Disrupting cancer cell function by targeting mitochondria

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Abstract

Although each cancer type is individually distinct, most cancers initially occur due to genomic mutations of oncogenes and tumor suppressor genes, leading to enhancement or disruption of specific cellular processes, including mitochondrial-mediated events. As an organelle necessary for both cell survival and cell death, the mitochondrion is involved in a variety of diseases, including cancer. Specific alterations to mitochondrial DNA in cancer can result in increased proliferation and avoidance of cell death pathways. Since cancer cells utilize mitochondria to enhance disease progression, specific targeting of mitochondrial-regulated processes and pathways may present advantageous anticancer treatments.

Introduction

Although overall cancer death rates have declined by 20% since climaxing in 1991 [1], this group of diseases is still of major importance regarding treatment and prevention. As cancer cells are continuously replicating, treatment regimens often fail to completely rid a patient of malignant cells, resulting in repopulation of the tumor [2]. Thus, ongoing research is necessary for continued observance and management of this complicated group of diseases.

Cancer is composed of a vast group of diseases characterized by unchecked cellular proliferation and metastasis of abnormal cells throughout the body. The development of cancer is initiated by three known factors. Firstly, genomic mutations constitutively activate oncogenes to promote uncontrolled cell growth [3]. Additionally, genetic modifications deactivate tumor suppressor genes so that they fail to inhibit the robust cell growth [4]. Last, stability genes necessary for genomic repair are inactivated, allowing for higher rates of mutations in the cellular genome [5]. All three genetic mutation types allow normal cells to progress to cancer. Once cells become cancerous they exhibit large metabolic imbalances [6] and increased resistance to cell death [7], two processes regulated by mitochondria.

These organelles are comprised of an Outer Membrane (OM), An Inner Membrane (IM), an intermembrane space, a cristae interior, and a matrix [8]. Mitochondria perform key roles in cellular function, including cell survival, energy generation, stabilization of Reactive Oxygen Species (ROS), and cell death pathway regulation. As mitochondria are largely involved in cell health, it is anticipated that they are involved in cancer development and progression [9-11].

Here, mitochondrial processes needed for cancer cell survival are discussed. Cell death pathways are examined in relation to enhanced tumor progression. Finally, presently available and potential treatment strategies are reviewed.

Mitochondrial function in cancer cells

Otto Warburg was one of the first investigators to implicate mitochondria in cancer. His phenomenon, termed the Warburg effect, demonstrates that tumor cells exhibit increased glycolytic Adenosine Triphosphate (ATP) production and reduced Oxidative Phosphorylation (OXPHOS) [12]. Since then, every aspect of the mitochondrion has undergone thorough investigation to shed light on the alterations promoting this aggressive disease.

Changed transcription factor activity in cancer

Mutations in oncogenes and tumor suppressor genes are leading factors promoting tumorigenesis and metastasis. These mutated genes encode transcription factors, which in turn control the gene expression patterns and signaling pathways that lead to cancer development [13]. Several transcription factor pathways are involved in tumorigenesis.

Nuclear Factor-κB (NF-κB) is involved in the regulation of inflammatory response genes, cell cycle regulatory genes, and anti-apoptotic genes. In a variety of human cancer cells, NF-κB activation inhibits apoptosis, leading to enhanced tumor resistance to chemotherapeutic agents [14]. Numerous studies have demonstrated that suppression of NF-κB leads to apoptosis induction and tumor regression [15-18]. Next, Activator Protein 1 (AP-1) regulates many cellular processes, including proliferation, differentiation, survival, and death. Overexpression of the AP-1 family has been demonstrated to induce tumor formation [19]. Similar to NF-κB, inhibition of AP-1 decreased cell viability [20] and reduced tumor volume [21] in numerous studies, suggestive of the potential of utilizing AP-1 in anticancer treatments. An additional transcription factor family involved in cancer is Signal Transducer and Activator of Transcription (STAT), which has roles in cell differentiation, development, proliferation, inflammation, and apoptosis. In many human cancer cell lines, STAT proteins often become constitutively activated, which promotes oncogenic transformation by regulating cell proliferation [22] and cell death

pathways [23]. Blockade of STAT proteins, especially STAT3, resulted in decreased proliferation and increased cell death in several studies [24,25]. In breast and prostate cancer, steroid hormone receptors play a key role in mediating the tumorigenic effects of testosterone, androgen, progesterone, and estradiol [26]. Finally, manipulation of steroid receptors, including inhibition of androgen receptors in prostate cancer cells [27] and silencing of estrogen-regulated genes in breast cancer cells [28], have provided novel strategies for the treatment of hormone-specific tumors.

