Mitochondrial Manipulation in Cancer Therapy –A Review

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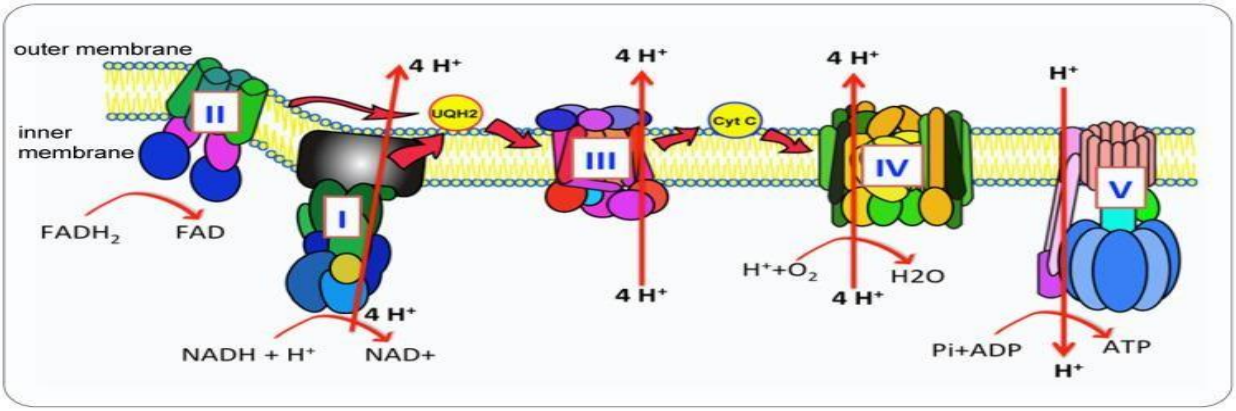
***Abstract*—Mitochondria are crucial for energy production and biosynthesis in cells, but they also play a significant role in cancer progression. Growing evidence suggests that mitochondrial bioenergetics, dynamics, and signalling are involved in cancer cell functions such as motility, stemness, proliferation, and survival. In some cancer cells, mitochondria adapt to the tumor's needs, potentially becoming "oncogenic mitochondria" that help spread cancer. Metabolic alterations, including changes in mitochondrial function, are key factors in cancer development. Reactive oxygen species, byproducts of various biological functions, have been extensively studied for their role in cancer. Modulating Reactive oxygen species levels has shown promise in cancer therapies, including immunotherapies, with positive results in preclinical studies. To target mitochondria more effectively, researchers are developing mitochondriotropic ligands and multifunctional nanoplatforms for cancer treatment. These platforms aim to induce mitochondria mediated apoptosis in tumor cells through strategies like chemotherapy, photothermal therapy, photodynamic therapy, chemodynamic therapy, sonodynamic therapy, radiodynamic therapy, and combined immunotherapy, though challenges remain in optimizing these approaches.**

***Index Terms*—Reactive oxygen species, Apoptisis, Sonodynamic therapies, oncogenic mitochondria.**

1. INTRODUCTION

ATP is the cell's primary energy source; it can be produced through two pathways: glycolysis in the cytosol and OXPHOS (Oxidative Phosphorylation) in the mitochondria. ATP production and consumption are critical for biosynthesis, metabolic regulation, and cellular maintenance. ATP is the cell's primary energy source; it can be produced through two pathways: glycolysis in the cytosol and OXPHOS in the mitochondria [1]. ATP production and consumption serve critical roles in biosynthesis, metabolic regulation, and cellular maintenance [2]. One of the "hallmarks of cancer" is altered energy metabolism, which serves as a molecular fingerprint for cancer cells. Glycolysis, mediated by phosphorfuctokinase1 (PFK1), produces pyruvate and NADH from glucose. The pyruvate then enters the mitochondria under aerobic circumstances and fuels the TCA cycle, which produces metabolites [3]. Mutations or deregulation of metabolites or enzymes including IDH, FH, SDH, and α-KGDHC are frequently observed in human cancer. Both the glycolysis and OXPHOS pathways have been identified as targets in cancer treatment.



