REVIEW

Mitochondrial dysfunction in oral cancer: A link between metabolic disorders and tumorigenesis

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Abstract

Development and spread of several malignancies, most notably oral cancer, are significantly influenced by mitochondrial dysfunction. Mitochondria is not only involve in energy production, it also regulate cellular function, apoptosis, calcium homeostasis, thermogenesis and mitochondrial dynamics. Some of the factors may affect the mitochondrial function such as increase level of ROS, enzyme abnormalities, mtDNA mutation, impaired oxidative phosphorylation and enhanced glycolysis (Warburg effect) are frequently observed in OSCC. Metabolic reprogramming favours cancer cells proliferation and survival. Mitochondrial dysfunction is contribute to aggressive progression of cancer cells. And also mitochondrial dysfunction is intricately linked to systemic disorders such as diabetes and obesity, which are recognized risk factor for oral cancer. Mitochondrial abnormalities also influence key oncogenic signaling pathways, including PI3K/AKT and p53, which are frequently deregulated in oral cancer. This review explores the abnormality of mitochondria and metabolic dysfunction in the advancement and progression of oral cancer, and highlighting their role in promoting cancer transformation, resistance to cell death and therapy option. Targeting mitochondrial pathways with treatments that increase mitochondrial activity, trigger mitophagy, or alter metabolic flux is holds promise for developing novel treatment approaches. And also targeting altered mtDNA copy number, respiratory enzyme activity, and ROS levels may serve as early diagnostic or prognostic biomarkers in oral cancer. Understanding the mechanism of mitochondrial dysfunction may discover novel diagnostic markers and therapeutic targets for oral cancer.

Keywords: Mitochondrial dysfunction, oral cancer, mtDNA mutations, metabolic reprogramming, reactive oxygen species, therapeutic targets.

Introduction

Mitochondria are the primary organelles for energy metabolism in eukaryotic cells.[1] Without them, cells would rely on aerobic glycolysis, a cytosolic process that yields only two ATP per glucose molecule and is energy-inefficient.[2] Mitochondria influence both health and disease.[3] Besides ATP production through oxidative phosphorylation and the TCA cycle, they regulate several mechanisms of cell death.[1] Metabolic disorders impair energy production and arise from factors such as cellular hypoxia, defective autophagy, elevated ROS, and reduced oxidative phosphorylation, all of which cause mitochondrial dysfunction. Because mitochondrial homeostasis depends on complex, interdependent proteins, treating metabolic disorders remains difficult.[4] Excess fat accumulation also contributes to interconnected conditions like obesity and cardiovascular disease, collectively termed metabolic syndrome, a growing global epidemic.[5]

Mitochondrial dysfunction is associated with metabolic syndrome, cancer, cardiovascular, neurological, infectious and inflammatory diseases.[3,6] Over the last two decades, understanding of mitochondrial roles in health and disease has expanded. Many common disorders including type 2 diabetes, cardiovascular disease, metabolic syndrome and cancer are linked to mitochondrial malfunction and altered cellular bioenergetics.[7] Diabetes mellitus, one of the most prevalent metabolic diseases, is defined by hyperglycemia

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due to inadequate insulin secretion or impaired insulin-mediated glucose uptake.[8]

Although physiology, genetics and environmental factors contribute to fat-related metabolic diseases, the precise mechanisms remain unclear.[5] Oral cancer is a malignant neoplasm of the lip or oral cavity, most often oral squamous cell carcinoma (OSCC), accounting for 90% of dental malignancies.[9] Its rising incidence makes it a major public health concern, especially among young males and females. Low awareness results in late diagnosis and higher mortality. Many cases are preceded by clinically detectable oral potentially malignant disorders (OPMDs), making early visual screening crucial for reducing morbidity and mortality.[10] Due to poor prognosis and delayed detection, oral cancer ranks among the top 10 cancers worldwide. Although its risk factors and disease course are well established, biomedical sciences especially dentistry can further improve clinical outcomes.[11]

This study extends its scope to understand the association between mitochondrial alterations and cancer progression, with a specific importance on OSCC. Analyzing the biological pathway, risk factors and disease progression is significantly improves the early detection of oral diseases and prevention. Overall, the study aims to provide a comprehensive understanding of mitochondrial involvement in both metabolic and oral squamous cell carcinoma.

