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The nuclear receptor subfamily 4 group A1 in human disease

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Abstract

Nuclear receptor 4A1 (NR4A1), a member of the NR4A subfamily, acts as a gene regulator in a wide range of signaling pathways and responses to human diseases. Here, we provided a brief overview of the current functions of NR4A1 in human diseases and the factors involved in its function. A deeper understanding of these mechanisms can potentially improve drug development and disease therapy.

1 Introduction

The nuclear receptor 4A (NR4A) subfamily, which belongs to the nuclear receptor (NR) superfamily, contains three members: NR4A1(mouse homologue Nur77, rat homologue NGFI-B, and human homologue TR3 or NAK-1), NR4A2 (Nurr1), and NR4A3 (NOR1, MINOR, Nor-1). NR4A1 is a member of the nuclear hormone receptor superfamily, an immediate early gene, and a class of intracellularly distributed ligand-dependent transcription factors that can regulate the transcription and expression of genes by binding to the corresponding ligands. However, since its ligands have not been identified, they are named orphan nuclear receptors[1, 2]. They have the typical structural features of nuclear receptors, including an N-terminal region that contains a ligand -independent activation function-1 (AF-1) transactivation domain (TAD), and a conserved central DNA-binding domain (DBD). The DBD consists of two main DNA-binding zinc finger structures that recognize and bind to the target gene's NGFI-B response element NBRE (sequence AAAGGTCA), thus, regulating gene expression[3]. The role of NR4A1 is closely related to its receptor's microenvironment, subcellular localization, expression, post-translational modifications, and interactions with other nuclear receptors[4-6]. In this paper, we will systematically discuss the pathophysiological mechanisms associated with human disease, the function of NR4A1, and the factors influencing its function.

2.nr4a1 In Human Diseases

NR4A1 can act as a hormone and ligand-dependent DNA-binding protein that translates endocrine, metabolic, and pathophysiological signals into changes in gene expression controlling metabolic homeostasis[7]. Whereas the function of NR4A1 is different under different pathological conditions. As a transcription factor, NR4A1 is involved in the onset and progression of multiple diseases[8-11].

2.1 NR4A1 in cancer

NR4A1 plays an important pro-oncogenic role and can be targeted by anticancer drugs that induce cell death via NR4A1-dependent and -independent pathways in cancer cells and tumors[12]. It is overexpressed in NSCLC, which is associated with tumor recurrence and poor survival in NSCLC patients[13]. Moreover, NR4A1 is also related to several primary solid tumors (lung, breast, prostate, colorectal, uterus, and ovarian)[14]. In triple-negative breast cancer cells, NR4A1/ specific protein 1 (Sp1) can regulate PD-L1 that can be targeted by bis-indole–derived NR4A1 antagonists, thereby inhibiting the occurrence and

development of the tumor[15]. In endometrial cancer cells, NR4A1 exhibits its pro-oncogenic activity by regulating cell growth, survival, and mTOR signaling[16].

Brousso chalcone A (BCA), a new NR4A1 inhibitor, downregulates the expression of the Sp1-mediated anti-apoptotic protein survivin, and activates endoplasmic reticulum stress-mediated apoptosis inhibiting the progression of pancreatic cancer[17]. In breast tumor models or in estrogen receptor-positive patients, the application of NR4A1 antagonists significantly inhibited breast cancer progression[18, 19]. In endometrial cancer, the silencing of NR4A1 or intervening with a bisindole-derived NR4A1 antagonist suppresses endometrial cancer cell growth via the mTOR signaling pathway in *vitro* and in *vivo*.

Furthermore, NR4A1 also exerts its anti-tumor effect in gastric cancer cells NR4A1 overexpression affects the growth of gastric cancer cells by decreasing excessive production of ROS and inducing the release of mPTP and Cyt-c enhancing caspase-9 dependent mitochondrial apoptosis[20]. Studies have shown that NR4A1 expression is significantly reduced in breast cancer patients and in mice with breast cancer demonstrating that NR4A1 expression levels in human TNBC are negatively correlated with tumor stage, lymph node metastasis, and disease recurrence[21]. Meanwhile, NR4A1 may also have an inhibitory role in relation to the invasion/metastasis of breast cancer cells[22].

Collectively, the function of NR4A1 remains controversial in most cancer cells because it plays different roles in different cancers. Further studies are needed to clarify the exact mechanisms in the future.

2.2 NR4A1 in kidney disease

Nr4a1 is a susceptibility gene for kidney disease. In a model of acute ischemia-reperfusion injury, the expression of NR4A1 was increased, which induced apoptosis significantly. NR4A1 silencing can inhibit apoptosis and alleviate renal injury by expressing the anti-apoptotic protein Bcl-2[23].

In chronic kidney disease, NR4A1 has a protective effect in many cases. The expression of NR4A1 was significantly reduced in the UUO rat model. NR4A1 was significantly increased after being treated with Chinese medicine, indicating that NR4A1 is closely related to chronic kidney disease[24]. It has been reported that deletion of Nr4a1 is associated with kidney injury and abnormal kidney function. Nr4a1-deficient rats ($Nr4a1^{-/-}$) appear to have increased kidney injury and reduced renal function[25]. Another study showed that Nur77 ameliorates age-associated renal tubular interstitial fibrosis by inhibiting the TGF-β/Smads signaling pathway[26]. Nr4a1/Ear2-expressing anti-inflammatory macrophages ameliorate macrophage-mediated progressive renal injury in anti-glomerular basement membrane crescentic glomerulonephritis[27]. Furthermore, NR4A1 inhibitors can aggravate the progression of renal fibrosis by increasing the expression of fibrosis related genes in HK-2 cells[28]. However, in diabetic mice, the activation of NR4A1 promotes hyperglycemia -mediated glomerular apoptosis and kidney fibrosis by activating the expression of p53, accelerating mitochondrial fission and inhibiting mitophagy [29].

In summary, according to the above research, NR4A1 can inhibit or prevent the progression of renal interstitial fibrosis, as well as promote the development of diabetes. Consequently, it has different effects on different kidney diseases.

2.3 NR4A1 in inflammation

Inflammation is essential for protection following biological, chemical, or physical stimuli; however, inappropriate inflammation occurs in inflammatory diseases, causing tissue damage. NR4A1 is a key mediator during the regulation of inflammatory disease factors[30, 31].

Nur77 has anti-inflammatory mechanisms of action by inhibiting NF-κB signaling. Nur77 inhibits the transcriptional activity of the p65 subunit of NF-κB, by directly binding to p65[32, 33]. Interestingly, there is an NF-κB binding site within the Nur77 gene promoter, indicating the existence of a negative feedback loop[34].

