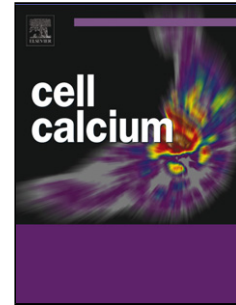# Journal Pre-proof

Mitochondria as the decision makers for cancer cell fate: from signaling pathways to therapeutic strategies

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# Mitochondria as the decision makers for cancer cell fate: from signaling pathways to therapeutic strategies

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Graphical abstract
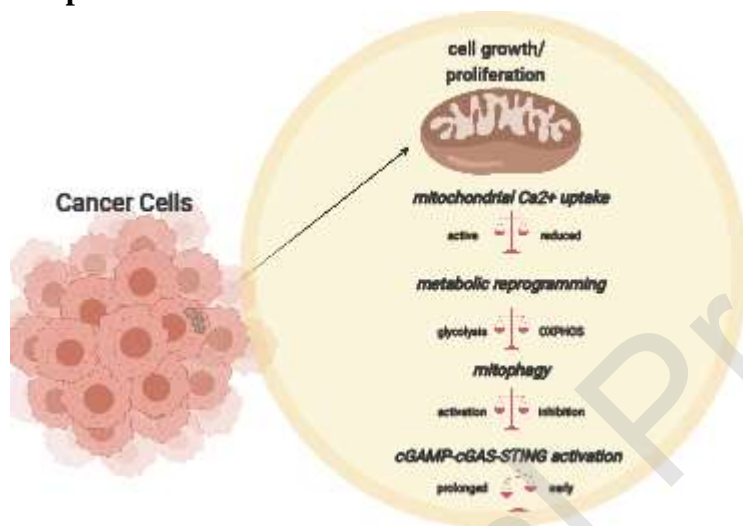
Highlights

- Mitochondria play a dual-faceted role in cancer cells death and proliferation

- $[Ca^{2+}]$ mito uptake might be either beneficial or detrimental to cancer cell survival

- Mitochondrial metabolic reprogramming is a key feature for cancer cell proliferation

- Mitophagic pathways can both arrest or enhance cancer cell proliferation

- The timing of inflammatory response to mtDNA release can be pro or anti-tumorigenic

Abstract
As pivotal players in cellular metabolism, mitochondria have a double-faceted role in the final decision of cell fate. This is true for all cell types, but it is even more important and intriguing in the cancer setting.
Mitochondria regulate cell fate in many diverse ways: through metabolism, by producing ATP and other metabolites deemed vital or detrimental for cancer cells; through the regulation of Ca^{2+}

homeostasis, especially by the joint participation of the endoplasmic reticulum in a membranous tethering system for Ca^{2+} signaling called mitochondria-ER associated membranes (MAMs); and by regulating signaling pathways involved in the survival of cancer cells such as mitophagy. Recent studies have shown that mitochondria can also play a role in the regulation of inflammatory pathways in cancer cells, for example, through the release of mitochondrial DNA (mtDNA) involved in the activation of the cGAS-cGAMP-STING pathway.

In this review, we aim to explore the role of mitochondria as decision makers in fostering cancer cell death or survival depending on the tumor cell stage and describe novel anticancer therapeutic strategies targeting mitochondria.

Keywords: Mitochondria, cancer, Ca^{2+} signaling, mitophagy, bioenergetics, cGAS-cGAMP-STING pathway.

Introduction

Cancer is the second leading cause of death worldwide. According to the World Health Organization, approximately 1 in 6 deaths are due to cancer. This pathology is driven by uncontrolled cell proliferation, where cells accumulate errors augmenting the dysregulation of vital cellular pathways. One of the hallmarks of cancer is the reprogramming of metabolic needs and energy metabolism [1]. A crucial role is played by mitochondria in this process.

Mitochondria are the powerhouses of cells, providing the energy and substrates necessary for a plethora of cell functions and orchestrating cell viability, apoptosis and differentiation [2]. In mitochondria, proteins necessary for oxidative phosphorylation (OXPHOS) and the electron transport chain (ETC) are involved in the tricarboxylic acid (TCA) cycle and other metabolic pathways. This organelle has its own genome (mitochondrial DNA, mtDNA) that encodes some of the mitochondrial proteins, whereas the other proteins are nuclear-encoded and imported into the organelle.

Given its importance, much recent scientific research has focused on the role of mitochondria in tumorigenesis, cell proliferation and metastasis dissemination. Indeed, the amount of energy required for cancer cell growth and dissemination is strictly dependent on the mitochondrial state and on its final decision of the cell fate.

For instance, during tumorigenic transformation, cells undergo significant metabolic remodeling that can result in the imbalance of mitochondrial anabolism and catabolism. Reactive oxygen species (ROS) are molecules produced as a result of OXPHOS or the electron transfer reaction catalyzed by the P450 system in mitochondria [3–5] in steroidogenic tissues. Once produced, ROS can be utilized by cells as signaling molecules, thus enhancing proper cell function. ROS overproduction represents a serious threat to cells since mitochondria can be driven toward the activation of programmed cell death [6]. Indeed, cancer cells often increase the production of NADPH as a strategy to detoxify ROS and escape apoptosis [7].

Moreover, there are other examples of alterations in mitochondrial metabolism that lead to the production of so-called oncometabolites, such as succinate, 2-hydroxyglutarate (2-HG) and fumarate, that accumulate in many tumors, supporting cancer cell proliferation [8–13].

As stated, damaged mitochondria drive cellular dysfunction, which stimulates a variety of pathological processes, such as aging, inflammation and cancer [14]. Mitochondria can influence the viability of cells by intervening in mitochondrial dynamics with processes known as mitophagy, mitofission and mitofusion. Mitophagy is a pathway that is activated when flawed mitochondria are

recognized and targeted for degradation by a specific autophagic pathway. There is much experimental evidence, both in *in vitro* and *in vivo* models, supporting that the suppression of autophagic players subsequently leads to an increase in mitochondrial mass and dysfunctions resulting in the accumulation of ROS and oncometabolites [15,16], possibly supporting tumor growth.

Evidence shows that most of the proteins involved in mitophagy modulation are dysregulated in cancer patients, but they can act as tumor suppressors or promoters depending on the cancer subtype and context [17–19], which is controversial. On the one hand, tumorigenesis is driven by the inhibition of mitophagy, while on the other hand, tumor progression depends on functional mitophagy [20].

Furthermore, mitochondria represent central hubs for the regulation of Ca^{2+} flux in cells, and even influence the decision between cell life or death. In recent years, many achievements have been made in the characterization of mitochondria-associated ER membranes (MAM)-mediated Ca^{2+} signaling in diverse pathological settings, from cancer to inflammation and from neurodegenerative disorders to cardiovascular diseases [21–24].

Ca^{2+} is fundamental for mitochondrial health, function and metabolism, and sufficient impairments in Ca^{2+} homeostasis have detrimental effects on ATP production and cell viability. Thanks to specialized proteins such as MCU, VDAC, NCLX and others, mitochondria are able to modulate their Ca^{2+} load in response to pathophysiological conditions, leading either to cell proliferation or cell growth arrest and death [25–29]. Nevertheless, the literature is still conflicting on the nature of Ca^{2+} transfer necessary to trigger programmed cell death.

In addition, the direct correlation between mitochondria-related pathways and cancer proliferation is worth introducing a novel link between cancer, mitochondria and inflammation deserving of investigation. This link correlates cytosolic DNA sensing, at the basis of the inflammatory response, to cancer, possibly paving the way for new investigations.

Once the mitochondria undergo persistent damage, they release mtDNA in the cytosol through the opening of the mitochondrial permeability transition pore complex (mPTPC) [30]. The release of mtDNA activates the cGAS-cGAMP-STING pathway, which is generally involved in microbial DNA recognition. It is thought that an inappropriate mtDNA-dependent inflammatory response can have a role in many pathologies and is mainly linked to inflammation/infection and cancer [31]. This pathway is based on cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase (cGAS), which functions as a DNA sensor triggering the innate immune response thanks to the production of cyclic AMP and GMP, which bind and activate the adaptor STING [32].

Thus, mitochondria are important either for cell growth, specifically in the cancer setting but also for cell death, upon certain stimuli. For this reason, they can be considered the ultimate decision makers for cancer cell fate. Novel therapies centered on mitochondrial-dependent signaling pathways are under increasing investigation since they can provide intriguing and successful strategies for cancer and other diseases treatment [33–37]. Nevertheless, there is still lack of clarity about their specific role in boosting or inhibiting cancer progression. In this review, we aim to shed light on mitochondrial controversy in cancer progression, focusing both on mitochondrial function/dysfunction, mitochondria-related signaling pathways and describing the latest findings in the field of mitochondria-oriented cancer therapy.

1. Mitochondria and Ca^{2+} signaling in cancer cell proliferation

1.1 Physiological mitochondrial Ca^{2+} homeostasis and MAMs

Ca^{2+} is a versatile second messenger involved in the control of numerous cellular processes, such as secretion, neuron excitability, muscle contraction, and cell migration [38–40] .

Given its importance, the cytoplasmic Ca^{2+} concentration is maintained at approximately 100 nM thanks to the cooperation of pumps, channels and exchangers located at the plasma membrane (PM) that are able to regulate the influx into the cytoplasm, as for the channels and pumps at ER or mitochondrial membranes that can modulate the Ca^{2+} intracellular homeostasis regulating ER-cytoplasm and ER-mitochondria Ca^{2+} transfer.

Moreover, much evidence demonstrates that this ion is important in cancer progression, especially during proliferation, invasion, migration and apoptosis [41].

At rest, cytoplasmic and mitochondrial Ca^{2+} concentrations are similar and maintained at low levels (~100 nM range or lower) [42]. In contrast, the endoplasmic reticulum (ER), the primary intracellular Ca^{2+} storage location, can reach a Ca^{2+} concentration range in the hundreds of μM [43]. Even though mitochondria are known as the cell powerhouse, they are, at the same time, a central hub for Ca^{2+} signaling in cooperation with the ER in a specialized tethering membranous system named MAMs. Indeed, for the proper activation of physiological processes, Ca^{2+} must transfer from the ER to mitochondria, and this transfer between the two organelles takes place at MAMs [44–46]. The latest findings have shown that Ca^{2+} signaling regulation at MAMs plays a role in many processes, one of which is cell proliferation [47,48].

Physiologically, upon cell stimulation with agonists, inositol 1,4,5-trisphosphate (IP$_3$) is produced and subsequently generates the release of Ca^{2+} from the ER through the opening of IP$_3$ receptors (IP3Rs), inducing transient Ca^{2+} uptake into the mitochondrion [49], which in turn activates various processes, such as secretion, neuron excitability, muscle contraction, and cell migration.

