Review Article

# Hypoxia-Inducible Factors-α as a Regulator for Forkhead Box Protein M1 in Pulmonary Artery Hypertension

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## Abstract

Hypoxia is defined as decreased levels of oxygen in the cells, which are caused by vascular and pulmonary diseases. The catalysts of hypoxia in the physiological role are important in all living cells, whereas its metabolic dysfunction is related to many diseases. Hypoxia-inducible factors (HIFs) activity should be controlled by providing HIF modules. Forkhead box protein M1 (FOXM1) plays a crucial role in the maintenance and differentiation of airways epithelial cell lining, especially during embryonic life, where it is essential in the formation and proliferation of pulmonary vessels. FOXM1 is overexpressed in the pulmonary artery smooth muscle in response to hypoxia through the elements that are present in the promoters of FOXM1; therefore, it was used to diagnose patients with pulmonary artery hypertension.

**Keywords:** Forkhead box protein M1, Hypoxia-inducible factors, pulmonary artery hypertension

## Introduction

Forkhead box protein M1 (FOXM1) has four subtypes (FOXM1a, FOXM1b, FOXM1c, and FOXM1d), which are transcription factors except FOXM1a.[1] It plays the role as a transcription factor through the activation of signaling pathways by targeting genes that control cell cycle processes such as cellular differentiation, cellular proliferation, cellular renewal, cellular migration, cellular survival, angiogenesis, and repairs damaged DNA.[1,2] FOXM1 plays a crucial role in the maintenance and differentiation of airways epithelial cell lining,[3] especially during embryonic life, where it is essential in the formation and proliferation of pulmonary vessels.[4] Pulmonary artery hypertension (PAH) results from alteration in the pulmonary artery smooth muscle cells (SMCs) type from contractile phenotype into proliferative ones and remodeling of vasculature. It is stimulated by hypoxia-inducible factors (HIFs), including two types: HIF1a and HIF2a.[5-7] FOXM1 is overexpressed in the pulmonary artery SMCs in response to hypoxia through the elements that are present in the FOXM1 promoters. Besides, reduced expression of miR-204, which in turn leads to the expression of FOXM1 from these cells in patients with PAH.[8,9] Under normal circumstances, HIF-1a regulates the action of FOXM1, whereas in the case of hypoxia, FOXM1 is stimulated by HIF-2a in the SMCs of the pulmonary arteries[5] by binding with target genes.[10] As a result, FOXM1 is induced by both HIF-1a and HIF-2a isoforms, but they differ in their response to oxygen (according to its concentration) and their distribution in the tissues.[5] In addition to HIF, there are other factors which are also thought to play an important role in the expression of FOXM1 in the SMCs enhancing their proliferation, and PAH includes CXCL12, PDGF-B, ET-1, or MIF,[11] which lead to hypertrophy of the right ventricle and remodeling of pulmonary artery SMCs;[7] furthermore, increase the number of endothelial cells in patients with PAH.[12] FoxM1 has an essential role in the controlling proliferation of SMCs; therefore, it is very necessary to understand the importance of FoxM1 in pulmonary hypertension and to illustrate the molecular mechanisms of it.[5] HIFs stimulated by the low level of oxygen supply in the

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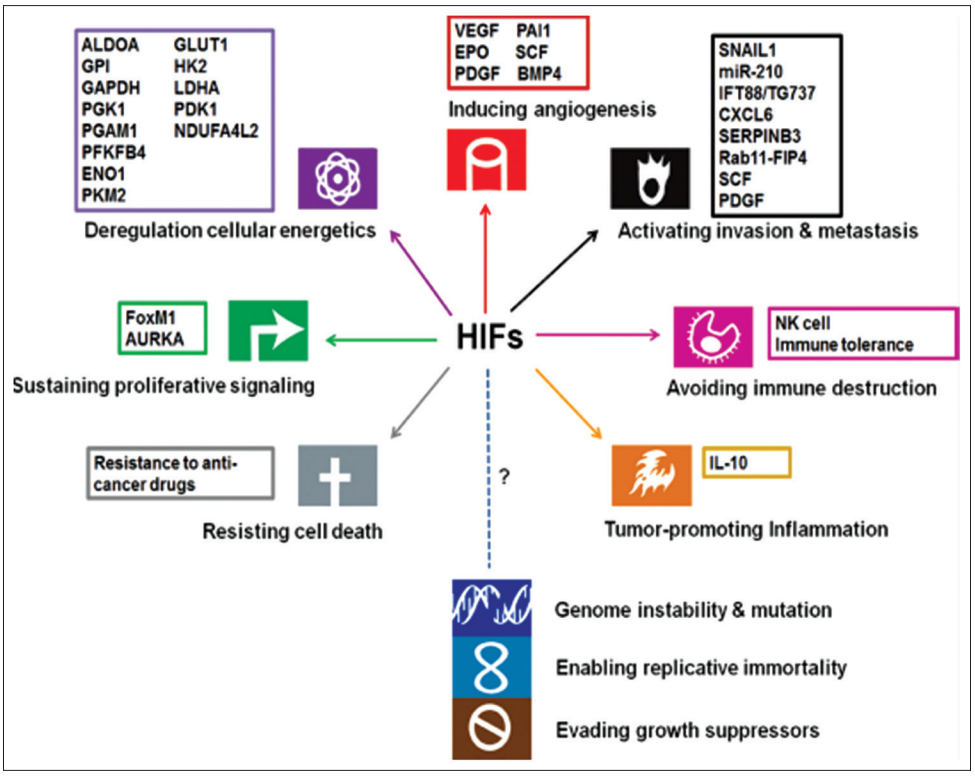


