

Mitochondria in Cancer Stem Cells: From an Innocent Bystander to a Central Player in Therapy Resistance

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Abstract: Cancer continues to rank among the world's leading causes of mortality despite advancements in treatment. Cancer stem cells, which can self-renew, are present in low abundance and contribute significantly to tumor recurrence, tumorigenicity, and drug resistance to various therapies. The drug resistance observed in cancer stem cells is attributed to several factors, such as cellular quiescence, dormancy, elevated aldehyde dehydrogenase activity, apoptosis evasion mechanisms, high expression of drug efflux pumps, protective vascular niche, enhanced DNA damage response, scavenging of reactive oxygen species, hypoxic stability, and stemness-related signaling pathways. Multiple studies have shown that mitochondria play a pivotal role in conferring drug resistance to cancer stem cells, through mitochondrial biogenesis, metabolism, and dynamics. A better understanding of how mitochondria contribute to tumorigenesis, heterogeneity, and drug resistance could lead to the development of innovative cancer treatments.

Keywords: mitochondria, cancer stem cells, drug resistance, therapy, metabolic dysfunction

Introduction

Despite several available therapies cancer is a leading cause of death worldwide. The failure of cancer cells to be eliminated by any kind of chemo or radiation therapy is attributed to a subpopulation of cells in the tumor, referred to as cancer stem cells (CSCs) or tumor-initiating cells (TICs).¹⁻⁴ In the early nineteenth century, several studies documented the presence of pluripotent stem cells in teratomas and hypothesized their role in tumorigenesis.^{5,6} However, the debate was rekindled when a study on human acute myeloid leukemia (AML) provided the first evidence for the involvement of stem cells in cancer. This study demonstrated that transplanting a population of cells from AML patients into severe combined immune-deficient (SCID) mice, initiated AML in the mice. These cells were then referred to as the AML-initiating cell population.² Similarly, CSCs were found in a variety of malignancies, including those of solid tissues.⁷ In fact, the existence of CSCs in solid tumors was first shown in breast cancer in the early 2000s, where as few as a hundred CSCs were able to form tumors in mice, in contrast to tens of thousands of cells with alternative phenotypes.⁸ These unusual cell subpopulations that cause tumors in vivo were later discovered in colon and brain malignancies.^{9,10} To date, CSCs have been isolated from almost all solid tumors, including pancreatic cancer, prostate cancer, melanoma, and ovarian cancer.¹¹⁻¹⁴

CSCs are subpopulations of cancer cells that share characteristics with healthy stem or progenitor cells, such as the ability to self-renew and differentiate into several cell types to aid in the growth and heterogeneity of tumors.¹⁵ It is well established that CSCs make up a relatively small fraction of tumor tissues, often between 0.01–2% of the overall tumor mass.^{4,16} CSCs act as drivers of tumor formation and growth and are frequently associated with aggressive, heterogeneous, and therapy-resistant tumors.¹⁷⁻²⁰ CSCs' resistance to chemotherapy or radiotherapy is linked to various factors, including the pivotal role of the cellular powerhouse – the mitochondrion. Mitochondria contribute to the maintenance of CSCs' survival and self-renewal, drug resistance, and tumor recurrence. Alterations in mitochondrial structure, function,

and location are commonly observed in CSCs.^{21–24} Consequently, exploring how mitochondrial function regulates CSCs holds promise in facilitating the creation of innovative CSC-targeted treatments to overcome cancer drug resistance.

In this review, we discuss the diverse attributes displayed by CSCs, exploring their connection with mitochondrial biology, and particularly emphasizing the role of mitochondria in CSC drug resistance.

Characteristics of Cancer Stem Cells

A common approach to reduce the tumor burden is to eliminate proliferating cells by chemotherapeutic agents. However, CSCs can undergo quiescence and resist such treatments, triggering a tumor relapse.^{25,26} Hence, it is essential to understand the basic cellular and molecular factors that influence the functioning and survival of CSCs. In this context, beyond the proliferative and self-renewal capabilities of CSCs, we elucidate several significant traits that govern their tumorigenicity.

Promoting Tumor Recurrence

Despite significant advancements in first-line anti-cancer medication, resection surgery, combination chemotherapy, and radiation, many patients still experience high rates of tumor recurrence and metastasis. The survival of CSCs following conventional therapy is assumed to be the cause of tumor recurrence, which poses a serious clinical problem in the successful treatment of cancer.^{25,27,28} Current anti-cancer medicines fail to effectively treat CSCs, which contributes to tumor recurrence, diversification, and a poor prognosis.^{29,30} There are several ways to understand CSCs' function in promoting cancer recurrence. The foremost cause of tumor recurrence is due to the ability of CSCs to withstand radiation and chemotherapy, thus maintaining a steady supply of tumor-causing cells.^{25,27} Another viewpoint on recurrence focuses on the significance of epithelial-mesenchymal transition (EMT), which involves the transformation of epithelial cells into mesenchymal phenotypes.³¹ Overexpression of EMT-related transcription factors (eg Twist and Snail) led to the expression of antigenic markers of neoplastic mammary stem cells in the non-tumorigenic, immortalized human mammary epithelial cells (HMLEs).³² These were able to form mammospheres, a characteristic of CSCs, and also expressed typical CSC markers such as CD44⁺/CD24^{−/low}.³² In a separate investigation, human breast tumor cells belonging to the claudin-low molecular subtypes demonstrated enrichment of cells that expressed elevated levels of CD44⁺/CD24^{−/low} markers and exhibited the ability to form mammospheres.³³ These cells had high expression of mesenchymal genes like Snail and low expression of cell-cell contact genes such as E-cadherin after treatment with endocrine therapy or chemotherapy.³³ Such evidence indicates that the CSCs undergo EMT and escape treatment resulting in tumor recurrence. Moreover, the establishment of CSCs can also occur due to abnormal activation of autocrine and paracrine signaling pathways.³⁴ This phenomenon is corroborated by a study that highlights the coordinated influence of TGFβ-SMAD and Wnt-β catenin pathways in inducing epithelial-mesenchymal transition (EMT) in both normal and tumorigenic human mammary epithelial cells (MECs).³⁵ According to certain studies, stem cell-like subpopulations of mesenchymal circulating tumor cells (CTCs) may serve as markers of micrometastatic status and predictors of the likelihood of tumor recurrence.³⁶

Tumorigenicity and Transplantation Potential

The tumorigenic and metastatic potential of CSC-containing malignancies surpasses that of non-CSC tumor cells, a well-established fact supported by numerous in vitro and in vivo studies. In particular, pancreatic cancer cells expressing CSC markers, such as CD133 and CXCR4, have demonstrated significantly higher tumorigenic and metastatic abilities.³⁷ Additionally, studies involving the transplantation of these CSCs into immunodeficient mice have shown their remarkable capacity to repopulate the original tumor even at low clonal densities, further exemplifying their potent tumorigenic potential.^{15,38} For instance, in one study, injection of a small number of CD44⁺/CD24[−] prostate cells into SCID mice resulted in tumor formation. These cells expressed stem-cell associated BMI1 and OCT-3/4, reinforcing their role as cancer stem cells.³⁸ Various xenograft models, both in vitro and in vivo, have consistently revealed that subpopulations of CSCs from different malignancies exhibit significantly higher proliferative capability, enhanced clonogenic potential, and an increased propensity for tumorigenesis and metastasis. Notably, numerous human malignancies, including leukemia, glioblastoma, breast, and skin cancers, harbor these clonogenic potential cells capable of reforming the parental tumors after transplantation. This underlines the critical role of CSCs in driving tumor initiation, growth, and dissemination, making them an essential target for developing effective cancer therapies.^{8,38–40}

Expression of Specific Markers

Recent advances in single-cell technologies have enabled genomic and proteomic profiling of individual cells. These advancements have also led to robust isolation and characterization protocols to identify CSCs from the rest of the tumor, based on a few molecular markers. However, the CSC isolation protocols are still limited by the cellular heterogeneity within the tumor and the diverse origins of tumors.^{41,42} It has been demonstrated that several cell surface markers, such as THY1 (THYmocyte differentiation antigen 1), EpCAM (epithelial cell adhesion molecule), ABCB5 (adenosine triphosphate (ATP) -binding cassette B5), CD24, CD133, CD200, CD44, etc may identify populations that are CSC-enriched (Table 1).^{10,43–45} Other markers have also been used to identify CSCs, like aldehyde dehydrogenase 1 (ALDH1), which is used to characterize CSCs in many types of cancers, including breast, leukemia, colon, liver,

