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At the Cutting Edge

Looking at nuclear receptors from a new angle

Christine Helsen, Frank Claessens *

Laboratory of Molecular Endocrinology, Department of Cellular and Molecular Medicine, KU Leuven, O&N1, Herestraat 49, 3000 Leuven, Belgium

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ABSTRACT

While the structures of the DNA- and ligand-binding domains of many nuclear receptors have been determined in great detail; the mechanisms by which these domains interact and possibly 'communicate' is still under debate. The first crystal structures of receptor dimers bound to ligand, DNA and coactivator peptides provided new insights in this matter. The observed binding modes revealed exciting new interaction surfaces between the different nuclear receptor domains. Such interfaces are proposed to be the route through which allosteric signals from the DNA are passed on to the ligand-binding domain and the activating functions of the receptor. The structural determinations of DNA-bound receptor dimers in solution, however, revealed an extended structure of the receptors. Here, we discuss these apparent contradictory structural data and their possible implications for the functioning of nuclear receptors.

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Contents

Abbreviations: AF1, activation function 1; AF2, activation function 2; AR, androgen receptor; CTE, carboxyterminal extension; DR, direct repeat; DBD, DNA binding domain; EM, electron-microscopy; ER, estrogen receptor; ERR2, estrogen-related receptor 2; FRET, fluorescence resonance energy transfer; GR, glucocorticoid receptor; HNF-4, hepatocyte nuclear factor 4; IR, inverted repeat; LBD, ligand binding domain; MR, mineralocorticoid receptor; NR, nuclear receptor; NTD, aminoterminal domain; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SANS, small-angle neutron scattering; SAXS, small-angle X-ray scattering; SF1, steroidogenic factor 1; TR, thyroid receptor; VDR, vitamin D receptor.

* Corresponding author. Address: Laboratory of Molecular Endocrinology, Department of Cellular and Molecular Medicine, Onderwijs & Navorsing 1, Box 901, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 330253; fax: +32 16 330735.
E-mail address: Frank.Claessens@med.kuleuven.be (F. Claessens).

1. Introduction

Nuclear receptors (NRs) play a crucial role in many physiological processes such as reproduction, metabolism, inflammation, immunity and lipid signaling (Hollman et al., 2012; Lamers et al., 2012; Pascual-Garcia and Valledor, 2012; Verhoeven et al., 2010). As much as 48 human NRs have been identified thus far (Xiao et al., 2013). Nuclear receptors are activated by their cognate ligands or other signals and function as transcription factors. Upon activation, the NR will bind to a specific DNA sequence, named the

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response element, located in the regulatory regions of their target genes.

When binding to the promoter or enhancer regions of the target genes, the receptor will affect transcription by recruiting specific co-regulators and components of the transcription initiation complex or RNA polymerase II (Acevedo and Kraus, 2004).

Detailed insight in the structure–function relationship of NRs originates from crystallographic studies on the two most conserved domains: the DNA binding domain (DBD) and the ligand binding domain (LBD). The aminoterminal domains of NRs are highly variable in length and in sequence. Structural studies indicate they are flexible and most likely intrinsically disordered (Khan et al., 2011; Kumar and Litwack, 2009; Kumar and Thompson, 2012). The hinge regions which connect the DNA- with the ligand-binding domains are the least conserved between the members of the NR family and their structures are poorly understood.

Crystallographic data for receptor dimers binding to DNA as well as coactivator peptides have now been reported for the PPARγ (peroxisome proliferator-activated receptor)–RXRα (retinoid X receptor) heterodimer and for the HNF-4α (hepatocyte nuclear factor 4) homodimer (Chandra et al., 2008, 2013). Solution structures of several receptor heterodimers were obtained via small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS) and electron-microscopy (EM) (Rochel et al., 2011). Here, we focus on how these different structures can be reconciled and what novel insights and questions are evoked by them, with regard to steroid receptor action.

