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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 health problem worldwide with poor clinical outcomes in patients diagnosed at advanced stages. Metabolic reprogramming is an important feature of oral cancer development and supports the growth and survival of malignant cells under changing tumor conditions. Oral cancer cells show increased glucose utilization and altered lipid metabolism. These changes provide energy and metabolic intermediates required for continuous tumor growth. At the same time the tumor microenvironment strongly influences cancer cell metabolism and immune function. Hypoxia, nutrient limitation, and interactions with stromal cells can promote an immunosuppressive environment that supports tumor progression. Metabolic changes within cancer cells can also affect immune cell activity and reduce effective antitumor responses. This interaction between tumor metabolism and immune regulation contributes to immune escape and may influence therapeutic resistance. Recent studies have identified several metabolic pathways and immune regulatory mechanisms that may serve as potential therapeutic targets. Approaches targeting glycolysis, lipid metabolism, and immunosuppressive pathways are being investigated for oral cancer treatment. This review discusses the major metabolic alterations associated with oral cancer and their influence on tumor immune evasion. It further examines the interaction between cancer metabolism and the tumor microenvironment and highlights emerging therapeutic strategies. Understanding these metabolic and immune interactions may support the development of more effective precision therapeutic approaches for oral cancer.

1. Introduction

Oral cancer remains an important health problem worldwide. Oral squamous cell carcinoma (OSCC) accounts for the majority of malignant tumors arising in the oral cavity. The clinical outcome remains unsatisfactory in many patients. Local invasion and lymph node metastasis further complicate treatment. Recurrence also remains a major concern after surgery and adjuvant treatment. These clinical features indicate that tumor progression cannot be explained only by genetic alterations within cancer cells. Changes in cellular metabolism and interactions with the tumor microenvironment have become important factors in oral cancer biology. Cancer cells require a continuous supply of energy and metabolic intermediates to maintain proliferation. They also need mechanisms that allow survival under hypoxia and nutrient limitation. OSCC cells therefore undergo metabolic changes that differ from those observed in normal oral epithelial cells (Tan et al., 2023). Increased glucose uptake and aerobic glycolysis are among the most recognized changes. However, OSCC metabolism is not restricted to glycolysis. Alterations in mitochondrial activity, lipid synthesis, fatty acid utilization, and nucleotide synthesis have also been described. These pathways provide energy and biosynthetic substrates for tumor growth. They also help cancer cells adapt to treatment and environmental stress (Eckert et al., 2016; Senlle et al., 2026). Metabolic changes also influence antitumor immunity. Tumor cells compete with immune cells for glucose and other nutrients.

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At the same time, they release metabolites that modify the surrounding microenvironment. Lactate is an important example and high glycolytic activity increases lactate production. Lactate accumulation lowers extracellular pH and can reduce the activity of cytotoxic lymphocytes. It can also alter macrophage function and promote an immunosuppressive environment. Recent work in OSCC has provided direct evidence that lactate can influence macrophage antigen presentation and T cell activation (M. Wang et al., 2026).

Hypoxia is another important link between metabolism and immunity. Poor vascularization creates areas with reduced oxygen availability. Hypoxia stabilizes hypoxia inducible factor 1 alpha (HIF-1α). HIF-1α then regulates genes involved in glucose transport. It also regulates glycolysis. It promotes angiogenesis and contributes to changes in the extracellular environment. Earlier studies in OSCC showed that HIF-1α and GLUT1 expression were associated with poor clinical outcome. Coexpression of these markers was associated with a higher risk of tumor related death (Eckert et al., 2016). The immune microenvironment of OSCC contains cytotoxic T cells and it also contains regulatory T cells. Tumor associated macrophages and myeloid derived suppressor cells are frequently present. Cancer associated fibroblasts further modify the tumor environment and these cells do not function independently. Their activity is strongly influenced by oxygen availability and nutrient distribution. Metabolic communication between cancer cells and stromal cells can therefore determine whether an immune response remains effective or becomes suppressed. Recent studies have strengthened this concept. Spatial transcriptomic analysis showed that metabolically active regions of OSCC contain distinct immune and stromal characteristics. These regions showed increased CD4 T cell infiltration and higher TGF-β expression. The same study suggested that lactate produced by glycolytic epithelial cells can influence fibroblast behavior and promote an inflammatory cancer associated fibroblast phenotype (Liu et al., 2024). These findings suggest that metabolic reprogramming and immune evasion should not be considered as separate processes. Understanding this relationship may help identify patients who are more likely to respond to immunotherapy. It may also provide new opportunities for combining metabolic inhibitors with immune checkpoint blockade. This review discusses the major metabolic alterations in oral cancer. It further examines how these changes shape the immune microenvironment and how this knowledge can be translated into precision therapeutic strategies.