These transcription factors, as well as others, propel cancer development through a variety of pathways, such as altering the cell cycle to enhance proliferation rate, blocking apoptosis to promote malignant cell survival, and changing gene expression patterns which affect cellular and mitochondrial processes.

Altered mitochondrial DNA in cancer

Mitochondria contain a DNA molecule (mtDNA) that encodes genes essential for normal mitochondrial function. Human mtDNA contains 37 genes that code for 13 polypeptides involved in respiration and OXPHOS, and two ribosomal RNAs in addition to 22 transfer RNAs important for protein synthesis [29]. Furthermore, mtDNA has a noncoding region with a displacement loop for control of mtDNA replication and transcription [30]. As mtDNA regulates vital processes, modifications to its genomic material can profoundly impact healthy cells.

Numerous studies have reported the effects of mtDNA mutations in tumors. To begin, mtDNA copy number has been examined in diverse cancers, indicating that changes in mtDNA content may be regulated in a tumor-specific manner [31,32]. Moreover, studies have shown that mutations in both the coded [33,34] and non-coded [35-37] mtDNA regions are associated with cancer growth. Interestingly, these alterations strongly correlate with patient outcome [38], as displacement loop mutations typically correlate with lower survival rates outcome [39]. Thus, the severity of mtDNA alterations in cancer cells and patient survival seem to depend on both mtDNA content deviations and mutation locations.

Modified energy metabolism in cancer

In healthy cells, ATP manufacturing is dependent upon oxygen uptake, the Tricarboxylic Acid (TCA) cycle, and the Electron Transport Chain (ETC). Dehydrogenases of the TCA cycle are stimulated by mitochondrial calcium (Ca^{2+}) intake (Figure 1.1), which propels the reduction of Nicotinamide Adenine Dinucleotide (oxidized NAD^+ to reduced NADH) [40]. In addition, succinate dehydrogenase, also known as complex II (succinate-ubiquinone oxidoreductase) of the ETC, catalyzes the oxidation of succinate to fumarate in the TCA cycle [41]. ETC complex I (NADH-ubiquinone oxidoreductase) receives electrons from NADH [42], while complex II gains electrons from succinate. Next, the accepted electrons are transferred to complex III (ubiquinol-cytochrome *c* oxidoreductase) and incorporated into Cytochrome c (cyto c) for delivery to complex IV (cytochrome *c* oxidase) [42], which are then used in the reduction of oxygen to water [43]. Protons are generated during the ETC process and used by ATP synthase (often referred to as complex V) in the OXPHOS pathway to generated ATP from Adenosine Diphosphate (ADP) and inorganic phosphate [44]. Once produced, ATP propels many activities in the cell, including signal transduction, active transport, and DNA synthesis. Consequently, changes in energy production due to mtDNA mutations can affect these processes.

Warburg initially discovered that tumor cells display increased glucose uptake, enhanced glycolytic ATP generation, and diminished OXPHOS [6]. Essentially, instead of utilizing pyruvate molecules in the TCA cycle to power the OXPHOS pathway for generation of ATP as is done by normal cells (Figure 1.2-1.4), cancer cells convert pyruvate into lactic acid for energy generation (Figure 2.1). A possible explanation for Warburg's findings involves ATP synthase malfunctioning as hyperglycemia in hepatocarcinoma cells reduced ATP synthase dimer stability in a new study [45]. Also, Isidoro et al. found that expression of the β-catalytic subunit of ATP synthase is decreased in cancer cells [46], further implicating the involvement of complex V.

Although the Warburg effect is widely recognized, several groups have challenged it, revealing that mitochondria in tumors are able to operate OXPHOS at lower capacities along with glycolysis [47]. In fact, malignant cells can switch from a glycolytic state to OXPHOS under glucose-limiting conditions to adjust to changes in the cellular environment [48]. Utilizing both respiration systems under diverse settings is important for tumor survival. For instance, glucose deprivation elevates OXPHOS in breast tumor cells while control cells remain unaffected [49]. Conversely, hypoxia improves respiration in control cells whereas it is impaired in breast cancer cells [50], signaling for tumor cells to switch to glycolysis. Therefore, cancer cells can direct the energy metabolism systems according to their specific needs under a variety of conditions; this likely aids in cancer cell growth and resistance to cell death.