Mitochondrial function and metabolism in healthy cells

Mitochondria are double-membrane organelles composed of an outer membrane, inner membrane, matrix, and intermembrane space (IMS).[12] Mitochondrial OXPHOS generates about 30 ATP per glucose molecule, making it essential for cellular metabolism since ATP cannot be efficiently stored.[13] The TCA cycle and ETC form the core of mitochondrial energy production.[6] Fatty acid metabolism and glutamine metabolism yield Acetyl-CoA and α-KG, which enter the Krebs cycle to support ATP generation, highlighting the central metabolic role of mitochondria.[6]

Beyond energy production, mitochondria participate in hormone and neurotransmitter synthesis, iron and calcium regulation, and melatonin production. They influence cellular communication through interactions with the nucleus, other organelles, and the extracellular environment.[3] Mitochondria also regulate multiple cell death pathways, including mitophagy, pyroptosis, oxeiptosis, apoptosis, NETosis, alkaliptosis, necroptosis, parthanatos, clockophagy, ferroptosis, and autosis.[1] (Figure 1).

As a key organelle shaping cell fate, mitochondria regulate calcium signaling, redox balance, and thermogenesis. To maintain their quantity and quality, they undergo mitophagy, fusion, and fission, enabling repair or replacement of damaged mitochondria.[4] Their dynamic nature allows rapid adaptation to metabolic and environmental changes, supporting coordination of diverse biological processes. Mitochondrial homeostasis governed by fission, fusion, mitophagy, and transport is essential for optimal signaling and metabolism.[14] Preclinical studies show that restoring or replacing damaged mitochondria with healthy ones may benefit several diseases.

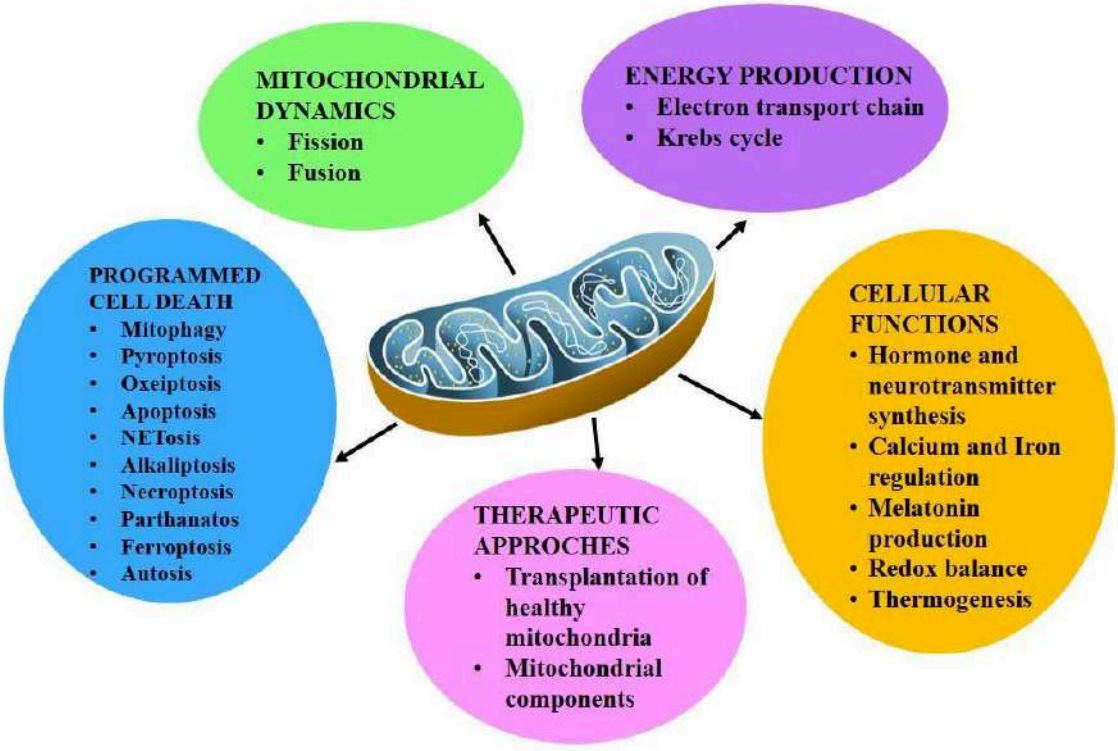

Fig. 1: Shows the role of mitochondria in dynamics, energy production, cell death regulation and its cellular function in cells.

Therapeutic strategies targeting mitochondrial function in immunometabolic disorders and tissue injury include mitochondrial components such as mtDNA, mitochondria-associated microRNAs, and specific mitochondrial proteins. Through quality control, metabolic regulation, and energy production, mitochondria remain crucial for maintaining cellular homeostasis.[6]

Mechanisms and consequences of mitochondrial dysfunction in cancer

A metabolic shift toward aerobic glycolysis is characteristic of cancers.[24] Due to the Warburg effect reduced mitochondrial respiration cancer cells rely on elevated glycolysis for ATP production. Although mitochondrial respiration is more efficient, how metabolically impaired cancer cells outcompete normal cells and develop drug resistance has remained unclear.[25] Disruption of mitochondrial dynamics can alter cell fate and contribute to cancer, metabolic disorders, cardiovascular diseases, and neurodegenerative conditions.[14]

