Crystal Structure of Human Indoleamine 2,3-dioxygenase

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Indoleamine 2,3-dioxygenase (IDO) catalyzes the cleavage of the pyrrole ring of indoleamines by the insertion of two oxygen atoms from molecular oxygen. This reaction is the first and the rate-limiting step in the kynurenine pathway, the major Trp catabolic pathway in mammals. IDO is a 45 kDa cytosolic protein containing heme as the prosthetic group that is essential for enzymatic activity. The crystallographic analysis of human IDO revealed that its polypeptide folds into two helical domains with unique folds. The heme is sandwiched between two domains. The heme iron is coordinated by His346 on the long helix in the proximal side of heme. A large pocket on the distal side of the heme is composed of hydrophobic residues, suggesting that the indole ring in the substarte are recognized only through hydrophobic interactions. It is unlikely that any amino acid group can interact with iron-bound oxygen. These findings suggest that the dioxygenase reaction would be triggered by subtracting the proton from the nitrogen atom in the 1-position of substrate indoleamine by the iron-bound oxygen.

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