2. Metabolic Reprogramming in Oral Cancer

2.1 Glycolytic reprogramming and Glucose utilization

Aerobic glycolysis is one of the most characteristic metabolic changes in OSCC. Cancer cells increase glucose uptake and convert a large proportion of glucose into lactate even when oxygen is available. This phenomenon is commonly referred to as the Warburg effect. The importance of this pathway in OSCC extends beyond ATP generation. Glycolysis provides intermediates required for nucleotide synthesis. It also supports amino acid production and lipid synthesis. GLUT1 is an important glucose transporter involved in this process. Increased GLUT1 expression has been reported in OSCC. HIF-1α can stimulate GLUT1 expression under hypoxic conditions. This allows tumor cells to maintain glucose uptake when mitochondrial respiration becomes less favorable. Earlier clinical observations found that tumors with high HIF 1α and GLUT1 expression had poorer outcomes. The study reported a 5.13 fold higher risk of tumor related death in patients showing high expression of both markers. Increased glucose uptake was also associated with reduced sensitivity to cisplatin based treatment (Eckert et al., 2016). Several glycolytic enzymes contribute to this metabolic phenotype. Hexokinase 2 promotes the first committed step of glycolysis. Phosphofructokinase regulates another rate limiting step. Pyruvate kinase M2 supports the final stage of glycolysis. Lactate dehydrogenase A converts pyruvate into lactate. Monocarboxylate transporters then facilitate lactate movement across the cell membrane. A recent review of OSCC metabolism emphasized that glycolytic activation is closely related to tumor progression and treatment resistance. It also highlighted the involvement of glycolytic pathways in the formation of an immunosuppressive tumor microenvironment (Shin, 2025). Glycolysis therefore provides a metabolic advantage to tumor cells. However, it also changes the environment surrounding the tumor. Increased lactate production creates extracellular acidity. This condition can damage the activity of immune effector cells. It can also favor tumor invasion and adaptation.

2.2 HIF-1α as a central metabolic regulator

Hypoxia is common in solid tumors. OSCC is

particularly affected because rapidly growing tumor tissue may outgrow its blood supply. HIF-1α acts as an important regulator of the response to reduced oxygen availability. Under normoxic conditions HIF-1α is continuously degraded. Under hypoxia it becomes stabilized. It then enters the nucleus and activates a broad group of genes. HIF-1α increases glycolytic activity by regulating glucose transporters and glycolytic enzymes. It also promotes angiogenesis through vascular endothelial growth factor. At the same time HIF-1α contributes to extracellular pH regulation. Carbonic anhydrase IX and other pH regulatory proteins help tumor cells survive acidic conditions. The importance of this pathway in OSCC has been demonstrated in clinical tissue studies. HIF-1α expression has been associated with tumor progression. HIF-1α has also been linked with lymphatic and vascular changes. These findings suggest that hypoxia does not simply represent a consequence of tumor growth. It actively contributes to tumor adaptation (Eckert et al., 2016). HIF-1α can also influence immune escape. Hypoxic regions are associated with reduced cytotoxic T cell activity. They can support recruitment of immunosuppressive myeloid cells. HIF 1α can also increase immune checkpoint expression. A clinical study involving 218 patients with advanced OSCC found an association between HIF-1α expression and PD-L1 expression in tumor tissue and metastatic lymph nodes (T.-C. Chen et al., 2015).

2.3 Mitochondrial metabolism and metabolic flexibility

The metabolic phenotype of OSCC should not be viewed as a complete loss of mitochondrial activity. Tumor cells can continue to use oxidative phosphorylation when environmental conditions permit. Mitochondria remain important for ATP production. They also participate in redox regulation and biosynthetic reactions. This metabolic flexibility may explain why single pathway inhibition often produces limited effects. When glycolysis is inhibited some tumor cells can increase mitochondrial metabolism. When glucose availability falls cancer cells may use fatty acids or amino acids as alternative substrates. Recent reports have emphasized that OSCC cells can maintain functional mitochondria despite increased aerobic glycolysis (Senlle et al., 2026). An earlier study using three OSCC cell lines demonstrated this heterogeneity. HSC 2 and HSC 3 cells showed greater dependence on glycolysis. PE15 cells maintained efficient oxidative phosphorylation. Treatment with dichloroacetate increased respiratory activity and produced strong cytostatic and proapoptotic effects in HSC 2 and HSC 3 cells. These findings provide an important example of why metabolic heterogeneity needs to be considered before selecting a metabolic therapy (Ruggieri et al., 2015).

