Gene name: **HIF1A**

External Ids for HIF1A Gene: HGNC: 4910 NCBI Gene: 3091 Ensembl: ENSG00000100644
OMIM®: 603348 UniProtKB/Swiss-Prot: Q16665

NCBI Gene Summary: This gene encodes the alpha subunit of transcription factor hypoxia-inducible factor-1 (HIF-1), which is a heterodimer composed of an alpha and a beta subunit. HIF-1 functions as a **master regulator of cellular and systemic homeostatic response to hypoxia by activating transcription of many genes, including those involved in energy metabolism, angiogenesis, apoptosis, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia.** HIF-1 thus plays an essential role in embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease. Alternatively spliced transcript variants encoding different isoforms have been identified for this gene.

GeneCards Summary: HIF1A (Hypoxia Inducible Factor 1 Subunit Alpha) is a Protein Coding gene. Diseases associated with HIF1A include Pheochromocytoma and Retinal Ischemia. Among its related pathways are Signaling by PTK6 and Autodegradation of the E3 ubiquitin ligase COP1. Gene Ontology (GO) annotations related to this gene include *DNA-binding transcription factor activity* and *protein heterodimerization activity*. An important paralog of this gene is EPAS1.

UniProtKB/Swiss-Prot Summary: Functions as a master transcriptional regulator of the adaptive response to hypoxia (PubMed:11292861, 11566883, 15465032, 16973622, 17610843, 18658046, 20624928, 22009797, 30125331, 9887100). Under hypoxic conditions, activates the transcription of over 40 genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor, HILPDA, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia (PubMed:11292861, 11566883, 15465032, 16973622, 17610843, 20624928, 22009797, 30125331, 9887100). Plays an essential role in embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease (PubMed:22009797). Heterodimerizes with ARNT; heterodimer binds to core DNA sequence 5'-TACGTG-3' within the hypoxia response element (HRE) of target gene promoters (By similarity). Activation requires recruitment of transcriptional coactivators such as CREBBP and EP300 (PubMed:16543236, 9887100). Activity is enhanced by interaction with NCOA1 and/or NCOA2 (PubMed:10594042). Interaction with redox regulatory protein APEX1 seems to activate CTAD and potentiates activation by NCOA1 and CREBBP (PubMed:10202154, 10594042). Involved in the axonal distribution and transport of mitochondria in neurons during hypoxia (PubMed:19528298). (HIF1A_HUMAN,Q16665)

Cellular localization: mostly in cytosol and nucleus.
Full Name: *Hypoxia-Inducible Factor 1 Alpha Subunit*
Protein Type: Transcription factor (bHLH-PAS family)

Biological Function of HIF1A

HIF1A encodes the α-subunit of HIF-1, a master transcriptional regulator of cellular responses to hypoxia (low oxygen).

🛠️ Main Functions:

1. **Oxygen sensing and adaptation**:
    - HIF1A is stabilized under hypoxic conditions.
    - Forms a heterodimer with HIF1B (ARNT) → HIF-1 complex.
    - Activates transcription of over 100 genes.

2. **Regulates metabolism**:
    - Increases glycolysis and decreases oxidative phosphorylation to help cells survive low oxygen.

3. **Drives angiogenesis**:
    - Promotes VEGF (vascular endothelial growth factor) expression for new blood vessel formation.

4. **Controls immune function**:
    - Modulates the activity and survival of:
        - Macrophages
        - Neutrophils
        - T cells
    - Shifts macrophages toward a pro-inflammatory (M1-like) phenotype.

🦠 Role of HIF1A in Sepsis

Sepsis often leads to tissue hypoxia, due to:

- Impaired perfusion
- Capillary leakage
- Mitochondrial dysfunction

Thus, HIF1A becomes activated and plays both protective and pathological roles:

Early Sepsis:

- HIF1A activation supports host defense:
    - Enhances neutrophil survival and function.
    - Boosts macrophage glycolysis and bactericidal activity.
    - Increases IL-1β, TNF-α, and other pro-inflammatory mediators.

Severe/Prolonged Sepsis:

- Chronic HIF1A activation contributes to:
    - Excessive inflammation
    - Endothelial dysfunction

    - Organ failure
    - Immunometabolic exhaustion of immune cells
- May also promote fibrosis, angiopathy, and maladaptive tissue repair.

