NR4A1 (nuclear receptor subfamily 4, group A, member 1)

Tzu-Min Chan, Shinn-Zong Lin, Tzyy-Wen Chiou, Horng-Jyh Harn

Center for Neuropsychiatry, China Medical University and Hospital, Taichung, 40447, Taiwan, ROC and Everfront Biotech Inc., F11, No 31, Ln169, Kangning St., Xizhi Dist., New Taipei City 221, Taiwan, ROC (TMC), Center for Neuropsychiatry, China Medical University and Hospital, Taichung, 40447, Taiwan, ROC (SZL), Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan, ROC (TWC), Department of Pathology, China Medical University Hospital, and Department of Medicine, China Medical University Hospital, Taichung, Taiwan, ROC (HJH)

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Identity

Other names: GFRP1, HMR, N10, NAK-1, NGFIB, NP10, NUR77, TR3
HGNC (Hugo): NR4A1
Location: 12q13.13
Note
This article is an update of: NR4A1, 2, 3--an orphan nuclear hormone receptor family involved in cell apoptosis and carcinogenesis (Li et al., 2006).

DNA/RNA

Description
The NR4A1 gene is located on human chromosome 12 at position 12q13.13.
The gene spans from 52416616 to 52453291 (36.7 Kb) on the forward strand (NCBI).

Transcription
NR4A1 encodes three transcript variants and variant 3 produces two protein isoforms.
Variant 1 mRNA NCBI Reference number: NM_002135.
Variant 2 mRNA NCBI Reference number: NM_173157.
Variant 3 mRNA NCBI Reference number: NM_001202233.

Protein

Description
NR4A1 is a steroid/thyroid hormone-responsive orphan nuclear receptor that contains three key functional domains: a steroid hormone receptor ligand-independent transactivation domain (AF-1), a nuclear hormone receptor zinc finger domain (ZnF_C4) and a hormone receptor ligand-binding domain (HOLI) (Figure).
No natural ligand for NR4A1 has yet been identified (Davis and Lau, 1994; Mohan et al., 2012). NR4A1 is thought to play a role in transcriptional regulation through binding of the ZnF_C4 domain to hormone response elements in DNA (Moehren et al., 2004). This domain contains multiple finger-like structures and interacts with several target molecules, including DNA, RNA, proteins, and/or lipid substrates (Laity et al., 2001). The range of interactions implies that the ZnF_C4 domain has multiple functions in different molecular processes. The HOLI domain influences NR4A1 nuclear translocation and its association with DNA (Bledsoe et al., 2004).

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Expression

NR4A1 has been detected at varying levels in different human tissues, with particularly high levels in the adrenal cortex, lungs, prostate, ovaries, testes, heart, muscle, thyroid, trachea, olfactory bulb and adrenal gland (Su et al., 2004).

Localisation

NR4A1 is a nuclear hormone receptor that is activated by association with its ligand to move into the nucleus. For example, in response to n-Butylidenephthalide induced cell death signals, NR4A1 translocates into mitochondria to enhance apoptosis (Chen et al., 2008; Liu et al., 2012).

Function

NR4A1 is involved in multiple molecular processes, including signal transmission, transcriptional regulation, mediation of cell growth, induction of apoptosis, and cell cycle control (Lee et al., 2011; McMorrow and Murphy, 2011; Mohan et al., 2012; van Tiel and de Vries, 2012). NR4A1 acts as a hormone receptor and is stimulated by ligand binding to move into the nucleus and associate with DNA to regulate transcription of multiple genes (Wu et al., 2002). NR4A1 is also involved in several complex pathways that mediate cell survival and apoptosis (Li et al., 2006; Lin et al., 2004). Furthermore, NR4A1 dysfunction has been associated with inflammation and carcinogenesis (Choi et al., 2004; Li et al., 2006). In terms of post-translational modifications, NR4A1 is phosphorylated by protein kinase B at Serine 350 and its acetylation is modulated by p300 and HDAC1 (Kang et al., 2010; Pekarsky et al., 2001).

