Hypoxia in Cancer

BASED ON THE REVIEW:

Oxygen sensing and hypoxia signalling pathways in animals: the implications of physiology for cancer

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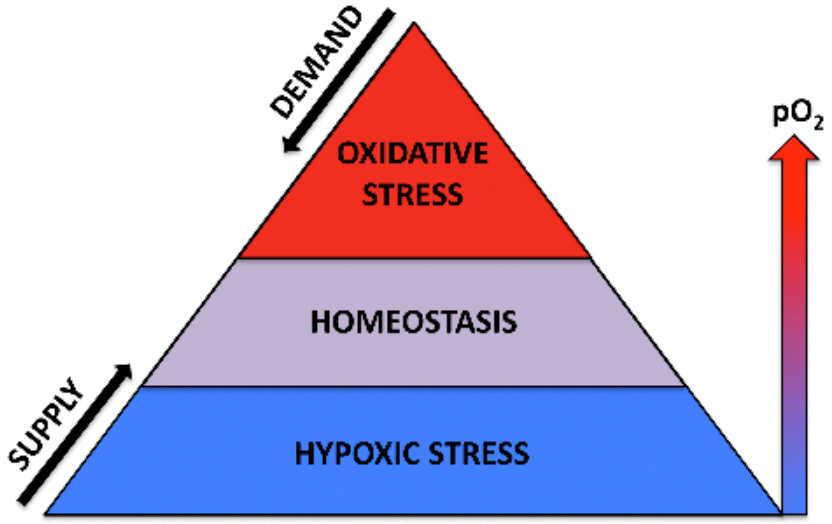
Lisbon, 2015

Oxygen demand

Maintenance of homeostasis requires robust mechanisms to detect and respond to alterations in O_2



Hypoxia induced factors - HIFs

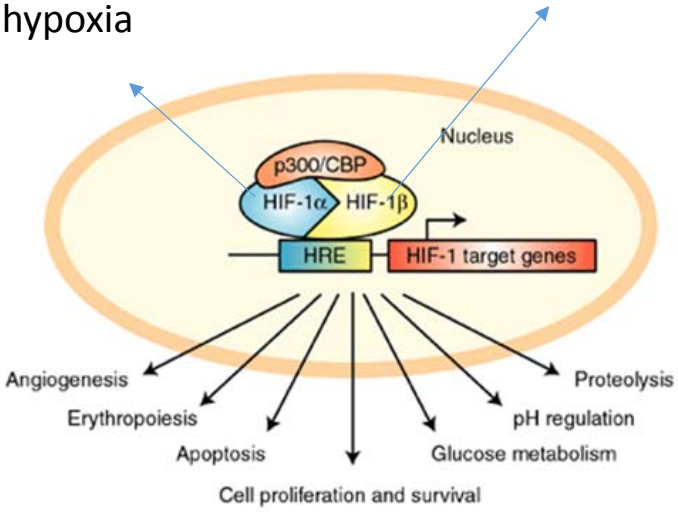
Transcription factor

Expressed widely in mammalian cells

500 different direct transcriptional targets

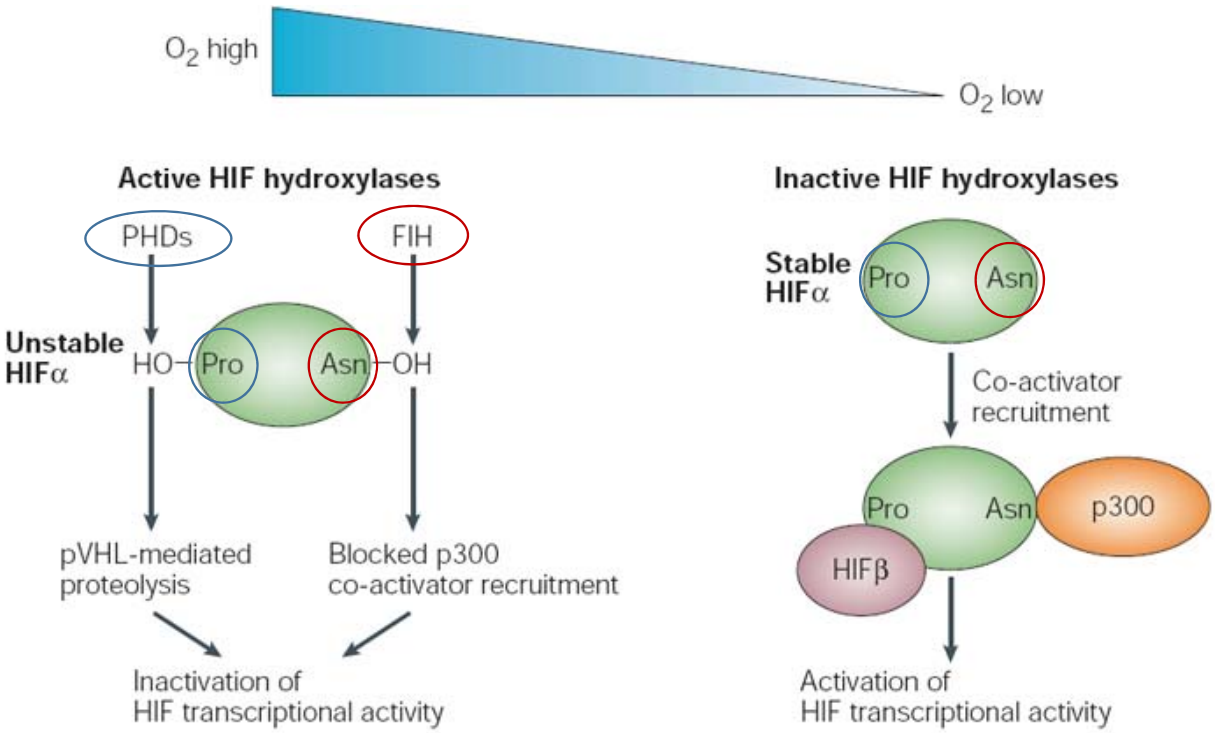
Specifically involved in response to hypoxia

