Received: 8 November 2024 | Revised: 27 February 2025 | Accepted: 7 March 2025

DOI: 10.1096/fj.202402775RR

REVIEW ARTICLE

The FASEB Journal

Controversy and multiple roles of the solitary nucleus receptor Nur77 in disease and physiology

Yanteng Wang | **Na Li** | **Wenwei Guan** | **Difei Wang**

Department of Gerontology and Geriatrics, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China

Correspondence
Difei Wang, Department of Gerontology and Geriatrics, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, China.
Email: dfwang@cmu.edu.cn

Funding information
MOST | National Natural Science Foundation of China (NSFC), Grant/Award Number: 92249305; Department of Science and Technology of Liaoning Province, Grant/Award Number: 2023-BSBA-334

Abstract

Neuron-derived clone 77 (Nur77), a member of the orphan nuclear receptor family, is expressed and activated rapidly in response to diverse physiological and pathological stimuli. It exerts complex biological functions, including roles in the nervous system, genome integrity, cell differentiation, homeostasis, oxidative stress, autophagy, aging, and infection. Recent studies suggest that Nur77 agonists alleviate symptoms of neurodegenerative diseases, highlighting its potential as a therapeutic target in such conditions. In cancer, Nur77 demonstrates dual roles, acting as both a tumor suppressor and promoter, depending on the cancer type and stage, making it a controversial yet promising anticancer target. This review provides a structured analysis of the functions of Nur77, focusing on its physiological and pathological roles, therapeutic potential, and existing controversies. Emphasis is placed on its emerging applications in neurodegenerative diseases and cancer, offering key insights for future research and clinical translation.

KEYWORDS

cancer, neurodegeneration, Nur77, physiological function, transcription

1 | INTRODUCTION

Neuron-derived Clone 77 (Nur77) is an orphan receptor in the nuclear receptor superfamily widely distributed across multiple human organs, including the heart, liver, spleen, lungs, kidneys, brain, adrenal glands, skeletal muscle, adipose tissue, genitalia, and blood. Its widespread presence suggests that Nur77 performs multiple biological functions. In recent years, Nur77 has garnered increasing research interest in cancer and neurological diseases, particularly regarding its complex roles in tumorigenesis and immune regulation. Although some studies have revealed Nur77's function as a transcription factor regulating target gene expression (Table 1) and its role as a transcription-independent regulator (Table 2), its functions in different biological contexts remain controversial.

The role of Nur77 in different tumor types shows a duality: it acts as a tumor suppressor in hematologic malignancies, while it may act as an oncogene in solid tumors. The molecular mechanisms of this dual action are still not fully understood, especially the interactions of Nur77 with cofactors and genomic targets. In particular, remarkable research gaps remain regarding the role of Nur77 in the cancer immune microenvironment and the mechanisms by which apoptosis pathways are regulated through subcellular localization, such as mitochondrial translocation.

Yanteng Wang and Na Li should be considered joint first authors.

TABLE 1 Transcriptional targets of Nur77.

Gene	Mechanism	Function	Reference
ABHD17B	Positive transcription	Lung cancer	[1]
ApoA5	Positive transcription	Lipid metabolism	[2]
Caspase-1	Negative transcription	Inflammasomes	[3]
Cbl-B	Positive transcription	ER stress/osteoprotection	[4,5]
Dact1	Negative transcription	Cell differentiation	[6]
Drp1	Negative transcription	Mitochondrial fission	[7]
Eno3	Positive transcription	Glycolysis	[8]
Esrra	Negative transcription	T-cell metabolism	[9]
FAM134B2	Positive transcription	Reticulophagy	[10]
FGF21	Positive transcription	Metabolic syndrome	[10]
FIS1	Negative transcription	Mitochondrial fission	[7]
Glut4	Positive transcription	Glucose metabolism	[11]
GPX1	Positive transcription	Oxidative stress	[12]
GSK-3β	Positive transcription	Cardiac fibrosis	[12]
HOXA10	Positive transcription	Embryo adhesion	[13]
IRF1	Negative transcription	Esophageal squamous cancer	[13]
Mapk3	Negative transcription	T-cell metabolism	[9]
MDM2	Negative transcription	Aging	[14]
Notch2	Negative transcription	T-cell metabolism	[9]
P21	Positive transcription	Pancreatic cancer	[15]
PGF	Positive transcription	Trophoblast invasion	[16]
Phka1	Positive transcription	Glucose metabolism	[11]
PSPC1	Positive transcription	Breast cancer	[17]
Pygm	Positive transcription	Glucose metabolism	[11]
Ritor	Negative transcription	T-cell metabolism	[9]
RLN3	Positive transcription	Apoptosis	[17]
RLN3	Positive transcription	Cardiac fibrosis	[18]
Rps6ka	Negative transcription	T-cell metabolism	[9]
SOD1	Positive transcription	Vascular endothelium	[19]
Syvn1	Positive transcription	Muscle function	[20]
WFDC21P	Positive transcription	Glycolysis	[21]

Abbreviation: ER, endoplasmic reticulum.

Therefore, addressing the dual role of Nur77 in cancer and its mechanisms is a key challenge for current research. In neurological diseases, most studies have shown that Nur77 has a protective effect against neuropathy, but its role in neurodegenerative diseases such as Alzheimer's disease (AD) has not been fully explored. The factors that influence Nur77's balance between neuronal survival and death, as well as its role in cellular events such as anti-inflammatory and proinflammatory responses, are still not fully understood.

Herein, we aim to fill this knowledge gap by focusing on the regulatory role of Nur77 in the nervous system and tumor microenvironment. By exploring the potential applications of Nur77 in neurodegenerative diseases and cancer immunotherapy, we hope to provide a new perspective and inspire further research on Nur77 as a therapeutic target.

2 | PHYSIOLOGICAL FUNCTION

2.1 | Functions in the nervous system

Nur77 is highly expressed in the mammalian central nervous system (CNS), particularly in the cerebral cortex and hippocampus, suggesting its potential role in neural functions. However, its specific neural function remains largely unknown. Recent studies have explored several molecular mechanisms of Nur77 neural action, improving our understanding of its role. In the CNS, oligodendrocytes (OL)

TABLE 2 Nontranscriptional functions of Nur77.

Gene	Subcellular localization	Mechanism	Function	Reference
Bcl-2	Mitochondria	Bcl-2 homology (BH) 3 domain exposure	Apoptosis	[22–24]
c-Abl	Mitochondria	Inhibitory phosphorylation	Autophagy	[25]
DNMT3b	Mitochondria	Increased GLS1 promoter methylation	Aging	[26]
FGFR1	Cytoplasm and nucleus	Nuclear accumulation	Embryonic stem cells	[27]
GATA4	Mitochondria	Inhibitory transcription	Transcription	[28]
Integrin α1	–	Promoter activity	Angiogenesis	[29]
NFATc3	Mitochondria	Inhibitory transcription	Transcription	[28]
p62/SQSTM1	Mitochondria	Liquid–liquid phase separation	Mitophagy	[30]
P63	–	Dicer expression regulation	Colorectal cancer	[31]
PEPCK1	–	PEPCK1 SUMOylation attenuation	Gluconeogenesis	[32]
pVHL	–	Ubiquitination inhibition	Oxidative stress	[33]
Smad3	Cytoplasm	Ubiquitination	Colonic tumorigenesis	[34]
Src-1	–	Competitive inhibition	Bladder cancer	[35]
STAT3	–	Activity enhancement/inhibitory phosphorylation	Leptin sensitivity/pulmonary arterial hypertension	[36,37]
TPβ	Mitochondria	Protection of TPβ from oxidation	Fatty acid oxidation	[38]
TRAF6	Cytoplasm	TRAF6 oligomerization modulation	Inflammatory bowel disease	[27,39]
TRAPγ	Cytoplasm	ER Ca^{2+} depletion/ubiquitination	ER stress/breast cancer	[40,41]
β-Catenin	Cytoplasm and nucleus	Proteasome pathway/negative transcription	Vascular remodeling	[42]

Abbreviations: ER, endoplasmic reticulum; SUMO, small ubiquitin-like modifier.

