BBA - Reviews on Cancer 1880 (2025) 189450

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review Article

Unraveling the role of mitochondrial dynamics in cancer stem cells: Molecular basis and therapeutic implications

Gaia Giannitti, Sara Marchesi, Riccardo Garavaglia, Ivan Preosto, Fabrizio Fontana *

Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy

ARTICLE INFO

Keywords:
Cancer stem cells
Mitochondrial dynamics
Mitochondrial biogenesis
Mitochondrial fission and fusion
Mitophagy
Cancer therapy

ABSTRACT

Many tumors consist of heterogeneous cell populations derived from a minority of cancer stem cells (CSCs), which possess distinct metabolic profiles that contribute to resistance against conventional anticancer therapy and increase the risk of tumor relapse. These unique CSC phenotypes are largely supported by altered mitochondrial function and turnover, regulated through continuous cycles of mitochondrial biogenesis, fission, fusion, and mitophagy. Consequently, understanding mitochondrial regulatory mechanisms in CSCs could reveal novel targets for cancer therapy. This article explores how mitochondrial dynamics contribute to CSC metabolic adaptation and drug resistance, alongside recent advances in the development of mitochondria-targeted drugs and their therapeutic usage.

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide [1]. Despite advances in therapy, recurrence and metastasis continue to limit patient survival [1]. A growing body of evidence supports the existence of a distinct subpopulation of cancer cells, namely cancer stem cells (CSCs), that may play a central role in tumor initiation, progression, and therapy resistance [2,3]. The origin of CSCs is not fully understood, but several hypotheses have been proposed. CSCs may arise from normal adult stem cells or progenitor cells that acquire oncogenic mutations, transforming them into tumor-initiating cells; on the other hand, differentiated or partially differentiated malignant cells may regain stem-like features under selective pressures, such as genetic instability or therapeutic stress [4]. Irrespective of these origins, CSCs exhibit several hallmark properties that distinguish them from the bulk tumor population: they can replicate indefinitely, maintaining their subgroup within the tumor over time; similar to normal stem cells, they can give rise to heterogeneous cell types that compose the tumor, contributing to its cellular diversity; only CSCs demonstrate the capacity to initiate cancer formation when transplanted into immunocompromised mice, often requiring far fewer cells than non-CSCs to generate a tumor mass; they are highly resistant to conventional therapies such as chemotherapy and radiation, attributed to mechanisms including quiescent cell cycle status, enhanced DNA repair capacity, high expression of drug efflux pumps, and anti-apoptotic signaling; CSCs are identified and isolated based on the expression of specific surface markers, such as CD44, CD133, and aldehyde dehydrogenase 1 (ALDH1) [2–4]. The identification of these stem-like traits has revolutionized our understanding of cancer heterogeneity and treatment failure. More importantly, targeting CSC biological characteristics offers a promising avenue for developing more effective and durable therapies [2–4].

Mitochondria, often described as the powerhouses of the cell, are central to a diverse array of essential cellular functions that extend well beyond their classical role in ATP generation via oxidative phosphorylation (OXPHOS) [3,5]. These organelles are intricately involved in the regulation of calcium homeostasis, modulation of intracellular reactive oxygen species (ROS) levels, and initiation and execution of programmed cell death pathways, particularly apoptosis. Collectively, these roles underscore mitochondrial function as a dynamic signaling hub that influences a wide spectrum of cellular outcomes [3,5]. Crucially, mitochondria possess the unique ability to integrate multiple intracellular signals and respond to various extracellular environmental cues—ranging from nutrient availability to oxidative and genotoxic stress. This integrative capacity enables cells, including CSCs, to dynamically and effectively adapt to changing physiological and pathological conditions, thereby promoting enhanced survival, metabolic flexibility, and proliferative capacity even under adverse or treatment-resistant microenvironments [5–7]. A key aspect of mitochondrial adaptability lies in their highly dynamic nature. Mitochondria constantly undergo morphological and functional remodeling through

* Corresponding author.
E-mail address: fabrizio.fontana@unimi.it (F. Fontana).

https://doi.org/10.1016/j.bbcan.2025.189450
Received 18 June 2025; Received in revised form 8 September 2025; Accepted 9 September 2025
Available online 10 September 2025

coordinated processes such as mitochondrial biogenesis, fusion, fission, and mitophagy. These dynamic events are not only fundamental for preserving mitochondrial integrity and maintaining overall cellular homeostasis, but are now recognized as critical regulators of cellular identity and fate decisions [5–7]. In CSCs, these processes have been shown to influence core properties associated with stemness, including self-renewal, differentiation blockade, and resistance to therapeutic stress. For instance, mitochondrial fusion promotes oxidative metabolism and supports the quiescent state characteristic of many CSCs, while fission is often linked to increased mitochondrial fragmentation, metabolic reprogramming, and readiness for cell division [8]. Similarly, mitophagy plays an essential role in the selective removal of damaged mitochondria, thereby preventing excessive ROS accumulation and ensuring mitochondrial quality control—features particularly important for maintaining the long-term viability and genomic stability of CSCs [9,10]. Importantly, these mitochondrial quality control mechanisms are not merely passive or background housekeeping processes. Instead, they are deeply embedded in the regulatory circuits that define the malignant behavior of CSCs. Through their influence on redox signaling, metabolite availability, and apoptotic threshold, mitochondrial dynamics actively shape the metabolic and signaling landscape within CSCs, reinforcing their tumor-initiating capacity, adaptability, and resilience to therapy. This mitochondrial-centric perspective highlights the dual role of these organelles as both facilitators of metabolic fitness and drivers of oncogenic signaling [11].

While the broader implications of mitochondrial metabolism and bioenergetics in CSC biology have been extensively reviewed in the literature [6,7], this article focuses specifically on the role of mitochondrial dynamics in supporting CSC identity, survival, and tumorigenic potential. In addition, we explore the emerging therapeutic potential of targeting mitochondrial dynamics as a novel strategy to selectively disrupt CSC function. By exploiting the unique mitochondrial dependencies and vulnerabilities of CSCs, such interventions hold significant promise for overcoming conventional treatment resistance, reducing tumor relapse, and ultimately improving long-term clinical outcomes in patients with various malignancies.

2. Mitochondrial biogenesis, content and distribution in cancer stem cells

As illustrated in Fig. 1, mitochondrial biogenesis is the cellular process of generating new mitochondria, typically in response to increased energy demands or to replace damaged organelles. This process involves coordinated synthesis of nuclear and mitochondrial components, including mitochondrial DNA (mtDNA) replication. A central regulator of this pathway is the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which stimulates the expression of genes that drive mitochondrial generation and distribution [12]. Remarkably, these mechanisms are deeply implicated in the control of CSC traits among a variety of malignancies.

2.1. PGC-1α

As previously mentioned, PGC-1α is widely recognized as a principal driver of mitochondrial biogenesis. Mechanistically, it activates nuclear respiratory factors (NRF1 and NRF2) and mitochondrial transcription factor A (TFAM) upon nuclear translocation, thereby promoting mitochondrial protein production and mitochondrial proliferation. Beyond this, it interacts with several nuclear receptors—including peroxisome proliferator-activated receptors (PPARs), estrogen-related receptors (ERRs), hepatic nuclear factors (HNFs), liver X receptors (LXRs), farnesoid X receptor (FXR), retinoic acid receptor (RARα), and the glucocorticoid receptor—to modulate broader aspects of energy metabolism [12]. Interestingly, Lisanti and colleagues were among the first to show that PGC-1α is significantly upregulated within the stem cell niche of breast tumors. This upregulation contributes to an increased mitochondrial mass specifically within these stem-like cellular compartments, suggesting that enhanced mitochondrial biogenesis supports the metabolic demands and self-renewal capacity of SCs in breast cancer [13,14]. Following this seminal work, subsequent studies have corroborated these findings across a range of other malignancies, including melanoma and cholangiocarcinoma, indicating that the elevation of PGC-1α expression and the associated mitochondrial expansion may represent a conserved metabolic adaptation within CSC populations in

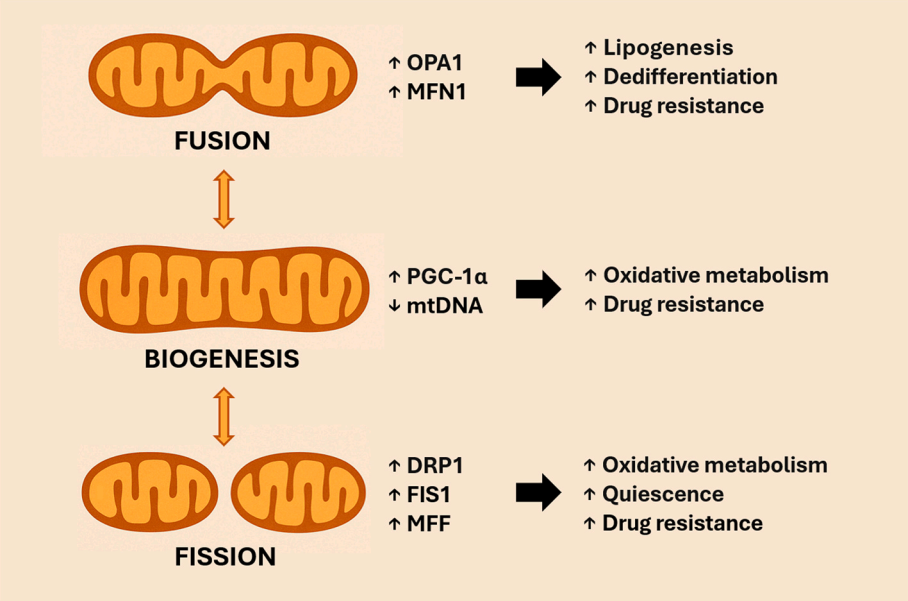

Fig. 1. Mitochondrial biogenesis, fission, and fusion in cancer stem cells. Emerging evidence indicates that cancer stem cells (CSCs) are characterized by improved mitochondrial dynamics. In particular, they display increased PGC-1α–driven mitochondrial biogenesis, leading to the perinuclear localization of a high number of mitochondria. However, some studies suggest that mitochondrial DNA (mtDNA) content in CSCs is lower than in their differentiated counterparts. Parallelly, both mitochondrial fission and fusion seem to be upregulated in cancer stem-like populations, due to overexpression of key mitochondrial proteins such as DRP1, FIS1, MFF, OPA1, and MFN1. Altogether, these processes finely orchestrate CSC state, metabolism, and drug resistance.

diverse tumor types [15,16]. More recently, PGC-1α has also been linked to drug resistance in CSCs. In a study by Viale et al., pancreatic tumor cells that survived $KRAS^{G12D}$ ablation—characterized by $CD133^{+}$ and $CD44^{high}$ expression—exhibited elevated PGC-1α levels and increased mitochondrial mass [17]. These surviving CSCs displayed altered mitochondrial morphology, greater reliance on OXPHOS, reduced glycolytic activity, and heightened sensitivity to OXPHOS inhibitors in relapse-prone mouse models [17]. These findings highlight the fundamental metabolic differences between bulk tumor cells and CSCs, emphasizing that the latter strongly rely on mitochondrial function for energy production and survival under stress. This metabolic distinction not only reinforces the unique vulnerabilities of CSCs but also supports the strategic targeting of mitochondrial pathways to selectively eliminate these therapy-resistant cell populations: by disrupting mitochondrial biogenesis in CSCs, it may be possible to prevent tumor relapse, reduce metastasis, and increase treatment efficacy.