Constitutively expressed, mediates several transcriptional responses



Adapted from: Expert Reviews in Molecular Medicine 2005

Regulation of HIF by HIF hydroxylases



3 Prolyl hydroxylases

PHD1 - prolyl hydroxylase domain 1

PHD2

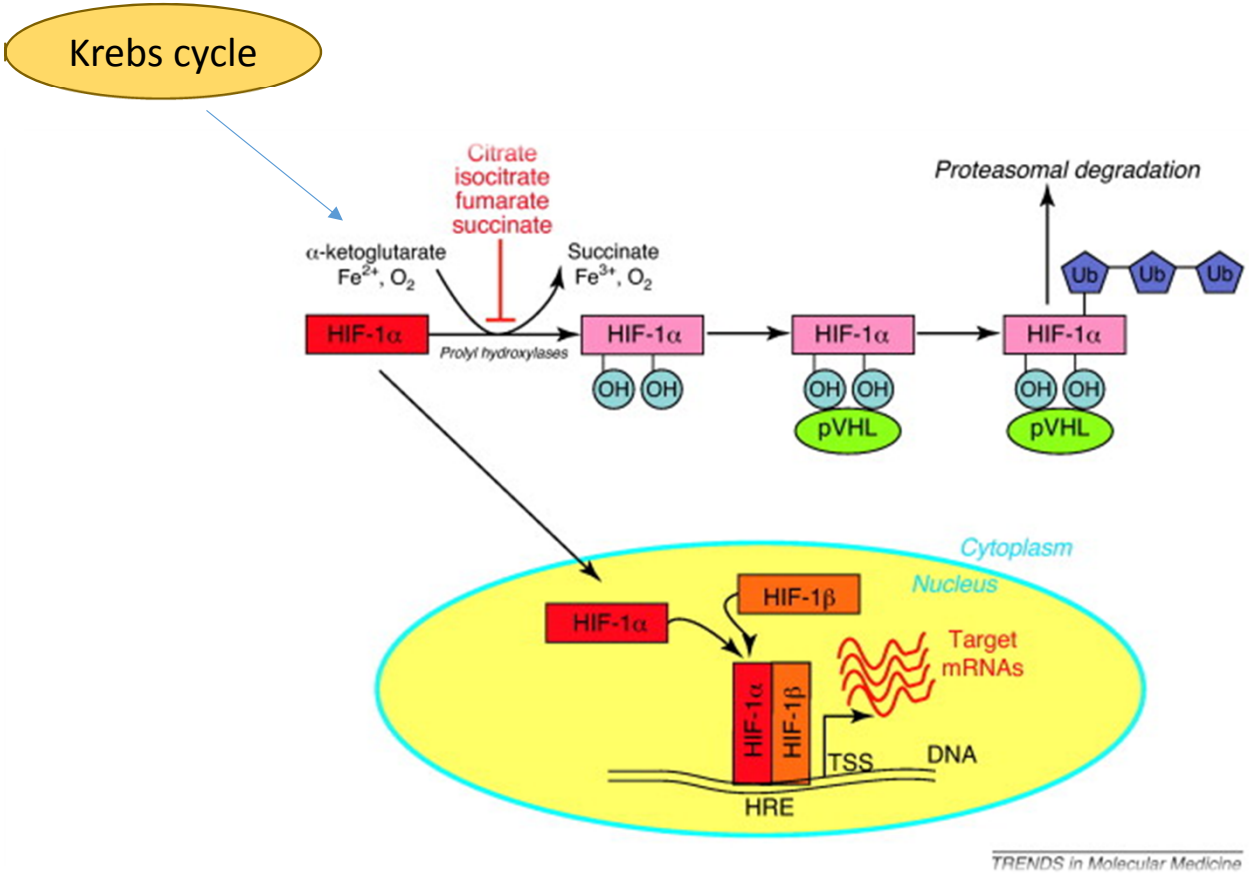
PHD3

1 asparaginyl hydroxylase

FIH – factor inhibiting hypoxia

Schofield, C. J. & Ratcliffe, P. J. Oxygen sensing by HIF hydroxylases. *Nature Reviews Molecular Cell Biology* 5, 347 (2004).

