The crystal structure of human Aldehyde Oxidase in native and inhibited forms

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Aldehyde oxidases (AOX; E.C. 1.2.3.1) are molybdo-flavoenzymes with broad substrate specificity, oxidizing aldehydes and N-heterocycles. AOX belongs to the xanthine oxidase (XO) family of Mo-containing enzymes. The true physiological function of AOX is still unknown, although it is recognized to play a role in the metabolism of compounds with medicinal and toxicological relevance [1]. AOX importance has increased in recent years since it is substituting Cyt-P450 as the central drug-metabolizing system in humans. We have solved the 3D structure of mouse AOX3 to 2.9 Å resolution [2] that was the first structure of an aldehyde oxidase, providing important evidences on substrate and inhibitor specificities between AOX and XO. The complement of AOX proteins in mammals varies from one in humans (hAOX1) to four in rodents (mAOX1, mAOX3, mAOX4 and mAOX3L1) as a result of evolutionary genetic events. Due to this unusual complement of AOX genes in different animal species, conclusions regarding protein metabolism in humans cannot be taken exclusively from the mouse model. Using the human aldehyde oxidase (hAOX1) purified after heterologous expression in Escherichia coli we were able to crystallize it and solve its 3D structure to 2.7 Å resolution (submitted). In addition to the native protein we also solved the structure of an inhibited form of the enzyme to 2.6Å resolution. Analysis of the protein active site and comparison with the structure of the mouse isoform (mAOX3) allowed us to identify, for the first time, the unique features that characterize hAOX1 as an important drug-metabolizing enzyme. In spite of the similarities of both enzymes, they show marked and relevant differences at the Mo active site, substrate tunnel as well as at the FAD site. The ensemble of these structures provides important insights into the role of aldehyde oxidases, contributing to elucidate the clinical metabolism implications of hAOX1 in humans which has particular relevance for novel drug design studies.


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