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Structures and regulation of non-X orphan nuclear receptors: A retinoid hypothesis

Xiaoyong Zhi[a,b,**], X. Edward Zhou[a], Karsten Melcher[a], H. Eric Xu[a,c,*]

[a] Laboratory of Structural Sciences, Van Andel Research Institute, 333 Bostwick Ave., N.E., Grand Rapids, MI 49503, USA
[b] Autophagy Research Center, University of Texas Southwestern Medical Center, 6000 Harry Hines Blvd., Dallas, TX 75390, USA
[c] VARI-SIMM Center, Key Laboratory of Receptor Research, Shanghai Institute of MateriaMedica, Chinese Academy of Sciences, Shanghai 201203, China

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ABSTRACT

Nuclear receptors are defined as a family of ligand regulated transcription factors [1–6]. While this definition reflects that ligand binding is a key property of nuclear receptors, it is still a heated subject of debate if all the nuclear receptors (48 human members) can bind ligands (ligands referred here to both physiological and synthetic ligands). Recent studies in nuclear receptor structure biology and pharmacology have undoubtedly increased our knowledge of nuclear receptor functions and their regulation. As a result, they point to new avenues for the discovery and development of nuclear receptor regulators, including nuclear receptor ligands. Here we review the recent literature on orphan nuclear receptor structural analysis and ligand identification, particularly on the orphan nuclear receptors that do not heterodimerize with retinoid X receptors, which we term as non-X orphan receptors. We also propose a speculative "retinoid hypothesis" for a subset of non-X orphan nuclear receptors, which we hope to help shed light on orphan nuclear receptor biology and drug discovery.

This article is part of a Special Issue entitled 'Orphan Nuclear Receptors'.

1. general introduction to the nuclear receptor family

Nuclear receptors are grouped as a family due to the significant identity in their primary sequences. The typical nuclear receptor comprises six regions (Fig. 1A). The N-terminal A/B region is the most variable one, both in terms of sequence and size, and contains the ligand-independent Activation Function 1 (AF1) transactivation domain. The activity of the AF1 domain is regulated by interacting cofactors and posttranslational modifications [7–12]. The underlying structural basis of this regulation remains unknown, because the intrinsically disordered property of the AF1 domain has prevented its structure determination. One potential solution might be to include an interacting peptide/protein in its crystallization [13].

The C region of a typical nuclear receptor is highly conserved and termed as the DNA binding domain (DBD) for its ability to bind specific DNA sequences (response elements) within the promoter/enhancer of transcriptionally regulated targets. The DBD also contributes to nuclear receptor homo/hetero dimerization. While the architectures of the DBD homodimers have already been identified between 1991 and 1993 [14–17], the architectures of the DBD heterodimers in the context of the full length (or almost full length) nuclear receptors has been revealed only recently [18,19]. Different RXR heterodimers assume different spatial arrangements when bound to DNA, due to the flexibility of RXR (compare the structures of the PPAR/RXR and LXR/RXR heterodimers in Fig. 1B). The DNA response elements are more than binding substrates. Rather, they could also function as allosteric ligands that regulate the receptor dimerization mode and transcriptional activity [17,20].

The D region has long been recognized as a hinge between the C (DBD) and E regions. However, it has become clear that it also contributes to the positioning of the DBD and to the control of DNA binding affinity [18]. Additionally, posttranslational modifications of amino acids within this region regulate receptor nuclear localization, cofactor recruitment, stability, and the response to ligand stimulation [21–24], suggesting that the hinge region plays diverse roles in modulating the receptor activity and the receptor activity and as such might be considered as a potential target for pharmaceutical intervention.

The E region is the second most conserved region and is responsible for ligand binding, for it harbors a hydrophobic ligand binding pocket. It is termed the ligand binding domain (LBD) and is present in all 48 human nuclear receptors. The canonical fold of the

* Corresponding author.
** Corresponding author.
E-mail addresses: Xiaoyong.Zhi@UTsouthwestern.edu (X. Zhi), Eric.Xu@vai.org (H. E. Xu).

