Mitochondrial Dynamics in Cancer: - Mechanisms, Implications, and Therapeutic Opportunities

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***Abstract*—Mitochondria are key players in cellular homeostasis, not just as major ATP production site but also as regulators of apoptosis, metabolic signalling, and innate immunity. One of their characteristic elements is the ability to dynamically change shape, size, and distribution by way of two stringently controlled processes: mitochondrial fission (division) and fusion (merging). Both are referred to collectively as mitochondrial dynamics and are vital to preserving mitochondrial function and cellular integrity. In cancer, this dynamic balance is commonly disrupted. Tumour cells tend to have increased mitochondrial fission, leading to fragmented mitochondria that are conducive to fast proliferation, apoptosis resistance, and enhanced metastatic ability. Suppression of fusion, on the other hand, inhibits mitochondrial repair and enhances oxidative stress, thereby enhancing malignancy. Moreover, mitophagy (exclusive breakdown of defective mitochondria) and biogenesis (production of new mitochondria) mechanisms of mitochondrial quality control are frequently usurped by cancer cells to cope with both metabolic and therapeutics stress. Considering the key role played by mitochondrial dynamics in the pathophysiology of cancer, these activities offer strong candidate targets for new therapeutic interventions.**

Pharmacological inhibition of excessive fission—e.g., by DRP1 inhibitors—or improvement of fusion by upregulation of proteins such as mitofusin-2 (MFN2), has been effective in preclinical models. Disrupting mitochondrial homeostasis in cancer cells by these manipulations may inhibit tumour growth, sensitize malignant cells to standard therapies, and eventually lead to improved patient outcomes. Greater insights into mitochondrial dynamics and their control within the tumour microenvironment would open avenues for development of more targeted and effective therapies against cancer.

***Index Terms*—Mitochondrial fission, Mitochondrial dynamics, Mitochondrial fusion, Mitochondrial biogenesis, Mitophagy,**

I. INTRODUCTION

Mitochondria are complex organelles long known to be "powerhouses" of the cell due to their central function in ATP generation through OXPHOS (oxidative phosphorylation). Aside from energy production, they play a crucial part in various cellular processes such as regulation of apoptosis, metabolic signalling, and innate immunity. Such diversity makes mitochondria regulators of cell fate, particularly in disease states like cancer.

Mitochondria catabolize substrates such as glucose and fatty acids by TCA (tricarboxylic acid) cycle to yield NADH and $FADH_2$, which energize the ETC (electron transport chain) located in inner mitochondrial membrane. This is followed by ATP production through oxidative phosphorylation, a major cellular energy source (Nelson et al., 2017; Alberts et al., 2015). ATP maintains its essential biological functions, such as proliferation, repair, motility, and intracellular communication. Mitochondria are key regulators of intrinsic apoptotic pathway. In response to stress or damage signals, MOMP (mitochondrial outer membrane permeabilization), leading to the release of pro-apoptotic factors, including cytochrome c, into cytosol, is achieved. This initiates caspase activation as well as choreographs programmed cell death in a regulated, non-inflammatory process (Green & Kroemer, 2004; Elmore, 2007). Evasion of this pathway is a characteristic of cancer. As a spin-off from respiration, mitochondria generate ROS (reactive oxygen species), which, at physiological concentrations, act as second messengers in signalling cascades. At high levels of ROS generation, oxidative stress leads to damage to DNA, proteins, and lipids. Chronic oxidative stress has been implicated in aging, inflammation, and carcinogenesis (Finkel et al., 2011; Murphy et al., 2009).

II. MITOCHONDRIAL DYNAMICS AND CANCER PROGRESSION

Dynamic character of the mitochondria, with a constant process of fission as well as fusion, is significant in maintaining mitochondrial integrity in addition to cellular plasticity. These processes, all collectively known as mitochondrial dynamics, enable mitochondria to adapt to metabolic requirements, eliminate defective parts, and maintain adequate distribution during cell division. The mitochondrial matrix, where the TCA cycle takes place, supplies the reducing equivalents (NADH, $FADH_2$) for ATP production through the ETC. Shifts in these dynamics have far-reaching consequences in oncogenesis. Enhanced fission, promoted by proteins such as DRP1, and diminished fusion, facilitated by MFN1/2 and OPA1, are prevalent in cancer cells and lend themselves to mitochondrial fragmentation, increased proliferation, and resistance to apoptosis (Vyas et al., 2016; Archer et al., 2013). Far from their previous characterization as static structures, mitochondria are now revealed to be very mobile and morphologically plastic. In resting cells, they tend to be organized as interconnected networks of tubes, while in cancer cells or when stressed, they break up into separate units. For instance, mitochondria in fibroblasts are usually long filaments, while those in hepatocytes are round (Youle & van der Bliek, 2012; Chan et al., 2012).