Table 1 Cancer Stem Cell Associated Markers Reported in Different Cancers

Cancer Type	Markers of CSCs
Breast	CD44, CD24, ALDH1A1, ESA, CD61, CD90, CD49f, CD29, LGR5, CD13, NANOG, KLF4, SOX2, BMI1, CXCR4, OCT4, SALL4, CD29, CD133
Cervical	CD44, CD29, CD13, CD105, ABCG2, CD133, CD49f, ALDH
Prostate	CD44, ALDH1A1, CD133, $\alpha 2\beta 1$, CD49f, CD166, NANOG, KLF4, SOX2, BMI1, OCT4, SALL4, CD151, EpCAM, CD117, $\alpha 2\beta 1$, EZH2, CXCR4, E-cadherin
Colorectal	CD44, CD24, ALDH1A1, CD133, ESA, CD166, CD29, CD26, LGR5, NANOG, KLF4, SOX2, Musashi-1, BMI1, SALL4, LETM1, CD200, EpCAM, CD206, CD49f
Ovarian	CD44, CD24, ALDH1A1, CD133, ESA, CD117, NANOG, SOX2, OCT4, SALL4, CD105, EpCAM
Lung	CD133, ALDH1, CD44, CD24, ALDH1A1, ESA, CD34, CD90, CD117, CD166, NANOG, SOX2, BMI1, OCT4, CD87, CD133
Liver	CD44, CD24, ALDH1A1, CD133, ESA, CD90, CD117, CD49f, CD13, OCT4, AFP, CD206, OV-6, EpCAM
Head/Neck	CD44, CD24, ALDH1A1, CD133, CD90, LGR5, BMI1, CD271, CD166
Pancreatic	CD133, CXCR4, SSEA-1, CD44, CD24, CD133, ESA, Nestin, SOX2, BMI1, CXCR4, OCT4, ALDH, ABCG2
Leukemia	ALDH1A1, NANOG, KLF4, SOX2, BMI1, OCT4, CD47
Gastric	CD44, HER2, APC, p53, KRAS, PTEN, LGR5, CCKBR, RHOA, CDH-1, SMAD5, ATP4B, PGA3, CD24, ALDH1A1, CD133, ESA, CD90, NANOG, SOX2, CXCR4, CD15, LINGO2, LETM1, MSI2, CD54, CD49f, CD71, EpCAM
Bladder	CD44, OCT4, CD47, CD66c, CD44v6, ALDH
Brain	CD44, CD133, ESA, SSEA-1, CD90, CD49f, NANOG, KLF4, Nestin, SOX2, Musashi-1, BMI1, CXCR4, CD15, CD36, EGFR, A2B5, L1CAM
Melanoma	CD133, CD166, Nestin, SOX2, OCT4, CD20, ABCB5, CD271, ALDH
Renal	CD133, ALDH, CXCR4, CD44, CD105
Gall bladder	CD44/CD133
Oral	CD44 ⁺ /CD24 ⁻ , ITGA7
Esophageal	ITGA7, CD44, ALDH, CD133, CD90
Nasopharyngeal	CD44, CD133, ALDH, CD24
Laryngeal	ALDH, CD44, CD133
Multiple myeloma	CD19, CD27
Blood	CD34, CD38, CD123, CD90, CD117, CD26, CD20, TIM3, SALL4, CD19

pancreatic, lung, prostate, brain and bladder (Table 1).^{46–51} The expression of CSC markers has been suggested to be associated with certain CSC characteristics like chemoresistance and the recurrence of invasive tumorigenicity.^{52,53} Numerous studies have also reported the expression of pluripotency factors such as KLF4, NANOG, SOX2, OCT4, and c-MYC as phenotypic markers of CSCs.^{54–57} A recent study utilizing triple-negative breast cancer cells has established Kruppel-like factor 8 (KLF8) as the master regulator for the expression of these pluripotency markers.⁵⁸ The study also showed the presence of a positive feedback loop with a metabolic enzyme, O-GlcNAc transferase (OGT). Increased expression of KLF8 correlated with increased resistance to paclitaxel, a commonly used chemotherapeutic agent for breast cancer.⁵⁸

CSCs and Acquisition of Therapeutic Resistance

Drug resistance in CSCs is a multifaceted phenomenon involving various mechanisms that enable these cells to survive and persist despite treatment.^{58,59} This resistance can stem from intrinsic factors, which may be inherited or acquired resistance to medication, as well as extrinsic factors, which result from tumor cells being exposed to chemicals. A few examples of these factors include the hypoxic microenvironment,^{60–62} disrupted cell cycle regulation,⁶³ increased autophagy,⁶⁴ epigenetic modifications,³⁰ microRNA dysregulation, interactions with the tumor microenvironment,⁶⁵ heterogeneity within CSC populations, quiescence,⁶⁵ interactions with the extracellular matrix, and paracrine signaling. These factors ultimately contribute to drug resistance through downstream processes that include epithelial-mesenchymal transition (EMT), drug efflux through ABC transporters, deregulation of essential signaling pathways, expression of multidrug-resistant (MDR) proteins, upregulation of DNA repair proteins, acquired mutations, evasion of apoptosis, and activation of the DNA damage response (DDR) pathway.^{66–69} Gaining a comprehensive understanding of these complexities is crucial to develop effective therapies targeting CSCs and ultimately enhancing cancer treatment outcomes. An overview of the processes responsible for drug resistance in CSCs is presented in the following section.

Quiescence

Quiescence is a biological condition in which the cells do not enter the cell cycle, remain in a state of rest but retain the ability to divide. Adult stem cells exhibit quiescence as a part of tissue homeostasis,⁷⁰ whereas CSCs undergo quiescence to escape drug exposure.⁷¹ CSCs can alternate between the phases of proliferation and quiescence, and the latter state is responsible for cancer recurrence and therapy resistance.^{72,73} CSCs often spend several years in a quiescent state (ie reversible G0 phase) within the body and endure prolonged periods of environmental stress.⁶⁵ These CSCs in the quiescent state are distinct from active CSCs because they lack unique surface markers and common genotypic and phenotypic traits. They do, however, have certain distinctive traits, such as label retention, low RNA content, and lack of expression of proliferative markers,⁷⁴ and have been studied in a variety of cancers.^{75,76} Chemotherapies drive CSCs to enter quiescence through upregulation of hairy and enhancer of split homolog-1 (HES1), a transcriptional repressor of Notch signaling, downregulation of c-MYC resulting in decreased Wnt signaling, increased expression of bone morphogenetic protein 7 (BMP7), which upregulates a metastasis suppressor gene, N-MYC downstream-regulated gene 1 protein (NDRG1) through activation of the p38-MAPK signaling pathway.^{77–79} Epigenetic modifications like DNA methylation and chromatin remodeling also drive CSCs into quiescence. Through H4K20me3 catalysis, SET domain-containing protein 4 (SETD4) induced quiescence in breast CSCs through tighter heterochromatin formation.⁷⁵ These genetic and epigenetic alterations act as a switch to regulate the growth arrest and quiescence of CSCs, which are linked to aggressive biology and chemoresistance of malignancies.^{80,81}

Dormancy

Dormancy is a stage in cancer progression in which cells stop proliferating. When the majority of the cancer population exhibits this phenomenon, the result is known as tumor dormancy, and when a single cancer cell exhibits this phenomenon, the process is referred to as quiescence.⁸² Dormancy is a special case of quiescence and is perhaps a deeper arrested state.⁸³ In contrast to quiescence, where cells resume proliferation more readily, dormancy requires a particular stimulus for cells to proliferate. When cells from the same tumor are disseminated, they have very distinct fates. Most of them experience senescence. Those that survive circulation and extravasation at secondary sites are

destined for a period of dormancy but might also enter quiescence based on the signals received from the microenvironment.⁸⁴ Tumor growth, metastasis, minimal residual disease (MRD), multidrug-resistance (MDR), and tumor expansion are all effects of tumor dormancy.^{85–88} It is a type of clinical remission in which cancer cells are occult (ie undetectable and asymptomatic), for a lengthy period.⁸⁹ CSCs and their clonal development are substantially responsible for tumor dormancy and treatment refractoriness in many forms of cancer.^{90,91} However, it is challenging to identify the precise or overlapping populations responsible for stimulating the processes of dissemination, intravasation, dormancy, and relapse due to the continual refining of the CSCs based on novel markers.⁹¹ Numerous malignancies, including pancreatic carcinoma, ovarian cancer, melanoma, lung cancer and chronic myeloid leukemia (CML) have been shown to have cells that combine stemness, drug resistance, and dormancy.^{92–97}