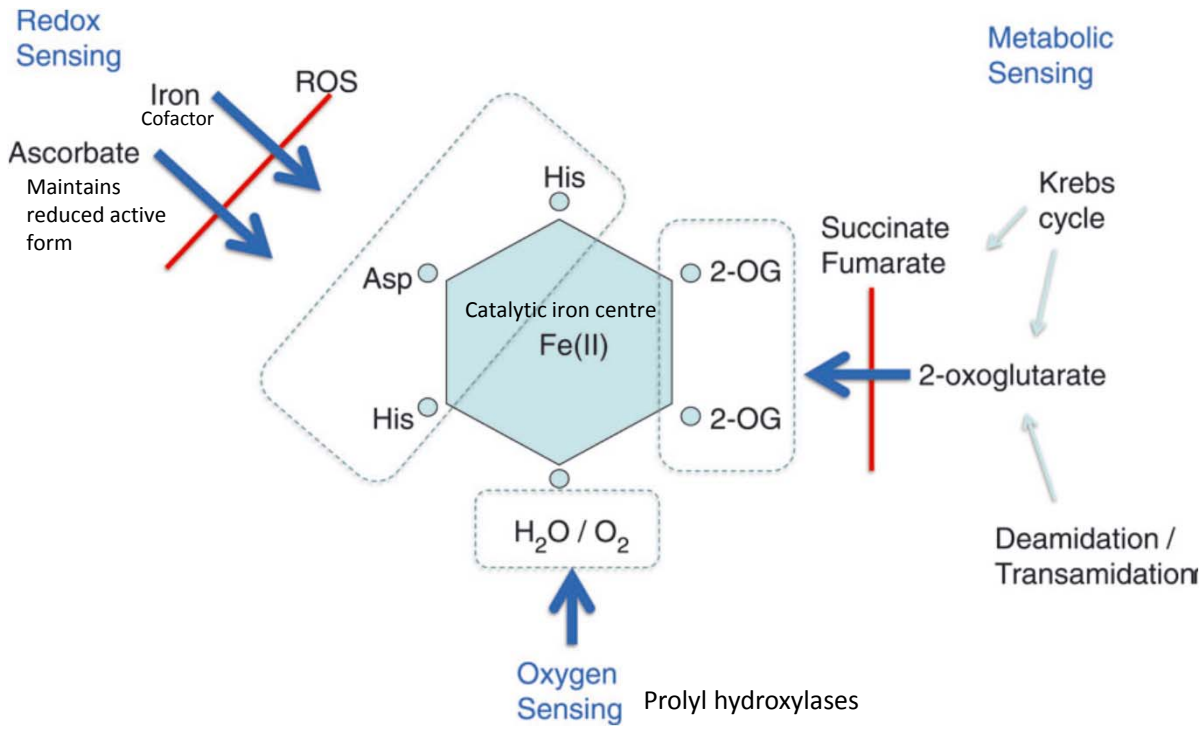
Hydroxylases - 2-oxoglutarate-dependent dioxygenases



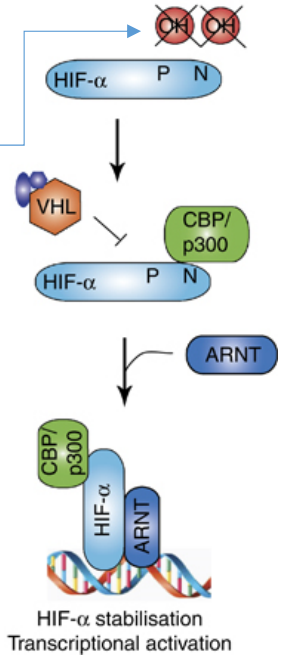
Sensing by HIF hydroxylases

Hydroxylase

Asparagynyl hydroxylases



When Krebs cycle is compromised, amount of 2-OG not enough to activate the enzime



Regulation of ‘hard-wired’ HIF hydroxylase pathways

Physiological ‘range finding’ mechanisms

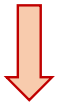
Oxygen homeostasis:

- Cardiopulmonary and ventilatory control

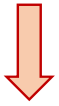
- Cell physiology dysregulation

Different ‘set points’ in different tissues

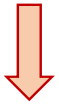
Oxidative stress



Inactivation of a proportion of HIF hydroxylases



Range finding mechanism

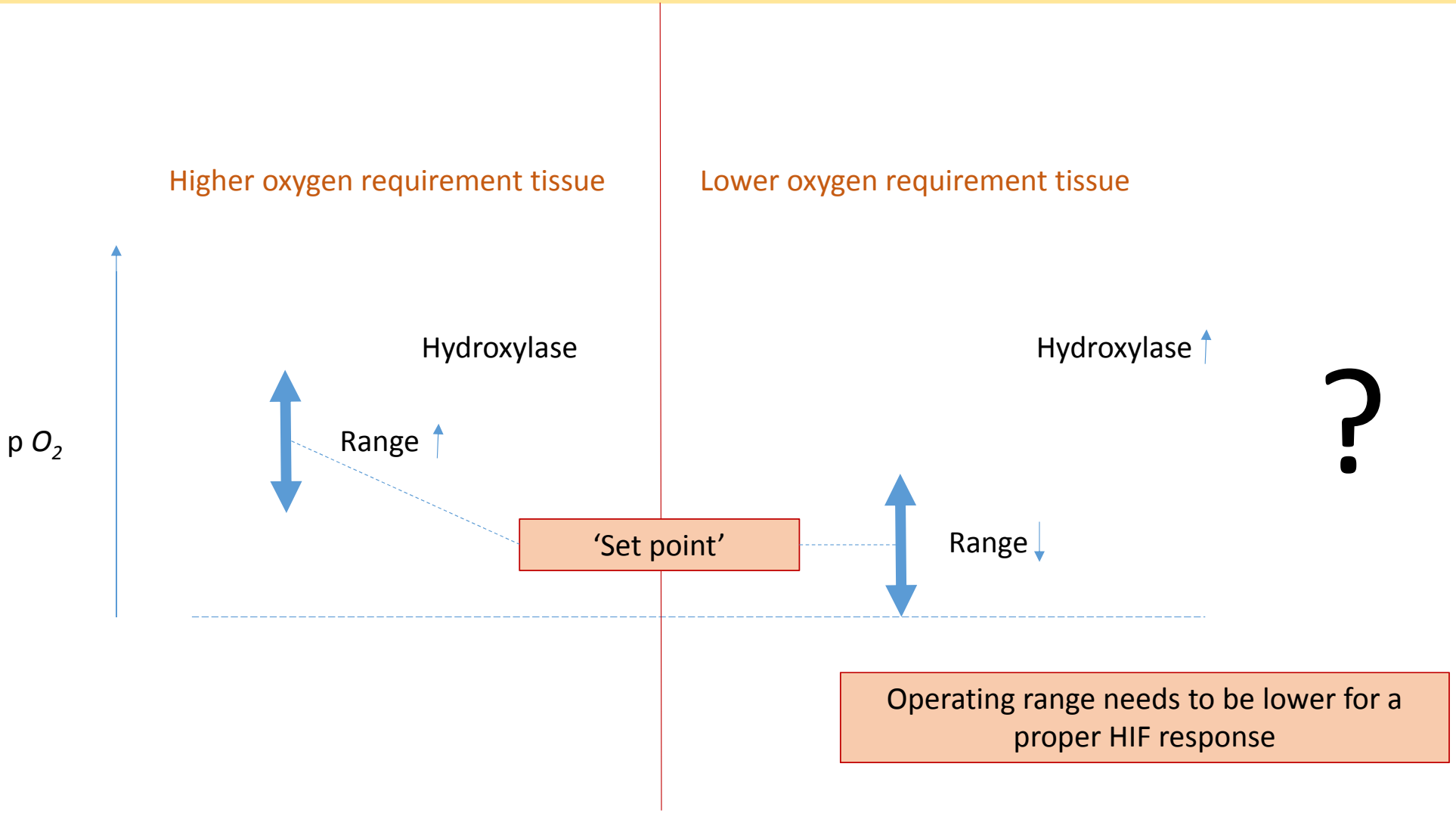


Alteration of oxygen sensing ‘set point’