Koenis's study showed that Nur77 induces an anti-inflammatory metabolic state in macrophages that protects against chronic inflammatory diseases such as atherosclerosis[30]. The absence of Nur77 in macrophages amplifies atherosclerosis development by shifting the profile of macrophages toward a pro-inflammatory, and pro-atherogenic phenotype in mice[35]. NR4A1 is a key endogenous inhibitor of chondrocyte inflammation, while its agonist cytosporone B reactivates and restores the inhibitory regulatory ability of NR4A1, preventing excessive inflammation, and ameliorating osteoarthritis[36]. In a model of acute E. coli pneumonia, the expression of macrophage NR4A1 was significantly increased. Moreover, when NR4A1 was inhibited, inflammatory cell infiltration was significantly reduced and the extent of lung injury significantly decreased[37]. NR4A1 is significantly upregulated in lipopolysaccharide-(LPS-) treated lung tissues. Knockout of NR4A1 overtly improved lung tissue morphology, inhibited inflammation, and reduced oxidative stress in LPS-treated lung tissue[38]. In brain microvascular endothelial cells, lipopolysaccharide increases the expression of circ0057583/NR4A1. Additionally, LPS-induced hBMEC injury is attenuated by inducing cell proliferation and angiogenesis and inhibiting apoptosis, autophagy, and inflammation once their expressions are inhibited[39]. The above findings suggest that NR4A1 is a key mediator in the regulation of inflammation and that NR4A1 may be a potential therapeutic target for inflammation-related diseases.

2.4 NR4A1 in neurological disease

In the nervous system, the research on NR4A1 primarily focuses on acute ischemic and traumatic diseases. Brain damage is aggravated with an increase in NR4A1 expression. NR4A1 expression was significantly increased in microglia after cerebral ischemia and the expression of chemokines, ICAM-1, and MPO was reduced after inhibition of NR4A1 expression. Moreover, NR4A1 can interact with NF-κB/p65. When p65 activation is inhibited, NR4A1 expression, M1 polarization, and neutrophil recruitment were reduced, thus, the inflammatory response was significantly suppressed[40]. NR4A1 was significantly increased within reperfused brain tissue. Knockdown of NR4A1 reduced cerebral infarct size and inhibited

apoptosis. The mechanism may be due to NR4A1 which induces a decrease in mitochondrial membrane potential, and cellular oxidative stress, interrupting ATP production, and initiates caspase-9-dependent apoptosis[41]. In a mouse model of traumatic brain injury, knockdown of CX3CR1 induced expression of CD36 and 15LO, followed by increased expression of NR4A1, which continuously exacerbated brain injury[30, 42-44].

However, NR4A1 plays a protective role in the early-stage brain injury model after ischemic stroke and subarachnoid hemorrhage. In a model of ischemic stroke, CX32 expression was significantly increased. Upon Cx32 inhibition Nur77 expression increases and is then translocated from the nucleus to the mitochondria stimulating autophagosome formation and regulating the expression of mitochondrial autophagy molecular markers to reduce brain injury[45]. In a late stage subarachnoid hemorrhage brain injury animal model, Akt activation negatively regulates NR4A1 by inducing NR4A1 phosphorylation, thus, inhibiting cellular apoptosis and reducing early-stage brain injury after a subarachnoid hemorrhage[46]. Similarly, in this model, activation of Nur77 induced the expression of anti-apoptotic protein Bcl-2, increasing the release of cytoc and inducing apoptosis. The application of NR4A1 agonist csn-b elevates apoptosis caused by NR4A1 activation and brain injury[47], while the administration of CSA significantly inhibits the expression of NR4A1 reducing brain injury[48].

2.5 NR4A1 in metabolic diseases

NR4A1 is an important regulator of glucose homeostasis and lipid metabolism in adipose tissue[49]. A previous study has shown that NR4A1 suppresses the transcription of key gluconeogenic genes, G6Pase and PEPCK, and further inhibits gluconeogenesis[50]. Glycerol kinase (GYK) plays a critical role in hepatic metabolism by converting glycerol to glycerol 3-phosphate in an ATP-dependent reaction. The cooperation of GYK with NR4A1 modulates lipid metabolism in the liver, independent of its metabolic enzyme activity[51]. It has been reported that NR4A1 is implicated in lipid metabolism by inhibiting adipogenesis or adipocyte maturation via enhancing GATA2 and p53 expression[52]. In addition, knockout of NR4A1 leads to amino acids, lipid, and glucose metabolic disorders in Zebrafish[53].

NR4A1 is highly expressed in diabetic models the silencing of NR4A1 significantly inhibits the expression of key gluconeogenic enzymes in the liver, reducing blood glucose to normal levels in T2DM db/db mice[54, 55]. NR4A1 also prevents the translocation of LKB1 from the nucleus to the cytoplasm by interacting with LKB1, which regulates the expression of key hepatic gluconeogenic enzymes, such as G6pc. Furthermore, it can significantly reduce hepatic glucose production, hepatic insulin resistance, and alter systemic glucose metabolism when NR4A1 null mice are fed a high-fat diet[56, 57]. Moreover, Csn-B, an NR4A1 agonist, increases fasting mice's hepatic glucose production and blood glucose levels [58]. In addition, the oral hypoglycemic agent berberine activates adenosine 5'-monophosphate activated protein kinase (AMPK) via NR4A1 and increases hepatic fibroblast growth factor 21 FGF21 expression. Thus, FGF21 may be a target gene of NR4A1 that exhibits multiple beneficial effects in energy metabolism[59,

[60]. In summary, this combined research indicates that NR4A1 is closely related to glucose and lipid metabolism, and maybe a key target in regulating or treating metabolic diseases.

2.6 NR4A1 in cardiovascular disease

A growing number of studies have shown that NR4A1 is closely associated with cardiovascular disease. NR4A1 interferes with cardiac microvascular ischemia reperfusion injury by triggering mitochondrial apoptosis[61]. Furthermore, NR4A1 also induces myocardial infarction through oxidative stress and exacerbates cardiac injury during myocardial infarction[39]. However, a study by Ji et al. showed that NR4A1 activation inhibits cardiac fibrosis by regulating glycolysis in a myocardial infarction rat model [62]. In an isoproterenol-induced myocardial fibrosis model, NR4A1 inhibits the process of fibrosis by inhibiting the phosphorylation of NR4A1[63]. According to these studies, the role of NR4A1 is closely associated with cardiovascular disease; however it is still controversial whether the activation of NR4A1 is beneficial or harmful for specific cardiovascular diseases. Thus, NR4A1 implications in cardiovascular disease need more in-depth research to determine its role in different cardiovascular disease models.

2.7 NR4A1 in liver disease

Previous studies have shown that NR4A1 has a correlation to liver disease. In the early stages of liver disease, the expression of NR4A1 was increased and further exacerbated liver disease damage[64, 65]. In hepatic ischemia-reperfusion injury, NR4A1 expression is increased; however NR4A1 silencing protects hepatocytes against hypoxia-reperfusion injury in vitro by activating liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK)[64].

In addition, NR4A1 also upregulates the expression of CYR61, leading to the activation of the NF-κB signaling pathway, which enhances the transcription of TGFβ1. When NR4A1 is silenced, the expression of CYR61/NF-κB/TGFβ1 is significantly reduced, thus alleviating the damage caused by liver ischemia/reperfusion[65]. Moreover, NR4A1 can lead to hepatocyte death and alcohol-related liver disease (ARLD) development. In addition, genetic ablation of NR4A1 ameliorates the progression of ARLD[66].

