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·综述·

线粒体代谢重编程驱动口腔鳞状细胞癌发展及治疗抵抗的研究进展

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【摘要】 口腔鳞状细胞癌(OSCC)是口腔癌最主要的组织学类型，局部侵袭、淋巴结转移及治疗抵抗是影响患者预后的重要因素。研究表明，线粒体代谢重编程贯穿OSCC发生、发展及治疗抵抗过程，并随疾病发展呈现不同的代谢适应特征。在肿瘤发生阶段，烟草、槟榔及酒精等长期致癌刺激可诱导线粒体功能紊乱并促进线粒体活性氧积累，激活丝裂原活化蛋白激酶、核因子κB及磷脂酰肌醇3-激酶/蛋白激酶B等应激相关信号通路，并伴随氧化还原缓冲能力增强，有利于受损细胞的适应性存活；在肿瘤发展阶段，无精子症缺失相关蛋白1-细胞色素c氧化酶组装因子16、趋化因子样受体1-磷脂酰肌醇3-激酶/蛋白激酶B-过氧化物酶体增殖物激活受体γ共激活因子1α、干扰素调节因子2结合蛋白2-动力蛋白相关蛋白1-肉碱棕榈酰转移酶1A等调控轴可通过调节线粒体呼吸、氧化代谢及脂肪酸氧化等过程，促进OSCC细胞增殖、侵袭及转移；在治疗抵抗阶段，线粒体微小RNA-2392/Argonaute蛋白2和线粒体微小RNA-5787-线粒体编码的细胞色素c氧化酶亚基3等线粒体调控机制可导致氧化磷酸化降低和糖酵解增强，促进化疗抵抗，甲基转移酶样蛋白1介导的转运RNA 7-甲基鸟苷修饰可驱动能量代谢由糖酵解向氧化磷酸化转换并促进安罗替尼治疗抵抗，醛脱氢酶1家族成员L1下调介导的谷氨酰胺合成酶-L-谷氨酸代谢异常可抑制$CD8^+$ T细胞线粒体氧化磷酸化并促进T细胞耗竭，降低抗程序性死亡受体1治疗反应。由此可见，OSCC线粒体代谢重编程并非单一代谢通路的改变，而是随病程演进、微环境变化及治疗压力动态调整的代谢适应过程。未来应结合单细胞多组学、空间代谢组学、稳定同位素示踪及患者来源模型，解析OSCC代谢异质性，筛选用于患者分层和疗效预测的代谢标志物，并探索基于代谢特征的精准联合治疗策略。

【关键词】 口腔鳞状细胞癌；　线粒体代谢重编程；　氧化磷酸化；　能量代谢；　线粒体活性氧；　代谢可塑性；　肿瘤微环境；　治疗抵抗
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Advances in mitochondrial metabolic reprogramming driving oral squamous cell carcinoma progression and therapeutic resistance

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【Abstract】 Oral squamous cell carcinoma (OSCC) is the predominant histological type of oral cancer. Local invasion, lymph node metastasis, and therapeutic resistance remain major factors affecting patient prognosis. Recent studies have

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demonstrated that mitochondrial metabolic reprogramming occurs throughout OSCC initiation, progression, and therapeutic resistance, exhibiting distinct metabolic adaptations during disease evolution. During tumor initiation, chronic exposure to carcinogenic factors, including tobacco, areca nuts, and alcohol, induces mitochondrial dysfunction and mitochondrial reactive oxygen species accumulation; activates stress-responsive signaling pathways such as mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT); and enhances redox buffering capacity to facilitate the adaptive survival of damaged cells. During tumor progression, regulatory axes including Deleted in Azoospermia Associated Protein 1-Cytochrome c oxidase assembly protein 16, Chemokine-like receptor 1-PI3K/AKT/Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and Interferon regulatory factor 2-binding protein 2-Dynamin-related protein 1-Carnitine palmitoyltransferase 1A promote OSCC cell proliferation, invasion, and metastasis by regulating mitochondrial respiration, oxidative metabolism, and fatty acid oxidation. During therapeutic resistance, mitochondrial microRNA-2392/Argonaute 2 and mitochondrial microRNA-5787-mitochondrially encoded cytochrome c oxidase subunit 3-associated regulatory mechanisms contribute to chemoresistance by reducing oxidative phosphorylation and enhancing glycolysis, whereas Methyltransferase-like protein 1-mediated m7G tRNA modification drives a metabolic shift from glycolysis toward oxidative phosphorylation and promotes anlotinib resistance. In addition, Aldehyde dehydrogenase 1 family member L1 downregulation-mediated Glutamine synthetase-L-glutamate metabolic dysregulation suppresses mitochondrial oxidative phosphorylation in $CD8^+$ T cells and promotes T-cell exhaustion, thereby reducing the response to programmed cell death protein 1 (PD-1) blockade. Collectively, mitochondrial metabolic reprogramming in OSCC is not limited to alterations in a single metabolic pathway but represents a dynamic adaptive process shaped by disease progression, changes in the tumor microenvironment, and therapeutic pressure. Future studies should integrate single-cell multi-omics, spatial metabolomics, stable isotope tracing, and patient-derived models to resolve metabolic heterogeneity, identify metabolic biomarkers for patient stratification and therapeutic response prediction, and develop metabolism-guided precision combination therapeutic strategies.