Abnormal metabolism is a hallmark of cancer. Tumor cells utilize both OXPHOS and aerobic glycolysis to support energy needs and biomass synthesis. Understanding this metabolic reprogramming can guide therapies targeting cancer metabolism.[15] Mitochondrial dysfunction is implicated in many diseases, driven by infections, aging, mtDNA mutations, and physical inactivity.[7] Deregulated cellular energetics one of the key cancer features arises from defects in mitochondrial enzymes, mtDNA mutations, and alterations in oncogenes or tumor suppressors.[16]

In cancers, point mutations and copy number changes are the two most common mitochondrial DNA abnormalities. Furthermore, resistance to chemotherapeutic agents or invasive characteristics develops more quickly in cancer cells, when mitochondrial malfunction is caused by chemically reducing mtDNA or affecting the electron transport chain.[16] Several prevalent illnesses, such as cancer, metabolic syndrome, dementia, and cardiovascular disorders, have been linked to mitochondrial dysfunction.[6] For the purposes to increase their survival and avoid apoptosis under different circumstances, cancer cells utilize a variety of approaches.[17] increased glucose uptake and glycolytic activity, enhanced lactate production, accumulation, and secretion, impaired mitochondrial function, and upregulated expression of monocarboxylate transporters all play a role in carcinogenesis and tumorigenesis. In carcinogenesis, aberrant cell signaling brought on by excessive and frequent elevated lactate levels creates a inappropriate positive feedback loop.[18] (Figure 2) TCA cycle enzyme mutations