However, NR4A1 provides a protective role in homocysteine-induced hepatic steatosis. The NR4A1 agonist significantly inhibits the progression of hepatic steatosis[67]. Moreover, NR4A1 inhibits the epithelial-mesenchymal transition of hepatic stellate cells and liver fibrosis[68]. In a lipopolysaccharide (LPS)/D-galactosamine (D-GaIN)-induced acute liver failure mouse model, upregulation of Gr-dependent Nr4a1 in Kupffer cells ameliorates acute liver failure[69]. In summary, according to all of these NR4A1 appears to have a multi mechanistic role in different liver disease states.

2.8 NR4A1 in other disease

NR4A1 is implicated in a variety of diseases. It has been reported that the expression of NR4A1 was upregulated in hypoxia reoxygenation induced mouse pulmonary vascular endothelial cells (MPVECs) in a time-dependent manner, thus reducing the apoptosis of MPVECs once NR4A1 expression was

inhibited[70]. Additionally, NR4A1 is involved in ovarian endometriosis fibrosis. Csn-B may be a potential candidate for the treatment of endometriosis due to its ability to slow or stop its progression[71, 72].

In conclusion, NR4A1 is implicated and has complex functions within human diseases. However, there are significant differences in the role of NR4A1. Next, this paper systematically defines the functions of NR4A1 in human diseases and summarizes the primary roles that affect its function.

3.0 Functions Of Nr4a1 And The Factors Influencing Nr4a1's Function

3.1 Functions of NR4A1

As a transcription factor, NR4A1 plays an important role in inflammation, fibrosis, tumors, metabolic diseases, stress and addiction[7-10]. It can also act as a hormone and a ligand-dependent DNA-binding protein that translates endocrine, metabolic, and pathophysiological signals into changes in gene expression, controlling metabolic homeostasis[11].

The function of NR4A1 is different under different pathological conditions. In cardiac ischemia-reperfusion injury, NR4A1 expression was upregulated, which disrupted mitochondrial homeostasis, enhanced endothelial apoptosis, and exacerbated microvascular dysfunction by facilitating Mff-mediated mitochondrial fusion and FUNDC1-required mitophagy[61]. Additionally, NR4A1 promotes cerebral ischemia reperfusion injury by repressing Mfn2-mediated mitophagy and inactivating the MAPK–ERK–CREB signaling pathway[73]. NR4A1 expression was also significantly increased and enhanced the expression of CYR61/NF-κB/TGF-β1, thus eventually exacerbating hepatic I/R injury[65]. However, as reported in the literature, NR4A1 is an endogenous inhibitor of fibrosis in the vocal folds and in ovarian endometriosis[71, 74]. It has been demonstrated that Nur77 knockout enhances endothelial-to-mesenchymal transition increasing cardiac dysfunction and fibrosis after myocardial infarction[75]. NR4A1 also attenuates fibrotic processes within intestinal myofibroblasts providing a valuable clinical target for its treatment[76]. These studies indicate that NR4A1 promotes ischemia-reperfusion injury and is an endogenous inhibitor of fibrosis. Therefore, Csn-B has the potential to become a therapeutic candidate for the treatment of fibrosis.

There is increasing evidence that NR4A1 plays an important pro-oncogenic role and can be targeted by anticancer drugs that induce cell death via NR4A1-dependent and -independent pathways in cancer cells and tumors[12]. It has been reported that NR4A1 is overexpressed in non-small-cell lung carcinoma, which is associated with tumor recurrence and poor survival rates in NSCLC patients[13]. Furthermore, NR4A1 is also related to several primary solid tumors (lung, breast, prostate, colorectal, uterus, and ovarian)[14]. In triple-negative breast cancer cells, NR4A1/Sp1 regulates PD-L1 targeted by bis-indole–derived NR4A1 antagonists[15]. In endometrial cancer cells, NR4A1 also exhibits its pro-oncogenic activity due to the regulation of cell growth, survival, and mTOR signaling[16]. Additionally, it has been suggested that NR4A1 exerts anti-tumor effects and can affect the susceptibility of gastric cancer cells to TNFα-induced

apoptosis through the inhibition of JNK/Parkin-dependent mitophagy[20]. Moreover, NR4A1 has an inhibitory role in relation to the invasion and metastasis of breast cancer cells[21]. Collectively, the function of NR4A1 remains controversial in most cancer cells. This may be due to the different roles NR4A1 play in various cancers. Further studies are needed to clarify these mechanisms in the future.

As mentioned above, NR4A1 possesses different regulatory roles under different pathological conditions, such as induction and inhibition of apoptosis and inflammation, pro-inflammatory and oncogenic properties as well as anti-tumor effects. Therefore, it is crucial to study the factors affecting NR4A1 functions.

3.2 The factors influencing NR4A1 function

The dual regulatory effects of NR4A1 have been shown in extensive studies. It is primarily related to its subcellular localization, and post-translational modifications.

3.2.1 Subcellular localization

Subcellular localization refers to the specific location of biomolecules within the cell, such as the nucleus, cytoplasm, or cell membrane. The function of many molecules is closely related to subcellular localization[77]. When NR4A1 is translocated to the nucleus, its transcriptional activity induces cell growth and proliferation. Furthermore, the transcriptional activity and function of NR4A1 can be affected to a certain extent once it is transferred to the cytoplasm or mitochondria. Previous studies have shown that Nur77 binds to the promoter region of its target gene in order to activate gene transcription within the nucleus; however, Nur77 can interact with Bcl-2 through its ligand binding domain (LBD) to induce apoptosis when it translocates from the nucleus to the cytoplasm[78, 79]. Another study indicated that ionomycin induces apoptosis in thymocytes through the intrinsic Nur77-mediated mitochondrial pathway[80]. It also has been demonstrated that Nur77 could translocate from the nucleus to mitochondria to promote renal epithelial apoptosis and inflammation by interacting with Bcl2 after acute kidney injury[81]. In addition, Csn-B induces the release of cytochrome C and apoptosis by inducing Nur77 expression, leading to its translocation from the nucleus to the mitochondria[58].

3.2.2 Post-translational modification

Post-translational modification (PTM) occurring during the late stages of protein biosynthesis is a protein chemical modification after translation, including phosphorylation, ubiquitination, methylation, and acetylation. The transcriptional activity and function of a protein are often altered after PTM. Previous studies have shown that the transcriptional activity of NR4A1 is altered once it is post-translationally modified[82-84]. Additionally, there are many PTMs in NR4A1 which may alter its subcellular localization, such as phosphorylation, SUMOylation, and acetylation.

Phosphorylation is the process of adding a phosphate group to an intermediate metabolite or protein, thus, the transcriptional activity of NR4A1 changes after phosphorylation[85, 86]. Moreover, NR4A1s

transcriptional activity and function depend on the phosphorylation site (see Table 1 for details). In another report, it has been demonstrated that Akt interacts with Nur77, inactivating Nur77 via phosphorylation at Ser-350 in a phosphatidylinositol 3-kinase-dependent manner, inducing apoptosis[87]. In addition, NR4A1that is phosphorylated at the threonine residues by the activated MAPK pathway, modulates neurokinin-1-receptor-mediated nonapoptotic programmed cell death[88]. Huang's study indicated that Nur77 is phosphorylated at Ser-154 by CK2, triggering Trim13-mediated ubiquitination of e thNur77 lysine 539 (K539); therefore, degrading it and inhibiting the expression of IL-6 and TNFα[89].

