of mitochondria and skew the cell's metabolic and signaling networks [11,12]. In cancer cells, a high load of mutated mtDNA can surpass a threshold at which the oxidative metabolism is compromised, driving cells to adopt glycolysis and other tumorigenic pathways [13]. This evolutionary dynamic underscores how "selfish" mtDNA variants could initiate or exacerbate malignant transformation.

2.3. Mitochondrial Retrograde Signaling and Metastatic Reprogramming

Recent comprehensive reviews have reinforced the centrality of mitochondrial dysfunction in the metabolic reprogramming and progression of cancer. There is compelling evidence that decreases in mtDNA copy numbers and somatic mutations in mtDNA—especially those affecting Complex I subunits—are prevalent across many tumor types and correlate with poor prognosis and chemoresistance. A synthesis of experimental studies [14] shows that depletion or impairment of the mitochondrial respiratory chain fosters

a shift toward glycolysis, enhances reactive oxygen species (ROS) signaling, and increases tumor invasiveness and drug resistance, all without reliance on nuclear driver mutations. Moreover, retrograde signaling serves as a critical conduit through which mitochondrial stress is conveyed to the nucleus, leading to altered gene expression that supports oncogenic reprogramming via ROS, calcium flux, and the accumulation of oncometabolites such as succinate and fumarate [14]. These insights lend mechanistic support to the hypothesis that mitochondria, through both genomic and metabolic alterations, can act as a primary instigator of malignant transformation.

2.4. Legacy Foundations and the Fusion Hybrid Model of Metastasis

The idea that mitochondrial dysfunction can initiate carcinogenesis builds upon a body of research developed over several decades. Studies using cytoplasmic–nuclear transfer models have demonstrated that normal mitochondria can suppress tumorigenic behavior in cancer-derived nuclei, whereas defective mitochondria can induce malignancy even in the presence of genetically intact nuclear DNA [15]. These findings have led to a reevaluation of the dominant nuclear-centric model and support the notion that cancer may originate primarily from the cytoplasm, particularly the mitochondria. One key extension of this hypothesis is the fusion hybrid model of metastasis, which posits that the hallmark of metastatic capability arises not solely from nuclear mutations but from mitochondrial dysfunction in myeloid-derived cells or their fusion hybrids. The hallmark of metastasis may arise from impaired respiration in cells of myeloid origin or their fusion hybrids, which inherently possess the capacity to survive in circulation and disseminate throughout the body [16,17]. These hybrid cells, by inheriting the migratory and immune-evasive characteristics of myeloid lineages and the proliferative potential of epithelial cells, may exploit mitochondrial dysfunction as a catalyst for systemic spread. Rather than claiming conceptual priority, the present work seeks to unify these evolutionary and experimental threads into a coherent mitochondria-first framework, emphasizing mitochondrial damage not merely as a consequence but as a possible origin of both tumorigenesis and metastatic progression.

2.5. Evolutionary Conflict Within an Ancient Symbiosis

The mitochondria-first hypothesis acquires greater coherence when situated within the evolutionary history of eukaryotic cells. Mitochondria originated through a singular endosymbiotic event in which an ancestral α-proteobacterium was engulfed by a proto-eukaryotic host. Over evolutionary time, this relationship stabilized into a cooperative arrangement, but not without cost. The mitochondrion retained a remnant genome and partial replication autonomy, creating the potential for conflict between mitochondrial and nuclear interests. These interests are normally aligned, but under cellular stress or mutational pressure, selection can act at the level of mtDNA, favoring variants that prioritize mitochondrial persistence—even at the expense of host cellular integrity. Cancer may represent a pathological reactivation of this latent evolutionary tension: a state in which the mitochondrial genome escapes host control, initiating metabolic reprogramming, immune evasion, and clonal expansion. This internal genomic competition reflects a broader evolutionary dynamic in which cooperation and conflict are intertwined even within a single organism's cells [18].