produce myelin sheaths that wrap around axons, thereby increasing nerve conduction speed. Maturation and myelination of OL are essential for the development of various social behaviors; however, the underlying molecular mechanisms are largely unknown. Nur77 is expressed in most O4+ OL. The effect of miR-124 on OL development is mediated through its target gene. Overexpression of Nur77 in the medial prefrontal cortex (mPFC) not only mitigates social impairments induced by isolation feeding but also enhances myelination. Conversely, inhibiting Nur77 expression substantially reduces myelin basic protein expression in cortical OL. Overexpression of Nur77 improves myelination in the mPFC of young socially isolated mice. However, the latent mechanism of Nur77 in myelination requires further study.[43] In vitro, enhanced Nur77 expression was observed during basic fibroblast growth factor-induced Schwann cell differentiation and nerve growth factor-induced PC12 cell neurite growth. In vitro and in vivo experiments showed that inhibiting Nur77 function by specific short hairpin RNA could inhibit Schwann cell myelination and axon regeneration. Therefore, Nur77 may be involved in Schwann cell differentiation and neurite elongation.[44] In neurons, Nur77 is induced by excitotoxicity and oxidative stress, acting as a mediator of cAMP response element-binding protein (CREB)-dependent neuroprotection.[45] The CREB pathway is crucial for OL progenitors, and CREB phosphorylation relies on protein kinase C (PKC) signaling cascades, which activate CREB-mediated transcription and promote the differentiation of immature to mature OL.[46] Therefore, Nur77 likely acts downstream of the CREB pathway, influencing OL development. However, direct evidence linking Nur77 to the regulation of oligodendrocyte differentiation and CNS myelination remains limited. Additionally, the molecular mechanisms via which Nur77 modulates transcriptional programs specific to myelin formation, such as interactions with CREB and downstream targets, are not fully elucidated. Future studies should focus on clarifying the specific contributions of Nur77 to oligodendrocyte maturation and myelin protein expression. Investigating its crosstalk with other nuclear receptors and signaling pathways in both peripheral and central nervous systems would enhance our understanding of its role in myelination and repair processes.

Microglia are immune effector cells in the CNS and exist in large numbers in the brain parenchyma. Microglia have a bidirectional role in inflammation: while these cells produce proinflammatory cytokines and reactive oxygen/nitrogen species involved in the progression of inflammation, additionally, they can produce anti-inflammatory cytokines and exhibit phagocytic activity that contributes to inflammation resolution. Neurons in the CNS cannot divide and replenish, so they need protection from pathogens, a key role for the immune system.[47] Overexpression

of Nur77 or application of the Nur77 agonist cytospora B inhibits proinflammatory gene expression such as inducible nitric oxide synthase,[48] cyclooxygenase-2, interleukin (IL)-1β, and tumor necrosis factor-α (TNF-α) in activated microglia, while silenced Nur77 exaggerated the inflammatory response of microglia. Moreover, in relation to microglia-mediated dopaminergic neurotoxicity, Nur77 improved cytotoxicity to MN9D dopaminergic cells in a microglia-conditioned medium system.[49] The immunosuppressive drug 6-mercaptopurine (6-MP) is mature, and the upregulation of Nur77 in microglia contributes to 6-MP-mediated inhibition of TNF-α production.[50]

Astrocytes connect the vascular system and the neurons, transporting glucose and other substances out of the bloodstream.[51–53] They undergo glycolysis of glucose to produce lactic acid, which serves as the main energy substrate of neurons. Extracellular ATP and chemical hypoxia induce Nur77 expression in RBA-2 astrocytes.[54] Currently, studies have found that Nur77 regulates glycolysis.[21,32,55] Therefore, Nur77 potentially plays a role in astrocytes and glycolysis, although direct evidence to support this hypothesis remains to be further explored. Additionally, astrocytes possess immune functions, and Nur77 dynamically regulates the expression of inflammatory genes in glial cells by regulating the transcriptional activity of NF-κB.[56]

The nuclear receptor Nur77 is a promising target for drug development in the treatment of CNS diseases. The activation of these receptors is expected to regulate the function and phenotype of glial cells by controlling the expression of specific gene subsets and regulating cell signaling mechanisms in a non-genomic manner. This in vivo and in vitro evidence suggests that Nur77 is an important regulator of neural function in the differentiation and survival of different nerve cells. Nur77 knockout (KO) has a damaging effect on the normal function of the nervous system, which may be age-related (Figure 1). In vivo studies of Nur77 conditional KO in different nerve cells in mice will enhance our understanding of its function in the nervous system.

2.2 | Mitosis regulation and genome integrity

Nur77 expression can be rapidly induced by several mitotic inducers, including serum growth factor, vascular endothelial growth factor, epidermal growth factor (EGF), and fibroblast growth factor.[57–60] It imparts growth-promoting activity to genes in the nucleus through transcriptional regulation. Ectopic Nur77 expression promotes cell cycle progression and BrdU incorporation, while silencing Nur77 expression inhibits the pro-mitotic effects of EGF and serum, and Nur77 DNA binding and trans-activation are required for its mitotic effects.[61] Furthermore, DNA-PKCs, a catalytic subunit of DNA-dependent protein kinases that, together with two other subunits, Ku70 and Ku80, form the DNA-PK complex, which plays a central role in DNA double-strand break repair and genome stabilization. Orphan nuclear receptor subfamily 4 Group A member 1 (Nur77) is the upstream signal for DNA-PKCs activation.[62–64]

Replication stress refers to the regulatory mechanism of DNA replication when it encounters obstacles, including uncoupling, reversal, restart, and translocation of replication forks, which are caused by an increasing number of different cell disturbances and significantly impact genome stability.[65–67] Reportedly, under acute replication stress, Nur77 isolates from the genome and releases a large number of immediate early gene transcripts. Its overexpression promotes breast tumor development, and its inhibition can trigger severe mitotic dysfunction and proliferative failure, suggesting that it is crucial in the adaptation of cancer cells to chronic replication stress.[68]

2.3 | Cell differentiation

Nur77 serves as a regulator of cell differentiation, assuming various roles across different cell types. As a nuclear receptor, Nur77 is a novel regulator of Paneth cell differentiation and function. Its deficiency leads to the loss of Pan's cells in the crypt of the ileum in mice. Intestinal tissues or organoids lacking Nur77 exhibit impaired intestinal stem cell niches following degranulation of Pan's cells and fail to enhance antimicrobial peptide expression; Nur77 transcription inhibits Dact1 expression to activate Wnt signal transduction activity, promoting Paneth cell differentiation.[6] Similarly, muscle tissue-specific knockdown of Nur77 increased Smad2 and FoxO3 activities, two negative regulators of muscle mass, and reduced the cross-sectional area of differentiated muscle fibers.[69] However, silencing Nur77 attenuates cantharidin CTD-induced apoptosis and reverses CTD-mediated cell cycle arrest and HL-60 cell differentiation.[24] Three members of the NR4A subfamily, Nur77, Nurr1, and NOR1, all strongly inhibit the differentiation of preadipocytes into adipocytes. The differentiation of preadipocytes 3T3-L1 was induced by standard differentiation mixture (DMI) or peroxisome proliferator-activated receptor-γ (PPARγ) ligand GW7845 and insulin within 1 h. Nur77 mRNA response to DMI was rapidly induced, Nur77 protein levels peaked at 2 h, and Nur77 inhibited the differentiation of preadipocytes by preventing the expansion of mitotic clones but had no significant effect on phenotypic markers such as PPARγ and aP2 that maintain mature adipocytes.[70] Nur77 reduced