Ca^{2+} enters the mitochondria, driven by the mitochondrial membrane potential ($\Delta\Psi$), crossing the outer mitochondrial membrane (OMM) by high conductance voltage-dependent anion channel 1 (VDAC1). Subsequently, through the mitochondrial calcium uniporter (MCU) the ion crosses the inner mitochondrial membrane (IMM) entering and accumulating in the mitochondrial matrix [50,51]. The MCU is crucial for mitochondrial Ca^{2+} uptake, and it works in cooperation with numerous proteins that contribute either to its formation or the regulation of its activity, as we will explain later in this section [52,53].

The Ca^{2+} signal released from the ER towards the mitochondria must be modulated in a spatiotemporal fashion to trigger apoptosis or cell proliferation [54,55]. Indeed, depending on the type of Ca^{2+} signaling that occurs, cell death or cell survival programs can be activated. In fact, the dysregulation of the ER-mitochondrion Ca^{2+} signaling axis can be associated with many types of diseases, such as diabetes, muscular-related diseases and cancer, in which uncontrolled proliferation and inhibition of apoptosis are major signatures [56]. For clarity sake, in the following paragraph we refer to ER-mitochondria association for Ca^{2+} transfer, not to be confused with MAMs themselves, formed by the association of mitochondria and ER membranes.

1.2 The current theories about Ca^{2+} signaling as proliferative or apoptotic stimulus

MAMs represent a hub for many tumor suppressors and oncogenes. The proper translation, expression and function of these proteins in healthy conditions prevents the survival and proliferation of damaged cells and enables the induction of programmed cell death in response to

persistent stress stimuli [57,58]. In contrast, altered expression or activity of tumor suppressors and oncogenes can influence Ca^{2+}-dependent resistance to cell death by the direct regulation of the main players of Ca^{2+} signaling at MAMs: IP3R3, SERCA (sarco/endoplasmic reticulum Ca^{2+}-ATPase) VDAC1 and the MCU complex, consequently modifying the homeostasis of mitochondrial Ca^{2+}. In particular, limited Ca^{2+} transfer from the ER to mitochondria by the action of activated oncogenes such as Bcl-2 [59–64], Bcl-XL [65–68] and Ras [69–71] or inhibited tumor suppressors such as PML [72–74] PTEN [75,76], and p53 [22,69,77–79] has been related to a reduced stress-induced cell death rate.

However, three recent studies contradicted the concept that a reduced ER-mitochondria Ca^{2+} signal is present in anti-apoptotic and pro-tumoral models. Indeed, they state that, in certain types of tumors, the overexpression of IP3R3, an IP3R isoform that can enable ER-mitochondrial Ca^{2+} transfers, can drive oncogenesis and malignant cell transformation. Initially, cell death is promoted by increased Ca^{2+} transfer to mitochondria, inducing the development of surviving antiapoptotic gene expression programs [80–82]. The link between IP3R expression and the real amount of Ca^{2+} transferred to the mitochondria subsequently leading to cell death susceptibility remains elusive and needs further elucidation.

Despite the fact that the three IP3R isoforms (IP3R1 and IP3R2) are involved ER-mitochondria Ca^{2+} transfer in different cell types, IP3R3 remains the most reported player in Ca^{2+} transfer between ER-mitochondria in cancer setting. Nonetheless, recent evidence show that also IP3R2 is one of the most effective in the regulation of ER-mitochondria Ca^{2+} transfer [83].

However, it is fascinating how this double-faceted role of ER-mitochondria Ca^{2+} transfer as a pro-apoptotic or anti-apoptotic signaling pathway resembles MCU complex observations.

Recent studies carried out on the individual components of the MCU complex, either in cell lines or in a mouse model, are still debating the role of mitochondrial Ca^{2+} signaling as an apoptosis trigger. In different neoplastic contexts, an increased function of the MCU complex has been observed [25]. The overexpression of MCU in HeLa cells [53,84], primary cortical neurons [85] and cerebellar granule neurons (CGNs) [84] enhances cell death in response to various stress stimuli (such as C2-ceramide, NMDA and H_2O_2) [53,84]; in contrast, when MCU is downregulated, cells are protected from apoptosis because of the reduced mitochondrial Ca^{2+} uptake that prevents mPTP opening and the release of cytochrome c through the OMM [85,86].

Considering that: i) since not all apoptotic stimuli are related to mitochondrial Ca^{2+} overload and ii) sustained Ca^{2+} uptake in the organelle is not toxic by itself , it is therefore important to understand the role played by the single components of the MCU complex in terms of expression levels and activity in order to correlate mitochondrial calcium homeostasis to various types of cancers [87]. Upon stress stimulus, apoptosis induction is generally related to high and persistent levels of mitochondrial Ca^{2+} uptake, which promote the activation and consequent opening of a key effector of cell death, the mPTP [88,89]. In contrast, tumorigenesis apoptosis escape, is supported by an alteration of Ca^{2+} signaling, where the reduction of mitochondrial Ca^{2+} uptake is related to the dissociation of F_0F_1 ATP synthase dimers at the base of mPTP openings and activation [90]. Several studies have also focused on MCU complex components and their role in mitochondrial Ca^{2+}-related cell viability. Briefly, MCU is organized as a pore forming complex consisting of multiple subunits [91], however it does not work alone, since its function strictly depends on other IMM proteins as: EMRE (Essential Mcu REgulatou), MICU1 (MItochondria Calcium Uptake 1), MICU2 (MItochondria Calcium Uptake 2), MCUR1 (Mitochondrial Calcium Uniporter Regulator 1) [91–96]. Moreover, it has been found a paralog of MCU (MCUb) that lacks of channel activity

and is generally less expressed, except for tissues as lung, heart and brain [50]. MCUR1 enhances MCU activity directly interacting with it but not with MICU1 [92]. MICU1 and 2 have an opposite effect on the regulation of MCU: MICU2 acts as a MCU inhibitor, while MICU1 limits the uptake of Ca^{2+} during basal conditions, but it can also support Ca^{2+} uptake when $[Ca^{2+}]_i$ increases [97] Even if its function is still under investigation, what it is known is that EMRE acts as a Ca^{2+} sensor on both sides of IMM and requires MICU1 and MICU2, besides its silencing abolishes MCU function. As a matter of fact, it plays a double role, depending on $[Ca^{2+}]_{cyt}$, it protects mitochondria both from both Ca^{2+} overload and depletion [98] (Figure 1).

For instance, MICU1 as a negative regulator of MCU acts as a gatekeeper to prevent Ca^{2+} mitochondrial overload. Although its role is not entirely clear, it has been related to different types of cancer. Loss of MICU1 leads to an increase in basal levels of Ca^{2+} in the mitochondrial matrix, promoting programmed cell death in both non-tumor and tumor cells. However, knockdown of MICU1 is also associated with the production of ROS in the mitochondrial matrix, a decrease in ATP and modification of mitochondrial morphology, reinforcing the cell death program [25,99,100].

Moreover, other evidence has shown that MICU1 is overexpressed in ovarian cancer cell lines and is related to chemoresistance and poor prognosis. Indeed, MICU1 *in vivo* and *in vitro* silencing experiments in OvCa ovarian cancer cell line have demonstrated both an improved sensitivity to chemotherapy, a reduction of tumor growth with better prognosis, and a reduction of cell proliferation, invasion and migration capacity [101].

On the other hand, other studies have described that MICU1 overexpression in the MDA-MB-231 breast cancer cell line is related to better prognosis, suggesting an oncosuppressive function [102]. Another study supports this oncosuppressive role of MICU1; it has been demonstrated that MICU1 maturation can be influenced by Akt, which seems to localize at the intermembrane space (IMS) of mitochondria. Akt phosphorylates a specific serine at the N-terminal region of MICU1. This post-translational modification induced by Akt causes the loss of MICU1 gatekeeper function, with a consequent increase in mitochondrial Ca^{2+} concentration at resting conditions, as well as the generation of ROS and tumor development [103].

In this regard, basal levels of mitochondrial Ca^{2+} and ROS production are re-established *in vivo*, inhibiting Akt-dependent tumor growth through the expression of a non-phosphorylable MICU1 mutant.

These data support the importance of the connection between tumor development and abnormal mitochondrial Ca^{2+} concentration under basal conditions, highlighting how MCU complex organization and activity modification contribute to the aggressiveness of some types of tumors [103].

Of note, MCUR1 is another MCU regulator and the interaction mechanism with the complex has not yet been well characterized. However, it seems that MCUR1 has a structural function in the MCU complex, interacting with both MCU and EMRE (another positive regulatory subunit of the MCU complex). MCUR1 is required for mitochondrial Ca^{2+} uptake and maintenance of cellular bioenergetics; indeed, the loss of MCUR1 causes a structural change of the complex [104,105]. Several studies have shown that in hepatocellular carcinoma (HCC) cells, MCUR1 expression is increased, leading consequently to MCU complex dysregulation, which entails an increase in mitochondrial Ca^{2+} uptake related to cell proliferation, resistance to apoptosis, metastasis and poor prognosis [106] [107]. In fact, MCUR1 silencing, without changing cytosolic Ca^{2+} content,

provokes a drastic decrease in the mitochondrial Ca^{2+} concentration that leads to cell death [93,107,108].

Furthermore, the connection between ER-IP3Rs and the mitochondria-MCU complex, in terms of Ca^{2+} transfer, is represented by VDAC, which, thanks to GRP75, forms a tethering system in the outer mitochondrial membrane that helps Ca^{2+} signal transmission directly from the ER lumen to mitochondria [109].

In particular, VDAC1 is responsible for Ca^{2+} uptake and, in a physiological context, is considered a regulator of programmed cell death, and it seems to have increased expression in cancer, contrary to what is expected [110]. It has been shown that increased expression of VDAC1 induces an enhanced Ca^{2+} flux into the mitochondria that contributes to tumor progression, influencing energy metabolism, inhibiting programmed cell death, and promoting cell proliferation in lung, colon and breast cancers, in addition to being associated with poor prognosis in these types of tumors [111]. Moreover, in numerous types of cancer, there is *in vivo* and *in vitro* evidence showing that proliferation, tumor growth and tumor regression are inhibited through VDAC1 RNA interference (RNAi) [112].

Furthermore, several studies have demonstrated that in addition to tumor suppressors and oncogenic proteins, microRNAs are also involved in cancer cell proliferation, particularly regulating mitochondrial Ca^{2+} signaling [78,113]. Notably, miR-7 targets the 3′-UTR of VDAC1 mRNA in human neuroblastoma SH-SY5Y cells and in mouse primary neurons. In fact, miR-7 overexpression causes a decrease in VDAC1 mRNA and protein levels, leading to a reduction in mitochondrial Ca^{2+} uptake and the inhibition of mitochondrial depolarization and fragmentation, which in turn prevents mPTP opening, cytochrome c release, and intracellular ROS generation, resulting in the blockage of the early stages of the apoptotic cascade [114].

