Metabolism Writes the Epigenome: Metabolite-Encoded Malignancy in Oral Squamous Cell Carcinoma

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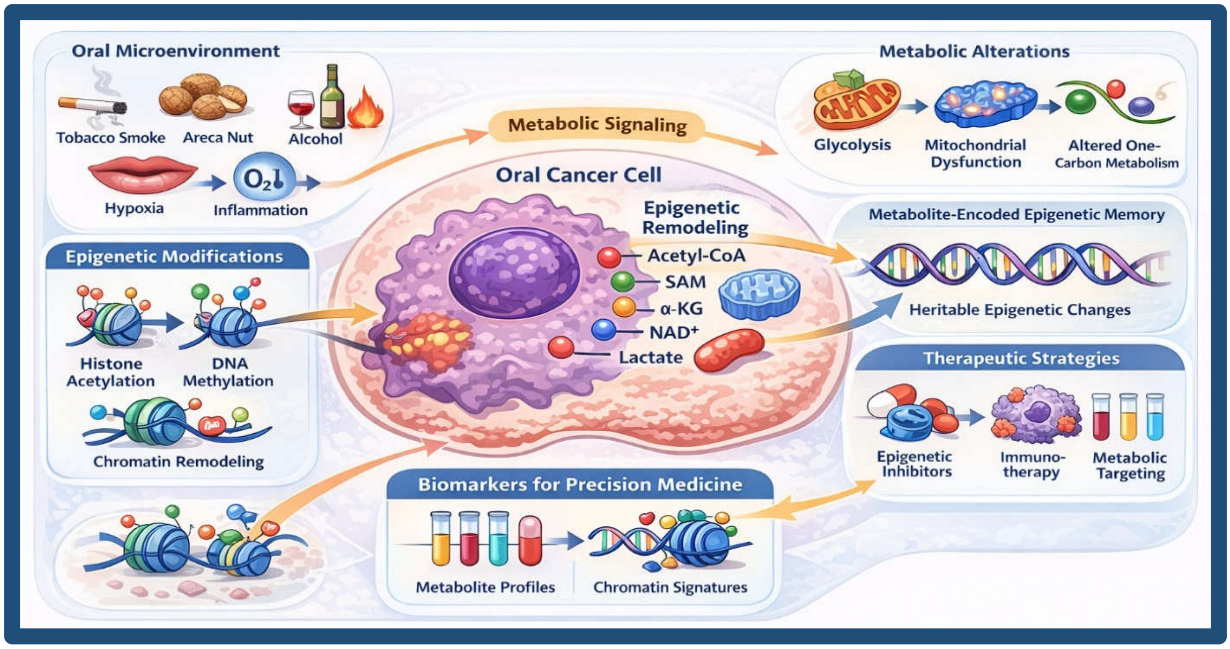
Abstract

Oral squamous cell carcinoma (OSCC) is increasingly recognized as a malignancy in which genetic alterations alone are insufficient to explain disease initiation and progression. Instead, coordinated interactions between cellular metabolism and epigenetic regulation have emerged as central drivers of OSCC pathogenesis. While metabolism and epigenetics were traditionally viewed as parallel processes, growing evidence indicates that metabolic intermediates directly regulate chromatin-modifying enzymes, thereby linking metabolic flux to transcriptional control. Metabolites such as acetyl-CoA, S-adenosylmethionine, α-ketoglutarate, NAD^+, and lactate function as essential cofactors for epigenetic modifications, enabling dynamic coupling of metabolic states with chromatin architecture. OSCC provides a unique context for studying this interplay due to chronic exposure to tobacco, areca nut, alcohol, hypoxia, and inflammation within the oral microenvironment. This review integrates recent findings demonstrating how glycolytic reprogramming, mitochondrial dysfunction, altered one-carbon metabolism, and lipid-derived acetyl-CoA production drive epigenetic remodeling in OSCC. We highlight lactate-mediated signaling, disrupted α-ketoglutarate–succinate balance, and metabolite-dependent regulation of histone acetyltransferase activity at oncogenic loci. Furthermore, we introduce the concept of metabolite-encoded epigenetic memory, wherein metabolic perturbations establish heritable epigenetic states that sustain malignant transcriptional programs beyond the initiating stress. Finally, we discuss therapeutic strategies targeting the metabolic–epigenetic interface, including combinatorial epigenetic and immunotherapeutic approaches, and the potential of metabolite and chromatin signatures as biomarkers for precision medicine in OSCC.



Graphical Abstract

Keywords: Oral squamous cell carcinoma; Metabolic reprogramming; Metabolite–chromatin interface; DNA methylation; Histone modifications; Metabolic memory; Tumor microenvironment.

1. Introduction: Metabolic–Epigenetic Integration in Oral Squamous Cell Carcinoma (OSCC)

Over 90% of OCC cases are represented by the type called Oral Squamous Cell Carcinomas (OSCC), which are the most common type of cancer of the jaw. It originates in the stratified squamous epithelium. Indeed, the high incidence of OSCC cases, its high malignancy potential, and its limited good clinical responses clearly indicate its high impact in the whole world. According to Global Cancer Observatories, oral cancer also ranks among the most common diseases globally, with 377,000 new cases and 177,000 annual deaths due to the disease annually (Koech, 2024). Incidence and death rates differ considerably globally. In particular, it has been observed that the highest health impact has been contributed by the people of South and South-East Asia, specifically by the Indian subcontinent. In this region, indeed, oral cancer has been observed to specifically represent “the most common type of cancer in men” (Wu et al., 2025). Although advanced diagnostic and therapeutic techniques such as surgery, radiation, and chemotherapy are available for diagnosing and treating this disease, the five-year survival rate for OSCC is only 50-60%, and this rate decreases dramatically for people with advanced-stage cancers (Yang et al., 2023). The poor prognosis is most often a consequence of late-diagnosed cases, locoregional recurrence, lymph node metastasis, and resistance to current treatments (Stawarz et al., 2025; Anand et al., 2025). These medical issues thereby emphasize the importance of having a deeper knowledge of OSCC aetiology at a molecular level as far as efficient early detection as well as effective targeted therapies are concerned. OSCC has multifactorial etiologies with both environmental as well as biological risk factors. The major etiological contributions of OSCC include tobacco smoking, use of smokeless tobacco, areca nut/chew, betel quid chewing, alcohol use, as well as the infection of human papillomavirus (Nokovitch et al., 2023; Eloranta et al., 2024; Yang et al., 2023), as shown in Figure 1. Chronic inflammation, oxidative damage, and instability of the genome, due to continuous exposure to carcinogens, lead to malignancy (Rembiałkowska et al., 2025; Mathur and Jha, 2020). Moreover, there is accumulating evidence that oral microbiota, diet, and socioeconomic factors exert influences on disease susceptibility, as well as disease development, as proposed by Nokovitch et al., (2023).

