The multifaceted roles of mitochondria at the crossroads of cell life and death in cancer

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ABSTRACT

Mitochondria are the cytoplasmic organelles mostly known as the “electric engine” of the cells; however, they also play pivotal roles in different biological processes, such as cell growth/apoptosis, Ca^{2+} and redox homeostasis, and cell stemness. In cancer cells, mitochondria undergo peculiar functional and structural dynamics involved in the survival/death fate of the cell. Cancer cells use glycolysis to support macromolecular biosynthesis and energy production (“Warburg effect”); however, mitochondrial OXPHOS has been shown to be still active during carcinogenesis and even exacerbated in drug-resistant and stem cancer cells. This metabolic rewiring is associated with mutations in genes encoding mitochondrial metabolic enzymes (“oncometabolites”), alterations of ROS production and redox biology, and a fine-tuned balance between anti-/proapoptotic proteins. In cancer cells, mitochondria also experience dynamic alterations from the structural point of view undergoing coordinated cycles of biogenesis, fusion/fission and mitophagy, and physically communicating with the endoplasmic reticulum (ER), through the Ca^{2+} flux, at the MAM (mitochondria-associated membranes) levels. This review addresses the peculiar mitochondrial metabolic and structural dynamics occurring in cancer cells and their role in coordinating the balance between cell survival and death. The role of mitochondrial dynamics as effective biomarkers of tumor progression and promising targets for anticancer strategies is also discussed.

Keywords Cancer, mitochondria, metabolic rewiring, OXPHOS, ROS, structural dynamics, MAMs

1. Introduction

Mitochondria are the renowed "power generators" of the cell, being the master intracellular producers of ATP through oxidative phosphorylation (OXPHOS). The activity of the OXPHOS system is supported by the coenzymes NADH and $FADH_2$ mainly formed through the TCA (tricarboxylic acid) cycle that also produces the building blocks for the synthesis of organic molecules such as proteins, nucleotides and lipids. TCA cycle metabolites are now known to be also involved in DNA methylation, chromatin remodelling and protein post-translational chemical modifications [1]. In addition to energy metabolism, mitochondria are involved in a wide array of biological processes, including intrinsic apoptosis, cell growth, intracellular Ca^{2+} and redox homeostasis, cell stemness, regulation of signaling pathways associated with cell proliferation [2-4]. Being dynamic organelles, mitochondria often undergo structural modifications such as biogenesis, fusion/fission, and degradation at the lysosomal level (mitophagy). The balance of these mechanisms supports the maintenance of mitochondrial integrity and, therefore, of their biological functions [5,6].

A deregulated energetic metabolism is now a well recognized hallmark of cancer, in its different phases of development and progression. During the process of carcinogenesis, cells undergo peculiar metabolic changes, including increased activity of the glycolytic pathway, altered lipid and glutamine metabolism and rewiring of mitochondrial functions [7-12]. Alterations of the structural dynamics of mitochondria were also widely shown to occur in several diseases, including cancer [6,12-15].

It is now recognized that mitochondria are not 'lonely' structures but rather communicate with different cytoplasmic organelles (nucleus, endoplasmic reticulum, Golgi apparatus, lysosomes, peroxisomes) by exchanging biological information through membrane contact sites; these interactions play a pivotal role in several cellular processes. In particular, mitochondria were shown to closely interact with the endoplasmic reticulum (ER) at the level of membrane contact sites, known as MAMs (mitochondria-associated membranes); this mitochondria-ER communication supports the key functions of the two organelles in regulating cell proliferation/death, cell metabolism, redox and Ca^{2+} homeostasis, in both physiological and pathological conditions, such as cancer [16-21].

Here, we aim to provide an update of the complex role of the mitochondrial functional and structural rewiring as well as of the mitochondria-ER physical interactions in the mechanisms underlying cancer development and progression; we will also address the role of these mitochondria-related mechanisms as novel molecular biomarkers and targets in cancer therapy.

2. Mitochondrial functional reprogramming in cancer

Cancer cells need high levels of energy and metabolites to support their aberrant proliferation, survival and metastatic behavior; to address these needs, in a hypoxic and hyponutrient microenvironmental condition, they adapt their metabolic activities through a process known as "metabolic reprogramming" [9,12,22-27]. Mitochondria are also deeply involved in reactive oxygen species (ROS) production and ROS homeostasis has been widely shown to play a crucial role in different aspects of tumor biology [28]

A diagrammatic representation of the mitochondrial functional dynamics occurring in cancer cells is depicted in Figure 1.

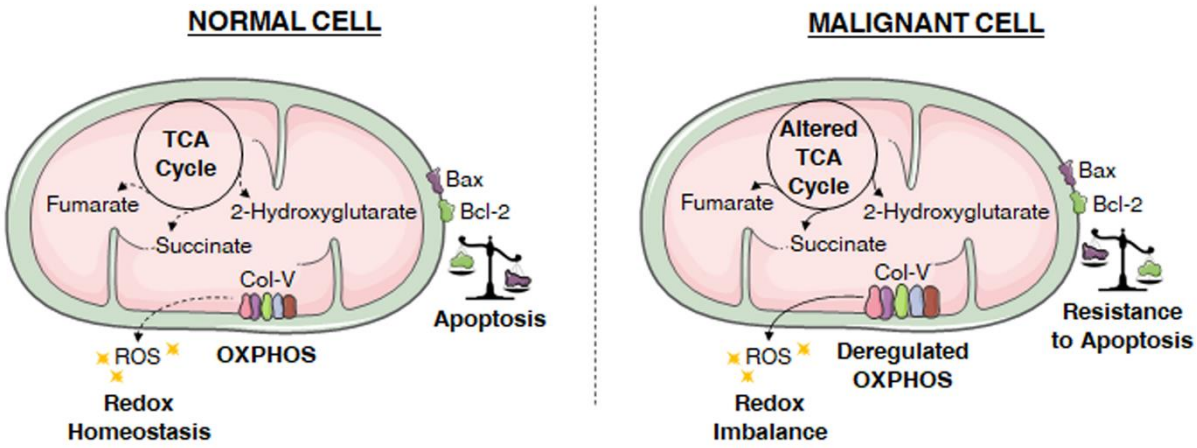

Fig. 1. Diagrammatic summary of the main mitochondrial functional dynamics in cancer cells. Metabolic rewiring: despite the presence of a highly active aerobic glycolysis, the mitochondrial OXPHOS machinery (complexes I-V, CoI-V) has been observed to be present and still functional in different tumors, and even exacerbated in their most aggressive invasive/metastatic and stem cell counterparts. Oncometabolites: in cancer cells, mitochondrial metabolic dysfunctions were also described to be related to mutations in genes encoding metabolic enzymes leading to the accumulation of the so called "oncometabolites", such as fumarate, succinate and 2-hydroxyglutarate, driving tumorigenesis. ROS production and redox homeostasis: altered ROS production and redox imbalance are a hallmark of cancer. Resistance to apoptosis: tumor cells develop resistance to anticancer drugs through a deregulation of the apoptotic cell death machinery, by shifting the balance from proapoptotic (Bax, Bak) to antiapoptotic (Bcl-2) proteins.

2.1. Metabolic rewiring

Otto Warburg, in the 1920s, first proposed that tumor cells are characterized by a high ability to uptake glucose and preferentially metabolize glucose through the glycolytic pathway ("aerobic glycolysis", also commonly referred to as the "Warburg effect"), even in the presence of sufficient amounts of oxygen to support OXPHOS at the mitochondrial level [29,30]. Glycolysis produces only two moles of ATP per mole of glucose, thus it does not exhaustively fulfill the energetic requirements of cancer cells. However, this metabolic process also produces a high amount of intermediate metabolites that function as building blocks to support the biosynthesis of organic molecules (amino acids, nucleotides and lipids) for proliferating cells [31,32]. Moreover, the increased lactate levels at the end of this pathway generate an acidic environment that promotes cancer cell invasion and migration [33,34] and affects the immune microenvironment to elicit an immune tolerant condition and tumor cell proliferation [35].

Despite the presence of a high glycolytic rate in cancer cells, chemotherapeutic strategies based on glycolytic inhibitors as well as genetic disruption affecting different steps of this metabolic pathway were reported to be unsuccessful in completely arresting the proliferation of tumor cells [36,37]. These observations support that mitochondrial OXPHOS is still present and active in tumor cells and highlight the notion that tumor cells are highly heterogeneous in terms of metabolic pathways [9,22,38-45]. The existence of an active mitochondrial metabolic network, specifically TCA cycle and ATP synthesis through the OXPHOS machinery has actually been demonstrated in different types of cancer cells to support the high demand on biomolecules, as building blocks for macromolecules, and energy for their proliferation and conversion to a metastatic phenotype (*i.e.*, epithelial-to-mesenchimal transition) [12,27,37,44,46-55]. We recently showed that, in melanoma cells, a functional OXPHOS machinery is strictly associated with mitochondrial Ca^{2+} and ROS homeostasis while a perturbation of the mitochondrial metabolic functions (decreased oxygen uptake, reduced expression of OXPHOS proteins and ATP production), together with a disruption of the Ca^{2+}/ROS homeostasis, triggers both canonical (apoptosis) and non-canonical (paraptosis) death mechanisms, thus regulating the cell survival/death balance [56,57]. A mitochondrial metabolic remodeling, characterized by a metabolic shift toward OXPHOS activity, has also been reported in cancer cells undergoing drug resistance [58-71]. In particular, an "exacerbated" dependency on OXPHOS is frequently observed in cancer stem cells (*i.e.*, the subpopulation of therapy-resistant cancer cells) to support their ability in self-renewal, stemness maintaining and evasion from apoptosis induced by anticancer treatments [45,63,65,72-81].

Interestingly, according to the theory of the "reverse Warburg effect", it has been proposed that cancer cells can induce oxidative stress in neighboring stromal cells (*i.e.*, cancer-associated fibroblasts, CAFs), forcing them towards a hyperglycolytic condition that leads to the overproduction of molecular intermediates. These glycolysis metabolites are then taken up by cancer cells that use them as precursors of macromolecules for their biomass synthesis, necessary to sustain their self-renewal, survival and proliferation [26,82-84].

