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Review article

Hypoxia Inducible Factor in signalling pathways of cancer: A commander of carcinogenesis

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ABSTRACT:

In hypoxic condition, cell undergoes variety of biological responses. These include activation of various regulatory pathways through hypoxia inducible factors. Hypoxia inducible factor is the essential mediator for cellular oxygen – signaling pathway that enhances oxygen delivery and adaptation to oxygen deprived condition through regulation of genes. The adaptation to cellular hypoxia and hypoxic microenvironment result in cell proliferation, migration and angiogenesis through various pathways. Cancer cell adapted this function result in survival of cells under any circumstances. Accumulation of HIF can induces variety of growth factors and play as common mediator to various pathways by maintaining relationship in voyage of tumorogenesis to distinct metastasis. There is great need of the hour is to understand the basic molecular pathways of carcinogenesis. Knowing pathways will facilitates research gateway for targeted therapeutics. This review highlights on various pathways HIF as it commands on various molecules and genes in pathways of carcinogenesis and it has a great potential in predicting malignant transformation in potentially malignant disorders. For this reason, HIF has surplus potential in prevention and treatment of early phases of carcinogenesis.

Key Words: Hypoxia, Hypoxia inducible factor, Cancer regulatory pathway, HIF pathway, Carcinogenesis.

INTRODUCTION:

Cancer has still great burden on world and leading cause of death. Many factors are responsible for death including behavioral and dietary risk. Interaction between genetic factor and stimuli result in to cell transformation from precancer to cancer. In carcinogenesis cells undergo hypoxic condition due to increased oxygen demand.[1] The get adapted to according to duration of hypoxia.[2] In acute hypoxia cells experience reoxygenation, with lacking of functional p53 is more susceptible to genetic mutation and tumorogenesis.[3]

In cyclic hypoxia, the reoxygenation in tumor tissue is the result of dysfunctional vascularity and diverse blood supply.[4] Undoubtedly hypoxia inducible factor (HIF) in the hypoxic regions in tumors directly affect the cells through the entire process of tumorogenesis, progression, and metastasis. To regulate stem cell biology, HIFs

attempt an important role in harmonizing cellular metabolism in stem cells and niches and provide a suitable environment to stem cells to hold undifferentiated status and multilineage differentiation potential of cells.[5] This review emphasis on multitasking role of hypoxia inducible factor in various steps involved in cancer development and distant metastasis along with pathways involved in these process and can be utilized securely in cancer treatment therapeutic.

Tumor and Hypoxia:

All cells demands constant oxygen to produce ATPs for tissue development and their functions. In tumor tissue, due to increased cellularity and sustainability, O_2 demand is maintained by the vascular system. The imbalance between oxygen consumption and oxygen delivery develops cellular hypoxia in the microenvironment.[6]

Vascular dysfunction, deteriorating genome, structural abnormality of a vessel, and disturbed microcirculation (Figure 1) results in to hypoxia and cell responses to it by activating various genes along with expression of various growth factors which are mainly induced by HIF. (Figure 2).This is responsible for adaptive mechanisms and regulates many functions like cell motility, metabolism, survival, the integrity of the basement membrane, angiogenesis, and many other functions.[7] HIF mediated adaptation said to be associated with malignant transformation and early carcinogenesis.[6]

Hypoxia in malignant transformation:

Hypoxia relatively less studied in oral premalignancy. Hypoxia related markers or proteins are strongly over expressed in stages of oral squamous cell carcinoma. It is observed that the predictability of malignant transformation was increased when few proteins were observed together like HIF-1α, Glut-1[8] and CA9.[9] Even Galetin-3 along HIF-1α strongly predict malignant transformation in epithelial dysplasia.[10] Neoangiogenesis in early dysplasia exhibits increased nutritional demand which is fulfilled by expressed HIF-1α resulting to increased vessels and microvessel density which facilitate malignant transformation.[11]