Notably, these factors not only induce genetic mutation but also play critical roles in influencing cellular metabolism as well as epigenetic regulation. In the past, metabolic rewiring and epigenetic alterations were identified as two separate characteristics of cancer. Metabolic rewiring: Cancer cells can proliferate in abundance because it helps to promote high glucose, glutamine, and lipid production even in hypoxic and nutrient-poor environments (Xu et al., 2023). Hence, there will be an attendant epigenetic process, such as dysfunctions involving DNA methylation, histone, and appropriate non-coding RNA expressions, resulting in the over-expression of oncogenes, as well as the suppression of tumour suppressor genes, without an accompanying change in the DNA sequence (Zhang et al., 2025; Farheen et al., 2024). As shown in the figure. 1. There has been recent insight into a new paradigm in which there is an intertwining relationship between metabolism and epigenetics through bidirectional regulation (Gantner et al., 2024). Substances such as S-adenosylmethionine (SAM), acetyl-CoA, α-ketoglutarate, fumarate, succinate, and NAD^+ are required components and cofactors for enzymes that modify chromatin (Zhang and Jagannath, 2025). This helps in rewiring metabolism to enable the proliferative growth of the cancerous cells under hypoxic conditions with low nutrition by increasing glucose, glutamine, and lipid synthesis. Therefore, there are concomitant changes in the epigenetics, especially in the form of aberrant DNA methylation patterns, histone modifications, as well as the inappropriate expression of non-coding RNAs (Jha et al., 2011). These contribute towards the activation of oncogenes as well as the down-regulation of tumor suppressor genes without any changes in the DNA (Gangwar and Jha, 2026). It was revealed by recent studies that there is a continually emerging paradigm of linkage between cellular metabolisms and epigenetics based on bidirectional regulatory systems. Metabolites, including S-adenosylmethionine (SAM), acetyl-CoA, alpha-ketoglutarate, fumarate, succinate, and NAD^+, act as substrates, cofactors, or regulators. Metabolic flux influences DNA methylation pattern, histone acetylation and methylation, chromatin accessibility, and hence global gene expression programs directly (Wang and Han, 2021). In contrast, epigenetic processes govern the transcription of metabolic enzymes and transporters, resulting in feedback loops that perpetuate carcinogenic metabolic states. Because of the distinct aetiology and the special microenvironment of OSCC, the latter is an ideal case to examine the interplay between the metabolic and epigenetic systems. Furthermore, the oral environment is continually exposed to diverse carcinogens and microbiologically generated metabolites. Therefore, the chronic and lifelong microenvironment in OSCC is unique and is particularly characterized by low oxygen levels and an inflammatory and metabolically diverse microenvironment (Chaudhary et al., 2020). Notably, OSCC is increasingly understood to evolve within a pervasive miRNA regulatory network that is intimately coupled to metabolic and epigenetic control layers, thereby coordinating transcriptional, post-transcriptional, and post-translational regulation of gene expression (Kim et al., 2022).

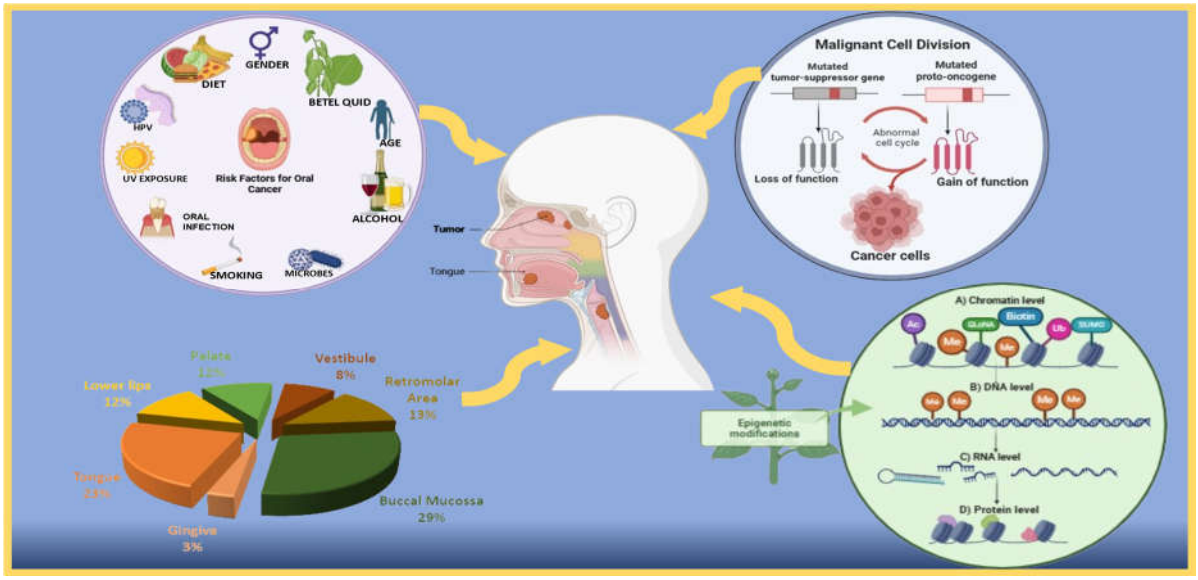


Figure 1: Introduction- Risk factors, Epigenetic Mechanism, Tumor Suppressor genes, and percentage of affected area

2. The Metabolite–Chromatin Interface: Mechanistic Foundations

Regulation of gene is increasingly recognized as a dynamic and integrated process governed by sustained interactions between the cellular metabolic network and chromatin organization, rather than as an isolated nuclear mechanism. Metabolic processes have long been known as a source of a variety of molecules of relevance far beyond their original purposes of energy supply and biosynthesis of important compounds. Instead, these metabolites directly control chromatin-modifying enzymes and shape higher-order chromatin structure as a means of transducing environmental and dietary signals into epigenetic responses (Singh et al., 2023; Church and Workman, 2024). The integration of metabolism and chromatin organization thus defines the metabolite/chromatin interface that plays a central role in all aspects of cellularity. Epigenetic enzymes responsible for post-translational modifications of histones and DNA are intrinsically dependent on the availability of specific metabolites. As a result, changes in metabolic flux rapidly translate into alterations in chromatin state and transcriptional output as depicted in Figure 2 (Fernández et al., 2025).

Acetyl-CoA occupies a pivotal position at the crossroads of glucose, lipid, and amino acid metabolism and serves as the obligatory acetyl donor for histone acetyltransferases (HATs). Higher intracellular acetyl-CoA concentrations intensify histone acetylation at lysine residues, remarkably at promoter and enhancer regions. This alteration neutralizes the positive charge of histones, thereby weakening histone–DNA interactions, and promoting an open chromatin configuration forbearing for transcription (Habazaki et al., 2023). The enhancer, acetylation marks like H3K27ac, enable the recruitment of bromodomain-containing proteins and transcriptional coactivators, which aid in stabilizing enhancer–promoter interactions (Tafessu and Banaszynski, 2020). The elevated rate of glycolysis and mitochondrial activity in both rapidly dividing cells and cancer cells leads to an increased pool of acetyl-CoA, which allows for the aberrant activation of enhancers and greater levels of transcription from oncogenes (Padinharayil et al., 2023). Therefore, acetyl-CoA acts as a metabolic rheostat linking the supply of nutrients to the transcriptional regulation of genes. The universal methyl donor for DNA methyltransferases (DNMTs) and histone methyltransferases (HMTs) is S-adenosylmethionine (SAM) (Abdelraheem et al., 2022).

Methylation reactions have critical roles in transcriptional repression, genomic imprinting, X-chromosome inactivation, and the prolongation of cellular identity. The cellular capability for methylation is determined not solely by SAM availability but rather by the SAM-to-S-adenosylhomocysteine (SAH) ratio, as SAH is a potential inhibitor of methyltransferases (Doherty, 2025). Disruption in one-carbon metabolism caused by alteration of methionine, folate, or vitamin B12 metabolism can disrupt methylation fidelity, resulting in to global hypomethylation or hypermethylation in a specific locus. These epigenetic aberrations are a common hallmark features in cancer and are linked with chromosomal instability, inappropriate gene silencing, and activation of oncogenic pathways (Lee et al., 2023).

α-Ketoglutarate (α-KG), a key intermediate of the tricarboxylic acid (TCA) cycle, is involved in epigenetic reprogramming by acting as a cofactor for ten–eleven translocation (TET) family DNA demethylases and Jumonji C (JmjC) domain-containing histone demethylases (Liu et al., 2022; Alcaraz Jr, 2025). The enzymes catalyze oxidative demethylation reactions of DNA and histone from which the methyl group is removed, also promoting chromatin attainability for transcriptional activation (Nie et al., 2024). The function of α-KG–dependent demethylases is extremely sensitive to metabolic homeostasis. Accumulation of structurally related metabolites such as succinate, fumarate, or 2-hydroxyglutarate competitively inhibits these enzymes, resulting in a hypermethylated chromatin condition. Such metabolic and epigenetic dysregulation is frequently observed in tumours with mitochondrial dysfunction or oncogenic mutations in metabolic enzymes (Naeini et al., 2023). Nicotinamide adenine dinucleotide (NAD^+) is regarded as essential for sirtuin activity; the latter are histone deacetylases/mono ADP-ribosyl-transferases that depend on the use of NAD^+. They are involved in the deacetylation of histone and non-histone proteins through the removal of acetyl groups in order to compact chromatin for transcription repression, particularly in heterochromatic regions and stress-responsive loci (Lu et al.,2025).