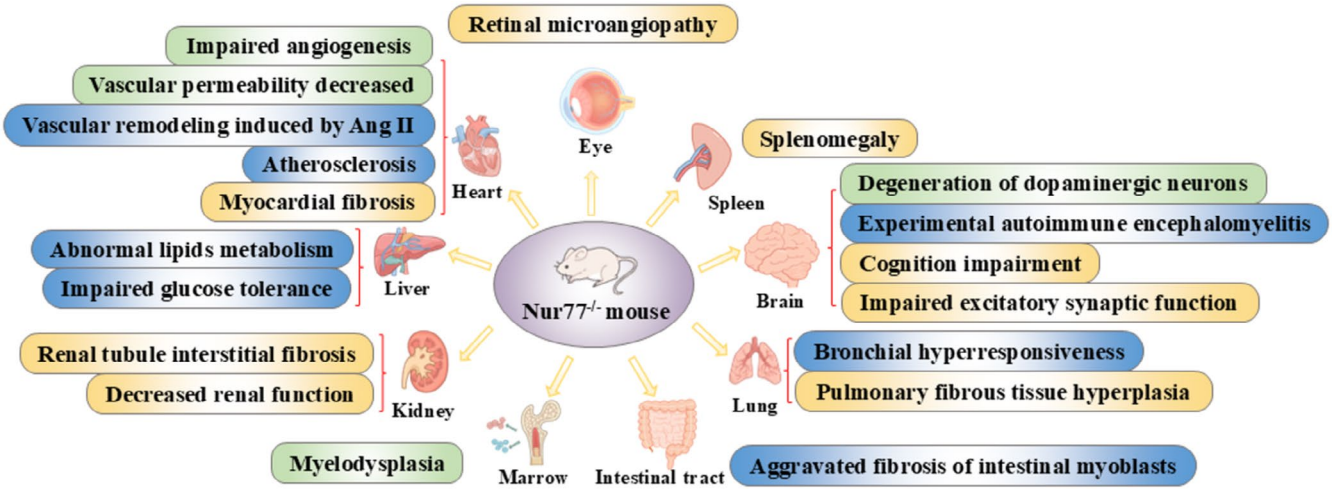

FIGURE 1 In vivo studies of physiological functions and disease models in Nur77$^{-/-}$ mice. Deletion of the Nur77 gene affects several crucial physiological functions in vivo, leading to degeneration of dopaminergic neurons, impaired angiogenesis, decreased vascular permeability, and myelodysplasia. As they age, Nur77$^{-/-}$ mice develop cognitive impairment, compromised excitatory synaptic function, myocardial fibrosis, pulmonary fibrous tissue hyperplasia, renal tubulointerstitial fibrosis, renal dysfunction, splenomegalysis, and retinal microangiopathopathy. In various disease models, Nur77$^{-/-}$ mice exhibit symptoms of experimental autoimmune encephalomyelitis, bronchial hyperresponsiveness, increased fibrosis of intestinal myoblasts, vascular remodeling, atherosclerosis, abnormal lipid metabolism, and impaired glucose tolerance. The green text box represents the effects on physiological function in Nur77$^{-/-}$ mice, the yellow box represents Nur77$^{-/-}$ mice used in aging-related studies, and the blue text box represents Nur77$^{-/-}$ mice induced by disease.

the initial differentiation of Treg lineages in autoreactive T-cell receptor transgenic and non-transgenic mice.[8] Nur77 inhibits osteoclast differentiation by inducing I κ B-α and inhibiting IKK-β in vivo and in vitro studies.[71]

Additionally, Nur77 is associated with stem cell differentiation. Previous studies reveal that genes specifically expressed by oocytes evolve rapidly, particularly through gene replication mechanisms. In 2007, Isabelle Callebaut et al. used the computer digital differential display method to identify two genes exclusively expressed in oocytes; one of these was identified as Nur77 downstream gene 1. Its specificity in oocytes was confirmed through RT-PCR and in situ hybridization. This gene does not exist in fish, chickens, or possums but appeared in the true mammalian genome, located between the Kcnq5 and Ddx43 genes, during evolutionary development.[72] Additionally, FGFR1 stimulates integrative nuclear FGFR1 signaling (INFS) to trigger cell cycle exit, morphological differentiation, neuron-specific protein expression, and the restoration of adult human brain neurogenesis in adult human brain-derived neuroprogenitor cells, as well as in cells from pheochromocytoma, medulloblastoma, and neuroblastoma. Concurrently, Nur77 promotes FGFR1 nuclear accumulation.[73–75] The transition from oxidative phosphorylation (OXPHOS) to glycolysis occurs during the transformation of somatic differentiated cells into induced pluripotent stem cells, reflecting metabolic reprogramming.[76] During metabolic reprogramming, mRNA levels of Nur77 decreased. Consistent with this, in vitro experiments knocking out Nur77 led to a notable reduction in OXPHOS and an increase in glycolysis.[77]

2.4 | Cell homeostasis

The liver is the main site for maintaining blood sugar levels, and in a state of limited energy, it reduces glucose surges during the feeding cycle by activating neogluconeogenesis and promoting glycogen synthesis while inhibiting gluconeogenesis.[78] The first and rate-limiting step of gluconeogenesis is catalyzed by phosphoenolpyruvate carboxykinase (PEPCK1). Nur77 attenuates ubiquitination and maintains PEPCK1 protein stability by impacting p300 activity and preventing Ubc9-PEPCK1 interactions, suggesting a potential mechanism by which Nur77 enhances gluconeogenesis, particularly at times of energy restriction.[32] Nur77 also can modulate glycolysis in cancer cells by regulating the activity of enzymes such as PFKP and PKM2, which are critical for glycolytic flux. Specifically, Nur77-activated lncRNA WFDC21P impedes the catalytic activity of PFKP and prevents PKM2 nuclear translocation, thereby suppressing glycolytic metabolism in hepatocellular carcinoma (HCC) cells.[21] Nur77 is associated with insulin sensitivity. Insulin mobilizes the glucose transporter 4 (GLUT4) into cell surface circulation pathways, accelerating glucose uptake.[79] Research suggests that Nur77 may enhance insulin sensitivity by activating the p-insulin receptor β (IRβ)/p-insulin receptor substrate

(IRS)/Akt/GLUT4 pathway and regulating autophagy.[80] Specifically, it increased the ratios of IRβ-Tyr1361 to IRβ, IRS-1Tyr612 to IRS-1, and p-Akt to Akt, while decreasing the ratio of p-IRS-1Ser307 to IRS-1. Additionally, the expression of glucose transporter type 1 decreased, and that of GLUT4 increased. Nur77 also enhanced the expression of the autophagy-related protein Beclin 1.

Besides, Serine 354 on Nur77 is phosphorylated by Src homology domain 3 binding kinase 1 (SBK1), which promotes liver FGF21 expression and increases insulin sensitivity.[81] Pharmacological and genetic inhibition can lead to insulin resistance.[82] In Nur77$^{-/-}$ mice, insulin-mediated tyrosine phosphorylation of the insulin receptor substrate-1 and phosphorylation of Akt were reduced, alongside glucose processing capacity.[83] These findings suggest that Nur77 may have a positive effect on glucose uptake in insulin-resistant conditions. Nur77 overexpression improves insulin sensitivity in insulin-resistant hepatocytes. In addition, siRNA silencing Nur77 reduces the expression of nuclear factor E2-related factor (Nrf2) and heme oxygenase 1 (HO-1), while the activation of the Nrf2/HO1 signaling pathway inhibits iron death.[84–90] Therefore, Nur77 may be involved in the metabolism of iron in cells.

Nur77 is involved in cellular homeostasis, especially glucose metabolism (Figure 2), but direct evidence linking Nur77 to glycolytic control across broader physiological and pathological contexts remains sparse. For instance, the precise mechanisms via which Nur77 interacts with metabolic pathways under varying conditions, such as hypoxia or nutrient stress, are poorly understood. Future research should focus on delineating the regulatory network of Nur77 in glycolysis and its crosstalk with other metabolic processes. Investigating its role in different tissues and disease models could provide a clearer picture of its physiological relevance and therapeutic potential in metabolic disorders and cancer.

