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Allosteric pathways in nuclear receptors — Potential targets for drug design

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ABSTRACT

The nuclear receptor family of transcription factor proteins mediates endocrine function and plays critical roles in the development, physiology and pharmacology. Malfunctioning nuclear receptors are associated with several disease states. The functional activity of nuclear receptors is regulated by small molecular hormonal and synthetic molecules. Multiple sources of evidence have identified and distinguished between the different allosteric pathways initiated by ligands, DNA and cofactors such as co-activators and co-repressors. Also, these biophysical studies are attempting to determine how these pathways that regulate co-activator and DNA recognition can control gene transcription. Thus, there is a growing interest in determining the genome-scale impact of allostery in nuclear receptors. Today, it is accepted that a detailed understanding of the allosteric regulatory pathways within the nuclear receptor molecular complex will enable the development of efficient drug therapies in the long term.

1. Introduction

Nuclear receptors (also nuclear hormone receptors and abbreviated as NR) are a family of transcription factors whose transcriptional activity is controlled by lipophilic hormone molecules and the ensuing recruitment of coactivator molecules (Evans, 1988; Evans & Mangelsdorf, 2014). There is a specific classification of nuclear receptors proposed by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) (Alexander et al., 2015; Auwerx et al., 1999). It is based on a phylogenetic tree that connects all known nuclear receptor sequences. This nomenclature also accounts for the evolution of the two well-conserved domains of nuclear receptors (described below).

2. Nuclear receptors, human disease and pharmacology

Nuclear receptors are widely expressed in all human tissue (Bookout et al., 2006; Kumar et al., 2013; McKenna & O'Malley, 2010). For instance, the peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) isoforms are expressed in tissues as diverse as the epidermis (Schmuth, Jiang, Dubrac, Elias, & Feingold, 2008) and in adipose tissue (Michalik et al., 2006). The estrogen receptor (ER) and PPAR are also expressed in neural tissue (Couse, Lindzey, Grandien, Gustafsson, & Korach, 1997; Cullingford et al., 1998) and ER is also expressed within the reproductive tract, hypothalamus and the lungs (Couse et al., 1997). The constitutive androstane receptor (CAR) whose activity is linked to xeno and endobiotic metabolism (Huang et al., 2003; Sonoda, Rosenfeld, Xu, Evans, & Xie, 2003; Sueyoshi & Negishi, 2001; Wei, Zhang, Egan-Hafley, Liang, & Moore, 2000; Zhang, Huang, Chua, Wei, & Moore, 2002; Zhang, Huang, Qatanani, Evans, & Moore, 2004) is most abundantly expressed in the liver and intestine (Bertilsson et al., 1998; Lamba et al., 2004) and is also expressed in the testis, adrenal tissue and the brain (Lamba et al., 2004). Multiple reviews on the many disease states associated with nuclear receptor malfunction already exist (McKenna & O'Malley, 2010). For instance, the PPARs are associated with diseases as diverse as diabetes (Cipolletta et al., 2012) and Alzheimer's (Moutinho & Landreth, 2017; Prakash & Kumar, 2014). Signaling through the glucocorticoid receptor (GR) has been linked with cardiovascular disease, psychiatric disorders and hyperglycemia, among many other ailments (Kadmiel & Cidlowski, 2013). Also, nuclear receptors have been linked to the progression of multiple cancers (McKenna & O'Malley, 2010; Tang et al., 2011), by the fatty liver disease and liver tumors by the farnesoid X (FXR) (Neuschwander-Tetri et al., 2015) and the constitutive androstane receptors (CAR) (Yamamoto, Moore, Goldsworthy, Negishi, & Maronpot, 2004).

