Molecular docking studies can shed light into the molecular determinants of ligand binding. When no experimental structures are available, docking can also be applied to homology models. Given that the model quality, especially in the binding site, greatly affects the accuracy of docking predictions, development of strategies able to include protein flexibility may help in the effective use of docking to homology models. In this work, ligand binding of structurally different ligands to the mouse Aryl hydrocarbon Receptor (mAhR) homology model is analyzed.

No experimental information is available for the AhR LBD but since last years the X-ray structures of many homologous PAS domains have been determined, in particular the Hypoxia-Inducible Factor 2a (HIF2a) shows nearly 30% of sequence identity with the mAhR LBD. We developed 10 homology models of the mAhR LBD using MODELLER, each one based on a different HIF2a template structure in order to describe the flexibility of the binding cavity. All the ligands and solvent molecules in the HIF2a internal cavity were maintained during the modeling and refinement stages.

AhR is a ligand-dependent transcription factor that responds to exogenous and endogenous chemicals with the induction of gene expression and production of diverse biological and toxic effects. The mechanism is initiated by ligand binding to the AhR, which is present in the cytosol as a multiprotein complex, and the PAS-B domain acts as ligand binding domain (LBD).

We identified three main arrangements within the binding cavity:

1. hydrophobic molecules interact mainly with residues located at the bottom of the cavity (TCDD);
2. others occupy the whole cavity and in some cases are stabilized by hydrogen bonds with residues in the middle (FICZ);
3. small and polar ligands stay at the entrance (leflunomide).

These poses will be validated by a mutagenesis study focused on the key stabilizing residues predicted for each ligand by the computational protocol here presented.

References:

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