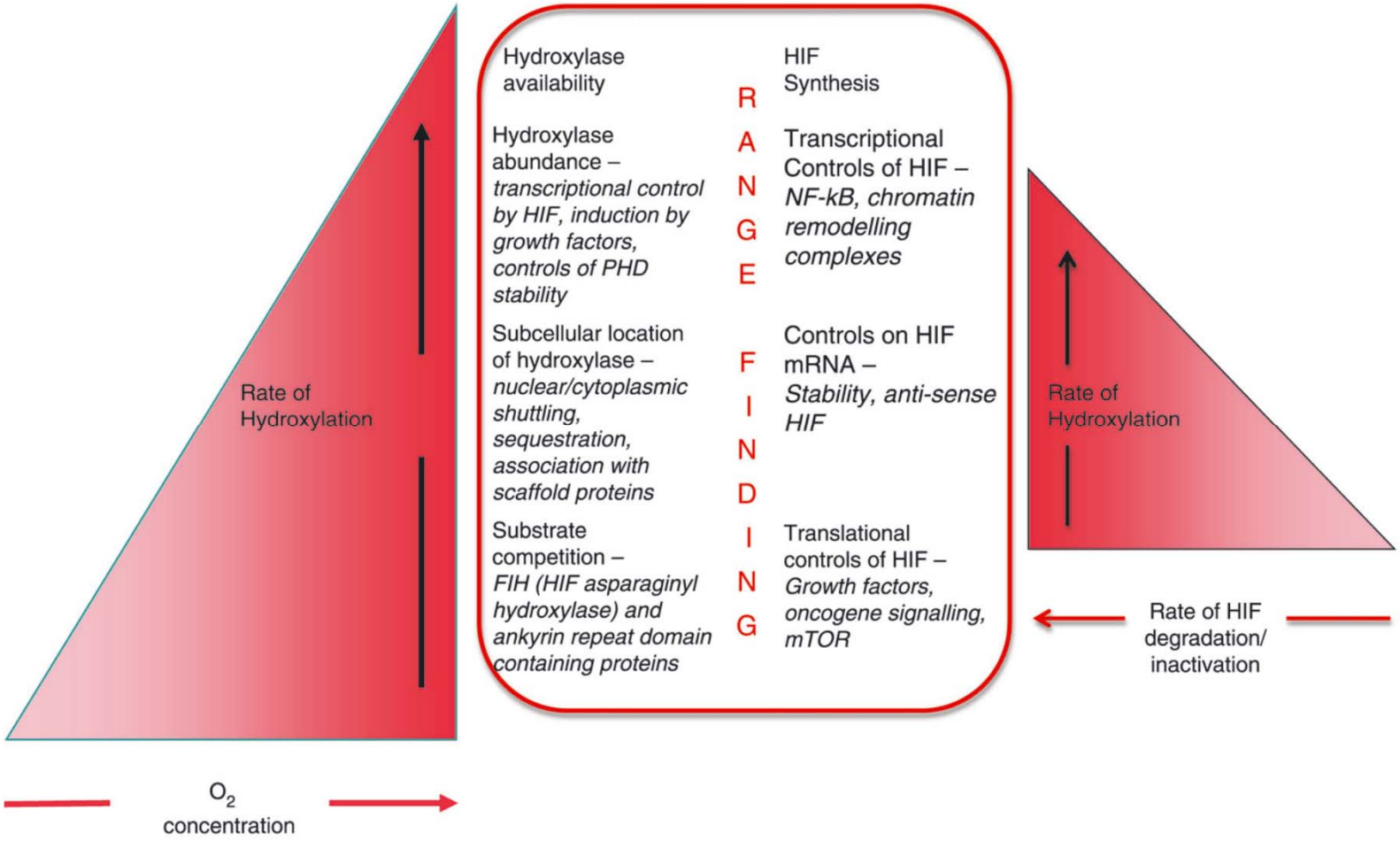
Range finding across cells operating at different oxygen tensions

Tissue operating at lower oxygen levels -> induction of PDH -> Lower operating range of HIF -> match more closely to tissue oxygen tension

Physiological ‘range finding’ mechanisms



‘Range finding’ by hydroxylases



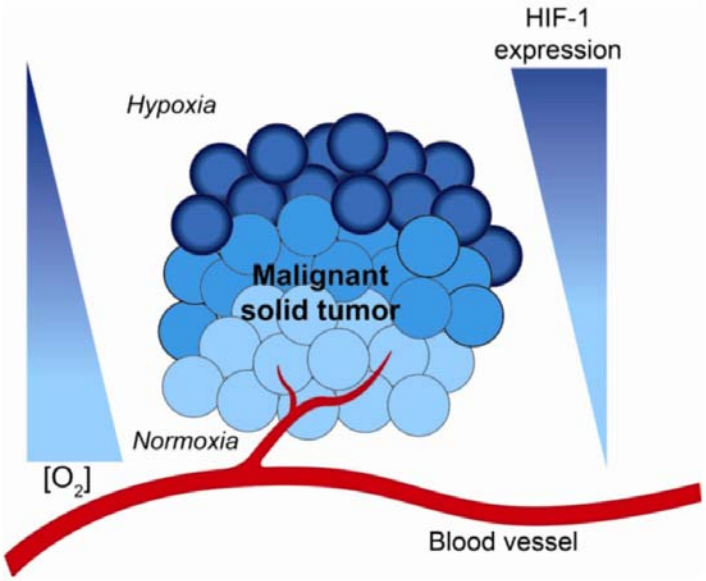
HIF control:

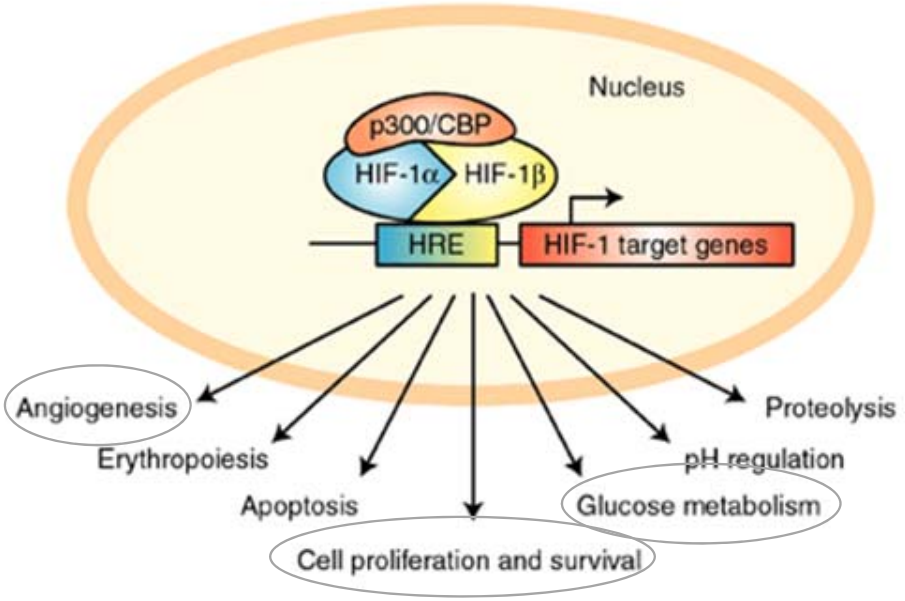
Rbx-2 : pVHL componente that promotes more rapid destruction of HIF α

HIF3α isoform

HIF pathway and cancer

Solid tumors have areas of severe hypoxia –> activation of HIF -> bad prognosis



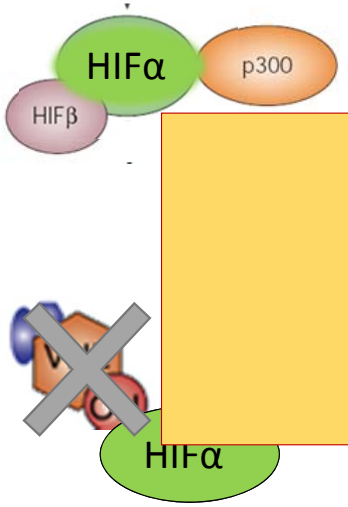


The effect of HIF activation leads to enhanced glucose uptake

This is why 18 fluorodeoxyglucose tomography is used in cancer diagnosis

HIF pathway and cancer

Does HIF signalling activation drive the malignant phenotype?



- Directly targets “cancer associated” genes (e.g. invasion, angiogenisis)
- Mechanistically linked to oncogenic pathways

However

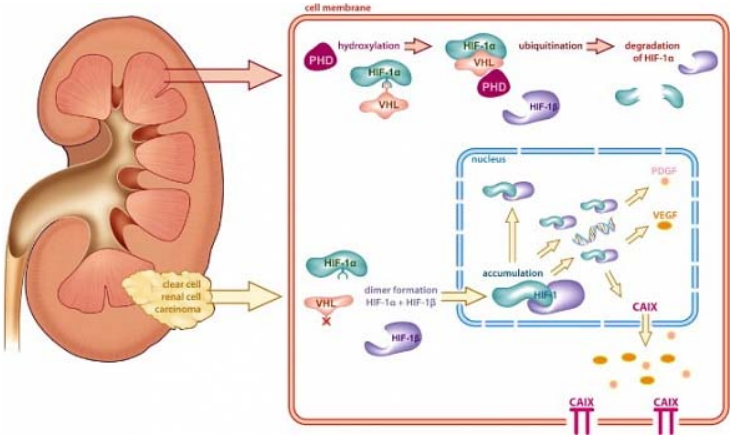
HIF mutations are not found in cancer

) leads to

Other tumor suppressor protein mutations (e.g. PTEN)

Mutation of Krebs cycle enzymes

HIF pathway and cancer – mixed results



- HIF can have beneficial or negative effects on tumour growth in pVHL deficient renal cancer (CCRC)