These transformations when studied in sequential basis from normal epithelium to dysplastic epithelium and regional lymph node metastasis shows significant increase in expression of HIF-1α[12] where epithelium adjacent to dysplasia shows negative expression this justifies its prominent role in oral carcinogenesis, invasion and metastasis.[13]

HIF Roles in Regulatory Pathways:

Von Hippel-Lindau Pathway:

The genetic mutation in the VHL gene has the potential for malignant transformation.[14] VHL senses altered oxygen level in the pathway and regulates and stabilizes HIF-1α through protein VHL (pVHL) (Figure 2). In hypoxic conditions, it did not bind with HIF-1α and activate the number of genes like VEGF, PDGF-B, erythropoietin which contribute to various cancer.[15,16,17] In hypoxic condition, pVHL along with HIF2α directly or indirectly affect the interaction of related genes and proteins like B-Myb, and CFB gene which involves in regulation of cell cycle and differentiation, angiogenesis, tumor invasion, migration, respectively.[18,19,20]

The experiment confirmed the physical interaction between pVHL and HIFα that targeted by pVHL as a part of the ubiquitin ligase complex by the interaction between the β-domain of pVHL and HIF-α ODDD (Figure 2).[21] These targets are regulated by hydroxylation of specific prolyl residues in the regulation of HIF1α.[22]

MDM2 Pathway:

Mouse double minute 2 homolog (MDM2), acts as a negative regulator of the P53 tumor suppressor gene and also known as E3 ubiquitin-protein ligase Mdm2 protein suppressor.[23] To maintain the stability of P53 signaling, MDM2

ligate P53 protein through E3 ubiquitin ligase and ubiquitinated P53 get degraded by proteasome as transferred to the cytoplasm (Figure 2). Under the hypoxic condition, P53 accumulation weakened HIF1α activity, and miR-17-92 (P53 trans represses anti-apoptotic genes) to relieve inhibition of pro-apoptotic genes like BIM. P53 stabilization is enhanced where more Mdm2 is associated with unacetylatedHIF1α.[24] A recent study proved that MDM2 is a major regulator of the pro-angiogenic mechanism involved directly in the control over VEGF transcription through HIF1α.[25]

Heat shock protein pathway:

Hsp properties are to prevent unfold protein to form an insoluble complex, maintain damage cell and participate in signaling transduction pathway of protein which regulate oncogenic factors.[26,27] Hsp90 activity stimulated by heat acclimation stabilizes HIF1α which further initiate collateral circulation.[28]

Increased Hsp90 precipitate phosphorylates and stabilizes HIF1α, independent of oxygen level. Increase HIF1 transcription factors bind to the hypoxic response element (HER) which results in increased growth factors. The relation between HIF and Hsp90 has been demonstrated modulation of Hsp90 and or HIF1α, which shows a profound effect on the severity of the injury or in the process of recovery.[29] Hsp70 and HIF1α are considered a cytoprotective proteins coordinate beneficial effect that provides long-standing protection to recurrent stress effects.[30]

Hypoxia and Angiogenesis:

HIF rapidly increase O2 supply by upregulation of vasodilator enzyme inducible nitric oxide synthase (iNOS) by relaxing vascular smooth muscle for short term and compensate by increasing blood flow and long term hypoxia is by stimulating angiogenesis. It regulated by pro-angiogenic genes including VEGF, angiopoietin-1, angiopoietin-2, Tie 2, Platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and monocyte chemo attractant protein-1 (MCP-1). HIF executes the angiogenic program by increasing endothelial cell proliferation, increased vascular permeability, sprouting, migration, and tube formation.[31] Even in highly vascularized tumors, stabilization of HIFα occurs due to leaky and poor functioning vessels. Other factors like RAS pathway hyperactivation, P53 mutation, and succinate accumulation are also responsible for HIF stabilization.[32] Endothelial cell in response to hypoxia synthesize Ang2 interfere Ang1 to normalize vasculature. Ang1 to promote angiogenesis recruits pericyte to mature vessels.[33]

Invasion and Metastasis:

