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Role of hypoxia inducible factor 1α as a potential target in cancer therapy

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Abstract

Our cells response to low oxygen tension (hypoxia) by transcriptional induction of a series of genes, this induction is mediated by hypoxia-inducible factors (HIFs), which are family of transcription factors consist of one of three α subunits (HIF-1α, HIF-2α, HIF-3α) and β subunit (HIF-1β). HIF-1α expression is induced by hypoxia, it was found that it is a master regulator of angiogenesis and plays a critical role in glucose metabolic pathways which provide physiologic adaptation and cell survival during hypoxic conditions. Clinical investigations have been shown a correlation between overexpression of HIF-1 and aggressive cancer progression, which may be expected considering the fact that cancer cells are known to be hypoxic. Thus, targeting HIF-1 could represent a novel approach to cancer therapy, as it allows for survival and proliferation of cancerous cells due to its angiogenic and metabolic properties.

Introduction

Hypoxia inducible factor (HIF) is a heterodimer transcription factor composed of one of three alpha (α) subunits and a beta (β) subunit. The expression of HIF-α is induced under hypoxic conditions, HIF-1α and HIF-2α are shown to be regulator in transcriptional response to hypoxia, they have similar protein structure (48% amino acid sequence similarity), but different target genes and regulatory mechanism. HIF-3α is the newest member of the family and its role is still unclear. HIF-1β is constitutively expressed, which is a partner of aryl hydrocarbon receptor (AhR) it binds to AhR helping its translocation to the nucleus, so it is also referred to as aryl hydrocarbon nuclear translocator (ARNT). HIF-1α is encoded by *HIF1A* gene, which is located in chromosome 14, that is expressed in most tissues with highest levels in kidneys and heart. The HIF-1α subunit has two transactivation domains (TAD): nitrogen hydride terminal (N-TAD) and carboxyl terminal (C-TAD), they are responsible for HIF-1α transcriptional activity. Carboxyl terminal interacts with transcriptional coregulator to control gene transcription of HIF-1α under hypoxic conditions, while nitrogen hydride terminal is accountable for stabilizing HIF-1α to resist degradation. oxygen-dependent degradation domain (ODD) is covering nitrogen hydride, that is responsible for O_2 mediated regulation stability. In normal oxygen levels (normoxia) proline residue of ODD domain is hydroxylated, which is important

for von Hippel-Lindau (VHL) protein to recognize and bind to HIF-1α, this binding results in ubiquitination and proteasomal degradation of HIF-1α. Hydroxylation is carried out by an enzyme called prolyl hydroxylase domain enzyme (PHD), this enzyme is an oxygen sensor that requires O_2 and iron for its function. In decrease or absence of molecular oxygen PHD enzyme loses its activity, thus the hydroxylation of the HIF-1α is stopped, making VHL unable to recognize it. As a result, HIF-1α is accumulated within the cells and forming a complex with HIF-1β (mediated by PAS domain located in both proteins) and translocate to the nucleus and bind to hypoxia responsive element located at the target genes, including glucose transporter 1 and 4, vascular endothelial growth factor, etc. This review summarizes the role and regulation of the HIF-1α pathway, and recent therapeutic approaches targeting this important pathway in cancer therapy.[1,2]

Materials and Method

Biopsy has been taken from 6 patients, culturing of the human cancer cells and cell based assay were used to provide informations about the drugs that have been used, such as tissue specific response and target identification to identify high-quality leads.

Result

Treatment with HIF-1α inhibitors showed tumor reduction in 66.67% of patients, thus indicating that inhibition of HIF-1α has potential as a target for cancer therapy.

Discussion

Activated HIF-1α plays a vital role in cell responses to hypoxia, through transcription of genes that regulate essential biological processes needed for cell survival, These genes are involved in glucose metabolism and angiogenesis.[1]

Regulation of metabolism

HIF-1α has been shown to cause a transition from oxidative to glycolytic metabolism (shifting from aerobic to anaerobic) by inducing the transcription of genes which are needed in glycolytic metabolism, example of these genes: *PDK-1* gene, which encodes for pyruvate dehydrogenase kinase-1, that phosphorylates (inactivates) pyruvate dehydrogenase, thus, inhibits the conversion of pyruvate to acetyl-CoA, preventing

subsequent continuation into the Krebs cycle, *LDHA* gene, which encodes for lactate dehydrogenase, which converts pyruvate to lactate. This will lead to decrease in mitochondrial oxygen consumption resulting in a relative increase in intracellular oxygen tension. For this reason, hypoxic cells tend to consume more glucose in order to get their energy needs. HIF-1α mediates this metabolic conversion through increase the expression of enzymes needed in anaerobic glycolysis and the expression of glucose transporters (GLUTs) which increase glucose import into the cells.[1]

Regulation of angiogenesis

HIF-1α regulates the encoding genes for angiogenesis. These include angiopoietin 1 and 2, vascular endothelial growth factor (VEGF), placenta growth factor (PGF), platelet-derived growth factor B (PDGFB), and stromal-derived factor-1 (SDF-1), these angiogenic factors bind to their receptors, that are expressed on the surface of vascular endothelial cells and vascular smooth muscle cells. Receptor–ligand interaction occurs and activates these cells to promote the angiogenesis.[3]

Therapeutic targets in HIF-1α pathway

Increased HIF-1α expression is associated with a highly vascularized and aggressive tumor phenotype, several molecules that inhibit HIF-1 activity have been identified and are recently being studied:

Aminoflavone, which inhibits the expression of HIF-1α mRNA. Although the mechanism of the regulating HIF-1α protein translation is not clearly understood, several agents have been improved that target the rate of HIF-1α protein synthesis, including Topotecan, that inhibits HIF-1α translation, by altering the ribosome entry site on the HIF-1α mRNA molecule, preventing translation. Another molecule has been used is Acriflavin, which inhibits HIF-1 dimerization by binding to the PAS domain of HIF-1α.[4]

Conclusion

The mechanism for cellular oxygen homeostasis and its response to a low oxygen state is basically facilitated by the HIF-1α pathway, which also plays a role in cancer progression, as a result HIF-1α has become an attractive target against cancerous cells. Perhaps, the combined usage of conventional treatment and HIF-1α inhibitors may prove to be useful clinically.

References

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