Hypoxia Inducible Factor – 1 (HIF-1): A High Impact Factor

Min Wang

Free Radical & Radiation Biology

College of Medicine

The University of Iowa

E-mail: min-wang@uiowa.edu

Phone: (319)335-6749; Fax: (319)335-8039

A. What is HIF-1?

HIF-1: Hypoxia Inducible Factor - 1

- **The studies of hypoxia response element of the erythropoietin gene leads to the discovery of HIF-1 by Semenza and Wang in 1992.**

  Semenza GL & Wang GL. (1992). *Mol. Cell. Biol.* 12: 5447-5454.

- **HIF-1 is a protein with DNA binding activity. It is composed of two subunits: HIF-1α and HIF-1β.**

HIF-1α is constitutively made and degraded *via* VHL.

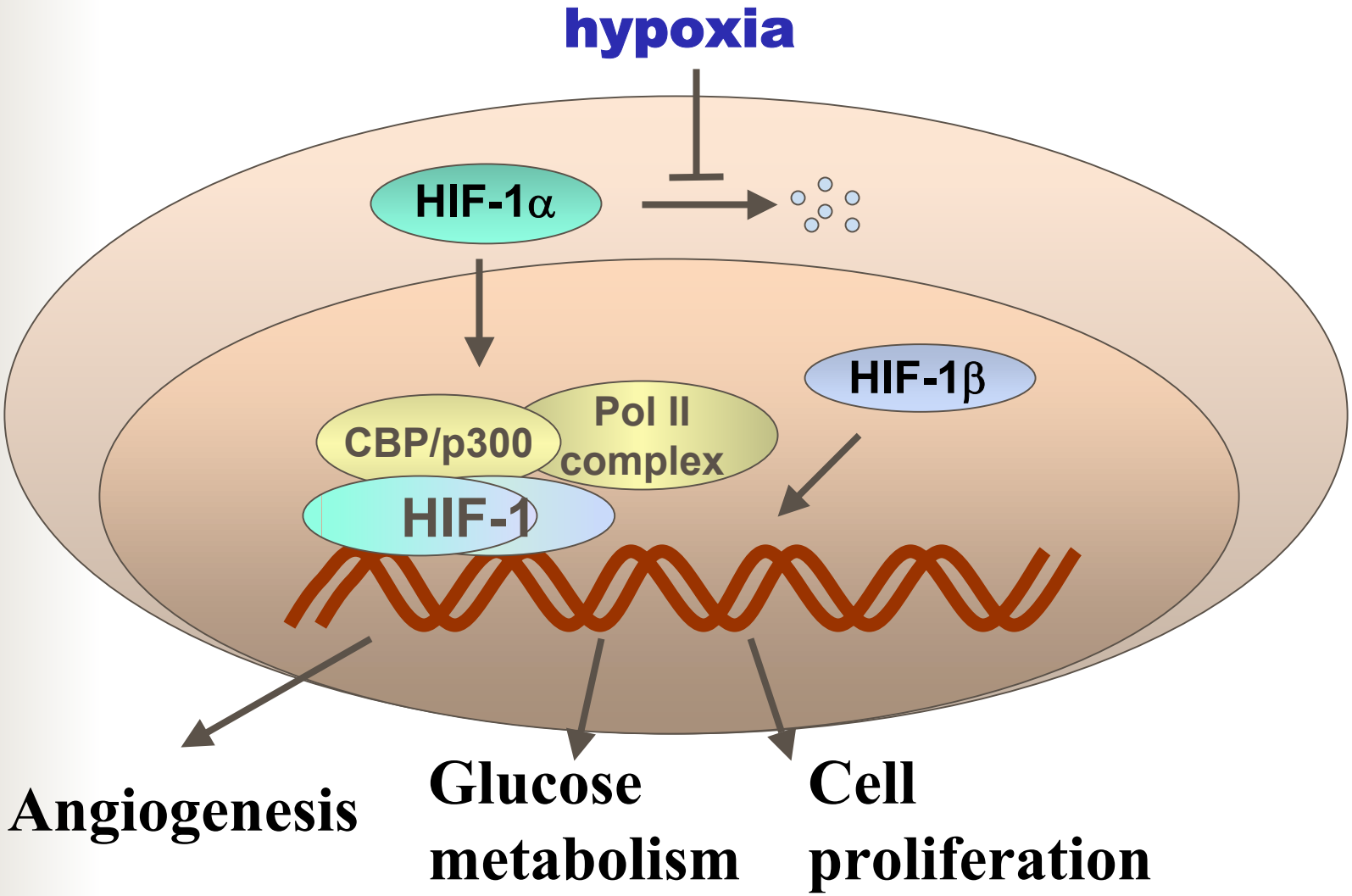
- Proline residue 402 & 564 in HIF-1α can be hydroxylated by prolyl hydroxylase.
- The hydroxylation of proline causes the binding of von Hippel-Lindau tumor suppressor (VHL).
- The binding of VHL leads to the ubiquitinylation of HIF-1α.
- Ubiquitinylation of HIF-1α results in degradation by proteasome.

