Review

Mitochondrial Hijacking and MicroRNA Crosstalk: Cancer Stem Cell-Mediated Immune Evasion and Metabolic Plasticity in the Tumor Microenvironment

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Mitochondrial Hijacking and MicroRNA Crosstalk: Cancer Stem Cell-Mediated Immune Evasion and Metabolic Plasticity in the Tumor Microenvironment

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Abstract

The tumor microenvironment (TME) is a highly adaptive and heterogeneous niche in which cancer stem cells (CSCs) promote immune evasion, metastatic dissemination, and therapy resistance. Among the mechanisms that support this phenotype, mitochondrial hijacking has emerged as a central strategy through which CSCs reprogram immune and stromal cells to favor tumor progression. This review synthesizes current evidence on how CSCs exploit mitochondrial transfer, particularly via tunneling nanotubes (TNTs) and extracellular vesicles (EVs), to impair antitumor immunity and remodel the metastatic niche. CSCs display marked metabolic plasticity, shifting between glycolysis and oxidative phosphorylation (OXPHOS) in response to environmental stress. They exploit this adaptability by transferring mitochondria and mitochondrial components to recipient cells, including tumor-associated macrophages (TAMs) and cytotoxic T cells, thereby disrupting ATP production, increasing oxidative stress, and skewing immune polarization. This mitochondrial hijacking contributes to an immunosuppressive milieu, stabilizes HIF-1α, and enhances PD-L1 expression, ultimately weakening T-cell activity and reinforcing CSC survival. EVs add another layer of regulation by transporting bioactive cargo, including oncogenic microRNAs (miRNAs) and mitomiRs such as miR-21, miR-210, and miR-34a. These molecules modulate mitochondrial gene expression, reshape immune signaling, and reinforce CSC phenotypes through autocrine and paracrine loops. Single-cell and spatial transcriptomic approaches have further revealed metabolic heterogeneity within CSC–immune synapses, identifying "metabolic hotspots" associated with profound immune dysfunction. Therapeutic strategies targeting OXPHOS, EV biogenesis, and miRNA activity are therefore being explored. In parallel, mitochondria-associated proteins such as TSGA10 may also contribute to CSC-driven immunometabolism regulation and deserve further investigation. Targeting downstream heterogeneity is like cutting the branches of a weed. Targeting the upstream mechanisms of mitochondrial hijacking and miRNA crosstalk aims to destroy the root (CSC plasticity) that generates the heterogeneity and drives therapy resistance in the first place. This review highlights mitochondrial hijacking and miRNA-mediated reprogramming as central determinants of CSC-driven immune escape and proposes a framework for precision interventions targeting CSC–immune interactions in metastatic cancer.

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1. Introduction

1.1. CSCs in the Tumor Microenvironment

Cancer stem cells (CSCs; also known as tumor-initiating stem cells) are a subpopulation of undifferentiated, highly plastic, self-renewing cells within the tumor bulk that drive tumor initiation, progression, metastasis, relapse, and resistance to therapy [1]. CSCs use the molecular tools to actively maintain the cellular heterogeneity and state-switching (plasticity) and have been identified across a wide range of malignancies, including breast cancer, colon cancer, glioblastoma, ovarian cancer, melanoma, pancreatic cancer, and liver cancer. Relative to non-CSCs, they often exhibit increased mitochondrial mass, elevated mitochondrial membrane potential ($\Delta\psi m$), and higher basal reactive oxygen species (ROS) levels. One of their most defining hallmarks is adaptive plasticity: the ability to rewire survival pathways in response to environmental stress, thereby maintaining persistence in conditions that eliminate more differentiated tumor cells. This plasticity helps CSCs establish a pro-tumor niche by resisting therapy and suppressing immunity [2]. Recent studies further emphasize that CSCs are critical mediators of immune escape and are highly treatment-resistant [3,4]. In this context, mitochondrial crosstalk is emerging as an important mechanism of CSC-mediated immunosuppression.

CSCs may arise from transformed normal stem or progenitor cells, or from dedifferentiated mature cancer cells [5]. In dynamic models of tumor evolution, non-CSCs can acquire stem-like features in response to microenvironmental cues such as hypoxia and inflammatory cytokines, as well as signaling pathways including Wnt/β-catenin, Notch, and Hedgehog. This plasticity is supported by epithelial–mesenchymal transition (EMT) programmes involving factors such as TGF-β and ZEB1 and may be further enhanced by mechanisms such as cell fusion [6].

Mesenchymal stem cells (MSCs) also prominently shape the TME by promoting angiogenesis, immunosuppression, and CSC enrichment. Through secretion of factors such as IL-6, IL-8, and PGE_2, together with the release of extracellular vesicles, MSCs help maintain CSC stemness and contribute to therapy resistance and metastatic recurrence in cancers including gastric, colon, prostate, and breast malignancies [7]. This crosstalk positions the MSC–CSC interaction as a key therapeutic target. As summarized in Figure 1, MSCs interact extensively with CSCs via paracrine signaling and EVs, thereby supporting CSC maintenance and immune evasion [7].

Beyond this broader stromal support, EV-mediated mitochondrial communication appears to be especially important in gastric CSC biology. Gastric CSCs can secrete EVs enriched in dysfunctional mitochondrial DNA (mtDNA), which are taken up by tumor-associated macrophages (TAMs). This transfer activates TLR9/NF-κB signaling in TAMs, drives polarization toward an immunosuppressive M2-like phenotype, and disrupts oxidative phosphorylation while shifting macrophage metabolism toward glycolysis. Clinically, elevated levels of these mtDNA-enriched EVs in patient serum are associated with more advanced disease and poorer prognosis, underscoring their role in tumor progression and immune evasion. Accordingly, therapeutic approaches targeting EV biogenesis are being investigated to interrupt this communication axis and limit macrophage reprogramming.

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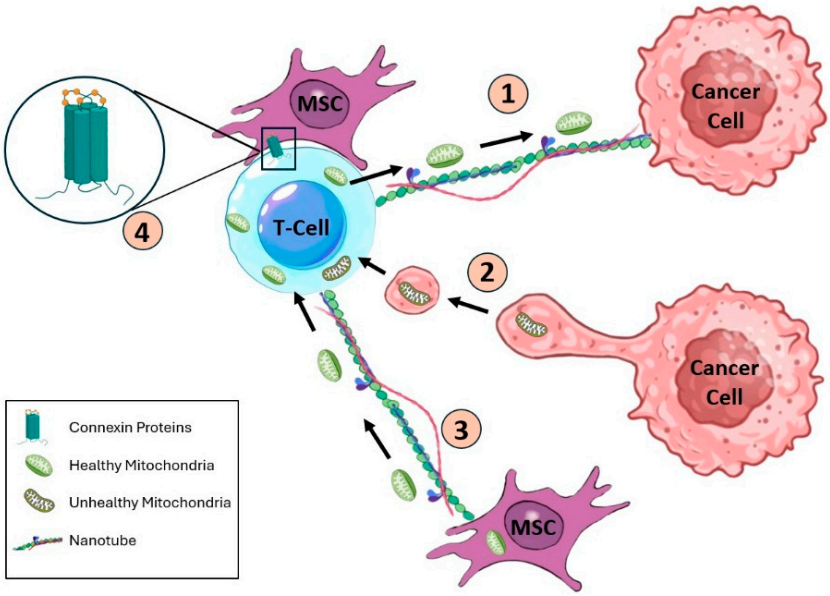

Figure 1. Mechanisms of intercellular mitochondrial transfer in the TME (based on Chun et al. 2025 [1,4]). Cancer cells (red) hijack mitochondria from T cells (blue) via tunneling nanotubes or EVs, while MSCs (pink) can donate healthy mitochondria to revive T cells. Gap junctions (Cx43) also allow direct transfer. (Adapted from BioRender.).