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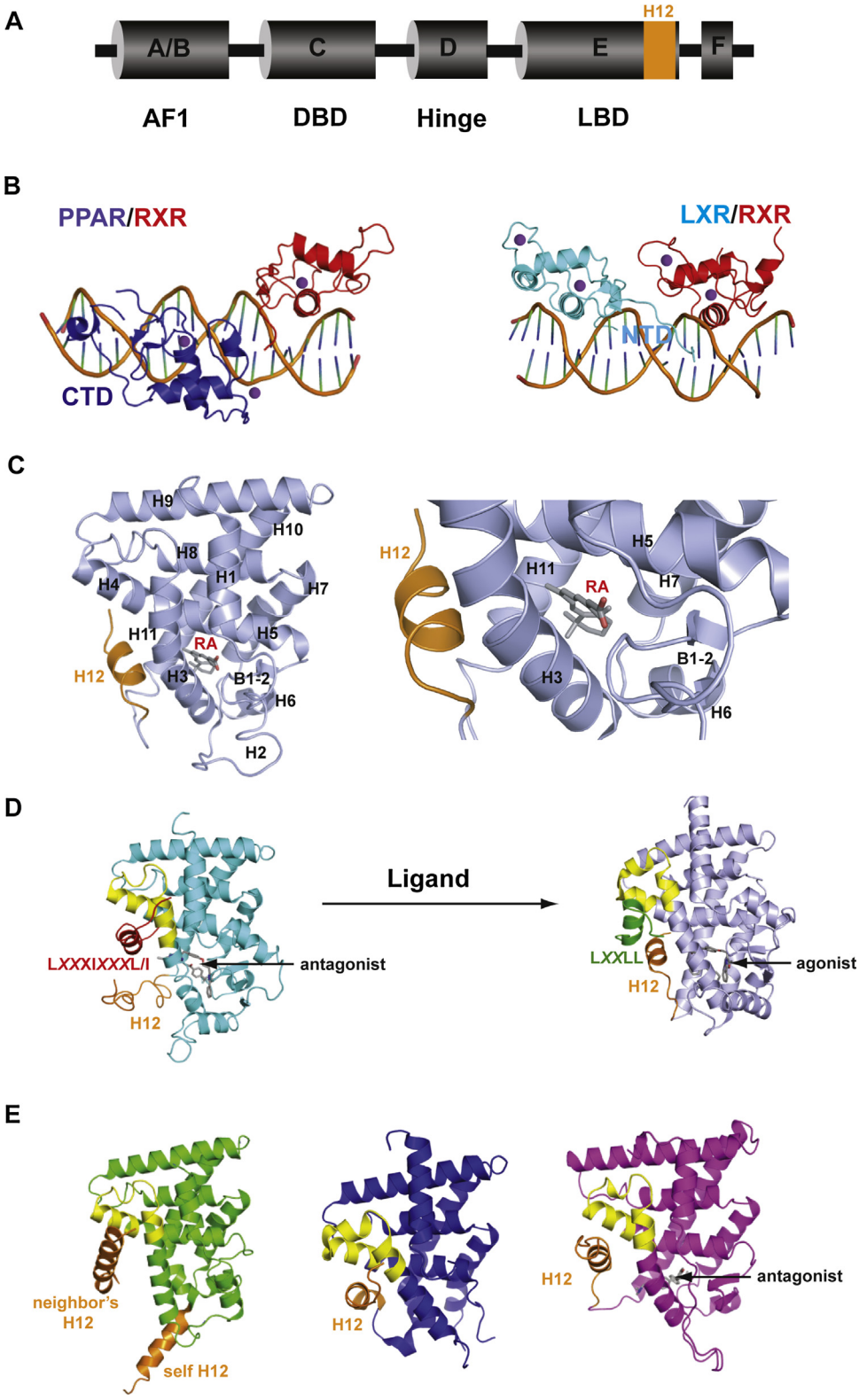

Fig. 1. A general introduction to the key structural features of nuclear receptors. (A). Domain organization of a typical nuclear receptor. Helix H12 is highlighted in orange. (B). Diverse DNA binding modes revealed in the DBD structures of PPAR (blue)/RXR (red) and LXR (cyan)/RXR. CTD stands for C-terminal domain and NTD for N-terminal domain. Zinc ions are represented by purple balls. (C). The overall architecture of a typical nuclear receptor LBD and its ligand binding mode. 9-cis retinoic acid (RA) bound RXR (light blue, PDB code = 1FM6) is used as an example to illustrate the overall fold of a typical nuclear receptor in the left panel. Helices H1–H11 and beta-strands (B1–2) are labeled. H12 is highlighted in orange and RA as stick model in blue. RA is bound inside RXR and contacts residues from helices H3, H5–H7, H11, and beta strands. In several nuclear receptors, H12 is involved in ligand binding, which is not shown here. (D). The conformational change of nuclear receptors in response to ligand binding. In the absence of agonist or in the presence of antagonist, the PPARα LBD (cyan, PDB code = 1KKQ) adopts a conformation in favor of interacting with the LXXX**I**XXXI/L motif-containing corepressor peptide (red, left panel), where H12 (orange) is dislodged from the main body of PPARα and an extended coactivator binding groove (yellow) is formed. In the presence of agonist, H12 (orange, right panel) undergoes a significant conformational change. In doing so, it packs tightly against the main body of the PPARγ LBD (light blue, PDB code = 1FM6), which favors the binding of the LXXLL motif containing coactivator peptide (green) to the coactivator binding groove (yellow). (E). The auto-repressed