


The NR4A subgroup: immediate early response genes with pleiotropic physiological roles

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The nuclear hormone receptor (NR) superfamily includes the orphan NR4A subgroup, comprised of Nur77 (NR4A1), Nurr1 (NR4A2) and NOR-1 (NR4A3). These NRs are classified as early response genes, are induced by a diverse range of signals, including fatty acids, stress, growth factors, cytokines, peptide hormones, phorbol esters, neurotransmitters, and physical stimuli (for example magnetic fields, shear stress). The ability to sense and rapidly respond to changes in the cellular environment thus appears to be a hallmark of this subfamily. The members of the NR4A subgroup are well conserved in the DNA binding domain (~91-95%) and the C-terminal ligand-binding domain (~60%), but are divergent in the N-terminal AB region. These receptors bind as monomers, homodimers and heterodimers with RXRs (to mediate retinoid signaling) to different permutations of the canonical NR binding motif. The NR4A subgroup activates gene expression in a constitutive ligand-independent manner. NR4A-mediated trans-activation (LBD) involves unusually active N-terminal AF-1 domains that mediate coactivator recruitment. Moreover, the NR4A receptors encode atypical LBDs and AF-2 domains. For example, the LBDs contain no cavity due to bulky hydrophobic residue side chains, and lack the classical coactivator-binding cleft constituted by helices 3, 4 and 12. However, a hydrophobic patch exists between helices 11 and 12, that encodes a novel cofactor interface that modulates transcriptional activity. In line with the pleiotropic physiological stimuli that induce the NR4A subgroup, these orphan NRs have been implicated in cell cycle regulation (and apoptosis), neurological disease, steroidogenesis, inflammation, carcinogenesis and atherogenesis.

Received September 14th, 2005; Accepted December 20th, 2005; Published February 8th, 2005 | **Abbreviations:** ACTH: adrenocorticotropic hormone; AICAR: 5'-phosphoribosyl-5-aminoimidazole-4-carboxamide; AMPK: AMP activated protein kinase; CAV3: caveolin 3; CRH: corticotropin releasing hormone; DMI: dexamethasone/3-iso-butyl-1-methylxanthine/insulin; EWS: Ewing's sarcoma gene; Glut4: glucose transporter 4; HPA: hypothalamic-pituitary-adrenal; IL-1 β : interleukin-1 β ; LBD: ligand binding domain; LDL: low density lipoprotein; NBRE: NBFI-B response element; NMR: nuclear magnetic resonance; NR: nuclear hormone receptor; NurRE: Nur-responsive element; POMC: pro-opiomelanocortin; PPAR γ : peroxisome proliferator activated receptor γ ; ROR α : RAR-related orphan receptor- α ; RXR: 9-cis retinoic acid receptor; SMC: smooth muscle cells; SRC: steroid receptor coactivator; TAF2N: TATA box binding protein (TBP)-associated factor, RNA polymerase II; TCF12: transcription factor 12; TNF- α : tumor necrosis factor α ; UCP3: uncoupling protein 3 | Copyright © 2006, Maxwell and Muscat. This is an open-access article distributed under the terms of the Creative Commons Non-Commercial Attribution License, which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

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NR4A orphan nuclear receptors

NR4A1 (Nur77, TR3, NGFI-B, N10, DHR38, NAK-1, TIS1) [Hazel et al., 1988; Milbrandt, 1988], NR4A2 (Nurr1, HZF-3, RNR-1, TINUR, NOT) [Law et al., 1992] and NR4A3 (NOR-1, TEC, MINOR, CHN) [Ohkura et al., 1996] comprise the NR4A subgroup of orphan nuclear receptors. The members of the NR4A subgroup are expressed in a wide variety of metabolically demanding and energy dependent tissues, such as skeletal muscle, adipose, heart, kidney, T-cells, liver and the brain [Arkenbout et al., 2002; Lim et al., 1995; Nakai et al., 1990; Winoto, 1997; Zetterstrom et al., 1996]. The NR4A subfamily of NRs activate gene expression in a constitutive ligand-independent manner [Davis et al., 1993; Maltais and Labelle, 2000; Paulsen et al., 1992; Paulsen et al., 1995]. The binding site for the NR4A receptors is the octanucleotide 5'-A/TAAAGGTCA (NGFI-B response element, NBRE; Fig. 1A) [Wilson et al., 1992; Wilson et al., 1991; Wilson et al., 1993b], and they can bind as monomers [Paulsen et al., 1995] and homodimers [Maira et al., 1999; Philips et al., 1997]. The transcriptional target of NR4A homodimers, called the Nur-responsive element (NurRE; Fig. 1B), is an everted repeat of the NBRE-related octanucleotide, AAAT(G/A)(C/T)CA, and this motif is found naturally

