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MITOCHONDRIA: INSIGHT TARGET OF DRUG DEVELOPMENT IN CANCER CELLS

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ABSTRACT

Mitochondria are involved in different physiological and pathological processes that are crucial for tumor cell physiology, growth and survival and its dysfunction leads to many human abnormalities, including cardiovascular diseases, neurodegenerative diseases, autoimmune disorders and cancer. The present review is focused on the different experimental and therapeutic cancer strategies addressed to either target mitochondria directly, or use mitochondria as mediators of apoptosis, although its total molecular mechanism has not been elucidated. Therefore, the role of mitochondria in the etiology and progression of several function and explore potential therapeutic benefits of targeting mitochondria in the disease processes. Newly evolving advances in disease diagnostics and therapy will further facilitate future growth in the field of mitochondrian biology, where there is a dire need for sensitive and more affordable diagnostic tools and an urgency to develop effective therapies and identify reliable drug to predict accurately the response to a cancer therapy. These approaches to treat mitochondrial dysfunction rationally could lead to selective protection of cells in different tissues and various disease states. To avoid mitochondrial liabilities, routine screens need to be positioned within the drug-development process as targets of drug-induced cytotoxicity or cancer promotion, as regulators of apoptosis, as sources of cell signalling through reactive oxygen species, and mitochondrial control of specific nuclear responses. However, several novel mitochondrial targets are now emerging, including the potential to manipulate the mitochondrial pool to maintain function via biogenesis and mitophagy. Forthcoming insights into the fine regulation of mitochondrial apoptosis will likely open future perspectives for cancer drug development.

INTRODUCTION: Mitochondria serve as a central hub for responses to cellular stress as well as injury. Mitochondria play key roles mediating intrinsic pathways of cell death by apoptosis, but non-apoptotic pathways have also been shown to involve mitochondrial mechanisms [1]. ‘‘Both pathways of cell death involve permeabilization of mitochondrial membranes, but the exact nature of the molecular complexes involved at the inner mitochondrial membrane (IMM) and outer mitochondrial membrane (OMM) remains uncertain in the light of recent gene knockout studies.’’

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The role of mitochondria is crucial in understanding their utility as potential targets against numerous human diseases. Mitochondria are therefore vital for normal cellular function, including intracellular metabolic activities and signal transduction of various cellular pathways. Human tissue affects and damages it by causing infection.

They are involved in cellular ion homeostasis, oxidative stress, and apoptotic and necrotic cell death. Indeed, recent studies have identified a host of common disorders with apparent ties to mitochondria, including metabolic (e.g., type 2 diabetes) and cardiovascular disorders, cancer, neurodegenerative diseases, psychiatric disorders, migraine headache, and the aging process. A thorough understanding of mitochondrial function in normal and pathological states is critical in developing the full therapeutic potential of the organelle in mitigating or preventing a given disease.

Mitochondrial-related diseases are vastly different and much of the science linking mitochondria to different disease states is still being intensively studied. Berridge *et al*., in 2010 has been addressed that the significance of metabolic flexibility and cell hierarchy in metastatic cancer [2]. The central premise of this review simply is that if mitochondrial abnormalities contribute to a pathological state (directly or indirectly), then alleviating the mitochondrial dysfunction should attenuate the severity or progression of the disease. Hence, the main objective of this review is to present the concept that mitochondria of varying cell types can be potentially targeted for therapeutic intervention in mitochondria-associated diseases.

Therefore, the review will focus on how the mitochondrion has become a potential therapeutic target in disease management.

Mitochondrial membrane as a Potential Therapeutic Target: The outer mitochondrial membrane (OMM), which encloses the entire organelle, has a protein-to-phospholipid ratio similar to the eukaryotic plasma membrane. It contains numerous integral proteins called *porins*, which contain a relatively large internal channel that is permeable to all molecules of 5000 daltons or less.

The elaborate structure of a mitochondrion is important for the normal functioning of the organelle and therefore as a potential therapeutic target. Two specialized membranes encircle each mitochondrion, dividing the organelle into a narrow intermembrane space (IMS) bordered by the OMM and the inner IMM. One of the membrane proteins is the peripheral benzodiazepine receptor (PBR).