- Small number of inactivating mutations of HIF1α in these types of cancer

- Pro- *versus* anti-tumourigenic actions of HIF are highly context specific

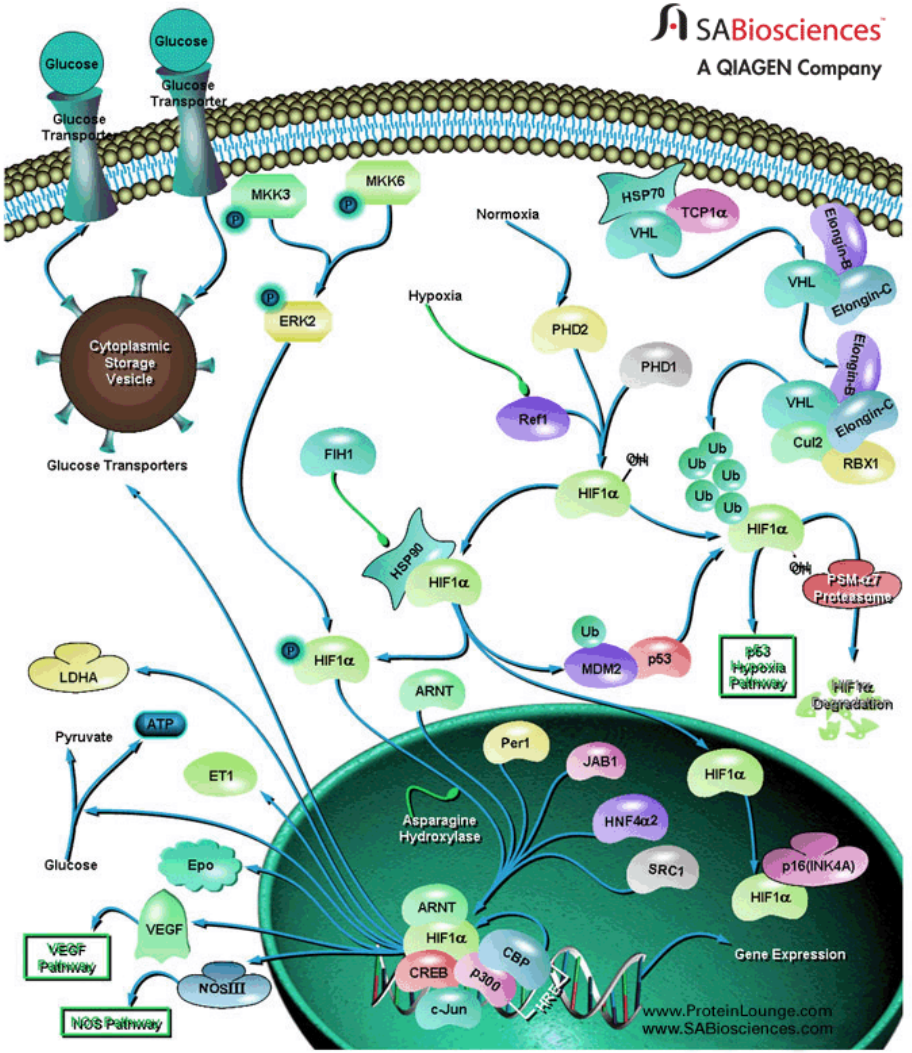
How does the complexity of the hypoxia response explain this paradox?

HIF pathway and cancer - considerations

HIF hydroxylase pathways are extremely complex
Oncogenic mutations interfere with whole cell metabolism and physiology

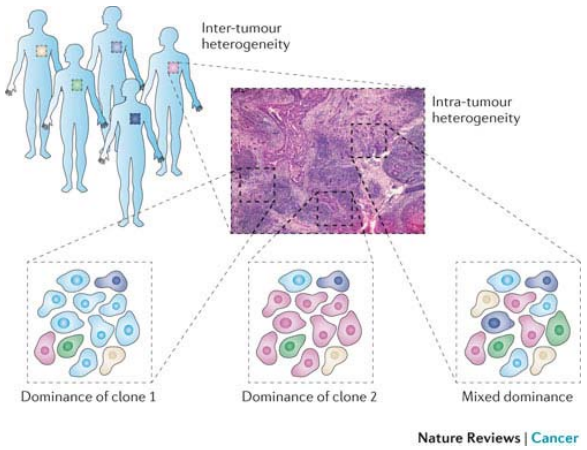
Cancer microenvironment
Activation of HIF response – 'Hard-wired' network dependent

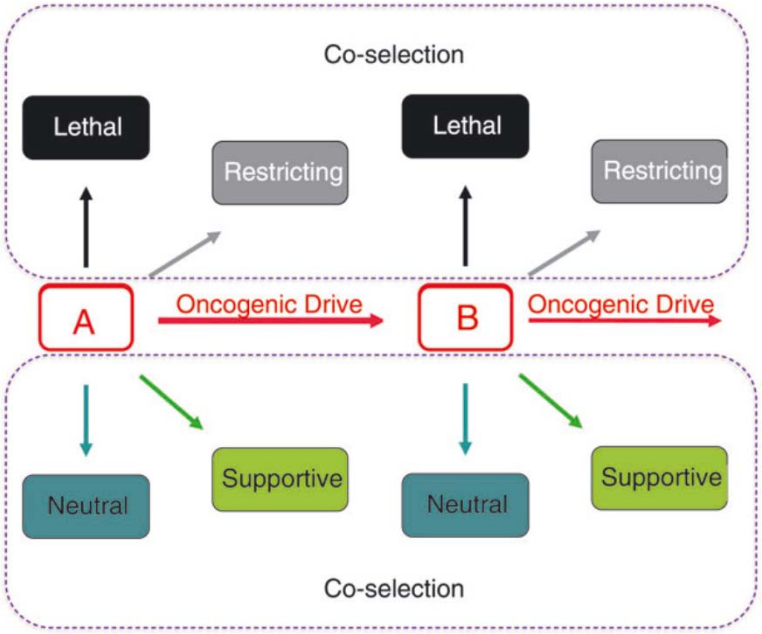
The balance between penalty and oncogenic advantage of dysregulating a physiological pathway is specific to the cellular context



Tumour clonal selection – Co-selection?

