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The Role of Hypoxia-Associated Genes in the Pathogenesis of Various Diseases and Therapeutic Targets: A Comprehensive Review

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ABSTRACT:
Hypoxia, characterized by low oxygen levels, induces a complex cellular response mediated by hypoxia-inducible factors (HIFs) and involves modulation of various signaling pathways and gene expression patterns. This review delves into the molecular mechanisms of hypoxia, emphasizing hypoxia-associated genes and their implications in different diseases. Key findings include the pivotal role of HIF proteins in arranging cellular adaptation to low-oxygen environments, the involvement of chromatin modifications in hypoxia response, and the identification of hypoxia-associated genes such as NF-KB, HIF1α, HK, PFKL, and PIM1. These genes play crucial roles in cancer progression, cardiovascular diseases, pulmonary hypertension, Alzheimer's disease, and liver diseases. Understanding the functions of these genes is essential for developing targeted therapeutic strategies. Targeting hypoxia-related pathways and genes holds promise for novel treatment options and may provide insights into disease mechanisms and potential biomarkers for prognosis and diagnosis. Further research is warranted to elucidate hypoxia-associated genes' intricate interactions and regulatory networks in disease progression and treatment resistance.

1. INTRODUCTION

Hypoxia is defined as a condition where the oxygen content, typically below 2%, is relatively lower and associated with the regular levels in a specific tissue, organ, or cell type. The pivotal element in hypoxia is the hypoxia-inducible factor (HIF) gene, which regulates the activation of genes downstream when oxygen levels decrease. HIFs play diverse roles, including facilitating angiogenesis, erythropoiesis, cell proliferation, and metabolic processes [1]. Their involvement has been implicated in the onset and advancement of cancers like lung cancer and the spread of metastatic tumors. Research primarily focuses on understanding the expression patterns of HIFs and their downstream targets in the context of human health and disease, offering avenues for potential therapeutic interventions [2]. In mammalian cells, molecular oxygen is essential for their functioning. Under normal oxygen conditions, these cells utilize oxygen and nutrients to produce adenosine 5'-triphosphate (ATP) [3]. Mammalian cells, rely on oxygen for crucial biochemical processes, maintaining a delicate balance to support their functions. When oxygen levels drop, cells trigger various responses to cope with the stress. These include activating pathways like HIF, autophagy, energy metabolism through mTOR complex 1 (mTORC1), and stress pathways like ER stress. These mechanisms help cells adapt to hypoxic conditions [4]. The primary mechanism by which cells react to low oxygen levels revolves around HIF transcription factors. These factors detect hypoxic conditions within cells, prompting adjustments in metabolism, overseeing cell growth, and managing inflammatory reactions, among other tasks [5]. At the same time, the HIF signal has also been shown to be linked with various illnesses, including cardiovascular, metabolic, inflammatory, and infection-related conditions [6,7,]. Several genes, including NF-KB, HIF1α, HK, PFKL, PIM1, ST3GAL4, TRIM8,

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STC2, TRPS1, and FAM207A, are implicated in hypoxia response [8]. They are involved in adapting to low oxygen levels in the body and have associations with conditions like cancer, osteosarcoma, and Alzheimer's disease. The way these genes are expressed can serve as indicators for predicting prognosis and drug resistance in specific types of cancer [9]. The discovery of this route provides a comprehensive molecular framework to comprehend how cells sense changes in oxygen concentration, send signals downstream, and present novel targets for the treatment of a range of human diseases. This review aims to comprehensively explore the molecular processes that trigger hypoxia, with an emphasis on genes linked to hypoxia and how they may affect different disorders. It will investigate into the cellular responses to hypoxia, the key signaling pathways involved, and the role of hypoxia-related genes in specific pathological conditions. Furthermore, it will discuss therapeutic implications and future directions in hypoxia research. Understanding hypoxia-related genes and their impact on disease mechanisms is crucial for designing targeted therapeutic approaches.