Balanced oxidative stress in cancer

Under homeostatic conditions, enhanced ATP production via enhanced ETC activity propels the reduction of oxygen to water. Consequently, this promotes leakage of free electrons from the ETC complexes, leading to the creation of superoxides, free radicals, and peroxides jointly known as ROS [51]. To compensate, ROS scavenging enzymes are also activated to neutralize oxidants [52]. Healthy cells tightly regulate the balance between oxidants and anti-oxidants to prevent destructive consequences (Figure 1.5). Nevertheless, ETC complex activity deficits are linked with reduced energy and heightened ROS generation [53]. Chiefly, reduced complex I, II, and IV respiratory capacities lead to increased risk of dysfunction [54]. Due to insufficient ROS scavenger levels, damaging oxidants accumulate within the cell and cause damage, such as mtDNA mutations [55]. Thus, unrestrained oxidative stress can propel cancer initiation and metastasis [56].

Elevated oxidative stress has been observed in many different tumors, with persistently high ROS levels seen in malignant cells (Figure 2.2) compared with paired controls [57]. Accordingly, cells are able to use mitochondrial ROS as a mechanism to increase their chance of cancer development through a kind of pro-cancer feedback loop. Also, extra-mitochondrial ROS production can affect cancer behavior, correlating with enhanced tumor growth and invasiveness [58,59]. Thus, cancer cells can utilize enhanced intra- and extra-mitochondrial ROS generation to increase tumor developmental and metastatic abilities.

However, elevated ROS levels can cause substantial damage to normal and cancerous cells, alike. As a result, tumor cells are capable of rebalancing ROS production and elimination by activating antioxidants (Figure 2.3) for restoration of an optimal redox state necessary for continuous proliferation [60]. For example, a study found that increasing ROS levels caused inhibition of glycolytic enzyme pyruvate kinase M2, which in turn activated the antioxidant systems required
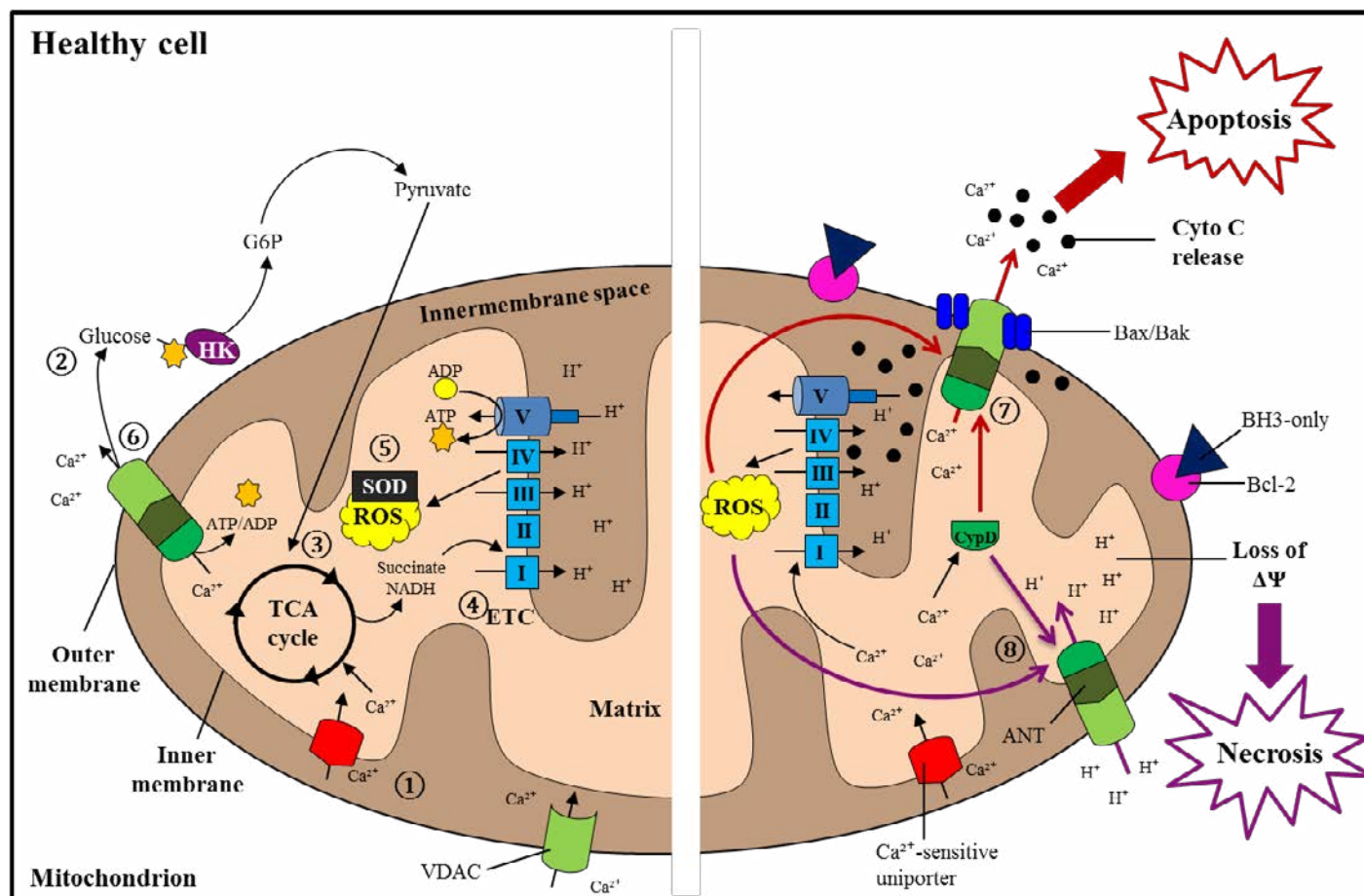
Figure 1: Mitochondrial processes and pathways in healthy cells

