

Comparative Evaluation of Mitochondrial Dysfunction in Oral Leukoplakia and Associated Oral Squamous Cell Carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC) represents a significant global oncologic burden, particularly in regions with prevalent tobacco and areca nut exposure. A substantial proportion of OSCC arises from oral leukoplakia (OL), the most common oral potentially malignant disorder (OPMD). Although histopathological grading of epithelial dysplasia remains the principal risk assessment tool, it does not fully capture underlying metabolic and molecular instability that precedes malignant transformation. Increasing evidence suggests that mitochondrial dysfunction represents a progressive and biologically significant driver of oral carcinogenesis. Chronic carcinogen exposure induces sustained oxidative stress, leading to mitochondrial DNA (mtDNA) instability, impaired oxidative phosphorylation, altered mitochondrial dynamics, metabolic reprogramming toward glycolytic dominance, and resistance to intrinsic apoptosis. These alterations appear to evolve across the continuum from OL to invasive OSCC. This narrative comprehensively reviews contemporary evidence regarding mitochondrial alterations in oral carcinogenesis, explores diagnostic and prognostic implications, examines therapeutic targeting strategies, and highlights current limitations and future research directions. Integration of mitochondrial profiling into oral oncology may refine early risk stratification and support precision redox-based therapeutic approaches.

Keywords: Oral leukoplakia, Oral squamous cell carcinoma, Mitochondrial DNA, Oxidative stress, Metabolic reprogramming

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1. Introduction

Oral cancer continues to represent a major global public health challenge, accounting for more than 350,000 new cases annually and over 170,000 deaths worldwide [1, 2]. Oral squamous cell carcinoma (OSCC) comprises approximately 90–95% of oral malignancies and remains associated with suboptimal five-year survival rates despite advances in surgical and adjuvant therapies [1–3]. The burden is disproportionately higher in South and Southeast Asia, where smokeless tobacco, betel quid, and areca nut consumption are prevalent risk factors (Figure 1 and 2) [2, 4].

Oral leukoplakia (OL), defined as a predominantly white plaque of questionable risk that cannot be characterized as any other disease, represents the most common oral potentially malignant disorder (OPMD) [4, 5]. Reported malignant transformation rates range between 1% and 20%, depending on lesion subtype,

anatomical location, patient-related factors, and duration of follow-up [5, 6]. Histopathological grading of epithelial dysplasia remains the gold standard for estimating transformation risk. However, discordance between dysplasia severity and biological behavior underscores the limitations of morphology-based assessment alone (Figure 3 and 4) [6].

Recent advances in molecular oncology suggest that metabolic remodeling and mitochondrial dysfunction may play pivotal roles in tumor initiation and progression [7–9]. While classical carcinogenesis models emphasize nuclear genetic instability, growing evidence indicates that bioenergetic alterations and redox imbalance actively shape the tumor microenvironment [8, 10]. Mitochondria are central regulators of cellular energy metabolism, apoptosis, redox signaling, calcium homeostasis, and biosynthetic pathways [9, 11]. Persistent

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Figure 1. (A) Intraoral Photographs Showing Exophytic-endophytic Growth Over the Ventrolateral Aspect of Tongue. (B) Exophytic Growth Over Right Buccal Mucosa.

mitochondrial perturbation may therefore influence both early transformation and tumor aggressiveness.

Emerging data demonstrate mitochondrial DNA alterations, dysregulated oxidative phosphorylation, enhanced glycolysis, and altered mitochondrial dynamics in head and neck squamous cell carcinoma [12-14]. However, the progressive relationship between mitochondrial dysfunction in OL and subsequent OSCC development remains incompletely understood. A comprehensive synthesis of contemporary evidence is therefore warranted.

2. Epidemiological and Molecular Context of Oral Carcinogenesis

OSCC development is strongly associated with chronic exposure to carcinogens such as tobacco nitrosamines, areca nut alkaloids, and alcohol metabolites [2, 4]. These agents induce sustained oxidative stress, DNA damage, and inflammatory responses within oral mucosa [15, 16]. Molecular characterization studies of head and neck squamous cell carcinoma have revealed alterations in TP53, CDKN2A, PI3K/AKT signaling, and other oncogenic pathways [3, 17].