It is now well established that tumor microenvironment (*i.e.*, CAFs) plays a pivotal role in the metabolic rewiring of cancer cells, by regulating their metabolic and phenotypic plasticity. Chiarugi and coworkers reported that lactate released by tumor-associated CAFs is taken up by cancer cells and triggers a metabolic reprogramming towards the mitochondrial OXPHOS energy production pathway, associated with an increase of mitochondrial mass. In tumor cells, CAF-derived lactate can also be converted into pyruvate, resulting in the production of oncometabolites (*i.e.*, succinate and fumarate) to fuel tumorigenesis and cancer progression [85-87].

Other aspects of mitochondrial metabolic reprogramming in cancer cells are the high rate of: glutaminolysis, converting glutamine into metabolic intermediates, as building blocks for nucleotide and amino acids synthesis, and into glutamate to fuel the TCA cycle; oxidation of fatty acids (FAs), derived by *de novo* biosynthesis as well as by exogenous FAs uptake, essential to meet the high ATP demand (*i.e.*, to provide the essential energy source) [23,88-93].

2.2. Oncometabolites

Alterations of cellular energetics and mitochondrial metabolic dysfunctions in cancer cells have been described to be related to mutations in nuclear genes encoding mitochondrial metabolic enzymes leading to the formation of metabolites, now called "oncometabolites". Oncometabolites have been recently reported to be involved in the different phases of cancer growth and progression. Specifically, point mutations in nuclear genes coding for fumarate hydratase (FH) and succinate dehydrogenase (SDH), enzymes involved in the TCA cycle, and isocitrate dehydrogenase 1 and 2 (IDH1/2), catalyzing the conversion of α-ketoglutarate into 2-hydroxyglutarate (2-HG), lead to the accumulation of the oncometabolites fumarate, succinate and 2-HG, respectively. These metabolites were widely shown to be involved in several processes, including epigenetic changes, driving tumorigenesis [94-99]. Cells harboring mutations in IDH1/2 (isocitrate dehydrogenase 1 and 2) were reported to display a high dependence on mitochondrial oxidative metabolism and to be highly sensitive to pharmacological OXPHOS inhibition [100,101].

Alterations of mitochondrial DNA (mtDNA) sequences, encoding proteins of the OXPHOS system, such as somatic point mutations and changes in copy number, were also observed in cancer cells. Increased mtDNA copy number, mitochondrial biogenesis and ATP production have been reported to be associated with an aberrant cell proliferation rate in some epithelial cancers [98,102-104]. Targeting the mitochondrial RNA polymerase with specific pharmacological inhibitors has been recently shown to induce a significant antitumor activity in cervical and ovarian cancer stem cells [65]. Mitochondrial functional rewiring, due to metabolic enzyme alterations or mtDNA mutations, also affect ROS and Ca^{2+} homeostasis, thus fueling the different processes of tumorigenesis [2,105]. Specifically, it has been demonstrated that ROS, Ca^{2+} and oncometabolites released from mitochondria affect the activity of cytosolic signaling pathways that in turn alter gene expression at the nuclear level (a process known as "retrograde signaling"), ultimately triggering tumor growth and progression [98].

Alterations in oncogenes, such as *HIF-1* (hypoxia-inducible factor-1), *BRAF*, *RAS*, *EGFR* (epidermal growth factor receptor), *MYC* and tumor suppressor genes, such as *TP53*, were also reported to trigger a metabolic rewiring in tumor cells to support cancer development and progression. In particular, metabolic changes induced by these genes include rewiring of glucose uptake, glycolytic and TCA cycle pathways, glutamine metabolism and fatty acid metabolism [98,106].

2.3. ROS production and redox homeostasis

Mitochondria are the the main source of ROS in cells and participate in redox homeostasis regulation [28]. ROS are a family of molecules that include highly reactive free oxygen radicals (superoxide anion, $O_2^{\bullet -}$ and the hydroxyl radical $^{\bullet}OH$) and the stable 'diffusable' non-radical oxidants (hydrogen peroxide, H_2O_2). ROS are generated primarily from the leakage of the electron transport chain during oxidative phosphorylation. Specifically, inhibition of ATP synthase in the inner mitochondrial membrane impairs the activity of the electron transport chain (ETC); the excess electrons are transferred directly to O_2 to generate superoxide ($O_2^{\bullet -}$) that can be further dismutated into H_2O_2. Increased levels of H_2O_2 then function as diffusible signalling molecules [107].

ROS are well known to play pleiotropic roles in tumor growth and progression. For instance, it has been proposed that, in cancer cells, ROS might behave as potent mitogens. In these cells, inhibition of apoptosis leads to elevated ROS production contributing to neoplastic transformation; moreover, in cancer cells undergoing adaptation to environmental stressors, elevation of ROS levels was reported to provide a survival advantage [28,108, 109]. In line with these observations, high

ROS levels and aberrant redox states have been recently shown to be a common feature of cancer cells, and specifically cancer stem cells (CSCs) [110]. Li and coworkers reported that high ROS levels increase telomerase activity, involved both in tumorigenesis and cancer cell stemness, through the Akt signaling pathway [111].

On the other hand, an opposite role for high ROS levels in cancer cell proliferation has also been described. It has been shown that most tumor cells resist to hypoxia-induced apoptosis by decreasing their ROS production, suggesting that, in these cells, a mechanism mediated by mitochondria might exist to regulate redox homeostasis, making them more tolerant to hypoxic microenvironment [112,113]. Moreover, elevated ROS levels were reported to induce toxic effects in cancer cells, inducing cell death mechanisms, such as apoptosis and necrosis [28]. In line with these observations, increased levels of mitochondrial ROS were widely shown to mediate the activity of different synthetic and natural anticancer compounds (see below).

2.4. Resistance to apoptosis

Mitochondria are also deeply involved in the drug-induced apoptosis process in most cancer cells [114-116]. In addition to their role as the "power plants" of the cells, mitochondria are the master regulators of the cell survival/death balance by playing a pivotal role in the intrinsic apoptosis pathway. This pathway involves the activity of the Bcl-2 (B-cell lymphoma 2) family of regulator proteins involved in the permeabilization of the mitochondrial outer membrane. This family consists of three groups of proteins based on their function: 1) antiapoptotic proteins (Bcl-2, Bcl-X_L, Bcl-W, MclL-1, Bfl-1/A1); 2) pro-apoptotic pore-formers (Bax, Bak, Bok); 3) pro-apoptotic BH3-only proteins (Bad, Bid, Bim, Noxa, Puma, Bik). When recruited to the mitochondrial outer membrane, the pro-apoptotic proteins Bax and Bak, through the formation of pores, induce the so called MOMP (mitochondrial outer membrane permeabilization) process. This initial event allows cytochrome *c* release that, in turn, triggers the activation of caspase-9 and, subsequently, of the intrinsic apoptotic pathway [117-119]. On the other hand, the antiapoptotic proteins Bcl-2 and Bcl-X inhibit this programmed cell death mechanisms by interfering with the activity of the pro-apoptotic members. An imbalance between anti- and proapoptotic proteins is frequently observed in cancer cells, specifically in drug-resistant cells, and is an effective target for the activity of anticancer compounds.

Interestingly, it has been showed that mitochondria are also involved in other cell death mechanisms, such as paraptosis, necroptosis, pyroptosis and ferroptosis [4,56,57,120,121].

Taken together, these observations support a crucial role of mitochondrial functional dynamics in tumorigenesis and respose to anticancer drugs. These organelles are well acknowledged as the master regulator of the intrinsice apoptosis pathway, by finely shaping the balance between antiapoptotic and proapoptotic proteins, thus serving as key effectors of both anticancer therapies and development of drug resistance. Importantly, there is now growing evidence that, in addition to the glycolytic pathway, a mitochondrial metabolic network (OXPHOS machinery, ATP production) is still present and functional in cancer cells, to support their energetic demands and the challenge of macromolecular synthesis for proliferation. Increased ROS production, due to elevated OXPHOS activity (as particularly evidenced in the most aggressive stem cell counterpart) and genetic mutations in genes involved in the TCA cycle and oncometabolite accumulation are also deeply involved in tumorigenesis. Based on these considerations, compounds targeting the mitochondrial functional reprogramming are gaining increasing interest in the development of cancer therapeutic approaches.

3. Mitochondrial structural dynamics in cancer

Mitochondria are organelles also characterized by distinctive structural dynamics. A stability of their structure, required for the mainenance of homeostasis in healthy cells, is allowed by the coordination of different biological processes, such as biogenesis, fusion, fission (fragmentation) and mitophagy (mitochondria degradation) [122,123]. On the other hand, alterations of mitochondrial structural dynamics have been shown to be deeply involved in different diseases, such as cancer, and represent an important growing and attractive area of research [12,124,125].

A schematic overview of the mitochondrial structural dynamics occurring in the subpopulation of cancer stem cells is depicted in Figure 2.