Enhanced ALDH Activity

A family of nicotinamide adenine dinucleotide phosphate [NAD(P)⁺]-dependent enzymes, the ALDHs detoxify a broad range of aldehydes to weak carboxylic acids, increasing the cell's resistance to injury from medicines.⁹⁸ ALDHs play a crucial role in stem cell maintenance and differentiation as well as in healthy development. Accumulating evidence suggests that the expression of ALDH is upregulated as a response to therapeutic intervention, which in turn facilitates the development of resistance to chemotherapy and radiotherapy.⁹⁹ By metabolizing harmful aldehydes and maintaining low reactive oxygen species (ROS) levels, ALDH enzymes help CSCs survive by regulating their capacity for self-renewal, cell differentiation, and chemoresistance. Through a variety of pathways, they support CSC immune evasion and metabolize retinoic acid, which promotes cancer progression and therapy resistance^{99–101} and are linked to the self-renewal abilities of stem cells in a variety of cancers, including breast cancer, colon cancer, hepatoma, and lung cancer.^{99,102–105} For example, increased ALDH gene expression was associated with high Snail expression. Knockdown of Snail decreased ALDH1 expression, inhibited cancer stem-like properties, and tumor formation ability of CD44+CD24–ALDH+ cells of head and neck squamous CSCs.¹⁰³ High ALDH1 is detected only in CSCs of various tumors like breast, oesophagus, lung, colon, and stomach epithelium and not in the cancer tissues, thus serving as a marker for the identification of CSCs.¹⁰⁶ Among the many isoforms, CSCs express high levels of ALDH1A1 and ALDH3. Normal human and mouse stem cells express high levels of ALDH1^{107,108} while normal human mammary cells have high ALDH3 and low ALDH1.¹⁰⁹ ALDHs mediate drug resistance by converting active 4-hydroperoxycyclophosphamide (4-Hc) to inactive carboxyphosphamide¹¹⁰ and this effect is reversed by pretreatment with N, N-diethylaminobenzaldehyde (DEAB).¹¹¹

Apoptosis Evasion Mechanisms

The hallmark features of malignancies are attributed to the intrinsic ability of CSCs to self-renew, proliferate, and disseminate, as well as evade apoptosis via aberrant regulation of signaling pathways involved in programmed cell death.¹⁰⁴ Cellular Fas-associated death domain-like IL-1 β -converting enzyme (FLICE)-inhibitory protein (c-FLIP) is a negative controller of the death receptor (DR) -initiated apoptotic pathway.¹¹² As a main anti-apoptotic regulator, c-FLIP interacts with Fas-associated death domain (FADD), caspase-8/10, and DR5, preventing the formation of death-inducing signaling complex (DISC) and subsequent activation of the caspase cascade.¹¹³ The CSC population was shown to have higher levels of c-FLIP expression than non-CSC-like cancer cells across a variety of malignancies, including leukemia, breast cancer, and glioblastoma.^{114–116} As a result, compared to their non-CSC-like counterparts, CSCs from these tumors show reduced sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. Several studies have demonstrated that c-FLIP isoforms sustain the survival and resistance of CSCs against apoptosis and anti-cancer treatments.^{117–119} Increasing the expression of c-FLIP in CD133⁺ cells, a marker associated with CSCs involved in metastasis, carcinogenesis, and chemoresistance, can serve as a way to inhibit apoptosis.¹¹²

Proteins from the inhibitor of apoptosis (IAP) family, which block apoptosis, are crucial for supporting cell survival. IAPs can directly or indirectly interact with caspases and thwart the apoptotic cascade. As an alternative, certain IAPs take part in signal transduction and activate the nuclear factor kappa B (NF- κ B) pathway and promote cell survival. Receptor-interacting protein kinase 1 (RIP1) mediates caspase-dependent activation of cell death. Downregulation of RIP1 levels is mediated by IAPs that recruits inhibitor of nuclear factor- κ B (I κ B) kinase (IKK) and E3 ligases and drive

the ubiquitination/degradation of RIP1, leading to cell survival.¹²⁰ IAPs are also involved in the maintenance of CSC properties by enhancing the stability of CSC markers like SOX2.¹²¹ For example, XIAPs blocked the autophagic degradation of SOX2 by inhibiting the activation of ERK1 in CSCs. In nasopharyngeal CSCs, autophagic degradation of SOX2 was inhibited by XIAPs which negatively regulated the activity of ERK1. SOX2 enhanced the stemness of CSCs, suggesting that IAPs can induce the expression of pluripotency markers.¹²¹ Contrary to many oncogenes, B-cell lymphoma-2 (Bcl-2) inhibits cell death and improves tumor cell survival rather than promoting cell proliferation.¹²² Studies have demonstrated elevated levels of Bcl-2 family proteins in CSCs, and these higher levels have been associated with reduced cell death and treatment resistance in CSCs.^{123,124} This resistance of cancer cells to treatment and programmed cell death is partially attributed to the balance between anti-apoptotic and pro-apoptotic protein levels, which promotes cell survival.⁶⁶

High Expression of Drug Efflux Pumps

CSCs have the unique ability to promote tumorigenesis, diversification, and metastasis. According to the CSC model of drug resistance, tumors include a population of pluripotent, drug-resistant cells that may withstand chemotherapeutic shock. CSCs in tumors are protected by ABC efflux pumps, which guard them against the negative effects of chemotherapy. ABCB1, ABCG2, and ABCC1 are among the drug efflux transporter proteins or ABC transporters that have been discovered to be expressed by CSCs. ABC transporters, such as ABCG2, ABCB1, and ABCC1, to mention a few, are linked to drug resistance and are significantly expressed in several malignancies.^{125–128}

Protective Niche

The niche is a term used to describe the unique microenvironment where stem cells divide, differentiate, or stay dormant. Chemokines, immune cells, stromal cells, cytokine networks, growth factors, hypoxic areas, and extracellular matrix (ECM) make up the tumor microenvironment (TME).¹²⁹ TME promotes CSC self-renewal, angiogenesis, modifying immunity, and other conditions that are favorable for metastasis. Dynamic alterations also contribute to treatment resistance, mostly by assisting CSCs in maintaining their stem-related signaling pathways.¹¹² To maintain CSCs in a stem-like state, the CSC niche modifies the signaling pathways of Wnt- β catenin, Notch, and Sonic Hedgehog (Shh), and/or interferes with the function of key transcriptional regulators such as NANOG, OCT4, and SOX2, among other factors.¹³⁰ Additionally, studies have also revealed that CSCs possess the ability not only to differentiate but to actively influence the surrounding microenvironment by recruiting niche components.¹³¹

Enhanced DNA Damage Response

CSCs are suggested to have an enhanced DDR to resolve DNA damage more effectively than bulk cancer cells.^{68,132–134} Studies have revealed that CSCs have a greater amount of inherent replicative stress than other types of cancer cells, leading to a constitutively active DDR. For example, in glioblastoma cancer stem-like cells expressing CD133, a CSC marker, increased expression of replicative stress response markers such as replication protein A2 (RPA2) and H2A histone family member X (H2AX) was observed when compared to CD133[−] cells. This phenomenon is due to the formation of DNA double-stranded breaks in glioblastoma cancer stem-like cells which results in increased DDR.¹³⁵ Additionally, CSCs share numerous characteristics with normal stem cells. Studies indicate that tissue-specific stem cells employ DNA repair pathways to mediate chemotherapy and radiation therapy resistance, and CSCs may exploit these same processes to their benefit.^{133,136,137} Also, the remarkable resistance of CSCs to standard chemotherapy and radiotherapy techniques results from their strong capacity to repair DNA damage caused by chemical agents or radiation. This increased DNA repair capacity may be a direct result of improved repair mechanisms or an indirect effect of slowed cell cycle progression.¹³⁸ Additionally, the CSCs evade therapeutic interventions through modulation of epigenetic marks (eg DNA methylation, promoter methylation/acetylation), long-range chromatin interactions, and altered splicing of nascent transcripts.³⁰

