REVIEW ARTICLE

Metabolic Reprogramming and Tumor Immune Evasion in Oral Cancer from Molecular Mechanisms to Precision Therapeutic Strategies

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Abstract

Oral cancer remains a major malignancy of the head and neck region. Oral squamous cell carcinoma represents the predominant histological form and is characterized by substantial metabolic heterogeneity. Increasing evidence indicates that metabolic alterations are not simply secondary consequences of malignant transformation. It can actively support the tumor progression by allowing cancer cells to adapt to changes in oxygen availability and nutrient supply. Glucose metabolism is extensively altered in oral cancer. Increased glycolysis and lactate production provide energy and biosynthetic intermediates required for tumor growth. Glutamine metabolism was also contributed to the nucleotide synthesis and antioxidant defense. Alterations in lipid metabolism further supports the membrane formation and tumor cell proliferation. These metabolic changes occur within a complex tumor microenvironment containing cancer associated fibroblasts, immune cells, endothelial cells and extracellular matrix components. Metabolic exchange between these populations can modify tumor behavior and promote immune suppression. Recent spatial transcriptomic studies have shown that metabolically active regions of oral squamous cell carcinoma are associated with increased regulatory T cell infiltration and TGF β activity. Lactate produced by tumor cells can also alter fibroblast and macrophage functions. Such findings indicate that metabolic plasticity is a shared feature of both tumor cells and their surrounding microenvironment. This review discusses the metabolic alterations associated with oral cancer initiation and progression. Particular attention is given to glucose metabolism, glutamine utilization, lipid metabolism, hypoxia, lactate signaling and metabolic interactions between cancer cells and stromal and immune populations. The potential relationship between metabolic plasticity and invasion, metastasis, treatment resistance and clinical outcome is also discussed. Understanding these metabolic interactions may provide new opportunities for developing therapeutic strategies that target both tumor metabolism and the surrounding microenvironment.

1. Introduction

Oral cancer remains an important clinical problem since most of the cases are diagnosed at an advanced stage. Oral squamous cell carcinoma (OSCC) accounts for the most of malignant tumors arising in the oral cavity. Tobacco exposure, alcohol consumption, and other environmental factors contribute to oral carcinogenesis. The clinical behavior of OSCC is also influenced by local invasion, lymph node involvement, and resistance to treatment (Tan et al., 2023). These features indicate that tumor progression cannot be explained only by genetic alterations within malignant cells. Cancer metabolism has received increasing attention as an important component of oral carcinogenesis. Malignant cells require continuous supplies of ATP and biosynthetic intermediates to support proliferation. Therefore, it modifies the way glucose, amino acids, lipids, and other nutrients are

utilized. This metabolic adaptation was initially described mainly through the Warburg effect (Gonçalves et al., 2025; Xu et al., 2017). In this model, cancer cells increase glucose uptake and lactate production even when oxygen is available. Tumor cells can shift between the glycolysis and mitochondrial oxidative phosphorylation based on the nutrient availability. This flexibility is particularly relevant in OSCC because the tumor contains areas with different oxygen and nutrient conditions. Cancer cells located near blood vessels may have access to oxygen and nutrients. Cells located in poorly perfused regions can experience hypoxia and nutrient limitation. The ability to switch between metabolic pathways allows malignant cells to survive these changing conditions (Eckert et al., 2020; S.-Y. Liu et al., 2008).

The tumor microenvironment also participates actively in this process. Cancer associated fibroblasts, macrophages, and extracellular matrix components interact with malignant cells. These cells exchange metabolites and signalling molecules. Lactate produced by highly glycolytic cancer cells can also alter the behavior of immune and stromal cells (Certo et al., 2021). Fibroblasts can undergo metabolic changes that provide additional nutrients to cancer cells. Recent spatial and single cell studies have demonstrated that metabolic activity is not uniform throughout OSCC tissue. Liu et al. reported distinct hypermetabolic, normal metabolic, and hypometabolic regions within OSCC specimens. Hypermetabolic regions showed greater CD4+ T cell infiltration and increased TGF β expression. These findings indicate that local metabolic conditions are closely associated with immune characteristics within the tumor microenvironment (Z. Liu et al., 2024). Metabolic plasticity therefore represents a connection between tumor cell biology and tumor microenvironment. It can support malignant transformation during early disease and later contribute to invasion, metastasis, and treatment resistance. This review discusses the major metabolic changes observed in oral cancer and examines how these changes interact with immune components during disease progression.

