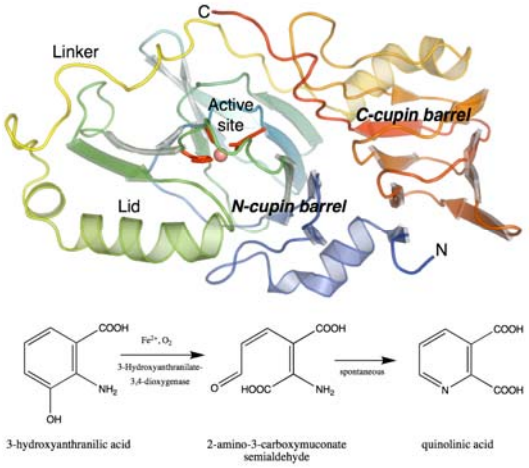
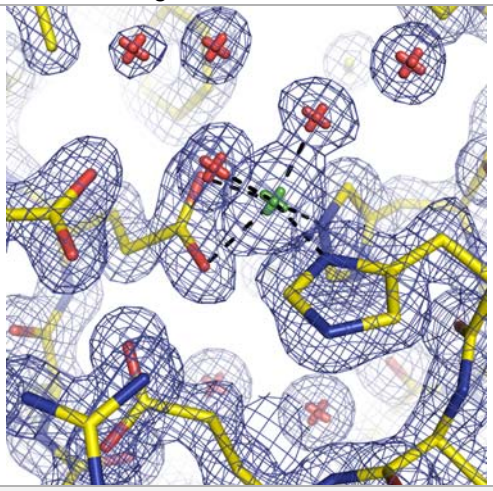
Center for Eukaryotic Structural Genomics

Protein Structure Initiative

Target ID	GO.43316	
Source Organism	*Homo sapiens*	
Target Name	BC029510	
PDB Entry	2QNK	Deposition: 17-Jul-2007
Function	3-hydroxyanthranilate-3,4-dioxygenase	
Produced From	*E. coli* BL834 p(RARE2) pVP-16-GW	
Structure by X-ray	Resolution: 1.60 Å	R-value (R-free): 15.7% (17.6%)
	No. of Residues/ASU: 286	Monomers/ASU: 1
Data Collected At	Advanced Photon Source GM/CA-CAT 23-ID-B, 06-July-2007	
Authors	E. Bitto, G.E. Wesenberg, G.N. Phillips, Jr., C.A. Bingman	





Structural Features

Ring-cleaving dioxygenases catalyze the oxygenolytic fission of catecholic compounds, an important step in the aerobic degradation of aromatic compounds. 3-hydroxyanthranilate-3,4-dioxygenase (3HAO) catalyzes fission of 3-hydroxyanthranilate (3HAA) to 2-amino-3-carboxymuconate semialdehyde, which spontaneously converts to quinolinic acid (QUIN). In normal metabolism, 3HAA is a key intermediate of catabolic metabolism of tryptophan, while QUIN is a crucial precursor in the biosynthesis of cofactors NAD^+ and $NADP^+$. Increased cerebral levels of the endogenous excitotoxin QUIN have been linked to neuronal damage in multiple neurological and inflammatory disorders, including Huntington's disease, epilepsy, Lyme boreliosis, and AIDS dementia.

The structure of human 3HAO revealed an internally dimerized protein with radius of gyration of 20.1 Å. The enzyme is comprised of an N-terminal cupin-barrel module with a helical lid, a linker, and a C-terminal cupin-barrel module. The two cupin-barrel modules are related by 2-fold symmetry. The N-terminal module shows high sequence identity (30 and 40%) as well as structural similarity to the 3HAO enzymes from *Ralstonia metallidurans* and *Saccharomyces cerevisiae*, respectively. The module contains a metal binding site in the active site as well as all important catalytic residues implicated in studies of *R. metallidurnas* 3HAO. The metal conducive to catalysis is Fe^{2+}. The structure was crystallized in the presence of non-catalytic Ni^{2+}. The C-terminal cupin-barrel module does not possess the metal site and is thus likely not catalytically functional. Interestingly, *R. metallidurans* and *S. cerevisiae* enzymes form homodimers from proteins containing a single cupin-barrel module. Human 3HAO bi-cupin core overlays closely with the homodimer core of these enzymes. It seems that the dimer interface of this enzyme remained highly conserved throughout evolution while underlying gene organization changed. Interestingly, it also seems that the C-terminal module lost catalytic function at certain point in evolution and underwent largely unconstrained evolution that still retained the overall fold.

Percent Identity with Nearest PDB Structure at Time Solved	26% (1IUQ)
Pfam Cluster	3-HAO
Sequence Cluster Size	126

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