2.2. mtDNA

In contrast to the above evidence, several studies suggest that a reduced mtDNA copy number is also associated with stemness in various CSC populations. In cancers such as colon, thyroid and lung carcinoma, CSCs have been shown to harbor significantly fewer mtDNA copies compared to their more differentiated counterparts [18,19]. Similar results have been observed in prostate, ovarian and esophageal squamous cell cancer models, where ethidium bromide-induced mtDNA depletion increased stem-related gene expression and resistance to radio- and chemotherapy [20,21]. This might represent a compensatory response to mitochondrial dysfunction or mtDNA damage caused by oxidative stress, hypoxia, or treatment pressure within the tumor microenvironment. While nuclear-encoded transcriptional coactivators can drive the production of mitochondrial proteins and promote biogenesis, defects in mtDNA replication or maintenance may limit mtDNA copy number. In this regard, it should be noted that CSCs often adopt a "lean" mitochondrial phenotype that sustains key functions such as redox homeostasis and apoptosis resistance, even with reduced mtDNA content [22]. In this scenario, the mitochondrial-to-nuclear communication is supposed to strongly influence dedifferentiation and self-renewal [8]. Supporting this hypothesis, a study in human mammary epithelial cells (hMECs) showed that reduced mtDNA levels activate a calcineurin-dependent mitochondrial retrograde signaling pathway, triggering epithelial-to-mesenchymal transition (EMT)-like reprogramming. This transition leads to loss of polarity, increased migration and invasion, and acquisition of self-renewing stem-like traits. Crucially, restoring mtDNA content reverses these stem-like characteristics, indicating that mitochondrial dysfunction precedes and potentially initiates changes in cell identity [23]. These insights unveil a compelling therapeutic opportunity: targeting the mitochondrial retrograde signaling cascade to selectively eliminate the stem-like cellular populations that persist despite conventional treatments. This strategy not only addresses a key driver of treatment failure and tumor recurrence but also opens the door to novel interventions that exploit the unique mitochondrial dependencies of CSCs.

2.3. Mitochondrial positioning

Numerous studies have demonstrated that the accumulation of mitochondria at the leading edge of the cell membrane enhances cell motility and invasive capacity, thereby promoting cancer cell metastasis [24]. However, unlike the mitochondrial distribution observed in differentiated cancer cells, CSCs typically exhibit a more pronounced perinuclear mitochondrial localization. For example, in acute myeloid leukemia (AML) stem populations, mitochondria are concentrated in a dense, crescent-shaped cluster around the nucleus, while in differentiated cells, they display a more diffuse distribution pattern [25]. Similar perinuclear mitochondrial arrangements have also been observed in lung and thyroid cancer stem-like subgroups [18,26]. Importantly, the perinuclear mitochondrial distribution in CSCs is not static. Mitochondria can be dynamically redistributed to respond to local needs for energy, calcium regulation, redox balance, and other cellular functions, which in turn can influence stemness and cell identity. Notably, a study found that aged mitochondria in hMECs are predominantly located near the nucleus, whereas younger mitochondria are more evenly dispersed across the mitochondrial network [27]. During cell division, hMEC daughter cells that inherit fewer aged mitochondria retain more stem-like properties—a process reliant on the differential subcellular localization of aged versus young mitochondria. Inhibiting mitochondrial division disrupts this perinuclear clustering of aged mitochondria, thereby impeding their asymmetric distribution and leading to a loss of stem-like characteristics [27]. Despite these observations, the functional significance of this specific mitochondrial positioning in CSCs remains unclear and warrants further investigation; we hypothesize that perinuclear mitochondrial clustering may help meet the energy demands of the nucleus during the CSC resting state or may act as a regulatory hub for nuclear signaling pathways that regulate CSC maintenance and propagation.

3. Mitochondrial fission and fusion in cancer stem cells

Mitochondrial morphology, governed by the dynamic balance between fission and fusion, plays a critical role in regulating both cellular metabolism and apoptosis [40]. Fission is primarily driven by dynamin-related protein 1 (DRP1), which translocates to the mitochondrial outer membrane (MOM), where it interacts with fission-related proteins, such as mitochondrial fission 1 protein (FIS1) and mitochondrial fission factor (MFF). In contrast, fusion is mediated by mitofusins 1 and 2 (MFN1 and 2) on the outer membrane and optic atrophy 1 (OPA1) on the inner mitochondrial membrane [40]. These opposing processes ensure mitochondrial homeostasis and adapt mitochondrial networks to cellular demands. More importantly, mitochondrial dynamics act both upstream and downstream of CSC signaling and are essential for maintaining the functional heterogeneity that characterizes CSC populations (Fig. 1).

3.1. DRP1, FIS1, and MFF

Xie et al. led the way in demonstrating that glioblastoma SCs exhibit a more fragmented mitochondrial morphology than their non-SC counterparts [28]. Although total DRP1 levels were comparable between the two cell populations, phosphorylation at DRP1-S616 (an activating modification) was significantly higher in CSCs, while phosphorylation at DRP1-S637 (an inactivating site) was lower. During CSC differentiation into non-CSCs, DRP1-S616 levels decreased and DRP1-S637 increased, indicating dynamic regulation of mitochondrial fission. To test functional relevance, the authors overexpressed DRP1 mutants mimicking S616 phosphorylation or preventing S637 phosphorylation in non-CSCs; these modifications led to reduced expression of differentiation markers (glial fibrillary acidic protein—GFAP, microtubule associated protein 2—MAP2) and increased expression of stemness genes (NANOG, octamer-binding transcription factor 4—OCT4, NES, stage-specific embryonic antigen 1—SSEA-1/FUT4,). Conversely, knockdown of DRP1 in CSCs caused a dramatic drop in basal and maximal oxygen consumption rate (OCR), reduced proliferation, impaired sphere formation in vitro, and significantly suppressed tumor growth in vivo [28]. Likewise, DRP1 is crucial in orchestrating the asymmetric division of hepatocellular carcinoma stem cells, sustaining the self-renewing CSC population while simultaneously producing differentiated tumor cells that contribute to intratumoral heterogeneity [29]. In this context, DRP1-mediated mitochondrial dynamics appear to be a critical determinant of how cellular fate decisions are regulated during cell division. Intriguingly, studies have revealed that the expression levels of DRP1 are inversely correlated with those of yin yang

2 (YY2), a zinc-finger transcription factor known for its tumor-suppressive properties across multiple cancer types. This inverse relationship suggests a potential regulatory axis wherein downregulation of YY2 may relieve inhibition on DRP1, thereby enhancing mitochondrial fission and promoting tumor persistence and recurrence over time [29]. In this scenario, it should be emphasized that environmental factors also influence mitochondrial morphology in CSCs. For example, under glutamine-limited conditions, ROS production activates the mitogen-activated protein kinase (MAPK) signaling pathway in ovarian and colorectal carcinoma, leading to phosphorylation of DRP1 at Ser616. This phosphorylated DRP1 promotes mitochondrial fragmentation and increases the population of stem-like cells marked by CD44 and CD117/CD45. In addition, glutamine deprivation causes fragmented mitochondria to cluster near the nucleus and reduces cell proliferation, both typical features of CSCs [30]. Similarly, a low extracellular pH (6.5) preserves stemness and a quiescent state in brain tumor-initiating cells by inducing a shift from tubular to circular mitochondrial morphology. This transformation is reversible: returning the pH to 7.4 reactivates CSCs and restores the tubular mitochondrial structure [31]. These observations not only point out the correlation between mitochondrial fission and cancer stem-like traits but also highlight how mitochondrial architecture responds to microenvironmental changes, with implications for cancer metabolism and therapy.

Recent evidence has sharpened our comprehension of DRP1 role in CSCs. In ovarian squamous cell carcinoma SCs, the mitochondrial network is notably fragmented, due to DRP1 upregulation [32]. When DRP1 expression is reduced through knockdown experiments, mitochondria become elongated, which results in increased levels of α-ketoglutarate (α-KG). This metabolic shift enhances glutaminolysis by increasing the expression of ASCT2, a key glutamine transporter, thereby fueling the tricarboxylic acid (TCA) cycle. Elevated α-KG then facilitates the demethylation of the histone marker H3K27me3, which in turn downregulates SLUG, a transcription factor closely associated with the maintenance of stemness and EMT. Importantly, this disruption of mitochondrial dynamics and the subsequent metabolic and epigenetic changes sensitize ovarian squamous cell carcinoma SCs cells to ferroptosis, a form of regulated cell death, thus amplifying the anticancer effects observed when DRP1 is suppressed [32]. Likewise, the depletion of DRP1 causes significant disruption to mitochondrial stability when osteosarcoma SCs are exposed to chemotherapeutic agents such as cisplatin or doxorubicin, compromising the ability of these cells to maintain proper function under drug-induced stress and markedly decreasing their resistance to chemotherapy [33]. Taken together, these works indicate that DRP1 plays a critical role in enabling CSCs to survive and adapt to the cytotoxic effects of commonly used cancer treatments and that targeting this protein may overcome mechanisms of drug resistance.

In AML, work from the Jordan lab has further clarified the connection between mitochondrial fission and CSC identity. Leukemic SCs from primary AML samples are identified by their low ROS levels compared to non-CSCs [34]. They are metabolically quiescent, with reduced glycolysis, mitochondrial respiration and ATP production, yet rely predominantly on OXPHOS to meet their limited energy needs. Morphologically, they contain fewer and more fragmented mitochondria, as a result of increased expression of the pro-fission protein FIS1, upregulated via AMPK activation [35]. When exposed to the mitochondrial stressor valinomycin, non-CSCs accumulated fused, dysfunctional mitochondria, whereas CSCs efficiently cleared damaged mitochondria via FIS1-mediated fission. Knockdown of FIS1 impaired this quality control mechanism, inactivated the anti-differentiation gene GSK3, and promoted cellular differentiation—thus undermining CSC identity [34,35]. These studies illustrate a CSC model in which mitochondrial fragmentation supports low ROS levels and the selective removal of damaged mitochondria, preserving overall stem-like properties. Indeed, by tightly regulating mitochondrial quality and function, mitochondrial fission not only protects leukemic SCs from oxidative damage but also supports their ability to survive and drive tumor progression under adverse conditions.