Scavenging of ROS

The physiological and functional activities of a living cell are greatly influenced by its oxidation-reduction (redox) state. Similar to normal stem cells such as hematopoietic stem cells, CSCs also show lower intracellular ROS contents than non-CSCs, which may be due to the increased expression of free radical scavenging systems. Modulation of the level of ROS plays a crucial role in chemoresistance and the upregulation of drug efflux during chemotherapy.^{139,140} ROS also mediate several processes, such as endoplasmic reticulum (ER) stress, autophagy, and disruption of the cell cycle, which contribute to the acquisition of chemoresistance in CSCs.^{141–143} For instance, ROS has been demonstrated to shift the ER-stress-mediated apoptosis to autophagy in methotrexate-resistant choriocarcinoma cells,¹⁴² highlighting their intricate role in drug resistance mechanisms. Enhanced ROS scavenging mechanism and decreased levels of ROS generation are associated with the increased radioresistance of CSCs in breast carcinoma.¹³² Upregulation of genes involved in ROS scavenging pathway such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase has been observed in breast cancer CSCs.¹³² Glutathione is an antioxidant, that plays a critical role in protecting cells against oxidative stress. Buthionine sulfoximine (BSO) inhibits gamma-glutamylcysteine synthetase,¹⁴⁴ which results in decreased synthesis of glutathione. In the absence of adequate levels of glutathione, an increase in ROS levels was observed, which significantly reduced the clonogenic characteristics and radiation therapy resistance of CSCs, supporting the hypothesis that ROS scavengers play a role in CSC radioresistance.¹³²

Hypoxic Stability

Hypoxia occurs when tissues receive insufficient oxygen levels, leading to an inability to maintain proper homeostasis. Tumor hypoxia refers to a condition in which the cells within excessively grown tumors receive less than 2% of the oxygen typically available in normal tissues.¹⁴⁵ It is strongly associated with CSC's resistance to radiation and chemotherapy, making the microenvironment an important factor in cancer progression.^{60,146} The role of hypoxia-inducible factors (HIFs), which function as transcription factors (TFs) in the cell's oxygen signaling pathways, is gaining increasing recognition due to their involvement in both CSC survival and tumor diversification. Moreover, a growing body of experimental evidence demonstrates that HIFs that are not destroyed in the hypoxic condition of tumor cells take part in the change of CSC phenotypes and regulate tumor radiation or chemotherapy resistance.¹⁴⁶ Studies have suggested the role of hypoxia in CSC resistance to radiation and chemotherapy, and that HIFs play a major regulatory role in the hypoxic microenvironment.^{60–62,146} Hypoxia maintains CSC stemness and promotes resistance through activation of self-renewal signaling pathways such as Notch, Wnt, and Shh.^{147,148}

Stemness Signaling Pathways

CSCs share many characteristics with tissue or embryonic stem cells, including the constant activation of highly conserved signaling pathways involved in tissue homeostasis and development, such as Wnt, Shh, Notch, and Hippo signaling pathways. These pathways have been studied to test potential novel CSC-targeting medications since they are linked to CSC self-renewal.^{58,149} These and other findings imply that some oncogenic cues can activate CSCs. These signals are followed by a rise in chemotherapeutic treatment resistance and, in certain situations, radiation resistance.^{58,150} Furthermore, a strong correlation exists between various mitochondrial activities, including mitochondrial biogenesis, metabolism, and dynamics, and the factors contributing to drug resistance in CSCs. A few such factors have been discussed earlier and include ALDH activity, apoptosis evasion mechanisms, ROS scavenging, hypoxic stability, elevated cryoprotective pathways, and more. This observation highlights the pivotal role of mitochondria in the growth and survival of CSCs.^{151–153} By dissecting the role of mitochondria in CSC survival, we can potentially uncover valuable therapeutic opportunities that could be harnessed for the development of effective cancer treatments and management strategies.

Mitochondrion - A Key Organelle in Cancer Stem Cells

Mitochondria are bioenergetic, metabolic, and signaling organelles that are essential for sensing stress and helping cells adapt to their surroundings. Numerous studies have been conducted on the involvement of mitochondria in the emergence and spread of cancer.^{154–156} Mitochondria, which are the primary ATP producers, supply the energy required

for carrying out cellular functions through a process known as oxidative phosphorylation (OXPHOS).¹⁵⁷ In addition to energy production, mitochondria are crucial for the generation of ROS, redox chemicals, and metabolites as well as for controlling cell signaling, cell death, and biosynthetic metabolism.^{158–160} Due to their wide range of functions, mitochondria play a key role in cells' capacity to detect stress and adapt to their surroundings.¹⁶¹ Mitochondria in cancer cells adapt to withstand challenging conditions such as hypoxia, nutrient scarcity, and cancer treatments. As a result, they play a pivotal role in tumor formation, necessitating adaptability to counter cellular and environmental changes, as well as the effects of cancer therapies.¹⁶² Besides bioenergetics, many other aspects of mitochondrial biology have been implicated in cellular transformation. Some of such processes are mitochondrial biogenesis and turnover, metabolism, fission and fusion dynamics, oxidative stress regulation, cell death susceptibility, and signaling.

The morphology, localization, and functions of mitochondria in CSCs differ from normal cells, normal stem cells, and cancer cells.^{163–166} CSCs express fewer mitochondrial DNA copies (mtDNA) and low levels of mitochondrial transcription factor A (TFAM) in contrast to normal cells which express many copies of mtDNA and TFAM.^{163,165,166} Notably, during the process of fibroblast remodeling into iPSCs, a significant reduction in the number of mitochondria takes place, accompanied by decreased mtDNA, mitochondrial mass, and low ROS levels in the stem cells. Conversely, as stem cells differentiate, there is an observable rise in mitochondrial biomass and mtDNA content, resulting in increased ROS and ATP production.¹⁶⁷ Structurally, mitochondria in CSCs are small and round in shape and highly perinuclear in localization whereas in normal cells, mitochondria are elongated and tubular in shape and mostly distributed in the cytoplasm.^{168,169} Cristae within mitochondria appear elongated in regular cells, and spherical in normal stem cells. In CSCs, the cristae become widened and fragmented.¹⁷⁰ Due to fragmented mitochondria, CSCs exhibit impaired aerobic function and reduced ETC, which leads to a decrease in ROS levels causing resistance to HIF-1 α and subsequent activation of MAPK that helps in the maintenance of stemness.^{171–173} Also, CSCs exhibit unique metabolic characteristics compared to cancer cells and normal stem cells. They switch between glycolysis and OXPHOS to produce ATP which is required for their activities. CSCs produce oncometabolites like fumarate, succinate, lactate, and 2-hydroxyglutarate which helps in tumor proliferation, angiogenesis, and invasion through accumulation of HIF-1 α , production of VEGF through activation of STAT3, activation of p65 via NF- κ B pathway and many others.^{174–176} Metabolically, mitochondria from CSCs vary from non-CSCs in terms of glucose uptake/consumption, ROS levels, ATP contents etc depending on the origin of the cancer.¹⁷⁷

In the following section, we discuss the role of different mitochondrial aspects in CSCs and their contribution to drug resistance in CSCs.