2. MOLECULAR MECHANISMS OF HYPOXIA

Hypoxia, marked by low oxygen levels, triggers a complex cellular response via the HIF signaling pathway. HIF is an essential component that controls the activation of genes associated with several physiological and pathological processes. The continuously expressed β-subunit and the oxygen-sensitive α-subunit make up the HIF protein. During hypoxic scenarios, the α-subunit undergoes stabilization and migrates to the nucleus. Within the nucleus, it combines with the β-subunit and other co-factors, facilitating the transcription of genes that help cells survive in low-oxygen environments [10]. In hypoxia, gene expression shifts to cope with low oxygen levels, enhancing angiogenesis, erythropoiesis, glucose metabolism, and cell survival. Crucially, the prolyl-hydroxylation of HIF-1α plays a vital role in regulating HIF activity. This modification targets HIF-1α for degradation in normal oxygen conditions, facilitated by prolyl hydroxylase domain (PHD) proteins, which utilize oxygen for their function. However, under hypoxia, PHD activity is hindered, leading to HIF-1α stabilization and subsequent activation of HIF target genes (**Fig.1)** [11].

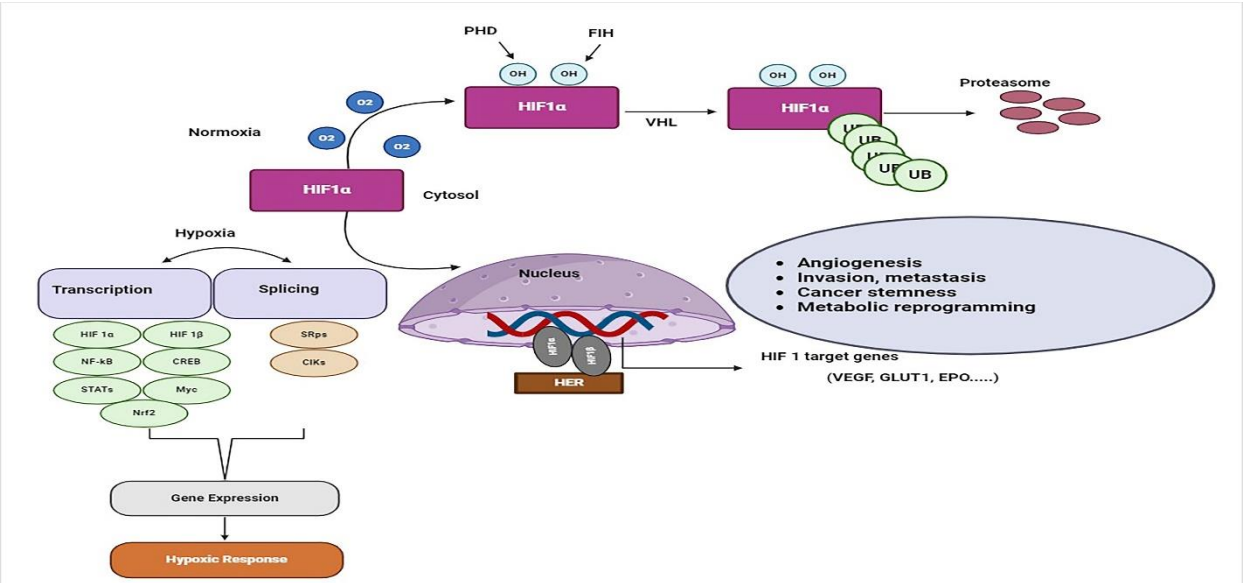

Figure 1: In normoxia, HIF-1α or HIF-2α undergo hydroxylation by PHDs using oxygen, leading to CO2 and succinate production. Hydroxy-HIF-α is recognized by pVHL, ubiquitinated by VBC, and degraded by the 26S proteasome. During low oxygen conditions, HIF-α stabilizes, enters the nucleus, forms a complex with HIF-1β, and activates gene expression related to hypoxic responses through binding to hypoxia response elements (HREs) in the genome.