In accordance with the above findings, MFF has been observed to be upregulated in prostate CSCs, where it promotes a substantial increase in OCR and spare respiratory capacity [36]. Remarkably, silencing MFF reduced CSC proliferation in prostasphere formation assays and significantly inhibited tumor growth in vivo [36]. On the other hand, overexpression of MFF in liver CSCs—where it is also significantly upregulated—enhanced mitochondrial fission, stemness, and tumor-initiating capacity in mice [37]. More recent mechanistic studies have shown that carnitine palmitoyltransferase 1A (CPT1A) facilitates the succinylation of MFF through its lysine succinyltransferase (LSTase) activity, a critical step for mitochondria-associated membrane formation and activation of sterol regulatory element-binding protein 1 (SREBP1); targeting CPT1A LSTase function reduces the stem-like properties of ovarian CSCs and potentiates the efficacy of cisplatin in both cell cultures and animal models [38]. Comparable results have been obtained in glioblastoma, where overexpression of CPT1A was found to suppress the self-renewal capacity of CSCs. Interestingly, this inhibitory effect on CSC maintenance occurred even though CPT1A upregulation was associated with increased phosphorylation of DRP1 at serine 637 (Ser637), which promotes mitochondrial fusion rather than fission [39]. Collectively, these data suggest that CSCs depend on unique patterns of mitochondrial dynamics that differ significantly from those observed in their more differentiated tumor cell counterparts. This specialized regulation of mitochondrial behavior may confer metabolic flexibility, enhanced stress resistance, and the capacity for sustained self-renewal, all of which are critical for CSC maintenance and tumor propagation. Understanding these distinct mitochondrial dynamics in CSCs offers important insights into their biology and highlights novel targets for therapeutic intervention aimed at selectively disrupting CSC function without affecting normal or differentiated tumor cells.

Based on the above evidence, we can conclude that mitochondrial fission plays a crucial role in maintaining cancer stemness. Recent studies suggest that enhanced mitochondrial fission, driven by increased expression or activation of DRP1, FIS1 and MFF, supports CSC properties such as self-renewal, metabolic plasticity, and resistance to therapy. By promoting a fragmented mitochondrial network, CSCs can more easily shift between glycolysis and OXPHOS, adapting their metabolism to environmental stress. Moreover, mitochondrial fission has been linked to the maintenance of a quiescent state and evasion of apoptosis, both of which are key contributors to CSC-mediated tumor relapse and metastasis. The upregulation of these mitochondrial mechanisms is therefore a critical determinant of CSC fate and represents a promising therapeutic target for disrupting tumor initiation and recurrence.

3.2. *OPA1 and MFN1*

In cervical and ovarian cancers, mitochondrial fusion has also been linked to CSC phenotypes. Kong et al. found that cisplatin-sensitive cells, which typically show an intermediate mitochondrial morphology, undergo extensive mitochondrial fragmentation and apoptosis upon cisplatin treatment. In contrast, chemoresistant cells maintain highly interconnected, tubular mitochondrial networks both before and after treatment [40]. A key mechanism supporting this fused morphology may involve reduced activity of OMA1 protease, which normally processes OPA1: in chemoresistant cells, cisplatin treatment does not significantly alter the ratio of long (L-OPA1, pro-fusion) to short (S-OPA1, fission-promoting) forms, while in chemosensitive cells, L-OPA1 decreases and S-OPA1 increases—shifting the balance toward fission [40]. However, the role of mitochondrial morphology in ovarian cancer drug resistance appears to vary by cell type. Zampieri and colleagues reported that cisplatin-resistant COV-362 cells show extensive mitochondrial networking compared to sensitive cells, while no such morphological differences are observed in SKOV-3 cell line; despite these differences, both cell types exhibit upregulated mitophagy and

rely on it to maintain CSC traits, such as clonogenic potential, under chemotherapeutic stress [41]. This suggests that targeting mitophagy may be a broadly effective strategy to eliminate CSCs, regardless of their mitochondrial structure. In particular, this approach holds promise for overcoming resistance mechanisms that allow CSCs to evade conventional treatments and contribute to tumor relapse.

As in gynecologic malignancies, high OPA1 expression and enhanced mitochondrial fusion have recently emerged as key metabolic features of the CSCs from pancreatic and lung carcinoma [42,43]. Specifically in the latter, stem-like populations have been reported to exhibit elevated lipogenesis, which upregulates OPA1 expression through SAM pointed domain–containing ETS transcription factor (SPDEF). As a result, high OPA1 levels promote mitochondrial fusion and reinforce cell stemness. These metabolic adaptations, characterized by elevated lipogenesis, SPDEF, and OPA1, were confirmed in primary CSCs isolated from lung cancer patients; consistently, inhibition of lipogenesis and mitochondrial fusion significantly suppressed CSC expansion and the growth of patient-derived lung cancer organoids [43]. Overall, these experimental observations demonstrate that lipogenesis regulates mitochondrial dynamics through SPDEF-mediated induction of OPA1, forming a critical axis that sustains CSC maintenance and tumor growth in human lung carcinoma; targeting this lipogenesis–mitochondrial fusion pathway may therefore represent a promising therapeutic strategy for eradicating CSCs and improving therapy outcomes.

Interestingly, mitochondrial fusion also plays a role in normal and cancerous hMECs undergoing EMT. In normal hMECs, EMT induced by SNAIL overexpression or transforming growth factor-beta (TGFβ) treatment enhances mitochondrial fusion through increased expression of MFN1 [44]. In this context, a MFN1–PKCζ complex tethers fused mitochondria to the cortical membrane, ensuring asymmetric mitochondrial segregation during cell division: the daughter cells that inherit more fused mitochondria exhibit increased glutathione synthesis and protection from ROS, promoting stem-like characteristics; conversely, the daughter cells receiving fewer mitochondria undergo luminal differentiation. Importantly, MFN1 knockdown reduces stemness, measured by reduced sphere-forming capacity, in both normal epithelial cells and BT549 and MDA-MB-231 breast cancer cell lines, which are enriched in stem-like populations [44]. Although these findings emphasize MFN1 role in promoting EMT and stemness through mitochondrial fusion, some studies associate MFN1-driven glycolysis with EMT in opposing ways [45]. This underscores the intricate and highly context-dependent nature of mitochondrial dynamics across different tumor types and experimental models, reflecting the diverse ways in which cancer cells regulate mitochondrial fission, fusion, and quality control to adapt to their specific microenvironmental and metabolic demands. Such complexity highlights the critical need for broader and more comprehensive investigations to unravel the nuanced roles of mitochondrial behavior in cancer progression and therapy resistance. Expanding research in this area will be essential for identifying universally applicable targets as well as tumor-specific vulnerabilities, ultimately informing the development of more precise and effective mitochondrial-targeted therapies.

Overall, it clearly emerges that mitochondrial fusion, mediated by proteins such as OPA1 and MFN1, is essential for regulating CSC function. A fused mitochondrial morphology promotes mitochondrial integrity, supports OXPHOS, and facilitates the efficient use of metabolic substrates—traits associated with CSC survival and self-renewal. In addition, it is linked to enhanced bioenergetic capacity and ROS buffering, both of which help sustain the stem-like phenotype and resistance to therapy. These observations highlight the potential of mitochondrial fusion as a target for cancer treatment.

4. Mitophagy in cancer stem cells

As shown in Fig. 2, mitophagy, a specialized form of autophagy, plays a critical role in maintaining cellular health by selectively removing damaged or dysfunctional mitochondria, thereby preserving essential cellular functions and metabolic homeostasis. This tightly regulated process ensures mitochondrial quality control and is fundamental to cellular adaptation under stress [46]. Interestingly, mitophagy exhibits a dual and context-dependent role in the landscape of cancer biology [47]. During the early stages of cellular transformation, mitophagy serves as a protective mechanism, safeguarding genomic integrity and preventing the accumulation of oxidative stress, thereby acting as a barrier against carcinogenesis. However, once cancer is established, mitophagy shifts from a tumor-suppressive function to a tumor-promoting one, particularly by supporting the survival of CSCs under hostile conditions such as cytotoxic therapy or hypoxia. This pro-survival role is achieved largely through the inhibition of apoptosis and the preservation of mitochondrial function, which collectively contribute to treatment resistance and disease progression [47]. For example, in hepatic CSCs, mitophagy inhibits the tumor suppressor protein p53, a key regulator of apoptosis and genomic stability; this suppression facilitates the activation of core pluripotency transcription factors, including NANOG, OCT4, and SOX2, which are essential for maintaining the stem-like characteristics of CSCs and promoting their expansion [48]. Within the same cell subtype, aberrant adenosine-to-inosine (A-to-I) RNA editing mediated by adenosine deaminase acting on RNA 1 (ADAR1) induces a metabolic reprogramming toward OXPHOS, enabling the maintenance of stem-like phenotypes via PINK1/Parkin-dependent mitophagy; this phenotypic switch confers adaptation to cellular stress and unique metastatic potential [49]. Likewise, in brain CSCs, the DRP1/FIS1 axis contributes to the mitophagy-mediated stabilization of mitochondrial respiratory cristae architecture, resulting in robust disease progression [50]; in particular, this process seems to be initiated by cyclin-dependent kinase 5 (CDK5) [28]. Comparable results have been obtained in lung CSCs, where a positive relationship between mitophagic activity and cell stemness was highlighted. At the mechanistic level, augmentation of mitophagy in the stem-like subpopulation is induced by FIS1 through mitochondrial fission [51]; more importantly, the accumulation of mtDNA within lysosomes functions as an endogenous ligand for Toll-like receptor 9 (TLR9) that supports mitochondrial metabolism through the Notch1/AMPK signaling cascade [52]. Interestingly, the AMPK/FIS1 axis also triggers the autophagic-dependent mitochondrial turnover in AML SCs, allowing this cell subpopulation to manage intracellular ROS levels effectively; of note, pharmacological or genetic inhibition of FIS1 disrupts mitophagy,

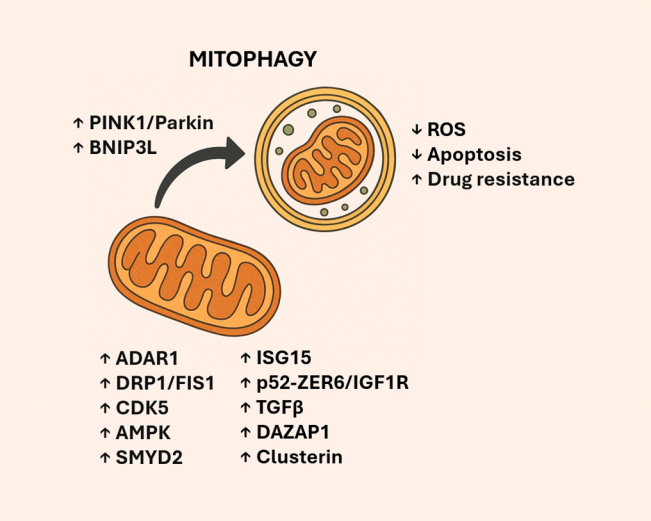

Fig. 2. Mitophagy in cancer stem cells. By exploiting a variety of signaling pathways, cancer stem cells (CSCs) activate PINK1/Parkin- and BNIP3L-mediated mitophagy to prevent oxidative stress and inhibit apoptosis, thus leading to increased resistance to stressful conditions, including chemotherapy.

leading to elevated oxidative stress and a significant reduction in stem-like properties [35]. In the context of bladder cancer, SET and MYND domain-containing protein 2 (SMYD2), a well-known protein-lysine methyltransferase, upregulates the expression of pyrroline-5-carboxylate reductase 1 (PYCR1) by catalyzing the trimethylation of histone H3 at lysine 4 (H3K4me3); this epigenetic modification culminates into the activation of the PINK1/Parkin-mediated mitophagic flux, determining the propagation of CSCs [53]. In pancreatic cancer, CSCs exploit mitophagy by modulating the interferon-stimulated gene 15 (ISG15) signaling pathway: trough ISGylation of mitochondrial proteins, these cells maintain mitochondrial integrity and sustain their self-renewal [54]. Finally, in oral and gastrointestinal tumors, mitophagy fuels cancer stemness by modulating a variety of signaling pathways, including the p52-ZER6/insulin-like growth factor 1 receptor (IGF1R) axis as well as molecular cascades associated with TGFβ, DAZ-associated protein 1 (DAZAP1), and clusterin [55–58]. Collectively, these findings underscore the pivotal role of mitophagic activity in modulating mitochondrial dynamics and turnover across various cancer types. This process not only facilitates metabolic flexibility and resistance to cell death but also reinforces stem-like traits and supports EMT, identifying mitophagy as a key player in cancer stem cell biology and a potential therapeutic target in oncology.