Mitochondrial DNA (mtDNA) integrity is important for mitochondrial function because it codes for key parts of the ETC. Experimental findings suggest that reduction in mtDNA copy number or existence of pathogenic mutations is associated with more virulent cancer phenotypes. As an example, colorectal and prostate cancer cells that have lost mtDNA are more invasive (Reznik et al., 2016). Analogously, APC-mutant mice that have lower mtDNA levels due to

TFAM heterozygosity exhibits enhanced intestinal tumorigenesis (Sai et al., 2019). Somatic mtDNA mutations were reported in an array of cancers including those of bone, kidney (renal adenocarcinoma), thyroid, colon, head and neck, and prostate (Brandon, Baldi, & Wallace, 2006). The biological relevance of such mutations is yet to be explored. Yet, hybrid models— created by combining enucleated donor cells with recipient nuclei—have allowed for the segregation of mitochondrial and nuclear genomic contributions under the same nuclear backgrounds (King & Attardi, 1989), which has given significant insights into the oncogenic potential of mtDNA aberrations.

2.1. Radiation-Induced Mitochondrial Effects

Radiation therapy has strong impacts on mitochondrial metabolism and structure, governing survival, cancer cell metabolism, and therapeutic response. Mitochondria adapt dynamically to radiation stress through multiple interdependent processes, which are biogenesis, fission-fusion equilibrium, regulation of apoptosis, and metabolic reprogramming.

Mitochondrial Biogenesis

Ionizing radiation has the ability to stimulate mitochondrial biogenesis, in a large part by enhancing peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), master regulator of mitochondrial gene expression and replication. This adaptive response could increase metabolic resilience of cancer cells to support them to maintain energy production under oxidative and therapeutic pressure (LeBleu et al., 2014). Enhanced mitochondrial mass was detected within irradiated tumour cells, which could be responsible for therapy resistance.

Mitochondrial Fusion and Fission

Radiation affects mitochondrial dynamics by interfering with balance between fission as well as fusion. Fission, which is mediated mostly by DRP1 (dynamin-related protein 1), results in fragmentation of the mitochondria, which correlates with augmented cell survival, apoptosis evasion, and therapy resistance in various cancers (Zhang et al., 2017; Archer et al., 2013). Fusion, under the regulation of MFN1(mitofusin-1), MFN2(mitofusin-2), and OPA1(optic atrophy protein 1), allows mitochondria to preserve functional integrity by exchanging contents and resisting damage. Pathological dysregulation after radiation can result in dysregulated mitochondrial quality control and aberrant bioenergetics. Apoptosis Regulation Mitochondria are key regulators of intrinsic apoptotic pathway. Radiation-induced MOMP leads to the release of cytochrome c and other pro-apoptotic proteins, triggering caspase activation and also programmed cell death. However, cancer cells tend to develop resistance to this pathway through changing mitochondrial dynamics or manipulating apoptotic regulators (Tait & Green, 2010; Youle & Strasser, 2008). Such resistance is usually associated with a

fragmented mitochondrial morphology and decreased expression of pro-apoptotic factors.

Metabolic Reprogramming

Metabolically, tumour cells are plastic and tend to revert to aerobic glycolysis (Warburg effect) to enable rapid growth. Radiation has the potential to further modulate this reprogramming by changing mitochondrial dynamics, subsequently influencing ATP production and metabolic flux. Mitochondrial-shaping protein variations in activity or expression, such as MFN1/2, OPA1, and DRP1, have a direct consequence on tumour cell bioenergetics and biosynthetic potential (Vyas et al., 2016; Ward & Thompson, 2012). Fusion promotes repair and maintenance of mitochondria, whereas fission aids in the elimination of dysfunctional components and Redistribution during cell division—processes both essential for adaptation to the metabolic needs of the cell. Collectively, these mechanisms highlight the significance of mitochondrial plasticity to radiation response. Elucidating the molecular regulation of these mitochondrial alterations might provide new paradigms that sensitize tumours to radiotherapy and enhance treatment outcome, as demonstrated in Table 2.1.

Table 2.1. Radiation Effect of Mitochondrial Dynamics

Mitochondrial Process	Radiation Effect	Molecular Markers/Pathways Affected	Functional Consequences	References/Notes
Fission	↑ Increased	↑ DRP1 (Dynamin-related protein 1), FIS1	Enhanced fragmentation, mitochondrial dysfunction	Common in response to oxidative stress from radiation
Fusion	↓ Decreased	↓ MFN1, MFN2 (Mitofusins), ↓ OPA1	Loss of mitochondrial network integrity, energy failure	Leads to imbalance in fission/fusion
Biogenesis	↓ Decreased (dose dependent)	↓ PGC-1α, NRF1, TFAM	Reduced mitochondrial mass, impaired ATP production	Particularly noted in chronic exposure

Mitophagy	↑ Increased (early phase) / ↓ Decreased (later phase or high dose)	↑ PINK1, Parkin (early); impaired autophagy flux (late)	Removal of damaged mitochondria (early), accumulation of dysfunctional mitochondria (late)	Biphasic response depending on dose/time
ROS Production	↑ Increased	↑ mtROS, ↑ NOX enzymes	Oxidative stress, DNA damage, signalling alterations	ntral mediator of mitochondrial and cellular damage
Mitochondrial Membrane Potential (ΔΨm)	↓ Decreased	Loss of ΔΨm	Apoptosis induction, energy crisis	Often correlates with cytochrome c release
Apoptosis Pathways	↑ Activated	↑ Bax, ↓ Bcl-2, ↑ Caspase-9, ↑ Cytochrome c release	Intrinsic apoptosis pathway activation	Mitochondria dependent apoptosis is frequently triggered by radiation

2.2. Regulators of Mitochondrial Dynamics: Fusion and Fission Proteins

Mitochondrial fusion and fission are tightly controlled by a conserved set of GTPase proteins that orchestrate a remodelling and functional adjustment of the mitochondrial network. These activities are critical for maintaining mitochondrial integrity, distribution, and quality control.