2. Metabolic Reprogramming During Oral Cancer Initiation

Glucose metabolism is one of the known characterized metabolic alterations in OSCC. Increased glucose consumption has been observed in tumor tissues compared with adjacent normal tissue (Chen et al., 2024). Ogawa et al. performed quantitative metabolomic analysis using paired OSCC and surrounding normal tissues from 32 patients. Their analysis showed increased glucose consumption and lactate production in OSCC. The findings were consistent with increased glycolytic activity. Interestingly, the reduction of glucose and several downstream glycolytic intermediates suggested that glucose was being directed toward biosynthetic processes rather than being used only for ATP generation. The same study also found evidence of increased glutamine utilization (Ogawa et al., 2014). These findings are important because rapid tumor growth requires more than ATP. Cancer cells need carbon sources for nucleotide synthesis, amino acid production, and membrane formation (Li & Zhang, 2016). Glycolysis provides several intermediates that can be redirected into these pathways. Increased glycolytic activity may therefore support both energy production and biomass generation. GLUT1 expression has been reported to increase in several oral cancer models and has been associated with aggressive tumor characteristics. Increased glucose uptake allows cancer cells to maintain metabolic activity even when the extracellular environment becomes unfavorable (Kumari et al., 2023). The glycolytic phenotype is also influenced by oncogenic signalling. PI3K and AKT stimulate glucose uptake and glycolytic activity. mTOR signaling promotes anabolic processes that support cell growth. Hypoxia provides another strong stimulus through HIF 1α. Stabilized HIF 1α increases the expression of genes involved in glucose transport and glycolysis (Chun & Kim, 2021; Hoxhaj & Manning, 2020; Luo et al., 2022). Recent work has further emphasized the importance of glycolysis in the OSCC microenvironment. A 2025 review summarized evidence linking increased aerobic glycolysis with OSCC proliferation, metastasis, immune evasion, and treatment resistance. The authors also highlighted the involvement of cancer associated fibroblasts, T lymphocytes, and tumor associated macrophages in the glycolytic environment of OSCC (Shin, 2025).

The Warburg model suggests that cancer cells mainly depend on glycolysis and reduce mitochondrial respiration. Evidence from OSCC indicates that this explanation is incomplete. Malignant cells can use both glycolysis and oxidative phosphorylation. The relative contribution of these pathways may change according to the metabolic environment. A useful example was reported in a study investigating garcinol in OSCC cells. Garcinol reduced mitochondrial respiration and decreased ATP production. However, the cells responded by increasing glycolysis. Lactate production increased together with glycolytic capacity. GLUT1 and GLUT4 expression also increased. HIF 1α and AKT signalling were upregulated after mitochondrial inhibition. This result provides direct evidence of metabolic compensation in OSCC. When oxidative phosphorylation was suppressed, the cells increased glycolytic activity to maintain metabolic function (G. Zhang et al., 2019). This observation is highly relevant to metabolic therapy. Blocking one pathway may not be sufficient if tumor cells can activate another pathway. Metabolic plasticity can therefore act as a survival mechanism. Further evidence comes from studies of PTP4A1. PTP4A1 has been associated with OSCC metastasis and mitochondrial metabolic reprogramming. Knockdown of PTP4A1 increased oxygen consumption and reduced extracellular acidification. The expression of PKM2 decreased while ACO2 increased. These findings

suggest that PTP4A1 can influence the balance between glycolysis and oxidative metabolism in OSCC cells (B. Liu et al., 2023). More recent work has identified another metabolic pathway involving CMKLR1. The recent study reported increased CMKLR1 expression in OSCC and an association with lymph node metastasis. CMKLR1 knockdown reduced mitochondrial function and oxidative phosphorylation. It also decreased ATP production and impaired proliferation, migration, invasion, and epithelial to mesenchymal transition. Mechanistic analysis linked this effect to the PI3K/AKT and PGC-1α pathway (Lin et al., 2026). Together, these studies suggest that OSCC cells should not be classified simply as glycolytic or oxidative (Figure 1). Their metabolic phenotype can change according to intracellular signalling and environmental conditions.