【Key words】 oral squamous cell carcinoma; mitochondrial metabolic reprogramming; oxidative phosphorylation; energy metabolism; mitochondrial reactive oxygen species; metabolic plasticity; tumor microenvironment; therapeutic resistance

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口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)是口腔癌的主要组织学类型,具有较强的局部浸润和转移倾向[1-2]。虽然以手术为基础的综合治疗模式不断完善,放疗、化疗、靶向治疗及免疫治疗也已逐步应用于临床,但部分患者仍会出现复发、转移或治疗抵抗,导致总体疗效提升有限[3-4]。因此,从新的生物学视角解析OSCC发展和治疗失败的内在机制,对于寻找潜在干预靶点具有重要意义。

肿瘤代谢重编程是恶性肿瘤的重要特征之一,也是肿瘤细胞适应恶劣微环境并维持恶性表型的重要基础[5-6]。传统观点认为,肿瘤细胞主要依赖糖酵解获取能量,即“Warburg效应”[7]。近年来研究表明,肿瘤细胞在持续致癌刺激、复杂微环境和治疗压力下形成的代谢适应,逐渐被认为是影响OSCC恶性发展和治疗抵抗的重要基础之一[8-9]。其中,线粒体作为细胞代谢的核心枢纽,不仅是能量代谢中心,还参与肿瘤代谢适应和细胞命运调控。肿瘤细胞可通过调节线粒体呼吸活性、碳源利用方式和不同代谢通路之间的协调,满足快速增殖、侵袭的代谢需求并增强微环境压力的适应能力[10-13]。同时,线粒体相关的活性氧稳态、细胞死亡调控和线粒体动力学过程,也是影响肿瘤细胞命运的重要因素[14-15]。

治疗压力可进一步筛选或诱导具有线粒体代谢适应优势的OSCC细胞亚群,使其在损伤修复、抗氧化防御、凋亡逃逸及免疫逃逸等方面获得更强适应能力[16-18]。然而,目前OSCC中线粒体代谢重编程的研究仍较为分散,多聚焦于单一代谢过程或特定分子机制,尚缺乏对其在肿瘤进展、微环境适应和治疗抵抗中整体作用的系统梳理。基于此,本文围绕线粒体代谢重编程与OSCC恶性发展及治疗抵抗的关系进行综述,并讨论其在OSCC代谢干预策略中的潜在应用价值。

1　线粒体代谢重编程与OSCC形成

在OSCC形成早期，口腔上皮细胞线粒体在长期致癌刺激下经历由损伤到适应的动态变化[19-20]。烟草、酒精及槟榔相关暴露可使口腔上皮细胞长期处于炎症、氧化应激和代谢压力并存的状态，并持续扰动线粒体功能稳态[21-22]。严重线粒体损伤可导致细胞死亡，而部分受损细胞可通过增强代谢适应、维持氧化还原稳态及提高应激耐受性，在持续损伤压力下获得存活优势[7,23]。因此，OSCC早期线粒体代谢重编程可被视为慢性致癌压力下的适应性生存机制，使受损口腔上皮细胞逃避清除并获得异常存活优势。

