Journal of Biosciences and Medicines, 2025, 13(1), 163-172
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Progress in the Regulation of Lipid Metabolism by the Orphan Nuclear Receptor Nur77

Hongjie He[1], Xiaohong Cen[1], Yejin Liang[1], Jinmei Zhong[1], Junhua Deng[2*], Yujie Jiang[2*]

[1]Graduate School, Youjiang Medical University for Nationalities, Baise, China
[2]Department of Pulmonary and Critical Care Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
Email: 1045532382@qq.com, 1402774324@qq.com, 952525378@qq.com, 1347360651@qq.com, *bsdengjunhua@163.com, *jiangyujie@ymcn.edu.cn

How to cite this paper: He, H.J., Cen, X.H., Liang, Y.J., Zhong, J.M., Deng, J.H. and Jiang, Y.J. (2025) Progress in the Regulation of Lipid Metabolism by the Orphan Nuclear Receptor Nur77. *Journal of Biosciences and Medicines*, **13**, 163-172.
https://doi.org/10.4236/jbm.2025.131013

Received: December 7, 2024
Accepted: January 13, 2025
Published: January 16, 2025

Abstract

Neuron-derived clone 77 (Nur77) is a member of the NR4A subfamily that plays critical roles in apoptosis, survival, proliferation, autophagy, angiogenesis, inflammatory responses, DNA repair, glycolipid metabolism and energy consumption. The deregulation of Nur77 signalling often relates to various serious diseases, including cancer and non-cancer diseases. A systematic review is necessary for the better understanding of Nur77 in clinical treatment. In this article, we comprehensively conclude the lipid regulation function and expression of Nur77, and its role in COPD. Finally, we prospect that development of drugs and clinical biochemical investigations targeting of Nur77 has considerable potential within healthcare.

Keywords

Orphan Nuclear Receptor, Nur77, NR4A1, Lipid Metabolism, COPD

1. Introduction

Nur77 is a kind of orphan nuclear receptor and belongs to the NR4A subfamily. Researchers have discovered that stimulation to tissues like lung, liver, muscle, testicle, ovary, thymus, prostate, adrenal gland, thyroid, or pituitary gland may rise Nur77's expression in each tissue. Also, Nur77 was found to participate in regulating glycolipid metabolism and energy metabolism. Abnormal regulation of Nur77 is closely associated with different diseases, suggesting its potential for drug and administration methods targeting Nur77, especially in chronic obstructive pulmonary disease (COPD) fields. Currently, there is a relative scarcity of research on the biological functions of Nur77 and its regulation of lipid metabolism in

various tissues. This article aims to provide a comprehensive review of Nur77 expression in the liver, skeletal muscle, adipose tissue, and tumor cells, as well as its mechanisms of lipid metabolism regulation, and to explore its role in COPD. The goal is to offer insights that may inform further research into respiratory diseases.

2. Biochemistry Foundation and Biological Function of Nur77

The NR4A subfamily is an isolated nuclear receptor, and its specific endogenous ligand has not yet been found. This family is observed overexpressed while induced by various signals inside and outside cells, so it is considered an immediate early gene. It consists of three highly homologous members: NR4A1 (Nur77), NR4A2 (Nurr1) and NR4A3 (NOR-1). Nur77 belongs to one of them and has typical characteristics of a nuclear receptor. It consists of a central double zinc DNA binding domain (DBD), an N-terminal trans-activation domain (TAD), and a C-terminal ligand binding domain (LBD). Nur77 is located on human chromosome 12 and consists of 598 amino acids. Its ligand binding pocket is filled with hydrophobic amino acid side chains, which will hinder the binding of small molecule ligands [1]. As an orphan nuclear receptor, Nur77 can serve as a transcription factor that can positively or negatively regulate the transcription and expression of downstream target genes through its DBD in the form of monomers, homodimers or heterodimers; it can also serve as a regulatory factor that regulates the biological functions of other proteins through protein-to-protein (PTP) interactions. As an immediate early gene, Nur77 can be overexpressed as a reaction to stimulations in various tissues and organs including lung, liver, muscle, testicle, ovary, thymus, prostate, adrenal gland, thyroid and pituitary gland. The stimulation can be hormones, TGF-β, inflammatory stimuli, cytokines, fatty acids or pathological factors [2]. Studies have also shown that Nur77 is related to the occurrence and development of multiple lung diseases, and has shown potential therapeutic effects in the treatment of asthma, acute lung injury and pulmonary fibrosis [3]-[5].

