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Editorial

New Sites for Old Suspects: Environmental Allosteric Modifiers of Nuclear Hormone Receptors

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EDITORIAL

Nuclear Hormone Receptors (NHRs) are implicated in various diseases including diabetes, infertility, muscular atrophy, hypoplasia, osteoporosis, and hormone receptor positive cancers [1]. X-ray crystal and Nuclear Magnetic Resonance (NMR) structures of NHRs and NHR-ligand complexes have been solved. To date, no high resolution structure of a full-length NHR has been solved. Hence, a holistic view of the full-length receptor structure in its activated state and inactivated state is far from understood. Peroxisome proliferator activated receptor gamma (PPARγ) - retinoid x receptor alpha (RXRα) heterodimeric structures with intact DNA binding (DBD), ligand binding (LBD) and hinge domains provide crucial structural clues pertinent to nuclear receptor domain architecture and potential conformational changes involved in activity [2].

NHRs, when bound to a ligand undergo conformational changes. Agonist binding induces conformational changes that facilitate the binding of nuclear coactivators to the activation function-2 (AF-2) pocket which is necessary to trigger associated the associated transcriptional activity. Antagonist binding induces a conformational change that either prevents co-activator binding or facilitate co-repressor recruitment, thereby blocking the transcriptional activity. The conformational flexibility of the ligand binding domain is critical for the overall receptor function and is mediated through the opening and closing of surface pockets/clefts to promote small molecular and protein-protein interactions.

The androgen receptor (AR) binding function-3 (BF-3) pocket, located close to the AF-2 pocket and the hinge rregion, connects the ligand and DNA binding domains, was identified [3]. Using X-ray crystallography and computational modeling several compounds have been identified to directly bind to the BF-3 pocket and allosterically modulate co-activator binding to the AF-2 site [3]. The residues R726/N727 bridge the AF-2 and BF-3 pockets and are speculated to relay conformational information from one pocket to the other [4]. A closer look at the X-ray crystal structures of nuclear receptors, reveal that the positive flag pole residue arginine (R726) is conserved in progesterone receptor (PR), mineralocorticoid receptor (MR), glucocorticoid receptor (GR), and vitamin D receptor (VDR) but not in estrogen receptor alpha (ERα; V368) and PPARγ (V307). in the BF3 pocket of NHRs are implicated in altered function [4]. Figure 1 illustrates the structural similarity of the conserved BF-3 pockets from AR and ER (Figure 1). To date no endogenous chemicals that specifically bind to BF-3 have been identified. Recently, a cochaperone protein which is known to regulate AR function, Bag-1L is replace to bind to the BF-3 domain. An N-terminal hexapeptide repeat sequence (GARRPR) from Bag-1L has been identified to specifically bind to the AR BF-3 pocket and regulate the AR-ARE mediated transcriptome [5]. Other cochaperones including FKBP52, a regulator of AR/Hsp90 complex, have been implicated in allosteric regulation of AR transactivation [6]. However, there is no concrete evidence yet that they interact with the AR BF-3 pocket.This highlights the importance of studying the role of BF-3 binding proteins in allosteric regulation of NR mediated transactivation.

Several endocrine disrupting chemicals have been classified as hormone mimics and are reported to bind directly to the NHR LBD and enable transcriptional activity via binding to appropriate nuclear response elements and accessory proteins [7]. While some of these EDCs have the required pharmacophore to induce functionally relevant conformations of NHR, many of them are classified as weak mimics, eventhough they produce considerable damage at low exposure. For example, Plasticizers, alkoxybisphenols and phthalate esters, do not share estrogen's pharmacophore but are often misclassified as compounds binding to estrogen receptor LBD.

Phthalates are found pervasively in the environment, plastic food wraps and containers, cosmetics, flooring, wall coverings, medical devices, tubing, rubber, polymers, sealants, toys and pharmaceutical products [8,9]. Phthalates are a known to be a contributor to aberrant health conditions such as infertility, decreased sperm counts, cryptorchidism, reproductive tract malformations, hypospadias, testicular tumors, reduced testosterone, anogenital distance, and nipple retention. Most of these actions are owing to their ability to alter hormone mediated activity. Phthalates are benzenedicarboxylic acid diesters. The