1.1　致癌刺激诱导线粒体适应性重塑

长期外源性致癌暴露可直接或间接扰动口腔上皮细胞线粒体稳态[21,24-25]。既往研究提示，烟草相关刺激可通过活性氧（reactive oxygen species，ROS）介导的氧化应激激活丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）等应激信号通路，并导致线粒体膜电位异常、氧化磷酸化障碍及线粒体DNA损伤；槟榔碱可诱导ROS/线粒体来源的活性氧（mitochondrial reactive oxygen species，mtROS）积累，进而激活MAPK/细胞外信号调节激酶、核因子κB（nuclear factor-κB，NF-κB）及转化生长因子β相关信号通路，促进OSCC发生发展；乙醇代谢产生的乙醛可诱导氧化应激和线粒体功能障碍，表现为线粒体超氧化物增加和膜电位下降[26-32]。这些证据提示，外源性致癌因素可诱导线粒体氧化应激、功能损伤及质量控制异常，推动口腔上皮细胞由急性损伤反应逐渐转向适应性存活状态。

1.2　线粒体氧化还原重编程与异常细胞存活

线粒体代谢重编程常伴随氧化还原状态的重塑，其中mtROS是连接代谢重塑与细胞命运改变的重要信号介质[33]。正常情况下，线粒体呼吸链产生的ROS可被谷胱甘肽、硫氧还蛋白和超氧化物歧化酶等抗氧化系统作用下受到有效控制，从而维持氧化还原稳态[19,26]。当致癌刺激导致呼吸链电子传递异常、膜电位改变或线粒体DNA损伤时，mtROS生成增加并超过细胞缓冲能力，使细胞进入持续氧化还原压力状态[26-27]。

mtROS的作用具有剂量和情境依赖性。过量mtROS可造成脂质过氧化、蛋白质氧化及核DNA/线粒体DNA损伤，诱导细胞衰老或死亡；而持续的中低水平mtROS则可激活缺氧诱导因子1α、NF-κB、MAPK、磷脂酰肌醇3-激酶/蛋白激酶B（phosphoinositide 3-kinase/protein kinase B，PI3K/AKT）等应激适应信号，促进受损细胞存活[28,33]。因此，OSCC形成早期的关键并非ROS单纯升高，而在于受损口腔上皮细胞能否通过增强还原型烟酰胺腺嘌呤二核苷酸磷酸（nicotinamide adenine dinucleotide phosphate，NADPH）供给、谷胱甘肽循环、硫氧还蛋白等抗氧化系统，将氧化压力维持在可耐受范围内[34-38]。这种氧化还原适应既可降低过量ROS诱导的细胞死亡风险，又保留mtROS介导的促存活信号，从而为受损细胞持续存活和恶性转化提供条件[27,39]。

OSCC形成早期的线粒体代谢改变可从损伤程度和缓冲能力两个方面理解。外源性致癌刺激可诱导线粒体功能紊乱和氧化应激，但其结果取决于受损细胞能否通过氧化还原缓冲系统维持相对稳定的细胞状态。因此，不同研究中ROS、糖酵解或氧化磷酸化结果不一致，可能反映了细胞所处损伤程度和代偿状态的差异。总体而言，这一阶段的线粒体代谢重编程体现了慢性致癌刺激下线粒体损伤积累与氧化还原适应之间的动态平衡。

2　线粒体代谢重编程促进OSCC发展

OSCC形成后线粒体代谢重编程逐渐由早期应激适应转向支持肿瘤持续增殖、侵袭和转移[40-42]。

2.1　线粒体代谢重塑促进OSCC增殖与存活

在肿瘤细胞持续增殖过程中，线粒体不仅通过氧化磷酸化产生三磷酸腺苷（adenosine triphosphate，ATP），还通过三羧酸循环（tricarboxylic acid cycle，TCA）为核苷酸、脂质和氨基酸合成提供碳源及代谢中间体，并通过还原型/氧化型烟酰胺腺嘌呤二核苷酸、还原型/氧化型黄素腺嘌呤二核苷酸和NADPH相关氧化还原网络维持细胞稳态[43-44]。线粒体能量代谢重编程涉及糖酵解、氧化磷酸化、谷氨酰胺代谢、脂质代谢及氧化还原代谢等多条途径的协同调控[45-46]。

OSCC代谢组学及^{13}C-葡萄糖示踪研究显示，OSCC细胞除葡萄糖消耗和乳酸生成增加外，部分葡萄糖来源碳流还可进入TCA循环和脂质合成通路，并伴随谷氨酰胺消耗及TCA循环相关代谢改变，提示糖酵解、TCA循环及生物合成通路可共同参与OSCC的代谢重编程[47-48]。这种代谢可塑性还体现在不同碳源对线粒体代谢的共同支持。整