2.6. Mitophagy as a Driver of Cancer Cell Survival and Adaptability

Recent evidence further emphasizes that cancer cells exploit mitophagy—a selective form of autophagy that removes dysfunctional mitochondria—to maintain metabolic plasticity and resist stress-induced cell death [19]. During mitochondrial stress, mitophagy acts as a quality control mechanism, but its dysregulation allows tumors to persist in hostile

microenvironments, including hypoxia and nutrient deprivation. Mitophagic signaling can also stabilize oncogenes, such as MYC and KRAS, while impairing apoptotic pathways through interactions with BCL2 family proteins. In cancer stem cells, mitophagy enhances survival, stemness, and therapy resistance. These insights suggest that mitochondrial dysfunction is not merely a consequence of tumor progression but a driving force in oncogenesis and resistance mechanisms, reinforcing the centrality of mitochondrial health in cancer biology.

3. Evidence for a Mitochondria-First Hypothesis

3.1. High Mutation Rate and ROS Feedback Loops

Mitochondrial DNA accumulates mutations at a rate significantly higher than nuclear DNA, which is attributable to limited repair systems and close proximity to the ROS produced during oxidative phosphorylation [7,20]. Elevated ROS levels not only damage mtDNA but can also diffuse into the nucleus, fostering secondary mutations in oncogenes and tumor suppressors [21]. This creates a cyclical interplay in which defective mitochondria generate more ROS, fueling broader genomic instability [22].

3.2. Metabolic Reprogramming as a Mitochondrial Survival Strategy

The shift to aerobic glycolysis in cancer cells—often referred to as the Warburg effect—can be viewed not merely as an adaptation to hypoxia but as a direct outcome of mitochondrial dysfunction [8]. When core components of the electron transport chain are compromised, cells become increasingly reliant on glycolysis for ATP production [13]. Additionally, certain "oncometabolites," such as succinate and fumarate, accumulate from dysfunctional Krebs cycle activity, stabilizing hypoxia-inducible factors and promoting tumorigenesis [22].

3.3. Immune Evasion via Mitochondrial Transfer

Tumor cells can transfer defective mitochondria to tumor-infiltrating lymphocytes (TILs) through structures like tunneling nanotubes or extracellular vesicles, impairing T cell mitochondrial dynamics, reducing oxidative capacity, and promoting metabolic exhaustion [10,23,24]. This sabotage of T cell function leads to diminished antitumor responses and contributes to immune evasion. Moreover, mitochondrial metabolites such as succinate and ROS further modulate T cell polarization, fostering a tolerogenic tumor microenvironment. These findings reinforce the mitochondria-first hypothesis, in which mitochondrial dysfunction not only reshapes the intracellular metabolism but also propagates intercellular immune suppression through mtDNA-driven mechanisms [25].

4. Mechanistic Insights

4.1. Mitophagy Evasion and USP30 Overexpression

Under physiological conditions, depolarized mitochondria are tagged for degradation via the PINK1-Parkin pathway. However, tumors often display elevated levels of the deubiquitinase USP30, which removes Parkin-mediated ubiquitin tags and prevents the destruction of damaged mitochondria [12,26]. Stabilizing these dysfunctional organelles perpetuates the pro-tumor metabolic phenotype and potentially drives further mtDNA mutation [26]. Ongoing research into USP30 inhibitors suggests that restoring mitophagy could limit tumor progression [27].

4.2. Retrograde Signaling and Nuclear Reprogramming

Mitochondria–nuclear "cross-talk" occurs through retrograde signaling, wherein mitochondrial distress signals recalibrate the nuclear gene expression [28]. Calcium and ROS

flux can activate transcription factors such as NF-κB and AP-1, accelerating cell proliferation and survival pathways [20]. Moreover, cytosolic leakage of mtDNA can trigger inflammatory cascades (e.g., via cGAS-STING) that alter the tumor microenvironment [29]. These feedback loops allow mitochondria to exert far-reaching control over cell fate decisions [3].

