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Review

Anti-mitochondrial Therapy: A New Dimension of Personalized Oncology

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Abstract: Energy is needed by cancer cells to stay alive and communicate with their surroundings. The primary organelles for cellular metabolism and energy synthesis are mitochondria. Researchers recently proved that cancer cells can steal immune cells' mitochondria using nanoscale tubes. This finding demonstrates the dependence of cancer cells on normal cells for their living and function. It also denotes the importance of mitochondria in cancer cells' biology. Emerging evidence has demonstrated how mitochondria are essential for cancer cells to survive in the harsh tumor microenvironment, evade the immune system, obtain more aggressive features, and resist treatments. For instance, functional mitochondria can improve cancer resistance against radiotherapy by scavenging the released reactive oxygen species. Therefore, targeting mitochondria can potentially enhance oncological outcomes, according to this notion. The patients' reactions to radiation are varied, ranging from a complete response to even cancer progression during treatment. This concept illustrates how different levels of mitochondrial metabolism might contribute to this heterogeneity. Considering this notion can help to improve personalized oncological treatments. This article outlines the importance of mitochondrial metabolism in cancer biology and personalized treatments.

Keywords: mitochondria; personalized oncology; cancer stem cell; T Cell

1. Introduction

Cancer is a heterogeneous illness made up of various biological entities that require various therapies. Due to this problem, the world is moving away from one-size-fits-all cancer treatment regimens toward ones that are risk-adapted (1). Recent researches aim to identify the predictive factors influencing outcomes to personalized therapies and enhance quality of life while preserving efficacy. Predictive indicators for therapy response and toxicity are as important to illness prognostic factors.

It has been demonstrated that normal cells are necessary for the survival and functionality of cancer cells. Saha et al noteworthy demonstrated that cancer cells can steal mitochondria from immune cells (CD8+ T cells and natural killer [NK] cells) via nanoscale tube-like structures(2). In addition to supplying energy, mitochondria are crucial organelles for the survival and development of cancer cells. Furthermore, mitochondria play a crucial role in the biology of cancer stem cells (CSCs), supporting their chemo- and radioresistance (3).

Here we give a thorough understanding of the crucial function of mitochondria in cancer metabolism and how it can serve as a basis to improve personalized treatments, with a special stress on radiotherapy. The radiotherapy schedule is based on the total dose, per fraction dose, overall treatment time, the interval between fractions, and dose rate. Personalized Radiotherapy aims to modulate the RT schedule to improve the therapeutic ratio. More than half of cancer patients receive

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radiation therapy (RT), which is a crucial component of their regimen (4). Delivering the highest dose to the target while protecting normal tissues as much as possible is the fundamental tenet of RT. Most of the RT recommendations in use are based on population averages. This mindset has two problems: tumors vary in terms of their genetic and epigenetic signature, and people with tumors vary in terms of their racial, ethnic, and genetic features (5). Enhancing evidence has demonstrated the effects of patient variables, including as age, gender, ethnicity, comorbidities, and even biological and lifestyle factors, on radiation response and toxicities (6). This strategy has become a discipline in Oncology called *Personalized Cancer Treatment* including *Radiotherapy*. The varied function of mitochondria in cancer metabolism is discussed in the following section, along with how essential healthy mitochondria are for the survival and development of cancer.

2. The Pivotal Role of Mitochondria in Cancer Cells' Metabolism

Influencing cancer cells' survival in the tumor microenvironment, immune evasion, progression, and resistance to treatment are a few areas of mitochondria's advantages for cancer cells (Figure 1). We previously demonstrated how mitochondria play a crucial role in cancer development, immune evasion, survival, and therapeutic resistance (7). The benefits of mitochondria for cancer cells are categorized as follows:

(A) Surviving in the tumor microenvironment's (TME): via promoting/meditating glycolysis, reactive oxygen species (ROS) clearance, cell cycle arrest, maintain pH homeostasis, autophagy, mitochondrial hijacking, and angiogenesis.