NAD^+ levels change depending on cellular energy status, oxidative stress, and circadian rhythms. Reduced NAD^+ availability inhibits sirtuin function, resulting in hyperacetylation of histones, loss of chromatin integrity, and altered gene expression. This pathway links metabolic stress, ageing, and epigenetic instability (Anaizi, 2020; Abbas et al., 2024). Lactate has long been regarded as a mere by-product of anaerobic glycolysis. However, the discovery of histone lactylation introduced lactate as a potential active regulator of the epigenome. Histone lactylation is a newly identified post-translational modification that builds up during states of high glycolysis flux, hypoxic stress, and inflammation (Gangwar et al., 2020). Histone lactylation marks have been demonstrated to trigger transcriptional processes related to cellular adaptability, tissue repair, immunological responses, and tumour growth (Xie et al., 2022). By providing cells with the ability to detect and react to metabolic stresses, the regulation of chromatin modifications by lactate shows how the repertoire of regulation by metabolites is expanded by these products, with significance in their roles in cellular regulation (Ziogas et al., 2025).

Metabolic and Energy-Dependent Regulation of Chromatin Accessibility, Genome Organization, and miRNA–Epigenetic Crosstalk

Metabolic intermediates also play a role in controlling chromatin structure independent of histone modifications. Chromatin remodelers like SWI/SNF, ISWI, and CHD families need optimum energy for nucleosome mobility and chromatin structure modulation (Prajapati et al., 2020; Church et al., 2024). Inhibition of energy metabolism

and mitochondrial impairment would affect chromatin remodeling and trigger a transcriptional repression state. Moreover, metabolic signals also affect three-dimensional genome structure, thereby regulating enhancer-promoter interactions and topologically associating domain dynamics (Baroux, 2021). Additionally, DNA structural properties play an important role in genome-wide regulation, together with other regulatory factors. Along with chromatin-level mechanisms, microRNA (miRNA) biogenesis regulates the intersection between cellular metabolism and post-transcriptional regulation (Agbu and Carthew, 2021). More precisely, miRNA processing and maturation through the activities of Drosha and Dicer endonucleases are highly sensitive to cellular ATP concentrations, redox homeostasis, and metabolic stresses. miRNA imbalances can also feedback to regulate chromatin-modifying enzymes and metabolic genes, hence their ability to create complex regulatory feedback mechanisms that link metabolism, epigenetics, and gene expression (Soci et al., 2022).

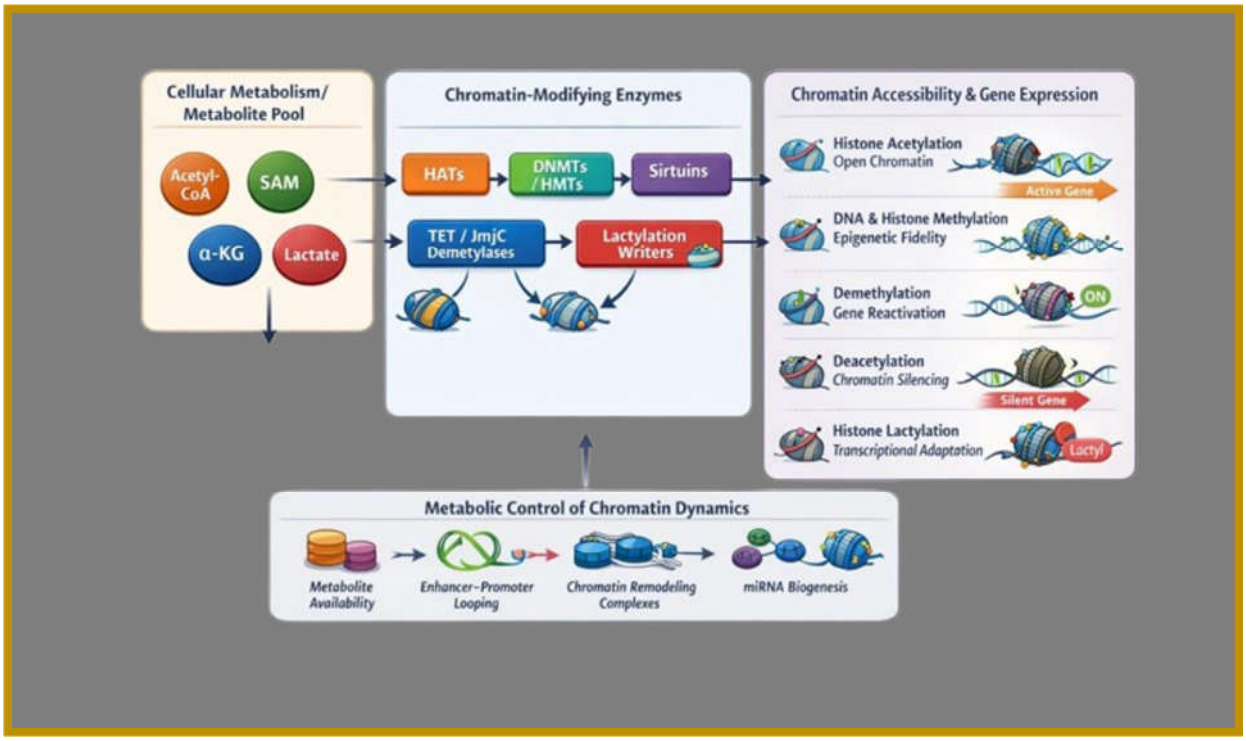


Figure 2: The Metabolite–Chromatin Interface: Mechanistic Foundations by different types of co-factors

3. Metabolic Reprogramming in OSCC as an Epigenetic Driver

Metabolic alterations have been reported, which have appeared to be one of the key driving forces responsible for the development and progression of OSCC (Gupta et al., 2024; Xu et al., 2023; Giulian et al., 2025). Besides the metabolic needs of dividing cells, metabolic processes are known to be extremely significant for influencing the epigenetic microenvironment through the regulation of intracellular concentrations of specific metabolites, which act as direct modulators for chromatin-modifying enzymes (Atlante et al., 202; Chapman, Chi, 2024). Metabolic changes operate as upstream regulators of gene expression in OSCC, resulting in chronic yet adaptable epigenetic processes that promote tumour growth, invasion, immune evasion, and treatment resistance (Xue et al., 2024; Sehgal and Chaturvedi, 2023). This introduces enzyme–metabolite–chromatin coupling; Table 1 provides structured mechanistic evidence. Metabolism and epigenetics are linked via bi-directional feedback. The

malignant signalling pathways reshape metabolism to create changes in the levels of key metabolites. At the same time, epigenetics maintains transcriptional activity toward such metabolism. (Lorenzo Pouso et al., 2022; Huang et al., 2024). In OSCC, there is great relevance. In OSCC, cancer cells are also subjected to constant hypoxia conditions, inflammation stress, cancer-causing chemicals from tobacco, and alcohol-related chemicals. All of them enhance linkage between metabolism and epigenetics. (Mesgari et al., 2023; Monabbati et al., 2025).

- **Glycolytic Rewiring and Lactate-Driven Epigenetic Signalling**

One of the major distinguishing metabolic features of OSCC is a higher dependency on aerobic glycolysis, which is often termed the Warburg phenotype (Heawchaiyaphum et al., 2023). Such a preference supports a higher uptake of glucose and a greater production of lactate even under normoxic conditions. Consequently, there is a greater accumulation of lactate within the tumor microenvironment due to higher rates of glycolysis and poor clearance under hypoxia usually seen in OSCC tissues (Gu et al., 2025). However, lactate is known to be much more than just a mere metabolite; rather, it has been identified to be a proactive modulator of chromatin dynamics (Yang et al., 2024; Jing et al.,2024). The mechanisms underlying this process have been understood to be largely dependent upon the capacity of lactate to downregulate the activity of histone deacetylases (HDACs) (Xue et al., 2024; Sehgal and Chaturvedi, 2023). By suppressing classes I and IIa HDACs, lactate stimulates higher levels of histone acetylation and relaxation of chromatin, making it easier to transcribe (Xue et al., 2024; Sehgal and Chaturvedi, 2023). In OSCC, this epigenetic change leads to the increased expression of epithelial-to-mesenchymal transition, extracellular matrix degradation, angiogenic, and immuno-modulatory genes, which together result in an aggressive cancer phenotype (Gan et al., 2024; Chaudhary et al., 2020).Until recently, great strides were made in understanding metabolic–epigenetic integration, with the identification of histone lactylation, which is a post-translational modification directly derived from lactate metabolism (Jing et al., 2024; Hu et al., 2025). This modification includes the addition of lactyl groups to the lysine residues on histone tails, catalyzed by the p300/CBP complex, utilizing lactyl-CoA as the donor (Chen et al.,2024). In contrast to transient events of histone acetylation, histone lactylation seems to be cumulative with sustained glycolysis and thus represents an imprint of lactate exposure.