An *in silico* study on five cancer-related miRNAs (miR-15, miR-17, miR-21, miR-25, miR-137) tested in HeLa cells showed that only miR-25 targeted the 3' UTR of MCU mRNA, reducing MCU protein levels, with a consequent decrease in mitochondrial matrix Ca^{2+} accumulation and susceptibility of cancer cells to apoptotic stimuli, leading to an increase in cell proliferation. Moreover, reduced MCU expression was observed, both in prostate cancer and colon cancer patient-derived cells, in correlation with an increase in the regulation of miR-25 [87].

Hong et al. showed that the cancer-like phenotype is related to high miR-138 and miR-25 expression. These miRNAs target MCU, reducing its expression, promoting a decrease in mitochondrial Ca^{2+} concentration and consequently inducing mitochondrial fission and an increase in $[Ca^{2+}]_{cyt}$ and aerobic glycolysis [115]. In contrast, Yu C. et al. demonstrated that metastasis in breast cancer is related to the downregulation of miR-340, which leads to increased MCU expression. The miR-340/MCU pathway requires high expression levels of MCU, which relate to a higher concentration of mitochondrial $[Ca^{2+}]$, which implies a switch from oxidative to glycolytic metabolism, recognized as the "Warburg effect", improving the invasion and migration capacity of breast cancer cells [116]. Given this evidence, the relationship between mitochondrial Ca^{2+} concentration and metabolic rewiring is still under debate and controversial.

Notably, Ca^{2+} homeostasis deregulation can be considered a general hallmark of cancer, since it has a crucial role in apoptosis resistance, tumor development, tumor cell proliferation, invasion, metastasis and chemoresistance in cancer cells [117].

The current literature is still not unanimous on how Ca^{2+} signaling triggers apoptosis. Some studies have demonstrated that reduced mitochondrial Ca^{2+} uptake leads to diminished ATP production and activation of autophagy, which sustains cancer cell proliferation [74,77,79,118–123]. In contrast,

other evidence indicates that active ER-mitochondria Ca^{2+} transfer activates MCU and induces a greater production of ATP, thus leading to cell proliferation [124] (Figure 1).

In conclusion, the data collected so far suggest that the aggressiveness of cancer cells could increase due to inhibition of effectors that regulate apoptosis. The role of mitochondrial Ca^{2+} concentration in this process is under continuous investigation; indeed, conflicting evidence still has not fully clarified whether mitochondrial Ca^{2+} transfer between the ER and mitochondria is tumor-promoting or toxic. To date, the evidence is still conflicting on the type of Ca^{2+} transfer needed by cancer cells to sustain proliferation; apparently, both an active or a reduced flux can sustain tumorigenesis upon agonist stimulus. We attempted to summarize the contradicting results in Figure 1.

2. Mitochondrial bioenergetics in cancer cell proliferation

In view of their leading role in energy production via OXPHOS, mitochondria are considered the bioenergetic powerhouse of the cell [125]. In addition to their energetic role, these dynamic organelles are central players in cellular metabolism, production of ROS, modulation of the redox status, control of Ca^{2+} homeostasis, regulation of cell signaling and programmed cell death (intrinsic apoptosis pathway) [126].

Alterations in these events can trigger a shift of the cell from a quiescent to a proliferating state [126]. Uncontrolled growth and proliferation are well-known cancer hallmarks [127]. In recent years, growing evidence has pointed out the pivotal role of mitochondria in tumors. It has been reported that dysfunctional mitochondria that are rewired in the cancer context contribute to the metabolic reprogramming of cancer cells, where they also modulate many cellular processes involved in oncogenesis [128].

Indeed, proliferating tumor cells exhibit profound metabolic rewiring to support their biosynthetic needs [129]. This metabolic remodeling is characterized by increased glucose uptake, a portion of which is redirected to the pentose phosphate pathway [130], and by the ability to oxidize or reduce glutamine to provide energy via the TCA cycle and the ETC [131], and interestingly, the capability to utilize glycolysis, OXPHOS and fatty acid oxidation in an interchangeable way to provide energy [11].

Alterations in the metabolic pathways of cancer cells were originally observed by Otto Warburg 70 years ago. Warburg and his collaborators noticed that even in oxygen-rich conditions, cancer cells predominantly rely on glycolysis, producing an excessive amount of lactate, while normal cells utilize OXPHOS to oxidize glucose inside the mitochondria [129]. Subsequently, this process has been defined as aerobic glycolysis or the 'Warburg effect', which he hypothesized to be related to a mitochondrial dysfunction that hampered cancer cells to effectively oxidize glucose carbon to CO_2. Today, this principle has been applied in clinics through the use of 18F-deoxyglucose positron emission tomography (FDG-PET) to image tumors with increased glucose uptake [132]. However, it is now recognized that properly functional mitochondria are essential for cancer cell proliferation and survival [127], as they are responsible for nutrient transformation into the building blocks required for cell growth [127]. Even if mitochondrial gene mutations are common in tumor cells, they do not suppress mitochondrial metabolism but rather alter mitochondrial bioenergetic and biosynthetic states. For example, defects in the genes for succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase 1 (IDH1 and IDH2), as reviewed by Wallace DC. 2012 [126], have been observed in a variety of human tumors [128]. Fumarate, succinate and 2-HG act as oncometabolites, behaving as mitochondrial signaling molecules altering gene expression and

epigenetics, meaning that their excessive accumulation is sufficient to trigger cell proliferation and resistance to death [10].

The ability of mitochondria to provide necessary building blocks for anabolic metabolism, their capability to generate ROS and their pivotal role in the regulation of cell death signaling make them a key player in cancer proliferation [11]

In most cancers, it has been reported that high levels of glycolysis are a follow-up of a deregulated PI3K/Akt signaling pathway and concomitant activation of oncogenes such as c-Myc and K-Ras or loss of PTEN and p53, which support the production of glycolytic intermediates that are conveyed into different biosynthetic pathways required for cell proliferation, such as the pentose phosphate pathway for NADPH and nucleotide synthesis [133,134]. Indeed, PI3K–PTEN–AKT pathway activation is one of the most common changes found in the cancer setting [132] that causes a shift from oxidative to glycolytic metabolism. The activation of this pathway increases the expression of glucose transporters on the cell surface and enhances glycolysis and protein translation through Akt-mediated mTOR stimulation, thus leading to changes in cellular metabolism that promote cancer cell growth and proliferation [126,132]. This occurs because cancer transformation generally comes with high and sustained proliferation together with mitochondrial alteration, so that cells try to provide essential metabolism through cytosolic glucose metabolism.

Both carbohydrates and amino acids, such as glutamine, are fundamental substrates for mitochondrial metabolism fueling [127]. Notably, glutamine is one of the most crucial nutrients utilized for cell proliferation. Moreover, the carbon backbone of glutamine is an important substrate for anaplerotic reactions that replenish TCA cycle intermediates [127].

Interestingly, it has been highlighted that cancer cells are able to increase the uptake and utilization of glutamine for their anabolic needs [135]. Upon activation of Myc, glutaminolysis is turned on, guaranteeing anaplerotic substrates for the mitochondrial TCA cycle. This event boosts the generation of citrate, which is exported to the cytosol where it is broken down to oxaloacetate and acetyl-CoA, which are required for lipid synthesis and protein modifications [126]. In addition, altered mitochondrial metabolism can increase the production of mitochondrial ROS, thus modifying the cellular redox status [126,136]. Moderately elevated ROS stimulates proliferation by inactivation of the tumor suppressor PTEN or by stabilization of HIF1-α [11].

Cell proliferation, similar to other cell functions, is regulated by Ca^{2+} release through ER-localized IP3R. IP3R-mediated Ca^{2+} signals also modulate cell metabolism, mainly by providing Ca^{2+} flux to mitochondria, where it stimulates OXPHOS and ATP production [137,138]. It has been shown that physiological low-level IP3R-mediated Ca^{2+} release is crucial for maintaining basal levels of OXPHOS and ATP production in multiple cell types [120]. Upon disruption of Ca^{2+} transfer from the ER to mitochondria, ATP levels drop, followed by autophagy induction. Interestingly, the blockade of Ca^{2+} flux from the ER to mitochondria results in decreased OXPHOS, AMPK activation and autophagy enhancement, although different evidence has been reported. On one hand, Cárdenas and coworkers found that in breast and prostate cancer cells, autophagy is not sufficient to guarantee cell survival [139]. While, Missiroli et al. demonstrated that autophagy activation has pro-survival effects in cancer cells [74]. Thus, the dependence of tumorigenic cells on constitutive Ca^{2+} transfer to mitochondria for their viability suggests that mitochondrial Ca^{2+} addiction is a feature of cancer cells (see paragraph 1) (Figure 2).

To conclude, it could be useful to understand how tumor cells rewire and adapt their mitochondrial metabolism during tumor progression to develop novel anticancer strategies and to identify malignant signs that can be used as prognostic indicators [12].

3. Mitophagy and mitochondrial dynamics in cancer cell proliferation

Mammalian cells are characterized by several highly interrelated mechanisms involving mitochondria that work as key quality controllers of many cellular processes. Among these processes, mitochondrial dynamics (fusion and fission) and macroautophagy (mitophagy) are particularly important.

3.1 Mitofusion and Mitofission

Mitochondrial fusion and fission are processes that determine the quality, quantity and shape of mitochondria [140,141]; these processes are closely intertwined with mitochondrial wellness; thus, they are involved in cellular functions such as proliferation, metabolism and migration [142]. Physiologically, mitofission is regulated by Drp1, a GTP-binding protein located at the mitochondrial membrane that forms a ring upon stimulus that induces the fission of the membrane, hydrolyzing ATP [143,144]. On the other hand, mitochondrial fusion is regulated at the outer mitochondrial membrane (OMM) by mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2) but is mediated by OPA1 at the inner mitochondrial membrane (IMM) [145]. Posttranslational modifications, such as sumoylation, phosphorylation and ubiquitination, influence Drp1, Mnf1 and Mnf2 stability and affect mitochondrial dynamics [146,147]. It has been reported that in lung cancer cells, Mfn2 is less expressed than in normal tissue; indeed, the combined overexpression of Mnf2 and Drp1 inhibits lung cancer proliferation [148].

Therefore, mitochondrial fission and fusion can play a crucial role in promoting cancer cell proliferation, providing nonfunctional mitochondria.

3.2 Mitophagy

The term mitophagy indicates a crucial process in which damaged, dysfunctional or obsolete mitochondria are recognized by the autophagic machinery in a self-degradation process that is typically stimulated upon cellular stress or nutrient deprivation conditions.