Abbreviations: 9c, 9-*cis* retinoic acid; AF1 (or 2), activation function 1(or 2); AR, androgen receptor; CAR, constitutive androstane receptor; ChIP, chromatin immunoprecipitation; DBD, DNA binding domain; ER, estrogen receptor; ERE, estrogen response elements; GR, glucocorticoid receptor; HRE, hormone response element; LBD, ligand binding domain; LBP, ligand binding pocket; LXR, liver X receptor; NCoR, nuclear receptor corepressor; NR, nuclear receptor; PPARγ, Peroxisome proliferator-activated receptor γ; RXR, retinoid X receptor; SMRT, silencing mediator of retinoid and thyroid-hormone receptors; SRC, steroid receptor coactivator; T3, *tri*iodothyronine; TR, thyroid receptor; TRE, thyroid receptor response element

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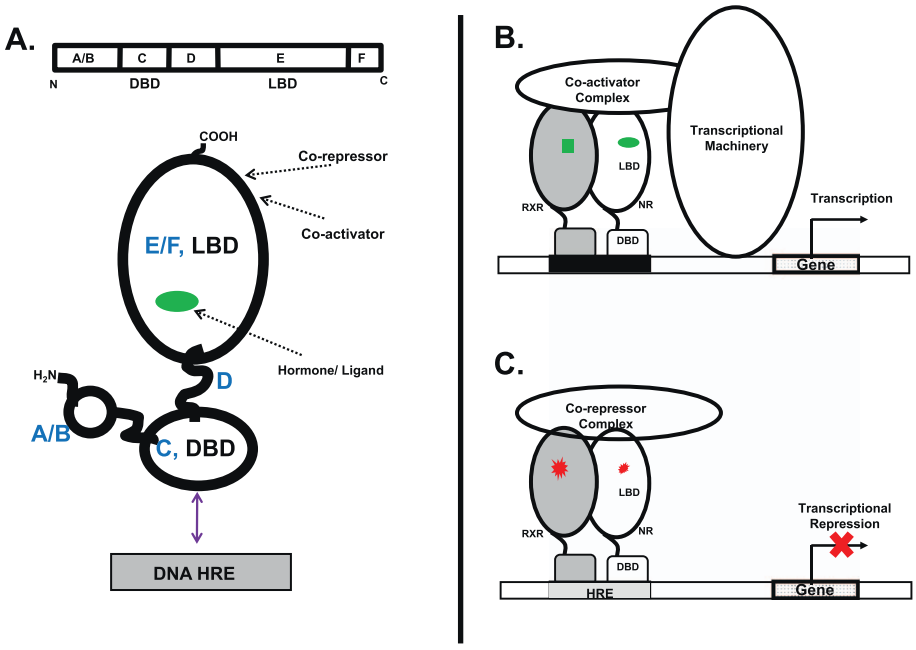

Fig. 1. *Nuclear Receptor (NR) Mode of Action and Molecular Topology*. A. The nuclear receptor topology and functional organization consists of distinct N-terminal A/B, a DNA-binding (C, DBD), linker D and C-terminal ligand-binding (EF, LBD) domains. Arrows show locations of the binding sites for ligand, co-activators/co-repressors and the DNA HRE. B. Ligand agonists (green) interact with the receptor (heterodimer of nuclear receptor (NR):retinoid X receptor, (RXR)). Ligand binding is accompanied by the recruitment of co-activators and the basal transcriptional machinery. C. In the absence of agonists or when bound to antagonists (red) the nuclear receptor is maintained in an inactive transcriptional state by co-repressor molecules. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Consequently, nuclear receptors are vital targets of therapeutic drugs (Alexander et al., 2015; Burris et al., 2013; Evans & Mangelsdorf, 2014; Moore, Collins, & Pearce, 2006; Safe, Jin, Hedrick, Reeder, & Lee, 2014). Multiple small-molecule scaffolds have been designed as pharmaceutical nuclear receptor ligands that function as agonists or antagonists. These include therapeutic drugs such as bicalutamide that bind to the androgen receptor (AR) and target prostate cancer (Blackledge, 1996), tamoxifen for ERs (that target breast cancer) (Ward, 1973), thiazolidinediones against PPARγ that target type II diabetes (Lehmann et al., 1995) and corticosteroids such as dexamethasone which targets the GR when treating ailments associated with inflammation (Madretsma, Dijk, Tak, Wilson, & Zijlstra, 1996).