2.4 Lipid metabolism

Lipid metabolism is another important component of OSCC progression. Cancer cells require lipids for membrane formation. Lipids also act as signalling molecules. Increased lipid synthesis can therefore support proliferation and survival. Fatty acid synthase and ATP citrate lyase are among the enzymes associated with altered lipid metabolism in OSCC. Changes in lipid composition have also been detected in tumor tissue and surrounding tissue. A study involving 30 patients with oral squamous cell carcinoma identified substantial differences in fatty acid composition between tumor tissue and adjacent tissue. The authors also observed relationships between fatty acid patterns and tumor grade (Halczy-Kowalik et al., 2019). Recent research has provided further evidence for stromal control of lipid metabolism. CAFs can release free fatty acids that are taken up by OSCC cells. These fatty acids can support lipid raft formation. Increased lipid raft formation can activate PI3K and AKT signalling. A recent study reported that CAF derived fatty acids promoted proliferation and invasion through this mechanism (Mu et al., 2025). CD36 is another relevant metabolic regulator. It functions as a fatty acid transporter and signalling molecule. Experimental inhibition of CD36 using sulfosuccinimidyl oleate sodium reduced OSCC proliferation. It also increased apoptotic cell death and altered immune accessory molecule expression. In an oral cancer mouse model, the treatment produced antitumor and immunomodulatory effects (Takaichi et al., 2024).