Mitochondrial Biogenesis and CSC Resistance

Mitochondrial biogenesis is the process by which cells increase the number and size of mitochondria, an essential process to maintain proper metabolism and the cell cycle. Several mitochondrial proteins involved in biogenesis are encoded in the nucleus and translated to the cytosol. The transport of these proteins from the cytosol to the mitochondria takes place through translocase of the outer membrane (TOM) complex. This process takes place during the M phase of the cell cycle. Thus, mitochondrial biogenesis is linked to cell cycle, thereby enabling proper functioning of the cell.^{178,179} Each cell contains many copies of mitochondrial DNA (mtDNA). The size of human mtDNA is 16.5 kb and comprises 37 genes responsible for coding 13 polypeptides vital for OXPHOS, along with 2 rRNAs and 22 tRNAs necessary for translating the respiratory subunit mRNAs within the mitochondrial matrix. Other mitochondrial proteins are coded in the nuclear genome.¹⁸⁰ Thus, mitochondrial biogenesis is a strictly controlled process that uses “mitonuclear communication” to coordinate a network of both mitochondrial and nuclear DNA (mtDNA and nDNA).¹⁸¹ During the process of mitochondrial biogenesis, a limited number of coactivators and nuclear TFs that are already present in the cell are gradually activated by signaling pathways, leading to the formation of new mitochondria from the pre-existing ones. Mitochondrial biogenesis is stimulated under increased energetic needs by a signaling pathway involving peroxisome proliferator-activated receptor-gamma co-activator 1 (PGC1) family members (such as PGC1 α , PGC1 β , and PPRC1), nuclear respiratory factors (NRF1 and NRF2), mitochondrial transcription factor A (TFAM), and estrogen-related receptors (ERRs) (ERR - α , - β , and - γ), and to a smaller extent, the peroxisome proliferator-activated receptor (PPAR) family of TFs (Figure 1a).¹⁸²

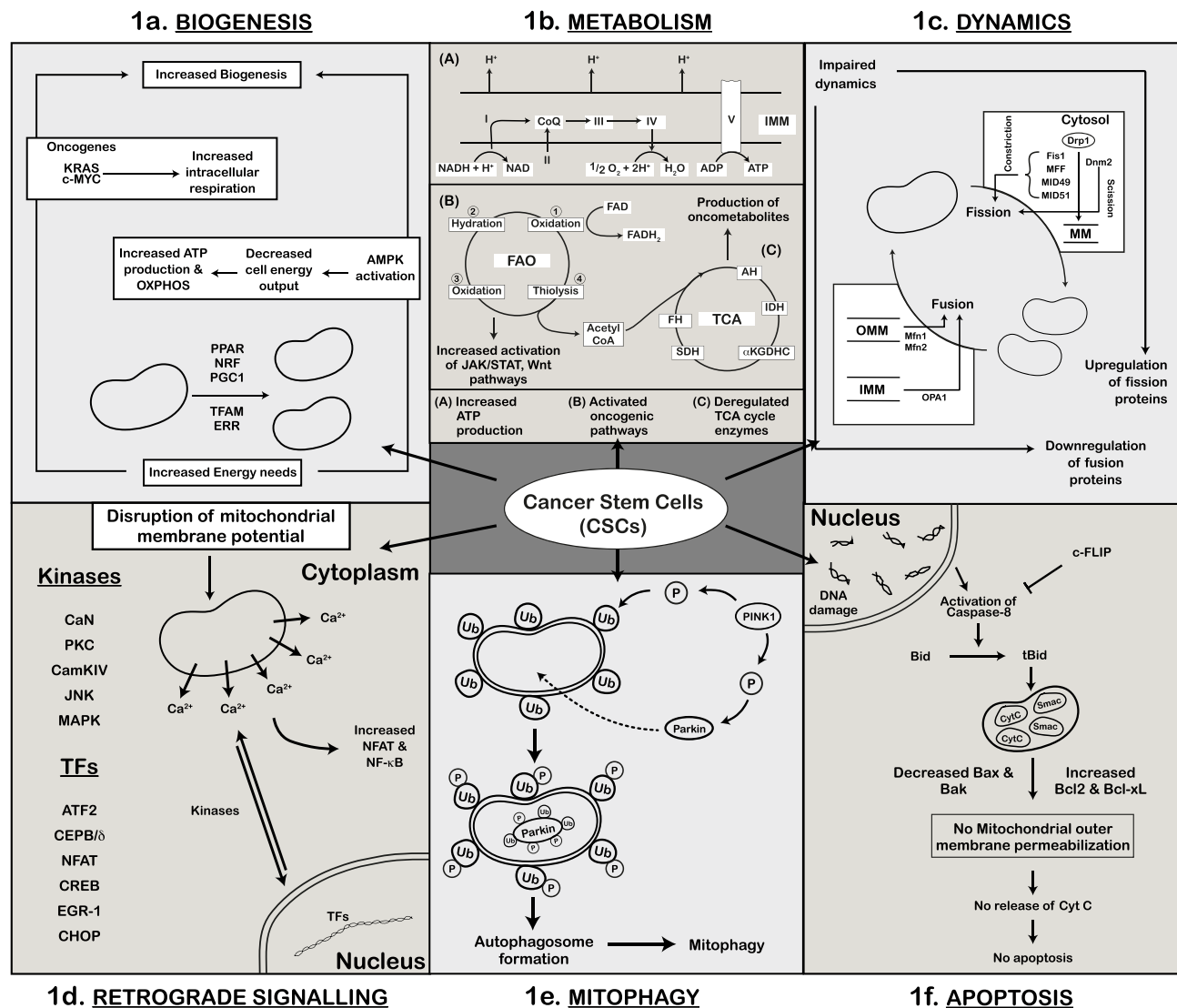


Figure 1 Mitochondrial Dysfunction and Cancer Stem Cells (CSCs). (a) Schematic of mitochondrial biogenesis and its regulation by transcription factors (PGC1, NRF, TFAM, PPAR, and ERR). Additionally, depicted are AMPK, oncogenic KRAS, and c-MYC-dependent mechanisms that lead to increase in biogenesis and energy production. This results in elevated oxidative phosphorylation (OXPHOS) and high ATP levels in CSCs. (b) Representation of mitochondrial metabolic dependency in CSCs. Cellular energy is derived through OXPHOS, fatty acid oxidation (FAO), and the TCA cycle within the mitochondria. CSCs exhibit increased oxidative phosphorylation for enhanced ATP production and elevated fatty acid oxidation through activation of oncogenic pathways. Deregulated TCA cycle enzymes in CSCs produce oncometabolites contributing to cancer progression. (c) Representation of altered mitochondrial dynamics in CSCs, where the balance between mitochondrial fission and fusion is disrupted. Upregulation of mitochondrial fission proteins (Drp1) and their regulators (Fis1, MID49, MID51, MFF) and downregulation of mitochondrial fusion proteins (Mfn1, Mfn2, OPA1) leads to impaired mitochondrial dynamics. (d) Increased activity of Ca²⁺-dependent kinases (PKC, CaN, CAMKIV, JNK, MAPK) due to altered membrane potential in CSCs is shown. Also indicated are the kinases and nuclear transcription factors involved in retrograde signaling. (e) Schematic representation of mitophagy in CSCs. Elevated cytoplasmic PINK1 phosphorylates Parkin and ubiquitinated-OMM proteins. Phosphorylated Parkin is transported into the mitochondria where it ubiquitinates itself and other mitochondrial substrates. These ubiquitin (Ub)-marked mitochondria are degraded by autophagosomes. (f) Mitochondria-mediated apoptosis in CSCs. Cells with damaged DNA activate caspase-8 mediated cell death. In CSCs, activation of caspase-8 is inhibited by high levels of c-FLIP; levels of pro-apoptotic proteins (Bax, Bak) are decreased while levels of anti-apoptotic proteins (Bcl-xL) are increased leading to cell survival and no apoptosis.

The process of mitochondrial biogenesis is different in CSCs from other cells. CSCs exhibit low levels of TFAM and mtDNA when compared to differentiated cancer cells. This phenomenon has been observed in different cancers like lung, thyroid, and colon.^{183,184} Reduced number of mtDNA copies helps in the maintenance of the stemness of cancer cells. Stem-cell like characteristics were observed in esophageal squamous cell carcinoma cells exhibiting low copies of mtDNA. Additionally, the knockdown of TFAM in these cells resulted in the formation of spheres.¹⁶⁶ Mitochondrial biogenesis and mtDNA alterations are frequently linked to increased tumorigenicity and resistance in CSCs. Ethidium bromide (EtBr) inhibits mtDNA replication. Ovarian cancer cells treated with EtBr showed upregulated proliferation

through increased expression of genes like ABCC3, VEGFA, ATF3, etc. They also showed downregulation of mitochondrial-related genes like TMEM165, PDK1, PDK2, etc. The expression of the chemoresistance factor ABCC3, tumorigenicity-related factor HES1 and angiogenesis-related factor VEGFA were upregulated in the cells treated with EtBr. The increased expression of CSC markers CD90 and CD117 was also observed in these cells.²¹

