Macromolecole della risposta alla pressione parziale di ossigeno

In mammals, O2 sensing occurs at many levels, leading to both **acute and chronic** adaptation

Quesiti

Erythrocyte regulation of 2,3-BPG





homeostatic mechanism for elevating 2,3-BPG levels, thereby enhancing oxygen release to tissues L'effetto Bohr: pH bassa \rightarrow bassa affinità \rightarrow rilascio di O₂



homeostatic mechanism for elevating 2,3-BPG levels enhancing oxygen release to tissues



Fig 1. The hypoxia-inducible factor (HIF) transcriptional cascade directly regulates genes with key functions in a broad range of processes. The complex binds in a sequence-specific manner to control elements in DNA, termed hypoxia-response elements, at target gene loci.

O2 sensing Regolazione di HIF ?





4-hydroxypyrrolidine-2-carboxylic acid



UBIQUITINIZZAZIONE



UBIQUITINA





UBIQUITINA





HIF e VHL fanno parte di complessi molecolari con molte componenti

VHL Function







The Cullin protein act as a scaffold that brings together the substrate recognized by pVHL and the E2-conjugating enzyme





HIF-2α is recruited to the complex via the β domain of pVHL, which recognizes the hydroxyproline posttranslation modification



Cul2 recruits pVHL at its N-terminal region through an adaptor subunit constituted by a dimeric complex formed by Elongin B (EloB) and Elongin C (EloC)

Rbx¹

ullin-2



Cullin RING E3 ubiquitin ligases catalyze the transfer of ubiquitin from the E2-conjugating enzyme to the target substrate



VHL Function: the difference in Kd for hydroxylated versus non-hydroxylated CODD is $\sim 1,000$ -fold (33 nM versus 34 µM)