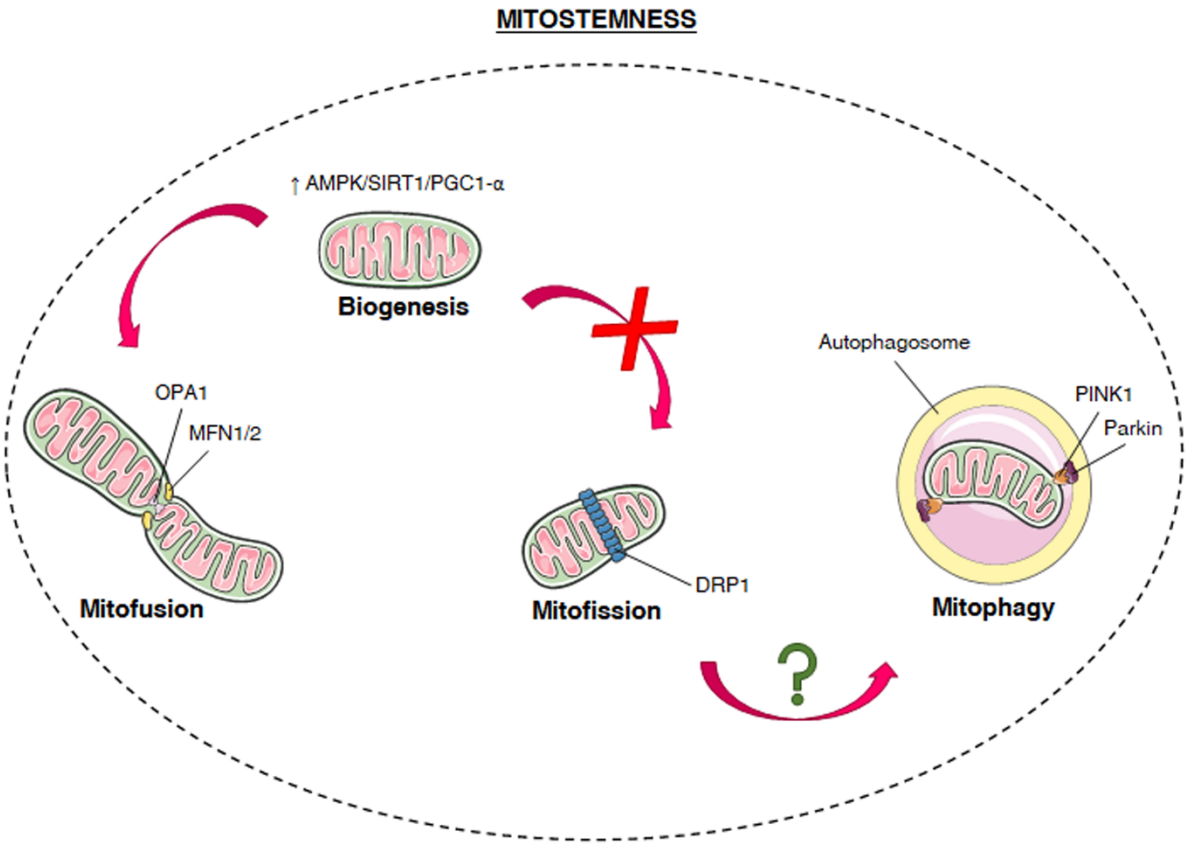

Fig. 2 Schematic overview of the main mitochondrial structural dynamics occurring in cancer stem cells. Biogenesis: the cellular mechanism responsible for the generation of new organelles, necessary to provide the essential amount of nutrients and energy to cancer cells, and specifically cancer stem cells. The AMPK/SIRT1/PGC1-α axis, by promoting mitochondrial biogenesis, has been reported to be deeply involved in the maintenance of the biological features (plasticity, cell renewal and stemness) of CSCs. Fusion and fission: the opposite processes of mitochondrial merging and separation. Fusion involves tethering of neighboring mitochondria followed by merging of the OMM and the IMM membranes. MFN1/2 (at the OMM level) and OPA1 (at the IMM level) are the key players in this dynamic process. Fission is the division of mitochondria to create new organelles, but it also involved in the removal of damaged mitochondria and in the apoptosis pathway during high levels of cellular stress. The cytosolic protein DRP1, recruited to the mitochondria, encircles and shrinkles the organelles to finally induce their fission. An increased fusion, or decreased fission, was observed in drug-resistant and, specifically, in stem cancer cells. Mitophagy: the process responsible for the removal of damaged mitochondria. Mitochondria damage activates the PINK1/Parkin pathway that triggers the autophagic elimination of the organelles. Notably, the specific relationship between mitochondrial autophagy and CSCs is still not clear.

3.1. Mitochondrial biogenesis

Mitochondrial biogenesis is the generation of new organelles and is required to provide the necessary amount of energy and nutrients in the cell [126]. It is usually triggered by cellular stress conditions or different stimuli from the microenvironment. This process foresees a tight coordinated regulatory network of both mtDNA and nuclear DNA, involving: mtDNA replication and transcription; nuclear DNA transcription and cytoplasmic synthesis of nuclear DNA-derived proteins and their import into the mitochondria via specific transporters [126]. In cancer cells, an increase of mitochondrial mass, together with a hyperactivated oxidative phosphorylation, has been shown to be deeply involved in cell proliferation, in the acquisition of an invasive and metastatic phenotype and in the development of drug resistance [64,125,127].

Different molecules are known to be involved in mitochondrial biogenesis. The well known "master regulator" of mitochondrial biogenesis is PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator-1alpha), belonging to the family of PGC multifunctional transcriptional coactivators (PGC-1, PGC-1α, PGC-β) [128,129]. Once activated by phosphorylation or deacethylation, PGC-1α cooperates with several nuclear transcription factors, such as nuclear respiratory factor-1 (NRF-1), NRF-2 and ERR-α (estrogen-related receptor-α) to increase the expression of mitochondrial transcription factor A (TFAM); TFAM is the final effector of mitochondrial biogenesis, through the regulation of mtDNA replication and transcription [130,131].

On the other hand, the expression of PGC-1α is finely regulated, through phosphorylation, by AMPK (adenosine monophosphate-activated protein kinase), the "energy sensor" of the cells. AMPK is activated in response to different conditions which deplete intracellular energy levels (decreased ATP/ADP ratio), such as hypoxia and glucose starvation. AMPK can also bind to mitochondria, thus directly stimulating the OXPHOS mechanisms and fatty acid oxidation [132].

In addition to the AMPK/PGC-1α axis, activation of mtDNA replication and transcription during mitochondrial biogenesis is regulated by different pathways. It is now well established that the factor silent information regulator-1 (SIRT1) activates PGC-1α (by inducing its deacetylation) thus triggering the transcription of genes, both at the nuclear and mitochondrial level, whose derived proteins are deeply involved in mitochondria biogenesis, OXPHOS and ATP production. On the other hand, SIRT3 promotes the synthesis of proteins involved in TCA cycle, OXPHOS and fatty acid oxidation [126,133]. It has been recently reported that, in pancreatic cancer stem cells, an active AMPK/SIRT1/PGC-1 α axis is involved in apoptosis inhibition and increased mitochondrial OXPHOS, required to maintain the stemness features of these cells [134].

Interestingly, in melanoma cells, expression of PGC-1α is regulated by the transcription factor MITF (microphtalmia-associated transcription factor); activation of the MITF-PGC-α axis induces upregulation of mitochondrial mass, OXPHOS activity and antioxidant gene expression [135-138].

The mTOR (mammalian target of rapamycin) serine/threonine protein kinase was shown to increase mtDNA transcription and, subsequently, mtRNA translation of TFAM as well as of proteins belonging to the OXPHOS complexes and mitochondrial ribosomal proteins [139].

Mitochondrial biogenesis has been recently reported to be involved in the ability of cancer stem cells (CSCs) to survive stress conditions associated with anticancer treatments [45,80,140].

3.2. Mitochondrial fusion and fission

A highly coordinated balance between the dynamic processes of fusion and fission ("mitochondrial dynamics") occurs not only in proliferating but also in resting cells, allowing appropriate mitochondrial structure, functions and intracellular distribution. A perturbation of this balance will lead to the formation of either interconnected/long or fragmented/punctiform mitochondria [5,16,50,105,141,142].

The process of fusion involves tethering between mitochondria, merging of the outer membrane (OMM), followed by fusion of the inner membrane (IMM) and the subsequent assortment of the biomolecules in the intermembrane space and mitochondrial matrix; these processes are dependent on the hydrolysis of GTP. Mitchondrial fusion is mediated by three membrane-anchored proteins belonging to the dynamin family of GTPases. Specifically, fusion of the outer membranes is controlled by the mitofusins MFN1 and MFN2 (mitochondrial fusion proteins 1 and 2), while fusion of the inner membranes is regulated by optic atrophy 1 (OPA1) [15]. Different OPA1 isoforms have been so far observed; in normal conditions, these forms are constitutively cleaved, to generate both the short and the long isoforms of the protein (S- and L-OPA1) [143]. Mechanistically, MFN1 physically interacts with MFN2 inducing the formation of strict connections between neighboring mitochondria, thus allowing the fusion of the OMM [144]. On the other hand, MFN1 heterodimerizes with OPA1 to trigger the fusion of the IMM [15,145,146].

During the process of fission, mitochondria divide, leading to the formation of different new organelles and the subsequent reorganization of the mitochondria network into the cell. This process is mediated by DRP1 (dynamin-related protein 1), a cytosolic GTPase member of the dynamin protein family. This process starts with the formation of contacts between the endoplasmic reticulum (ER) and the mitochondrial membranes. First, the InsP3R (inositol 1,4,5-trihpsphate receptor) channel in the ER membrane comes in contact with the VDAC (voltage-dependent anion

channel) in the OMM; this allows a Ca^{2+} flux from ER into the mitochondria leading to actin polimerization at the level of the contact site; then, DRP1 is recruited from the cytosol to these sites and further gathers additional OMM-anchored proteins, such as MID49, MID51 and MFF, and FIS1. Together, these proteins encircle and shrinkle the mitochondrion leading to its division into new and functional organelles [147-150]. The activity of the different proteins involved in both fusion and fission is finely regulated by post-translational modifications, such as phosphorylation, ubiquitination and sumoylation [151,152].

An alteration of the balance between fusion and fission has been widely demonstrated to be involved in cancer growth and progression; however, the specific role of fusion *vs.* fission in the tumorigenic process is still a matter of debate, supporting a specific role of these processes in different cell contexts [6,12,50,142,153]. Interestingly, in a very recent paper, Kleele and coworkers highlighted the presence, in Cos-7 cells, of two "distinct fission signatures" that can predict either the biogenesis or the degradation of mitochondria. Specifically, they reported that mitochondrial fission at the cell periphery involves the elimination of damaged organelles by mitophagy, while mitochondrial division at the cell midzone is responsible for organelle proliferation [154]. The relevance of the intracellular localization of the fission process (cell periphery *vs*. midzone) in the role of fission/fusion balance in driving cell survival/death in cancer cells still has to be investigated.