CSCs harness mitophagy not only to sustain their defining stem-like properties but also as a crucial mechanism for preserving intracellular homeostasis under stressful conditions, including chemotherapy [47]. By selectively eliminating damaged or dysfunctional mitochondria, CSCs can mitigate oxidative stress, maintain metabolic flexibility, and prevent the accumulation of cytotoxic mitochondrial byproducts, thereby enhancing their survival and contributing to treatment resistance. This capacity to finely tune mitochondrial quality control positions mitophagy as a central player in the development of chemoresistance across various tumor types [47]. A clear example of this is observed in colorectal CSCs, where exposure to the chemotherapeutic agent doxorubicin leads to an upregulation of BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L)-mediated mitophagy; this increase in mitophagic flux facilitates the clearance of impaired mitochondria and lowers the overall oxidative burden, allowing CSCs to better withstand the cytotoxic effects of the drug [59]. These data align with findings in glioblastoma, where CSCs residing in hypoxic niches within the tumor microenvironment display elevated levels of both BNIP3L and mitophagic activity in comparison to non-CSC populations: BNIP3L plays a pivotal role in maintaining mitochondrial integrity under low-oxygen conditions and supports the stemness of these cells by regulating key pluripotency and CSC markers, including CD133, OCT4, and SOX2; experimental knockdown of BNIP3L impairs mitochondrial quality control, reduces CSC viability, and notably improves survival outcomes in xenograft models, underscoring its therapeutic relevance [60]. Similarly, in oral squamous cell carcinoma, increased mitophagic activity has been linked to resistance against cisplatin, a commonly used chemotherapeutic agent; in this context, elevated mitophagy not only promotes drug tolerance but also reinforces the expression of stemness-associated traits, enabling CSCs to persist and repopulate the tumor following treatment [61]. Finally, PIWI-like protein 1 (PIWIL1), a key member of the Argonaute protein family, induces the formation of autophagosomes, particularly mitophagosomes, in multiple myeloma cells by disrupting mitochondrial calcium signaling and regulating components of the canonical PINK1/Parkin mitophagy pathway; this process increases the proportion of side population cells and upregulates stem cell-associated gene expression, eventually contributing to chemotherapeutic resistance both in vitro and in vivo [62]. Taken together, these insights highlight mitophagy as a critical cellular defense strategy that enables CSCs to resist chemotherapy by mitigating mitochondrial dysfunction and oxidative stress. This protective mechanism contributes not only to therapeutic resistance but also to the persistence and recurrence of cancer following treatment. As such, targeting mitophagy—either directly or by disrupting its regulatory networks, including those involved in mitochondrial fission and fusion—represents a promising avenue for sensitizing CSCs to treatment and overcoming drug resistance in a variety of malignancies.

5. Mitochondrial dynamics as a target for cancer stem cell eradication

CSCs represent a small but highly influential subpopulation within tumors, acting as principal drivers of tumor initiation, progression, recurrence, metastasis, and resistance to conventional therapies. Mitochondria are deeply integrated into the biology of CSCs, serving not only as powerhouses for energy production but also as hubs for metabolic flexibility, redox regulation, and apoptotic signaling. This centrality of mitochondria to CSC function makes them a compelling therapeutic target [6,7]. In particular, targeting the entire mitochondrial life-cycle—from biogenesis to mitophagy, through fission and fusion—offers a promising strategy to reduce mitochondrial adaptability and restore CSC sensitivity to standard treatments (Table 1).

Traditional inhibitors of the ETC, such as oligomycin, rotenone, and CCCP, have laid the groundwork for targeting mitochondrial metabolism. In particular, a number of small-molecule inhibitors that specifically target mitochondrial OXPHOS complex I, including BAY 87-2243, IACS-010759, metformin, and phenformin, have demonstrated significant antitumor activity in different preclinical cancer models, positioning them as promising antitumor therapeutic agents [63]. Mechanistically, these compounds interfere with mitochondrial respiration, thereby reducing ATP production and inducing metabolic stress in CSCs, which often rely heavily on OXPHOS for survival and proliferation. Despite their encouraging efficacy, the clinical translation of these inhibitors remains substantially limited due to concerns regarding their toxicity profiles. Indeed, because of their broad and largely non-selective mechanisms of action, these agents tend to affect not only malignant cells but also healthy, metabolically active tissues. As a result, patients frequently experience a range of adverse side effects, including but not limited to fatigue, nausea, vomiting, diarrhea, lactic acidosis, elevated blood lactate levels, and peripheral neuropathy [63]. These toxicities present significant challenges to the safe and effective use of complex I inhibitors in clinical settings and highlight the need for more targeted strategies or combination therapies that can mitigate off-target effects while preserving antitumor efficacy. In this setting, recent years have witnessed the emergence of more sophisticated and selective agents targeting other aspects of mitochondrial function. Notably, inhibitors of PGC-1α, such as XCT790 and SR-18292, have demonstrated potent anti-CSC activity in preclinical models of breast cancer, cholangiocarcinoma, and melanoma. These compounds block mitochondrial expansion and metabolic reprogramming, impairing CSC propagation [14,16,64]. In parallel, repurposing of widely used antibiotics, including doxycycline, tigecycline, and azithromycin, has opened a new avenue in CSC-targeted therapy. These antibiotics exert off-target effects by inhibiting mitochondrial ribosomes and biogenesis, ultimately suppressing CSC viability and self-renewal capacity. Their safety profiles and existing clinical approval make them attractive candidates for combination therapy with standard chemotherapeutic agents, potentially as part of first-line treatment regimens [65]. Finally, a promising class of therapeutics includes mitochondrial RNA polymerase inhibitors like IMT1, which block mtDNA transcription and protein synthesis without disrupting overall OXPHOS or causing damage to non-malignant cells. These agents represent a more targeted approach, exploiting the reliance of CSCs on mitochondrial-encoded proteins while sparing normal tissue metabolism [66].

Targeting mitochondrial structure has also shown therapeutic potential. Inhibitors of mitochondrial fission, such as Mdivi-1, which blocks the activity of DRP1, have been found to reduce proliferation and promote apoptosis in CSCs derived from glioblastoma, breast, lung, pancreatic, and oral cancers in vitro [67–72]. On the opposite side of the dynamic balance, fusion inhibition by targeting OPA1 with compounds

Table 1
Mitochondrial inhibitors in cancer therapy.

Drug	Mechanism of action	Tumor type	Clinical development	References
BAY 87-2243, IACS-010759, metformin, and phenformin	OXPHOS inhibition	Various	Preclinical studies; phase I trial (metformin)	[63]
XCT790 and SR-18292	PGC-1α inhibition	Breast cancer, cholangiocarcinoma, and melanoma	Preclinical studies	[14,16,64]
Doxycycline, tigecycline, and azithromycin	Inhibition of mitochondrial ribosomes	Various	Preclinical studies	[65]
IMT1	Inhibition of mitochondrial DNA transcription	Osteosarcoma	Preclinical studies	[66]
Mdivi-1	DRP1 inhibition	Glioblastoma, breast, lung, and pancreatic cancer	Preclinical studies	[67–72]
MYLS22, BTM-3528, BTM-3566, and AOH1996	OPA1 inhibition	Breast and lung cancer, lymphoma, and leukemia	Preclinical studies	[73–76]
MFI8	MFN1 inhibition	Breast cancer	Preclinical studies	[77]
PKI-402, liensinine, sanguinarine, fluorizoline, and XRK3F2	Pro-survival mitophagy inhibition	Breast, liver, and lung cancer, leukemia	Preclinical studies	[78–83]
PMI and LCL-461	Pro-death mitophagy activation	Leukemia and liver cancer	Preclinical studies	[84,85]
Genipin, alternol, lupeol, tocotrienols, mensacarcin, gracillin, polyphillin I, berberine, cordycepin, and quambalarine B	Mitochondrial dysfunction	Various	Preclinical studies	[87–98]

like MYLS22, BTM-3528, BTM-3566, and AOH1996 has also demonstrated efficacy, leading to tumor growth suppression in vivo [73–76]. Likewise, pharmacological inhibition of MFN1 by MFI8 has been found to restore tamoxifen-induced apoptosis in resistant breast cancer cells, emphasizing the role of mitochondrial fusion in acquired drug resistance and the potential benefit of its modulation in overcoming therapeutic barriers [77]. Although much of this research remains in the early stages, these findings underscore the vulnerability of cancers to disturbances in mitochondrial morphology and distribution, suggesting that these alterations might be employed to selectively deplete CSC populations. Strategically disrupting mitochondrial structural organization offers a potential means to impair the metabolic adaptability and survival pathways of CSCs, thereby diminishing tumor aggressiveness and therapeutic resistance. These reports highlight a promising direction for the development of targeted treatments that modulate mitochondrial dynamics to improve the overall effectiveness of cancer therapies.

The above review highlights the importance of mitophagy in tumor initiation and progression, as well as its involvement in supporting metabolic reprogramming, cancer cell stemness, and resistance to chemotherapy. In particular, this mechanism plays a dual role in cancer: on the one hand, regulated mitophagic flux helps remove damaged mitochondria, preserves cellular homeostasis and metabolic function, and promotes cell survival in hostile environments; on the other hand, excessive mitophagy can eliminate healthy mitochondria, impair mitochondrial function, and disrupt energy production, ultimately leading to cell death [47]. Therefore, targeting the mitophagic pathway could influence the balance between tumor growth and cell death, making the modulation—either inhibition or activation—of this process a potential therapeutic approach in cancer treatment. In this context, both mitophagy inhibitors and inducers are now under extensive study for cancer management. For example, it has been shown that inhibition of mitophagy through PKI-402, a potent inactivator of PI3K and mTOR, isoquinoline alkaloids (i.e. liensinine and sanguinarine), and fluorizoline, a synthetic molecule that targets mitochondrial prohibitins, leads to apoptosis in a variety of tumor models [78–82]. Parallelly, XRK3F2 and PMI, two compounds that block and trigger p62-mediated mitophagy respectively, have shown great potential in eliminating neuroblastoma, hepatocarcinoma, and hematopoietic cancer cells [83,84]. Similarly, activation of the ceramide stress pathway by LCL-461 can induce mitophagy to promote cell death in AML [85]. Even though these data still need to be confirmed in the context of CSCs, they open to the possibility of specifically targeting mitophagy to eradicate essentially all tumor types.