2.5 | Aging

Emerging evidence highlights that the NR4A subfamily of orphan nuclear receptors (NUR77/NUR77, NR4A2/NURR1, and NR4A3/NOR1) is a key transcriptional regulator of cytokine and growth factor action in diseases affecting our aging population. Nur77 emerges as a promising target for anti-aging therapies. Our previous research revealed that loss of Nur77 increases DNA damage response and cellular senescence with age, accelerating the aging process in several mouse tissues. We observed that Nur77 reduced Sirt1 protein degradation by the proteasome through negative transcriptional regulation of its E3 ligase MDM2, thereby stabilizing Sirt1 protein. In addition, we confirmed the important role of Nur77 in the prevention of aging nephropathy through Sirt1. However, such findings need to be validated in other diseases of aging to elucidate the general anti-aging role of NUR77-stabilized Sirt1.[14] With age, Nur77 levels decrease during cardiac remodeling, and it directly initiates GSK-3β transcription through the GSK-3β/β-catenin pathway to alleviate cardiac fibrosis. Specifically, Nur77 defects induced overproduction of type I collagen (Col-1) and alpha-smooth muscle actin in transforming growth factor β (TGF-β)-treated H9c2 cells, whereas Nur77 overexpression attenuated the effect. Nur77 in vitro and in vivo defects downregulated glycogen synthase kinase (GSK)-3β expression and increased β-catenin activity, while its overexpression increased GSK-3β expression. In addition, GSK-3β knockdown negated the antifibrotic effect of Nur77 on TGFβ-treated H9c2 cells.[91] Additionally, our research group demonstrated that Nur77 improves age-related renal tubulointerstitial fibrosis by inhibiting transforming growth factor β (TGF-β)/Smads signaling pathways. Mechanistically, Nur77 interacts with Smad7, the main inhibitor of Smad2/3 nuclear translocation, and stabilizes Smad7 protein homeostasis. Nur77 defects lead to Smad7 degradation, intensify Smad2/3 phosphorylation, and promote transcription of its downstream target gene ACTA2 and collagen I.[92] The osmotic effect of increased glutamine synthesis in astrocytes is often associated with cerebral edema and complications of acute liver failure (intracranial hypertension, cerebral hernia caused by detoxification products in the brain). Nur77 KO can block glutamyl amino decomposition and induce hepatic stellate cell (HSC) senescence.[26] Nur77 enhances the transcriptional activity of the signal transduction and activation of transcription 3 (STAT3) by recruiting acetylase p300 and histone deacetylase 1 (HDAC1), regulating the expression of the *Pomc* gene in the middle and lower hypothalamus. This interaction promotes STAT3-mediated leptin sensitivity, contrasting with the severe leptin resistance observed in Nur77 KO mice with hyperleptinemia that leads to age-induced obesity.[36] Xu Jing et al. demonstrated that Nur77, as an important target of HDAC7, is involved in the formation of contextual fear conditioning memory in the regulation of situational fear, potentially offering a therapeutic target for preventing memory deficits in aging and neurological diseases.[93] The thymus undergoes age-related gradual atrophy or degeneration, leading to impaired central T-cell tolerance, reducing Nur77 in some cell subsets in the atrophic thymus compared with those in the young thymus.[94] Overall, the findings underscore the therapeutic potential of Nur77 in mitigating senescence-driven pathologies and promoting healthy aging, so that targeting drugs to prevent the age-related decline of Nur77 in late adulthood may be a new approach

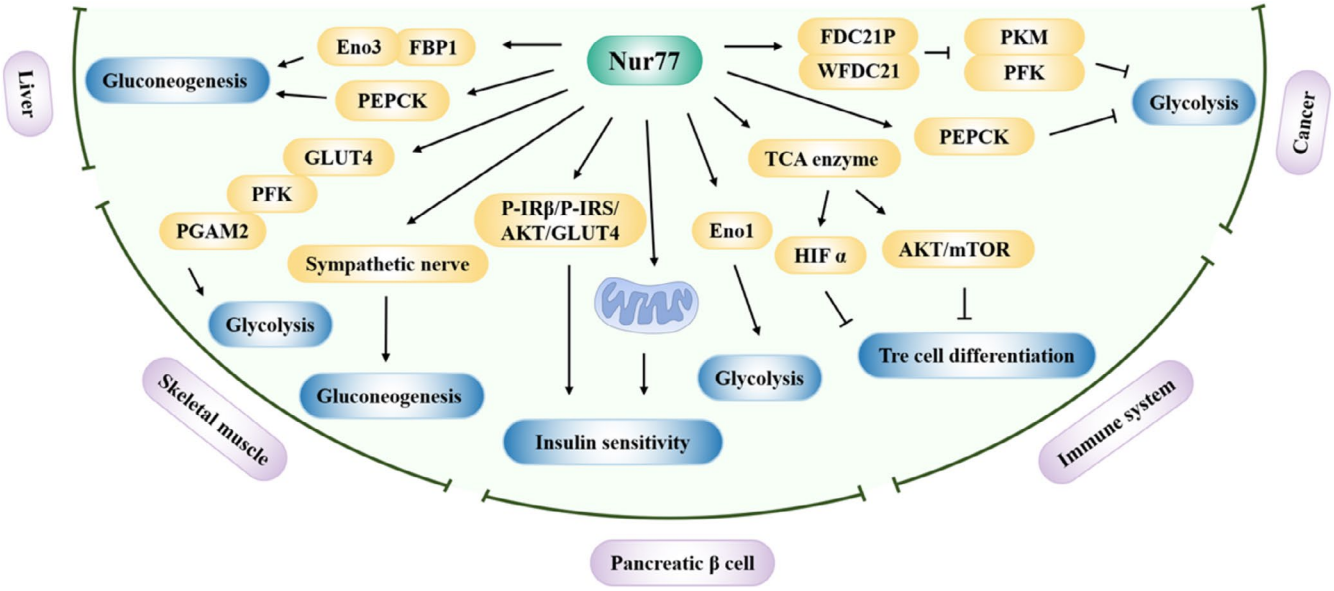

FIGURE 2 Nur77 in glucose metabolism. In the liver, Nur77 overexpression induces the expression of genes associated with gluconeogenesis in mice, such as fructose diphosphatase 1 (FBP1) and enolase-3 (Eno3), thereby stimulating glucose production in vivo and in vitro and raising blood sugar levels. In addition, the first and rate-limiting step of gluconeogenesis is catalyzed by phosphoenolpyruvate carboxykinase (PEPCK1); Nur77 enhances gluconeogenesis by modulating p300 activity and preventing Ubc9-PEPCK1 interactions, which attenuate ubiquitination and maintain PEPCK1 stability—especially during energy restriction. In skeletal muscle, Nur77 is involved in the expression of glycolytic genes, including glucose transporter 4 (GLUT4), phosphofructokinase (PFK), and phosphoglycerate mutase 2 (PGAM2). Nur77 also activates the sympathetic nervous system during acute stress, thereby promoting gluconeogenesis. In islet β cells, Nur77 may enhance insulin sensitivity by activating the p-insulin receptor β (IRβ)/p-insulin receptor substrate (IRS)/Akt/GLUT4 pathway and regulating autophagy. Overexpression of Nur77 induces β cell proliferation and enhances mitochondrial respiration, which promotes insulin secretion; it also increases the expression of the glycolytic gene Eno3. In the immune system, Nur77 participates in the activation of glycolytic and TCA cycle enzymes, thereby driving cellular energy production and activating the Akt/mTOR axis, which leads to a decrease in Treg differentiation. Transcriptional activation of glycolysis preferentially promotes Th17 differentiation rather than Treg via a hypoxia-inducible factor 1α (HIF1α)-dependent mechanism. In tumor cells, Nur77 binds to response elements on the promoter of the WAP four-disulfide core domain 21 pseudogene (WFDC21P) to induce its transcription. WFDC21P inhibits liver cancer cell glycolysis through simultaneous interaction with phosphofructokinase (PFK) and the pyruvate kinase M2 isoform (PKM2), a key glycolytic enzyme. Moreover, Nur77 interacts with PEPCK1 to promote gluconeogenesis in hepatocellular carcinoma by reducing the SUMOylation and ubiquitination of PEPCK1, thereby effectively inhibiting glycolysis in hepatocellular carcinoma.

for treating age-related diseases. Future research should explore the detailed molecular mechanisms of Nur77 in different aging contexts to fully realize its translational applications.

