Prolyl-hydroxylase domain containing protein 2: Structural insight from MD Simulations

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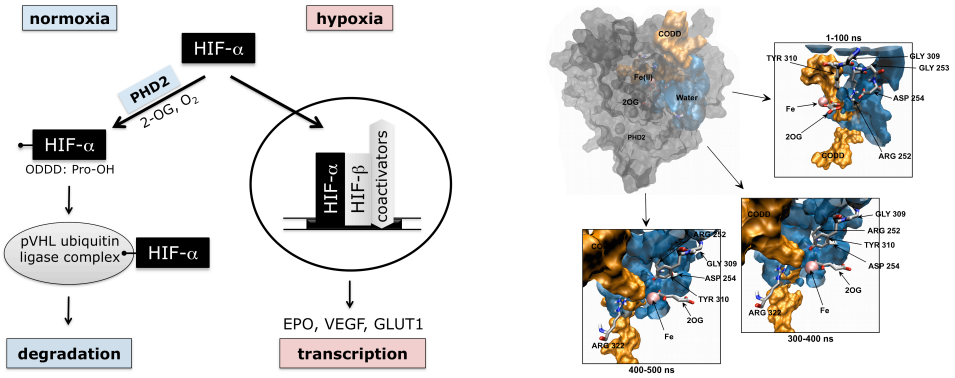
Prolyl-hydroxylase domain containing protein 2 (PHD2) is an iron(II), oxygen and 2-oxoglutarate (2OG) dependent dioxygenase that catalyses the hydroxylation of two proline residues (oxygen dependent degradation domains, ODDD) of the α-subunit of hypoxia-inducible factor (HIF-1α), one part of an α,β heterodimeric transcription factor.[1] Hydroxylation at one ODDD triggers recognition by the Von Hippel-Lindau tumor suppressor (pVHL) protein and leads to degradation of HIF-1α via the proteasome. In situations with low oxygen availability (hypoxia), HIF-1α levels increase in the cytoplasm and the transcription factor can translocate into the nucleus, where it up-regulates the transcription of genes that enable mammalian cells to adapt to hypoxia (e.g. EPO, VEGF, GLUT1).[2]

We describe computational studies of the mode of action of PHD2. Long-term Molecular Dynamics (MD) Simulations were performed to investigate the rigidity of the crystallographically observed conformations of PHD2 in solution. Furthermore we describe the influence of the C-terminal ODDD on the overall behavior of the protein, including the effect of the natural ligand 2-oxoglutarate and an isoquinoline inhibitor.



[1] J. Cassavaugh, K. M. Lounsbury, *J. Cell. Biochem.* **2011**, *112*, 735-744.
[2] R. Chowdhury, A. Hardy, C. J. Schofield, *Chem. Soc. Rev.* **2008**, *37*, 1308-1319.