While nuclear genomic instability remains central

to carcinogenesis, metabolic dysregulation has emerged as a parallel hallmark of malignant transformation [7, 8]. Cancer cells exhibit adaptive metabolic plasticity that supports proliferation under stress conditions. Mitochondrial dysfunction may contribute both to the initiation of genetic instability and to the metabolic reprogramming necessary for tumor survival [9, 11].

In OPMDs such as OL, early molecular alterations including oxidative DNA damage and dysregulated redox signaling have been documented prior to invasive transformation [6, 18]. These findings suggest that mitochondrial perturbations may precede overt carcinoma.

3. Carcinogen-Induced Oxidative Stress and Mitochondrial Vulnerability

Reactive oxygen species (ROS) are generated physiologically as byproducts of mitochondrial respiration. Under normal conditions, antioxidant systems maintain redox homeostasis [19]. However, chronic exposure to carcinogens increases ROS production beyond buffering capacity, resulting in oxidative stress [15, 19].

Tobacco-derived nitrosamines and areca nut constituents stimulate ROS generation within oral epithelial cells [4, 15]. Alcohol metabolism further

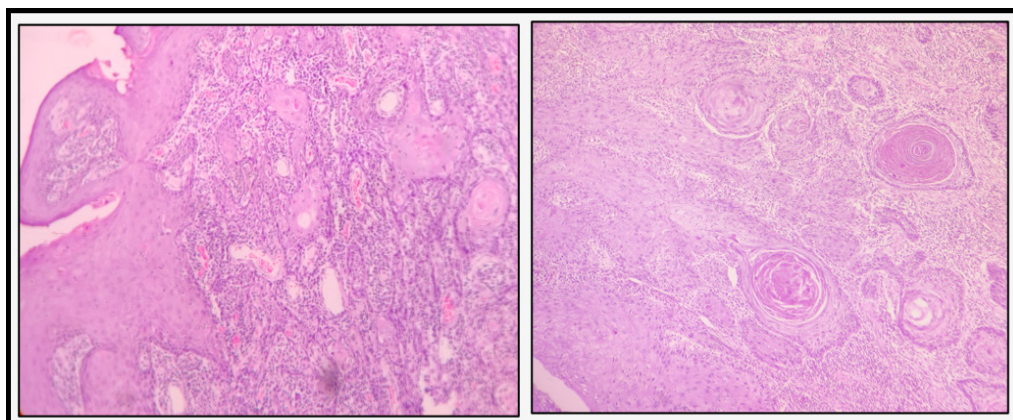


Figure 2. H & E-stained Sections Reveal the Presence of Parakeratotic Stratified Squamous Epithelium which is Discontinuous at Places and Showing Varying Degrees of Atypia. The most striking feature is the presence of tumor islands in the subadjacent connective tissue stroma, being composed of neoplastic epithelial cells showing cellular atypia and nuclear pleomorphism and arranged in nests and cords, with profuse keratin differentiation at multiple places.



Figure 3. (A&B) Intraoral Photographs Showing Greyish-white Lesions on Left Buccal Mucosa and Left Retro-commissural Area.

contributes to acetaldehyde-induced oxidative injury [16]. Sustained ROS accumulation damages lipids, proteins, and nucleic acids, including mitochondrial DNA (mtDNA).

Mitochondria are particularly susceptible to oxidative injury due to the absence of protective histones and limited DNA repair mechanisms [11]. Damage to electron transport chain (ETC) complexes increases electron leakage, further amplifying ROS production in a self-perpetuating cycle (Table 1) [20].

4. Mitochondrial DNA Alterations and Genomic Instability in Oral Carcinogenesis

Mitochondrial DNA (mtDNA) is a 16.6 kb circular genome encoding 13 essential subunits of the electron transport chain (ETC), 22 transfer RNAs, and 2 ribosomal RNAs. Unlike nuclear DNA, mtDNA lacks protective histone proteins and possesses comparatively limited repair capacity, rendering it highly susceptible to oxidative damage [11, 20].

4.1 mtDNA Mutations in OSCC

Recent sequencing-based analyses in head and neck squamous cell carcinoma have demonstrated frequent mtDNA mutations, particularly within genes encoding

components of complexes I and III of the ETC [12, 21]. Such mutations may impair respiratory efficiency, increase electron leakage, and amplify reactive oxygen species (ROS) production.