occurring in the pro-opiomelanocortin (POMC) gene promoter [Philips et al., 1997]. Nur77 and Nurr1 (but not NOR-1) can also bind as heterodimers with RXR to mediate retinoid signaling [Perlmann and Jansson, 1995; Zetterstrom et al., 1996]. These RXR heterodimers bind a motif called DR5 (Fig. 1C), comprised of two direct repeats of the consensus NR binding motif separated by five nucleotides [Perlmann and Jansson, 1995]. Furthermore, heterodimers can also be formed between members of the subgroup [Maira et al., 1999] (Fig 1B).



Figure 1. NR4A response elements. The NR4A family members can bind as monomers to the NBRE (panel A), homodimers and NR4A heterodimers to the NurRE (panel B), or heterodimers with RXR to the DR5 motif (panel C). The naturally occurring NurRE from the pro-opiomelanocortin (POMC) promoter is shown.

It has been suggested that the NR4A subfamily evolved from a common ancestral gene, as the genomic structures for these receptors are extremely similar [Saucedo-Cardenas et al., 1997]. The members of the NR4A subgroup are well conserved in the DNA binding domain (~91-95%) and the C-terminal ligand-binding domain (LBD) (~60%), but are divergent in the N-terminal AB region [Murphy et al., 1996; Paulsen et al., 1995; Saucedo-Cardenas et al., 1997]. In the classical model of NR regulation, a hydrophobic cleft in the LBD recruits cofactors that function as coactivators or corepressors of transcription. However, the NR4A receptors encode unusual and atypical LBDs, which do not function in a classical manner [Paulsen et al., 1992]. However, it has been demonstrated that the LBD of Nurr1 (and to a lesser extent, NOR-1) can activate transcription, but this activation is not observed in all cell types [Castro et al., 1999]. Interestingly, it has been reported that NR4A-mediated transcription and cofactor recruitment also involves the N-terminal AF-1 domain [Castro et al., 1999; Maira et al., 2003; Wansa et al., 2002; Wansa et al., 2003]. In this context, phosphorylation of serine 105 in the N-terminal AF-1 domain has been implicated in growth factor dependent nucleo-cytoplasmic shuttling of Nur77 [Kang et al., 2000]. In summary, the NR4A subgroup encodes atypical NRs with very potent AF-1 domains, and LBDs with unique structures and regulatory properties.

NR4A genes encode atypical LBDs

This receptor subgroup initially proved refractory to the understanding of LBD mediated coactivator recruitment in the context of constitutive agonist independent trans-activation [Castro et al., 1999]. Moreover, the NR4A LBDs lack intrinsic and classical activation domains; nevertheless, site-specific mutations and deletions in helix 12 compromise the activity of this unique subgroup of orphan receptors [Paulsen et al., 1992]. Molecular modelling studies demonstrated that the LBDs of the NR4A1 and 3 receptors encode unusually hydrophilic surfaces with unique topography, rather than the classical hydrophobic cleft that mediates steroid receptor coactivator (SRC) recruitment [Wansa et al., 2002; Wansa et al., 2003]. Subsequently, X-ray crystallography studies demonstrated that the LBD of the orphan NR4A2 (Nurr1) adopts a canonical fold resembling that of agonist activated LBDs [Wang et al., 2003]. This is reminiscent of modelling studies with ROR α that demonstrated the AF2 domain is locked permanently in the holo-conformation described for other liganded receptors, and thus enables ligand independent recruitment of coactivators [Harris et al., 2002]. The Nurr1 LBD had two distinctive features. Firstly, the Nurr1 LBD lacks a cavity as a result of bulky side chains from hydrophobic residues in the region normally occupied by agonists [Wang et al., 2003]. This is very similar conclusion to modelling studies from Renaud and coworkers, that showed the Rev-erb α and β encode LBDs occupied by bulky side chains [Renaud et al., 2000]. The crystal studies rigorously concluded that Nurr1 lacked a classical binding site for coactivators and polar side chains occupy the classical

