JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

A Review on the Interplay between Immune Responses, Hypoxia Signaling, and Cellular Dynamics and their Implications for Disease Pathogenesis

Quazia Ifaq*[1], Imran Rashid[1], Rajip Nepal[1], Abhishek Kumar[1], Vishal Kajla[2]

[1]*UG Scholar, College of Pharmacy, B-Pharmacy, RIMT University, Gobindgarh, Punjab, India.*
[2]*Assistant Professor, Dept of Pharmacology, College of Pharmacy, RIMT University, Gobindgarh, Punjab, India.*

Publication history: Received on 24th March; Revised on 30th March; Accepted on 4th April

Article DOI: 10.5281/zenodo.11116448

Abstract: The complex orchestration of immune and cellular responses is crucial for maintaining homeostasis and combating disease. This review discusses the intricate interplay between toll-like receptors (TLRs), hypoxia-inducible factors (HIFs), and cellular dynamics, elucidating their roles in immune function, angiogenesis, and disease progression. TLRs, as pattern recognition receptors, play a pivotal role in innate immunity by recognizing microbial products and initiating adaptive immune responses through dendritic cell activation. Understanding their function in bridging innate and adaptive immunity holds therapeutic potential for autoimmune disorders and infectious diseases. Moreover, the hypoxia-induced stabilization of HIFs triggers the transcriptional activation of genes involved in angiogenesis, shedding light on the pathophysiology of retinal angiomatous proliferation (RAP) and neovascular age-related macular degeneration (AMD). The differential roles of HIF-α isoforms, HIF-1α and HIF-2α, in hypoxia transcription control are explored, highlighting their distinct physiological functions and target gene specificities. Furthermore, the review examines the implications of hypoxia signaling and HIF-mediated modulation of epithelial-mesenchymal transition pathways in cancer metastasis. Understanding these intricate mechanisms, novel therapeutic strategies can help in developing drugs that target immune dysfunction, angiogenesis, and cancer progression.

Keywords: Toll-like receptors; Hypoxia; Hypoxia-inducible factors; Angiogenesis; Epithelial-mesenchymal transition

1. Introduction

The immune system's intricate orchestration of innate and adaptive responses is essential for maintaining health and combating disease. At the forefront of this complex network lies the family of toll-like receptors (TLRs), which play a pivotal role in recognizing and responding to microbial threats [1-3]. These pattern recognition receptors (PRRs) serve as sentinels, detecting conserved molecular patterns associated with pathogens (PAMPs) and initiating appropriate immune responses [4-7].

TLRs are type I transmembrane proteins characterized by an extracellular leucine-rich repeat (LRR) domain and an intracellular Toll/IL-1 receptor (TIR) domain [8]. The LRR domain facilitates the recognition of a wide range of PAMPs, including bacterial lipopolysaccharides, viral nucleic acids, and fungal cell wall components. Upon ligand binding, TLRs undergo conformational changes that trigger downstream signaling cascades, ultimately leading to the production of inflammatory cytokines, chemokines, and the activation of various immune effector mechanisms [9].

The significance of TLRs in animal immunity extends beyond their role in pathogen recognition. They serve as a crucial link between the innate and adaptive arms of the immune system, a process facilitated by their interaction with dendritic cells (DCs). Immature DCs, strategically positioned in peripheral tissues, express a comprehensive repertoire of TLRs, enabling them to detect and capture microbial invaders [10-14]. Upon TLR engagement, DCs undergo maturation, upregulating the expression of major histocompatibility complex (MHC) molecules and co-stimulatory signals. These mature DCs then migrate to draining lymph nodes, where they present processed antigens to naive T cells, initiating adaptive immune responses tailored to the specific pathogenic threat [15-16].

The TLR signaling pathway also influences the polarization of T helper (Th) cell responses, a crucial determinant of the ensuing immune response. For instance, TLR-mediated recognition promotes the development of Th1 responses, characterized by the production of interferon-gamma (IFN-γ) and IgG2a antibodies, which are essential for combating intracellular pathogens like

* Corresponding author: Quazia Ifaq

bacteria, viruses, and protozoa. Conversely, Th2 responses, typified by the secretion of interleukins like IL-4 and IL-13, are less dependent on TLR signaling and are critical for defense against extracellular parasites such as helminths [17-18].

This review article aims to provide a comprehensive understanding of the pivotal roles played by toll-like receptors in animal immunity, with a particular focus on their functions in pathogen recognition, bridging innate and adaptive immunity, and shaping subsequent immune responses. By elucidating the intricate mechanisms underlying TLR-mediated immunity, we seek to unravel potential therapeutic avenues for modulating immune function in the context of autoimmune disorders, infectious diseases, and immune-related pathologies.

2. Function of Hypoxia and HIF Factors in Age-Related Macular Degeneration (AMD) and Retinal Angiomatous Proliferation (RAP)

Age-related macular degeneration (AMD) and retinal angiomatous proliferation (RAP) are sight-threatening ophthalmic conditions characterized by abnormal neovascularization in the retina [19]. While the underlying mechanisms driving these pathologies remain incompletely understood, accumulating evidence points to the pivotal roles played by hypoxia and hypoxia-inducible factors (HIFs) in their pathogenesis [20, 21].

Hypoxia, a state of reduced oxygen availability, is a potent stimulus for the activation of various cellular responses aimed at restoring tissue oxygenation [22]. Central to this adaptive process are the HIFs, a family of transcription factors that orchestrate the expression of genes involved in angiogenesis, metabolic reprogramming, and various other cellular processes. The HIF complex comprises an oxygen-sensitive α-subunit (HIF-1α, HIF-2α, or HIF-3α) and a constitutively expressed β-subunit (HIF-1β) [23-25].