During regular conditions, healthy cells chiefly use mitochondrial OXPHOS for generation of ATP. **1)** Ca^{2+} is readily taken up into mitochondria through VDAC and Ca^{2+}-sensitive uniporter channels on the OM and IM, respectively; these ions go on to stimulate ATP production. **2)** During glycolysis, glucose molecules are converted into pyruvate molecules, **3)** which are taken up into mitochondria for use in the TCA cycle. **4)** Reduced forms of NADH and succinate are used by the ETC to drive ATP assembly. **5)** Anti-oxidants (superoxide dismutase, SOD) maintain the levels of ROS generated during the ETC process. **6)** The MPTP, comprised of VDAC, ANT, and CypD, expels surplus Ca^{2+} ions from mitochondria. **7)** During cell injury, apoptotic cell death (red pathway) is instigated as a result of uncontrolled Ca^{2+} and/or ROS levels. Anti-apoptotic Bcl-2 is repressed by BH3-only proteins, which allows pro-apoptotic Bax and Bak to interact. This induces opening of the MPTP for release of cyto c and Ca^{2+} into the cytosol, propelling the organized collapse of the cell. **8)** Necrosis (purple pathway) occurs due to excessive Ca^{2+} and/or ROS accumulation and reduction of ATP stores, leading to loss of $\Delta\Psi$ and the unplanned rupture of the cell [123].

for detoxifying ROS in cancer cells [61]. Therefore, tumor cells regulate ROS levels for initial development and long-term management of cancer progression.

Reduced MPTP formation in cancer

A nonselective mitochondrial Ca^{2+}-activated pore was initially discovered to take in and extrude ions during membrane permeability oscillations [62]. Currently called the mitochondrial permeability transition pore (MPTP, Figure 1.6), this pore is often connected with cell death provoked by stress and C^{a2+} overload [63]. Under stress conditions in healthy cells, the MPTP forms in the IM where its induction can lead to mitochondrial swelling, loss of transmembrane potential ($\Delta\Psi$), apoptotic mediator release, and eventual cell death [64]. However, MPTP-mediated cell death is suppressed in tumor cells, rendering them resistant to therapies [65]. Many factors participate in protecting cancer cells from MPTP-regulated membrane disruption and cell death induction, a few of which are presently discussed.