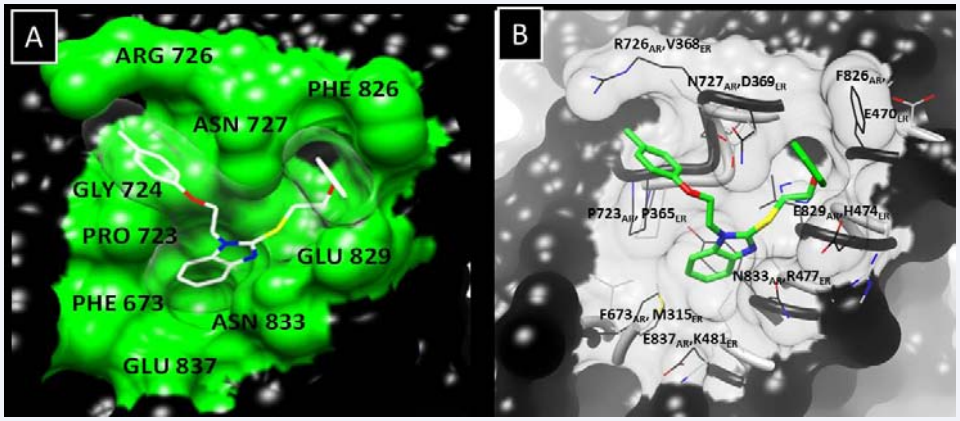

Figure 1 (A) - AR Binding Function-3 pocket (highlighted in green) with bound small molecular ligand 1-[2-(4-methylphenoxy) ethyl]-2-(2-phenoxyethylsulfanyl) benzimidazole (PDB: 2YLO).
(B) - Comparison of estrogen receptor (PDB: 1ERE) and androgen receptor BF-3 pockets. Residues pertinent to each receptor pocket are identified with AR or ER in the suffix.

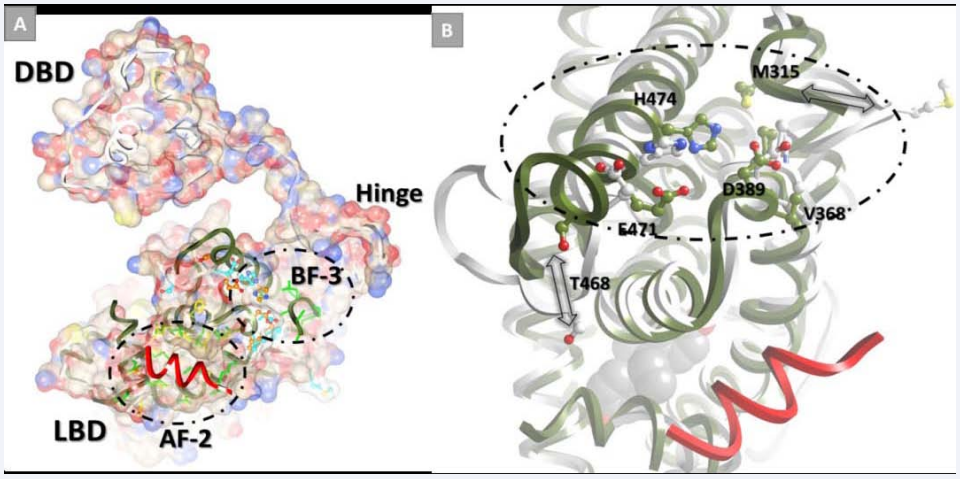

Figure 2 (A) Theoretical homology model of human Estrogen receptor. The hinge region orchestrates both local and global conformational changes required for ER mediated transcriptional activity. The Activation Function-2 and Binding Function-3 pockets are highlighted by dotted circles. The coactivator (red) bound to AF-2 pocket can be regulated by ligand or protein bound to BF-3 pocket.
(B) Superposition of ER LBD (PDB: 3ERD; rendered in olive green) with the full length ER model (rendered in grey) reveals potential conformational changes transmitted via the hinge region and AF-2 domain in addition to the V368/D369 bridge.

Abbreviations: NHR: Nuclear Hormone Receptor; LBD: Ligand Binding Domain; DBD: DNA Binding Domain; AF-2: Activation Function-2; BF-3: Binding Function -3; EDC: Endocrine Disrupting Chemicals; ER: Estrogen Receptor; AR: Androgen Receptor; PR: Progesterone Receptor; MR: Mineralocorticoid Receptor; GR: Glucocorticoid Receptor; PPAR: Peroxisome Proliferator Activated Receptor; RXR: Retinoid X Receptor; VDR: Vitamin D Receptor; NRE: Nuclear Response Element; PDB: Protein Data Bank; NMR: Nuclear Magnetic Resonance; Actor: Aggregated Computational Toxicology Resource

1,2-benzenedicarboxylic acid and the o-phthalates are the primary biologically active phthalates. Phthalates undergo both hydrolysis and phase I biotransformation to form monoesters or oxidative metabolites respectively. These metabolites can undergo phase II biotransformation and result in glucuronide conjugates which can then be excreted [10]. Phthalates are absorbed through the skin or ingested, and have been shown to have "weak" estrogenic and/or androgenic activity in vitro, which doesn't fully resolve the pronounced effects observed in vivo.

Monoalkyl/aryl phthalates bind to AR BF-3 pocket via tight ion-pair like interactions with the flag pole arginine (R726) and the carboxylic acid moiety of the phthalate, while the alkyl/aryl moieties are accommodated easily by hydrophobic interactions. Similarly, several phthalates bind to ER AF-2 and BF-3 pockets, suggesting new sites for these old suspect endocrine disruptors. This provides a molecular bases for their pronounced in vivo effect in spite of poor in vitro activity. The hinge region orchestrates both local and global conformational changes required for NHR activity and the BF-3 pocket relays conformational information to the co-activator and ligand binding sites (Figure 2).

Most of the current cell-based in vitro assays that are currently in use to screen for potential EDCs do not have the resolution

nor have the capability to screen for allosteric regulators. It is imperative to design new assay systems to test suspect environmental chemicals not only against multiple nuclear receptors for their ability to compete with cognate hormones but also be able to screen for contributions from these new sites.

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