Despite these advances, a significant challenge remains: achieving specificity in mitochondrial-targeted therapies. Because mitochondria are essential to virtually all cell types, including healthy tissues, off-target toxicity is a major concern. To overcome this critical limitation, researchers are increasingly turning to nanotechnology as a promising strategy to enhance the precision of drug delivery specifically to cancer cell mitochondria [86]. Nanocarriers, such as liposomes, dendrimers, micelles, and various polymeric or inorganic nanoparticles, can be custom-designed with highly specific physicochemical properties, including size, surface charge, ligand functionalization, and controlled-release mechanisms. These design features allow nanocarriers to selectively home in on tumor cells, penetrate cellular membranes, and deliver therapeutic agents directly into the mitochondrial compartment. By enhancing intracellular targeting and accumulation within cancer cells, particularly CSCs, nanotechnology-based systems not only increase drug efficacy but also reduce systemic exposure and toxicity to normal tissues. Moreover, mitochondrial-targeting ligands, such as triphenylphosphonium (TPP) cations, are often conjugated to nanocarriers to further enhance mitochondrial localization and therapeutic precision [86]. In parallel, a growing body of research is exploring the potential of naturally derived compounds to selectively target mitochondrial vulnerabilities in CSCs. These compounds, many of which originate from traditional medicinal plants, exhibit unique bioactive properties that interfere with mitochondrial function in cancer cells while exhibiting low toxicity toward healthy tissues. Examples include terpenoids (i.e. genipin, alternol, lupeol, and tocotrienols), flavonoids (i.e. mensacarcin), saponins (i.e. gracillin and polyphillin I), alkaloids (i.e. berberine and cordycepin), and quinones (i.e. quambalarine B). Preclinical studies have reported promising anti-cancer activity for these agents, often accompanied by minimal side effects, making them attractive candidates for further development [87–98]. Together, these advances reflect a multifaceted approach to refining mitochondrial-targeted therapy—leveraging both engineered nanotechnologies and bioactive natural compounds. Such strategies offer considerable potential for integration into personalized or combinatory oncology regimens, ultimately aiming to improve therapeutic efficacy while reducing harm to normal tissues. Continued research in this direction is essential to

realize the full clinical potential of mitochondrial-targeted cancer treatments.

In summary, therapies targeting mitochondrial dynamics offer a promising strategy to disrupt CSC maintenance and overcome treatment resistance. Indeed, by disrupting the dynamic equilibrium between mitochondrial processes, these pharmacological strategies can selectively target the unique mitochondrial dependencies of CSCs, impairing their self-renewal and tumor-initiating capacity. Combining mitochondrial dynamics modulators with conventional treatments holds potential for improving clinical outcomes by eliminating CSC populations that often drive relapse and metastasis.

6. Conclusions and future perspectives

Mitochondria serve as pivotal regulators of multiple critical cellular processes in CSCs, including metabolism, differentiation, survival, and resistance to therapeutic interventions. Their central role in these functions makes these organelles highly attractive and promising targets for anticancer therapies. However, the inherent dynamic nature of mitochondrial structure and distribution within heterogeneous cancer cell populations poses significant challenges for the development and efficacy of mitochondria-targeted drugs. Different mitochondrial subpopulations within a tumor can govern distinct cellular activities, such as energy production, ROS management, and apoptotic signaling, complicating efforts to design interventions that uniformly impact all relevant mitochondrial functions. This complexity often results in the partial failure of current therapeutic approaches that do not fully account for mitochondrial heterogeneity. Moreover, broad-spectrum mitochondrial inhibitors risk unintended collateral damage to healthy, non-cancerous tissues, given that mitochondria are essential organelles in virtually all cell types. This off-target toxicity underscores critical gaps in our understanding of the regulation of mitochondrial dynamics specifically within cancerous versus normal cells. To address these challenges effectively, it is imperative to consider the metabolic and functional heterogeneity that exists not only between tumors but also within individual tumors—referred to as intratumor heterogeneity—which encompasses variations in metabolic signatures and distinct behaviors of cancer subpopulations, including CSCs and more differentiated cancer cells. Recent technological advances, particularly in single-cell sequencing and lineage-tracing methodologies, provide unprecedented opportunities to dissect this complexity at a granular level. These approaches enable researchers to map mitochondrial phenotypes and metabolic states in individual cancer cells, uncovering the intricate interplay between mitochondrial dynamics and cellular identity within the tumor microenvironment. From a therapeutic point of view, promising avenues currently under exploration include the repurposing of FDA-approved drugs—such as certain antibiotics—that have off-target effects on mitochondrial biogenesis and function, offering a potentially faster route to clinical application. In addition, innovative delivery platforms like nanocarriers are being developed to improve the precision and efficacy of mitochondrial-targeted agents, minimizing systemic toxicity by ensuring selective accumulation within tumor mitochondria. Parallel to this, the use of non-toxic, naturally derived phytochemicals offers an alternative or complementary strategy to modulate mitochondrial dynamics with reduced side effects. Ultimately, future progress in combating CSC-driven tumor growth and therapeutic resistance hinges on deepening our mechanistic understanding of mitochondrial dynamics and their regulatory networks within CSCs. By focusing on the precise manipulation of key mitochondrial regulators involved in biogenesis, fission, fusion, and mitophagy, it may be possible to develop refined therapies that selectively eradicate cancer cells while preserving normal tissue function. Such targeted approaches hold great promise for overcoming current treatment limitations and achieving durable cancer remission.

Funding

This research was funded by MIUR Progetto di Eccellenza (Department of Pharmacological and Biomolecular Sciences “Rodolfo Paoletti”, Università degli Studi di Milano) and PSR 2023 (F.F.).

Declaration of competing interest

All authors have no conflict of interest to declare.

Data availability

No data was used for the research described in the article.

References

[1] P. Piña-Sánchez, A. Chávez-González, M. Ruiz-Tachiquín, E. Vadillo, A. Monroy-García, J.J. Montesinos, R. Grajales, M. Gutiérrez de la Barrera, H. Mayani, Cancer biology, epidemiology, and treatment in the 21st century: current status and future challenges from a biomedical perspective, Cancer Control 28 (2021), https://doi.org/10.1177/10732748211038735.

[2] M. Marzagalli, F. Fontana, M. Raimondi, P. Limonta, Cancer stem cells—key players in tumor relapse, Cancers (Basel) 13 (2021) 376, https://doi.org/10.3390/cancers13030376.

[3] X. Chu, W. Tian, J. Ning, G. Xiao, Y. Zhou, Z. Wang, Z. Zhai, G. Tanzhu, J. Yang, R. Zhou, Cancer stem cells: advances in knowledge and implications for cancer therapy, Signal Transduct. Target. Ther. 9 (2024) 170, https://doi.org/10.1038/s41392-024-01851-y.

[4] L. Walcher, A.-K. Kistenmacher, H. Suo, R. Kitte, S. Dluczek, A. Strauß, A.-R. Blaudszun, T. Yevsa, S. Fricke, U. Kossatz-Boehlert, Cancer stem cells—origins and biomarkers: perspectives for targeted personalized therapies, Front. Immunol. 11 (2020), https://doi.org/10.3389/fimmu.2020.01280.

[5] F. Fontana, P. Limonta, The multifaceted roles of mitochondria at the crossroads of cell life and death in cancer, Free Radic. Biol. Med. 176 (2021) 203–221, https://doi.org/10.1016/j.freeradbiomed.2021.09.024.

[6] Y. Liu, Y. Sun, Y. Guo, X. Shi, X. Chen, W. Feng, L.-L. Wu, J. Zhang, S. Yu, Y. Wang, Y. Shi, An overview: the diversified role of mitochondria in cancer metabolism, Int. J. Biol. Sci. 19 (2023) 897–915, https://doi.org/10.7150/ijbs.81609.

[7] X. Zheng, J. Chen, Y. Sun, T. Chen, J. Wang, S. Yu, Mitochondria in cancer stem cells: Achilles heel or hard armor, Trends Cell Biol. 33 (2023) 708–727, https://doi.org/10.1016/j.tcb.2023.03.009.

[8] M. Fan, Y. Shi, J. Zhao, L. Li, Cancer stem cell fate determination: mito-nuclear communication, Cell Commun. Signal. 21 (2023) 159, https://doi.org/10.1186/s12964-023-01160-x.

[9] P.P. Praharaj, D.P. Panigrahi, C.S. Bhol, S. Patra, S.R. Mishra, K.K. Mahapatra, B. P. Behera, A. Singh, S. Patil, S.K. Bhutia, Mitochondrial rewiring through mitophagy and mitochondrial biogenesis in cancer stem cells: a potential target for anti-CSC cancer therapy, Cancer Lett. 498 (2021) 217–228, https://doi.org/10.1016/j.canlet.2020.10.036.

[10] P.P. Praharaj, B.S. Patro, S.K. Bhutia, Dysregulation of mitophagy and mitochondrial homeostasis in cancer stem cells: novel mechanism for anti-cancer stem cell-targeted cancer therapy, Br. J. Pharmacol. 179 (2022) 5015–5035, https://doi.org/10.1111/bph.15401.

[11] W. Chen, H. Zhao, Y. Li, Mitochondrial dynamics in health and disease: mechanisms and potential targets, Signal Transduct. Target. Ther. 8 (2023) 333, https://doi.org/10.1038/s41392-023-01547-9.

[12] L. Qian, Y. Zhu, C. Deng, Z. Liang, J. Chen, Y. Chen, X. Wang, Y. Liu, Y. Tian, Y. Yang, Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) family in physiological and pathophysiological process and diseases, Signal Transduct. Target. Ther. 9 (2024) 50, https://doi.org/10.1038/s41392-024-01756-w.

[13] A.F. Salem, D. Whitaker-Menezes, A. Howell, F. Sotgia, M.P. Lisanti, Mitochondrial biogenesis in epithelial cancer cells promotes breast cancer tumor growth and confers autophagy resistance, Cell Cycle 11 (2012) 4174–4180, https://doi.org/10.4161/cc.22376.

[14] A. De Luca, M. Fiorillo, M. Peiris-Pagès, B. Ozsvari, D.L. Smith, R. Sanchez-Alvarez, U.E. Martinez-Outschoorn, A.R. Cappello, V. Pezzi, M.P. Lisanti, F. Sotgia, Mitochondrial biogenesis is required for the anchorage-independent survival and propagation of stem-like cancer cells, Oncotarget 6 (2015) 14777–14795, https://doi.org/10.18632/oncotarget.4401.

[15] C. Raggi, M.L. Taddei, E. Sacco, N. Navari, M. Correnti, B. Piombanti, M. Pastore, C. Campani, E. Pranzini, J. Iorio, G. Lori, T. Lottini, C. Peano, J. Cibella, M. Lewinska, J.B. Andersen, L. di Tommaso, L. Viganò, G. Di Maira, S. Madiai, M. Ramazzotti, I. Orlandi, A. Arcangeli, P. Chiarugi, F. Marra, Mitochondrial oxidative metabolism contributes to a cancer stem cell phenotype in cholangiocarcinoma, J. Hepatol. 74 (2021) 1373–1385, https://doi.org/10.1016/j.jhep.2020.12.031.