📈 Clinical Relevance of HIF1A in Sepsis

Diagnostic Role:

- HIF1A is upregulated in immune cells (especially macrophages and neutrophils) from septic patients.
- Included in sepsis-related transcriptomic signatures.

Prognostic Role:

- Persistently elevated HIF1A correlates with:
    - Greater organ dysfunction
    - Higher mortality
    - Poor immune recovery

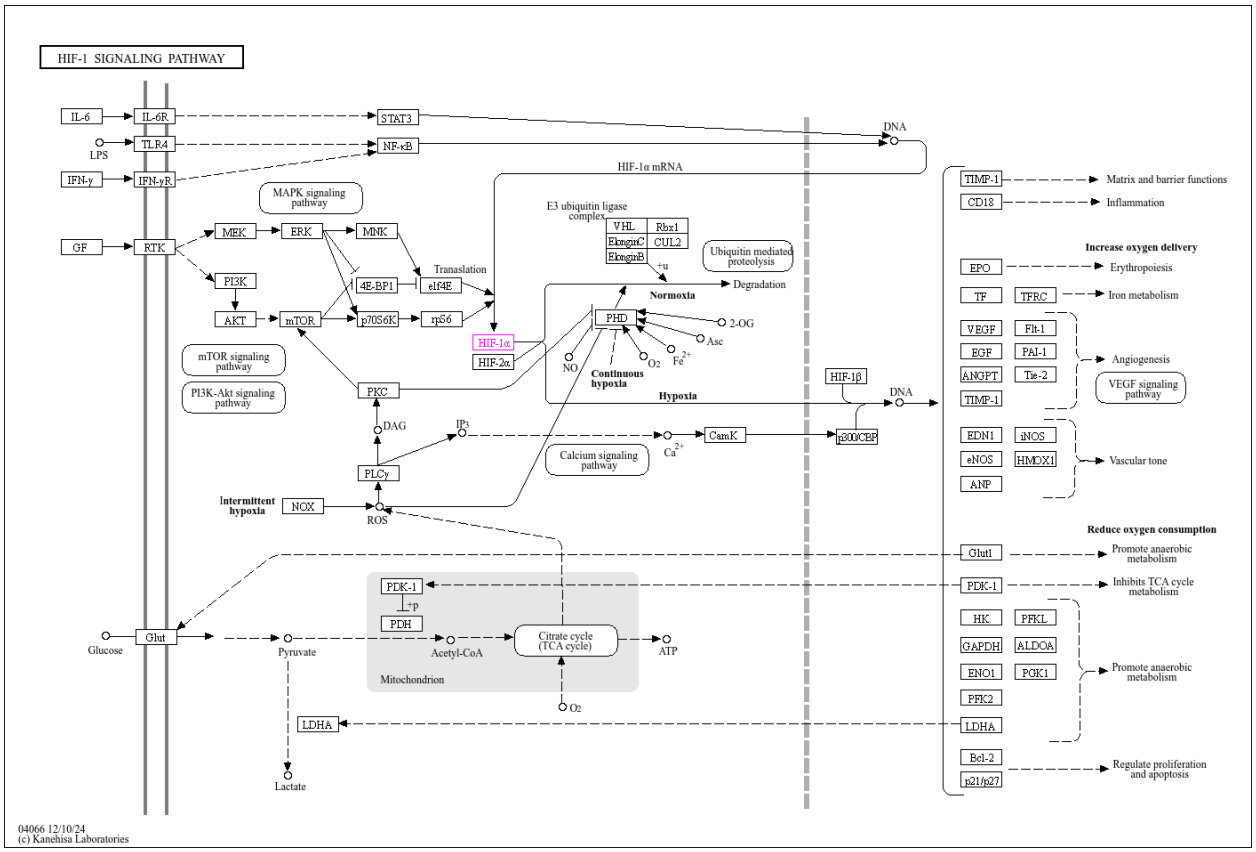
Therapeutic Potential:

- Modulating HIF1A is a target of interest:
    - Inhibitors could reduce tissue inflammation and oxidative damage.
    - Activators might boost host defense in immune-compromised phases.
- However, its dual role requires careful timing and context-specific modulation.

📚 Key Supporting Studies

Doi: 10.3389/fmolb.2019.00085
Doi: 10.1186/s13054-024-04885-4
Doi: 10.1097/SHK.0000000000001694
Doi: 10.1111/febs.15222

KEGG:



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