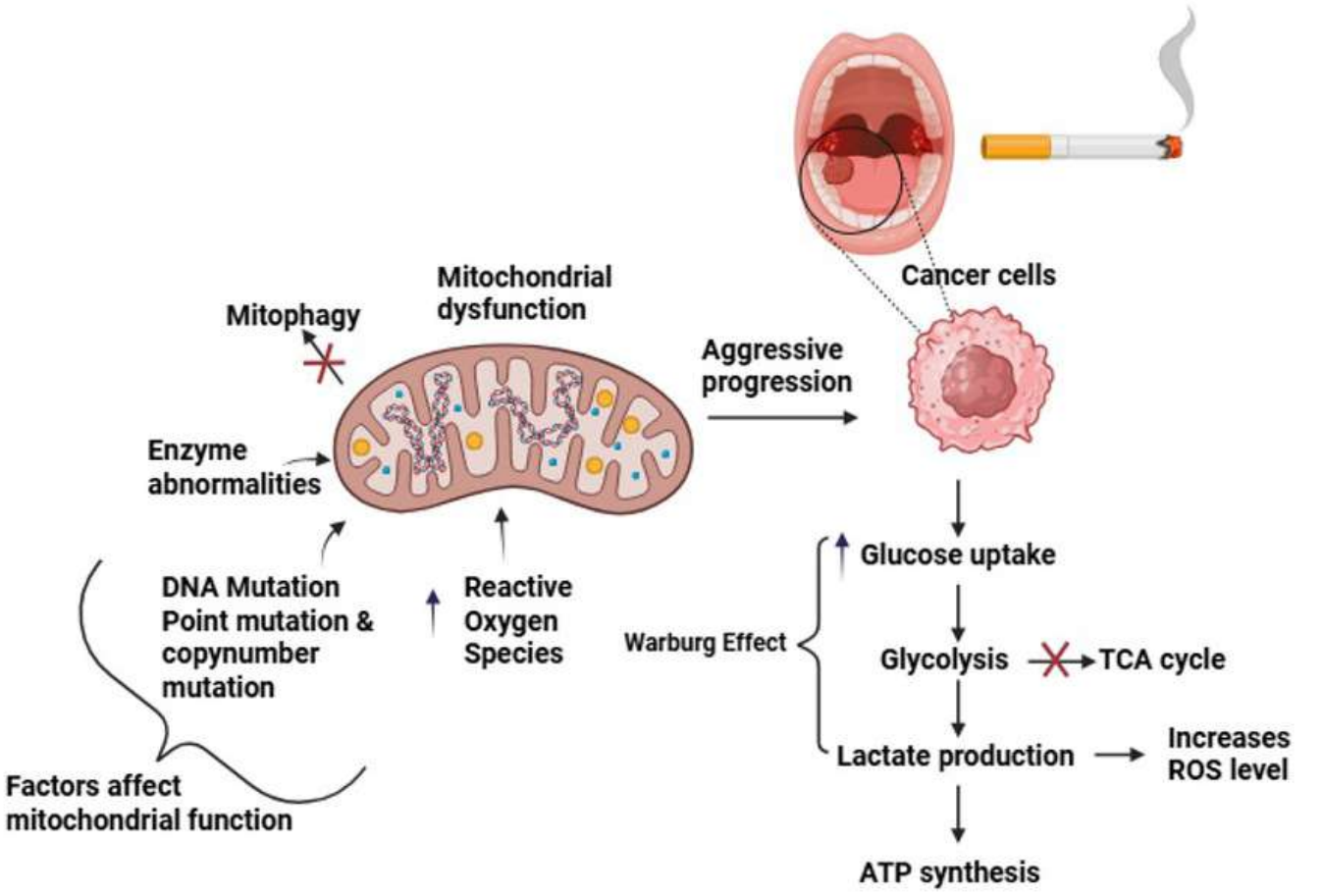

Fig. 2: Schematic representation shows a various factor triggers mitochondrial dysfunction and their involvement in cancer progression.

are frequently observed in cancer and may be connected to the progression of the disease by reprogramming the metabolism of the cancer and producing oncometabolites.[55]

Many studies show the effectiveness of mitochondria-based therapies, supporting their potential in treating diverse diseases.[1] Both familial and sporadic cancers are associated with abnormalities in mitochondrial enzymes such as fumarate hydratase, isocitrate dehydrogenase, and succinate dehydrogenase. Dysregulation of the mitochondrial deacetylase SIRT3 can also promote cancer by altering oxidative stress and metabolism. Mitochondrial defects activate cytosolic signaling pathways that modify nuclear gene expression through retrograde signaling. Changes in ROS or oncometabolite levels are key drivers of this mitochondrial retrograde signaling, contributing to cancer development and neoplastic transformation.[16]

Relevance of mitochondrial dysfunction to oral carcinogenesis

Oral cancer is a major global health challenge and ranks among the top 10 most common cancers. Despite advances in research and treatment, survival rates have shown little improvement.[11] Over 370,000 new OSCC cases and nearly 170,000 deaths occur annually.[23] Metabolic by-products such as ROS contribute to disease progression. Mitochondrial dysfunction has long been implicated in disease, and recent studies show that aging further disrupts mitochondria-regulated pathways, worsening mitochondrial health.[4] Because mitochondria influence cellular metabolism, signaling, and lifespan, their dysfunction contributes to many polygenic disorders, including cardiovascular and neurological diseases. Mitochondrial abnormalities are also increasingly linked to OIDs and systemic disorders.[21]

Mitochondria regulate calcium signaling, redox balance, and thermogenesis and maintain their integrity through mitophagy, fusion, and fission.[4] Cancer cells frequently exhibit mutations in nuclear genes associated with the TCA cycle and mtDNA, contributing to metabolic remodeling.[54] Proper mitochondrial shape, distribution, and selective removal of damaged mitochondria depend on dynamic fission–fusion processes. The TCA cycle and electron transport chain are central to mitochondrial ATP production.[6] Oxidative damage impairs mitochondrial activity and increases ROS due to electron leakage, particularly affecting Complex I (ND2) and Complex III (succinate–CoQ reductase).[40] Cytochrome c immunostaining is detected in 63.3% of malignant parotid tumors.[29] Mutations in PI3K–AKT–mTOR, RAS, HIF-1, and MYC further remodel cancer metabolism by altering OXPHOS and fatty acid, glutamine, and one-carbon metabolism.[55]

Earlier studies showed that NOFs and OSCC cells engage in metabolic coupling before acquiring an activated phenotype without senescence.[24] Targeting key mitochondrial regulators such as MFN and UCP may limit mitochondrial damage and improve metabolic diseases, including obesity and type 2 diabetes. Smoking-induced ND2 mtDNA mutations have been found in histologically normal parotid tissue, suggesting their use as molecular markers of mtDNA damage.[39]

Mitochondrial dysfunction and metabolic disorders in OSCC

Mitochondria play a central role in cancer biology. The Warburg effect, identified by Otto Warburg in 1924, shows that cancer cells rely on glycolysis for ATP production even in the presence of oxygen.[27] In obese individuals, cancer cells frequently display altered lipid metabolism including increased lipid uptake, storage, and lipogenesis which supports rapid proliferation, membrane synthesis, tumor aggressiveness, and therapy resistance. 42 Obesity is strongly associated with cancer progression, recurrence, metastasis, and treatment resistance.[51]

Earlier research demonstrated that NOFs transfer mitochondria to OSCC cells through direct and indirect mechanisms. When co-cultured with OSCC, NOFs acquire a cancer-associated fibroblast–like metabolic phenotype, marked by aerobic glycolysis, elevated oxidative stress, increased L-lactate, and upregulated MCT-4, leading to hypoxia, mitophagy, and mPTP activation. Cav-1 low NOFs supply L-lactate that fuels OSCC growth and mitochondrial metabolism. Reduced PGC-1α and AMPK activity may regulate ROS balance, maintaining ATP and redox homeostasis during carcinogenesis.[24]