Under normoxic conditions, the HIF-α subunits are rapidly degraded via the proteasomal pathway, a process mediated by the von Hippel-Lindau (VHL) tumor suppressor protein and prolyl hydroxylase enzymes [26]. However, in hypoxic environments, the hydroxylation of HIF-α subunits is inhibited, leading to their stabilization and subsequent translocation to the nucleus. There, they form transcriptionally active complexes with HIF-1β, binding to hypoxia-responsive elements (HREs) and activating the expression of target genes, such as vascular endothelial growth factor (VEGF) [27-30].

In the context of AMD and RAP, hypoxia and HIF activation play critical roles in driving pathological angiogenesis and disease progression. Several lines of evidence [31-35] support this notion:

- Choroidal perfusion deficits and vascular abnormalities have been documented in AMD patients, indicating the presence of tissue hypoxia in the retinal pigment epithelium (RPE) and outer retina [36].
- Transdifferentiated RPE cells and surgically excised choroidal neovascular membranes from AMD patients exhibit significant VEGF expression, a direct target of HIF-mediated transcription [37].
- Stable HIF-1α and HIF-2α have been detected in the endothelium and macrophages of human choroidal neovascular membranes associated with AMD [38].
- Elevated vitreous levels of VEGF have been observed in patients with RAP compared to control subjects [39].
- Anti-VEGF therapies, such as intravitreal injections of anti-VEGF agents, have demonstrated efficacy in inhibiting neovascularization and improving visual outcomes in both RAP and neovascular AMD [40].

The hypoxic microenvironment in RAP is thought to be exacerbated by the presence of large drusen deposits and Bruch's membrane thickening, which may limit oxygen supply to the outer retina and photoreceptors. Furthermore, RPE detachment, a characteristic feature of RAP, can further increase the hypoxic challenge by increasing the distance between the photoreceptors and the choroidal vasculature, their primary source of oxygen and nutrients [41-43].

Immunohistochemical studies on RAP specimens have revealed the expression of HIF-1α and HIF-2α in the vicinity of VEGF-positive neovascular regions, suggesting a hypoxia-driven mechanism underlying VEGF production and subsequent angiogenesis in this condition. The intricate interplay between hypoxia, HIF activation, and VEGF signaling appears to play a central role in the pathogenesis of AMD and RAP [44]. Understanding these molecular pathways not only sheds light on the etiology of these sight-threatening conditions but also provides potential therapeutic targets for the development of novel treatment strategies targeting angiogenesis and disease progression.

3. Target Gene Regulation by HIF-1α and HIF-2α: Dissecting the Various Functions of HIF-α Isoforms

While hypoxia-inducible factors (HIFs) are best known for their pivotal role in orchestrating cellular responses to oxygen deprivation, the specific functions of individual HIF-α isoforms have been the subject of intense investigation. Despite sharing

similar biochemical properties, such as the ability to heterodimerize with HIF-1β and bind to hypoxia-responsive elements (HREs), HIF-1α and HIF-2α exhibit distinct cellular expression patterns and differential regulation of target gene expression [45, 46].

The HIF-α family comprises three members: HIF-1α, HIF-2α (also known as EPAS1, MOP2, or HLF), and HIF-3α. While all three isoforms share a high degree of protein conservation, a common domain structure, and hypoxia-dependent regulatory mechanisms, accumulating evidence suggests that HIF-1α and HIF-2α play non-redundant physiological roles and regulate distinct sets of target genes [47]. One of the most striking observations regarding the differential functions of HIF-α isoforms is their tissue-specific expression patterns. For instance, in the kidney, HIF-1α is predominantly expressed in epithelial cells, while HIF-2α is primarily found in endothelial and interstitial fibroblast cells. This differential expression pattern suggests that these isoforms may regulate distinct physiological processes within the same organ [48].

The functional non-redundancy of HIF-1α and HIF-2α is further underscored by the fact that embryos lacking either isoform are nonviable, indicating that they cannot compensate for each other's absence during development. This observation highlights the unique and essential roles played by each isoform in embryogenesis and fetal development. Studies investigating the transcriptional targets of HIF-α isoforms have revealed intriguing differences in their gene regulation capabilities. While some genes, particularly those involved in glycolytic pathways, appear to be exclusively transactivated by HIF-1α, others are regulated by both HIF-1α and HIF-2α. Interestingly, a subset of genes has been identified that is transactivated solely by HIF-2α, suggesting a more selective role for this isoform in hypoxic gene regulation [49].

One notable example of a gene selectively regulated by HIF-2α is the erythropoietin (EPO) gene, which plays a crucial role in erythropoiesis. Although HIF-1 was initially identified through affinity purification with the EPO hypoxia-responsive element (HRE), subsequent studies have firmly established HIF-2α as the physiological regulator of EPO production. This finding is further supported by the association between gain-of-function mutations in HIF-2α and familial erythrocytosis, a condition characterized by excessive red blood cell production. The mechanisms underlying the differential target gene regulation by HIF-α isoforms remain an active area of investigation [50-54]. While the sequences of the HREs themselves do not appear to dictate isoform specificity, several potential explanations have been proposed:

3.1. Tissue-specific expression patterns

The distinct cellular and tissue distribution of HIF-1α and HIF-2α may influence their accessibility to specific target gene promoters, thereby shaping their transcriptional regulation profiles [55].

