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Review Article

Role of HIF 1 α in Covid-19 Disease

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Abstract

This review article aims to point out the many roles of HIF-1α in COVID-19 diseases. World health organization named the newly emerged virus SARS-CoV-2 or 2019-nCoV or covid-19. At beginning of coronavirus symptoms of pneumonia were appeared in December 2019 near Wuhan city of China. The Coronavirus Disease 2019 outbreak spread rapidly worldwide and is associated with the high death rate in humans. However, there are currently fewer safe and effective drugs available for targeting SARS-CoV-2. So, there is an emergency for the invention of effective prevention and treatment options for the SARS-CoV-2 outbreak. SARS-CoV-2 recognizes the human ACE2 more strongly than SARS-CoV. SARS-CoV-2 spike supermolecule having a very high robust binding affinity to human ACE2. Relatively limited information is understood about the transcriptional regulation of ACE2. Hypoxic condition reduces the synthesis of ACE2, Further experimentation has shown that hypoxic condition induced HIF-1α protein leads to increases ACE synthesis which, prompts to rise the amount of Ang II and overall this process modulates the reduction in ACE2 synthesis with the help of Ang II. Activation of HIF-1 is related to numerous physiological and pathological processes. HIF-1 will manage ACE2 regulation and several natural components exhibit the role in activation and stabilization of the HIF-1α protein. The level of HIF-1α in cells gives us future opportunities for new, safe, and effective treatment options for the novel coronavirus.

Keywords: COVID-19; SARS-COV; HIF-1α Pathway; Influenza A Virus; Natural HIF-1α Activators

Introduction

World health organization named the newly emerged virus SARS-CoV-2 or 2019-nCoV or covid-19. At beginning of coronavirus symptoms of pneumonia were appeared in December 2019 near Wuhan city of China. One phylogenetic analysis of whole-genome sequences showed that bats are the main reservoir of COVID-19. The responsible intermediate host has not been found till now. However, there are presently fewer promising medications are available on 2019-nCoV/SARS-CoV-2. There is a relationship between the HIF-1 α and SARS-CoV-2, therefore HIF-1 will manage ACE2 regulation. Synthetic as well as naturally occurring HIF-1 alpha activators may show a promising effect in COVID-19.

HIF-1 (Hypoxia-inducible factor) is a fundamental protein of human physiology that has a [1] helix-circle helix kind of construction [1]. A Heterodimer, crown-like structure present on the SARS-CoV virus, has 2 subparts HIF-1α and HIF-1β. HIF-1α is a protein activated by the low amount of oxygen in mammals. The synthesis of HIF-1α protein is controlled with the help of amount of O2 in

cells and O2 homeostasis. HIF-1 α activation plays important role in hypoxic conditions. Hypoxic conditions are generally caused by, for example, high-temperature levels, a low number of RBCs in the blood, and wound healing. Hypoxic condition activates the HIF-1α that prompts the synthesis of various genes in the human body. Synthesized transcript genes encode numerous components are Hematopoietic hormone, Enzymes (involve in glycolysis like hexokinase, phosphofructokinase, and pyruvate kinase), Glucose carrier proteins (GLUT6, GLUT8, GLUT10, GLUT12, and GLUT13), andVEGF. HIF-1 is significant in the early stages of development, endurance, cardiovascular capacities, Vascularization, and oncogenic tumors.

Hypoxia and HIF 1 α responses

HIFs are present in all cells of the body, and partial pressure of oxygen plays an important role in the activation HIFs protein. The whole process depends upon the environment to which the cells are exposed. Following is the flowchart of the hypoxic condition and its corresponding HIF 1 α response (Figure 1).

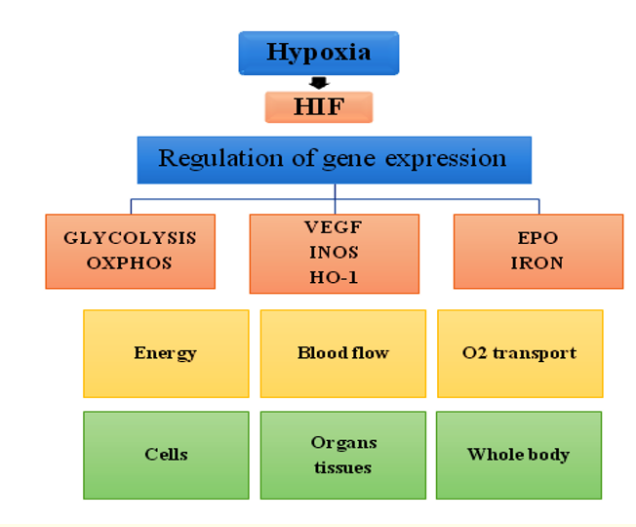

Figure 1: The flowchart of transcription genes and hypoxic responses regulated by HIF.
(OXPHOS: Oxidative phosphorylation, INFOS: Inducible nitric oxide synthase, EPO: Erythropoietin, HO-1Heme oxygenase-1, VEGF: Vascular endothelial growth factor).

SARS-CoV and SARS-CoV-2

It is detected that SARS-CoV-2 has less risk as compared to SARS-CoV or influenza virus, but the rate of transmission from one to another is high. Gene sequencing studies of identical two SARS viruses showed that both possess the nearly same gene sequencing [2]. The spike proteins of both viruses have nearly the same structures and also having similarities in amino acid sequences about 76.5% [3,4]. SARS-CoV-2 has a high power of binding for human ACE2 [5]. SARS-CoV-2 identifies the ACE2 of humans more strongly than SARS-CoV, which leads to rising the power of SARS-CoV-2 to transfer from one person to another (Figure 2).