2.6 | Infection and inflammation

During infection, pathogens affect the transcriptional machinery of the host cell for their own benefit; however, the underlying mechanism of this change remains elusive. In wild-type mice infected with *Listeria*, $CD8^+$ T cells showed a specific response to *Listeria monocytogenes*, with early activation marker Nur77 induced within a few hours.[95] The orphan nuclear receptor Nur77 regulates the macrophage response to *Mycobacterium tuberculosis* (Mtb) infection. Nur77 is induced in the early stage of infection. Metabolism is regulated by directly binding isocitrate dehydrogenase 2 (IDH2) to the promoter of the Tricarboxylic acid circulating enzyme, acting as its inhibitor. This interaction shifts the balance from a proinflammatory phenotype to an anti-inflammatory phenotype. The depletion of Nur77 increases IDH2 transcription, increasing intracellular levels of succinic acid and leading to elevated levels of the proinflammatory cytokine IL-1β. Additionally, Nur77 inhibited the production of antimicrobial nitric oxide and IL-1β in a succinate dehydrogenase-dependent manner, suggesting its induction favored bacterial survival by inhibiting the bactericidal response. Nur77 depletion inhibits the intracellular survival of Mtb. Conversely, Nur77 consumption enhanced liposome formation, indicating a decrease in Nur77 levels as the infection progresses may favor foam macrophage formation and long-term survival of Mtb in the host environment.[96] However, preliminary experiments in $Nur77^{-/-}$ mice suggest that Nur77 is required for *Gardnerella* exposure to trigger recurrent urinary tract

infections in the host of uropathogenic *Escherichia coli*.[97] It is not active in the host response to *E. coli* in the peritoneum and blood compartments. However, Nur77 regulates bacterial influx into the organ by increasing vascular permeability, thus exacerbating distant organ damage.

Furthermore, Nur77 is involved in viral infections. EBNA2 is a transcriptional trans-activator encoded by the Epstein–Barr virus. EBNA2 exerts its anti-apoptotic function by retaining Nur77 in the nucleus and preventing it from targeting mitochondria in response to apoptotic stimulation. Targeting Nur77 could be another strategy by which the virus fights apoptosis.[98] Hepatitis B virus X protein (HBx) induces Fas ligand (FasL) expression and Nur77, an orphan nuclear receptor associated with FasL upregulation, and blocking Nur77 function inhibits FasL induction by introducing antisense or a dominant negative mutant Nur77. Nur77 may help direct the HBX-induced Fas/FasL signaling pathway, eliminating invading Fas-expressing lymphocytes.[99]

Since Nur77 was found to regulate the expression of specific NF-κB-dependent genes, more studies have begun to investigate the relationship between Nur77 and inflammation. We found that overexpression of Nur77 alleviates siIκB-α-induced inflammation in RAW264.7 cells, while siIKK-β alleviated ShNur77-induced inflammation.[71,100] Research on Nur77 and intestinal microecology revealed that obesity in Nur77-deficient mice is related to low-grade systemic inflammation mediated by intestinal microecology disorder.[101] Intracellular induction of mouse caspase 11 or human caspase 4 to lipopolysaccharide (LPS) initiates a protease cascade called the atypical inflammasome, leading to gasdermin D processing and subsequent nucleotide-binding and leucine-rich repeating immune receptor family containing 3 (NLRP3) inflammasome activation. Nur77 binds directly to LPS through its C-terminal domain, and the association between Nur77 and NLRP3 requires the presence of LPS and dsDNA, so Nur77 functions as an intracellular LPS sensor. The binding of mitochondrial DNA and LPS activates the non-classical NLRP3 inflammasome.[102,103] Additionally, siRNA knockdown of Nur77 in pulmonary microvascular endothelial cells decreased VE-cadherin and β-catenin expression and increased the number of fluorescein isothiocyanate-labeled glucans transported in LPS-damaged endothelial monolayers. Nur77 plays a key role in protecting the lung endothelial barrier against LPS.[104] Docosahexaenoic acid (DHA) has a strong anti-inflammatory effect and can bind to the ligand binding domain of the anti-inflammatory regulator Nur77, and DHA ethanolamine (DHA-EA) plays an anti-inflammatory role as the Nur77 regulator. The DHA-EA derivative J9, which targets Nur77, is a potential candidate for developing anti-inflammatory and acute lung injury therapeutics.[105] Compound B7 binds strongly to Nur77 ($K_d = 3.55 \times 10^{-7}$ M) and inhibits inflammation; mechanistically, B7 regulates Nur77 colocalization in mitochondria and inhibits LPS-induced inflammation by blocking NF-κB activation in a Nur77-dependent manner.[106] Nur77 appears essential for inflammation; however, the mechanisms involved are not fully understood.

In conclusion, the immunomodulatory role of Nur77 in infection and inflammation is increasingly attracting attention, and its association with the clinical outcomes of infectious diseases is particularly important. As a key regulator of the immune system, Nur77 plays an anti-inflammatory and immunohomeostasis role by inhibiting the NF-κB signaling pathway and regulating T-cell activity. In bacterial and viral infections, upregulation of Nur77 can reduce excessive inflammatory responses and reduce tissue damage. For example, Nur77 improves survival in bacterial sepsis by regulating the inflammatory response of macrophages and clearing infection. Furthermore, in viral infections, Nur77 regulates the balance between apoptosis and antiviral immune response, and its absence may lead to chronic inflammation and infection persistence. For example, Nur77 improves infection-related clinical outcomes by modulating T-cell function and limiting virus-induced immunopathological responses. Although such studies preliminarily revealed the role of Nur77 in infection, its specific regulatory mechanisms in different pathogen infections and its effects on host immune tolerance still require further exploration. In-depth studies of the Nur77 regulatory network in infection and inflammation would facilitate the development of Nure77-based immunotherapy strategies and improve clinical outcomes for infectious diseases.

2.7 | Oxidative stress

Angiotensin II (AngII) induces disruption of mitochondrial homeostasis and oxidative stress. Nur77 knockdown exacerbated AngII-induced oxidative stress in vascular smooth muscle cells, and Nur77 can directly bind the promoter regions of mitochondrial fission-related genes Fis1 and Drp1 and inhibit their transcription.[7] Glutathione peroxidase 1 (GPX1) is the most common antioxidant enzyme in the glutathione peroxidase family. Nur77 enhances the trans-activation of the GPX1 promoter by binding to a putative binding site on the GPX1 promoter, increasing GPX1 expression. Nur77 may protect pancreatic beta cells from oxidative stress-induced apoptosis by increasing GPX1 expression.[12] However, fibroblast growth factor 1 (FGF1), a classical mitogen, was treated with the FGF1 variant with reduced proliferative potency (FGF1ΔHBS), increased antioxidant gene expression, and decreased Nur77 expression. Reduced mitochondrial

fragmentation, reactive oxygen species (ROS) production, and cytochrome c leakage enhance the mitochondrial respiration rate and β oxidation to exert these beneficial effects. Activation of Nur77 using Csn-B inhibits the beneficial effects of FGF1.[57]

2.8 | Autophagy

Autophagy is an evolutionarily conserved catabolic process that attenuates cellular stress by digesting cytoplasmic contents and disposing of intracellular waste. The liquid–liquid separation function of Nur77 is related to mitochondrial autophagy. Nur77 mediates autophagy in celastrol, strongly inducing LC3-II (an autophagy marker) after treating HepG2 cells with celastrol for 6 h, a response absent in Nur77$^{-\backslash-}$ mice.[107] The specific mechanism involves liquid-liquid phase separation that promotes the formation of membrane-less condensates with ubiquitinated mitochondria Nur77 and is able to isolate damaged mitochondria by interacting with the ubiquitin-associated (UBA) domain of p62/SQSTM1. Mitochondrial autophagy is affected by the N-terminal inherently disordered region of Nur77 and the N-terminal PB1 domain of p62/SQSTM1.[30] The transcriptional function of Nur77 is involved in endoplasmic reticulum (ER) autophagy. Overexpression of Nur77 induces FAM134B2, which regulates the autophagic degradation of secreted proteins synthesized in the ER, such as apolipoprotein C3 (APOC3). FAM134B2 can directly bind to lipidized LC3B (LC3B-II) and APOC3. They are delivered to lysosomes in an autophagy-related 7 (ATG7)-dependent manner.[10] Small ubiquitin-like modifier (SUMO)ylation is a post-translational modification that affects protein stability and transcriptional activity and alters protein–protein interactions and the intracellular localization of target proteins. This modification can enhance the transcriptional activity of Nur77 and alter the intracellular distribution to induce autophagy-dependent cell death.[108] Nur77 enhanced the expression of autophagy-associated protein Beclin1 and the ratio of LC3II/LC3I, thereby enhancing the insulin sensitivity of HTR-8/SVneo cells.[80] Conversely, Nur77 enhances mitochondrial fission, inhibits BNIP3-associated mitochondrial autophagy, disrupts the mitochondrial structure, and impairs respiratory function, and Nur77 knockdown is associated with enhanced autophagy flux, which is highly dependent on the microtubule (MT) network.[64,109] Overexpression of Nur77 inhibits Parkin-dependent mitochondrial autophagy by inhibiting c-Jun N-terminal kinase (JNK). Reactivation of the JNK/Parkin pathway eliminated the inhibitory effect of Nur77 on mitochondrial autophagy, ultimately limiting apoptosis.[110] Other studies have shown that Nur77 regulates mitochondrial respiration without affecting autophagy.[111] Regardless of whether Nur77 interferes with autophagy in different pathological processes or stimuli, Nur77 influences autophagy by regulating autophagy-related proteins through transcription or protein interaction, necessitating further mechanism studies.