Since mitochondria have been implicated in a considerable number of vital processes (see introduction, Ca^{2+} signaling and bioenergetics paragraphs) and these organelles are also apoptosis hubs, it is not surprising that a defective mitophagic process may lead to many human pathologies, including neurodegenerative disease [149,150], cardiac defects [151], type 2 diabetes [152] and, above all, cancer [153]. The tumor-mitophagy interplay is not yet well characterized, but it is assumed to be connected to oxidative metabolism and energy homeostasis, since mitochondria are the primary site for ATP production, ROS production and glucose metabolism. Moreover, mitochondria are indispensable for cancer cells, where mitochondrial-harbored metabolic pathways are rewired to handle oxidative stress and to meet the increased bioenergetic needs. Most of the main proteins that take part in the mitophagic process have been shown to be dysregulated in cancer cells derived from patients, but whether they behave as tumor promoters or suppressors seems to be highly cancer subtype-related.

One of the most studied tumor suppressors, p53, acts on mitophagy in a context-dependent fashion by either promoting [154] or inhibiting [155] this degradation process. Conversely, the tumor suppressive activity of p53 is in turn regulated by mitophagy, indicating that there is a complex molecular circuit between p53 and mitophagy that supports cancer cell proliferation [156].

To date, the three best characterized mitophagy pathways in mammalian cells include the following: i) PTEN-induced putative kinase 1 (PINK1)/E3 ubiquitin ligase Parkin, ii) BCL2/adenovirus E1B

19 kDa protein-interacting protein 3 (BNIP3)/BNIP3-like (NIX) and iii) FUN14 Domain Containing 1 (FUNDC1) pathways (Figure 3).

PINK1/Parkin is certainly the most studied pathway of mitophagy; these two proteins are activated upon the loss of mitochondrial membrane potential to promote mitochondrial outer membrane protein proteasomal degradation and the selective elimination of damaged mitochondria by mitophagy.

Parkin is a p53 target gene that regulates p53-mediated glucose metabolism and mitochondrial respiration [157].

It has been shown that mitophagy is of considerable importance in onset of the Warburg effect, which consists of a metabolic shift where tumor cells generate ATP mostly through glycolysis rather than OXPHOS, even in the presence of oxygen [158]. Stabilization of the hypoxia-inducible factor 1-alpha (HIF1α) subunit under hypoxic conditions activates the expression of glycolytic factors, promoting the conversion of pyruvate into lactate and enhancing the transcription of the promitophagic receptors BNIP3 and NIX. The resulting increase in mitophagic activity leads to a mitochondrial mass reduction and an enhancement of cancer cell survival under low oxygen conditions [159]. As previously stated, Parkin can mediate the p53-dependent reduction of the Warburg effect, decreasing cellular glucose uptake and lactate release [157]. Parkin-deficient mice are highly prone to spontaneous hepatocellular carcinoma (HCC), and mutated Parkin has been found in lung cancer, colorectal cancer, breast cancer, and glioma. Parkin results deleted in 25% cases of colorectal cancer as well as in HCC. Parkin also exerts a tumor suppressive function in breast cancer, where the blockage of mitophagy boosts tumor progression [160–163].

Similarly, PINK1, which is known to be a sensor for mitochondrial dysfunction, plays an important role in tumor contexts. PINK1 expression loss induces ROS production and tumor growth through the stabilization of HIF1α both *in vitro* and *in vivo*, although its overexpression has been reported in lung cancer and esophageal squamous cell carcinoma (ESCC) patients [164].

Moreover, PINK1 expression is altered in other malignancies, such as neuroblastoma, glioblastoma, and ovarian cancer [165–167]. TANK-binding kinase 1 (TBK1) is a serine/threonine protein kinase that promotes mitophagy via the PINK-PARKIN pathway that seems to be involved in Kirsten rat sarcoma (K-Ras) activity, a proto-oncogene that plays a pivotal role in a variety of cancers, promoting readjustment of cell metabolism [168]. TBK1 mitophagy effector is overexpressed in different kinds of malignancies, such as breast, lung and colon cancer [169], and its depletion causes proliferation and survival defects in cancer cells [170].

It has also been shown that PINK1-Parkin-mediated mitophagy is responsible for iron importer degradation, which correlates with the HIF1α-dependent Warburg effect and inflammasome activation, consequent to tumor cell mitochondrial iron accumulation. In this context, PINK1-Parkin loss of function accelerates mutant K-Ras-driven pancreatic tumorigenesis, suggesting that mitochondrial iron homeostasis may contribute to cancer development [171].

The BNIP3/NIX mitophagy pathway is usually triggered by hypoxic conditions, which leads to mitophagy-mediated growth suppression in several tumor types. BNIP3 prevents tumor progression in primary cells by inhibiting damaged mitochondrial accumulation; its lack, on the contrary, increases ROS accumulation and activates HIF1α, promoting cancer cell growth [172]. Currently, there is evidence in support of both an oncogenic and an oncosuppressive role of BNIP3. The role of NIX in tumor progression remains relatively obscure; however, it has been shown that NIX loss promotes tumorigenesis by avoiding p53-dependent apoptosis under hypoxic conditions in mouse xenografts and in glioblastoma models [173].

In addition to BNIP3/NIX, FUNDC1 represents a hypoxia-induced mitophagy receptor. It is located at the outer mitochondrial membrane, and it is involved in hypoxia-induced mitophagy by binding to LC3 via its LIR motif ($Y_{18}xxL_{21}$) [174], thus playing an important role in the modulation of cancer onset and progression. Indeed LC3 is a crucial effector of autophagy/mitophagy, since it participates to the formation and stabilization of the autophagosome that subsequently blend into lysosomes for the organelle degradation.

Recent findings on the role of this protein are still controversial; indeed, it has been reported that FUNDC1 suppresses the development of HCC by inhibiting inflammasome activation through mitophagy, while FUNDC1 expression is particularly increased in cervical cancer tissue [175,176]. A key role in the mitophagic process is also played by a large number of modulators and adaptors that can, in turn, participate in mitophagy-dependent tumor onset and progression. Of particular importance is p62, an autophagy substrate involved in the proteasomal degradation of ubiquitinated proteins that is used as a reporter of autophagy activity. p62-induced mitophagy maintains mitochondrial integrity, and its loss in human acute myeloid leukemia (AML) delays the elimination of dysfunctional mitochondria, thus increasing mitochondrial ROS levels leading to the inhibition of cancer growth both *in vitro* and *in vivo* [177].

New insights into previously unexplored mitophagy functions in relation to cancer pathologies are promising, and increasing knowledge of this peculiar mitochondrial self-degradation process may eventually lead to novel therapeutic approaches to treat cancer.

4. cGAS-cGAMP-STING inflammatory pathway links mtDNA to cancer proliferation

The importance of mitochondria in the development of tumors is based not only on their capability to control cancer cell proliferation but also on their ability to activate and modulate the innate immune response. Innate immunity is the key player in host defense; it protects the host not only from microbial pathogens but also from host-damaged tissues and cells. In the first scenario, host cells activate the immune response by recognizing conserved pathogen-associated molecular patterns (PAMPs) with different pattern recognition receptors (PRRs), while in the second scenario, PRRs recognize host damage-associated molecular patterns (DAMPs) [178,179]. Increasing research demonstrates the involvement of mitochondria in the innate immune response by their participation in PRR signaling, mainly in antiviral immunity [180–182]. Interestingly, mitochondria are not only crucial players in controlling inflammation but also represent an important source of DAMPs. Because of their bacterial origin, it is not surprising that mitochondria retain the bacterial ability to elicit robust inflammatory responses once damaged and released in the extracellular space [183]. This feature is due to the presence of *N*-formylated proteins that are recognized by PRRs and by the presence of hypomethylated CpG within mtDNA that, by resembling bacterial CpG DNA, activates Toll-like receptor 9 (TLR9) [184]. Supporting this hypothesis, administration of mtDNA *in vivo* or *in vitro* results in the development of inflammatory conditions or in increased pro-inflammatory cytokine secretion [185–187]. TLR9 is localized in intracellular compartments, mainly the endoplasmic reticulum (ER) and is responsible for the recognition of mtDNA that has been released in the extracellular space from necrotic cells [188]. A parallel mechanism aimed to sense cytoplasmic double stranded DNA (dsDNA), and as a result, the abnormal release of mtDNA, is the newly discovered cGAS–STING signaling. Cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) is an innate immune sensor able to monitor the presence of cytosolic dsDNA, triggering innate immune response activation in the case of antimicrobial defense, senescence, autoimmunity, and cancer [189,190]. Detection of dsDNA in the

cytosol results in the establishment of a complex consisting of 2 molecules of cGAS bound to 2 DNA molecules [191,192]. At this point, cGAS undergoes molecular changes to transform ATP and GTP into the second messenger 2',3'-cyclic GMP-AMP (cGAMP) [193,194] which binds to its ER-resident adaptor protein stimulator of interferon genes (STING) [189,195]. Once activated, STING induces type 1 interferon (IFN 1) production by activating the transcription factors NF-ƙB and IRF3 via IκB kinase (IKK) and TANK binding kinase-1 (TBK1) pathways [196–199]. This cascade results in the massive production of type I interferons, pro-inflammatory cytokines and other immune mediators that are responsible for the activation of the inflammatory response (Figure 4) (for a complete review on the molecular mechanism and cellular function of this pathway we suggest a recently published review by Hopfner and Hornung [200]). Interestingly, in addition to the antiviral and antibacterial functions of the cGAS-STING pathway, recent studies have suggested its involvement in different human diseases, mainly of inflammatory origin, including cancer [32,201]. In fact, as described, cGAS is able to detect both cytosolic dsDNA derived from pathogens and self-DNA leaked into the cytosol due to genome instability or cellular damage [202,203]. Interestingly, some evidence suggests that cGAS-STING signaling can be activated differently by nuclear self-DNA and by mitochondrial self-DNA, even though definitive evidence is still missing [204].

The effects of the activation of this mechanism on carcinogenesis are still debated due to the presence of evidence proving both its antitumorigenic and protumorigenic effects. It has been proposed that at the initial stages of tumorigenesis, the cGAS-STING pathway boosts immune surveillance against cancer cells, exerting an antitumorigenic effect. However, once the transformation has been overstepped, the dsDNA sensing pathway might help in the establishment of a chronic inflammatory state, enhancing tumor growth (Figure 4) [204].

