The orphan nuclear receptors at their 25-year reunion

Shannon E Mullican*, Joanna R DiSpirito* and Mitchell A Lazar

Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, and The Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA

*(S E Mullican and J R DiSpirito contributed equally to this work)

Correspondence
should be addressed
to M A Lazar
Email
lazar@mail.med.upenn.edu

Abstract

The nuclear receptor superfamily includes many receptors, identified based on their similarity to steroid hormone receptors but without a known ligand. The study of how these receptors are diversely regulated to interact with genomic regions to control a plethora of biological processes has provided critical insight into development, physiology, and the molecular pathology of disease. Here we provide a compendium of these so-called orphan receptors and focus on what has been learned about their modes of action, physiological functions, and therapeutic promise.

Key Words

► orphan nuclear receptor

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Introduction

In the late 1980s the observation that the steroid hormone receptors shared highly conserved domains encouraged researchers to search for additional members of the nuclear receptor (NR) family (Mangelsdorf *et al.* 1995, Giguère 1999, Willson & Moore 2002, Benoit *et al.* 2006). Unlike that of the classic NRs that had previously been identified with prior knowledge of a naturally occurring ligand, these new members were initially without ligand, and therefore referred to as orphans. Over the span of a decade, using probes designed from conserved NR domains to screen cDNA libraries and degenerate primers for target amplification, as well as automated searches of EST databases, 36 vertebrate orphan NRs were identified (Fig. 1; Willson & Moore 2002).

Orphan NRs consist of the four major domains that characterize classic nuclear hormone receptors (Aranda & Pascual 2001, Huang *et al.* 2010, Helsen *et al.* 2012). The amino terminus contains the A/B domain consisting of activation function 1 (AF1) and among orphans, this region is quite variable in size. The DNA-binding domain (DBD) consists of two zinc finger motifs and confers response element specificity; it is typically highly

conserved within orphan receptor subgroups. Linking the DBD to the carboxy-terminal ligand-binding domain (LBD) is the hinge region, whose length varies between subfamilies. The pocket formed by the LBD can also vary greatly in size and by the absence or presence of the AF2 region that mediates coactivator interaction.

Classic NRs are transcription factors regulated by the high affinity binding of naturally occurring small molecules, which dictate receptor subcellular localization and conformation. The latter determines coactivator–repressor interactions and thereby transactivation potential (Mangelsdorf *et al.* 1995, Aranda & Pascual 2001). In contrast, while the regulation of gene transcription by orphan NRs also depends on interactions with coactivator and corepressor complexes, the role of ligand varies (Benoit *et al.* 2004, Markov & Laudet 2011). Nevertheless, once an endogenous ligand has been identified, the corresponding orphan is then considered ‘adopted’ (Benoit *et al.* 2006).

Due to their potential ligand regulation, orphan NRs have the prospect of serving as therapeutic targets of small molecules (Mukherjee & Mani 2010). Thus, there has been an intense focus on the physiological roles and molecular

Figure 1

Orphan NR Timeline. From the late 1980s till the end of the 1990s, there was rapid growth of the NR superfamily with the addition of 36 orphan members. Once the cloning and discovery of novel members plateaued, the

focus of the field shifted to intense functional characterization. Here each orphan is listed by its common name and color-coded based on its designated NR subfamily.

mechanisms of orphan NRs over the last 25 years (Benoit *et al.* 2006). All vertebrate orphan NRs have been globally deleted in mice and some have been overexpressed and/or selectively targeted spatially and/or temporally. To illustrate the enormous impact of this technology on our understanding of orphan NR biology, all relevant mouse models are summarized in Table 1.

There are many orphan NRs in mammals as well as in lower organisms. Orphan NRs in *Drosophila melanogaster* and *Caenorhabditis elegans* have been reviewed elsewhere (Taubert *et al.* 2011, Fahrback *et al.* 2012). Here, we review current knowledge about each of the 36 orphan NRs that has a human ortholog. The entire NR superfamily has been categorized into six structurally distinct groups based on phylogenetic analysis, producing a unified nomenclature system that identifies each NR with less ambiguity (Laudet 1997, Nuclear Receptors Nomenclature Committee 1999, Germain *et al.* 2006). In this review, each orphan is introduced as part of its official NR group, then addressed by its most commonly used name. The discussion of each is necessarily brief, highlighting its discovery, regulation, and physiological functions, particularly those with therapeutic implications. For

more detailed information on individual NRs, readers are directed to the NURSA website (www.nursa.org) and to more comprehensive reviews.

The odd ones: orphans of the NROB group

Nr0b1/Dax1 and Nr0b2/Shp

DAX1 and SHP are atypical NRs harboring a classifiable NR LBD in their carboxyl-terminus, but lack a classic NR DBD and instead have a region resembling the NR interaction motifs characteristic of coactivators (Zanaria *et al.* 1994, Seol *et al.* 1996, Lalli & Sassone-Corsi 2003, Båvner *et al.* 2005, Ehrlund & Treuter 2012). The name small heterodimer partner (*Shp*) reflects the ability of SHP and DAX1 to bind to the AF2 of other NRs, preventing coactivator recruitment while recruiting corepressor complexes and acting as transcriptional repressors (Lalli & Sassone-Corsi 2003, Båvner *et al.* 2005, Ehrlund & Treuter 2012). While most reports indicate that DAX1 and SHP function as transcriptional repressors, they may also enhance transcription (Kim *et al.* 2001, Nishizawa *et al.* 2002, Xu *et al.* 2009, Kelly *et al.* 2010).

Table 1 Phenotypes of orphan receptor mutant mouse strains. Orphan NR mutant strains that have been published and are listed in the Mouse Genome Informatics (MGI) database. We have listed the general physiological systems and functions affected by each mutation. For more details, see the MGI resource (www.informatics.jax.org) from which this information was collated

Receptor	Embryonic lethal	Whole body mutants	Tissue-specific mutants
DAX1 (NR0B1)	No	KO: fertility (males)	NR
SHP (NR0B2)	No	KO: fertility; energy expenditure, cholesterol metabolism, hepatic inflammation (diet-induced)	Liver: cholesterol and TG metabolism
PPAR α (NR1C1)	No	KO: fatty acid oxidation (fasting); cholesterol and TG metabolism; glycemic control (HFD); cardiac fibrosis; wound healing	Muscle (transgene): glycemic control (HFD) Heart (transgene): TG and cholesterol metabolism
PPAR β/δ (NR1C2)	Yes	KO: placentation; growth; dyslipidemia; cancer; myelination; energy expenditure; cholesterol and TG metabolism	Adipose/brain/macrophage: normal Pan-hematopoietic: atherosclerosis; glycemic control (HFD); hematopoietic Myeloid: autoimmunity; glycemic control (HFD) Skeletal muscle: glycemic control; fiber type; regeneration Pancreas: insulin secretion Heart (transgene): glycemic control
PPAR γ (NR1C3)	Yes	KO: death by E10.5 (placentation) KI (hypomorphic): premature death, AT deposition, glycemic control, TG metabolism KI (Pro12Ala): body weight; glycemic control; TG + cholesterol metabolism KI (P465L): embryonic lethal; BAT activity (het) KI (L466A): embryonic lethal; AT deposition, TG metabolism, glycemic control (hets) KI (S112A): glycemic control KO (Mox2-Cre): AT deposition, glycemic control, blood pressure; circadian rhythm KO (γ 2 isoform only): AT deposition (strain-dependent); glycemic control KO (γ 2 isoform only): AT deposition (strain-dependent); glycemic control	Pancreas: beta cell mass I-Pancreas: no beta cell defects Heart: hypertrophy, systolic function Myeloid: autoimmunity; glycemic control; polarization; glycemic control (HFD), immunity to infection; atherosclerosis Kidney: body weight, blood volume Liver: TG metabolism, glycemic control Muscle: AT deposition; glycemic control Lung epithelium: lung structure Mammary epithelium: no mammary defects Ovary: ovulation (pre-ovulatory follicles) Endothelium/BM: TG metabolism; blood pressure rhythms Treg: adipose inflammation (HFD) B cell: antibody production CNS: no abnormalities reported Adipose (aP2): AT deposition; body weight; glycemic control I-Adipose (aP2): AT maintenance
REV-ERB α (NR1D1)	No	KO: postnatal lethality; fertility; circadian (behavior, cholesterol and TG metabolism, immune response); bile acids; cerebellar	NR
REV-ERB β (NR1D2)	No	KO: no reported abnormalities	NR
REV-ERB α/β	No	NR	DKO liver: circadian; dyslipidemia
ROR α (NR1F1)	No	ENU: postnatal lethality; cerebellar; paralysis KO: viability; atherosclerosis; cerebellar; cholesterol and TG homeostasis; fertility; adrenal; hematopoietic	NR
ROR β (NR1F2)	No	KO: postnatal lethality; growth; fertility; learning/memory; motor; ocular	NR
ROR γ (NR1F3)	No	KO: hematopoietic	T cell: autoimmunity
LXR β (NR1H2)	No	KO: fertility; skin; CNS (amyloid deposition)	NR
LXR α (NR1H3)	No	KO: cholesterol and TG homeostasis (high cholesterol diet); infection KI: constitutively active LXRA confers resistance to LPS-induced lung injury	Liver: cholesterol and TG homeostasis (high cholesterol diet); atherosclerosis

Table 1 Continued

Receptor	Embryonic lethal	Whole body mutants	Tissue-specific mutants
LXR α/β	No	DKO: CNS (lipid deposits); cholesterol and fertility	TG metabolism; immunity to infection;
FXR (NR1H4)	No	KO: bile acids; dyslipidemia	Liver: bile acids; dyslipidemia Intestine: bile acids
PXR (NR1I2)	No	KO: xenobiotic response KI: species-specific xenobiotic responses (human)	NR
CAR (NR1I3)	No	KO: xenobiotic response; lipid homeostasis; body weight (caloric restriction) KI: species-specific xenobiotic responses (human)	NR
HNF4 α (NR2A1)	Yes	KO: embryogenesis, die before E10.5 KI: glycemic control (a1 isoform only)	Liver: hepatogenesis; glycogen; lipid homeostasis body weight; viability
HNF4 γ (NR2A2)	No	KO: body weight; locomotor activity and energy expenditure (circadian)	Beta cell: insulin secretion NR
RXR α (NR2B1)	Yes	KO: cardiac, ocular and placental defects, die before E16.5 KO AF-1 only: partial postnatal lethality; cardiac; ocular; growth retardation	Liver: lipid and cholesterol metabolism, bile acids (high cholesterol diet); body weight, glycemic control (HFD) I-Liver: regeneration I-Adipose (aP2): body weight Macrophage: autoimmunity; endotoxin response Epicardium: cardiovascular developmental defects Retina: photoreceptors Skin: hair and coat color Prostate: pre-neoplastic lesions NR
RXR β (NR2B2)	Partial	KO: viability, fertility KO AF2 only: cholesterol metabolism	NR
RXR γ (NR2B3)	No	KO: thyroid; cholinergic neurons; CNS re-myelination	NR
RXR $\alpha/\beta/\gamma$	Multiple combinatorial	KO, see MGI database for details	
TR2 (NR2C1)	No	KO: fetal hemoglobin	NR
TR4 (NR2C2)	Partial	KO: viability; aging; growth; fertility; cerebellar; body weight, glycemic control, lipid homeostasis, energy expenditure, inflammation (HFD)	NR
TR2/4	Yes	DKO: embryogenesis, die before E12	
TLX (NR2E1)	No	KO: CNS (limbic development); neurogenesis (adult); growth; fertility; ocular; aggression	CNS: aggression I-CNS: spatial learning
PNR (NR2E3)	No	KO: ocular (retina, rods and cones)	NR
COUP-TFI (NR2F1)	No	KO: viability (brain development)	
COUP-TFII (NR2F2)	Yes	KO: angiogenesis and cardiac development I-KO: lymphatic (induction of systemic Cre at E8.5); fertility (induction of Cre at P14)	Uterus: placentation Endothelium: venous and lymphatic development Beta cells: insulin secretion Stomach: morphogenesis DKO eye: morphogenesis NR
COUP-TFI/II	No		
EAR-2 (NR2F6)	No	KO: circadian rhythm; thermal nociception; autoimmunity	NR
ERR α (NR3B1)	No	KO: adipose deposition; stress susceptibility (cardiac, temperature, infection); bone structure	NR
ERR β (NR3B2)	Yes	KO: death by E10.5 (placentation)	Embryonic: hearing (inner ear development)
ERR γ (NR3B3)	No	KO: viability; cardiac; spinal cord; kidney	NR

Table 1 Continued

Receptor	Embryonic lethal	Whole body mutants	Tissue-specific mutants
NURR77 (NR4A1)	No	KO: body weight (HFD); atherosclerosis	NR
NURR1 (NR4A2)	No	KO: complete postnatal lethality by 12 h; selective loss of dopaminergic neurons	NR
NOR1 (NR4A3)	Yes	KO: death by E8.5 (gastrulation); seizures; inner ear; atherosclerosis	NR
NURR77/NOR1 DKO	No	KO: viability; leukemia (growth, hepatomegaly, anemia)	NR
SF1 (NR5A1)	No	KO: viability (adrenals); gonads; hypothalamus KI: K119 and K194 mutated to R, loss of sumoylation on those residues associated with abnormal adrenal function and infertility	Anterior pituitary: fertility (gonad maturation) Gonads: fertility (gonad maturation) CNS: behavior (anxiety); body weight (HFD)
LRH-1 (NR5A2)	Yes	KO: death before E7.5 HET: intestinal crypts	Liver: slight dyslipidemia; bile acid composition Intestine: slight dyslipidemia Gonads: fertility (ovulation)
GCF (NR6A1)	Yes	KO: death by E10.5 (cardiac development)	Oocyte: fertility (oocyte morphology, steroidogenesis)

KO, knock-out; DKO, double knock-out; KI, knock-in; I, inducible Cre transgene; NR, not yet reported; AT, adipose tissue; HFD, high-fat diet; TG, triglyceride.

To date, no ligands for the NR0B receptors have been well-established, although retinoid-related molecules have been reported to bind and enhance the repressive function of SHP (Miao *et al.* 2011, Ehrlund & Treuter 2012). Indeed, a crystal structure study of DAX1 demonstrated a ligand-binding pocket (LBP) filled with amino acid side chains, suggesting typical ligand regulation of this orphan to be unlikely (Sablin *et al.* 2008). Sequence conservation between *Nr0b* group members suggests this to be a shared characteristic, and thus, it appears that the *Nr0b* group is regulated at the level of expression, alternative splicing, posttranslational modifications, and miRNA targeting (Hossain *et al.* 2004, Miao *et al.* 2009, Xiao *et al.* 2012, Seok *et al.* 2013).

Although DAX1 and SHP are mechanistically very similar, their tissue expression patterns are distinct, suggesting different physiological roles (Ehrlund & Treuter 2012). *Nr0b1* was originally identified as a gene frequently deleted or mutated in X-linked adrenal hypoplasia congenita (AHC) and also duplicated in dosage-sensitive sex reversal (DSS), leading to its more common name, DSS-AHC critical region on the X, gene 1, or *Dax1* (Muscatelli *et al.* 1994, Zanaria *et al.* 1994, Lalli & Sassone-Corsi 2003). *Dax1* is highly expressed in the hypothalamic–pituitary–adrenal–gonadal axis and has essential roles in gametogenesis and sex specification mediated in part by

repression of NR5A1 (SF1; Lalli & Sassone-Corsi 2003, Iyer & McCabe 2004). In contrast, Shp is highly expressed in the liver and small intestine, where it represses NR5A2 (LRH1) to regulate cholesterol, bile acid (BA), and glucose metabolism (Bävner *et al.* 2005, Chanda *et al.* 2008).

Both members of the *Nr0b* group have also been reported to repress the transcriptional activity of other factors besides NRs (Kim *et al.* 2004, 2012, Suh *et al.* 2006, Kinsey *et al.* 2009, Sun *et al.* 2009, Yuk *et al.* 2011). For example, SHP functions as a corepressor of NF-κB during inflammatory Toll-like receptor signaling (Yuk *et al.* 2011). Moreover, the ability to bind and repress OCT4 activity has identified DAX1 as a critical component in maintaining embryonic stem cell pluripotency (Wang *et al.* 2006, Kim *et al.* 2008, Sun *et al.* 2009). Finally, the potential role of *Nr0b* receptors in carcinogenesis is highlighted by the functional interaction of DAX1 with the EWS/FLI fusion protein in Ewing's sarcoma (Kinsey *et al.* 2009).

There for dinner: orphans of the NR1C group

Nr1c1/Pparα, Nr1c2/Pparβ or δ, and Nr1c3/Pparγ

Peroxisome proliferator-activated receptors (PPARs) regulate carbohydrate and lipid metabolism in major metabolic organs (liver, adipose, and muscle) as well as

in peripheral tissues with metabolic roles (intestine, hematopoietic, and hypothalamic). The 'PPAR' name followed the discovery that PPAR α was activated by clofibrate, a lipid-lowering drug that causes peroxisome proliferation in the rodent liver (Issemann & Green 1990); however, the β/δ and γ subtypes have not been shown to cause peroxisomal proliferation. Despite ongoing searches for dominant endogenous ligands, the PPARs are now commonly thought of as 'sensors' for a wide range of fatty acid molecules, a promiscuity that may be explained by their large LBP (Nolte *et al.* 1998, Uppenberg *et al.* 1998, Xu *et al.* 1999, 2001, Michalik 2006). However, high affinity and relatively specific synthetic ligands exist for each PPAR (Bensinger & Tontonoz 2008). As noted earlier, lipid-lowering fibrates activate PPAR α , and agonists of PPAR γ function as anti-diabetic drugs (Lehrke & Lazar 2005).

Activation of PPAR α and PPAR β/δ supports fatty acid oxidation (FAO) in the heart, liver, and muscle, while PPAR γ promotes lipid storage in adipose tissue (Michalik 2006). Thus, loss of PPAR α in the liver blocks elevated FAO in response to fasting, leading to hepatic and myocardial lipid accumulation, hypoglycemia, and elevated serum-free fatty acids (Kersten *et al.* 1999, Leone *et al.* 1999). Similarly, PPAR β/δ activity in the muscle promotes formation of highly oxidative slow-twitch fibers, in part through its positive regulation of PGC1 α (Evans *et al.* 2004, Schuler *et al.* 2006). Interestingly, these two receptors have opposing roles in cardiac myocytes of the diabetic heart, where PPAR β/δ promotes glucose uptake, utilization, and overall cardiac health, while the PPAR α pathway decreases glucose utilization and promotes the myocardial lipid accumulation associated with cardiac disease (Burkart *et al.* 2007). PPAR γ is strongly induced during adipocyte differentiation and its activity is necessary and, in some cases, sufficient for adipogenesis (Chawla & Lazar 1994, Tontonoz *et al.* 1994, Tontonoz & Spiegelman 2008). Two isoforms, γ 1 and γ 2, identical except for an additional 30 amino acids at the N-terminus of γ 2, are highly expressed in adipocytes, while other cell types express comparatively lower levels of the γ 1 isoform (Tontonoz *et al.* 1994, Nagy *et al.* 2013). Loss of PPAR γ expression causes lipodystrophy in mice as do dominant negative mutants of PPAR γ in both mice and humans (Barak *et al.* 2002, Freedman *et al.* 2005, Semple 2006, Duan *et al.* 2007). PPAR γ also regulates lipid metabolism in macrophages and appears to have an overlapping but non-redundant role with PPAR δ in the regulation of macrophage polarization and homeostatic scavenging of apoptotic cells (Ahmadian *et al.* 2013).

PPARs bind DNA as obligate heterodimers with Nr2b1 (Rxr) family members to a direct repeat (DR) of the sequence AGGTCA separated by one nucleotide, usually an adenine (Kliewer *et al.* 1992b, Ijpenberg *et al.* 1997, Varga *et al.* 2011). This DR1 element was initially defined using *in vitro* binding and transactivation assays and has been confirmed as the predominant recognition motif at PPAR binding sites identified on a genome-wide scale *in vivo* (Dreyer *et al.* 1992, Kliewer *et al.* 1992b, Tugwood *et al.* 1992, Lefterova *et al.* 2008, 2010, Nielsen *et al.* 2008, Mikkelsen *et al.* 2010, Boergesen *et al.* 2012).

It's about time: orphans of the NR1D group

Nr1d1/Rev-erb α and Nr1d2/Rev-erb β

Rev-erb α was discovered as a coding sequence on the reverse strand of the *c-erbA* gene, which encodes a thyroid hormone receptor, and the identification of Rev-erb β followed several years later (Lazar *et al.* 1989, Dumas *et al.* 1994, Forman *et al.* 1994, Retnakaran *et al.* 1994). Structurally, the Rev-erbs are unique among NRs because they lack a critical alpha-helix (H12) in the AF2 domain that mediates coactivator interaction, resulting in a conformation more suitable for corepressor recruitment (Renaud *et al.* 2000, Ramakrishnan & Muscat 2006, Yin *et al.* 2010). Both Rev-erb α and Rev-erb β act as receptors for heme, which binds within the classic NR LBP (Reinking *et al.* 2005, Raghuram *et al.* 2007, Yin *et al.* 2007, Burris 2008). Several synthetic agonists have been developed and show potential for modulating Rev-erb *in vivo* (Yin *et al.* 2010, Solt *et al.* 2012). Besides ligand binding, regulation of Rev-erb activity also occurs at the level of gene expression, posttranslational modifications, and protein-protein interactions (Yin *et al.* 2010, Chini *et al.* 2013). For example, Rev-erb expression in most tissues is circadian and is tightly controlled by the core circadian clock TFs, BMAL1 and CLOCK, as well as repressing its own transcription (Feng & Lazar 2012). Furthermore, Rev-erb α is stabilized by GSK3 β -mediated phosphorylation that can be blocked by lithium exposure; in hippocampal neurons, oligophrenin 1 alters cellular localization of Rev-erb α , blocking its repressive function (Valnegri *et al.* 2011, Feng & Lazar 2012).