2.2.1. Mitochondrial Fusion**:** - Mitochondrial fusion is a process where 2 mitochondria merge to create a larger, healthier organelle.0 This maintains mitochondrial function by allowing the contents to mix such as proteins and mitochondrial DNA, which can dilute damage and enhance energy production. The most important proteins involved are MFN1 & MFN2, which fuse outer membranes, and OPA1, which fuses inner membranes. Fusion plays a significant role in maintaining cellular energy homeostasis, guarding against mitochondrial stress, and promoting overall cell survival. In healthy cells, this process is regulated and synchronized with fission to maintain mitochondria in proper working condition. But this balance is compromised in cancerous cells. Some cancer cells indicate enhanced fusion, which protects them against stress, prevents cell death, and supplies them with high energy demands. Overexpression of the fusion proteins OPA1 and MFN2 was correlated with tumour development as well as unfavourable outcomes in some cancers (Chen & Chan, et al., 2017; Xin, Zhang, & Chen, et al., 2018). Fusion Proteins

• Mitofusin 1 (MFN1) and Mitofusin 2 (MFN2): MFN1 and MFN2 are dynamin-like GTPases on outer mitochondrial membrane. They bring about a tethering as well as later outer membrane fusion between neighbouring mitochondria. The two proteins have overlapping functions, with MFN2 also being involved in endoplasmic reticulum–mitochondria tethering, with other functions in signalling and metabolism.

• Optic Atrophy 1 (OPA1): OPA1 is an inner mitochondrial membrane-anchored dynamin GTPase. It supports a fusion of inner mitochondrial membranes and is critical in maintaining cristae structure and mitochondrial respiratory efficiency. OPA1 also acts in inhibiting release of pro-apoptotic factors during stress conditions.

Fusion allows mitochondrial contents to commingle, including mitochondrial DNA, proteins, and metabolites, supporting functional complementation of partially damaged mitochondria. This action is especially protective under cellular stress, as it supports mitochondrial membrane potential and bioenergetics capacity.

2.2.2. Mitochondrial Fission: Mitochondrial fission is dynamic cellular phenomenon in which single mitochondrion splits into 2 distinct organelles. This procedure is largely mediated by GTPase Drp1, which is recruited to mitochondrial outer membrane by adaptor proteins including Mff, MiD49, and MiD51. When recruited, Drp1 aggregates into oligomeric formations that narrow and cleave a mitochondrion, a process that is further assisted by interactions with actin cytoskeleton and the endoplasmic reticulum. Physiologically, mitochondrial fission plays a crucial role in maintaining cellular homeostasis Fission makes it possible to separate dysfunctional or impaired mitochondrial fragments so that they can be eliminated through mitophagy.

Excessive fission is also essential during cell division to provide appropriate mitochondrial distribution. Yet, aberrant fission is often observed in cancerous cells and is also associated with enhanced invasiveness, apoptosis resistance, and metabolic adaptation. Mitochondrial fission is a crucial process that guarantees adequate mitochondrial distribution during cell division, promotes energy homeostasis, and allows the degradation of defective mitochondrial fragments through mitophagy. This tightly controlled process involves a complex network of proteins that regulate the constriction and division of mitochondrial membranes. Although crucial for cellular health, this process is usually dysregulated in cancer cells and becomes overactive. Overactive mitochondrial fission sustains cancer cell proliferation, increases metastatic ability, and sustains viability under stress like hypoxia or chemotherapy. This is due to the fact that frequent fission increases energy generation, assists in evading apoptosis, and supports cancer cell movement and invasion into tissue. For this reason, increased mitochondrial fission is associated with aggressive tumour phenotypes and treatment resistance. Consequently, inhibiting mitochondrial fission has been as a promising therapeutic strategy to sensitize cancer cells as well as enhance treatment efficacy (Chen & Chan, et al., 2017; Rehman et al., 2012; Senft & Ronai, et al., 2016). Fission Proteins • Dynamin-related Protein 1 (DRP1): DRP1 is a cytosolic GTPase with key role in mitochondrial fission. Activated DRP1 moves to outer mitochondrial membrane, where it oligomerizes and forms spiral structures that wrap around mitochondria. DRP1 produces mechanical force through GTP hydrolysis to constrict and finally cut a mitochondrial membrane, splitting one mitochondrion into two daughter organelles.

•Mitochondrial Fission Factor (MFF), Fission 1 (Fis1), Mitochondrial Dynamics Protein of 49 and 51 kDa (MiD49 and MiD51): These outer mitochondrial membrane resident adaptor proteins act as docking sites for DRP1. They promote recruitment, assembly, as well as activation of DRP1 to precise fission locations. MFF acts as a major receptor for DRP1, whereas MiD49 and MiD51 fine-tune localization. Fis1, while less active in mammals than yeast, also has the ability to support DRP1 recruitment under specific conditions. Fission of mitochondria plays an important role in a number of cellular activities:

•Cell growth: Secures an even distribution of mitochondria during cell division. •\energy homeostasis: Regulates the size and number of mitochondria in relation to metabolic requirements.