3.2. Cooperative interactions

HIF-α isoforms may exhibit preferential cooperation with specific transcription factors, coactivators, or corepressors, modulating their ability to regulate certain target genes [56].

3.3. Epigenetic regulation

Epigenetic mechanisms, such as histone modifications and DNA methylation patterns, could differentially influence the binding and activity of HIF-1α and HIF-2α at target gene promoters [57].

3.4. Protein-protein interactions

The unique interactomes of HIF-1α and HIF-2α, including their associations with distinct protein partners, may contribute to their functional specificity. Unraveling the intricate mechanisms governing the differential target gene regulation by HIF-α isoforms has significant implications for our understanding of tissue homeostasis, disease pathogenesis, and the development of targeted therapeutic interventions [58]. By elucidating the specific roles of HIF-1α and HIF-2α in various physiological and pathological contexts, researchers can gain insights into the complex hypoxic signaling networks and leverage this knowledge to modulate specific cellular responses in a more precise and effective manner.

4. Dominant Role of Hypoxia-Inducible Factors (HIFs) in Hypoxic Signaling and Cellular Responses

Hypoxia, or the deprivation of adequate oxygen supply, is a ubiquitous stress condition that cells and tissues encounter in various physiological and pathological contexts. To adapt to this challenging environment, cells have evolved sophisticated signaling pathways that orchestrate a coordinated transcriptional response, enabling them to maintain homeostasis and survival. At the forefront of this intricate hypoxic response lie the hypoxia-inducible factors (HIFs), a family of transcriptional regulators that play a dominant role in mediating cellular adaptations to oxygen deprivation [59]. The HIF family consists of three main members: HIF-1, HIF-2, and HIF-3, each composed of an oxygen-sensitive α-subunit (HIF-1α, HIF-2α, or HIF-3α) and a constitutively expressed β-subunit (HIF-1β). Under normoxic conditions, the HIF-α subunits are rapidly degraded via the proteasomal pathway,

a process mediated by the von Hippel-Lindau (VHL) tumor suppressor protein and prolyl hydroxylase enzymes. However, in hypoxic environments, the hydroxylation of HIF-α subunits is inhibited, leading to their stabilization and subsequent translocation to the nucleus [60].

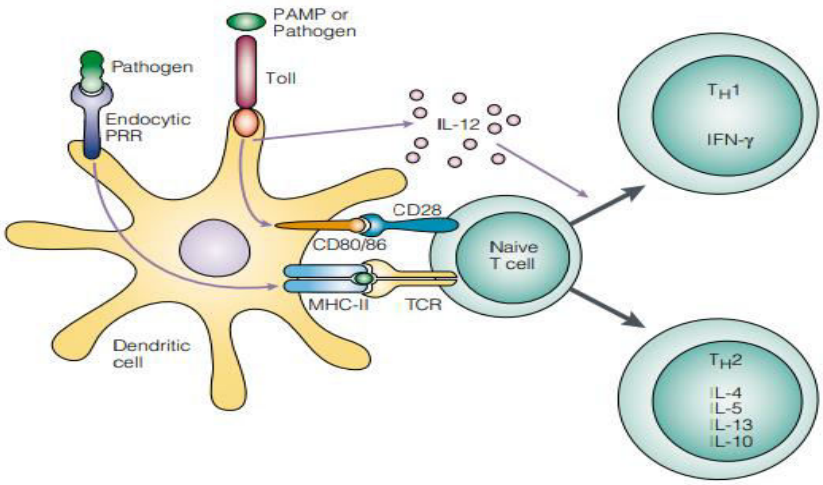
Once in the nucleus, the stabilized HIF-α subunits form transcriptionally active complexes with HIF-1β, binding to hypoxia-responsive elements (HREs) in the promoter regions of target genes. This binding initiates a remarkable transcriptional program that coordinates a wide array of cellular responses aimed at mitigating the effects of oxygen deprivation and promoting survival. One of the most well-characterized functions of HIFs is their ability to regulate angiogenesis, the process of forming new blood vessels [61]. By inducing the expression of potent angiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin-2 (ANGPT2), HIFs play a crucial role in promoting neovascularization, thereby facilitating oxygen and nutrient delivery to hypoxic tissues.

Table 1 Summary of immune factors, their responses, and their role in cancer metastasis

Pathway/Factor	Role in Immune Response	Role in Hypoxic Response	Role in Cancer Metastasis
Toll-Like Receptors (TLRs)	- Recognize microbial patterns (PAMPs) - Initiate innate and adaptive immune responses - Shape T helper cell polarization (Th1/Th2)	- Indirect role through regulation of inflammatory responses	- Potential role in tumor immune evasion and inflammation-driven metastasis
Hypoxia-Inducible Factor 1α (HIF-1α)	- Indirect role in regulating inflammatory responses	- Central regulator of hypoxic gene expression- Induces angiogenesis (VEGF), glycolytic switch, cell survival/proliferation	- Promotes EMT, angiogenesis, metabolic reprogramming- Modulates tumor microenvironment- Contributes to cancer stem cell maintenance
Hypoxia-Inducible Factor 2α (HIF-2α)	- Indirect role in regulating inflammatory responses	- Regulates erythropoiesis (EPO), angiogenesis- Distinct target gene specificity from HIF-1α	- Promotes EMT, angiogenesis, metabolic reprogramming- Contributes to cancer stem cell maintenance
TGF-β Pathway	- Regulates immune cell differentiation and function	- Induced by hypoxia/HIFs- Mediates EMT	- Potent inducer of EMT- Facilitates metastasis through EMT and immunosuppression
Notch Pathway	- Regulates T cell development and function	- Induced by hypoxia/HIFs- Mediates EMT	- Promotes EMT, cancer stem cell maintenance- Contributes to therapy resistance