Acting as dedicated transcriptional repressors, both Rev-erbs bind to extended half-sites (AGGTCA) with an A/T-rich 5' end (RORE), a sequence identical to that recognized by NR1F (ROR) orphan receptors but with opposing effects. Importantly, Rev-erb monomer's association with isolated ROREs is not sufficient for active transcriptional repression (although it can still compete

with ROR binding to the RORE); however, two neighboring monomeric Rev-erbs can cooperate to recruit corepressors to repress gene expression (Yin *et al.* 2010). Heme stabilizes the interaction with NCoR, augmenting repression of transcription and defining the Rev-erb group as ligand-stimulated transcriptional repressors (Pardee *et al.* 2009). Rev-erb α and β also dimerize and function at a DR of their unique half-site spaced by two additional nucleotides (Rev-DR2; Yin *et al.* 2010).

The Rev-erbs have been implicated in a variety of physiological processes, including cerebellar development, osteoarthritis, adipogenesis, and mitochondria biogenesis, but the most well-known cellular function is to act as integrators of circadian rhythm and metabolic pathways (Chomez *et al.* 2000, Chaturvedi *et al.* 2006, Ramakrishnan & Muscat 2006, Wang & Lazar 2008, Yin *et al.* 2010, Woldt *et al.* 2013). Genome-wide studies have indicated that the cyclic expression and genomic presence of both Rev-erbs result in the proper rhythmic expression of circadian clock and lipid metabolism genes and underscoring the importance of this convergence, Rev-erb deficiency in the liver results in hepatic steatosis and dysregulation of the cell autonomous hepatic clock (Bugge *et al.* 2012, Cho *et al.* 2012). Recent work has also described that Rev-erbs represent a key link between the cellular clock and macrophage function, where they function cyclically to limit the expression of cytokines impacting responses to pathogens (Fontaine *et al.* 2008, Gibbs *et al.* 2012, Chandra *et al.* 2013, Lam *et al.* 2013).

More time for discussion: orphans of the NR1F group

Nr1f1/Ror α , Nr1f2/Ror β , and Nr1f3/Ror γ

The RAR-related orphan NRs comprise three structurally related orphan NRs with roles in retinal development, lipid and glucose homeostasis, atherosclerosis, carcinogenesis, circadian rhythm, bone formation, and immunity (Becker-André *et al.* 1993, Medvedev *et al.* 1996, Jetten 2009, Solt & Burris 2012). Of particular note, ROR α is required for cerebellar development, and ROR γ plays a critical role in lymphoid cells (Hamilton *et al.* 1996, Kurebayashi *et al.* 2000, Ivanov *et al.* 2006, Solt & Burris 2012).

RORs bind as monomers to the same RORE sequence bound by Rev-erbs and are described as constitutive activators, recruiting coactivators in absence of ligand (Jetten 2009). However, independent investigations have suggested that oxysterols and cholesterol derivatives act as

agonist and inverse agonist ligands of ROR α and γ (Kallen *et al.* 2002, Jin *et al.* 2010, Wang *et al.* 2010). In addition, retinoids and retinoic acid have been shown to antagonize the activity of ROR β (Stehlin-Gaon *et al.* 2003). Despite the uncertainty surrounding endogenous ligand regulation of RORs, the generation of synthetic agonists and inverse agonists has great therapeutic promise, particularly in modulating the function of the ROR γ -t isoform in T_H17 lymphocytes during autoimmunity (Yang *et al.* 2008, Huh *et al.* 2011, Solt *et al.* 2011).

Like other NRs, activity of RORs can be regulated by posttranslational modifications, including phosphorylation and sumoylation (Hwang *et al.* 2009, Onishi *et al.* 2009, Lee *et al.* 2010). Intriguingly, a 'methyl degraon' sequence has been recently described in ROR α , making it the first non-histone substrate targeted by methyltransferases to regulate protein stability (Lee *et al.* 2012). Antagonism with other TFs also mediates ROR activity, demonstrated by the recent observation that ROR γ function is inhibited by direct interaction with Foxp3 (Ichiyama *et al.* 2008, Zhou *et al.* 2008). Furthermore, the ability of ROR α and Rev-erb α to bind to overlapping sites and counteract each other's activity at target genes has been demonstrated in the circadian control of Bmal1 and Rev-erb α expression (Guillaumond *et al.* 2005). In addition to direct transcriptional regulation at specific response elements, the transrepression of Wnt/ β -catenin-mediated gene activation has been reported (Lee *et al.* 2010). Furthermore supporting the DNA-binding independent functions of RORs, ROR α has been reported to bind and stabilize p53 protein and thereby indirectly regulate p53 target gene expression (Kim *et al.* 2011, Wang *et al.* 2012).

Watching what they eat: orphans of the NR1H group

Nr1h2/Lxr β , Nr1h3/Lxr α , and Nr1h4/Fxr α

The *Nr1h* family includes liver X receptors, LXR α and LXR β , and farnesol X receptors, FXR α and FXR β , although FXR β is found in mice but not in humans (Moore *et al.* 2006). LXRs and FXRs have metabolically intertwined roles that converge on minimizing the buildup of cholesterol by responding to elevated levels of sterols and BAs respectively (Calkin & Tontonoz 2012). Endogenous LXR ligands that have been reported include: 24(S), 25-epoxycholesterol in the liver, 24(S)-hydroxycholesterol in the brain, and 27-hydroxycholesterol in macrophages (Moore *et al.* 2006). Synthetic, high affinity pan-LXR

agonists are in wide experimental use. These compounds promote the cholesterol-lowering activity of LXRs, but this benefit is offset by activation of the SREBP1C pathway of *de novo* lipogenesis in the liver, which has hindered the advancement of LXR agonists as therapies for human metabolic disorders (Repa *et al.* 2000, Joseph *et al.* 2002, Tangirala *et al.* 2002, Levin *et al.* 2005). FXR was initially named based on its activation by very high concentrations of farnesol and its metabolites *in vitro*, but was later found to respond to physiological concentrations of BAs and is now widely viewed as a nuclear BA receptor and central regulator of BA homeostasis (Forman *et al.* 1995, Makishima *et al.* 1999, Parks *et al.* 1999, Wang *et al.* 1999). BAs vary in their affinity for FXR with the strongest agonist being the primary BA chenodeoxycholic acid (CDCA; Modica *et al.* 2010). Importantly, synthetic FXR agonists are efficacious in treating mouse models of cholestatic diseases (Moschetta *et al.* 2004).

Subtype and cell type-specific deletions of LXR have uncovered their roles in the regulation of whole-body cholesterol homeostasis. In atherosclerosis-prone mouse strains, LXR α is required for preventing cholesterol overload in several tissues including the liver, where LXR α activation cannot be compensated for by LXR β ; macrophages, where it contributes equally with LXR β ; and likely other tissues including adipose and intestine (Lehrke *et al.* 2005, Bradley *et al.* 2007, Hong *et al.* 2012, Zhang *et al.* 2012). Similarly, LXR β has a non-redundant role in preventing cholesterol accumulation in BA-metabolizing cholangiocytes, the CNS, spinal cord, and male gonadal cells (Gabbi *et al.* 2009, Xia *et al.* 2012). For FXR, activation by BAs initiates a negative feedback loop that limits BA synthesis and promotes their transit from hepatocytes to the enterohepatic circulation. Consistent with this, FXR-deficient mice challenged with high levels of dietary BAs suffer severe hepatotoxicity (Sinal *et al.* 2000).

All *Nr1h* members heterodimerize with RXR and recent genome-wide binding studies have demonstrated widespread use of sequence motifs identified using older low-throughput methods. In liver, the vast majority of FXR-binding sites identified by ChIP-seq, contained an IR1 motif (inverted repeats of the canonical NR half site AGGTCA separated by one nucleotide) which was initially reported as the preferred motif for FXR-RXR heterodimers (Laffitte *et al.* 2000, Chong *et al.* 2010, Thomas *et al.* 2010). Similarly, genome-wide profiling confirmed co-occupancy of LXR-RXR at DR4 motifs, initially characterized almost 20 years ago (Willy *et al.* 1995, Boergesen *et al.* 2012).

The defenders: orphans of the NR1l group

Nr1i2/Pxr and Nr1i3/Car

The pregnane X receptor (PXR) and constitutive androstane receptor (CAR) play a key role in the body's defense against xenobiotics (foreign materials encountered in the environment). Mouse and human PXR were discovered almost simultaneously, revealing PXR as a conserved, direct regulator of *Cyp3a* family enzymes important in xenobiotic and endobiotic metabolism (Bertilsson *et al.* 1998, Blumberg *et al.* 1998, Kliewer *et al.* 1998, Lehmann *et al.* 1998). PXR can bind structurally distinct ligands that range in size from 268 to 823 Da and are highly species-specific, in accordance with the relatively low conservation of the PXR LBP among orthologs (Reschly & Krasowski 2006). This diverse array of xenobiotics, dietary compounds, and endobiotics includes rifampicin, clotrimazole, phenobarbital, the herbal antidepressant St John's wort, HIV protease inhibitors, and BAs (Zhou *et al.* 2009, Tolson & Wang 2010). Initial cloning of CAR reported its transcriptional activity in the absence of an exogenous ligand, leading to the name constitutive active receptor before androstanes were identified as inverse agonists (Baes *et al.* 1994, Forman *et al.* 1998). To date, many xenobiotic agonists have been identified with phenobarbital-like compounds being the most widely used to study CAR's function (Gao & Xie 2010).

Both receptors induce phase I and II drug metabolizing enzymes in the liver and intestine (Tolson & Wang 2010, Ihunnah *et al.* 2011). Though this activity is clearly beneficial, it can also enhance drug toxicity, such as during the PXR-mediated accumulation of toxic aspirin metabolites (Guo *et al.* 2004). Similarly, CAR deficiency is protective against hepatotoxicity caused by the breakdown of phenobarbital and related compounds (Wei *et al.* 2000). Roles of PXR and CAR in endobiotic metabolism have also come to light. PXR can promote BA excretion from the liver into the urine, which may explain the profound susceptibility of PXR-deficient mice to challenge with a high cholesterol-BA diet (Staudinger *et al.* 2001, Xie *et al.* 2001, Sonoda *et al.* 2005). Ligand-activated PXR can also suppress hepatic gluconeogenesis and fasting-induced FAO and has been implicated in the regulation of reverse cholesterol transport, steroid hormone synthesis, and the catabolism of androgen, bilirubins, and retinoic acid (Ihunnah *et al.* 2011). Ligand-activated CAR protects against diet-induced obesity and its related metabolic complications (Gao *et al.* 2009).

Ligand activation of both PXR and CAR induces cytoplasmic to nuclear shuttling that can be regulated by

phosphorylation (Squires *et al.* 2004, Pondugula *et al.* 2009). Once in the nucleus, PXR binds DNA as a heterodimer with RXR, predominantly at DR4 motifs, as revealed by recent genome-wide binding analysis in the liver (Kliewer *et al.* 1998, Cui *et al.* 2010). Notably, this study found no evidence for PXR binding to everted repeats (ER6 or ER8), as was previously reported (Kliewer *et al.* 2002). CAR also binds as an obligate heterodimer with RXR to DR4 motifs, but this preference has yet to be shown on a genome-wide scale (Kawamoto *et al.* 1999, Sueyoshi & Negishi 2001).

Arrested development: orphans of the NR2A group

Nr2a1/Hnf α and Nr2a2/Hnf γ

The hepatocyte nuclear factors HNF4 α and HNF4 γ are encoded by two distinct but highly homologous genes (Drewes *et al.* 1996). Cloning of HNF4 α from human liver revealed several variants regulated by alternative promoter usage and splicing (Chartier *et al.* 1994, Kritis *et al.* 1996). There are two predominant isoforms: the longer HNF4 α 1 containing an additional N-terminal AF1 domain expressed highly in liver, and the shorter HNF4 α 7 expressed highly in the pancreas (Eeckhoutte *et al.* 2003). HNF4 γ was cloned from a human kidney cDNA library and an early report found it in the pancreas, liver, brain, and lung (Plengvidhya *et al.* 1999). HNF4 α appears to function as a ligand-independent, constitutively active receptor (Ruse *et al.* 2002). However, several crystal structures of purified LBDs identified fatty acids in its binding pocket and there is evidence that linoleic acid binds to HNF4 α in the livers of fed, but not fasted, mice (Dhe-Paganon *et al.* 2002, Wisely *et al.* 2002, Yuan *et al.* 2009).

Mutations in HNF4 α are associated with a rare form of early-onset, autosomal dominant diabetes called maturity onset diabetes of the young, and therefore HNF α is considered a MODY1 gene (Yamagata *et al.* 1996, Navas *et al.* 1999). Mouse models have shown that it is required in the pancreas for glucose-stimulated insulin secretion and beta cell expansion (Gupta *et al.* 2005, 2007). HNF4 α has pleiotropic roles in other enterohepatic tissues, most prominently in the liver, where it is required for the maturation, maintenance, and differentiated functions of hepatocytes (Sladek *et al.* 1990, Chen *et al.* 1994b). Disruption of this program by hepatocyte-specific ablation of HNF4 α results in hepatomegaly, fatty liver, reduced serum cholesterol and TG, increased serum BAs, and premature death (Hayhurst *et al.* 2001). In intestinal

epithelial cells, HNF4 α regulates fatty acid re-absorption and barrier function (Cattin *et al.* 2009, Frochot *et al.* 2012). Importantly, HNF4 α is required for endoderm formation during development and at multiple stages of liver maturation (Duncan 2003, Parviz *et al.* 2003). Less is known about the physiological roles of HNF4 γ , but it appears to be dispensable for embryogenesis. Rather, it promotes normal energy expenditure and locomotor activity (Gerdin *et al.* 2006).

HNF4 α can bind as a homodimer or as a heterodimer with HNF4 γ to DR1 recognition motifs (Daigo *et al.* 2011, Fang *et al.* 2012). Although many other NRs bind the DR1, one specific half-site motif (CAAAGTCCA) is preferred by HNF4 α *in vitro* and *in vivo*, suggesting a mechanism underlying its distinct target gene networks and functions (Odom *et al.* 2004, Gupta *et al.* 2005, Fang *et al.* 2012).

Partners for life: orphans of the NR2B group

Nr2b1/Rxr α , Nr2b2/Rxr β , and Nr2b3/Rxr γ

The Nr2b family includes retinoid X receptors, RXR α , RXR β , and RXR γ . Cloning of RXR α as a retinoic acid-responsive factor that shared modest homology with retinoic acid receptors (RARs) was followed shortly by identification of RXR β and RXR γ (Mangelsdorf *et al.* 1990, Rowe *et al.* 1991, Yu *et al.* 1991). RXRs dimerize with and strengthen the DNA-binding and transcriptional activity of other NRs, a list that now includes TR, RARs, VDR, PPARs, LXRs, FXR, PXR, CAR, NGFIB, and NURR1 (Yu *et al.* 1991, Kliewer *et al.* 1992a, Leid *et al.* 1992, Marks *et al.* 1992, Mark & Chambon 2003). RXRs bind 9-*cis*-retinoic acid with high affinity, and their heterodimer partners can be defined as 'permissive' or 'non-permissive' based on whether an RXR ligand activates the complex (Levin *et al.* 1992, Mangelsdorf *et al.* 1992, Lefebvre *et al.* 2010). The production of 9-*cis*-RA *in vivo* is controversial, but several specific and high affinity pharmacological ligands have been developed (Wolf 2006, Pérez *et al.* 2012).

Because of their wide array of binding partners, RXRs may have the most disparate biological roles of all NRs. For instance, RXR α ablation is embryonic lethal due to cardiac defects likely to result from its participation in complexes with RAR (Kastner *et al.* 1994, Sucov *et al.* 1994, Gruber *et al.* 1996). In the liver, where RXR α is the most abundant subtype, hepatocyte-specific deletion results in elevated serum triglycerides, serum cholesterol, and dramatic intolerance to a high cholesterol diet, likely via a loss of LXR, FXR, and possibly PXR and CAR activities (Mangelsdorf *et al.* 1992, Wan *et al.* 2000). Ablation of

RXR β is lethal in some genetic backgrounds and it has a non-redundant role in spermatogenesis (Kastner *et al.* 1996). RXR γ is not essential for development but appears to be important for proper sensitivity to thyroid hormone, as knock-out mice have increased metabolic activity, serum T₄ and TSH, and are resistant to diet-induced obesity (Brown *et al.* 2000, Haugen *et al.* 2004). It is also required in the CNS for proper functioning of cholinergic and dopaminergic pathways and for oligodendrocyte differentiation (Saga *et al.* 1999, Krzyzosiak *et al.* 2010, Huang *et al.* 2011). Compound mutants in RXR family members have been generated and have been comprehensively reviewed elsewhere (Mark *et al.* 2006).

Recent ChIP-seq studies have profiled the binding specificities of RXRs on a genome-wide scale, revealing extensive co-occupancy of RXRs with PPAR γ in adipocytes and LXR in liver. These studies also reported substantial numbers of RXR-only binding sites, suggesting the likely cooperation of RXR with additional NR partners in these tissues (Nielsen *et al.* 2008, Boergesen *et al.* 2012). A similar study found RXR α bound near ~80% of genes expressed in the liver, though expression of only a small fraction were affected by hepatocyte-specific RXR α knockout, illustrating the challenge of elucidating the role of RXRs in tissue-specific regulatory networks (Zhan *et al.* 2012).

What's in a name: orphans of the NR2C group

Nr2c1/Tr2 and Nr2c2/Tr4

Testicular orphan NR 2 (*Tr2*) was originally identified by screening a human testis cDNA library for novel genes containing sequences similar to previously identified NR DBDs and the identification of related receptor *Tr4* (*Tak1*) was reported a few years later (Chang *et al.* 1989, 1994, Hirose *et al.* 1994, Law *et al.* 1994, Lee *et al.* 2002). *Tr2* and *Tr4* display a widespread expression pattern in embryonic and adult tissues, suggesting pleiotropic physiological functions (Lee *et al.* 2002). Indeed, loss of function studies implicated TR4 in many diverse biological systems, including the CNS, reproduction, and metabolism (Kim *et al.* 2003, Chen *et al.* 2005b, Kang *et al.* 2011, Lin *et al.* 2012). Interestingly, mice lacking TR2 appeared normal suggesting that the *Nr2c* group may function redundantly and this is supported by the dramatic defect in stem cell self-renewal, commitment, and differentiation observed in mice lacking both orphan NRs (Shyr *et al.* 2002a, 2009).

TR2 and 4 can bind to response elements consisting of a DR of the canonical NR half site (AGGTCA) with various

types of spacing (DR1–5) and, consistent with this relatively promiscuous binding, part of the group's functions seems to be mediated by sharing or competing with other NRs for response elements (Lin *et al.* 1995, Yan *et al.* 1998, Xie *et al.* 2009a). Direct regulation of transcription appears to be dependent on homo- or heterodimerization between the *Nr2c* group members (Lee *et al.* 1998, Zhou *et al.* 2011). In contrast, the analysis of TR4-enriched genomic regions obtained with ChIP-seq revealed no obvious DR element, suggesting that the genomic localization of NR2C members may be indirect (O'Geen *et al.* 2010). Consistent with this, several studies have reported interaction with and regulation of other NRs independent of NR2C binding to DNA (Hu *et al.* 2002, Shyr *et al.* 2002b, Mu & Chang 2003).

To date, ligands for *Nr2c* group members have not been described, although there is some evidence that they can be bound and activated by polyunsaturated fatty acids (Xie *et al.* 2009a). A recent crystal structure showed ligand-free TR4 to be in an autorepressed conformation that can be modulated by retinoid treatment introducing another potential ligand of the *Nr2c* group (Zhou *et al.* 2011). Receptor phosphorylation, acetylation, and sumoylation status can also cause the exchange of corepressors and coactivators and thereby convert NR2C receptors from transcriptional repressors to activators and vice versa (Khan *et al.* 2005, Gupta *et al.* 2009, Xie *et al.* 2011). This is exemplified by the regulation of the *Oct4* promoter in stem cells by TR2, where phosphorylation of the receptor causes repression of *Oct4*, a critical switch in the balance of pluripotent cell self-renewal and differentiation (Gupta *et al.* 2008). In addition to posttranslational modification, the expression level of TR2/4 appears to be an important means of activity modulation and showing therapeutic promise, genetic overexpression of *Tr2/Tr4* in the erythroid lineage of a sickle cell disease model conferred enhanced expression of target gene fetal hemoglobin and alleviated disease symptoms (Campbell *et al.* 2011).

Seeing is believing: orphans of the NR2E group

Nr2e1/Tlx and Nr2e3/Pnr

Tlx is the vertebrate homologue of the *Drosophila* gene *tailless* (*tll*), which was characterized in 1990 (Gui *et al.* 2011). A screening for similar genes led to the photoreceptor NR (PNR), making it the latest vertebrate NR to be described (Chen *et al.* 1999, Kobayashi *et al.* 1999). TLX and PNR negatively regulate target gene transcription as

monomers or homodimers, recruiting corepressors to the half sites or DR1 elements although there have been reports of gene activation as well (Chen *et al.* 2005a, Zhang *et al.* 2006, Sun *et al.* 2007, Yokoyama *et al.* 2008, Qu *et al.* 2010). Furthermore, a recent study has reported the ability of PNR to interact with and positively regulate p53 in a manner independent of PNR DNA-binding (Wen *et al.* 2012). While very little is known about the ligand dependency of the *Nr2e* group, activity of PNR and TLX is regulated by interaction with other NRs, posttranslational modification, alternative splicing, and miRNA targeting (Cheng *et al.* 2004, Wolkenberg *et al.* 2006, Onishi *et al.* 2009, Zhao *et al.* 2009, 2010, Shibata *et al.* 2011, Qin *et al.* 2013b).