Studies evaluating OSCC tissues have reported increased mutation burden compared with adjacent non-tumorous mucosa [13, 22]. Importantly, certain mtDNA mutations have been associated with altered tumor behavior and poorer clinical outcomes [23]. However, the heterogeneity of reported mutations suggests that mtDNA alterations may contribute to carcinogenesis through cumulative bioenergetic disruption rather than through single driver events.

4.2 mtDNA Copy Number Variability

Alterations in mtDNA copy number represent another important dimension of mitochondrial genomic instability. Both mtDNA depletion and compensatory amplification have been described in OSCC [12, 24]. Increased mtDNA copy number may reflect a cellular attempt to compensate for impaired oxidative phosphorylation, whereas depletion may indicate severe mitochondrial dysfunction.

Recent studies have suggested that altered mtDNA copy number may hold prognostic value in OSCC patients, although findings remain inconsistent across populations [24, 25]. Standardization of quantification techniques is necessary before clinical application.

The observed heterogeneity in mtDNA copy number across studies likely reflects biological and methodological variability. From a biological standpoint, early-stage lesions such as oral leukoplakia may demonstrate compensatory mtDNA amplification in response to oxidative phosphorylation impairment, whereas advanced tumors may exhibit mtDNA depletion due to cumulative mitochondrial damage and metabolic rewiring [26]. Tumor site-specific differences, particularly between tongue and buccal mucosa, may further contribute to variability due to differences in vascularity, carcinogen exposure, and microenvironmental hypoxia. Additionally, tumor stage and differentiation status influence mitochondrial biogenesis and turnover. Methodologically, discrepancies may arise from variations in quantification techniques, normalization strategies, and sample types (tissue vs. saliva vs. blood). Therefore, mtDNA copy number

Table 1. Environmental Risk Factors and Mitochondrial Consequences in Oral Carcinogenesis.

Risk Factor	Primary Mitochondrial Effect	Downstream Cellular Impact
Tobacco nitrosamines	ETC complex disruption	Increased ROS generation
Areca nut alkaloids	Persistent oxidative burden	mtDNA mutations
Alcohol metabolites	Membrane depolarization	Reduced ATP production
Chronic inflammation	Cytokine-mediated ROS amplification	NF- κ B activation
Nutritional deficiency	Reduced antioxidant defenses	Enhanced lipid peroxidation

Major environmental carcinogens implicated in oral carcinogenesis induce progressive mitochondrial injury through oxidative mechanisms. Persistent mitochondrial dysfunction may therefore serve as a bridge linking environmental exposure to molecular transformation.

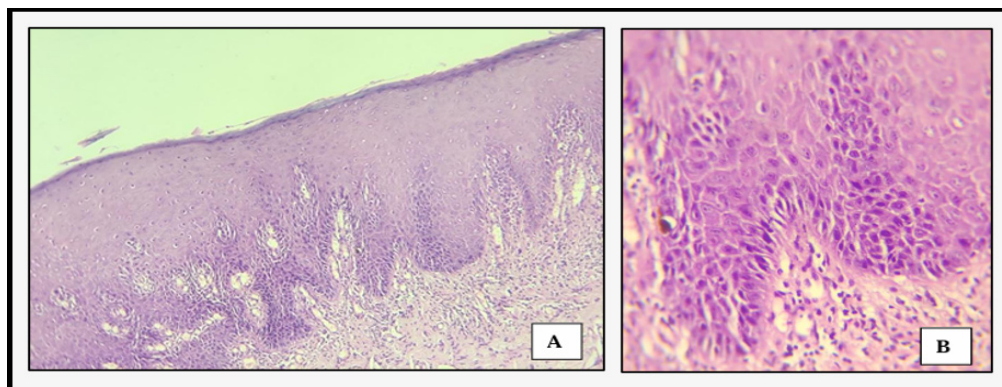


Figure 4. [A-10X, B-40X]: The Sections Stained with H and E Revealed the Presence of Hyperplastic, Hyper-parakeratinized, Stratified Squamous Surface Epithelium Having Broad, Bulbous Rete Ridges with Fibro-vascular Connective Tissue Stroma. The epithelium showed increase in the thickness of the spinous cell layer with cellular atypia involving basal, supra-basal and in some areas it involve half of the prickle cell layers. The connective tissue shows presence of non-specific chronic inflammatory cell infiltrate.

alterations should be interpreted within a contextual framework incorporating lesion stage, anatomical site, and methodological standardization [12].

