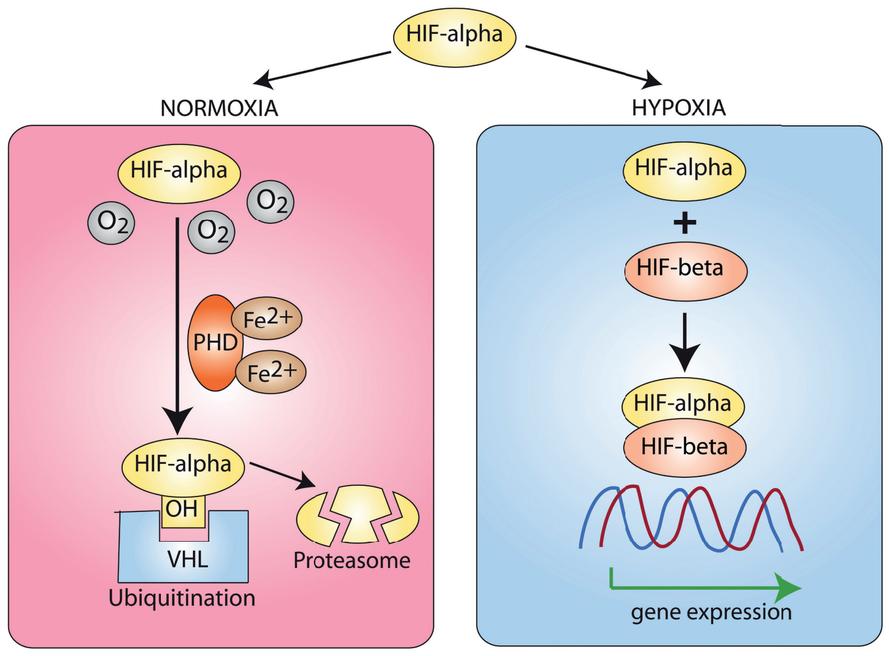
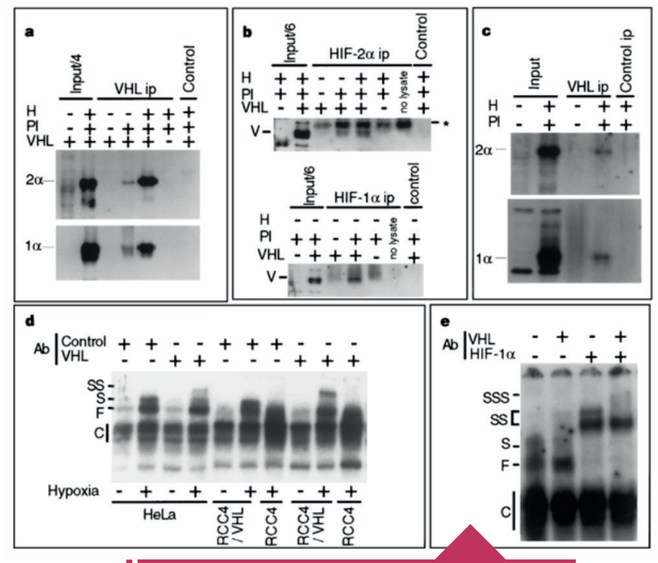
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

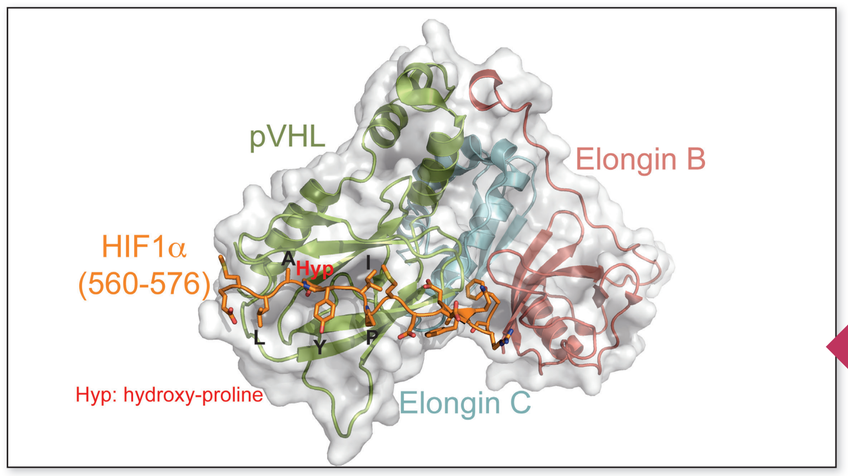
Cancer cells reveal a ubiquitous mechanism of adaptation to changing levels of oxygen

Oxford professor John Scott Haldane (left) studied the effects of altitude on respiration at Pike's Peak in Colorado in 1911. His assistant Mabel Purefoy Fitzgerald (second from left) travelled alone to remote mining communities to collected blood samples between 6000 and 12,500 feet, showing that the haemoglobin levels increased continuously with altitude





Immunoblots showing association of pVHL with HIF-1



The crystal structure of a hydroxylated HIF-1α peptide bound to VCB (pVHL, elongins C and B) reveals a single, conserved hydroxyproline-binding pocket in pVHL

WHAT WAS KNOWN

- At low oxygen concentrations (e.g. at altitude) the body increases production of red blood cells (erythropoiesis) and blood vessels (angiogenesis)
- Some kidney cancers are associated with excessive erythropoiesis and angiogenesis. These cancers carry mutations in the gene for the von Hippel Lindau (VHL) tumour suppressor protein
- HIF is continually produced and destroyed in the cell in the presence of oxygen, but stabilised by hypoxia
- Cobalt, which competes for sites with iron, also increases erythropoiesis, indicating that a ferroprotein oxygen sensor may be involved

WHAT WE DID

- Examined gene expression in response to hypoxia in VHL-deficient cell lines and after transfection with a normal VHL gene
- Tested for physical association between VHL and HIF proteins
- Measured the effect of VHL on HIF stability

WHAT THIS ADDS

- Demonstrates a critical role for the VHL gene product pVHL in regulating HIF-1 and hence regulating a broad range of responses to hypoxia
- VHL-defective cells stabilise HIF subunits, mimicking the effects of hypoxia
- Oxygen-dependent destruction of HIF can be restored by re-expression of pVHL
- pVHL and HIF form complexes, but in cells exposed to cobalt ions, HIF dissociates from pVHL, suggesting that iron-dependent interaction between VHL and HIF is necessary for the oxygen-dependent degradation of HIF
- Subsequent work demonstrated that the key modification promoting association between VHL and HIF is prolyl hydroxylation and elucidated the structural basis of this key oxygen dependent switch

REFERENCES

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