•Quality control: Segregates defective mitochondrial sections to be degraded through mitophagy, maintaining mitochondrial integrity.

Under disease conditions like cancer, increased fission, which may be stimulated by enhanced DRP1 activity, has been linked with tumour growth, metabolic reprogramming, and apoptosis resistance.

Mitophagy, or selective degradation of mitochondria via autophagy, plays a critical role in the maintenance of cellular homeostasis, especially during mitosis, under stress conditions, as well as in the control of mitochondrial quality. During mitosis, mitophagy ensures proper distribution of mitochondria to daughter cells through promotion of mitochondrial fission, a process controlled by cyclin B1–CDK1 and DRP1 phosphorylation. Coordination plays a significant role in equal mitochondrial inheritance; also, it is involved in cancer progression because it is involved in cell division and proliferation.

Mitophagy is used as a quality control mechanism in stress responses through the elimination of damaged mitochondria. In hypoxia or nutrient starvation conditions, mitophagy occurs via pathways with PINK1/Parkin and receptors such as BNIP3 and NIX, controlled by stress-activated transcription factors HIF-1 and p53. In addition, mitophagy forms an essential part of mitochondrial quality control through identification and elimination of damaged mitochondria to avoid accumulation of non-functional organelles. Such a point is where mitophagy comes into play, where defective mitochondria are not just removed but the biosynthesis of new mitochondria is encouraged, thus ensuring mitochondrial homeostasis. The coordination between mitophagy and mitochondrial biogenesis is fundamental to cellular adaptation to metabolic stress and demand. Cumulatively, mitophagy is an essential process for cellular adaptation and survival that maintains mitochondrial integrity during cell division, prevents damage during stress, and maintains mitochondrial function through quality control mechanisms (Palikaras, Lionaki, & Tavernarakis, et al., 2018; Vara-Perez, Felipe-Abrio, & Agostinis, et al., 2019).

2.3. Mitophagy: Guardian of Mitochondrial Quality and Cellular Health

Mitophagy is a specialized form of autophagy that degrades defective or damaged mitochondria. It is crucial for maintaining mitochondrial quality control. Mitophagy ensures a maintenance of healthy mitochondria and avoids an accumulation of faulty organelles that can generate toxic ROS as well as disrupt cellular energy metabolism. Through the elimination of damaged mitochondria, mitophagy saves cellular energy, limits oxidative stress, and maintains cellular homeostasis. Effective mitophagy is therefore critical for avoiding the development of many diseases, including neurodegenerative disease, cancer, as well as age-related disease (Palikaras, Lionaki, & Tavernarakis, 2018; VaraPerez, Felipe-Abrio, & Agostinis, 2019). The PINK1/Parkin Pathway: Central Regulator of Mitophagy - Among the most significant regulators of mitophagy is PINK1/Parkin pathway.

Normally, PINK1 (PTEN-induced kinase 1) is imported quickly into healthy mitochondria as well as degraded. When mitochondria are depolarized due to injury, PINK1 accumulates on the outer mitochondrial membrane, acting as a molecular signal for mitophagy induction. Such accumulation brings Parkin, an E3 ubiquitin ligase, from the cytosol. PINK1 phosphorylation activated Parkin ubiquitinates many of the outer mitochondrial membrane proteins, essentially marking damaged mitochondria for autophagy destruction. This process is crucial in maintaining mitochondrial integrity as well as avoiding cellular dysfunction. Dysfunction in the PINK1/Parkin pathway has a close connection with pathogenesis of Parkinson's disease, thereby underscored as crucial in neuroprotection and cellular health (Palikaras et al., 2018; Vara-Perez et al., 2019). Mitochondria are point-of-entry hubs for cellular stress response through the regulation of metabolic processes to sustain survival in stressful conditions such as hypoxia, nutrient starvation, or exposure to toxins.

In mitophagy, cells adapt mitochondrial function to suit shifting environmental and metabolic demands. It is coordinated by principal signalling molecules like AMPK (AMP-activated protein kinase) and HIF-1(hypoxia inducible factor-1), which monitor energy status and oxygen levels, respectively, and trigger mechanisms to re-establish cellular homeostasis (Zhang et al., 2021). Mitophagy has a context-dependent dual function in cancer, acting as a tumour suppressor and as a survival strategy for cancer cells. During early tumorigenesis, mitophagy—especially through the PINK1/Parkin pathway—has a defensive role by removing defective mitochondria, thus minimizing levels of ROS and ensuring mitochondrial quality.

This prevents genomic instability and cancerous transformation.

But in advanced tumours, mitophagy promotes cancer progression. By constantly eliminating damaged mitochondria, mitophagy allows cancer cells to

survive with adverse conditions, such as hypoxia along with nutrient deprivation, which are prevalent in tumour microenvironment. This metabolic adjustment makes the tumour more resilient, facilitates growth, and helps build resistance against chemotherapy and other treatments. The step-by-step mechanism of mycophagy through the PINK1/Parkin pathway, from sensing mitochondrial damage to autophagy degradation, is depicted in figure 2. Thus, mitophagy is a double-edged sword in cancer biology—inhibiting tumour initiation and promoting tumour survival during later phases. A critical appreciation of such duality is essential for development of successful cancer therapy that targets mitochondrial dynamics and quality control (Li, Yang, Hu, Ling, & Zhang, 2021).