OSSC invasiveness is further linked to increased ROS1 tyrosine kinase, an oncogene that can localize to mitochondria. Mitochondrial ROS1 reduces mitochondrial biogenesis but increases OXPHOS, ATP generation, and mitochondrial fission,

S.No	Key aspect	Finding	Reference
1.	Mitochondrial dysfunction in cancer	Promotes cancer metastasis, aggressiveness, and resistance to treatment; associated with EMT.	37
2.	PSMA2 Role in OSCC	Contributes to carcinogenesis and resistance via cell cycle regulation, mitochondrial dysfunction, and mitophagy.	26
3.	Lactate Metabolism & OSCC Growth	NADH oxidation from CAF-derived lactate in mitochondrial OXPHOS may enhance OSCC proliferation.	30
4.	Antioxidant Enzymes & OSCC Progression	GPX1, GPX4, and catalase levels decrease, while GLRX2, PXR3, TXN2, and GSH increase; SOD2 decreases in Stages II & III but rises in Stage IV.	31
5.	PGC-1 Expression & Prognosis	A poor prognosis for OSCC is associated with negative PGC-1 expression; vascular invasion and low PGC-1 may be clinical markers.	53

Table 1: Represents the mitochondrial dysfunction role in OSCC, by highlighting PSMA2 role, Lactate metabolism, Antioxidant enzyme alterations, PGC-1 expression and prognosis in OSCC. These mitochondrial changes contribute to OSCC progression, therapy resistance, and metabolic adaptation.

supporting OSCC metabolic flexibility and invasiveness.[41] Another study showed that SQD9 cells gaining radiation resistance shift from glycolysis toward more oxidative metabolism, indicating a greater reliance on OXPHOS in radioresistant cells.[43]

Mitochondrial dysregulation and OSCC aggressiveness

Mitochondrial dysfunction contributes to cancer aggressiveness, metastasis, and treatment resistance, features also associated with epithelial–mesenchymal transition (EMT).[37] Previous studies show that PSMA2 promotes carcinogenesis and resistance by regulating the cell cycle, mitochondrial dysfunction, and mitophagy, and that mitophagy inducers exert anticancer effects in OSCC xenograft models overexpressing PSMA2.[26]

Mitochondrial damage-related genes (MDGs) are strongly linked to OSCC incidence, progression, and metastasis.[38] The mitochondrial OXPHOS pathway may further support OSCC proliferation by oxidizing NADH derived from CAF-produced lactate.[30] (Table 1) During OSCC progression, GPX1, GPX4, and catalase levels decrease, whereas GLRX2, PRX3, TXN2, and GSH levels increase. In addition, SOD2 expression decreases in Stages II–III but rises again in Stage IV.[31] Low PGC-1 expression is associated with poor OSCC prognosis, and its negative expression along with vascular invasion may serve as useful prognostic indicators.[53]

Therapeutic implications of targeting mitochondrial dysfunction in OSCC

1. Targeting mitochondrial metabolism in OSCC therapy:

Hypoxia-related glucose metabolism is closely linked to OSCC carcinogenesis and mitochondrial OXPHOS activity. Acidosis and increased OXPHOS can shift cancer cell metabolism toward the pentose phosphate pathway (PPP), and inhibition of the PPP or glycolysis along with targeted anti-mitochondrial ROS-inducing therapies may enhance apoptosis in OSCC.[44] Alantolactone similarly suppresses OSCC proliferation by disrupting mitochondrial homeostasis and modulating Drp1-dependent mitochondrial fission.[28] Cancer cells further enhance survival by activating NFκB and PI3K–Akt pathways and upregulating antiapoptotic Bcl-2 and Bcl-XL