合素β2亚基高表达癌相关成纤维细胞（cancer-associated fibroblasts，CAFs）可通过激活PI3K/AKT/西罗莫司机制靶蛋白（mechanistic target of rapamycin，mTOR）信号通路增强糖酵解并促进乳酸释放，乳酸随后被OSCC细胞摄取利用，并促进线粒体氧化磷酸化和ATP生成，从而支持肿瘤细胞增殖。脂肪酸β氧化可为线粒体代谢提供乙酰辅酶A，而脂滴积累及脂肪酸代谢异常也可改变线粒体功能和细胞氧化应激状态；谷氨酰胺则可经谷氨酰胺酶分解生成α-酮戊二酸进入TCA循环，同时参与谷胱甘肽代谢，并影响细胞抗氧化能力和铁死亡敏感性[14,49-52]。在OSCC进展过程中，线粒体功能增强可作为促进恶性适应的重要代谢策略。例如，白细胞介素-1受体拮抗剂可通过调控线粒体代谢促进表皮生长因子受体/ c-Jun N端激酶/ SRY盒转录因子2信号轴活化，促进恶性表型形成；蛋白酶体激活因子28γ通过调控补体成分1 Q亚成分结合蛋白，增强线粒体功能和氧化磷酸化水平，从而促进肿瘤细胞增殖、迁移[53-55]。

2.2　线粒体代谢重编程促进OSCC上皮间充质转化、侵袭与转移

随着OSCC发展，线粒体代谢重编程可通过增强能量供应和线粒体适应能力，参与肿瘤上皮间充质转化、侵袭和转移[56-57]。在低氧压力下，OSCC干细胞可激活B细胞淋巴瘤2相互作用蛋白3/B细胞淋巴瘤2相互作用蛋白3样蛋白驱动的线粒体自噬程序，从而维持干性、上皮间充质转化及侵袭能力；与此同时，其氧化磷酸化依赖性增强，线粒体质量控制和呼吸功能维持可能共同参与肿瘤干细胞的低氧适应[58-59]。进一步机制研究显示，无精子症缺失相关蛋白1－细胞色素c氧化酶组装因子16轴通过促进线粒体呼吸链复合物Ⅳ组装增强氧化磷酸化，线粒体定位的ROS原癌基因1受体酪氨酸激酶可通过促进线粒体裂变增强线粒体呼吸，趋化因子样受体1－PI3K/AKT－过氧化物酶体增殖物激活受体γ共激活因子1α轴也可参与线粒体代谢重编程并促进OSCC细胞增殖、侵袭及转移[53,60-61]。长链非编码RNA介导的异质核糖核蛋白C－锌指E盒结合同源盒1调控轴通过增强糖酵解和线粒体呼吸，促进OSCC细胞侵袭及体内转移；干扰素调节因子2结合蛋白2则通过诱导动力蛋白相关蛋白1磷酸化介导的线粒体分裂，增强肉碱棕榈酰转移酶1A依赖性脂肪酸氧化，将线粒体动力学与能量代谢重编程相耦联，从而促进OSCC淋巴结转移[56,62]。

2.3　线粒体代谢可塑性与OSCC微环境适应

CAFs是OSCC微环境中参与基质重塑、血管生成和肿瘤进展的重要细胞。与正常成纤维细胞相比，CAFs可表现出更高的氧耗率和ATP生成水平，提示其线粒体氧化代谢活性增强。肿瘤坏死因子受体相关蛋白1可通过调控CAFs的氧化磷酸化影响OSCC发展[63]；头颈部鳞状细胞癌（head and neck squamous cell carcinoma，HNSCC）研究进一步显示，肿瘤来源碱性成纤维细胞生长因子可增强CAFs的氧化磷酸化，并通过肝细胞生长因子/c-Met信号促进肿瘤生长[64]。除CAFs外，内皮细胞的线粒体功能改变也可影响肿瘤血管表型。尽管OSCC中相关直接证据仍有限，但更广泛的内皮代谢研究提示，mtROS、脂肪酸氧化和氧化还原稳态异常可促进血管渗漏和结构紊乱，进而加重肿瘤缺氧与微环境失衡[65-67]。与效应T细胞在代谢受限环境中容易发生功能衰竭不同，部分免疫抑制性细胞可通过重塑线粒体能量代谢获得更强的环境适应能力，从而在肿瘤微环境中持续发挥免疫抑制作用。OSCC相关研究提示调节性T细胞可通过脂肪酸氧化支持线粒体氧化磷酸化，分化簇36介导的脂质摄取可能进一步增强调节性T细胞对乳酸富集、葡萄糖受限微环境的适应能力[68-70]。肿瘤相关巨噬细胞通常表现出以脂肪酸氧化依赖的氧化磷酸化代谢特征，该代谢状态与其免疫抑制、组织修复和促血管生成等功能相关[71-72]。口腔癌模型和泛癌研究提示髓源性抑制细胞也可依赖脂肪酸氧化维持其免疫抑制功能；抑制脂肪酸氧化可削弱髓源性抑制细胞的免疫抑制作用，并增强抗肿瘤治疗效果[73-74]。总体而言，目前OSCC中关于调节性T细胞、肿瘤相关巨噬细胞、髓源性抑制细胞及内皮细胞线粒体代谢调控的直接证据仍较少，相关结论仍需进一步验证。