Mitochondrial fusion was reported to be inversely correlated with tumor development. Specifically, overexpression of mitofusins (MFN2) was found to be associated with an antiproliferative and proapoptotic effect in some tumor cell lines [124,155]. In line with these observations, DRP1 expression levels were shown to positively correlate with cell survival and proliferation by promoting cell cycle progression. A mitochondrial fragmentation was suggested to be a peculiar morphological feature in different types of cancer cells [142,156-160]. In line with these data, a higher activity of DRP1 and lower expression of mitofusins was shown to be associated with morphological changes and metasiatic behaviors in some type of cancer cells [124,161-164].

However, an opposite role of the fusion/fission dynamics in cancer cells has also been reported. There is now substantial evidence that fission is strictly associated with mitophagy, the process responsible for the removal of damaged mitochondria [165,166], and with the intrinsic apoptosis pathway, through an increased release of cytochome *c* form the mitochondria [167]. Similarly, a decreased mitochondrial fission (or increased fusion) was observed in cisplatin-resistant gynecological tumors [168,169], supporting a strict association of chemotherapy resistance with mitochondrial fusion; in line with these observations, a fused mitochondrial morphology was

recently observed in aggressive, metastatic Triple-Negative Breast Cancer cells [170]. Moreover, Sanchez-Alvarez and coworkers recently reported that overexpression of the mitochondrial fission factor MFF in MCF7 breast cancer cells decreases both mitochondrial mass and activity, as evidenced by inhibition of the OXPHOS and glycolytic pathways; MFF overexpression also reduces CSCs activity/propagation, supporting the activation of a quiescence program. Taken together, these data support that, in these cells, activation of the fission process leads to an impairment of the mitochondrial metabolism associated with inhibition of CSC propagation [171].

In cancer cells, an increased ROS production has been shown to correlate with mitochondrial membrane potential loss, mitochondrial fission, mitophagy and apoptosis [105]. Recent *in vitro* and *in vivo* studies consistently reported that mitochondrial fission, associated with mitochondrial metabolic alterations, is deeply involved in the proapoptotic activity of different chemotherapeutic drugs [105,172-174]. In line with these data, we recently showed that, in prostate cancer cells, mitochondrial Ca^{2+} and ROS overload-associated cell death (apoptosis, paraptosis) is mediated by the activation of the mitochondrial fission and mitophagic pathways [56].

3.3. Mitophagy

Mitophagy (the selective degradation of mitochondria through autophagy) is the process that removes damaged or dysfunctional mitochondria with the aim to maintain their functions and integrity. Damaged mitochondria are engulfed in autophagosomes (double-membrane-delimited vesicles) by which they are transferred to lysosomes for their degradation [165]. The PINK1 (PTEN-induced kinase 1)/Parkin pathway plays a pivotal role in the mitophagy program [175,176]. PINK is a mitochondrial serine/threonine protein kinase while Parkin functions as an E3 ubiquitin ligase. In normal conditions, after its import into mitochondria through its specific mitochondria-targeting sequence, PINK1 is cleaved at the level of the IMM by the PARL (presenilin-associated rhomboid-like) protease and then translocates back from mitochondria to the cytosol where it is degraded at the proteasomal level [177]. In conditions of mitochondrial damage (*i.e.*, depolarization), PINK accumulates at the OMM level where, through phosphorylation, it activates Parkin that in turn induces ubiquitination of different membran-bound proteins, such as MFN1, MFN2 and VDAC1. Ubiqutinated proteins recruit the autophagy cargo adaptors p62/SQSTM1 and OPTN (optineurin) and interact with the autophagosomal marker LC3 forming a complex that is ultimately degraded through the autophagic process [178-182].

Alterations of the mitophagy process, and the associated accumulation of damaged/dysfunctional mitochondria, have been observed in different pathological conditions, such as cancer

[12,13,50,183,184]. In particular, in cancer cells, this process has been found to be involved both in cell proliferation/survival or death, according to the cell context. Mitophagy was initially suggested be an oncosuppressor process that maintains cellular homeostasis and prevents oncogenic transformation, at least in the early phases of carcinogenesis; on the other hand, in cancer cells subjected to stressful conditions, such as hypoxia and nutrient starvation, increased mitophagy was reported to be involved in cell evasion from apoptosis through the removal of damaged mitochondria and the decrease of mitochondrial ROS species [185]. The role of mitophagy in cancer drug resistance is still controversial, being shown to reduce or to increase the sensitivity of cancer cells to chemotherapeutic drugs [186]. Interestingly, in cancer stem cells, mitophagy has been demonstrated to be involved in cell plasticity and their adaptive/survival behavior to anticancer drugs [80,81,187,188]. In a recent paper, we reported that a perturbation of the mitochondrial Ca^{2+}/ROS homeostasis, associated with impaired respiration and mitochondrial fission accompanied by mitophagy, triggers cell death mechanisms (*i.e.*, autophagy, apoptosis and paraptosis) in prostate cancer cells [56]. Recently, it is becoming clear that mitophagy pathways are intricately linked to the metabolic rewiring of cancer cells to support the high bioenergetic demand of the tumor.

In summary, recent emerging evidence strongly supports a deep involvement of mitochondrial structural dynamics in tumor growth and progression. However, while the role of mitochondrial biogenesis (the generation of new organelles, required to provide the essential amount of nutrients and energy to cancer cells) is now well established, the specific roles of mitochondrial fusion (merging)/fission (separation) and mitophagy (removal of damaged organelles) in tumorigenesis is still a matter of debate. Recent data from our as well as from others' laboratories evidenced that the fission process, associated with Ca^{2+} overload and ROS overproduction and followed by mitophagy, is linked to cell death mechanisms (apoptosis, paraptosis) triggered by anticancer compounds; these data are in line with the observation of an increased mitochondrial fusion in drug-resistant and stem cancer cells. Further investigations of the role of the mitochondrial structural dynamics in carcinogenesis and development of drug resistance are warranted.

4. Mitochondria-organelle interactions in cancer

It is now well established that the communication between intracellular organelles, through their physical interaction at the level of membrane contact sites (MCS), plays a pivotal role in different cellular physiological processes. In particular, mitochondria physically interact with different subcellular organelles and cytoplasmic structures, such as plasma membrane, ER, nucleus,

lysosomes, peroxisomes, cytoskeleton, to regulate fundamental cellular processes such as coordinated cellular homeostasis, mitochondria bioenergetics and cell fate (survival *vs.* death). Dysregulations of these dynamic inter-organelle communications, and especially the mitochondria-ER crosstalk, were widely reported to be involved in different health disorders, such as cardiovascular and neurodegenerative diseases, as wel as tumor development and progression.

An illustrative representation of the mitochondria-ER interactions, and Ca^{2+} shuttling, at the MAM level is given in Figure 3.

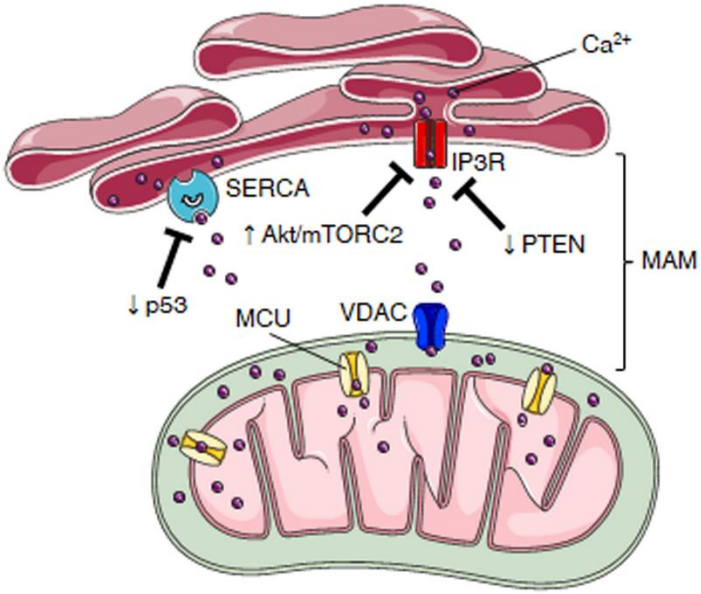

Fig. 3 Representation of Ca^{2+} transfer at the level of mitochondria-ER interactions (MAMs) and its role in cancer cell growth. At the MAM level, the SERCA pump, located in the ER membrane, favors Ca^{2+} uptake from the cytosol in the ER lumen. On the other hand, the IP3R channel, in the ER membrane, gets in contact with the VDAC channel, located in the OMM. This IP3R/VDAC axis allows Ca^{2+} transfer from ER to the mitochondrial intermembrane space, where it is uptaken by the MCU uniporters to be transferred into the mitochondrial matrix. Alterations of the ER-mitochondria Ca^{2+} flux, and therefore of mitochondrial Ca^{2+} homeostasis, were reported to be involved in tumor cell growth and development of resistance to anticancer drugs. Specifically, in these cells, it was reported that: a downregulation of the expression/activity of the oncosuppressors p53 and PTEN (known to activate the SERCA and IP3R Ca^{2+} channels, respectively) is associated with a reduction of cytosolic Ca^{2+} uptake in the ER and of the ion flux from the ER to the mitochondria; activation of the Akt/mTORC2 axis triggers the phosphorylation (*i.e.*, inactivation) of IP3 thus inhibiting the ER-mitochondria Ca^{2+} transfer. Ultimately, both these pathways prevent mitochondrial Ca^{2+} overload, thus supporting cancer cell survival *vs.* apoptosis.

4.1. Mitochondria-ER interactions

The first sites of intracellular organelle physical communications to be discovered were the mitochondria-ER contact sites [189,190]. These contacts, known as MAMs (mitochondrial associated membranes), are mainly involved in Ca^{2+} exchange from ER to mitocohondria but also in lipid (*i.e.*, phospholipids) synthesis and exhange, as well as in mitochondrial metabolism and structural dynamics [17-21,191-193].