4.3. Mitochondrial Heterogeneity and Selective Pressure

An emerging dimension in the mitochondria–cancer interface is the observation that mitochondrial phenotypes differ significantly by tissue context. A recent large-scale mitochondrial proteomics study created a high-resolution spatial atlas of mitochondrial specialization across human brain regions. Although focused on neurobiology, the findings underscore a fundamental principle: mitochondrial structure and oxidative capacity are tailored to cellular demands and can vary even within a single tissue. Applying this principle to cancer suggests that tumor-specific mitochondrial phenotypes—shaped by both mtDNA content and nuclear–mitochondrial co-regulation—may confer selective advantages under metabolic or immune pressure. Mitochondria that evade degradation and support rapid proliferation or immune evasion would be positively selected, echoing natural selection dynamics within the tumor microenvironment [30].

5. Clinical and Therapeutic Implications

5.1. Diagnostic Biomarkers

The detection of circulating mtDNA in plasma or serum shows promise as a biomarker for early-stage cancers, correlating with disease burden and progression [31]. Furthermore, imaging modalities such as ^18F-fluorodeoxyglucose PET highlight regions of elevated glucose uptake—a hallmark of cells that have undergone metabolic shifts, potentially due to mitochondrial damage [32].

Supporting this view, a pan-cancer analysis demonstrated that mtDNA content correlates with tumor metabolic phenotype and aggressiveness. Tumors with low mtDNA copy numbers were more glycolytic and exhibited worse patient outcomes, whereas tumors retaining higher mtDNA levels preserved oxidative phosphorylation and were associated with slower progression. This data supports our core hypothesis: mtDNA mutations and depletion may act as early switches that trigger metabolic remodeling and influence the trajectory of malignancy. Importantly, this study also raises the possibility that mtDNA content could serve as a predictive biomarker for both prognosis and response to therapies targeting cancer metabolism [33].

5.2. Mitochondrial Remodeling and Neuro-Tumoral Signaling in Cancer Progression

Beyond the intracellular consequences of mitochondrial dysfunction, accumulating evidence showcases how tumors exploit systemic networks—metabolic, immunological, and even neuronal—to sustain their progressions. Recent studies have uncovered a surprising dimension to tumor behavior: the ability to form functional synapse-like connections with neurons, hijacking glutamatergic signaling to stimulate their own growth. Glioma cells are capable of receiving excitatory input from neurons via specialized neuron-to-glioma synapses, which amplify intracellular calcium signaling and drive tumor proliferation [34]. Moreover, neuronal activity promotes glioma growth through the release of neuroligin-3, highlighting a bidirectional neuro-tumor communication that actively shapes disease progression [35]. These findings emphasize that cancer progression is not solely a function of autonomous cell mutation but also of strategic co-option of host signaling systems—likely initiated or facilitated by early mitochondrial reprogramming. By altering energy metabolism and redox states, mitochondria may set the stage for such adaptive cross-talk, further supporting their role as central players in oncogenesis.

5.3. Mitochondria-Targeted Therapies

Efforts to restore or maintain mitochondrial function in cancer cells and immune cells are gaining momentum. Antioxidants and redox regulators such as MitoQ localize to mitochondria to neutralize ROS, potentially slowing cancer progression by preserving mitochondrial integrity [36]. The modulation of mitochondrial dynamics through small-molecule inhibitors of the dynamin-related protein DRP1 (e.g., Mdivi-1) can disrupt excessive fission, promoting the selective removal of severely damaged mitochondria and limiting cancer cell adaptability [27]. Exogenous mitochondrial transfer from mesenchymal stem cells has rejuvenated defective T cell populations in preclinical studies, bolstering anti-tumor immunity [37]. Emerging techniques for the direct modification of mtDNA, such as mitochondria-targeted TALENs or CRISPR-like systems, may eventually correct pathogenic mtDNA variants that initiate malignancy [38].

