Exploring the Interplay of Hypoxia-Inducible Factors: Unveiling Genetic Connections to Diseases Through Bioinformatics Analysis

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ABSTRACT

Objective: Hypoxia-inducible factor (HIF) is a transcription factor that is effective in the ability of cells to sense and adapt to changes in oxygen levels. HIF1α gene is located in the 14q23.2 chromosome region and consists of 15 exons and 14 introns. It is a transcriptional regulator of metabolic processes such as angiogenesis and erythropoiesis and is required for immunological responses.

Material and Methods: Our study examined the function of HIF1α and its relations with other genes and diseases using various bioinformatics database tools. GENEMANIA/GeneCard databases were used to detect the relationship of HIF gene with other genes, miRDB to show target miRNAs, STRING to detect protein-protein interaction, and GWAS databases to show its relationship with diseases. In addition, organs and tissues in which it is expressed were determined using the UniProt database.

Results: The bioinformatic analysis yielded significant results, revealing that 189 miRNAs target HIF1α and exhibits close interactions with 10 genes, among which important genes like STAT3, MDM2, TP53, SMAD3, and VHL were identified. The most predominant pathway utilized by the HIF1α gene was determined to be the HIF-1 signaling pathway. A co-expression relationship was also established with proteins EPO, PLIN2, BNIP3, and the enzyme ENO1. Furthermore, it was ascertained that HIF1α exhibits the highest expression levels in the kidney and the perivenous region of the liver. Moreover, close associations have been established between HIF1α and diseases such as renal cell carcinoma and bladder cancer.

Conclusion: Identifying the pathways associated with HIF1α, other genes, and epigenetic factors with the help of Bioinformatics Tools may enable experimental studies to be carried out with large cohorts and using a broad perspective. Thus, it may contribute to our understanding of how this gene affects diseases and anomalies and to accelerate the studies of targeted therapeutic treatment.

Keywords: Hypoxia-inducible factor, HIF1-alpha gene, bioinformatics, diseases

INTRODUCTION

Every cell necessitates a certain level of oxygen for its proper functioning. When oxygen concentration drops below a critical threshold, such circumstances are termed as hypoxic conditions. In such scenarios, the operations of organs, tissues, and cells may either pause or deteriorate (1). Cells exposed to hypoxia activate a transcription factor known as "hypoxia-inducible factor (HIF)" in order to transcribe a series of genes responsible for regulating angiogenesis, iron metabolism, glucose metabolism, cell proliferation, and survival. HIF protein binds to the 5’-(A/G)CGTG-3’ sequence, found in the enhancer region of target genes and referred to as the hypoxia response element (HRE), thereby ensuring the expression of these genes (2).

The HIF-1 transcription factor serves as one of the primary mediators of homeostasis in human tissues facing hypoxia. HIF-1 participates in nearly all rapid gene expression processes in response to diminished oxygen levels (3,4). Under hypoxic conditions, the alpha and beta subunits of HIF-1 form an active heterodimer, consequently orchestrating the transcription of over 60 genes pivotal for cell survival, adaptation, anaerobic metabolism, immune responses, cytokine production, vascularization, and overall tissue homeostasis (2,5).
Furthermore, HIF-1 plays a pivotal role in the development of physiological systems during fetal and postnatal life, and it is a critical mediator in conditions such as cancer, lung diseases, and cardiovascular disorders. Gaining a better comprehension of HIF-1’s functions and pharmacological modulation of its activity could potentially pave the way for successful therapeutic interventions for these diseases (6-8).

**MATERIAL and METHODS**

The sequencing projects in the Human Genome Project and other organisms have generated a vast wealth of biological data. The substantial need for analyzing and interpreting this data has been met by the advancement of bioinformatics science. Bioinformatics is described as the implementation of calculation and analysis devices for collecting and interpretation of biological data, and is an interdisciplinary area benefitting from computer science, mathematics, physics and biology (9). In our study, we investigated the function of HIF, and its associations with other genes and diseases using various bioinformatics database mediums.

We employed GENEMANIA/GeneCard to identify the associations of the HIF1α gene with other genes. For showcasing the target miRNAs, we utilized miRDB. The protein-protein interactions were detected using STRING, and the association of HIF1α with diseases was demonstrated through GWAS databases. Furthermore, we utilized the UniProt database to determine the organs and tissues where HIF is expressed.

**RESULTS**

The bioinformatics analysis conducted on the miRDB database revealed that HIF-1α is targeted by 189 miRNAs.

