Poster Presentation

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Structural basis for the histamine synthesis by human histidine decarboxylase

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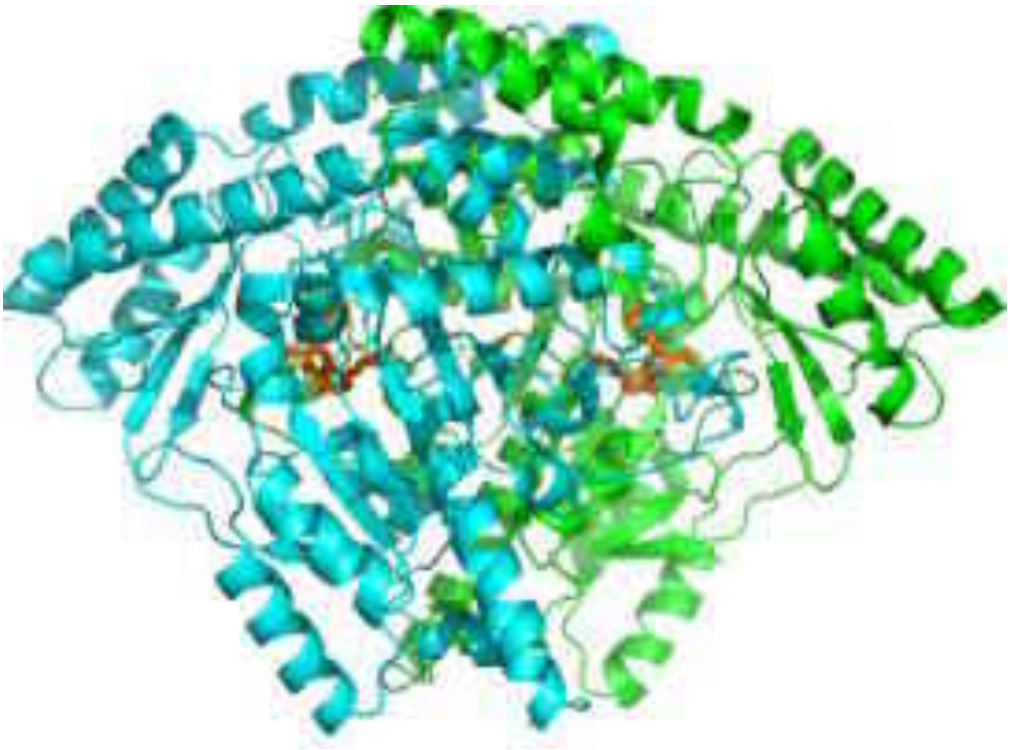
Histamine is a bioactive amine responsible for a variety of physiological reactions, including allergy, gastric acid secretion, and neurotransmission. In mammals, histamine production from histidine is catalyzed by histidine decarboxylase (HDC). Mammalian HDC is a pyridoxal 5'-phosphate (PLP)-dependent decarboxylase and belongs to the same family as mammalian glutamate decarboxylase (GAD) and mammalian aromatic L-amino acid decarboxylase (AroDC). The decarboxylases of this family function as homodimers and catalyze the formation of physiologically important amines like GABA and dopamine via decarboxylation of glutamate and DOPA, respectively. Despite high sequence homology, both AroDC and HDC react with different substrates. For example, AroDC catalyzes the decarboxylation of several aromatic L-amino acids, but has little activity on histidine. Although such differences are known, the substrate specificity of HDC has not been extensively studied because of the low levels of HDC in the body and the instability of recombinant HDC, even in a well-purified form. However, knowledge about the substrate specificity and decarboxylation mechanism of HDC is valuable from the viewpoint of drug development, as it could help lead to designing of novel drugs to prevent histamine biosynthesis. We have determined the crystal structure of human HDC in complex with inhibitors, histidine methyl ester (HME) and alpha-fluoromethyl histidine (FMH). These structures showed the detailed features of the PLP-inhibitor adduct (external aldimine) in the active site of HDC. These data provided insight into the molecular basis for substrate recognition among the PLP-dependent L-amino acid decarboxylases.

[1] *Y. Nitta et al. Food Chemistry 138, 1551-1556, (2013),* ***[2]*** *H. Komori et al. J. Biol. Chem. 287, 29175 - 29183, (2012),* ***[3]*** *H. Komori et al. Acta Cryst. F 68, 675 - 677, (2012)*



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