S.No	Key aspects of therapeutic targets in OSCC	Finding	Reference
1.	mtDNA mutations	Higher 8-OdG and mtDNA deletion is occur in OSC cells after γ radiation.	32
2.	mtDNA repair proteins	TFAM and POLG expression levels decreased after the PI3K/Akt signaling pathway was inhibited.	34
		Activation of NFκB and PI3K/Akt and increased production of Bcl-2, XL is enhance cancer cells ability to survive.	17
3.	Mitochondrial tumor suppressors	Reduced SIRT3 expression cause OGG1 to be more acetylated and degraded, which enhance the production of ROS and carcinogenesis.	35
		Mitochondrial suppressor proteins like SIRT3 and MTUS1 malfunction affect the energy metabolism of mitochondria.	36
4.	Therapeutic targets	SLC25A20 is a mitochondrial protein for fatty acid oxidation & BID a protein involved in apoptosis as independent diagnostic and therapeutic biomarkers for OSCC prognosis	38
5.	Metabolic enzyme and proteins	The expression of glycolysis-associated proteins (GLUT-1, HK2, LDHA, TKTL1), mitochondrial enzymes (SDHA, SDHB, ATP synthase), and IGF-R1 was significantly increased during OSCC carcinogenesis	44
		Glycolytic enzymes such as PKM2, HK2, PFK, G6PD are upregulated during metabolic processor and their over expression of this enzymes observed in OSCC.	49
6.	Mitocondrial dynamics	MAP, ROS, mitochondrial fission, Fusion, Loss of mitophagy.	4, 33
7.	Metabolic pathway	Targeting a mitochondrial metabolic pathways like PPP, Glycolysis, OXPHOS	44
8.	Mitochondrial targeted antioxidants	GLRX2, Reduced GSH, GPX, SOD2, TXN2 protects against mitochondrial oxidative stress	31
9.	Mitochondrial respiration	Modifying the expression of the tumor suppressor p53 and hypoxia-inducible factor 1 regulates mitochondrial respiration.	16
10.	Cell Growth, Survival, and Metabolism in OSCC	ITGB2-high pro-tumoral cancer-associated fibroblasts (CAFs) enhance mitochondrial oxidative phosphorylation by promoting NADH oxidation, which activates the PI3K/AKT/mTOR signaling pathway.	50

Table 2: Represent the mitochondrial modulation in OSCC influences the proliferation, survival, and metabolic processes of cancer cells by targeting critical pathways and mtDNA mutations, repair proteins, tumor suppressors, and metabolic pathways. Therapeutic strategies include controlling mitochondrial dynamics, and using antioxidants that target the mitochondria.

proteins, which inhibit mitochondria-mediated apoptosis and counteract Bak/Bax activity.[17] HL156A has been reported as a potential therapeutic agent for OSCC, and the mitochondrial ETC inhibitor phenformin also shows strong anticancer activity across multiple cancers.[43]

2. Mitochondrial-targeted antioxidants:

The prognosis of patients with OSCC is still significantly impacted by locoregional failure, which is mostly caused by tumor resistance to chemotherapy or radiation.[26] Excessive production of reactive oxygen species by OXPHOS damages mtDNA and causes progressive respiratory chain malfunction, which can result in a number of illnesses, including cancer. Because mitochondria lack protective DNA repair enzymes, histones, and introns, they are vulnerable to oxidative stress (OS). However, many antioxidants, including reduced glutathione (GSH), glutaredoxin 2 (GLRX2), thioredoxin 2 (TXN2), glutathione peroxidase (GPX), catalase, and glutathione dismutase 2 (SOD2), protect mitochondria against OS (oxidative stress).[31] Resistance to chemotherapy and radiation in OSCC is frequently linked to mitochondrial adaptations, such as enhanced antioxidant defenses and mitophagy which is protect cancer cells from oxidative stress induces therapy. Mitophagy removes damaged mitochondria, reducing the effectiveness of ROS-mediated therapies. The mitochondrial antioxidants like glutathione (GSH), glutaredoxin 2 (GLRX2), thioredoxin 2 (TXN2), and superoxide dismutase 2 (SOD2) further shields cancer cells from oxidative damage. Targeting these mitochondrial processes can sensitize cancer cells to treatment and overcome resistance.[56] (Table 2)

3. Mitochondrial dynamics as therapeutic targets:

Key therapeutic strategies for OSCC target MAP, ROS, and mitochondrial fission.[33] Disruption of mitochondrial fission–fusion dynamics and impaired mitophagy contribute to metabolic diseases and cellular senescence by increasing ROS, altering calcium uptake, and affecting membrane potential and ATP production. Fission facilitates removal of damaged mitochondria, while fusion supports mitochondrial repair.[4]

In OSCC, ITGB2-high pro-tumoral CAFs enhance tumor growth by stimulating the PI3K/AKT/mTOR pathway through NADH oxidation–driven OXPHOS.30 Fisetin, a natural