Cell growth/survival

As a steroid/thyroid hormone receptor, NR4A1 acts as a transcription factor, activating several genes involved in cell growth and survival (Bras et al., 2000). The expression of NR4A1 can be induced by tumor necrosis factor, growth factor, nerve growth factor and T-cell receptor-mediated signaling, implying a role of NR4A1 in cell proliferation (Bras et al., 2000). In addition, nerve growth factor IB and nuclear receptor subfamily 4 response elements, suggesting that NR4A1 functions in growth and cell cycle control (Pei et al., 2006). A dominant negative mutation in the transactivation domain of NR4A1 reduces cultured mouse embryonic cell growth in a tumor necrosis factor-dependent manner (Suzuki et al., 2003). Silencing of NR4A1 by siRNA treatment causes a dramatic reduction in growth/survival of HeLa, DLD1, HCT116, PC3, U87, and AsPC1 cell lines (Ke et al., 2004). Thus, NR4A1 appear to be involved in cell growth and survival, but the detailed mechanisms are still largely unknown.

Apoptosis

Contradictory to its apparent role in cell survival, NR4A1 also activates several genes involved in cell apoptosis as well as translocating directly into mitochondria to enhance the apoptotic signal (Li et al.,
For example, NR4A1 induces apoptosis in cultured prostate cancer cells through activation of the transcription factor E2F1 (Mu and Chang, 2003; Wilson et al., 2003). NR4A1 also mediates apoptosis through translocation from the nucleus into mitochondria where it interacted with the apoptosis regulating protein Bcl-2 to release cytochrome c (Lin et al., 2004; Suzuki et al., 2003). Another apoptosis regulating protein, BAX, is thought to recruit NR4A1 into the mitochondria to mediate apoptosis (Wilson et al., 2003). NR4A1 further induces apoptosis by reacting with self-recognizing major histocompatibility complex molecules in T cell (Zhang et al., 1999). NR4A1 acts as an inflammatory factor in T-cell, and T-cell receptor-mediated apoptosis can be prevented by inhibiting NR4A1 function (Liu et al., 1994; Woronicz et al., 1994). Thus, it appears that NR4A1 plays different and opposing roles in cell survival and apoptosis depending on the cell status and molecular environment (Moham et al., 2012).

**Neuronal regulation**

GFP-tagged NR4A1 is associated with dopamine receptor D1 positive neurons in brain tissue of transgenic mice (Davis and Puhl, 2011). NR4A1 activity closely correlates with dopamine neurotransmission in the central nervous system of mice (Gilbert et al., 2006). Furthermore, NR4A1 induces immediate early genes within central nervous system cells and basal ganglia of adult mice (Heiman et al., 2008; Lobo et al., 2006). NR4A1 deficient mice exhibit dysfunctional locomotor behavior due to alteration of dopamine neuron activity (Gilbert et al., 2006). Although NR4A1 is clearly involved in dopamine neuron activity, the specific mechanisms of this involvement remain unknown (Perlmann and Wallen-Mackenzie, 2004).

**Muscle homeostasis and metabolism**

In skeletal muscle, NR4A1 expression is enhanced by activation of the beta-adrenergic signaling pathway during muscle hypertrophy and endurance exercise (Mahoney et al., 2005; Maxwell et al., 2005; Pearen et al., 2006). Knockdown of NR4A1 by siRNA treatment causes repression of several genes associated with lipid, carbohydrate and glucose metabolism including the genes for AMP-activated protein kinase subunit gamma 3, fatty acid translocase and glucose transporter 4 (Maxwell et al., 2005; Chao et al., 2007). Interestingly, NR4A1 appears to influence energy balance and thermogenesis control through uncoupling of mitochondrial respiration (Kanzleiter et al., 2005). These findings suggest that NR4A1 is involved in energy metabolism and muscle energetics and function.