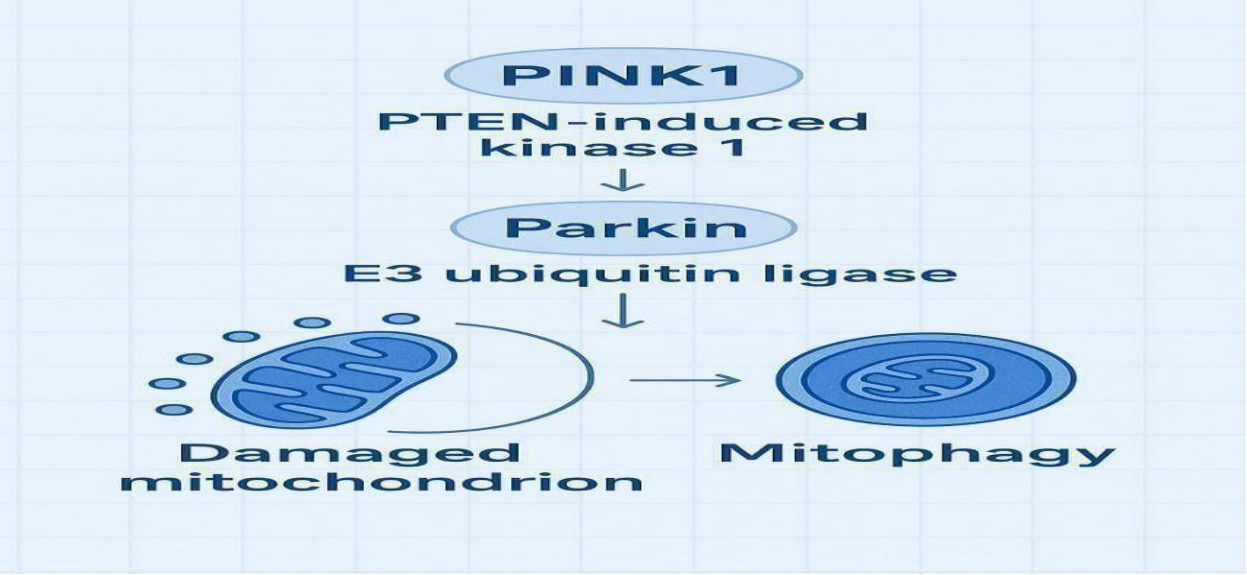

Figure No. 2: Mitophagy Pathway

2.4. Mitochondrial Biogenesis: Coordinating Energy Demands and Cellular Health Mitochondrial biogenesis is cellular process of generating new mitochondria to accommodate augmented energy requirements, particularly under conditions of physiological stress, growth, exercise, or cellular maintenance. This tightly regulated phenomenon provides a sufficiency supply of operational mitochondria to sustain ATP generation and cellular metabolism. It complements mitophagy, selective elimination of defective mitochondria, for the preservation of mitochondrial homeostasis. At the molecular level, mitochondrial biogenesis is regulated by a number of regulatory proteins and transcription factors, and master regulator being PGC1α(Peroxisome proliferator-activated receptor gamma coactivator 1-alpha). It induces the expression of nuclear-encoded mitochondrial genes and thus boosts synthesis of proteins required for mitochondrial replication and function. This process plays a particularly important role in energy-requiring tissues, such as skeletal muscle, cardiac muscle, and brain (Scapula, Vega, & Kelly et al., 2012).

Regulators of Mitochondrial Biogenesis: Regulation of mitochondrial biogenesis is a coordinated set of proteins that respond to energy status and stimulate gene expression cascades, which are:

•PGC-1α: Central coordinator that sequesters transcription factors like NRF1 & NRF2 and results in the expression of genes necessary for mitochondrial structure as well as function. It is stimulated in response to physiological stimuli, such as cold exposure, exercise, and caloric restriction.

- TFAM (Mitochondrial Transcription Factor A): Functions downstream of PGC-1α and has a pivotal role in mitochondrial DNA (mtDNA) replication as well as transcription. TFAM ensures that newly formed mitochondria contain functional genomes necessary for oxidative phosphorylation.
- AMPK (AMP-Activated Protein Kinase): Serves as cell's energy sensor. In response to low ATP levels, AMPK activates PGC-1α, thereby stimulating

mitochondrial biogenesis and restoring energy balance.

•SIRT3: An enzyme deacetylase within the mitochondria, which modulates the activity of mitochondrial enzymes and improves oxidative capacity. It is a modulator that interacts and activates AMPK and PGC-1α, augmenting the mitochondrial biogenesis pathway and energy efficiency.

These proteins together create a feedback-regulated axis that maintains mitochondrial quantity and quality under basal and stress-induced conditions.