PBR is a small evolutionarily conserved protein involved in cholesterol transport and steroid synthesis; it is also a regulator of apoptosis [3-5]. The PBR is also involved in OMM permeabilization by interaction with the pro-apoptotic Bcl family of proteins. However, OMM permeability may be independent of mitochondrial permeability transition pore (mPTP) opening because blocking PBR with 4′-chlorodiazepam (CDZ) protects against ischemia-induced cyto-chrome *c* release independent of damage to the IMM [5-7]; CDZ also reduces ischemia-induced arrhythmias [6].

This close association also suggests that PBR-VDAC may serve as a target for modulating apoptosis and may have implications for drug design to treat such disorders as cancer and neurodegenerative diseases[4, 5]. During the activation of cell death programs, permeation of the OMM occurs through the unopposed activation of effector proteins Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak) [8]. These proteins are located in the cytosol but oligomerize and translocate to the OMM as a consequence of oxidative stress. They are activated by interaction with activator peptides including truncated-bid (t-bid) or Bim.

The activator proteins are initially sequestered and inhibited by the anti-apoptotic proteins Bcl-2 and Bcl-Xl [8-11]. Bcl-2 and Bcl-Xl also interact with sensitizer BH3-only domain peptides including Bcl-2-associated death proteins (Bad), Bcl-2-interacting killer (Bik) protein, and perhaps Bcl-2/adenovirus E1B 19 kd-interacting protein (Bnip). These peptides preferentially interact with and sequester B-cell lymphoma (Bcl-2) and Bcl-2 X protein (Bcl-Xl), tilting the balance toward unopposed action of the activator peptides [9]. When activated, Bak and Bax homo-oligomerize at the OMM and promote the release of apoptotic factors cytochrome *c*, AIF, HtrA22/Omi and other factors.

The inner mitochondrial membrane (IMM) forms internal compartments known as cristae, which allow greater space for the proteins such as cytochromes to function properly and efficiently. The electron transport chain is located on the inner membrane of the mitochondria. Within the inner mitochondrial membrane are also transport proteins that transport in a highly controlled manner metabolites across this membrane. The IMM is highly impermeant and allows only certain small molecules to pass through. Cation permeation is regulated by ion channels and exchangers whose functions are governed by a high IMM potential ($\Delta\Psi_m$).

Mitochondrial cation anti-porters/exchangers (proton-linked) regulate any osmotic differential across the IMM that would result from the high proton motive force ($\Delta\mu H^+$). It is important that mitochondrial ion channels and exchangers are controlled in order to provide the balance between energy supply and demand that is crucial for normal cell function. Achieving this goal from a pharmacological standpoint could "spur the development of novel and specific therapeutic agents targeted to the mitochondria [7].

Mitochondrial Permeability Transition Pore: The Mitochondrial permeability transition pore (mPTP**)** is defined as an increase in the permeability of the mitochondrial membranes to molecules of less than 1500 Daltons. The mPTP pore is a protein pore that is formed in the inner membrane of the mitochondria under certain pathological conditions such as traumatic brain injury and stroke. Induction of the permeability transition pore can lead to mitochondrial swelling and cell death through apoptosis or necrosis depending on the particular biological settins [12].

The role of the mPTP in the survival and death of the cell is therefore critical in selective targeting of the pore for therapeutic interventions. Similarly, an understanding of the constituents of the pore and its molecular structure are paramount in this therapeutic goal. Moreover, the opening of the pore has been associated with numerous pathological conditions (e.g., stroke accompanied by brain ischemia). In this case, prolonged pore opening led to loss of mitochondrial proteins, most notably cytochrome *c*, second mitochondria-derived activator caspase/direct inhibitors of apoptosis protein (IAP)-binding protein (Smac/Diablo), apoptosis-inducing factor (AIF), endonuclease G (Endo G), and HtrA2/Omi [13-15]. Once released into the cytosol, these mitochondrial proteins trigger both caspase-dependent (by cytochrome *c*, Smac/DIABLO, or HtrA2/Omi), and caspase-independent (by AIF, Endo G, or HtrA2/Omi) apoptosis [16, 17].