Small ubiquitin-like modifier (SUMO) is a post-translational modification that affects the proteins stability, and transcriptional activity. As reported in the literature, SUMO modification of NR4A1 triggers polyubiquitination eliminating its stability and mitigating the inhibition of innate immune signaling, such as TNF-α and IL-1β-induced NF-κB activation[83]. To our knowledge, SUMO modification of transcription factors usually inhibits their transcriptional activity. It has been shown that NR4A1 SUMOylation impairs its transcriptional activity inducing autophagic cell death[90]. Furthermore, recent research has clarified that Nur77 transcriptional activity can be potently repressed by protein inhibitors of activated STAT gamma (PIASγ) and SUMO2[91]. These recent investigations have revealed that the SUMOylation sites of NR4A1 (Nur77) may be at K102 and K577.

As a major PTM, acetylation of transcriptional factors regulates protein stability and transcriptional activity. It has been shown that expression of p300 enhances the acetylation and protein stability of Nur77, whereas histone deacetylase 1 decreases its acetylation and protein levels, as well as its transcriptional activity[84].

Table 1: post translational modification sites, stimuli and functions

Post-translational modifications	Site	Stimulate	Function
Phosphorylation	Ser95	Pin1	Enhanced stability
Phosphorylation	Ser431	Pin1	Trans-activation enhancement
Phosphorylation	Ser95	JNK	Promotes ubiquitination and eliminates mitotic activity
Phosphorylation	Ser350	NGF	Inhibits transcriptional activity and DNA binding activity
Phosphorylation	Ser350	AKT	Transcriptional inactivation and induction of apoptosis
Phosphorylation	Ser	SP/nk1r	Altered transcriptional activity and induction of autophagy
Phosphorylation	Ser142	EGF	Altered transcriptional activity and induction of apoptosis
Ubiquitination	Lys539	Trim	Transcriptional inactivation, mediating inflammation
Phosphorylation	Ser154	CK2	Induces ubiquitination and inhibits inflammation
Phosphorylation	Ser351	AKT	Nucleoplasmic translocation, targeting mitochondria to induce apoptosis
SUMO	K577	PIASγ	Reduced transcriptional activity
SUMO	K102	PIASγ	Reduced transcriptional activity

4 Discussion And Outlook

NR4A1 is located on human chromosome 12. NR4A1, first identified in 1988 by Hazel et al. and has been confirmed to be present in various species and is considered a member of NR subfamily group 4A[92]. As an immediate early response gene and transcription factor, it can regulate physiological activity in three ways. One is that it can bind to the neural growth factor-induced gene B response element (NBRE) in a monomeric form. Second it has a structure that allows it to form homodimers with itself and acts on the Nur response element (NurRE). Third, it can form heterodimers with other nuclear receptors such as RXR, NR4A2 and NR4A3, specifically binding to DB5 or the NBRE elements. In all three forms of action, they can bind to DNA and promote or repress the expression of downstream genes or proteins, thus performing different biological functions[93].

NR4A1 significantly impacts almost all physiological processes in mammalian cells, tissues, and organs at all levels of the organism. The NR subfamily group 4A acts as an interface between changes in cellular or systemic environments and the genome, facilitating the fusion of various extra- and intracellular signals. They play an important role in initiating intercellular physiological transcriptional programs. Their

close association with many human diseases means that they have the potential to become new and novel therapeutic targets. Over the past 30 years, advances in NR4A1 biochemistry and molecular biology have led to a better understanding of its functions and the factors influencing its functions.

As a nuclear transcription factor, NR4A1 plays an important role in numerous human diseases; however, there may be a two-way regulation in most diseases. NR4A1 an oncogene, can be overexpressed in a variety of cancer microenvironments. Additionally, it can also be used as an anti-oncogene to inhibit the occurrence and development of tumors. The main mechanism of its role is closely related to oxidative stress, mitochondrial dysfunction, and apoptosis. As a key mediator regulating inflammation, NR4A1 plays a prominent anti-inflammatory role by inhibiting the NF κB signaling pathway, indicating the existence of a negative feedback loop, thereby inhibiting inflammation. In kidney disease, the mechanism of its role may be closely related to the microenvironment of the disease. In the acute phase of the disease, NR4A1 is an early response gene, with its expression rising rapidly, exacerbating renal injury. During the chronic development phase of the disease, the mechanisms of NR4A1 are closely related to mitochondrial dysfunction and oxidative stress. Its role in cardiovascular and liver disease is similar to that in kidney disease and is closely related to the microenvironment of the receptor. Its mechanism primarily involves inflammation, oxidative stress, mitochondrial function, angiogenesis, and cell phenotype transformation. Therefore, it is critical to study the role of NR4A1 in human diseases systematically.

NR4A1s function is complex, due to the differences in subcellular localization, post-translational modifications, and various tissues and cellular microenvironments. Studies have shown that NR4A1 is originally located in the nucleus and is transferred to the cytoplasm upon various stimul. Once NR4A1 is translocated to the cytoplasm, its transcriptional activity is altered. This process is accompanied by post-translational modifications including phosphorylation, acetylation, and ubiquitination. The functional differences in various tissues and cellular microenvironments markedly effects NR4A1s physiological role. In this paper, we have systematically summarized the relevant factors affecting the function of NR4A1. However, further studies should be conducted to specify the function of NR4A1 in various microenvironments as well as the relevant factors affecting NR4A1.

Previous studies on NR4A1 have focused on human diseases, such as cancer, inflammation, metabolic, and other related diseases[94]. Recent studies have shown that NR4A1 is correlated to human diseases and has an impact on the pathophysiological mechanisms, that regulate the pathology of human diseases from various aspects such as inflammation, hypoxia, oxidative stress, mitochondrial function, vascular neogenesis and epithelial cell phenotype transformation. It is crucial to investigate the role of NR4A1 in its ability to regulate chronic kidney disease's pathophysiological mechanisms for subsequent clinical studies. New drugs targeting the expression levels, transcriptional activity, and nuclear export of NR4A1 hold great clinical promise.

In conclusion, NR4A1 has a complex function and regulates multiple pathophysiological mechanisms in human disease, making it an important target for research. In-depth studies may help clarify NR4A1s

function and its influencing factors, providing new strategies for further research and the development of new drugs against human diseases.

Declarations

Conflicts of Interest: The authors declare no conflict of interest.