Clusters or even in cells away from the blood vessels are undergoes hypoxic condition.[34] Therefore HIF1 pathways are expected to activate in a very early phase of tumor progression. Indeed premalignant condition and carcinoma in situ also express HIF1 overexpression, suggesting early HIF pathway activation towards progression and metastasis.[35] HIF1stimulate genetic transcription like protease, which is responsible for the degradation of cathepsin C, MMP2, 9, and 14 and lysyl oxidase (LOX).[36] LOX forms a "premetastatic niche" by mediating bone marrow-derived cells recruited by accumulating at a new site.[37] In cancer cell CXCR4 induced by hypoxia plays a role as cell trafficking.[38] Invadopodia (actin-rich membrane protrusions) are mainly upregulated in hypoxia facilitating the invasion of the tumor cell through extracellular proteolysis.[39] HIF signaling promotes epithelial-mesenchymal transitional transcription factors by a direct or indirect mechanism whish are also responsible for cell adhesion capacity of cells and reliving it to metastatic cascade. [40] Hypoxia induced EMT shows decreased in epithelial-associated gene expression and an increase in mesenchymal-like gene expressions (Figure 3). The protein which

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holds the rigid cytoskeleton and cell to cell adhesion is inhibited by HIF 1α by activating repressor gene, which stimulate flexible cytoskeleton and hence prove its role.[41]

In cancer therapy:

The agent affects HIF protein synthesis and acts as a pathway inhibitor are tyrosin kinase, cyclin dependent kinase, oncogene pathway inhibitor, thioredoxinreductase inhibitor. Recently the agent used as an inhibitor is topotecan which generates double-strand DNA breaks and cytotoxicity. Another agent is cardiac glycosides of which Digoxin is a potent HIF-1 inhibitor. It inhibits HIF-1 translation by mTOR-independent mechanism and exhibits antitumor activity. PX478 is another inhibitor that is in phase I trial of advanced metastatic cancer it shows antitumoral activity in correlation with HIF-1 expression. Translation of HIF-1 protein can be regulated and these pathways are the target for HIF inhibitor. HIF-1 mRNA levels affect protein translation. Aminoflevone (AF) is an agent act as a ligand of the aryl-hydrocarbon receptor (AhR) which affects the expression of HIF-1 mRNA.42[49] EZN- 2968is a RNA modulator that inhibits HIF-1α mRNA expression.43[50] It shows tumor reduction and in the clinical study observed reduced HIF-1α mRNA in post-treatment biopsies.44[51] Inhibition of these pathways indicates that inhibition of HIF- 1α has potential in the treatment of cancer.

CONCLUSION:

Hypoxia in many human cancers plays a critical and decisive role in initiation, progression, and metastasis of malignant cells and appears to be controlled by HIF α factor. In malignancy the molecule that controls and controlled by HIF is large in numbers and growing with new research, to identify target molecule in the pathway of malignancy, but the common binding factor observed to be HIF. The role of HIF molecule is found to be as if supplying oxygen to ignition and spread fire beyond their boundaries. It was even observed that controlling hypoxia controls the havoc. The new approach in the development of pharmacology that initiates or inhibit HIF or its target gene products can provide new dawn in cancer therapeutics.

Figure 1:

In normoxia HIF1α is hydroxylated and recognized further by VHL, ubiquitin ligase and degrade HIF1α through proteosomal pathway. In hypoxic condition, hydroxylation is restricted, resulting in combination of HIF1α and HIF1β association with hypoxic response element (HER) of targeting gene by activating their transcription and modulate cell survival, angiogenesis, invasion and glycolysis.