Cyclophilin D (CypD) is a prolyl isomerase located within the mitochondrial matrix and has been established as a modulatory component of the MPTP [66-68]. During oxidative stress or Ca^{2+} overload in healthy cells, CypD translocation to the IM activates the MPTP, inducing cell death [69]. Interestingly, cancer cells overexpress CypD, leading to the suppression of cell death by interacting with anti-apoptotic Bcl-2 to inhibit the release of cyto c [70]. CypD-mediated inhibition of cell death also correlates with mitochondrial-bound hexokinases (HK, Figure 2.4). Inactivation of CypD results in the release of bound HK-II and enhances pro-apoptotic Bax/Bak-mediated apoptosis [71]. In addition, heat shock protein interactions with CypD inhibit normal CypD-dependent MPTP opening and cell death in some tumors [72]. Thus, CypD expression seems necessary for cancer growth, and is regulated by many molecular interactions.

The Translocator Protein (TSPO; initially known as the peripheral benzodiazepine receptor) is another recognized component, first linked to the MPTP due to its ligand interactions [73]. Moreover, the OM has been shown to have a regulatory role in MPTP formation, primarily through TSPO [74]. Similar to CypD, TSPO is elevated in many types of cancer, especially breast cancer [75]. Increased levels of TSPO are associated with enhanced invasiveness of breast cancer
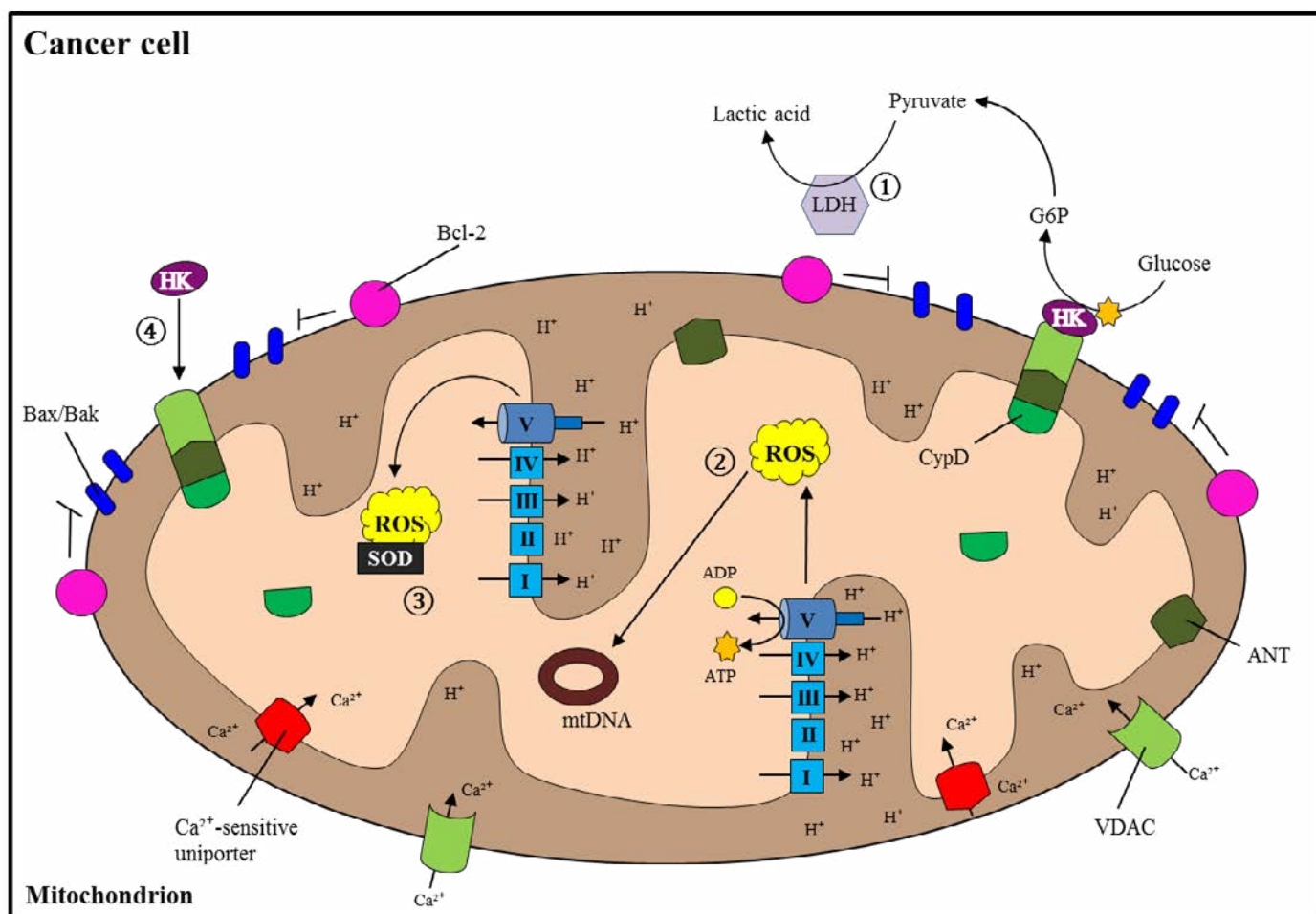
Figure 2: Altered mitochondrial processes during cancer
In cancer cells, there is a shift from OXPHOS to glycolytic ATP production, **1)** producing large amounts of lactic acid via Lactate Dehydrogenase (LDH). **2)** High levels of ROS induce carcinogenic mutations in mtDNA, but are **3)** balanced by activated antioxidants (such as superoxide dismutase, SOD). **4)**HK inhibits opening of the MPTP, and as a result blocks cell death induction. Thus, the combination of increased carcinogenicity and decreased cell death promote cancer cell growth [123].