3. Nuclear receptor structural topology, assembly and signaling

Nuclear receptors have common modular structural features that include an N-terminal domain (A/B domain, Fig. 1A). This A/B domain is of variable length and amino acid sequence and is critical for regulating transactivation (Dieken & Miesfeld, 1992; Kato et al., 1995; O'Malley et al., 1995; Tora et al., 1989; Werman et al., 1997). With a few exceptions, the A/B domain encompasses a ligand-independent transactivation function (AF1) domain (Tora et al., 1989; Tsai & O'Malley, 1994). Following the A/B domain is a highly conserved DNA-binding domain (DBD) (C domain, Fig. 1B) that binds palindromic or direct repeat DNA sequences (six nucleotide segments of varied arrangements), or response elements (RE). A short 'hinge' sequence (D domain) connects the DBD to a C-terminal ligand-binding domain (LBD) (E & F domain, Fig. 1A). Upon binding agonist-ligands the LBD undergoes conformational changes and recruits coactivator molecules to the ligand-dependent transactivation function (AF2) domain within the LBD (Suino et al., 2004; Wright et al., 2011; Wright, Vincent, & Fernandez, 2007; Xu et al., 2004). Inverse agonists disrupt the 'active' AF2 conformation and the resulting LBD conformation functions as a docking site for co-repressors (Dussault et al., 2002; Shan et al., 2004).

These receptors function as monomers, homodimers and as heterodimers, most commonly in a bimolecular complex with the nuclear receptor, the retinoid X receptor (RXR) (Auwerx et al., 1999; Evans & Mangelsdorf, 2014; Kliewer, Umesono, Noonan, Heyman, & Evans, 1992; Moore, Kato, et al., 2006). When activated, nuclear receptors bind specific DNA sequences called hormone response elements (HRE) which are usually labeled to signify the activity-initiating hormone. For instance, the estrogen response elements (ERE) are HREs that bind the estrogen hormone receptor (ER) (Klock, Strahle, & Schutz, 1987), the androgen response elements (ARE) bind the androgen hormone receptor (AR) (Cato, Henderson, & Ponta, 1987), glucocorticoid response elements (GRE) bind the glucocorticoid receptor (Klock et al., 1987), and the thyroid hormone response elements (TRE) bind the thyroid hormone receptor (Fig. 1B) (Umesono, Giguere, Glass, Rosenfeld, & Evans, 1988), among others (Evans, 1988; Olefsky, 2001). This DNA/nuclear receptor complex recruits and binds to transcriptional coactivator proteins such as the steroid receptor coactivators (SRC) (Johnson & O'Malley, 2012), TIF-2/GRIP-1/NcoA-2 (transcriptional intermediary factor 2/glucocorticoid receptor interacting protein 1/nuclear receptor coactivator 2) (Min, Kemper, & Kemper, 2002), peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1α) (Ding, Lichti, Kim, Gonzalez, & Staudinger, 2006; Shiraki, Sakai, Kanaya, & Jingami, 2003), Activating signal cointegrator-2 (ASC-2) (Choi et al., 2005) and others (Arnold, Eichelbaum, & Burk, 2004). Coactivator recruitment can be accompanied by histone acetylation, recruitment of the RNA polymerase II complex and gene expression (Dasgupta, Lonard, & O'Malley, 2014; Glass & Rosenfeld, 2000; Kamei et al., 1996; Rastinejad, Huang, Chandra, & Khorasanizadeh, 2013; Yao, Ku, Zhou, Scully, & Livingston, 1996). Within the nucleus, the transcriptional activity of nuclear receptors can be maintained in a repressed state by antagonists and inverse agonists (Weatherman, Fletterick, & Scanlan, 1999) which promote the recruitment of transcriptional co-repressors (Lonard & O'Malley, 2012) such as the silencing mediator of retinoid and thyroid-hormone receptors (SMRT) (Chen & Evans, 1995; Sande & Privalsky, 1996) and the nuclear receptor co-repressor (NCoR) (Fig. 1C) (Horlein et al., 1995; Seol, Mahon, Lee, & Moore, 1996).

4. Noncanonical nuclear receptor signaling

Several additional mechanisms can also control the action of nuclear receptors and alter target gene expression. For instance, RNA-seq studies on CAR in hepatocyte-like (HepaRG) cell lines have shown distinct ligand (CITCO)-dependent and ligand-independent (phenobarbital, PB, activated) gene expression profiles (Li et al., 2015; Mutoh et al., 2009). Likewise, diverse mechanisms can control the DNA-binding-site specificity of nuclear receptors. Genome-scale studies with