[16] F. Fontana, C. Macchi, M. Anselmi, A.S. Rizzuto, M. Ruscica, P. Limonta, PGC1-α-driven mitochondrial biogenesis contributes to a cancer stem cell phenotype in melanoma, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 2024 (1870) 166897, https://doi.org/10.1016/j.bbadis.2023.166897.

[17] A. Viale, P. Pettazzoni, C.A. Lyssiotis, H. Ying, N. Sánchez, M. Marchesini, A. Carugo, T. Green, S. Seth, V. Giuliani, M. Kost-Alimova, F. Muller, S. Colla, L. Nezi, G. Genovese, A.K. Deem, A. Kapoor, W. Yao, E. Brunetto, Y. Kang, M. Yuan, J.M. Asara, Y.A. Wang, T.P. Heffernan, A.C. Kimmelman, H. Wang, J.B. Fleming, L. C. Cantley, R.A. DePinho, G.F. Draetta, Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function, Nature 514 (2014) 628–632, https://doi.org/10.1038/nature13611.
[18] X. Ye, Q. Li, G. Wang, F. Sun, G. Huang, X. Bian, S. Yu, G. Qian, Mitochondrial and energy metabolism-related properties as novel indicators of lung cancer stem cells, Int. J. Cancer 129 (2011) 820–831, https://doi.org/10.1002/ijc.25944.
[19] T. Liu, Q. Ma, W. Li, Y. Hu, J. Yang, Q. Yao, Ubiquilin 1 suppresses the cancer stem cell–like traits of non-small cell lung cancer cells by regulating reactive oxygen species homeostasis, Bioengineered 12 (2021) 7132–7144, https://doi.org/10.1080/21655979.2021.1979353.
[20] R. Huang, J. Wang, Y. Zhong, Y. Liu, T. Stokke, C.G. Trope, J.M. Nesland, Z. Suo, Mitochondrial DNA deficiency in ovarian cancer cells and cancer stem cell-like properties, Anticancer Res. 35 (2015) 3743–3753.
[21] Y. Masuike, K. Tanaka, T. Makino, M. Yamasaki, Y. Miyazaki, T. Takahashi, Y. Kurokawa, K. Nakajima, M. Mori, Y. Doki, Esophageal squamous cell carcinoma with low mitochondrial copy number has mesenchymal and stem-like characteristics, and contributes to poor prognosis, PLoS One 13 (2018) e0193159, https://doi.org/10.1371/journal.pone.0193159.
[22] J.M. García-Heredia, A. Carnero, Role of mitochondria in cancer stem cell resistance, Cells 9 (2020) 1693, https://doi.org/10.3390/cells9071693.
[23] M. Guha, S. Srinivasan, G. Ruthel, A.K. Kashina, R.P. Carstens, A. Mendoza, C. Khanna, T. Van Winkle, N.G. Avadhani, Mitochondrial retrograde signaling induces epithelial–mesenchymal transition and generates breast cancer stem cells, Oncogene 33 (2014) 5238–5250, https://doi.org/10.1038/onc.2013.467.
[24] M. Furnish, M.C. Caino, Altered mitochondrial trafficking as a novel mechanism of cancer metastasis, Cancer Rep. 3 (2020), https://doi.org/10.1002/cnr2.1157.
[25] R.P. Singh, A.D. Schimmer, Mitochondria regulate AML differentiation independent of oxidative phosphorylation and metabolism, Mol. Cell. Oncol. 7 (2020) 1815503, https://doi.org/10.1080/23723556.2020.1815503.
[26] Y. Ren, H. Liang, X. Wang, Z. Cao, Y. Ma, X. Liu, Alterations in mitochondrial function and energy metabolism-related properties in thyroid cancer stem cells, Acta Biochim. Pol. (2021), https://doi.org/10.18388/abp.2020_5370.
[27] P. Katajisto, J. Döhla, C.L. Chaffer, N. Pentinmikko, N. Marjanovic, S. Iqbal, R. Zoncu, W. Chen, R.A. Weinberg, D.M. Sabatini, Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness, Science 348 (2015) (1979) 340–343, https://doi.org/10.1126/science.1260384.
[28] Q. Xie, Q. Wu, C.M. Horbinski, W.A. Flavahan, K. Yang, W. Zhou, S. M. Dombrowski, Z. Huang, X. Fang, Y. Shi, A.N. Ferguson, D.F. Kashatus, S. Bao, J. N. Rich, Mitochondrial control by DRP1 in brain tumor initiating cells, Nat. Neurosci. 18 (2015) 501–510, https://doi.org/10.1038/nn.3960.
[29] M. Wei, U. Nurjanah, J. Li, X. Luo, R. Hosea, Y. Li, J. Zeng, W. Duan, G. Song, M. Miyagishi, V. Kasim, S. Wu, YY2-DRP1 axis regulates mitochondrial fission and determines CANCER stem cell asymmetric division, Adv. Sci. 10 (2023), https://doi.org/10.1002/advs.202207349.
[30] P. Prasad, S. Ghosh, S.S. Roy, Glutamine deficiency promotes stemness and chemoresistance in tumor cells through DRP1-induced mitochondrial fragmentation, Cell. Mol. Life Sci. 78 (2021) 4821–4845, https://doi.org/10.1007/s00018-021-03818-6.
[31] F.J. Aulestia, I. Néant, J. Dong, J. Haiech, M.-C. Kilhoffer, M. Moreau, C. Leclerc, Quiescence status of glioblastoma stem-like cells involves remodelling of Ca2+ signalling and mitochondrial shape, Sci. Rep. 8 (2018) 9731, https://doi.org/10.1038/s41598-018-28157-8.
[32] Z. Wang, S. Tang, L. Cai, Q. Wang, D. Pan, Y. Dong, H. Zhou, J. Li, N. Ji, X. Zeng, Y. Zhou, Y. Shen, Q. Chen, DRP1 inhibition-mediated mitochondrial elongation abolishes cancer stemness, enhances glutaminolysis, and drives ferroptosis in oral squamous cell carcinoma, Br. J. Cancer 130 (2024) 1744–1757, https://doi.org/10.1038/s41416-024-02670-2.
[33] B. Tian, Y. Wu, X. Du, Y. Zhang, Osteosarcoma stem cells resist chemotherapy by maintaining mitochondrial dynamic stability via DRP1, Int. J. Mol. Med. 55 (2024) 10, https://doi.org/10.3892/ijmm.2024.5451.
[34] E.D. Lagadinou, A. Sach, K. Callahan, R.M. Rossi, S.J. Neering, M. Minhajuddin, J. M. Ashton, S. Pei, V. Grose, K.M. O'Dwyer, J.L. Liesveld, P.S. Brookes, M. W. Becker, C.T. Jordan, BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells, Cell Stem Cell 12 (2013) 329–341, https://doi.org/10.1016/j.stem.2012.12.013.
[35] S. Pei, M. Minhajuddin, B. Adane, N. Khan, B.M. Stevens, S.C. Mack, S. Lai, J. N. Rich, A. Inguva, K.M. Shannon, H. Kim, A.-C. Tan, J.R. Myers, J.M. Ashton, T. Neff, D.A. Pollyea, C.A. Smith, C.T. Jordan, AMPK/FIS1-mediated mitophagy is required for self-renewal of human AML stem cells, Cell Stem Cell 23 (2018) 86–100.e6, https://doi.org/10.1016/j.stem.2018.05.021.
[36] G. Civenni, R. Bosotti, A. Timpanaro, R. Vàzquez, J. Merulla, S. Pandit, S. Rossi, D. Albino, S. Allegrini, A. Mitra, S.N. Mapelli, L. Vierling, M. Giurdanella, M. Marchetti, A. Paganoni, A. Rinaldi, M. Losa, E. Mira-Catò, R. D'Antuono, D. Morone, K. Rezai, G. D'Ambrosio, L. Ouafik, S. Mackenzie, M.E. Riveiro, E. Cvitkovic, G.M. Carbone, C.V. Catapano, Epigenetic control of mitochondrial fission enables self-renewal of stem-like tumor cells in human prostate cancer, Cell Metab. 30 (2019) 303–318.e6, https://doi.org/10.1016/j.cmet.2019.05.004.