Released in the cytosol Smac/Diablo and HtrA2/Omi bind to and cleave IAPs and thereby induce apoptosis [18, 19]. For example, increased expression of HtrA2/Omi in cells increases cleavage of XIAP, while suppression of HtrA2/Omi by siRNA has the opposite effect [20]. Therefore, release of these pro-apoptotic peptides could initiate and/or amplify cell death that occurs via apoptosis [18, 21].

Recent studies have also shown that the mitochondrial apoptotic protein Smac can abrogate the protective function of IAPs [22, 23, 15]. These findings suggest the potential clinical utility of Smac mimetics to trigger apoptosis and overcome drug resistance conferred by IAPs. Knowledge of the structural constituents of the mPTP and how agents modulate the dynamic function and structure of the mPTP is essential to understand the role of mitochondria as a therapeutic target for human diseases. The goal here would be to selectively manipulate mPTP protein function by therapeutic intervention, either to activate it to induce apoptosis for cancer therapy.

Electron Transport Chain and Oxidative Phosphorylation: Mitochondrial ETC function is modulated by several trans-matrix ions that enter and exit via several mitochondrial ion channels, exchangers, and symports [24]. Mitochondrial outer membrane permeabilization and cytochrome c release promote caspase activation and execution of apoptosis through cleavage of specific caspase substrates in the cell.

Among the first targets of activated caspases are the permeabilized mitochondria themselves, leading to disruption of electron transport, loss of mitochondrial transmembrane potential, decline in ATP levels, production of reactive oxygen species (ROS), and loss of mitochondrial structural integrity [25]. ATP is involved in a myriad of cellular processes that are essential for cell survival such as maintaining ionic homeostasis, cell

proliferation, and gene regulation. For example, cancer cells and astrocytes can survive well on ATP generated from glycolysis and are much less dependent on mitochondrial OXPHOS to generate ATP. Other cells such as neurons and cardiomyocytes depend almost entirely on mitochondrial OXPHOS for their function. Preservation of the constituents of the mitochondrial ETC is paramount in maintaining the bioenergetics status of the mitochondrion and the cell homeostasis. Indeed, mitochondrial defects encompassing complex I–IV of the ETC characterize a large number of neurodegenerative diseases [26, 27].

In the mitochondrion, a principal cation uptake pathway is via K^+ channels. There is a concerted interplay between K^+ uptake, via one or more K^+ channels, and the primary K^+ efflux route via the K^+/H^+ exchanger (KHE), which controls mitochondrial volume homeostasis [28, 29]. The existence of regulated pathways for both K^+ uptake and K^+ efflux may allow for a very fine-tuning of mitochondrial volume, and thus the rate of respiration. Changes in mitochondrial volume regulate mitochondrial energy metabolism through their effects on the TCA cycle enzymes and respiratory chain [30, 31].

During the steady state, respiration is balanced by K^+ influx into mitochondria through K^+ channels and efflux through the KHE. An imbalance in this dynamic relation could lead to matrix swelling and on to cellular damage by apoptosis or necrosis.

Mitochondrian reactive Oxygen species and its Biological role: Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. Examples include oxygen ions and peroxides. Reactive oxygen species are highly reactive due to the presence of unpaired valence shell electrons. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis. However, during times of environmental stress (e.g., UV or heat exposure), ROS levels can increase dramatically [32].

Mitochondrial ROS are involved in cell signal pathways as noted for ischemic and pharmacological pre- and postconditioning [24]. Indeed, ROS are important in normal cellular development and a limited amount of ROS in specific cells is necessary to mediate the programmed cell death that is required for cell elimination and mitochondrial autophagy during development and elimination of injured mitochondria or poorly performing cells. So, one would assume that teleologically mitochondria produce some ROS that are important for normal cellular function and survival despite the elaborate scavenging system [24].