Scientific research has recently revealed that the orphan nuclear receptor Nur77 plays multiple roles in organisms, especially in fields involving basic life activities, such as glycan decomposition pathways and fat storage and consumption process. Of all the organs in human body, Nur77 is found to be primely distributed in liver, skeletal muscle and adipose tissue, which are related with glycolipid metabolism and energy metabolism, indicating that Nur77 play a crucial role in regulating the dynamic balance of lipid metabolism.

3. Pathogenic Mechanisms of Nur77's Misregulation

3.1. The Relationship between Liver and Nur77's Misregulation

The liver is one of the most crucial organs in metabolism process, which involves almost all metabolic activities in the body, including the process of lipid

metabolism. Nur77 is essential for hepatic lipid metabolism, and hepatic steatosis can be observed in Nur77$^{-/-}$ knockout mice [6]. It is also worth noting that after knockout of Nur77 in mouse model, the expression of lipid synthesis-related genes such as SREBP1c and FAS will be up-regulated in the liver [6]. Follow-up studies found that Nur77 affected the content of triglycerides in the liver of mice by down-regulating the expression of SREBP1c [7]. By injecting recombinant adenovirus to overexpress Nur77 in the livers of mice, changes in plasma lipid components and hepatic triglyceride levels were observed. The results showed a 12% decrease in plasma high-density lipoprotein (HDL) cholesterol compared to the control group, while low-density lipoprotein (LDL) cholesterol and low-density triglycerides increased by 98% and 67%, respectively, and hepatic triglyceride levels were found to be reduced concurrently. Upon activation of Nur77, heatmap-illustrated data from individual mouse models revealed a pattern of decreased mRNA expression levels for numerous genes implicated in hepatic lipid metabolism, with a particularly significant reduction observed in the expression of SREBP1 under the influence of Nur77. Concurrently the expression levels of SREBP1's direct target genes, Ldlr and Scd1, as well as three downstream genes associated with lipid metabolism (Gpam, Fas, and Acaca), also showed a tendency towards reduction. This suggests that Nur77 may lead to a reduction in SREBP1c activity, which could subsequently impact the synthesis of triglycerides within the liver. Glycerol kinase (GK), a key enzyme in glycerol metabolism, is capable of synthesizing triglycerides via the phosphatidic acid pathway in the liver. When glycerol kinase (GK) is deficient, signaling pathways associated with glucose and lipid metabolism, including SREBP1, PPARα, and STAT3, are suppressed, thereby affecting the metabolic processes of glucose, lipids, and insulin in the body. Liu Yue *et al.* discovered through in vitro cellular experiments based on the results of the yeast two-hybrid screen that Nur77 can interact with glycerol kinase, with the interaction sites located in the DNA-binding domain and the ligand-binding domain (LBD) of Nur77 [8]. Follow up examinations used co-transfection of Nur77 and glycerol kinase into the human L02 liver cell line and mice and confirmed that upon binding to glycerol kinase, Nur77 significantly modulates the activities of SREBP1c and other key enzymes involved in lipid biosynthesis. The interaction between them may modulate hepatic lipid metabolism by influencing the activity and stability of Nur77 [8]. Liu Tingting *et al.* elucidated that Nur77 plays a pivotal role in promoting liver lipid degradation during the onset and progression of non-alcoholic fatty liver disease in the elderly by regulating chaperone-mediated autophagy (CMA) and autophagic flux through the establishment of wild-type and Nur77 gene-mutated mouse models [9]. In hepatocytes, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), a key regulatory enzyme in the cholesterol biosynthesis pathway, catalyzes the formation of mevalonic acid (MVA). Inhibition of its function can effectively prevent cholesterol biosynthesis. Simultaneously, the low-density lipoprotein receptor (LDLR) plays a pivotal role in maintaining cholesterol homeostasis. Nur77 can modulate cholesterol metabolism in