[76,77], and correlate with shortened disease-free survival in lymph node-negative patients [78]. It has been postulated that high TSPO levels may render malignant cells more resistant to MPTP formation and cell death, comparable to CypD. This seems plausible, though additionally research is needed to determine the function of elevated TSPO levels in cancer.

Two other mitochondrial membrane channels were proposed as MPTP components [79], but have since been shown to be unnecessary for MPTP formation.

First, mitochondria take up small molecules and ions through Voltage Dependent Anion Channels (VDAC) along the OM [80]. VDAC was originally hypothesized to play a role in MPTP configuration [81], however recent findings suggest otherwise [82,83]. In cancer cells, VDAC channels are significantly upregulated. As expected, downregulation of VDAC directly affects proliferation [84,85]. HK expression is also linked with VDAC quantities; in tumor cells, overexpression of HK-I and -II induces VDAC closure and prevents MPTP opening [86]. This HK-mediated closure of VDAC may allow for CypD-induced MPTP inhibition (Figure 2.4), thus enhancing tumor cell proliferative abilities.

Second, Adenine Nucleotide Translocase (ANT) was another postulated component of the MPTP [87], as it functions to catalyze the exchange of mitochondrial ATP for cytosolic ADP through the IM [88]. However, studies demonstrated it is not essential for MPTP induction [89]. Of the four isoforms of ANT, increased expression of ANT-1 and -3 promotes cancer cell death [90,91]. In contrast, enhanced expression of ANT-2 and -4 renders malignant cells more resistant [92,93]. Furthermore, ANT-2 seems to be critical for importation of glycolytic ATP in cancer cells [94]. Connecting ANT to the MPTP, overexpression of CypD inhibits ANT-1-mediated apoptosis in tumor cells [95]. Hence, the ANT isoforms oppositely participate in MPTP regulation in cancer, with CypD interactions vital in control cancer cell survival.

Collectively, this suggests that altered interactions between CypD, TSPO, VDAC, and ANT may play important roles in promoting cancer growth. Therefore, MPTP-induced cell death via manipulation of any of these factors may hold the key to future cancer treatment methods.