In gliomas, there are both OXPHOS-dependent cells and glycolytic-dependent cells; the mechanism lies in the lactate dehydrogenase (LDH). The former expressed both LDH -A and -B isoforms, whereas the latter only expressed LDH-B, and LDH-B would be expected to be essential for the use of extracellular lactate to fuel cell activities [4]. Mitochondrial lipid homeostasis and transport between different organelles within the cell are crucial to mitochondrial function [5]. Phospholipids such as cardiolipin (CL) and phosphatidylethanolamine (PE), which are necessary for mitochondrial respiratory processes, can be synthesized by mitochondria [6]. DNA replication and RNA creation are critical activities in cell division and proliferation; their manufacture is enhanced in the late G1 phase [7]. To provide adequate energy and precursors for RNA production, a high ATP/ADP ratio must be preserved, with ATP content typically remaining over 1 mm [8].

2. MITOCHONDRIAL DYNAMICS IN CANCER

The process of mitochondrial biogenesis occurs mostly in healthy cells. Surprisingly, in malignant cells, increased oxidative phosphorylation and mitochondrial biogenesis were associated with invasion and metastasis [9]. It engages co-ordination between the mitochondrial and the nuclear genomes, in a complex and multistep process (Figure 1).

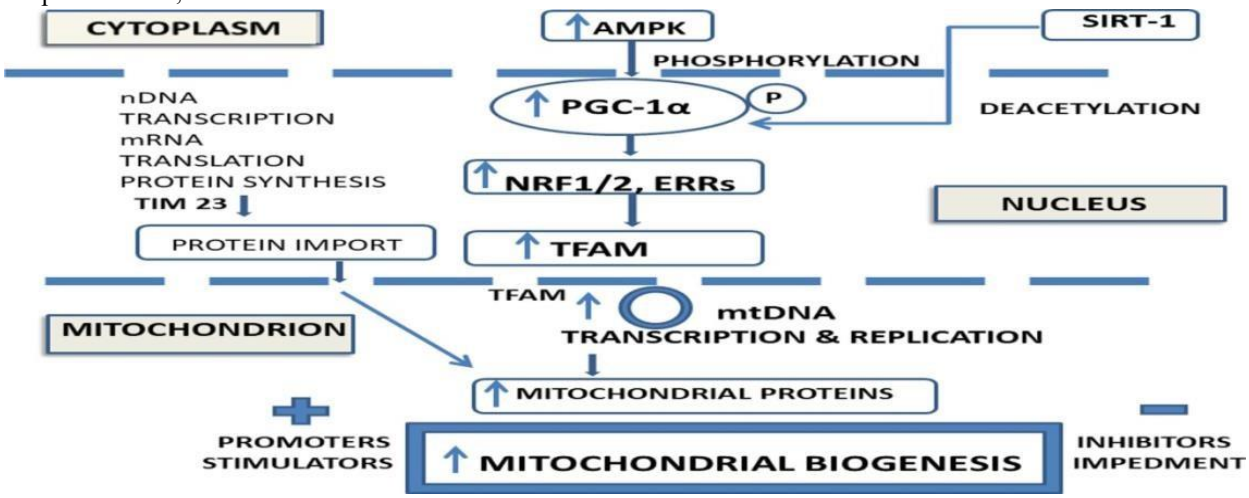


Fig 1: Dynamics in cancer

2.1. Mitochondrial biogenesis inductors/promoters: - Induction of mitochondrial biogenesis is connected with the activation of transcription factors that operate on mitochondrial genes, as well as an increase in mitochondrial protein translation at the local level. These effects are created in reaction to many natural compounds, such as 6gingerol (the major active component in the ginger extracts [10].