(B) Immune evasion via facilitating TME acidification, glucose influx, PD-1 upregulation on T cells (by mitochondrial hijacking) (8), recruiting myeloid-derived suppressor cells (MDSCs), PD-L1 overexpression on cancer cells, MHC-1 downregulation, and the secretion of immunosuppressants, mitochondria help cancer cells avoid being recognized by immune cells. Additionally, T cells' mitochondrial hijacking depletes their energy and prevents long-term cancer-fighting action.

(C) Aggressiveness: mitochondria are crucial for cancer progression via mediating genomic instability, quiescence evasion, and epithelial-to-mesenchymal transition (EMT). Production of reactive oxygen species (ROS) mediates these activities.

(D) Treatment resistance: mitochondria can protect cancer cells from chemotherapy and RT by eliminating the released ROS. Additionally, they increase chemotherapy resistance by encouraging the function of efflux pumps (by providing ATP) and inducing cell cycle arrest. Additionally, mitochondrial hijacking from T cells impairs the long-term effects of anti-PD-1 treatment.

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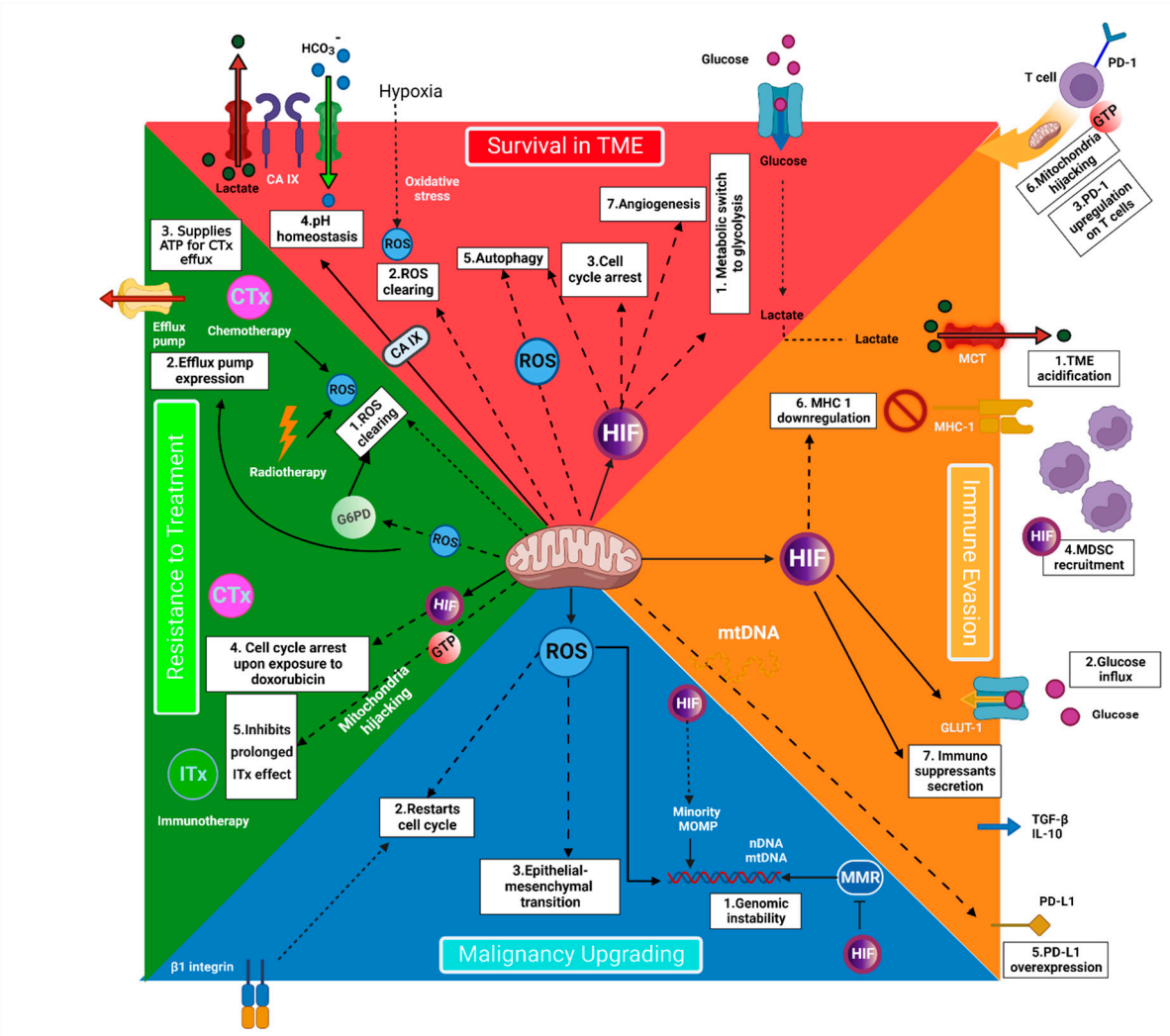