2.9 | GlcNAcylation

Glycosylation is the transfer of sugars to proteins via glycosyltransferase and the formation of glycosidic bonds with amino acid residues on the proteins. Proteins undergo glycosylation to form glycoproteins. Glycosylation is an important modification of protein, regulating protein and aiding protein folding. Dysregulated O-GlcNAcylation can lead to diabetic complications. One potential mechanism leading to elevated O-GlcNAcylation is increased flux through the hexosamine biosynthesis pathway. Glutamino-fructose-6-phosphoamyltransferase (GFAT) is a rate-limiting enzyme that inhibits this pathway. Normal expression of Nur77 was sufficient to promote GFAT2 mRNA expression and O-GlcNAcylation in cultured retinal cells. High-fat diet (HFD) increases the retinal protein O-GlcNAcylation by promoting Nur77-dependent GFAT2 expression.[112]

2.10 | Post-translational modifications of Nur77

Nur77 participates in complex biological processes, and its function is strictly regulated, with multi-level precision and complexity. Nur77 can form several homologous proteins at the translation level and create homologous or heterodimers or cooperate with other protein factors for specific cellular functions. It is involved in signal transduction pathways that respond to various extracellular signals through protein modifications, including phosphorylation, acetylation, ubiquitination, SUMOylation, methylation, oxidation, and glycosylation.

Phosphorylation of Nur77 can regulate its transcriptional activation activity. Mst1 promotes the transcriptional activity of Nur77 by phosphorylating the Nur77 threonine 366 site, increasing the expression of the downstream target β3-integrin, and improving the embryo implantation rate in delayed implantation mouse models.[113] Phosphorylation of Nur77 at threonine 88, induced by Chk2, inhibits the transcriptional activation activity of Nur77, and phosphorylation enables Nur77 to bind to the response elements on the promoter of BABAM2–BRISC and BRCA1 A complex member 2 (BRE) and RNF-7 genes, negatively regulating these two anti-apoptotic

genes and promoting cisplatin-induced apoptosis.[114] SBK1 phosphorylates Nur77 serine 344 to promote liver FGF21 expression and inhibit transcription of genes involved in lipid anabolism.[81]

Phosphorylation of Nur77 can affect the expression of the Nur77 protein. JNK induces phosphorylation of serine 95 at the N-terminal of Nur77, blocking the DNA-binding properties of Nur77 and reducing its trans-activation activity.[115] The Ser95-Pro motif of Nur77 is a key site where Pin1 enhances Nur77 stability by delaying its degradation. Pin1 can catalyze Nur77 by phosphorylating the Ser431-Pro motif, which is phosphorylated by extracellular signal-regulated kinase 2 (ERK2), thereby enhancing Nur77 trans-activation.[116]

Phosphorylation of Nur77 can affect its protein interactions. GSK3β phosphorylated threonine 27 and 143 of Nur77, weakening its inhibition of Wnt signaling.[117] Additionally, Lp38α phosphorylated threonine 27 and 143 of Nur77, inhibiting Nur77's binding to p65, compromising its ability to inhibit NF-κB activity, and activating the inflammatory response.[100]

Phosphorylation of Nur77 alters its subcellular localization. TGF-β enhances the invasion of breast and lung cancer cells through the phosphorylation-dependent nuclear output of the nuclear receptor Nur77.[118,119] Ribosomal S6 kinase (RSK) phosphorylates Nur77 at serine 354, regulating its nuclear output and intracellular translocations during T-cell death.[120] Akt phosphorylates cytoplasmic Nur77 through physical interaction with the N terminus of Nur77, inhibits the interaction between Nur77 and Bcl-2, impedes Nur77 mitochondrial localization, and inhibits the occurrence of apoptosis.[121] Conversely, the highly active Akt2 in tumor cells can phosphorylate Serine 533 of Nur77, retaining Nur77 in the nucleus and preventing its mitochondrial localization.[122]

Additionally, Serpina3c$^{-/-}$ inhibits Nur77 acetylation and increases its degradation. Serpina3c inhibits the transcriptional activation of enolase ENO1 by regulating Nur77 acetylation, thereby reducing fibrosis after myocardial infarction by inhibiting glycolysis.[123] Methylmercury inhibits the recruitment of the CREB-binding protein (CBP) complex to the Nur77 promoter region and impairs neuronal function associated with Nur77 inhibition by reducing acetylation of histone H3 lysine 14 levels.[124] The expression of p300 with histone acetyltransferase activity enhances the acetylation and protein stability of Nur77. HDAC1 reduces the acetylation level of Nur77, reducing its protein level and transcriptional activity; treatment with the HDAC inhibitor trogoustatin A increases Nur77 acetylation.[125,126] The post-practice Nr4a gene expression requires the CREB interaction domain of histone acetyltransferase CBP. Mutations in the CREB–CBP interaction domain reduce Nr4a promoter acetylation after learning.[127] SUMOylation of Nur77 inhibits its transcriptional activity in HEK-293T cells. By replacing arginine residues at two phylogenetically conserved putative SUMO receptor sites, Lysine 102 (K102) and 577 (K577), Nur77 transcriptional activity is regulated. Specifically, the Nur77-k102r and Nur77-K102R/K577R mutants significantly reduce Nur77 transcriptional activity. Conversely, a single K577R substitution increases Nur77 transcriptional activity. The K577R mutation reduced the inhibition of SUMO2 and PIASγ on Nur77 transcriptional activity, while the K102R mutant remained insensitive to SUMO2.[128] Under glucose starvation, ERK2 phosphorylation is activated, leading to the translocation of Nur77 to the mitochondria. The cysteine residues at positions 505, 551, and 566 of Nur77 undergo oxidation and modification. These modifications protect the rate-limiting enzyme TP-β in fatty acid oxidation (FAO) from oxidation, thereby regulating the FAO process.[38] TRAF2, a scaffold protein, and E3 ubiquitin ligase promote the ubiquitination of Nur77 in mitochondria, making it sensitive to autophagy.[107] PPARγ promotes the ubiquitination and degradation of Nur77 mediated by ubiquitin ligase Trim13 through binding to Nur77 and then affects the interaction of Nur77 with CD36 and FABP4 promoters, which promotes the occurrence and progression of breast cancer.[129,130] The E3 ubiquitin ligase Smad ubiquitination regulator 1 mitigated the JNK-mediated downregulation by mediating its unconventional ubiquitination to prevent Nur77 degradation, resulting in Nur77 accumulation and subsequent translocation to mitochondria to trigger apoptosis[131] (Figure 3).

2.11 | Summary

Nur77 plays an important role in cell physiological activities, indicating its complex, multi-level regulation; although the description of Nur77's physiological function remains vague and unclear, our understanding of the function is constantly improving.