Bruick RK. (2002) *Science.* 295:807-808.

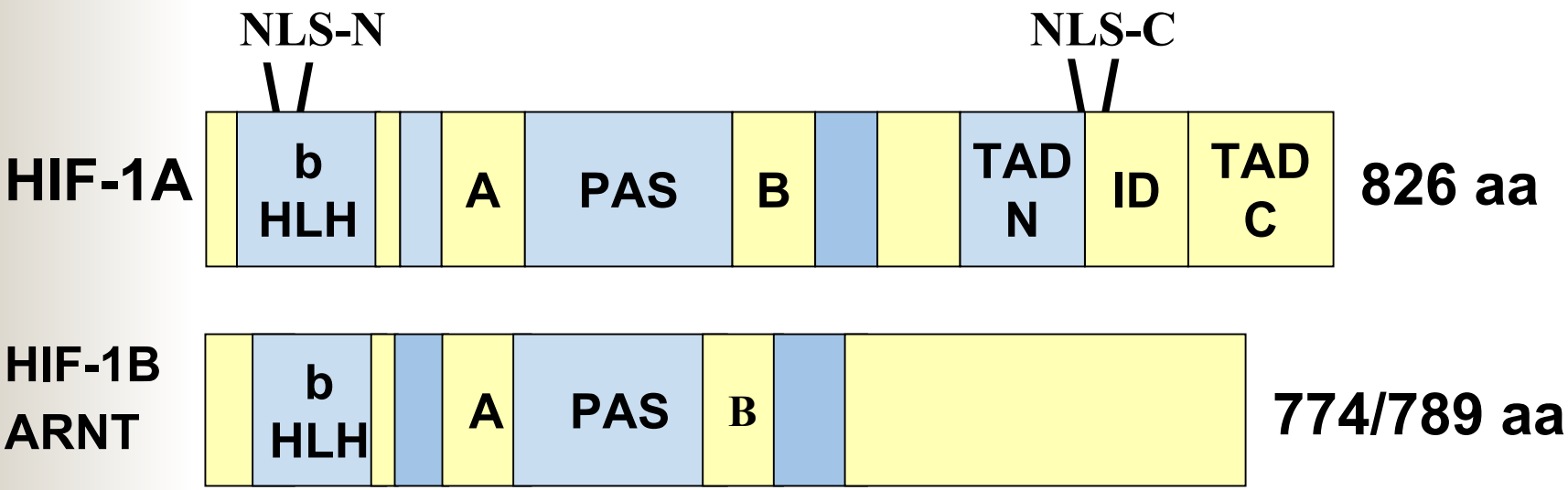
Prolyl hydroxylase is O_2-dependent

- The activation of prolyl hydroxylase depends on several co-factors such as O_2, Fe^{2+}, α-ketoglutarate and ascorbate.
- Under hypoxia, prolyl hydroxylase cannot be activated. Thus,
- HIF-1 accumulates and translocates into nucleus. In the nucleus, it binds to HIF-1β forming HIF-1.
- HIF-1 binds to co-activators CBP/p300 and is then activated.

HIF-1 is a heterodimer



Human HIF1A and HIF1B gene structures



Both bHLH and PAS are essential for dimerization and DNA-binding.
bHLH: basic helix-loop-helix domain;
PAS: domain with A and B repeats, amino-terminal (N) and carboxyl-terminal (C) nuclear localization signal (NLS);
TAD: transactivation domain;
ID: transcriptional inhibitory domain.