CSCs exhibit increased energy demands for their survival. This results in the activation of TFs like PGC1, NRFs, etc resulting in increased production of ATP and OXPHOS by the activation of AMPK. Adenosine monophosphate (AMP) - activated protein kinase (AMPK) is frequently activated by decreasing cellular bioenergetic output to create ATP and OXPHOS, which in turn triggers mitochondrial biogenesis.¹⁸⁵ AMPK promotes the catabolic pathways performed by the cell resulting in the generation of ATP. The expression of NRF2 was higher in CD44⁺/CD24⁻ doxorubicin-resistant MCF7 cells. Silencing of NRF2 resulted in higher levels of ROS, decreased tumor growth, and reduced sphere formation and invasion in these cells when compared to controls.¹⁸⁶ It is also required for the self-renewal of CSCs. Knockdown of NRF2 decreased the expression of BMI1, SOX2, and Cyclin E in glioma stem cells.¹⁸⁷ Increased levels of NRF2 are crucial for the survival of CSCs and attaining drug resistance. In cervical cancer cells with SP phenotype, increased NRF2 expression resulted in enhanced expression of ABC transporter ABCG2 than in the non-SP cells.¹⁸⁸ PGC1 α plays an important role in causing drug resistance in cancer cells. In ovarian cancer, PGC1 α overexpressing cells were resistant to chemotherapy. They expressed drug resistance-related proteins, MDR1 and ABCG2 and this was observed in tumorspheres than differentiated cells. Additionally, the spheres showed elevated mitochondrial mass and fragmented mitochondria at the perinuclear region. Knockdown of PGC1 α showed decreased mitochondrial mass, downregulated expression of MDR1 and ABCG2, and sensitized the spheres to cisplatin treatment.¹⁸⁹ Oncogenes like KRAS and c-MYC also regulate mitochondrial biogenesis and increase intracellular respiration and biosynthesis, which promotes the development of cancer (Table 2).^{154,190,191}

Mitochondrial Metabolism and CSC Resistance

Mitochondria are subcellular organelles that are maternally inherited and are responsible for fundamental mechanisms of ATP production, including OXPHOS and electron transport chain (ETC), fatty acid oxidation (FAO), and tricarboxylic acid (TCA) cycle. In addition to these roles, mitochondria also play a crucial role in other cellular processes such as calcium signaling, apoptosis, and biosynthesis of important molecules such as heme, pyrimidines, and iron-sulfur (Fe-S) clusters. CSCs mostly depend on these processes to meet the energy demands for their survival. Unlike normal stem cells

Table 2 Drug Category and Mode of Acquired Resistance in Cancer Stem Cells in Different Cancers

Drug	Cancer Type	Impact of the Molecule Involved	Mode of Action	Ref.
Metformin	Pancreatic	Reduced MYC and increased PGC-1 α levels	Lowers ROS levels	[190]
Paclitaxel	Triple Negative Breast Cancer	Increased expression of Myc	Increased mtOXPHOS and ROS levels	[191]
Sorafenib	Hepatocellular	Increased NANOG	Increased FAO	[192]
Gefinitib	Non Small Cell Lung Cancer	Increased expression of HIF-1	Increased IGF1 expression	[193]
Gefinitib	Non Small Cell Lung Cancer	Loss of PTEN	Akt activation; increased TSPYL5 expression	[194]
Temozolomide	Glioma	Loss of PTEN	Promotes SP phenotype	[195]
Paclitaxel & gemcitabine	Triple Negative Breast Cancer	Increased expression of HIF	Increased IL-6 and IL-8 signaling; Increased MDR expression	[196]
Doxorubicin	Breast	Overexpression of Bcl-2	Upregulation of IL-6/STAT3 pathway	[124]

and differentiated cancer cells, CSCs exhibit distinct metabolic characteristics for the maintenance of stemness and self-renewal.¹⁷²

Oxidative phosphorylation (OXPHOS) plays a critical role in the metabolism of CSCs.^{197,198} CSCs utilize ATP produced from OXPHOS for their metabolism. It has been observed that CSCs derived from the ovaries of patients exhibited elevated expression of mitochondrial OXPHOS enzymes.¹⁹⁹ Unlike differentiated cancer cells, which undergo glycolysis, cancer stem cells depend on OXPHOS for their energy needs. In glioma, the comparison of oxygen consumption rate, glucose uptake, lactate production, and intracellular ATP levels between differentiated cancer cells and CSCs, CSCs showed less glycolytic activity, consumed less glucose, and produced less lactate. The increased levels of ATP were also observed in CSCs than the differentiated cells. Additionally, glioma stem cells were found to be radioresistant.²⁰⁰ In gliomaspheres, OXPHOS is known to be regulated by oncofetal insulin-like growth factor 2 mRNA-binding protein 2 (IMP2, IGF2BP2). IMP2 participates in the assembly and function of mitochondrial respiratory chain complex subunits by binding to mRNAs that code them. Depletion of IMP2 impaired OXPHOS by affecting complex I and complex IV mRNA and protein levels in gliomaspheres.²⁰¹

Fatty Acid Oxidation (FAO) is required for the maintenance of stemness in CSCs. In a study on liver tumor-initiating stem-like cells (TICs), NANOG was found to be essential for FAO. Knockdown of NANOG resulted in decreased mRNA and protein levels of FAO-associated genes like *Echs1*, *Acads*, and *Acadv1*. The FAO flux analysis with ¹⁴C-radiolabeled-palmitic acid to produce acid-soluble ¹⁴C metabolites and ¹⁴CO₂ demonstrated that NANOG⁺ TICs showed higher levels of FAO activity compared to controls.¹⁹² Carnitine palmitoyl transferase I (CPTI) and carnitine palmitoyl transferase II (CPTII) enzymes are crucial in increasing FAO in radioresistant breast cancer cells. Downregulation of the ERK pathway was observed in cells by blocking FAO by CRISPR-mediated CPTI/CPTII knockdown and inhibited the formation of tumorspheres in radioresistant breast CSCs.²⁰² FAO is also regulated by JAK/STAT3 and is critical for CSC self-renewal and chemoresistance. Inhibition of JAK/STAT3 blocked the self-renewal of breast CSCs. It also resulted in reduced expression of the CPT1B gene, which codes for an enzyme involved in FAO.²⁰³ The reduced products formed during FAO, FADH₂ and NADH, are funnelled back to the respiratory chain where they are oxidized to produce ATP which is required for the survival of CSCs.²⁰⁴ Elevated levels of FAO contribute to chemoresistance in different cancers by increased levels of oncogenic pathways like JAK/STAT3, and Wnt (Table 2).^{192,203,205,206}

The TCA cycle, sometimes referred to as the Krebs cycle or the citric acid cycle, is a sequence of chemical processes that take place in a closed loop and function as an internal metabolic engine in cells oxidizing carbohydrates, proteins, and lipids.²⁰⁴ In a simplistic view, the TCA cycle is a continuous cyclic mitochondrial pathway that is continually oxidizing the acetyl moiety of acetyl-CoA to carbon dioxide (CO₂), creating NADH and FADH₂, whose electrons power the mitochondrial respiratory chain for ATP production.²⁰⁴

In normal cells, the TCA cycle is fuelled by glucose whereas in CSCs the products of the glutamine pathway fuel the TCA cycle.²⁰⁷ In human malignancies, several mitochondrial enzymes, involved in the TCA cycle like Aconitate Hydratase (AH), Isocitrate Dehydrogenase (IDH), Fumarate Hydratase (FH), Succinate Dehydrogenase (SDH), and α -ketoglutarate dehydrogenase complex (α -KGDHC) are often altered or deregulated (Figure 1b) and have been linked to cancer progression.²⁰⁸ Moreover, these mutations lead to the aberrant accumulation of various metabolites, known as oncometabolites like (R)-2-hydroxyglutarate, fumarate, and succinate. These oncometabolites can interfere with fundamental cellular processes, particularly epigenetic regulation, and contribute to cancer development and progression.²⁰⁹ Oncometabolites can alter epigenetic regulation by inhibiting enzymes involved in the removal of epigenetic marks, such as DNA and histone demethylases, or by promoting the activity of epigenetic writers, such as DNA methyltransferases and histone acetyltransferases. For example, mutations in SDH and FH cause the accumulation of succinate and fumarate and inhibit multiple α -KG-dependent dioxygenases such as histone and DNA demethylases in cancers.²¹⁰ Also, mutations in SDH and FH result in the stabilization of HIF-1 α , a transcription factor responsible for promoting tumor survival and metastasis.²¹¹ Another prominent example is the inhibition of the activity of the ten-eleven translocation (TET) methyl-cytosine hydroxylases and Jumonji (JmjC) domain-containing histone demethylases in gliomas and acute myelogenous leukemia due to mutant IDH.^{30,212} The dysregulation of epigenetic regulation by oncometabolites is thought to play a critical role in the development and progression of several cancers, including renal cell carcinoma

and certain types of leukemia. Targeting the metabolism of cancer cells, including the production and accumulation of oncometabolites, is an area of active research for cancer therapy development.