**Figure 1:** Hypoxia inducible factors are involved in several metabolisms[18]

cells by a special transcriptional program.[13] The deficiency of oxygen in the cells and tissues results from imbalance between metabolic requirements and oxygen availability, for example, during vigorous exercise or embryos growing, ischemia and cancer which reduced consumption of oxygen by metabolic alterations and intensifying the mechanisms responsible for transferring oxygen to cells such as erythrocyte regulation and angiogenesis, and these modifications are involved increased levels of gene expression.[14,15] There are three types of hypoxia: acute hypoxia, hypoxia reperfusion, and chronic hypoxia. In chronic hypoxia, the percentage of oxygen stress is about 2%–3%, especially cause unlimited cell proliferation. There are two types of hypoxia, acute hypoxia and hypoxia reperfusion, observed in these types, increase oxidative stress and blood toxicity.[16] The expression of HIF-1α in the macrophages increased by internal inflammation, atheroma, and arteries wall thickness often exceed the oxygen limit to 100–200 μm,[5] which may develop to plaques formation by affecting on low-density lipoprotein-cholesterol flow and apoptosis. On the other hand, primary inflammatory genes, influence on the secretion of monocyte chemoattractant protein-1 from cells,[17] and partially induces vascular endothelial growth factor expression, in addition to glycolysis stimulation and glucose transporter by hexokinase and lactate dehydrogenase both promote glucose conversion to pyruvate by dehydrogenase, which inhibits the carboxylic acid cycle; therefore, unstable hypoxia may lead to increased mitochondrial activity, resulting in accumulation of reactive oxygen species and deregulation of cellular energetic as shown in Figure 1.[18]

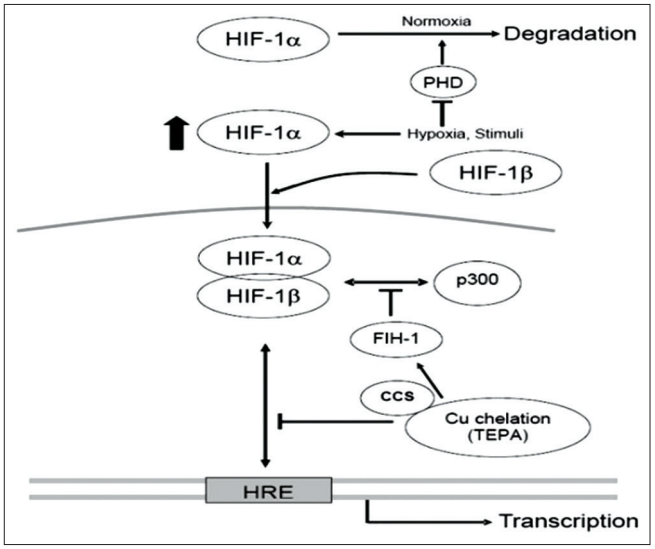


**Figure 2:** Copper chelating by TEPA on hypoxia-inducible factor-1 transactivity.[19] VEGF: Vascular endothelial growth factor, TEPA: Tetraethylenepentamine, HRE: Hypoxia-responsive element, FIH-1: Factor inhibiting hypoxia-inducible factor 1, CCS: Copper chaperone for superoxide dismutase 1, PHD: Hypoxia-inducible factor prolyl hydroxylase

When hypoxia or other stimuli are stable, HIF-1-α is associated with HIF-1-β transferred to a nucleus, the heterodimer is then linked to the HRE sequence and the p300 helper starts to copy the target gene, the removal of copper using tetraethylenepentamine stimulate FIH-1, leads to HIF-1 hydroxylation and prevents its binding to the p300. It also