Different techniques were utilized to unravel the structure and functions of MAMs. Their isolation, achieved in subcellular fractionation-based experiments, highlighted the role of these structures as membrane sites of lipid biosynthesis and transfer [194]. Electron microscopy and electron tomography studies demonstrated that mitochondria and smooth ER are juxtaposed at a distance of approximately 10-25 nm [195-197]. More recently, techniques based on targeted fluorescent proteins, and in particular, green fluorescent protein-based contact site sensors (SPLICS), evidenced the presence of both narrow and wide mitochondria-ER contact sites in human cells by means of confocal microscopy [198]. It is important to underline that, at the level of MAMs, the organelle membranes are not fused but instead they form a tethered structure [199]

It is now well established that MAMs are deeply involved in the regulation of Ca^{2+} signaling and homeostasis [200]. In basal conditions, Ca^{2+} levels are low in the cytoplasm and ER is the main storage organelle of this ion within cells. On the other hand, in the presence of extracellular stimuli, Ca^{2+} is released from ER to be distributed to the cytosol, to fulfil its functions as an intracellular messenger (*i.e.*, binding to calmodulin and activation of the downstream Ca^{2+}/calmodulin-dependent protein kinase), or to enter cytosolic organelles such as mitochondria. ER Ca^{2+} storage/depletion mainly depends on channels and pumps present on ER membranes, such as SERCA (sarco/endoplasmic reticulum Ca^{2+} ATPase, involved in Ca^{2+} uptake from the cytosol), RyRs (ryanodine receptors, mainly responsible for the release of Ca^{2+} from the sarcoplasmic/endoplasmic reticulum during excitation-contraction coupling in both cardiac and skeletal muscle) and IP3Rs (inositol 1,4,5-triphosphate receptors) [201]. Specifically, IP3Rs are involved in Ca^{2+} transfer from the ER to mitochondria intermembrane space through the VDAC, located in the OMM. From the intermembrane space, Ca^{2+} is then transferred to the mitochondrial matrix through the MCU (mitochondrial calcium unipoter) uniporter present in the IMM that is not permeable to the ion [202,203]. Different ER-mitochondria tethering proteins, essential for the Ca^{2+} flux at the MAM level and implicated in Ca^{2+} homeoastasis, are: GRP75, the molecular chaperone glucose regulated protein 75; MFN1/MFN2, located in the ER and mitochondrial membranes;

PDZD8 (PDZ domain-containing protein 8) and DJ-1 (the oncoprotein encoded by the *PARK7* gene), involved in the maintenance of contact site structure [204-207].

4.2. Mitocondria-ER interactions: role of Ca^{2+} transfer in cancer

A strict control of mitochondrial Ca^{2+} levels is crucial for its role in the regulation of bioenergetics, metabolism and cell survival/death [208]. Physiologically, Ca^{2+} homeostasis in the mitochondria matrix was shown to increase the activity of rate-limiting enzymes of the TCA cycle and fatty acid oxidation [209]. On the other hand, alterations of Ca^{2+} levels, in particular its overaccumulation, results in the opening of the mitochondrial permeability transition pores (PTPs), leading to ROS generation, increased IMM permeability, loss of membrane potential, mitochondrial swelling, OMM dysruption and cytochrome *c* release, thus switching the cell death/survival balance towards apoptosis and non-canonical cell death mechanisms [210-217].

Different oncogenes and tumor suppressor genes were found to be gathered at the MAM levels and to affect cell growth through the regulation of the key processes involved in ER/mitochondria Ca^{2+} flux and homeoastasis [218,219].

As discussed above, IP3R is a key player in the Ca^{2+}-mediated communication between ER and mitochondria, thus its expression/activation is crucially involved in the molecular mechanisms underlying tumor growth and progression. IP3R receptor overexpression has been reported to be associated with altered mitochondrial bioenergetics and apoptosis in cancer cells [220,221]. Akt is a serine threonine kinase belonging to the PI3K/Akt/mTOR signaling pathway and deeply involved in the pathogenesis of different diseases, including cancer [222]. Akt has been found to be enriched at the MAM levels where it phosporylates (*i.e.*, inactivates) IP3R, thus inhibiting the ER/mitochondria Ca^{2+} transfer and, consequently, supporting cell survival *vs.* apoptosis [223,224]. Interestingly, regulators of Akt activity, such as PTEN (phosphatase and tensin homolog) and PML (promyelocytic leukemia protein), with a suppressor activity, and mTORC2, with activating properties, were also reported to be located at the MAM level. Bononi and coworkers demonstrated that, based on its phosphatase activity, PTEN directly induces the dephosphorylation of IP3R, thus favoring Ca^{2+} release and its mitochondrial accumulation triggering downstream apoptotic events; in line with these observations, PTEN downregulation was found to reduce the ER-mitochondrial Ca^{2+} transfer and this ultimately results in a decreased sensitivity of the cells to Ca^{2+}-induced apoptosis [225]. At the MAM level, PML forms a molecular complex together with Akt and the phosphatase PP2A (protein phosphatase 2A). When PML is not present, the phosphatase PP2A is inactive and this leads to an increased Akt phosphorylation and subsequent phosphorylation (*i.e.*,

inactivation) of IP3R with reduced mitochondrial Ca^{2+} levels and increased cell resistance to apoptosis [226]; IP3R activity can also be downregulated through ubiquitination and degradation at the proteasomal level [227]. On the other hand, mTORC2, forming a multiprotein complex with IP3R, GRP75 and VDAC at the ER-mitochondria contact sites, triggers IP3R phosphorylation, thus reducing mitochondrial Ca^{2+} levels to favor cell survival. mTORC2 was also reported to phosphorylate hexokinase 2 to promote Warburg effect through the activation of the glycolytic pathway [228].

The tumor suppressor protein p53 is the well-known key player in cell cycle arrest, and apoptosis. At the MAM level, this transcription factor interacts with the SERCA pump located in the ER membrane favoring Ca^{2+} uptake in the ER lumen. Activation of p53 by oxidative stress conditions or antitumor drugs leads to an increased ER-mitochondrial Ca^{2+} flux thus increasing cell sensitivity to apoptosis [229].

The role of the VDAC Ca^{2+} channel in cancer is still a matter of debate. Downregulation of this channel was shown to inhibit cell proliferation, supporting its relevant role in tumor growth [230,231]. In line with this observation, VDAC overexpression was observed in several tumor tissues (breast, lung, head and neck cancers) and to correlate with poor survival outcome [20]. On the other hand, an increased expression of both VDAC and SERCA following progesterone treatment was reported to inhibit the proliferation, and to trigger the non-canonical cell death ferroptosis, in breast cancer cells [232].

MCU is the well known uniporter located at the IMM and responsible for Ca^{2+} transfer from the intermembrane space into the mitochondrial matrix [202,203]. Similarly to IP3R and VDAC, MCU is also involved in the mechanisms regulating the survival/death balance in cancer cells [233]. MCU was shown to be overexpressed in different types of cancer cells. Li and coworkers recently reported that *MCU* silencing decreases the proliferation of glioblastoma cells [234]. Knockdown of this uniporter was also found to potentiate caspase-independent cell death and to decrease cell motility, reducing mitochondrial ROS levels, in cancer cells [235-238]. In contrast to these observations, other investigators observed that this uniporter is associated with antitumor activities. For instance, Marchi and coworkers reported that in colon cancer cells, downregulating MCU expression with its specific microRNAs (miR-25) suppresses Ca^{2+} entry in the mitochondrial matrix thus promoting cell survival [239]. Further studies are therefore needed to definitely highlight the role of MCU in tumorigenesis.

Taken together, these data strongly support that ER-mitochondria Ca^{2+} transfer is deeply involved in cancer development and progression and represents an effective target for novel therapeutic strategies. In line with this obervation, different anticancer drugs, including natural

compounds, were widely reported to induce cell death, such as paraptosis, a type of programmed cell death characterized by cytoplasmic vacuolation, consisting of both ER and mitochondrial swelling. Mechanistically, it has been shown that the antitumor activity of these compounds is accompanied by ER stress due to proteostasis disruption, inducing protein misfolding and accumulation in the ER lumen, and leading to the opening of IP3R receptors and Ca^{2+} release. ER-derived Ca^{2+} ions are then uptaken into mitochondria, through the VDAC channels at the MAM level, inducing their swelling and dysfunction. Specifically, we demonstrated that, in melanoma cells, mitochondrial Ca^{2+} overload triggers ROS overproduction culminating in mitochondrial fission, mitophagy, and activation of apoptosis paraptosis [57].

5. Targeting mitochondrial dynamics in cancer therapies

As discussed above, despite the dependency of cancer cells on aerobic glycolysis as a source of energy even in the presence of oxygen (the "Warburg Effect"), it is now well accepted that mitochondrial metabolism (TCA cycle, OXPHOS, ATP production) is not impaired, but it is actually still active in different types of tumor cells to fulfill their high demands of energy and intermediates as biomolecule precursors to sustain cancer growth and progression. A mitochondrial metabolic reprogramming was also consistently demonstrated to represent a hallmark of drug resistance and stemness in different tumors.

It is now well established that mitochondria are highly dynamic organelles also from the structural point of view; mitochondrial morphological dynamics, such as biogenesis, fusion/fission and mitophagy, are deeply involved in the development of numerous diseases, including cancer.
Moreover, mitochondria are very "chatterbox" structures that keep in touch with other cytoplasmic organelles, such as ER; alterations of ER-mitochondria communications were reported to be involved in different disorders, such as tumorigenesis and progression.

Based on these observations, mitochondrial functional and structural dynamics as well as organelle interactions are now considered a promising molecular target for novel and effective therapeutic strategies in cancer.

5.1. Targeting mitochondrial functional and structural dynamics

Several synthetic and natural compounds were recently reported to exert a significant antitumor activity by targeting mitochondrial functional and structural dynamics [46,53,77,240-243] (see Table 1).