In addition to advanced gene-editing strategies, a range of affordable, low-risk interventions may leverage mitochondrial vulnerabilities in cancer cells. Fasting and dietary glucose restriction, for instance, exploit the glycolytic dependency of tumor cells by reducing available glucose—a critical nutrient for cancer energy metabolism [39,40]. Alkalizing strategies that elevate the pH of the tumor microenvironment (TME) can hinder tumor proliferation, as acidic conditions favor oncogenesis [41,42]. Moreover, mitochondrial respiratory Complex IV may be stimulated through low-level red-light (photobiomodulation) therapy [43,44], while compounds like methylene blue, known to accumulate in mitochondrially compromised cells, can enhance oxidative phosphorylation and reduce oxidative stress [45,46]. These low-cost interventions—dietary, photonic, or pharmacologic—may potentiate conventional treatments and represent promising complementary strategies to restore mitochondrial function and suppress tumor progression.

6. Conclusions and Future Directions

The mitochondria-first hypothesis posits that these dynamic, semi-autonomous organelles lie at the heart of cancer initiation [3,7]. By linking mtDNA mutations, metabolic reprogramming, and immune system disruption, this framework challenges traditional views that emphasize nuclear mutations as the sole drivers of oncogenesis [1]. Future studies should focus on mapping the temporal relationship between mtDNA variants and nuclear DNA alterations in early preneoplastic lesions [9], exploring gene-editing tools for mtDNA repair [38], and conducting clinical trials of agents that target mitochondrial quality-control pathways [27].

If validated, the mitochondria-first model may revolutionize oncology. Therapies aimed at repairing, replacing, or removing dysfunctional mitochondria could become frontline interventions, while mtDNA-centric diagnostics could enable earlier and more precise cancer detection [30]. Ultimately, the interplay of host and organellar genomes, once a foundational step in eukaryotic evolution, may hold the key to understanding—and defeating—human malignancies.

To highlight the conceptual distinctions between the classical nuclear-centric model and the mitochondria-first hypothesis proposed here, Table 1 provides a comparative summary of the key features across both frameworks. This contrast underscores the unique mechanistic, evolutionary, and therapeutic implications of centering mitochondrial dysfunction in models of cancer initiation.

Table 1. Comparison of the nuclear-centric and mitochondria-first models of cancer initiation.

Feature	*Nuclear-Centric Model*	*Mitochondria-First Hypothesis*
Primary Driver of Oncogenesis	Nuclear DNA mutations (e.g., TP53, KRAS)	mtDNA mutations and mitochondrial dysfunction
Role of Mitochondria	Downstream metabolic reprogramming	Initiating role through metabolic and redox disruption
Mutation Rate	Lower (protected by histones and repair machinery)	Higher (lack of histones, limited repair mechanisms)
ROS Impact	Secondary effect of oncogenic signaling	Primary driver of genomic instability and signaling
Immune Modulation	Tumor antigens drive immune escape	mtDNA transfer alters T cell metabolism and function
Predictive Biomarkers	PD-L1, TMB, driver mutations	mtDNA copy number, metabolic phenotype, mitophagy status
Therapeutic Targets	Checkpoints, kinases, oncogenes	Mitophagy pathways (e.g., USP30), mitochondrial transfer
Evolutionary Perspective	Clonal selection of nuclear mutations	Selection of "selfish" mitochondria under stress

Note: This table contrasts the traditional nuclear-driven model of cancer with the emerging mitochondria-first hypothesis, emphasizing mechanistic and therapeutic distinctions that may have diagnostic or clinical relevance.

