

Hypoxia and Epigenetic Reprogramming in Cancer: A Narrative Review of Mechanisms and Therapeutic Implications

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Abstracts

Background: Epigenetic mechanisms are fundamental regulators of gene expression and cell identity; their dysregulation contributes significantly to cancer initiation and pathological development. Tumor hypoxia, a prevalent characteristic of the tumor microenvironment that profoundly alters epigenetic regulation, results in promoting tumor aggressiveness, cancer stem cell maintenance, immune evasion, and therapeutic resistance.

Objectives: This narrative review summarizes current evidence regarding hypoxia-driven epigenetic reprogramming in cancer, focusing on hypoxia-inducible factors (HIFs), DNA methylation, histone modifications, chromatin remodelling, non-coding RNAs, hypoxic memory, epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs) and therapeutic resistance.

Methods: A narrative review of the literature was performed using PubMed, Scopus, and Google Scholar. Peer-reviewed studies published mainly between 2015 and 2025 were evaluated according to their relevance to hypoxia-associated epigenetic mechanisms in cancer. All articles were chosen if they were relevant to the topic and added scientific value to hypoxia associated epigenetic regulation in cancer. As this was a narrative review, there were no inclusion/ exclusion criteria or a PRISMA flow diagram.

Results: Hypoxia stabilizes HIF-1 α and HIF-2 α , which cooperate with multiple epigenetic regulators, including DNA methyltransferases, histone-modifying enzymes, chromatin remodelling complexes, and non-coding RNAs. These interactions promote EMT, CSC maintenance, immune escape, metastasis, and resistance to chemotherapy and immunotherapy. Emerging evidence also indicates that hypoxic memory sustains epigenetic alterations after reoxygenation, contributing to persistent malignant phenotypes.

Conclusions: Epigenetic hypoxia acts as a primary driver of cancer progression and therapeutic resistance by sustaining epigenetic reprogramming and preserving cancer stemness. Although histone deacetylase inhibitors and hypomethylating agents show therapeutic potential, their inconsistent clinical efficacy necessitates the development of optimized combination and personalized treatment strategies. Consequently, further investigation into hypoxia-driven epigenetic mechanisms is essential to enhance treatment efficacy and advance precision oncology.

Keywords: Cancer progression; Cancer stem cells; Epigenetic regulation; Hypoxia; Hypoxic memory.

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Introduction

Hypoxia and its effect on the body

Hypoxia is a condition that occurs when there is an inadequate supply of oxygen to the body tissues (1). This condition is particularly relevant in the context of cancer, since insufficient oxygen is a fundamental feature of tumours and is connected with cancer growth and progress (2). It can also occur due to a variety of factors, including high altitude, lung diseases, and heart conditions, among others (3). When the body experiences hypoxia, it triggers a series of physiological responses that aim to increase oxygen delivery to the tissues, including increased heart rate and breathing rate. However, if hypoxia persists, it can have significant effects on the body, including, increased risk of heart disease and stroke, impaired cognitive function, and reduced immune function (4).

Hypoxia has multiple consequences on the growth of cancer, including changes in genetic repair procedures cellular metabolism, and tumor immune responses (3). Hypoxic conditions affect tumor progression via various epigenetic modifications, including acetylation, methylation, and demethylation, among others (5). A study published in *Cancer Letters* found that hypoxia promotes the metastatic progression of pancreatic cancer by regulating NOX4/KDM5A-mediated histone methylation modifications via a HIF1 α -dependent mechanism (6). These epigenetic modifications can alter gene expression and contribute to the development and progression of cancer. Low oxygen availability can also impact cancer progression by altering the activity of important carcinogenic pathways through changes in the status of histone modification (7). Under hypoxic conditions, cancer cells reconfigure their metabolic pathways, supporting aerobic glycolysis over oxidative phosphorylation. This can contribute to cancer growth and metastasis (8). Additionally, hypoxia can induce T and NK effector cell dysfunction through HIF1 α -mediated chromatin modifications, leading to immune evasion by cancer cells (9). These findings elucidate the intricate relationships between hypoxia and cancer

advancement, highlighting the importance of epigenetic modifications in hypoxic environments for cancer treatment (3).