2.2. Mitochondrial biogenesis stimulators/inhibitors: -

In physiological situations, cells' responses to energy demands result in up- or down-regulation of transcription factors that stimulate and/or inhibit mitochondrial biogenesis. Pathology-related mitochondrial biogenesis problems include inhibited mitochondrial biogenesis, which requires stimulation of the declining process, or abnormally high levels of this process, which necessitates a decrease. The following are examples of effective stimulators of mitochondrial biogenesis: Formoterol is used in the treatment of podocytopathies [11].

2.3. Mitochondrial fission and fusion: -

Drp1(Dentatorubral–pallidoluysian atrophy) is primarily responsible for mediating the mitochondrial fission process. Drpl, a GTP-binding protein, can be recruited from the cytoplasm to the mitochondrial membrane with the assistance of mitochondrial receptor proteins Fis1(Fund for International Service Learning), MFF (Mitochondrial fission factor), MID49(Mitochondrial dynamics protein of 49kDa), and MID51(Mitochondrial dynamics proteins of 51kDa) [12].

Phosphorylation, ubiquitination, and sumoylation of Drp1 can modulate mitofission by affecting its stability and recruitment [13].

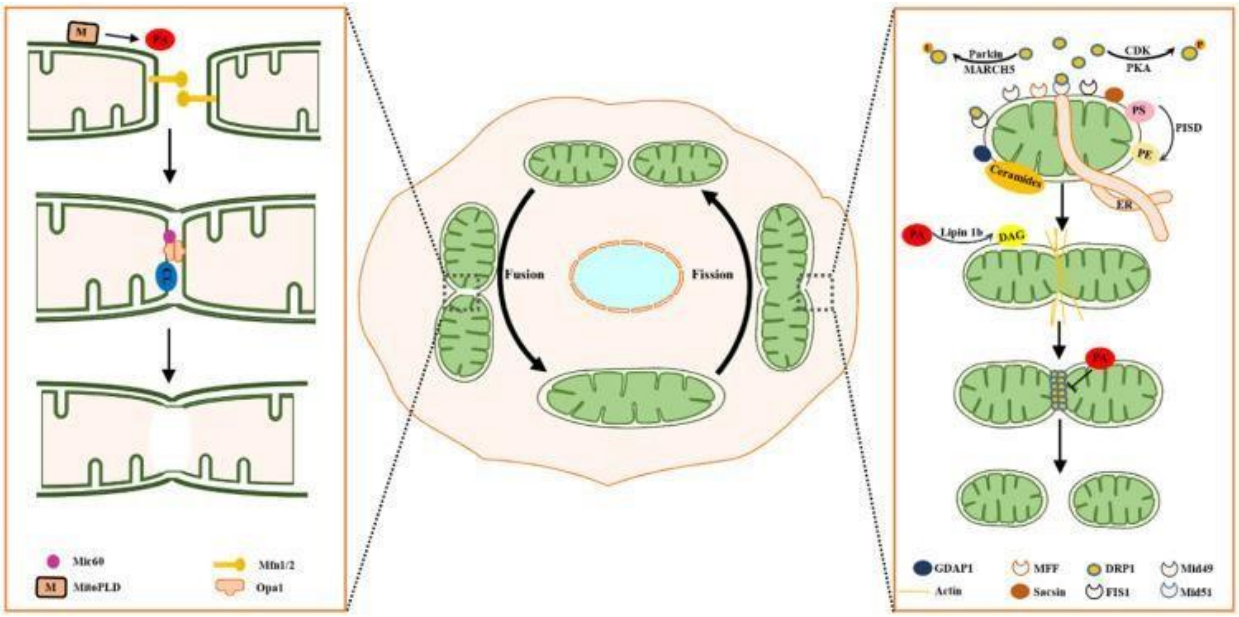


Fig 2: Mitochondrial fission and fusion

Mitophagy plays a varied role at various stages of tumour growth. Mitophagy supports normal cell metabolism and suppresses tumorigenesis in the early stages of carcinogenesis, but it enhances cell tolerance and promotes tumor growth in the later stages. The deletion, mutation, or functional change in numerous key genes causes the buildup of damaged mitochondria and suppression of mitophagy, which eventually induces cancer [14].