In contrast to most orphan NRs, the *Nr2e* members have very specialized physiological roles limited mainly to the development of the rods and cones of the retina and CNS function (Gui *et al.* 2011, Forrest & Swaroop 2012). The essential role for PNR in retinal development is reflected in its mutation being highly associated with enhanced S-cone syndrome, retinitis pigmentosa, and other retinopathy in humans (Forrest & Swaroop 2012). Retinal degeneration also occurs in mice with either a spontaneous or targeted deletion (Forrest & Swaroop 2012). TLX also functions in preventing retinal degeneration and in addition, mouse models have demonstrated a critical role in the development of the limbic system, where deletion leads to extreme aggression (Monaghan *et al.* 1997, Yu *et al.* 2000, Young *et al.* 2002). More recently, the essential role of TLX in maintaining adult neural stem cells in an undifferentiated, proliferative state has come to light and this cellular function has been reported to impact both spatial learning and brain tumor expansion, suggesting its potential as a therapeutic target (Shi *et al.* 2004, Liu *et al.* 2010, Zou *et al.* 2012).

Leaders of the chicken dance: orphans of the NR2F group

Nr2f1/Coup-tfI, Nr2f2/Coup-tfII, and Nr2f6/Ear2

Chicken ovalbumin upstream promoting TF 1 (COUP-TFI) was identified as a long-sought after regulator of the chicken ovalubulin gene (Wang *et al.* 1989). It, as well as ERBA-related protein 2 (EAR2), was originally described as the genes encoding proteins with homology to thyroid receptor, while COUP-TFII, a *Nr2f* member highly related to COUP-TFI, was identified in a later screen (Miyajima *et al.* 1988, Ritchie *et al.* 1990, Ladas & Karathanasis 1991).

COUP-TFI and II bind as dimers to repress transcription via DR1 elements (Tsai & Tsai 1997, Alfano *et al.* 2013). The COUP-TFs can also promiscuously recognize many other direct, inverted and everted NR half-site (AGGTCA) repeats, enabling them to compete with and antagonize the action of other NRs (Tsai & Tsai 1997, Alfano *et al.* 2013). These receptors also have transrepressive effects mediated by heterodimerization with other TFs or their partner RXR. EAR2 also appears to be a transcriptional repressor able to heterodimerize with other NRs including the COUP-TFs (Jonk *et al.* 1994, Zhu *et al.* 2000, Warnecke *et al.* 2005). For example, EAR2 was recently demonstrated to bind and inhibit the function of ROR γ t in T_H17 lymphocytes (Hermann-Kleiter *et al.* 2012). Despite the large body of evidence describing this family as transcriptional repressors, there have been some reports of NR2F-mediated gene activation but *in vivo* relevance of these findings has not been substantiated (Tsai & Tsai 1997). To date, the *Nr2f* members remain as true orphan NRs, but in addition to their level of gene expression, activity of these TFs is regulated by posttranslational modifications including phosphorylation (Tsai & Tsai 1997, Hermann-Kleiter *et al.* 2008).

The *Nr2f* group is widely expressed and loss of function models has been a key in the dissection of their many physiological roles (Lin *et al.* 2011). By influencing cellular processes including, survival, migration, fate determination, and differentiation, COUP-TFI and II have unique and essential functions in neural development and organogenesis respectively (Lin *et al.* 2011). However, they do share nearly identical DBDs and LBDs and recent analyses of mice deficient in both receptors have uncovered a redundant role in retinal development (Satoh *et al.* 2009, Tang *et al.* 2010). In addition to loss of function studies, genome-wide profiling of histone modifications and analyses of enhancer sequences predicted a role for both COUP-TFI and II in the phenotype of embryonic neural crest cells (NCC) which was further supported by knockdown experiments in human NCCs (Rada-Iglesias *et al.* 2012). Besides direct developmental roles, the NR2F receptors have recently been implicated as potential targets in cancer therapeutic intervention (Litchfield & Klinge 2012). For example, overexpression of COUP-TFII results in the inhibition of SMAD4-mediated transactivation, which normally prevents cancer progression in prostate epithelium (Qin *et al.* 2013a). In contrast to COUP-TFI and II, much less is known about EAR2; however, knock-out mouse studies have suggested the roles in the CNS and immune system (Warnecke *et al.* 2005, Hermann-Kleiter *et al.* 2008).

Lots of energy: orphans of the NR3B group

Nr3b1/Err α , Nr3b2/Err β , and Nr3b3/Err γ

Estrogen-related receptors, α (Err α) and β (Err β) were discovered by screening libraries with a probe consisting of the sequence of the DBD of estrogen receptor (ER) and were the first orphan NRs to be discovered (Giguère *et al.* 1988, Deblois & Giguère 2011). Nearly a decade later, Err γ was discovered as a gene deleted in a critical region of Usher syndrome, a genetic disorder resulting in hearing and vision loss, and subsequently described by two additional groups (Eudy *et al.* 1998, Hong *et al.* 1999, Heard *et al.* 2000). The ERRs are constitutive activators and crystal structure studies suggest that classic ligand binding modulation is unlikely due to an inaccessible LBP. However, the presence of certain inverse agonists are able to induce a conformational change favoring corepressor interaction (Kallen *et al.* 2007, Xie *et al.* 2009b). Although no endogenous ligand for the ERRs has been reported, many inverse agonists and antagonists have been described, including pesticides, synthetic and phyto-estrogens, and 4-hydroxytamoxifen (4-OHT), underscoring the notion of functional crosstalk between ERR and ER signaling (Coward *et al.* 2001, Tremblay *et al.* 2001a,b, Bonnelye & Aubin 2013). Adding to this complexity, bisphenol A, the synthetic estrogen and endocrine disruptor found in many plastics, binds Err γ and prevents 4-OHT-induced coactivator dissociation (Takayanagi *et al.* 2006). Posttranslational modifications including phosphorylation, acetylation, and sumoylation also influence ERR activity (Ariazi *et al.* 2007, Tremblay *et al.* 2008, Wilson *et al.* 2010). The constitutive activity of the ERR group is also negatively regulated by DAX1 and SHP (Sanyal *et al.* 2002, Uranishi *et al.* 2013). The ERRs all recognize an extended half-site termed the ERRE (TNAAGGTCA) as monomers, homodimers, or heterodimers (Dufour *et al.* 2007, Tremblay & Giguère 2007). Although ERRs may also have affinity for classic estrogen and thyroid receptor elements *in vitro*, recent genome wide localization studies have suggested that the ERRE is the main site of ERR occupancy (Johnston *et al.* 1997, Vanacker *et al.* 1998, Dufour *et al.* 2007, Tremblay & Giguère 2007).

Err α and Err γ are widely expressed and regulate genes that modulate cellular energy metabolism by directing mitochondrial biogenesis and function impacting a variety of tissues under various physiological stresses including bone, adipose, heart, immune cells, kidney, and liver, implicating them as important therapeutic targets in a variety of metabolic disorders (Tremblay & Giguère 2007, Giguère 2008, Deblois & Giguère 2011). In addition, ERRs

have the potential to modulate cancer cell energy production and, recently, Err γ has been identified as a miRNA target in breast cancer cells, leading to a shift from oxidative to glycolytic metabolism (Eichner *et al.* 2010, Deblois & Giguère 2013). Err β has emerged as a component of cell pluripotency, being a key target of both NANOG and GSK/TCF3 pathways that modulates the expression of genes important in self-renewal (Ivanova *et al.* 2006, Chen *et al.* 2008, Festuccia *et al.* 2012, Martello *et al.* 2012). Err β also functions during development of the placenta, retina, and endolymph of the inner ear and, mutations have been linked to hearing loss in humans (Chen & Nathans 2007, Collin *et al.* 2008, Onishi *et al.* 2010, Ben Saïd *et al.* 2011, Lee *et al.* 2011b).

First to the party: orphans of the NR4A group

Nr4a1/Nur77, Nr4a2/Nurr1, and Nr4a3/Nor1

The Nr4a group consists of three related genes with many names reflecting discovery by many different groups: Nur77 (*Ngfi-b*, *Tr3*, *N10*, *Nak-1*, *St-59*), Nurr1 (*Rnr-1*, *Not*, *Tinur*) and Nor1 (*Tec*, *Minor*, *Chn*) (Hazel *et al.* 1988, Milbrandt 1988, Chang *et al.* 1989, Ryseck *et al.* 1989, Nakai *et al.* 1990, Law *et al.* 1992, Searce *et al.* 1993, Mages *et al.* 1994, Ohkura *et al.* 1994, Hedvat & Irving 1995, Labelle *et al.* 1995, Clark *et al.* 1996, Chen & Nathans 2007, Collin *et al.* 2008, Onishi *et al.* 2010, Ben Saïd *et al.* 2011, Lee *et al.* 2011b). Depending on cellular and signal context, these receptors can function uniquely or redundantly as developmental modulators or immediate early genes whose expression is rapidly induced by a variety of stimuli to control cellular proliferation, function, or death (Li *et al.* 2006, Maxwell & Muscat 2006). Key roles for the NR4A receptors have been demonstrated in many cell types including neuronal, immune, hematopoietic, cancer, endocrine, and metabolic (Li *et al.* 2006, Maxwell & Muscat 2006, Pei *et al.* 2006, Pearen & Muscat 2010, Zhao & Bruemmer 2010, Luo 2012, Mohan *et al.* 2012, van Tiel & de Vries 2012).

Nr4a orphans harbor a unique LBD filled with bulky hydrophobic residues that is unlikely to accommodate a typical ligand (Baker *et al.* 2003, Wang *et al.* 2003). Furthermore, nonclassical coactivator interfaces have been described for these receptors (Wansa *et al.* 2002, Codina *et al.* 2004). Therefore, regulation of the NR4A receptor activity depends on gene expression, alternative splicing, posttranslational modification, interaction with other NRs, microRNA targeting, and cellular localization (Maruyama *et al.* 1998, Maxwell & Muscat 2006, Malewicz

et al. 2011, McMorro & Murphy 2011, Yang *et al.* 2012, Li *et al.* 2013). It should be noted that despite the unique structure of the LBD, pharmacological agonists have been described including 1,1-bis(3-indolyl)-1-(p-anisyl)-methane, anti-neoplastic and anti-inflammatory agent 6-mercaptopurine, and cytosporone B (Wansa *et al.* 2003, Chintharlapalli *et al.* 2005, Zhan *et al.* 2008).

NURR1, NUR77, and NOR1 can bind as monomers to half-site recognition motifs called the NBRE (AAAGGTCA), but they can also homodimerize or heterodimerize with each other and with RXR and bind NurRE, a DR element (Maruyama *et al.* 1998, Maxwell & Muscat 2006). The importance of the transactivation function of the NR4A receptors has been demonstrated *in vivo*. For example, *Nor1* is a gene component within chromosomal translocations that occur frequently in human extraskeletal myxoid sarcoma (Labelle *et al.* 1995, Clark *et al.* 1996). The oncogenic fusion protein product of this translocation is frequently a strong activation domain of another TF such as EWS linked to a full length NOR1 leading to misregulation of NOR1 gene targets (Filion & Labelle 2012). Critical gene regulation by NR4A receptors is also exemplified by the direct regulation of tyrosine hydroxylase in neurons by NURR1 to maintain the dopaminergic phenotype which is hampered in Parkinson's disease and by obligatory direct regulation of *Foxp3* by all three NR4A members acting redundantly during the development of regulatory T cells thereby preventing autoimmunity (Sakurada *et al.* 1999, Luo 2012, Sekiya *et al.* 2013). Like other NRs, transrepression by the NR4A group has been reported. Specifically, NURR1 in concert with the CoREST complex is able to dock on the p65 subunit of NFκB and drive its clearance from inflammatory target genes in astrocytes and microglia, providing an additional mechanism for the protective function of NURR1 in Parkinson's disease (Saijo *et al.* 2009). Finally, NUR77 and NOR1 play essential roles in apoptosis in many cells and there is mounting evidence that this is accomplished in a non-genomic manner by converting BCL-2 proteins into pro-apoptotic molecules at the mitochondria (Li *et al.* 2006, Mohan *et al.* 2012). Underscoring the potential impact of this finding, small peptide mimics of NUR77 have been designed successfully to induce cancer cell death (Kolluri *et al.* 2008).

On steroids: orphans of the NR5A group

Nr5a1/Sf1 and Nr5a2/Lrh1

Steroidogenic factor 1 (SF1) was discovered by Lala *et al.* (1992) as a major regulator of steroidogenic enzyme gene

expression. Liver receptor homolog 1 (LRH-1) was cloned by several groups as a regulator of hepatitis virus and albumin gene expression (Tsukiyama *et al.* 1992, Becker-André *et al.* 1993, Galarneau *et al.* 1996, Li *et al.* 1998, Nitta *et al.* 1999). SF1 and LRH1 have large, hydrophobic LBDs (Schimmer & White 2010). Initial studies reported stable active state conformations of both receptor LBDs without addition of an exogenous ligand (Desclozeaux *et al.* 2002, Sablin *et al.* 2003). However, in 2005, three groups discovered phospholipid species in the LBDs of SF1 and LRH1 purified from bacteria (Krylova *et al.* 2005, Li *et al.* 2005, Ortlund *et al.* 2005). Intriguingly, an unusual phosphatidylcholine species was identified as an LRH1 ligand that, when administered to WT, but not *Lrh1*^{-/-} mice, improved their glucose homeostasis and ameliorated hepatic steatosis during high fat diet feeding (Lee *et al.* 2011a).

SF1 and LRH1 are transcriptional activators that bind DNA as monomers recognizing consensus of AGGTCA sequences. An apparent preference for YCA (where Y is a pyrimidine) 5' to the hexamer may be due to a C-terminal extension (CTE) of the DBD shared with other monomeric DNA-binding NRs (Wilson *et al.* 1993, Solomon *et al.* 2005). SF1 and LRH1 also contain an additional 20 amino acid extension after the CTE called the Ftz-f1 motif (after *Drosophila* Ftz-f1) that is unique to NR5A family members (Ingraham & Redinbo 2005). Crystal structures revealed that this motif does not contact DNA but rather affects interactions with co-activating proteins (Solomon *et al.* 2005). Recent genome-wide profiling of SF1 binding in adrenocortical cells found the NR half site as its preferential motif, but did not find enrichment of the predicted 5' pyrimidine, suggesting that it may not be required for SF1 binding to DNA in chromatin (Doghman *et al.* 2013).

SF1 is required for the differentiation of steroidogenic tissues, with homozygous null mice dying shortly after birth due to corticosteroid insufficiency (Luo *et al.* 1994, Sadosky *et al.* 1995). SF1 function is also required for cell autonomously in pituitary gonadotropes, developing gonads and postnatal ovarian granulosa cells (Schimmer & White 2010). These mouse models of sexual maturation defects are important to human disease, as shown by the reproductive dysfunction in patients with naturally occurring SF1 mutations (El-Khairi & Achermann 2012, Lalli *et al.* 2013). LRH1 is involved in the regulation of steroid, BA and cholesterol homeostasis, processes that are consistent with its restricted expression in the pancreas, liver, intestines, and ovaries (Fernandez-Marcos *et al.* 2011). Hepatocyte-specific deletion of LRH1 changes the composition of the BA pool, resulting in decreased

intestinal lipid absorption and BA recycling (Mataki *et al.* 2007, Lee *et al.* 2008). LRH1 has also been implicated in regulating glucose metabolism in the liver and proliferation in the intestine and pancreas (Schoonjans *et al.* 2005, Oosterveer *et al.* 2012). Intriguingly, GWAS studies have found a link between LRH1 SNPs and pancreatic cancer susceptibility (Petersen *et al.* 2010).

The family jewel: orphans of the NR6A group

Nr6a1/Gcnf

Germ cell nuclear factor (*Gcnf*, *Rtr*, *Ncnf*) is unique enough within the NR superfamily to be the only member of the NR6 subfamily (Hummelke & Cooney 2001, Germain *et al.* 2006). Originally named because of its robust and restricted expression in the germ cells, GCNF lacks a classic AF2 domain and acts as a transcriptional repressor through ligand-independent interactions with corepressor complexes (Chen *et al.* 1994a, Hirose *et al.* 1995, Bauer *et al.* 1997, Hummelke & Cooney 2001, Mullen *et al.* 2007). To date, a ligand for GCNF has not been identified, and its activity appears to be controlled by regulation of its gene expression (Heinzer *et al.* 1998, Gurtan *et al.* 2013, Krill *et al.* 2013, Wang *et al.* 2013). While recombinant GCNF forms homodimers upon binding to a DR of the classic NR half-site (AGGTCA) with no additional central nucleotides (DR0), endogenous DR0-bound GCNF exists as an oligomer in a DNA-dependent manner unlike that of typical NR dimerization (Gu *et al.* 2005b).

One of the direct targets of GCNF is *Oct4*, a core TF in the maintenance of embryonic stem cell pluripotency (Fuhrmann *et al.* 2001). Indeed, loss of function studies in mice has demonstrated that the GCNF-mediated repression of *Oct4* is essential for stem cell differentiation during embryogenesis (Chung *et al.* 2001, Gu *et al.* 2005a). The regulation of *Oct4* and other pluripotency factors makes GCNF an attractive target for therapeutic manipulation and biomarking in stem cells (Mullen *et al.* 2007, Akamatsu *et al.* 2009, Wang *et al.* 2013).

Summary and future perspectives

Advances in chemistry and molecular biology have led to an enormous accumulation of knowledge about the number, regulation, and function of orphan NRs over the past 25 years since their initial discovery. This review has attempted to provide a high-level overview of this progress, focusing on how each orphan was discovered, its regulation by ligand, and its regulation of gene

expression in different tissues in health and disease. Much more is known about each orphan NR, and readers are encouraged to seek out additional information from the printed and virtual scientific literature.

Although the family is much grown up, current rapid progress in high throughput nucleotide sequencing, proteomics, metabolomics, and computational biology promises to lead to a more complete and integrated understanding of the orphan NRs and how they are regulated in different tissues, and what they regulate at many developmental stages, and in disease states. This approach is presently somewhat limited by the lack of adequate antibodies and data analysis pipelines, and by the added complexity of many orphan NRs playing critical roles in cell types that are minority components of heterogeneous tissues. Technical advances in these areas will be critical for the discovery of novel therapeutic targets as well as strategies that avoid off target effects while maintaining beneficial actions.

Possibly the largest question still unanswered concerns the identification of the most relevant endogenous ligands for most, if not all, of the orphan NRs. Beginning shortly after the initial discovery of orphan NRs, the issue of whether they would all have endogenous ligands was hotly debated ('Do Orphan Receptors Have Ligands?', see www.sarah-greene.net/previous/hmsbeagle/html/content/03/cutedge/overview.htm) and this question still remains. While endogenous and synthetic ligands have been discovered for many of the orphan NRs, others seem likely to be bona fide ligand-independent TFs, yet this is almost impossible to prove (Schupp & Lazar 2010). Further, in most cases, there is not a consensus about the physiological role of putative endogenous ligands. This is in clear contrast with NR superfamily members that are receptors for hormones, where the hormones were discovered before the ligands and, in most cases, are produced by discrete endocrine organs such as the thyroid and adrenals, whose function is largely based on secretion of their cognate hormones.