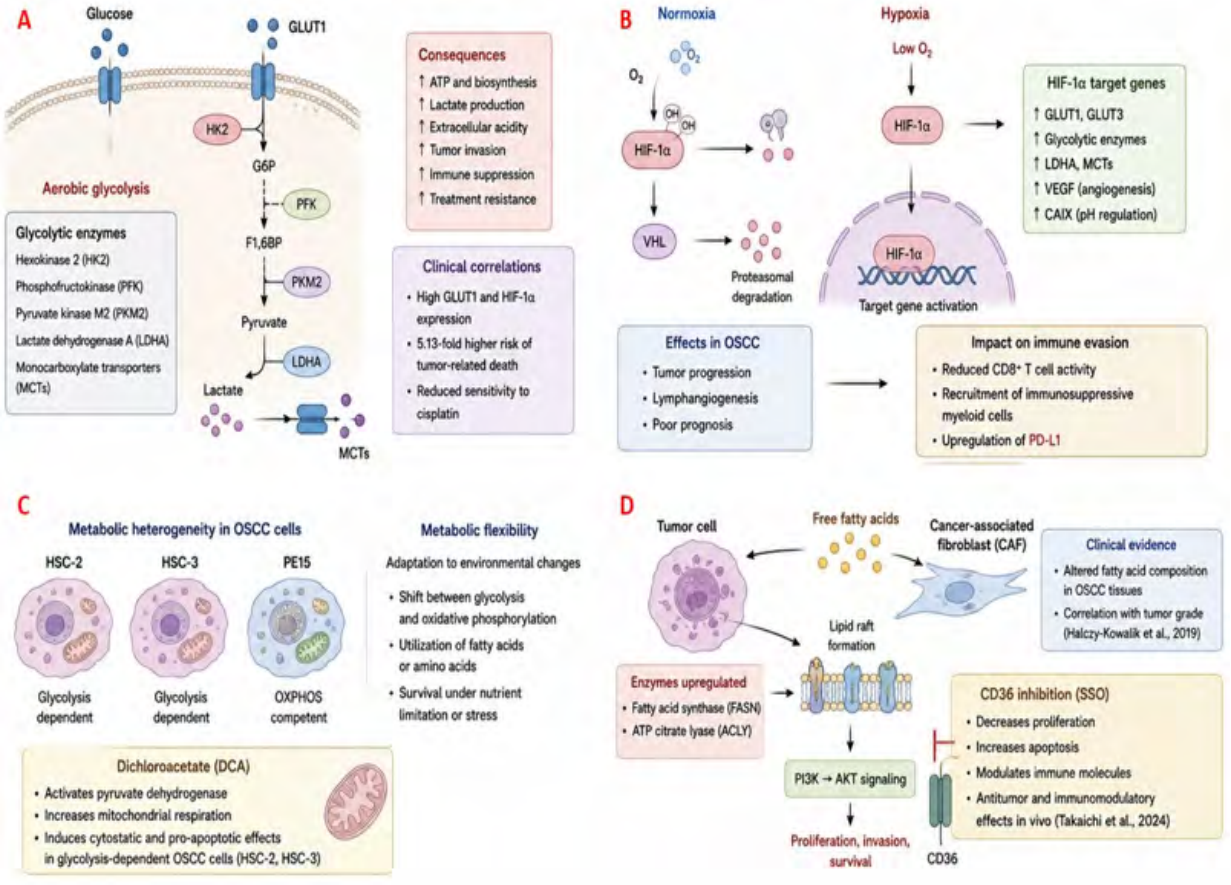


Figure 1: (A) Enhanced glucose uptake through GLUT1 promotes aerobic glycolysis and increases lactate production. (B) HIF-1α becomes stabilized under hypoxic conditions and regulates genes involved in glycolysis, angiogenesis, and pH control. (C) OSCC cells also show metabolic flexibility with differences in their dependence on glycolysis and oxidative phosphorylation. (D) Altered lipid metabolism further supports tumor growth through fatty acid utilization and lipid raft formation. Cancer associated fibroblasts can provide free fatty acids to tumor cells and promote PI3K AKT signaling. These metabolic changes contribute to tumor proliferation, invasion, immune suppression, and treatment resistance.

3. Metabolic Regulation of the Oral Cancer Tumor Microenvironment

The tumor microenvironment is composed of cancer cells and several nonmalignant populations. Endothelial cells and extracellular matrix components contribute to the local environment. Metabolic changes in tumor cells can alter the behavior of each of these components. Lactate is one of the most important metabolites connecting glycolysis with immune suppression. Increased glycolysis increases lactate production. MCT proteins transport lactate out of tumor cells. This process contributes to extracellular acidification. An acidic environment is unfavorable for several immune functions. CD8 positive T cells show reduced cytotoxic activity under high lactate conditions. NK cell function can also be impaired. Reduced production of granzyme and perforin has been reported under hypoxic and lactate rich conditions in oral cancer models (Chaudhary et al., 2020). Recent OSCC research has provided more direct mechanistic evidence. Wang and colleagues used single cell analysis and experimental models to investigate macrophage dysfunction. They found that lactate accumulation caused metabolic changes in tumor associated macrophages and this change increased C/EBPα acetylation. CD74 expression was subsequently reduced. The loss of CD74 impaired antigen presentation and reduced T cell activation. The authors further linked this pathway with tumor progression and recurrence (M. Wang et al., 2026). This finding is important because it shows that lactate does not simply suppress immune cells through acidity. It can also modify transcriptional programs within immune cells. Metabolic products can therefore act as signalling molecules.

Activated T cells require substantial amounts of glucose. Tumor cells can consume glucose at a much higher rate. This creates a nutrient restricted environment for immune cells. B7-H3 has recently emerged as an important regulator of this process in OSCC. Wu and colleagues reported that B7-H3 expression was associated with advanced tumor stage and lymph node metastasis. Their experimental work showed that B7-H3 influenced glucose competition between OSCC cells and CD8 positive T cells. Increased tumor glycolysis

reduced the availability of glucose for T cells. This impaired their immune function (M. Wang et al., 2026). These findings provide a direct connection between metabolic competition and immune checkpoint biology. The tumor cell does not need to completely eliminate immune cells. It can instead create a metabolic environment in which immune cells cannot function efficiently.

Regulatory T cells are important suppressive populations within the OSCC microenvironment. They inhibit excessive immune activation under normal conditions. In cancer they can suppress antitumor responses. Their function is strongly influenced by metabolism. Tregs can adapt to nutrient restricted conditions. They can use fatty acid oxidation and other metabolic pathways to maintain their suppressive phenotype. Tryptophan metabolism also contributes to Treg biology. IDO1 converts tryptophan into kynurenine. Kynurenine can activate the aryl hydrocarbon receptor and promote regulatory immune responses. Recent work on OSCC has emphasized the interaction between glycolysis and Treg function. Lactate rich conditions can support Treg activity. Adenosine metabolism can provide another suppressive signal. CD39 and CD73 convert extracellular ATP into adenosine. Adenosine then acts through adenosine receptors to reduce immune cell activity (Gan et al., 2024). The metabolic environment can therefore favor Tregs over cytotoxic lymphocytes. This shift contributes to immune tolerance within the tumor.