Indeed, overexpression of matrix scavenger proteins (e.g., manganese superoxide dismutase (MnSOD), the mitochondrial variant of SOD), could provide effective scavenging, but because $O_2^{\bullet-}$ plays an important physiological role, excess scavenging may be deleterious. Under physiological conditions, a net amount of $O_2^{\bullet-}$ is produced (i.e., $O_2^{\bullet-}$ emission), as determined by the rate of $O_2^{\bullet-}$ generated minus the rate of $O_2^{\bullet-}$ scavenged.

To maintain this delicate balance, mitochondria are equipped with a variety of endogenous antioxidant defenses that regulate $O_2^{\bullet-}$ within a physiological range. However, under pathological conditions, as in cardiac I/R and in the aging process, the delicate balance (generation—scavenging) that keeps the level of $O_2^{\bullet-}$ to a minimum is altered so that the rate of $O_2^{\bullet-}$ generation exceeds the rate of scavenging. This can result in further damage to mitochondria and may exacerbate ROS-induced ROS damage [32, 33]. In normal healthy aerobic cells, oxidation and the generation of $O_2^{\bullet-}$ occur at a controlled rate.

But under high stress conditions or in disease states including cancer, nervous system disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), or cardiovascular disorders, ROS production is greatly increased, causing peroxidative changes of many proteins and lipids [34-36]. Increased mitochondrial ROS production, for example during hyperglycemia, may be a major factor in the pathology of diabetes. Glucose-stimulated insulin secretion by isolated islet cells can be used as an index for oxidative stress and/or impaired oxidative metabolism [37].

Less intense mitochondrial ROS generation has been associated with pathophysiological signaling. Mitochondrial-derived H_2O_2 is responsible for redox activation of c-Jun N-terminal kinase which inhibits mitochondrial metabolic enzymes [38]. This serves as a potential feedback mechanism to regulate metabolic

processes. In endothelial cells, H_2O_2 derived from mitochondria induces growth factor transactivation including receptors for vascular endothelial growth factor-2 and platelet-derived growth factor [39]. These responses are inhibited by endogenous antioxidants. In human coronary arterioles, mitochondrial-derived H_2O_2 is responsible for flow-mediated vasodilation [40].

Thus, ROS are not simply a byproduct of respiration, but can serve as a control mechanism by which the mitochondria signal changes in vascular function and growth.

Mitochondrian ROS scavenging and its therapeutic value: Reactive oxygen species (ROS) is closely linked to degenerative diseases such as Alzheimer's disease, Parkinson's, and neuronal death including ischemic and hemorrhagic stroke, acute and chronic degenerative cardiac myocyte death, and cancer. As a byproduct of oxidative phosphorylation, a steady stream of reactive species emerges from our cellular energy plants, the mitochondria [41].

ROS are clearly involved in normal cellular functions because they act as signaling agents in cellular protection, such as in cardiac preconditioning [42-48], postconditioning [42, 49-51], and cold preservation [52, 53]. But ROS can induce cell damage if their levels are not controlled within acceptable physiological limits. With this dual role, can modulation of ROS be an effective therapeutic tool? To address this question, the need to effectively detoxify pathologic ROS has to be balanced with the need to maintain physiological ROS.

It is this delicate balance that is used to control and manage cancer. Increased generation of ROS, which challenges ROS scavenging systems, can lead to increased apoptosis of tumor cells, or alternatively increase the scavenging capability to reduce ROS needed for tumor growth, in this case a desirable effect [54].

During pathological stress with a sustained increase in ROS levels, an ideal strategy would be to boost $O_2^{\bullet-}$ scavenging by using nontoxic catalytic antioxidants that are either delivered tissue-specifically or produced where needed from inactive precursors. Another strategy would be to decrease the primary $O_2^{\bullet-}$ production by preventing the over-reduction of intra-mitochondrial NADH [55] or by using mild uncouplers, that is, decrease $\Delta\Psi_m$ [55, 56, 24], or to pharmacologically stimulate the expression of endogenous mitochondrial and intracellular antioxidant systems [57].

ROS escape results in the activation of cytosolic stress pathways, DNA damage, and the upregulation of JNK, p38, and p53. Incomplete scavenging of ROS and RNS particularly affects the mitochondrial lipid cardiolipin (CL), triggers the release of mitochondrial cytochrome *c*, and activates the intrinsic death pathway [41].