Figure 1. Schematic model of mitochondria's role in cancer survival, immune evasion, progression, and treatment resistance. The white boxes depict the mitochondria regulation outcomes.

ATP indicates adenosine triphosphate; CA IX, carbonic anhydrase IX; EMT, epithelial–mesenchymal transition; GLUT-1, Glucose transporter-1; GTP, guanosine triphosphate; G6PD, glucose 6-phosphate dehydrogenase; HIF, hypoxia-inducible factor;; IFN, interferon; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell; MHC-1, major histocompatibility complex class I; mtDNA, mitochondrial DNA; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; ROS, reactive oxygen species; TGF-β,transforming growth factor-beta; TME, tumor microenvironment; VEGF, vascular endothelial growth factor;. (retrieved from Taghizadeh-Hesary et al., 2022) (7).

3. Mitochondria Individualized Role in Cancer Metastasis

Metastasis happens in a very diverse and individualized pattern. The players in the molecular pathway of metastasis and the therapeutic response to metastasis should also be considered in a personalized and idealized context. EMT is the prerequisite for metastasis by inhibiting cell adhesion and promoting local migration, vascular invasion, and resistance to apoptotic stimuli (9). EMT and cancer-cell stemness are correlated phenomena regulated by common mediators, including HIFs, SNAIL, and SLUG/SOX9 (10, 11). Mitochondrial ROS (mtROS) can promote EMT through different pathways, such as MAPK, PI3K/Akt/mTOR, and VEGFA–SOX2–SNAI2 pathways (11-13).In addition, mitochondria are involved in cancer proliferation, invasion, and metastasis by providing the crosslink between β1 integrin and the extracellular matrix is (14). This process is mediated by

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lysyl oxidase (LOX), which is enhanced by mitochondria via stabilizing and securing HIF-1α function (15, 16). Therefore, targeted anti-mitochondrial therapy has the potential to disrupt EMT and metastasis. Precisional targeting of cancer-specific mitochondria can reduce their ability to de-differentiate, proliferate, and metastasize, and help to improve the treatment results and overall prognosis.

4. Targeting Mitochondria: A Practical Strategy for Personalized Cancer Treatment

As a result of developments in medical genetics and molecular biology, the function of mitochondria in several cellular functions, including apoptosis, redox balance, macromolecule production, and calcium homeostasis, has been demonstrated (17, 18). In contrast to the ancient Warburg theory, the mitochondria of cancer cells are functional, supporting their survival and function(7). As noted earlier, mitochondria can contribute the development, progression, and metastasis of cancer. In addition, it has a crucial role in treatment resistance. As noted in section 2, functional mitochondria can help cancer cells to overcome chemotherapy effects by scavenging released ROS and activating multidrug resistance pumps (7). Also, they can improve the resistance against immunotherapy, by inhibiting the immune cells entry to the TME by depleting the glucose content of TME, acidifying the TME, and mediating the mitochondria hijacking from immune cells(7, 19). Next, we outline how mitochondria can improve the cancer cells resistance against radiotherapy. In a recent study, Taghizadeh-Hesary et al. demonstrated that mitochondria have a contributing role in tumor response to radiotherapy. They demonstrated that mitochondria are involved in so-called 6Rs of radiobiology (20)(Figure 2). The details of this link were presented as follows:

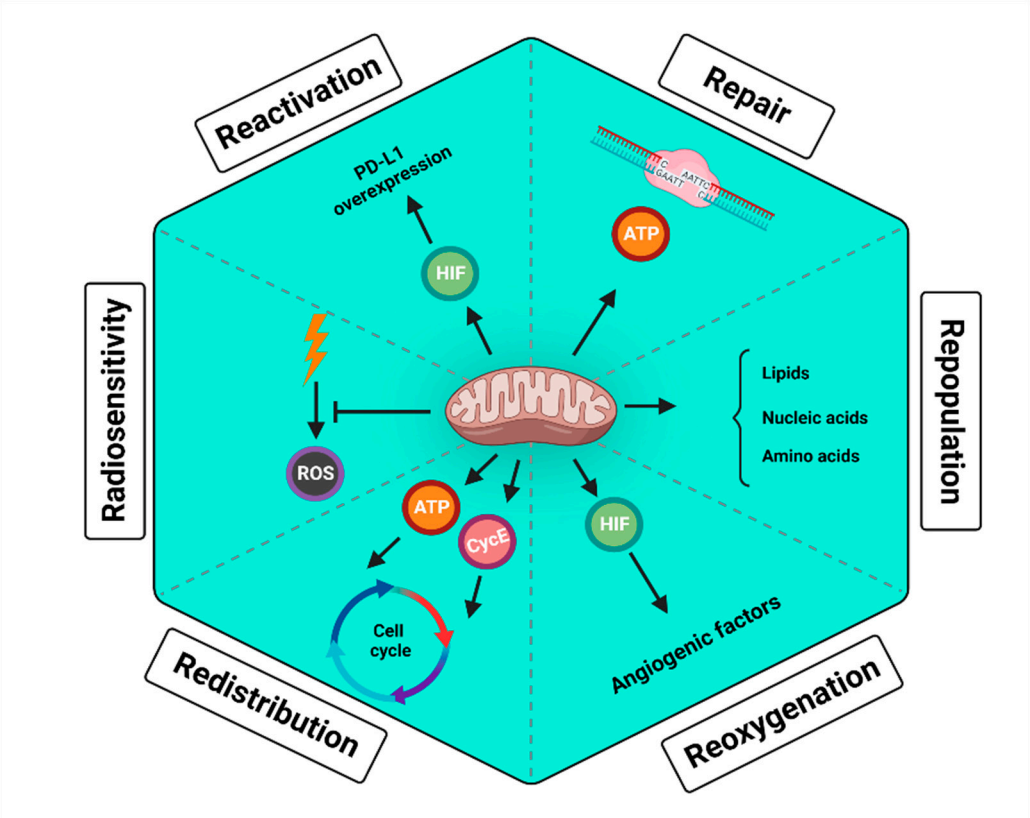

Figure 2. The contribution of mitochondrial metabolism to 6Rs of radiobiology. (retrieved from Taghizadeh-Hesary et al. study (20)).

(a) Repair: DNA damage is the primary cause of RT's cytotoxic effects. Cancer cells with improved DNA repair mechanisms can counteract this effect. Mitochondrial can support ATP-dependent proteins responsible for DNA integrity-related, including PARP-1 (21), XRCC1 (22), ATM(23), and DNA ligases (24), by providing enough ATP molecules..

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(b) Repopulation: Mitochondria can support cancer cells proliferation by supplying the building materials, including nucleic acids, amino acids, and lipids through stabilizing HIF-1 and metabolic switching to glycolysis.(25) .

(c) Reoxygenation: HIF-1 can mediate tissue reoxygenation by promoting the expression of different angiogenic factors and shielding endothelial cells from radiation effects (26). HIF-1 needs functional mitochondria to function properly (16). Consequently, healthy mitochondria can aid in the reoxygenation of tumor tissue.

(d) Redistribution: Cyclin-Cdk complexes carefully control the cancer cells' cell cycle (27). The radiosensitive phases of cell cycle are G2 and M and the radioresistant phases are G1 and S. (28). Cell cycle progression depends on dynamic responses of mitochondria in order that during the G1 and S phases, mitochondria fuse to form a hyperactive network; after that, they undergo fission to ensure proper partitioning between the two daughter cells (27). In addition, functional mitochondria can help the cell cycle progression by supplying enough energy (29).