综上，OSCC进展阶段的代谢表型不宜简单套用“糖酵解增强”或“氧化磷酸化增强”解释。现有研究更支持一种随肿瘤生物学行为和微环境动态变化的代谢重编程模式：当肿瘤细胞以持续增殖为主要需求时，线粒体代谢主要服务于ATP生成和生物合成底物供给；当肿瘤进入低氧、侵袭或转移状态时，代谢重编程则更多体现为线粒体质量控制、氧化还原稳态维持和替代性底物利用。不同研究结论存在差异，可能与细胞模型、肿瘤分期、缺氧程度和微环境组成不同有关。随着肿瘤

分期升高和微环境复杂化，局部底物供给、氧供状态和免疫代谢环境改变可能进一步影响肿瘤细胞对线粒体代谢的依赖。因此，后续研究需要进一步明确线粒体代谢在不同病程阶段和空间区域中的功能差异及生物学意义。

3　线粒体代谢重编程与OSCC治疗抵抗

3.1　线粒体代谢重编程与OSCC放化疗抵抗

放疗是OSCC联合治疗的重要组成部分，其抗肿瘤作用主要依赖DNA损伤和ROS累积[75]。在放疗压力下，OSCC细胞可通过增强抗氧化代谢适应降低放疗敏感性。例如，放疗抵抗细胞中核因子E2相关因子2持续上调，并通过促进糖酵解和谷胱甘肽合成增强抗氧化能力，从而减轻放疗诱导的氧化损伤并维持细胞存活[76]。除抗氧化代谢外，线粒体质量控制也可能参与放疗抵抗，蛋白酶体亚基α2型可通过影响线粒体功能和线粒体自噬促进OSCC放化疗抵抗[77]。

传统化疗主要通过干扰DNA复制或有丝分裂杀伤来消除快速增殖的肿瘤细胞。而线粒体代谢重编程可降低药物诱导的细胞毒性。OSCC常用的化疗药物包括铂类、氟尿嘧啶类及紫杉类药物，其中相关线粒体代谢研究主要集中于顺铂耐药[78-79]。顺铂可通过形成核DNA和mtDNA交联加合物诱导DNA损伤和细胞凋亡，但OSCC细胞可通过重塑线粒体呼吸、葡萄糖代谢、线粒体DNA稳定性及氧化还原代谢降低药物敏感性[16,80-81]（The Japan Registry of Clinical Trials：jRCTs031180135[80]）。线粒体微小RNA-5787下调可抑制线粒体编码的细胞色素c氧化酶亚基3翻译，促进代谢由氧化磷酸化向有氧糖酵解转变并增强顺铂耐药[17]。此外，5-氟尿嘧啶敏感性降低可能与ROS/ NOD样受体热蛋白结构域相关蛋白3/白细胞介素-1β轴、c-Jun N末端激酶1/2激活及线粒体凋亡调控有关[82-83]。紫杉类耐药则可伴随线粒体DNA含量升高、ROS生成减少及线粒体膜电位改变[84-85]。

