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The Role of Nur77 in Glucose Metabolism Regulation: Implications for ARDS Pathophysiology

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Abstract: Nur77 (Neuron-derived clone 77) is one of the members of the orphan nuclear receptor family, and its expression and activation are rapidly triggered under a variety of physiological and pathological stimuli and have complex biological activities. Studies indicate that Nur77 regulates glucose metabolism in a tissue-dependent manner, and this mechanism may play a role in the occurrence and progression of acute respiratory distress syndrome (ARDS). Understanding how Nur77 regulates glucose metabolism and how it influences the onset and progression of ARDS is expected to provide an opportunity to alter Nur77 to regulate glucose metabolism and explore novel targets for ARDS medication therapy. In this review, we will discuss the molecular biological functions and expression of Nur77, the regulation of glucose metabolism by Nur77, and its putative role in ARDS.

Keywords: Nur77, NR4A1, Glucose metabolism, Gene expression, acute respiratory distress syndrome

1 Introduction

The orphan nuclear receptor NUR77 is a significant member of the nuclear receptor superfamily, extensively present in tissues including lung, liver, skeletal muscle, adipose tissue, heart, brain, kidney, and thymus. It plays a crucial role in energy conversion, energy metabolism, and various pathophysiological processes, exhibiting complex biological functions. NUR77 modulates glucose metabolism, lipid metabolism, and energy equilibrium. Increasing research indicates that, beside its critical function in metabolic illnesses, Nur77's regulation of glucose metabolism may significantly influence the onset and advancement of acute respiratory distress syndrome (ARDS). This study aims to examine the molecular biological function and expression characteristics of Nur77, as well as to investigate its regulatory influence on glucose metabolism and the associated mechanisms and research advancements in ARDS.

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1.1 Nur77

The nuclear receptor superfamily comprises transcription factor families activated by ligands, including steroid and non-steroid hormone receptors, which have roles in growth, development, metabolism, cell differentiation, and several physiological processes in the body. The orphan nuclear receptor subfamily comprises three members: Nur77 (NR4A1), Nurr1 (NR4A2), and NOR1 (NR4A3)(Zhao & Bruemmer, 2010). Nur77, a member of the nuclear receptor superfamily, is an early response gene that modulates the expression of various target genes. It shares a common nuclear receptor architecture with two other members, consisting of an N-terminal binding domain, a DNA binding domain (DBD), and a ligand binding domain (LBD) within its genomic structure and DNA. The conserved region of the binding zone has a uniform structure and a significant degree of homology (Saucedo-Cardenas et al., 1997).

Nur77 is situated on chromosome 12, and its protein consists of 598 amino acids, featuring atypical A/B, C, D, and E ligand-binding domains **(Figure 1)**, with no identified unique endogenous ligand (Maxwell & Muscat, 2006). However, an increasing amount of research has demonstrated that numerous small compounds and lipophilic ligands can engage with Nur77 by targeting the ligand-binding domain and altering receptor activity through the induction of conformational changes at the Nur77 ligand-binding site (Banno et al., 2019a). The NR4A receptor is an early immediate response gene that is swiftly activated and expressed in diverse metabolic and energy-dependent tissues following various physiological and pathological stimuli, including growth factors, inflammatory agents, cytokines, hormones, and cellular stress (Pearen & Muscat, 2010). Recent research indicate that Nur77 plays a role in the pathophysiology of lung disorders including as asthma, acute lung damage, and pulmonary fibrosis, and its activation holds significant therapeutic potential for these conditions.

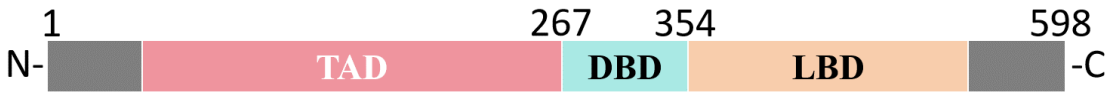

Fig. 1 Schematic diagram of Nur77 structure

2 Regulation of glucose metabolism by Nur77

2.1 Nur77regulates hepatic glucose metabolism

2.1.1 Nur77 promotes hepatic gluconeogenesis via cAMP

Nur77 functions as a transcriptional regulator of hepatic gluconeogenesis and serves as a downstream mediator of cyclic adenosine monophosphate (cAMP) in the regulation of glucose metabolism. Physiological stimuli, including hunger, fasting, and glucagon, can activate the cAMP pathway to enhance the expression of Nur77 in the liver, which is elevated in a mouse model of pathological gluconeogenesis (Oita et al., 2009). NR4A1 is upregulated by fasting and glucagon in vivo, and its expression in the murine liver enhances the expression of many

genes associated with glucose production and transport, promotes hepatic gluconeogenesis, and elevates blood glucose levels (Kovalovsky et al., 2002; Maxwell et al., 2005b). Pei et al.,(2006) found that the administration of 8-Br-cAMP, a cAMP analog that activates gluconeogenesis, rapidly promotes NR4A1 expression in mouse hepatic primary cells and directly regulates target gene expression to influence glucose metabolism.