cleft [Wang et al., 2003]. Similar X-ray crystal studies on DHR38, the *Drosophila* ortholog of mammalian NR4A1, in the same way revealed the absence of a classic ligand binding pocket and classical coactivator binding site, features common to all the NR4A subgroup [Baker et al., 2003]. Recent crystal and NMR studies identified a hydrophobic patch between helices 11 and 12 that interacts with cofactors and modulates transcriptional activity [Codina et al., 2004; Flaig et al., 2005].

The NR4A receptors respond to diverse stimuli

The NR4A subgroup are immediate early or stress response genes, and can be induced by a wide range of physiological signals (see Fig. 2), such as fatty acids, stress, prostaglandins, growth factors, calcium, inflammatory cytokines, peptide hormones, phorbol esters, and neurotransmitters [Borghaei et al., 1998; Fahrner et al., 1990; Hazel et al., 1988; Honkaniemi et al., 1994; Honkaniemi et al., 2000; Kagaya et al., 2005; Katagiri et al., 1997; Roche et al., 1999; Tetradis et al., 2001a; Tetradis et al., 2001b; Tippetts et al., 1988; Williams and Lau, 1993]. Physical stimuli - for example magnetic fields, mechanical agitation (causing fluid shear stress), and membrane depolarization [Bandoh et al., 1997; Hazel et al., 1991; Katagiri et al., 1997; Miyakoshi et al., 1998] - have also been shown to induce expression of the NR4A receptors. The ability to sense and rapidly respond to changes in the cellular environment thus appears to be a hallmark of this subfamily of orphan nuclear receptors.

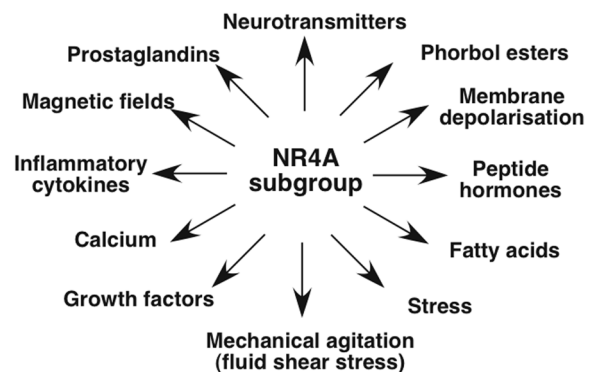


Figure 2. Diverse stimuli induce the NR4A subgroup. Nur77, NOR-1 and Nurr1, immediate early response genes that sense and respond to changes in the cellular environment, are induced by physiological and physical stimuli.

NR4A function in the central nervous system

There is widespread expression of all three NR4A receptors in the central nervous system [Zetterstrom et al., 1996], including the dopaminergic neurons. Nurr1 plays a role in the transcriptional activation of tyrosine hydroxylase (an enzyme involved in the synthesis of dopamine) [Sakurada et al., 1999], and is essential for the development of dopaminergic neurons in the midbrain [Zetterstrom et al., 1997]. Nurr1 mutations have also been

linked to Parkinson's disease [Le et al., 2003]. Anti-psychotic drugs can induce NOR-1, but the role of NOR-1 may be distinct from Nur77 in the dopamine receptor signaling response to these drugs, possibly due to the inability of NOR-1 to form heterodimers with RXR [Maheux et al., 2005]. Anti-psychotic drugs can also induce Nur77 [Beaudry et al., 2000]. Knockout mouse studies of the NR4A members have provided particularly useful insights into the role of the subfamily in the central nervous system.

