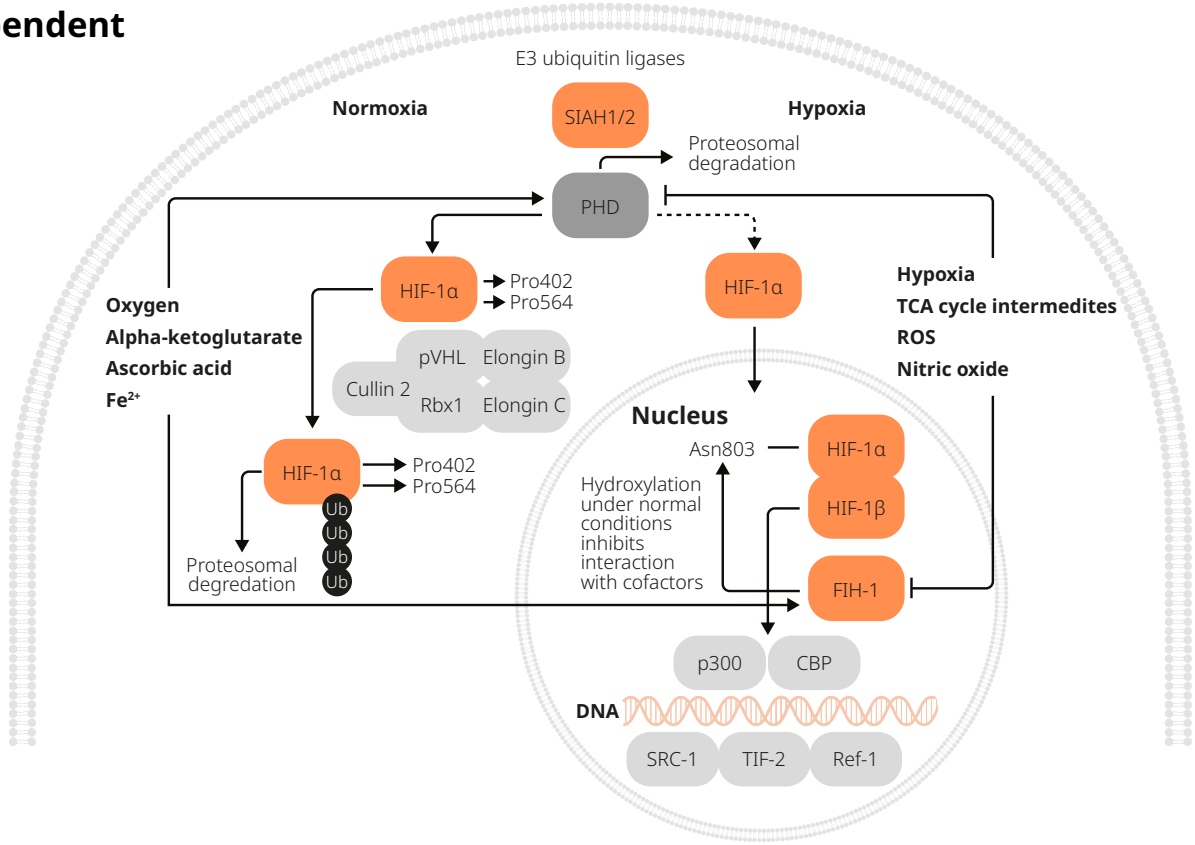
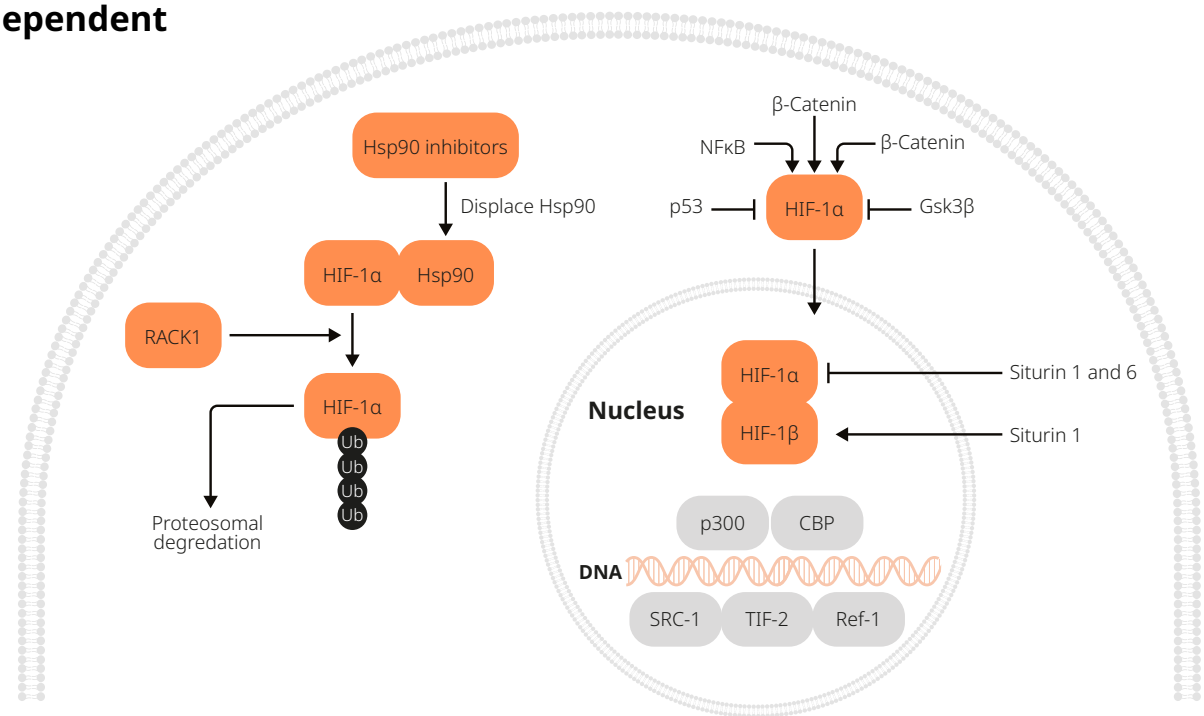
HIF-1α pathways

Oxygen dependent



Under normoxic conditions, HIF-1α is hydroxylated by oxygen-sensing HIF-1α-specific prolyl hydroxylases (PHD1-3). Hydroxylation triggers poly-ubiquitination of HIF-1α, which targets it for proteosomal degradation by an E3 ubiquitin ligase - the von Hippel-Lindau protein (pVHL) complex. HIF-1α subunits are also substrates for an asparaginyl hydroxylase, FIH-1 (factor inhibiting HIF-1α). FIH-1 also senses oxygen, and hydroxylation by FIH-1 disrupts a critical interaction between HIF-1α a subunits and co-activators such as p300/CBP, impairing HIF transcriptional activity. Hypoxia and TCA cycle intermediates inhibit hydroxylation, stabilizing the protein and allowing interaction with co-activators, resulting in transcription of target genes.

Oxygen independent



Regulation of HIF-1α stability can also be mediated by an oxygen-independent pathway. In the cytoplasm, HIF-1α is bound to heat-shock protein 90 (Hsp90), leading to enhanced HIF-1α stability. Displacement of Hsp90 by inhibitors allows RACK (receptor of activated protein C kinase) to bind and recruit ubiquitin ligase machinery, leading to HIF-1α degradation.

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