2.1.2 *Nur77 regulates hepatic glucose metabolism through the LKB1-AMPK axis*

Adenosine monophosphate-activated protein kinase (AMPK) is a conserved metabolic sensor that is crucial for the regulation of cellular energy metabolism. Like FGF21, berberine possesses antihyperglycemic and antidyslipidemic characteristics. Studies indicate:(F. Zhou et al., 2018) Berberine can markedly enhance the expression of FGF21 in mouse hepatocytes via Nur77 in a dose- and time-dependent manner by activating the AMPK signaling pathway. This effect is negated by AMPK inhibitors, suggesting that FGF21 may be a target gene of Nur77, thereby aiding in the amelioration of metabolic disorders. The study found that mice with NR4A1 knockout had increased phosphorylation of the AMPKα subunit in the liver, which reduced blood sugar levels; Conversely, NR4A1 overexpression inhibits hepatic AMPKα phosphorylation and elevates blood glucose levels(Zhan et al., 2012).

Furthermore, the connection between NR4A1 and LKB1 was discovered to activate the AMPK/SIRT1 signaling pathway while inhibiting the NF-κB signaling pathway, therefore preserving glucose homeostasis and mitigating the symptoms in T2DM rats (Ming et al., 2020). Consequently, while NR4A1 does not directly engage with AMPKα, it interacts with TMPA via the LKB1-AMPK axis to release LKB1 sequestered in the nucleus. LKB1 is then translocated to the cytoplasm to activate its kinase activity, while NR4A1 inhibits AMPK phosphorylation by binding to LKB1, thereby facilitating gluconeogenesis to enhance blood glucose levels (Kurakula et al., 2014; Zhan et al., 2012).

2.1.3 *Nur77 interacts with other factors and is involved in hepatic glucose metabolism*

Hwang et al., (2012) found that B-cell translocation gene 2 (BTG2) is a co-activator of CREB, which plays an important role in regulating hepatic gluconeogenesis, and glucagon-CREB signaling induces an increase in BTG2 and increases hepatocyte gluconeogenesis. Kim et al.,(2014) found that the BTG2-CREB axis stimulates NR4A1 gene expression in fasting or diabetic states, and BTG2 and NR4A1 upregulate G6pc gene expression through physical interaction to increase hepatic gluconeogenesis. Gyk inhibits NR4A1 transcriptional activity by weakening the binding of NR4A1 to the target gene promoter NBRE element and inhibits NR4A1 transcriptional activity, and Gyk inhibits hepatic gluconeogenesis through protein-protein interaction with NR4A1. This effect is not affected by the kinase activity of Gyk in the cytoplasm(Miao et al., 2019).

2.2 *Nur77 regulates glucose metabolism in muscle tissues*

Skeletal muscle constitutes approximately 40% of body weight yet is responsible for 70% to 80% of glucose uptake following postprandial insulin stimulation. In skeletal muscle, β-

adrenergic signaling, insulin, and endurance exercise stimulate Nur77 expression (Mahoney et al., 2005; Maxwell et al., 2005a; Pearen et al., 2006). Impairments in glucose uptake and muscle glycogen synthesis subsequent to insulin stimulation have been recognized as significant initial occurrences in the development of insulin resistance (Petersen & Shulman, 2006). Nur77 is the predominant member of the Nr4a family expressed in skeletal muscle and regulates gene expression related to glucose use in this tissue.

2.2.1 *Nur77 regulates glycolysis in skeletal muscle*

Nur77 directly influences the glucose utilization pathway in skeletal muscle, and β-adrenergic stimulation can promote the expression of two NR4A family members, specifically Nur77 and NOR1 (Praslicka et al., 2017). Muscle cells exhibited the expression of NR4A1 during exercise via the epinephrine and AMP-PKA pathways(Kanzleiter et al., 2010) . The overexpression of NR4A1 did not influence lipid oxidation in rat (Rattus norvegicus) muscle cells, but enhanced glucose oxidation and glycogen production (Kanzleiter et al., 2009). The response of NR4A1 to insulin is augmented by aerobic exercise training, and insulin administration elevates the expression of NR4A1 in human primary skeletal muscle cells (Mey et al., 2019a). The muscle-specific overexpression of NR4A1 enhances mitochondrial DNA content, diminishes mitochondrial fission, and elevates oxidative metabolism in muscle (Chao et al., 2012), indicating that NR4A1 may modify metabolic pathways by shifting metabolic patterns towards oxidative metabolism in the context of sustained chronic stress, thus enhancing energy efficiency.