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References

1. Safe S, Shrestha R, Mohankumar K. Orphan nuclear receptor 4A1 (NR4A1) and novel ligands [J]. Essays Biochem, 2021, 65(6): 877–86.
2. Liu X, Wang Y, Lu H, Li J, Yan X, Xiao M, Hao J, Alekseev A, Khong H, Chen T, Huang R, Wu J, Zhao Q, Wu Q, Xu S, Wang X, Jin W, Yu S, Wang Y, Wei L, Wang A, Zhong B, Ni L, Liu X, Nurieva R, Ye L, Tian Q, Bian X W, Dong C. Genome-wide analysis identifies NR4A1 as a key mediator of T cell dysfunction [J]. Nature, 2019, 567(7749): 525–9.
3. Wilson T E, Fahrner T J, Milbrandt J. The orphan receptors NGFI-B and steroidogenic factor 1 establish monomer binding as a third paradigm of nuclear receptor-DNA interaction [J]. Mol Cell Biol, 1993, 13(9): 5794–804.
4. Peng J, Zhao S, Li Y, Niu G, Chen C, Ye T, Zhao D, Zeng H. DLL4 and Jagged1 are angiogenic targets of orphan nuclear receptor TR3/Nur77 [J]. Microvasc Res, 2019, 124: 67–75.
5. Wingate A D, Campbell D G, Peggie M, Arthur J S. Nur77 is phosphorylated in cells by RSK in response to mitogenic stimulation [J]. Biochem J, 2006, 393(Pt 3): 715–24.
6. Niu G, Lu L, Gan J, Zhang D, Liu J, Huang G. Dual roles of orphan nuclear receptor TR3/Nur77/NGFI-B in mediating cell survival and apoptosis [J]. Int Rev Cell Mol Biol, 2014, 313: 219–58.
7. Wang S C, Muscat G E. Nuclear receptors and epigenetic signaling: novel regulators of glycogen metabolism in skeletal muscle [J]. IUBMB Life, 2013, 65(8): 657–64.
8. Chen L, Fan F, Wu L, Zhao Y. The nuclear receptor 4A family members: mediators in human disease and autophagy [J]. Cell Mol Biol Lett, 2020, 25(1): 48.
9. Mohan H M, Aherne C M, Rogers A C, Baird A W, Winter D C, Murphy E P. Molecular pathways: the role of NR4A orphan nuclear receptors in cancer [J]. Clin Cancer Res, 2012, 18(12): 3223–8.
10. Wu H, Lin Y, Li W, Sun Z, Gao W, Zhang H, Xie L, Jiang F, Qin B, Yan T, Chen L, Zhao Y, Cao X, Wu Y, Lin B, Zhou H, Wong A S, Zhang X K, Zeng J Z. Regulation of Nur77 expression by β-catenin and its mitogenic effect in colon cancer cells [J]. Faseb j, 2011, 25(1): 192–205.
11. McMorrow J P, Murphy E P. Inflammation: a role for NR4A orphan nuclear receptors? [J]. Biochem Soc Trans, 2011, 39(2): 688–93.

12. Lee S O, Li X, Khan S, Safe S. Targeting NR4A1 (TR3) in cancer cells and tumors [J]. Expert Opin Ther Targets, 2011, 15(2): 195–206.
13. Zhu B, Yang J R, Jia Y, Zhang P, Shen L, Li X L, Li J, Wang B. Overexpression of NR4A1 is associated with tumor recurrence and poor survival in non-small-cell lung carcinoma [J]. Oncotarget, 2017, 8(69): 113977–86.
14. Ramaswamy S, Ross K N, Lander E S, Golub T R. A molecular signature of metastasis in primary solid tumors [J]. Nat Genet, 2003, 33(1): 49–54.
15. Karki K, Wright G A, Mohankumar K, Jin U H, Zhang X H, Safe S. A Bis-Indole-Derived NR4A1 Antagonist Induces PD-L1 Degradation and Enhances Antitumor Immunity [J]. Cancer Res, 2020, 80(5): 1011–23.
16. Mohankumar K, Li X, Sridharan S, Karki K, Safe S. Nuclear receptor 4A1 (NR4A1) antagonists induce ROS-dependent inhibition of mTOR signaling in endometrial cancer [J]. Gynecol Oncol, 2019, 154(1): 218–27.
17. Lee H S, Kim S H, Kim B M, Safe S, Lee S O. Broussochalcone A Is a Novel Inhibitor of the Orphan Nuclear Receptor NR4A1 and Induces Apoptosis in Pancreatic Cancer Cells [J]. Molecules, 2021, 26(8).
18. Karki K, Mohankumar K, Schoeller A, Martin G, Shrestha R, Safe S. NR4A1 Ligands as Potent Inhibitors of Breast Cancer Cell and Tumor Growth [J]. Cancers (Basel), 2021, 13(11).
19. Hedrick E, Li X, Cheng Y, Lacey A, Mohankumar K, Zarei M, Safe S. Potent inhibition of breast cancer by bis-indole-derived nuclear receptor 4A1 (NR4A1) antagonists [J]. Breast Cancer Res Treat, 2019, 177(1): 29–40.
20. Yan H, Xiao F, Zou J, Qiu C, Sun W, Gu M, Zhang L. NR4A1-induced increase in the sensitivity of a human gastric cancer line to TNFα-mediated apoptosis is associated with the inhibition of JNK/Parkin-dependent mitophagy [J]. Int J Oncol, 2018, 52(2): 367–78.
21. Alexopoulou A N, Leao M, Caballero O L, Da Silva L, Reid L, Lakhani S R, Simpson A J, Marshall J F, Neville A M, Jat P S. Dissecting the transcriptional networks underlying breast cancer: NR4A1 reduces the migration of normal and breast cancer cell lines [J]. Breast Cancer Res, 2010, 12(4): R51.
22. Wu H, Bi J, Peng Y, Huo L, Yu X, Yang Z, Zhou Y, Qin L, Xu Y, Liao L, Xie Y, Conneely O M, Jonkers J, Xu J. Nuclear receptor NR4A1 is a tumor suppressor down-regulated in triple-negative breast cancer [J]. Oncotarget, 2017, 8(33): 54364–77.
23. Shi W, Dong J, Liang Y, Liu K, Peng Y. NR4A1 silencing protects against renal ischemia-reperfusion injury through activation of the β-catenin signaling pathway in old mice [J]. Exp Mol Pathol, 2019, 111: 104303.
24. Safe S, Jin U H, Morpurgo B, Abudayyeh A, Singh M, Tjalkens R B. Nuclear receptor 4A (NR4A) family - orphans no more [J]. J Steroid Biochem Mol Biol, 2016, 157: 48–60.
25. Westbrook L, Johnson A C, Regner K R, Williams J M, Mattson D L, Kyle P B, Henegar J R, Garrett M R. Genetic susceptibility and loss of Nr4a1 enhances macrophage-mediated renal injury in CKD [J]. J Am Soc Nephrol, 2014, 25(11): 2499–510.