Nevertheless, the identification of biological functions and ligands that activate the orphan NRs has yielded remarkable insight into dozens of diverse physiological processes, from embryonic stem cell self renewal and differentiation to inflammation, circadian rhythm, and metabolism. This has led to a more complete understanding of the mechanism of action for certain drug classes, the identification of targets mediating adverse effects of environmental pollutants, better strategies for the reprogramming of pluripotent cells, and development of novel small molecules for the treatment of human disease. Further dissection of orphan NR networks, including their

mechanisms of action and the genes and cellular processes that they regulate, continues to have great potential to elucidate the molecular pathology of diseases as well as the underlying physiology, leading to safer, more specific, and more effective therapeutic strategies that are likely to be evident at the next orphan NR reunion.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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References

- Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M & Evans RM 2013 PPAR γ signaling and metabolism: the good, the bad and the future. *Nature Medicine* **19** 557–566. (doi:10.1038/nm.3159)
- Akamatsu W, DeVeale B, Okano H, Cooney AJ & van der Kooy D 2009 Suppression of Oct4 by germ cell nuclear factor restricts pluripotency and promotes neural stem cell development in the early neural lineage. *Journal of Neuroscience* **29** 2113–2124. (doi:10.1523/JNEUROSCI.4527-08.2009)
- Alfano C, Magrinelli E, Harb K & Studer M 2013 The nuclear receptors COUP-TF: a long-lasting experience in forebrain assembly. *Cellular and Molecular Life Sciences* [in press]. (doi:10.1007/s00018-013-1320-6)
- Aranda A & Pascual A 2001 Nuclear hormone receptors and gene expression. *Physiological Reviews* **81** 1269–1304.
- Ariazi EA, Kraus RJ, Farrell ML, Jordan VC & Mertz JE 2007 Estrogen-related receptor α 1 transcriptional activities are regulated in part via the ErbB2/HER2 signaling pathway. *Molecular Cancer Research* **5** 71–85. (doi:10.1158/1541-7786.MCR-06-0227)
- Baes M, Gulick T, Choi HS, Martinoli MG, Simha D & Moore DD 1994 A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Molecular and Cellular Biology* **14** 1544–1552.
- Baker KD, Shewchuk LM, Kozlova T, Makishima M, Hassell A, Wisely B, Caravella JA, Lambert MH, Reinking JL, Krause H *et al.* 2003 The *Drosophila* orphan nuclear receptor DHR38 mediates an atypical ecdysteroid signaling pathway. *Cell* **113** 731–742. (doi:10.1016/S0092-8674(03)00420-3)
- Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R & Evans RM 2002 Effects of peroxisome proliferator-activated receptor δ on placental, adiposity, and colorectal cancer. *PNAS* **99** 303–308. (doi:10.1073/pnas.012610299)
- Bauer UM, Schneider-Hirsch S, Reinhardt S, Pauly T, Maus A, Wang F, Heiermann R, Rentrop M & Maelicke A 1997 Neuronal cell nuclear factor – a nuclear receptor possibly involved in the control of neurogenesis and neuronal differentiation. *European Journal of Biochemistry/FEBS* **249** 826–837. (doi:10.1111/j.1432-1033.1997.t011-00826.x)
- Båvner A, Sanyal S, Gustafsson J-Å & Treuter E 2005 Transcriptional corepression by SHP: molecular mechanisms and physiological consequences. *Trends in Endocrinology and Metabolism* **16** 478–488. (doi:10.1016/j.tem.2005.10.005)
- Becker-André M, André E & DeLamarier JF 1993 Identification of nuclear receptor mRNAs by RT-PCR amplification of conserved zinc-finger motif sequences. *Biochemical and Biophysical Research Communications* **194** 1371–1379. (doi:10.1006/bbrc.1993.1976)
- Benoit G, Malewicz M & Perlmann T 2004 Digging deep into the pockets of orphan nuclear receptors: insights from structural studies. *Trends in Cell Biology* **14** 369–376. (doi:10.1016/j.tcb.2004.05.007)
- Benoit G, Cooney A, Giguere V, Ingraham H, Lazar M, Muscat G, Perlmann T, Renaud J-P, Schwabe J, Sladek F *et al.* 2006 International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacological Reviews* **58** 798–836. (doi:10.1124/pr.58.4.10)
- Ben Saïd M, Ayedi L, Mnejja M, Hakim B, Khalfallah A, Charfeddine I, Khifagi C, Turki K, Ayadi H, Benzina Z *et al.* 2011 A novel missense mutation in the ESRRB gene causes DFNB35 hearing loss in a Tunisian family. *European Journal of Medical Genetics* **54** e535–e541. (doi:10.1016/j.ejmg.2011.06.008)
- Bensinger SJ & Tontonoz P 2008 Integration of metabolism and inflammation by lipid-activated nuclear receptors. *Nature* **454** 470–477. (doi:10.1038/nature07202)
- Bertilsson G, Heidrich J, Svensson K, Asman M, Jendeborg L, Sydow-Bäckman M, Ohlsson R, Postlind H, Blomquist P & Berkenstam A 1998 Identification of a human nuclear receptor defines a new signaling pathway for CYP3A induction. *PNAS* **95** 12208–12213. (doi:10.1073/pnas.95.21.12208)
- Blumberg B, Sabbagh W Jr, Juguilon H, Bolado J Jr, van Meter CM, Ong ES & Evans RM 1998 SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes and Development* **12** 3195–3205. (doi:10.1101/gad.12.20.3195)
- Boergesen M, Pedersen TÅ, Gross B, van Heeringen SJ, Hagenbeek D, Bindsøll C, Caron S, Lalloyer F, Steffensen KR, Nebb HI *et al.* 2012 Genome-wide profiling of liver X receptor, retinoid X receptor, and peroxisome proliferator-activated receptor α in mouse liver reveals extensive sharing of binding sites. *Molecular and Cellular Biology* **32** 852–867. (doi:10.1128/MCB.06175-11)
- Bonnelye E & Aubin JE 2013 An energetic orphan in an endocrine tissue: a revised perspective of the function of estrogen receptor-related receptor α in bone and cartilage. *Journal of Bone and Mineral Research* **28** 225–233. (doi:10.1002/jbmr.1836)
- Bradley MN, Hong C, Chen M, Joseph SB, Wilpitz DC, Wang X, Lusis AJ, Collins A, Hseuh WA, Collins JL *et al.* 2007 Ligand activation of LXR β reverses atherosclerosis and cellular cholesterol overload in mice lacking LXR α and apoE. *Journal of Clinical Investigation* **117** 2337–2346. (doi:10.1172/JCI31909)
- Brown NS, Smart A, Sharma V, Brinkmeier ML, Greenlee L, Camper SA, Jensen DR, Eckel RH, Krezel W, Chambon P *et al.* 2000 Thyroid hormone resistance and increased metabolic rate in the RXR- γ -deficient mouse. *Journal of Clinical Investigation* **106** 73–79. (doi:10.1172/JCI9422)
- Bugge A, Feng D, Everett LJ, Briggs ER, Mullican SE, Wang F, Jager J & Lazar MA 2012 Rev-erb α and Rev-erb β coordinately protect the circadian clock and normal metabolic function. *Genes and Development* **26** 657–667. (doi:10.1101/gad.186858.112)
- Burkart EM, Sambandam N, Han X, Gross RW, Courtois M, Gierasch CM, Shoghi K, Welch MJ & Kelly DP 2007 Nuclear receptors PPAR β / δ and PPAR α direct distinct metabolic regulatory programs in the mouse heart. *Journal of Clinical Investigation* **117** 3930–3939. (doi:10.1172/JCI32578)
- Burris TP 2008 Nuclear hormone receptors for heme: REV-ERB α and REV-ERB β are ligand-regulated components of the mammalian clock. *Molecular Endocrinology* **22** 1509–1520. (doi:10.1210/me.2007-0519)
- Calkin AC & Tontonoz P 2012 Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. *Nature Reviews. Molecular Cell Biology* **13** 213–224. (doi:10.1038/nrm3312)

- Campbell AD, Cui S, Shi L, Urbonya R, Mathias A, Bradley K, Bonsu KO, Douglas RR, Halford B, Schmidt L *et al.* 2011 Forced TR2/TR4 expression in sickle cell disease mice confers enhanced fetal hemoglobin synthesis and alleviated disease phenotypes. *PNAS* **108** 18808–18813. (doi:10.1073/pnas.1104964108)
- Cattin A-L, Le Beyec J, Barreau F, Saint-Just S, Houllier A, Gonzalez FJ, Robine S, Pinçon-Raymond M, Cardot P, Lacasa M *et al.* 2009 Hepatocyte nuclear factor 4 α , a key factor for homeostasis, cell architecture, and barrier function of the adult intestinal epithelium. *Molecular and Cellular Biology* **29** 6294–6308. (doi:10.1128/MCB.00939-09)
- Chanda D, Park J-H & Choi H-S 2008 Molecular basis of endocrine regulation by orphan nuclear receptor small heterodimer partner. *Endocrine Journal* **55** 253–268. (doi:10.1507/endocrj.K07E-103)
- Chandra V, Mahajan S, Saini A, Dkhar HK, Nanduri R, Raj EB, Kumar A & Gupta P 2013 Human IL10 gene repression by Rev-erb α ameliorates *Mycobacterium tuberculosis* clearance. *Journal of Biological Chemistry* **288** 10692–10702. (doi:10.1074/jbc.M113.455915)
- Chang C, Kokontis J, Liao SS & Chang Y 1989 Isolation and characterization of human TR3 receptor: a member of steroid receptor superfamily. *Journal of Steroid Biochemistry* **34** 391–395. (doi:10.1016/0022-4731(89)90114-3)
- Chang C, Da Silva SL, Ideta R, Lee Y, Yeh S & Burbach JP 1994 Human and rat TR4 orphan receptors specify a subclass of the steroid receptor superfamily. *PNAS* **91** 6040–6044. (doi:10.1073/pnas.91.13.6040)
- Chartier FL, Bossu JP, Laudet V, Fruchart JC & Laine B 1994 Cloning and sequencing of cDNAs encoding the human hepatocyte nuclear factor 4 indicate the presence of two isoforms in human liver. *Gene* **147** 269–272. (doi:10.1016/0378-1119(94)90079-5)
- Chaturvedi P, Pratta M, Steplewski K, Connor J & Kumar S 2006 Functional characterization of an orphan nuclear receptor, Rev-ErbA α , in chondrocytes and its potential role in osteoarthritis. *Arthritis and Rheumatism* **54** 3513–3522. (doi:10.1002/art.22170)
- Chawla A & Lazar MA 1994 Peroxisome proliferator and retinoid signaling pathways co-regulate preadipocyte phenotype and survival. *PNAS* **91** 1786–1790. (doi:10.1073/pnas.91.5.1786)
- Chen J & Nathans J 2007 Estrogen-related receptor β /NR3B2 controls epithelial cell fate and endolymph production by the stria vascularis. *Developmental Cell* **13** 325–337. (doi:10.1016/j.devcel.2007.07.011)
- Chen F, Cooney AJ, Wang Y, Law SW & O'Malley BW 1994a Cloning of a novel orphan receptor (GCNF) expressed during germ cell development. *Molecular Endocrinology* **8** 1434–1444. (doi:10.1210/me.8.10.1434)
- Chen WS, Manova K, Weinstein DC, Duncan SA, Plump AS, Prezioso VR, Bachvarova RF & Darnell JE 1994b Disruption of the HNF-4 gene, expressed in visceral endoderm, leads to cell death in embryonic ectoderm and impaired gastrulation of mouse embryos. *Genes and Development* **8** 2466–2477. (doi:10.1101/gad.8.20.2466)
- Chen F, Figueroa DJ, Marmorstein AD, Zhang Q, Petrukhin K, Caskey CT & Austin CP 1999 Retina-specific nuclear receptor: a potential regulator of cellular retinaldehyde-binding protein expressed in retinal pigment epithelium and Müller glial cells. *PNAS* **96** 15149–15154. (doi:10.1073/pnas.96.26.15149)
- Chen J, Rattner A & Nathans J 2005a The rod photoreceptor-specific nuclear receptor Nr2e3 represses transcription of multiple cone-specific genes. *Journal of Neuroscience* **25** 118–129. (doi:10.1523/JNEUROSCI.3571-04.2005)
- Chen Y-T, Collins LL, Uno H & Chang C 2005b Deficits in motor coordination with aberrant cerebellar development in mice lacking testicular orphan nuclear receptor 4. *Molecular and Cellular Biology* **25** 2722–2732. (doi:10.1128/MCB.25.7.2722-2732.2005)
- Chen X, Xu H, Yuan P, Fang F, Huss M, Vega VB, Wong E, Orlov YL, Zhang W, Jiang J *et al.* 2008 Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. *Cell* **133** 1106–1117. (doi:10.1016/j.cell.2008.04.043)
- Cheng H, Khanna H, Oh ECT, Hicks D, Mitton KP & Swaroop A 2004 Photoreceptor-specific nuclear receptor NR2E3 functions as a transcriptional activator in rod photoreceptors. *Human Molecular Genetics* **13** 1563–1575. (doi:10.1093/hmg/ddh173)
- Chini CCS, Escande C, Nin V & Chini EN 2013 DBC1 (deleted in breast cancer 1) modulates the stability and function of the nuclear receptor Rev-erb α . *Biochemical Journal* **451** 453–461. (doi:10.1042/BJ20121085)
- Chintharlapalli S, Burghardt R, Papineni S, Ramaiah S, Yoon K & Safe S 2005 Activation of Nur77 by selected 1,1-bis(3'-indolyl)-1-(p-substituted phenyl)methanes induces apoptosis through nuclear pathways. *Journal of Biological Chemistry* **280** 24903–24914. (doi:10.1074/jbc.M500107200)
- Cho H, Zhao X, Hatori M, Yu RT, Barish GD, Lam MT, Chong L-W, DiTacchio L, Atkins AR, Glass CK *et al.* 2012 Regulation of circadian behaviour and metabolism by REV-ERB- α and REV-ERB- β . *Nature* **485** 123–127. (doi:10.1038/nature11048)
- Chomez P, Neveu I, Mansén A, Kiesler E, Larsson L, Vennström B & Arenas E 2000 Increased cell death and delayed development in the cerebellum of mice lacking the rev-erbA(α) orphan receptor. *Development* **127** 1489–1498.
- Chong HK, Infante AM, Seo Y-K, Jeon T-I, Zhang Y, Edwards PA, Xie X & Osborne TF 2010 Genome-wide interrogation of hepatic FXR reveals an asymmetric IR-1 motif and synergy with LXR-1. *Nucleic Acids Research* **38** 6007–6017. (doi:10.1093/nar/gkq397)
- Chung AC, Katz D, Pereira FA, Jackson KJ, DeMayo FJ, Cooney AJ & O'Malley BW 2001 Loss of orphan receptor germ cell nuclear factor function results in ectopic development of the tail bud and a novel posterior truncation. *Molecular and Cellular Biology* **21** 663–677. (doi:10.1128/MCB.21.2.663-677.2001)
- Clark J, Benjamin H, Gill S, Sidhar S, Goodwin G, Crew J, Gusterson BA, Shipley J & Cooper CS 1996 Fusion of the EWS gene to CHN, a member of the steroid/thyroid receptor gene superfamily, in a human myxoid chondrosarcoma. *Oncogene* **12** 229–235.
- Codina A, Benoit G, Gooch JT, Neuhaus D, Perlmann T & Schwabe JWR 2004 Identification of a novel co-regulator interaction surface on the ligand binding domain of Nurr1 using NMR footprinting. *Journal of Biological Chemistry* **279** 53338–53345. (doi:10.1074/jbc.M409096200)
- Collin RWJ, Kalay E, Tariq M, Peters T, van der Zwaag B, Venselaar H, Oostrik J, Lee K, Ahmed ZM, Caylan R *et al.* 2008 Mutations of ESRB encoding estrogen-related receptor β cause autosomal-recessive non-syndromic hearing impairment DFNB35. *American Journal of Human Genetics* **82** 125–138. (doi:10.1016/j.ajhg.2007.09.008)
- Coward P, Lee D, Hull MV & Lehmann JM 2001 4-Hydroxytamoxifen binds to and deactivates the estrogen-related receptor γ . *PNAS* **98** 8880–8884. (doi:10.1073/pnas.151244398)
- Cui JY, Gunewardena SS, Rockwell CE & Klaassen CD 2010 ChIPing the cistrome of PXR in mouse liver. *Nucleic Acids Research* **38** 7943–7963. (doi:10.1093/nar/gkq654)
- Daigo K, Kawamura T, Ohta Y, Ohashi R, Katayose S, Tanaka T, Aburatani H, Naito M, Kodama T, Ihara S *et al.* 2011 Proteomic analysis of native hepatocyte nuclear factor-4 α (HNF4 α) isoforms, phosphorylation status, and interactive cofactors. *Journal of Biological Chemistry* **286** 674–686. (doi:10.1074/jbc.M110.154732)
- Deblois G & Giguère V 2011 Functional and physiological genomics of estrogen-related receptors (ERRs) in health and disease. *Biochimica et Biophysica Acta* **1812** 1032–1040. (doi:10.1016/j.bbdis.2010.12.009)
- Deblois G & Giguère V 2013 Oestrogen-related receptors in breast cancer: control of cellular metabolism and beyond. *Nature Reviews. Cancer* **13** 27–36. (doi:10.1038/nrc3396)
- Desclozeaux M, Krylova IN, Horn F, Fletterick RJ & Ingraham HA 2002 Phosphorylation and intramolecular stabilization of the ligand binding domain in the nuclear receptor steroidogenic factor 1. *Molecular and Cellular Biology* **22** 7193–7203. (doi:10.1128/MCB.22.20.7193-7203.2002)
- Dhe-Paganon S, Duda K, Iwamoto M, Chi Y-I & Shoelson SE 2002 Crystal structure of the HNF4 α ligand binding domain in complex with

- endogenous fatty acid ligand. *Journal of Biological Chemistry* **277** 37973–37976. (doi:10.1074/jbc.C200420200)
- Doghman M, Figueiredo BC, Volante M, Papotti M & Lalli E 2013 Integrative analysis of SF-1 transcription factor dosage impact on genome-wide binding and gene expression regulation. *Nucleic Acids Research* **41** 8896–8907. (doi:10.1093/nar/gkt658)
- Drewes T, Senkel S, Holewa B & Ryffel GU 1996 Human hepatocyte nuclear factor 4 isoforms are encoded by distinct and differentially expressed genes. *Molecular and Cellular Biology* **16** 925–931.
- Dreyer C, Krey G, Keller H, Givel F, Helftenbein G & Wahli W 1992 Control of the peroxisomal β -oxidation pathway by a novel family of nuclear hormone receptors. *Cell* **68** 879–887. (doi:10.1016/0092-8674(92)90031-7)
- Duan SZ, Ivashchenko CY, Whitesall SE, D'Alecy LG, Duquaine DC, Brosius FC III, Gonzalez FJ, Vinson C, Pierre MA, Milstone DS *et al.* 2007 Hypotension, lipodystrophy, and insulin resistance in generalized PPAR γ -deficient mice rescued from embryonic lethality. *Journal of Clinical Investigation* **117** 812–822. (doi:10.1172/JCI28859)
- Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M, Evans RM, Blanchette M & Giguère V 2007 Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERR α and γ . *Cell Metabolism* **5** 345–356. (doi:10.1016/j.cmet.2007.03.007)
- Dumas B, Harding HP, Choi HS, Lehmann KA, Chung M, Lazar MA & Moore DD 1994 A new orphan member of the nuclear hormone receptor superfamily closely related to Rev-Erb. *Molecular Endocrinology* **8** 996–1005. (doi:10.1210/me.8.8.996)
- Duncan SA 2003 Mechanisms controlling early development of the liver. *Mechanisms of Development* **120** 19–33. (doi:10.1016/S0925-4773(02)00328-3)
- Eeckhoutte J, Moerman E, Bouckenooghe T, Lukoviak B, Pattou F, Formstecher P, Kerr-Conte J, Vandewalle B & Laine B 2003 Hepatocyte nuclear factor 4 α isoforms originated from the P1 promoter are expressed in human pancreatic β -cells and exhibit stronger transcriptional potentials than P2 promoter-driven isoforms. *Endocrinology* **144** 1686–1694. (doi:10.1210/en.2002-0024)
- Ehrlund A & Treuter E 2012 Ligand-independent actions of the orphan receptors/corepressors DAX-1 and SHP in metabolism, reproduction and disease. *Journal of Steroid Biochemistry and Molecular Biology* **130** 169–179. (doi:10.1016/j.jsbmb.2011.04.007)
- Eichner LJ, Perry M-C, Dufour CR, Bertos N, Park M, St-Pierre J & Giguère V 2010 miR-378(*) mediates metabolic shift in breast cancer cells via the PGC-1 β /ERR γ transcriptional pathway. *Cell Metabolism* **12** 352–361. (doi:10.1016/j.cmet.2010.09.002)
- El-Khairi R & Achermann JC 2012 Steroidogenic factor-1 and human disease. *Seminars in Reproductive Medicine* **30** 374–381. (doi:10.1055/s-0032-1324720)
- Eudy JD, Yao S, Weston MD, Ma-Edmonds M, Talmadge CB, Cheng JJ, Kimberling WJ & Sumegi J 1998 Isolation of a gene encoding a novel member of the nuclear receptor superfamily from the critical region of Usher syndrome type IIa at 1q41. *Genomics* **50** 382–384. (doi:10.1006/geno.1998.5345)
- Evans RM, Barish GD & Wang Y-X 2004 PPARs and the complex journey to obesity. *Nature Medicine* **10** 355–361. (doi:10.1038/nm1025)
- Fahrbach SE, Smagghe G & Velarde RA 2012 Insect nuclear receptors. *Annual Review of Entomology* **57** 83–106. (doi:10.1146/annurev-ento-120710-100607)
- Fang B, Mane-Padros D, Bolotin E, Jiang T & Sladek FM 2012 Identification of a binding motif specific to HNF4 by comparative analysis of multiple nuclear receptors. *Nucleic Acids Research* **40** 5343–5356. (doi:10.1093/nar/gks190)
- Feng D & Lazar MA 2012 Clocks, metabolism, and the epigenome. *Molecular Cell* **47** 158–167. (doi:10.1016/j.molcel.2012.06.026)
- Fernandez-Marcos PJ, Auwerx J & Schoonjans K 2011 Emerging actions of the nuclear receptor LRH-1 in the gut. *Biochimica et Biophysica Acta* **1812** 947–955. (doi:10.1016/j.bbadis.2010.12.010)
- Festuccia N, Osorno R, Halbritter F, Karwacki-Neisius V, Navarro P, Colby D, Wong F, Yates A, Tomlinson SR & Chambers I 2012 Esrrb is a direct Nanog target gene that can substitute for Nanog function in pluripotent cells. *Cell Stem Cell* **11** 477–490. (doi:10.1016/j.stem.2012.08.002)
- Filion C & Labelle Y 2012 Identification of genes regulated by the EWS/NR4A3 fusion protein in extraskeletal myxoid chondrosarcoma. *Tumour Biology* **33** 1599–1605. (doi:10.1007/s13277-012-0415-2)
- Fontaine C, Rigamonti E, Pourcet B, Duez H, Duhem C, Fruchart J-C, Chinetti-Gbaguidi G & Staels B 2008 The nuclear receptor Rev-erb α is a liver X receptor (LXR) target gene driving a negative feedback loop on select LXR-induced pathways in human macrophages. *Molecular Endocrinology* **22** 1797–1811. (doi:10.1210/me.2007-0439)
- Forman BM, Chen J, Blumberg B, Kliewer SA, Henshaw R, Ong ES & Evans RM 1994 Cross-talk among ROR α 1 and the Rev-erb family of orphan nuclear receptors. *Molecular Endocrinology* **8** 1253–1261. (doi:10.1210/me.8.9.1253)
- Forman BM, Umesono K, Chen J & Evans RM 1995 Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81** 541–550. (doi:10.1016/0092-8674(95)90075-6)
- Forman BM, Tzamelis I, Choi HS, Chen J, Simha D, Seol W, Evans RM & Moore DD 1998 Androstane metabolites bind to and deactivate the nuclear receptor CAR- β . *Nature* **395** 612–615. (doi:10.1038/26996)
- Forrest D & Swaroop A 2012 Minireview: the role of nuclear receptors in photoreceptor differentiation and disease. *Molecular Endocrinology* **26** 905–915. (doi:10.1210/me.2012-1010)
- Freedman BD, Lee E-J, Park Y & Jameson JL 2005 A dominant negative peroxisome proliferator-activated receptor- γ knock-in mouse exhibits features of the metabolic syndrome. *Journal of Biological Chemistry* **280** 17118–17125. (doi:10.1074/jbc.M407539200)
- Frochot V, Alqub M, Cattin A-L, Carrière V, Houllier A, Baraille F, Barbot L, Saint-Just S, Ribeiro A, Lacasa M *et al.* 2012 The transcription factor HNF-4 α : a key factor of the intestinal uptake of fatty acids in mouse. *American Journal of Physiology. Gastrointestinal and Liver Physiology* **302** G1253–G1263. (doi:10.1152/ajpgi.00329.2011)
- Fuhrmann G, Chung AC, Jackson KJ, Hummelke G, Baniahmad A, Sutter J, Sylvester I, Schöler HR & Cooney AJ 2001 Mouse germline restriction of Oct4 expression by germ cell nuclear factor. *Developmental Cell* **1** 377–387. (doi:10.1016/S1534-5807(01)00038-7)
- Gabbi C, Warner M & Gustafsson J-A 2009 Minireview: liver X receptor β : emerging roles in physiology and diseases. *Molecular Endocrinology* **23** 129–136. (doi:10.1210/me.2008-0398)
- Galarneau L, Paré JF, Allard D, Hamel D, Levesque L, Tugwood JD, Green S & Bélanger L 1996 The α 1-fetoprotein locus is activated by a nuclear receptor of the *Drosophila* FTZ-F1 family. *Molecular and Cellular Biology* **16** 3853–3865.
- Gao J, He J, Zhai Y, Wada T & Xie W 2009 The constitutive androstane receptor is an anti-obesity nuclear receptor that improves insulin sensitivity. *Journal of Biological Chemistry* **284** 25984–25992. (doi:10.1074/jbc.M109.016808)
- Gao J & Xie W 2010 Pregnane X receptor and constitutive androstane receptor at the crossroads of drug metabolism and energy metabolism. *Drug Metabolism and Disposition* **38** 2091–2095. (doi:10.1124/dmd.110.035568)
- Gerdin AK, Surve VV, Jönsson M, Bjursell M, Björkman M, Edenro A, Schuelke M, Saad A, Björström S, Lundgren EJ *et al.* 2006 Phenotypic screening of hepatocyte nuclear factor (HNF) 4- γ receptor knockout mice. *Biochemical and Biophysical Research Communications* **349** 825–832. (doi:10.1016/j.bbrc.2006.08.103)
- Germain P, Staels B, Dacquet C, Spedding M & Laudet V 2006 Overview of nomenclature of nuclear receptors. *Pharmacological Reviews* **58** 685–704. (doi:10.1124/pr.58.4.2)
- Gibbs JE, Blaikley J, Beesley S, Matthews L, Simpson KD, Boyce SH, Farrow SN, Else KJ, Singh D, Ray DW *et al.* 2012 The nuclear receptor REV-ERB α mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *PNAS* **109** 582–587. (doi:10.1073/pnas.1106750109)