2.2.2 *Nur77 regulates glycolysis in skeletal muscle*

Expression of NR4A1 increases the expression of insulin-like growth factor 1 (IGF1), mature myogenic factor, and many developing myosin genes (Myh3, Myh8, and Myl4). At the same time, NR4A1 downregulates the expression of two E3 ligases, Trim63 (MuRF1) and Fbxo32 (atrogin1 or MAFbx), which encode amyotrophy(Tontonoz et al., 2015). Glucose oxidation and glycogen synthesis were significantly increased following overexpression of NR4A1 in L6 myotubes and rat skeletal muscle(Mohankumar et al., 2018).

In accordance with animal studies, the expression of NR4A1 and its target glycogen protein in the muscles of obese men diminished, closely correlating with body fat content and insulin sensitivity; however, the variation in Glut4 expression did not achieve statistical significance (Mohankumar et al., 2018). Mey et al., (2019b) conducted hyperinsulin-euglycemic clamp studies and skeletal muscle biopsies in healthy, obese, and type 2 diabetic individuals, discovering that insulin responsiveness of Nur77 and NOR1 was diminished in obese and type 2 diabetic patients, thereby confirming that Nur77 is a crucial regulator of glucose metabolism in skeletal muscle in vivo. Therefore, NR4A1 promotes the decomposition and utilization of glucose in muscle and reduces glucose accumulation by promoting the expression of glucose transport-related genes or glycolysis genes in muscle.

2.3 *Nur77 regulates glucose metabolism in pancreatic islet β cells*

Nur77 functions as a pressure sensor in pancreatic β cells and inhibits glucose-stimulated insulin release. NR4A1 has been demonstrated to modulate β cell proliferation (Ardid-Ruiz et al., 2018) and insulin secretion (Reynolds et al., 2016). Nur77 diminishes the density of β cells in pancreatic islets, and its overexpression promotes β cell proliferation. Furthermore, β cell mitochondrial respiration is contingent upon Nur77 and NR4A3; in their absence, mitochondrial respiratory function is markedly impaired, thereby inhibiting glucose-stimulated insulin secretion (Reynolds et al., 2016). Recent studies (Herring et al., 2024) indicate that Nur77 is essential for the effective secretion of insulin through glucose uptake and metabolic processes. Evidence suggests that Nr4a1 is pivotal in the β cell's response to feeding states, fuel metabolism, and β cell functionality, with its expression modulated by glucose levels through the cAMP/PKA/CREB pathway. Furthermore, Nr4a1 regulates the expression of Glut2, Ndufa4, Ins1, In2, Sdhb, and Idh3g in response to glucose treatment.

Sasaki et al., (2023) indicated that Sox4 modulates β cell quality through the regulation of the type 2 diabetes mellitus (T2D) susceptibility gene GRK5. β cell-specific Grk5 knockout mice demonstrate compromised glucose tolerance and diminished β cell quality, accompanied by the upregulation of the cell cycle repressor gene Cdkn1a, potentially influenced by pathways involving HDAC5 phosphorylation and subsequent transcription of immediate early genes (IEGs) such as Nr4a1, Fosb, Junb, Arc, Egr1, and Srf. A study on NUR77-deficient zebrafish (Xu et al., 2022) revealed that numerous genes associated with amino acid, lipid, and carbohydrate metabolism exhibited alterations exceeding twofold. The increased glucose levels were attributed not to variations in glucose uptake, but rather to disorders in glycolysis and gluconeogenesis, alongside compromised β cell functionality, which included down-regulation of INSB expression, reduced β cell mass, and inhibition of insulin secretion. Furthermore, targeted expression of NUR77 in β cells effectively rescued the overall defective β cells in larval zebrafish lacking NUR77. Nur77 and NR4A3 can modulate the expression of glycolytic genes in pancreatic β cells, thereby influencing glucose utilization and insulin secretion (Yu et al., 2015).