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References

1. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The Next Generation. *Cell* **2011**, *144*, 646–674. [CrossRef] [PubMed]
2. Gray, M.W. Mitochondrial Evolution. *Science* **1999**, *283*, 1476–1481. [CrossRef] [PubMed]
3. Wallace, D.C. Mitochondria and Cancer. *Nat. Rev. Cancer* **2012**, *12*, 685–698. [CrossRef] [PubMed]
4. Gustafsson, C.M.; Falkenberg, M.; Larsson, N.G. Maintenance and Expression of Mammalian Mitochondrial DNA. *Annu. Rev. Biochem.* **2016**, *85*, 133–160. [CrossRef]
5. Alexeyev, M.; Shokolenko, I.; Wilson, G.; LeDoux, S. The Maintenance of Mitochondrial DNA Integrity—Critical Analysis and Update. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a012641. [CrossRef]
6. Grandemange, S.; Herzig, S.; Martinou, J.C. Mitochondrial Dynamics and Cancer. *Semin. Cancer Biol.* **2009**, *19*, 50–56. [CrossRef]
7. Kopinski, P.K.; Singh, L.N.; Zhang, S.; Lott, M.T.; Wallace, D.C. Mitochondrial DNA Variation and Cancer. *Nat. Rev. Cancer* **2021**, *21*, 431–445. [CrossRef]
8. Martínez-Reyes, I.; Chandel, N.S. Cancer Metabolism: Looking Forward. *Nat. Rev. Cancer* **2021**, *21*, 669–680. [CrossRef]
9. Ju, Y.S.; Alexandrov, L.B.; Gerstung, M.; Martincorena, I.; Nik-Zainal, S.; Ramakrishna, M.; Davies, H.R.; Papaemmanuil, E.; Gundem, G.; Shlien, A.; et al. Origins and Functional Consequences of Somatic Mitochondrial DNA Mutations in Human Cancer. *eLife* **2014**, *3*, e02935. [CrossRef]
10. Ikeda, H.; Kawase, K.; Nishi, T.; Watanabe, T.; Takenaga, K.; Inozume, T.; Ishino, T.; Aki, S.; Lin, J.; Kawashima, S.; et al. Immune Evasion through Mitochondrial Transfer in the Tumour Microenvironment. *Nature* **2025**, *638*, 225–236. [CrossRef]
11. Mishra, P.; Chan, D.C. Mitochondrial Dynamics and Inheritance during Cell Division, Development and Disease. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 634–646. [CrossRef] [PubMed]
12. Bingol, B.; Tea, J.S.; Phu, L.; Reichelt, M.; Bakalarski, C.E.; Song, Q.; Foreman, O.; Kirkpatrick, D.S.; Sheng, M. The Mitochondrial Deubiquitinase USP30 Opposes Parkin-Mediated Mitophagy. *Nature* **2014**, *510*, 370–375. [CrossRef] [PubMed]
13. Vyas, S.; Haigis, M.C. Mitochondria and Cancer. *Cell* **2016**, *166*, 555–566. [CrossRef] [PubMed]
14. Hsu, C.C.; Tseng, L.M.; Lee, H.C. Role of Mitochondria in Cancer Therapy—A Potential Target for Chemotherapy. *Exp. Biol. Med.* **2016**, *241*, 1281–1291. [CrossRef]
15. Seyfried, T.N. Cancer as a mitochondrial metabolic disease. *Front. Cell Dev. Biol.* **2015**, *3*, 43. [CrossRef]

