

P026 The role of histidine in tryptophan 2,3-dioxygenase
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Tryptophan 2,3-dioxygenase (TDO) from *Xanthomonas campestris* is a heme-containing enzyme from a small family of homologous enzymes, which includes indoleamine 2,3-dioxygenase (IDO). TDO is a homotetrameric enzyme and displays high specificity for L-tryptophan (L-Trp) and related derivatives such as 6-F-Trp. TDO and IDO have been implicated in a number of physiological conditions, including suppression of T cell proliferation and the immune escape of cancers, making them attractive targets for drug discovery.

The structure of wild-type TDO in the catalytically active, ferrous form in complex with L-Trp revealed that TDO is an induced-fit enzyme with significant structural changes on substrate binding. Histidine 55 hydrogen bonds to L-Trp, precisely positioning it in the active-site and may act as an active site base. The substitution of histidine 55 by alanine and serine (H55A and H55S) provides insight into the precise molecular mechanism used to control substrate binding. The crystal structures of H55A and H55S in complex with L-Trp, in conjunction with potentiometric and kinetic studies, reveal that histidine 55 is not essential for turnover, but controls the binding of substrate to the active site. The possibility that this residue acts as an active site base is discussed in relation to the catalytic mechanism and related heme proteins.