4.3 Field Cancerization and Mitochondrial Genomic Alterations

The concept of field cancerization proposes that widespread molecular alterations occur within clinically normal mucosa exposed to carcinogens [17]. Mitochondrial genomic instability has been detected in histologically normal mucosa adjacent to OSCC lesions [13]. This observation supports the hypothesis that mitochondrial alterations may precede overt malignant transformation.

In oral leukoplakia, preliminary data indicate the presence of oxidative DNA damage and early mitochondrial perturbation even in lesions without severe dysplasia [18, 27]. Such findings raise the possibility that mitochondrial biomarkers could enhance risk stratification beyond histopathology.

5. Redox Signaling and Oncogenic Pathway Activation

While excessive ROS induce molecular damage, sublethal ROS levels function as signaling intermediates that modulate transcriptional programs [19]. Persistent mitochondrial ROS production can therefore promote oncogenic signaling.

5.1 MAPK and PI3K/AKT Pathways

ROS-mediated activation of the mitogen-activated protein kinase (MAPK) pathway enhances cellular proliferation and survival [28]. Similarly, redox modulation of the PI3K/AKT pathway promotes metabolic adaptation and resistance to apoptosis [28, 29].

In OSCC, activation of PI3K/AKT signaling is frequently observed and has been associated with tumor progression and therapeutic resistance [3, 17].

5.2 NF- κ B Activation and Inflammatory Microenvironment

Chronic inflammation represents a recognized driver of oral carcinogenesis. Mitochondrial ROS activate nuclear factor-kappa B (NF- κ B), leading to transcription of

pro-inflammatory cytokines and anti-apoptotic genes [19, 30]. Sustained NF- κ B signaling fosters a tumor-promoting microenvironment and may facilitate immune evasion.

5.3 Hypoxia-Inducible Factor-1 α (HIF-1 α) Stabilization

Hypoxic microenvironments emerge within expanding dysplastic lesions and invasive tumors. Mitochondrial ROS can stabilize hypoxia-inducible factor-1 α (HIF-1 α), even under normoxic conditions [31, 32]. Stabilized HIF-1 α upregulates genes involved in angiogenesis (VEGF), glycolysis (GLUT1, HK2), and survival pathways.

Overexpression of HIF-1 α has been correlated with poor prognosis in head and neck cancers (Table 2) [33].

6. Metabolic Reprogramming and Bioenergetic Plasticity

Metabolic remodeling is increasingly recognized as a fundamental feature of tumor biology [7, 9]. In OSCC, mitochondrial dysfunction frequently coincides with enhanced glycolytic activity.

6.1 Shift Toward Aerobic Glycolysis

Although oxidative phosphorylation (OXPHOS) remains functional in many tumors, cancer cells often exhibit increased reliance on glycolysis for ATP production, even in the presence of oxygen [9]. This metabolic shift allows rapid ATP generation and supports biosynthetic pathways necessary for proliferation.

Table 2. Major Oncogenic Pathways Influenced by Mitochondrial ROS.

Pathway	Mechanism of Activation	Functional Consequence
MAPK	ROS-mediated phosphorylation cascades	Enhanced proliferation
PI3K/AKT	Redox-sensitive signaling modulation	Survival and metabolic adaptation
NF- κ B	Mitochondrial retrograde signaling	Inflammation and anti-apoptosis
HIF-1 α	ROS-induced stabilization	Glycolytic reprogramming and angiogenesis

Persistent mitochondrial ROS activate multiple oncogenic signaling pathways that support malignant progression in oral epithelium.

Enhanced expression of glycolytic enzymes including hexokinase-2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA) has been documented in head and neck cancers [25, 34]. Glycolytic upregulation has also been observed in premalignant lesions, suggesting early metabolic adaptation [27].

Accumulation of lactate within the tumor microenvironment contributes to extracellular acidification, promoting invasion, angiogenesis, and immune modulation [35].

6.2 Glutamine Metabolism and TCA Cycle Adaptation

Beyond glucose metabolism, glutamine serves as a key substrate for biosynthesis and replenishment of tricarboxylic acid (TCA) cycle intermediates [36]. Under conditions of impaired mitochondrial respiration, glutamine-derived carbon can sustain anabolic processes.

Recent investigations have identified altered glutamine metabolism in head and neck squamous cell carcinoma, highlighting metabolic flexibility as a therapeutic target [36, 37].