Mitochondrial Dynamics and CSC Resistance

The process of mitochondrial fission (constriction and scission) and fusion, known as mitochondrial dynamics, regulates the shape, quality, and number of mitochondria. In contrast to mitochondrial fusion, which involves joining two mitochondria to form a single mitochondrion, mitochondrial fission is characterized by the division of a single mitochondrion into two daughter mitochondria. Large GTPase proteins from the Dynamin (Dnm) family make up the majority of the core machinery proteins.²¹³ These mechanoenzymes can oligomerize and alter conformation to promote membrane remodeling, constriction, scission, and/or fusion.²¹⁴ Mitochondrial fission is carried out by the Dnm-related-like protein 1 (Drp1) that can be recruited to the mitochondrial membrane (MM) from cytoplasm with the help of mitochondrial receptor proteins Fis1, MID49, MID51, MFF (for constriction) and Dnm2 (for scission) (Figure 1c).²¹⁵ On the other hand, mitochondrial fusion is ensured by mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1), which mediate outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM) fusion, respectively (Figure 1c).²¹⁶ Up-regulation of fission-related proteins and down-regulation of fusion-related proteins have been implicated in the onset, development, metastasis, CSC survival, and treatment resistance of several cancers.^{217–220} The inhibition of Drp1, a fission-related protein using mdivi-1 resulted in the inhibition of cell migration and CSC signaling in breast cancer. The inhibition also reduced the formation of tumorspheres in a dose-dependent manner in breast, lung, and melanoma cells.²²¹ In another study, high expression of OPA1 was observed in the tumorspheres of NSCLC CSCs, which was due to overexpression of SPDEF, a SAM Pointed Domain containing ETS transcription factor.²²² Mitochondrial fission and fusion enhance CSC stemness and maintain self-renewal. Knockdown of fission-related genes such as Drp1, and MFF reduces the expression of stemness-associated genes like OCT4, NANOG, etc, and the tumorsphere formation capability of CSCs in brain and prostate cancer.^{220,223} Moreover, the inhibition of Drp1 by mdivi-1 reduces the capacity of CD44⁺ CSCs to form tumors in vitro and in vivo in nasopharyngeal cancer.²²⁴ Similarly reduced populations of CD133+CD15+ brain tumor-initiating cells and decreased levels of stemness genes in EpCAM+CD133+ liver cancer stem cells were observed upon Drp1 inhibition with mdivi-1.^{220,225} Phosphorylation of Drp1 induces mitochondrial fragmentation to promote metabolic adaptation and chemoresistance as seen in acute lymphoblastic leukemic T-cells.²²⁶

Mitochondrial Retrograde Signaling and CSC Resistance

Mitochondrial retrograde signaling refers to the cellular response to changes in mitochondrial activity and state and is a vital component in maintaining cellular homeostasis. Mitochondrial retrograde signaling enables the transmission of information regarding alterations in mitochondrial bioenergetics and redox potential to the rest of the cell. Altered nuclear gene transcription due to mitochondrial dysfunction opens new avenues in mitonuclear communication.²²⁷ Under both normal and pathological circumstances, mitochondria can communicate with the nucleus through mitochondrial retrograde signaling. Disruption of the MM potential and poor absorption of Ca²⁺ leads to increased intracellular Ca²⁺. This triggers the activity of Ca²⁺ dependent kinases such as protein kinase C (PKC), c-Jun N-terminal kinase (JNK), calcium/calmodulin-dependent protein kinase IV (CamKIV), and mitogen-activated protein kinase (MAPK) which then function through various transcription factors like activating transcription factor 2 (ATF2), nuclear factor of activated T-cells (NFAT), CCAAT/enhancer-binding protein delta (CEBP/δ), early growth response protein 1 (Egr-1), cAMP-response element binding protein (CREB), C/EBP homologous protein (CHOP), and NF-κB, to alter the nuclear gene expression (Figure 1d). Additionally, increased Ca²⁺ levels activate calcineurin (CaN), a calcium-dependent serine-threonine phosphatase that is thought to have developed from RTG-dependent retrograde (RTG) signaling and increases NFAT and NF-κB.²²⁸ The ongoing maintenance of the organelle may be viewed as a delicate balance between its biogenesis and the quality control systems (engaged in remodeling and mitophagy) that ensure cell homeostasis and function. Numerous antioxidant enzymes like GPX1, PRDX3, PRDX5, SOD2, chaperones, and quality control proteases work together to maintain this function by promoting protein folding and stability on the mitochondria while degrading accumulating unfolded or misfolded proteins.²²⁹

The molecular connection between the nucleus and mitochondria, which involves ATP, calcium, and ROS, is crucial for this regulation.²³⁰ Mitochondrial-to-nucleus communication, also activates a coordinated expression of nuclear genes to relieve the stress and/or to compensate for the defect upon organelle dysfunction which are caused by many events, such as mtDNA depletion, deletions, mutations, aggregation of misfolded proteins, oxidative stress, or dramatic changes in morphology and dynamics.²³¹ The dysfunction of mitochondria due to these factors results in the activation of retrograde signaling, which alters the transcription of nuclear genes that encode mitochondrial proteins involved in retrograde signaling. This alteration can lead to the acquisition of stemness, EMT induction, resistance to apoptosis, and drugs in CSCs.^{232–234} For example, the reduction of mtDNA activated CaN-dependent mitochondrial retrograde signaling and generated breast CSCs. This CaN-mediated mitochondrial retrograde signaling led to the induction of EMT by increased mesenchymal gene expression in mtDNA-reduced cells.²³⁵ These changes occur through dysregulation of TFs involved in mitochondrial retrograde signaling. Also, the triggering of the signaling pathways involved in retrograde signaling converges on the upregulation of genes affecting several cellular functions, including apoptosis resistance, MDR, invasion, and EMT.¹⁵¹ In prostate cells depleted of mitochondria, PARP inhibitor AGD14699 activates Ca²⁺-mediated retrograde signaling and downregulates BRCA2 levels. Decreased levels of BRCA2, a tumor suppressor protein that regulates the homologous DNA repair process, make the prostate cells sensitize to PARP inhibitor, resulting in cell death. This demonstrates that the presence of mitochondria in the cells provides resistance to drugs.²³³

Increased ROS obtained after mtDNA depletion in hepatocellular carcinoma cells, activates NRF2 signaling pathway and multidrug-resistance proteins MRP1 and MRP2 to help tumor cells fight against ROS and resist cisplatin and doxorubicin treatment.²³⁶ Also, mitochondrial stress-related ROS modulates the expression of PGC1 α , a key regulator of mitonuclear communication, to promote OXPHOS and confer cisplatin resistance in SKOV3 ovarian cancer cells.²³⁷ Porporato et al have shown that dysfunction in the ETS results in ROS overproduction that activates Src, which in turn induces the expression of Pyk2, a FAK family protein tyrosine kinase known to promote cytoskeletal remodeling, migration, and EMT in SiHa cells.²³⁸ The above studies indicate a key role for mitochondrial retrograde signaling in maintaining stemness and in drug resistance of cancer cells. However, the role of mitochondrial retrograde signaling in CSC drug resistance is still being explored.