1.2. Metabolic Plasticity of CSCs: Glycolysis vs. OXPHOS

The metabolic plasticity of CSCs is a direct outcome of the mitochondrial hijacking mechanisms detailed later in this manuscript, orchestrated by CSCs to control their own fate and the fate of the tumor ecosystem and microenvironment. CSCs can flexibly switch between glycolysis and oxidative phosphorylation (OXPHOS) in response to environmental cues [8]. Unlike many differentiated tumor cells, CSCs may rely on either glycolysis or mitochondrial respiration depending on context. Particularly, "CSCs show a distinct metabolic phenotype that, depending on the cancer type, can be highly glycolytic or OXPHOS-dependent" [9]. Mitochondria are thus central to CSCs' function in all cases; however, this centrality extends beyond mere bioenergetics. Acting as a metabolic "command hub", mitochondria orchestrate the delicate balance of redox signaling and stemness maintenance, thereby equipping CSCs with the resilience to withstand extreme environmental duress [7,10]. Various factors, such as oxygen, nutrient levels, and oncogenic signaling, which drive CSCs' plasticity and metabolic switching, support stemness (via redox balance), regulate reactive oxygen species (ROS) levels, and promote survival under stress [11]. It is crucial to consider that ROS functions as a biological double-edged sword: while unchecked surges lead to exhaustion, a calibrated baseline is required to fuel the cell cycle machinery [12].

For a T cell to mount an effective defense, it must undergo rapid clonal expansion. However, this proliferation is strictly gated by oxidative stress; if ROS levels breach a certain threshold, the cell cycle arrests at the G1/S checkpoint to prevent DNA damage [13]. The acquisition of healthy mitochondria (e.g., from MSCs) effectively hits a 'Redox Reset' button. By delivering antioxidant enzymes such as Manganese Superoxide Dismutase (MnSOD, or SOD2) and stabilizing the electron transport chain, these donated organelles maintain the T cell within a permissive metabolic window [14]. This ensures that the immune cell avoids premature senescence and sustains the massive proliferation needed to overwhelm the tumor [15]. It is important to look beyond simple energetics to appreciate that mitochondrial transfer restores the delicate 'Redox Balance' essential for proliferation.

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1.3. Mitochondrial Hijacking by CSCs: Tunneling Nanotubes and Extracellular Vesicles

Recent studies show that tumor cells form intercellular conduits (tunneling nanotubes, TNTs; Figure 1) or secrete extracellular vesicles (EVs) containing mitochondrial components to relay mitochondria between cells [16–18]. For example, mitochondrial transfer occurs across different cells and alters mitochondrial metabolism in recipient cells [19]. Both TNTs and EVs fusion have been shown to carry whole mitochondria or mtDNA to immune cells [20]. Evidence (especially from human tumors) shows that CSCs use these routes to reprogram immune and stromal cells. Studies show that cancer cells can obtain mitochondria from T cells via TNTs to blunt immune attacks, and EVs can deliver mitochondrial content across cells [21]. Crucially, this interaction is far from a one-way street; it operates as a distinct 'parasitic bidirectional exchange.' Cancer cells do not merely steal healthy mitochondria to revitalise themselves; they actively dump their own damaged, ROS-laden organelles back into the T cells [22]. Direct physical evidence of this heist is reported, revealing how cancer cells extend tunneling nanotubes to siphon mitochondria from immune defenders. This act of 'metabolic theft' critically drains the T cell's respiratory capacity, accelerating its exhaustion and paving the way for immune escape [23].

1.4. Effects of CSC Mitochondrial Transfer on Immune Cells

Mitochondrial transfer can enhance oxidative metabolism, induce oxidative stress and cause metabolic dysfunction in the recipient cells. This could tip macrophages toward an M2 (tumor-supportive) phenotype and impair T-cell cytotoxicity [24,25]. A Nature study demonstrates that T cells that inherit mutant mitochondria from cancer cells become senescent and exhibit defective effector functions [26]. Altered metabolism in immune cells often increases PD-L1 expression, further suppressing antitumor immunity (e.g., by stabilizing HIF-1α and PD-L1 in the tumor microenvironment) [27–29]. Also, reports show that EV-bound mtDNA activates TLR9/NF-κB in tumor-associated macrophages (TAMs), inducing an M2-like immunosuppressive state (as seen in gastric CSCs models) [30].

Mitochondria in cancer cells have emerged as a highly promising therapeutic target due to the profound metabolic differences between malignant cells and their normal counterparts [31,32]. Unlike healthy cells, tumor cells exhibit a hyperactive metabolic phenotype, preferentially relying on aerobic glycolysis, the hallmark Warburg effect, even when oxygen is abundant, while undergoing extensive metabolic rewiring to survive and proliferate within the nutrient and oxygen-deprived tumor microenvironment. This metabolic plasticity not only drives early carcinogenic events by exacerbating hypoxia but also sustains stemness, metastatic potential, tumor progression, and chemoresistance. Given their central role as the primary energy hub and key regulators of apoptosis, mitochondria have become a focal point for next-generation anticancer strategies [33,34].

Among the most actively investigated agents are mitocans small molecule drugs specifically designed to disrupt mitochondrial function in cancer cells, which are currently classified into eight distinct groups based on their molecular targets: Hexokinase 2 (Class I), Bcl-2 family proteins (Class II), Thiol redox systems (Class III), VDAC/ANT (Class IV), the electron transport chain (Class V), the inner mitochondrial membrane (Class VI), the Krebs cycle (Class VII), and mitochondrial DNA (Class VIII) [35,36]. Among mitocans, hexokinase 2 (HK2) stands out as an exceptionally attractive target because it is dramatically overexpressed in most cancers, remains anchored to the outer mitochondrial membrane (facilitating easier access than inner-membrane or matrix targets), and catalyzes the rate-limiting first step of glycolysis while simultaneously inhibiting apoptosis through VDAC blockade [37]. Although numerous HK2 inhibitors (2-deoxy-D-glucose, 3-bromopyruvate, and benserazide) and broader-spectrum mitocans have shown remarkable preclinical efficacy and several have entered clinical trials, their therapeutic success remains limited, largely due to poor specificity and inefficient mitochondrial delivery [38]. Mitochondria produce ATP (adenosine triphosphate) and simultaneously regulate lethal processes, such as apoptosis and necrosis. These lethal functions are primarily regulated by permeabilization of the mitochondrial outer membrane (MOMP), triggered by apoptotic signals and facilitated by the pore-forming activity of proapoptotic

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proteins, such as the Bcl-2 (B-Cell lymphoma 2) family, Bax (Bcl-2-associated X protein), and Bak (Bcl-2 antagonist/killer protein) [39].

The double-membrane architecture and highly negative membrane potential of mitochondria pose significant barriers to drug penetration, often resulting in off-target effects and suboptimal intracellular concentrations. Consequently, there is an urgent need for advanced, mitochondria-targeted delivery platforms capable of selectively transporting mitocans, particularly HK2-directed agents, directly to the outer mitochondrial membrane of cancer cells, especially the therapy-resistant CSCs subpopulation, thereby maximizing on-target efficacy while minimizing systemic toxicity [40,41].