Cell death manipulation in cancer

Cells often become damaged, infected, or malignant. When this happens, survival is no longer a priority. If this occurs, mitochondria have control of signal transduction pathways, such as apoptosis and necrosis, for proper destruction of the cell.
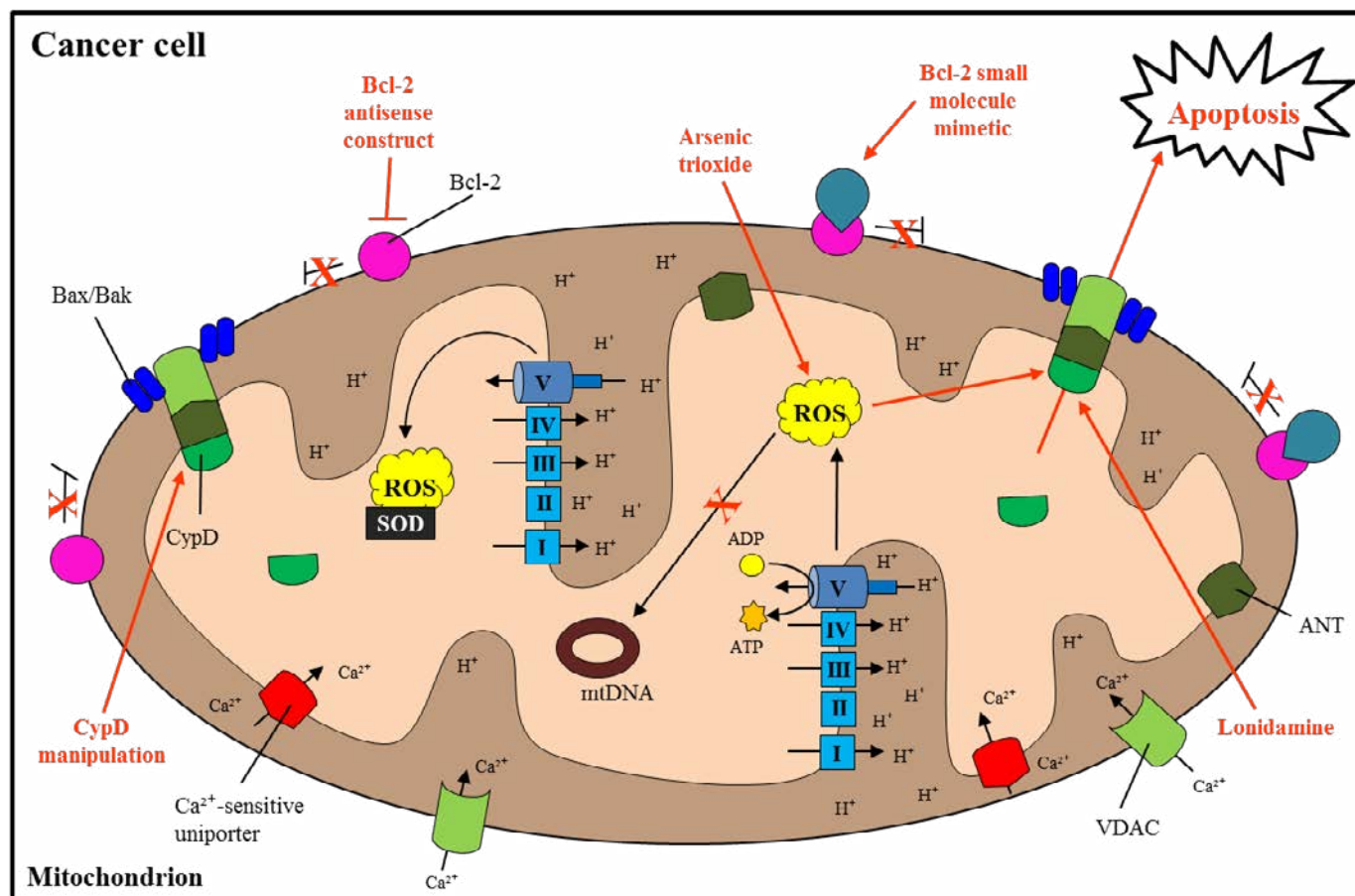
Figure 3: Mitochondrial targets for treatment of cancer
Since cancer mitochondria are vastly altered, specific targeting of dysfunctional processes and pathways may lead to novel treatment regiments (labeled in red). In cancer cells, manipulation of Bcl-2 antiapoptotic proteins can be used to induce apoptosis. Bcl-2 antisense constructs and Bcl-2 small molecular mimeticshave been used in animal and clinical trials to inactivate Bcl-2 specifically, with varied results. Lonidaminehas been observed to disrupt ΔΨ and propel MPTP-regulated cell death. Moreover, arsenic trioxide together with lonidamine further increases ROS output, leading to apoptosis. Manipulation of CypD may aid in the sensitization of cancer cells to anticancer therapeutics. Essentially, disrupting cancer cell resistance by inducing cell death using the indicated therapeutics/target areas could provide additional anticancer treatment options [123].

Apoptosis

Two alternative pathways can initiate apoptosis within cells. Death receptors on the cell surface initiate apoptosis via the extrinsic path [96], while mitochondria activate the intrinsic route [97] (Figure 1.7). Apoptosis signaling stimulates initiator caspases [98], which propel the cleavage of death substrates through activation of executioner caspases [99]. Upon activation by caspases, anti-apoptotic proteins release pro-apoptotic proteins [100], driving the release of cyto c and other apoptotic factors from the opened MPTP [101]. The apoptotic factors exacerbate the process, causing the organized collapse and shrinkage of the cell until the cell body is engulfed by neighboring cells for removal [102]. Also known as programmed cell death as it can be purposefully initiated; apoptosis is a pathway that can be activated specifically by mitochondria.