6.3 Mitochondrial OXPHOS in OSCC: Suppressed or Rewired?

Contrary to earlier assumptions that mitochondrial respiration is universally suppressed in cancer, contemporary evidence suggests that many tumors retain functional OXPHOS while augmenting glycolysis [8, 10]. In OSCC, both enhanced glycolysis and residual mitochondrial respiration have been described [21, 37].

This dual metabolic capacity confers adaptive advantages under fluctuating microenvironmental conditions (Table 3).

7. Hypoxia and Microenvironmental Adaptation

As dysplastic lesions enlarge, local hypoxia develops due to inadequate vascular supply. Hypoxia not only stabilizes HIF-1 α but also modulates mitochondrial respiration to reduce oxygen consumption [31].

Hypoxia-driven metabolic adaptation enhances angiogenesis and promotes epithelial–mesenchymal transition (EMT), facilitating invasion and metastasis [32, 33].

In leukoplakia lesions exhibiting severe dysplasia, early microvascular alterations may contribute to localized hypoxia, reinforcing metabolic remodeling.

8. Mitochondrial Dynamics and Structural Remodeling in Oral Carcinogenesis

Mitochondria are not static organelles; they exist as dynamic networks that continuously undergo fission and fusion to maintain structural and functional integrity [38]. These processes are tightly regulated and essential for mitochondrial quality control, bioenergetic balance, and apoptosis regulation.

Disruption of mitochondrial dynamics has increasingly been implicated in cancer biology, including head and neck squamous cell carcinoma.

8.1 Mitochondrial Fission

Mitochondrial fission is primarily mediated by dynamin-related protein 1 (Drp1), a cytosolic GTPase that translocates to the outer mitochondrial membrane and facilitates organelle division [38]. Increased Drp1 activity leads to mitochondrial fragmentation, a phenotype frequently observed in malignant cells.

Enhanced mitochondrial fission has been associated with:

- Increased reactive oxygen species production
- Altered metabolic flexibility
- Resistance to apoptosis
- Enhanced migratory capacity

Studies in head and neck cancers have demonstrated elevated Drp1 expression correlating with tumor aggressiveness [39]. Fragmented mitochondria may facilitate metabolic reprogramming by optimizing glycolytic adaptation and altering mitochondrial membrane potential.

8.2 Mitochondrial Fusion

Fusion processes are mediated by mitofusin-1 (MFN1), mitofusin-2 (MFN2), and optic atrophy protein 1 (OPA1) [38]. Fusion enables mixing of mitochondrial contents, allowing functional complementation of damaged components.

Reduced expression of fusion proteins has been described in multiple malignancies. Impaired fusion can exacerbate mitochondrial dysfunction and promote oxidative stress.

Although specific data in oral leukoplakia remain limited, it is plausible that early dysregulation of fission–fusion balance contributes to progressive mitochondrial instability during transformation.

Table 3. Metabolic Alterations Across Disease Continuum.

Parameter	Normal Epithelium	Oral Leukoplakia	OSCC
ROS Levels	Physiological	Moderately elevated	Markedly elevated
OXPHOS	Efficient	Partially impaired	Rewired/variable
Glycolysis	Basal	Increased	Dominant
Lactate Production	Minimal	Elevated	High
Glutamine Utilization	Baseline	Altered	Enhanced

Progressive metabolic reprogramming accompanies transformation from oral leukoplakia to invasive OSCC.

9. Mitophagy and Mitochondrial Quality Control

Mitophagy represents a selective autophagic process that eliminates damaged mitochondria, thereby preserving cellular homeostasis [40]. The PINK1–Parkin pathway plays a central role in identifying and targeting dysfunctional mitochondria for degradation.

Under physiological conditions, mitophagy prevents accumulation of ROS-producing organelles. However, impaired mitophagy may allow persistence of dysfunctional mitochondria, amplifying oxidative stress and genomic instability.

Recent evidence suggests that alterations in mitochondrial quality control pathways may contribute to tumor progression and therapeutic resistance [37, 40]. In OSCC, aberrant autophagic signaling has been linked to altered survival pathways, though precise mechanistic relationships with mitochondrial dysfunction require further clarification.

10. Intrinsic Apoptotic Dysregulation

Mitochondria are central regulators of intrinsic apoptosis. In response to severe cellular stress, mitochondrial outer membrane permeabilization (MOMP) results in release of cytochrome c, activation of caspases, and programmed cell death [41].

