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Review

NR4A nuclear receptors are orphans but not lonesome

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ABSTRACT

The NR4A subfamily of nuclear receptors consists of three mammalian members: Nur77, Nurr1, and NOR-1. The NR4A receptors are involved in essential physiological processes such as adaptive and innate immune cell differentiation, metabolism and brain function. They act as transcription factors that directly modulate gene expression, but can also form trans-repressive complexes with other transcription factors. In contrast to steroid hormone nuclear receptors such as the estrogen receptor or the glucocorticoid receptor, no ligands have been described for the NR4A receptors. This lack of known ligands might be explained by the structure of the ligand-binding domain of NR4A receptors, which shows an active conformation and a ligand-binding pocket that is filled with bulky amino acid side-chains. Other mechanisms, such as transcriptional control, post-translational modifications and protein–protein interactions therefore seem to be more important in regulating the activity of the NR4A receptors. For Nur77, over 80 interacting proteins (the interactome) have been identified so far, and roughly half of these interactions has been studied in more detail. Although the NR4As show some overlap in interacting proteins, less information is available on the interactome of Nurr1 and NOR-1. Therefore, the present review will describe the current knowledge on the interactomes of all three NR4A nuclear receptors with emphasis on Nur77.

1. Introduction

The nuclear receptor family of 48 proteins comprises steroid hormone receptors, nuclear receptors that heterodimerize with retinoid X receptors (RXRs), and a number of so called orphan receptors. A typical nuclear receptor contains a central double zinc finger DNA-binding domain (DBD), a carboxyl-terminal ligand-binding domain (LBD) composed of 12 α-helices, and an unstructured amino-terminal domain (N-term) (Fig. 1) [1]. The ligands of nuclear receptors are usually small, non-protein compounds such as steroid hormones, retinoids, fatty acids or cholesterol derivatives. In this review we describe the NR4A-subfamily of orphan receptors comprised of Nur77 (also known as NR4A1, TR3, NGFI-B), Nurr1 (NR4A2) and NOR-1 (NR4A3), for which no ligand has been identified yet. The amino acid sequences of the different NR4A DBDs are almost identical, whereas the LBDs show a sequence similarity of 58–65%. Meanwhile, the N-terminal domains are most divergent, with only 26–28% amino acid sequence similarity between the NR4As.This domain is therefore also the most likely to exhibit diversity in protein–protein interactions (Fig. 1). NR4A receptors are involved in a plethora of cellular processes and their activity is mainly regulated through alterations in gene expression, post-translational modifications and interactions with coregulatory proteins. In this review we put together the wealth of information that is available on the interactome of the NR4A receptors with a focus on Nur77, for which most protein–protein interactions have been described. We categorized the Nur77-binding proteins into three groups: transcription factors, transcriptional coregulators and kinases. The proteins interacting with Nurr1 and NOR-1 are described in a separate part of the review. The protein–protein interactions described in this review are summarized in Tables 1 through 5, while the protein–protein interactions of Nur77 that have a known binding site are also shown schematically in Fig. 2.

2. Interactions between Nur77 and other transcription factors

Nur77 acts as a transcription factor with its two zinc fingers in the DBD mediating direct binding to DNA. Nur77 binds as a monomeric factor on the NGFI-B response element (NBRE; AAAGGTCA) or as a homodimer to Nur-response elements (NurREs; TGATATTTn$_6$AAATGCCA) in

Abbreviations: 6-MP, 6-mercaptopurine; 9-cis-RA, 9-cis-retinoic acid; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; Cam-kinase, calcium/calmodulin-dependent protein kinase; CREB, cAMP response element binding protein; DBD, DNA-binding domain; DSB, DNA double-strand break; E2, 17-β-estradiol; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIF-1α, hypoxia inducible factor-1α; HPA, hypothalamo-pituitary-adrenal; LBD, ligand-binding domain; LXRs, liver X receptors; MDM2, mouse double minute 2; NBRE, NGFI-B response element; NES, nuclear export sequence; N-term, amino-terminal domain; NurRE, Nur-response elements; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol(3,4,5)phosphate; PKC, protein kinase C; POMC, pro-opiomelanocortin; PPARs, peroxisome proliferator-activated receptors; βRARE, RA-response element of the RARβ promoter; RXRs, retinoid X receptors; StAR, steroidogenic acute regulatory protein; Treg, regulatory T cells

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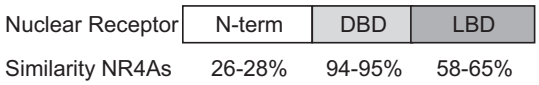

Fig. 1. Schematic representation of the domain structure of nuclear receptors. Nuclear receptors are composed of an N-terminal domain (N-term), a central DNA-binding domain (DBD) and a ligand-binding domain (LBD). The amino acid similarity between the individual domains of Nur77 with Nurr1 and NOR-1 is given in percentages below the domains.

promoter sequences of its downstream target genes. The interaction of Nur77 with other transcription factors modulates its transcriptional activity. Vice versa, such protein–protein interactions can also result in enhancement or inhibition of the activity of the interacting transcription factor itself (see Table 1). The following paragraphs will focus on those interactions between Nur77 and other transcription factors for which the outcome on transcriptional activity has been determined in a physiological context.