hepatocytes by adjusting the activity states of LDLR and HMGCR. Levels of LDLR and HMGCR increase with the downregulation of Nur77 expression and decrease with the upregulation of Nur77 expression [10]. This observation is consistent with the findings of Chao and colleagues in animal studies [6]. FGF21, a stress-responsive factor in the liver, is activated during the process of steatosis, leading to its increased production [11]. Its expression is influenced by various transcription factors, including Nur77 [12]. Research by Ahuja P *et al.* reports that Src homology 3 (SH3) domain-binding kinase 1 (SBK1) in the liver regulates lipid metabolism and enhances FGF21 production by phosphorylating Nur77 [13]. This mechanism effectively prevents excessive fat accumulation in the livers of obese mice by inhibiting the transcription of genes associated with lipid synthesis. In summary, Nur77 plays an indispensable role in the dynamic regulation of liver fat storage and lipid metabolism, with its functional mechanism involving the interplay of multiple key enzymes and stress response factors.

3.2. Metabolism Process in Skeletal Muscle and Nur77's Misregulation

Skeletal muscle, a primary peripheral tissue, accounts for 50% of energy expenditure and is a major site for lipid metabolism, playing a crucial role in obesity and dyslipidemia. Reports indicate that β-adrenergic signaling can trigger muscle glycogenolysis, lipolysis, and energy metabolism, and β-adrenergic receptor agonists also modulate the expression of NR4A. The NR4A family is intimately associated with lipid, glucose, and energy metabolism in skeletal muscle. Maxwell MA *et al.* have demonstrated that Nur77 regulates lipolysis in skeletal muscle cells [14]. By upregulating Nur77 expression in C2C12 skeletal muscle cells using β-adrenergic receptor agonists, they observed a reduction in the expression of genes and proteins related to energy expenditure and lipid homeostasis regulation, such as CD36, UCP3, AMPKγ3, GLUT4, and Caveolin-3. Conversely, when Nur77 expression is suppressed, lipolysis is significantly inhibited. Additionally, as reported in relevant literature, Nur77 knockout mice on a high-fat diet exhibit skeletal muscle insulin resistance, and an increase in lipid content within skeletal muscles is observed in these knockout mice, findings that align with the conclusions of Maxwell MA *et al.* [6] [14]. Therefore Nur77 is recognized as a key factor in ameliorating the decline in muscle mass associated with obesity [15]. Furthermore, Nur77 can mitigate the inflammatory response induced by oxidized low-density lipoprotein (oxLDL) by reducing the excessive proliferation of smooth muscle cells and the uptake of oxLDL by macrophages [16].

3.3. Metabolism Process in Adipose Tissue and Nur77's Misregulation

Members of the NR4A family are prevalent in various adipose tissues, including white and brown adipose tissues. Luo *et al.* have reported that the NR4A family plays a role in glucose metabolism and lipidogenesis within white adipose tissue

[17]. Within adipocytes, insulin and its thiazolidinedione agonists can induce Nur77 activation. Notably, in their studies of obese and diabetic mouse models, they observed a significant downregulation of Nur77 expression in white adipose tissue, a phenomenon that appears to be closely associated with disease progression. Additionally, the NR4A family appears to play a collaborative role in lipid signaling and transcriptional activities. Research indicates that Nur77 (NR4A1) and Nurr1 (NR4A2) interact with the glucocorticoid receptor system, which is indispensable for adipogenesis [18]. In adipose precursor cells, the overactivity of Nur77 can significantly impede adipogenesis. It modulates the fat synthesis process in the following ways: 1) By enhancing the functions of gap junction protein 1 (GJA1) and Tolloid-like protein 1 (TLL1), it achieves significant inhibition of adipogenesis [19]; 2) By regulating cellular status to induce an inactive state in precursor cells, it further suppresses fat synthesis. Conversely, the absence of Nur77 stimulates the proliferation of adipose precursor cells and enhances their adipogenic potential [20]. On the other hand, the research by QinD and colleagues has unraveled the molecular mechanisms of Nur77. They discovered that Nur77 can directly activate the expression of GATA2, thereby indirectly suppressing the transcriptional activity of PPARγ. Furthermore, Nur77 can upregulate the levels of p53, indirectly inhibiting the expression of SREBP1c and consequently affecting FAS, which hinders adipocyte maturation and lipid formation. This intricate regulatory network further highlights the central role of Nur77 in adipocyte fate determination [21].