e) Reactivation: Emerging evidence has demonstrated that cancer cells can evade the activated immune cells using immune inhibitory molecules, such as programmed death-ligand 1 (PD-L1) (30). In the hypoxic TME, HIF-1α increases PD-L1 expression on cancer cells (31). Functional mitochondria can facilitate this process by stabilizing HIF-1α (16). On the other hand, Akbari et al. found that programmed death protein-1 (PD-1) expression of T cells is inversely related to their mitochondrial capacity; so that a decrease in T cells' mitochondrial capacity can give rise to PD-1 overexpression on T cells and their inactivation (8). A recent study by Saha et al. demonstrated that cancer cells can hijack mitochondria from T cells via nanotubes (2). With this strategy, cancer cells can attain both goals (increasing PD-L1 and PD-1 expression on cancer cells and T cells, respectively), thereby enhancing the immunoescape.

f) Radiosensitivity: Functional mitochondria can reduce the radiosensitivity of cancer cells by scavenging the released ROS and mediating the removal of damaged mitochondria, a process called mitophagy. Hitherto, numerous biological factors have been linked to the intrinsic radiosensitivity of cancer cells, including p53, transforming growth factor beta (TGF-β), and isocitrate dehydrogenase 1 (IDH1) among others. For instance, p53 can improve radioresistance by enhancing the mitochondrial DNA integrity and PGC-1α (peroxisome proliferator-activated receptor γ coactivator-1α) overexpression. For the detailed mechanisms of other corresponding factors, the readers are referred to the study by Taghizadeh-Hesary et al (20). (**Table 1**)

This section illustrated how functional mitochondria can improve the tumor resistance against the various treatments. Therefore, inhibiting the cancer cells' mitochondria can potentially improve the treatment results.

Table 1. The biological factors of radioresistance from the mitochondria perspective.

Factors	Cancer	Ref.	Interaction with mitochondria	Ref.
Increasing radioresistance				
Mutated P53	Various	(32)	- Mutated p53 preserves mtDNA integrity - Mutated p53 improves mt capacity (PGC1α-mediated) - More functional mt scavenge more RT-induced ROS	(33) (34) (7)
TGF-β	HCC	(35)	- TGF-β signalling in CAFs mediates reverse Warburg effect - CAFs' lactate and pyruvate feed cancer cells' mt OxPhos - Activated OxPhos helps to restore NADPH - NADPH supports the antioxidant defense system	(36) (37) (38) (39)

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IDH1	Glioblastoma	(40)	- Mutated IDH1 enhances mt OxPhos (ROS generation) - Mutated IDH1 downregulates cytochrome c - Cytochrome c can nullify ROS - Thus, IDH1 mutation disrupts the ROS balance	(41) (42) (43)
PARP	Breast Ovarian Prostate Pancreatic HCC	(44) (45)	- PARP requires RAD51 for HR - BRCA2 regulates RAD51 function - BRCA2 requires mt support - Thus, functional mt improves radioresistance by mediating HR	(46) (46) (47)
PI3K/Akt/mTOR pathway	Prostate	(48)	- mTOR upregulates mt proteins responsible for mt metabolism - More functional mt scavenge more RT-induced ROS	(49) (7)
Wnt/β-catenin pathway	Esophageal SCC	(50)	- Wnt upregulates HMGB1 - HMGB1 activates mitochondria - More functional mt scavenge more RT-induced ROS	(50) (51) (7)
NF-κB pathway	Breast Glioma HCC Melanoma NSCLC	(52)	- Enhances mt respiration - Regulates mt dynamics - Regulates mt gene expression	(53)
8-oxo-dG	Esophageal Gastric	(54)	- Serum 8-oxo-DG level represents cellular ROS - Cellular ROS is dependent on mt metabolism	(54) (7)
ATM	Glioma	(55)	- Preserves mtDNA	(56)
XRCC1	NSCLC HNC	(57)	- Preserves mt respiratory chain	(58)
NOTCH2	NSCLC	(59)	- Regulates mitochondrial function	(60)
KEAP1	NSCLC	(59)	- Regulates mitochondrial function - Regulates mitophagy	(61) (62)
FGFR1/3	NSCLC	(59)	- Regulates mitochondrial energy metabolism	(63)
HOTAIR	Breast	(64)	- Regulates mitochondrial function	(65), (66)
AMPK	Glioblastoma	(67)	- Preserves mt biogenesis upon energy stress	(68)
RPA1	Glioblastoma	(69)	- Preserves mtDNA	(70)
RSK2	NSCLC	(71)	- Stimulates mt OxPhos	(72)
LAPTM4B	NPC	(73)	- Activates mTOR - mTOR upregulates mt proteins responsible for mt metabolism - More functional mt scavenge more RT-induced ROS	(74) (49) (7)
Decreasing radioresistance				
TNFα	NSCLC	(75)	- Impairs mt complex I and III - Complex III is essential for NADPH activity - Thus, reduces mt capacity to scavenge RT-induced ROS	(76) (77)