In addition to angiogenesis, HIFs orchestrate a diverse range of cellular processes in response to hypoxia, including metabolic reprogramming, cell proliferation, and survival. For instance, HIF-1α upregulates the expression of glycolytic enzymes, enabling cells to shift their energy production from oxidative phosphorylation to the more oxygen-independent glycolytic pathway, a phenomenon known as the Warburg effect. This metabolic adaptation allows cells to maintain energy production under hypoxic conditions, a strategy commonly employed by rapidly proliferating cells, such as cancer cells. Furthermore, HIFs play a pivotal role in regulating cell cycle progression and apoptosis, two critical processes that determine cellular fate under hypoxic stress. By modulating the expression of cell cycle regulators and pro-apoptotic or anti-apoptotic factors, HIFs can either promote cell survival or induce programmed cell death, depending on the severity and duration of the hypoxic insult. One of the most intriguing and clinically relevant functions of HIFs is their involvement in cancer progression and metastasis. In the hypoxic tumor microenvironment, HIFs are frequently stabilized and contribute to various aspects of tumor biology, including angiogenesis, metabolic reprogramming, and epithelial-mesenchymal transition (EMT). The latter process, mediated by HIF-induced expression of transcriptional regulators such as TWIST and SNAIL, promotes the acquisition of a more invasive and migratory phenotype in cancer cells, facilitating metastasis to distant sites. Importantly, the roles of HIFs extend beyond hypoxic signaling and encompass a diverse array of physiological and pathological processes [62]. For instance, HIF-2α has been identified as the primary regulator of erythropoietin (EPO) production, a critical factor in erythropoiesis and oxygen delivery. Additionally, HIFs have been implicated in various pathologies, including ischemic disorders, pulmonary hypertension, and inflammatory diseases, highlighting their broader significance in human health and disease. Hypoxia-inducible factors (HIFs) play a dominant role in orchestrating cellular responses to oxygen deprivation. By regulating the expression of a vast array of target genes, HIFs coordinate intricate transcriptional programs that govern processes such as angiogenesis, metabolic adaptation, cell survival, and metastasis [63]. Unraveling the intricate mechanisms underlying HIF-mediated signaling pathways has profound implications for our understanding of disease pathogenesis and the development of novel therapeutic interventions targeting hypoxia-related disorders

Cancer metastasis, the spread of malignant cells from the primary tumor to distant sites, is a complex and multistep process that accounts for the majority of cancer-related deaths. One of the key drivers of metastasis is the hypoxic tumor microenvironment, which arises due to the rapid proliferation of cancer cells and the inadequate supply of oxygen and nutrients. In this hostile milieu, hypoxia-inducible factors (HIFs) play a pivotal role in mediating cellular adaptations and promoting metastatic dissemination [64]. HIFs, as previously discussed, are transcriptional regulators that orchestrate a vast array of cellular responses to oxygen deprivation. In the context of cancer metastasis, HIFs exert their influence through various mechanisms, including the modulation of epithelial-mesenchymal transition (EMT), a critical process that endows cancer cells with increased motility, invasiveness, and



resistance to apoptosis.

Figure 1. TLRs detect PAMPs, triggering APCs to increase surface molecules and produce cytokines, guiding adaptive immunity. TLRs induce T cell activation, leading to TH1 cell development via IL-12. Their role in TH2 responses remains unclear.

The EMT program is characterized by the loss of epithelial characteristics, such as cell-cell adhesion and polarity, and the acquisition of a mesenchymal phenotype, which includes enhanced migratory and invasive capabilities. This transition is governed by a complex interplay of transcriptional regulators, including SNAIL, SLUG, TWIST, and ZEB families, which are known to suppress the expression of epithelial markers, such as E-cadherin, and induce the expression of mesenchymal markers, like vimentin and N-cadherin. HIFs have been shown to directly and indirectly modulate the expression and activity of these EMT-associated transcription factors. For instance, the promoter region of the TWIST1 gene contains hypoxia-responsive elements (HREs), allowing for direct transcriptional activation by HIFs under hypoxic conditions. Additionally, HIFs can induce EMT through the activation of signaling pathways that converge on EMT regulators, such as the TGF-β and Notch pathways. The TGF-β pathway is a potent inducer of EMT and is closely linked to hypoxia signaling. Under hypoxic conditions, HIF-1α stabilization can lead to the upregulation of TGF-β1, which in turn activates the SMAD transcriptional complex. This complex can then directly or indirectly enhance the expression of EMT-associated transcription factors, such as SNAIL and TWIST, thereby promoting the transition towards a mesenchymal phenotype [65-67]. Similarly, the Notch signaling pathway, which has been implicated in cancer stem cell maintenance and therapy resistance, is also known to interact with hypoxia signaling. Hypoxia can induce the expression of Notch ligands and receptors, leading to the activation of the Notch pathway and subsequent upregulation of EMT-associated transcription factors, such as SNAIL and SLUG. Beyond EMT, HIFs contribute to metastasis through various other mechanisms, including the regulation of angiogenesis, metabolic reprogramming, and the modulation of cell survival and proliferation pathways. By inducing the expression of pro-angiogenic factors like VEGF and ANGPT2, HIFs promote the formation of new blood vessels, facilitating the escape of cancer cells from the primary tumor and their dissemination to distant sites. Furthermore, the metabolic adaptations orchestrated by HIFs, such as the Warburg effect and the upregulation of glycolytic enzymes, provide cancer cells with a metabolic advantage, enabling them to thrive in the nutrient-deprived and hypoxic microenvironment encountered during metastasis. Interestingly, recent evidence suggests that HIFs may play a role in the formation and maintenance of cancer stem cells (CSCs), a subpopulation of cells within tumors that exhibit stem cell-like properties, including self-renewal, differentiation potential, and enhanced resistance to therapy. CSCs are thought to contribute significantly to metastasis and disease recurrence, making them an attractive therapeutic target. Moreover, HIFs have been implicated in the regulation of various signaling pathways involved in cell survival and proliferation, such as the PI3K/AKT and MAPK pathways [68]. By modulating these pathways, HIFs can promote the survival and proliferation of cancer cells, further enhancing their metastatic potential.