3.4. Nur77 Participates in Lipid Metabolism in Tumor

Orphan nuclear receptors exhibit time-dependent roles in the progression of cancer, playing complex and multifaceted roles in tumorigenesis and development, functioning both as oncogenes and tumor suppressors. In the development and metastasis of breast cancer, aberrant lipid metabolism plays a pivotal role. Nur77 is regarded as a tumor suppressor in breast cancer. Peng-bo Yang and his team initially discovered that the orphan nuclear receptor Nur77 can downregulate the transcription of key molecules in fatty acid uptake, CD36 and fatty acid-binding protein 4, by recruiting the SWI/SNF complex and HDAC1, thereby preventing breast cancer cells from taking up exogenous fatty acids and effectively suppressing tumor cell proliferation [22]. Additionally, it has been confirmed that the Nur77 agonist cytosporone B (Csn-B) exhibits potent anti-breast cancer activity. In breast cancer, PPARγ can regulate Nur77 by recruiting Trim13, facilitating Nur77 ubiquitination and degradation. The compound Csn-B can precisely target the ligand-binding domain (LBD) of Nur77, thereby preventing the interaction between PPARγ and Nur77, and subsequently enhancing Nur77's inhibitory effect on the progression of breast cancer. Csn-B not only strengthens the formation of Nur77 homodimers but also blocks the Nur77-PPARγ interaction, antagonizing PPARγ-mediated Nur77 degradation. This ensures Nur77's inhibition of exogenous fatty acid uptake and further delays the development of breast cancer.

These findings offer new possibilities for breast cancer treatment strategies and highlight the significant potential of Csn-B as a potential antineoplastic agent. Research by Bian H *et al.* has also revealed similar outcomes; after downregulating Nur77 gene expression in human breast cancer cells, they observed that Nur77 downregulation promotes the proliferation of breast cancer cells and enhances the cells' ability to absorb long-chain fatty acids, indicating that Nur77 plays a crucial role in inhibiting the proliferation and lipid metabolism of breast cancer cells [23]. Additionally, it has been observed that breast cancer patients with high levels of Nur77 expression exhibit longer postoperative overall survival, whereas patients with elevated PPARγ expression tend to have a poorer prognosis, as PPARγ can suppress the expression of Nur77 protein. In contrast to its role in breast cancer, Nur77 behaves as an oncogenic molecule in melanoma. Studies have revealed that Nur77 enhances the survival of melanoma cells by safeguarding TPβ, a key catalyst for fatty acid oxidation (FAO), from oxidative damage, particularly under conditions of glucose scarcity, thereby maintaining the FAO process [24]. Specifically, during glucose deprivation, the phosphorylation of ERK2 is triggered, which in turn facilitates the translocation of Nur77 to the mitochondria. Within the mitochondria, Nur77 interacts with TPβ to prevent its oxidation under low-glucose conditions. Collectively, Nur77 plays a crucial role in the lipid metabolism of melanoma by modulating fatty acid oxidation and preserving an antioxidant state, thereby aiding the survival of melanoma cells under metabolic stress.

4. Nur77's Role in COPD

Chronic Obstructive Pulmonary Disease (COPD), often induced by smoking, manifests as a broad systemic inflammatory condition. Previous research has highlighted the significant role of Nur77 in smoking-related pulmonary inflammatory responses [25]. Studies have observed a downregulation of Nur77 expression in the lung tissues of COPD patients, in mice exposed to cigarette smoke, and in airway epithelial cells treated with smoke extracts. Additionally, it has been discovered that the activation of Nur77 can effectively suppress the inflammatory response in a mouse COPD model induced by brief exposure to cigarette smoke [25]. Subsequent research has revealed that the expression levels of Nur77 in the serum of COPD patients exhibit a negative correlation with disease progression, and this variation is closely associated with pulmonary function and inflammatory markers [26]. This strongly supports the notion that Nur77 could be a potential therapeutic target for COPD. As a significant nuclear transcription factor, Nur77 is recognized for its crucial role in the regulation of autophagy, a key process in the initiation and progression of smoking-induced COPD. In contrast to previous findings that tobacco smoke exposure reduces Nur77 activity, other studies have shown that tobacco smoke can increase Nur77 expression and promote its translocation from the nucleus to the cytoplasm, where it interacts with Bcl2, leading to the dissociation of Bcl2 and Beclin-1. This interaction diminishes Bcl2's inhibitory effect on autophagy, thereby initiating the autophagic mechanism and