16. Huysentruyt, L.C.; Seyfried, T.N. Perspectives on the mesenchymal origin of metastatic cancer. *Cancer Metastasis Rev.* **2010**, *29*, 695–707. [CrossRef]
17. Seyfried, T.N.; Huysentruyt, L.C. On the origin of cancer metastasis. *Crit. Rev. Oncog.* **2013**, *18*, 43–73. [CrossRef]
18. Da Silva, S. The Extended vs. The Modern Synthesis of Evolutionary Theory. *Philosophies* **2025**, *10*, 58. [CrossRef]
19. Behera, B.P.; Mishra, S.R.; Patra, S.; Mahapatra, K.K.; Bhol, C.S.; Panigrahi, D.P.P.; Praharaj, P.P.; Klionsky, D.J.; Bhutia, S.K. Molecular Regulation of Mitophagy Signaling in Tumor Microenvironment and Its Targeting for Cancer Therapy. *Cytokine Growth Factor Rev.* **2025**, *73*, 102207. [CrossRef]
20. Sabharwal, S.S.; Schumacker, P.T. Mitochondrial ROS in Cancer: Initiators, Amplifiers or an Achilles' Heel? *Nat. Rev. Cancer* **2014**, *14*, 709–721. [CrossRef]
21. Weinberg, F.; Chandel, N.S. Mitochondrial Metabolism and ROS Generation Are Essential for Kras-Mediated Tumorigenicity. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 8788–8793. [CrossRef] [PubMed]
22. Sullivan, L.B.; Chandel, N.S. Mitochondrial Reactive Oxygen Species and Cancer. *Cancer Metab.* **2014**, *2*, 17. [CrossRef] [PubMed]
23. Soto-Heredero, G.; Desdín-Micó, G.; Mittelbrunn, M. Mitochondrial Dysfunction Defines T Cell Exhaustion. *Cell Metab.* **2021**, *33*, 470–472. [CrossRef] [PubMed]
24. Desdín-Micó, G.; Soto-Heredero, G.; Aranda, J.F.; Oller, J.; Carrasco, E.; Gabandé-Rodríguez, E.; Blanco, E.M.; Alfranca, A.; Cussó, L.; Desco, M.; et al. T Cells with Dysfunctional Mitochondria Induce Multimorbidity and Premature Senescence. *Science* **2020**, *368*, 1371–1376. [CrossRef]
25. Miller, B.C.; Sen, D.R.; Al Abosy, R.; Bi, K.; Virkud, Y.V.; LaFleur, M.W.; Yates, K.B.; Lako, A.; Felt, K.; Naik, G.S.; et al. Subsets of Exhausted $CD8^+$ T Cells Differentially Mediate Tumor Control and Respond to Checkpoint Blockade. *Nat. Immunol.* **2019**, *20*, 326–336. [CrossRef]
26. Rusilowicz-Jones, E.V.; Jardine, J.; Kallinos, A.; Pinto-Fernandez, A.; Guenther, F.; Giurrandino, M.; Barone, F.G.; McCarron, K.; Burke, C.J.; Murad, A.; et al. USP30 Sets a Trigger Threshold for PINK1-PARKIN Amplification of Mitochondrial Ubiquitylation. *Life Sci. Alliance* **2020**, *3*, e202000768. [CrossRef]
27. Rodrigues, T.; Ferraz, L.S. Therapeutic Potential of Targeting Mitochondrial Dynamics in Cancer. *Biochem. Pharmacol.* **2020**, *182*, 114282. [CrossRef]
28. Cárdenas, C.; Miller, R.A.; Smith, I.; Bui, T.; Molgó, J.; Müller, M.; Vais, H.; Cheung, K.-H.; Yang, J.; Parker, I.; et al. Essential Regulation of Cell Bioenergetics by Constitutive InsP3 Receptor Ca^{2+} Transfer to Mitochondria. *Cell* **2010**, *142*, 270–283. [CrossRef]
29. Lam, W.Y.; Becker, A.M.; Kennerly, K.M.; Wong, R.; Curtis, J.D.; Llufrio, E.M.; McCommis, K.S.; Fahrmann, J.; Pizzato, H.A.; Nunley, R.M.; et al. Mitochondrial Pyruvate Import Promotes Long-Term Survival of Antibody-Secreting Plasma Cells. *Immunity* **2016**, *45*, 60–73. [CrossRef]
30. Mosharov, E.V.; Rosenberg, A.M.; Monzel, A.S.; Osto, C.A.; Stiles, L.; Rosoklija, G.B.; Dwork, A.J.; Bindra, S.; Junker, A.; Zhang, Y.; et al. A Human Brain Map of Mitochondrial Respiratory Capacity and Diversity. *Nature* **2025**, *641*, 749–758. [CrossRef]