2.4 *Nur77 Regulates Glucose Metabolism in the Immune System*

The orphan nuclear receptor subfamily modulates diverse immune cell types and is particularly significant in T cells. Nur77 is an early response gene activated in T cells shortly after stimulation, and it is associated with increased basal and maximal respiratory capacity, as well as higher glycolytic ability in T cells. Nur77 facilitates the activation of glycolytic and TCA enzymes, thereby enhancing cellular energy production, whereas the suppression of glycolysis genes elevates Tre cell populations. Additionally, the activation of the Akt/mTOR pathway to enhance glucose metabolism may result in a reduction of Tre differentiation (Fassett et al., 2012).

The research indicated that the influence of Nur77 on mitochondrial respiration and aerobic glycolysis was detectable as early as 24 hours post α CD3 stimulation, suggesting that Nur77,

as a transcription factor, may primarily regulate T cell metabolism through interactions with other transcription factors (Liebmann et al., 2018). NR4A1 facilitates glycolysis via essential enzymes, including glucose transporters (GLUTs), in cancer and contributes to tumor immunity through metabolic reprogramming (Deng et al., 2022).

3 Nur77 and Acute Respiratory Distress Syndrome (ARDS)

ARDS, a severe respiratory condition, is associated with elevated mortality and morbidity rates (*Acute Respiratory Distress Syndrome in Adults: Diagnosis, Outcomes, Long-Term Sequelae, and Management - the Lancet*, n.d.; Lopes-Pacheco et al., 2020). The pathogenesis of ARDS involves extensive alveolar injury due to neutrophil-mediated epithelium necrosis, succeeded by interstitial hyperemia and subsequent endothelial injury(*Acute Respiratory Distress Syndrome in Adults: Diagnosis, Outcomes, Long-Term Sequelae, and Management - the Lancet*, n.d.). The pathogenesis of ARDS is intricate, encompassing the activation and deregulation of various interrelated processes associated with lung and systemic damage, inflammation, and coagulation (Bos & Ware, 2022).

The patient exhibits a hypermetabolic condition attributable to stress hormones, inflammatory mediators, and cytokines, resulting in significant metabolic dysregulation. Notably, glucose metabolism is disrupted, characterized by heightened gluconeogenesis, diminished direct oxidative energy provision from glucose, increased anaerobic digestion, and impaired glucose utilization due to insulin resistance. Given that Nur77 participates in pathophysiological processes such as energy metabolism and inflammatory response in vivo, it is essential to investigate the role and mechanism of Nur77 in the pathophysiology of ARDS, potentially offering a foundation for a deeper understanding of ARDS pathogenesis and novel therapeutic interventions.

Studies in the rat model of ARDS demonstrated that Nur77 exerted a protective effect via suppressing NF-κB and p38MAPK to diminish the expression of ET-1 in A549 cells of a rat model of LPS-induced acute respiratory distress syndrome(Coulthard et al., 2009; Jiang et al., 2016a). Ding et al., (2021a) found that the orphan nuclear receptor Nur77 is a crucial element in controlling inflammasome activation in vascular endothelial cells (ECs). Ectopic overexpression of Nur77 effectively suppressed LPS-induced inflammasome activation, probably by transcriptional suppression of caspase-1 expression. In the lung endothelial cells of Nur77 mutant mice, LPS-induced inflammasome activation was dramatically amplified. This inhibitory action is connected with Nur77 downregulating IRF1 (IFN regulator 1) expression and lowering its binding to the caspase-1 promoter. In LPS-induced mice models of ALI, Nur77 knockdown resulted in increased caspase-1 activity in the lungs, increased IL-1β levels, and exacerbated ALI illness, and these effects could be dramatically mitigated by caspase-1 inhibitors. This result reveals that Nur77 plays a significant function in suppressing inflammasome activation in ECs and may represent a potential target for the treatment of inflammation-related disorders such as ALI and atherosclerosis.

Wang et al., (2024) discovered that airway epithelial cells infected with SARS-CoV-2 exhibited diminished responses to interferons and immediate early genes (such as FOS, FOSB, and NR4A1) that are typically activated by other coronaviruses. In contrast to the low-pathogenic coronaviruses HCoV-229E and HCoV-OC43, SARS-CoV-2 demonstrates marked suppression of critical host response genes. Further experiments indicated that modulation of the NR4A1 signaling pathway could significantly decrease the RNA copy numbers of SARS-CoV-2 and MERS-CoV, implying its vital role in viral replication. Additionally, the pivotal function of interferon-related pathways in differentiating between high and low pathogenic coronaviruses underlines a crucial foundation for therapeutic strategies.