In the last years, it has become increasingly clear that some antibiotics, in addition to their antibacterial activity, are endowed with a high potential as anticancer drugs. This assessment is based on the so called "endo-symbiotic theory of mitochondrial evolution" affirming that some of the organelles present in eukaryotic cells were initially prokaryotic microbes. Specifically, this theory states that mitochondria derive from aerobic bacteria that were engulfed by eukariotic cells during their evolution to give rise to novel lineages at the highest taxonomic levels. Lisanti and coworkers widely investigated the antitumor activity of antibiotics in different cancers cells. By means of vHTS (virtual high-throughput screening) and computational chemistry analyses, they identified four classes of antibiotics (also named "mitoriboscins") that, in breast cancer cell lines, as well as in their stem cell counterpart, bind to the two subunits of mitoribosomes, thus ultimately impairing mitochondrial respiration [244]. These authors also reported that the antibiotics doxycycline and azithromycin (two FDA-approved antibiotics), in combination with vitamin C, significantly reduce the stemness features of the stem cell subpopulation in MCF7 breast cancer cells, by impairing mitochondrial metabolism and ATP production while increasing a compensatory glycolytic pathway. Mechanistically, vitamin C is a mild pro-oxidant which induces the formation of free radicals while doxocycline and azithromycin act by inhibiting the small and the large mitochondrial ribosome subunits respectively, thus impairing the synthesis of proteins involved in the OXPHOS axis [245]. The authors propose that "driving mitochiondrial oxidative stress followed by inhibition of mitochondrial protein translation ultimately prevents CSC mitochondria from recovery". In these experiments, the two antibiotics were utilized at sub-antimicrobial levels, thereby avoiding the development of undesired antibiotic resistance [245,246]. Doxocycline and azithromycin were also shown to be associated with antitumor effects by inhibiting respiration in melanoma cells [49].

Ozsvari and coworkers also demonstrated that, in MCF7 cells, the antibiotic diphenyleneiodomium chloride (DPI) significantly impairs mitochondrial respiration, specifically targeting the CSCs subpopulation through the inhibition of flavin-containing enzymes, located in complex I and II of the ETC and endowed with autofluorescent properties [247]. In a pilot clinical study, it was reported that a short-term pre-operative treatment of breast cancer patients with oral doxycyline is effective in eradicating the subpopulation of CSCs in tumor tissues [248]. Based on these data, Lisanti and colleagues proposed the relevance of the treatment with "a mitochondrial based oncology platform (MITO-OC-RX)", to specifically target mitochondrial metabolism in the most aggressive stem cell subpopulation in different types of tumors [72,249].

In line with these observations, the FDA-approved antibiotic tigecycline, was shown to exert a significant antitumor activity in different type of cancer cells (hematologic tumors, melanoma,

neuroblastoma, hepatocellular carcinoma, triple negative breast cancer), by inducing mitochondrial dysfunctions, through inhibition of the OXPHOS pathway, and mitochondrial translation, likely by interacting with mitochondrial ribosome subunits. In hepatocarcinoma cells, tigecycline was also shown to increase the levels of mitochondrial superoxide, hydrogen peroxide and ROS levels. Importantly, antioxidant N-acetyl-l-cysteine (NAC) reversed these effects, suggesting that oxidative stress is required for the action of tigecycline in cancer cells [250]. Combination treatments of this antibiotic with chemotherapeutic compounds was then proposed as a promising treatment for cancer therapeutical strategies [49,250-255].

Similar results were obtained with other antibiotics: quinoprustin/dalfopristin, shown to suppress glioblastoma CSC growth by dysregulating OXPHOS complexes [256]; acriflavine, effectively reducing the growth of pancreatic cancer cells, *in vitro* and *in vivo*, through the downregulation of mitochondrial metabolic pathways [257]; bedaquiline, an antibiotic recently developed to treat tuberculosis infections that are resistant to conventional treatments, impairing mitochondrial ATP production by targeting the gamma subunit of the ATP synthase [258].

Interestingly, some antibiotics were reported to exert their anticancer activity also by targeting mitochondrial structural dynamics, and specifically by impairing the biogenesis process [251,259].

Clinical studies demonstrated that antibiotics such as azithromycin and tygecycline increase the favorable effects (*i.e.*, overall survival) of anticancer compounds in some malignancies (lung cancer, hematologic tumors), being well tolerated and relatively safe [260,261]. On the other hand, doxycline given in combination with bone-targeted therapy in patients with metastatic breast cancer did not show positive effects in terms of bone markers and was found to be associated with serious gastrointestinal side effects [262]. Thus, given these contrasting results from clinical application, future studies should focus on the effects of antibiotic drugs to effectively treat cancer patients.

Cisplatin is a chemotherapy drug widely used for the treatment of different types of cancers, such as ovarian, bladder, head and neck, testicular, lung and cervical cancer. Its antitumor activity has been linked to its ability to crosslink with the purine bases on the DNA, preventing DNA repair mechanisms of DNA, thus causing DNA damage and subsequently inducing apoptosis [263]. On the other hand, it was also reported to rapidly accumulate in mitochondria altering both their metabolic and structural functions [264,265]. Specifically, it was shown to decrease the expression levels of enzymes involved in the TCA cycle while increasing mitochondrial ROS levels, thus triggering apoptosis [265,266]. Choi and coworkers demonstrated that the main reason of cisplatin-related cytotoxicity is related to the generation of mitochondrial ROS that influence multiple signaling pathways. Alteration of these pathways results in the collapse of mitochondrial ATP production, which in turn sensitizes the cells to death. The quenching of ROS leads to the

amelioration of the affected pathways [265]. Moreover, in *in vitro* and *in vivo* studies, it was also demonstrated to induce mitochondrial fragmentation and apoptosis via regulating key factors related to the p53 tumor suppressor pathway, in different cancer cells [172,267,268]. Interestingly, these data could be confirmed by clinical trials [172].

The biguanide metformin, approved by FDA in the 1990s, is the first-line medication for the treatment of type 2 diabetes [269]. Diabetic patients more likely develop cancer with respect to healthy subjects; on the other hand, it is now well established that diabetic patients treated with metformin have a significantly lower incidence of cancer than diabetic patients treated with other antidiabetic drugs [270-272]. These observations led to the development of several clinical trials investigating the possible anticancer activity of metformin in diabetic patients affected by different types of cancers [273-276]. More recently, clinical studies were developed to assess the potential antitumor activity in non-diabetic cancer patients; however, contrasting results were reported [276-281]. These data stimulated basic research efforts with the aim to dissect the molecular mechanisms of the potential direct anticancer activity of this drug.

Several *in vitro* and *in vivo* studies have demostrated the efficacy of metformin, alone or in combination with standard drugs, in impairing the growth of different types of cancer cells, as well as of their CSC counterpart [45,259,282-284]. Although the precise molecular mechanisms behind the antitumor activity of metformin (and the other biguanide antidiabetic drug phenformin) are still only partly understood, this drug has been widely demonstrated to inhibit mitochondrial respiration through the inhibition of complex I of the ETC (electron transport chain), leading to a disruption of the NAD^+/NADH balance (*i.e.*, decreased NADH oxidation), decreased oxygen conumption and ATP production [285-288]. This is accompanied by a reduced TCA cycle activity/metabolite production and AMPK activation, thus resulting in downstream suppression of the mTOR pathway followed by apoptosis and autophagy [289]. Both a direct effect, assuming the accumulation of the drug into the mitochondria, and an indirect effect were suggested to be involved in this activity [284,290]. However, it must be underlined that the involvement of AMPK in metformin activity is still a matter of debate [276,291].

STAT3 (signal transducer and activator of transcription 3) has been reported to be localized to the mitochondria where it is involved in the link between oncogene-related signaling pathways and cancer cell metabolism. Metformin was shown to target the STAT3-OXPHOS pathway in drug-resistant oncogene-addicted tumors [292]. ASK1 (apoptosis signaling regulating kinase 1) is known to be associated with cell death and mitochondria damage. In ovarian cancer cells, metformin was recently reported to induce apoptosis via ASK1-mediated functional mitochondrial damage, by means of *in vitro* and *in vivo* experiments [293]. Recent studies have underlined a synergistic

anticancer effect of metformin when given in combination with other therapeutic agents as well as its capacity to overcome chemotherapy resistance [294,295]. Based on these promising basic results, clinical trials are presently ongoing to assess the potential activity of metformin, either alone or in combination with standard antitumor compounds, in non diabetic patients with cancer [295-298].

Last but not least, metformin was also widely reported to exert its cytotoxic effects in cancer cells through the upregulation of ROS production. In colon cancer cells, metformin was found to disturb the mitochondrial activity via increased ROS levels and SIRT3 activity, and these rapid alterations play a key role in its cytotoxic property [299]. In human osteosarcoma cells, metformin was shown to induce cell cycle arrest and programmed cell death, including apoptosis and autophagy, through the ROS-dependent JNK/c-Jun cascade [300]. Similar observations were reported in gastric adenocarcinoma cells [301]. In colon cancer cells, the antidiabetic drug, combined with cisplatin, inhibited cell viability, decreased colony formation, and induced the intrinsic apoptosis pathway through increased ROS-mediated PI3K/Akt signaling pathway activity [302]. In lung cancer cells, by means of *in vitro and in vivo* studies, it has been shown that metformin, in combination with celecoxib, induces ROS aggregation, leading to mitochondrial membrane potential alteration, DNA double-strand breaks and increased expression of the tumor suppressor factor p53, causing cell cycle arrest and cell proliferation inhibition [303]; similar mechanisms were reported to mediate the antitumor activity of metformin, in combination with standard therapies, in different types of cancer cells [304-307].

Systematic reviews and meta-analysis of randomized controlled studies, supporting that metformin possesses beneficial effects for cancer prevention and treatment in different tumors, have recently been published [297,298,308-314]. Clinical outcomes of the ongoing trials are urgently required to further support the therapeutic use of metformin in cancer.