Studies have revealed histone lactylation in OSCC on elements controlling genes related to immune suppressive mechanisms, angiogenesis, and metabolic adaptation (Cheng et al., 2024). Perhaps most interestingly, lactylation of histone H3 on lysine 18 has been directly associated with the transcriptional upregulation of immune checkpoint molecules such as PD-L1. Thus, this provides a direct molecular link between altered tumor metabolism and immune evasion, allowing OSCC cells to translate metabolic stress into durable, immunosuppressive gene expression programs (Jia et al., 2025). The effects of lactate are not just seen in cancer cells but also in the presence of immune cells within the microenvironment. High levels of lactate impair the proliferation and cytotoxic activity of effector T cells but promote the generation of regulatory T cells and the differentiation of macrophages towards an immunosuppressive subset. These activities are now being increasingly attributed to the role of epigenetic reprogramming by lactate in immune cells themselves. The microenvironment of the immune system, caused by lactate, also has the ability to modulate the enzymatic change of the chromatin state.

- **Mitochondrial Dysfunction and One-Carbon Metabolism**

Despite the prevalent role of glycolysis in energy/metabolism in OSCCs, mitochondrial metabolism is an essential regulator of epigenetic integrity (Bernasocchi and Mostoslavsky, 2024). The TCA cycle is an important source of vital cofactors for DNA and histone-modifying enzymes. The impairment of TCA cycle activity in OSCC affects the levels of α-KG, succinate, and fumarate. The three compounds play an important role in controlling α-KG-dependent dioxygenases directly, as illustrated in Figure 3 (Agarwal and Jha, 2025).

DNA demethylation by the ten–eleven translocation enzymes and histone demethylation by the Jumonji C domain-containing enzymes is also dependent on α-KG. Both succinate and fumarate inhibit the enzymatic activities. In OSCC, the succinate levels are elevated due to the pseudohypoxia signaling effect of hypoxia, resulting in the reduction of demethylase enzymatic activity, thereby causing the maintenance of the DNA and histone methyl repressive marks (Lorenzo Pouso et al., 2022). Genome-scale studies on DNA methylation have confirmed that such alterations were locus-specific, showing a preference for the promoter region of the tumor suppressor genes CDKN2A, PTEN, and MGMT (Gopalakrishnan et al., 2025). One-carbon metabolism is another connection point between mitochondrial activity and epigenetic regulation. This set of interconnected folate and methionine cycles is responsible for generating S-adenosylmethionine (SAM), which is the primary methyl group donor for DNA methyltransferases and histone methyltransferases (Jha et al., 2016). In OSCC cells, there is often an augmentation of serine and glycine metabolism and an enhancement of one-carbon mitochondrial enzymes such as MTHFD2 and SHMT2 to ensure an adequate level of SAM to support such dysregulated methylation (Jiang et al.,2023). Nevertheless, due to the elevated availability of the methyl group donors, the paradoxical epigenetics observed in OSCC reveals global DNA hypomethylation concomitant with hypermethylation within the region of the CpG islands. Apart from the concentration of SAM, this was found to be affected by the cumulative effect of S-adenosylhomocysteine (SAH), a strong inhibitor of methyltransferase activity. A disturbance in the metabolism and redox state was also seen to affect the movement of the one-carbon pool (Zhou et al., 2025).

- **Lipid and Acetate Metabolism in Chromatin Remodelling**

Lipid metabolism plays a crucial role in OSCC's epigenetic profile, regulating the availability of nuclear acetyl-CoA (Miao et al., 2022). Acetyl-CoA is the obligate substrate of histone acetyltransferases; therefore, its intracellular localization is one of the key factors determining the status of transcriptionally active chromatin. In OSCC, nuclear acetyl-CoA is primarily produced by the conversion the amount of citrate exported from mitochondria via ACLY. However, overexpression of ACLY is a common feature in OSCC, and this is accompanied by increased histone acetylation at the promoter and enhancer regions of oncogenes. It is imperative to note that the production of acetyl-CoA, which is dependent on ACLY, is essential in the maintenance of super-enhancers that control the transcriptional expression of master oncogenes like MYC, EGFR, and TP63. There is a need for the continuous production of acetyl-CoA, and this is crucial in the maintenance of the oncogenic transcriptional program in OSCC (Hazawa et al., 2024; Chakkarappan et al., 2024). In situations where there is metabolic stress, acetate metabolism becomes a crucial bioavailable source of acetyl-CoA. ACSS2 is responsible for converting acetate to acetyl-CoA because it catalyzes this reaction. In addition to this, it is also able to traverse to the nucleus where it is able to perform histone acetylation. During the hypoxic and nutrient-deficient

microenvironment present in OSCC, acetate may originate either from direct dietary uptake or the metabolic breakdown of ethanol. This can be a potential mechanism for the origin of OSCC in patients who consume alcohol. (Bradshaw et al., 2021).

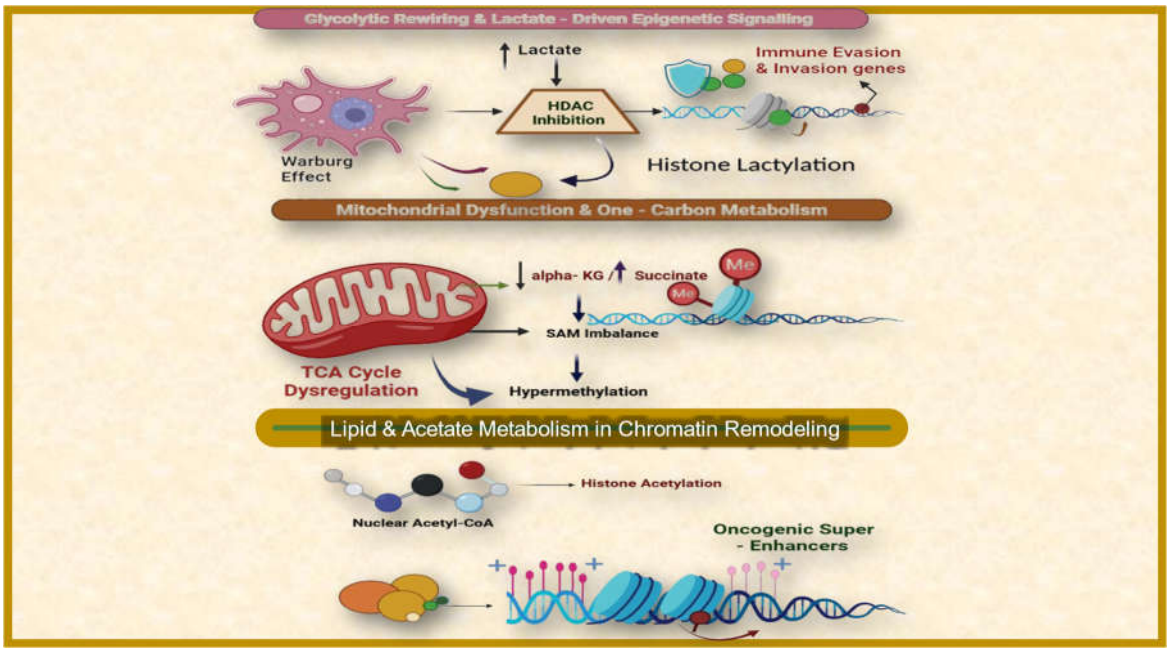


Figure 3: Mitochondrial Dysfunction and One-Carbon Metabolism

Table 1: Metabolite-Sensitive Epigenetic Enzymes and Their Functional Roles in Oral Squamous Cell Carcinoma

