Homology modelling of Endoplasmic Reticulum associated Amyloid β-peptide Binding protein (ERAB)

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ERAB (1) is believed to be involved in Alzheimer's disease, where it is supposed to interact with the amyloid β-peptide. The amyloid β-peptide forms fibrils in neuronal tissue, which cause cell death. ERAB's natural catalytic activity is reduction of L-3-Hydroxy-acyl-CoA and the protein is a member of the SDR family (Short-chain Dehydrogenases/Reductases)(2). SDR is a divergent family of NAD(P)H dependent dehydrogenases or reductases. The members of the family are distantly homologous but have a conserved three dimensional structure.

The model is created to search for clues to how the amyloid β-peptide and ERAB might interact. The NMR structure of the amyloid β-peptide was determined and published earlier this year, so we hope that use our model to get more information about possible interactions between ERAB and the amyloid β-peptide which could be validated in laboratory experiments.

ERAB is a homotetrameric protein with subunits of 261 amino acid residues, whose closest homologues are 20-β-hydroxysteroid dehydrogenase (20β-HSD) (PDB code 2hsd)(3) and 7-α-hydroxy steroiddehydrogenase (7α-HSD)(PDB code 1fmc)(4). Higher sequence identity between ERAB and 20β HSD made us chose the 20β HSD as the template for the homology modelling. The resulting model showed more similarity to 7α-HSD so we felt that a switch of templates were justified. ICM (4) was used for the homology modelling of one subunit. The placement of the NAD+ was taken directly from the pdb-file.

The two models converge to the general SDR fold with a central seven-stranded β-sheet surrounded by helices arranged in β-α-β folds. The catalytic tyrosine (position 168) is located in a cleft that is covered by the substrate-binding loop (207-221) similarly to the experimentally determined structures of the SDR family. This supports that the general structural features of our model reflect the true three-dimensional structure of ERAB.

References:
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