NR4A receptors, steroidogenesis and inflammation

Activation of the HPA axis starts with the secretion of hypothalamic corticotropin releasing hormone (CRH), followed by the activation of pituitary POMC gene transcription and adrenocorticotrophic hormone (ACTH) secretion in response to CRH, resulting in ACTH-induced stimulation of adrenal glucocorticoid synthesis. NOR-1, Nur77 and NURR1 have been shown to play a key role in regulating expression of various genes in the HPA axis related to inflammation and steroidogenesis [Crawford et al., 1995; Fernandez et al., 2000; Stocco et al., 2002]. Furthermore, transcriptional antagonism between the glucocorticoid receptor and the NR4A subgroup has been described for many years [Martens et al., 2005]. CRH treatment of adrenal and pituitary cells induces Nur77 [Philips et al., 1997], and Nur77 activates expression of CRH [Murphy et al., 2001]. These events lead to the activation of the gene encoding steroid 21 α -hydroxylase [Davis and Lau, 1994; Wilson et al., 1993a]. The NR4A subfamily also regulates steroid 17-hydroxylase and the 20 α -hydroxysteroid dehydrogenase promoters [Davis and Lau, 1994; Stocco et al., 2000; Wilson et al., 1993a]. In response to CRH, the NR4A subfamily enhances the gene expression of POMC, the precursor to ACTH (the chief regulator of adrenal steroidogenesis and CRH [Murphy and Conneely, 1997; Murphy et al., 1996; Philips et al., 1997]. In response to inflammatory cytokines (e.g IL-1 β , TNF- α) there is local up-regulation of CRH in rheumatoid arthritis synovial tissue, indicating CRH as a component of the inflammatory cascade in arthritis [Murphy et al., 2001].

The NR4A subfamily has been extensively investigated in the context of inflammation. Two recent studies have shown that Nur77, NOR-1 and Nurr1 are rapidly induced in macrophages following lipopolysaccharide (LPS) stimulation [Barish et al., 2005; Pei et al., 2005], and that treatment with oxidised lipids and various cytokines can also stimulate Nur77 induction [Pei et al., 2005]. Interestingly, IFN γ also induced the expression of the NR4A subfamily in macrophages, but the induction was delayed compared to LPS, peaking at 16 to 24 hours after IFN γ exposure. In addition, the latter study showed a link between the NR4A response and the NF- κ B signaling pathway [Pei et al., 2005]. Nur77 and Nurr1 are similarly induced in response to inflammatory cytokines in rheumatoid arthritis [Murphy et al., 2001]. TNF α upregulates the expression of Nur77 in human umbilical vein endothelial cells, and in turn, the PAI-1 (plasminogen

activator inhibitor 1) promoter contains a Nur77 binding region that mediates the TNF α induction of PAI-1 [Gruber et al., 2003]. High plasma levels of PAI-1 have been linked to increased risk of vascular diseases, and Nur77 and PAI-1 co-localise in atherosclerotic vessels [Gruber et al., 2003]. Interestingly, it has recently been shown that the thiazolidinediones rosiglitazone and pioglitazone attenuate the induction of Nur77 (and Nurr1) in endothelial cells stimulated with TNF α [Liu et al., 2005]. The complex and diverse role of the NR4A members, in particular the involvement of Nur77 in modulating apoptosis in the inflammatory response, continues to be investigated.

NR4A receptors in smooth muscle cells and atherogenesis

The NR4A subgroup is expressed in multiple human atherosclerotic lesions from type II to V stages of atherosclerosis [Arkenbout et al., 2002]. The three members of the subgroup are expressed in neointimal (but not medial) smooth muscle cells (SMCs) [Arkenbout et al., 2003]. Moreover, the NOR-1 (NR4A3) gene is a target of the cAMP responsive element binding protein-mediated mitogenic effects of low-density lipoprotein (LDL) on vascular SMCs. Inhibition of NR4A3 expression inhibits the LDL induced proliferation [Rius et al., 2004]. Furthermore, emerging evidence demonstrates in a 'carotid artery ligation induced SMC proliferation mouse model' that NR4A1 inhibition results in increased neointimal formation, whereas neointimal formation is inhibited in transgenic mice expressing full length NR4A1. The process involves the NR4A1 mediated increase in the synthesis of the cyclin dependent kinase inhibitor, p27 (kip1) [Arkenbout et al., 2002]. In conclusion, this will require further investigation to resolve the role of the NR4A subgroup in atherosclerosis. For example, the link between PAI-1, Nur77, and vascular disease has to be reconciled in the context of Nur77 expression in neointimal formation.