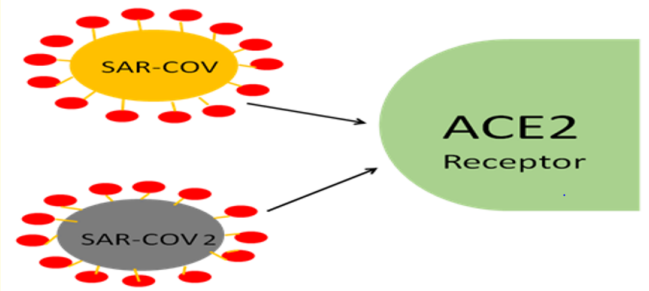

Figure 2: Interaction of SAR-COV and SAR-COV 2 with the ACE2 receptor.

ACE2 and HIF-1α in coronavirus pathophysiology

Relatively very little data available regarding the detailed transcription of ACE2. Although angiotensin proteins, some other peptides, and steroid hormones seem to modulate ACE2 protein level. Decreased amount of oxygen leads to a hypoxic condition called hypoxia, which increases the hypoxic HIF-1α protein level and simultaneously decreases the level of ACE2 in the human body. Further experimentation has shown that hypoxic condition induced HIF-1α protein enhances the ACE synthesis which, prompts an increased amount of Ang II (angiotensin) enzyme [4] and overall this process modulates the reduction in ACE2 with the help of the Ang II enzyme (Figure 3).

The function of HIF 1 α in the ACE expression

Hypoxia directs ACE and ACE2 articulation in extremely alternative manners [6]. HIF-1 α up-managed ACE, yet it down-directed ACE2. Besides, excessive expression of HIF-1 α activates the move-

Figure 3: HIF-1α increased concentration of Ang II (angiotensin)and mediates a decrease in ACE2.

ment of the ACE Promoter, however not ACE2. One test performed on the Effects of hypoxia on angiotensin-changing over a catalyst (ACE) and ACE2 synthesis in hPASMCs cells showed that excessive expression of HIF-1 could up-manage ACE protein articulation, however down-direct ACE2, without hypoxia. Furthermore, noticed that the average up-regulation of ACE during the hypoxic condition, however not in HIF-1α treated cells. Conversely, the ACE2 protein level was particularly expanded in HIF-1α treated cells contrasted and controls during the hypoxic environment of cells [4]. This investigation exhibits that HIF-1 can up-direct ACE and down-manage ACE2.

Role of HIF 1 α in influenza A virus

It is found that the amount of HIF-1α contributes to the multiplication of the influenza A virus in the infected human cells. HIF-1α promotes autophagy in type II epithelial cells of alveoli. Various cytokines are released in the infectious condition of the virus such as TNF-α and IL-6 and their expression regulation is also done with the help of HIF-1α. Nuclear accumulation of HIF-1α enhances the level of proinflammatory cytokine in influenza A virus-infected cells. The overall process shows that the HIF-1α synthesize and activates proinflammatory cytokine in influenza A virus infection [7].

Natural HIF-1 alpha modulators

Several natural components exhibit the role in stabilization of the HIF-1α protein [8].

Desferri-exochelin DFE 722 SM	Inhibits the Fe(II)-dependent asparaginyl and prolyl hydroxylases.	[9]
Ciclopirox olamine and 8-methyl-pyridoxatin	Inhibition of asparaginyl and prolyl hydroxylases.	[10]
N-oxaloylglycine	Inhibition of 2-oxoglutarate,prolyl-4-hydroxylase, and Fe(II) dependent oxygenases.	[11]
Alahopcin and dealanylalahopcin	Inhibition of collagen prolyl hydroxylase.	[12]
3-carboxy-N-hydroxy pyrollidone and 3-carboxy-methylene N-hydroxy succinimide	HPH(Hif prolyl-hydroxylase) inhibitors.	[13]
Indirubin 5-iodoindirubin-3'-oxime and 5-methyl-indirubin-3'-oxime	Inhibits GSK3β(glucogen synthase kinase 3β) and prevents a decrease in HIF-1α protein.	[14]
NO donor L-penicillamine, S-nitroso-N-acetyl-D, and S-nitrosoglutathione	Increases HIF-1α protein accumulation and activate HIF-1 transcription from the VEGF promoter in A-172 human glioblastoma and Hep3B cells.	[15]
Vinblastine and Colchicine, and the synthetic MDA nocodazole	Increases the level of HIF-1α protein.	[16]
Dibenzoylmethane,(Glycyrrhiza glabra)	Stabilize of the HIF-1α protein.	[17]
Quercetin	Activates HIF-1α protein in normoxic conditions.	[18]
Green tea catechins	At high concentrations (100 μM) Activates HIF-1.	[19,20]
Dihydrotestosterone	Increases the amount of HIF-1α protein and activates HIF-1.	[17]

Table 1: Natural HIF-1α modulators.

Conclusion

It is found that there is a relationship between HIF-1 and ACE2, therefore HIF-1 will help us to discover new treatment options for COVID-19 virus infection. HIF-1 α protein plays a crucial function in various processes of the mammalian body. By further research on the concurrent effect of HIF-1 on the regulation of ACE2 will give us more information related to the new target for coronavirus and the new drug development studies. Several natural components exhibit the role in the stabilization and activation of the HIF-1α protein. Repurposing of the drug from natural origin could abbreviate the time and lessen the expense contrasted with all over again drug discovery process. The level of HIF-1α in cells gives us the future opportunities for the new, safe and effective treatment options for the novel coronavirus.

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