Mitochondrial Dynamics in Cancer: Biogenesis and Adaptation to Metabolic Stress Cancer cells exhibit modified metabolic profiles to maintain rapid proliferation and survival under stress. Warburg effect is an indicator of cancer metabolism. It is a phenomenon when cells use glycolysis to produce energy rather than oxidative phosphorylation, even in the presence of oxygen. Such a change in metabolism enables cancer cells to not only generate ATP but also biosynthetic precursors required for growth. To fuel this changed metabolism, cancer cells reprogram mitochondrial function by dynamically regulating mitophagy and mitochondrial biogenesis. While mitophagy clears the way for dysfunctional mitochondria to decrease oxidative stress, mitochondrial biogenesis provides the supply of effective organelles to sustain energy generation. Regulators such as PGC-1α, AMPK, and SIRT3, which are normally linked to metabolic well-being, paradoxically facilitate cancer cell survival in adverse microenvironments. By facilitating metabolic flexibility, they enable tumour cells to survive in hypoxic or starvation environments and make them resistant to therapies aimed against mitochondrial metabolism (Vyas et al., 2016). Mitochondrial biogenesis, together with mitophagy, constitutes a mechanism for cellular energy homeostasis. The network comprising

PGC-1α, TFAM, AMPK, and SIRT3 not only sustains normal physiology but also pathological processes like cancer.

III. MITOCHONDRIAL DYNAMICS AND CANCER BIOLOGY

Mitochondrial dynamics, which include coordinated fission (division) and fusion (merging) processes of mitochondria, play essential roles in maintaining mitochondrial integrity, bioenergetics functions, as well as cellular survival. In normal cells, equilibrium between fission and fusion sustains mitochondrial shape, supports energy generation, and allows for the clearance of damaged mitochondria by mitophagy. But in cancer cells, the balance is often lost, causing metabolic reprogramming and increased tumorigenicity (Seo et al., 2019). Dysregulation of mitochondrial dynamics plays a major role in tumour initiation and tumour progression. Cancer cells often display enhanced mitochondrial fission and decreased fusion, facilitating quick proliferation, high migration, and tumour cell resistance to cellular stress and therapy. Overactive fission, primarily mediated by Drp1, enables the segregation of damaged mitochondria for elimination while ensuring mitotic advancement and adaptation to hypoxia. By contrast, defective fusion hinders mitochondrial repair and genomic stability. All these changes collectively provide a permissive condition for tumorigenesis (Kasha Tus et al., 2018).

Mitochondrial dynamics have cancer-type–specific changes that play a role in tumorigenesis and disease progression. In breast cancer, increased mitochondrial fission along with inhibited fusion has been found to be associated with accelerated proliferation of tumour cells, increased aggressiveness, and chemotherapy resistance. In colorectal cancer as well, dysregulation of both fission and fusion mechanisms enhances tumour development and maintains metastatic potential, highlighting the dual function of abnormal mitochondrial remodelling in disease progression. In lung cancer, the overexpression of fission-related proteins like dynamin-related protein 1 (DNM1L/DRP1) in combination with the downregulation of fusion mediators like mitofusin 1 (MFN1) leads to the fragmented mitochondrial morphology, thereby increasing cancer cell survival, adaptability, and invasive capacity. Together, these findings emphasize how differences in mitochondrial fission–fusion machinery not only differ between malignancies but actually mandate tumour aggressiveness and therapeutic resistance, rendering them appealing yet complicated targets for cancer therapy.

These changes toward a pro-fission phenotype are uniformly correlated with more aggressive disease and

worse patient prognoses (Zhang, Li, & Wang et al., 2020).

Mutations in mtDNA are strongly correlated with cancer formation. These mutations disable OXPHOS, enhance ROS generation, and also facilitate metabolic reprogramming. A hallmark effect is the transition from OXPHOS to glycolysis under normoxic conditions, referred to as the Warburg effect. Such a transition not only sustains anabolic growth but also remodels the tumour microenvironment and modulates immune reaction. Therefore, mtDNA mutations are both drivers and indicators of oncogenesis (Lee & Wei et al., 2009). Warburg Effect and Metabolic Reprogramming- To meet high energy as well as biosynthetic requirements for rapid growth, cancer cells alter their utilization of energy. Rather than depending on OXPHOS, most tumours use glycolysis, even under conditions of plenty of oxygen, effect referred to as Warburg effect. Though less effective in ATP production, glycolysis supplies intermediates for nucleotide, lipid, and amino acid synthesis, thus maintaining cell growth and survival under oxygen- and nutrient-limited conditions (Vander Heiden, Cantley, & Thompson et al., 2009). Mitochondrial fission and mitophagy are pivotal in metabolic reprogramming in cancer. Fission mediated by Drp1 enables division of defective mitochondria and drives the transition to glycolysis. In parallel, mitophagy facilitates selective removal of dysfunctional mitochondria, preventing accumulation of ROS as well as promoting cell survival. Such coordinated modulation of mitochondrial architecture and dynamics allows tumours to survive hypoxia, resist apoptosis, and preserve energy homeostasis (Toyama & Youle et al., 2011). Cytokine Secretion and Immunosuppression- Tumours use cytokine signalling to repress antitumor immune responses. Immunosuppressive cytokines such as IL-10, TGFβ, & IL-6 secreted by cancer cells and stromal elements suppress the function of cytotoxic T cells and enhance expansion of regulatory T cells (Trigs) and MDSCs (myeloid-derived suppressor cells).