31. Peng, F.; Wang, S.; Feng, Z.; Zhou, K.; Zhang, H.; Guo, X.; Xing, J.; Liu, Y. Circulating Cell-Free mtDNA as a New Biomarker for Cancer Detection and Management. *Cancer Biol. Med.* **2023**, *21*, 105–110. [CrossRef] [PubMed]
32. Pavlova, N.N.; Thompson, C.B. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab.* **2016**, *23*, 27–47. [CrossRef] [PubMed]
33. Reznik, E.; Miller, M.L.; Şenbabaoğlu, Y.; Riaz, N.; Sarungbam, J.; Tickoo, S.K.; Al-Ahmadie, H.A.; Lee, W.; Seshan, V.E.; Hakimi, A.A.; et al. Mitochondrial DNA Copy Number Variation Across Human Cancers. *eLife* **2016**, *5*, e10769. [CrossRef]
34. Venkataramani, V.; Tanev, D.I.; Strahle, C.; Studier-Fischer, A.; Fankhauser, L.; Kessler, T.; Körber, C.; Kardorff, M.; Ratliff, M.; Xie, R.; et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature* **2019**, *573*, 532–538. [CrossRef] [PubMed]
35. Venkatesh, H.S.; Johung, T.B.; Caretti, V.; Noll, A.; Tang, Y.; Nagaraja, S.; Gibson, E.M.; Mount, C.W.; Polepalli, J.; Mitra, S.S.; et al. Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell* **2015**, *161*, 803–816. [CrossRef]
36. Jin, H.; Kanthasamy, A.; Ghosh, A.; Anantharam, V.; Kalyanaraman, B.; Kanthasamy, A.G. Mitochondria-Targeted Antioxidants for Treatment of Parkinson's Disease: Preclinical and Clinical Outcomes. *Biochim. Biophys. Acta* **2014**, *1842*, 1282–1294. [CrossRef]
37. Keshtkar, S.; Azarpira, N.; Ghahremani, M.H. Mesenchymal Stem Cell-Derived Extracellular Vesicles: Novel Frontiers in Regenerative Medicine. *Stem Cell Res. Ther.* **2018**, *9*, 63. [CrossRef]
38. Lim, K. Mitochondrial Genome Editing: Strategies, Challenges, and Applications. *BMB Rep.* **2024**, *57*, 19–29. [CrossRef]
39. Banu, I.I.; Waseem, M.; Banerjee, S. Understanding the Clinical Link between Fasting and Response to Cancer Therapy. *Curr. Pharmacol. Rep.* **2022**, *8*, 290–299. [CrossRef]
40. Ibrahim, E.M.; Al-Foheidi, M.H.; Al-Mansour, M.M. Energy and Caloric Restriction, and Fasting and Cancer: A Narrative Review. *Support Care Cancer* **2020**, *28*, 4017–4030. [CrossRef]
41. Hamaguchi, R.; Uemoto, S.; Wada, H. Editorial: The Impact of Alkalizing the Acidic Tumor Microenvironment to Improve Efficacy of Cancer Treatment. *Front. Oncol.* **2023**, *13*, 1223025. [CrossRef] [PubMed]
42. Kachi, S.; Hamaguchi, R.; Narui, R.; Morikawa, H.; Okamoto, T.; Wada, H. Cancer Can Be Suppressed by Alkalizing the Tumor Microenvironment: The Effectiveness of "Alkalization Therapy" in Cancer Treatment. *Oncologie* **2025**, *27*, 393–401. [CrossRef]

43. Hamblin, M.R.; Nelson, S.T.; Strahan, J.R. Photobiomodulation and Cancer: What Is the Truth? Photomed. *Laser Surg.* **2018**, *36*, 241–245. [CrossRef]
44. Da Silva, T.G.; Rodrigues, J.A.; Siqueira, P.B.; Soares, M.S.; Mencalha, A.L.; Fonseca, A.S. Effects of photobiomodulation by low-power lasers and LEDs on the viability, migration, and invasion of breast cancer cells. *Lasers Med. Sci.* **2023**, *38*, 191. [CrossRef]
45. Wainwright, M.; Crossley, K.B. Methylene Blue—A Therapeutic Dye for All Seasons? *J. Chemother.* **2002**, *14*, 431–443. [CrossRef]
46. Taldaev, A.; Terekhov, R.; Nikitin, I.; Melnik, E.; Kuzina, V.; Klochko, M.; Reshetov, I.; Shiryaev, A.; Loschenov, V.; Ramenskaya, G. Methylene Blue in Anticancer Photodynamic Therapy: Systematic Review of Preclinical Studies. *Front. Pharmacol.* **2023**, *14*, 1264961. [CrossRef]