3.2　线粒体代谢重编程与OSCC靶向治疗抵抗

在靶向治疗方面，HNSCC的表皮生长因子受体靶向治疗抵抗可伴随脂质和谷氨酰胺代谢重编程。西妥昔单抗耐药中，过氧化物酶体增殖物激活受体α介导的脂肪酸氧化增强，抑制过氧化物酶体增殖物激活受体α或肉碱棕榈酰转移酶1A可恢复治疗敏感性[86]。同时，靶向线粒体代谢调控因子丙酮酸脱氢酶激酶1可促进ROS积累和细胞凋亡，从而改善HNSCC对西妥昔单抗的治疗反应[87]。此外，甲基转移酶样蛋白1可通过转运RNA 7-甲基鸟苷修饰驱动OSCC细胞由糖酵解向氧化磷酸化转变并促进安罗替尼耐药[88]。

3.3　线粒体代谢重编程与OSCC免疫治疗抵抗

现有HNSCC研究显示，在复发或转移性HNSCC患者中，肿瘤低氧水平与抗程序性死亡受体1治疗反应不佳相关，提示缺氧性免疫抑制可能是影响免疫检查点抑制剂疗效的重要微环境因素[89]（ClinicalTrials.gov NCT04114136）。机制研究表明，高氧化磷酸化可通过增加耗氧、加重肿瘤低氧，促进T细胞耗竭并降低抗程序性死亡受体1治疗反应[90]。在非小细胞肺癌和肾细胞癌模型中，较高的氧化磷酸化依赖性均与免疫治疗疗效不佳相关，而抑制氧化磷酸化或线粒体复合体I可减轻缺氧、增强$CD8^+$ T细胞功能并改善抗程序性死亡受体1/程序性死亡配体1治疗效果[91-92]。此外，肿瘤微环境还可抑制T细胞过氧化物酶体增殖物激活受体γ共激活因子1α相关线粒体生物发生，导致线粒体含量和功能下降，进一步削弱其代谢和效应功能[93]。醛脱氢酶1家族成员L1下调可通过谷氨酰胺合成酶介导谷氨酸积累，抑制$CD8^+$ T细胞PI3K/AKT/叉头框蛋白O1信号和线粒体氧化磷酸化，并促进T细胞耗竭，而靶向醛脱氢酶1家族成员L1的化合物甜菊苷可增强抗程序性死亡受体1治疗效果，提示氨基酸代谢-线粒体氧化磷酸化轴可能是改善OSCC免疫治疗反应的可干预节点[94]。最新研究进一步提出，癌细胞可向肿瘤浸润淋巴细胞转移携带线粒体DNA突变的线粒体，使T细胞出现线粒体代谢异常，并与黑色素瘤和非小细胞肺癌患者免疫检查点抑制剂预后不良相关[95]。由此可见，线粒体代谢重编程参与免疫治疗抵抗主要体现在两个层面：一是肿瘤细胞氧化磷酸化增强导致耗氧增加和缺氧驱动的免疫抑制微环境，二是肿瘤浸润淋巴细胞线粒体生物发生、质量控制或代谢适应受损，限制程序性死亡受体1/程序性死亡配体1阻断后的免疫功能恢复。不同治疗方式下的线粒体代谢重编程及关键调控机制见表1。

3.4　靶向线粒体代谢的OSCC治疗策略

靶向线粒体代谢的治疗策略主要围绕氧化磷酸化抑制、氧化还原稳态干预和关键代谢酶靶向展开。首先，氧化磷酸化抑制剂可通过干预线粒体呼吸链，降低ATP生成和细胞耗氧水平，从而影

表1　OSCC治疗抵抗中的线粒体代谢重编程及关键调控机制

Table 1　Mitochondrial metabolic reprogramming and key regulatory mechanisms associated with therapeutic resistance in oral squamous cell carcinoma

Therapeutic intervention	Mitochondrial metabolic reprogramming	Regulators/pathways	Resistance phenotype
Cisplatin[16]	Decreased OXPHOS and increased glycolysis	mitomiR-2392/AGO2	Increased cisplatin resistance
Cisplatin[17]	Decreased OXPHOS and increased glycolysis	mitomiR-5787 - MT-CO3	Decreased cisplatin sensitivity
Anlotinib[88]	Decreased glycolysis and increased OXPHOS	METTL1-m7G tRNA modification	Increased anlotinib resistance
Anti-PD-1 therapy[94]	Glutamate accumulation and impaired $CD8^+$ T-cell OXPHOS	ALDH1L1-GLUL-L-glutamate axis	Reduced anti-PD-1 efficacy