Most often, cancer cells display increased inhibition of apoptosis due to mutations that either disrupt pro-apoptotic proteins [103,104] or elevate anti-apoptotic proteins [105]. On the contrary, a recent study found that enhanced levels of pro-apoptotic Bad promote prostate cancer growth [106]. This discrepancy illustrates that cancer cells tightly regulate all apoptotic protein levels in accordance with their proliferative needs. Additionally, in the event of apoptosis initiation, some cancer cells can reverse the process and survive [7]. Clearly,

tumors manipulate many aspects of apoptosis to avoid death, which render cancer therapies ineffective. However, simultaneously targeting cancer cell-specific apoptotic inhibitory pathways while administering current anticancer agents is a novel avenue that may eliminate the resistance seen in tumors.

Necrosis

In the event of cellular injury, an unplanned cell death pathway called necrosis can be activated (Figure 1.8). Death receptor adaptor activation causes their translocation to the IM [107,108], which interferes with ANT-mediated ATP/ADP exchange. This disruption leads to ATP depletion and ROS accumulation [109]. Heightened ROS and Ca^{2+} levels stimulate mitochondrial uncoupling, swelling, and loss of ΔΨ due to opening of the MPTP [110,111]. These disparities initiate degradative enzymes which aggravate the process until plasma membrane rupture [112] and leakage of the intracellular contents in an unorganized manner.

Studies have shown that necrotic cell death is impaired in cancer cells, although the particular mechanisms are still being examined. Nakagawa and colleagues found that inhibiting CypD protects malignant cells from necrosis [113]. Also, although Leucine zipper/ EF hand-containing Tansmembrane-1 (LETM1) induces necrosis

in normal cells, LETM1 overexpression is common in many forms of cancer, leading to the inhibition of necrotic cell death [114]. Due to inconsistent outcomes with apoptosis-mediated treatments, the induction of necrosis may provide an alternative tool for treating cancer cells resistant to apoptosis-inducing methods.

Treatment strategies targeting mitochondria in cancer

As many cancers become resistant to chemotherapy and radiation regimens, targeting of mitochondrial-mediated processes is being investigated for enhancement of available anticancer agents. A large variety of drugs are approved for cancer treatment, such as cisplatin [115], paclitaxel [116], and trastuzumab [117]. However, due to cell repopulation and resistance, many antitumor agents fail to reduce cancer progression and metastasis in the long run. Concurrent treatment may aid the antitumor effects of available treatments.

Apoptosis manipulation is a popular target as programmed cell death is inhibited in cancer cells. Reducing the levels of antiapoptotic proteins in tumor cells using antisense constructs (Genasense) showed promising results for sensitizing cancer cells to apoptosis-mediated anticancer drugs in animals [118], but less desirable effects in clinical trials. Instead, small molecule mimetics that bind and inactivate antiapoptotic proteins have been proposed as an alternative method [119]. In essence, inhibition of antiapoptotic proteins could help sensitize malignant cells to available antineoplastic treatments (Figure 3).

Looking specifically at the MPTP, a few drugs are being tested for anticancer ability. As shown in Figure 3, targeting lonidamine to malignant cell mitochondria causes ΔΨ disruption and MPTP-induced apoptosis [120]. Furthermore, co-treatment with lonidamine and arsenic trioxide enhances ROS generation and leads to MPTP-mediated cell death in human leukemia cells [121]. Also, CypD seems to play a role in cisplatin-mediated pancreatic cancer cell death [122]. As CypD overexpression typically enhances cancer cell resistance, it will be interesting to see whether manipulation of CypD or other MPTP components has an effect on sensitizing tumor cells to antitumor agents.

Conclusion

Mitochondrial dysfunction and tight regulation of cellular activities allows for cancer cell growth and resistance to cell death. With effective treatment options limited for cancer, research has shifted to target-specific and/or concurrent therapeutic regimens. Since mitochondrial dysfunction is highly implicated in cancer, targeting specific mitochondrial processes may enhance the susceptibility of diseased cells to available drugs. This novel approach toward disease treatment would increase the quantity and quality of therapeutic options.

Acknowledgements

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