2.4. Role of mitochondrial dynamics in tumorigenesis and metastasis: -

- *Mitophagy and Carcinogenesis: -*

Mitophagy dysfunction is closely associated with carcinogenesis and tumor formation. Mitophagy's role varies with tumor stage [15]. Mitophagy supports normal cell metabolism and suppresses carcinogenesis in the early stages of tumor growth, but it enhances cell tolerance and promotes tumor development in the later stages [16]. Inhibiting mitophagy results in an increase in reactive oxygen species, which affects the function of cells, tissues, organs, and even entire systems [17]. Furthermore, the findings revealed that Parkin-deficient hepatocytes continue to multiply and have an antiapoptotic effect by upregulating endogenous follistatin, hence promoting cancer progression. PARK2 gene, situated on human chromosome 6 (FRA6E, 6q26), encodes Parkin protein and is particularly sensitive to gene mutations [18].

- *Mitophagy and cancer Metastasis: -*

During cancer growth, certain cancer cells switch aerobic mitochondrial respiration to glycolysis to meet their energy needs. This is known as the Warburg effect [19]. Cancer cells are often characterized by a Warburg effect, aberrant mitochondrial quality control, ROS production, modulation of cell redox state, and a lack of apoptotic signals [20]. In the process of mitophagy, Parkin enhances the degree of oxidative metabolism and inhibits the Warburg effect downstream of the p53 tumor suppressor, which is likely to be achieved by strengthening the integrity of the mitochondria [21]. As a p53 target gene, Parkin may have tumor-suppressive effect. Another study confirmed that Parkin reduced tumor migration and invasion in breast cancer via targeting HIF-1α for ubiquitination and destruction [22].

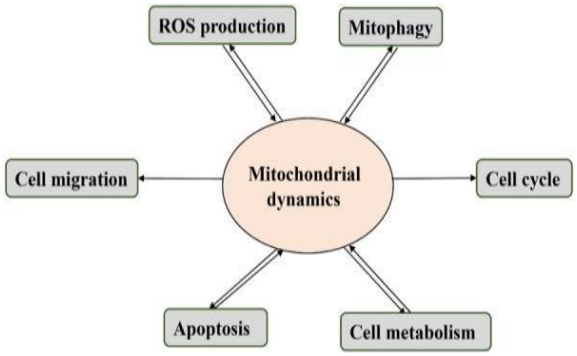


Fig 3: Biological functions of mitochondrial dynamics

3. MITOCHONDRIAL ROS AND CANCER

3.1. Reactive oxygen species (ROS) production in mitochondria: -

Reactive Oxygen Species (ROS) are unstable and reduced oxygen derivatives created during regular metabolic activities. ROS are primarily composed of superoxide anion (•O2-), singlet oxygen (1O2), hydrogen peroxide (H2O2), hypochlorous acid (HOCl), and hydroxyl radical. Due to their role in causing cell death, ROS is regarded as a tumor-suppressing agent when its creation is a mechanism that most chemotherapeutic drugs share [23]. On the contrary, because of their metabolic need for energy and biomass creation, cancer cells thrive in environments with higher levels of ROS generated from the mitochondria. Thus, it appears that focusing on mitochondria and adjusting the amount of ROS produced by them could be a useful strategy for causing cancer cells to die [24]. Mitochondrial damaging peptides are a class of peptides that use their self-assembly properties in conjunction with nanotargeted ligands to change their morphology in vivo and ultimately cause cell malfunction [25]. Malignant cells are afforded significant metabolic plasticity by some mitochondrial pathways that adjust to the distinct bioenergetic or biosynthetic metabolic functions of tumors [26]. In order to impact suitable interventions at an early and crucial stage of illness transition into resistance, it may be helpful to develop reliable and precise methods of monitoring ROS status both before and during treatments [27]. Higher levels of ROS may result from increased mitochondrial metabolic activity, particularly in drug-resistant situations, such as tumor cells resistant to cisplatin, and in people who do not react to cisplatin [28]. Reactive oxygen species (ROS) are produced in large quantities by the mitochondria, which have been linked to DNA damage and genetic instability [29]. A group of unstable, reactive, partially reduced oxygen derivatives are collectively referred to as "ROS." These include hydroxyl radicals (•OH), hydrogen peroxide (H2O2), superoxide anion (O2−), hypochlorous acid (HOCl), and singlet [30].