Iyer NV (1998). *Genomics.* 52:159-165.

B. Where is HIF-1?

Ubiquitous Expression

- **mRNA:**
  brain, heart, kidney, lung, liver, pancreas, plancenta, skeletal muscle and all human tissues checked so far.

- **BLAST Search:**
  Bone, fetal and adult brain, pancreatic islets, retina, uterus and white blood cells.
  Wiener CM (1996). *Biochem Biophys Res Commun.* **225**: 485-488.

C. What does HIF-1 do?

1. **Helps normal tissues as well as tumors to survive under hypoxic conditions**
2. **HIF-1 is a transcription factor that turns on genes needed for survival under hypoxic conditions.**
3. **So far, more than 40 target genes have been found to be regulated by HIF-1.**
4. **These genes can be classified into 3 main groups:**

HIF-1 Target Genes

- Erythropoeitin (EPO)
- Nitric oxide synthase 2 (NOS2)
- Transferrin
- Transferrin receptor
- Vascular endothelial growth factor (VEGF)
- VEGF receptor FLT-1

Group 1: O_2 Delivery

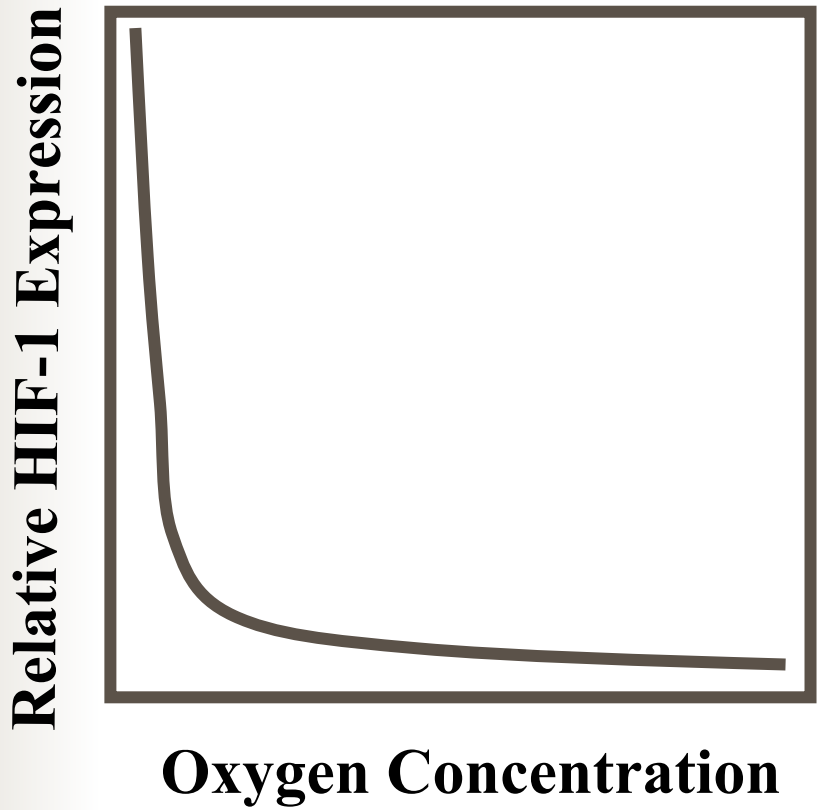
Aldolase A
Aldolase C
Enolase 1 (ENO1)
Glucose transporter 1
Glyceraldehyde phosphate dehydrogenase
Hexokinase 1
Hexokinase 2
Lactate dehydrogenase A
Phosphofructokinase L
Phosphoglycerate kinase 1
Pyruvate kinase M

Group 2: Glucose /Energy Metabolism

Insulin-like growth factor 2 (IGF-2) **IGF binding protein 1** **IGF binding protein 3** **p21** **p35srj**	**Group 3: Cell Proliferation /Viability**

D. How does HIF-1 do the job?

Protein Expression as a Function of [O_2]



HIF-1 expression increases exponentially when O_2 concentration decreases. The curve shows a point of inflection around 4-5% O_2, which is the O_2 concentration in normal human tissues.