These alterations establish an immunosuppressive tumour microenvironment under which cancer cells can escape immune recognition as well as resistance to immunotherapy. Targeting cytokine networks is an exciting approach to re-establish immune surveillance and improve therapeutic results (Kumar, Patel, Tcyganov, & Gabrilovich et al., 2016). Radiation Therapy and Tumour Microenvironment -Modulation Radiation therapy (RT) does not only because immediate DNA damage to tumour cells but also alters the tumour microenvironment. RT provokes release of DAMPs (damage-associated molecular patterns) and inflammatory cytokines, triggering tumour antigen presentation and activation of immunity. Yet, RT can also promote immunosuppressive mechanisms via enhancing TGF-β release and overexpression of immune checkpoint proteins such as PD-L1, creating an immunosuppressive environment. Furthermore, senescence induced by RT in stromal fibroblasts enhances cytokine secretion such as CCL2, attracting MDSCs and tumour-associated macrophages (TAMs), which further suppress immunity (Deng et al., 2014). Mitochondria play a critical role in modulating cellular responses to radiation. As dysregulated mitochondrial dynamics, impaired apoptosis pathways, and increased mitophagy underlie radio resistance. Cancer cells that have defective mitochondria resist radiation-induced apoptosis, sustain bioenergetics homeostasis through metabolic adaptations, and eliminate radiation-damaged mitochondria, enabling unlimited proliferation. Disrupting mitochondrial processes like fission, oxidative metabolism, and mitophagy has the potential to sensitize tumour cells to radiation and enhance therapeutic outcomes (Desai, Kaur, & Rani et al., 2020). DNA damage resulting from radiation or chemotherapeutic agents usually triggers the DNA damage response (DDR) and initiates apoptosis when the damage is irreversible. However, cancer cells usually develop resistance through inhibiting apoptosis by overexpression of anti-apoptotic proteins such as Bcl-2, as well as through activation of prosurvival signals such as PI3K/AKT, Fib, & MAPK/ERK. In addition, numerous tumours maintain partial DDR function—sufficient to endure DNA insults but not adequate to avoid mutagenesis—thereby encouraging tumour as well as resistance evolution. Therapeutic targeting of these mutated survival and repair processes is a major emphasis towards the success in breaking treatment resistance as well as in optimizing cancer outcomes (Hanahan & Weinberg et al., 2011).

IV. THERAPEUTIC IMPLICATIONS OF TARGETING MITOCHONDRIAL DYNAMICS IN CANCER

The mitochondrial dynamics targeting in the therapy is a new and promising approach in oncology. Mitochondria are key modulators of cell metabolism, survival, and stress responses—processes often usurped by cancer cells to support growth, resist treatment, as well as avoid apoptosis. Through the modulation of proteins that participate in mitochondrial fission, fusion, mitophagy, and biogenesis, scientists hope to interrupt the intrinsic survival mechanism of tumour cells instead of attacking their DNA or cell membranes directly (Sabouny & Shutt et al., 2020). This new direction promises potential for creating more efficient and less toxic cancer therapies. The proteins DRP1, MFN2, and OPA1 are central regulators of mitochondrial morphology, as illustrated in Figure 3. Therapeutic inhibition of DRP1 has shown promise in reducing tumour growth and sensitizing cancer cells to chemotherapy and radiotherapy. In contrast, restoration or activation of MFN2 and OPA1 can restore dysfunctional mitochondria and inhibit tumorigenic signalling.

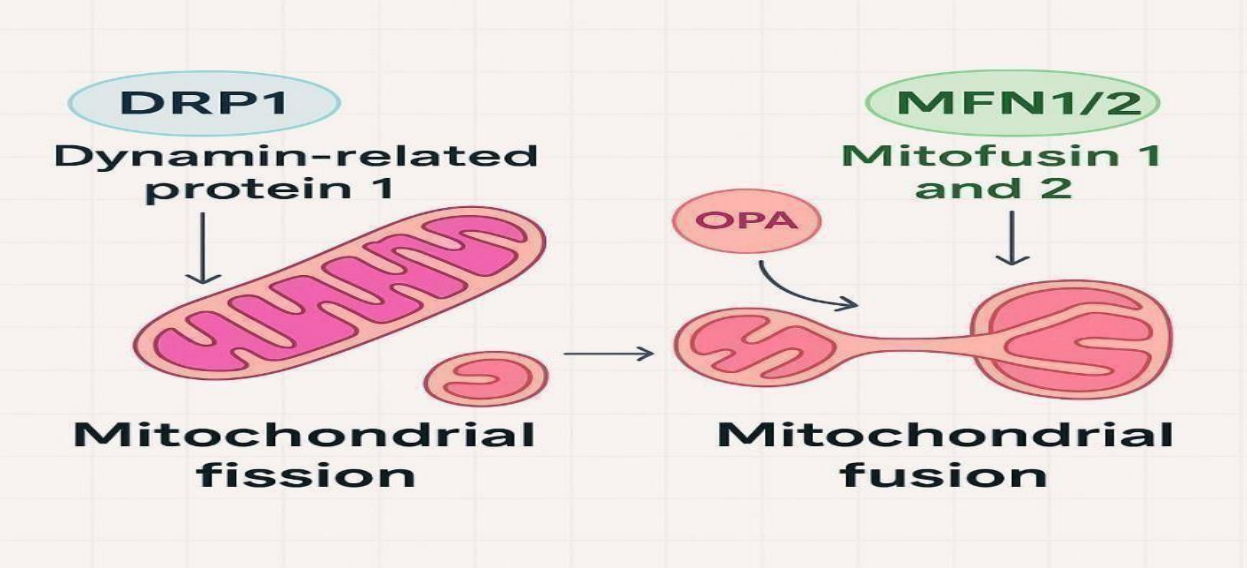

Figure No. 3: *Role of DRP1, OPA1, and MFN1/2 in mitochondrial dynamics and cancer progression.*