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Chromatin is involved in detecting low oxygen levels in cells and actively participates in responding to hypoxia. Since many hypoxia responses hinge on transcription, chromatin needs to adjust quickly to changes in ATP levels and ensure the proper access of transcription factors to specific parts of the genome during low oxygen situations [12]. In the realm of cancer, hypoxia represents a fundamental aspect of the tumor's surroundings and significantly influences the advancement of cancer as well as its response to treatments. Tumor cells adjust to low oxygen levels by triggering HIF signaling and employing other adaptive strategies, fostering their resilience and aggressive traits. Researchers are investigating the modulation of hypoxia-related pathways as a strategy for targeting therapy in solid tumors, intending to revive immune cells and reshape the tumor's environment to bolster immune reactions against the tumor [13]. Implicated in diseases like cancer and ischemia, the HIF-1 pathway is a potential therapeutic target. Regulated by oxygen-dependent and independent mechanisms, its dysregulation is linked to various diseases, making it a focus of therapeutic research. Targeting HIF-1 for therapeutic purposes in cancer, ischemia, and other diseases is under investigation, promising novel treatment options in the future.

3. HYPOXIA-ASSOCIATED GENES

Hypoxia-associated genes contain several important actors, especially when it comes to cancer. The research found that nearly all hypoxia-inducible genes exhibited PO2-dependent up- and down-regulated expression, and potential hypoxia biomarker genes such NF-KB, HIF1α, HK, PFKL, and PIM1 were expressed in all hypoxic cells. [8,14]. The dimeric protein complex known as HIF-1 is a transcription factor for several target genes and is essential to the body's response to hypoxia [15]. Furthermore, two hypoxia-inducible factors, HIF-1 and HIF-2, which have distinct transcriptional targets and varying effects on different physiological processes, are the main mediators of the transcriptional response to hypoxia [16]. **Fig. 2** illustrates key genes targeted by the HIF and their respective functions in cellular adaptation to low oxygen levels (hypoxia). These genes and factors may be candidates for therapeutic intervention in diseases including cancer and ischemia because of their important roles in the cellular and developmental response to hypoxia.

3.1. Role of Transcription Factors in Gene Regulation

Proteins called transcription factors (TFs) are essential for controlling the process of genetic information being transferred from DNA to messenger RNA. They bind to specific DNA sequences, controlling the transcription of target genes, and thus playing a vital role in gene regulation [17]. TFs can activate or suppress gene expression, allowing for varied gene expression across the genome. They typically consist of a DNA binding domain (DBD) for recognizing and binding to transcription factor binding sites (TFBSs) and an effector domain (ED) for sensing signals. TFs execute their functions through mechanisms like steric hindrance, roadblock, deformation, and anti-activation [18]. In contexts like hypoxia and cancer, HIFs are a subset of TFs upregulated during low oxygen conditions in cancer, promoting the expression of genes crucial for metabolic adaptation, survival, and migration. Dysregulation of TFs, including HIFs, has been linked to various pro-oncogenic processes such as proliferation, survival, metabolism, invasion, metastasis, and resistance to chemotherapy, as well as poorer prognoses [19].

3.2. Functional Categories of Hypoxia-Associated Genes

Various functional categories of hypoxia-associated genes have been identified, spanning a wide array of biological processes. These include glycolytic enzymes, proapoptotic genes, prolyl hydroxylase, antioxidant pathways, NAD(P), and ER stress response pathways. HIFs play a pivotal role in sensing and responding to low oxygen levels, composing the expression of downstream genes involved in diverse cellular functions such as metabolism, cell growth, immune response, and tumorigenesis [20]. Furthermore, through techniques like WGCNA (Weighted Gene Co-Expression Network Analysis) analysis, key hub genes associated with hypoxia have been pinpointed, particularly those implicated in angiogenesis, cell cycle regulation, and immune response [21]. Investigating hypoxia-associated genes across various diseases, including Alzheimer's

