Aldehyde oxidase and its role in drug and xenobiotic metabolism

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Aldehyde oxidases (AOX) belong to the xanthine oxidase (XO) family of molybdenum containing enzymes. These enzymes contain Mo bound to an organic molybdopterin cofactor (Moco) with two spectroscopically distinct [2Fe2S] centres and an FAD site involved in electron transfer [1]. Reactivity appears to be conferred solely by the Mo centre, while specificity is controlled by the amino acid residues in the substrate binding pocket. The human AOX1 has great toxicological importance since, along with cytochrome P450, it metabolizes different classes of drugs and xenobiotics being an enzyme of emerging significance in phase I drug metabolism and pharmacokinetics [2]. The crystallization and structure determination of human AOX1 [3] and mouse AOX3 [4] have brought new insights into the structure and the mechanisms underlying substrate/inhibitor binding as well as the catalytic activity of this class of enzymes.

The elucidation of the 3D crystal structure of human AOX in the substrate free form (PDB ID: 3UHW) and in complex with the substrate phthalazine and the noncompetitive inhibitor thioridazine (PDB ID: 4UHX) revealed novel and important structural features. Contrary to the mouse enzyme, (mAOX3; PDB ID: 3ZYV) in the human AOX1 structure, the substrate and inhibitor molecules were found to be simultaneously bound to the protein at different binding sites. Moreover, the structural analysis of the complex revealed a new and unexpected inhibition site structurally conserved among mammalian AOX and XO.
To clarify the hAOX enzymatic and inhibition mechanisms, several variants were prepared and, kinetic studies in combination with computational and structural studies, allowed identifying the structural determinants for the specific of hAOX1.

The ensemble of the published and novel crystal structures has provided important structural insights into the catalytic and inhibition mechanisms of AOX1 and will be presented.

References

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