Macrophages show substantial metabolic flexibility. Their phenotype can change in response to cytokines. It can also change in response to nutrients and metabolites. Lactate is an important factor in this process. Hypoxic oral tumors produce high levels of lactate. Lactate can favor a tumor supporting macrophage phenotype. These macrophages can produce growth factors and immunosuppressive cytokines. They may also reduce antigen presentation. The recent lactate C/EBPα-CD74 study provides a more specific mechanism. The findings suggest that tumor derived lactate can directly modify macrophage transcriptional activity (Gan et al., 2024). This mechanism may be particularly relevant when considering immunotherapy. Checkpoint inhibitors require functional immune cells. A metabolically suppressed macrophage compartment may therefore contribute to poor therapeutic response.

4. Metabolic Reprogramming and Immune Evasion

PD-L1 is one of the major immune escape mechanisms in OSCC. Tumor cells expressing PD-L1 can inhibit PD-1 positive T cells. This reduces T cell mediated tumor killing. Metabolism and PD-L1 expression are closely connected. Hypoxia can stimulate PD-L1 expression through HIF dependent mechanisms. Glycolytic activity can also correlate with PD L1 expression. A study of advanced OSCC reported an association between HIF-1α and PD-L1 expression. This finding suggests that hypoxic tumor regions may possess both metabolic adaptation and immune suppressive properties (T.-C. Chen et al., 2015). Recent research has identified additional connections between metabolic signalling and PD L1. A 2026 study found that RUVBL1 promoted mTORC1 activation in OSCC. This pathway increased PD-L1 expression and reduced T cell infiltration and effector function. Pharmacological inhibition of RUVBL1 suppressed tumor growth and showed synergy with PD-L1 blockade in experimental models (X. Wang et al., 2026). Another recent study identified the NFIC DEPTOR mTOR axis as a regulator of glycolysis and immune escape. NFIC increased DEPTOR expression and reduced mTOR activity. This decreased glycolytic activity and improved CD8 positive T cell killing. The same pathway reduced tumor growth and tumor microenvironment acidification in experimental models (Xu et al., 2026).

T cell exhaustion develops when immune cells experience persistent antigen stimulation. The metabolic environment can accelerate this process and high lactate levels can reduce T cell cytotoxic activity. Low glucose availability further limits T cell metabolism. Hypoxia can reduce mitochondrial function and change cytokine production. These changes can reduce interferon gamma production and granzyme activity. A recent OSCC study reported that excessive lactate accumulation promoted PD-L1 enrichment on tumor cells. Lactate exposure also reduced the secretion of interferon gamma. It reduced tumor necrosis factor alpha and cytotoxic molecules such as granzyme B and perforin (Cui et al., 2025; W. Zhao et al., 2026). These results suggest that controlling lactate metabolism may improve the function of existing immune cells. This approach could complement immune checkpoint blockade. NK cells provide an early defense against malignant cells and their cytotoxic function depends on metabolic activity. Hypoxia and high lactate levels can reduce NK cell function. Studies in oral cancer models indicate that hypoxic conditions can reduce NK cell expression of cytotoxic mediators. These changes can decrease tumor cell killing. The combination of hypoxia and lactate therefore creates a microenvironment that protects malignant cells from innate immune surveillance (Chaudhary et al., 2020).

5. Metabolic Crosstalk Between Cancer Cells and Stromal Cells

CAFs are abundant stromal cells in many OSCC lesions. They influence tumor growth through extracellular matrix remodeling. It also release growth factors and cytokines.

Recent evidence indicates that CAFs participate directly in metabolic communication. A recent study showed that CAFs secreted free fatty acids that were taken up by OSCC cells. The fatty acids increased lipid raft formation. This activated PI3K and AKT signalling. The result was increased proliferation and invasion (Mu et al., 2025). Spatial transcriptomic research has added another dimension to this interaction. Hypermetabolic areas of OSCC were associated with increased CD4 T cell infiltration and higher TGF-β expression. Fibroblasts in these regions could utilize tumor derived lactate. This was associated with an inflammatory CAF phenotype and increased HIF-1A signalling (Liu et al., 2024). These findings suggest that tumor metabolism can change the phenotype of stromal cells. The altered stromal cells can then return nutrients and signals to the tumor. This creates a metabolic feedback loop.