3.2 Dual role of ROS in cancer progressionand apoptosis:

Massive ROS buildup contributes to carcinogenesis. Because of the activation of the mitochondrial, P53, ER stress, and ferroptosis pathways in cancer, a significant buildup of ROS can prevent tumor cell development and cause cancer cell death [31]. When ROS levels exceed the tipping threshold, their carcinogenic activities in proliferation and invasion are converted to antitumor effects through the production of regulated cell death (RCD) programs, which primarily include apoptosis, necroptosis, and ferroptosis [32]. Initiating apoptosis is a crucial function of mitochondria, which are thought to be both a source and a target of ROS. Excessive quantities of ROS in the mitochondria can trigger intrinsic apoptosis, which releases cytochrome- C from the mitochondrial intermembrane gap into the cytosol [33]. As a transcription factor, TP53 promotes pro-apoptotic genes like BAX in colorectal cancer cells while suppressing the presence of survival proteins including MCL1, MYC, and BCL2 to induce intrinsic apoptosis [34]. Many of the conventional chemotherapeutic drugs used in clinical settings, such doxorubicin (DOX) and pirarubicin, can cause the formation of ROS inside cells and initiate the mitochondrial apoptotic pathway, which ultimately results in the death of cancer cells [35].

4. MITOCONDRIAL DNA IN CANCER:

Somatic mitochondrial DNA (mtDNA) mutations have become more common in primary human malignancies [36]. Most mutations in coding regions, but few result in major ammutations Mostino acid changes, raising doubts about their biological consequences [37]. The origins of somatic mtDNA mutations in human cancer, as well as their possible diagnostic and therapeutic implications, are reviewed [38,39].

4.1. Mitochondrial Genome Mutations in Cancer:

The nuclear genome encodes most of the protein subunits of the respiratory complexes, whereas the mt-genome encodes only 13 protein subunits. However, as oxidative phosphorilation (OXPHOS) activity occurs within the mt-environment, these organelles are in large extent the “power plant” of the cell. Therefore, mtDNA molecules are markedly exposed to reactive oxygen species (ROS) and are highly sensitive to them due to the lack of the protective action of histones. The replication and repair of mt-genomes depends on

nuclear genes and is error prone with bulky adducts being the lesion most inefficiently repaired, followed by slipped strand mispairing and ROS damage [40, 41, 42].

Due to the high rate of spontaneous mutations, the hundreds to thousands of mtDNA molecules found is a somatic cell have a diverse range of random polymorphisms [43]. It is still unclear how a particular mt-haplotype, out of the numerous haplotypes that most likely exist in the original transformed cell, could become frequent enough to be identified as a heteroplasmic or homoplasmic haplotype during the process of clonal expansion, given that the majority of cancers have a monoclonal origin [44]. To date, two theories have been put forth to explain why heteroplasmic or homoplasmic mtGI appears in cancer cells: (a) mutant mt-genomes have a selective advantage and take the place of wild mt-genomes in the subsequent divisions that result in the transformed cell's expansion [45] and (b) a single mitochondrion would regulate its own replication [46].