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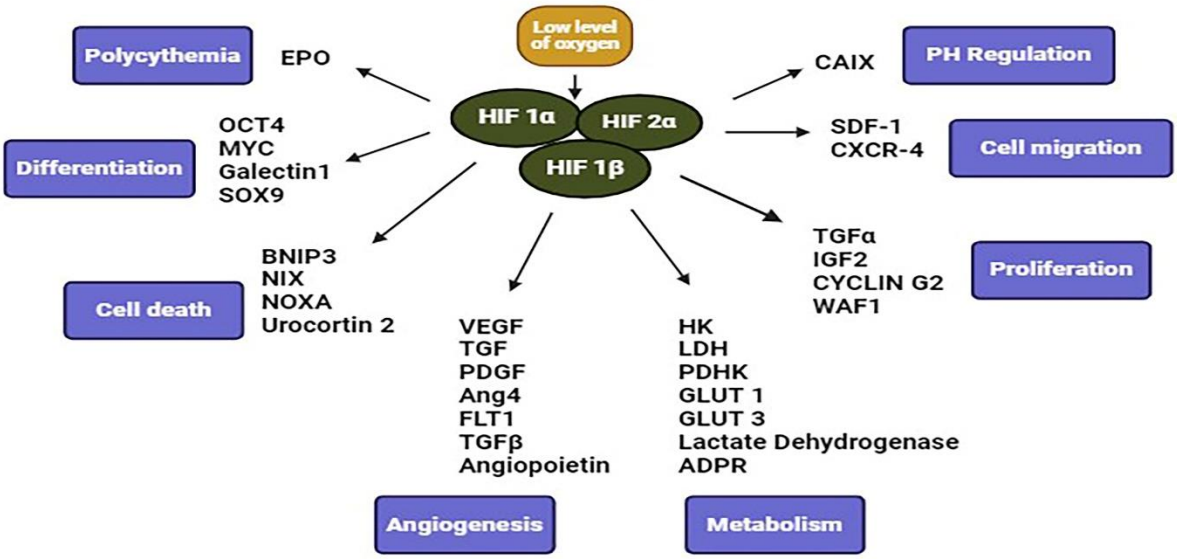

Figure 2: Illustrates HIF target gene activation includes a diverse array of roles, including crucial tumor-promoting actions like angiogenesis, evasion of cell death, cellular metabolism, cell migration, PH regulation, cell proliferation, and differentiation. The activation of these targets supports adaptive cellular survival in hypoxic conditions.

disease, holds promise for uncovering novel therapeutic targets to combat these conditions.

4. ROLE OF HYPOXIA-RELATED GENES IN SPECIFIC DISEASES

Hypoxia, characterized by insufficient oxygen levels, is a pivotal factor observed in both normal physiological processes and various health conditions. These range from cancer, myocardial ischemia, and chronic heart and kidney diseases to metabolic disorders, and reproductive illnesses like preeclampsia and endometriosis [22]. Significantly, hypoxia influences the development of these conditions by altering cellular functions, including metabolism, proliferation, cell viability, glycolysis, immune responses, susceptibility to microbial infections, tumor formation, and the spread of cancer cells [2]. Table 1 presents an overview of the diseases, along with the corresponding hypoxia-related genes and their significant roles within each disease context (**Table 1)**.

4.1. Cardiovascular disease (CVD)

Hypoxia, characterized by reduced oxygen levels, is a key contributor to the development of CVD conditions such as ischemic heart disease (IHD). Several studies have identified and validated genes linked to hypoxia that are associated with coronary artery disease (CAD) and IHD. For instance, a study discovered and confirmed four central hypoxia-related genes ADM, PPFIA4, FAM162A, and TPBG that could serve as diagnostic indicators for CAD (**Fig.3**) [23]. In the heart tissue affected by inadequate blood flow, genes that respond to low oxygen levels are activated by a protein called HIF-1. In treating ischemic heart disease, gene therapy involves introducing genes that code for substances promoting blood vessel growth and preventing cell death as therapeutic agents [24]. Research has delved into the involvement of hypoxia signaling in the development of cardiovascular conditions like IHD, examining its role in tissue remodeling and the seriousness of heart-related illnesses [25]. Researching genes associated with hypoxia and examining hypoxia signaling within the context of IHD offers a valuable understanding of the molecular processes driving the illness and could influence the creation of potential treatment approaches.