Release of Cytochrome *c*: The Cytochrome complex, or cyt *c* is a small heme protein found loosely associated with the inner membrane of the mitochondrion. Cytochrome c is a component of the electron transport chain in mitochondria. The heme group of cytochrome c accepts electrons from the b-c1 complex and transfers electrons to the cytochrome oxidase complex [58]. Cytochrome *c* can accept or donate an electron depending on the redox state of its heme (Fe).

Thus, it is also a scavenger of $O_2^{\bullet-}$through its capacity to be reduced alternatively by the transfer of electrons or by $O_2^{\bullet-}$, thereby reducing ROS emission [57, 59]. The reduced cytochrome *c* is reinstituted by donating its electron to cytochrome *c* oxidase. In neurodegenerative diseases, loss of cytochrome *c* inhibits respiration, which leads to increased electron leak [60, 61]; the outcome is more $O_2^{\bullet-}$ production and more cell damage.

Another possible reason for an increase in $O_2^{\bullet-}$ after mPTP opening is the loss of cytochrome *c*. It was shown that addition of exogenous cytochrome *c* to cytochrome *c*-depleted mitochondria reduced $O_2^{\bullet-}$ levels by 7–8-fold [61, 62].

Therefore, an adequate concentration of cytochrome *c* in the ETC is necessary to maintain ROS at physiological levels [61]. Hence, maintaining the integrity of cytochrome *c* could represent a potential strategy for mitigating mitochondria-related cellular injury. Cytochrome c is also involved in initiation of apoptosis. Upon release of cytochrome c to the cytoplasm, the protein binds apoptotic protease activating factor [58].

Mitochondrian DNA and Therapeutic Target: Mitochondrial nonchromosomal DNA (mtDNA) damage plays a causative role in various disorders that are associated with aging, cancer, neurodegenerative diseases, and other diseases [63]. Currently, it is believed that various mutations are responsible for more than 120 syndromes associated with mitochondrial proteins [64, 65, 24].

There are also a number of mitochondrial diseases associated with specific mutations in mtDNA or in nDNA coding for mitochondrial proteins [66, 67, 24]. In all these diseases, the genetic mutations lead to impaired mitochondrial energy-generating machinery. Indeed, the most common source of somatic mutation of mtDNA is $O_2^{\bullet-}$ generated from the ETC.

The $O_2^{\bullet-}$ produced in the mitochondrion can continue in a self-perpetuating process leading to even more damage and more $O_2^{\bullet-}$ generation [24]. It is likely that gene replacement has potential to be used to correct a mutant mitochondrial genome similar to classical gene transfer therapies that have replaced defective nuclear genes [68]. Indeed, genetic maneuvers of different sorts have been employed to reverse mitochondrial related diseases.

Pharmacology and Therapeutic Potential: It is important to consider how pharmacological agents affect mitochondrial biochemistry, not only because of toxicological concerns but also because of potential therapeutic applications. Several potential targets could be envisaged at the mitochondrial level that may underlie the toxic effects of some drugs seem to depend on free radical production, although the mechanisms have not yet been clarified [69].

In a recent review, Armstrong [70] proposed the potential therapeutic application of mitochondrial targeting to include: a) delivery of antioxidants to prevent I/R injury, diabetes, and neurodegenerative diseases; b) delivery of apoptotic drugs that target BCl-2 proteins or deliver toxic drugs to neutralize cancer cells; c) targeting of the mPTP in I/R and stroke; and d) use of uncoupling proteins or activation of endogenous uncoupling proteins in diabetes and obese patients. In addition to these approaches, other recent approaches include the use of techniques in molecular biology involving mitochondrial and nuclear genes, siRNA, and targeting of the mitochondrial reticular network and mitochondrial interactions with the nucleus and the ER. These new approaches include targeting the mitochondrial fusion and fission proteins, targeting the communication between ER and mitochondria via the IP3R response to cytochrome *c* release, and targeting oxidative stress and mitochondrial modulation of nuclear transcription factors [24, 70-73].