26. Ma G, Chen F, Liu Y, Zheng L, Jiang X, Tian H, Wang X, Song X, Yu Y, Wang D. Nur77 ameliorates age-related renal tubulointerstitial fibrosis by suppressing the TGF-β/Smads signaling pathway [J]. Faseb j, 2022, 36(2): e22124.
27. Chen J, Huang X R, Yang F, Yiu W H, Yu X, Tang S C W, Lan H Y. Single-cell RNA Sequencing Identified Novel Nr4a1(+) Ear2(+) Anti-Inflammatory Macrophage Phenotype under Myeloid-TLR4 Dependent Regulation in Anti-Glomerular Basement Membrane (GBM) Crescentic Glomerulonephritis (cGN) [J]. Adv Sci (Weinh), 2022, 9(18): e2200668.
28. Wang S, Zuo A, Jiang W, Xie J, Lin H, Sun W, Zhao M, Xia J, Shao J, Zhao X, Liang D, Yang A, Sun J, Wang M. JMJD1A/NR4A1 Signaling Regulates the Procession of Renal Tubular Epithelial Interstitial Fibrosis Induced by AGEs in HK-2 [J]. Front Med (Lausanne), 2021, 8: 807694.
29. Sheng J, Li H, Dai Q, Lu C, Xu M, Zhang J, Feng J. NR4A1 Promotes Diabetic Nephropathy by Activating Mff-Mediated Mitochondrial Fission and Suppressing Parkin-Mediated Mitophagy [J]. Cell Physiol Biochem, 2018, 48(4): 1675–93.
30. Koenis D S, Medzikovic L, van Loenen P B, van Weeghel M, Huveneers S, Vos M, Evers-van Gogh I J, Van den Bossche J, Speijer D, Kim Y, Wessels L, Zelcer N, Zwart W, Kalkhoven E, de Vries C J. Nuclear Receptor Nur77 Limits the Macrophage Inflammatory Response through Transcriptional Reprogramming of Mitochondrial Metabolism [J]. Cell Rep, 2018, 24(8): 2127-40.e7.
31. Jiang Y, Zeng Y, Huang X, Qin Y, Luo W, Xiang S, Sooranna S R, Pinhu L. Nur77 attenuates endothelin-1 expression via downregulation of NF-κB and p38 MAPK in A549 cells and in an ARDS rat model [J]. Am J Physiol Lung Cell Mol Physiol, 2016, 311(6): L1023-l35.
32. Hong C Y, Park J H, Ahn R S, Im S Y, Choi H S, Soh J, Mellon S H, Lee K. Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha [J]. Mol Cell Biol, 2004, 24(7): 2593–604.
33. Harant H, Lindley I J. Negative cross-talk between the human orphan nuclear receptor Nur77/NAK-1/TR3 and nuclear factor-kappaB [J]. Nucleic Acids Res, 2004, 32(17): 5280–90.
34. Pei L, Castrillo A, Chen M, Hoffmann A, Tontonoz P. Induction of NR4A orphan nuclear receptor expression in macrophages in response to inflammatory stimuli [J]. J Biol Chem, 2005, 280(32): 29256–62.
35. Hanna R N, Shaked I, Hubbeling H G, Punt J A, Wu R, Herrley E, Zaugg C, Pei H, Geissmann F, Ley K, Hedrick C C. NR4A1 (Nur77) deletion polarizes macrophages toward an inflammatory phenotype and increases atherosclerosis [J]. Circ Res, 2012, 110(3): 416–27.
36. Xiong Y, Ran J, Xu L, Tong Z, Adel Abdo M S, Ma C, Xu K, He Y, Wu Z, Chen Z, Hu P, Jiang L, Bao J, Chen W, Wu L. Reactivation of NR4A1 Restrains Chondrocyte Inflammation and Ameliorates Osteoarthritis in Rats [J]. Front Cell Dev Biol, 2020, 8: 158.
37. Cui P, Wu S, Xu X, Ye H, Hou J, Liu X, Wang H, Fang X. Deficiency of the Transcription Factor NR4A1 Enhances Bacterial Clearance and Prevents Lung Injury During Escherichia Coli Pneumonia [J]. Shock, 2019, 51(6): 787–94.

38. Zhu P, Wang J, Du W, Ren J, Zhang Y, Xie F, Xu G. NR4A1 Promotes LPS-Induced Acute Lung Injury through Inhibition of Opa1-Mediated Mitochondrial Fusion and Activation of PGAM5-Related Necroptosis [J]. Oxid Med Cell Longev, 2022, 2022: 6638244.
39. Peng X, Wang W, Wang W, Qi J. NR4A1 promotes oxidative stresses after myocardial ischemia reperfusion injury in aged mice [J]. Exp Gerontol, 2022, 162: 111742.
40. Zhang Y J, Song J R, Zhao M J. NR4A1 regulates cerebral ischemia-induced brain injury by regulating neuroinflammation through interaction with NF-κB/p65 [J]. Biochem Biophys Res Commun, 2019, 518(1): 59–65.
41. Wu X, Fu S, Liu Y, Luo H, Li F, Wang Y, Gao M, Cheng Y, Xie Z. NDP-MSH binding melanocortin-1 receptor ameliorates neuroinflammation and BBB disruption through CREB/Nr4a1/NF-κB pathway after intracerebral hemorrhage in mice [J]. J Neuroinflammation, 2019, 16(1): 192.
42. Wang W, Wang J, Tang Q, Zhu X, Zhu R, Cui D, Wei C, Liu X, Liu X, Ran S, Pan Y, Yu J. CX3CR1 deficiency aggravates brain white matter injury and affects expression of the CD36/15LO/NR4A1 signal [J]. Biochem Biophys Res Commun, 2021, 549: 47–53.
43. Hamers A A, Argmann C, Moerland P D, Koenis D S, Marinković G, Sokolović M, de Vos A F, de Vries C J, van Tiel C M. Nur77-deficiency in bone marrow-derived macrophages modulates inflammatory responses, extracellular matrix homeostasis, phagocytosis and tolerance [J]. BMC Genomics, 2016, 17: 162.
44. Li J, Zhou H, Fu X, Zhang M, Sun F, Fan H. Dynamic role of macrophage CX3CR1 expression in inflammatory bowel disease [J]. Immunol Lett, 2021, 232: 39–44.
45. Ping F, Zhang C, Wang X, Wang Y, Zhou D, Hu J, Chen Y, Ling J, Zhou J. Cx32 inhibits the autophagic effect of Nur77 in SH-SY5Y cells and rat brain with ischemic stroke [J]. Aging (Albany NY), 2021, 13(18): 22188–207.
46. Dai Y, Zhang W, Zhou X, Shi J. Activation of the Protein Kinase B (Akt) Reduces Nur77-induced Apoptosis During Early Brain Injury after Experimental Subarachnoid Hemorrhage in Rat [J]. Ann Clin Lab Sci, 2015, 45(6): 615–22.
47. Dai Y, Zhang W, Sun Q, Zhang X, Zhou X, Hu Y, Shi J. Nuclear receptor nur77 promotes cerebral cell apoptosis and induces early brain injury after experimental subarachnoid hemorrhage in rats [J]. J Neurosci Res, 2014, 92(9): 1110–21.
48. Dai Y, Sun Q, Zhang X, Hu Y, Zhou M, Shi J. Cyclosporin A ameliorates early brain injury after subarachnoid hemorrhage through inhibition of a Nur77 dependent apoptosis pathway [J]. Brain Res, 2014, 1556: 67–76.
49. Miao L, Yang Y, Liu Y, Lai L, Wang L, Zhan Y, Yin R, Yu M, Li C, Yang X, Ge C. Glycerol kinase interacts with nuclear receptor NR4A1 and regulates glucose metabolism in the liver [J]. Faseb j, 2019, 33(6): 6736–47.
50. Li X, Xu M, Wang F, Ji Y, Davidso N W, Li Z, Tso P. Interaction of ApoA-IV with NR4A1 and NR1D1 Represses G6Pase and PEPCK Transcription: Nuclear Receptor-Mediated Downregulation of Hepatic Gluconeogenesis in Mice and a Human Hepatocyte Cell Line [J]. PLoS One, 2015, 10(11): e0142098.