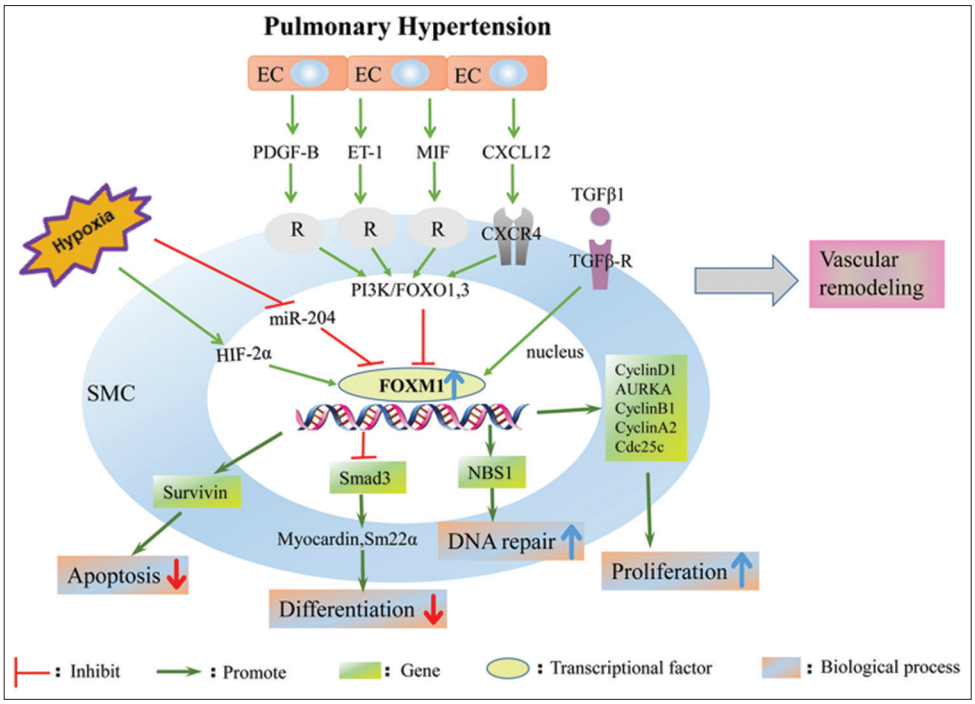


**Figure 3:** Forkhead box protein M1 promotes pulmonary arterial hypertension progression and initiation.[24] PDGF-B: Platelet-derived growth factor, ET-1: Endothelin-1, MIF: Macrophage migration inhibitory factor, CXCL12: Chemokine ligand 12, SMC Smooth muscle cell, NBS1: Nijmegen breakage syndrome 1

reduces the HIF-1 link in the target gene sequence and inhibits transcription activity by CCS. In this regard, copper can be converted from FIH-1 activity to maintain the binding capacity of HIF-1 as shown in Figure 2.[19]

Scientists explain all these mechanisms by protein translation according to low intracellular oxygen.[20] HIF is catalyzed in response to hypoxia in the cells and tissues, which new drugs are HIF prolyl-hydroxylase inhibitors used to regulate HIF in chronic renal anemia.[21] New clinical factors depending on the hypoxia-inducible factor mechanism stimulate erythropoietin to increase iron concentration by physiological action to treat anemia.[22] Correspondence studies suggest that cells distribution of HIF-prolyl hydroxylases between the cytosol and the nucleus plays a role in the management of chronic kidney anemia, but irregular distribution of HIF-prolyl hydroxylases cells between these compartments is responded to hypoxia condition.[23]

Hypoxia upregulates FOXM1 expression in SMCs through elevated growth factor and inflammatory cytokine from endothelial cells, and the increased FOXM1 targets different pathways, such as increasing SMC and proliferation, inhibition of SMC differentiation and apoptosis, resulting in PAH vascular remodeling as shown in Figure 3.[24]

## Conclusion

1. Hypoxia is an important factor in the development of PAH through the stimulation of FOXM1 expression in SMCs of the pulmonary artery in addition to that hypoxia also occurs in the other types of pulmonary hypertension
2. Protein translation is stimulated according to low oxygen levels inside the cells, playing a role in the pulmonary hypertension progression
3. The expression of HIF-1α in the macrophages increases internal inflammation and stimulates atheroma formation and arteries wall thickness.

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## Conflicts of interest

There are no conflicts of interest.