2. DNA binding by nuclear receptors

Extensive study of DNA binding by NRs has shown that the global composition of the DNA response element determines which NR can bind to it. Response elements are typically composed of two hexameric sequence organized as a direct, inverted or everted repeat. Each hexameric sequence or half-site is recognized by a receptor (Roemer et al., 2006). The half-sites are usually separated from each other by a spacer with variable length. Less common are response elements that consist of only 1 hexameric sequence which is recognized by a NR in monomeric binding mode. The exact composition and hence recognition by the correct NR is dependent on orientation and sequence of the hexamer and on the spacer length. Steroid receptors prefer the 5′-AGAACA-3′-like motifs while non-steroid receptors and the ER bind to the 5′-AGGTCA-3′-like motifs. The specific DNA binding properties of each receptor will enable or disable binding to a certain response element. Properties such as the flexibility and the length of the hinge, the specific recognition of the half-site and the strength of intermolecular dimerization via the DBDs and LBDs allow adaptation for the correct positioning of the receptors. Roughly, the NRs can be subdivided into three groups based on their DNA binding characteristics: receptors that homodimerize, receptors that heterodimerize with one of the retinoid X receptors (RXRs) and receptors that bind as a monomer (Table 1).

Table 1
DNA binding by the NR family.

	NR	Consensus RE	Dimerization	Configuration
I. Steroid receptors	AR, PR	5′-AGAACA-3′	Homodimer	IR3, DR3
	GR, MR	5′-AGAACA-3′	Homodimer	IR3
	ER	5′-AGGTCA-3′	Homodimer	IR3
II. Non-steroid receptors	RAR	5′-AGGTCA-3′	Homodimer	IR0
			Heterodimer	DR1 DR2 DR5
	VDR	5′-AGGTCA-3′	Homodimer	DR3
			Heterodimer	DR3
	PPAR	5′-AGGTCA-3′	Heterodimer	DR1
	TR	5′-AGGTCA-3′	Monomer	Half-site
			Homodimer	DR4, IP6, P0
			Heterodimer	DR4
	RXR	5′-AGGTCA-3′	Homodimer	DR1
			Heterodimer	DR1 DR2 DR3 DR4 DR5
III. Orphan receptors	Nurr77	5′-AAA AGGTCA-3′	Monomer	Extended half-site
	SF1, ERR2	5′-TCA AGGTCA-3′	Monomer	Extended half-site

The first group of homodimeric receptors consists of the steroid receptors: the estrogen receptor (ER), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the progestagen receptor (PR) and the androgen receptor (AR). They can homodimerize on an inverted repeat of 5′-AGAACA-3′-like motifs with a 3-nucleotide spacer (IR3) (5′-AGGTCA-3′ for the ER) (Table 1). The AR and the PR can also bind to 3-nucleotide spaced direct repeats of the same hexamer (DR3) (Denayer et al., 2010; Kerkhofs et al., 2012). The second group of receptors comprises the receptors that can heterodimerize with RXR, although some of them can also homodimerize. They recognize direct repeats of 5′-AGGTCA-3′-like motifs with receptor-specific spacer lengths (Table 1) (Rastinejad et al., 1995). Monomeric DNA binders, such as Nur77 (Meinke and Sigler, 1999), SF1 (steroidogenic factor 1) (Little et al., 2006) and ERR2 (estrogen receptor-related receptor 2) (Gearhart et al., 2003), are known to extend the DBD-DNA interface outside the major groove of the DNA. Additional contacts are formed between the CTE of the orphan receptor and the minor groove of the DNA upstream of the hexameric consensus sequence (Table 1).

Alternatively, receptors are recruited to DNA indirectly via other sequence-specific transcription factors (Heldring et al., 2011; Sahu et al., 2011), but this will not be discussed here.

3. Domain organization of nuclear receptors

3.1. The ligand-binding domain

The 3-dimensional structure of the LBD consists of 12 α-helices in antiparallel sandwich-like arrangement (Wurtz et al., 1996). A comparison of the structures in absence and in presence of hormone led to the 'mouse trap' hypothesis (Parker and White, 1996) which was later confirmed by the structures of many NR-LBDs. When an agonist binds the ligand-binding pocket, helix 12 serves as a lid and covers the ligand-binding pocket. This repositioned helix 12 forms a platform for coactivator binding (Brzozowski et al., 1997; Parker and White, 1996). Co-crystals of LBDs with coactivator peptides that contain the nuclear receptor binding signature motif (Heery et al., 1997) illustrated how helix 12 forms the activation function 2 (AF2) surface first proposed by Cavailles (Cavailles et al., 1994). Antagonist binding will reposition helix 12 differently and, as a result, the LBD fails to recruit coactivators. The alternative surface can even lead to binding of corepressors which results in a transcriptionally repressed target gene (Heldring et al., 2007). Structures of agonist and antagonist bound LBDs have had a major impact and have provided valuable

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