3 | NUR77 AND NEUROLOGICAL DISEASES

Nur77 is associated with various neurological disorders, such as Parkinson's disease, multiple sclerosis, ischemic encephalopathy, AD, and depression. Many models of CNS disease in existing studies have shown that the lack of Nur77 can lead to increased symptoms and mortality in mice, suggesting that Nur77 has a protective effect in

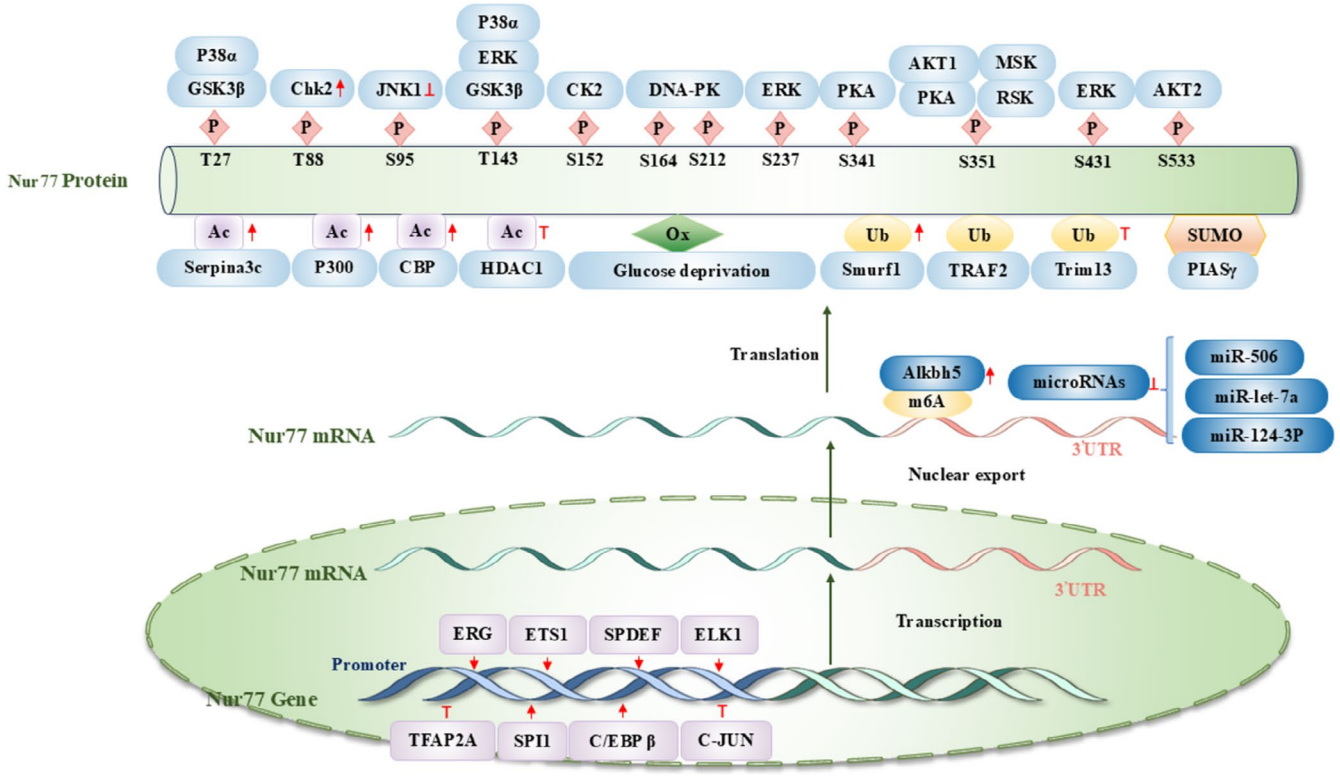

FIGURE 3 Molecular regulation of Nur77 at various levels. At the transcriptional level, transcription factors ERG, ETS1, SPDEF, ELK1, TFAP2A, SPI1, C/EBP-β, and c-Jun bind to the Nur77 promoter and regulate its expression. At the post-transcriptional level, Alkbh5 interacts with Nur77 mRNA, leading to the ablation of m6A modification and enhancing its stability. Some miRNAs also target the 3′UTR of the Nur77 gene, which leads to mRNA degradation. At the post-translational level, Nur77 can be phosphorylated at various sites by different phosphokinases. Additionally, Nur77 can be regulated by other post-translational modifications, such as acetylation, ubiquitination, and oxidation.

nervous system diseases, and its corresponding regulatory mechanisms need to be further studied.

3.1 | Parkinson's disease

Parkinson's (PD) usually involves the progressive loss of dopaminergic (DA) neurons in the substantia nigra and the accumulation of Lewy bodies composed mainly of alpha-synuclein (α-syn).[132] Studies have confirmed that genetic or drug promotion of Nur77 salvaged α-syn toxicity and altered inclusion body morphology in PD cell models and that treatment with the Nur77 agonist CN-B prevented DA cell death. Under alpha-SYN, Nur77 translocated from cytoplasm to mitochondria to improve prohibitin (PHB)-mediated mitochondrial autophagy by regulating c-Abl phosphorylation. Overexpression of Nur77 alleviates the expression level of pS129-α-syn and the loss of DA neurons in α-syn pre-formed fibrils mice, suggesting therapeutic potential for PD.[25] Microglia-mediated neuroinflammation plays a key role in PD pathological development. In vitro and experimental 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD mouse models exhibited reduced Nur77 expression in microglia. Overexpression of Nur77 or application of the Nur77 agonist cytosporone B inhibited the expression of proinflammatory genes such as inducible nitric oxide synthase, cyclooxygenase-2, IL-1β, and TNF-α in activated microglia, and activation of Nur77 inhibited LPS-induced NF-κB activation.[49,56,84] Additionally, studies have shown that the neurotoxin 6-hydroxydopamine causes rapid upregulation of Nur77 in the substantia nigra of rats. Genetic disruption of Nur77 in rats reduced neurotoxin-induced dopamine cell loss and L-dopa-induced dyskinesis, while viral-driven Nur77 striatal overexpression enhanced or partially restored chronic L-dopa-induced involuntary movement in wild-type and Nur77-deficient rats, respectively.[133] Compared with the WT 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine MPTP-treated control group, Nur77-deficient MPTP-treated mice demonstrated reduced levels of dopamine and 3,4-dihydroxyphenylacetic acid in the striatum and elevated postsynaptic FosB activity, indicating increased nigra striatum damage. Notably, in the nigrostriatal system, ectopic Nur77 expression salvaged this sensitization in Nur77-deficient mice.[134] Nur77 has an inhibitory effect on PD pathology, enhancing its potential as a therapeutic intervention target for PD.

3.2 | AD

Studies investigating the function of Nur77 in AD are limited. Amyloid-beta peptide (Aβ) is the most important biomarker for AD, and the amyloid-producing pathway of Aβ and Tau hyperphosphorylation are the most studied targets. An early study showed that compared with wild-type mice, the mRNA level of Nur77 in amyloid precursor protein (APP)+presenilin 1 (PS1) transgenic mice decreased, while the mRNA expression level of presynaptic markers (including synaptic vesicular and synaptic fusion proteins.) was relatively stable. Nur77 may regulate cognitive dysfunction before synaptic and neuronal degeneration.[135] Other studies indicated that Nur77 expression levels are normal in young APP + PS1 mice prior to amyloid deposition but decline as the mice age and amyloid deposit accumulation.[136] A genome-wide scan of the human promoter region nbrs found that SerpinA3 (1-anticoagulant trypsin), a major component of plaques that interacts with neurotoxic Aβ during the production of AD, can be identified as a novel Nur77 regulatory gene.[137] In NR4A family gene expression in the peripheral blood of patients with AD, only Nur77 gene expression was significantly downregulated.[138] Conversely, compared with wild-type mice, Nur77 expression is increased in the hippocampus of APP/PS1 transgenic mice, and overexpression of Nur77 in HT22 cells upregulates APP and BACE1 levels, downregulates the expression of ADAM10, and promotes amyloidosis. The results showed that α-CTF levels decreased and β-CTF levels increased. Nur77 accelerates tau hyperphosphorylation via GSK3β signaling.[139] Therefore, Nur77 plays a certain role in AD; however, it is necessary to deeply understand the mechanism of Nur77 in the AD process.