1.5. Extracellular Vesicles Cargo and microRNA-Mediated Crosstalk

CSCs secrete EVs rich in oncogenic microRNAs (mitomiRs) that tune immune and metabolic pathways [42]. Exosomal miRNAs can reprogram multiple immune cells: for example, CSC-derived EVs have been shown to polarize macrophages toward a pro-tumor M2 state and to impair dendritic cell (DC) and T-cell function [43,44]. Notable examples include miR-21 and miR-210. miR-21-carrying exosomes promote macrophage M2 polarization (via RhoB/MAPK) and can upregulate PD-L1 in target cells [45,46]. miR-210, often induced by hypoxia, can rewire recipient cell metabolism and angiogenesis [47]. microRNAs, including miR-21, miR-210, and miR-34a, collectively drive immunosuppression, metabolic rewiring, and therapy resistance. EVs are not merely organelle carriers but vehicles for a comprehensive 'metabolic code'. This code comprises both the 'hardware' (mitochondria/mtDNA) and the regulatory 'software' (miRNAs), which act in concert to ensure that the recipient cell's metabolism is precisely rewired to serve the tumor's agenda. This section could include a table or bullets summarizing key EV-miRNAs and their targets in immune cells [48]. Meanwhile, CSCs secrete exosomes containing miRNAs that specifically target immune cells to suppress anti-tumor immunity, creating a spatially and functionally heterogeneous immune response. The spatial and functional heterogeneity of the immune system within the TME is a direct consequence of the mitochondrial and miRNA-based mechanisms CSCs use to hijack and suppress anti-tutor immunity.

Studies show that chronic kidney disease (CKD) is an independent risk factor for the development of coronary artery disease (CAD). In both CKD and CAD, the intercellular transfer of microRNAs via elevated levels of endothelial-derived vesicles (eEVs) is an important factor in disease development [49].

Given the high endothelial expression of miR-126-3p and miR-130a-3p, it is important to understand how CKD alters eEVs production and content in vitro. Zietzer et al. (2022) used human coronary artery endothelial cells (HCAECs) to isolate large EVs (Annexin V, Flotillin-1). To model CKD in vitro, HCAECs were treated with indoxyl sulfate (IS). A 250 M IS dose, which did not affect cell viability, was used. This treatment led to a significant reduction in miR-130a-3p levels packaged into EVs, whereas miR-126-3p levels were unaffected. Furthermore, recipient HCAECs that took up EVs from IS-treated cells (EVIS250) exhibited lower miR-130a-3p levels, indicating impaired functional transfer [49]. Additional experiments using oxidized LDL (to mimic CAD) or hypoxia did not significantly affect the vesicular export of these miRNAs, confirming the specific effect of IS. Consequently, IS treatment alone was selected for further study. Using an alternative EV isolation method yielded a more homogeneous EV population and confirmed the strong decrease in vesicular miR-130a-3p following IS treatment. Functionally, EVs isolated by both methods exerted comparable anti-proliferative effects on recipient HCAECs [49,50].

Among the key signaling molecules carried by EVs, miRNAs have emerged as pivotal regulators of glucose and lipid metabolism [51]. miR-141-3p, a member of the miR-200 family, is widely involved in the progression and metastasis of various cancers [52]. Notably, miR-141-3p is associated with adipose tissue-derived EVs and has been implicated in alleviating obesity-induced hepatic insulin resistance and type 2 diabetes; however, research in this area remains relatively scarce [53]. Additionally, previous studies have reported that phosphatase and homolog may be a target of miR-

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141-3p [54]. The PTEN gene (Phosphatase and Tensin homolog) is a critical tumor suppressor gene located on chromosome 10q23 and regulates cell growth, survival, and proliferation by antagonising the PI3K/AKT/mTOR signaling pathway. Loss or mutation of PTEN is common in various cancers, including prostate, breast, glioblastoma, and endometrial cancers. PTEN also plays a pivotal role in insulin signaling as a negative regulator of the pathway. It suppresses downstream signaling cascades to maintain metabolic homeostasis [55,56]. A study demonstrated that exosomes containing miR-141-3p from lean adipose tissue can improve hepatic insulin resistance by targeting PTEN. Nonetheless, the precise molecular mechanism underlying its effect remains unclear. In our previous study, we demonstrated that EVs released from obese adipose tissue impair insulin sensitivity and glucose uptake in hepatocytes by transferring reduced miR-141-3p. However, whether adipose tissue-derived EVs regulate obesity-induced hepatic insulin resistance via miR-141-3p and the underlying mechanisms remain unexplored. In this study, miR-141-3p-knockout and overexpressing EVs were generated to further investigate the potential regulatory role and molecular mechanisms of miR-141-3p-mediated adipose tissue-derived EVs in obesity-induced hepatic insulin resistance [53]. Overall, the miRNA crosstalk is the instructional language that CSCs use to sculpt the cellular and immunological heterogeneity.

1.6. Single-Cell and Spatial Insights: Metabolic Niches and CSCs–Immune Synapses

Recent findings show single-cell and spatial transcriptomics linking metabolic heterogeneity to immune dysfunction. Studies show “metabolic hotspots” within tumors where CSCs and immune cells interact [57]. For instance, spatial analysis of head-and-neck cancers revealed that hypoxic, high-glycolysis regions coincide with immunosuppressive signaling (e.g. increased TGF-β and Treg recruitment), creating a specialised, hostile environment that promotes tumor survival and immune escape [58]. Single-cell profiling can identify CSC subpopulations with hybrid glycolytic/OXPHOS states that engage in dysfunctional synapses with T cells or macrophages. This could illuminate how metabolic gradients in the TME shape CSCs and immune crosstalk and highlight potential biomarkers of immune escape (e.g., co-localization of CSC markers with M2 macrophages in hypoxic niches) [59].

Building on these insights, a recent single-cell RNA sequencing (scRNA-seq) study of pancreatic adenocarcinoma (PAAD) has revealed significant metabolic reprogramming of epithelial glycosphingolipids, which serve as a pivotal driver of malignancy, proliferation, and metastasis [60]. As previously reported, the single-cell landscape of pancreatic adenocarcinoma includes a UMAP projection of 43,580 cells colored by 23 clusters and an annotation of those clusters into 16 major cell types, including cancer stem cells (CSCs), epithelial cells, fibroblasts, and various immune subsets. Utilizing scRNA-seq data from the GSE212966 dataset, encompassing 43,580 cells clustered via Uniform Manifold Approximation and Projection (UMAP) into 16 distinct subgroups, including cancer stem cells (CSCs), epithelial cells, fibroblasts, and various immune populations, the investigation identified elevated glycosphingolipid (GSL) metabolism in tumor-associated epithelial cells, characterised by pathways such as glycolysis, O-glycan biosynthesis, and EMT-related transitions. [61].

Employing computational tools like scMetabolism for metabolic quantification and LASSO-Cox regression for prognostic modelling, the researchers constructed a six-gene signature (*KLK10, MT1X, LAMA3, MET, KRT7, SFTA2*) that stratifies PAAD patients into high- and low-risk groups, with the former exhibiting poorer overall survival, higher mutation rates in genes like *KRAS* and *TP53*, immunosuppressive tumor microenvironments enriched in regulatory T cells and M2 macrophages, and differential drug sensitivities (e.g., increased responsiveness to Acetalax and Selumetinib). Validated across cohorts, including TCGA-PAAD, ICGC-PAAD-US, and GSE71729, this model, when integrated into a nomogram incorporating clinical variables such as age and tumor stage, offers a robust prognostic indicator, underscoring the therapeutic potential of targeting epithelial GSL metabolism to overcome chemoresistance and immune evasion in pancreatic cancer [61,62].

