Substrate selectivity of prolyl hydroxylases

The cellular response to chronic hypoxia is regulated by the hypoxia inducible factor (HIF) system in animals. Under normoxic conditions the human prolyl hydroxylases (PHD) 1 and 2 efficiently catalyse the stereo selective prolyl-4-hydroxylation of either of two residues in the HIF oxygen degradation domains CODD (Pro564) and NODD (Pro402), having a preference for CODD. Extensive structural and biochemical studies on prolyl-4-hydroxylases including human PHD2, *Tricoplax adherens* PHD, *Pseudomonas* PHD, (*Bacillus*, algal and viral) collagen PHs (CPHs) and the human prolyl-3-hydroxylase OGFOD1 have informed on similarities and differences in their substrate- and stereo-selectivity determinants. These findings have implications for inhibitor design and are actively leading to an assortment of novel compounds targeting PHDs.