Title

Cysteine Dioxygenase: The Importance of Key Residues and Insight into the Mechanism of the Metal Center

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Abstract

Cysteine dioxygenase (CDO) is a non-heme iron enzyme that can be found in mammalian tissue. It is mainly localized in the liver but is also present in the brain, kidney, and adipose tissue. CDO converts cysteine to cysteine sulfinic acid, which is the first step in cysteine metabolism in the human body. CDO contains a novel cofactor located near the metal binding site that is present in another enzyme, galactose oxidase, where it is essential for redox function. This suggests that the linkage may play an important role in CDO as well. The cofactor consists of Y157 and C93. Mutation of the C93S causes a drop in activity to 57.1% and a mutation of the Y157F causes a drop to 8.1%. The metal center was studied using XAS revealing that the addition of cysteamine, an activator of CDO, changes the conformation of the binding site significantly. CDO differs from the rest of the cupin super family in that it does not contain a 2-his-1-carboxylate binding motif but rather the carboxylate is replaced with another histidine. A mutation of one of the binding residues, H140D, caused the enzyme to be non-active. Also the mechanism of the CDO was studied by conducting activity assays with various inhibitors and activators that yielded contradicting results with previously published work.

First Advisor

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