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To bridge the gap between single-cell metabolic findings and clinical practice, a six-gene prognostic risk model was constructed from differentially expressed genes (DEGs) associated with epithelial glycosphingolipid metabolism in pancreatic adenocarcinoma (PAAD) [61]. Using univariate Cox regression, LASSO regression, and multivariate Cox regression, six pivotal genes, *KLK10, MT1X, LAMA3, MET, KRT7, and SFTA2*, were identified to build a risk score that stratified patients into high- and low-risk groups based on the median value. The high-risk group consistently showed significantly worse overall survival in the TCGA-PAAD training set and two independent validation cohorts (ICGC-PAAD-US and GSE71729), with highly consistent expression patterns of the signature genes across datasets. Additionally, high-risk patients had higher somatic mutation burdens, particularly in key driver genes such as *KRAS* and *TP53*, and exhibited an immunosuppressive tumor microenvironment, characterised by greater infiltration of regulatory T cells and M2-polarised macrophages. This subgroup also exhibited increased sensitivity to specific chemotherapies, such as Acetalax and Selumetinib. For improved clinical utility, a prognostic nomogram was developed by integrating the risk score with clinicopathological variables (age, T stage, N stage, and tumor grade). This nomogram achieved superior predictive performance for 1-, 3-, and 5-year survival, as confirmed by calibration curves and decision curve analysis (DCA) [61,63].

Building on these single-cell findings in pancreatic cancer, recent reviews on liver cancer highlight the pivotal role of TME in CSC metabolic rewiring. For instance, TME stimuli such as hypoxia and immune cell interactions drive CSC plasticity, aligning with the metabolic niches and dysfunctional synapses discussed earlier [64].

Despite substantial evidence on metabolic adaptations in liver cancer, the direct interplay between metabolic rewiring of CSCs and tumor microenvironment (TME) stimuli remains underexplored, particularly in cholangiocarcinoma (CCA) [65]. TME-driven metabolic niches shaped by hypoxia, nutrient scarcity, and metabolite accumulation regulate CSC plasticity, promoting shifts toward glycolysis or oxidative phosphorylation to enhance survival and therapy resistance. Moreover, bidirectional CSC-TME crosstalk disrupts the formation of effective CSC-immune synapses, thereby enabling immune evasion [65,66]. Crucially, CSCs actively contribute to immunosuppressive niches by secreting mediators that recruit and polarise immune cells (e.g., macrophages to an M2 phenotype, myeloid-derived suppressor cells, and regulatory T cells) via factors such as CCL2, IL-6, CCL22, VEGF, IL-13, and IL-34. Nutrient deprivation and metabolites like lactate further amplify immunosuppression, impairing effector T cell function and promoting angiogenesis. Disrupting this metabolic-immune crosstalk by inhibiting CSC-derived factors could dismantle protective niches, restore functional immune synapses, and overcome CSC resilience. Targeting TME-modulated metabolic niches alongside immune boosters thus holds promise for more effective combination therapies in liver cancers [25,26,67].

As illustrated in Figure 2, cancer stem cells act as master conductors, directing the creation of a tumor environment that suppresses the immune system. They achieve this through constant two-way communication with two key accomplices: tumor-associated macrophages and regulatory T cells [68]. In this alliance, both cancer stem cells and macrophages release signaling factors such as CCL2, CSF1, IL-13, and TGF-β that actively push macrophages into a pro-tumor, healing mode (called M2 polarization). In a vicious cycle, these reprogrammed macrophages then send back their own signals, such as WNT, IL-6, and TGF-β, which act as fuel to sustain the cancer cells' stem-like, resilient properties. To make matters worse, the cancer stem cells deploy a multi-layer defense: they hide their cellular "ID tags" by downregulating MHC-I, display "do not attack" signals such as PD-L1 and CTLA-4, and flood the area with inhibitory cytokines, including CCL2, CCL5, and TGF-β. This combined assault cripples the immune response by disrupting how threats are presented to immune cells, paralyzing the killer T cells, and recruiting more suppressor T cells. The result is a breakdown in the crucial immune attack connection, effectively allowing the tumor to cloak itself and evade destruction [27,69].

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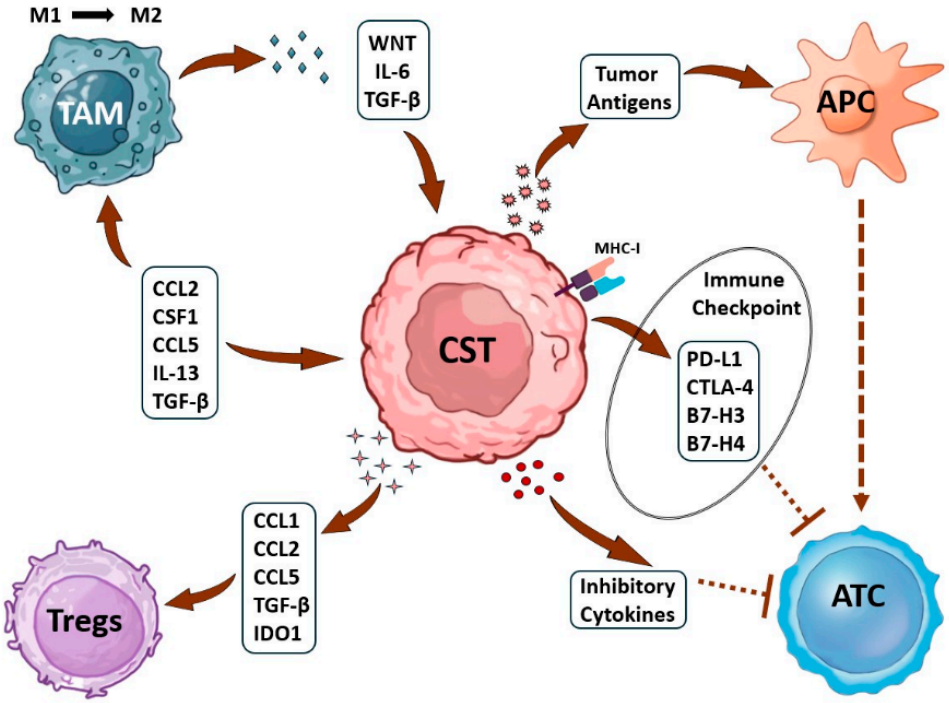

Figure 2. The details of how cancer stem cells (CSCs) evade immune destruction. Their key strategies include hiding by reducing antigen presentation (like MHC-I); building a suppressive niche by recruiting regulatory cells and releasing cytokines (e.g., CCL2, TGF-β); and overexpressing immune "brakes" such as PD-L1. Additionally, they exploit pro-survival signaling pathways. Together, these mechanisms shield CSCs from T and NK cells, often allowing them to enter a dormant state that contributes to tumor relapse and spread [10].

Immune synapses formed by cytotoxic T lymphocytes (CTLs) represent a highly specialized, transient interface that facilitates targeted cell killing during adaptive immune responses. Upon T cell receptor-mediated recognition of antigens on target cells, CTLs rapidly reorganize their cytoskeleton, polarizing the centrosome, the primary microtubule-organizing center, directly to the synaptic plasma membrane. This polarization positions the centrosome as a focal point for directed secretion, where it docks via distal appendages of the mother centriole, creating a secretory domain within the synapse. Lytic granules containing perforin and granzymes traffic along microtubules toward this docked centrosome and undergo polarized exocytosis precisely at the synapse [28]. As illustrated in Figure 3, the formation of the immune synapse in cytotoxic T lymphocytes involves sequential stages from initial T cell APC encounter and stable contact to the mature synapse where centrosome polarization and docking at the plasma membrane creates a focal secretory domain. This mirrors yet functionally diverging from the centrosome-to-basal body conversion and axoneme nucleation seen in primary ciliogenesis [70,71].