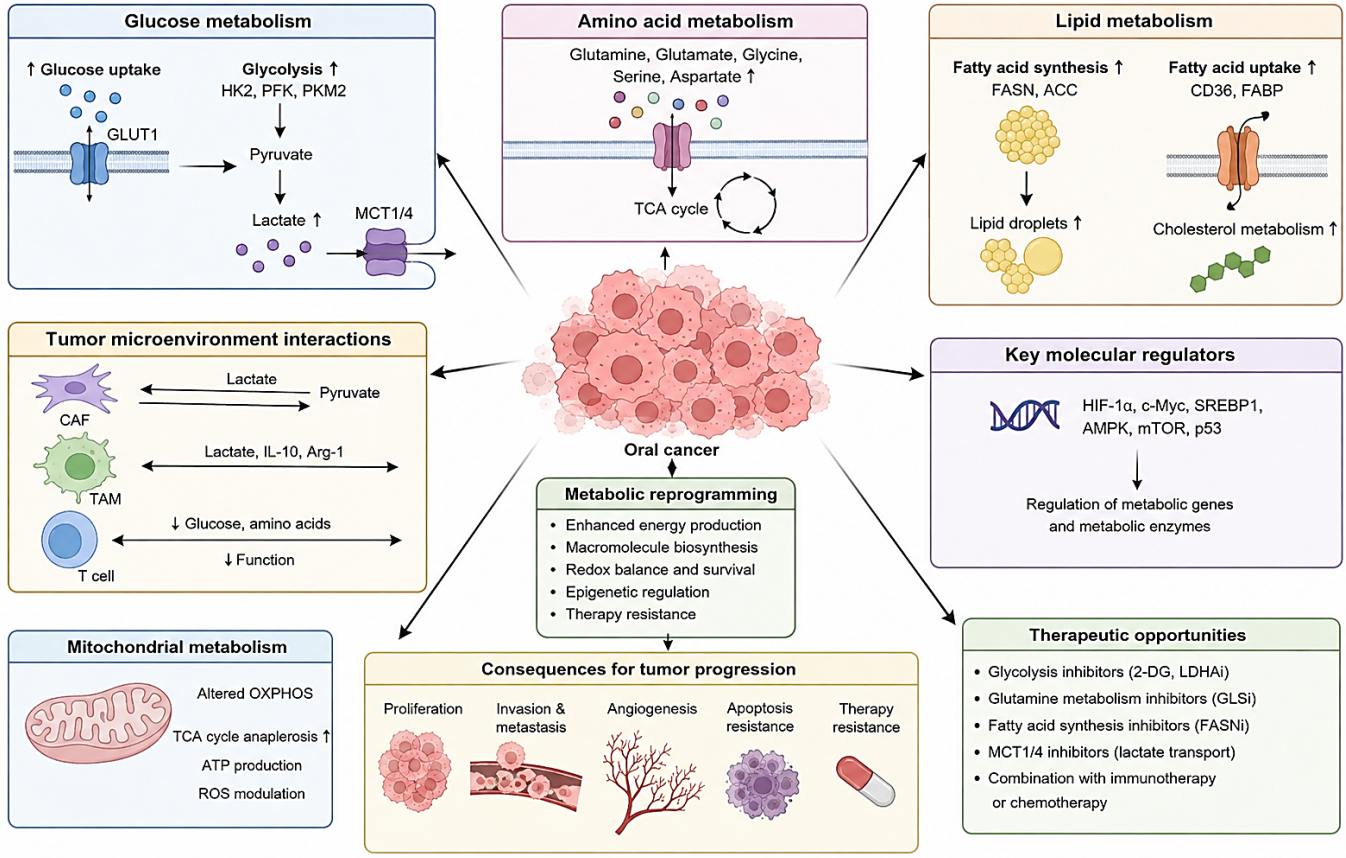

Figure 1: Oral cancer cells undergo metabolic reprogramming that increases glycolysis, glutamine utilization, lipid metabolism, and adaptation to oxidative stress. These changes interact with the tumor microenvironment through metabolic exchange and signalling between cancer cells, cancer associated fibroblasts, tumor associated macrophages, endothelial cells, immune cells, and extracellular matrix components. Altered glucose and lactate metabolism supports tumor cell proliferation and survival. Changes in lipid and amino acid metabolism provide additional metabolic substrates required for tumor growth. The tumor microenvironment further promotes angiogenesis, immune suppression, extracellular matrix remodeling, invasion, and therapeutic resistance. This metabolic interaction creates a dynamic environment that supports oral cancer progression from early disease development to advanced clinical stages.

3. Glutamine and Amino Acid Metabolism in Oral Cancer

Amino acid metabolism provides a carbon and nitrogen for biosynthesis and supports redox control. Among the amino acids, glutamine has received particular attention. Glutamine can enter the tricarboxylic acid cycle after conversion to glutamate and subsequently to α ketoglutarate. It can therefore provide an alternative carbon source when glucose metabolism is altered. Glutamine also contributes to nucleotide synthesis and glutathione production (Alapati et al., 2023; Ogawa et al., 2014). The investigators analyzed normal oral mucosa, precursor lesions, and OSCC tissues. SLC1A5 or ASCT2 and glutaminase were significantly overexpressed in OSCC compared with normal tissue. Their expression also increased during progression from precursor lesions to OSCC. GLDH expression remained relatively weak. The authors suggested that glutamine metabolism in OSCC may be used mainly for nucleotide and protein biosynthesis and for antioxidant defense rather than simply for ATP production (Cetindis et al., 2016). This finding supports the broader concept of metabolic plasticity. Glutamine does not necessarily replace glucose as an energy source. Instead, it can provide specific metabolic intermediates needed for tumor growth.

Glutamine metabolism also supports the antioxidant system. Glutamate is required for glutathione synthesis. Increased glutathione production can protect tumor cells from reactive oxygen species. This mechanism may become particularly important in OSCC because malignant cells often

experience increased oxidative stress. Tobacco exposure, inflammatory reactions, mitochondrial activity, and hypoxia can all increase reactive oxygen species. Cancer cells that develop stronger antioxidant defenses may therefore gain a survival advantage. Recent metabolomic work has expanded the understanding of amino acid reprogramming in OSCC. A 2024 study identified increased γ aminobutyrate in cancerous OSCC tissues. The authors linked this change to altered glutamate and glutamine metabolism. In OSCC derived cells, glutamate was converted to glutamine through glutamine synthetase and subsequently converted back to glutamate through glutaminase (Wu et al., 2024). This metabolic cycling illustrates how cancer cells can reorganize amino acid metabolism according to their biosynthetic and redox requirements.