10.1 BCL-2 Family Proteins

The BCL-2 family of proteins governs mitochondrial membrane integrity. Anti-apoptotic members (BCL-2, BCL-xL, MCL-1) counteract pro-apoptotic proteins (BAX, BAK) [42].

Overexpression of anti-apoptotic BCL-2 family proteins has been documented in various cancers, including OSCC [42, 43]. Such dysregulation suppresses apoptosis, allowing survival of cells harboring mitochondrial and nuclear genomic damage.

10.2 Caspase Activation and Mitochondrial Membrane Potential

Reduced caspase activation and altered mitochondrial membrane potential have been observed in head and neck squamous cell carcinoma [43]. Loss of apoptotic sensitivity enables clonal expansion of metabolically

adapted cells.

In oral leukoplakia, apoptotic dysregulation may represent an intermediate stage, with partial resistance emerging prior to invasive transformation.

11. Integrated Model of Progressive Mitochondrial Dysfunction

Collectively, mitochondrial alterations in oral carcinogenesis can be conceptualized as a progressive continuum (Table 4):

1. Chronic carcinogen exposure induces oxidative stress.
2. ROS damage mtDNA and ETC components.
3. Mitochondrial dysfunction amplifies ROS production.
4. Redox-sensitive oncogenic pathways are activated.
5. Metabolic reprogramming toward glycolysis occurs.
6. Dysregulated fission–fusion balance increases fragmentation.
7. Apoptotic resistance enables survival of unstable clones.
8. Invasive OSCC develops (Figure 5 and 6).

12. Mitochondrial Biomarkers in Oral Potentially Malignant Disorders

Given the progressive nature of mitochondrial alterations, several biomarkers have been proposed for risk stratification.

12.1 mtDNA Copy Number

Altered mtDNA copy number has been explored as a potential early transformation marker [12, 24]. Some studies report increased copy number in early lesions, while others note depletion in advanced tumors.

12.2 Oxidative Stress Markers

Salivary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) have been reported at elevated levels in OPMDs and OSCC [23]. Salivary diagnostics offer non-invasive assessment potential.

12.3 Metabolic Enzyme Expression

Overexpression of glycolytic enzymes such as HK2 and LDHA may reflect metabolic reprogramming [25, 34].

Table 4. Progressive Mitochondrial Alterations from OL to OSCC.

Feature	Normal Mucosa	Oral Leukoplakia	OSCC
ROS	Physiological	Elevated	Markedly elevated
mtDNA mutations	Rare	Emerging	Frequent
OXPPOS efficiency	Intact	Reduced	Rewired/variable
Glycolysis	Basal	Increased	Dominant
Fission activity	Balanced	Increasing	Enhanced
Apoptotic sensitivity	Preserved	Partially reduced	Suppressed

Conceptual progression of mitochondrial dysfunction during oral malignant transformation.

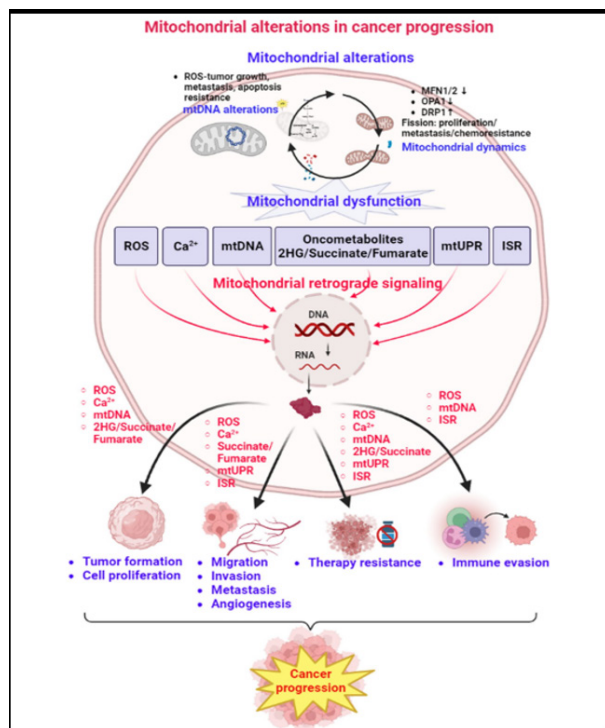


Figure 5. Mitochondrial Alterations Driving Cancer Progression Through Retrograde Signaling Pathways.