ultimately leading to cell death through autophagy. This form of autophagic cell death plays a pivotal role in the pathogenesis of COPD, particularly in the context of airway and alveolar damage [27]. The pathological characteristics of COPD encompass chronic bronchitis, airway remodeling, and emphysema. Nur77 exacerbates the progression of COPD by intervening in autophagic processes. The complexity of COPD extends beyond respiratory issues, often accompanied by various comorbidities, including hypertension and dysregulation of glucose and lipid metabolism. Disturbances in fat metabolism may contribute to the development and exacerbation of COPD [28]. Previous research has observed a close association between the extent of emphysema in COPD patients and weight loss as well as fat loss [29]. Research conducted both in vivo and in vitro experiments has demonstrated that exposure to tobacco smoke can lead to a reduction in total body fat and adipose tissue atrophy, likely due to enhanced lipolysis [30]. In patients with COPD, adipose tissue loss, which manifests as weight loss, is a notable clinical characteristic. Furthermore, studies indicate that dysregulation of fatty acid metabolism contributes to the development of chronic pulmonary inflammation and emphysema by initiating oxidative stress, inflammation, pulmonary structural remodeling, and autophagy, thereby influencing the pathogenesis of COPD [31]. However, the specific role of Nur77 under the influence of tobacco smoke and the underlying pathophysiological mechanisms that lead to lipid metabolism disorders and weight loss in COPD patients remain unclear and warrant further investigation.

5. Conclusion and Prospect

As a member of the orphan nuclear receptor family, Nur77 is influenced by a diverse array of physiological and pathological factors and plays a pivotal role in lipid metabolism across various tissues and cells. While current pharmacological treatments and integrated strategies of Chinese and Western medicine can effectively manage COPD and enhance patients' quality of life, no drug has yet been found that can halt the progression or reverse the pathological state of the disease. Hence, further exploration of Nur77's physiology mechanism, its regulation of lipid metabolism, and its functions in inflammation-related lung diseases, may offer new avenues for the prevention and treatment of COPD. To sum up, more relevant mechanistic research should be conducted at the prospect of Nur77's regulation of lipid metabolism process and its relevant potential of halting the progression of COPD.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81860021).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wu, L. and Chen, L. (2018) Characteristics of Nur77 and Its Ligands as Potential Anticancer Compounds (Review). *Molecular Medicine Reports*, **18**, 4793-4801. https://doi.org/10.3892/mmr.2018.9515

[2] Zhang, C., Xu, X., Shang, Y., *et al.* (2014) Orphan Nuclear Receptor Nur77 and Pulmonary Disease. *International Journal of Respiration*, **34**, 1900-1904.

[3] Wang, K., Wang, M., Shang, Y., He, Y., Li, Q., Gao, W., *et al.* (2020) Regulatory Effects of Nur77 on Airway Remodeling and ASMC Proliferation in House Dust Mite-Induced Asthma. *Oxidative Medicine and Cellular Longevity*, **2020**, Article ID: 4565246. https://doi.org/10.1155/2020/4565246

[4] Ding, R., Sun, X., Yi, B., Liu, W., Kazama, K., Xu, X., *et al.* (2021) Nur77 Attenuates Inflammasome Activation by Inhibiting Caspase-1 Expression in Pulmonary Vascular Endothelial Cells. *American Journal of Respiratory Cell and Molecular Biology*, **65**, 288-299. https://doi.org/10.1165/rcmb.2020-0524oc

[5] Palumbo-Zerr, K., Zerr, P., Distler, A., Fliehr, J., Mancuso, R., Huang, J., *et al.* (2015) Orphan Nuclear Receptor NR4A1 Regulates Transforming Growth Factor-β Signaling and Fibrosis. *Nature Medicine*, **21**, 150-158. https://doi.org/10.1038/nm.3777

[6] Chao, L.C., Wroblewski, K., Zhang, Z., Pei, L., Vergnes, L., Ilkayeva, O.R., *et al.* (2009) Insulin Resistance and Altered Systemic Glucose Metabolism in Mice Lacking Nur77. *Diabetes*, **58**, 2788-2796. https://doi.org/10.2337/db09-0763

[7] Pols, T.W.H., Ottenhoff, R., Vos, M., Levels, J.H.M., Quax, P.H.A., Meijers, J.C.M., *et al.* (2008) Nur77 Modulates Hepatic Lipid Metabolism through Suppression of SREBP1c Activity. *Biochemical and Biophysical Research Communications*, **366**, 910-916. https://doi.org/10.1016/j.bbrc.2007.12.039

[8] Liu, Y. (2012) Study on GK-Nur77Interaction and Its Regulation of Lipid Metabolism in Liver. Master's Thesis, Pharmaceutical Engineering.