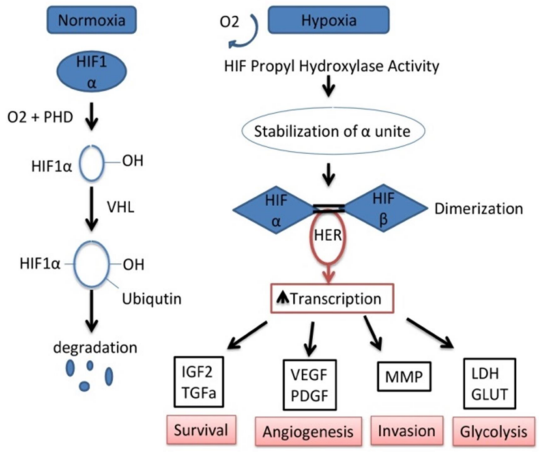


Figure 2:

Figure shows factors responsible for hypoxia causing genetic instability which leads to increased HIF transcription through various pathways. Growth factor activation from clonal mutation till distant growth of tumor. In HSP pathway, HSP binding with HIF1α is inhibited by Inhibitor Geldanamycin (GA), leading to increased HIF1α transcription (which is nullify by inhibitor in normoxia). VHL - In absence of oxygen VHL form hetrodimer leading to increased growth factors in absence of hydroxylation which inhibits proteolysis. MDM2 - The bond between HIF1α and P53 is

inhibited by MDM2 mediated ubiquitination leading to increased HIF protein.

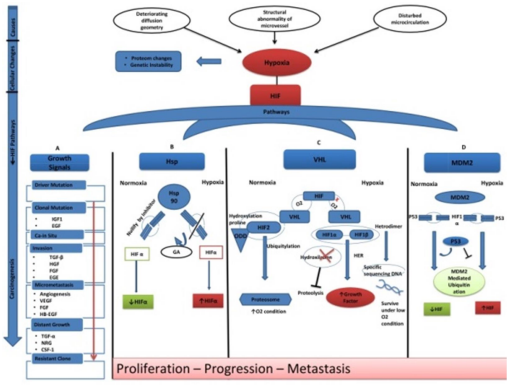
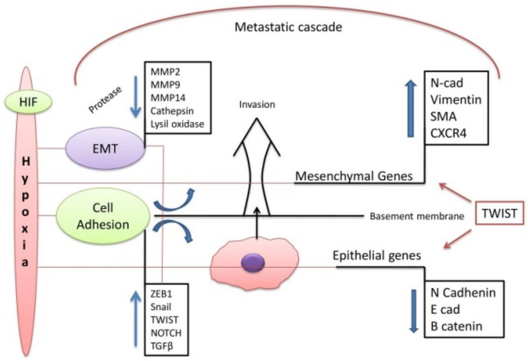


Figure 3:

In metastatic cascade, HIF expression stimulates genetic transcription like protease degrading bunch of proteins. HIF signaling promotes epithelial-mesenchymal transitional transcription factors (by degrading or upgrading) and responsible for cell adhesion molecule, basement membrane and ECM of cells and relieved it to cascade. TWIST causes shift of expression marker from mesenchymal to epithelial marker.



References:

1. Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckland, N.Z.) 2015; 3:83–92. https://doi.org/10.2147/HP.S93413.
2. Luoto KR, Kumareswaran R, Bristow RG. Tumor hypoxia as a driving force in genetic instability. Genome Integr 2013; 4(1):5-20.
3. Pires IM, Bencokova Z, Milani M, Lisa K. Folkes LK, Li Ji-Liang, Mike R. Stratford MR, et al. Effects of acute versus chronic hypoxia on DNA damage responses and genomic instability. Cancer Res. 2010; 70(3):925–935.
4. Kimura H, Braun RD, Ong ET, Hsu R, Secomb TW, Papahadjopoulos D, et al. Fluctuations in red cell flux in tumor microvessels can lead to transient hypoxia and reoxygenation in tumor parenchyma. Cancer Res.1996; 56(23):5522–5528.
5. Huang X, Trinh T, Aljoufi A, Broxmeyer HE. Hypoxia Signaling Pathway in Stem Cell Regulation: Good and Evil. Curr. Stem Cell Rep. 2018; 4(2):149-157.
6. Patel NR, Jain L, Mahajan AR, Hiray PV, Shinde SS, Patel PA. An Immunohistochemical Study of HIF-1 Alpha in Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma.Indian J. Otolaryngol. Head Neck Surg. 2019; 7(4):435–441.
7. Pouysségur J, Dayan F. Mazure NM. Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature 2006; 441(7092):437–443.
8. Wang X-X, Sun H-Y, Yang Q-Z, Guo B, Sai Y, Zhang J. Hypoxia-inducible factor-1α and glucose transporter 1 in the malignant transformation of oral lichen planus. Int J Clin Exp Pathol 2017; 10(8):8369-8376
9. Zhang X, Han S, Han H-Y, Ryu MH, Kim K-Y, Choi E-J, et al. Risk Prediction for Malignant Conversion of Oral Epithelial Dysplasia by Hypoxia Related Protein Expression. Pathology 2013; 45(5):478-83.
10. Radi NA, Balbola GA. Association of galectin-3 and hypoxia-inducible factor-1α with progression of oral squamous cell carcinoma. J Nat Sci Med. 2019; 2:123-9
11. Rzepakowska A, Żurek M, Grzybowski J, et al. Microvascular density and hypoxia-inducible factor in intraepithelial vocal fold lesions. Eur Arch Otorhinolaryngol.2019; 276:1117–1125.