Enzyme / Complex	Epigenetic Category	Key Metabolite Regulator	Chromatin Target	Functional Consequence in OSCC	Clinical / Translational Relevance	References
HDAC1/2	Histone Deacetylase	Lactate	H3/H4 acetylation sites	Chromatin relaxation, EMT and invasion gene activation	Therapeutic HDAC targeting: metabolic sensitization	Minisini et al., 2024; Patel et al., 2023
p300/CBP	Histone Acetyltransferase	Acetyl-CoA / Lactyl-CoA	H3K18, H3K27	Histone acetylation and lactylation; immune evasion	Predicts response to metabolic–epigenetic inhibitors	Patel et al., 2023; Marsh et al., 2025

TET2	DNA Demethylase	α-Ketoglutarate	CpG islands	Tumor suppressor gene reactivation	Methylation-based prognostic biomarker	Joshi et al., 2022; Goel et al., 2021
JMJD3 (KDM6B)	Histone Demethylase	α-KG/ Succinate	H3K27me3	Inflammatory and EMT gene activation	Links hypoxia to epigenetic dysregulation	Ding et al., 2021
DNMT1	DNA Methyltransferase	SAM / SAH	CpG promoters	Tumor suppressor gene silencing	Targetable with methylation inhibitors	Liu et al., 2024; Nikbakht et al., 2017
ACSS2 (nuclear)	Metabolic-Epigenetic Enzyme	Acetate	Histone acetylation sites	Sustains oncogenic transcription under stress	Alcohol-associated OSCC risk stratification	Miller et al., 2021
GCN5/PCAF (SAGA complex)	Histone Acetyltransferase	Acetyl-CoA	H3K9, H3K14	Activation of proliferation- and survival-associated transcription	Potential vulnerability in highly glycolytic OSCC	Ononye and Downey, 2022
TET2 (TET2–OGT chromatin complex)	DNA Demethylase	α-Ketoglutarate	CpG islands	Tumor suppressor gene reactivation	Methylation-based prognostic biomarker	Agarwal and Jha, 2025
TET3 complexes	DNA Demethylase	α-KG / Ascorbate	Enhancers and promoters	Epigenetic plasticity and lineage instability	Indicator of metabolic control over DNA demethylation	Martinez-Colin et al., 2025

UTX/KDM6A (COMPASS-like complex)	Histone Demethylase	α-KG	H3K27me3	Derepression of differentiation-associated genes	Prognostic relevance in squamous malignancies	Wang et al., 2024
LSD1/KDM1A (CoREST complex)	Histone Demethylase	FAD	H3K4me1/2	Suppression of epithelial differentiation programs	Targetable epigenetic vulnerability	Kim et al., 2020
EZH2 (PRC2 complex)	Histone Methyltransferase	SAM	H3K27me3	Stable transcriptional repression of tumor suppressor genes	Clinically actionable epigenetic target	Gupta et al., 2024
SETD2 (elongation-associated complex)	Histone Methyltransferase	SAM	H3K36me3	Genome stability and transcriptional fidelity	Mutation-associated prognosis	Bradshaw et al., 2021; Hazawa et al., 2024
ATP-citrate lyase (ACLY–chromatin complex)	Metabolic-Epigenetic Enzyme	Citrate	Histone acetylation sites	Links glucose metabolism to histone acetylation	Metabolic–epigenetic therapeutic target	Zhao et al., 2025

4. Oral-Specific Carcinogen Exposure as a Metabolic–Epigenetic Stressor in OSCC

The diagnosis of oral squamous cell carcinoma develops in a particularly hostile biochemical environment that is marked by long-term, localized exposure to alcohol, nicotine, and areca nut carcinogens. In contrast to systemic cancers, the oral epithelium is subjected to frequent and direct metabolic insults that cause long-term disruptions in cellular bioenergetics, redox homeostasis, and metabolite availability. These exposures function as long-lasting metabolic-epigenetic stressors that can change transcriptional identity and chromatin architecture long before overt malignant transformation occurs, in addition to being causes of genotoxic damage (Krishnan et al., 2024). Metabolic intermediates operate as epigenetic cofactors, directly connecting environmental exposures to persistent gene regulation alterations, according to recent discoveries in cancer metabolism. Oral-specific carcinogens in OSCC modify metabolic fluxes in ways that change chromatin accessibility, DNA methylation, and histone alterations, integrating carcinogenic signals into the epigenome and fostering long-term oncogenic memory as described in Figure 4 (Vatsa et al., 2023).

- **Tobacco-Induced Metabolic Rewiring and Persistent Epigenetic Repression**

Tobacco exposure is the most thoroughly researched causal factor in OSCC and has a significant impact on cellular metabolism. Components of tobacco smoke produce high levels of reactive oxygen species (ROS), mainly by disturbing the mitochondrial electron transport chain. Persistent ROS exposure harms mitochondrial DNA, disrupts oxidative phosphorylation, and triggers compensatory metabolic adjustments toward glycolysis and reductive glutamine metabolism (Viet et al., 2024). Tobacco-induced mitochondrial dysfunction significantly modifies the NAD^+/NADH ratio, which is a crucial factor in both metabolic enzyme activity and epigenetic regulation. Histone hyperacetylation at certain genomic locations and loss of transcriptional fidelity resulted from reduced NAD^+ availability, which impairs the activity of NAD^+-dependent deacetylases, including sirtuin family members. Ten-eleven translocation (TET) enzyme activity and other demethylation processes are simultaneously disrupted by altered redox balance, favoring abnormal DNA methylation patterns (Berthiaume et al., 2019). In OSCC, these metabolic changes result in enduring epigenetic suppression of tumor suppressor genes, which include regulators of cell cycle arrest, apoptosis, and genomic integrity. The hypermethylation of promoters and the presence of repressive histone modifications at these loci are frequently irreversible, remaining even after tobacco exposure ends (Gupta et al., 2024). Additionally, the oral mucosa experiences chronic inflammation and hypoxia due to tobacco-induced metabolic stress, which reinforces epigenetic repression through hypoxia-inducible metabolic pathways (Paul et al., 2022).

- **Areca Nut Alkaloids, One-Carbon Metabolism Disruption, and Epigenetic Instability**

Chewing areca nut presents a unique carcinogenic mechanism in OSCC, mainly influenced by alkaloids like arecoline that cause direct metabolic harm. In contrast to tobacco, areca nut mainly interferes with one-carbon metabolism, a key biochemical system that connects folate metabolism, methionine cycling, and nucleotide synthesis. Prolonged exposure to areca nut disrupts folate absorption and use, resulting in reduced production of S-adenosylmethionine (SAM), the main methyl donor for DNA and histone methylation processes (Muthukumaran et al., 2023). Global methylation stress occurs due to SAM depletion and is characterized by localized hypermethylation in regulatory regions alongside widespread DNA hypomethylation. This combined instability specifically inhibits genes necessary for differentiation and tumor suppression, while undermining genomic integrity (Yang et al., 2025). A defining feature of areca nut–associated OSCC is the development of oral submucous fibrosis, a premalignant condition marked by excessive extracellular matrix deposition and stromal remodeling. Fibrosis imposes additional metabolic constraints, including altered amino acid metabolism, increased proline synthesis, and changes in tissue stiffness. These biomechanical and metabolic signals further influence epigenetic regulation through mechanosensitive chromatin remodelling pathways (Yuan et al.,2025)

- **Alcohol Metabolism, Acetyl-CoA Overflow, and Aberrant Chromatin Activation**

Through metabolic mechanisms that directly affect chromatin control, alcohol use is linked to OSCC. Acetate produced by ethanol metabolism is quickly transformed into acetyl-CoA, a key molecule that connects energy metabolism to histone acetylation. Recurrent alcohol consumption causes a persistent buildup of acetyl-CoA in the oral epithelium that surpasses the metabolic requirements of central carbon pathways (Mews et al., 2019). Histone acetyltransferase activity is fueled by this acetyl-CoA overflow, which results in extensive histone hyperacetylation and long-lasting chromatin relaxation. Alcohol-driven acetylation creates long-term chromatin

accessibility at loci regulating proliferation, inflammation, angiogenesis, and the epithelial–mesenchymal transition, in contrast to transitory signalling-induced acetylation (Kriss et al., 2018). Crucially, in nutrient-limited circumstances, acetate produced from ethanol metabolism can act as a substitute carbon source, giving premalignant and malignant cells a metabolic advantage (Bose et al., 2019). This metabolic adaptability is closely linked to epigenetic permissiveness, allowing OSCC cells to adjust to varying microenvironmental stressors (Obeid and Damaghi, 2024). Alcohol induced chromatin opening, in conjunction with tobacco exposure, interacts with DNA methylation irregularities, intensifying transcriptional dysregulation and hastening malignant progression (Ferraguti et al., 2022).