Mitochondrial quality control depends on the dynamic equilibrium between mitophagy (elimination of dysfunctional mitochondria) and mitochondrial biogenesis (formation of new mitochondria). Cancer cells tend to use these processes to survive in hostile microenvironments, including hypoxia or starvation. Blocking overactive mitophagy can block cancer cells from eliminating dysfunctional mitochondria, leading to increased oxidative stress, and apoptosis. Downregulation of biogenesis can decrease mitochondrial mass and bioenergetics capacity, making cancer cells more sensitive to treatment-induced stress. Strategic modulation of these pathways can compromise the tumour's ability to adapt, thereby enhancing the efficacy of existing treatments. A number of preclinical and early-phase clinical studies are ongoing in order to assess therapeutic value of the targeting of mitochondrial dynamics: Experimental drugs that target DRP1, MFN2, and OPA1 are currently tested for their ability to limit tumour growth as well as to enhance sensitivity towards chemotherapy and radiotherapy.

Mitophagy inhibitors, including PINK1/Parkin pathway regulators, are investigated for their ability to enhance mitochondrial stress and promote cancer cell killing. Combination approaches, combining mitochondrial modulators with standard cancer treatments, exhibit synergistic activity in preclinical models. These studies form a rapidly expanding field of mitochondrialtargeted oncology and may open the door to novel class of anti-cancer therapeutics targeting cellular energy homeostasis and organelle dynamics.

V. CHALLENGES AND FUTURE DIRECTIONS IN MITOCHONDRIA-TARGETED CANCER THERAPY

Although targeting mitochondrial function represents a new and promising approach to cancer therapy, there are many challenges to overcome. These involve deficiencies in our knowledge of mitochondrial behaviour in various tumours, the shortcomings of existing experimental models, and the requirement for individualized therapeutic approaches. The majority of current research in mitochondrial-targeted cancer therapies is based on in vitro cell cultures or in vivo animal models that, while rich in biological detail, usually don't more accurately reflect the tumour microenvironment and genetic heterogeneity of human cancers. Such shortcomings have the potential to result in differences between laboratory achievement and clinical efficacy.

In spite of remarkable progress toward the understanding of mitochondrial biology, there are some shortcomings that still hamper the advancement in translating mitochondrial-targeted approaches to cancer therapy. Traditional in vitro models like two-dimensional cell lines, although beneficial for mechanistic analysis, cannot reflect the metabolic and structural complexity of actual tumours. Analogously, animal models, especially rodents, also fail to consistently accurately recapitulate mitochondrial responses to stress or therapy in humans, which poses questions regarding the clinical Trans lability of preclinical data. Furthermore, the absence of patient-specific information highlights the imperative for human-derived models, such as patient-derived organoids, xenografts, and sophisticated imaging and omics tools, to better assess mitochondrial function in the clinic. Considering the natural heterogeneity of cancer, there is a low likelihood for a one-size-fits-all strategy to be successful in mitochondrialtargeted treatments. Rather, emerging treatment paradigms should focus on personalized profiling of mitochondrial phenotypes and tumour metabolic signatures, treatment selection based on biomarkers, and rational combination regimens that combine mitochondrial modulators with conventional therapies to maximize efficacy while reducing toxicity. Meanwhile, basic knowledge gaps linger. The specific mechanistic roles of mitochondrial dynamics—including fission, fusion, biogenesis, and mitophagy—in tumour initiation, progression, and resistance to therapy remain incompletely understood. Moreover, the heterogeneity in therapeutic responses indicates the importance of defining which patient subgroups are most likely to harbour beneficial effects from these interventions. Lastly, the cancer-type specificity of mitochondrial physiology and differential function across malignancies and stages of disease make therapeutic development even more challenging, highlighting the need for more profound, context-based investigations.

VI. CONCLUSION

Mitochondrial dynamics involving fission, fusion, mitophagy, and biogenesis are being identified as key controllers in cancer biology. Alteration of these processes facilitates tumour cells to rewire their metabolism, evade apoptosis, and survive in aggressive microenvironments, thereby contributing to cancer development and therapeutic resistance. Such regulatory proteins as DRP1, MFN2, and OPA1 act as pivotal nodes in this network, making them promising targets for new cancer therapies. Therapeutic manipulation of mitochondrial activity has great potential for increasing the effectiveness of standard treatments such as chemotherapy and radiotherapy, and maybe decreasing toxicity. However, a number of challenges still persist, such as uncomplete mechanistic insight, heterogeneity among cancer types, and the requirement for robust predictive biomarkers. Future studies ought to be aimed at elucidating the function of mitochondria in various malignancies, making more representative disease models, and pushing forward personalized therapeutic strategies. By incorporating mitochondrial biology into cancer diagnostics and treatment models, there is great potential to enhance clinical outcomes and enable next-generation, mitochondria-targeted cancer treatments.

VII. ACKNOWLEDGEMENT

The authors gratefully acknowledge the support of our institution and the valuable contributions of researchers whose work formed the basis of this review.

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