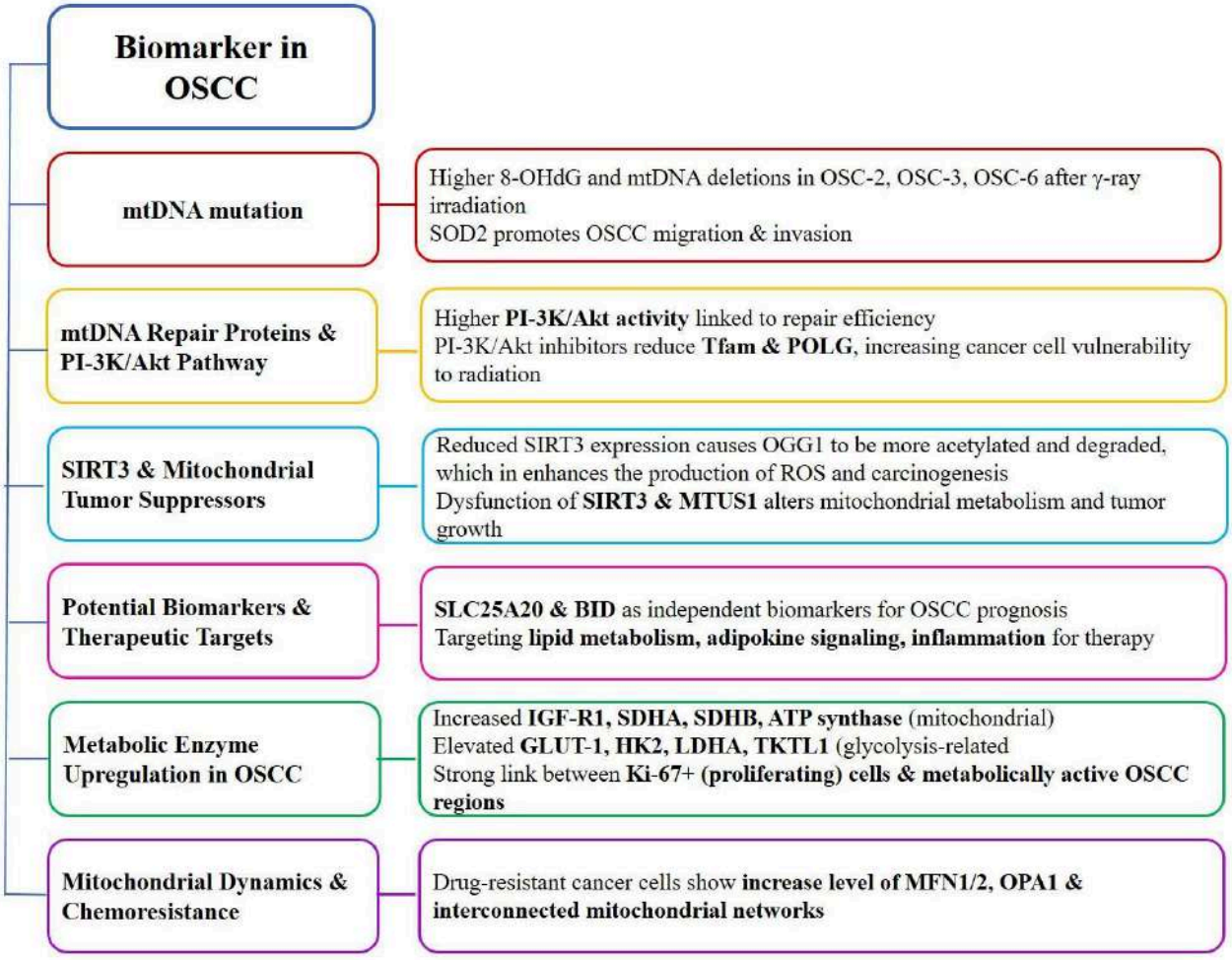

Fig. 3: Shows mitochondrial dysfunction in OSCC, highlighting mitochondrial mutations, metabolic adaptation, tumor progression, and chemoresistance. Key pathways include mtDNA repair, PI-3K/Akt signaling, antioxidant regulation, and mitochondrial dynamics in therapy response.

flavonoid, inhibits SCC-4 oral cancer cells by inducing G2/M arrest and caspase-dependent apoptosis accompanied by Bcl-2 downregulation, release of EndoG, AIF, and cytochrome c, and triggering ER stress.[50]

4. Metabolic intervention through lifestyle changes:

Immunohistochemistry revealed that OSCC had considerably higher PPIA expression than normal oral mucosa.[19] In 96.9% of OSCC cases, LGALS7B immunoexpression was detected, and it was substantially correlated with histological malignancy grading systems.[20] BCAT-1 (RNAi) knockdown can cause oxidative damage and overactivate nerve cell mitochondria, which may trigger symptoms of Parkinson's disease.[22] Mitochondrial respiration and cellular metabolism are regulated by oncogenes and tumor suppressors, including HIF-1 and p53, through transcriptional control of downstream target genes.[16] Obesity affects the activity of cancer cells by changing the release of cytokines (like TNF-α and IL-6) and adipokines (like leptin and adiponectin). These mediators accelerate up the growth of tumors by fostering an environment that is immunosuppressive and pro-tumorigenic.[42]