4.2. Pulmonary Hypertension (PH)

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Table 1: This table highlights the diseases, the associated hypoxia-related genes, and their key roles or findings in each disease.

Disease	Hypoxia-Associated Genes	Key Findings	Therapeutic Target	References
Cancer	NF-KB, HIF1α, HK, PFKL, PIM1, GLUT1, VEGF, MDR1	Crucial for tumor progression, metastasis, and drug resistance.	Targeting HIFs, VEGF, or MDR1 as potential therapies.	[41, 42]
Cardiovascular Disease	ADM, PPFIA4, FAM162A, TPBG	Potential diagnostic indicators for coronary artery disease.	Understanding hypoxia-related genes may lead to better diagnostic markers.	[23, 24]
Pulmonary Hypertension	HIF-1α, HIF-2α, Aldh6a1, Mmp2, Gpx3	Essential in pulmonary vascular remodeling and metabolic changes.	Targeting HIF signaling pathways as a therapeutic approach.	[29, 31]
Alzheimer's Disease	BACE1, NEP, VEGF, BDNF	Implicated in neurodegenerative processes, oxidative stress, and amyloid production.	Investigating drugs targeting BACE1 or VEGF for AD treatment.	[34, 36]
Liver Disease	HIF-1α, LOX, HBx, MDR1	Influence liver fibrosis, hepatocellular carcinoma, and metabolic changes.	Targeting HIF signaling or LOX as therapeutic strategies for liver diseases.	[38, 39]

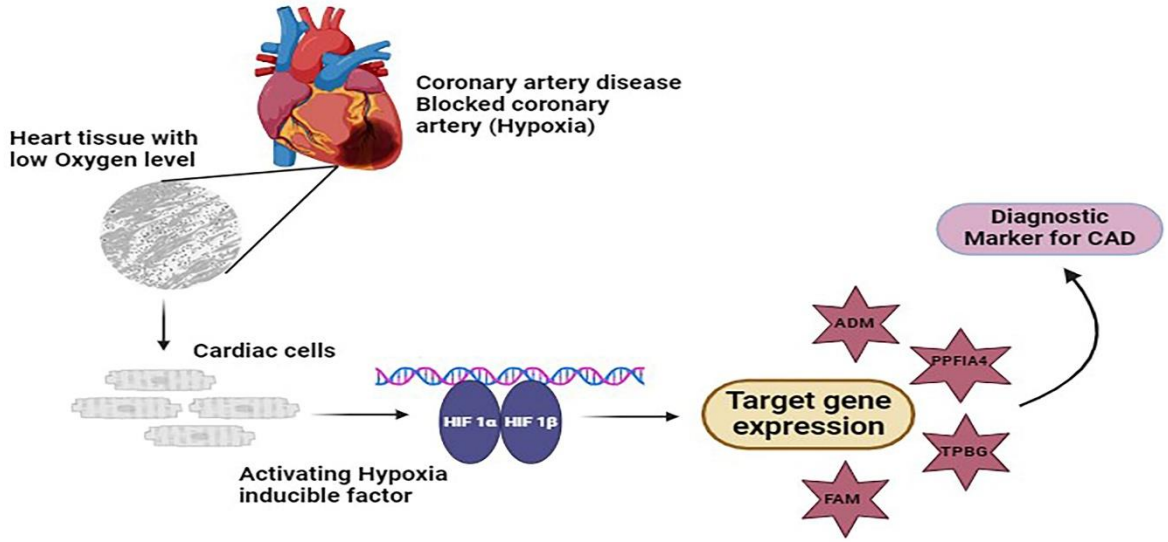

Figure 3: The figure depicts the progression from coronary artery disease to hypoxia in heart tissue due to blocked coronary arteries. In response, cardiac cells activate the Hypoxia-Inducible Factor (HIF), leading to the expression of target genes. These genes serve as diagnostic markers for CAD, reflecting cellular adaptation to low oxygen levels in the heart.