OXPHOS: oxidative phosphorylation; mitomiR: mitochondrial microRNA; miR: microRNA; AGO2: argonaute 2; MT-CO3: mitochondrially encoded cytochrome c oxidase subunit Ⅲ; METTL1: methyltransferase 1; m^7G; N7-methylguanosine; tRNA: transfer RNA; PD-1: programmed cell death protein 1; ALDH1L1: aldehyde dehydrogenase 1 family member L1; GLUL: glutamate-ammonia ligase; CD8: cluster of differentiation 8; OSCC: oral squamous cell carcinoma

响氧化磷酸化依赖型肿瘤细胞的代谢适应。OSCC研究显示，二甲双胍可增强顺铂抗肿瘤作用，其机制可能与抑制NF-κB/缺氧诱导因子1α信号及诱导细胞凋亡有关[96]；HNSCC早期临床研究（ClinicalTrials.gov：NCT02949700）也提示二甲双胍联合铂类放疗具有一定可行性，但其疗效仍需进一步验证[97]。

其次，靶向氧化还原稳态可能提高OSCC对放化疗的敏感性，核因子E2相关因子2介导的抗氧化应激反应参与放疗抵抗和代谢调节，提示核因子E2相关因子2/谷胱甘肽轴具有潜在的干预价值[76,98]。此外，诱导铁死亡可能成为克服治疗抵抗的另一策略。核因子E2相关因子2介导的抗氧化防御可降低顺铂耐药细胞对青蒿琥酯的敏感性；而荜茇酰胺可通过促进ROS积累和脂质过氧化诱导OSCC细胞铁死亡，联合谷氨酰胺酶1抑制剂CB-839则可进一步增强该效应[99-101]。总体而言，这类策略的价值在于削弱肿瘤细胞的氧化还原缓冲能力，但目前仍主要停留在临床前研究阶段。

此外，关键代谢酶靶向主要集中于丙酮酸脱氢酶激酶/丙酮酸脱氢酶轴和谷氨酰胺代谢。丙酮酸脱氢酶激酶抑制剂二氯乙酸在OSCC细胞模型中显示出一定抗肿瘤活性，提示调控丙酮酸进入线粒体氧化代谢可能成为潜在干预策略；谷氨酰胺酶1抑制剂则更多用于联合治疗，以削弱谷氨酰胺依赖的抗氧化能力并增强铁死亡诱导效果[101-102]。总体而言，现有证据虽提示氧化磷酸化相关代谢酶具有潜在干预价值，但其靶向治疗的临床转化仍有待验证[103]。

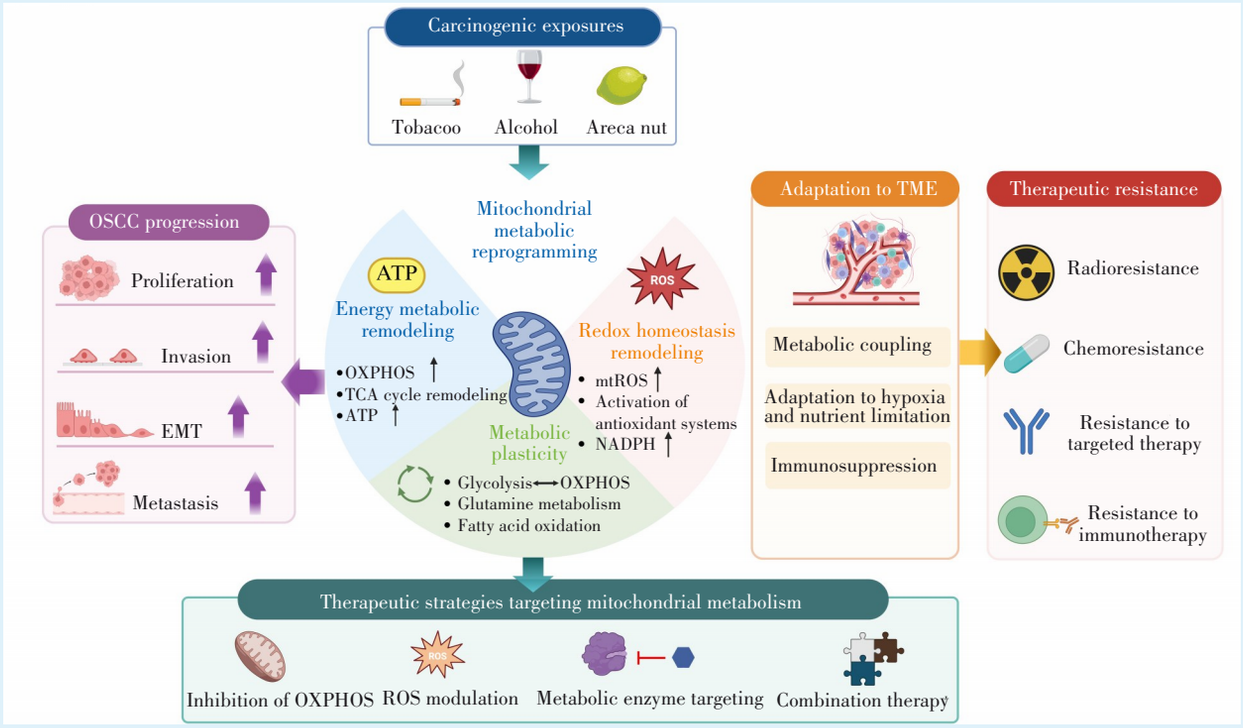
基于更高层级证据提示，线粒体代谢靶向目前更适合作为联合治疗中的增敏策略。其他实体瘤的临床研究表明，干预线粒体代谢可改善肿瘤缺氧，并具有增强放化疗疗效的潜力；在HNSCC中，二甲双胍联合铂类同步放化疗已开展早期临床探索，并显示出一定的可行性和耐受性[97,104-106]。（ClinicalTrials.gov：NCT02949700[97]；ClinicalTrials.gov：NCT02186847[103]；ClinicalTrials.gov:NCT02394652[105]；ClinicalTrials.gov：NCT02325401[106]）。