[9] Liu, T.T. (2022) Nur77 Promotes Chaperon-Mediated Autophagy to Alleviate Aging-Related Non-Alcoholic Fatty Liver Disease. Ph.D. Thesis, China Medical University.

[10] Wang, Q. (2012) The Orphan Nuclear Receptor Nur77 Regulates Hepatic Cholesterol Metabolism through the Suppression of LDLR and HMGCR Expression. *Molecular Medicine Reports*, **5**, 1541-1547. https://doi.org/10.3892/mmr.2012.850

[11] Chukijrungroat, N., Khamphaya, T., Weerachayaphorn, J., Songserm, T. and Saengsirisuwan, V. (2017) Hepatic FGF21 Mediates Sex Differences in High-Fat High-Fructose Diet-Induced Fatty Liver. *American Journal of Physiology-Endocrinology and Metabolism*, **313**, E203-E212. https://doi.org/10.1152/ajpendo.00076.2017

[12] Min, A., Bae, K., Jung, Y., Choi, Y., Kim, M., Kim, J., *et al.* (2014) Orphan Nuclear Receptor Nur77 Mediates Fasting-Induced Hepatic Fibroblast Growth Factor 21 Expression. *Endocrinology*, **155**, 2924-2931. https://doi.org/10.1210/en.2013-1758

[13] Ahuja, P., Bi, X., Ng, C.F., Tse, M.C.L., Hang, M., Pang, B.P.S., *et al.* (2022) SRC Homology 3 Domain Binding Kinase 1 Protects against Hepatic Steatosis and Insulin Resistance through the Nur77-FGF21 Pathway. *Hepatology*, **77**, 213-229. https://doi.org/10.1002/hep.32501

[14] Maxwell, M.A., Cleasby, M.E., Harding, A., Stark, A., Cooney, G.J. and Muscat, G.E.O. (2005) Nur77 Regulates Lipolysis in Skeletal Muscle Cells. *Journal of Biological Chemistry*, **280**, 12573-12584. https://doi.org/10.1074/jbc.m409580200

[15] Chen, F., Yu, Y., Tian, H., Ma, G., Ma, R., Tian, T., *et al.* (2023) Nur77 Is Involved in the Regulation of Obesity-Related Lower Muscle Mass by Promoting Pten Degradation. *The FASEB Journal*, **37**, e23083. https://doi.org/10.1096/fj.202201983rr

[16] Shao, Q., Han, F., Peng, S. and He, B. (2016) Nur77 Inhibits oxLDL Induced Apoptosis of Macrophages via the P38 MAPK Signaling Pathway. *Biochemical and Biophysical Research Communications*, **471**, 633-638. https://doi.org/10.1016/j.bbrc.2016.01.004

[17] Fu, Y., Luo, L., Luo, N., Zhu, X. and Garvey, W.T. (2007) NR4A Orphan Nuclear Receptors Modulate Insulin Action and the Glucose Transport System: Potential Role in Insulin Resistance. *Journal of Biological Chemistry*, **282**, 31525-31533. https://doi.org/10.1074/jbc.m701132200

[18] Carpentier, R., Sacchetti, P., Ségard, P., Staels, B. and Lefebvre, P. (2007) The Glucocorticoid Receptor Is a Co-Regulator of the Orphan Nuclear Receptor Nurr1. *Journal of Neurochemistry*, **104**, 777-789. https://doi.org/10.1111/j.1471-4159.2007.05055.x

[19] Chao, L.C., Bensinger, S.J., Villanueva, C.J., Wroblewski, K. and Tontonoz, P. (2008) Inhibition of Adipocyte Differentiation by Nur77, Nurr1, and Nor1. *Molecular Endocrinology*, **22**, 2596-2608. https://doi.org/10.1210/me.2008-0161