Receptor tyrosine kinases (RTKs) are cell surface receptors for different biomolecules such as growth factors, hormones and cytokines. These receptors are not only involved in physiological cellular processes but they also have a crucial role in cancer growth and progression [315,316]. Tyrosine kinase inhibitors (TKIs) have recently gained a great interest in the oncology field based on their ability to specifically target oncogenic signaling pathways in cancer cells, while sparing normal healthy cells [317]. From the clinical point of view, they are characterized by some significant advantages such as minimal side effects, high selectivity and oral administration [318]. In a recent review, Rodríguez-Hernández and coworkers discussed in depth the molecular mechanisms involved in the anticancer activity of different TKIs. Specifically, they highlighted that sorafenib, dasatinib and regorafenib induce cancer cell death and antitumoral autophagy, by

triggering mitochondrial dysfunction through the inhibition of the ETC complexes, AMPK activation and mTOR inhibition, and a dysregulation of the mitochondrial Ca^{2+} and ROS homeostasis [319]. Sorafenib was also demonstrated to act synergystically with FH535 (an inhibitor of the Wnt/β-catenin pathway) in inducing hepatocellular carcinoma cell death by dysrupting cell bioenergetics and mitochondrial functions [54,320].

Recently, different "small-molecule" inhibitors of mitochondrial metabolic functions (*i.e.*, targeting ETC complexes, OXPOHOS pathway, ATP production, mitochondrial DNA transcription) were developed with the aim to improve cancer tratment strategies; these drugs include: ONC201, ONC206 and ONC212 (belonging to the imipridone family); IACS-010759; ME-344 (isoflavone derivative); IMT1 and IMT1B (inhibitor of mitochondrial transcription 1 and 1B) [42,65].

ONC201 is orally administered and crosses the intact blood brain barrier. In clinical trials, its administration was reported to be associated with tumor regression and increased disease-free survival in patients with advanced solid tumors and hematological malignancies. Synergistic effects with chemotherapy, targeted therapy and immune-checkpoint agents have been observed in preclinical models and are being evaluated in clinical trials [321].

Ivosidenib and enasidenib, are two inhibitors of mutant IDH 1/2, recently approved by the US FDA for the treatment of some types of cancers, such as refractory or relapsed acute myeloid leukemia; they prevent the synthesis and accumulation of the oncometabolite 2-HG but their clinical application is limited by their poor ability to cross the blood-brain barrier. Vorasidenib, an oral mutant IDH1/2 inhibitor, with a satisfactory brain penetration, has been recently developed and its clinical application is currently under investigation in patients with advanced/recurrent glioma and hematological malignancies [322].

It is now well established that several natural compounds are endowed with a significant antitumor activity, notably attributed to their potent antioxidant effects. On the other hand, several molecular mechanisms and intracellular signaling pathways were demonstrated to be involved in their activity purposing their role as potential effective compounds in chemopreventive/treatment anticancer strategies, either alone or in combination with canonical drugs [121,323-333]. Specifically, it has recently become clear that these compounds may exert their antitumor effects also by targeting mitochondrial dynamics, both at the functional and structural level.

Vitamin E consists of eight hydrophobic compounds, named tocotrienols (TTs) and tocopherols (TPs). TTs and TPs are divided into two groups: α-, β-, δ- and γ-TT and the corresponding TPs. TTs are present in different plant sources, such as annatto (Bixa orellana) seed, palmo il and rice bran [334,335]. In the last decades, TTs attracted great interest for their beneficial health effects in

preventing or treating different chronic diseases (*i.e.*, osteoporosis, neurodegenerative and cardiovascular diseases) [336-338]. In particular, several *in vitro* and *in vivo* studies underlined that these compounds are also endowed with a significant antitumor activity based on their ability to trigger cell death and to impair the metastatic and angiogenic behavior of different types of cancer cells [339-344]. In our laboratory, we showed that, in prostate cancer cells, the δ-TT isoform induces apoptosis, involving ER stress, as well as the non-canonical cell death paraptosis [345]. Mechanistically, we demonstrated that this antitumor activity is associated with a remarkable impairment of both mitochondrial functional and structural dynamics. Specifically, δ-TT reduces mitochondrial respiration by decreasing O_2 consumption and ATP production and downregulating OXPHOS protein levels. From the structural point of view, the tocotrienol induces mitochondrial fission as well as the Ca^{2+}- and ROS-mediated mitophagic process, leading to a dysruption of the mitochondrial network [56]. We also reported that δ-TT exerts a significant antitumor activity in human melanoma cells, as well as in their stem cell counterpart [346]. In human A375 and BLM melanoma cells, this compound significantly impairs mitochondrial respiration, as demonstrated by reduced expression of the OXPHOS complex I, decreased O_2 consumption, ATP production and mitochondrial membrane potential, culminating in paraptosis induction [57].

From the clinical point of view, it was reported that orally administered δ -TT in preoperative patients with pancreatic ductal neoplasia is well tolerated, reaches bioactive levels in blood, and induces apoptosis in the neoplastic cells of cancer specimens [347]. More recently, a phase-II clinical trial demonstrated that the combination of bevacizumab and δ-TT is effective in increasing the progression-free and the overall survival in multiresistant ovarian cancer patients [348].

Gracillin, a natural product-derived steroidal saponin, is another mitochondria-targeting natural compound. By means of *in vitro* and *in vivo* studies, it was reported that, in NSCLC (non-small cell lung cancer) and breast cancer cells, gracillin inhibits the OXPHOS-mediated bioenergetics through the dysruption of the mitochondrial complex II-mediated energy production, resulting in ROS overproduction and cell death; the glycolytic pathway was also found to be reduced by this compound [349,350]. Similarly, a mixture of bergamot-derived polyphenols (brutieridin and melitidin) and the catechin-enriched matcha green teawere shown to inhibit the breast cancer stem cell propagation by targeting mitochondrial respiration and fatty acid oxidation [351,352].

As discussed above, mitochondrial glutaminolysis is a metabolic process deeply involved in cancer growth and progression. Glutamine is taken up by cancer cells through specific transporters, such as SLC1A5 (also named ASCT2). It has been shown that resveratrol potentiates the cisplatin-induced cell death in cancer cells, by reducing SLC1A5 expression [353]. However, glutamine must enter the mitochondria to be converted to glutamate to fuel the TCA cycle. It is accepted that it can

diffuse through the OMM into the intermembrane space and it is then transported into the mitochondrial matrix through a specific inner membrane transporter; the structure of this specific transporter is still a matter of debate. Recently, Yoo and coworkers reported the presence of a novel variant of SLC1A5, localized into the IMM; they found that overexpression of this variant triggers a metabolic reprogramming and chemotherpy resistance in cancer cells [354]. The role of this transporter as a molecular target for anticancer therapeutic strategies still has to be investigated.

Last but not least, different pharmacological strategies (*i.e.*, "mitochondria-targeted therapeutics", MTTs) have been recently developed to specifically get drugs into mitochondria. Notably, triphenuphosphonium (TPP) is a lypophilic cationic compound that has been utilized as an anticancer drugs-carrier since, based on its chemical structure, it can diffuse and accumulate into the mitochondrial matrix and can also be easily conjugated with bioactive compounds. Thus, TPP derivatives were developed by linking the TPP molecule with different conventional cytostatic drugs (*i.e.*, doxorubicin, paclitaxel, platinum, tamoxifen), metformin, antioxidants as well as natural compounds (*i.e.*, betulinic acid, glycyrrhetinic acid) [355,356]. These compounds were reported to inhibit proliferation and induce cell death in different cancer cells lines, *in vitro* and *in vivo*; interestingly, they were also shown to impair mitochondrial bioenergetics and metabolism, specifically by targeting complex I activity and triggering ROS generation [357]. De Francesco and coworkers recently reported that TTP derivatives, by targeting mitochondrial OXPHOS activity, significantly eradicate the CSC subpopulation in breast cancer cell lines; interestingly, these compounds also synergistically act with both synthetic and natural anticancer drugs, supporting a novel therapeutic strategy to concurrently target both the bulk of cancer cells and their stem cell counterpart [358]. The promising results from these *in vitro* and preclinical studies support potential prospects for the clinical application of these compounds in the future.

Table 1

Anticancer drugs targeting mitochondrial functional and structural dynamics and ER-mitochondria crosstalk.

Drug	Therapy class	Effects	References
Doxycycline, azithromycin, tigecycline, acriflavine, quinupristin/dalfopristin, bedaquiline	Antibiotics with anticancer activity	Inhibition of OXPHOS protein translation and mitochondrial respiration; dysregulation of OXPHIOS complexes and induction of mitochondrial oxidative stress; inhibition of mitochondrial biogenesis	[245-248, 250-259]

Diphenyleneidonium-Cl	Antimicrobics with anticancer activity	Inhibition of flavin-containing enzymes (complex I and II of the ETC); impairment of mitochondrial respiration	[247]
Cisplatin	Platinum-based chemotherapy	Decreased expression of TCA enzymes; overload of mitochondrial ROS; activation of mitochondrial fission	[172,264-268]
Metformin	Antidiabetic (type 2 diabetes) drugs	Inhibition of ETC complex I; decreased O_2 consumption and ATP production; AMPK activation; induction of autophagy and apoptosis: suppression of the STAT/OXPHOS pathway; upregulation of ROS production	[285-289,292,293,299-307]
Sorafenib, dasatinib, regorafenib	Tyrosine kinase inhibitors (TKIs)	Inhibition of ETC complexes; AMPK activation; alteration of Ca^{2+}/ROS homeostasis	[319,320]
ONC201, 206, 212	Small molecules	Inhibition of ETC complexes and OXPHOS; decreased ATP production; alteration of mitochondrial DNA transcription	[42,65]
Ivosidenib, enasidenib, vorasidenib	Mutant IDH1/2 inhibitors	Prevention of 2-HG oncometabolite accumulation	[322]
Vitamin E-derived tocotrienols, gracilin, bergamot-derived polyphenos	Natural antioxidants	Reduced O_2 consumption, OXPHOS protein levels and ATP; disruption of complex II functions; altered Ca^{2+}/ROS homeostasis; mitochondrial fission, mitophagy; apoptosis and paraptosis; glutaminolysis	[56,57,349-354]
Cytostatic drug-linked TTP	Mitochondria-targeted therapeutics (MTTs)	Inhibition of ETC complex I and OXPHOS;	[357-358]

(triphenylphosphonium)	mitochondrial ROS generation

5.2. Targeting ER-mitochondria interactions and Ca^{2+} transfer

Based on their key role in cancer growth and progression, MAMs and Ca^{2+} flux, mediated by specific channels located both in ER and in mitochondrial channels, are considered a promising molecular target for novel therapeutic approaches. ER-mitochondria Ca^{2+} transfer has been reported to be involved in the anticancer activity of different synthetic and natural compounds (see Table 2).