Clonal selection is done thorwards the alteration in balance that represents a more oncogenic profile



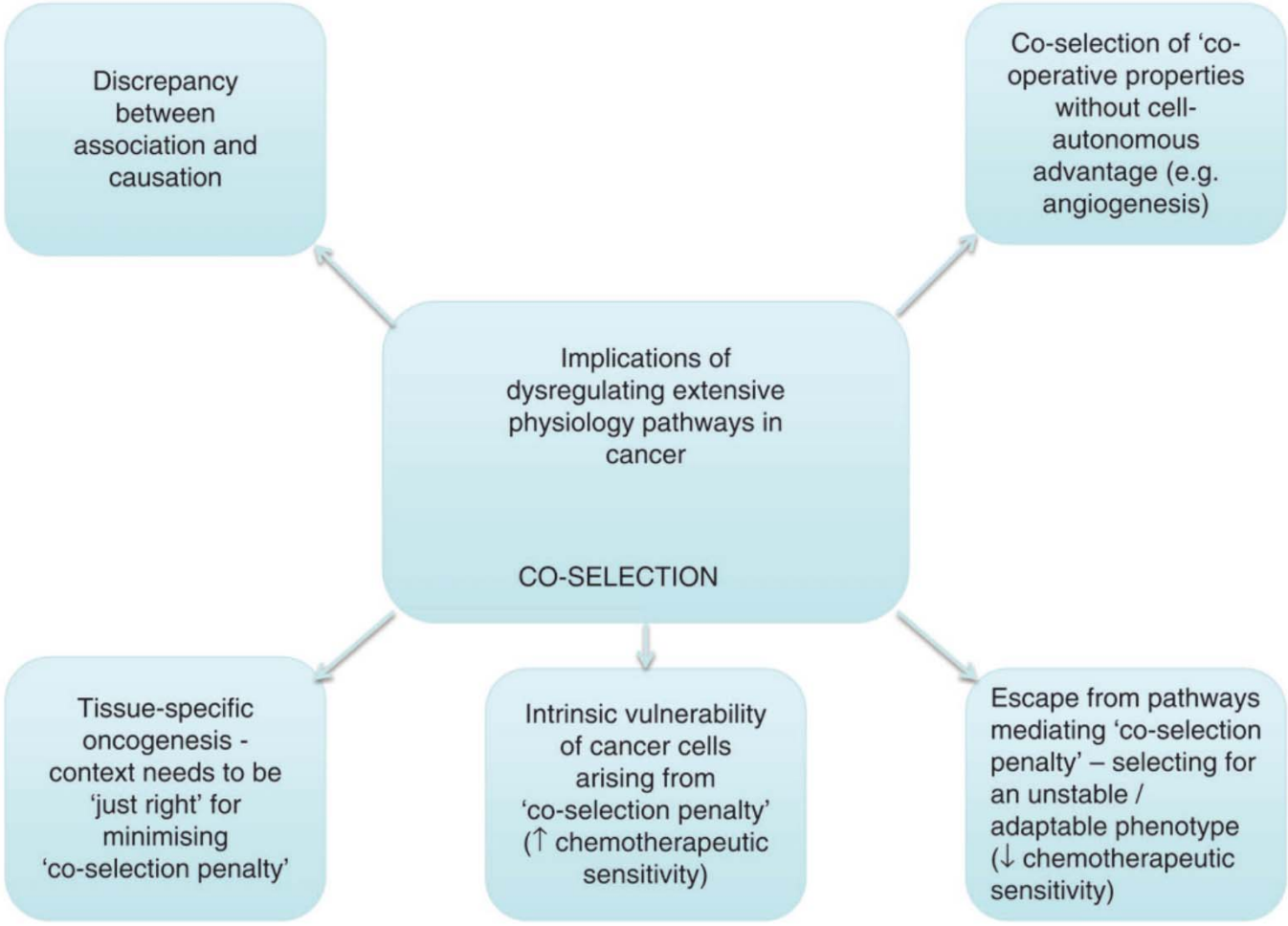


Co-Selection might explain observation of cancer properties that are difficult to rationalize

Selection of ‘hard-wired’ pathways can be positive or negative for tumour

Depending on resulting phenotype after ‘range finding’and specific cellular context

Implications of co-selection penalty in cancer



Conclusion

HIF activation has to be ‘just right’ so the tumor compensates for the penalty that might occur from co-selection

Co-selection leads to adaptable phenotype

Therapy resistance

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