Opening of the Safety-belt Loop of Human Aldose Reductase

Marianna Biadene[a], Isabel Hazemann[b], Thomas R. Schneider[c], [a]*Department of Inorganic Chemistry, University of Goettingen, Germany.* [b]*IGBMC, Illkirch, France.* [c]*IFOM-The FIRC Institute of Molecular Oncology, Milano, Italy.* E-mail: marianna@shelx.uni-ac.gwdg.de

Aldose reductase (ALR2; EC 1.1.1.21) is a member of the aldo-keto reductase superfamily and it catalyzes the NADPH-dependent reduction of aldeydes to their corresponding alcohols. It is implicated in the polyol pathway and in diabetic complication.

The crystal structure of native aldose reductase has been determined to a resolution of 0.82 Å with a final R = 9.50 and R_{free} = 10.90 and a mean coordinate error for the fully occupied sites of the protein of 0.011 Å (from fully matrix inversion). The structure contains a large number of multiple conformations: 78 out of 316 residues were modeled in two conformations.

The overall structure folds into an eight-stranded α/β barrel with the active site located at the C-terminal end of the barrel and the $NADP^+$-binding site near the hydrophobic binding pocket [1]. The cofactor is held in place by the so-called 'safety-belt' (a loop between residue 216 and 227 of the canonical α/β barrel) [2].

The active site of the structure contains a citrate molecule in two conformations. One of the conformations stabilizes the closed position of the safety-belt, whereby the other permits the safety-belt to open. Due to the high resolution, the partially opened conformation of the safety-belt can be observed in the electron density.

[1] El-Kabbani O., Wilson D., Petrash J. M., Quiocho F. A., *Molecular Vision*, 1998, 4. [2] Wilson D.W., Bohren K.M., Gabbay K.H and Quiocho F.A., *Science*, 1992, **257**, 81.

Keywords: high-resolution refinement, active-site structure, loop modeling