In addition to their direct effects on cancer cells, HIFs can also influence the tumor microenvironment in ways that facilitate metastasis. For instance, HIF-mediated regulation of extracellular matrix remodeling enzymes, such as matrix metalloproteinases (MMPs), can promote the degradation of the extracellular matrix, enabling cancer cell invasion and dissemination [69]. Furthermore, HIFs can modulate the behavior of other cell types within the tumor microenvironment, such as cancer-associated fibroblasts (CAFs) and immune cells, creating a more permissive environment for metastasis. For example, HIF-mediated alterations in the secretion of cytokines and chemokines can lead to the recruitment of immunosuppressive cells, facilitating immune evasion and tumor progression. The multifaceted roles of HIFs in metastasis underscore their potential as therapeutic targets in cancer treatment. Several strategies have been explored to inhibit HIF activity, including the use of small molecule inhibitors targeting HIF-α subunits or their upstream regulators, as well as the development of HIF-targeted gene therapy approaches [70, 71]. However, it is important to note that the effects of HIF inhibition may be context-dependent, as HIFs also play crucial roles in normal physiological processes, such as erythropoiesis and vascular homeostasis. Therefore, a comprehensive understanding of the tissue-specific and cell-type-specific functions of HIFs is essential for the development of safe and effective HIF-targeted therapies. The role of hypoxia-inducible factors in the hypoxic response and metastasis is multifaceted and complex. By orchestrating cellular adaptations, such as EMT, angiogenesis, metabolic reprogramming, and the modulation of cell survival and proliferation pathways, HIFs endow cancer cells with enhanced metastatic potential [72]. Unraveling the intricate mechanisms by which HIFs contribute to metastasis not only deepens our understanding of this lethal process but also paves the way for the development of novel therapeutic strategies targeting the hypoxic tumor microenvironment and its key mediators

5. Conclusion

The complex interplay between immune responses, hypoxia signaling, and cellular dynamics highlights the complexity of physiological processes and disease pathogenesis. Toll-like receptors (TLRs) play a pivotal role in innate immunity by recognizing microbial products and initiating adaptive immune responses through dendritic cell activation. Understanding their function in bridging innate and adaptive immunity holds therapeutic potential for autoimmune disorders and infectious diseases. The hypoxia-induced stabilization of hypoxia-inducible factors (HIFs) elucidates the molecular mechanisms underlying angiogenesis and disease progression in conditions such as retinal angiomatous proliferation (RAP) and neovascular age-related macular degeneration (AMD). The differential roles of HIF-α isoforms, HIF-1α and HIF-2α, in regulating hypoxic transcription underscore their distinct physiological functions and potential therapeutic implications. Moreover, the dominance of HIFs in orchestrating cellular responses to hypoxia, including angiogenesis, metabolic reprogramming, and epithelial-mesenchymal transition (EMT), highlights their central role in cancer metastasis and progression. By modulating these processes, HIFs endow cancer cells with enhanced metastatic potential, making them attractive therapeutic targets.

References

[1] Hashimoto C, Hudson KL, Anderson KV. The Toll gene of Drosophila, required for dorsal-ventral embryonic polarity, appears to encode a transmembrane protein. Cell. 1988 Jan 29;52(2):269-79.

[2] Rock FL, Hardiman G, Timans JC, Kastelein RA, Bazan JF. A family of human receptors structurally related to Drosophila Toll. Proceedings of the National Academy of Sciences. 1998 Jan 20;95(2):588-93.

[3] Kobe B, Deisenhofer J. Proteins with leucine-rich repeats. Current opinion in structural biology. 1995 Jun 1;5(3):409-16.

[4] Aravind L, Dixit VM, Koonin EV. Apoptotic molecular machinery: vastly increased complexity in vertebrates revealed by genome comparisons. Science. 2001 Feb 16;291(5507):1279-84.

[5] Muzio M, Ni J, Feng P, Dixit VM. IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling. Science. 1997 Nov 28;278(5343):1612-5.

[6] Burns K, Martinon F, Esslinger C, Pahl H, Schneider P, Bodmer JL, Di Marco F, French L, Tschopp J. MyD88, an adapter protein involved in interleukin-1 signaling. Journal of biological chemistry. 1998 May 15;273(20):12203-9.

[7] Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998 Mar 19;392(6673):245-52

[8] Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nature immunology. 2001 Aug;2(8):675-80

[9] Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. Nature immunology. 2001 Oct 1;2(10):947-50.

[10] Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, Kriegsheim AV, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH. Targeting of HIF-α to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001 Apr 20;292(5516):468-72.