4. Lipid Metabolism and Redox Adaptation

Lipid metabolism is another important component of OSCC biology. Tumor cells require lipids for membrane formation and signalling. Rapidly proliferating cells therefore increase lipid synthesis and alter lipid uptake. The recent studies have investigated the lipid metabolism in oral cancer through examination of fatty acid synthesis in the TCA 83 oral squamous carcinoma cell line. The incorporation of radio labelled acetate into cellular lipids was significantly higher in cancer cells than in normal gingival fibroblasts. The measured incorporation was approximately 68 ± 12.7 cpm compared with 13 ± 4.2 cpm in normal fibroblasts. The study also examined cerulenin as an inhibitor of fatty acid synthase and suggested that increased fatty acid synthesis could represent a metabolic vulnerability in oral cancer (Y. Zhang et al., 2005). Fatty acid synthase has subsequently received considerable attention in cancer research. De novo fatty acid synthesis provides membrane components for rapidly dividing cells. Fatty acids can also influence signalling pathways and membrane properties. Recent research has expanded this concept beyond malignant epithelial cells. Lipid metabolism within the stromal compartment may also support OSCC progression (Alapati et al., 2023). Liu et al. investigated lipid metabolism in OSCC associated fibroblasts. Their study showed increased phosphorylation of ATP citrate lyase in CAFs compared with normal fibroblasts. The CAFs contained higher cytosolic acetyl CoA and more lipid droplets. These findings indicated enhanced lipid synthesis and demonstrated functional importance. Blocking lipid synthesis in CAFs reduced their ability to promote OSCC cell proliferation, invasion, and migration. Inhibition of fatty acid uptake by OSCC cells produced similar effects. Mechanistic analysis identified an IL8 AKT phosphorylated ACLY pathway. OSCC derived IL8 activated AKT in fibroblasts and increased ACLY phosphorylation (P. Liu et al., 2024). This study provides an important example of metabolic cooperation. The metabolic phenotype of the tumor is not produced only by cancer cells. CAFs can become metabolically active and supply lipid resources that support tumor progression.

Lipid metabolism can also influence immune cells. SOAT1 is an enzyme involved in cholesterol esterification. A study of OSCC reported increased SOAT1 expression in tumor tissue and an association with M2 like macrophage infiltration. SOAT1 increased OSCC proliferation, tumor sphere formation, migration, and invasion. It also activated the SREBP1 regulated lipid pathway and the PI3K AKT mTOR pathway. Importantly, increased SOAT1 activity promoted M2 like polarization of macrophages (Y. Liu et al., 2024). These findings connect lipid metabolism with immune suppression. Altered lipid handling can therefore affect both tumor cell behavior and macrophage phenotype. A recent study provided another example of this relationship. Tumor derived progranulin was associated with macrophage cholesterol efflux through a SORT1 linked pathway involving PPARγ, LXRα, ABCA1, and ABCG1. This metabolic change was accompanied by immunosuppressive macrophage features and increased IL6, IL10, and TGF β secretion (Luan et al., 2026). Although these findings are recent, they support a broader concept. Lipid metabolism should be considered as an immunometabolic process rather than an isolated pathway within cancer cells.

5. Hypoxia, Lactate and Metabolic Remodeling of the Tumor Microenvironment

Hypoxia is a major feature of solid tumors and OSCC is no exception. Rapid proliferation increases oxygen demand while abnormal tumor vessels limit efficient oxygen delivery. HIF 1α is a central mediator of the cellular response to low oxygen. Stabilization of HIF 1α increases glycolytic activity and promotes angiogenic signaling. This response allows tumor cells to maintain ATP production under hypoxic conditions (Kierans & Taylor, 2021). The clinical relevance of HIF 1α in OSCC has been investigated extensively. A meta-analysis involving 18 studies and 1474 patients found that HIF 1α overexpression was associated with larger tumor size, advanced disease, and lymph node metastasis. High HIF 1α expression was also associated with poorer overall survival. The pooled hazard ratio for overall survival was 1.70 (Zhou et al., 2017). These findings suggest that hypoxia is not simply a consequence of tumor growth. It can contribute to aggressive disease behavior and increased glycolysis results in increased lactate production. Lactate was traditionally considered a metabolic waste product. Current evidence shows that lactate has important signaling functions. Cancer derived lactate can alter extracellular pH. Acidification promotes changes in stromal cells and can impair immune cell activity. Lactate can also be transported between different cell populations and used as an energy substrate. The broader cancer literature shows that high lactate concentrations can suppress cytotoxic T cell and natural killer cell function. Lactate can also favor immunosuppressive populations. These effects link tumor metabolism directly with immune escape (Z.-H. Wang et al., 2021). Evidence specific to OSCC is emerging. Cui et

al. recently examined lactate accumulation and immune escape in OSCC. Their study found that reducing lactate accumulation with baicalin decreased OSCC proliferation and migration. It also improved antitumor activity in activated peripheral blood mononuclear cells (Cui et al., 2025). This result suggests that lactate reduction may influence both cancer cell behavior and immune function.