4　小结与展望

综上，OSCC中的线粒体代谢重编程是肿瘤细胞及其微环境在持续致癌刺激、微环境变化和治疗压力下形成的系统性代谢适应，贯穿肿瘤形成、进展及治疗抵抗全过程（图1）。随着疾病演进，其功能由早期应激适应逐步转向支持肿瘤增殖、侵袭转移和治疗抵抗。

代谢可塑性使OSCC细胞能够适应不同生存需求，而氧化还原稳态重塑可能是连接肿瘤进展与治疗抵抗的重要共性机制。此外，线粒体代谢异常还涉及间质细胞和免疫细胞，并通过细胞间代谢互作共同塑造促肿瘤和免疫抑制性微环境。因此，靶向线粒体代谢及其氧化还原调控网络，可能为提高现有治疗敏感性和克服治疗抵抗提供新的联合干预方向。

然而，现有研究仍存在基础机制与临床转化衔接不足、单一模型验证较多、患者分层及干预性证据有限等问题。未来应重点从代谢异质性、因果机制和临床转化三个层面推进。首先，可结合单细胞多组学、空间代谢组学和同位素示踪等技术，解析原发灶、侵袭前沿、淋巴结转移灶及治疗后残留病灶中不同细胞亚群的代谢特征及动态变化。其次，应依托患者来源样本、类器官和人源化



OSCC: oral squamous cell carcinoma; TME: tumor microenvironment; EMT: epithelial-mesenchymal transition; ATP: adenosine triphosphate; OXPHOS: oxidative phosphorylation; TCA: tricarboxylic acid cycle; ROS: reactive oxygen species; mtROS: mitochondrial reactive oxygen species; NADPH: reduced nicotinamide adenine dinucleotide phosphate. This figure was created using BioRender. The authors reviewed and edited the output and take full responsibility for the figure

Figure 1　The relationship between mitochondrial metabolic reprogramming, oral squamous cell carcinoma progression, and therapeutic resistance

图1　线粒体代谢重编程与口腔鳞状细胞癌发展及治疗抵抗的关系

模型，筛选反映氧化代谢、氧化还原状态及线粒体功能依赖性的代谢标志物，为患者分层和联合治疗提供依据；同时，应关注口腔微生物-代谢-免疫互作，阐明菌群及其代谢产物对肿瘤线粒体功能、局部免疫状态和治疗反应的影响。最后，还需明确代谢可塑性及代偿通路对线粒体靶向治疗的影响，优化适用人群、治疗时序和联合方案，从而推动线粒体代谢研究向OSCC风险评估、疗效预测和精准治疗转化。

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【Generative AI statement】 Figure in this manuscript was created with BioRender. The authors reviewed and edited the output and take full responsibility for the figures. No other generative AI technology was used in the creation of this manuscript.

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