51. Miao L, Su F, Yang Y, Liu Y, Wang L, Zhan Y, Yin R, Yu M, Li C, Yang X, Ge C. Glycerol kinase enhances hepatic lipid metabolism by repressing nuclear receptor subfamily 4 group A1 in the nucleus [J]. Biochem Cell Biol, 2020, 98(3): 370–7.
52. Qin D D, Yang Y F, Pu Z Q, Liu D, Yu C, Gao P, Chen J C, Zong C, Zhang Y C, Li X, Wang X D, Liu Y T. NR4A1 retards adipocyte differentiation or maturation via enhancing GATA2 and p53 expression [J]. J Cell Mol Med, 2018, 22(10): 4709–20.
53. Xu Y, Tian J, Kang Q, Yuan H, Liu C, Li Z, Liu J, Li M. Knockout of Nur77 Leads to Amino Acid, Lipid, and Glucose Metabolism Disorders in Zebrafish [J]. Front Endocrinol (Lausanne), 2022, 13: 864631.
54. Berriel Diaz M, Lemke U, Herzig S. Discovering orphans' sweet secret: NR4A receptors and hepatic glucose production [J]. Cell Metab, 2006, 4(5): 339–40.
55. Pei L, Waki H, Vaitheesvaran B, Wilpitz D C, Kurland I J, Tontonoz P. NR4A orphan nuclear receptors are transcriptional regulators of hepatic glucose metabolism [J]. Nat Med, 2006, 12(9): 1048–55.
56. Chao L C, Wroblewski K, Zhang Z, Pei L, Vergnes L, Ilkayeva O R, Ding S Y, Reue K, Watt M J, Newgard C B, Pilch P F, Hevener A L, Tontonoz P. Insulin resistance and altered systemic glucose metabolism in mice lacking Nur77 [J]. Diabetes, 2009, 58(12): 2788–96.
57. Pearen M A, Muscat G E. Minireview: Nuclear hormone receptor 4A signaling: implications for metabolic disease [J]. Mol Endocrinol, 2010, 24(10): 1891–903.
58. Zhan Y, Du X, Chen H, Liu J, Zhao B, Huang D, Li G, Xu Q, Zhang M, Weimer B C, Chen D, Cheng Z, Zhang L, Li Q, Li S, Zheng Z, Song S, Huang Y, Ye Z, Su W, Lin S C, Shen Y, Wu Q. Cytosporone B is an agonist for nuclear orphan receptor Nur77 [J]. Nat Chem Biol, 2008, 4(9): 548–56.
59. Bai M, Liu Y, Zhou F, Zhang Y, Zhu Q, Zhang L, Zhang Q, Wang S, Zhu K, Wang X, Zhou L. Berberine inhibits glucose oxidation and insulin secretion in rat islets [J]. Endocr J, 2018, 65(4): 469–77.
60. Zhou F, Bai M, Zhang Y, Zhu Q, Zhang L, Zhang Q, Wang S, Zhu K, Liu Y, Wang X, Zhou L. Berberine-induced activation of AMPK increases hepatic FGF21 expression via NUR77 [J]. Biochem Biophys Res Commun, 2018, 495(2): 1936–41.
61. Zhou H, Wang J, Zhu P, Zhu H, Toan S, Hu S, Ren J, Chen Y. NR4A1 aggravates the cardiac microvascular ischemia reperfusion injury through suppressing FUNDC1-mediated mitophagy and promoting Mff-required mitochondrial fission by CK2α [J]. Basic Res Cardiol, 2018, 113(4): 23.
62. Ji J J, Qian L L, Zhu Y, Jiang Y, Guo J Q, Wu Y, Yang Z W, Yao Y Y, Ma G S. Kallistatin/Serpina3c inhibits cardiac fibrosis after myocardial infarction by regulating glycolysis via Nr4a1 activation [J]. Biochim Biophys Acta Mol Basis Dis, 2022, 1868(9): 166441.
63. Yang H X, Sun J H, Yao T T, Li Y, Xu G R, Zhang C, Liu X C, Zhou W W, Song Q H, Zhang Y, Li A Y. Bellidifolin Ameliorates Isoprenaline-Induced Myocardial Fibrosis by Regulating TGF-β1/Smads and p38 Signaling and Preventing NR4A1 Cytoplasmic Localization [J]. Front Pharmacol, 2021, 12: 644886.
64. Zheng Y, Tao Y, Zhan X, Wu Q. Nuclear receptor 4A1 (NR4A1) silencing protects hepatocyte against hypoxia-reperfusion injury in vitro by activating liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) signaling [J]. Bioengineered, 2022, 13(4): 8349–59.

65. Cao J, Xu T, Zhou C, Wang S, Jiang B, Wu K, Ma L. NR4A1 knockdown confers hepatoprotection against ischaemia-reperfusion injury by suppressing TGFβ1 via inhibition of CYR61/NF-κB in mouse hepatocytes [J]. J Cell Mol Med, 2021, 25(11): 5099–112.
66. Zhou H, Zhu P, Wang J, Toan S, Ren J. DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy [J]. Signal Transduct Target Ther, 2019, 4: 56.
67. Liang H, Xie X, Song X, Huang M, Su T, Chang X, Liang B, Huang D. Orphan nuclear receptor NR4A1 suppresses hyperhomocysteinemia-induced hepatic steatosis in vitro and in vivo [J]. FEBS Lett, 2019, 593(10): 1061–71.
68. Huang Q, Xu J, Ge Y, Shi Y, Wang F, Zhu M. NR4A1 inhibits the epithelial-mesenchymal transition of hepatic stellate cells: Involvement of TGF-β-Smad2/3/4-ZEB signaling [J]. Open Life Sci, 2022, 17(1): 447–54.
69. Deng J W, Yang Q, Cai X P, Zhou J M, E W G, An Y D, Zheng Q X, Hong M, Ren Y L, Guan J, Wang G, Lai S J, Chen Z. Early use of dexamethasone increases Nr4a1 in Kupffer cells ameliorating acute liver failure in mice in a glucocorticoid receptor-dependent manner [J]. J Zhejiang Univ Sci B, 2020, 21(9): 727–39.
70. Dong W, Yang H, Cheng M, Zhang X, Yin J, Zeng Z, Huang G. Dexmedetomidine alleviates pulmonary ischemia-reperfusion injury through modulating the miR-21-5p/Nr4a1 signaling pathway [J]. Acta Biochim Pol, 2020, 67(4): 521–9.
71. Zeng X, Yue Z, Gao Y, Jiang G, Zeng F, Shao Y, Huang J, Yin M, Li Y. NR4A1 is Involved in Fibrogenesis in Ovarian Endometriosis [J]. Cell Physiol Biochem, 2018, 46(3): 1078–90.
72. Mohankumar K, Li X, Sung N, Cho Y J, Han S J, Safe S. Bis-Indole-Derived Nuclear Receptor 4A1 (NR4A1, Nur77) Ligands as Inhibitors of Endometriosis [J]. Endocrinology, 2020, 161(4).
73. Zhang Z, Yu J. NR4A1 Promotes Cerebral Ischemia Reperfusion Injury by Repressing Mfn2-Mediated Mitophagy and Inactivating the MAPK-ERK-CREB Signaling Pathway [J]. Neurochem Res, 2018, 43(10): 1963–77.
74. Hiwatashi N, Mukudai S, Bing R, Branski R C. The effects of cytosporone-B, a novel antifibrotic agent, on vocal fold fibroblasts [J]. Laryngoscope, 2018, 128(12): E425-e8.
75. Chen J, Jia J, Ma L, Li B, Qin Q, Qian J, Ge J. Nur77 deficiency exacerbates cardiac fibrosis after myocardial infarction by promoting endothelial-to-mesenchymal transition [J]. J Cell Physiol, 2021, 236(1): 495–506.
76. Pulakazhi Venu V K, Alston L, Iftinca M, Tsai Y C, Stephens M, Warriyar K V V, Rehal S, Hudson G, Szczepanski H, von der Weid P Y, Altier C, Hirota S A. Nr4A1 modulates inflammation-associated intestinal fibrosis and dampens fibrogenic signaling in myofibroblasts [J]. Am J Physiol Gastrointest Liver Physiol, 2021, 321(3): G280-g97.
77. Wette S G, Lamb G D, Murphy R M. Nuclei isolation methods fail to accurately assess the subcellular localization and behaviour of proteins in skeletal muscle [J]. Acta Physiol (Oxf), 2021, 233(3): e13730.