[11] Grimm C, Wenzel A, Groszer M, Mayser H, Seeliger M, Samardzija M, Bauer C, Gassmann M, Remé CE. HIF-1-induced erythropoietin in the hypoxic retina protects against light-induced retinal degeneration. Nature medicine. 2002 Jul 1;8(7):718-24.

[12] Caprara C, Grimm C. From oxygen to erythropoietin: relevance of hypoxia for retinal development, health, and disease. Progress in retinal and eye research. 2012 Jan 1;31(1):89-119.

[13] Cash TP, Pan Y, Simon MC. Reactive oxygen species and cellular oxygen sensing. Free Radical Biology and Medicine. 2007 Nov 1;43(9):1219-25.

[14] Dehne N, Brüne B. HIF-1 in the inflammatory microenvironment. Experimental cell research. 2009 Jul 1;315(11):1791-7.

[15] Joyal JS, Sun Y, Gantner ML, Shao Z, Evans LP, Saba N, Fredrick T, Burnim S, Kim JS, Patel G, Juan AM. Retinal lipid and glucose metabolism dictates angiogenesis through the lipid sensor Ffar1. Nature medicine. 2016 Apr;22(4):439-45.

[16] Arjamaa O, Nikinmaa M, Salminen A, Kaarniranta K. Regulatory role of HIF-1α in the pathogenesis of age-related macular degeneration (AMD). Ageing research reviews. 2009 Oct 1;8(4):349-58.

[17] Kent DL. Age-related macular degeneration: beyond anti-angiogenesis. Molecular vision. 2014;20:46.

[18] Chung HS, Harrisa A, Ciulla TA, Kagemann L. Progress in measurement of ocular blood flow and relevance to our understanding of glaucoma and age-related macular degeneration. Progress in retinal and eye research. 1999 Apr 1;18(5):669-87.

[19] Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. Investigative ophthalmology & visual science. 1996 Aug 1;37(9):1929-34.

[20] Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. Investigative ophthalmology & visual science. 1996 Apr 1;37(5):855-68.

[21] Inoue Y, Yanagi Y, Matsuura K, Takahashi H, Tamaki Y, Araie M. Expression of hypoxia-inducible factor 1α and 2α in choroidal neovascular membranes associated with age-related macular degeneration. British Journal of Ophthalmology. 2007 Dec 1;91(12):1720-1.

[22] Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews. 2014(8).

[23] Engelbert M, Zweifel SA, Freund KB. "Treat and extend" dosing of intravitreal antivascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. Retina. 2009 Nov 1;29(10):1424-31.

[24] Atmani K, Voigt M, Le Tien V, Querques G, Coscas G, Soubrane G, Souied EH. Ranibizumab for retinal angiomatous proliferation in age-related macular degeneration. Eye. 2010 Jul;24(7):1193-8.

[25] Hartnett ME, Weiter JJ, Staurenghi G, Elsner AE. Deep retinal vascular anomalous complexes in advanced age-related macular degeneration. Ophthalmology. 1996 Dec 1;103(12):2042-53.

[26] Kim JH, Kim JR, Kang SW, Kim SJ, Ha HS. Thinner choroid and greater drusen extent in retinal angiomatous proliferation than in typical exudative age-related macular degeneration. American journal of ophthalmology. 2013 Apr 1;155(4):743-9.

[27] Shimada H, Kawamura A, Mori R, Yuzawa M. Clinicopathological findings of retinal angiomatous proliferation. Graefe's Archive for Clinical and Experimental Ophthalmology. 2007 Feb;245:295-300.

[28] Vavilala DT, O'Bryhim BE, Ponnaluri VC, White RS, Radel J, Symons RA, Mukherji M. Honokiol inhibits pathological retinal neovascularization in oxygen-induced retinopathy mouse model. Biochemical and Biophysical Research Communications. 2013 Sep 6;438(4):697-702.

[29] Huang LE, Bunn HF. Hypoxia-inducible factor and its biomedical relevance. Journal of Biological Chemistry. 2003 May 30;278(22):19575-8.

[30] Rosenberger C, Mandriota S, Ju JS, Wiesener MS, Ho JH, Frei U, Ratcliffe PJ, Maxwell PH, Bachmann S, Eckardt KU. Expression of hypoxia-inducible factor-1α and-2α in hypoxic and ischemic rat kidneys. Journal of the American Society of Nephrology. 2002 Jul 1;13(7):1721-32.

[31] Sowter HM, Raval R, Moore J, Ratcliffe PJ, Harris AL. Predominant role of hypoxia-inducible transcription factor (Hif)-1α versus Hif-2α in regulation of the transcriptional response to hypoxia. Cancer research. 2003 Oct 1;63(19):6130-4.

[32] Raval RR, Lau KW, Tran MG, Sowter HM, Mandriota SJ, Li JL, Pugh CW, Maxwell PH, Harris AL, Ratcliffe PJ. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. Molecular and cellular biology. 2005 Jul 1.

[33] Hu CJ, Wang LY, Chodosh LA, Keith B, Simon MC. Differential roles of hypoxia-inducible factor 1α (HIF-1α) and HIF-2α in hypoxic gene regulation. Molecular and cellular biology. 2003 Dec 1;23(24):9361-74.

[34] Aprelikova O, Wood M, Tackett S, Chandramouli GV, Barrett JC. Role of ETS transcription factors in the hypoxia-inducible factor-2 target gene selection. Cancer research. 2006 Jun 1;66(11):5641-7.