From an antitumorigenic perspective, it was initially assumed that due to its key role in prompting inflammation and immune surveillance, the cGAS-STING pathway primarily functions as a tumor suppressor [204]. At the early stages of cancer cell transformation, mtDNA is released in the cytosol upon mitochondrial dysfunction, subsequently to the mitochondrial outer membrane permeabilization (MOMP) [205]. MOMP not only causes the release of mtDNA but also of mitochondrial intermembrane space proteins, such as cytochrome c, which in turn activate caspases, resulting in apoptosis, a non-inflammatory form of cell death. Caspase activity is essential for the absence of inflammation in cases of mitochondrial-induced apoptosis because it is responsible for the inactivation of cGAS-STING signaling. If MOMP-induced caspase activition is blocked, released mtDNA will activate the cGAS-STING pathway, resulting in NF-ƙB activation and INF release [206,207]. This cascade of events, called caspase-independent cell death (CICD), leads to proinflammatory cytokine production, with the consequent activation of the immune response against the dying cell. Therefore, it has been proposed that if CICD is activated in a cancer cell, it will stimulate antitumour immunity [208], leading to the paradoxical hypothesis that cGAS-STING signaling is responsible for the induction of an immune suppressive tumor microenvironment [209,210]. Moreover, STING knockout mice show an increased susceptibility to colorectal tumorigenesis once induced by chronic DNA damage and inflammation [211,212]. In *KRAS* mutant non-small cell lung cancer cells, it has been shown that cytosolic leakage of mtDNA activates STING signaling and that this specific type of tumor, which harbors its malignancy in mitochondrial dysfunction, epigenetically silences STING, therefore blocking downstream IFN signaling [213]. The ability to selectively downregulate cGAS and STING has also been shown in melanoma and colorectal adenocarcinoma cells [214,215], and the inhibition of STING in

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melanoma and pancreatic cancer cells resulted in decreased immune cell infiltration, with consequent increased tumor growth *in vivo* [216,217]. Remarkably, caspase activation is able to inactivate the cGAS–STING pathway, thus suppressing sterile inflammation, suggesting the presence of a control mechanism in the case of abnormal cytosolic dsDNA in the case of apoptosis [206,207]. This control mechanism, not yet fully characterized, is altered in cancer cells due to their ability to escape apoptosis. This scenario supports the protumorigenic vision of cGAS-STING signaling, which exerts its protumoral function by triggering chronic inflammation and thus prompting an altered immune response [168,218]. Accordingly, the cGAS-STING pathway has the ability to trigger the formation of the NLRP3 inflammasome via either IFN I release or initiating potassium efflux upstream of NLRP3 activation [219,220]. As described, the activation of this pathway mediates the secretion of a variety of proinflammatory cytokines that can exert a dual effect. On the one hand, these cytokines work as immune-stimulatory factors that decrease cancer growth and recruit immune cells for tumor clearance, while on the other hand, the release of TNF-α elicits inflammatory-derived carcinogenesis, exacerbating tumorigenesis [204,221]. Interestingly, cancer cells are able to recruit mtDNA from the extracellular space to restore mitochondrial function and their metastatic potential [222,223]. This ability suggests that cancer cells seek extracellular mtDNA to sustain cGAS-STING-driven tumorigenesis in addition to supplementing mitochondrial functions [204], supporting protumorigenic vision.

In conclusion, the DNA sensing cGAS–STING pathway has a dual role in tumorigenesis: it is responsible for cytosolic mtDNA and dsDNA sensing, creating antitumoral immunity via the release of several proinflammatory cytokines, but at the same time, cancer cells have learned how to customize this mechanism to stimulate their survival and metastasizing ability. Therefore, other studies are needed to better understand this complex mechanism to develop pharmaceutical strategies to boost the cGAS–STING antitumor mechanisms.

5. Targeting mitochondria as a cancer therapeutic strategy

There is increasing evidence showing that mitochondrial targeting may represent an antitumoral strategy option with great potential. In this section, we aimed to describe scientific literature data from the last 5 years (Table 1). The latest evidence seems to confirm that targeting mitochondria is associated with an improved survival rate and remarkable clinical effects in oncologic patients, although sometimes with a lack of uniform outcomes across different cancer types.

5.1 Conjugating mitochondria-targeting compounds

Several conventional drugs have been redesigned by conjugating mitochondria-targeting compounds to improve antitumoral effects. For instance, triphenylphosphonium ion-conjugated doxorubicin seems to reduce drug resistance; the mitochondria-targeted analog of glycyrrhetinic acid induces apoptosis in cancer cell lines through the induction of membrane permeability transition; F16 conjugated with chlorambucil causes mitochondrial DNA damage and apoptosis; mitochondria-targeted pro-delocalized charge conjugated with carboplatin accumulates in cancer cells and seems to increase in transmembrane potential and hamper glutathione system, involved in redox detoxification [224]. The concept of pro-delocalized charge has been introduced by Reshetnikov et al [225]: the induction of delocalized charge within the cell is due to N-alkylamino ferrocene structure reacting with ROS; this is considered a highly selective method for targeting tumor cells, as the positive charge is activated only in cancer cells, where ROS are overexpressed. A mitochondria-targeted pro-delocalized charge conjugated with carboplatin has been clinically

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approved and seems to accumulate in human ovarian cancer cells where: i) increases the transmembrane potential and ii) hampers glutathione system, involved in redox detoxification [224].

5.2 Mitochondria-targeted synthetic peptides

Biomedical research is also focused on mitochondria-targeted synthetic peptides, known as MPPs, due to their biocompatibility and feasible synthesis. Compounds such as MPP-conjugated doxorubicin and MPP-conjugated mtPt (analog of platinum) have shown excellent cellular uptake and specific mitochondrial targeting [224]. Mitochondria-targeted peptides elicit mitochondrial dysfunction by either direct or indirect induction of OMM permeabilization, mPTPC or membrane disruption [226].

5.3 Photodynamic therapy

Furthermore, photodynamic therapy has been considered among mitochondria-targeted anticancer strategies, particularly combining photosensitizers with MPPs [224]. Mitochondria-targeted photodynamic therapy has been assessed to effectively induce tumor cell death, probably because of its inhibitory effect on the mitochondrial respiratory system [224].

Among mitochondria-targeted metal complexes, iridium-based complexes are the most studied photosensitizers, while among mitochondria-targeted small molecules, boron-dipyrromethane or cyanine dye showed better deep tissue penetration [224].

5.4 Targeting mitochondria bioenergetics

Mitochondrial metabolism represents a crucial element in malignant cells; thus, targeting metabolic pathways could be an effective antitumoral strategy. Among the most significant mitochondrial targets, the ETC and OXPHOS activity are the most studied. Substances such as tamoxifen, α-tocopheryl succinate, phenformin, and 3-bromopyruvate, acting as electron transport chain inhibitors, induce an increase in ROS concentration and tumor cell mitochondrial-mediated apoptosis [227]. Metformin has been shown to reduce OXPHOS activity and tumor growth in several cancer types by inhibiting mitochondrial complex I, with a positive safety profile [228,229]. Furthermore, tagging complex I inhibitors with the triphenylphosphonium group seems to improve the specificity of the compound towards cancer cells, leading to effective cancer cell death in colorectal, lung and breast cancers [230].

Moreover, some ECT inhibitors are currently undergoing clinical trials for different types of cancer. One of them is the complex I inhibitor ME344, which is undergoing a clinical trial for the treatment of human epidermal growth factor 2-negative breast cancer; another inhibitor, named atovaquone, has been shown to inhibit complex III, and it is in a clinical trial for the treatment of acute myeloid leukemia; arsenic trioxide has also been reported to inhibit complex IV, representing an FDA-approved treatment for promyelocytic leukemia [229].

Furthermore, synergic administration with glycolytic inhibitors (such as hexokinase inhibitors) has been observed to further impair mitochondrial function and to further suppress cancer cell proliferation [231]. Glycolysis targeting could be an effective strategy to obtain selective anticancer activity towards electron transport chain-mutated tumor cells [228].

Isocitrate dehydrogenase inhibitors (such as AGI-5198, AGI-6780, AG-120, AG-221, 3BP, and dichloroacetate) have been assessed to be effective as antitumoral agents in several cancer types, hampering the TCA cycle and blocking the accumulation of the 2-HG oncometabolite [232].

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Furthermore, a possible mitochondrial metabolic reprogramming strategy has been proposed: silencing of pyruvate carboxylase in succinate dehydrogenase-deficient cancer cells has been shown to hamper tumor progression, while the administration of proline dehydrogenase with glutaminase inhibitors has been shown to reduce tumor growth in several breast cancer cell lines [229].

5.5 Targeting ROS homeostasis

ROS homeostasis represents another intriguing mitochondrial target in cancer therapy. According to some studies, targeting thioredoxin and the glutathione system, inducing oxidative stress and apoptosis, and targeting elevated ROS production in tumor cells seem to be effective in sparing normal cells both *in vitro* and *in vivo* [228]. In fact, Rozanov and collaborators demonstrated that the 1,4-naphthoquinine derivative NSC130362 was able to suppress the antioxidant glutathione system, consequently inducing oxidative stress and apoptosis in tumor cells while sparing normal human primary hepatocytes [233]. NSC130362 has been shown to potentiate the cytotoxic activity of several pancreatic and prostate cancer drugs. Conversely, triphenylphosphonium ion-conjugated terpyridine-Pt has been demonstrated to inhibit the thioredoxin system and to induce apoptosis [224].

It has been observed that elesclomol sodium (STA-4783) increases mROS production and induces cytotoxicity and apoptosis processes in cancer cells [229]; similarly, β-phenylethylisothiocyanates (PEITC), in combination with metformin, have been stated to induce apoptosis, with an antiproliferative effect in ovarian cancers. On the other hand, LBL21, a PEITC analog, causes a superior cytotoxic effect in lung cancer cell lines and animal models [229].

Compounds such as oxymatrine, capsaicin, casticin, and myricetin were reported to kill cancer cells, enhancing ROS generation and interfering with mitochondrial redox balance [232], thus confirming that targeting mitochondrial ROS production may represent a possible therapeutic target, enhancing chemotherapy activity [227].

5.6 Targeting mitochondria-mediated apoptotic pathway

Several drugs have been developed to target apoptotic pathways to induce cancer cell death by mitochondria-mediated apoptosis. Bcl-2 and/or Bcl-xL inhibitors (such as Venetoclax, Navitoclax, Obatoclax, TW-37, and BM-1197)) or Bcl-2 expression inhibitors (such as Oblimersen) showed antitumoral activity in several cancer types, increasing apoptotic priming in cancer cells [227,229,232]; Bcl-2 homology-3 domain mimetics (such as navitoclax, ABT-737, and α-TOS) also induce tumor cell death, activating Bax or Bak oligomerization and the apoptotic pathway [227]. Particularly, ABT-737 has been observed to resensitize tumor cells to drug-induced death when administered in combination with chemotherapy and radiotherapy [229] and to alter the mitochondrial membrane potential, hampering the glutathione system and consequently increasing ROS production [224].

5.7 Targeting mitochondrial Ca^{2+} homeostasis

An alternative approach to mitochondrial-oriented cancer therapy could be the modulation of mitochondrial Ca^{2+} homeostasis. Indeed, it has been proposed as a possible antitumoral strategy, given the central importance of mitochondrial Ca^{2+} uptake for tumor cell survival and proliferation [234]. Several drugs targeting channels, transporters, and pump structures involved in Ca^{2+} homeostasis have been studied [235], many of which pinpoint proteins at cell membranes and ER, indirectly perturbing mitochondrial Ca^{2+} concentration.