Notably, the immunological synapse displays striking morphological and molecular similarities to primary ciliogenesis, while exhibiting a clear functional divergence. In primary cilia, stable docking of the centrosome (the basal body) promotes axonemal outgrowth, enabling sustained environmental sensing. By contrast, the immune system involves brief centrosomal docking, described as a frustrated cilium lacking axoneme extension, thereby repurposing this conserved mechanism for rapid, precisely targeted secretion, which is essential to cytotoxic T lymphocyte function [28].

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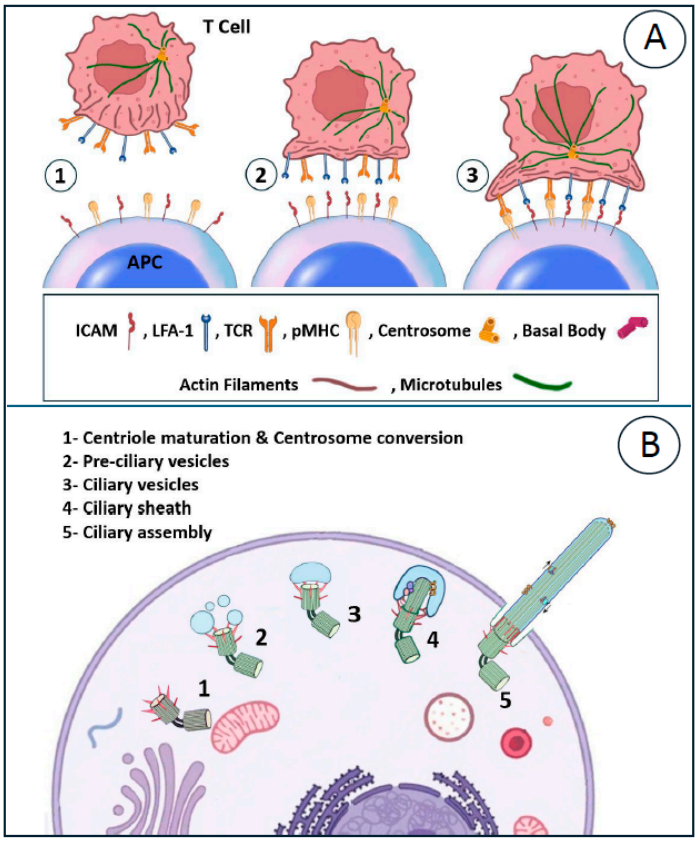

Figure 3. Schematic comparison of key steps in immunological synapse (IS) formation in T cells and primary ciliogenesis. (a) IS assembly is triggered by TCR recognition of pMHC on an APC, leading to centrosome polarization, docking at the synaptic membrane, and polarized secretion. Actin initially clusters TCRs in the cSMAC before retracting to the dSMAC, forming a ring around the LFA-1-enriched pSMAC. (b) Ciliogenesis is induced by stressors (e.g., serum starvation), involving centrosome-to-basal-body conversion, mother centriole docking with cap vesicle formation, actin redistribution for symmetry breaking, and axoneme nucleation. Both processes feature centrosome docking with local cortical actin clearance, highlighting shared mechanisms adapted for distinct functions [12].

1.7. Ciliary–Mitochondrial Interactions in CSCs

This section would explore the emerging theme of organelle crosstalk; especially how primary cilia interface with mitochondria in CSCs. Recent work identified TSGA10 as a key linker: “TSGA10 is a ciliary-centrosomal protein” that physically connects basal bodies/primary cilia to mitochondrial complex III [72,73]. We would explain how ciliary signaling and mitochondrial metabolism are coordinated; for example, cilia-associated proteins can recruit mitochondria to the ciliary base to supply ATP or trigger mitochondrial depolarisation to support Ca^2+ signaling [74]. Given that many CSCs possess primary cilia and high mitochondrial content, this ciliary–mitochondrial “hub” may support CSC energy demands and immune privilege. We would also mention that TSGA10 is overexpressed in tumors and may influence HIF-1α and metabolic pathways [6,72,74]. This section thus connects cell-biological features of CSCs (e.g., cilia) with mitochondrial hijacking and could suggest new angles (e.g., targeting cilia/TSGA10) to disrupt CSC immunometabolism.

This physical tethering is not accidental but designed for the precise coordination of energy demands. Cilia-associated proteins recruit mitochondria to the ciliary base to supply ATP directly at the site of consumption for signaling, or to trigger mitochondrial depolarisation for the fine-tuning of calcium signaling [75]. Given that many CSCs possess primary cilia and high mitochondrial content, the "Miro1 hub" supports CSC survival and immune privilege by ensuring immediate energy availability to process environmental signals. It is also noteworthy that TSGA10 is overexpressed in

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tumors and may influence HIF-1α pathways and metabolic adaptation. Thus, targeting this axis (e.g., inhibiting TSGA10 or ciliary signaling) could represent a novel strategy to disrupt CSC immunometabolism [76].

An emerging area of research highlights the fascinating crosstalk between primary cilia and mitochondria in CSCs, in which these organelles work together to meet the unique demands of tumor-initiating cells. Many CSCs retain primary cilia while maintaining robust mitochondrial activity, much like certain protected postmitotic cells in the body that are rich in both structures and enjoy a degree of immune privilege. A key player in this connection is the protein TSGA10, originally discovered for its role in sperm development but now recognized as a ciliary-centrosomal protein that also influences mitochondrial function. Recent work proposes that TSGA10 acts as a bridge, directly binding to a component of mitochondrial Complex III (cytochrome c1), thereby helping to streamline electron flow in the respiratory chain [77,78].

TSGA10 enhances mitochondrial efficiency by promoting effective ATP production via oxidative phosphorylation, while reducing wasteful electron leaks that produce harmful ROS and unnecessary heat. Acting like a cellular thermostat, it optimises the coupling between proton gradients and energy synthesis, ensuring high ATP yields in demanding cells without risking overheating or oxidative stress, crucial protection in vulnerable tissues such as the brain and testis, where excess ROS or thermal damage could trigger dysfunction or degeneration [72,78]. In cancer, however, TSGA10 exhibits paradoxical behavior. It is frequently overexpressed in tumors such as melanoma, colon, liver, ovarian, and prostate cancers, as well as leukaemias, with context-dependent effects. On one side, it acts as a tumor suppressor by blocking HIF-1α, a key regulator of hypoxia responses, from entering the nucleus, thereby inhibiting the activation of downstream genes (e.g., *VEGF, MMP2, MMP9*) that drive angiogenesis, invasion, glycolysis shift, metabolic reprogramming, and metastasis [79].

On the other hand, reduced TSGA10 in some scenarios allows HIF-1α to run unchecked, encouraging cancer cells to adopt inefficient but survival-friendly glycolysis, accumulate ROS for mutagenic advantage, and adapt to harsh tumor microenvironments (such as cold stress or hypoxia) by mimicking heat-generating strategies seen in brown fat. This flexibility helps CSCs thrive under stress, maintain stem-like properties, and resist therapy. By linking ciliary positioning (via its centrosomal/basal body role) with mitochondrial efficiency and HIF-1α control, TSGA10 emerges as a critical node in the ciliary-mitochondrial hub that sustains CSC energy needs, redox balance, and immune evasion. Disrupting this axis, perhaps by modulating TSGA10 expression or its interactions, could render CSCs metabolically vulnerable, reducing their ability to reprogram energy pathways or tolerate stress, and opening new avenues for targeting the immunometabolism that drives tumor relapse and resistance. This dual-edged role underscores why context-specific strategies will be key to harnessing TSGA10-related mechanisms therapeutically [72,80].