12. Lin P-Y, Yu C-H, Wang J-T, Chen H-H, Cheng S-J, Kuo MY-P, et al. Expression of hypoxia-inducible factor-1α is significantly associated with the progression and prognosis of oral squamous cell carcinomas in Taiwan. J Oral Pathol Med.2008; 37:18–25
13. Costa A, Coradini D, Carrassi A, Erdas R, Sardella A, Daidone Re MG. Levels of Hypoxia-Inducible Factor-1 During Breast Carcinogenesis. Journal of the National Cancer Institute 2001; 93(15):1175–1177.
14. Richard S, Gardie B, Couvé S, Gad S. Von Hippel-Lindau: How a rare disease illuminates cancer biology. Semin. Cancer Biol. 2013; 23(1):26–37.
15. Kaelin WG Jr. Von Hippel-Lindau Disease. Annual Review of Pathology: Mechanisms of Disease 2007;2(1):145-173.
16. Bader HL, Hsu T. Systemic VHL gene functions and the VHL disease. FEBS Lett 2012; 586(11):1562–1569.
17. Pasupuleti SK, Katari V, Srikanth L, Krishna Sarma PVG, Reddy AR, Subramanian S, et al. Novel three missense mutations observed in Von Hippel-Lindau gene in a patient reported with renal cell carcinoma. Indian J. Hum. Genet 2013; 19(3):373–376.
18. Okumura F, Joo-Okumura A, Nakatsukasa K, Kamura T. Hypoxia-inducible factor-2α stabilizes the von Hippel-Lindau (VHL) disease suppressor, Mybrelated protein 2. PloS one 2017; 4:e0175593. https://doi.org/10.1371/journal.pone.0175593.
19. Rutkowski MJ, Sughrue ME, Kane AJ, Mills SA, Fang S, Parsa AT. Complement and the central nervous system: Emerging roles in development, protection and regeneration. Immunology and Cell Biology 2010; 88(8):781-786.
20. Pio R, Ajona D, Lambris JD. Complement inhibition in cancer therapy. Semin Immunol 2013; 25(1):54-64.
21. Ohh M, Park CW, Ivan M, Hoffman HA, Kim TY, Huang LE, et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the β-domain of the von Hippel - Lindau protein. Nat. Cell Biol. 2000; 2(7):423–427.
22. Evan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, et al. HIF and targeted for VHL-mediated distruction by proline hydroxylation: implications for O2 sensing. Science 2001; 292(5516):464-468.
23. Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature 1992; 358:80–83.
24. Zhou CH, Zhang XP, Liu F, Wang W. Modeling the interplay between the HIF-1 and p53 pathways in hypoxia. Sci. Rep. 2015; 5:1–10.
25. Muthumani P, Alagarsamy K, Dhandayuthapani S, Venkatesan T. Rathinavelu A. Pro-angiogenic effects of MDM2 through HIF-1α and NF-κB mediated mechanisms in LNCaP prostate cancer cells. Mol. Biol. Rep. 2014; 41(8):5533–5541.
26. Miller OJ. Harlequin Chromosomes. Encycl. Genet 2001:914. doi:10.1006/rwgn.2001.0586.
27. Saporita AJ, Ai J, Wang Z. The Hsp90 Inhibitor, 17-AAG, Prevents the Ligand-Independent Nuclear Localization of Androgen Receptor in Refractory Prostate Cancer Cells. Prostate 2007; 67(5):509–520.
28. Semenza, GL. Hypoxia-inducible factor 1 (HIF-1) pathway. Sci. STKE 2007; 2007(407): 9-12. DOI: 10.1126/stke.4072007cm8.
29. Eickelberg O, Seebach F, Riordan M, Thulin G, Mann A, Reidy KH, et al. Functional activation of heat shock factor and hypoxia-inducible factor in the kidney. J. Am. Soc. Nephrol. 2002; 13(8):2094–2101.
30. Horowitz M, Assadi H. Heat acclimation-mediated cross-tolerance in cardioprotection: Do HSP70 and HIF-1α play a role? Ann. N. Y. Acad. Sci. 2010; 1188: 199–206.
31. Krock BL, Skuli N, Simon MC. Hypoxia-Induced Angiogenesis: Good and Evil. Genes and Cancer 2011; 2(12):1117–1133.
32. Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase. Cancer Cell 2005; 7:77–85.
33. Skuli N,Liu L, Runge A, Wang T, Yuan L, Patel S, et al. Endothelial deletion of hypoxia-