- Giguère V 1999 Orphan nuclear receptors: from gene to function. *Endocrine Reviews* **20** 689–725. (doi:10.1210/er.20.5.689)
- Giguère V 2008 Transcriptional control of energy homeostasis by the estrogen-related receptors. *Endocrine Reviews* **29** 677–696. (doi:10.1210/er.2008-0017)
- Giguère V, Yang N, Segui P & Evans RM 1988 Identification of a new class of steroid hormone receptors. *Nature* **331** 91–94. (doi:10.1038/331091a0)
- Gruber PJ, Kubalak SW, Pexieder T, Sucov HM, Evans RM & Chien KR 1996 RXR α deficiency confers genetic susceptibility for aortic sac, conotruncal, atrioventricular cushion, and ventricular muscle defects in mice. *Journal of Clinical Investigation* **98** 1332–1343. (doi:10.1172/JCI118920)
- Gu P, LeMenuet D, Chung AC-K, Mancini M, Wheeler DA & Cooney AJ 2005a Orphan nuclear receptor GCNF is required for the repression of pluripotency genes during retinoic acid-induced embryonic stem cell differentiation. *Molecular and Cellular Biology* **25** 8507–8519. (doi:10.1128/MCB.25.19.8507-8519.2005)
- Gu P, Morgan DH, Sattar M, Xu X, Wagner R, Raviscioni M, Lichtarge O & Cooney AJ 2005b Evolutionary trace-based peptides identify a novel asymmetric interaction that mediates oligomerization in nuclear receptors. *Journal of Biological Chemistry* **280** 31818–31829. (doi:10.1074/jbc.M501924200)
- Gui H, Li M-L & Tsai C-C 2011 A tale of tailless. *Developmental Neuroscience* **33** 1–13. (doi:10.1159/000321585)
- Guillaumond F, Dardente H, Giguère V & Cermakian N 2005 Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. *Journal of Biological Rhythms* **20** 391–403. (doi:10.1177/0748730405277232)
- Guo GL, Moffit JS, Nicol CJ, Ward JM, Aleksunes LA, Slitt AL, Klierer SA, Manautou JE & Gonzalez FJ 2004 Enhanced acetaminophen toxicity by activation of the pregnane X receptor. *Toxicological Sciences* **82** 374–380. (doi:10.1093/toxsci/kfh286)
- Gupta RK, Vatamaniuk MZ, Lee CS, Flaschen RC, Fulmer JT, Matschinsky FM, Duncan SA & Kaestner KH 2005 The MODY1 gene HNF-4 α regulates selected genes involved in insulin secretion. *Journal of Clinical Investigation* **115** 1006–1015. (doi:10.1172/JCI22365)
- Gupta RK, Gao N, Gorski RK, White P, Hardy OT, Rafiq K, Brestelli JE, Chen G, Stoeckert CJ Jr & Kaestner KH 2007 Expansion of adult β -cell mass in response to increased metabolic demand is dependent on HNF-4 α . *Genes and Development* **21** 756–769. (doi:10.1101/gad.1535507)
- Gupta P, Ho P-C, Huq MM, Ha SG, Park SW, Khan AA, Tsai N-P & Wei L-N 2008 Retinoic acid-stimulated sequential phosphorylation, PML recruitment, and SUMOylation of nuclear receptor TR2 to suppress Oct4 expression. *PNAS* **105** 11424–11429. (doi:10.1073/pnas.0710561105)
- Gupta P, Ho P-C, Ha SG, Lin Y-W & Wei L-N 2009 HDAC3 as a molecular chaperone for shuttling phosphorylated TR2 to PML: a novel deacetylase activity-independent function of HDAC3. *PLoS ONE* **4** e4363. (doi:10.1371/journal.pone.0004363)
- Gurtan AM, Ravi A, Rahl PB, Bosson AD, JnBaptiste CK, Bhutkar A, Whittaker CA, Young RA & Sharp PA 2013 Let-7 represses Nr6a1 and a mid-gestation developmental program in adult fibroblasts. *Genes and Development* **27** 941–954. (doi:10.1101/gad.215376.113)
- Hamilton BA, Frankel WN, Kerrebrock AW, Hawkins TL, FitzHugh W, Kusumi K, Russell LB, Mueller KL, van Berkel V, Birren BW *et al.* 1996 Disruption of the nuclear hormone receptor ROR α in staggerer mice. *Nature* **379** 736–739. (doi:10.1038/379736a0)
- Haugen BR, Jensen DR, Sharma V, Pulawa LK, Hays WR, Krezel W, Chambon P & Eckel RH 2004 Retinoid X receptor γ -deficient mice have increased skeletal muscle lipoprotein lipase activity and less weight gain when fed a high-fat diet. *Endocrinology* **145** 3679–3685. (doi:10.1210/en.2003-1401)
- Hayhurst GP, Lee Y-H, Lambert G, Ward JM & Gonzalez FJ 2001 Hepatocyte nuclear factor 4 α (nuclear receptor 2A1) is essential for maintenance of hepatic gene expression and lipid homeostasis. *Molecular and Cellular Biology* **21** 1393–1403. (doi:10.1128/MCB.21.4.1393-1403.2001)
- Hazel TG, Nathans D & Lau LF 1988 A gene inducible by serum growth factors encodes a member of the steroid and thyroid hormone receptor superfamily. *PNAS* **85** 8444–8448. (doi:10.1073/pnas.85.22.8444)
- Heard DJ, Norby PL, Holloway J & Vissing H 2000 Human ERR γ , a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development and in the adult. *Molecular Endocrinology* **14** 382–392. (doi:10.1210/me.14.3.382)
- Hedvat CV & Irving SG 1995 The isolation and characterization of MINOR, a novel mitogen-inducible nuclear orphan receptor. *Molecular Endocrinology* **9** 1692–1700. (doi:10.1210/me.9.12.1692)
- Heinzer C, Süsens U, Schmitz TP & Borgmeyer U 1998 Retinoids induce differential expression and DNA binding of the mouse germ cell nuclear factor in P19 embryonal carcinoma cells. *Biological Chemistry* **379** 349–359. (doi:10.1515/bchm.1998.379.3.349)
- Helsen C, Kerkhofs S, Clinckemalie L, Spans L, Laurent M, Boonen S, Vanderschueren D & Claessens F 2012 Structural basis for nuclear hormone receptor DNA binding. *Molecular and Cellular Endocrinology* **348** 411–417. (doi:10.1016/j.mce.2011.07.025)
- Hermann-Kleiter N, Gruber T, Lutz-Nicoladoni C, Thuille N, Fresser F, Labi V, Schiefermeier N, Warnecke M, Huber L, Villunger A *et al.* 2008 The nuclear orphan receptor NR2F6 suppresses lymphocyte activation and T helper 17-dependent autoimmunity. *Immunity* **29** 205–216. (doi:10.1016/j.immuni.2008.06.008)
- Hermann-Kleiter N, Meisel M, Fresser F, Thuille N, Müller M, Roth L, Katopodis A & Baier G 2012 Nuclear orphan receptor NR2F6 directly antagonizes NFAT and ROR γ t binding to the IL17a promoter. *Journal of Autoimmunity* **39** 428–440. (doi:10.1016/j.jaut.2012.07.007)
- Hirose T, Fujimoto W, Tamaai T, Kim KH, Matsuura H & Jetten AM 1994 TAK1: molecular cloning and characterization of a new member of the nuclear receptor superfamily. *Molecular Endocrinology* **8** 1667–1680. (doi:10.1210/me.8.12.1667)
- Hirose T, O'Brien DA & Jetten AM 1995 RTR: a new member of the nuclear receptor superfamily that is highly expressed in murine testis. *Gene* **152** 247–251. (doi:10.1016/0378-1119(94)00656-D)
- Hong H, Yang L & Stallcup MR 1999 Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptor ERR3. *Journal of Biological Chemistry* **274** 22618–22626. (doi:10.1074/jbc.274.32.22618)
- Hong C, Bradley MN, Rong X, Wang X, Wagner A, Grijalva V, Castellani LW, Salazar J, Realegeno S, Boyadjian R *et al.* 2012 LXR α is uniquely required for maximal reverse cholesterol transport and atheroprotection in ApoE-deficient mice. *Journal of Lipid Research* **53** 1126–1133. (doi:10.1194/jlr.M022061)
- Hossain A, Li C & Saunders GF 2004 Generation of two distinct functional isoforms of dosage-sensitive sex reversal-adrenal hypoplasia congenita-critical region on the X chromosome gene 1 (DAX-1) by alternative splicing. *Molecular Endocrinology* **18** 1428–1437. (doi:10.1210/me.2003-0176)
- Hu Y-C, Shyr C-R, Che W, Mu X-M, Kim E & Chang C 2002 Suppression of estrogen receptor-mediated transcription and cell growth by interaction with TR2 orphan receptor. *Journal of Biological Chemistry* **277** 33571–33579. (doi:10.1074/jbc.M203531200)
- Huang P, Chandra V & Rastinejad F 2010 Structural overview of the nuclear receptor superfamily: insights into physiology and therapeutics. *Annual Review of Physiology* **72** 247–272. (doi:10.1146/annurev-physiol-021909-135917)
- Huang JK, Jarjour AA, Nait Oumesmar B, Kerninon C, Williams A, Krezel W, Kagechika H, Bauer J, Zhao C, Baron-Van Evercooren A *et al.* 2011 Retinoid X receptor γ signaling accelerates CNS remyelination. *Nature Neuroscience* **14** 45–53. (doi:10.1038/nn.2702)
- Huh JR, Leung MWL, Huang P, Ryan DA, Krout MR, Malapaka RRV, Chow J, Manel N, Ciofani M, Kim SV *et al.* 2011 Digoxin and its derivatives

- suppress TH17 cell differentiation by antagonizing ROR γ t activity. *Nature* **472** 486–490. (doi:10.1038/nature09978)
- Hummelke GC & Cooney AJ 2001 Germ cell nuclear factor is a transcriptional repressor essential for embryonic development. *Frontiers in Bioscience: A Journal and Virtual Library* **6** D1186–D1191. (doi:10.2741/Hummelke)
- Hwang EJ, Lee JM, Jeong J, Park JH, Yang Y, Lim J-S, Kim JH, Baek SH & Kim KI 2009 SUMOylation of ROR α potentiates transcriptional activation function. *Biochemical and Biophysical Research Communications* **378** 513–517. (doi:10.1016/j.bbrc.2008.11.072)
- Ichiyama K, Yoshida H, Wakabayashi Y, Chinen T, Saeki K, Nakaya M, Takaesu G, Hori S, Yoshimura A & Kobayashi T 2008 Foxp3 inhibits ROR γ t-mediated IL-17A mRNA transcription through direct interaction with ROR γ t. *Journal of Biological Chemistry* **283** 17003–17008. (doi:10.1074/jbc.M801286200)
- Ihunnah CA, Jiang M & Xie W 2011 Nuclear receptor PXR, transcriptional circuits and metabolic relevance. *Biochimica et Biophysica Acta* **1812** 956–963. (doi:10.1016/j.bbadis.2011.01.014)
- Ijpenberg A, Jeannin E, Wahli W & Desvergne B 1997 Polarity and specific sequence requirements of peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor heterodimer binding to DNA. A functional analysis of the malic enzyme gene PPAR response element. *Journal of Biological Chemistry* **272** 20108–20117. (doi:10.1074/jbc.272.32.20108)
- Ingraham HA & Redinbo MR 2005 Orphan nuclear receptors adopted by crystallography. *Current Opinion in Structural Biology* **15** 708–715. (doi:10.1016/j.sbi.2005.10.009)
- Isseman I & Green S 1990 Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* **347** 645–650. (doi:10.1038/347645a0)
- Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelletier A, Lafaille JJ, Cua DJ & Littman DR 2006 The orphan nuclear receptor ROR γ t directs the differentiation program of proinflammatory IL-17+T helper cells. *Cell* **126** 1121–1133. (doi:10.1016/j.cell.2006.07.035)
- Ivanova N, Dobrin R, Lu R, Kotenko I, Levorse J, DeCoste C, Schafer X, Lun Y & Lemischka IR 2006 Dissecting self-renewal in stem cells with RNA interference. *Nature* **442** 533–538. (doi:10.1038/nature04915)
- Iyer AK & McCabe ERB 2004 Molecular mechanisms of DAX1 action. *Molecular Genetics and Metabolism* **83** 60–73. (doi:10.1016/j.ymgme.2004.07.018)
- Jetten AM 2009 Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. *Nuclear Receptor Signaling* **7** e003. (doi:10.1621/nrs.07003)
- Jin L, Martynowski D, Zheng S, Wada T, Xie W & Li Y 2010 Structural basis for hydroxycholesterols as natural ligands of orphan nuclear receptor ROR γ . *Molecular Endocrinology* **24** 923–929. (doi:10.1210/me.2009-0507)
- Johnston SD, Liu X, Zuo F, Eisenbraun TL, Wiley SR, Kraus RJ & Mertz JE 1997 Estrogen-related receptor α 1 functionally binds as a monomer to extended half-site sequences including ones contained within estrogen-response elements. *Molecular Endocrinology* **11** 342–352. (doi:10.1210/me.11.3.342)
- Jonk LJ, de Jonge ME, Pals CE, Wissink S, Vervaart JM, Schoorlemmer J & Kruijer W 1994 Cloning and expression during development of three murine members of the COUP family of nuclear orphan receptors. *Mechanisms of Development* **47** 81–97. (doi:10.1016/0925-4773(94)90098-1)
- Joseph SB, McKilligan E, Pei L, Watson MA, Collins AR, Laffitte BA, Chen M, Noh G, Goodman J, Hagger GN *et al.* 2002 Synthetic LXR ligand inhibits the development of atherosclerosis in mice. *PNAS* **99** 7604–7609. (doi:10.1073/pnas.112059299)
- Kallen JA, Schlaeppi J-M, Bitsch F, Geisse S, Geiser M, Delhon I & Fournier B 2002 X-ray structure of the hROR α LBD at 1.63 Å: structural and functional data that cholesterol or a cholesterol derivative is the natural ligand of ROR α . *Structure* **10** 1697–1707. (doi:10.1016/S0969-2126(02)00912-7)
- Kallen J, Lattmann R, Beerli R, Blechschmidt A, Blommers MJJ, Geiser M, Ottl J, Schlaeppi J-M, Strauss A & Fournier B 2007 Crystal structure of human estrogen-related receptor α in complex with a synthetic inverse agonist reveals its novel molecular mechanism. *Journal of Biological Chemistry* **282** 23231–23239. (doi:10.1074/jbc.M703337200)
- Kang HS, Okamoto K, Kim Y-S, Takeda Y, Bortner CD, Dang H, Wada T, Xie W, Yang X-P, Liao G *et al.* 2011 Nuclear orphan receptor TAK1/TR4-deficient mice are protected against obesity-linked inflammation, hepatic steatosis, and insulin resistance. *Diabetes* **60** 177–188. (doi:10.2337/db10-0628)
- Kastner P, Grondona JM, Mark M, Gansmuller A, LeMour M, Decimo D, Vonesch JL, Dollé P & Chambon P 1994 Genetic analysis of RXR α developmental function: convergence of RXR and RAR signaling pathways in heart and eye morphogenesis. *Cell* **78** 987–1003. (doi:10.1016/0092-8674(94)90274-7)
- Kastner P, Mark M, Leid M, Gansmuller A, Chin W, Grondona JM, Décimo D, Krezel W, Dierich A & Chambon P 1996 Abnormal spermatogenesis in RXR β mutant mice. *Genes and Development* **10** 80–92. (doi:10.1101/gad.10.1.80)
- Kawamoto T, Sueyoshi T, Zelko I, Moore R, Washburn K & Negishi M 1999 Phenobarbital-responsive nuclear translocation of the receptor CAR in induction of the CYP2B gene. *Molecular and Cellular Biology* **19** 6318–6322.
- Kelly VR, Xu B, Quirk R, Koenig RJ & Hammer GD 2010 Dax1 up-regulates Oct4 expression in mouse embryonic stem cells via LRH-1 and SRA. *Molecular Endocrinology* **24** 2281–2291. (doi:10.1210/me.2010-0133)
- Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B & Wahli W 1999 Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting. *Journal of Clinical Investigation* **103** 1489–1498. (doi:10.1172/JCI6223)
- Khan SA, Park SW, Huq M & Wei L-N 2005 Protein kinase C-mediated phosphorylation of orphan nuclear receptor TR2: effects on receptor stability and activity. *Proteomics* **5** 3885–3894. (doi:10.1002/pmic.200402062)
- Kim YS, Han CY, Kim SW, Kim JH, Lee SK, Jung DJ, Park SY, Kang H, Choi HS, Lee JW *et al.* 2001 The orphan nuclear receptor small heterodimer partner as a novel coregulator of nuclear factor- κ B in oxidized low density lipoprotein-treated macrophage cell line RAW 264.7. *Journal of Biological Chemistry* **276** 33736–33740. (doi:10.1074/jbc.M101977200)
- Kim E, Xie S, Yeh S-D, Lee Y-F, Collins LL, Hu Y-C, Shyr C-R, Mu X-M, Liu N-C, Chen Y-T *et al.* 2003 Disruption of TR4 orphan nuclear receptor reduces the expression of liver apolipoprotein E/C-I/C-II gene cluster. *Journal of Biological Chemistry* **278** 46919–46926. (doi:10.1074/jbc.M304088200)
- Kim J-Y, Chu K, Kim H-J, Seong H-A, Park K-C, Sanyal S, Takeda J, Ha H, Shong M, Tsai M-J *et al.* 2004 Orphan nuclear receptor small heterodimer partner, a novel corepressor for a basic helix–loop–helix transcription factor BETA2/neuroD. *Molecular Endocrinology* **18** 776–790. (doi:10.1210/me.2003-0311)
- Kim J, Chu J, Shen X, Wang J & Orkin SH 2008 An extended transcriptional network for pluripotency of embryonic stem cells. *Cell* **132** 1049–1061. (doi:10.1016/j.cell.2008.02.039)
- Kim H, Lee JM, Lee G, Bhin J, Oh SK, Kim K, Pyo KE, Lee JS, Yim HY, Kim KI *et al.* 2011 DNA damage-induced ROR α is crucial for p53 stabilization and increased apoptosis. *Molecular Cell* **44** 797–810. (doi:10.1016/j.molcel.2011.09.023)
- Kim YD, Li T, Ahn S-W, Kim D-K, Lee J-M, Hwang S-L, Kim Y-H, Lee C-H, Lee I-K, Chiang JYL *et al.* 2012 Orphan nuclear receptor small heterodimer partner negatively regulates growth hormone-mediated induction of hepatic gluconeogenesis through inhibition of signal transducer and activator of transcription 5 (STAT5) transactivation. *Journal of Biological Chemistry* **287** 37098–37108. (doi:10.1074/jbc.M112.339887)
- Kinsey M, Smith R, Iyer AK, McCabe ERB & Lessnick SL 2009 EWS/FLI and its downstream target NR0B1 interact directly to modulate transcription and oncogenesis in Ewing's sarcoma. *Cancer Research* **69** 9047–9055. (doi:10.1158/0008-5472.CAN-09-1540)