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In the pathophysiology of pulmonary hypertension (PH), HIF signaling is essential and crucial. HIFs have a role in the pathophysiology of several illnesses, including PH, and coordinate the body's response to hypoxia [26]. Increased pulmonary artery pressure and pulmonary vascular remodeling result from the upregulation of HIF-1α and HIF-2α in pulmonary artery smooth muscle cells (PASMCs) and endothelial cells (PAECs) in the setting of PH. It has been demonstrated that HIF-1α in PASMCs reduces myosin light chain phosphorylation, which in turn lowers vascular tone [27]. Inflammation, mechanical strain, oxidative stress, and genetic susceptibility are additional variables that impact HIF signaling. These factors converge on HIF signaling pathways to cause changes in angiogenesis, vascular tone, metabolism, and cell survival [26,28]. The study identified six key genes linked to metabolism affected by hypoxia, which are crucial for understanding hypoxic PH. These genes, such as Aldh6a1, Mmp2, and Gpx3, were highlighted as central players in hypoxia-induced metabolic changes. Additionally, the research revealed that utilizing a hub gene-based LASSO model enables accurate prediction of PH occurrence [29]. Another study indicated that sets of genes mediated by HIF2α could potentially serve as a means to distinguish pulmonary arterial hypertension from other conditions [30]. Mutations in genes associated with hypoxia, such as loss-of-function mutations in VHL and the HIF-2α mutation G537R, have been connected to PH [31]. The pathophysiology of PH is aided by the dysregulation of HIFs, which are crucial mediators of the hypoxic response. HIF signaling pathway targeting could be a cutting-edge PH treatment approach.

4.3. Alzheimer's disease (AD)

Alzheimer's disease (AD) and hypoxia are closely linked. Studies have shown that inadequate oxygen levels can trigger oxidative stress, disrupt cellular energy metabolism, and facilitate the accumulation of misfolded proteins such as tau and beta-amyloid (Aβ), which are hallmarks of AD [32]. Prolonged inflammation and impaired neurovascular functions can be exacerbated by hypoxia, which can also worsen neurodegenerative processes [33]. In addition, the lack of oxygen in the body can increase the activity of the BACE1 gene which, in turn, escalates the production of Aβ while simultaneously decreasing the expression of enkephalin (NEP), the primary enzyme responsible for Aβ degradation [34]. Disruption of calcium regulation by hypoxia can lead to neuronal cell death and microglial activation, initiating a neuroinflammatory response that contributes to AD pathogenesis [35]. Additionally, a lack of oxygen in the body can cause a change in the way the brain processes amyloid precursor protein, resulting in an increase in the production of amyloid. This can also lead to a decrease in the expression of brain-derived neurotrophic factor (BDNF), which can ultimately result in cognitive impairment [36]. So, genes associated with low oxygen levels might make someone more prone to Alzheimer's disease, and bringing oxygen levels in the brain back to normal could potentially improve or even reverse the process of neurodegeneration.