In differentiated thyroid cancer, the interaction between primary cilia and mitochondria is mediated by VDAC1, a protein that localizes to both the mitochondrial outer membrane and the basal body of the cilium. Loss of primary cilia, achieved through thyroid-specific Ift88 knockout in mice or IFT88/KIF3A silencing in TPC1 and BCPAP cell lines, disrupts this interaction, leading to mitochondrial fragmentation, elevated VDAC1 expression and oligomerization, cytochrome c release, and robust activation of the mitochondria-dependent apoptotic pathway [81]. Mouse thyroids lacking cilia showed irregular dilated follicles, markedly increased TUNEL-positive apoptotic thyrocytes, reduced BCL-2, and eventual development of solid proliferative nodules. In cell lines, ciliogenesis defects reduced ciliation by 80–90 %, produced globular fragmented mitochondria, raised apoptosis to 15–27 % (measured by Annexin V/PI and TUNEL), and the effect was largely reversed by the VDAC1 oligomerization inhibitor DIDS [82]. Patient samples from oncocytic PTC and PTC with Hashimoto's thyroiditis exhibited 3-18% ciliation (versus 68% in conventional PTC), higher VDAC1 expression, more apoptosis, and less extrathyroidal invasion, indicating indolent behavior. Pharmacological inhibition of ciliogenesis with ciliobrevin A decreased viability by 40-45

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%, suggesting that deliberate disruption of this ciliary-mitochondrial interaction offers a selective therapeutic strategy for cilia-preserving thyroid cancers [83,84].

1.8. Therapeutic Implications and Future Directions

Heterogeneity and plasticity are the primary reasons targeted therapies and chemotherapies fail. A drug may kill 99% of the tumor, but the pre-existing or inducibly plastic subpopulation (CSCs) survives and repopulates the tumor. The therapy-resistant phenotypes that arise from cellular heterogeneity and plasticity are mechanistically driven by the mitochondrial and miRNA regulatory networks within CSCs.

This section would discuss strategies to disrupt the CSC–immune metabolic axis. Potential interventions include OXPHOS inhibitors (to cut off CSC energy supply) and blockers of EV biogenesis or TNT formation (to prevent mitochondrial transfer) [6,19]. For example, the "Hallmarks of CSC metabolism" review highlights mitochondrial function as an Achilles◎ heel: inhibiting mitochondrial respiration in CSCs could prevent relapse [18,19]. miRNA antagonists (e.g. antagomiRs against miR-21/210) might restore immune cell function [85]. We would also mention the possibility of targeting ciliary signaling, given the role of TSGA10 and cilia in CSCs; disrupting this organelle crosstalk may sensitize CSCs (as suggested by recent conclusions) [20,24]. Finally, we would identify gaps (e.g., the need for in vivo validation of mitochondrial-EV mechanisms) and propose how future research (perhaps using CRISPR screens or organoid co-cultures) could address them. This section could end by proposing a "precision intervention framework" targeting the CSC-immune metabolic niche, as alluded to in the abstract.

To conclude, disrupting the CSC-immune metabolic axis represents a transformative strategy for eradicating cancer stem cells and preventing relapse. Inhibitors of oxidative phosphorylation (e.g. metformin, IACS-010759) can starve CSCs of their preferred mitochondrial energy source, while blocking extracellular vesicle biogenesis or TNT (tunneling nanotube) formation can interrupt direct mitochondrial transfer from stromal cells to CSCs [86]. As elegantly shown in the thyroid cancer study, deliberate ablation of primary cilia triggers a rapid increase in mitochondrial VDAC1 oligomerization, mitochondrial fragmentation, and caspase-dependent apoptosis, turning the CSC mitochondrial hub from a survival advantage into its Achilles◎heel. Targeting ciliary signaling (via TSGA10 disruption or ciliogenesis inhibitors such as cilobrevin A) offers an additional orthogonal approach that simultaneously sensitises CSCs to immune attack by collapsing their immunosuppressive organelle crosstalk [87]. Future work must validate these mechanisms in vivo using CRISPR-based screens in CSC-enriched organoid co-cultures with immune cells. Ultimately, a precision intervention framework that combines OXPHOS blockade, TNT inhibition, and ciliary–mitochondrial disruption could create a synthetic lethal niche for CSCs, a niche in which they lose both metabolic resilience and immune privilege, paving the way for durable remission in patients.

1.9. Intercellular Mitochondrial Transfer and Metabolic Crosstalk: A Conceptual Framework

Intercellular transfer of mitochondria and mitochondrial components is emerging as a paradigm-shifting process in cancer, immunity, and viral disease. In the tumor microenvironment (TME), cancer cells can hijack healthy mitochondria from immune T cells and simultaneously transfer damage (Figure 1), ROS-generating mitochondria back to T cells [1,2]. This bidirectional exchange has a dual role: pathological transfer enables tumor immune evasion (by inducing T cell exhaustion), whereas therapeutic transfer (e.g. from mesenchymal stem cells to T cells) can revitalize antitumor immunity [2,6]. Multiple pathways mediate this transfer: tunneling nanotubes (TNTs), extracellular vesicles, or direct cell–cell contact (gap junctions) [2,7,88]. A crucial mechanistic detail often overlooked is the role of Miro1 (Mitochondrial Rho GTPase 1) [89]. Studies have identified this protein as the primary 'molecular motor' driving mitochondrial trafficking along the microtubules within TNTs, with Miro1 overexpression directly correlating to the velocity and efficiency of this 'metabolic hijacking' [90]. For example, as illustrated below, an exhausted T cell may receive a "sabotaged" mitochondrion from a cancer cell (via TNT or EV) that impairs its function, while a

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healthy T cell can receive a donated mitochondrion from a mesenchymal stem cell (MSC) that boosts its metabolism [6,49]. Computational tools (such as the mitochondrial-enabled reconstruction of cellular interactions, MERCI) are being developed to quantify these exchanges; high MERCI scores have been linked to poorer clinical outcomes in cancer [2]. In summary, oxidative stress drives TNT formation and exosome release, enabling tumors to rewire immune-cell metabolism [91,92]. Harnessing this knowledge could guide next-generation immunotherapies (e.g., improving CAR-T cell efficacy via mitochondrial donation) and identify circulating biomarkers (e.g., circulating mtDNA, mitochondrial transfer scores) of treatment response [2,93].

1.10. Extracellular Vesicles and Mitochondria in Cancer Therapy

Extracellular vesicles, including exosomes and microvesicles, are membrane-bound packages that shuttle proteins, RNAs, and even organelles between cells. In non-small cell lung cancer (NSCLC), radiation resistance has been linked to aberrant mitochondrial function, and EVs appear to play a key role [25,94]. EVs released by tumor or stromal cells can carry whole mitochondria, mitochondrial DNA (mtDNA), or mitochondrial proteins (MtS) to recipient cells [22,95]. For instance, metastatic NSCLC cells use EVs to prepare pre-metastatic niches and may transfer “healthy” mitochondria to support nearby stromal cells, while other tumor cells cannibalise mitochondria from the microenvironment via TNTs [24,32]. Importantly, studies have shown that EV-mediated mitochondrial delivery to cancer cells can alter radiation response [96]. In some cases, providing functional mitochondria via EVs makes cancer cells more radiosensitive (thereby enhancing therapy), whereas in other contexts it may promote radio-resistance by boosting tumor metabolism. A key molecular mechanism supported by recent literature involves 'ROS Scavenging'. Since radiotherapy primarily eliminates cancer cells by inducing lethal oxidative stress, the acquisition of functional mitochondria significantly boosts the tumor cells' antioxidant capacity. These mitochondria effectively act as 'metabolic shields,' neutralizing radiation-induced free radicals and thereby preventing cell death.