## References

1. Liao GB, Li XZ, Zeng S, Liu C, Yang SM, Yang L, *et al.* Regulation of the master regulator FOXM1 in cancer. Cell Commun Signal 2018;16:57.
2. Lam EW, Brosens JJ, Gomes AR, Koo CY. Forkhead box proteins: Tuning forks for transcriptional harmony. Nat Rev Cancer 2013;13:482-95.
3. Wang IC, Zhang Y, Snyder J, Sutherland MJ, Burhans MS, Shannon JM, *et al.* Increased expression of foxM1 transcription factor in respiratory epithelium inhibits lung sacculation and causes clara cell hyperplasia. Dev Biol 2010;347:301-14.
4. Ustiyan V, Wang IC, Ren X, Zhang Y, Snyder J, Xu Y, *et al.* Forkhead box M1 transcriptional factor is required for smooth muscle cells during embryonic development of blood vessels and esophagus. Dev Biol 2009;336:266-79.

5. Raghavan A, Zhou G, Zhou Q, Ibe JC, Ramchandran R, Yang Q, *et al.* Hypoxia-induced pulmonary arterial smooth muscle cell proliferation is controlled by forkhead box M1. Am J Respir Cell Mol Biol 2012;46:431-6.
6. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease: Pulmonary arterial hypertension. Nat Rev Cardiol 2011;8:443-55.
7. Dai J, Zhou Q, Tang H, Chen T, Li J, Raychaudhuri P, *et al.* Smooth muscle cell-specific foxM1 controls hypoxia-induced pulmonary hypertension. Cell Signal 2018;51:119-29.
8. Courboulin A, Paulin R, Giguère NJ, Saksouk N, Perreault T, Meloche J, *et al.* Role for miR-204 in human pulmonary arterial hypertension. J Exp Med 2011;208:535-48.
9. Bourgeois A, Lambert C, Habbout K, Ranchoux B, Paquet-Marceau S, Trinh I, *et al.* FOXM1 promotes pulmonary artery smooth muscle cell expansion in pulmonary arterial hypertension. J Mol Med (Berl) 2018;96:223-35.
10. Xia LM, Huang WJ, Wang B, Liu M, Zhang Q, Yan W, *et al.* Transcriptional up-regulation of foxM1 in response to hypoxia is mediated by HIF-1. J Cell Biochem 2009;106:247-56.
11. Dai Z, Zhu MM, Peng Y, Jin H, Machireddy N, Qian Z, *et al.* Endothelial and smooth muscle cell interaction via foxM1 signaling mediates vascular remodeling and pulmonary hypertension. Am J Respir Crit Care Med 2018;198:788-802.
12. Guignabert C, Tu L, Le Hiress M, Ricard N, Sattler C, Seferian A, *et al.* Pathogenesis of pulmonary arterial hypertension: Lessons from cancer. Eur Respir Rev 2013;22:543-51.
13. Påhlman S, Mohlin S. Hypoxia and hypoxia-inducible factors in neuroblastoma. Cell Tissue Res 2018;372:269-75.
14. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell 2012;148:399-408.
15. Mylonis I, Simos G, Paraskeva E. Hypoxia-inducible factors and the regulation of lipid metabolism. Cells 2019;8:E214.
16. Chen L, Endler A, Shibasaki F. Hypoxia and angiogenesis: Regulation of hypoxia-inducible factors via novel binding factors. Exp Mol Med 2009;41:849-57.
17. Aarup A, Pedersen TX, Junker N, Christoffersen C, Bartels ED, Madsen M, *et al.* Hypoxia-inducible factor-1α expression in macrophages promotes development of atherosclerosis. Arterioscler Thromb Vasc Biol 2016;36:1782-90.
18. Chen C, Lou T. Hypoxia inducible factors in hepatocellular carcinoma. Oncotarget 2017;8:46691-703.
19. Feng W, Ye F, Xue W, Zhou Z, Kang YJ. Copper regulation of hypoxia-inducible factor-1 activity. Mol Pharmacol 2009;75:174-82.
20. Ivanova IG, Park CV, Kenneth NS. Translating the hypoxic response-the role of HIF protein translation in the cellular response to low oxygen. Cells 2019;8:E114.
21. Kaplan JM, Sharma N, Dikdan S. Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. Int J Mol Sci 2018;19:E389.
22. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. Am J Kidney Dis 2017;69:815-26.
23. Yasumoto K, Kowata Y, Yoshida A, Torii S, Sogawa K. Role of the intracellular localization of HIF-prolyl hydroxylases. Biochim Biophys Acta 2009;1793:792-7.
24. Li Y, Wu F, Tan Q, Guo M, Ma P, Wang X, *et al.* The multifaceted roles of FOXM1 in pulmonary disease. Cell Commun Signal 2019;17:35.