- Kliwer SA, Umesono K, Mangelsdorf DJ & Evans RM 1992a Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. *Nature* **355** 446–449. (doi:10.1038/355446a0)
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA & Evans RM 1992b Convergence of 9-*cis* retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature* **358** 771–774. (doi:10.1038/358771a0)
- Kliwer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterström RH *et al.* 1998 An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92** 73–82. (doi:10.1016/S0092-8674(00)80900-9)
- Kliwer SA, Goodwin B & Willson TM 2002 The nuclear pregnane X receptor: a key regulator of xenobiotic metabolism. *Endocrine Reviews* **23** 687–702. (doi:10.1210/er.2001-0038)
- Kobayashi M, Takezawa S, Hara K, Yu RT, Umesono Y, Agata K, Taniwaki M, Yasuda K & Umesono K 1999 Identification of a photoreceptor cell-specific nuclear receptor. *PNAS* **96** 4814–4819. (doi:10.1073/pnas.96.9.4814)
- Kolluri SK, Zhu X, Zhou X, Lin B, Chen Y, Sun K, Tian X, Town J, Cao X, Lin F *et al.* 2008 A short Nur77-derived peptide converts Bcl-2 from a protector to a killer. *Cancer Cell* **14** 285–298. (doi:10.1016/j.ccr.2008.09.002)
- Krill KT, Gurdziel K, Heaton JH, Simon DP & Hammer GD 2013 Dicer deficiency reveals microRNAs predicted to control gene expression in the developing adrenal cortex. *Molecular Endocrinology* **27** 754–768. (doi:10.1210/me.2012-1331)
- Kritis AA, Argyrokastritis A, Moschonas NK, Power S, Katrakili N, Zannis VI, Cereghini S & Talianidis I 1996 Isolation and characterization of a third isoform of human hepatocyte nuclear factor 4. *Gene* **173** 275–280. (doi:10.1016/0378-1119(96)00183-7)
- Krylova IN, Sablin EP, Moore J, Xu RX, Waitt GM, MacKay JA, Juzumiene D, Bynum JM, Madausk K, Montana V *et al.* 2005 Structural analyses reveal phosphatidyl inositols as ligands for the NRS orphan receptors SF-1 and LRH-1. *Cell* **120** 343–355. (doi:10.1016/j.cell.2005.01.024)
- Krzyzosiak A, Szyszka-Niagolov M, Wietrzyk M, Gobaille S, Muramatsu S & Krezel W 2010 Retinoid X receptor γ control of affective behaviors involves dopaminergic signaling in mice. *Neuron* **66** 908–920. (doi:10.1016/j.neuron.2010.05.004)
- Kurebayashi S, Ueda E, Sakaue M, Patel DD, Medvedev A, Zhang F & Jetten AM 2000 Retinoid-related orphan receptor γ (ROR γ) is essential for lymphoid organogenesis and controls apoptosis during thymopoiesis. *PNAS* **97** 10132–10137. (doi:10.1073/pnas.97.18.10132)
- Labelle Y, Zucman J, Stenman G, Kindblom LG, Knight J, Turc-Carel C, Dockhorn-Dworniczak B, Mandahl N, Desmazière C & Peter M 1995 Oncogenic conversion of a novel orphan nuclear receptor by chromosome translocation. *Human Molecular Genetics* **4** 2219–2226. (doi:10.1093/hmg/4.12.2219)
- Ladisa JA & Karathanasis SK 1991 Regulation of the apolipoprotein AI gene by ARP-1, a novel member of the steroid receptor superfamily. *Science* **251** 561–565. (doi:10.1126/science.1899293)
- Laffitte BA, Kast HR, Nguyen CM, Zavacki AM, Moore DD & Edwards PA 2000 Identification of the DNA binding specificity and potential target genes for the farnesoid X-activated receptor. *Journal of Biological Chemistry* **275** 10638–10647. (doi:10.1074/jbc.275.14.10638)
- Lala DS, Rice DA & Parker KL 1992 Steroidogenic factor I, a key regulator of steroidogenic enzyme expression, is the mouse homolog of fushi tarazu-factor I. *Molecular Endocrinology* **6** 1249–1258. (doi:10.1210/me.6.8.1249)
- Lalli E & Sassone-Corsi P 2003 DAX-1, an unusual orphan receptor at the crossroads of steroidogenic function and sexual differentiation. *Molecular Endocrinology* **17** 1445–1453. (doi:10.1210/me.2003-0159)
- Lalli E, Doghman M, Latre de Late P, Wakil AE & Mus-Veteau I 2013 Beyond steroidogenesis: novel target genes for SF-1 discovered by genomics. *Molecular and Cellular Endocrinology* **371** 154–159. (doi:10.1016/j.mce.2012.11.005)
- Lam MTY, Cho H, Lesch HP, Gosselin D, Heinz S, Tanaka-Oishi Y, Benner C, Kaikkonen MU, Kim AS, Kosaka M *et al.* 2013 Rev-Erbs repress macrophage gene expression by inhibiting enhancer-directed transcription. *Nature* **498** 511–515. (doi:10.1038/nature12209)
- Laudet V 1997 Evolution of the nuclear receptor superfamily: early diversification from an ancestral orphan receptor. *Journal of Molecular Endocrinology* **19** 207–226. (doi:10.1677/jme.0.0190207)
- Law SW, Conneely OM, DeMayo FJ & O'Malley BW 1992 Identification of a new brain-specific transcription factor, NURR1. *Molecular Endocrinology* **6** 2129–2135. (doi:10.1210/me.6.12.2129)
- Law SW, Conneely OM & O'Malley BW 1994 Molecular cloning of a novel member of the nuclear receptor superfamily related to the orphan receptor, TR2. *Gene Expression* **4** 77–84.
- Lazar MA, Hodin RA, Darling DS & Chin WW 1989 A novel member of the thyroid/steroid hormone receptor family is encoded by the opposite strand of the rat c-erbA α transcriptional unit. *Molecular and Cellular Biology* **9** 1128–1136.
- Lee CH, Chinpaisal C & Wei LN 1998 A novel nuclear receptor heterodimerization pathway mediated by orphan receptors TR2 and TR4. *Journal of Biological Chemistry* **273** 25209–25215. (doi:10.1074/jbc.273.39.25209)
- Lee Y-F, Lee H-J & Chang C 2002 Recent advances in the TR2 and TR4 orphan receptors of the nuclear receptor superfamily. *Journal of Steroid Biochemistry and Molecular Biology* **81** 291–308. (doi:10.1016/S0960-0760(02)00118-8)
- Lee Y-K, Schmidt DR, Cummins CL, Choi M, Peng L, Zhang Y, Goodwin B, Hammer RE, Mangelsdorf DJ & Kliwer SA 2008 Liver receptor homolog-1 regulates bile acid homeostasis but is not essential for feedback regulation of bile acid synthesis. *Molecular Endocrinology* **22** 1345–1356. (doi:10.1210/me.2007-0565)
- Lee JM, Kim IS, Kim H, Lee JS, Kim K, Yim HY, Jeong J, Kim JH, Kim J-Y, Lee H *et al.* 2010 ROR α attenuates Wnt/ β -catenin signaling by PKC α -dependent phosphorylation in colon cancer. *Molecular Cell* **37** 183–195. (doi:10.1016/j.molcel.2009.12.022)
- Lee JM, Lee YK, Mamrosh JL, Busby SA, Griffin PR, Pathak MC, Ortlund EA & Moore DD 2011a A nuclear-receptor-dependent phosphatidylcholine pathway with antidiabetic effects. *Nature* **474** 506–510. (doi:10.1038/nature10111)
- Lee K, Khan S, Ansar M, Santos-Cortez RLP, Ahmad W & Leal SM 2011b A novel ESRRB deletion is a rare cause of autosomal recessive nonsyndromic hearing impairment among Pakistani families. *Genetics Research International* **2011** 368915. (doi:10.4061/2011/368915)
- Lee JM, Lee JS, Kim H, Kim K, Park H, Kim J-Y, Lee SH, Kim IS, Kim J, Lee M *et al.* 2012 EZH2 generates a methyl degron that is recognized by the DCAF1/DBP1/CUL4 E3 ubiquitin ligase complex. *Molecular Cell* **48** 572–586. (doi:10.1016/j.molcel.2012.09.004)
- Lefebvre P, Benomar Y & Staels B 2010 Retinoid X receptors: common heterodimerization partners with distinct functions. *Trends in Endocrinology and Metabolism* **21** 676–683. (doi:10.1016/j.tem.2010.06.009)
- Lefterova MI, Zhang Y, Steger DJ, Schupp M, Schug J, Cristancho A, Feng D, Zhuo D, Stoeckert CJ, Liu XS *et al.* 2008 PPAR and C/EBP factors orchestrate adipocyte biology via adjacent binding on a genome-wide scale. *Genes and Development* **22** 2941–2952. (doi:10.1101/gad.1709008)
- Lefterova MI, Steger DJ, Zhuo D, Qatanani M, Mullican SE, Tuteja G, Manduchi E, Grant GR & Lazar MA 2010 Cell-specific determinants of peroxisome proliferator-activated receptor γ function in adipocytes and macrophages. *Molecular and Cellular Biology* **30** 2078–2089. (doi:10.1128/MCB.01651-09)
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT & Kliwer SA 1998 The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *Journal of Clinical Investigation* **102** 1016–1023. (doi:10.1172/JCI3703)
- Lehrke M & Lazar MA 2005 The many faces of PPAR γ . *Cell* **123** 993–999. (doi:10.1016/j.cell.2005.11.026)

- Lehrke M, Leberherz C, Millington SC, Guan H-P, Millar J, Rader DJ, Wilson JM & Lazar MA 2005 Diet-dependent cardiovascular lipid metabolism controlled by hepatic LXR α . *Cell Metabolism* **1** 297–308. (doi:10.1016/j.cmet.2005.04.005)
- Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen J-Y, Staub A, Garnier J-M, Mader S *et al.* 1992 Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell* **68** 377–395. (doi:10.1016/0092-8674(92)90478-U)
- Leone TC, Weinheimer CJ & Kelly DP 1999 A critical role for the peroxisome proliferator-activated receptor α (PPAR α) in the cellular fasting response: the PPAR α -null mouse as a model of fatty acid oxidation disorders. *PNAS* **96** 7473–7478. (doi:10.1073/pnas.96.13.7473)
- Levin AA, Sturzenbecker LJ, Kazmer S, Bosakowski T, Huselton C, Allenby G, Speck J, Kratzseisen C, Rosenberger M & Lovey A 1992 9-*cis* retinoic acid stereoisomer binds and activates the nuclear receptor RXR α . *Nature* **355** 359–361. (doi:10.1038/355359a0)
- Levin N, Bischoff ED, Daige CL, Thomas D, Vu CT, Heyman RA, Tangirala RK & Schulman IG 2005 Macrophage liver X receptor is required for antiatherogenic activity of LXR agonists. *Arteriosclerosis, Thrombosis, and Vascular Biology* **25** 135–142. (doi:10.1161/01.ATV.0000178996.91277.fb)
- Li M, Xie YH, Kong YY, Wu X, Zhu L & Wang Y 1998 Cloning and characterization of a novel human hepatocyte transcription factor, hB1F, which binds and activates enhancer II of hepatitis B virus. *Journal of Biological Chemistry* **273** 29022–29031. (doi:10.1074/jbc.273.44.29022)
- Li Y, Choi M, Cavey G, Daugherty J, Suino K, Kovach A, Bingham NC, Klier SA & Xu HE 2005 Crystallographic identification and functional characterization of phospholipids as ligands for the orphan nuclear receptor steroidogenic factor-1. *Molecular Cell* **17** 491–502. (doi:10.1016/j.molcel.2005.02.002)
- Li Q-X, Ke N, Sundaram R & Wong-Staal F 2006 NR4A1, 2, 3 – an orphan nuclear hormone receptor family involved in cell apoptosis and carcinogenesis. *Histology and Histopathology* **21** 533–540.
- Li P, Liu Y, Yi B, Wang G, You X, Zhao X, Summer R, Qin Y & Sun J 2013 MicroRNA-638 is highly expressed in human vascular smooth muscle cells and inhibits PDGF-BB-induced cell proliferation and migration through targeting orphan nuclear receptor NOR1. *Cardiovascular Research* **99** 185–193. (doi:10.1093/cvr/cvt082)
- Lin TM, Young WJ & Chang C 1995 Multiple functions of the TR2-11 orphan receptor in modulating activation of two key *cis*-acting elements involved in the retinoic acid signal transduction system. *Journal of Biological Chemistry* **270** 30121–30128. (doi:10.1074/jbc.270.50.30121)
- Lin F-J, Qin J, Tang K, Tsai SY & Tsai M-J 2011 Coup d'Etat: an orphan takes control. *Endocrine Reviews* **32** 404–421. (doi:10.1210/er.2010-0021)
- Lin S-J, Ho H-C, Lee Y-F, Liu N-C, Liu S, Li G, Shyr C-R & Chang C 2012 Reduced osteoblast activity in the mice lacking TR4 nuclear receptor leads to osteoporosis. *Reproductive Biology and Endocrinology* **10** 43. (doi:10.1186/1477-7827-10-43)
- Litchfield LM & Klinge CM 2012 Multiple roles of COUP-TFII in cancer initiation and progression. *Journal of Molecular Endocrinology* **49** R135–R148. (doi:10.1530/JME-12-0144)
- Liu H-K, Wang Y, Belz T, Bock D, Takacs A, Radlwimmer B, Barbus S, Reifemberger G, Lichter P & Schütz G 2010 The nuclear receptor tailless induces long-term neural stem cell expansion and brain tumor initiation. *Genes and Development* **24** 683–695. (doi:10.1101/gad.560310)
- Luo Y 2012 The function and mechanisms of Nurr1 action in midbrain dopaminergic neurons, from development and maintenance to survival. *International Review of Neurobiology* **102** 1–22. (doi:10.1016/B978-0-12-386986-9.00001-6)
- Luo X, Ikeda Y & Parker KL 1994 A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. *Cell* **77** 481–490. (doi:10.1016/0092-8674(94)90211-9)
- Mages HW, Rilke O, Bravo R, Senger G & Kroczeck RA 1994 NOT, a human immediate-early response gene closely related to the steroid/thyroid hormone receptor NAK1/TR3. *Molecular Endocrinology* **8** 1583–1591. (doi:10.1210/me.8.11.1583)
- Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ & Shan B 1999 Identification of a nuclear receptor for bile acids. *Science* **284** 1362–1365. (doi:10.1126/science.284.5418.1362)
- Malewicz M, Kadkhodaei B, Kee N, Volakakis N, Hellman U, Viktorsson K, Leung CY, Chen B, Lewensohn R, van Gent DC *et al.* 2011 Essential role for DNA-PK-mediated phosphorylation of NR4A nuclear orphan receptors in DNA double-strand break repair. *Genes and Development* **25** 2031–2040. (doi:10.1101/gad.16872411)
- Mangelsdorf DJ, Ong ES, Dyck JA & Evans RM 1990 Nuclear receptor that identifies a novel retinoic acid response pathway. *Nature* **345** 224–229. (doi:10.1038/345224a0)
- Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A & Evans RM 1992 Characterization of three RXR genes that mediate the action of 9-*cis* retinoic acid. *Genes and Development* **6** 329–344. (doi:10.1101/gad.6.3.329)
- Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P *et al.* 1995 The nuclear receptor superfamily: the second decade. *Cell* **83** 835–839. (doi:10.1016/0092-8674(95)90199-X)
- Mark M & Chambon P 2003 Functions of RARs and RXRs *in vivo*: genetic dissection of the retinoid signaling pathway. *Pure and Applied Chemistry* **75** 1709–1732. (doi:10.1351/pac200375111709)
- Mark M, Ghyselinck NB & Chambon P 2006 Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signaling pathway during mouse embryogenesis. *Annual Review of Pharmacology and Toxicology* **46** 451–480. (doi:10.1146/annurev.pharmtox.46.120604.141156)
- Markov GV & Laudet V 2011 Origin and evolution of the ligand-binding ability of nuclear receptors. *Molecular and Cellular Endocrinology* **334** 21–30. (doi:10.1016/j.mce.2010.10.017)
- Marks MS, Hallenbeck PL, Nagata T, Segars JH, Appella E, Nikodem VM & Ozato K 1992 H-2RIIBP (RXR β) heterodimerization provides a mechanism for combinatorial diversity in the regulation of retinoic acid and thyroid hormone responsive genes. *EMBO Journal* **11** 1419–1435.
- Martello G, Sugimoto T, Diamanti E, Joshi A, Hannah R, Ohtsuka S, Göttgens B, Niwa H & Smith A 2012 Esrrb is a pivotal target of the Gsk3/Tcf3 axis regulating embryonic stem cell self-renewal. *Cell Stem Cell* **11** 491–504. (doi:10.1016/j.stem.2012.06.008)
- Maruyama K, Tsukada T, Ohkura N, Bandoh S, Hosono T & Yamaguchi K 1998 The NGFI-B subfamily of the nuclear receptor superfamily (review). *International Journal of Oncology* **12** 1237–1243.
- Mataki C, Magnier BC, Houten SM, Annicotte J-S, Argmann C, Thomas C, Overmars H, Kulik W, Metzger D, Auwerx J *et al.* 2007 Compromised intestinal lipid absorption in mice with a liver-specific deficiency of liver receptor homolog 1. *Molecular and Cellular Biology* **27** 8330–8339. (doi:10.1128/MCB.00852-07)
- Maxwell MA & Muscat GEO 2006 The NR4A subgroup: immediate early response genes with pleiotropic physiological roles. *Nuclear Receptor Signaling* **4** e002. (doi:10.1621/nrs.040002)
- McMorrow JP & Murphy EP 2011 Inflammation: a role for NR4A orphan nuclear receptors? *Biochemical Society Transactions* **39** 688–693. (doi:10.1042/BST0390688)
- Medvedev A, Yan ZH, Hirose T, Giguère V & Jetten AM 1996 Cloning of a cDNA encoding the murine orphan receptor RZR/ROR γ and characterization of its response element. *Gene* **181** 199–206. (doi:10.1016/S0378-1119(96)00504-5)