Leonov et al. (2024) review a “controversy” in NSCLC: EV/mitochondria exchange could either exacerbate or overcome radiation resistance [94]. They propose novel theragnostic approaches: profiling circulating EVs (e.g., chips to detect mitochondrial cargos) as predictive biomarkers, and engineering EVs or EV secretion modulators to sensitize tumors to radiation [94,97]. In summary, EVs are emerging as both mediators of cancer therapy resistance and potential vehicles for mitochondria-based treatments in NSCLC [67,98].

1.11. Exosomes and Microvesicles as Mitochondrial Carriers

Extracellular microvesicles (exosomes) act as “magic bullets” for horizontal transfer of mitochondria and their regulators [99]. All cells secrete these vesicles, which carry diverse cargo (RNAs, proteins, lipids) and can fuse with target cells to modulate their function [7]. Notably, ExMVs can incorporate whole mitochondria (forming mito-exosomes) or release them in a “naked” form [100]. Through these routes, donor cells effectively transplant mitochondria into recipients. Ratajczak et al. (2025) describe multiple mechanisms of mitochondrial transfer: mitochondria may be engulfed by a secreted microvesicle (path 1), released into the medium and taken up by endocytosis (path 2), or shuttled directly via nanotubules (path 3) [100,101]. Our graphical model below illustrates these routes. In addition to mitochondria, EVs often carry regulatory miRNAs and proteins that reprogram the metabolism of target cells [102]. For example, an EV might deliver miRNAs that suppress oxidative phosphorylation genes, complementing the effect of mitochondrial transfer. Remarkably, recent evidence shows that EV-mediated mitochondrial transfer can induce mitophagy in recipient cells: by donating healthy mitochondria, ExMVs trigger clearance of damaged organelles, thereby improving cellular energetics [103,104]. Thus, exosomes not only supply new mitochondria but also carry “metabolic code” (mtDNA signatures, miRNAs) that tune mitochondrial function in target cells [83,91,105].

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Furthermore, studies revealed that this targeting is not random; exosomes are equipped with specific surface integrins that act as 'molecular zip codes,' dictating precisely which tissue or immune cell receives the cargo [105,106]. Consistent with immunometabolism principles, evidence also suggests that CSCs can transfer mutated metabolic enzymes (e.g., IDH1), thereby producing toxic oncometabolites (such as D-2HG) in the recipient cell. This mechanism effectively 'poisons' immune cells from within, causing metabolic paralysis and further ensuring tumor survival [107].

1.12. Viral Infection, Mitochondria, and Metabolic Dysregulation

Viral pathogens and their therapies also impinge on mitochondrial and metabolic networks. Chronic hepatitis B virus (HBV) infection, a major cause of hepatocellular carcinoma (HCC), illustrates this interplay [108]. Liang et al. (2023) used a mouse model (HBV transgene × miR-122 knockout) to show that HBV replication causes profound metabolic stress, including hepatic steatosis, altered lipid metabolism (Warburg effect), suppression of the TCA cycle, ER stress, and mitochondrial dysfunction [108]. Loss of the hepatocyte miR-122 (a fatty-acid regulator) exacerbated these effects, highlighting miR-122's tumor-suppressor role [109]. Crucially, antiviral treatment (nucleoside analogues) reduced HCC incidence by ~30–35% even in mice with normal liver enzymes, by suppressing HBV and relieving stress pathways. This improvement was linked to activation of the ER stress response (ATF4), clearance of the autophagy cargo p62, and inhibition of the CHOP-mediated apoptosis cascade [108,112]. In summary, HBV-driven liver injury involves ER stress, accumulated p62 (blocked autophagy), and mitochondrial defects that drive carcinogenesis; antiviral therapy can reverse these mitochondrial and metabolic dysfunctions [108,113].

To further explain ER stress, we must look at the structural level involving Mitochondria-Associated Membranes (MAMs), which act as physical contact sites and signaling hubs. Viruses target this region to execute a dual strategy: 1) disrupting calcium transfer between the ER and mitochondria, which is a primary driver of the observed ER stress, and 2) degrading the MAM-resident MAVS protein, thereby severing the antiviral signaling link [110].

Another critical immunometabolic mechanism highlighted in recent studies is the neutralization of the cGAS-STING sensing pathway [114]. Typically, mtDNA leakage resulting from mitochondrial damage should trigger innate immunity. However, viruses accelerate 'mitophagy' to clear leaked mtDNA before cGAS detects it. This strategy, effectively a form of 'mitochondrial camouflage,' prevents type I interferon production, allowing the viral infection to persist within an immune-silent niche [110,115].

Similarly, other viruses rewire host metabolism. For example, miR-124 (a liver-expressed miRNA) has been shown to repress genes involved in fatty acid β-oxidation, causing triglyceride accumulation [116]. Shaw et al. found that miR-124 downregulates enzymes like AADAC and ATGL, tipping hepatoma cells toward lipid storage. Interestingly, miR-124 also inhibits hepatitis C virus (HCV) production (since HCV hijacks lipid pathways), consistent with its targeting of AADAC [117]. Together, these studies show that miRNAs integrate metabolic and immune/viral signals: loss of miR-122 (in an HBV model) or gain of miR-124 can dramatically alter lipid homeostasis and viral susceptibility [117,118].

1.13. Non-Coding RNAs and Metabolic Regulation

Non-coding RNAs (miRNAs, lncRNAs) emerge as key coordinators of mitochondrial and metabolic biology. In the context of EVs, many miRNAs packaged into exosomes target metabolic pathways in recipient cells [91,109,119]. For instance, Ratajczak et al. (2025) note that ExMVs often contain miRNA species “that regulate the function of mitochondria in the target cells” [100]. In NSCLC, such miRNAs could modulate radiation response by reshaping metabolic networks. In viral infections, computational profiling has identified specific lncRNAs and miRNAs that are dysregulated in COVID-19 lung tissue. Aishwarya et al. (2022) found that SARS-CoV-2 infection upregulates mitochondrial respiration genes, induces cytokine production, and perturbs iron and glucose transport pathways [120]. Their analysis highlighted lncRNAs (e.g. C058791.1, TTTY15,

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TPTEP1) as potential regulators of COVID-19 pathology, and suggested drug candidates (digoxin, proscillaridin) that reverse the expression signature [102,120]. Notably, the study predicted that MDH1 and SGCE were upregulated and PFKFB3 was downregulated as biomarker candidates [120]. This illustrates how non-coding RNAs and metabolic genes form a network in disease, where changes in mitochondrial gene expression and miRNA/lncRNA profiles can drive pathology or identify therapeutic targets [120–122].

We should also highlight the role of circular RNAs (circRNAs). Due to their closed-loop structure, these molecules are highly stable and often act as 'sponges' that absorb specific miRNAs, preventing them from interfering with metabolic genes (as seen with circACC1) [123]. Beyond simple regulation, lncRNAs can also serve as physical scaffolds. For instance, SAMMSON was shown to bind directly to the mitochondrial protein p32, effectively creating a bridge between the nucleus and mitochondria. As demonstrated by Leucci et al. (2016) breaking this connection causes mitochondrial collapse, proving that these RNAs are actual structural components of the cancer cell's metabolic machinery, not just background signals [124].