Moreover, some studies have demonstrated that Nur77 modulates the pathogenic progression of ARDS/ALI via NF-κB, JNK, p38 MAPK, and other signaling pathways, or by other mechanisms that directly or indirectly influence Nur77. These studies demonstrate that the Nur77/NR4A1 receptor serves as a fundamental regulator of inflammatory diseases and represents a significant target for the treatment of various related conditions, facilitating drug development, elucidating the pathological mechanisms of inflammation, and advancing precision medicine. Future study can further the investigation of its involvement in disorders like as ARDS and sepsis, offering novel insights for both basic and clinical research **(Table 1)**.

Table 1 Research on Nur77 and ARDS/ALI

Citations	Signaling pathways /Mechanisms	Key findings
2024(Wang et al., 2024)	NR4A1 Early gene response	NR4A1 inhibition was found to be a unique response in SARS-CoV-2-infected airway epithelial cells, distinct from other coronaviruses.
2023(H. Zhou et al., 2023)	JNK/c-Jun	Glycyrrhizin was found to significantly alleviate LPS-induced ALI by inhibiting the phosphorylation of JNK, Nur77 and c-Jun.
2023(Fang, Li, et al., 2023)	NF-κB	The DHA-EA derivative J9 was found to alleviate ALI inflammation by inhibiting NF-κB activation in a Nur77-dependent manner.
2023(Fang, Cao, et al., 2023)	Nur77 PEs/TGs hydrolyze	DPA-EA and DHA-EA mixtures modulate lipid profiles through Nur77 activation.
2022(Li et al., 2022)	NR4A1 activation	Astragalus significantly alleviate LPS-induced ALI through activation of NR4A1.
2022(Xie et al., 2022)	JNK/Nur77/c-Jun	Rhodopsin reduced LPS-induced ALI by JNK/Nur77/c-Jun pathway.
2022(P. Zhu et al., 2022)	PGAM5/Opa1 mitochondrial fusion	NR4A1 exacerbating ALI by mitochondrial dysfunction and necrotic apoptosis.

continued

2022(Ao et al., 2022)	Nur77-mitochondria/ NF-κB	Compound B7 showed significant anti-inflammatory activity by modulating Nur77 and inhibiting NF-κB activation.
2022(Sunil et al., 2022)	PI3K/Akt2/ERK	Nitrogen mustard exposure effectson type II alveolar cells, cause reduced Nur77 expression and impaired energy metabolism and surfactant production.
2021(Sommer et al., 2021)	Nur77-inflammasome axis	Nur77-inflammasome axis regulating inflammatory vesicle activity in ALI.
2021(Ding et al., 2021b)	Caspase-1/IRF1	Nur77 inhibits caspase-1 expression through modulation of IRF1, thereby suppressing inflammasome activity. It's a new mechanism.
2020(Fang et al., 2020)	NF-κB	PUFA-AA derivatives were synthesized, of which compound 4k showed potent anti-inflammatory effects by targeting Nur77 and inhibiting NF-κB activation.
2019(Banno et al., 2019b)	NF-κB	Nur77 inhibits NF-κB signaling to attenuate pro-inflammatory responses.
2019(N. Zhu et al., 2019)	β- catenin Degradation inhibition	Nur77 maintaining endothelial barrier integrity during LPS-induced lung injury in mice.
2016(Jiang et al., 2016b)	NF-κB/p38 MAPK	Nur77 reduces endothelin-1 expression and attenuates the associated injury through inhibition of NF-κB and p38 MAPK pathways in an ARDS model.
2006(Dolinay et al., 2006)	Nur77 Mediated signaling pathways	Nur77 was identified as a candidate gene for ventilator-associated lung injury, and its expression was found to correlate with inflammatory and apoptotic gene regulation.

4 Conclusion

Nur77, a significant member of the nuclear orphan receptor family, is controlled by many physiological and pathological events, and is crucial for glucose metabolism across various tissues and cells. Currently, there remains an absence of effective pharmacological interventions for ARDS, necessitating the urgent exploration of novel therapeutic targets. Recent research indicate that Nur77 can modulate the pathophysiological processes of ARDS by blocking mechanisms such as the NF-κB and p38 MAPK pathways, establishing it as a possible therapeutic target. The etiology of ARDS is intricately linked to inflammatory responses and metabolic problems, both of which are substantially modulated by NUR77. Consequently, a comprehensive examination of the mechanism of action and targets of NR4A1, together with the development of targeted pharmaceuticals founded on its regulatory attributes

to reestablish homeostasis, is anticipated to yield novel insights for the diagnosis and treatment of inflammatory and metabolic disorders.

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