Mitophagy and CSC Resistance

To ensure a robust and healthy mitochondrial population, cells employ a controlled catabolic process known as mitophagy, which serves to eliminate any damaged or defective mitochondria. By doing so, mitophagy plays a crucial role in reducing cell damage, promoting cellular homeostasis, and supporting overall cell survival.²³⁹ Mitophagy plays a crucial role in conferring tumor resistance to various cancer therapies (Table 2) by facilitating the degradation of impaired mitochondria, consequently leading to a reduction in mitochondrial ROS levels.^{240,241} Different routes can be used to activate mitophagy. One such mechanism is through the phosphatase and tensin homolog (PTEN) -induced putative kinase 1 (PINK1) and Parkin signaling pathway. The PINK1/Parkin pathway is in-charge of preparing damaged mitochondria for selective autophagic identification. In general, PINK1 is transported into the IMM by translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) complexes, where it is digested by the proteasome and cleaved by the mitochondrial protease PARL (presenilin-associated rhomboid-like) (Figure 1e).²⁴² When the mitochondria are depolarized, PINK1 remains connected to the OMM and recruits PARKIN which helps in ubiquitylation of OMM substrates. This ubiquitylation pattern acts as a signal for the sequestration of damaged mitochondria (Figure 1e).²⁴³ Thus, depolarization of MM results in increased OMM expression of PINK1 following recruitment of Parkin to the mitochondria allowing selective and effective turnover of damaged mitochondria.²⁴⁴

Another mechanism that contributes to the removal of mitochondria under physiological and diseased conditions is MM receptor-mediated mitophagy. This includes different receptors like BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), BNIP3L/NIX, FUN14 domain-containing protein 1 (FUNDC1), an activating molecule in Beclin 1-regulated autophagy (AMBRA1), FK506-binding protein 8 (FKBP8), ATPase family AAA domain-containing protein 3B (ATAD3B), and some kinds of lipids (cardiolipin (CL) and C18-ceramide).²⁴⁵ The key mediators of hypoxia-induced mitophagy include BNIP3 and BNIP3L/NIX. Interestingly, the transcription of BNIP3 and NIX is influenced by HIF-1.

Mitophagy contributes significantly to the mitochondrial stress response through these two pathways, as well as to the regulation of mitochondrial quality and the maintenance of homeostasis.^{246–249} CSCs utilize mitophagy to promote their survival.^{248–250} For example, in hepatic CSCs, enhanced mitophagy promoted the recruitment of phosphorylated p53 to the mitochondria thereby increasing the nuclear expression of NANOG and promoting stemness.²⁴⁷ This process facilitates the selective distribution of mitochondria between stem-like and non-stem-like cells. For example, when mammary epithelial stem-like cells divide, the daughter cells with stem cell characteristics inherit fewer older mitochondria, whereas the differentiated cells receive a higher proportion of older mitochondria. Consequently, stem-like cells inherit the newest and most efficient mitochondria, promoting their continued function, while the differentiated daughter cells that receive older mitochondria are eventually eliminated.²⁵¹ Enhanced mitophagy within the CSC population facilitates the removal of aberrant mitochondria, promoting cell growth and survival across various tumor types.²⁵² The ability of CSCs to enter a state of cell quiescence is tied to mitophagy. Mitophagy results in a decrease of mitochondrial mass and subsequently reduced OXPHOS activity. As a result, cells switch to glycolysis to meet their energy demands.¹⁷⁸ Glycolysis drives CSCs to enter a quiescent state and is also crucial to increase antioxidant compensative capacity, enhancing stemness, and improving self-renewal capacity.^{253–255} As mentioned above, BNIP3 is highly expressed under hypoxic conditions. In glioblastoma cells, growing in hypoxic situations, it has been demonstrated by Jung et al that BNIP3-mediated mitophagy promotes cell survival by clearing ROS levels.²⁴⁹ In oral squamous cell carcinoma, CD44⁺/ABCBI⁺/ADAM17⁺ CSCs exhibited resistance to cisplatin. Higher autophagic flux and mitophagy were observed in drug-resistant FaDu cells compared to parental cells. Mitophagy is a key contributor to doxorubicin resistance in CSCs of HCT8 human colorectal cells. The CD133⁺/CD44⁺ cells were more resistant to doxorubicin treatment. Silencing of BNIP3L prevented mitophagy and increased sensitivity to doxorubicin therapy.²⁵⁶ Deletion or mutation of PARK2 and BNIP3 inhibits mitophagy and thereby promotes carcinogenesis. Loss of function mutation in the PARK2 gene has been detected in colorectal cancer.²⁵⁷ Therefore targeting mitophagy in CSCs could sensitize cells to various chemotherapeutic drugs.

Apoptosis and CSC Resistance

Mitochondria play a central role in apoptotic cell death. The intrinsic apoptosis process is triggered by DNA damage, the loss of survival factors, and alterations in cell cycle checkpoints. As part of the intrinsic pathway, BH3-interacting domain death agonist (Bid) is cleaved to truncated Bid (tBid) in the presence of activated caspase-8. This results in tBid translocation to the mitochondria and causes mitochondrial outer membrane permeabilization (MOMP) by activating Bcl-2 associated x -protein (Bax) and Bcl-2 homologous antagonist/killer (Bak), resulting in the release of Cyt C and mitochondria-derived activator of caspase (Smac) from mitochondria which are transported to the cytosol. In the cytosol, Cyt C interacts with ATP, apoptosis peptidase-activating factor-1 (Apaf-1), and initiator pro-caspase-9 to form a signaling complex called apoptosome where caspase-9 is activated, in turn causing the activation of effector caspases-3, -6, and -7 to cause apoptosis (Figure 1f).²⁵⁸ It has been demonstrated that higher levels of Bcl-2 family proteins are related to drug resistance in many cancers. Bcl-2 deregulation hinders the oligomerization of Bax and Bak, preventing MOMP, which in turn blocks the release of Cyt C into the cytosol and thereby inhibits apoptosis (Figure 1f).²⁵⁹ Increased levels of Bcl-2 proteins were detected in many CSCs like breast and colon.^{123,124} Additionally, mitochondria to nuclear retrograde signaling is related to increased transcription of anti-apoptotic Bcl-2 family members and activation of survival signals like Akt. CSCs also show apoptosis resistance by increased expression of anti-apoptotic proteins like c-FLIP and IAPs (as discussed in the earlier sections) that can block the activation of caspases, thereby inhibiting apoptosis.^{39,260} Acquired resistance to drugs by CSCs through dysregulation of apoptosis-regulating proteins is a recurrent theme observed in many cancers (Table 2).

Conclusion

Resistance to chemotherapeutic agents has grown into a major issue in the treatment of cancers. CSCs evolve diverse mechanisms to enable this therapeutic evasion of tumors, contributing to poor prognosis. Mitochondria play a central role in imparting drug resistance to the CSCs by altering many pathways involved in biogenesis, metabolism, dynamics, and retrograde signaling. Developing strategies to target different molecules involved in resistance pathways especially those

associated with mitochondria, either alone or in combination with various chemotherapeutic agents could help in the sensitization of CSCs, promoting effective treatment.

Mitochondria-targeting therapies for CSCs are a new and promising approach, but still in the preclinical stages. Mitochondrial uncouplers selectively disrupt the proton gradient across the mitochondrial membrane, leading to oxidative stress-induced apoptosis in CSCs. Mitochondrial-targeting drugs, such as elesclomol, induce mitochondrial ROS production and lead to apoptosis in CSCs.²⁶¹ Targeting mtDNA mutations using drugs or other therapies is another promising strategy for eliminating CSCs. Additionally, targeting mitochondrial dynamics, including fusion and fission, using drugs like mdivi-1 can induce mitochondrial fission, leading to the selective elimination of CSCs. However, it is essential to note that this is still an area of ongoing research, and the development of therapies targeting mtDNA mutations to eliminate CSCs is complex and may face challenges. Understanding the mechanisms and vulnerabilities of CSCs, as well as potential off-target effects of such treatments, will be critical in realizing the full potential of this approach.

Mitochondrial retrograde signaling is a process by which mitochondria communicate with the nucleus to alter gene expression in response to changes in mitochondrial function. Dysregulation of mitochondrial function, such as through mutations or environmental stressors, can lead to the activation of retrograde signaling pathways and alterations in nuclear gene expression that can promote stemness, EMT, drug resistance, and other hallmarks of cancer. Thus, by understanding the link between mitochondrial function and nuclear gene expression, novel strategies to target CSCs and prevent tumor recurrence can be developed. Targeting mitochondrial function or the pathways involved in mitochondrial retrograde signaling could potentially be used to induce apoptosis or differentiation of CSCs, sensitize them to traditional cancer therapies, or prevent the emergence of drug-resistant CSCs. Despite the promising results of these mitochondria-based therapies in preclinical models, there are still several challenges such as potential toxicity to normal cells and the heterogeneity of CSCs that need to be addressed to translate these therapies into clinical applications.

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