A common connection between cancer and low oxygen levels

Hypoxia, defined as an insufficient supply of oxygen, is a feature of many solid tumors and can actually promote tumor growth (2). This is achieved by stimulation of angiogenesis, the formation of new blood vessels into the tumor which supplies the growing tumor cells with nutrients and oxygen (10). Furthermore it causes genetic mutations and alterations in the DNA repair mechanisms, leading to further genetic instability and promoting tumor progression (8). It helps promote the appearance of therapeutic resistance, which is a substantial challenge in cancer therapy. Identifying the processes by which hypoxia stimulates tumor growth and resistance will allow researchers to build more efficient cancer therapies. Under hypoxic conditions, cancerous cells undergo metabolic alterations, changing from phosphate oxidation to aerobic glycolysis (11). This metabolism reprogramming can boost cancer cells' survival and migration, which leads to increased aggressiveness and metastasis, altering tumoral immunity, and reducing the immune system's ability to recognise and kill cancer cells (12). Hypoxia can further enhance cancer cell malignancy and render them less susceptible to treatment. Epigenetic modifications control gene expression and are sequence independent and heritable. The effects of epigenetic modifications induced by hypoxia include promotion of tumor initiation and progression including metastasis and chemoresistance (5). Tumor metabolism is also affected by a metabolic change that encourages cancer cell survival and proliferation in addition to the classical Warburg effect induced by hypoxia (13).

Understanding the intersection of hypoxia and epigenetic modifications will enable researchers to develop novel therapeutics that could translate into better patient outcomes by targeting these pathways (3). A historical overview of the development of this subject is given in Figure 1, which outlines the key turning points in epigenetic research and its connection with hypoxia biology in cancer (14).

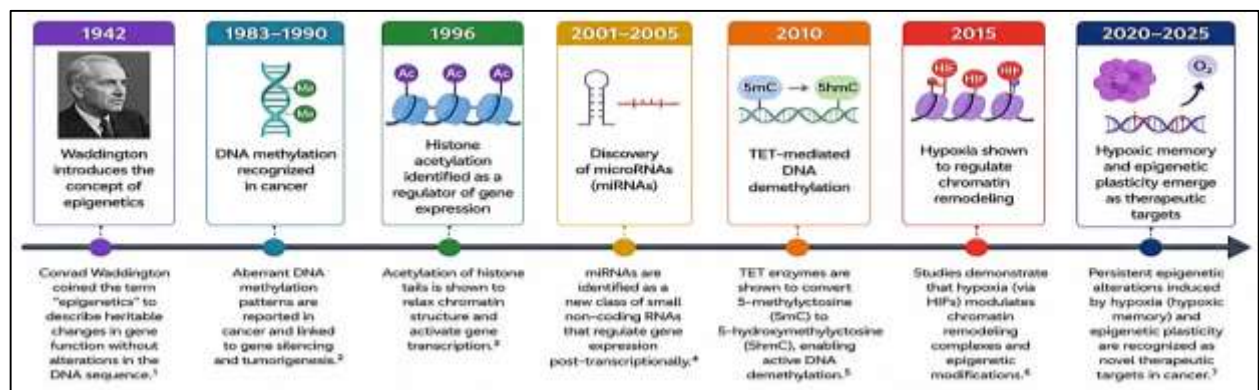


Figure 1: Historical evolution of epigenetic discoveries and their relationship to hypoxia in cancer. The schematic was created by the authors based on published evidence (14).