[35] Elvert G, Kappel A, Heidenreich R, Englmeier U, Lanz S, Acker T, Rauter M, Plate K, Sieweke M, Breier G, Flamme I. Cooperative interaction of hypoxia-inducible factor-2α (HIF-2α) and Ets-1 in the transcriptional activation of vascular endothelial growth factor receptor-2 (Flk-1). Journal of Biological Chemistry. 2003 Feb 28;278(9):7520-30.

[36] Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1 (*). Journal of biological chemistry. 1995 Jan 20;270(3):1230-7.

[37] Kojima I, Tanaka T, Inagi R, Kato H, Yamashita T, Sakiyama A, Ohneda O, Takeda N, Sata M, Miyata T, Fujita T. Protective role of hypoxia-inducible factor-2α against ischemic damage and oxidative stress in the kidney. Journal of the American Society of Nephrology. 2007 Apr 1;18(4):1218-26.

[38] Gruber M, Hu CJ, Johnson RS, Brown EJ, Keith B, Simon MC. Acute postnatal ablation of Hif-2 α results in anemia. Proceedings of the National Academy of Sciences. 2007 Feb 13;104(7):2301-6.

[39] Percy MJ, Furlow PW, Lucas GS, Li X, Lappin TR, McMullin MF, Lee FS. A gain-of-function mutation in the HIF2A gene in familial erythrocytosis. New England Journal of Medicine. 2008 Jan 10;358(2):162-8.

[40] Wenger RH, Stiehl DP, Camenisch G. Integration of oxygen signaling at the consensus HRE. Science's STKE. 2005 Oct 18;2005(306):re12-.

[41] Foster JG, Wong SC, Sharp TV. The hypoxic tumor microenvironment: driving the tumorigenesis of non-small-cell lung cancer. Future Oncology. 2014 Dec;10(16):2659-74.

[42] Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. Proceedings of the National Academy of Sciences. 1993 May 1;90(9):4304-8.

[43] Eales KL, Hollinshead KE, Tennant DA. Hypoxia and metabolic adaptation of cancer cells. Oncogenesis. 2016 Jan;5(1):e190-.

[44] Dabral S, Muecke C, Valasarajan C, Schmoranzer M, Wietelmann A, Semenza GL, Meister M, Muley T, Seeger-Nukpezah T, Samakovlis C, Weissmann N. A RASSF1A-HIF1α loop drives Warburg effect in cancer and pulmonary hypertension. Nature communications. 2019 May 13;10(1):2130.

[45] Iliopoulos O, Kibel A, Gray S, Kaelin Jr WG. Tumour suppression by the human von Hippel-Lindau gene product. Nature medicine. 1995 Aug 1;1(8):822-6.

[46] Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999 May 20;399(6733):271-5.

[47] Franovic A, Holterman CE, Payette J, Lee S. Human cancers converge at the HIF-2α oncogenic axis. Proceedings of the National Academy of Sciences. 2009 Dec 15;106(50):21306-11.

[48] Sarella PN, Maddali SS, Asogwa PO, Kakarparthy R. Persistent Infection in a Patient with Tibial Non-union. Journal of Clinical and Pharmaceutical Research. 2023 Jul 17:1-3.

[49] Wiesener MS, Jürgensen JS, Rosenberger C, Scholze C, Hörstrup JH, Warnecke C, Mandriota S, Bechmann I, Frei UA, Pugh CW, Ratcliffe PJ. Widespread, hypoxia-inducible expression of HIF-2α in distinct cell populations of different organs. The FASEB Journal. 2003 Feb;17(2):271-3.

[50] Eales KL, Hollinshead KE, Tennant DA. Hypoxia and metabolic adaptation of cancer cells. Oncogenesis. 2016 Jan;5(1):e190-.

[51] Xiao D, He J. Epithelial mesenchymal transition and lung cancer. Journal of thoracic disease. 2010 Sep;2(3):154.

[52] Gulei D, Magdo L, Jurj A, Raduly L, Cojocneanu-Petric R, Moldovan A, Moldovan C, Florea A, Pasca S, Pop LA, Moisoiu V. The silent healer: miR-205-5p up-regulation inhibits epithelial to mesenchymal transition in colon cancer cells by indirectly up-regulating E-cadherin expression. Cell Death & Disease. 2018 Jan 19;9(2):66.

[53] Wei L, Sun JJ, Cui YC, Jiang SL, Wang XW, Lv LY, Xie L, Song XR. Twist may be associated with invasion and metastasis of hypoxic NSCLC cells. Tumor Biology. 2016 Jul;37:9979-87.

[54] He P, Qiu K, Jia Y. Modeling of mesenchymal hybrid epithelial state and phenotypic transitions in EMT and MET processes of cancer cells. Scientific Reports. 2018 Sep 25;8(1):14323.

[55] Jolly MK, Boareto M, Huang B, Jia D, Lu M, Ben-Jacob E, Onuchic JN, Levine H. Implications of the hybrid epithelial/mesenchymal phenotype in metastasis. Frontiers in oncology. 2015 Jul 20;5:155.

[56] Lecharpentier A, Vielh P, Perez-Moreno P, Planchard D, Soria JC, Farace F. Detection of circulating tumour cells with a hybrid (epithelial/mesenchymal) phenotype in patients with metastatic non-small cell lung cancer. British journal of cancer. 2011 Oct;105(9):1338-41.

[57] Grigore AD, Jolly MK, Jia D, Farach-Carson MC, Levine H. Tumor budding: the name is EMT. Partial EMT. Journal of clinical medicine. 2016 Apr 29;5(5):51.