Recently, antiviral nucleoside analogs have displayed mitochondrial toxicity through the inhibition of DNA polymerase-γ (pol-γ). Other drugs that target different components of mitochondrial channels can disrupt ion homeostasis or interfere with the mitochondrial permeability transition pore [69].

Mitochondrial antioxidant systems are important in cancer chemotherapy. Tamoxifen, a synthetic nonsteroidal antiestrogen widely used to treat breast cancer, is known to have antioxidant and cardioprotective effects in part by induction of MnSOD [74]. However, normal tissue injury is a major problem that limits the success of cancer therapy in protocols involving chemotherapeutic drugs (e.g., adriamycin). Generation of ROS is implicated in the toxicity of a large number of these agents and the injury is manifested at the mitochondrial level [74].

Meanwhile, drugs targeting mitochondria have been used to treat mitochondrial dysfunctions. Importantly, drugs that target the mitochondria of cancer cells have been developed recently; such drugs can trigger apoptosis or necrosis of the cancer cells [69].

Restrictions in Mitochondrian Drug Development: Given the multiple pathways potentially affected by a change in mitochondrial function, development of drugs targeting mitochondria requires judicious safety assessment and risk management [75]. The use of mitochondria as a therapeutic target can also be limited by the changes the organelle undergoes during the different phases of development.

For example, the younger heart shows greater sensitivity to anesthetic preconditioning (APC) than the older heart [76], which may correspond to the period during which bioenergetic function may begin to decline. Ontogenetic defects in mitochondrial function that lead to depressed mitochondrial bioenergetics

due to inherited mitochondrial cytopathies could result in altered responses to pharmacological interventions. For example, an anesthetic given in the APC paradigm could unintentionally lead to pathologic levels of ROS that cause cell damage[77] instead of the small amount of ROS needed to mediate cellular protection. The risk associated with using uncouplers to mitigate mitochondrial-related pathologies has been recognized. DNP was once used as a weight-loss drug but was abruptly discontinued due to undesirable side effects and even death [78].

Aside from their very limited window of action, another major problem with uncouplers is that they must be designed for tissue specificity to maximize their therapeutic potential and minimize side effects. A broad usage of uncouplers could lead to reduction in ATP production in untargeted mitochondria [79]. Another pharmacologic delivery problem is how to target brain mitochondria due to the relative impermeability of the blood–brain barrier (BBB). For example, MnTBAP is effective in ameliorating numerous pathological cardiovascular abnormalities and in extending the lifespan of *sod2*-deficient mice [80, 81].

However, MnTBAP does not cross the BBB and consequently, ROS can accumulate in the brain of these animals and cause abnormalities such as ALS, tremor, and other movement disorders[82, 83]. It is evident that an overarching concern in development of mitochondria-targeted drugs is to make the distinctions between nonadverse drug effects that are physiologic, pharmacologic, or adaptive, and the adverse effects that lead to unacceptable deleterious consequences.

Despite these limitations and challenges, the approaches outlined in this review have features that suggest a potential utility of targeting mitochondria for therapeutic purposes.

CONCLUSION: Selective stimulation of cell death in tumor cells remains a primary strategic aim in cancer therapy. This review has focused on different cells and tissues have distinct sensitivities and responses to mitochondrial dysfunction. Appreciation of these differences will be important when considering mitochondrial therapeutic strategies to combat diverse groups of maladies such as coronary heart disease, heart failure, hypertension, diabetes, cancer, and neurodegenerative diseases. Therefore, the goal in development of effective treatments for each of these diseases becomes a more pressing issue. The success of an anticancer attack must be based on the concerted modulation of cellular energy metabolism, mitochondrial stability, and other mechanisms responsible for the resistance of tumor cells to death stimuli.

In this regard, mitochondrial targeting appears to be a promising tool for promotion of tumor cell death. It is evident that much future work is required to develop novel and more tissue specific mitochondria-targeted approaches or interventions that intimate interplay between apoptotic regulators and mitochondrial energy metabolism should therefore be considered during the search for novel anticancer drugs.

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