6. Metabolic Interactions Between Cancer Cells and the Tumor Microenvironment

6.1 Cancer associated fibroblasts

The tumor microenvironment contains multiple cell types that can alter cancer metabolism. Among these populations, cancer associated fibroblasts and macrophages have received particular attention in OSCC. CAFs are major stromal components of many OSCC lesions. It influences extracellular matrix remodeling, angiogenesis, immune regulation, and metabolic exchange. A particularly important study investigated the metabolic relationship between normal oral fibroblasts and OSCC cells. The researchers developed an indirect co culture system and found that normal oral fibroblasts underwent metabolic changes after exposure to OSCC cells. The fibroblasts increased aerobic glycolysis and reactive oxygen species production. Lactate secretion also increased together with MCT4 expression. The study further showed that fibroblasts could transfer mitochondria toward OSCC cells (Z. Zhang et al., 2020). This observation is significant because it demonstrates that metabolic communication can begin before fibroblasts acquire the complete characteristics of activated CAFs. More recent work has identified specific signalling pathways responsible for fibroblast recruitment. A 2025 study found that OSCC derived ISG15 promoted fibroblast migration and activation. ISG15 expressing tumors showed increased collagen and α SMA expression. Fibroblasts exposed to ISG15 showed increased glycolysis related gene expression, glucose uptake, and lactate production (S.-H. Wang et al., 2025). These findings indicate that tumor cells can actively reprogram stromal metabolism. A related mechanism has been described in head and neck squamous cell carcinoma. CAF derived HGF increased glycolysis and lactate production in cancer cells. In return, cancer derived bFGF increased mitochondrial oxidative phosphorylation and HGF secretion in CAFs. Inhibition of both c MET and FGFR significantly reduced CAF mediated tumor growth in experimental models (Kumar et al., 2018). Although this study involved HNSCC rather than only oral cavity tumors, it provides a useful model for understanding metabolic symbiosis within the oral cancer microenvironment.

6.2 Tumor associated macrophages

Macrophages are another major population in the OSCC microenvironment. Their functional state can vary according to cytokines, metabolites, oxygen availability, and signals released by cancer cells. Lipid metabolism can influence this process. As discussed earlier, SOAT1 expression in OSCC was associated with M2 like macrophage polarization. SOAT1 activation increased lipid metabolism and promoted tumor growth (Y. Liu et al., 2024). The relationship between macrophages and metabolism may extend beyond lipids. A recent integrated proteomic and metabolomic analysis identified macrophage associated signals in OSCC and reported significant changes in tryptophan metabolism. C1QC positive macrophages were identified as an important source of altered proteins. High infiltration of these macrophages was associated with poor prognosis (Yang et al., 2025). These findings indicate that amino acid metabolism can also participate in immune regulation within OSCC (Table 1).

Table 1: Major metabolic alterations reported in oral cancer and their potential biological significance

Tumor Microenvironment	Metabolic alterations	Potential Biological Significance	Reference
Lactate reduction therapy	OSCC treated with baicalin	Lowering lactate accumulation reduced proliferation/migration and improved antitumor activity of activated PBMCs	(Cui et al., 2025)
Spatial metabolic heterogeneity	Spatial transcriptomics of OSCC tissue	Hypermetabolic tumor regions showed greater regulatory T-cell/CD4+ infiltration, TGF-β activity and iCAF transformation.	(Z. Liu et al., 2024)
Fibroblast metabolic reprogramming	Indirect co-culture of normal oral fibroblasts with OSCC cells	Fibroblasts shifted toward glycolysis and ROS production, raised MCT4/lactate secretion, and transferred mitochondria to tumor cells.	(Z. Zhang et al., 2020)
Tumor-to-fibroblast signaling (ISG15)	OSCC-derived ISG15 acting on fibroblasts	ISG15 recruited and activated fibroblasts, increasing their glycolytic gene expression, glucose uptake and lactate output.	(S.-H. Wang et al., 2025)
CAF-tumor metabolic loop (HGF/bFGF)	HNSCC co-culture model	CAF-derived HGF raised tumor glycolysis; tumor-derived bFGF raised CAF oxidative phosphorylation. Dual c-MET/FGFR blockade reduced CAF-driven growth.	(Kumar et al., 2018)

CAF lipid biosynthesis (IL8/AKT/ACLY)	OSCC-associated fibroblasts	Tumor-derived IL8 activated AKT and ACLY phosphorylation in CAFs; blocking CAF lipid synthesis reduced tumor proliferation, invasion and migration.	(P. Liu et al., 2024)
Macrophage lipid metabolism (SOAT1)	OSCC tissue and cell models	SOAT1 activated SREBP1 and PI3K-AKT-mTOR signaling, promoted tumor growth and drove M2-like macrophage polarization.	(Y. Liu et al., 2024)
Macrophage cholesterol efflux	Tumor-derived progranulin acting on macrophages	SORT1-linked signaling (PPARγ/LXRα/ABCA1/ABCG1) drove cholesterol efflux and an immunosuppressive macrophage phenotype (↑IL-6, IL-10, TGF-β).	(Luan et al., 2026)
Macrophage amino-acid signaling	Integrated proteomic/metabolomic analysis of OSCC	Altered tryptophan metabolism and $C1QC^{+}$ macrophage infiltration were linked to poor prognosis.	(Yang et al., 2025)
Metabolism-driven EMT/invasion	OSCC cells, CMKLR1 overexpression	Elevated mitochondrial respiration promoted proliferation, migration, invasion and EMT; OXPHOS suppression reversed these effects.	(Lin et al., 2026)
Metabolic flexibility in metastasis	OSCC cells, PTP4A1 knockdown	Shift toward oxidative metabolism (↑O2 consumption, altered PKM2/ACO2) accompanied reduced metastatic behavior.	(B. Liu et al., 2023)
Metabolic rewiring and drug resistance	OSCC cells treated with garcinol	Compensatory glycolytic activation after mitochondrial inhibition illustrates a route by which tumor cells evade single-pathway metabolic therapy.	(G. Zhang et al., 2019)