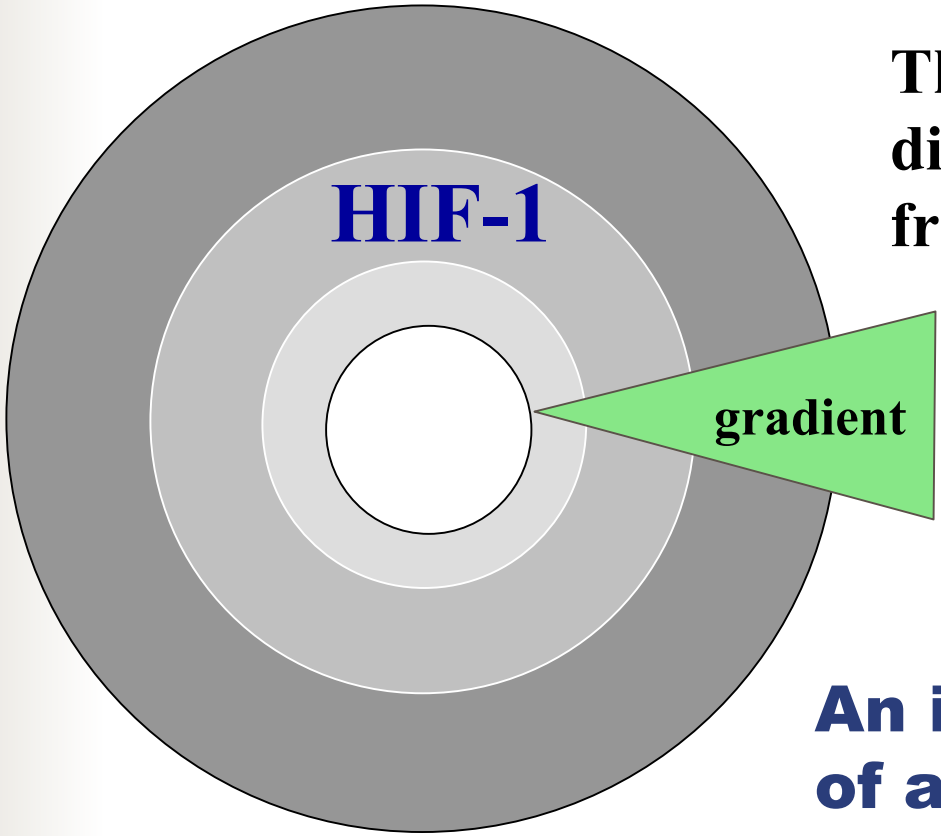
Semenza GL. (1997) *Kidney Int.* **51**:553-555

Hypoxia is widespread in tumors

- Tumor blood vessels are highly irregular and disorganized.
- Most human solid tumors have pO_2 values lower than their normal tissues of origin.
- Severe hypoxia can rarely be found in normal tissues, but these regions always exist in tumors.

- So, tumor cells are living in a low oxygen and low nutrient environment.
- But tumor cells are usually proliferating faster than normal cells.
- Therefore, the ability of tumor cells to sense and adapt to low oxygen (hypoxia) is essential for tumor growth.

Among the first responses at the onset of hypoxia is an increase in the protein levels of hypoxia-inducible factor-1 (HIF-1)



The oxygen and nutrients display a gradient away from the necrotic center

O_2, glucose, growth factors

An idealized diagram of a tumor cross section

HIF-1α Correlates with Tumor Vascularity

- **Low oxygen tension is associated with increased metastasis and decreased survival of patients**
- **The expression of HIF-1α is positively correlated with tumor vascularity.**

Zagzag D. (2000) *Cancer.* 88:2606

Summary

- **HIF-1 is a transcription factor that is composed of HIF-1α and HIF-1β subunits.**
- **More than 40 target genes have been found to be regulated by HIF-1.**
- **HIF-1 expression is positively correlated with tumor vascularity, indicating HIF-1 plays a crucial role in tumor angiogenesis progression.**
- **HIF-1α is degraded by proteasome *via* VHL.**

Finally…

Thank you for stopping by.