4.2. Implications of mtdna Alterations on Tumor Progression:

The circular, 16.5 kb double-stranded DNA molecule known as mtDNA differs from nDNA in a number of ways. MtDNA is exclusively inherited from the mother; although hundreds of mtDNA molecules can be found in mammalian cells, they only make up a small portion of the total DNA [47]. A mitochondrion includes five to ten copies of mtDNA, each of which can have a different composition due to the fact that mtDNA is polyploid. When a cell has homoplasmy, all of its mtDNA copies are the same, whereas heteroplasmy is a mixture of wild-type and variant copies [48]. Malignant cell transformation is a complex process that often consists of a series of events whereby a gene malfunction sets off a series of other gene malfunctions, resulting in modifications to the cell cycle that start the transformation. NGI is produced by mutation, epigenetic factors such aberrant methylation [49] and LOH in one or more genes of the cohort of DNA repair genes in a large number of hereditary and sporadic malignancies. According to the data in this review, all other tumors examined to date demonstrate varying rates and types of mtGI, with the exception of testicular germ cell malignancies [50]. The ability of mitochondria to eliminate large adducts from mtDNA molecules is severely lacking. As a result, mtDNA contains 10–50 times more adducts than nuclear DNA in cells treated with anticancer medications [51].

5. MITOCHONDRIA APOPTOSIS PATHWAY: -

5.1. Role of Mitochondria in intrinsic apoptosis pathway:

The intrinsic route, which is apoptosis mediated by mitochondria, is typified by the permeability transition pore (PTP) opening and cytochrome c being released, which permits the production of apoptosomes and the subsequent activation of the caspase cascade [52]. Thus, mechanisms that restore this function should reserve resistance in CSCs (cancer stem cells), as the cell's incapacity to elicit apoptosis might lead to treatment resistance [53]. Autophagic and apoptotic machinery are thought to converge mostly in mitochondria [54]. Apoptosis has been linked in the past to cellular reactions that relate aging and mitochondrial activity [55]. To safeguard with a recent study that found CISD-1 has an anti-apoptotic function in C. elegans [56]. We then evaluated the impact of the intrinsic, mitochondrially derived apoptotic pathway on longevity that is dependent on CISD-1. Pro-apoptotic BH3 (BCL2 homology domain 3)-only protein EGL-1, anti-apoptotic BCL2 ortholog protein CED-9, pro-apoptotic APAF1 ortholog protein CED-4, and caspase 9 ortholog protein CED-3 are the four primary components of the canonical route. CED-9 is attached to the OMM, where it binds to CED-4 to inhibit it. When EGL-1 binds to CED-9, its conformation is altered, enabling CED-4 to activate the executor caspase CED-3. By detecting abnormalities in mitochondrial activity, the CED-13 apoptotic pathway has been proposed to promote survival rather than death. CED-1 is an alternative BH3 negative regulator of CED-9 [57]. Pro and anti-apoptotic proteins are important regulators that belong to the B-cell lymphoma 2 (BCL-2) protein family. Healthy cells have a delicate balance of these regulators. In actuality, they have the power to either permanently prevent cells from undergoing apoptosis and creating a cancerous clone, or they can induce cells to irreversibly go toward cell death [58]. Since cancerous cells express the BCL-2 protein to significantly higher levels than normal cells, normal cells are not significantly affected by inhibitors that target this protein. An innovative treatment approach based on tumor pathophysiology is thus to block the

BCL-2 anti-apoptotic protein in order to overcome the tumor cell's resistance to apoptosis [59].

6. CONCLUSION

Being a subcellular organelle involved in metabolism, mitochondria are a key target because of their roles in cellular signalling pathways, proliferation, and apoptotic cell death. Numerous obstacles remain for the continued use of the mitochondria-targeting approach in the future. First, the most successful method has been found to be mitochondria-targeting CT, which destroys cancer cells by causing mtDNA damage and triggering apoptosis. Therefore, in cancer treatment, mitochondria are a desirable subcellular target. The effectiveness of anticancer therapy has been enhanced by the development of several mitochondria-targeted nanomedicines for chemotherapy, photothermal therapy, photodynamic therapy, chemodynamic therapy, Sonodynamic therapy, radiodynamic therapy, and combination immunotherapy. Finally, our analysis suggests that pharmacological approaches to modulate new tumor cell death pathways could be very beneficial in cancer treatment, and we recommend further research utilizing animal models to find further results. We also expect that additional clinical trials will be carried out to examine the application of novel cell death modulations in cancer patients.

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