Convergence of Metabolic and Epigenetic Stress Pathways in OSCC

Alcohol, areca nut, and tobacco all have different metabolic consequences, but their carcinogenic effects all lead to the same result: long-lasting epigenetic reprogramming caused by ongoing metabolic stress. The availability of epigenetic cofactors is altered when mitochondrial function, redox balance, one-carbon metabolism, and acetyl-CoA homeostasis are disrupted, integrating environmental exposure into the chromatin landscape (Mesgari et al., 2023). The continuous exposure of the oral cavity to these agents guarantees that metabolic stress is both repetitive and localized, leading to the accumulation of epigenetic changes over cell generations. This model clarifies why OSCC frequently shows significant epigenetic dysregulation, even in initial lesions, and offers a mechanistic foundation for field cancerization (Cabra et al., 2025). By using a metabolic-epigenetic lens to frame OSCC pathogenesis, new therapeutic and preventative potential are revealed in addition to deepening mechanistic knowledge. For OSCC treatments, focusing on metabolic vulnerabilities to restore epigenetic balance may be a potential approach, especially in high-risk populations with prolonged exposure to carcinogens (Yang et al., 2025).

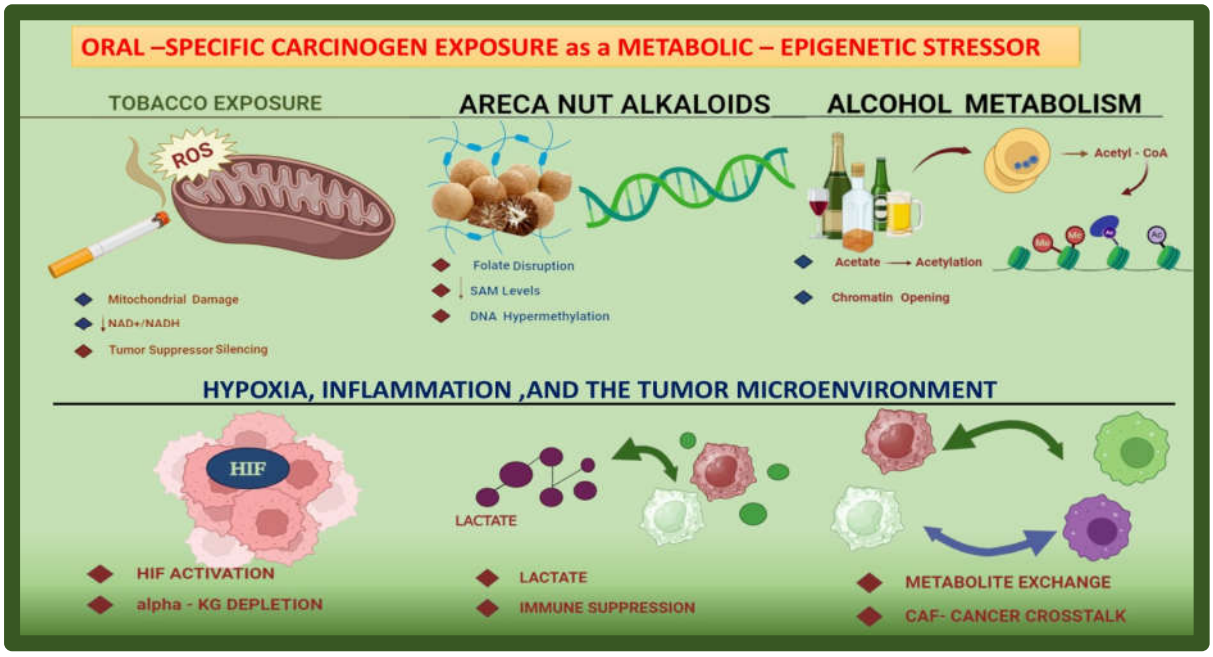


Figure 4: Oral- Specific Carcinogenic Exposure as a Metabolite- Epigenetic Stressor

5. Hypoxia, Inflammation, and the Tumor Microenvironment in OSCC

The tumor microenvironment (TME) of oral squamous cell carcinoma (OSCC) is a varied and metabolically strained ecosystem influenced by ongoing hypoxia, persistent inflammation, stromal alteration, and immune imbalance (Tan et al., 2023). In contrast to typical oral mucosa, OSCC arises in an environment of persistent exposure to carcinogens like tobacco, alcohol, areca nut, and microbial damage, resulting in prolonged inflammatory signalling and vascular impairment (Veerasamy et al., 2025). These factors significantly impact cellular metabolism and epigenetic control, allowing tumor cells to adjust, endure, and advance (Xu et al., 2023). In the TME, hypoxia and inflammation work together to alter the metabolic and epigenetic architecture of both malignant and non-malignant cells. Transcriptional pathways that support tumor development, immune evasion, invasion, and treatment resistance are established by this coordinated remodelling as described in Table 2 (Khalaf et al., 2021).

Hypoxia-Induced Metabolic Shifts and HIF-Dependent Chromatin States

OSCC is characterized by hypoxia, especially in advanced and poorly vascularized tumors. Insufficient oxygen transport caused by rapid cellular growth and aberrant angiogenesis leads in areas of intermittent and chronic hypoxia (Acuña-Pilarte et al., 2025). In reaction to reduced oxygen supply, OSCC cells stabilize hypoxia-inducible factors (HIFs), mainly HIF-1α and HIF-2α, which coordinate a worldwide transcriptional response (Eghbalifard et al., 2025). Enhanced glucose absorption, overexpression of glycolytic enzymes, and inhibition of mitochondrial oxidative phosphorylation are the hallmarks of a dramatic metabolic reprogramming driven by HIF signaling (Li et al., 2025). This change minimizes damage caused by reactive oxygen species (ROS) while promoting ATP synthesis from glycolysis in hypoxic environments. However, HIFs have an impact on chromatin regulation and epigenetic control in addition to metabolism (Palma et al., 2024). Histone acetyltransferases, chromatin remodelers, and transcriptional co-activators are drawn to hypoxia-responsive regions of the genome by HIFs. Increased histone acetylation and particular histone methylation alterations at promoters and enhancers of genes involved in angiogenesis, invasion, epithelial–mesenchymal transition (EMT), and stemness are the hallmarks of hypoxia-specific chromatin landscapes created by this interaction (Kim et al., 2022). These HIF-dependent chromatin modifications increase the propensity for metastasis, enable local invasion, and encourage aggressive behaviors in OSCC (Hill et al., 2022).

α-Ketoglutarate Depletion and Inhibition of Epigenetic Demethylases

The intracellular availability of metabolites that serve as crucial cofactors for epigenetic enzymes is dramatically changed by metabolic reprogramming under hypoxic settings (Ge et al., 2022). Among these metabolites, α-ketoglutarate (α-KG) is essential as a co-substrate for α-KG-dependent dioxygenases, such as histone demethylases that include the Jumonji C (JmjC) domain and TET DNA demethylases (Jumonji and Demethylases, 2021). Hypoxia-induced inhibition of the tricarboxylic acid (TCA) cycle in OSCC increases competitive metabolites, including succinate and fumarate, while decreasing α-KG synthesis (Rajneesh et al., 2025). Because of the imbalance that results, demethylase activity is inhibited, which causes repressive epigenetic marks to accumulate widely. Tumor suppressor, differentiation-associated, and immune-related genes are silenced by DNA hypermethylation and elevated histone methylation at important regulatory loci (Chatoff et al., 2025). OSCC cells are locked into undifferentiated, stem-like states with increased survival potential due to this

epigenetic rigidity. (Bamodu et al., 2024) Furthermore, cancer cells are able to sustain long-term adaptation to hypoxic stress due to defective demethylation, which also contributes to tumor heterogeneity and therapeutic resistance (Zaarour et al., 2023).