Tumor metabolism is closely connected to angiogenesis. Hypoxia increases HIF-1α activity. HIF-1α promotes VEGF expression. New blood vessels may improve nutrient delivery. However, tumor vessels are often structurally abnormal. Poor perfusion can therefore persist even after angiogenesis. This produces regions with variable oxygen and nutrient availability. Tumor cells located in these regions must continuously adapt. HIF-1α also promotes lymphatic changes. Earlier OSCC studies found an association between HIF-1α expression and VEGF C expression. Higher HIF-1α expression was also associated with increased lymphatic vessel density (Eckert et al., 2016). This mechanism may help explain the relationship between hypoxia and lymph node metastasis. The oral cavity contains a complex microbial community. Changes in the oral microbiota have been associated with oral carcinogenesis. Microorganisms can produce metabolites that influence epithelial cells and immune cells. Recent research has proposed a microbiome metabolite host axis in OSCC. Microbial metabolites may influence energy metabolism. They can also affect epigenetic regulation and oxidative stress. Tryptophan derived microbial products may influence immune signalling through the aryl hydrocarbon receptor. Short chain fatty acids may also affect immune responses (Wu et al., 2026).

6. Metabolic Features as Biomarkers of Oral Cancer Progression

6.1 Glycolytic biomarkers

GLUT1 and HIF 1α are among the most investigated metabolic markers. Their expression has been linked with aggressive disease. Other glycolytic proteins include HK2. PKM2 and LDHA have also been investigated. A study examining HIF related glycolytic proteins in oral potentially malignant disorders and OSCC evaluated GLUT1, GLUT3, HK2, PFKL, PKM2, phosphorylated PDH, LDHA, MCT4 and CAIX. Such studies support the possibility that metabolic changes occur before advanced malignant progression (GHOLAMI et al., 2023). The clinical value of these markers will depend on validation in larger cohorts. A single marker is unlikely to capture the metabolic heterogeneity of OSCC.

6.2 Lipid metabolic markers

Lipid metabolism also shows potential for risk stratification. FASN and ACLY are associated with increased lipid synthesis. CES2 has attracted interest because its loss can disturb lipid homeostasis. A study of CES2 found that altered lipid metabolism was associated with malignant behavior in OSCC. Experimental modulation of CES2 produced changes in lipid composition and tumor cell behavior. The findings support the concept that lipid homeostasis is important for tumor adaptation (X. Chen et al., 2022). More recent studies have examined lipid metabolic patterns using single cell and transcriptomic approaches. A recent study identified metabolic subgroups associated with hypoxia and lipid metabolism. The work suggested that integrated metabolic profiles may provide better prognostic information than isolated genes (L. Zhao et al., 2026).

6.3 Metabolic and immune biomarkers

The most useful biomarkers may combine metabolic and immune information. For example, a tumor with high glycolysis and high PD-L1 expression may represent a different biological state from a tumor with high glycolysis and strong CD8 T cell infiltration. A recent study of 80 OSCC patients examined PI3K/AKT/mTOR pathway activation and PD-L1 expression. p-PI3K was positive in 58.8% of tumors. p-AKT was positive in 62.5%. p-mTOR was positive in 51.3%. PD-L1 was positive in 41.3%. p AKT expression showed a significant association with PD-L1 expression. p-AKT was also an independent predictor of shorter survival (Gu, 2026). These findings support a combined biomarker approach. Metabolic signalling may help identify tumors that require both pathway inhibition and immune checkpoint treatment.

7. Precision Therapeutic Strategies Targeting Metabolism and Immunity

The connection between metabolism and immune evasion provides a rationale for combination therapy. The goal is not simply to kill metabolically active tumor cells. It is also to restore a microenvironment that permits immune cells to function. Dichloroacetate is an example of a metabolic drug that has been studied in OSCC. It inhibits pyruvate dehydrogenase kinase. This promotes pyruvate entry into mitochondrial oxidation. Preclinical OSCC studies showed that DCA increased mitochondrial respiration. It

also induced cytostatic and proapoptotic effects in glycolysis dependent cell lines (Ruggieri et al., 2015). Clinical evidence remains more limited. A randomized phase II study in locally advanced head and neck squamous cell carcinoma evaluated DCA with cisplatin based chemoradiotherapy. The study included 45 patients. Complete response at treatment completion was higher in the DCA group than in the placebo group at 71.4% versus 37.5%. However long term survival did not differ significantly. DCA treatment reduced serum pyruvate and lactate levels (Powell et al., 2022). These findings show the difference between metabolic modulation and clinical benefit. A metabolic drug may change its intended biochemical target without producing a durable survival advantage.