**Homology**

NR4A1 is an evolutionarily conserved gene and shows similar genomic synteny across species. The NR4A family includes three proteins (NR4A1, NR4A2 and NR4A3) with highly conserved protein sequences (NCBI).

**Mutations**

**Note**

No single site, nonsense or frameshift mutations in NR4A1 have been associated with cancer and/or disease in humans, but disruption of NR4A1 in mice by insertion of the neomycin resistance gene in exon 2 leads to development of acute myeloid leukemia (Mullican et al., 2007).

**Implicated in**

**Cancer and clinical translation**

**Note**

It is well known that tumor growth depends on new blood vessel formation to facilitate nutrient delivery (Liu et al., 2003; Mohan et al., 2012). NR4A1 expression is enhanced by vascular endothelial growth factor (Arkenbout et al., 2003; Liu et al., 2003). VEGF also stimulates CREB-dependent NR4A1 expression which in turn enhances angiogenesis through its transcription factor activity (Zeng et al., 2006; Zhao et al., 2011b). In addition, NR4A1 is activated by overexpression of hypoxia-inducible factor-1 alpha and thereby promotes overproduction of the hormone precursor proopiomelanocortin in VHL-mutated renal cell carcinoma (Choi et al., 2004).

Although the studies cited above indicate that NR4A1 contributes to carcinogenesis, many others report the opposite effect of NR4A1 on tumor growth (Mohan et al., 2012). NR4A1 expression is modified to inhibit tumor formation in many tumor types, including colon, breast, bladder, liver, thyroid, lung, prostate, and renal cell carcinoma (Choi et al., 2004; Mohan et al., 2012; Mu and Chang, 2003). As noted earlier, NR4A1 promotes apoptosis in a human prostate cancer cell line through stimulation of E2F1 expression (Mu and Chang, 2003). Early induction of NR4A1 in a human breast cancer cell line causes A23187-induced cell death via the CREB signaling pathway (Ohkubo et al., 2000). Recruitment of NR4A1 to the mitochondria and the subsequent release of cytochrome c have been associated with the Bcl-2 apoptotic pathway in several different cancer cell types (Lin et al., 2004; Wilson et al., 2003). NR4A1 enhances p53 transactivation of ionizing radiation-induced apoptosis in hepatoma cells, indicating that it may be a potential target for cancer radiotherapy (Zhao et al., 2011a). Loss of NR4A1 correlates with malignancy in follicular thyroid carcinomas presumably due to the reduction in apoptosis that allows cell growth (Camacho et al., 2009). Retinoic acid receptors (RARs) are often lost during carcinogenesis. NR4A1 was found to form apoptosis-inducing heterodimers with RARs in cultured lung cancer cells (Wu et al., 1997). Up-regulation of
NR4A1 and the resulting increase in apoptosis of human hepatocellular carcinoma cells is also RARβ dependent (Yang et al., 2011).

NR4A1 has begun to be incorporated into new cancer therapeutic strategies. These therapies rely on apoptosis induced by NR4A1 mitochondrial localization (Lin et al., 2004; Mohan et al., 2012). For example, glioblastoma multiforme is inhibited by local interstitial delivery of z-butylidenephthalalde, which enhances NR4A1 expression and translocation into mitochondria (Harn et al., 2011; Lin et al., 2008). N-butylidenephthalalde derivative also inhibit cell growth in hepatocellular carcinoma, oral squamous cell carcinoma and balloon injured rat carotid artery by inducing apoptosis (Chen et al., 2008; Liu et al., 2011; Liu et al., 2012). Moreover, 1,1-Bis(3'-indolyl)-1-(p-substituted phenyl)methanes induce apoptosis through NR4A1 activation in cultured pancreatic carcinoma cells (Chinthatlapalli et al., 2005).

To be noted

Note

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