Mitochondrial dysfunction as a biomarker in OSCC

The sensitivity of cancer cells to anticancer drugs is closely linked to mitochondrial DNA (mtDNA) repair capacity. Radiosensitive OSC-2, OSC-3, and OSC-6 cells show higher 8-hydroxy-2′-deoxyguanosine levels and mtDNA deletions after γ-irradiation compared to OSC-1, OSC-4, and OSC-5 cells.34 SOD2 has also been shown to promote migration and invasion in tongue squamous cell carcinoma.[32]

Different OSCC cell lines display distinct mtDNA repair profiles. OSC-1, OSC-4, and OSC-5 exhibit higher expression of POLG, OGG1, and Tfam, as well as increased PI-3K/Akt activity, than OSC-2, OSC-3, and OSC-6. Downregulating these mtDNA repair components sensitizes OSC-2 and OSC-5 to γ-irradiation, and PI-3K/Akt inhibitors reduce Tfam and POLG expression. These findings suggest that combining PI-3K/Akt inhibitors or OGG1 suppressors with radiation or chemotherapy may enhance therapeutic response by weakening mtDNA repair.[34] Reduced SIRT3 expression promotes OGG1 acetylation and degradation, elevating ROS and supporting carcinogenesis.[35] Dysfunction of mitochondrial tumor suppressors such as SIRT3 and MTUS1 disrupts mitochondrial energy metabolism, driving cellular transformation and tumor progression.[36] SLC25A20 and BID have emerged as promising prognostic biomarkers for OSCC.[38]

Therapeutic strategies targeting lipid metabolism including lipid-modulating drugs, dietary interventions, and adipokine-directed treatments aim to reduce inflammation, restore metabolic balance, and impair tumor growth.[42] OSCC carcinogenesis is also marked by upregulation of IGF-R1, mitochondrial enzymes (SDHA, ATP synthase, SDHB), and glycolysis-related proteins (TKTL1, GLUT-1, LDHA, HK2), which correlate with proliferating (Ki-67+) and metabolically active tumor regions.[44]

According to recent developments in mitochondrial medicine, tumor cells undergoes metabolic adaptability to chemotherapeutic drugs is mediated by mitochondrial fusion and fission. The elevation of MFN1/2 and OPA1 expression, along with correlation mitochondrial networks in drug-resistant of cancer cells are the main indicators of the importance of mitochondrial fusion in chemoresistance. For example, when acute myeloid leukemia (AML) cells are treated with venetoclax for an extended period of time, increased OPA1 produces resistance to cytochrome c release.[52]

Emerging research and future directions

Mitochondrial involvement in OSCC therapy has been recognized, yet only limited studies or reviews are available, making comprehensive analysis challenging. Expanding this research could clarify mitochondrial roles in OSCC treatment, improve therapy effectiveness, and support the development of novel anticancer strategies.[33] Although mitochondrial mechanisms are gaining interest, several pathways remain poorly understood. Mitochondria can enhance treatment response while also contributing to therapy resistance. Targeting them with nanoparticles has emerged as a promising approach to modulate resistance and optimize therapeutic outcomes.[33]

Integrins, key coordinators of intracellular and extracellular signaling, are frequently dysregulated in cancers and can alter the tumor microenvironment.[30] Glycolytic enzymes such as PFK, HK2, PKM2, and G6PD are upregulated in OSCC, reflecting enhanced metabolic activity.45–48 Elevated lactate dehydrogenase (LDH) levels in serum and saliva of OSCC patients further support its potential as a diagnostic biomarker.[49] Drug resistance remains a major challenge in cancer therapy. The ability of cancer cells to adapt to therapeutic stress is poorly understood. Since mitochondria serve as the primary hub for cellular energy, their metabolic flexibility provides cancer cells with robust bioenergetic and biosynthetic capacity, contributing to treatment resistance and tumor survival.[42]

Conclusion

Mitochondrial dysfunction plays a central role in oral cancer development and is closely linked to various metabolic disorders. Disrupted mitochondrial dynamics, mtDNA mutations, and altered metabolic pathways drive cancer progression by enhancing glycolysis, oxidative stress, and therapy resistance. The metabolic shift toward aerobic glycolysis and altered OXPHOS the Warburg effect supports rapid proliferation and inhibits apoptosis. Mutations in mtDNA and mitochondrial enzymes promote abnormal signaling, genomic instability, and increased ROS production. Impaired retrograde signaling further alters nuclear gene expression, facilitating invasion, metastasis, and treatment resistance. Accumulation of ROS and lactate creates a tumor-supportive microenvironment that enhances immune evasion and metastatic potential. Understanding these mitochondrial contributions offers opportunities for targeted therapies aimed at restoring mitochondrial function, correcting metabolic reprogramming, and improving treatment responses. Future research should prioritize mitochondria-focused strategies to enhance oral cancer management and patient outcomes.

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