7. Metabolic Plasticity During Invasion, Metastasis and Treatment Resistance

7.1 Metabolism and epithelial to mesenchymal transition

Metabolic plasticity becomes increasingly important when OSCC progresses from localized disease to invasive and metastatic disease. Cancer cells at the invasive front encounter different conditions from cells located in the center of the tumor. The oxygen levels and nutrient availability can change rapidly. Cells capable of adjusting their metabolic pathways may therefore survive more effectively. Epithelial to mesenchymal transition is an important process during tumor invasion. EMT increases cellular motility and promotes the ability of cancer cells to invade surrounding tissue. Metabolic pathways are closely connected with EMT. Increased oxidative phosphorylation has been linked with aggressive phenotypes in several cancers. In OSCC, the CMKLR1 study provided direct evidence for this relationship. CMKLR1 overexpression increased mitochondrial respiration and promoted proliferation, migration, invasion, and EMT. Suppression of oxidative phosphorylation reduced these tumor promoting effects (Lin et al., 2026). This finding challenges the idea that advanced OSCC is always dependent on glycolysis. Some aggressive tumors may rely strongly on mitochondrial metabolism.

7.2 Metabolic flexibility and metastasis

PTP4A1 promoted OSCC metastasis through altered mitochondrial metabolism. PTP4A1 knockdown increased oxygen consumption while reducing glycolytic activity. Changes in PKM2 and ACO2 expression accompanied this metabolic shift (B. Liu et al., 2023). These findings suggest that the relationship between glycolysis and oxidative phosphorylation can change during metastatic progression. Metabolic adaptation may also help disseminated cells survive after leaving the primary tumor. The metastatic environment does not provide the same nutrients or oxygen conditions as the primary tumor. Flexible metabolism may therefore increase the probability of successful colonization.

7.3 Metabolism and therapeutic resistance

Metabolic plasticity also creates an important barrier to treatment. If a drug blocks one metabolic pathway, surviving cancer cells may increase the use of another pathway. The garcinol study provides an experimental example. Inhibition of mitochondrial respiration resulted in compensatory activation of glycolysis. This response was associated with increased lactate production and increased expression of glycolysis related factors (G. Zhang et al., 2019). A similar problem may occur when glycolysis is targeted. Cells with sufficient mitochondrial capacity may increase oxidative phosphorylation. This suggests that combination strategies may be more effective than single pathway inhibition. The metabolic environment may also influence radiotherapy. Hypoxic cells are less sensitive to radiation induced damage because oxygen is required for fixation of several forms of radiation induced molecular injury. Hypoxia driven metabolic adaptation may therefore contribute to radioresistance. Metabolic interactions with CAFs can add another level of protection. CAFs can provide nutrients and survival signals to tumor cells. Targeting only the cancer cell may therefore have limited efficacy if stromal support remains intact.