[37] M. Tang, M. Yang, G. Wu, S. Mo, X. Wu, S. Zhang, R. Yu, Y. Hu, Y. Xu, Z. Li, X. Liao, J. Li, L. Song, Epigenetic induction of mitochondrial fission is required for maintenance of liver cancer–initiating cells, Cancer Res. 81 (2021) 3835–3848, https://doi.org/10.1158/0008-5472.CAN-21-0436.
[38] Y. Zhu, S. Chen, H. Su, Y. Meng, C. Zang, P. Ning, L. Hu, H. Shao, CPT1A-mediated MFF succinylation promotes stemness maintenance in ovarian cancer stem cells, Commun. Biol. 8 (2025) 250, https://doi.org/10.1038/s42003-025-07720-w.
[39] M. Luo, Y.-Q. Liu, H. Zhang, C.-H. Luo, Q. Liu, W.-Y. Wang, Z.-C. He, C. Chen, X.-N. Zhang, M. Mao, K.-D. Yang, C. Wang, X.-Q. Chen, W.-J. Fu, Q. Niu, X.-W. Bian, Y. Shi, Y.-F. Ping, Overexpression of carnitine palmitoyltransferase 1A promotes mitochondrial fusion and differentiation of glioblastoma stem cells, Lab. Investig. 102 (2022) 722–730, https://doi.org/10.1038/s41374-021-00724-0.
[40] B. Kong, H. Tsuyoshi, M. Orisaka, D. Shieh, Y. Yoshida, B.K. Tsang, Mitochondrial dynamics regulating chemoresistance in gynecological cancers, Ann. N. Y. Acad. Sci. 1350 (2015) 1–16, https://doi.org/10.1111/nyas.12883.
[41] L.X. Zampieri, D. Grasso, C. Bouzin, D. Brusa, R. Rossignol, P. Sonveaux, Mitochondria participate in chemoresistance to cisplatin in human ovarian cancer cells, Mol. Cancer Res. 18 (2020) 1379–1391, https://doi.org/10.1158/1541-7786.MCR-19-1145.
[42] C.A. Carmona-Carmona, E. Dalla Pozza, G. Ambrosini, B. Cisterna, M. Palmieri, I. Decimo, J.M. Cuezva, E. Bottani, I. Dando, Mitochondrial elongation and OPA1 play crucial roles during the stemness acquisition process in pancreatic ductal adenocarcinoma, Cancers (Basel) 14 (2022) 3432, https://doi.org/10.3390/cancers14143432.
[43] Z. Liu, J. Lei, T. Wu, W. Hu, M. Zheng, Y. Wang, J. Song, H. Ruan, L. Xu, T. Ren, W. Xu, Z. Wen, Lipogenesis promotes mitochondrial fusion and maintains cancer stemness in human NSCLC, JCI Insight 8 (2023), https://doi.org/10.1172/jci.insight.158429.
[44] M.-J. Wu, Y.-S. Chen, M.R. Kim, C.-C. Chang, S. Gampala, Y. Zhang, Y. Wang, C.-Y. Chang, J.-Y. Yang, C.-J. Chang, Epithelial-mesenchymal transition directs stem cell polarity via regulation of mitofusin, Cell Metab. 29 (2019) 993–1002.e6, https://doi.org/10.1016/j.cmet.2018.11.004.
[45] Z. Zhang, T.-E. Li, M. Chen, D. Xu, Y. Zhu, B.-Y. Hu, Z.-F. Lin, J.-J. Pan, X. Wang, C. Wu, Y. Zheng, L. Lu, H.-L. Jia, S. Gao, Q.-Z. Dong, L.-X. Qin, MFN1-dependent alteration of mitochondrial dynamics drives hepatocellular carcinoma metastasis by glucose metabolic reprogramming, Br. J. Cancer 122 (2020) 209–220, https://doi.org/10.1038/s41416-019-0658-4.
[46] A. Picca, J. Faitg, J. Auwerx, L. Ferrucci, D. D'Amico, Mitophagy in human health, ageing and disease, Nat. Metab. 5 (2023) 2047–2061, https://doi.org/10.1038/s42255-023-00930-8.
[47] C. Song, S. Pan, J. Zhang, N. Li, Q. Geng, Mitophagy: a novel perspective for insighting into cancer and cancer treatment, Cell Prolif. 55 (2022), https://doi.org/10.1111/cpr.13327.
[48] K. Liu, J. Lee, J.Y. Kim, L. Wang, Y. Tian, S.T. Chan, C. Cho, K. Machida, D. Chen, J.-H.J. Ou, Mitophagy controls the activities of tumor suppressor p53 to regulate hepatic cancer stem cells, Mol. Cell 68 (2017) 281–292.e5, https://doi.org/10.1016/j.molcel.2017.09.022.
[49] J. Luo, L. Gong, Y. Yang, Y. Zhang, Q. Liu, L. Bai, X. Fang, B. Zhang, J. Huang, M. Liu, B. Liu, Y. Tang, C.N. Wong, J. Huang, S. Liu, S. Li, T. Ding, K. Man, V.H.-F. Lee, Y. Li, S. Ma, X.-Y. Guan, Enhanced mitophagy driven by ADAR1-GLI1 editing supports the self-renewal of cancer stem cells in HCC, Hepatology 79 (2024) 61–78, https://doi.org/10.1097/HEP.0000000000000299.
[50] X. Li, J. Tie, Y. Sun, C. Gong, S. Deng, X. Chen, S. Li, Y. Wang, Z. Wang, F. Wu, H. Liu, Y. Wu, G. Zhang, Q. Guo, Y. Yang, Y. Wang, Targeting DNM1L/DRP1-FIS1 axis inhibits high-grade glioma progression by impeding mitochondrial respiratory cristae remodeling, J. Exp. Clin. Cancer Res. 43 (2024) 273, https://doi.org/10.1186/s13046-024-03194-6.
[51] D. Liu, Z. Sun, T. Ye, J. Li, B. Zeng, Q. Zhao, J. Wang, H.R. Xing, The mitochondrial fission factor FIS1 promotes stemness of human lung cancer stem cells via mitophagy, FEBS Open Bio 11 (2021) 1997–2007, https://doi.org/10.1002/2211-5463.13207.
[52] Z. Liu, S. Shan, Z. Yuan, F. Wu, M. Zheng, Y. Wang, J. Gui, W. Xu, C. Wang, T. Ren, Z. Wen, Mitophagy bridges DNA sensing with metabolic adaption to expand lung cancer stem-like cells, EMBO Rep. 24 (2023), https://doi.org/10.15252/embr.202154006.
[53] J. Chen, S. Xiao, X. Yan, Y. Wei, W. Song, Mechanism of SMYD2 promoting stemness maintenance of bladder cancer stem cells by regulating PYCR1 expression and PINK1/Parkin mitophagy pathway, Int. J. Oncol. 66 (2025) 1–15, https://doi.org/10.3892/ijo.2025.5747.
[54] S. Alcalá, P. Sancho, P. Martinelli, D. Navarro, C. Pedrero, L. Martín-Hijano, S. Valle, J. Earl, M. Rodríguez-Serrano, L. Ruiz-Cañas, K. Rojas, A. Carrato, L. García-Bermejo, M.Á. Fernández-Moreno, P.C. Hermann, B. Sainz, ISG15 and ISGylation is required for pancreatic cancer stem cell mitophagy and metabolic plasticity, Nat. Commun. 11 (2020) 2682, https://doi.org/10.1038/s41467-020-16395-2.
[55] K.A. Whelan, P.M. Chandramouleeswaran, K. Tanaka, M. Natsuizaka, M. Guha, S. Srinivasan, D.S. Darling, Y. Kita, S. Natsugoe, J.D. Winkler, A.J. Klein-Szanto, R. K. Amaravadi, N.G. Avadhani, A.K. Rustgi, H. Nakagawa, Autophagy supports generation of cells with high CD44 expression via modulation of oxidative stress and Parkin-mediated mitochondrial clearance, Oncogene 36 (2017) 4843–4858, https://doi.org/10.1038/onc.2017.102.
[56] W. Li, C. Huang, L. Qiu, Y. Tang, X. Zhang, L. Zhang, H. Zhao, M. Miyagishi, V. Kasim, S. Wu, p52-ZER6/IGF1R axis maintains cancer stem cell population to promote cancer progression by enhancing pro-survival mitophagy, Oncogene 43 (2024) 2115–2131, https://doi.org/10.1038/s41388-024-03058-5.
[57] P. Zhang, W. Wang, H. Xiang, Y. Zhou, Q. Peng, G. Liu, Z.-X. Xu, L. Lu, DAZAP1 maintains gastric cancer stemness by inducing mitophagy, JCI Insight 10 (2025), https://doi.org/10.1172/jci.insight.175422.
[58] P.P. Praharaj, S. Patra, S.R. Mishra, S. Mukhopadhyay, D.J. Klionsky, S. Patil, S. K. Bhutia, CLU (clusterin) promotes mitophagic degradation of MSX2 through an