Note: This table is retrieved from Taghizadeh-Hesary et al. study (20).
Abbreviations:8-oxo-dG, 8-hydroxy-2′-deoxyguanosine; Akt, protein kinase B; AMPK, serine/threonine kinase AMP-activated protein kinase; ATM, ataxia-telangiectasia mutated; BRCA2,

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breast cancer gene 2; CAF, cancer-associated fibroblasts; FGFR1/3, fibroblast growth factor 1/3; HCC, hepatocellular carcinoma; HMGB1, high mobility group box 1; HOTAIR, HOX transcript antisense RNA; HR, homologous recombination; IDH1, Isocitrate dehydrogenase 1; KEAP1, Kelch-like ECH-associated protein; LAPTM4B, lysosome-associated transmembrane protein 4B; mt, mitochondrial; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor κB; NOTCH2, neurogenic locus notch homolog protein 2; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OxPhos, oxidative phosphorylation; PARP, poly (ADP-ribose) polymerase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1α; PI3K, phosphoinositide 3-kinases; ROS, reactive oxygen species; RPA1, replication protein A1; RSK2, ribosomal S6 kinase; RT, radiotherapy; SCC, squamous cell carcinoma; TGF-β, transforming growth factor β; TNFα, tumor necrosis factor α; XRCC1, X-ray repair cross complementing 1.

5. Enhancing the Normal Cells' Mitochondria Reduces the Radiotherapy Toxicity

Normal tissue response to irradiation is primarily determined by Repair, Repopulation, and Radiosensitivity, among others (78). As alluded to above, functional mitochondria are essential for DNA repair, cellular proliferation, and scavenging radiation-induced ROSs. Radiation-induced inflammation is an important phase in the development of normal tissue toxicity, happening upon ROS release from damaged cells (79). Functional mitochondrial can alleviate the resultant inflammation (and thus the ultimate tissue damage) by scavenging ROSs (80). With this information in mind, enhanced mitochondrial content of normal cells can reduce radiation-induced toxicities. In the following, it is outlined how mitochondrial metabolism is linked to the recognized predictive factors of radiosensitivity of normal tissue.

Recruiting genotypic and proteomic data of patients with breast or head and neck cancer, a series of proteins are recognized as determinant for normal tissue toxicity to radiation; including CHIT1, PDGFB, STIM1, and THPO proteins as improving radiosensitivity, and SERPINC1 and SLC4A as enhancing radioresistance (81). Mitochondrial metabolism interprets the mechanism of action of STIM1, SERPINC1, and SLC4A. STIM1 (stromal interaction molecule 1) regulates intracellular calcium level (82) and downregulates mitochondrial metabolism as its knock-out leads to more metabolically active mitochondria (83). STIM1 exacerbates radiation toxicity by preventing mitochondrial function from neutralizing the radiation-induced ROSs. Apoptosis and mitochondrial dysfunction are instead encouraged by SERPINC1 knockout because it activates the Bax pathway (84). In the mitochondrial anti-oxidative system, SLC4 (solute carrier 4) scavenges ROS to improve radioresistance (85). Hence, SERPINC1 and SLC4 may enhance radioresistance by enhancing mitochondrial metabolism and their capacity to scavenge ROS molecules.

TGF-β overexpression increases the susceptibility of radiation-induced pulmonary fibrosis (86) and its activation affects mitochondrial respiration via impairing the mitochondrial complex IV in lung epithelial cells (87).