- Miao J, Xiao Z, Kanamaluru D, Min G, Yau PM, Veenstra TD, Ellis E, Strom S, Suino-Powell K, Xu HE *et al.* 2009 Bile acid signaling pathways increase stability of small heterodimer partner (SHP) by inhibiting ubiquitin-proteasomal degradation. *Genes and Development* **23** 986–996. (doi:10.1101/gad.1773909)
- Miao J, Choi S-E, Seok SM, Yang L, Zuercher WJ, Xu Y, Willson TM, Xu HE & Kemper JK 2011 Ligand-dependent regulation of the activity of the orphan nuclear receptor, small heterodimer partner (SHP), in the repression of bile acid biosynthetic CYP7A1 and CYP8B1 genes. *Molecular Endocrinology* **25** 1159–1169. (doi:10.1210/me.2011-0033)
- Michalik L 2006 Involvement of PPAR nuclear receptors in tissue injury and wound repair. *Journal of Clinical Investigation* **116** 598–606. (doi:10.1172/JCI27958)
- Mikkelsen TS, Xu Z, Zhang X, Wang L, Gimble JM, Lander ES & Rosen ED 2010 Comparative epigenomic analysis of murine and human adipogenesis. *Cell* **143** 156–169. (doi:10.1016/j.cell.2010.09.006)
- Milbrandt J 1988 Nerve growth factor induces a gene homologous to the glucocorticoid receptor gene. *Neuron* **1** 183–188. (doi:10.1016/0896-6273(88)90138-9)
- Miyajima N, Kadowaki Y, Fukushige S, Shimizu S, Semba K, Yamanashi Y, Matsubara K, Toyoshima K & Yamamoto T 1988 Identification of two novel members of erbA superfamily by molecular cloning: the gene products of the two are highly related to each other. *Nucleic Acids Research* **16** 11057–11074. (doi:10.1093/nar/16.23.11057)
- Modica S, Gadaleta RM & Moschetta A 2010 Deciphering the nuclear bile acid receptor FXR paradigm. *Nuclear Receptor Signaling* **8** e005. (doi:10.1621/nrs.08005)
- Mohan HM, Aherne CM, Rogers AC, Baird AW, Winter DC & Murphy EP 2012 Molecular pathways: the role of NR4A orphan nuclear receptors in cancer. *Clinical Cancer Research* **18** 3223–3228. (doi:10.1158/1078-0432.CCR-11-2953)
- Monaghan AP, Bock D, Gass P, Schwäger A, Wolfer DP, Lipp HP & Schütz G 1997 Defective limbic system in mice lacking the tailless gene. *Nature* **390** 515–517. (doi:10.1038/37364)
- Moore DD, Kato S, Xie W, Mangelsdorf DJ, Schmidt DR, Xiao R & Kliewer SA 2006 International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnene X receptor, farnesoid X receptor α , farnesoid X receptor β , liver X receptor α , liver X receptor β , and vitamin D receptor. *Pharmacological Reviews* **58** 742–759. (doi:10.1124/pr.58.4.6)
- Moschetta A, Bookout AL & Mangelsdorf DJ 2004 Prevention of cholesterol gallstone disease by FXR agonists in a mouse model. *Nature Medicine* **10** 1352–1358. (doi:10.1038/nm1138)
- Mu X & Chang C 2003 TR2 orphan receptor functions as negative modulator for androgen receptor in prostate cancer cells PC-3. *Prostate* **57** 129–133. (doi:10.1002/pros.10282)
- Mukherjee S & Mani S 2010 Orphan nuclear receptors as targets for drug development. *Pharmaceutical Research* **27** 1439–1468. (doi:10.1007/s11095-010-0117-7)
- Mullen EM, Gu P & Cooney AJ 2007 Nuclear receptors in regulation of mouse ES cell pluripotency and differentiation. *PPAR Research* **2007** 61563. (doi:10.1155/2007/61563)
- Muscattelli F, Strom TM, Walker AP, Zanaria E, Récan D, Meindl A, Bardoni B, Guioli S, Zehetner G, Rabl W *et al.* 1994 Mutations in the DAX-1 gene give rise to both X-linked adrenal hypoplasia congenita and hypogonadotropic hypogonadism. *Nature* **372** 672–676. (doi:10.1038/372672a0)
- Nagy ZS, Czimmerer Z & Nagy L 2013 Nuclear receptor mediated mechanisms of macrophage cholesterol metabolism. *Molecular and Cellular Endocrinology* **368** 85–98. (doi:10.1016/j.mce.2012.04.003)
- Nakai A, Kartha S, Sakurai A, Toback FG & DeGroot LJ 1990 A human early response gene homologous to murine nur77 and rat NGFI-B, and related to the nuclear receptor superfamily. *Molecular Endocrinology* **4** 1438–1443. (doi:10.1210/mend-4-10-1438)
- Navas MA, Munoz-Elias EJ, Kim J, Shih D & Stoffel M 1999 Functional characterization of the MODY1 gene mutations HNF4(R127W), HNF4(V255M), and HNF4(E276Q). *Diabetes* **48** 1459–1465. (doi:10.2337/diabetes.48.7.1459)
- Nielsen R, Pedersen TA, Hagenbeek D, Moulos P, Siersbaek R, Megens E, Denissov S, Børgesen M, Francois K-J, Mandrup S *et al.* 2008 Genome-wide profiling of PPAR γ :RXR and RNA polymerase II occupancy reveals temporal activation of distinct metabolic pathways and changes in RXR dimer composition during adipogenesis. *Genes and Development* **22** 2953–2967. (doi:10.1101/gad.501108)
- Nishizawa H, Yamagata K, Shimomura I, Takahashi M, Kuriyama H, Kishida K, Hotta K, Nagaretani H, Maeda N, Matsuda M *et al.* 2002 Small heterodimer partner, an orphan nuclear receptor, augments peroxisome proliferator-activated receptor γ transactivation. *Journal of Biological Chemistry* **277** 1586–1592. (doi:10.1074/jbc.M104301200)
- Nitta M, Ku S, Brown C, Okamoto AY & Shan B 1999 CPF: an orphan nuclear receptor that regulates liver-specific expression of the human cholesterol 7 α -hydroxylase gene. *PNAS* **96** 6660–6665. (doi:10.1073/pnas.96.12.6660)
- Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK & Milburn MV 1998 Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor- γ . *Nature* **395** 137–143. (doi:10.1038/25931)
- Nuclear Receptors Nomenclature Committee 1999 A unified nomenclature system for the nuclear receptor superfamily. *Cell* **97** 161–163. (doi:10.1016/S0092-8674(00)80726-6)
- Odom DT, Zizlsperger N, Gordon DB, Bell GW, Rinaldi NJ, Murray HL, Volkert TL, Schreiber J, Rolfe PA, Gifford DK *et al.* 2004 Control of pancreas and liver gene expression by HNF transcription factors. *Science* **303** 1378–1381. (doi:10.1126/science.1089769)
- O'Geen H, Lin Y-H, Xu X, Echipare L, Komashko VM, He D, Fietze S, Tanabe O, Shi L, Sartor MA *et al.* 2010 Genome-wide binding of the orphan nuclear receptor TR4 suggests its general role in fundamental biological processes. *BMC Genomics* **11** 689. (doi:10.1186/1471-2164-11-689)
- Ohkura N, Hijikuro M, Yamamoto A & Miki K 1994 Molecular cloning of a novel thyroid/steroid receptor superfamily gene from cultured rat neuronal cells. *Biochemical and Biophysical Research Communications* **205** 1959–1965. (doi:10.1006/bbrc.1994.2900)
- Onishi A, Peng G-H, Hsu C, Alexis U, Chen S & Blackshaw S 2009 Pias3-dependent SUMOylation directs rod photoreceptor development. *Neuron* **61** 234–246. (doi:10.1016/j.neuron.2008.12.006)
- Onishi A, Peng G-H, Poth EM, Lee DA, Chen J, Alexis U, de Melo J, Chen S & Blackshaw S 2010 The orphan nuclear hormone receptor ERR β controls rod photoreceptor survival. *PNAS* **107** 11579–11584. (doi:10.1073/pnas.1000102107)
- Oosterveer MH, Matak C, Yamamoto H, Harach T, Moullan N, van Dijk TH, Ayuso E, Bosch F, Postic C, Groen AK *et al.* 2012 LRH-1-dependent glucose sensing determines intermediary metabolism in liver. *Journal of Clinical Investigation* **122** 2817–2826. (doi:10.1172/JCI62368)
- Ortlund EA, Lee Y, Solomon IH, Hager JM, Safi R, Choi Y, Guan Z, Tripathy A, Raetz CRH, McDonnell DP *et al.* 2005 Modulation of human nuclear receptor LXR-1 activity by phospholipids and SHP. *Nature Structural & Molecular Biology* **12** 357–363. (doi:10.1038/nsmb910)
- Pardee KI, Xu X, Reinking J, Schuetz A, Dong A, Liu S, Zhang R, Tiefenbach J, Lajoie G, Plotnikov AN *et al.* 2009 The structural basis of gas-responsive transcription by the human nuclear hormone receptor REV-ERB β . *PLoS Biology* **7** e43. (doi:10.1371/journal.pbio.1000043)
- Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD *et al.* 1999 Bile acids: natural ligands for an orphan nuclear receptor. *Science* **284** 1365–1368. (doi:10.1126/science.284.5418.1365)
- Parviz F, Matullo C, Garrison WD, Savatski L, Adamson JW, Ning G, Kaestner KH, Rossi JM, Zaret KS & Duncan SA 2003 Hepatocyte nuclear factor 4 α controls the development of a hepatic epithelium and liver morphogenesis. *Nature Genetics* **34** 292–296. (doi:10.1038/ng1175)
- Pearren MA & Muscat GEO 2010 Minireview: nuclear hormone receptor 4A signaling: implications for metabolic disease. *Molecular Endocrinology* **24** 1891–1903. (doi:10.1210/me.2010-0015)

- Pei L, Waki H, Vaitheeswaran B, Wilpitz DC, Kurland IJ & Tontonoz P 2006 NR4A orphan nuclear receptors are transcriptional regulators of hepatic glucose metabolism. *Nature Medicine* **12** 1048–1055. (doi:10.1038/nm1471)
- Pérez E, Bourguet W, Gronemeyer H & de Lera AR 2012 Modulation of RXR function through ligand design. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids* **1821** 57–69. (doi:10.1016/j.bbalip.2011.04.003)
- Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M *et al.* 2010 A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nature Genetics* **42** 224–228. (doi:10.1038/ng.522)
- Plengvidhya N, Antonellis A, Wogan LT, Poleev A, Borgschulze M, Warram JH, Ryffel GU, Krolewski AS & Doria A 1999 Hepatocyte nuclear factor-4γ: cDNA sequence, gene organization, and mutation screening in early-onset autosomal-dominant type 2 diabetes. *Diabetes* **48** 2099–2102. (doi:10.2337/diabetes.48.10.2099)
- Pondugula SR, Dong H & Chen T 2009 Phosphorylation and protein–protein interactions in PXR-mediated CYP3A repression. *Expert Opinion on Drug Metabolism & Toxicology* **5** 861–873. (doi:10.1517/17425250903012360)
- Qin J, Wu S-P, Creighton CJ, Dai F, Xie X, Cheng C-M, Frolov A, Ayala G, Lin X, Feng X-H *et al.* 2013a COUP-TFII inhibits TGF-β-induced growth barrier to promote prostate tumorigenesis. *Nature* **493** 236–240. (doi:10.1038/nature11674)
- Qin Q, Knapinska A, Dobri N, Madoux F, Chase P, Hodder P & Petrukhin K 2013b In pursuit of synthetic modulators for the orphan retina-specific nuclear receptor NR2E3. *Journal of Ocular Pharmacology and Therapeutics* **29** 298–309. (doi:10.1089/jop.2012.0135)
- Qu Q, Sun G, Li W, Yang S, Ye P, Zhao C, Yu RT, Gage FH, Evans RM & Shi Y 2010 Orphan nuclear receptor TLX activates Wnt/β-catenin signalling to stimulate neural stem cell proliferation and self-renewal. *Nature Cell Biology* **12** 31–40 sup pp 1–9. (doi:10.1038/ncb2001)
- Rada-Iglesias A, Bajpai R, Prescott S, Bruggmann SA, Swigut T & Wysocka J 2012 Epigenomic annotation of enhancers predicts transcriptional regulators of human neural crest. *Cell Stem Cell* **11** 633–648. (doi:10.1016/j.stem.2012.07.006)
- Raghubar S, Staybrook KR, Huang P, Rogers PM, Nosie AK, McClure DB, Burris LL, Khorasanizadeh S, Burris TP & Rastinejad F 2007 Identification of heme as the ligand for the orphan nuclear receptors REV-ERBα and REV-ERBβ. *Nature Structural & Molecular Biology* **14** 1207–1213. (doi:10.1038/nsmb1344)
- Ramakrishnan SN & Muscat GEO 2006 The orphan Rev-erb nuclear receptors: a link between metabolism, circadian rhythm and inflammation? *Nuclear Receptor Signaling* **4** e009. (doi:10.1621/nrs.04009)
- Reinking J, Lam MMS, Pardee K, Sampson HM, Liu S, Yang P, Williams S, White W, Lajoie G, Edwards A *et al.* 2005 The *Drosophila* nuclear receptor e75 contains heme and is gas responsive. *Cell* **122** 195–207. (doi:10.1016/j.cell.2005.07.005)
- Renaud JP, Harris JM, Downes M, Burke LJ & Muscat GE 2000 Structure–function analysis of the Rev-erbA and RVR ligand-binding domains reveals a large hydrophobic surface that mediates corepressor binding and a ligand cavity occupied by side chains. *Molecular Endocrinology* **14** 700–717. (doi:10.1210/me.14.5.700)
- Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL & Mangelsdorf DJ 2000 Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRα and LXRβ. *Genes and Development* **14** 2819–2830. (doi:10.1101/gad.844900)
- Reschly EJ & Krasowski MD 2006 Evolution and function of the NR11 nuclear hormone receptor subfamily (VDR, PXR, and CAR) with respect to metabolism of xenobiotics and endogenous compounds. *Current Drug Metabolism* **7** 349–365. (doi:10.2174/138920006776873526)
- Retnakaran R, Flock G & Giguère V 1994 Identification of RVR, a novel orphan nuclear receptor that acts as a negative transcriptional regulator. *Molecular Endocrinology* **8** 1234–1244. (doi:10.1210/me.8.9.1234)
- Ritchie HH, Wang LH, Tsai S, O'Malley BW & Tsai MJ 1990 COUP-TF gene: a structure unique for the steroid/thyroid receptor superfamily. *Nucleic Acids Research* **18** 6857–6862. (doi:10.1093/nar/18.23.6857)
- Rowe A, Eager NS & Brickell PM 1991 A member of the RXR nuclear receptor family is expressed in neural-crest-derived cells of the developing chick peripheral nervous system. *Development* **111** 771–778.
- Ruse MD Jr, Privalsky ML & Sladek FM 2002 Competitive cofactor recruitment by orphan receptor hepatocyte nuclear factor 4α1: modulation by the F domain. *Molecular and Cellular Biology* **22** 1626–1638. (doi:10.1128/MCB.22.6.1626-1638.2002)
- Ryseck RP, Macdonald-Bravo H, Mattéi MG, Ruppert S & Bravo R 1989 Structure, mapping and expression of a growth factor inducible gene encoding a putative nuclear hormonal binding receptor. *EMBO Journal* **8** 3327–3335.
- Sablin EP, Krylova IN, Fletterick RJ & Ingraham HA 2003 Structural basis for ligand-independent activation of the orphan nuclear receptor LRH-1. *Molecular Cell* **11** 1575–1585. (doi:10.1016/S1097-2765(03)00236-3)
- Sablin EP, Woods A, Krylova IN, Hwang P, Ingraham HA & Fletterick RJ 2008 The structure of corepressor Dax-1 bound to its target nuclear receptor LRH-1. *PNAS* **105** 18390–18395. (doi:10.1073/pnas.0808936105)
- Sadovsky Y, Crawford PA, Woodson KG, Polish JA, Clements MA, Tourtellotte LM, Simburger K & Milbrandt J 1995 Mice deficient in the orphan receptor steroidogenic factor 1 lack adrenal glands and gonads but express P450 side-chain-cleavage enzyme in the placenta and have normal embryonic serum levels of corticosteroids. *PNAS* **92** 10939–10943. (doi:10.1073/pnas.92.24.10939)
- Saga Y, Kobayashi M, Ohta H, Murai N, Nakai N, Oshima M & Taketo MM 1999 Impaired extrapyramidal function caused by the targeted disruption of retinoid X receptor RXRγ1 isoform. *Genes to Cells* **4** 219–228. (doi:10.1046/j.1365-2443.1999.00253.x)
- Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, Gage FH & Glass CK 2009 A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. *Cell* **137** 47–59. (doi:10.1016/j.cell.2009.01.038)
- Sakurada K, Ohshima-Sakurada M, Palmer TD & Gage FH 1999 Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain. *Development* **126** 4017–4026.
- Sanyal S, Kim J-Y, Kim H-J, Takeda J, Lee Y-K, Moore DD & Choi H-S 2002 Differential regulation of the orphan nuclear receptor small heterodimer partner (SHP) gene promoter by orphan nuclear receptor ERR isoforms. *Journal of Biological Chemistry* **277** 1739–1748. (doi:10.1074/jbc.M106140200)
- Satoh S, Tang K, Iida A, Inoue M, Kodama T, Tsai SY, Tsai M-J, Furuta Y & Watanabe S 2009 The spatial patterning of mouse cone opsin expression is regulated by bone morphogenetic protein signaling through downstream effector COUP-TF nuclear receptors. *Journal of Neuroscience* **29** 12401–12411. (doi:10.1523/JNEUROSCI.0951-09.2009)
- Scearce LM, Laz TM, Hazel TG, Lau LF & Taub R 1993 RNR-1, a nuclear receptor in the NGFI-B/Nur77 family that is rapidly induced in regenerating liver. *Journal of Biological Chemistry* **268** 8855–8861.
- Schimmer BP & White PC 2010 Minireview: steroidogenic factor 1: its roles in differentiation, development, and disease. *Molecular Endocrinology* **24** 1322–1337. (doi:10.1210/me.2009-0519)
- Schoonjans K, Dubuquoy L, Mebis J, Fayard E, Wendling O, Haby C, Geboes K & Auwerx J 2005 Liver receptor homolog 1 contributes to intestinal tumor formation through effects on cell cycle and inflammation. *PNAS* **102** 2058–2062. (doi:10.1073/pnas.0409756102)
- Schuler M, Ali F, Chambon C, Duteil D, Bornert J-M, Tardivel A, Desvergne B, Wahli W, Chambon P & Metzger D 2006 PGC1α expression is controlled in skeletal muscles by PPARβ, whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metabolism* **4** 407–414. (doi:10.1016/j.cmet.2006.10.003)
- Schupp M & Lazar MA 2010 Endogenous ligands for nuclear receptors: digging deeper. *Journal of Biological Chemistry* **285** 40409–40415. (doi:10.1074/jbc.R110.182451)

- Sekiya T, Kashiwagi I, Yoshida R, Fukaya T, Morita R, Kimura A, Ichinose H, Metzger D, Chambon P & Yoshimura A 2013 Nr4a receptors are essential for thymic regulatory T cell development and immune homeostasis. *Nature Immunology* **14** 230–237. (doi:10.1038/ni.2520)
- Semple RK 2006 PPAR and human metabolic disease. *Journal of Clinical Investigation* **116** 581–589. (doi:10.1172/JCI28003)
- Seok S, Kanamalluru D, Xiao Z, Ryerson D, Choi S-E, Suino-Powell K, Xu HE, Veenstra TD & Kemper JK 2013 Bile acid signal-induced phosphorylation of small heterodimer partner by protein kinase C is critical for epigenomic regulation of liver metabolic genes. *Journal of Biological Chemistry* **288** 23252–23263. (doi:10.1074/jbc.M113.452037)
- Seol W, Choi HS & Moore DD 1996 An orphan nuclear hormone receptor that lacks a DNA binding domain and heterodimerizes with other receptors. *Science* **272** 1336–1339. (doi:10.1126/science.272.5266.1336)
- Shi Y, Chichung Lie D, Taupin P, Nakashima K, Ray J, Yu RT, Gage FH & Evans RM 2004 Expression and function of orphan nuclear receptor TLX in adult neural stem cells. *Nature* **427** 78–83. (doi:10.1038/nature02211)
- Shibata M, Nakao H, Kiyonari H, Abe T & Aizawa S 2011 MicroRNA-9 regulates neurogenesis in mouse telencephalon by targeting multiple transcription factors. *Journal of Neuroscience* **31** 3407–3422. (doi:10.1523/JNEUROSCI.5085-10.2011)
- Shyr C-R, Collins LL, Mu X-M, Platt KA & Chang C 2002a Spermatogenesis and testis development are normal in mice lacking testicular orphan nuclear receptor 2. *Molecular and Cellular Biology* **22** 4661–4666. (doi:10.1128/MCB.22.13.4661-4666.2002)
- Shyr C-R, Hu Y-C, Kim E & Chang C 2002b Modulation of estrogen receptor-mediated transactivation by orphan receptor TR4 in MCF-7 cells. *Journal of Biological Chemistry* **277** 14622–14628. (doi:10.1074/jbc.M110051200)
- Shyr C-R, Kang H-Y, Tsai M-Y, Liu N-C, Ku P-Y, Huang K-E & Chang C 2009 Roles of testicular orphan nuclear receptors 2 and 4 in early embryonic development and embryonic stem cells. *Endocrinology* **150** 2454–2462. (doi:10.1210/en.2008-1165)
- Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G & Gonzalez FJ 2000 Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102** 731–744. (doi:10.1016/S0092-8674(00)00062-3)
- Sladek FM, Zhong WM, Lai E & Darnell JE Jr 1990 Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily. *Genes and Development* **4** 2353–2365. (doi:10.1101/gad.4.12b.2353)
- Solomon IH, Hager JM, Safi R, McDonnell DP, Redinbo MR & Ortlund EA 2005 Crystal structure of the human LRH-1 DBD–DNA complex reveals Ftz-F1 domain positioning is required for receptor activity. *Journal of Molecular Biology* **354** 1091–1102. (doi:10.1016/j.jmb.2005.10.009)
- Solt LA & Burris TP 2012 Action of RORs and their ligands in (patho)physiology. *Trends in Endocrinology and Metabolism* **23** 619–627. (doi:10.1016/j.tem.2012.05.012)
- Solt LA, Kumar N, Nuhant P, Wang Y, Lauer JL, Liu J, Istrate MA, Kamenecka TM, Roush WR, Vidović D *et al.* 2011 Suppression of TH17 differentiation and autoimmunity by a synthetic ROR ligand. *Nature* **472** 491–494. (doi:10.1038/nature10075)
- Solt LA, Wang Y, Banerjee S, Hughes T, Kojetin DJ, Lundasen T, Shin Y, Liu J, Cameron MD, Noel R *et al.* 2012 Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature* **485** 62–68. (doi:10.1038/nature11030)
- Sonoda J, Chong LW, Downes M, Barish GD, Coulter S, Liddle C, Lee C-H & Evans RM 2005 Pregnane X receptor prevents hepatorenal toxicity from cholesterol metabolites. *PNAS* **102** 2198–2203. (doi:10.1073/pnas.0409481102)
- Squires EJ, Sueyoshi T & Negishi M 2004 Cytoplasmic localization of pregnane X receptor and ligand-dependent nuclear translocation in mouse liver. *Journal of Biological Chemistry* **279** 49307–49314. (doi:10.1074/jbc.M407281200)
- Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, LaTour A, Liu Y, Klaassen CD, Brown KK, Reinhard J *et al.* 2001 The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *PNAS* **98** 3369–3374. (doi:10.1073/pnas.051551698)
- Stehlin-Gaon C, Willmann D, Zeyer D, Sanglier S, Van Dorselaer A, Renaud J-P, Moras D & Schüle R 2003 All-trans retinoic acid is a ligand for the orphan nuclear receptor ROR β . *Nature Structural Biology* **10** 820–825. (doi:10.1038/nsb979)
- Sucov HM, Dyson E, Gumeringer CL, Price J, Chien KR & Evans RM 1994 RXR α mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis. *Genes and Development* **8** 1007–1018. (doi:10.1101/gad.8.9.1007)
- Sueyoshi T & Negishi M 2001 Phenobarbital response elements of cytochrome P450 genes and nuclear receptors. *Annual Review of Pharmacology and Toxicology* **41** 123–143. (doi:10.1146/annurev.pharmtox.41.1.123)
- Suh JH, Huang J, Park Y-Y, Seong H-A, Kim D, Shong M, Ha H, Lee I-K, Lee K, Wang L *et al.* 2006 Orphan nuclear receptor small heterodimer partner inhibits transforming growth factor- β signaling by repressing SMAD3 transactivation. *Journal of Biological Chemistry* **281** 39169–39178. (doi:10.1074/jbc.M605947200)
- Sun G, Yu RT, Evans RM & Shi Y 2007 Orphan nuclear receptor TLX recruits histone deacetylases to repress transcription and regulate neural stem cell proliferation. *PNAS* **104** 15282–15287. (doi:10.1073/pnas.0704089104)
- Sun C, Nakatake Y, Akagi T, Ura H, Matsuda T, Nishiyama A, Koide H, Ko MSH, Niwa H & Yokota T 2009 Dax1 binds to Oct3/4 and inhibits its transcriptional activity in embryonic stem cells. *Molecular and Cellular Biology* **29** 4574–4583. (doi:10.1128/MCB.01863-08)
- Takayanagi S, Tokunaga T, Liu X, Okada H, Matsushima A & Shimohigashi Y 2006 Endocrine disruptor bisphenol A strongly binds to human estrogen-related receptor γ (ERR γ) with high constitutive activity. *Toxicology Letters* **167** 95–105. (doi:10.1016/j.toxlet.2006.08.012)
- Tang K, Xie X, Park J-I, Jamrich M, Tsai S & Tsai M-J 2010 COUP-TFs regulate eye development by controlling factors essential for optic vesicle morphogenesis. *Development* **137** 725–734. (doi:10.1242/dev.040568)
- Tangirala RK, Bischoff ED, Joseph SB, Wagner BL, Walczak R, Laffitte BA, Daige CL, Thomas D, Heyman RA, Mangelsdorf DJ *et al.* 2002 Identification of macrophage liver X receptors as inhibitors of atherosclerosis. *PNAS* **99** 11896–11901. (doi:10.1073/pnas.182199799)
- Taubert S, Ward JD & Yamamoto KR 2011 Nuclear hormone receptors in nematodes: evolution and function. *Molecular and Cellular Endocrinology* **334** 49–55. (doi:10.1016/j.mce.2010.04.021)
- Thomas AM, Hart SN, Kong B, Fang J, Zhong X & Guo GL 2010 Genome-wide tissue-specific farnesoid X receptor binding in mouse liver and intestine. *Hepatology* **51** 1410–1419. (doi:10.1002/hep.23450)
- van Tiel CM & de Vries CJM 2012 NR4A1 in the vessel wall. *Journal of Steroid Biochemistry and Molecular Biology* **130** 186–193. (doi:10.1016/j.jsbmb.2011.01.010)
- Tolson AH & Wang H 2010 Regulation of drug-metabolizing enzymes by xenobiotic receptors: PXR and CAR. *Advanced Drug Delivery Reviews* **62** 1238–1249. (doi:10.1016/j.addr.2010.08.006)
- Tontonoz P & Spiegelman BM 2008 Fat and beyond: the diverse biology of PPAR γ . *Annual Review of Biochemistry* **77** 289–312. (doi:10.1146/annurev.biochem.77.061307.091829)
- Tontonoz P, Hu E, Graves RA, Budavari AI & Spiegelman BM 1994 mPPAR γ 2: tissue-specific regulator of an adipocyte enhancer. *Genes and Development* **8** 1224–1234. (doi:10.1101/gad.8.10.1224)
- Tremblay AM & Giguère V 2007 The NR3B subgroup: an overReview. *Nuclear Receptor Signaling* **5** e009. (doi:10.1621/nrs.05009)
- Tremblay GB, Bergeron D & Giguère V 2001a 4-Hydroxytamoxifen is an isoform-specific inhibitor of orphan estrogen-receptor-related (ERR) nuclear receptors β and γ . *Endocrinology* **142** 4572–4575. (doi:10.1210/en.142.10.4572)
- Tremblay GB, Kunath T, Bergeron D, Lapointe L, Champigny C, Bader JA, Rossant J & Giguère V 2001b Diethylstilbestrol regulates trophoblast