[58] Garg M. Epithelial, mesenchymal and hybrid epithelial/mesenchymal phenotypes and their clinical relevance in cancer metastasis. Expert Reviews in Molecular Medicine. 2017 Jan;19:e3.

[59] Schliekelman MJ, Taguchi A, Zhu J, Dai X, Rodriguez J, Celiktas M, Zhang Q, Chin A, Wong CH, Wang H, McFerrin L. Molecular portraits of epithelial, mesenchymal, and hybrid States in lung adenocarcinoma and their relevance to survival. Cancer research. 2015 May 1;75(9):1789-800.

[60] Zhang J, Tian XJ, Xing J. Signal transduction pathways of EMT induced by TGF-β, SHH, and WNT and their crosstalks. Journal of clinical medicine. 2016 Mar 28;5(4):41.

[61] Lakshmi SS, Sarella PN, Adarsh K, Padmini PL, Kumar MV. Concurrent Diagnosis of Renal Calculi, Uterine Fibroids and Ovarian Cysts: A Complex Case Study. Journal of Clinical and Pharmaceutical Research. 2023 Oct 24:22-7..

[62] Moreno Roig E, Groot AJ, Yaromina A, Hendrickx TC, Barbeau LM, Giuranno L, Dams G, Ient J, Olivo Pimentel V, van Gisbergen MW, Dubois LJ. HIF-1α and HIF-2α differently regulate the radiation sensitivity of NSCLC cells. Cells. 2019 Jan 12;8(1):45.

[63] Gort EH, Van Haaften G, Verlaan I, Groot AJ, Plasterk RH, Shvarts A, Suijkerbuijk KP, van Laar T, van der Wall E, Raman V, Van Diest PJ. The TWIST1 oncogene is a direct target of hypoxia-inducible factor-2α. Oncogene. 2008 Mar;27(11):1501-10.

[64] Asogwa PO, Sarella PN. Observational Studies of Prescription Pattern and Use of Antibiotics in Selected Rural Areas. Int J Pharm Sci and Medicine. 2023;8:21-30.

[65] Vincent T, Neve EP, Johnson JR, Kukalev A, Rojo F, Albanell J, Pietras K, Virtanen I, Philipson L, Leopold PL, Crystal RG. A SNAIL1–SMAD3/4 transcriptional repressor complex promotes TGF-β mediated epithelial–mesenchymal transition. Nature cell biology. 2009 Aug;11(8):943-50.

[66] Kang Y, Chen CR, Massagué J. A self-enabling TGFβ response coupled to stress signaling: Smad engages stress response factor ATF3 for Id1 repression in epithelial cells. Molecular cell. 2003 Apr 1;11(4):915-26.

[67] Sarella PN, Dadishetti JP, Asogwa PO, Kakarparthy R. Pharmacological and Non-pharmacological Management of Bipolar Disorder with Comorbid Huntington's Disease: A Case Report. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:5-8..

[68] Sahlgren C, Gustafsson MV, Jin S, Poellinger L, Lendahl U. Notch signaling mediates hypoxia-induced tumor cell migration and invasion. Proceedings of the National Academy of Sciences. 2008 Apr 29;105(17):6392-7.

[69] Donnem T, Andersen S, Al-Shibli K, Al-Saad S, Busund LT, Bremnes RM. Prognostic impact of Notch ligands and receptors in nonsmall cell lung cancer: coexpression of Notch-1 and vascular endothelial growth factor-A predicts poor survival. Cancer. 2010 Dec 15;116(24):5676-85.

[70] Li Y, Burns JA, Cheney CA, Zhang N, Vitelli S, Wang F, Bett A, Chastain M, Audoly LP, Zhang ZQ. Distinct expression profiles of Notch-1 protein in human solid tumors: Implications for development of targeted therapeutic monoclonal antibodies. Biologics: Targets and Therapy. 2010 Jun 24:163-71.

[71] Yuan X, Wu H, Xu H, Han N, Chu Q, Yu S, Chen Y, Wu K. Meta-analysis reveals the correlation of Notch signaling with non-small cell lung cancer progression and prognosis. Scientific reports. 2015 May 21;5(1):10338.

[72] Hassan KA, Wang L, Korkaya H, Chen G, Maillard I, Beer DG, Kalemkerian GP, Wicha MS. Notch pathway activity identifies cells with cancer stem cell–like properties and correlates with worse survival in lung adenocarcinoma. Clinical cancer research. 2013 Apr 15;19(8):1972-80.

Author's short biography

Quazia Ifaq

As a pharmacist-turned-author, Im interested in pharmaceutical research, blending scientific accuracy with recent advances

Imran Rashid

With a background in pharmacy research, my research works seamlessly integrates cutting-edge discoveries and ethical dilemmas, offering readers a glimpse into the dynamic world of healthcare innovation

Rajip Nepal

Drawing from my experience in the pharmacy department, my research aims to explore the human side of scientific exploration, capturing the passion, perseverance, and ethical challenges inherent in groundbreaking research

Abhishek Kumar

Through my work as a researcher rooted in the pharmacy realm, I aim to bridge the gap between scientific inquiry and societal impact, crafting narratives that inspire dialogue and introspection on the role of pharmaceutical advancements in shaping our collective future

Vishal Kajla

From the lab bench to the pages of research, my journey as a pharmacist-author intertwines the complexities of drug development inviting readers to ponder the profound implications of scientific progress on humanity