[20] Zhang, Y., Federation, A.J., Kim, S., O'Keefe, J.P., Lun, M., Xiang, D., *et al.* (2018) Targeting Nuclear Receptor NR4A1-Dependent Adipocyte Progenitor Quiescence Promotes Metabolic Adaptation to Obesity. *Journal of Clinical Investigation*, **128**, 4898-4911. https://doi.org/10.1172/jci98353

[21] Qin, D., Yang, Y., Pu, Z., Liu, D., Yu, C., Gao, P., *et al.* (2018) NR4A1 Retards Adipocyte Differentiation or Maturation via Enhancing GATA2 and p53 Expression. *Journal of Cellular and Molecular Medicine*, **22**, 4709-4720. https://doi.org/10.1111/jcmm.13715

[22] Yang, P., Hou, P., Liu, F., Hong, W., Chen, H., Sun, X., *et al.* (2020) Blocking PPARγ Interaction Facilitates Nur77 Interdiction of Fatty Acid Uptake and Suppresses Breast Cancer Progression. *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 27412-27422. https://doi.org/10.1073/pnas.2002997117

[23] Bian, H., Liang, X., Lu, D., Lin, J., Lu, X., Jin, J., *et al.* (2024) In Silico Discovery of Stapled Peptide Inhibitor Targeting the Nur77-PPARγ Interaction and Its Anti-breast-Cancer Efficacy. *Advanced Science*, **11**, e2308435. https://doi.org/10.1002/advs.202308435

[24] Li, X., Wang, Z., Zheng, Y., Guan, Y., Yang, P., Chen, X., *et al.* (2018) Nuclear Receptor Nur77 Facilitates Melanoma Cell Survival under Metabolic Stress by Protecting Fatty Acid Oxidation. *Molecular Cell*, **69**, 480-492.e7. https://doi.org/10.1016/j.molcel.2018.01.001

[25] Reddy, A.T., Lakshmi, S.P., Banno, A., Jadhav, S.K., Pulikkal Kadamberi, I., Kim, S.C., *et al.* (2020) Cigarette Smoke Downregulates Nur77 to Exacerbate Inflammation in Chronic Obstructive Pulmonary Disease (COPD). *PLOS ONE*, **15**, e0229256. https://doi.org/10.1371/journal.pone.0229256

[26] Deng, J.H., Wang, Z.B. and Huang, B.H. (2021) Expression and Clinical Significance of Serum NR4A1 in Chronic Obstructive Pulmonary Disease. *Journal of Clinical Pulmonary Medicine*, **26**, 1034-1037.

[27] Qin, H., Gao, F., Wang, Y., Huang, B., Peng, L., Mo, B., *et al.* (2019) Nur77 Promotes Cigarette Smoke-Induced Autophagic Cell Death by Increasing the Dissociation of Bcl2 from Beclin-1. *International Journal of Molecular Medicine*, **44**, 25-36. https://doi.org/10.3892/ijmm.2019.4184

[28] Azimzadeh, S., Mirzaie, M., Jafari, M., Mehrani, H., Shariati, P. and Khodabandeh, M. (2015) Signaling Network of Lipids as a Comprehensive Scaffold for Omics Data Integration in Sputum of COPD Patients. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular and Cell Biology of Lipids*, **1851**, 1383-1393. https://doi.org/10.1016/j.bbalip.2015.07.005

[29] Kurosaki, H., Ishii, T., Motohashi, N., Motegi, T., Yamada, K., Kudoh, S., *et al.* (2009) Extent of Emphysema on HRCT Affects Loss of Fat-Free Mass and Fat Mass in COPD. *Internal Medicine*, **48**, 41-48. https://doi.org/10.2169/internalmedicine.48.1102

[30] Wang, L., van Iersel, L.E.J., Pelgrim, C.E., Lu, J., van Ark, I., Leusink-Muis, T., *et al.* (2022) Effects of Cigarette Smoke on Adipose and Skeletal Muscle Tissue: *In Vivo* and *in Vitro* Studies. *Cells*, **11**, Article 2893. https://doi.org/10.3390/cells11182893

[31] Ye, M. and Li, F. (2022) Role of Fatty Acid Metabolism in the Pathogenesis of Chronic Obstructive Pulmonary Disease. *International Journal of Respiration*, **42**, 895-900.