- stem cell differentiation as a ligand of orphan nuclear receptor ERR β . *Genes and Development* **15** 833–838. (doi:10.1101/gad.873401)
- Tremblay AM, Wilson BJ, Yang X-J & Giguère V 2008 Phosphorylation-dependent sumoylation regulates estrogen-related receptor- α and - γ transcriptional activity through a synergy control motif. *Molecular Endocrinology* **22** 570–584. (doi:10.1210/me.2007-0357)
- Tsai SY & Tsai MJ 1997 Chick ovalbumin upstream promoter-transcription factors (COUP-TFs): coming of age. *Endocrine Reviews* **18** 229–240. (doi:10.1210/er.18.2.229)
- Tsukiyama T, Ueda H, Hirose S & Niwa O 1992 Embryonal long terminal repeat-binding protein is a murine homolog of FTZ-F1, a member of the steroid receptor superfamily. *Molecular and Cellular Biology* **12** 1286–1291.
- Tugwood JD, Issemann I, Anderson RG, Bundell KR, McPheat WL & Green S 1992 The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *EMBO Journal* **11** 433–439.
- Uppenberg J, Svensson C, Jaki M, Bertilsson G, Jendeborg L & Berkenstam A 1998 Crystal structure of the ligand binding domain of the human nuclear receptor PPAR γ . *Journal of Biological Chemistry* **273** 31108–31112. (doi:10.1074/jbc.273.47.31108)
- Uranishi K, Akagi T, Sun C, Koide H & Yokota T 2013 Dax1 associates with Esrrb and regulates its function in embryonic stem cells. *Molecular and Cellular Biology* **33** 2056–2066. (doi:10.1128/MCB.01520-12)
- Valnegri P, Khelfaoui M, Dorseuil O, Bassani S, Lagneaux C, Gianfelice A, Benfante R, Chelly J, Billuart P, Sala C *et al.* 2011 A circadian clock in hippocampus is regulated by interaction between oligophrenin-1 and Rev-erb α . *Nature Neuroscience* **14** 1293–1301. (doi:10.1038/nn.2911)
- Vanacker JM, Bonnelye E, Delmarre C & Laudet V 1998 Activation of the thyroid hormone receptor α gene promoter by the orphan nuclear receptor ERR α . *Oncogene* **17** 2429–2435. (doi:10.1038/sj.onc.1202167)
- Varga T, Czimmerer Z & Nagy L 2011 PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. *Biochimica et Biophysica Acta* **1812** 1007–1022. (doi:10.1016/j.bbadis.2011.02.014)
- Wan Y-JY, An D, Cai Y, Repa JJ, Chen TH-P, Flores M, Postic C, Magnuson MA, Chen J, Chien KR *et al.* 2000 Hepatocyte-specific mutation establishes retinoid X receptor α as a heterodimeric integrator of multiple physiological processes in the liver. *Molecular and Cellular Biology* **20** 4436–4444. (doi:10.1128/MCB.20.12.4436-4444.2000)
- Wang J & Lazar MA 2008 Bifunctional role of Rev-erb α in adipocyte differentiation. *Molecular and Cellular Biology* **28** 2213–2220. (doi:10.1128/MCB.01608-07)
- Wang LH, Tsai SY, Cook RG, Beattie WG, Tsai MJ & O'Malley BW 1989 COUP transcription factor is a member of the steroid receptor superfamily. *Nature* **340** 163–166. (doi:10.1038/340163a0)
- Wang H, Chen J, Hollister K, Sowers LC & Forman BM 1999 Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Molecular Cell* **3** 543–553. (doi:10.1016/S1097-2765(00)80348-2)
- Wang Z, Benoit G, Liu J, Prasad S, Aarnisalo P, Liu X, Xu H, Walker NPC & Perlmann T 2003 Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors. *Nature* **423** 555–560. (doi:10.1038/nature01645)
- Wang J, Rao S, Chu J, Shen X, Levasseur DN, Theunissen TW & Orkin SH 2006 A protein interaction network for pluripotency of embryonic stem cells. *Nature* **444** 364–368. (doi:10.1038/nature05284)
- Wang Y, Kumar N, Solt LA, Richardson TI, Helvering LM, Crumbley C, Garcia-Ordóñez RD, Stayrook KR, Zhang X, Novick S *et al.* 2010 Modulation of retinoic acid receptor-related orphan receptor α and γ activity by 7-oxygenated sterol ligands. *Journal of Biological Chemistry* **285** 5013–5025. (doi:10.1074/jbc.M109.080614)
- Wang Y, Solt LA, Kojetin DJ & Burris TP 2012 Regulation of p53 stability and apoptosis by a ROR agonist. *PLoS ONE* **7** e34921. (doi:10.1371/journal.pone.0034921)
- Wang H, Wang X, Xu X, Zwaka TP & Cooney AJ 2013 Epigenetic re-programming of the germ cell nuclear factor gene is required for proper differentiation of induced pluripotent cells. *Stem Cells* [in press]. (doi:10.1002/stem.1367)
- Wansa KDSA, Harris JM & Muscat GEO 2002 The activation function-1 domain of Nur77/NR4A1 mediates trans-activation, cell specificity, and coactivator recruitment. *Journal of Biological Chemistry* **277** 33001–33011. (doi:10.1074/jbc.M203572200)
- Wansa KDSA, Harris JM, Yan G, Ordentlich P & Muscat GEO 2003 The AF-1 domain of the orphan nuclear receptor NOR-1 mediates trans-activation, coactivator recruitment, and activation by the purine anti-metabolite 6-mercaptopurine. *Journal of Biological Chemistry* **278** 24776–24790. (doi:10.1074/jbc.M300088200)
- Warnecke M, Oster H, Revelli J-P, Alvarez-Bolado G & Eichele G 2005 Abnormal development of the locus coeruleus in Ear2(Nr2f6)-deficient mice impairs the functionality of the forebrain clock and affects nociception. *Genes and Development* **19** 614–625. (doi:10.1101/gad.317905)
- Wei P, Zhang J, Egan-Hafley M, Liang S & Moore DD 2000 The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature* **407** 920–923. (doi:10.1038/35038112)
- Wen Z, Pyeon D, Wang Y, Lambert P, Xu W & Ahlquist P 2012 Orphan nuclear receptor PNR/NR2E3 stimulates p53 functions by enhancing p53 acetylation. *Molecular and Cellular Biology* **32** 26–35. (doi:10.1128/MCB.05513-11)
- Willson TM & Moore JT 2002 Minireview: genomics versus orphan nuclear receptors - a half-time report. *Molecular Endocrinology* **16** 1135–1144. (doi:10.1210/me.16.6.1135)
- Willy PJ, Umeson K, Ong ES, Evans RM, Heyman RA & Mangelsdorf DJ 1995 LXR, a nuclear receptor that defines a distinct retinoid response pathway. *Genes and Development* **9** 1033–1045. (doi:10.1101/gad.9.9.1033)
- Wilson TE, Mouw AR, Weaver CA, Milbrandt J & Parker KL 1993 The orphan nuclear receptor NGFI-B regulates expression of the gene encoding steroid 21-hydroxylase. *Molecular and Cellular Biology* **13** 861–868.
- Wilson BJ, Tremblay AM, Deblois G, Sylvain-Drolet G & Giguère V 2010 An acetylation switch modulates the transcriptional activity of estrogen-related receptor α . *Molecular Endocrinology* **24** 1349–1358. (doi:10.1210/me.2009-0441)
- Wisely GB, Miller AB, Davis RG, Thornquest AD Jr, Johnson R, Spitzer T, Seffler A, Shearer B, Moore JT, Miller AB *et al.* 2002 Hepatocyte nuclear factor 4 is a transcription factor that constitutively binds fatty acids. *Structure* **10** 1225–1234. (doi:10.1016/S0969-2126(02)00829-8)
- Woldt E, Sebt Y, Solt LA, Duhem C, Lancel S, Eeckhoutte J, Hesselink MKC, Paquet C, Delhay S, Shin Y *et al.* 2013 Rev-erb- α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. *Nature Medicine* **19** 1039–1046. (doi:10.1038/nm.3213)
- Wolf G 2006 Is 9-*cis*-retinoic acid the endogenous ligand for the retinoic acid-X receptor? *Nutrition Reviews* **64** 532–538.
- Wolkenberg SE, Zhao Z, Kapitskaya M, Webber AL, Petrukhin K, Tang YS, Dean DC, Hartman GD & Lindsley CW 2006 Identification of potent agonists of photoreceptor-specific nuclear receptor (NR2E3) and preparation of a radioligand. *Bioorganic & Medicinal Chemistry Letters* **16** 5001–5004. (doi:10.1016/j.bmcl.2006.07.056)
- Xia X, Jung D, Webb P, Zhang A, Zhang B, Li L, Ayers SD, Gabbi C, Ueno Y, Gustafsson J-Å *et al.* 2012 Liver X receptor β and peroxisome proliferator-activated receptor δ regulate cholesterol transport in murine cholangiocytes. *Hepatology* **56** 2288–2296. (doi:10.1002/hep.25919)
- Xiao J, Gong A-Y, Eischeid AN, Chen D, Deng C, Young CYF & Chen X-M 2012 miR-141 modulates androgen receptor transcriptional activity in human prostate cancer cells through targeting the small heterodimer partner protein. *Prostate* **72** 1514–1522. (doi:10.1002/pros.22501)
- Xie W, Radominska-Pandya A, Shi Y, Simon CM, Nelson MC, Ong ES, Waxman DJ & Evans RM 2001 An essential role for nuclear receptors SXR/PXR in detoxification of cholestatic bile acids. *PNAS* **98** 3375–3380. (doi:10.1073/pnas.051014398)
- Xie S, Lee Y-F, Kim E, Chen L-M, Ni J, Fang L-Y, Liu S, Lin S-J, Abe J, Berk B *et al.* 2009a TR4 nuclear receptor functions as a fatty acid sensor to modulate CD36 expression and foam cell formation. *PNAS* **106** 13353–13358. (doi:10.1073/pnas.0905724106)

- Xie Y-B, Park J-H, Kim D-K, Hwang JH, Oh S, Park SB, Shong M, Lee I-K & Choi H-S 2009b Transcriptional corepressor SMILE recruits SIRT1 to inhibit nuclear receptor estrogen receptor-related receptor γ transactivation. *Journal of Biological Chemistry* **284** 28762–28774. (doi:10.1074/jbc.M109.034165)
- Xie S, Ni J, Lee Y-F, Liu S, Li G, Shyr C-R & Chang C 2011 Increased acetylation in the DNA-binding domain of TR4 nuclear receptor by the coregulator ARA55 leads to suppression of TR4 transactivation. *Journal of Biological Chemistry* **286** 21129–21136. (doi:10.1074/jbc.M110.208181)
- Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM *et al.* 1999 Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Molecular Cell* **3** 397–403. (doi:10.1016/S1097-2765(00)80467-0)
- Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Kliewer SA, Gampe RT, McKee DD *et al.* 2001 Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *PNAS* **98** 13919–13924. (doi:10.1073/pnas.241410198)
- Xu B, Yang W-H, Gerin I, Hu C-D, Hammer GD & Koenig RJ 2009 Dax-1 and steroid receptor RNA activator (SRA) function as transcriptional coactivators for steroidogenic factor 1 in steroidogenesis. *Molecular and Cellular Biology* **29** 1719–1734. (doi:10.1128/MCB.01010-08)
- Yamagata K, Furuta H, Oda N, Kaisaki PJ, Menzel S, Cox NJ, Fajans SS, Signorini S, Stoffel M & Bell GI 1996 Mutations in the hepatocyte nuclear factor-4 α gene in maturity-onset diabetes of the young (MODY1). *Nature* **384** 458–460. (doi:10.1038/384458a0)
- Yan ZH, Karam WG, Staudinger JL, Medvedev A, Ghanayem BI & Jetten AM 1998 Regulation of peroxisome proliferator-activated receptor α -induced transactivation by the nuclear orphan receptor TAK1/TR4. *Journal of Biological Chemistry* **273** 10948–10957. (doi:10.1074/jbc.273.18.10948)
- Yang XO, Pappu BP, Nurieva R, Akimzhanov A, Kang HS, Chung Y, Ma L, Shah B, Panopoulos AD, Schluns KS *et al.* 2008 T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR α and ROR γ . *Immunity* **28** 29–39. (doi:10.1016/j.immuni.2007.11.016)
- Yang D, Li T, Wang Y, Tang Y, Cui H, Tang Y, Zhang X, Chen D, Shen N & Le W 2012 miR-132 regulates the differentiation of dopamine neurons by directly targeting Nurr1 expression. *Journal of Cell Science* **125** 1673–1682. (doi:10.1242/jcs.086421)
- Yin L, Wu N, Curtin JC, Qatanani M, Szewergold NR, Reid RA, Waitt GM, Parks DJ, Pearce KH, Wisely GB *et al.* 2007 Rev-erb α , a heme sensor that coordinates metabolic and circadian pathways. *Science* **318** 1786–1789. (doi:10.1126/science.1150179)
- Yin L, Wu N & Lazar MA 2010 Nuclear receptor Rev-erb α : a heme receptor that coordinates circadian rhythm and metabolism. *Nuclear Receptor Signaling* **8** e001. (doi:10.1621/nrs.08001)
- Yokoyama A, Takezawa S, Schule R, Kitagawa H & Kato S 2008 Transrepressive function of TLX requires the histone demethylase LSD1. *Molecular and Cellular Biology* **28** 3995–4003. (doi:10.1128/MCB.02030-07)
- Young KA, Berry ML, Mahaffey CL, Saionz JR, Hawes NL, Chang B, Zheng QY, Smith RS, Bronson RT, Nelson RJ *et al.* 2002 Fierce: a new mouse deletion of Nr2e1; violent behaviour and ocular abnormalities are background-dependent. *Behavioural Brain Research* **132** 145–158. (doi:10.1016/S0166-4328(01)00413-2)
- Yu VC, Delsert C, Andersen B, Holloway JM, Devary OV, Näär AM, Kim SY, Boutin J-M, Glass CK & Rosenfeld MG 1991 RXR β : a coregulator that enhances binding of retinoic acid, thyroid hormone, and vitamin D receptors to their cognate response elements. *Cell* **67** 1251–1266. (doi:10.1016/0092-8674(91)90301-E)
- Yu RT, Chiang MY, Tanabe T, Kobayashi M, Yasuda K, Evans RM & Umesono K 2000 The orphan nuclear receptor Tlx regulates Pax2 and is essential for vision. *PNAS* **97** 2621–2625. (doi:10.1073/pnas.050566897)
- Yuan X, Ta TC, Lin M, Evans JR, Dong Y, Bolotin E, Sherman MA, Forman BM & Sladek FM 2009 Identification of an endogenous ligand bound to a native orphan nuclear receptor. *PLoS ONE* **4** e5609. (doi:10.1371/journal.pone.0005609)
- Yuk J-M, Shin D-M, Lee H-M, Kim J-J, Kim S-W, Jin HS, Yang C-S, Park KA, Chanda D, Kim D-K *et al.* 2011 The orphan nuclear receptor SHP acts as a negative regulator in inflammatory signaling triggered by Toll-like receptors. *Nature Immunology* **12** 742–751. (doi:10.1038/ni.2064)
- Zanaria E, Muscatelli F, Bardoni B, Strom TM, Guioli S, Guo W, Lalli E, Moser C, Walker AP, McCabe ERB *et al.* 1994 An unusual member of the nuclear hormone receptor superfamily responsible for X-linked adrenal hypoplasia congenita. *Nature* **372** 635–641. (doi:10.1038/372635a0)
- Zhan Y, Du X, Chen H, Liu J, Zhao B, Huang D, Li G, Xu Q, Zhang M, Weimer BC *et al.* 2008 Cytosporone B is an agonist for nuclear orphan receptor Nur77. *Nature Chemical Biology* **4** 548–556. (doi:10.1038/nchembio.106)
- Zhan Q, Fang Y, He Y, Liu H-X, Fang J & Wan Y-JY 2012 Function annotation of hepatic retinoid X receptor α based on genome-wide DNA binding and transcriptome profiling. *PLoS ONE* **7** e50013. (doi:10.1371/journal.pone.0050013)
- Zhang C-L, Zou Y, Yu RT, Gage FH & Evans RM 2006 Nuclear receptor TLX prevents retinal dystrophy and recruits the corepressor atrophin1. *Genes and Development* **20** 1308–1320. (doi:10.1101/gad.1413606)
- Zhang Y, Breevoort SR, Angdisen J, Fu M, Schmidt DR, Holmstrom SR, Kliewer SA, Mangelsdorf DJ & Schulman IG 2012 Liver LXR α expression is crucial for whole body cholesterol homeostasis and reverse cholesterol transport in mice. *Journal of Clinical Investigation* **122** 1688–1699. (doi:10.1172/JCI59817)
- Zhao Y & Brummer D 2010 NR4A orphan nuclear receptors transcriptional regulators of gene expression in metabolism and vascular biology. *Arteriosclerosis, Thrombosis, and Vascular Biology* **30** 1535–1541. (doi:10.1161/ATVBAHA.109.191163)
- Zhao C, Sun G, Li S & Shi Y 2009 A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. *Nature Structural & Molecular Biology* **16** 365–371. (doi:10.1038/nsmb.1576)
- Zhao C, Sun G, Li S, Lang M-F, Yang S, Li W & Shi Y 2010 MicroRNA let-7b regulates neural stem cell proliferation and differentiation by targeting nuclear receptor TLX signaling. *PNAS* **107** 1876–1881. (doi:10.1073/pnas.0908750107)
- Zhou L, Lopes JE, Chong MMW, Ivanov II, Min R, Victora GD, Shen Y, Du J, Rubtsov YP, Rudensky AY *et al.* 2008 TGF- β -induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing ROR γ t function. *Nature* **453** 236–240. (doi:10.1038/nature06878)
- Zhou C, King N, Chen KY & Breslow JL 2009 Activation of PXR induces hypercholesterolemia in wild-type and accelerates atherosclerosis in apoE deficient mice. *Journal of Lipid Research* **50** 2004–2013. (doi:10.1194/jlr.M800608-JLR200)
- Zhou XE, Suino-Powell KM, Xu Y, Chan C-W, Tanabe O, Kruse SW, Reynolds R, Engel JD & Xu HE 2011 The orphan nuclear receptor TR4 is a vitamin A-activated nuclear receptor. *Journal of Biological Chemistry* **286** 2877–2885. (doi:10.1074/jbc.M110.168740)
- Zhu XG, Park KS, Kaneshige M, Bhat MK, Zhu Q, Mariash CN, McPhie P & Cheng SY 2000 The orphan nuclear receptor Ear-2 is a negative coregulator for thyroid hormone nuclear receptor function. *Molecular and Cellular Biology* **20** 2604–2618. (doi:10.1128/MCB.20.7.2604-2618.2000)
- Zou Y, Niu W, Qin S, Downes M, Burns DK & Zhang C-L 2012 The nuclear receptor TLX is required for gliomagenesis within the adult neurogenic niche. *Molecular and Cellular Biology* **32** 4811–4820. (doi:10.1128/MCB.01122-12)

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