Tissue-based immunohistochemistry may support adjunct risk assessment (Table 5).

13. Therapeutic Targeting of Mitochondrial Dysfunction in OSCC

Recognition of mitochondrial dysfunction as a contributor to oral carcinogenesis has stimulated investigation into metabolism-oriented therapeutic strategies. Unlike conventional cytotoxic therapies that primarily target rapidly dividing cells, mitochondrial-targeted approaches aim to exploit bioenergetic vulnerabilities and redox imbalance.

13.1 Redox Modulation Strategies

Tumor cells often maintain elevated baseline reactive oxygen species (ROS) levels while upregulating antioxidant systems to avoid lethal oxidative damage [19, 44]. Therapeutic approaches may therefore pursue one of two strategies:

1. Pro-oxidant therapy – further increasing ROS to exceed cytotoxic thresholds.
2. Antioxidant pathway inhibition – suppressing tumor redox buffering systems.

Agents targeting glutathione metabolism and thioredoxin systems have shown potential in preclinical cancer models [44, 45]. In head and neck cancers, modulation of oxidative stress pathways may enhance radiosensitivity and chemotherapy response [21].

However, the paradox of antioxidant supplementation in cancer prevention remains unresolved, as excessive antioxidant use may theoretically protect tumor cells from ROS-mediated death.

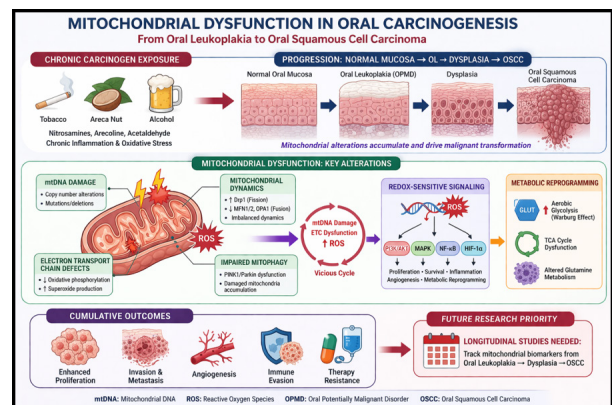


Figure 6. Integrated Model of Mitochondrial Dysfunction in Oral Carcinogenesis: from Oral Leukoplakia to Oral Squamous Cell Carcinoma.

13.2 Targeting Oxidative Phosphorylation (OXPHOS)

Inhibition of mitochondrial respiration has emerged as an attractive strategy in tumors exhibiting OXPHOS dependence [8, 46]. Pharmacologic inhibitors of mitochondrial complex I and ATP synthase are under investigation in various malignancies.

In head and neck squamous cell carcinoma, metabolic profiling suggests that subsets of tumors retain functional OXPHOS and may be susceptible to mitochondrial inhibitors [21, 37].

Selective targeting remains challenging due to the essential role of mitochondria in normal tissues.

13.3 Glycolysis Inhibition

Given enhanced glycolytic flux in OSCC, inhibition of glycolytic enzymes represents another potential strategy [25, 34]. Agents targeting hexokinase-2 (HK2), LDHA, and glucose transporters have demonstrated preclinical efficacy.

2-deoxy-D-glucose (2-DG) has been explored as a glycolytic inhibitor and radiosensitizer in various cancers, including head and neck malignancies [47]. By limiting glycolytic compensation, such agents may increase susceptibility to oxidative damage.

13.4 Targeting Glutamine Metabolism

Glutamine metabolism supports nucleotide synthesis and redox homeostasis [36]. Inhibition of glutaminase and related enzymes may disrupt anabolic pathways essential for tumor growth.

Recent studies suggest metabolic vulnerabilities in head and neck cancers that may be therapeutically exploited [37].

13.5 Modulation of Mitochondrial Dynamics and Apoptosis

Inhibition of excessive mitochondrial fission through Drp1 modulation has shown tumor-suppressive effects in experimental systems [39]. Additionally, BH3 mimetics targeting anti-apoptotic BCL-2 family proteins may restore intrinsic apoptotic signaling [42].

Combination approaches integrating mitochondrial targeting with conventional therapy may overcome

Table 5. Candidate Mitochondrial and Redox Biomarkers in OPMDs.