Thapsigargin (TG), a selective inhibitor of the SERCA (ER/SR Ca^{2+}-ATPase) pump, has been observed to induce the programmed cell death pathway due to the enhancement of endoplasmic reticulum stress, the prevention of Ca^{2+} uptake into the endoplasmic reticulum and the depletion of the endoplasmic reticulum Ca^{2+} store [235], thus diminishing Ca^{2+} transfer at MAMs (see relevant section). Nonetheless, TG has not yet been used in clinical practice due to its nonselectivity for tumor cells. In contrast, mipsagargin (G202), an analog to thapsigargin conjugated to specific targeting peptides, has been shown to significantly reduce tumor progression in breast, bladder, and prostate cancers, with a good safety profile in animal trials [235] Furthermore, targeting the MAMs and Ca^{2+} channels/transporters/pumps, could represent another possibility to modulate mitochondrial Ca^{2+}: BCL-2-IP3R disruptor 2 (BIRD-2) increases mitochondrial Ca^{2+} uptake, inducing cancer cell apoptosis [229,236,237]; xestospongin B, an IP3R inhibitor, reduces cancer cell proliferation, inducing necrosis in tumorigenic breast cells [235]; caffeine and 4-chloro-m-cresol, ryanodine receptor agonists, induce apoptosis in prostate cancer and breast cancer cell growth reduction [235].

Thus far, MCU appears to be another promising target for mitochondrial Ca^{2+} homeostasis in the cancer setting, although to date, there is still no MCU-targeted effective therapy. Indeed, a study demonstrated that counteracting the inhibitory effect on MCU expression exerted by miR-25 through the overexpression of an anti-miR-25, it is possible to restore mitochondrial Ca^{2+} uptake and reverse apoptosis resistance [87].

The mitochondrial permeability transition pore complex (mPTPC) represents a crucial element in maintaining the mitochondrial membrane potential, and upon ROS overproduction or mitochondrial Ca^{2+} signaling impairment, its opening is triggered. Clodronate has been assessed to depolarize the mitochondrial membrane potential, inhibiting adenine nucleotide transporter activity and oxygen consumption in macrophages *in vitro*; AppCCl$_2$P, a clodronate metabolite, has been shown to induce apoptosis, inhibiting adenosine triphosphate translocation in isolated human osteoclasts [224].

5.8 Targeting overexpressed mitochondrial proteins

Furthermore, targeting overexpressed mitochondrial proteins has been considered among possible antitumor strategies; for instance, triphenylphosphonium ion-conjugated SMTIN-P01 has been shown to induce apoptosis by inhibiting the mitochondrial HSP90 (heat shock protein 90) isoform, known as TRAP1 (tumor necrosis factor receptor associated protein 1), an overexpressed chaperone in cancer cells [224].

5.9 Targeting mitochondrial dynamics and mitophagy

Another valid anticancer strategy is represented by mitochondrial fission modulators, both inhibitors and inducers. Mitochondrial division inhibitor-1 (MDIVI-1) targeting DRP-1 inhibitor has been the only one tested as a fission inhibitor, showing an effective role as an adjuvant to cisplatin, promoting cancer cell death in several cancer types and to TNF-related apoptosis-inducing ligand (TRAIL) in ovarian cancer [229]. Saikosaponin is an upregulator of DRP-1 and a mitochondrial fission inducer; this compound showed synergy with cisplatin, inducing apoptosis in cisplatin-resistant ovarian cancer cells [229]. In colon, cervical, liver and breast cancers, resveratrol has been assessed to cause mitochondrial fragmentation and cancer cell death by DRP-1 upregulation [229].

Targeting mitophagy pathways could represent a particularly effective therapeutic option as an enhancer of anticancer drug action. Selective mitophagy modulation may cause a disruption of the balance between cell death and tumorigenesis, inhibiting tumor growth and promoting the elimination of cancer cells [17]. Several mitophagy inducers have been reported. Ceramides and their analogues have been demonstrated to induce cancer cell death by autophagy and reduce drug resistance in a broad range of tumor types [238]. Wang et al showed that low-intensity ultrasound therapy was able to induce mitophagy and cell death in nasopharyngeal carcinoma cells incubated with curcumin [239]. Phenanthroline, a metal chelating agent, has shown to induce DRP-1 dependent mitochondria fragmentation, following ROS production [240]. Deferiprone, an iron chelator, in known as another mitophagy inducer: it affects the respiratory chain complexes and function, binding to their iron-sulfur clusters [241]. Dihydroergotamine tartrate has been assessed to suppress lung cancer cell growth, by inducing mitophagy [242]. Linamarase, linamarin and glucose oxidase systems are known to activate mitophagy by suppressing glycolysis and oxidative phosphorylation [17,229,238,243]. However, a high level of mitophagy has also been correlated with anticancer therapy resistance, probably either due to a higher OXPHOS state and enhanced cell proliferation or to better control of ROS production and mitochondrial transmembrane potential and the consequent reduction of the apoptotic process [244] [18]. These findings have been pointed out in cisplatin-resistant oral squamous cell carcinoma and in doxorubicin-resistant or oxaliplatin-resistant human colorectal cancer stem cells, suggesting that mitophagy could possibly play a dual role in tumor treatment [19].

To date, there is limited evidence about mitophagy inhibitors as useful antitumoral treatments to promote tumor cell death while sparing normal cells, which are usually less susceptible to mitophagy inhibition [245]. For instance, cyclosporine A inhibits mitophagy by reducing mitochondrial outer membrane permeability; mitochondrial division inhibitor-1 disrupts the mitochondrial fragmentation process; liensinin has been observed to increase breast cancer cell sensitivity to doxorubicin, thus confirming the usefulness of mitophagy inhibitors in association with conventional antitumoral therapies [17,229,243].

Furthermore, genetic mitophagy suppression (downregulation of PINK1/Parkin-mediated mitophagy and Rab9a-mediated mitophagy and downregulation of FUNDC1, PINK1, and AMBRA1) has been shown to render tumor cells more sensitive to death induced by radio- and chemotherapy [19].

Moreover, mitochondrial clearance has been suggested to play a possible regulatory role during immunogenic cancer cell death induced by anthracyclines [246].

Nonetheless, to date, several issues about targeting mitophagy as an anticancer therapeutic option and the reaction of healthy cells to mitophagy modulators remain uncleared and deserve further investigation.

5.10 Mitochondrial-related immunotherapy

The latest novelties in the field of cancer therapy are related to immunotherapy, which represents an innovative therapeutic strategy aimed at increasing innate immunity and promoting a tumoral environment with CD8+ T cell infiltration [247].

Considering that cGAS stimulates endogenous anticancer immunity and is sensitive to mitochondrial DNA released after mitochondrial damage, several therapeutic strategies focused on the cGAS-STING axis have been tested in various cancer models: synthetic and natural STING agonists, radiotherapy, chemotherapy, antibody-based therapy, viral-based therapy, and vaccines

have shown effective antitumor activity [247]. One STING agonist, 5,6-dimethylxanthenon-4-acetic acid (DMXAA), promotes tumor regression *in vivo in* mouse models by inducing tumor hemorrhagic necrosis and has undergone phase II clinical trials [248–250].

Nevertheless, data in the literature are still inconsistent, since there is evidence that the cGAS-STING axis may represent a protumoral pathway in some cancer types. To date, the issue of cGAS-STING-targeted therapeutic strategies is still under debate.

5.11 Latest novel approaches

Finally, novel approaches to mitochondrial targeted treatment have been suggested. For instance, targeting mitochondria trafficking has been proposed as a possible antitumoral strategy; mitochondrial relocation to the periphery of the cancer cell is crucial for cellular movement and invasiveness, thus the use of compounds inhibiting mitochondria trafficking could represent an innovative strategy to reduce cancer cell migration, but further investigations are needed [229]. The mitochondrial unfolded protein response pathway, a transcriptional program aimed at repairing and recovering a mitochondrial perturbation or dysfunction, has been hypothesized to represent a novel strategy for oncologic patient treatment [251]. Of note, "drug-free" agents represent a brand-new therapeutic approach. This therapeutic strategy points towards i) intramitochondrial aggregation, ii) intramitochondrial self-assembly, and iii) intramitochondrial biomineralization, all mechanisms postulated to lead to cell death and overcome drug resistance [224].

Concluding remarks

Given its crucial function in promoting both viability and cell death, mitochondria represent one of the most intriguing targets for successful cancer treatment. The main obstacle is still its dual role in many vital cell pathways. Indeed, mitophagy and its related pathways can be either supportive of tumor growth or hinder them depending on cancer subtype, as mitochondrial Ca^{2+} uptake can sustain tumor growth to assist bioenergetics as though being toxic stimulus and induce apoptosis. Nevertheless, mitochondrial bioenergetics is still the most intriguing focus for the development of novel cancer therapies. Tumor cells, with dysfunctional mitochondria, mainly take advantage of glycolysis and the pentose phosphate pathway to produce ATP and reducing equivalents such as NADPH, as well as catabolism of amino acids such as glutamine, to sustain cancer cell energetic needs. Although, dysfunctional mitochondria are still able to perceive the activation of alternative anabolic and catabolic pathways in the cytoplasm. A recent study has demonstrated that in malignant prostate cancer patients, OXPHOS is rewired to a metabolism mostly based on succinate oxidation, supported by the overexpression of respiratory complex II [252]. This means that mitochondria adapt to preserve cancer cell proliferation.

Of growing interest is also the role played by mitochondria in cancer-related inflammation, specifically by the release of mtDNA in the activation of the cGAS-STING pathway. This signaling, however, depends on the timing of its activation during cancer transformation, and can either activate immune surveillance or support chronic inflammation, thus enhancing cancer cell growth.

Mitochondria-oriented cancer therapeutic strategies have been developed in recent years, some of them with successful results. Many efforts are still needed to unveil all the controversies still existing in the mechanisms behind mitochondria-mediated cancer cell regulation to address the clinical unmet needs.