The JAK/STAT signaling in human cells has been considered as a radioprotective factor. STAT3 activation improves the radioresistance of normal cells by increasing the generation of NADPH (for redox homeostasis) and ATP (for DNA stability); hence, enhances the mitochondrial electron transport chain in normal cells (88).

Radiation toxicities are more likely to affect older people. Higher ROS production and decreased antioxidant capability in older people have been blamed for this impact (89). As people get older, there is mounting evidence that their ability to produce ATP and NADPH is reduced because of an accumulation of mtDNA mutations and ROS damage to the mitochondrial substructures (90). The cellular redox processes (such as glutathione) and the ATP-dependent enzymes responsible for repairing DNA damage are each impaired, necessitating NAPDH to function (91). As a result, its relationship with radiation damage may be influenced by aging's impact on mitochondrial metabolism.

Several mechanisms have been proposed to explain how smoking during RT may increase the frequency and severity of radiation-induced acute and delayed toxicities (92). Through endothelial

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damage and coagulation, it impairs tissue repair and triggers an inflammatory cascade, which increases the rate and severity of acute radiation toxicities and causes late toxicities (93). Both acute and late radiation toxicities from tobacco smoke affect mitochondria negatively. Smoke exposure alters the mitochondrial membrane potential, which causes the release of ROS from the mitochondria and ultimately results in cellular death DAMPs are then released into the extracellular matrix, where they connect to toll-like receptors (TLRs) on tissue macrophages and trigger the NF-kB pathway. Inflammatory cytokines are released as a result, which damages healthy tissue and exacerbates acute radiation-induced inflammation (93). The main cause of delayed radiation toxicities, which manifest at least three months after RT, is the replacement of normal tissues by fibrotic tissues with inadequate blood flow (94). In order for tissue regeneration and angiogenesis to be mediated by wound macrophages—the key players in wound healing—proper mitochondrial function is a crucial precondition and determining factor in the early stages of wound repair (95). Therefore, increased radiation toxicity in smokers is justified by mitochondrial damage.

Alcohol intake can also enhance the incidence and severity of tissue fibrosis after radiation exposure, which can aggravate radiation-induced toxicities (96). In order for macrophages to effectively repair the damaged tissue, as mentioned above, functional mitochondria are necessary (95). Since ethanol can harm normal cells' mitochondria by inducing oxidative stress, its detrimental effects on mitochondrial metabolism may contribute to the radiotherapy's delayed toxicities (97). As a result, continued use of cigarettes or alcohol during RT may each cause certain radiation-induced toxicities.

6. Immune cells' Mitochondria: A Chance to Improve Treatment Results

In addition to immunotherapy, powerful immune system can improve the treatment results of radiotherapy and chemotherapy []. To improve the normal cells' mitochondrial content and activity several strategies can be employed y. The mitochondria quality can increase by two strategies; (1) improving the lifestyle by regular exercise (98), specific diets (low-specific dynamic action diet (99), branched-chain amino acid-rich diet (100), and Mediterranean diet (101)); good sleep (102), healthy weight (103), alcohol abstinence (104), and smoking cessation (105); and (2) mitochondria boosting agents (e.g., coenzyme Q10, activators of adenosine AMPK, acetyl-L-Carnitine; mammalian target of rapamycin [mTOR], PGC-1α, etc.) (106, 107). In addition, the human gut microbiota is another modulator of mitochondrial fitness. It has been demonstrated that microbiota-derived metabolites are necessary for the proper action of mitochondrial metabolisms, including glycolysis, tricarboxylic acid (TCA) cycle, oxidative phosphorylation, as well as amino acid and fatty acid metabolism. The mitochondrial boosting strategies are diverse. Detailed information is presented in the following sources (107, 108).