Biomarker	Sample Type	Clinical Potential	Limitation
mtDNA copy number	Tissue/Saliva	Early transformation indicator	Technical variability
8-OHdG	Saliva/Serum	Oxidative DNA damage	Non-specific
MDA	Saliva	Lipid peroxidation	Systemic confounding
HK2 expression	Tissue	Glycolytic activation	Requires biopsy
LDHA expression	Tissue	Metabolic shift	Stage-dependent

treatment resistance.

14. Clinical Translation: Challenges and Considerations

Despite compelling mechanistic evidence, translation of mitochondrial biomarkers and therapies into routine clinical practice faces several limitations.

14.1 Heterogeneity of Findings

Variability in mtDNA mutation patterns and copy number changes complicates biomarker standardization [12, 24]. Differences in tissue sampling, quantification methods, and patient demographics contribute to inconsistency.

14.2 Lack of Longitudinal OPMD Studies

A critical limitation in the current literature is the lack of well-designed longitudinal studies evaluating mitochondrial alterations in oral potentially malignant disorders. Most available data are derived from cross-sectional analyses, which preclude definitive conclusions regarding temporal progression and causal relationships. There is a pressing need for prospective cohort studies that track mitochondrial biomarkers including mtDNA copy number, oxidative stress markers, and metabolic enzyme expression from Oral Leukoplakia through dysplasia to invasive carcinoma. Such studies would enable validation of mitochondrial parameters as predictive biomarkers for malignant transformation and facilitate risk stratification beyond conventional histopathology. Addressing this gap should be considered a priority in future oral oncology research. [6, 27].

14.3 Metabolic Plasticity and Therapeutic Resistance

Cancer cells exhibit metabolic flexibility, allowing adaptation to metabolic inhibitors [9, 37]. Targeting a single pathway may therefore yield limited durability.

14.4 Specificity and Toxicity

Given the essential role of mitochondria in normal tissues, therapeutic selectivity remains a major challenge. Mitochondrial-targeted agents must minimize systemic toxicity.

Limitations and Controversies

While evidence supports the involvement of mitochondrial dysfunction in oral carcinogenesis, several unresolved questions persist:

1. Cause versus Consequence: Whether mitochondrial

alterations initiate transformation or arise secondary to oncogenic signaling remains debated [17].

2. mtDNA Copy Number Directionality: Studies report both increased and decreased mtDNA copy numbers in OSCC, suggesting context-dependent regulation [12, 24].

3. Field Cancerization Complexity: Detection of mitochondrial alterations in adjacent clinically normal mucosa complicates specificity of biomarkers [13].

4. Antioxidant Therapy Paradox: The dual role of ROS in promoting both carcinogenesis and apoptosis complicates redox-based interventions [44].

Addressing these issues requires mechanistic experimentation and well-designed clinical studies.

Future Directions: Toward Precision Redox Oncology

Future research priorities include:

- Integration of multi-omics profiling combining genomics, transcriptomics, proteomics, and metabolomics [9].
- Standardization of mtDNA quantification techniques.
- Development of composite biomarker panels incorporating mitochondrial and redox markers.
- Artificial intelligence-based risk modeling for OPMD progression.
- Clinical trials evaluating mitochondrial-targeted therapies in OSCC.

Precision oncology approaches incorporating metabolic profiling may improve early detection and personalized therapy selection.

In conclusion, mitochondrial dysfunction represents a progressive and biologically meaningful component of oral carcinogenesis. Chronic carcinogen exposure induces sustained oxidative stress, leading to mtDNA instability, impaired oxidative phosphorylation, redox-driven oncogenic signaling, metabolic reprogramming, dysregulated mitochondrial dynamics, and resistance to intrinsic apoptosis. These alterations evolve from oral leukoplakia to invasive OSCC, suggesting potential diagnostic and therapeutic relevance.

While mitochondrial biomarkers and metabolic targeting strategies show promise, clinical translation requires rigorous validation and mechanistic clarification. Integration of mitochondrial assessment with conventional histopathology may refine risk stratification and support precision redox-based interventions in oral oncology.

Conflict of Interest

There is no conflict of interest.

Acknowledgments

Statement of Transparency and Principles

- The authors declare no conflict of interest.
- The study was approved by the Research Ethics Committee of the authors' affiliated institution.
- All authors contributed to the implementation of this research.

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