The chemotherapeutic drug cisplatin has been demonstrated to trigger Ca^{2+} flux from the ER to the mitochondria at the MAM level in different types of cancer cells. The IP3R channel was found to be dysregulated in cancer cells resistant to this drug [359,360]; moreover, the antiapoptotic protein Bcl-2 was reported to counteract cisplatin cytostatic activity by decreasing the number of mitochondria-ER contact sites, thus impairing Ca^{2+} flux [360]. In line with these data, it was shown that the Bcl-2 inhibitor ABT737, known to increase mitochondrial Ca^{2+} levels, potentiates cisplatin activity in resistant ovarian cancer cells [361]. The Bcl-2/IP3R dysruptor 2 (BIRD2), interfering with the Bcl-2/IP3R interactions, favors Ca^{2+} release from the ER and its subsequent accumulation in mitochondria thus inducing apoptosis [362]. Similarly, oxaliplatin was demonstrated to trigger IP3R-mediated Ca^{2+} flux and apoptosis in human neuroblastoma cells [363]. Novel anticancer compounds that specifically target the Bcl-2/IP3R interaction, thus impacting on Ca^{2+} signaling, have recently been developed and progressed into clinical studies [364].

Doxorubicin (*i.e.*, adriamycin) is another cytostatic drug widely used in cancer treatment [365-369]. It is known to impair the activity of topoisomerase II and to intercalate in DNA triggering the accumulation of p53 at the MAM level and increasing the activity of the ER channel SERCA thus leading to elevated ER Ca^{2+} levels and its transfer to the mitochondria, followed by apoptosis [229,370].

Arsenic trioxide is a chemotherapy drug widely utilized in combination with all-*trans*-retinoic acid for the treatment of acute promyelocytic leukemia patients based on its ability to induce proteasomal degradation of the PML/RARα (retinoic acid receptor) fusion protein [371,372]. As discussed above, PML is a tumor suppressor protein localized at the MAM level to favor ER-mitochondrial Ca^{2+} flux, ultimately repressing the prosurvival autophagic pathway. Interestingly, arsenic trioxide was shown to promote the degradation of the fusion protein PML/RARα (but not of

PML itself) while increasing PML levels at the ER-mitochondrial contact sites, thus inhibiting autophagy [373].

The energy disruptor metformin induces cancer cell death by targeting complex I and, therefore, the respitatory chain functions. Loubiere and coworkers reported that metformin also triggers Ca^{2+} release from ER and its accumulation into the mitochondria, thus leading to mitochondrial swelling and apoptosis [374].

Recently, some natural compounds have been also shown to be endowed with a significant antitumor activity by impairing the mitochondria-ER interaction.

Osthole is a natural coumarin present in a wide variety of plants, such as *Cnidium monnieri*, *Angelica arcangelica* and *Angelica pubescens* [375]. It was demonstrated to possess different pharmacological properties, including anticancer activities [376-378]. Specifically, it was shown that, in ovarian cancer cells, osthole inhibits cell cycle progression and triggers apoptosis; these anticancer effects are related to mitochondrial Ca^{2+} overload and ROS overgeneration, associated with altered expression of Ca^{2+} channels at the MAM level (*i.e.*, IP3R, VDAC1), leading to the impairment of the mitochondria-ER axis functions [379].

Resveratrol is a stilbenoid polyphenol present in different plants, such as red grape skin and berries, and known to exert a wide variety of beneficial health effects, mainly based on its antioxidant activity [380]. In tumor cells, it is endowed with anticancer properties (*i.e.*, antiproliferative, proapoptotic) through modulation of different molecular signaling pathways. Resveratrol was also shown to inhibit ATP synthesis and SERCA activity within MAMs, by enhancing the mitochondria-ER tethering at these contact sites, thus resulting in increased MCU-dependent mitochondrial Ca^{2+} uptake and cancer cell death [381].

As discussed above, we recently reported that the natural compound δ-TT exerts a significant antitumor activity in melanoma cells mediated by an impairment of the mitochondrial respiratory functions. In addition, by using inhibitors of both IP3R and VDAC channels (*i.e.*, the key regulators of Ca^{2+} permeability in MAMs), we could also demonstrate that δ-TT triggers Ca^{2+} homeostasis dysruption, with mitochiondrial accumulation of ER-derived Ca^{2+} ions and subsequent ROS generation, responsible for triggering the paraptotic process [57]. Similar data were recently reported by a wide variety of natural compounds [216].

Taken together, these observations strongly support the notion that mitochondrial functional and structural dynamics as well as mitochondrial-ER contact sites represent an interesting and promising molecular target for novel therapeutic strategies in cancer.

Several clinical studies in cancer patients assessing the safety and efficacy of antitumor compounds targeting the mitochondrial functional and structural dynamics are presently oingoing and can be found on https://clinicaltrials.gov.

Table 2

Anticancer drugs targeting Ca^{2+} flux at the mitochondria-ER contact sites.

Drug	Therapy class	Effects	References
Cisplatin, oxiplatin	Platinum-based chemotherapy	Increased number of IP3R Ca^{2+} channels and Ca^{2+} flux	[360,361,363]
Doxorubicin	Antibiotics with anticancer activity	Accumulation of p53 at the MAM level; increased activity of the SERCA channel; elevated ER-mitochondria Ca^{2+} flux	[229,370]
Arsenic trioxide	Chemoterapeutics	Increased levels of PML at the ER-mitochondria contact sites and Ca^{2+} flux; inhibition of autophagy	[371-373]
Metformin	Antidiabetic (diabete type 2) drugs	Increased Ca^{2+} release from the ER and accumulation into mitochondria	[374]
Osthole, resveratrol, vitamin E-derived tocotrienols	Natural antioxidants	Increased expression of Ca^{2+} channels at the MAM level; increased mitochondria-ER tethering at contact sites; induction of Ca^{2+} flux through IP3R and VDAC channels; increased MCU-dependent Ca^{2+} uptake; mitochondrial Ca^{2+} overload and ROS generation	[57,378,379,381]

6. Conclusions

It is now well recognized that mitochondria are not only the central hub in the overall metabolic network of cells; they are also involved in the regulation of Ca^{2+} and redox homeostasis, cell proliferation, cell death (poptosis, paraptosis, necroptosis, autophagy,) and cell signaling. Due to their central role in cell survival and death mechanisms, mitochondria also behave as key players in the development and progression of cancer. Notably, in cancer cells, they act as dynamic organelles undergoing both a metabolic rewiring and a structural reshaping, thus playing a peculiar role in the coordination of the different mechanisms involved in tumorigenesis.

Cancer cells are known to depend on an overactive glycolytic pathway for the production of intermediate metabolites that function as building blocks to support the biosynthesis of organic molecules, and therefore, their proliferative activity ("Warburg effect"). On the other hand, it is now established that a tightly coordinated TCA cycle/OXPHOS axis is still present and active in the tumor cell mitochondria; a peculiar "exacerbated" mitochondrial metabolic rewiring, characterized by high OXPHOS activity, was also observed in drug-resistant cancer cells as well as in cancer stem cells. Alterations of mitochondrial ROS production and redox biology were reported to occur during carcinogenesis. A reshaping of metabolic functions in cancer cells was also found to be related to mutations in genes encoding mitochondrial metabolic enzymes leading to the formation of metabolites ("oncometabolites) recently reported to be involved in the different phases of tumorigenesis. Mitochondria are also the master regulators of the cell survival/death balance by playing a pivotal role in the intrinsic apoptosis pathway, involving apoptotic proteins at the mitochondrial membrane level.

Significant alterations in mitochondrial structural dynamics (biogenesis, fusion/fission, mitophagy, organelle communication) were also widely reported to be typical features of cancer cells. Mitochondrial biogenesis, the formation of new organelles, has been shown to positively correlate with cell proliferation, acquisition of an invasive and metastatic phenotype and drug resistance. Mitochondrial fusion and fission are peculiar structural dynamics that shape cancer metabolism. An altered balance between these processes has been widely reported to be involved in cancer growth and progression; however, data so far available show conflicting evidence for their function in tumor progression. Mitochondrial fusion was reported to inversely correlate with tumor development. On the other hand, mounting evidence indicates that fission is strictly associated with mitophagy and apoptosis; in particular, in CSCs, activation of fission triggers an impairment of the mitochondrial metabolism associated with inhibition of stem cells propagation. Recent *in vitro* and *in vivo* studies consistently support that fission is deeply involved in the proapoptotic activity of different chemotherapeutic drugs. Mitophagy is the dynamic process responsible for the removal of damaged or dysfunctional mitochondria. Data so far available

highlight a dual role of this mechanism in cancer development, being shown to both reduce or increase the sensitivity of cancer cells to chemotherapeutic drugs. Thus, further studies are needed to definitely prove the role of mitophagy in cancer cell fate.

Mitochondria physically interact and communicate with different subcellular organelles, such as ER, to regulate cellular homeostasis, mitochondrial bioenergetics and cell fate. Specifically, mitochondria-ER contact sites are deeply involved in the Ca^{2+} transfer from the ER to mitocohondria, resulting in ROS generation, loss of membrane potential, swelling, cytochrome *c* release and cell death.

Growing evidence indicates that mitochondrial functional and structural dynamics might represent effective biomarkers of tumor progression and development of drug resistance. Moreover, a marked rewiring of the mitochondrial metabolic pathways (OXPHOS activity, O_2 consumption, ATP production) as well as alterations of mitochondrial structural dynamics (specifically, the fusion/fission balance) were shown to be deeply involved in the anticancer activity of a wide range of both synthetic and natural compounds. However, most of these observations are based on results reported from *in vitro* and *in vivo* studies. Therefore, additional clinical studies are needed to definitely support the role of mitochondrial dynamics, both functional and structural, as a biomarker of tumor progression and an effective molecular target for novel mitochondria-based chemopreventive/anticancer strategies.

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Declaration of competing interest

None.

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