7. Heteroplasmy Provides Unique Profiles in Cancer

Heteroplasmy is the presence of more than one type of organellar genome (mitochondrial DNA or plastid DNA) within a cell. The amount of heteroplasmy is determined during oogenesis and is inherited from the mother. There are variations in the percentage of mutant alleles between oocytes and then between children. Heteroplasmy or the presence of at least two mtDNA variants within the single cell, and its level (the proportion of mutated mtDNA) are frequently seen with and in accompanying with tumor heterogeneity. One of the major challenges to understanding and elucidating the role of the variations in tumor growth is the heteroplasmy levels of the mtDNA variants. In turn, intratumor genetic heterogeneity affects personalized medicine strategies in a significant way since it can reduce the effectiveness of treatments and result in treatment resistance. It is interesting to note that numerous studies have linked heteroplasmic levels to both cancer risk and survival (109-113). It would be essential to advance knowledge of the biological mechanisms at play, including proliferation, metastasis, and intratumoral heterogeneity, as well as the clinical implications of heteroplasmy, via recognizing the crucial role of heteroplasmy in cancer. The high mutation rate found in mtDNA, which is between 10 and 17 times higher than that of the nuclear genome, is explained by the lack of histones, effective DNA repair mechanisms, and closeness to

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reactive oxygen species (ROS) produced by the OXPHOS system (mostly from Complex I and III) (nDNA) (114-117). In humans, mtDNA is only inherited via the maternal line as a single unit called a haplotype, which may be shared by populations with similar ancestries. Factually, a set of haplotypes or a haplogroup can be used to distinguish across populations or ethnic groupings while certain haplogroups have advantages for environmental adaptation but are also linked to cancer (118-125).

The degree of heteroplasmy varies greatly between different cancer kinds and individuals. It has been demonstrated that when tumors progressed, heteroplasmy varied amongst tissues. Based on the idea that some heteroplasmic variations are finally able to become dominant or lost in cancer cells based on their tumor-promoting impact, a likely bottleneck process was proposed. The G1576C and G12009A mutations are the most prevalent in tumor cells compared to normal cells (7.8% versus 0.35 % and 68.8% versus 0.35 %, respectively) (126).

Although very limited number of studies have been done on the mechanisms of heteroplasmy shifting in cancer, there is proof that cell niche and the nucleus-mitochondrial environment regulate the OXPHOS system's energy performance, choosing particular mutant alleles (127) . For instance, it has been demonstrated that fumarate accumulation in renal cancer alters the mitochondrial content by inactivating core components necessary for mtDNA replication (128). Alterations in DNA polymerase gamma (POLG) and mitochondrial transcription factor A (TFAM) expression, mutations in nDNA-encoded genes involved in mitochondrial biogenesis, nuclear and mitochondrial epigenetic modifications, as well as intrinsic and extrinsic stimuli, may all result in anomalies in mtCNVs (129-131). Examples include the dysregulated expression of nuclear genes such as *dynamin 1 (DRP1), mitofusin 1 (MFN1)* and *2 (MFN2)* mitochondrial fusion and fission proteins, *BCL2 inter-acting protein 3* (*BNIP3*), *PTEN-induced kinase 1* (PINK1), and *hypoxia inducible factor 1 (HIF1)*, observed in lung, bladder, and breast cancers (132, 133). The role of the tumor microenvironment in altering the allelic frequencies of mtDNA mutations was also hypothesized based on an investigation of primary tumors and their distant metastasis (134). Additionally, NOX2-derived redox signaling has been shown to be used by bone marrow stromal cells to transfer functioning mitochondria to acute myeloid leukemia blasts (135, 136). Together, these pathways may be crucial for the emergence of a tumorigenic environment-adaptive-unique response that is represented in the alteration of the allelic frequencies of mtDNA mutations. The nuclear insertions of mitochondrial origin (NumtS), which have been linked to cancer, should be considered in next investigations on heteroplasmy. NumtS, or mtDNA segments integrated into the nucleus during evolution, are thought to occur at a rate of ~5 x $10e^{-6}$ per germ cell every generation (137).

Currently, methods based on mitochondrial gene editing have been proposed as a treatment choice for reestablishing the OXPHOS system in conditions brought on by mtDNA mutations. A possible therapeutic target for cancer has been suggested to include components involved in mitochondrial biogenesis and metabolism (138-140).

8. Conclusions

This article illustrated how mitochondria is involved the tumor response to different treatments as well as the normal tissue toxicity. With this concept in mind, future works can design more personalized treatments to improve the treatment results with fewer toxicities. Although there are clear links between heteroplasmy and cancer-related phenotypes, it is still unclear whether heteroplasmy or the variation in mtDNA copy number in cancer is a cause or an effect.

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