NR4A null mutants: functional redundancy?

Interestingly, despite the dynamic role of Nur77 in the regulation of gene expression in the hypothalamic-pituitary-adrenal (HPA) axis, there is normal basal regulation of the hypothalamic and pituitary systems, and steroidogenesis in Nur77 $^{-/-}$ mice [Crawford et al., 1995]. Nurr1 and NOR-1 have also been shown to be involved in HPA function [Fernandez et al., 2000; Murphy et al., 2001], raising the possibility that the Nur77 $^{-/-}$ mice are rescued by compensatory expression of the other NR4A subfamily members. Along these lines, Nur77 mediates T cell receptor mediated T cell apoptosis [Liu et al., 1994; Woronicz et al., 1994; Woronicz et al., 1995], however, Nur77 $^{-/-}$ mice do not have dysfunctional thymic and peripheral T cell death. Again this can be accounted for by functional redundancy in the subgroup, for example, NOR-1 also has pro-apoptotic activity in thymocytes [Cheng et al., 1997; Lee et al., 1995].

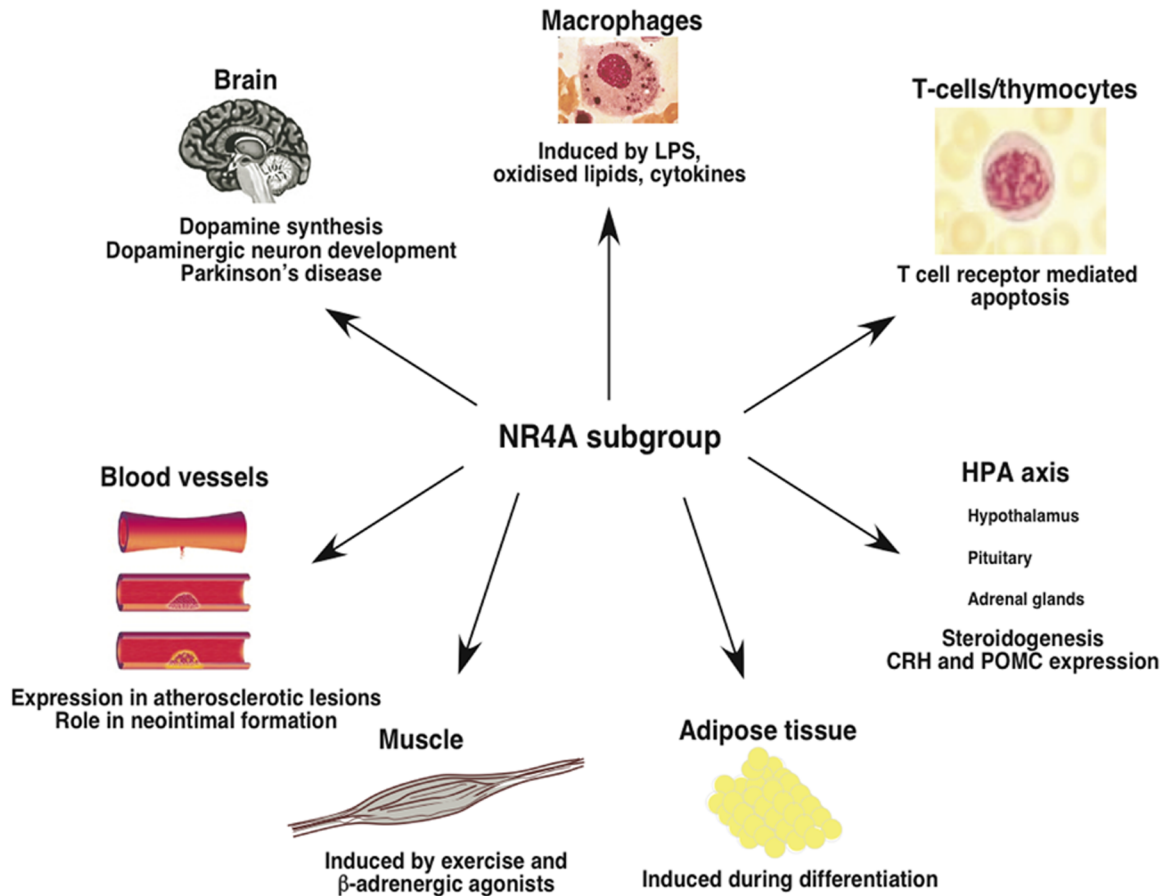


Figure 3. Organ and tissue specific effects of the NR4A subgroup. Schematic summarising the pleiotropic, cell-specific effects of this NR subgroup, that function as immediate early response genes in a variety of pathophysiological conditions.

Nurr1^{-/-} mice develop to full-term [Castillo et al., 1998]. However, neonates die at birth, apparently due to a severe defect in respiratory function [Nsegbe et al., 2004]. Nurr1 ablation leads to selective agenesis of midbrain dopaminergic neurons [Saucedo-Cardenas et al., 1998; Zetterstrom et al., 1997]. The homozygous and heterozygous mice lack (or have substantially reduced levels of) dopamine in the brain, consistent with the absence of tyrosine hydroxylase, L-aromatic amino decarboxylase and other dopamine neuronal markers [Castillo et al., 1998]. Recently, it has been demonstrated that Nurr1 is required for the neurotransmitter identity of ventral midbrain dopaminergic neurons, and Nurr1 expression is also required for the induction of the vesicular monoamine transporter 2 and dopamine transporter expression [Smits et al., 2003]. Furthermore, a recent report has established that decreased Nurr1 expression