Epigenetics in Hypoxic Solid tumor Microenvironment

Waddington first came up with the idea of epigenetics in 1942 to show how genes and the environment affect each other (15). His initial research sought to elucidate the role of epigenetics in embryonic development; however, the concept has since expanded to cover a wide array of biological phenomena (16). Recent progress in epigenetics has revealed that human cancer cells carry comprehensive aberrations in epigenetic patterns, as also many genetic changes (17). The cellular response to oxygen deficiency is predominantly directed by hypoxic-inducible factors, a collection of transcription regulators responsible for regulating the activation of multiple genes that enable tumor cells to adapt to this difficult microenvironment (18). Hypoxia-inducible factors (HIFs) are heterodimeric transcription factors that consist of one of three oxygen-sensitive α subunits (HIF-1 α , HIF-2 α , or HIF-3 α) plus a constitutively expressed HIF-1 β subunit (19,20). Methylation of DNA and histone alterations are examples of epigenetic processes that play a role in cancer control during hypoxia (2). Histone modifications were shown to impact HIF stability, thereby affecting hypoxia signalling. In contrast, HIFs have the ability to regulate the activity of chromatin modifications. Furthermore, these enzymes rely on oxygen-sensitive metabolic intermediates as cofactors. HIFs may potentially exert their transcriptional functions through interactions with chromatin remodelers (21). These epigenetic alterations may influence various pathways related to carcinogenesis, such as proliferation, the acquisition of stem cell-type features, and the onset of aberrant clonal expansion, predisposing cells to malignant transformation. This modification is critical for the maintenance and survival of cancer-initiating cells (CICs), an atypical subpopulation that is characterised by self-renewal ability and the potential to differentiate into the various cell types that form the tumour. There is increasing evidence that hypoxia facilitates the maintenance of cancer stem cells (CSCs) through HIF-mediated epigenetic reprogramming, thus increasing tumour plasticity, therapeutic resistance and disease recurrence (22,23). Numerous studies have identified hypoxia as a mechanism that regulates epigenetic changes during cancer development and progression. However, information remains scattered across various studies that typically examine single mechanisms without necessarily establishing a complete mechanistic picture. For instance, activation of DNA methyltransferases and histone deacetylases has been shown to be regulated by hypoxia in certain studies (24). In contrast, some studies have found activation of these enzymes to be context-dependent, or even repression of these enzymes in response to hypoxia, dependent on the type of cancer, hypoxia gradient, and cancer cell metabolism (25). The role of Ten-Eleven Translocation enzymes (TET) and histone modifications has also been shown to be regulated by hypoxia. However, studies have concluded that these

modifications promoted cancer progression, as well as studies that have found these modifications to serve as a protective mechanism with no ties to cancer progression. Additionally, hypoxia-induced epigenetic changes have been studied primarily in acute settings (26). This is problematic as solid tumors typically experience chronic hypoxia. There is no current model that explains how acute hypoxia can lead to long term epigenetic reprogramming and phenotypic plasticity.

Among the proposed CSC markers, CD133 has been widely investigated as a representative marker of cancer stemness in haematological malignancies and solid tumors. Increased gene expression of CD133 is linked to enhanced tumor development, metastatic potential and poor clinical outcome in various cancers such as glioblastoma, breast, liver and colorectal cancer (27–33). Under hypoxia, HIF1 α stabilization promotes CD133- positive stem-like cell maintenance via epigenetic mechanisms, including DNA methylation, histone modifications, and TET-mediated DNA demethylation. In a triple-negative breast cancer, low oxygen increases the proportion of CD133- positive cells, improves vasculogenic mimicry, and promotes chemoresistance via autophagy-dependent pathways (32,33). Together these results suggest that CD133 should be viewed as a representative downstream effect of epigenetic regulation by hypoxia, rather than a separate mechanism of tumour progression.