inducible factor-2α (HIF-2α) alters vascular function and tumor angiogenesis. Blood 2009; 114(1):469–477.

34. Gatenby RA, Kessler HB, Rosenblum JS, Coia LR, Moldofsky PJ, Hartz WH, et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 1988; 14(5):831–838.
35. Zhong H, Marzo AMD, Laughner E, Lim M, Hilton DA, Zagzag D, Buechler P, et al. Overexpression of hypoxia-inducible factor 1α in common human cancers and their metastases. Cancer Res. 1999; 59(22):5830–5835.
36. Soni S, Padwad Y. HIF-1 in cancer therapy: two decade long story of a transcription factor. Acta Oncologica 2017; 56(4):503-515.
37 Erler JT. Bennewith KL, Cox TR, Lang G, Bird D, Koong A, et al. Hypoxia-Induced Lysyl Oxidase Is a Critical Mediator of Bone Marrow Cell Recruitment to Form the Premetastatic Niche. Cancer Cell 2009; 15(1):35–44.
38 Azab AK, Azab F, Blotta S, Pitsillides CM, Thompson B, Runnels JM, et al. RhoA and Rac1 GTPases play major and differential roles in stromal cell-derived factor-1-induced cell adhesion and chemotaxis in multiple myeloma. Blood 2009; 14(3):619–629.
39. Hoffmann C, Mao X, Brown-Clay J, Moreau F, Al Absi A, Wurzeret H, et al. Hypoxia promotes breast cancer cell invasion through HIF-1α-mediated up-regulation of the invadopodial actin bundling protein CSRP2. Sci Rep. 2018; 8:10191.
40. Martin TA, Jiang WG. Loss of tight junction barrier function and its role in cancer metastasis. Biochim. Biophys. Acta-Biomembr. 2009; 1788(4):872–891.
41. Semenza GL. Hypoxia-Inducible Factors in Physiology and Medicine. Cell 2012; 148(3):399-408.
42. Onnis B, Rapisarda A, Melillo G. Development of HIF-1 inhibitors for cancer therapy. J. Cell. Mol. Med. 2009; 13(9a):2780–2786.
43. Masoud GN, Li W. HIF-1α pathway: Role, regulation and intervention for cancer therapy. Acta Pharm. Sin. 2015; 5(5):378–389.
44. Yu T, Tang B, Sun X. Development of inhibitors targeting hypoxia-inducible factor 1 and 2 for cancer therapy. Yonsei Med. J. 2017; 58(3):489–496.

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