results in the increased vulnerability of dopaminergic neurons to dopaminergic toxins. This cascade involves nitric oxide, increased expression of nitric oxide synthase and 3-nitrotyrosine in the striatum of heterozygous Nurr1^{+/-} mice. Moreover, induction of Caspase-3 and p53, and reduced expression of Bcl-2 were also observed [Imam et al., 2005].

NOR-1 null mice have inner ear defects, and impaired bi-directional circling behavior associated with diminished endolymphatic fluid space in the canals. This is

concordant with NOR-1 expression in the semi-circular canal forming fusion plates, and the non-sensory epithelial cells [Ponnio et al., 2002; Ponnio and Conneely, 2004]. Furthermore, the NOR-1^{-/-} mice are sensitive to excitotoxic glutamate receptor agonists and display increased limbic seizure activity. This phenotype is associated with impaired postnatal hippocampal development, abnormal axon guidance and postnatal death of hippocampal pyramidal neurons [Ponnio and Conneely, 2004].

In summary, the phenotypes reported for NR4A null mutants are consistent with central nervous system expression and function, but analysis of the many other reported roles of these immediate early genes is complicated by functional redundancy. Hopefully, future analysis of double and triple knockouts, and/or tissue-specific NR4A attenuation will provide further insights into the pleiotropic functions of these receptors.

NR4A receptors and cancer

Chimeric fusions of NOR-1 with EWS [Clark et al., 1996; Labelle et al., 1999], TCF12 [Sjogren et al., 2000] and TAF2N [Attwooll et al., 1999; Panagopoulos et al., 1999; Sjogren et al., 1999] have been linked to extraskelatal myxoid chondrosarcoma. Furthermore, the role of the NR4A subfamily members in cancer is also largely defined

by the implication of the subfamily in the regulation of apoptosis. Apoptosis in many tumor types, including colon, breast, prostate, lung, and gastric cancers, have been shown to involve the NR4A family members [Li et al., 1998; Ohkubo et al., 2000; Wilson et al., 2003; Wu et al., 2002; Zhang, 2002]. Ongoing research continues to define the precise role of the NR4A subgroup in cell cycle regulation.