Lactate-Rich Niches and Immune-Suppressive Epigenetic Programs

In hypoxic OSCC cells, increased glycolytic flux leads to excessive lactate synthesis, which is actively exported into the extracellular environment by monocarboxylate transporters (Gu et al., 2025). Lactate buildup causes the tumor microenvironment to become acidic, resulting in metabolically unfriendly yet tumor-permissive niches (Pranzini et al., 2025). Immune cell activity is significantly impacted by these lactate-rich areas. Acidic environments hinder the activation of cytotoxic T lymphocytes, decrease the synthesis of interferon-γ, and prevent natural killer cells from destroying tumor cells. Lactate simultaneously strengthens immunological evasion by encouraging the growth of regulatory T cells and the polarization of macrophages toward an immunosuppressive phenotype (Wang et al., 2024). Recent studies suggest that lactate also serves as a direct epigenetic regulator via histone lactylation. In OSCC, lactate-driven histone lactylation initiates transcriptional programs that promote immune tolerance, angiogenesis, and wound-healing–like responses (Xiao et al., 2025). These epigenetic changes help maintain chronic inflammation while hindering effective anti-tumor immunity, enabling tumor cells to survive and proliferate within the oral microenvironment (Xie et al., 2023).

TABLE 2: Hypoxia-linked Metabolic–Epigenetic Events

Hypoxia-linked Event	Molecular Drivers	Cellular Consequences	Epigenetic Output	Functional Impact in OSCC	Representative Citations
HIF stabilization under low O_2	HIF-1α, HIF-2α activation	↑ Glycolysis, ↓ OxPhos, adaptive survival in nutrient-poor niches	Recruitment of HATs & chromatin remodelers; hypoxia-specific enhancer activation	Promotes EMT, angiogenesis, stemness, invasion	Silveira et al., 2025; Eghbalifard et al., 2025; Cabral et al., 2025
Chromatin remodeling at hypoxia-responsive loci	HIF-dependent transcriptional coactivators	Remodeling of promoter/enhancer accessibility	↑ Histone acetylation, selective H3/H4 methylation shifts	Increases aggressiveness & metastatic potential	Kim et al., 2022; Hill et al., 2022
Metabolic reprogramming & TCA suppression	Reduced α-KG; ↑ succinate & fumarate	Dioxygenase inhibition	Global DNA hypermethylation; ↑ histone methylation	Silencing of tumor suppressors; differentiation blockade	Rajneesh et al., 2025; Mendiratta et al., 2025; Bamodu et al., 2024

Lactate accumulation in TME	MCT-mediated lactate export	Acidic microenvironment formation	Histone acetylation-mediated transcriptional shifts	Immune suppression, angiogenesis, and chronic inflammation	Gu et al., 2025; Gan et al., 2024

6. Therapeutic Implications: Targeting the Metabolic–Epigenetic Axis

The blending of metabolism and epigenetic regulation has emerged as a determining factor of cellular identity, plasticity, and disease progression (Zhang et al.,2025; Pal et al., 2025). Contrary to serving as separate regulatory levels, metabolic pathways and epigenetic chromatin-modifying processes act rather as a system, whereby the levels of metabolites directly influence the activity of epigenetic enzymes (Vatapalli et al., 2025). Key metabolic intermediates include acetyl-CoA, S-adenosylmethionine (SAM), α-ketoglutarate, NAD^+, and lactate which serve as substrates or cofactors for histone acetyltransferases, methyltransferases, demethylases, and deacetylases, therefore, linking cellular metabolic state to transcriptional control (Bradshaw 2021; Bernasocchi and Mostoslavsky, 2024). This is the intrinsic, self-reinforcing, bidirectional interface between metabolism and epigenetics as conceptualised in Figure 6. Metabolic dysfunctions directly modify chromatin structure and gene expression, while epigenetics further perpetuates pathological metabolic phenotypes by regulating gene expression of metabolic enzymes and transporters (Newman and Maddocks, 2017). The strategy of therapeutically targeting this interface is advantageous: it takes advantage of disease-specific, cellular metabolic dependencies, and it allows for indirect but stable epigenetic reprogramming and combinatorial approaches which would be able to overcome resistance against single-agent treatments (Qu et al., 2023). Moreover, the link between cancer and metabolic reprogramming is clear, and metabolic aberrancies contribute to the maintenance of the oncogenic and epigenetically active chromosomal instability and DNA damage response network (Cao et al.,2025).

Metabolic Modulators as Epigenetic Therapeutic Agents

Targeting metabolism for epigenetic intervention thus stands out as a paradigm shift in therapeutic design (Ewida et al., 2024). Perhaps among the most studied nodes are those that control pathways acetyl-CoA production, one-carbon metabolism, and lactate signalling, all of which exert direct control over chromatin architecture. Acetyl-CoA is a central metabolic intermediate, and, importantly, it is the only acetyl donor in histone acetylation (Bradshaw 2021; Ling et al., 2022). Its intracellular abundance is strictly controlled by glucose metabolism through ATP citrate lyase, acetate utilization through acyl-CoA synthetase short-chain family member 2 (ACSS2), and fatty acid oxidation. Again, cancer cells increase their dependency on glucose-derived acetyl-CoA to maintain global and locus-specific histone acetylation, especially at promoters and enhancers of growth-promoting genes. By pharmacological inhibition of ACLY, nuclear acetyl-CoA availability decreases, thereby inducing selective loss of histone acetylation at metabolically active chromatin regions and suppression of oncogenic transcriptional programs (Ewida et al., 2024). However, alternative pathways such as ACSS2-mediated acetate utilization can give a partial response; there is emerging evidence that multiple parallel disruptions of acetyl-CoA-generating routes are required to dismantle epigenetic resilience fully. Systemic metabolic interventions, ketogenic and low-

carbohydrate diets, further illustrate how nutrient availability influences chromatin states. By shifting acetyl-CoA sourcing from glucose to ketone bodies, these approaches induce distinct epigenetic outcomes that can selectively affect tumor cells. However, locus specificity and long-term consequences of such dietary modulation are incompletely defined, with a mechanistically informed clinical implementation in need.

One-carbon metabolism is another major hub that is linked to epigenetics through SAM-mediated methylation reactions on both DNA and histones. The elevation of the folate and methionine cycles is shown to enhance hypermethylated states of chromatin, which is indicative of malignancy (Bernasocchi and Mostoslavsky, 2024). A methionine restriction or pharmacologic suppression of the synthesis of SAM reduces the levels of methyl groups, and this impacts the ratio of methylation marks on the state of histones on chromatin that distinguish between activated and repressed gene expression and transcriptional adaptation towards lower proliferative states (Cao et al., 2025). Cancer cells, which retain their increased sensitivity towards methionine, would also increase sensitivity towards this therapy. The serine/glycine metabolism pathways, which play a very important role in one-carbon metabolism and thus the use of cancer cells, if inhibited, inhibit SAM synthesis and prevent tumor growth with preferential and specific killing of cancer cells, specifically those transcriptionally activated towards serine metabolism. Lactate has become a metabolic molecule with autologous epigenetic signalling properties, evidenced by the discovery of histone lactylation. Enhanced lactate secretion, indicative of glycolytic reprogramming, has been shown to support lactylation-mediated transcription programs in various processes, including malignancy and tissue remodelling (Fan et al., 2025).