Author contributions statement:

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Paolo Pinton: Funding acquisition; Review and editing;

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Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1 – Mitochondria-targeted approaches

Class	Compound	Target
Conventional drug conjugate with mitochondria targeting ligand	- Triphenylphosphonium ion-conjugated doxorubicin - Mitochondria-targeted analog of glycyrrhetinic acid - F16 conjugated with chlorambucil - Mitochondria-targeted pro-delocalized charge	Redox detoxification systems
Mitochondria penetrating peptide conjugated with cargo	- MPPs-conjugated doxorubicin - MPPs-conjugated mtPt	OMM permeabilization mPTPc opening
Photosensitizer conjugate with mitochondria targeting ligand	- Iridium-based complexes - Boron-dipyrromethane - Cyanine dye	Electron transport chain
Electron transport chain and oxidative phosphorylation activity inhibitors	- Tamoxifen - α-Tocopheryl succinate - Metformin - Phenformin	Complex I, III, IV

	• 3-Bromopyruvate • ME344 • Atovaquone • Arsenic trioxide	
Glycolytic inhibitors	• Hexokinase inhibitors	Glycolysis
Isocitrate dehydrogenases inhibitors	• AGI-5198 • AGI-6780 • AG-120 • AG-221 • 3BP • Dichloroacetate	Tricarboxylic acid cycle
ROS regulators	• NSC130362 • Triphenylphosphonium ion-conjugated terpyridine-Pt • STA-4783 • PEITC • LBL21 • Oxymatrine • Capsaicin • Casticin • Myricetin	ROS homeostasis, glutathione system, thioredoxin system
Apoptotic pathway modulators	Bcl-2 and/or Bcl-xL modulators: • Venetoclax • Navitoclax • Obatoclax • Oblimersen • TW-37 • BM-1197 • ABT-737 • α-TOS	Bcl-2, Bcl-xL
Mitochondrial Ca^{2+} modulators	Ca2+-ATPase inhibitors: • Thapsigargin • G202 Ca^{2+} channel/transporters/pumps modulators • BIRD-2 • Xestospongin B • Caffeine • 4-chloro-m-cresol	Mitochondrial Ca^{2+} uniporter, mitochondrial-associated endoplasmic reticulum membranes
Mitochondrial permeability transition pore modulators	• Clodronate • AppCCI$_2$P	Adenine nucleotide transporter, adenosine triphosphate translocation
Overexpressed mitochondrial proteins modulators	• Triphenylphosphonium ion-conjugated SMTIN-P01	Chaperones
Mitochondrial fission modulators	Fission inhibitor: • MDIVI-1 Fission inducer: • Saikosaponin	DRP-1 inhibitor

|	• Resveratrol	
Mitophagy modulators	Mitophagy inducers: • Ceramides • Low-intensity ultrasound therapy with curcumin exposition • Phenanthroline • Deferiprone • Dihydroergotamine • Linamarase, linamarin and glucose oxidase system Mitophagy inhibitors: • Cyclosporine A • Mitochondrial division inhibitor-1 • Liensinin • Genetic mitophagy suppression (downregulation of PINK1/Parkin-mediated mitophagy, downregulation of FUNDC1, PINK1, and AMBRA1)	Mitophagy pathway
Synthetic lethal interaction	• Silencing pyruvate carboxylase in succinate dehydrogenase deficient-cancer cells • Proline dehydrogenase with glutaminase inhibitors	Mitochondrial metabolic reprogramming
Immunotherapy	• Synthetic and natural STING agonist (DMXAA) • Radiotherapy • Chemotherapy • Antibody therapy • Viral therapy • Vaccines	cGAS-STING pathway

Figures and Figure legends:
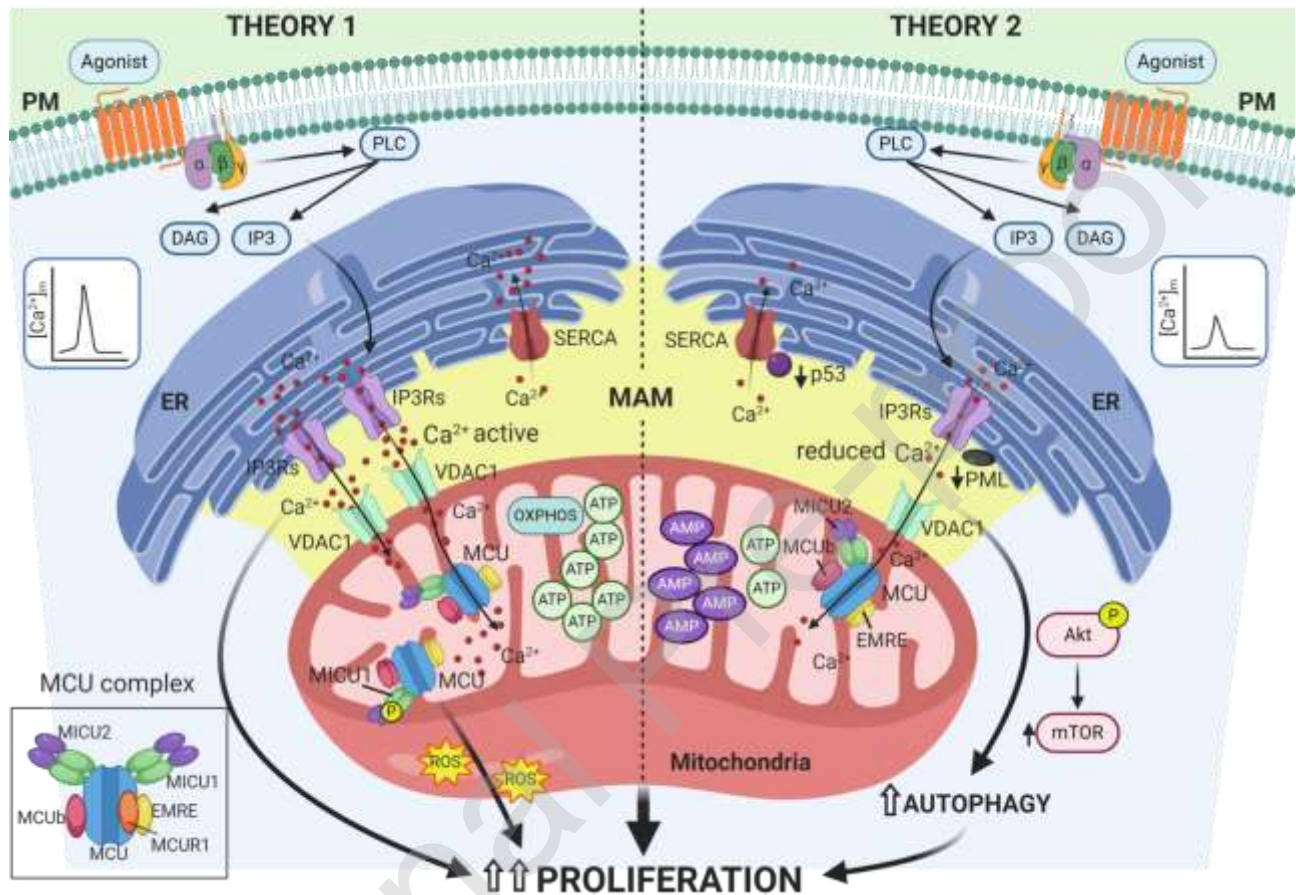
Figure 1: ER mitochondrial Ca^{2+} transfer upon agonist stimulus can have two possible outcomes in cancer cells according to the current literature. On the one hand (left side of the figure), active Ca^{2+} uptake through the MCU complex leads to increased ATP production from OXPHOS that sustains cancer cell proliferation. MICU1 phosphorylation by Akt can also support basal mitochondrial Ca^{2+} uptake through MCU in an agonist-independent fashion that can provide for mitochondrial metabolism and cancer cell survival and proliferation through the production of metabolites such as ROS. On the right side of the figure, the opposite body of evidence shows that a reduced mitochondrial Ca^{2+} uptake from the ER upon agonist stimulus, due to the downregulation of oncosuppressors such as PML and p53, leads to a decrease in ATP production that is sustained by the activation of autophagy. This coordinated action supports cancer cell proliferation (figure created with Biorender.com)
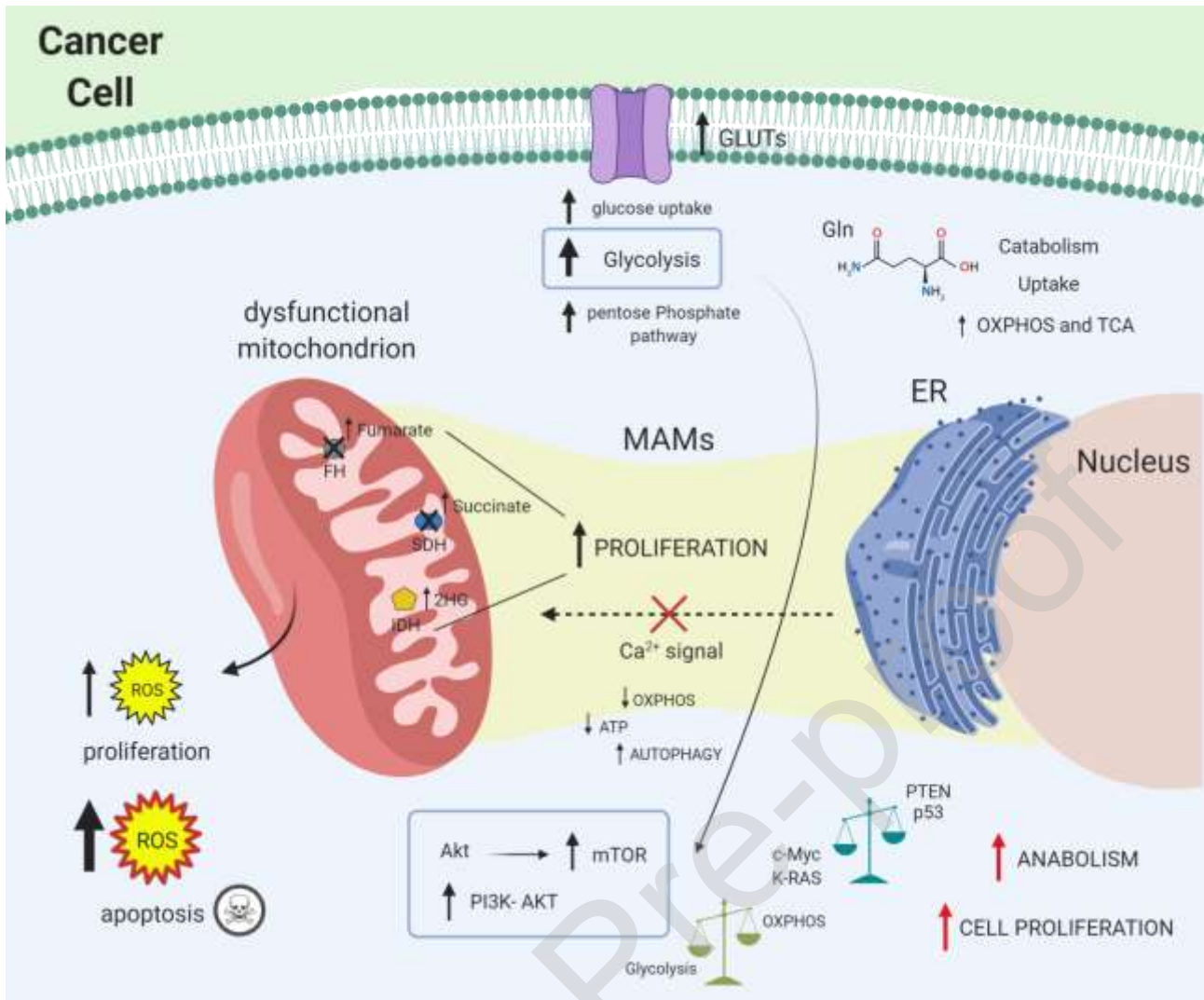
23