4.4. Liver disease (LD)

HIF 1 alpha has a notable impact on several liver conditions such as liver fibrosis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma (HCC) and viral hepatitis. When oxygen levels decrease, the activity of HIF-1α, a type of transcription factor, increases, contributing to the development and advancement of liver disorders [37]. Liver fibrosis progression is a crucial phase in liver disease advancement, in which HIF-1α plays a part. Low oxygen levels stimulate liver fibrosis by controlling the activity of numerous genes, including those responsible for generating the extracellular matrix (ECM) and triggering the activation of hepatic stellate cells (HSCs) [38]. The expression of the VEGF gene induces the transformation of liver sinusoidal endothelial cells (LSECs) into capillary endothelium, leading to hypoxia in the liver and contributing to the progression of liver fibrosis. The HIF/LOX pathway in liver cancer is impacted by Lysyl oxidase (LOX) which modifies the extracellular matrix. This effect is particularly notable in cases of hepatitis B virus (HBV) infection [39]. The HBx protein, encoded by the hepatitis B virus (HBV), has been implicated in promoting extracellular matrix modification in liver cancer through the HIF/LOX pathway. Furthermore, hepatitis C virus (HCV) infection can induce the expression of HIF-1α, which in turn enhances autotaxin protein expression, leading to liver fibrosis and hepatocellular carcinoma (HCC) [37]. These genes and their regulatory mechanisms are important in the understanding and potential treatment of live

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diseases, providing potential targets for therapeutic intervention.

4.5. Cancer

Hypoxia-related genes play a significant role in cancer progression, treatment resistance, and the tumor microenvironment (TME). When oxygen levels drop, triggering hypoxia, HIF transcription factors become activated. These factors then govern the expression of various genes related to processes such as angiogenesis, cell survival, metabolism, and resistance to drugs [40]. HIF-1α, a key HIF transcription factor, can induce the expression of genes such as VEGF, GLUT1, and MDR1 (ABCB1), which promote angiogenesis, glycolysis, and multidrug resistance, respectively [41]. HIF-1α can activate both the Rap1 signal transduction pathway and the Hedgehog signal transduction pathway, both of which play crucial roles in cell motility and the process of metastasis (**Fig. 4)** [42]. Hypoxic cells can upregulate drug transporters like MDR1, which pumps chemotherapeutic agents out of the cell, leading to reduced drug efficacy. Hypoxia can also inhibit cell cycle progression and induce apoptosis, which contributes to treatment resistance [40]. TME is a complex network of cells, extracellular matrix, and signaling molecules that influence cancer progression and treatment response. Hypoxia can alter the TME by modulating the expression of genes related to immune cell infiltration, immune suppression, and immune evasion [43].

5. Therapeutic implications and future prospectives

Hypoxia, hypoxia-associated genes, and diseases have significant prospective and therapeutic implications. Research has shown that HIFs play a pivotal role in adapting cells to hypoxic conditions, affecting various physiological systems. In the context of cancer, HIF-targeted therapy has been a focus, with HIFs being associated with tumor progression, metastasis, and drug resistance [44]. Additionally, intermittent hypoxia (IH) has been studied for its potential therapeutic effects in various clinical disorders, with evidence suggesting that "low dose" IH may be a simple, safe, and effective treatment with considerable therapeutic potential [45]. Furthermore, the expression of hypoxia-inducible genes such as NF-KB, HIF1α, HK, PFKL, and PIM1 has bee