AKT-DNM1L/Drp1 axis to maintain SOX2-mediated stemness in oral cancer stem cells, Autophagy 19 (2023) 2196–2216, https://doi.org/10.1080/15548627.2023.2178876.
[59] C. Yan, L. Luo, C.-Y. Guo, S. Goto, Y. Urata, J.-H. Shao, T.-S. Li, Doxorubicin-induced mitophagy contributes to drug resistance in cancer stem cells from HCT8 human colorectal cancer cells, Cancer Lett. 388 (2017) 34–42, https://doi.org/10.1016/j.canlet.2016.11.018.
[60] J. Jung, Y. Zhang, O. Celiku, W. Zhang, H. Song, B.J. Williams, A.J. Giles, J. N. Rich, R. Abounader, M.R. Gilbert, D.M. Park, Mitochondrial NIX promotes tumor survival in the hypoxic niche of glioblastoma, Cancer Res. 79 (2019) 5218–5232, https://doi.org/10.1158/0008-5472.CAN-19-0198.
[61] P.P. Naik, S. Mukhopadhyay, P.K. Panda, N. Sinha, C.K. Das, R. Mishra, S. Patil, S. K. Bhutia, Autophagy regulates cisplatin-induced stemness and chemoresistance via the upregulation of CD44, ABCB1 and ADAM17 in oral squamous cell carcinoma, Cell Prolif. 51 (2018), https://doi.org/10.1111/cpr.12411.
[62] Y. Wang, L. Yao, Y. Teng, H. Yin, Q. Wu, PIWIL1 drives chemoresistance in multiple myeloma by modulating mitophagy and the myeloma stem cell population, Front. Oncol. 11 (2022), https://doi.org/10.3389/fonc.2021.783583.
[63] O. Cadassou, L.P. Jordheim, OXPHOS inhibitors, metabolism and targeted therapies in cancer, Biochem. Pharmacol. 211 (2023) 115531, https://doi.org/10.1016/j.bcp.2023.115531.
[64] C. Raggi, M.L. Taddei, E. Sacco, N. Navari, M. Correnti, B. Piombanti, M. Pastore, C. Campani, E. Pranzini, J. Iorio, G. Lori, T. Lottini, C. Peano, J. Cibella, M. Lewinska, J.B. Andersen, L. di Tommaso, L. Viganò, G. Di Maira, S. Madiai, M. Ramazzotti, I. Orlandi, A. Arcangeli, P. Chiarugi, F. Marra, Mitochondrial oxidative metabolism contributes to a cancer stem cell phenotype in cholangiocarcinoma, J. Hepatol. 74 (2021) 1373–1385, https://doi.org/10.1016/j.jhep.2020.12.031.
[65] I. Karp, A. Lyakhovich, Targeting cancer stem cells with antibiotics inducing mitochondrial dysfunction as an alternative anticancer therapy, Biochem. Pharmacol. 198 (2022) 114966, https://doi.org/10.1016/j.bcp.2022.114966.
[66] Y. Kong, X. Li, H. Zhang, B. Fu, H.-Y. Jiang, H.-L. Yang, J. Dai, Targeting POLRMT by a first-in-class inhibitor IMT1 inhibits osteosarcoma cell growth in vitro and in vivo, Cell Death Dis. 15 (2024) 57, https://doi.org/10.1038/s41419-024-06444-9.
[67] Q. Xie, Q. Wu, C.M. Horbinski, W.A. Flavahan, K. Yang, W. Zhou, S. M. Dombrowski, Z. Huang, X. Fang, Y. Shi, A.N. Ferguson, D.F. Kashatus, S. Bao, J. N. Rich, Mitochondrial control by DRP1 in brain tumor initiating cells, Nat. Neurosci. 18 (2015) 501–510, https://doi.org/10.1038/nn.3960.
[68] M. Peiris-Pagès, G. Bonuccelli, F. Sotgia, M.P. Lisanti, Mitochondrial fission as a driver of stemness in tumor cells: mDIVI1 inhibits mitochondrial function, cell migration and cancer stem cell (CSC) signalling, Oncotarget 9 (2018) 13254–13275, https://doi.org/10.18632/oncotarget.24285.
[69] L. Zhang, H. Cao, H. Tao, J. Yang, W. Gong, Q. Hu, Effect of the interference with DRP1 expression on the biological characteristics of glioma stem cells, Exp. Ther. Med. 22 (2021) 696, https://doi.org/10.3892/etm.2021.10128.
[70] D. Liu, Z. Sun, T. Ye, J. Li, B. Zeng, Q. Zhao, J. Wang, H.R. Xing, The mitochondrial fission factor FIS1 promotes stemness of human lung cancer stem cells via mitophagy, FEBS Open Bio 11 (2021) 1997–2007, https://doi.org/10.1002/2211-5463.13207.
[71] S. Courtois, B. de Luxán-Delgado, L. Penin-Peyta, A. Royo-García, B. Parejo-Alonso, P. Jagust, S. Alcalá, J.A. Rubiolo, L. Sánchez, B. Sainz, C. Heeschen, P. Sancho, Inhibition of mitochondrial dynamics preferentially targets pancreatic cancer cells with enhanced tumorigenic and invasive potential, Cancers (Basel) 13 (2021) 698, https://doi.org/10.3390/cancers13040698.
[72] F. Wu, S. Chen, S. Ren, R. Wang, Y. Tan, R. Chen, B. Li, H. Cao, J. Li, Regulating lipid metabolism via mitochondrial dynamics in tongue squamous cell carcinoma cancer stem cells, Recent Pat. Anticancer Drug Discov. 20 (2025) 445–459, https://doi.org/10.2174/0115748928275772231226063458.
[73] M. Zamberlan, A. Boeckx, F. Muller, F. Vinelli, O. Ek, C. Vianello, E. Coart, K. Shibata, A. Christian, F. Grespi, M. Giacomello, I. Struman, L. Scorrano, S. Herkenne, Inhibition of the mitochondrial protein opa1 curtails breast cancer growth, J. Exp. Clin. Cancer Res. 41 (2022) 95, https://doi.org/10.1186/s13046-022-02304-6.
[74] Z. Liu, J. Lei, T. Wu, W. Hu, M. Zheng, Y. Wang, J. Song, H. Ruan, L. Xu, T. Ren, W. Xu, Z. Wen, Lipogenesis promotes mitochondrial fusion and maintains cancer stemness in human NSCLC, JCI Insight 8 (2023), https://doi.org/10.1172/jci.insight.158429.
[75] A. Schwarzer, M. Oliveira, M.-J. Kleppa, S.D. Slattery, A. Anantha, A. Cooper, M. Hannink, A. Schambach, A. Dörrie, A. Kotlyarov, M. Gaestel, T. Hembrough, J. Levine, M. Luther, M. Stocum, L. Stiles, D.M. Weinstock, M. Liesa, M.J. Kostura, Targeting aggressive B-cell lymphomas through pharmacological activation of the mitochondrial protease OMA1, Mol. Cancer Ther. 22 (2023) 1290–1303, https://doi.org/10.1158/1535-7163.MCT-22-0718.
[76] H. Kang, M. Valerio, J. Feng, L. Gu, D.H. Hoang, A. Blackmon, S. Sharkas, K. Pathak, J. Jossart, Z. Li, H. Zhang, B. Zhang, P. Pirrotte, J.J.P. Perry, R.J. Hickey, L. Malkas, G. Marcucci, L.X.T. Nguyen, AOH1996 targets mitochondrial dynamics and metabolism in leukemic stem cells via mitochondrial PCNA inhibition, Exp. Hematol. Oncol. 13 (2024) 123, https://doi.org/10.1186/s40164-024-00586-4.
[77] Y. Song, S. Ren, X. Chen, X. Li, L. Chen, S. Zhao, Y. Zhang, X. Shen, Y. Chen, Inhibition of MFN1 restores tamoxifen-induced apoptosis in resistant cells by disrupting aberrant mitochondrial fusion dynamics, Cancer Lett. 590 (2024) 216847, https://doi.org/10.1016/j.canlet.2024.216847.
[78] J. Sheng, L. Shen, L. Sun, X. Zhang, R. Cui, L. Wang, Inhibition of PI3K/mTOR increased the sensitivity of hepatocellular carcinoma cells to cisplatin via interference with mitochondrial-lysosomal crosstalk, Cell Prolif. 52 (2019), https://doi.org/10.1111/cpr.12609.
[79] X. Zhang, X. Wang, T. Wu, B. Li, T. Liu, R. Wang, Q. Liu, Z. Liu, Y. Gong, C. Shao, Isoliensinine induces apoptosis in triple-negative human breast cancer cells through ROS generation and p38 MAPK/JNK activation, Sci. Rep. 5 (2015) 12579, https://doi.org/10.1038/srep12579.
[80] J. Zhou, G. Li, Y. Zheng, H.-M. Shen, X. Hu, Q.-L. Ming, C. Huang, P. Li, N. Gao, A novel autophagy/mitophagy inhibitor liensinine sensitizes breast cancer cells to chemotherapy through DNM1L-mediated mitochondrial fission, Autophagy 11 (2015) 1259–1279, https://doi.org/10.1080/15548627.2015.1056970.
[81] Q. Su, J. Wang, F. Liu, Y. Zhang, Blocking Parkin/PINK1-mediated mitophagy sensitizes hepatocellular carcinoma cells to sanguinarine-induced mitochondrial apoptosis, Toxicol. in Vitro 66 (2020) 104840, https://doi.org/10.1016/j.tiv.2020.104840.
[82] S. Núñez-Vázquez, J. Saura-Esteller, I. Sánchez-Vera, E. Guilbaud, A.M. Cosialls, G. Pons, J.-E. Ricci, D. Iglesias-Serret, S. Marchetti, J. Gil, The prohibitin-binding compound fluorizoline inhibits mitophagy in cancer cells, Oncogenesis 10 (2021) 64, https://doi.org/10.1038/s41389-021-00352-9.
[83] Y. Li, Y. Li, J. Yin, C. Wang, M. Yang, J. Gu, M. He, H. Xu, W. Fu, W. Zhang, Y. Ru, X. Liu, Y. Li, Y. Xin, H. Gao, X. Xie, Y. Gao, A mitophagy inhibitor targeting p62 attenuates the leukemia-initiation potential of acute myeloid leukemia cells, Cancer Lett 510 (2021) 24–36, https://doi.org/10.1016/j.canlet.2021.04.003.
[84] D.A. East, F. Fagiani, J. Crosby, N.D. Georgakopoulos, H. Bertrand, M. Schaap, A. Fowkes, G. Wells, M. Campanella, PMI: a ΔΨm independent pharmacological regulator of mitophagy, Chem. Biol. 21 (2014) 1585–1596, https://doi.org/10.1016/j.chembiol.2014.09.019.
[85] M. Dany, S. Gencer, R. Nganga, R.J. Thomas, N. Oleinik, K.D. Baron, Z.M. Szulc, P. Ruvolo, S. Kornblau, M. Andreeff, B. Ogretmen, Targeting FLT3-ITD signaling mediates ceramide-dependent mitophagy and attenuates drug resistance in AML, Blood 128 (2016) 1944–1958, https://doi.org/10.1182/blood-2016-04-708750.
[86] C. Ganji, V. Muppala, M. Khan, G.P. Nagaraju, B. Farran, Mitochondrial-targeted nanoparticles: delivery and therapeutic agents in cancer, Drug Discov. Today 28 (2023) 103469, https://doi.org/10.1016/j.drudis.2022.103469.
[87] J. Kreiter, A. Rupprecht, L. Zimmermann, M. Moschinger, T.I. Rokitskaya, Y. N. Antonenko, L. Gille, M. Fedorova, E.E. Pohl, Molecular mechanisms responsible for pharmacological effects of genipin on mitochondrial proteins, Biophys. J. 117 (2019) 1845–1857, https://doi.org/10.1016/j.bpj.2019.10.021.
[88] C. Li, C. He, Y. Xu, H. Xu, Y. Tang, H. Chavan, S. Duan, A. Artigues, M.L. Forrest, P. Krishnamurthy, S. Han, J.M. Holzbeierlein, B. Li, Alternol eliminates excessive ATP production by disturbing Krebs cycle in prostate cancer, Prostate 79 (2019) 628–639, https://doi.org/10.1002/pros.23767.
[89] K. Sinha, S. Chowdhury, S. Banerjee, B. Mandal, M. Mandal, S. Majhi, G. Brahmachari, J. Ghosh, P.C. Sil, Lupeol alters viability of SK-RC-45 (renal cell carcinoma cell line) by modulating its mitochondrial dynamics, Heliyon 5 (2019) e02107, https://doi.org/10.1016/j.heliyon.2019.e02107.
[90] F. Fontana, R.M. Moretti, M. Raimondi, M. Marzagalli, G. Beretta, P. Procacci, P. Sartori, M. Montagnani Marelli, P. Limonta, Δ-Tocotrienol induces apoptosis, involving endoplasmic reticulum stress and autophagy, and paraptosis in prostate cancer cells, Cell Prolif. (2019), https://doi.org/10.1111/cpr.12576.
[91] F. Fontana, M. Raimondi, M. Marzagalli, M. Audano, G. Beretta, P. Procacci, P. Sartori, N. Mitro, P. Limonta, Mitochondrial functional and structural impairment is involved in the antitumor activity of δ-tocotrienol in prostate cancer cells, Free Radic. Biol. Med. (2020), https://doi.org/10.1016/j.freeradbiomed.2020.07.009.
[92] M. Raimondi, F. Fontana, M. Marzagalli, M. Audano, G. Beretta, P. Procacci, P. Sartori, N. Mitro, P. Limonta, Ca2+ overload- and ROS-associated mitochondrial dysfunction contributes to δ-tocotrienol-mediated paraptosis in melanoma cells, Apoptosis (2021), https://doi.org/10.1007/s10495-021-01668-y.
[93] B. Plitzko, E.N. Kaweesa, S. Loesgen, The natural product mensacarcin induces mitochondrial toxicity and apoptosis in melanoma cells, J. Biol. Chem. 292 (2017) 21102–21116, https://doi.org/10.1074/jbc.M116.774836.
[94] H.-Y. Min, H.-J. Jang, K.H. Park, S.Y. Hyun, S.J. Park, J.H. Kim, J. Son, S.S. Kang, H.-Y. Lee, The natural compound gracillin exerts potent antitumor activity by targeting mitochondrial complex II, Cell Death Dis. 10 (2019) 810, https://doi.org/10.1038/s41419-019-2041-z.
[95] G.-B. Li, R.-Q. Fu, H.-M. Shen, J. Zhou, X.-Y. Hu, Y.-X. Liu, Y.-N. Li, H.-W. Zhang, X. Liu, Y.-H. Zhang, C. Huang, R. Zhang, N. Gao, Polyphyllin I induces mitophagic and apoptotic cell death in human breast cancer cells by increasing mitochondrial PINK1 levels, Oncotarget 8 (2017) 10359–10374, https://doi.org/10.18632/oncotarget.14413.
[96] Y. Sun, J. Yu, X. Liu, C. Zhang, J. Cao, G. Li, X. Liu, Y. Chen, H. Huang, Oncosis-like cell death is induced by berberine through ERK1/2-mediated impairment of mitochondrial aerobic respiration in gliomas, Biomed. Pharmacother. 102 (2018) 699–710, https://doi.org/10.1016/j.biopha.2018.03.132.
[97] C.-W. Wang, W.-H. Hsu, C.-J. Tai, Antimetastatic effects of cordycepin mediated by the inhibition of mitochondrial activity and estrogen-related receptor α in human ovarian carcinoma cells, Oncotarget 8 (2017) 3049–3058, https://doi.org/10.18632/oncotarget.13829.
[98] K. Vališ, V. Grobárová, L. Hernychová, M. Bugáňová, D. Kavan, M. Kalous, J. Černý, E. Stodůlková, M. Kuzma, M. Flieger, J. Černý, P. Novák, Reprogramming of leukemic cell metabolism through the naphthoquinonic compound Quambalarine B, Oncotarget 8 (2017) 103137–103153, https://doi.org/10.18632/oncotarget.21663.