Figure 2: Cancer cells are often accompanied by dysfunctional mitochondria. Altered mitochondria cause rewired metabolism, where glucose and amino acids (glutamine) are the main sources sustaining cancer cell proliferation. Generally, cancer cells have a higher glucose uptake (through GLUTs) that supports glycolysis, the pentose phosphate pathway and, through the PI3K-AKT pathway, autophagy, shifting towards glycolysis and oncogene expression that enhance cancer cell proliferation. Moreover, the reduced Ca^{2+} transfer from the ER to mitochondria at MAMs affects both OXPHOS and ATP production. Dysfunctional mitochondria also produce certain oncometabolites, such as ROS, succinate, fumarate and 2-HG. ROS, when produced at normal concentrations, induce cancer cell proliferation; once overproduced, it is an apoptosis inducer. Succinate, fumarate and 2-HG are the result of loss-of-function mutations (for the first two) or mutations that help in the accumulation of these oncometabolites and the impairment of the TCA cycle, both in the mitochondria and in the cytoplasm, where they act on gene expression and epigenetic regulation to sustain cell proliferation (figure created with Biorender.com)
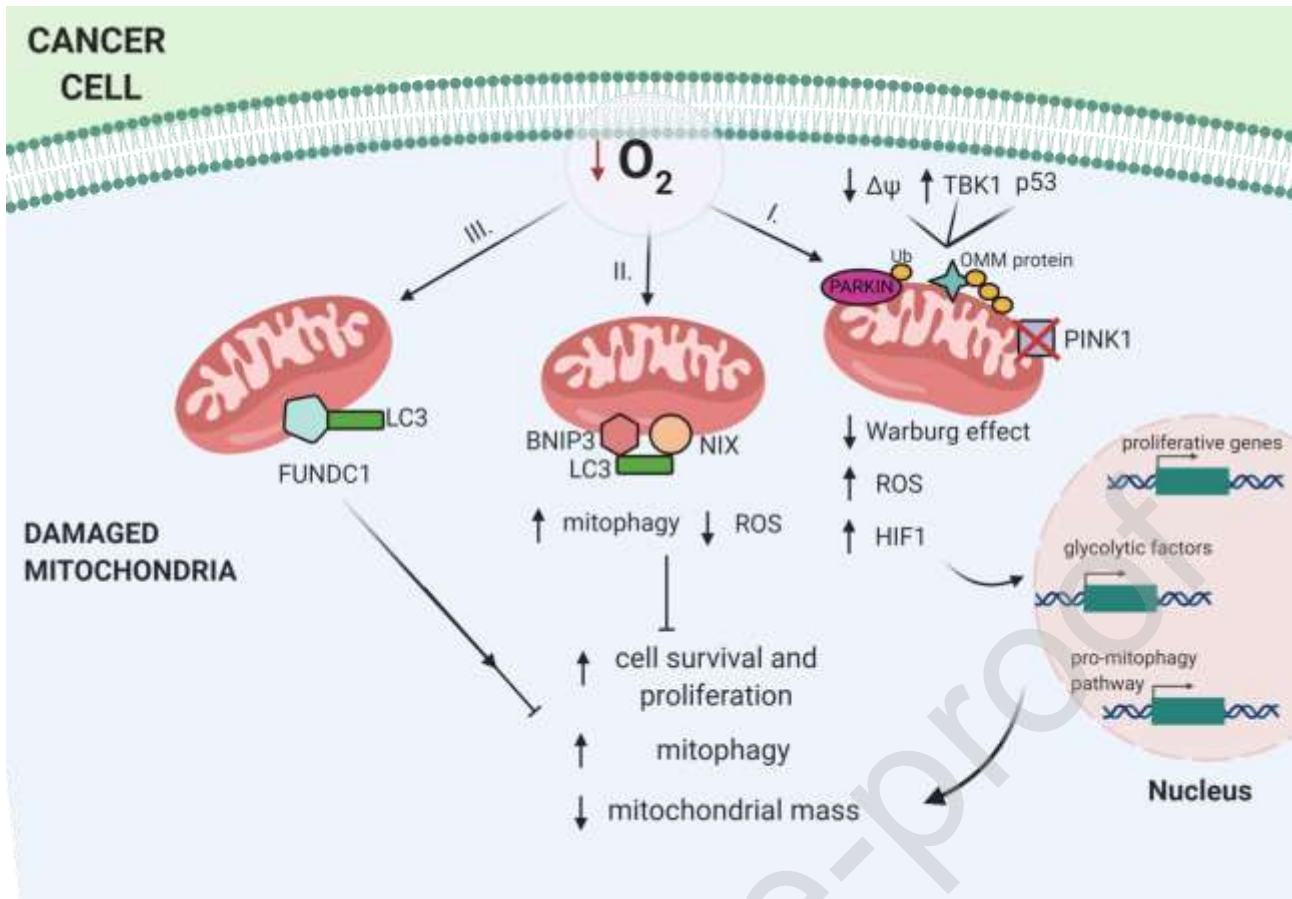
Figure 3: Mitophagy is a controversial mechanism of damaged mitochondrial clearance that can have both antiproliferative or proproliferative effects on cancer cells. There are three main mitophagic pathways, all of which are typically triggered by the reduction of O_2 in the organelle. The first pathway involves the action of PARKIN and PINK1, which can also be activated by p53 and TBK1 and reduce mitochondrial membrane potential. PARKIN, as an E3 ubiquitin ligase, can posttranslationally modify OMM proteins, favoring their degradation via the proteasome, thus enhancing mitochondrial clearance. They both have an effect on metabolism, reducing the Warburg effect in the cytoplasm and increasing ROS production, activating HIF1. This in turn activates a transcription program that culminates with the activation of mitophagy, reduction of mitochondrial mass and cell proliferation. The second pathway involves BNIP3/NIX, which are both able to bind to LC3, activating mitophagy, which in this case, has a tumor suppressive function. BNIP3/NIX have a controversial role, since in some tumors, it has been reported that their transcription, via HIF1, supports cancer pro-proliferative mitophagy. The last pathway is also controversial; it involves the activation of a mitochondrial membrane receptor named FUNDC1, which can bind to LC3. This activation, however, can either inhibit or activate mitophagy-mediated cell proliferation (figure created with Biorender.com).
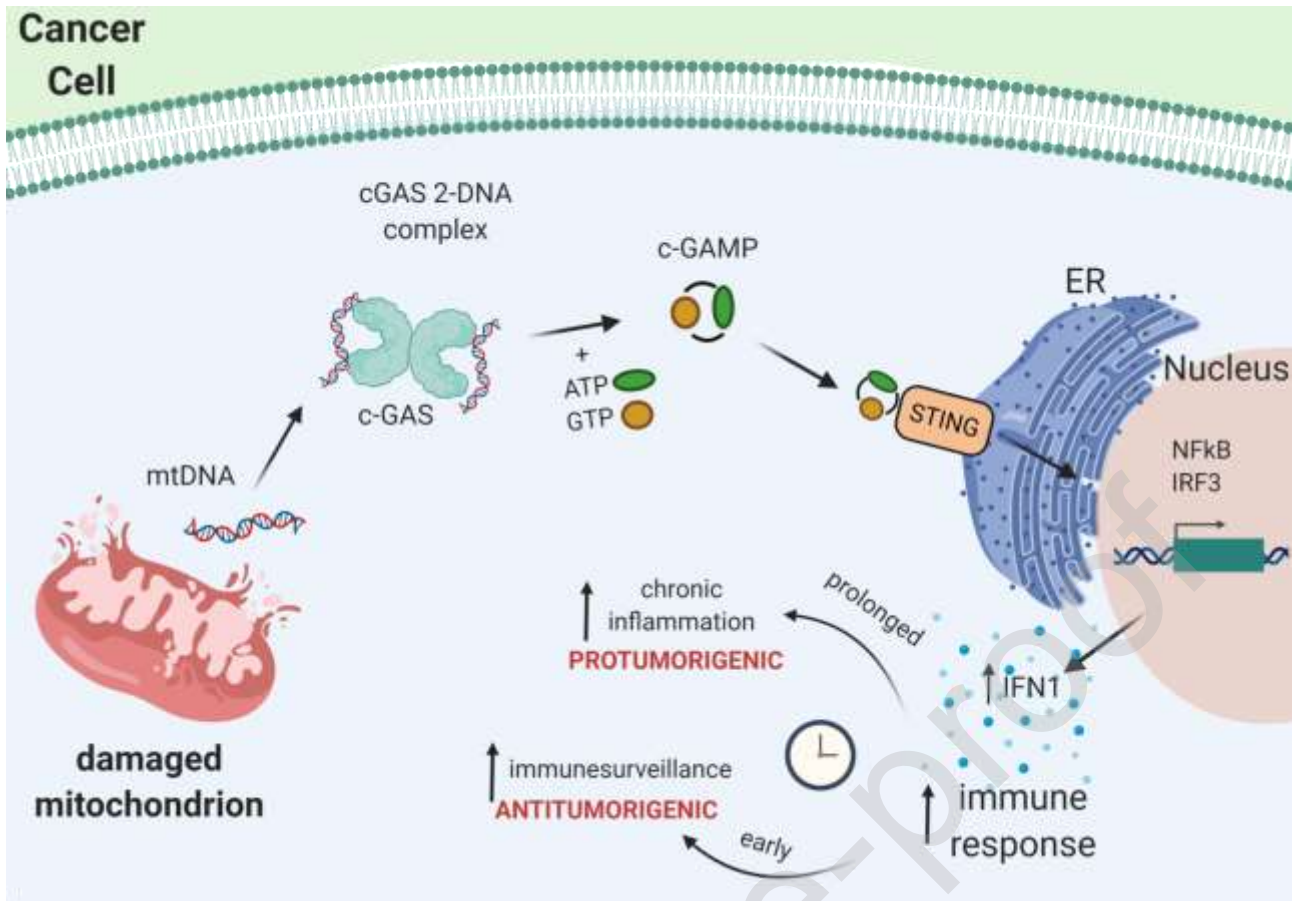
Figure 4: The c-GAS-cGAMP-STING pathway links the release of mtDNA due to mitochondrial damage to inflammation pathway activation and cancer cell proliferation. This pathway is physiologically employed by cells to recognize microbial DNA to activate the innate immune response. In the cancer context, it has been reported that released mtDNA is recognized by cGAS, which forms a complex with 2 mtDNA molecules. This enzyme, thanks to ATP and GTP, can convert mtDNA into cGAMP. This is then sensed by an ER receptor named STING, which activates the transcription of the inducer of innate immune response. This activation leads to the release of IFN1. Depending on the activation timing of this pathway, there could be an antitumorigenic effect (early) that induces the intervention of immune surveillance in the clearance of cancer cells. When sustained, IFN1 production can permit the establishment of chronic inflammation, which elicits tumor progression and cell proliferation (figure created with Biorender.com).

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