Epigenetics regulates the expression of the CD133 antigen in early cancers of the ovarian and endometrium cell lines. More specifically, it is responsible for controlling the levels of CD133 expression. The expression of CD133 has been found to be enhanced by the administration of 5-aza-2'-deoxycytidine (DAC), while its regulation is influenced in a cell-line-specific manner by Trichostatin A (TSA) (34,35). Furthermore, the opposite relationship has been established between CD133 expression and the amount of methylation in the CD133 P2 promoter (34).

DNA methylation is one of the earliest and most studied epigenetic mechanisms implicated in the hypoxic response. HIF signalling is known to interact with DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) under low-oxygen conditions, resulting in promoter hypermethylation and transcriptional silencing of tumour suppressor genes. These alterations promote tumor cell survival, immune evasion and resistance to chemotherapy, while maintaining stable gene expression patterns that are maintained during tumour progression. Thus, the coordinated regulation of DNA methylation by hypoxia provides a mechanistic link between oxygen deprivation and long-term epigenetic modification (5,36). Histone modifications are another important regulatory mechanism that hypoxia utilises to change gene expression. Histone acetyltransferases and histone deacetylases (HDACs) dynamically modulate chromatin accessibility through modifications of lysine residues on histone proteins. Under hypoxic conditions, HIFs cooperate with HDACs to induce

chromatin condensation and facilitate the expression of genes involved in angiogenesis, epithelial-mesenchymal transition (EMT), cancer stem cell maintenance, and metastatic progression. HDAC inhibitors have therefore received considerable attention as potential therapeutic agents that can reverse hypoxia-induced transcriptional reprogramming and restore sensitivity to treatment (36–38). A recent study revealed that the genome demethylation caused by (TET) enzymes are an important molecular link between oxygen sensing and epigenetic regulation. These oxygen-dependent dioxygenases catalyse the oxidation of 5-methylcytosine to promote active DNA demethylation. In hypoxia, TET1 expression is induced via HIF-1 α signalling and acts as a co-regulator of hypoxia-responsive genes promoting epithelial-mesenchymal transition, cellular plasticity and metastatic dissemination (39,40). In addition to regulating individual genes, TET enzymes are involved in setting up stable epigenetic states that can persist after reoxygenation, supporting the concept of hypoxic memory. Recent studies show that cellular responses to hypoxia play crucial roles in promoting the epithelial-mesenchymal transition (EMT) and in maintaining cancer stem-like cell populations by inducing hypoxia inducible factors HIF-1 α and HIF-2 α (41). Under conditions of low oxygen, stabilization of HIFs induces transcriptional programs that suppress epithelial characteristics, while enhancing mesenchymal traits, thereby increasing tumor cell motility, invasiveness, and the metastatic potential (42). HIF-1 α has been shown to transcriptionally activate Twist and Snail, leading to repression of E-cadherin expression and disruption of cell-cell adhesion, while HIF-2 α is essential to the preservation of stem-like tumor cell groups, by reinforcing self-renewal and cellular plasticity (2,5). This coordinated regulation of EMT and stemness under hypoxic conditions promotes tumor

heterogeneity, therapy resistance, and disease recurrence, underlining the fact that hypoxia-driven transcriptional reprogramming is a fundamental mechanism in cancer progression (3). Hypoxia can induce lasting epigenetic changes that persist even after reoxygenation, a phenomenon named hypoxic memory, and it also promotes epithelial-mesenchymal transition (EMT). Hypoxic memory allows tumor cells to maintain transcriptional programs related to stemness, invasiveness, immune escape and therapy resistance via permanent changes in DNA methylation, histone modifications and chromatin architecture even when oxygen levels rebound. This lasting epigenetic plasticity is increasingly recognised as a crucial mechanism driving tumour relapse and treatment failure, emphasising the need for therapeutic strategies targeting both the hypoxic microenvironment and the underlying epigenetic machinery (43).

Most recently, histone lactylation emerged as a new epigenetic mechanism that links tumour metabolism to gene regulation. In hypoxia, elevated lactate production can enhance histone lactylation, affecting macrophage polarisation, inflammatory signalling, and immune system suppression in the tumour microenvironment. This mechanism highlights the collaborative role of metabolic adaptation and epigenetic regulation in driving tumour progression and offers a promising path for future treatment investigation (42).