The bioinformatics analysis conducted using the Genemania, GeneCard, and STRING databases unveiled a close interaction between HIF1α and 10 genes, including prominent ones like STAT3, MDM2, TP53, SMAD3, and VHL (Figure1).

The bioinformatics analysis conducted on Genecard and UniProt databases revealed that HIF-1α is expressed in various tissues, with the highest levels observed in the kidney and heart. The HIF-1α is overexpressed in most of the common human cancers, and in their metastases as a consequence of the mutations in the genes encoding the oncoproteins and tumor suppressors, and in the presence of intramural hypoxia. HIF-1α shows a higher expression level in pituitary gland tumors compared with the pituitary gland (Figure2).

The bioinformatics analysis conducted using Genecards, UniProt, and GWAS databases highlighted that in hypoxic conditions, HIF activates the transcription of over 40 genes. This set includes erythropoietin, glucose carriers, glycolytic enzymes, vascular endothelial growth factor, HILPDA, and protein products that enhance oxygen transmission or facilitate metabolic adaptation to hypoxia. Furthermore, diseases like retinal ischemia and polycythemia were associated with HIF-1α. Notably, HIF protein played a crucial role in embryonic vascularization, tumor angiogenesis, and the pathophysiology of ischemic conditions.

![Figure 1. HIF-1α associated genes](image-url)
DISCUSSION

Inflammation, poor circulation or the combination of both are the most common causes of tissue hypoxia. Infected tissues and areas surrounding the malignant tumors are characterised by lower glucose concentrations. Severe and widespread inflammation can lead to sepsis and circulatory collapse, which in turn can trigger acute or chronic tissue hypoxia in critical organs. This prompts a swift homeostatic response in all nucleated cells of the affected organs within the human body. The main transcriptional regulator of metabolic adaptation to changes in oxygen environment of hypoxia-inducible factor 1 (HIF-1) is involved in various physiologic and pathological processes of the body, and is closely associated with the pathogenesis of multiple number of diseases (10).

In studies in the literature, it has been reported that hsa-miR-18a-5p is effective in hypertrophic cardiomyopathy by interacting with HIF1α, and in the bioinformatic analysis we performed in our study, it was determined that HIF1α gene and hsa-miR-18a-5p were closely related (11). As a result of the bioinformatic analysis performed in our study, it was determined that HIF1α gene is in close interaction with 10 genes, including important genes such as STAT3, MDM2, TP53, SMAD3, VHL, and it has been reported that STAT3-dependent activation of HIF1α leads to high VEGF expression in breast, kidney and cervical cancer models (12-14). Research focused on breast tumors has demonstrated that both STAT3 and HIF1α play a direct role in the progression and metastasis of breast tumors. They achieve this by regulating the expression of genes associated with cell motility and invasion (15-18).

In a study with pancreatic cancer cells, it was reported that HIF1α may exert a tumour suppressor effect by preventing PPP1R1B expression and degradation of p53 protein in pancreatic cancer cells and that
loss of HIF1α in pancreatic cancer cells may increase invasive and metastatic activity (19). In a separate study involving RAS mutant cells, it was revealed that the expression of wild-type p53 led to an increase in HIF-1α turnover in ovarian and lung cancer cells (20). A recent study in the literature reported that MDM2 promotes the survival of Retinoblastoma cells by regulating the expression of pVHL and HIF1α and that targeting MDM2 and/or HIF1α may be a potentially effective approach for Retinoblastoma treatment (21). In addition, studies have reported that HIF1α is also associated with regulating programmed death ligand (PD-L1) expression in some malignancies. In a study involving glioma patients, it was observed that both HIF1α and PD-L1 were significantly overexpressed in advanced glioma tissues. Furthermore, this finding was linked to a poor prognosis of the disease and reduced survival rates among the patients. In the same study, HIF1α inhibitor and anti-PD-L1 antibody combination therapy applied to murine glioma models was shown to have an effective suppressive effect on tumour growth (22).

CONCLUSION

The literature is replete with studies corroborating the involvement of HIF1α in numerous molecular pathways, exerting its influence on the pathogenesis and prognosis of various diseases. Employing bioinformatics tools to identify associated pathways, other genes, and epigenetic factors could facilitate the execution of experimental studies with broader cohorts and perspectives. This, in turn, could aid in comprehending the impact of this gene on diseases and abnormalities, accelerating targeted and specific therapeutic research endeavors.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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