2.1. Nur77 in the regulation of endocrine signals and steroid hormone synthesis

Nur77 is expressed in endocrine tissues and in organs that are crucial for steroid hormone synthesis such as the adrenal glands, the pituitary gland and the testes. The first functional NurRE was identified in the promoter of the pro-opiomelanocortin (POMC) gene of pituitary-derived AtT-20 cells [2]. Nur77 can bind this NurRE either as a homodimer or as a heterodimer with either one of the other two NR4A receptors Nurr1 and NOR-1. Interestingly, it was shown that these heterodimers enhance POMC gene transcription more potently than homodimers of Nur77 do, suggesting that there is interdependency between the NR4A receptors in activating their target genes [3].

The NurRE sequence in the POMC promoter also partially overlaps with a STAT1-3 response element. Philips et al. showed that Nur77 and STAT1-3 bind simultaneously to this so called NurRE-STAT composite site and synergistically enhance transcription of the POMC gene. However, Nur77 and STAT1-3 do not interact directly, which suggests that one or more facilitating factors are involved in NurRE-STAT driven transcription. Mynard et al. showed that this third factor is cAMP response element binding protein (CREB), which binds both STAT1-3 and Nur77 and indirectly enhances transcription of the POMC gene by facilitating the synergistic activation of the NurRE-STAT composite site by STAT1-3 and Nur77 [4].

Nur77 also plays an important role in the steroidogenic acute regulatory protein (StAR)-mediated testosterone production by Leydig cells. StAR is required for the transport of cholesterol through the mitochondrial membrane to initiate steroid hormone synthesis. Nur77 binds to an NBRE in the StAR promoter, which is in close proximity to an AP-1 response element. In response to cAMP stimulation c-Jun and Nur77 synergistically increase StAR gene expression [5], presumably through a direct interaction between c-Jun and the LBD of Nur77 [6]. On the other hand, c-Jun has also been shown to suppress expression of the hydroxylase P450c17 gene by blocking the DNA-binding activity of Nur77 in response to stimulation of Leydig cells with reactive oxygen species [7]. The effect of c-Jun on the transcriptional activity of Nur77 therefore seems to depend on other factors as well. One of these factors could be the atypical nuclear receptor DAX1 (NR0B1), which lacks a DBD and associates with multiple coregulatory proteins. DAX1 binds Nur77 directly and represses its ability to enhance transcription of the previously mentioned P450c17 gene. This inhibition is mainly the result of competition

Table 1
Transcription factors interacting with Nur77.

Transcription factor	Also known as	Interacting domain of Nur77	References
Coactivators of Nur77			
CREB	CREB1	N-term	[4]
NOR-1	NR4A3; MINOR		[3]
Nur77	NR4A1; TR3; NGFI-B		[3]
Nurr1	NR4A2; NOT		[3]
RXRγ	NR2B3; RXRC; RXRgamma	N-term; LBD	[15]
Coactivated by Nurt77			
c-Jun	AP-1; AP1; c-Jun; C-JUN; cJun	LBD	[7]
RXRα	NR2B1; RXR alpha	LBD	[16,17]
SP1			[34,35]
SP4			[34,35]
p53	TP53; TRP53	DBD–LBD	[67]
Corepressed by Nur77			
COUP-TFI	NR2F1; EAR3		[26]
COUP-TFII	NR2F2; COUPTFB		[26]
GR	NR3C1; GCR; GRL; GCCR	DBD	[11]
NF-κB (p65)	EBP-1; KBF1; NF kappa B; NFκB		[42]
p53	TP53; TRP53	DBD–LBD	[38]
RXRα	NR2B1; RXR alpha	LBD	[21]
Corepressor of Nur77			
AR	NR3C4	N-term	[12]
DAX1	NR0B1; DAX-1; DSS	LBD	[8]
ERα	NR3A1; ER; ESR1; Era; ESRA;	DBD–LBD	[13]
GR	NR3C1; GCR; GRL; GCCR	DBD	[9,10]
c-JUN	AP-1; AP1; c-Jun; C-JUN; cJun	LBD	[6]
NF-κB (p65)	EBP-1; KBF1; NF kappa B; NFκB	LBD	[14]
Notch-1	hN1; TAN1	DBD–LBD	[37]
PML	MYL; TRIM19	DBD	[36]
RARα	NR1B1; RAR		[22]
RXRα	NR2B1; RXR alpha	DBD	[22]
SHP	NR0B2; SHP-1	N-term	[28]
Other function			
ß-catenin	CTNNB1; armadillo	Nur77 inhibits β-catenin signaling by inducing its degradation	[33]
RXRα	NR2B1; RXR alpha	Translocation of hetero-dimers to the cytoplasm	[17,20,21,24]
VHL	pVHL; VHL1	Nur77 inhibits VHL-associated E3-ligase activity	[40]