Structural Insight into the Prolyl Hydroxylase PHD2

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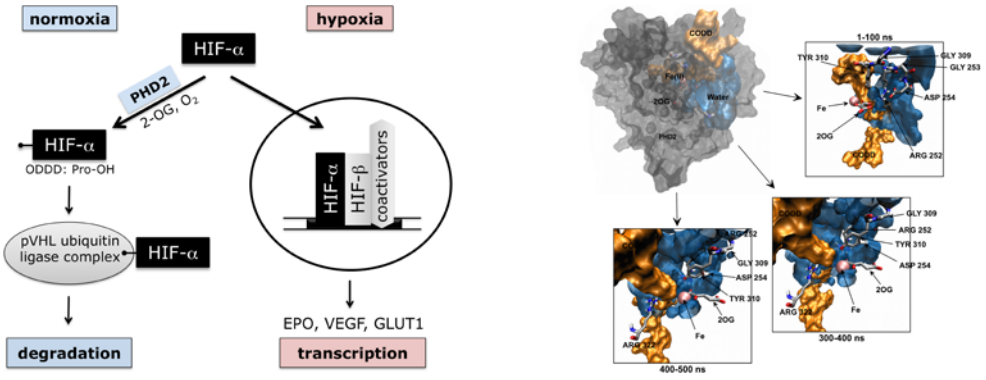
Hypoxia-inducible factors (HIF) take an constitutive part in the cellular response to hypoxia at the transcriptional level.[1] In states of low oxygen availability (hypoxia), the levels of the α-subunit of these α,β heterodimeric transcription factors (HIF-1α) increase in the cytoplasm. Therefore, HIF-1α can translocate into the nucleus, where it dimerizes with the β subunit and up-regulates the transcription of genes that enable mammalian cells to adapt to hypoxia (e.g. EPO, VEGF, GLUT1).[2] In situations with normal oxygen supply (normoxia), continued degradation of HIF-1α takes place in the cytoplasm. This degradation is directly connected to oxygen availability by α-ketoglutarate (α-KG) dependent dioxygenases, e.g. the prolyl hydroxylase domain containing protein 2 (PHD2). PHD2 is an iron(II), oxygen and α-KG dependent dioxygenase that catalyses the hydroxylation of two proline residues (oxygen dependent degradation domains, ODDD) of HIF-1α. 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.

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.