1.14. Artificial Intelligence and Computational Modelling

The complexity of mitochondrial and EV-mediated communication calls for advanced computational approaches. Deep bioinformatic analyses are already uncovering hidden patterns: for example, gene expression profiling of COVID-19 samples (using tools such as GEO2R/limma) has revealed a surge in mitochondrial respiration and changes in miRNA biogenesis [120]. These large-scale studies can be considered early AI-driven efforts that integrate multi-omics data to identify dysregulated pathways and repurposable drugs [106,120]. In cancer immunology, machine-learning–based image analysis (e.g., single-cell imaging of TNTs) and network reconstruction tools (such as MERCI) could be used to quantify mitochondrial exchanges [125–127]. Future AI frameworks might integrate single-cell transcriptomics, proteomics, and spatial imaging to map the "mitochondrial connectome" of tissues. For instance, identifying which T cells have acquired tumor mitochondria (as opposed to those donated by MSCs) could be automated using classifier algorithms trained on multimodal data. Similarly, AI could help predict which miRNAs or EV cargos most strongly influence metabolic reprogramming in recipient cells. In sum, computational AI methods are poised to synthesize data from diverse studies (genomic, imaging, functional assays) to construct predictive models of mitochondrial and metabolic crosstalk [2,120].

Looking forward, a promising frontier lies in the concept of 'Mitochondrial Digital Twins.' Rather than relying solely on experimental models, these virtual systems would enable us to test complex scenarios in silico, such as predicting exactly how a tumor might react if we blocked specific EV pathways or severed TNT connections. This approach could move us beyond trial-and-error, allowing clinicians to design precise, personalized metabolic interventions for each patient before a single drug is administered.

1.15. Integrative Conceptual Model

Combining these findings suggests a unified model where mitochondrial exchange and metabolic signaling form a regulatory network across disease contexts:

- Tumor–Immune Crosstalk: Cancer cells hijack mitochondria from T cells and use oxidative stress–induced pathways (TNTs/EVs) to exhaust immunity, while therapeutic strategies aim to reverse this by delivering healthy mitochondria back to T cells [2,6,83].
- EV-Mediated Signaling: Extracellular vesicles act as vehicles for mitochondria, mtDNA, and regulatory RNAs. They enable horizontal transfer of metabolic capacity and information between tumor, stromal, and immune cells [23,24,91]. EV cargo profiles (mtO/MtS) may predict radio resistance and metastatic potential [128].
- Viral and Metabolic Coupling: Viral infections (HBV, SARS-CoV-2, etc.) induce ER stress and mitochondrial dysfunction, which in turn trigger compensatory metabolic changes (e.g. lipid

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accumulation). Host miRNAs (miR-122, miR-124) and lncRNAs modulate these processes, linking infection to cancer and metabolic disease [116,118,120].

- MicroRNA Control: MiRNAs serve as master regulators of metabolic enzymes (e.g. miR-124 repressing fatty acid oxidation) and impact viral lifecycles (miR-124 inhibiting HCV) [116]. Changes in miRNA networks can thus amplify mitochondrial effects and alter intercellular communication.
- AI-Driven Integration: Advanced computational models can integrate gene-expression patterns, EV contents, and imaging data to identify key nodes in this network. For instance, unsupervised algorithms might cluster cells by mitochondrial content, or neural networks could predict how altering miRNA levels will shift metabolism.
- Metabolo-Epigenetic Reprogramming: It is crucial to recognise that mitochondria act as the primary suppliers of substrates for chromatin modification. Transferred mitochondria alter the intracellular pool of Acetyl-CoA and alpha-Ketoglutarate. Since Acetyl-CoA is the essential donor for histone acetylation (which opens chromatin structure), an influx of tumor-derived mitochondria can essentially "rewrite" the epigenetic landscape of the recipient T cell. This creates a lasting 'metabolic memory', locking the immune cell into an exhausted state that persists even if the tumor signal is removed [129,130].

This framework (schematically illustrated above) bridges cancer biology, immunology, virology, and metabolism. It emphasizes that mitochondrial dynamics are not confined to a single cell but are shared and regulated in the tissue environment. In practical terms, it suggests multi-targeted interventions: for example, combining antivirals (to reduce viral stress), metabolic therapies (to restore mitochondrial function), and engineered exosomes or mitochondrial transfers (to reprogram immune cells) could synergize. Finally, we should not overlook the critical dimension of time—specifically, 'chronometabolism.' Mitochondrial dynamics do not operate in a vacuum; they are tightly gated by the body's circadian clock. A striking example is seen in Colorectal Cancer, where the circadian regulator BMAL1 directly drives mitochondrial fission and metabolic activity. This opens the door for 'chronotherapy': rather than administering drugs arbitrarily, we could time metabolic interventions to coincide with the tumor's peak mitochondrial activity. This strategy allows us to strike when the cancer is most vulnerable, potentially maximizing efficacy while sparing healthy tissues [131].

All components of this model are supported by current literature [2,93,120], yet it remains a hypothesis to be tested. Future research, aided by AI/ML, should aim to map this “mitochondrial signaling network” in detail and translate it into personalized therapies for cancer and infectious diseases.

2. Conclusion

2.1. Beyond Bioenergetics: The Rise of the "Mitochondrial Internet"

Taking together, the evidence presented in this review points to a tipping point in our understanding of tumor biology. We can no longer view mitochondria merely as isolated intracellular powerhouses; they have emerged as dynamic intercellular messengers. It is becoming clear that Cancer Stem Cells (CSCs) are orchestrating a sophisticated biological warfare; not just by stealing energy, but by actively colonizing the immune microenvironment. By establishing physical networks (TNTs) and dispatching encrypted metabolic codes (via EVs), tumors effectively overwrite the 'operating system' of immune cells, turning defenders into accomplices.

This realization offers a plausible explanation for why many current immunotherapies fall short: they attack the tumor mass but ignore its communication grid. The path forward, therefore, lies in a fusion of biology and technology. We must move toward deploying 'Digital Twins' to simulate these complex exchanges and utilize 'chronotherapy' to sever the tumor's supply lines at their most vulnerable moments. Ultimately, we are not just fighting a static collection of cells; we are confronting an intelligent metabolic ecosystem. To defeat it, we must learn to hack its network.

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2.2. Hypothesis: The "Mito-Epigenetic Lock"

Building on these integrated findings, we propose a unifying hypothesis: the 'Mito-Epigenetic Lock'; in which the transfer of tumor-derived mitochondria into T cells may function as a metabolic "Trojan Horse" within the tumor microenvironment. These hijacked organelles may not merely compromise bioenergetic efficiency but could alter the intracellular availability of key metabolic substrates, including acetyl-CoA and potentially immunomodulatory metabolites such as D-2-hydroxyglutarate (D-2HG), thereby reshaping cellular metabolic signaling. We hypothesize that such metabolic perturbations may influence chromatin remodeling processes and contribute to durable transcriptional reprogramming consistent with T-cell exhaustion phenotypes. Rather than representing a fully irreversible state, this process may establish a persistent epigenetic memory, or "metabolic scar", that sustains functional impairment even after the initiating tumor-derived signals are reduced.

From a therapeutic perspective, these considerations suggest that interventions targeting mitochondrial transfer alone may be necessary but not sufficient to fully restore immune competence; for example, through disruption of intercellular transport pathways mediated by proteins such as Miro1 or by inhibiting tunneling nanotubes and extracellular vesicle trafficking. A more effective strategy may involve a combinatorial or "dual-hit" approach that simultaneously limits pathological mitochondrial exchange and modulates epigenetic regulatory circuits to reprogram exhausted immune cells and restore antitumor immunity.

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