Combined Metabolic–Epigenetic Targeting and Therapeutic Synergy

This is attributed to the fact that a combinational strategy would be needed because the relationships between metabolic and epigenetic deregulations are so intertwinedto realize long-term clinical benefits. Monochemical targeting of either metabolic or epigenetic enzymes will, after all, lead to adaptive resistance mechanisms through the activation of a compensatory pathway (Zhang et al., 2025). On the contrary, a strategy that will abrogate self-feeding loops will inhibit concurrent metabolic components together with the direct targeting of the epigenetic apparatus. Application of a strategy against convergent metabolic pathways supporting the same epigenetic event reduces metabolic route plasticity. The combination of metabolic and epigenetic therapy with immunotherapy has shown a high synergistic value. Metabolic reprogramming of the TME with a decrease in lactate levels provides a mechanism to overcome immune suppression and restore effector T cell functionality (Parab et al., 2023).

Biomarkers for Metabolic–Epigenetic Therapeutic Response

Acetylation, methylation, and lactylation, histone modifications known to be directly associated with the availability of metabolites (Xu et al., 2025; Noerenberg and Damm, 2024), can be used as a mechanistic indicator of metabolic dysruption. Modifications of specific histone residues can identify the scope of targeted metabolic pathways and compensatory responses. DNA methylation patterns represent a complementary and stable marker platform (Yang et al., 2025; Lavoro et al., 2025). Whole and specific loci DNA methylation Analysis can help detect therapeutic modification of one-carbon metabolism and unravel genes for which epigenetic reactivation is predictive of clinical response. Improved technology of high-throughput DNA methylation studies and modeling allows predictive DNA methylation signatures to be developed. Sources of non-invasive biomarkers, especially saliva, have been considered for longitudinal studies (Rapado-González et al., 2025). Lactate, amino acids, and

short-chain fatty acids, which are salivary metabolites involved in epigenetic regulation, represent systemic conditions, offering a possible means to track treatment efficacy (Zhao et al., 2025). Data is emerging on salivary DNA and chromatin fragments being viable substrates for epigenetic information regarding disease status, although further verification is necessary. In functional assays that combine the results of metabolic flux analysis with epigenetic profiling, there is additional predictive capacity. Stable isotope tracing, chromatin accessibility analysis, and ex vivo drug sensitivity phenotype measurements jointly provide information about the interplay between metabolism and chromatin structure, which allows personalized medicine (Miro-Blanch et al., 2023).

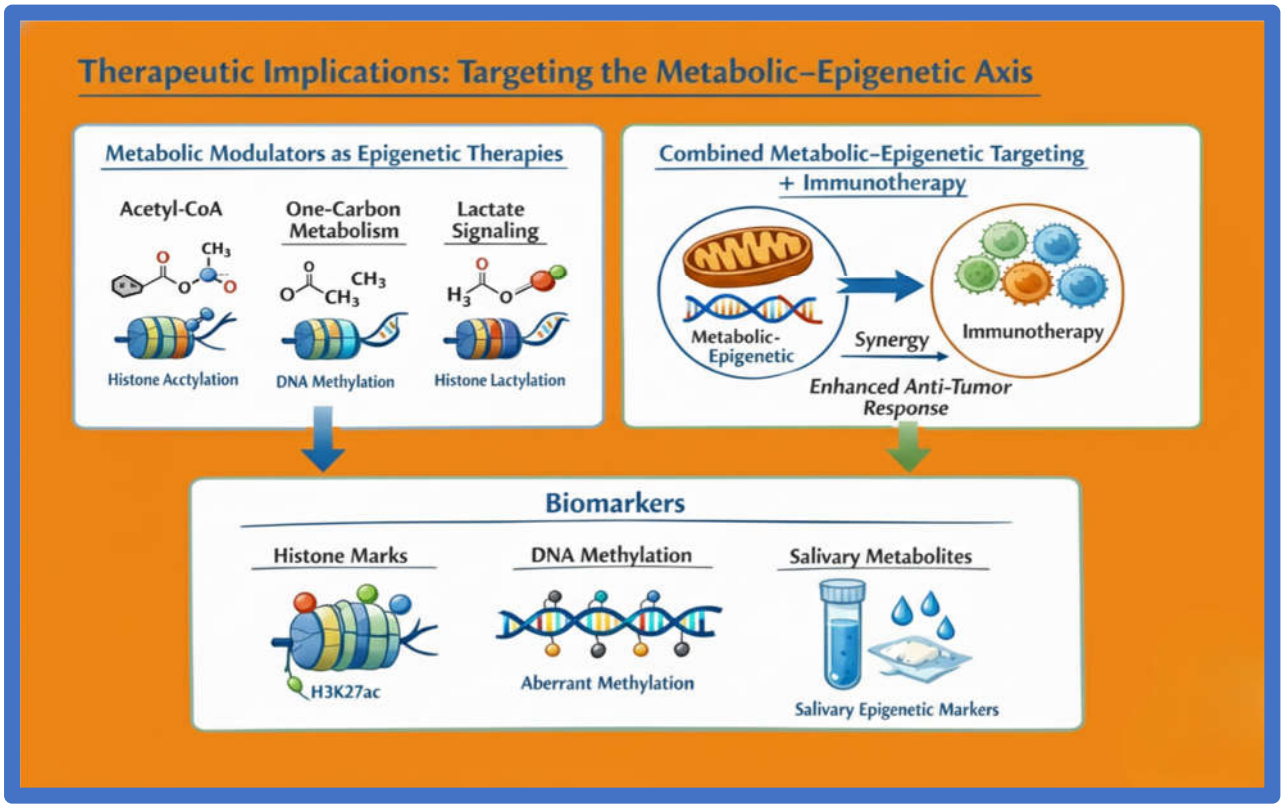


Figure 5: Therapeutic Implications: Metabolic Modulators as Epigenetic Therapies and Biomarkers

7. Future Directions

Oral squamous cell carcinoma is increasingly understood as a disease shaped by dynamic coupling between metabolic reprogramming and epigenetic dysregulation, yet the causal hierarchy and temporal integration of these processes remain unresolved. Pronounced intertumoral metabolic heterogeneity suggests that distinct metabolic states differentially condition epigenetic programs governing invasion, immune evasion, and therapy resistance. Future advances are likely to arise from integrating single-cell and spatial metabolomics with single-cell epigenomic profiling, enabling high-resolution mapping of metabolic–epigenetic dependencies within native tumor architecture. Longitudinal models incorporating patient-derived organoids, lineage tracing, and time-resolved metabolic imaging will be critical to determine whether early metabolic perturbations precede and stabilize oncogenic chromatin states, thereby defining windows for metabolic intervention and chemoprevention. A central unresolved question is the reversibility of metabolic–epigenetic memory, which will require experimental frameworks combining metabolic perturbation with targeted epigenetic editing. Looking ahead, patient-specific metabolic–epigenetic profiling integrated with AI-driven modelling is expected to stratify OSCC

into actionable subtypes and guide rational combination therapies, while non-invasive metabolic and epigenetic monitoring may enable real-time treatment adaptation and early relapse detection.

8. Conclusion

OSCC exemplifies a malignancy in which metabolic reprogramming and epigenetic alterations are not parallel consequences of transformation but are interdependent modulators of tumor initiation, progression, and therapy resistance. Chronic metabolic stress imposed by carcinogen exposure, hypoxia, and inflammation in the oral cavity reshapes chromatin architecture through metabolite-dependent regulation of DNA methylation, histone modifications, and non-coding RNA networks, thereby stabilizing malignant transcriptional programs. A central outcome of this coupling is metabolic–epigenetic memory, wherein transient metabolic perturbations establish persistent epigenetic states that promote phenotypic plasticity, immune evasion, and disease recurrence. Targeting the metabolic–epigenetic axis, therefore, represents a promising therapeutic strategy, particularly when combined with epigenetic or immunomodulatory approaches. Successful clinical translation will require robust biomarkers that capture dynamic metabolic–epigenetic states, supported by emerging single-cell and spatial profiling technologies to resolve intertumoral heterogeneity and temporal evolution in OSCC.

Declaration

I hereby declare that the information given above and in the enclosed documents is true to the best of my knowledge and belief, and nothing has been concealed therein.

Conflict of Interest

The authors declare no conflict of interest

Acknowledgment

The authors acknowledge the help provided by the **School of Biosciences and Technology, Galgotias University, Greater Noida, India**

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