A summary of key hypoxia-associated epigenetic regulators and their functions in tumor progression is provided in (Table 1, Figure 2). Table 1 provides an overview of key hypoxia-related epigenetic regulators, their molecular mechanisms, biological effects and implications for cancer progression. It summarises representative findings reported in the cited literature and provides an overview of the main mechanisms discussed throughout this narrative review.

Table 1: Hypoxia-driven epigenetic mechanisms in cancer.

Hypoxia-associated factor	Epigenetic regulator	Mechanism	Biological outcome	Cancer relevance	Key references
HIF-1 α	DNMTs	DNA hypermethylation	Tumour suppressor gene silencing	Tumour progression	(5, 19, 33)
HIF-1 α / HIF-2 α	HDACs	Histone deacetylation	Chromatin condensation	Therapy resistance	(5, 19, 40)
Hypoxia	TET enzymes	DNA demethylation	EMT activation	Metastasis	(33, 35, 36)
Hypoxic metabolism	Histone lactylation	Epigenetic activation	Immune suppression	Immune escape	(13, 39)
Hypoxic niche	Chromatin remodelers	Stable transcriptional programs	CSC maintenance	Tumour recurrence	(19, 20, 35)

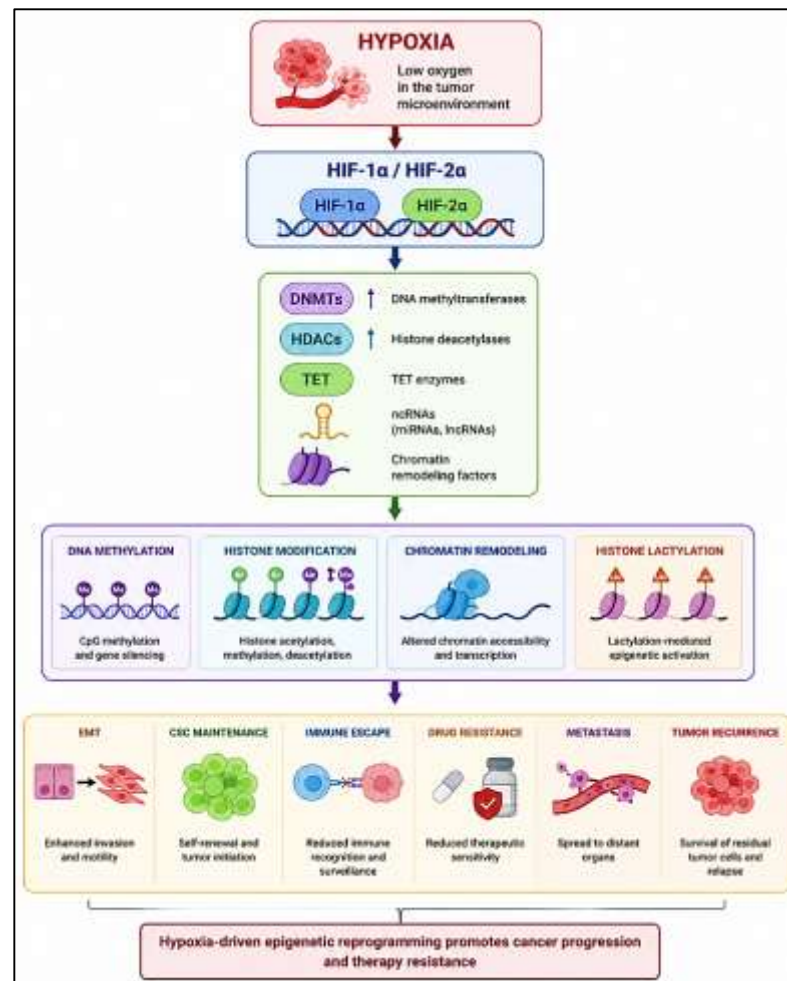


Figure 2: Hypoxia-driven epigenetic reprogramming in cancer

Schematic illustration of hypoxic regions within solid tumours stabilize hypoxia-inducible factors (HIF-1 α and HIF-2 α), that engage with epigenetic controllers that includes DNA methyltransferases, histone-modifying enzymes, and chromatin remodeling complexes. These interactions induce widespread epigenetic alterations that promote epithelial-mesenchymal transition, cancer stem-like phenotypes, immune evasion, and resistance to therapy. Targeting hypoxia-associated epigenetic pathways represents a promising therapeutic strategy in cancer treatment. The schematic was created by the authors based on published evidence (5,19,33,35,37,40)

Hypoxia, Epigenetics, Treatment Resistance, and Prospects for the Future

Hypoxia-associated epigenetic reprogramming plays a major role in resistance to standard chemotherapy, radiation therapy, and immunological therapy (44). Epigenetic silencing of the DNA repair genes, modulation of apoptotic pathways, and suppression of antigen presentation collectively reduces the treatment efficacy (45). Furthermore, hypoxia-induced immune dysfunction limits the success of an immune checkpoint blockade (46). Given these challenges, therapeutic strategies targeting epigenetic modifiers such as DNA methyltransferase and histone deacetylase inhibitors have gained increasing attention. Combination approaches integrating

epigenetic therapy with conventional treatments or immunotherapy may help overcome hypoxia-mediated resistance (47).