The NR4A receptors in metabolism

Previous reports described the induction of Nur77 by adrenergic agonists in muscle [Lim et al., 1995], and brain [Bing et al., 1991]; however, these isolated reports had not been reproduced. A recent study demonstrated that Nur77 mRNA is rapidly and transiently induced in C2C12 skeletal muscle cells by isoprenaline (a general β -adrenergic receptor agonist) [Maxwell et al., 2005]. These studies also showed that siRNA-mediated attenuation of Nur77 expression in C2C12 cells results in a decrease in the mRNA and/or protein expression of genes involved in energy expenditure and lipid homeostasis, such as UCP3, Glut4, CD36, CAV3 and AMPK γ 3 [Maxwell et al., 2005]. These findings are in concordance with a number of recently published reports. The coupled suppression of UCP3 and AMPK γ 3 is consistent with the activation of UCP3 in type II muscle fibers by the AMPK activator, AICAR [Suwa et al., 2003]. Furthermore, in rat skeletal muscle L6 cells, β -adrenergic receptor agonists increase glucose transport [Nevzorova et al., 2002]. Interestingly, it has been reported that Nur77, along with NOR-1 and Nurr1, are induced in skeletal muscle during recovery from endurance exercise. Nur77 and Nurr1 are moderately increased, but strikingly, NOR-1 is highly increased under these conditions [Mahoney et al., 2005].

In recent studies utilizing the 3T3-L1 adipocyte model, Nur77, NOR-1 and Nurr1 are rapidly and transiently induced by both rosiglitazone, and dexamethasone/IBMX/insulin (DMI) induction of adipocyte differentiation [Fu et al., 2005]. The NR4A members were induced within 2-4 hours of DMI treatment, and expression had subsided by 12-24 hours. Interestingly, the expression of Nur77 and NOR-1 were increased by rosiglitazone induction of adipocyte differentiation, but Nurr1 was not induced, and in fact exhibited decreased expression [Fu et al., 2005]. These studies in both skeletal muscle and adipocyte systems indicate that the NR4A subfamily has a critical role in the regulation of metabolism, consistent with the abundant expression of this subgroup in peripheral tissues with onerous energy demands.

In summary, adipose tissue and skeletal muscle are major sites of lipid and glucose metabolism, and are important target tissues for metabolic therapies. The possibility that modulating the activity of the NR4A subfamily may have pharmacological application in the treatment of metabolic disorders is supported by the observation that β -adrenergic and PPAR γ agonists, that regulate energy expenditure, insulin sensitivity and lipid storage,

respectively, induce the expression of the NR4A family members in these tissues.

Concluding remarks

The therapeutic utility of the subgroup (see Fig. 3) will depend on whether reverse endocrinology, coupled to novel chemistry, can identify small molecule regulators (agonists, antagonists and/or selective modulators) of this orphan NR family. X-ray crystallography studies suggest that this will be difficult because of bulky side chains occupying the traditional LBD cavity. Perhaps novel small molecule regulators will be identified, that selectively modulate the activity of this atypical NR subgroup. For example, the anti-neoplastic compound 6-mercaptopurine has been shown to activate NOR-1 and Nurr1, in an AF-1-dependent manner, independently of direct binding [Ordentlich et al., 2003; Wansa et al., 2003]. Secondly, prostaglandin A2 has recently been identified as a novel transactivator of NOR-1. The N-terminal AF-1 domain and the LBD were both necessary for activation. Prostaglandin A2 was also shown to directly bind the LBD of NOR-1 [Kagaya et al., 2005].

A very recent report suggested that E75 (the *Drosophila* homolog of the orphan nuclear receptor Rev-erb α) contains a heme prosthetic group, and functions as a redox and/or diatomic gas sensor [Reinking et al., 2005]. This exciting development and the studies above, highlight the possibility that orphan nuclear receptors with small ligand binding pockets may be modulated by novel and unexpected signaling cascades.

Recent X-ray and NMR studies have identified a novel hydrophobic patch at the C-terminal region that mediates cofactor interaction [Codina et al., 2004; Flaig et al., 2005], which suggests boutique peptides may be utilized to regulate the activity of this orphan NR subgroup. There is also the possibility that novel cofactors will be identified, that specifically modulate the actions of the NR4A subgroup.

The observations that this NR subgroup react as immediate early response genes to a diverse range of stimuli, including magnetic fields, shear stress, growth factors, fatty acids, calcium etc, in a variety of tissues (see Fig. 3), suggests the biomedical exploitation of this NR subgroup will require meticulous and painstaking studies.

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