8. Therapeutic Opportunities and Future Directions

The close relationship between metabolic plasticity and the tumor microenvironment provides several opportunities for developing new therapeutic strategies against oral cancer. Conventional treatment approaches such as surgery, radiotherapy, chemotherapy, and immunotherapy have improved clinical management. However, treatment resistance and tumor recurrence remain major concerns. Metabolic adaptation may contribute to these limitations by allowing oral cancer cells to maintain energy production under hypoxia and nutrient deprivation. Therefore, targeting tumor metabolism together with the surrounding microenvironment may provide a more effective therapeutic approach. Glycolysis represents one of the potential targets because many oral cancer cells show increased glucose utilization and lactate production. Inhibition of glycolytic regulators such as GLUT1, hexokinase 2, phosphofructokinase, and lactate dehydrogenase has been investigated as a strategy to reduce tumor growth. Studies using oral squamous cell carcinoma models have shown that interference with glycolytic metabolism can reduce cellular proliferation and increase sensitivity to therapeutic stress (Kumari et al., 2026). Mitochondrial metabolism also represents an important target because metabolically adaptable tumor cells can switch between glycolysis and oxidative phosphorylation according to changes in nutrient and oxygen availability. Agents that interfere with mitochondrial respiration may therefore be useful in metabolically flexible tumors. Lipid metabolism provides another therapeutic opportunity because fatty acid synthesis and lipid uptake contribute to membrane formation, energy storage, and signalling during tumor progression. Targeting fatty acid synthase or other lipid metabolic regulators may restrict tumor growth and reduce the ability of cancer cells to adapt to metabolic stress. At the same time, metabolic inhibition should be carefully designed because normal oral tissues also depend on many of these metabolic pathways. The tumor microenvironment provides additional therapeutic targets. Cancer associated fibroblasts can supply metabolites and growth signals to malignant cells and may therefore support metabolic adaptation. Targeting fibroblast mediated signalling could reduce this metabolic support and potentially improve the response to anticancer treatment. Tumor associated macrophages are another important target because their metabolic state influences inflammation, angiogenesis, immune suppression, and tumor progression. Reprogramming macrophages toward an antitumor phenotype may improve immune activity within the tumor. Hypoxia is also an important component of the oral cancer microenvironment. Hypoxia inducible factors regulate several metabolic pathways and promote angiogenesis and treatment resistance. Strategies targeting hypoxia related signaling may therefore interfere with both metabolic adaptation and tumor progression. The interaction between metabolism and immune responses also provides an opportunity to improve immunotherapy. Metabolic competition between cancer cells and immune cells can restrict glucose and amino acid availability within the tumor and reduce immune cell function. High extracellular lactate can further contribute to an immunosuppressive environment. Combining metabolic interventions with immune checkpoint inhibitors may help restore immune activity and improve therapeutic responses. Nanotechnology may provide another useful approach for this combination because nanocarriers can improve drug delivery and increase accumulation within tumor tissues. Future studies should focus on developing systems that simultaneously target metabolic pathways and specific components of the tumor microenvironment. Patient selection will also be important because metabolic characteristics can vary between tumors and between individual patients. Metabolomic profiling together with genomic and transcriptomic analysis may help identify patients who are more likely to respond to specific metabolic therapies. Liquid biopsy approaches may further assist in monitoring metabolic changes during treatment and detecting early signs of therapeutic resistance. Despite these opportunities, several challenges need to be addressed before metabolism based therapies can be widely translated into clinical practice. Metabolic pathways are highly interconnected and inhibition of one pathway may result in activation of an alternative pathway. Tumor cells can therefore escape metabolic inhibition through metabolic rewiring. Combination strategies will probably be required to overcome this adaptive capacity. Future research should also place greater emphasis on three dimensional tumor models, patient derived organoids, spatial transcriptomics, and single cell analysis because these approaches can provide a more realistic understanding of metabolic differences within individual tumors. Overall, therapeutic strategies that consider oral cancer as a dynamic metabolic system rather than a population of malignant cells alone may provide new opportunities for disease control. A combined approach targeting tumor metabolism, stromal interactions, hypoxia, immune suppression, and therapeutic resistance could improve treatment efficacy and may support the development of more precise treatment strategies for patients with oral cancer.

9. Conclusion

These findings support a shift from studying tumor metabolism as an isolated cancer cell process toward understanding it as a property of the entire tumor ecosystem. Future treatment strategies may therefore need to target metabolic pathways in both malignant and stromal cells. The combination of metabolic intervention with immunotherapy or conventional treatment could provide a useful strategy for overcoming metabolic adaptation and treatment resistance. Overall, metabolic plasticity should be considered as a dynamic process that links tumor growth with the changing conditions of the oral tumor microenvironment. Better understanding of this relationship may help identify

metabolic biomarkers and develop more selective therapeutic strategies for patients with oral cancer

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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References