While there is a lot of evidence suggesting that hypoxia-induced epigenetic changes enhance cancer progression, some critical elements remain unexplained. Much of the argument relies on the role of oxygen-sensitive epigenetic enzymes, particularly the TET enzymes. Other studies have demonstrated reduced TET activity in hypoxia condition as the enzymes are reliant on molecular oxygen for their catalytic function, while some research has indicated that hypoxia can lead to increased TET expression through HIF-dependent mechanisms, promoting epithelial-mesenchymal transition (EMT) and tumor progression (43,48). These apparently contradicting observations imply that the biological effects of TET enzymes are very context-dependent and may vary depending on tumor type, length of hypoxia, metabolic status and interactions with the cancer microenvironment. Similarly, DNA

methyltransferase inhibitors and histone deacetylase inhibitors have showed promising outcomes in preclinical trials, but their clinical success has been uneven among different malignancies (49). Tumor heterogeneity, adaptive resistance, and diversity in the hypoxic micro-environment may all contribute to these discrepancies. The concept of hypoxia memory, where epigenetic modifications are maintained after

reoxygenation, is a new concept which is not yet fully elucidated. The molecular mechanisms that maintain such long-term changes deserve further investigation. Collectively, research results point to future research directions integrating hypoxia biology with epigenomic profiling, single-cell sequencing, and biomarker-guided therapeutics. A better understanding of the epigenetic plasticity induced by hypoxia will allow us to design rational combination therapies to overcome treatment resistance and improve clinical outcome in cancer patients.

Conclusion

Hypoxia is the central driver of epigenetic plasticity in cancer, shaping tumor evolution, immune escape, and therapeutic resistance. Hypoxia induces persistent malignant characteristics that promote tumor growth by coordinating chromatin structure and gene expression. Targeted hypoxia-associated epigenetic mechanisms may provide chances for developing more effective and long-lasting cancer therapies.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

Study conception & design: (Yasamin Al-Qassab). Literature search: (Yasamin Al-Qassab, Tharwa H. Al-Tai & Suha A. AL-Fakhar). Literature acquisition: (Wifaq M. Ali & Tariq. Nadeem). Literature interpretation: (Yasamin Al-Qassab). Manuscript preparation: (Yasamin Al-Qassab, Hayfaa S. AL-Hadithi & Khalil I. Mohammed). Manuscript editing & review: (Yasamin Al-Qassab).