78. Woronicz J D, Lina A, Calnan B J, Szychowski S, Cheng L, Winoto A. Regulation of the Nur77 orphan steroid receptor in activation-induced apoptosis [J]. Mol Cell Biol, 1995, 15(11): 6364–76.
79. Lin B, Kolluri S K, Lin F, Liu W, Han Y H, Cao X, Dawson M I, Reed J C, Zhang X K. Conversion of Bcl-2 from protector to killer by interaction with nuclear orphan receptor Nur77/TR3 [J]. Cell, 2004, 116(4): 527–40.
80. Stasik I, Rapak A, Kalas W, Ziolo E, Strzadala L. Ionomycin-induced apoptosis of thymocytes is independent of Nur77 NBRE or NurRE binding, but is accompanied by Nur77 mitochondrial targeting [J]. Biochim Biophys Acta, 2007, 1773(9): 1483–90.
81. Balasubramanian S, Jansen M, Valerius M T, Humphreys B D, Strom T B. Orphan nuclear receptor Nur77 promotes acute kidney injury and renal epithelial apoptosis [J]. J Am Soc Nephrol, 2012, 23(4): 674–86.
82. Chen H Z, Zhao B X, Zhao W X, Li L, Zhang B, Wu Q. Akt phosphorylates the TR3 orphan receptor and blocks its targeting to the mitochondria [J]. Carcinogenesis, 2008, 29(11): 2078–88.
83. Zhang L, Xie F, Zhang J, Dijke P T, Zhou F. SUMO-triggered ubiquitination of NR4A1 controls macrophage cell death [J]. Cell Death Differ, 2017, 24(9): 1530–9.
84. Kang S A, Na H, Kang H J, Kim S H, Lee M H, Lee M O. Regulation of Nur77 protein turnover through acetylation and deacetylation induced by p300 and HDAC1 [J]. Biochem Pharmacol, 2010, 80(6): 867–73.
85. Xiong J, Kuang X, Lu T, Liu X, Cheng B, Wang W, Wei D, Li X, Zhang Z, Fang Q, Wu D, Wang J. Fenretinide-induced Apoptosis of Acute Myeloid Leukemia Cells via NR4A1 Translocation into Mitochondria and Bcl-2 Transformation [J]. J Cancer, 2019, 10(27): 6767–78.
86. Liu N, Wu Z, Chen A, Chai D, Li L, Zhang L, Zheng J. ISG12a and its interaction partner NR4A1 are involved in TRAIL-induced apoptosis in hepatoma cells [J]. J Cell Mol Med, 2019, 23(5): 3520–9.
87. Pekarsky Y, Hallas C, Palamarchuk A, Koval A, Bullrich F, Hirata Y, Bichi R, Letofsky J, Croce C M. Akt phosphorylates and regulates the orphan nuclear receptor Nur77 [J]. Proc Natl Acad Sci U S A, 2001, 98(7): 3690–4.
88. Castro-Obregón S, Rao R V, del Rio G, Chen S F, Poksay K S, Rabizadeh S, Vesce S, Zhang X K, Swanson R A, Bredesen D E. Alternative, nonapoptotic programmed cell death: mediation by arrestin 2, ERK2, and Nur77 [J]. J Biol Chem, 2004, 279(17): 17543–53.
89. Huang B, Pei H Z, Chang H W, Baek S H. The E3 ubiquitin ligase Trim13 regulates Nur77 stability via casein kinase 2α [J]. Sci Rep, 2018, 8(1): 13895.
90. Zárraga-Granados G, Muciño-Hernández G, Sánchez-Carbente M R, Villamizar-Gálvez W, Peñas-Rincón A, Arredondo C, Andrés M E, Wood C, Covarrubias L, Castro-Obregón S. The nuclear receptor NR4A1 is regulated by SUMO modification to induce autophagic cell death [J]. PLoS One, 2020, 15(3): e0222072.
91. Dodat F, Cotnoir-White D, Dianati E, Vallet A, Mader S, Lévesque D. Complex regulation of orphan nuclear receptor Nur77 (Nr4a1) transcriptional activity by SUMO2 and PIASγ [J]. Biochim Biophys Acta Mol Cell Res, 2021, 1868(2): 118908.

92. Wu L, Chen L. Characteristics of Nur77 and its ligands as potential anticancer compounds (Review) [J]. Mol Med Rep, 2018, 18(6): 4793–801.
93. Drouin J, Maira M, Philips A. Novel mechanism of action for Nur77 and antagonism by glucocorticoids: a convergent mechanism for CRH activation and glucocorticoid repression of POMC gene transcription [J]. J Steroid Biochem Mol Biol, 1998, 65(1–6): 59–63.

Figures

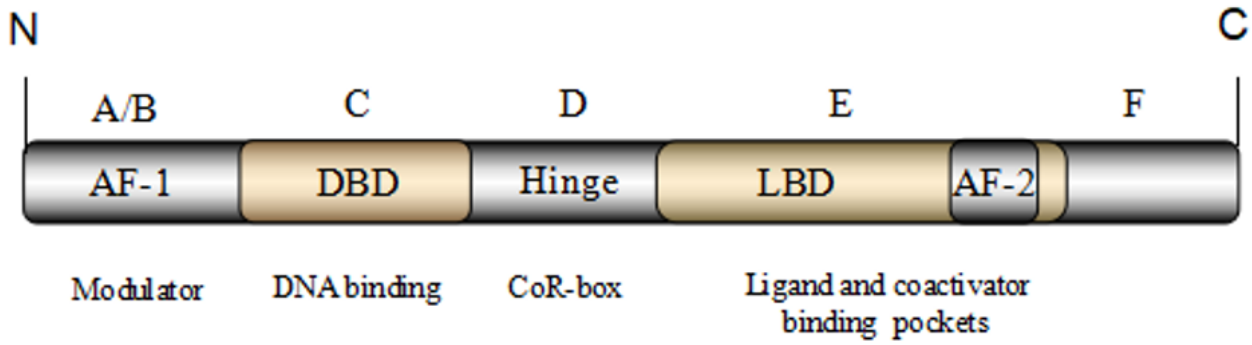

Figure 1

Structural organization of NR4A1