1. Cetindis, M., Biegner, T., Munz, A., Teriete, P., Reinert, S., & Grimm, M. (2016). Glutaminolysis and carcinogenesis of oral squamous cell carcinoma. European Archives of Oto-Rhino-Laryngology, 273(2), 495–503. https://doi.org/10.1007/s00405-015-3543-7
2. Cui, Y., Liu, J., Wang, X., Wu, Y., Chang, Y., Hu, X., & Zhao, W. (2025). Baicalin attenuates the immune escape of oral squamous cell carcinoma by reducing lactate accumulation in tumor microenvironment. Journal of Advanced Research, 77, 721–732. https://doi.org/10.1016/j.jare.2025.01.021
3. Kumar, D., New, J., Vishwakarma, V., Joshi, R., Enders, J., Lin, F., Dasari, S., Gutierrez, W. R., Leef, G., Ponnurangam, S., Chavan, H., Ganaden, L., Thornton, M. M., Dai, H., Tawfik, O., Straub, J., Shnayder, Y., Kakarala, K., Tsue, T. T., … Thomas, S. M. (2018). Cancer-Associated Fibroblasts Drive Glycolysis in a Targetable Signaling Loop Implicated in Head and Neck Squamous Cell Carcinoma Progression. Cancer Research, 78(14), 3769–3782. https://doi.org/10.1158/0008-5472.CAN-17-1076
4. Lin, Y., Zhao, L., Huang, Y., Chen, Y., Wan, Q., Lu, Z., & Zhang, X. (2026). Chemokine-Like Receptor 1 Knockdown Suppresses Oral Squamous Cell Carcinoma Progression by Reducing Oxidative Phosphorylation. International Dental Journal, 76(3), 109479. https://doi.org/10.1016/j.identj.2026.109479
5. Liu, B., Si, W., Wei, B., Zhang, X., & Chen, P. (2023). PTP4A1 promotes oral squamous cell carcinoma (OSCC) metastasis through altered mitochondrial metabolic reprogramming. Cell Death Discovery, 9(1), 360. https://doi.org/10.1038/s41420-023-01657-x
6. Liu, P., Wang, Y., Li, X., Liu, Z., Sun, Y., Liu, H., Shao, Z., Jiang, E., Zhou, X., & Shang, Z. (2024). Enhanced lipid biosynthesis in oral squamous cell carcinoma cancer-associated fibroblasts contributes to tumor progression: Role of IL8 /AKT / p-ACLY axis. Cancer Science, 115(5), 1433–1445. https://doi.org/10.1111/cas.16111
7. Liu, Y., Shen, L., Li, Y., Sun, X., Liang, L., Jiang, S., Zhang, Z., Tang, X., Tao, Y., Xie, L., Jiang, Y., & Cong, L. (2024). ETS1-mediated Regulation of SOAT1 Enhances the Malignant Phenotype of Oral Squamous Cell Carcinoma and Induces Tumor-associated Macrophages M2-like Polarization. International Journal of Biological Sciences, 20(9), 3372–3392. https://doi.org/10.7150/ijbs.93815
8. Liu, Z., Zhang, Z., Zhang, Y., Zhou, W., Zhang, X., Peng, C., Ji, T., Zou, X., Zhang, Z., & Ren, Z. (2024). Spatial transcriptomics reveals that metabolic characteristics define the tumor immunosuppression microenvironment via iCAF transformation in oral squamous cell carcinoma. International Journal of Oral Science, 16(1), 9. https://doi.org/10.1038/s41368-023-00267-8
9. Luan, Y., Xu, Y., Zhao, S., Li, H., Liu, Z., Yang, P., & Yang, C. (2026). Tumor-derived progranulin promotes macrophage cholesterol efflux and associated immunosuppressive features in oral squamous cell carcinoma. Journal of Translational Medicine. https://doi.org/10.1186/s12967-026-08422-5
10. Ogawa, T., Washio, J., Takahashi, T., Echigo, S., & Takahashi, N. (2014). Glucose and glutamine metabolism in oral squamous cell carcinoma: insight from a quantitative metabolomic approach. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 118(2), 218–225. https://doi.org/10.1016/j.oooo.2014.04.003
11. Shin, J.-A. (2025). Glycolytic Reprogramming in Oral Squamous Cell Carcinoma: Molecular Regulators and Natural Product-Based Therapies. International Dental Journal, 75(6), 103949. https://doi.org/10.1016/j.identj.2025.103949
12. Wang, S.-H., Chen, Y.-L., Huang, S.-H., Fu, Y.-K., Lin, S.-F., Jiang, S. S., Liu, S.-C., Hsiao, J.-R., Chang, J.-Y., & Chen, Y.-W. (2025). Tumor cell-derived ISG15 promotes fibroblast recruitment in oral squamous cell carcinoma via CD11a-dependent glycolytic reprogramming. Oncogenesis, 14(1), 6. https://doi.org/10.1038/s41389-025-00549-2
13. Wang, Z.-H., Peng, W.-B., Zhang, P., Yang, X.-P., & Zhou, Q. (2021). Lactate in the tumour microenvironment: From immune modulation to therapy. EBioMedicine, 73, 103627. https://doi.org/10.1016/j.ebiom.2021.103627
14. Wu, S.-L., Zha, G.-Y., Tian, K.-B., Xu, J., & Cao, M.-G. (2024). The metabolic reprogramming of γ-aminobutyrate in oral squamous cell carcinoma. BMC Oral Health, 24(1), 418. https://

doi.org/10.1186/s12903-024-04174-0

15. Yang, B., Zhang, Z., Liu, Y., Gong, Z., & Wu, G. (2025). Integrated proteomics and metabolomics analysis revealed that macrophage-related signals may be potential biomarkers for oral squamous cell carcinoma. Scientific Reports, 16(1), 2217. https://doi.org/10.1038/s41598-025-31899-x
16. Zhang, G., Fu, J., Su, Y., & Zhang, X. (2019). Opposite Effects of Garcinol on Tumor Energy Metabolism in Oral Squamous Cell Carcinoma Cells. Nutrition and Cancer, 71(8), 1403–1411. https://doi.org/10.1080/01635581.2019.1607409
17. Zhang, Y., Guo, C., & Yu, G. (2005). A pilot study of fatty acid metabolism in oral squamous cell carcinoma. International Journal of Oral and Maxillofacial Surgery, 34(1), 78–81. https://doi.org/10.1016/j.ijom.2004.03.001
18. Zhang, Z., Gao, Z., Rajthala, S., Sapkota, D., Dongre, H., Parajuli, H., Suliman, S., Das, R., Li, L., Bindoff, L. A., Costea, D. E., & Liang, X. (2020). Metabolic reprogramming of normal oral fibroblasts correlated with increased glycolytic metabolism of oral squamous cell carcinoma and precedes their activation into carcinoma associated fibroblasts. Cellular and Molecular Life Sciences, 77(6), 1115–1133. https://doi.org/10.1007/s00018-019-03209-y
19. Zhou, J., Huang, S., Wang, L., Yuan, X., Dong, Q., Zhang, D., & Wang, X. (2017). Clinical and prognostic significance of HIF-1α overexpression in oral squamous cell carcinoma: a meta-analysis. World Journal of Surgical Oncology, 15(1), 104. https://doi.org/10.1186/s12957-017-1163-y