AI Declaration

No artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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نقص الأكسجة وإعادة البرمجة فوق الجينية في السرطان: مراجعة سردية للآليات والآثار العلاجية

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³ كلية الطب، جامعة اشور، بغداد، العراق.

الخلاصة:

خلفية البحث: الآليات اللاجينية هي منظمات أساسية للتعبير الجيني وهوية الخلية، يساهم خللها بشكل كبير في بدء السرطان والتطور المرضي. يؤدي نقص الأكسجة في الورم، وهو سمة سائدة في البيئة الدقيقة للورم التي تغير بشكل عميق التنظيم اللاجيني، إلى تعزيز عدوانية الورم، والحفاظ على الخلايا الجذعية السرطانية، والتهرب المناعي، والمقاومة العلاجية.

الأهداف: تلخص هذه المراجعة السردية الأدلة الحالية المتعلقة بإعادة البرمجة الشرسة المدفوعة بنقص الأكسجة في السرطان، مع التركيز على العوامل التي تحفز نقص الأكسجة (HIFs)، مثيلة الحمض النووي، وتعديلات الهيستون، وإعادة تشكيل الكروماتين، والحمض النووي الريبي غير المشفر، والذاكرة الناقصة الأكسجين، والانتقال الظهاري المتوسط (EMT)، والخلايا الجذعية السرطانية (CSCs) والمقاومة العلاجية.

المنهجية: تم إجراء مراجعة سردية للأدبيات باستخدام PubMed و Scopus و Google Scholar. تم تقييم الدراسات التي تمت مراجعتها من قبل الأقران والتي نشرت بشكل رئيسي بين عامي 2015 و 2025 وفقا لمدى صلتها بالآليات اللاجينية المرتبطة بنقص الأكسجة في السرطان. تم اختيار جميع المقالات إذا كانت ذات صلة بالموضوع وأضافت قيمة علمية إلى التنظيم اللاجيني المرتبط بنقص الأكسجة في السرطان. نظرا لأن هذه مراجعة سردية، لم تكن هناك معايير إدراج/ استبعاد أو مخطط تدفق PRISMA.

النتائج: يعمل نقص الأكسجة على استقرار HIF-1α و HIF-2α، اللذان يتعاونان مع منظمات جينية متعددة، بما في ذلك إنزيمات مثيل ترانسفيراز الحمض النووي، والإنزيمات المعدلة للهيستون، ومجموعات إعادة تشكيل الكروماتين، والحمض النووي الريبي غير المشفر. تعزز هذه التفاعلات EMT، والحفاظ على CSC، والهروب المناعي، والانبثاث، ومقاومة العلاج الكيميائي والعلاج المناعي. تشير الأدلة الناشئة أيضا إلى أن الذاكرة ناقصة الأكسجين تحافظ على التغيرات الجينية بعد إعادة الأكسجة، مما يساهم في الأنماط الظاهرية الخبيثة المستمرة.

الاستنتاج: يعمل نقص الأكسجة اللاجيني كمحرك أساسي لتطور السرطان والمقاومة العلاجية من خلال الحفاظ على إعادة البرمجة اللاجينية والحفاظ على جذع السرطان. على الرغم من أن مثبطات نازعة الأسيتيل الهيستون وعوامل نقص المثيل تظهر إمكانات علاجية، إلا أن فعاليتها السريرية غير المتسقة تتطلب تطوير مزيج محسن واستراتيجيات علاج شخصية. وبالتالي، فإن إجراء مزيد من التحقيق في الآليات اللاجينية التي يحركها نقص الأكسجة أمر ضروري لتعزيز فعالية العلاج وتعزيز علم الأورام الدقيق.

الكلمات المفتاحية: تطور السرطان؛ الخلايا الجذعية السرطانية؛ التنظيم اللاجيني؛ نقص الأكسجة؛ ذاكرة نقص الأكسجين