[P14] Discriminating agonist and antagonist ligands of the Nuclear Receptors using 3D pharmacophores

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Introduction Nuclear receptors (NRs) are transcription factors naturally switched on and off by small-molecule hormones that monitor a wide range of physiological key functions. A large amount of compounds has been proposed, some of them are still marketed, whether to activate (agonist ligands) or inhibit (antagonist ligands) the activity of one or more NRs. Even if the molecular bases of agonism and antagonism have been elucidated [1], discriminating agonist and antagonist ligands based on their sole structure remains a challenge [2-4]. We decided, in this study, to evaluate the use of 3D pharmacophore models to discriminate agonist ligands from antagonist ligands of the NRs.

Material and Methods

NRLiSt BDB. The NRLiSt BDB [5] is a public benchmarking dataset dedicated to the NRs that contains agonist datasets and antagonist datasets for 27 targets (out of 48 known NRs). Each dataset consists in three elements: all of the available human holo PDB structures, all of the ligands found to be agonists or antagonists in the scientific literature, and their corresponding computed decoys obtained using the DUD·E decoy generation tool.

Preparation of Ligands and Decoys. All of the ligands provided in SMILES format in the NRLiSt BDB were converted in .ldb format. Agonists were used as decoys for antagonist ligands and reciprocally.

LigandScout. Defaults settings of LigandScout (version 4.0) [6] were used to construct both structure-based 3D pharmacophores from the holo PDB structures and ligand-based 3D pharmacophores from the structures of agonist and antagonist ligands.

Results and Discussion Using only the structure-based 3D pharmacophore approach, it was possible to obtain 3D pharmacophores that were selective to agonist ligands and 3D pharmacophores that were selective to antagonist ligands. However, these pharmacophores were not able to recognize neither all NRs agonist ligands nor all NRs antagonist ligands. We thus used a combination of structure-based and ligand-based 3D pharmacophores, and succeeded to obtain a complete discrimination of agonist ligands from antagonist ligands for 21 NRs out of the 27 studied and to discriminate antagonist ligands from agonist ligands for 23 out of the 27 NRs.

Conclusion 3D pharmacophores represent a powerful tool to discriminate NRs agonist ligands and antagonist ligands based on their sole structure. 3D pharmacophores can be used as a predictor of the pharmacological activity of NRs ligands.

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