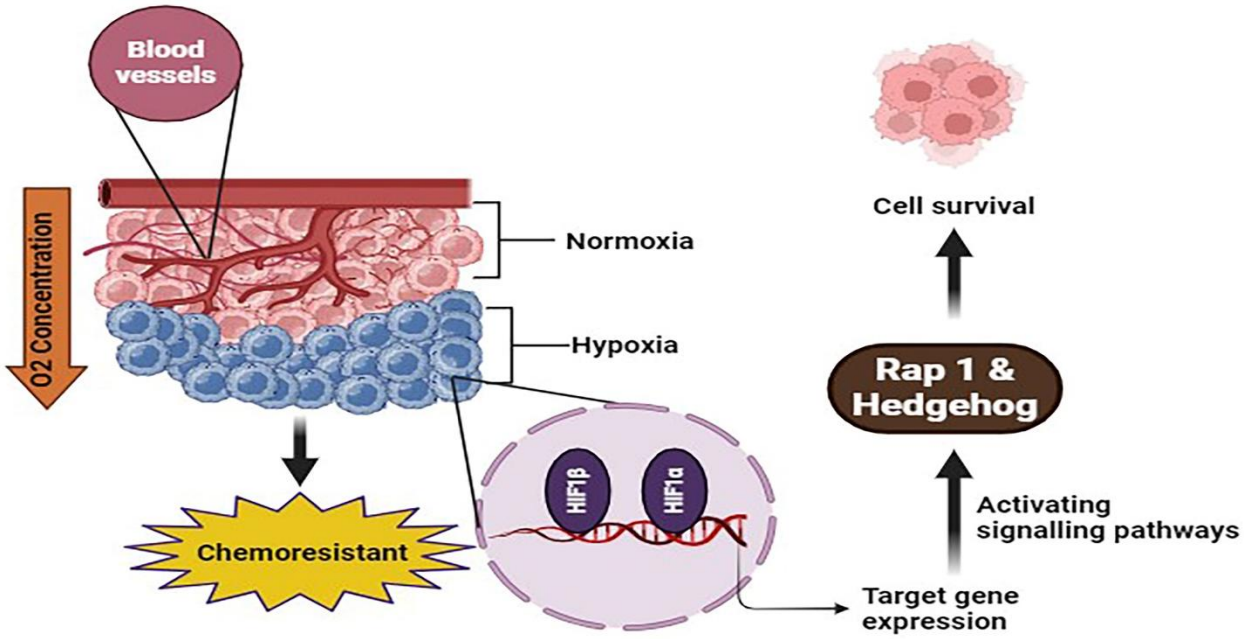

Figure 4: Hypoxic tumor regions lack oxygen due to distance from blood vessels. Hypoxia activates HIF transcription factors, which control genes related to angiogenesis, cell survival, metabolism, and drug resistance. HIF-1α activates Rap1 and Hedgehog pathways, crucial for cell motility and metastasis.

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identified in different cancer cell lines, providing possible targets for therapy [46]. In the context of diseases, conditions such as heart or lung diseases, infections, and cancer can lead to hypoxia, which can be life-threatening and cause organ damage [47]. In the specific case of bladder cancer, hypoxia modification has been a focus of research, with promising methods such as histopathological markers, protein expression biomarkers, and novel therapies being explored for their potential to improve treatment outcomes [48]. Efforts spanning over a century have aimed to combat tumor hypoxia by developing therapies targeting hypoxic cells and improving tumor oxygenation. Strategies involve inhibiting hypoxia-related pathways like HIFs and mTOR, as well as exploring supplemental hyperoxia therapy. Oxygen therapy, a common medical intervention, also helps alleviate tissue hypoxia in critically ill patients [49, 50]. These findings underscore the importance of understanding the implications of hypoxia and hypoxia-associated genes in disease development and potential therapeutic interventions.

6. CONCLUSION

In conclusion, hypoxia, characterized by low oxygen levels, triggers a complex cellular response mediated by hypoxia-inducible factors and involves the modulation of various signaling pathways and gene expression patterns. The molecular mechanisms underlying hypoxia involve the stabilization of HIF proteins, chromatin modifications, and the activation of downstream genes crucial for cellular adaptation to low-oxygen environments. Hypoxia-associated genes, including NF-KB, HIF1α, HK, PFKL, and PIM1, play pivotal roles in cellular responses to hypoxia and are implicated in various diseases, such as cancer, cardiovascular diseases, pulmonary hypertension, Alzheimer's disease, and liver diseases. Understanding the functions of these genes and their implications in specific pathological conditions is essential for the development of targeted therapeutic strategies. Targeting hypoxia-related pathways and genes holds promise for novel treatment options and may provide insights into disease mechanisms and potential biomarkers for prognosis and diagnosis. However, further research is warranted to elucidate hypoxia-associated genes' intricate interactions and regulatory networks and their roles in disease progression and treatment resistance.

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ETHICAL APPROVAL

This study does not involve experiments with animals or human subjects.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used/analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that there are no conflicts of interest.

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AUTHOR'S CONTRIBUTIONS

All authors equally contributed to this work, read and approved the final manuscript.

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