Lipid metabolism represents another therapeutic opportunity. FASN inhibitors may reduce de novo fatty acid synthesis. CD36 inhibition may interfere with fatty acid uptake. Targeting lipid raft formation may also affect oncogenic signalling. The recent CD36 study provides preliminary evidence that metabolic inhibition can influence tumor immunity. CD36 blockade inhibited OSCC growth and altered immune accessory molecules (Takaichi et al., 2024). The CAF fatty acid pathway provides another potential target. Blocking fatty acid release from CAFs could reduce lipid availability to tumor cells. It may also weaken PI3K/AKT signalling (Mu et al., 2025). mTOR integrates nutrient availability with cell growth. It also regulates glycolysis and protein synthesis. The recent RUVBL1 study provides an example of how mTOR signalling can connect metabolism with immune escape. RUVBL1 promoted mTORC1 activity. This increased PD-L1 expression and impaired T cell function. RUVBL1 inhibition showed synergy with PD-L1 blockade in experimental models (X. Wang et al., 2026). The NFIC DEPTOR study provides complementary evidence. Activation of DEPTOR reduced mTOR signaling. This suppressed glycolysis and improved CD8 T cell activity (Xu et al., 2026). These findings support combination strategies that target metabolic signalling together with immune checkpoints. Lactate represents a particularly attractive target because it sits at the intersection of tumor metabolism and immune suppression. Blocking lactate production could reduce extracellular acidity. Blocking lactate transport could prevent lactate accumulation outside tumor cells. MCT1 and MCT4 are therefore potential targets. Recent OSCC research showed that MCT1 inhibition reduced lactate secretion and extracellular acidification. It also reduced PD-L1 enrichment and improved CD8 T cell mediated antitumor activity. In the same study baicalin reduced MCT1 mRNA stability and improved immune activity in experimental models (Cui et al., 2025; W. Zhao et al., 2026). This finding is particularly relevant because it provides a direct link between metabolic intervention and immune restoration.

8. Future Perspectives

Metabolic reprogramming has become an important feature of oral cancer biology. OSCC cells increase glycolysis and modify mitochondrial metabolism. They also alter lipid and amino acid utilization. These changes allow tumor cells to maintain growth under hypoxia and nutrient limitation. More importantly they influence the surrounding immune environment. The relationship between metabolism and immunity is not one directional. Tumor cells consume nutrients required by immune cells. They release lactate and other metabolites. These metabolites alter macrophage function. They also reduce cytotoxic T cell activity and support regulatory immune populations. Hypoxia further strengthens these effects through HIF 1α signaling. CAFs contribute additional metabolic substrates such as fatty acids. The result is a microenvironment that supports tumor survival while reducing immune surveillance.

Recent studies have provided direct evidence for this interaction. The lactate C/EBPα-CD74 pathway shows how tumor derived lactate can impair macrophage antigen presentation. B7 H3 mediated glucose competition demonstrates how tumor metabolism can restrict CD8 T cell function. RUVBL1 and mTOR signalling provide another connection between metabolic regulation and PD-L1 expression. CAF derived fatty acids further demonstrate that stromal metabolism can directly support malignant behavior (M. Wang et al., 2026; X. Wang et al., 2026; Wu et al., 2024). These findings provide a strong basis for metabolic immunotherapy. However metabolic targeting should be approached carefully. Tumors are metabolically heterogeneous. Different cancer cell populations may use different substrates. Metabolic inhibition can therefore produce adaptation rather than complete tumor control.

9. Conclusion

Overall evidence indicates that metabolic reprogramming is not simply a consequence of oral cancer progression. It actively contributes to immune escape and treatment resistance. Understanding this relationship may allow metabolic characteristics to become useful biomarkers. It may also support the development of combination therapies that target both tumor metabolism and immune suppression. Such an approach could move OSCC treatment toward a more precise strategy in which therapy is selected according to the metabolic and immune characteristics of each tumor.

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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