3.3 | Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease characterized by the central role of $CD4^+$ T cells in its pathogenesis. These peripherally activated T cells migrate to the CNS, leading to demyelination and axonal degeneration.[140] During the development of MS, various regulatory mechanisms were driven by Nur77. In a proteomic analysis of dysregulated pathways in activated T cells from healthy individuals and patients with MS, the Nur77 pathway was identified as a biological pathway known to limit the abnormal effect of T-cell responses.[141] Subsequent studies revealed that Esrra promoters can directly bind to the Nur77 protein, affecting T-cell mitochondrial metabolism, such as oxidative respiration and glycolysis. Nur77-deficient T cells are highly proliferative, and the lack of Nur77 is associated with enhanced T-cell activation and increased susceptibility to the T-cell-mediated inflammatory disease MS, identifying Nur77 as a transcriptional regulator of T-cell metabolism, which raises the threshold for T-cell activation.[9] Proper expression of Nur77 can promote the development of Treg cells by stimulating Foxp3 expression.[142] In the preclinical stage of MS, Nur77 expression is low in peripheral blood mononuclear cells. Knocking out the Nur77 gene in mice exacerbates symptoms of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. After treatment with Csn-B, the clinical symptoms of EAE in mice were significantly reduced. The percentage of $CD4^+$ T and $F4/80^+$ cells in the CNS decreased.[143,144] Thus, Nur77, as a major regulatory gene of T-cell metabolism, enhances its potential as a therapeutic intervention target for MS.

Additionally, the adrenal signaling system is involved in the development of MS. Transcription factor Nur77 regulates the production of norepinephrine (NE) in macrophages, limiting EAE. Nur77 inhibits autocrine NE production in macrophages by recruiting the corepressor protein to the Th promoter. NE and proinflammatory IL-6 reactivate monocyte-derived macrophages through adrenergic and gp130 receptors, respectively, leading to the aggravation of the vicious cycle of the inflammatory response and promoting the recruitment of T cells and other inflammatory cells to the CNS. Nur77 serves as a regulator of inflammation and the sympathetic nervous system.[145] Moreover, microglia play a critical role in the development and progression of MS, and Nur77 loss triggers spontaneous and excessive microglia activation, leading to increased cytokine and nitric oxide production and accelerated and worsened forms of EAE. Ligand-induced Nur77 activation correspondingly improves disease outcomes.[48] Fingomode and Sinimode (BAF312) are selective agonists of the sphingosine-1-phosphate receptor and are approved for the treatment of relapsing remission and secondary progression MS, respectively. BAF312 enhances Nur77 expression in the N9 microglia cell line and exerts pro-myelination and neuroprotective functions on CNS resident cells.[146]

Nur77 has been identified as a regulator of microglia activation and a potential new target for treating inflammatory CNS diseases such as MS.

3.4 | Cerebrovascular diseases

Cerebrovascular diseases are often characterized by cerebral tissue ischemia or bleeding accidents, such as cerebral atherosclerosis, moyamoya disease (MMD), cerebral hemorrhage, and cerebral ischemia. Arterial remodeling is a key process in vascular diseases such as aneurysm formation and atherosclerosis, and lipid-rich foam cells

derived from subcutaneous macrophages contribute to the occurrence and progression of atherosclerosis. SLAMF7 is upregulated in mouse bone marrow-derived macrophages and RAW264.7 cells stimulated with oxidized low-density lipoprotein (ox-LDL). SLAMF7 responds to ox-LDL by downregulating Nur77 and upregulating RUNX3. Overexpression of Nur77 reverses SLAMF7-induced lipid uptake and M1 polarization by inhibiting RUNX3 expression, thereby alleviating carotid atherosclerosis progression.[147–149] Furthermore, activation of the pyrin domain of the NLRP3 inflammatory-mediated IL-1β secretion is a vital part of the inflammatory process of atherosclerosis formation. Nur77$^{-/-}$ mice showed severe plaque load associated with increased lipid deposition, decreased smooth muscle cells, macrophage infiltration, and decreased collagen expression, and Nur77 deletion promotes atherosclerosis formation by exacerbating NLRP3-mediated inflammation.[150] MMD is a rare progressive cerebrovascular disease characterized by stenosis and occlusion. A gene expression profile of intracranial arteries in MMD patients revealed gender-specific differentially expressed genes. Examples include aquaporin-4, superoxide dismutase 3, and Nur77, a member of the nuclear receptor subfamily 4 Group A. These findings highlight sex differences in gene expression in intracranial arteries and offer new insights into the pathogenesis of MMD.[149] Additionally, Nur77 promotes apoptosis of brain cells by mediating early brain injury and triggering conformational changes of BCL-2, resulting in the release of cytochrome C. Nur77 activity and brain cell apoptosis peaked 24 h after the onset of subarachnoid hemorrhage (SAH). Following SAH induction, the Nur77 agonist Csn-B was injected to enhance Nur77 expression and function.[151] In the thrombotic focal ischemia model, at an early point (1–4 h), nerve growth factor-induced gene A was rapidly induced throughout the ipsilateral cortex, with no significant differences between distal cortical regions.[152] Nur77 expression significantly increased in microglia after ischemic brain injury. Nur77 KO reduces infarct volume and ischemia-induced neuronal injury, inhibits neuronal apoptosis, and alleviates M1 polarization in microglia and neutrophil recruitment. The expression of M1 markers, chemokines, intracellular adhesion molecule-1, and myeloperoxidase levels was reduced, while the expression of anti-inflammatory factors in oxygen-glucose deprivation (OGD)-treated microglia was salvaged to alleviate ischemic stroke.[153,154] In contrast, Nur77 expression was upregulated in cerebral ischemia–reperfusion or OGD/reoxygenation (OGD/R) models, and in SiNur77-transfected cells, the number of dysfunctional mitochondria increased and mitochondrial autophagy was inhibited, which exacerbated OGD/R-induced neuronal damage.[155] Therefore, Nur77 tends to promote apoptosis in hemorrhagic stroke while inhibiting neuronal apoptosis in ischemic stroke. It acts as a bridge between mitochondria-mediated apoptosis and autophagy in CNS-related inflammation and metabolism.

3.5 | Other neurological disorders

Nur77 has been linked to depression. At high latitudes, approximately 10% of the population suffers from depression during the winter months, and levels of Nur77 are observed to be suppressed in the brains of muskefish during this period. Cytosporone B, a chemical activator of Nur77, reverses winter depression-like behavior.[156] Other studies have shown that Nur77 mRNA levels in the dentate gyrus are decreased in patients with major depression compared with control subjects with normal mental health.[157]

Nur77 plays a crucial role in neurological diseases, particularly neurodegenerative diseases. Currently, most studies have shown that Nur77 protects against neuropathy (Figure 4). However, its role in AD and other neurodegenerative diseases has not been explored comprehensively. Existing studies have shown that Nur77 may play a role in the pathological process of AD by regulating oxidative stress, autophagy, and mitochondrial function. The absence of Nur77 may aggravate beta-amyloid protein (Aβ) accumulation and hyperphosphorylation of tau protein, which may further exacerbate neuroinflammation and apoptosis. In addition, Nur77 is strongly associated with mitochondria-related apoptotic pathways, and its studies in Huntington's disease and amyotrophic lateral sclerosis (ALS) have shown similar neuroprotective potential. For example, Nur77 may improve Huntington protein aggregation by regulating autophagy mechanisms, while alleviating oxidative stress-induced motor neuron degeneration in ALS. Although such findings provide clues to the neuroprotective effects of Nur77, its specific molecular mechanisms in AD and other neurodegenerative diseases still require further investigation.

Future research should focus on the factors that affect Nur77's balance between neuronal survival and death, as well as its roles in anti-inflammatory, proinflammatory responses, and other cellular events. Key considerations should include subcellular localization, cell type, cell environment, interactions with other signaling molecules, and the types of stimuli that regulate Nur77's expression and activity. More conditional KO animal models and clinical data are needed to elucidate the therapeutic potential of Nur77 in neurological diseases.

4 | NUR77 AND CANCER

Many studies have linked Nur77 with cancer, where Nur77 expression is always disorganized.

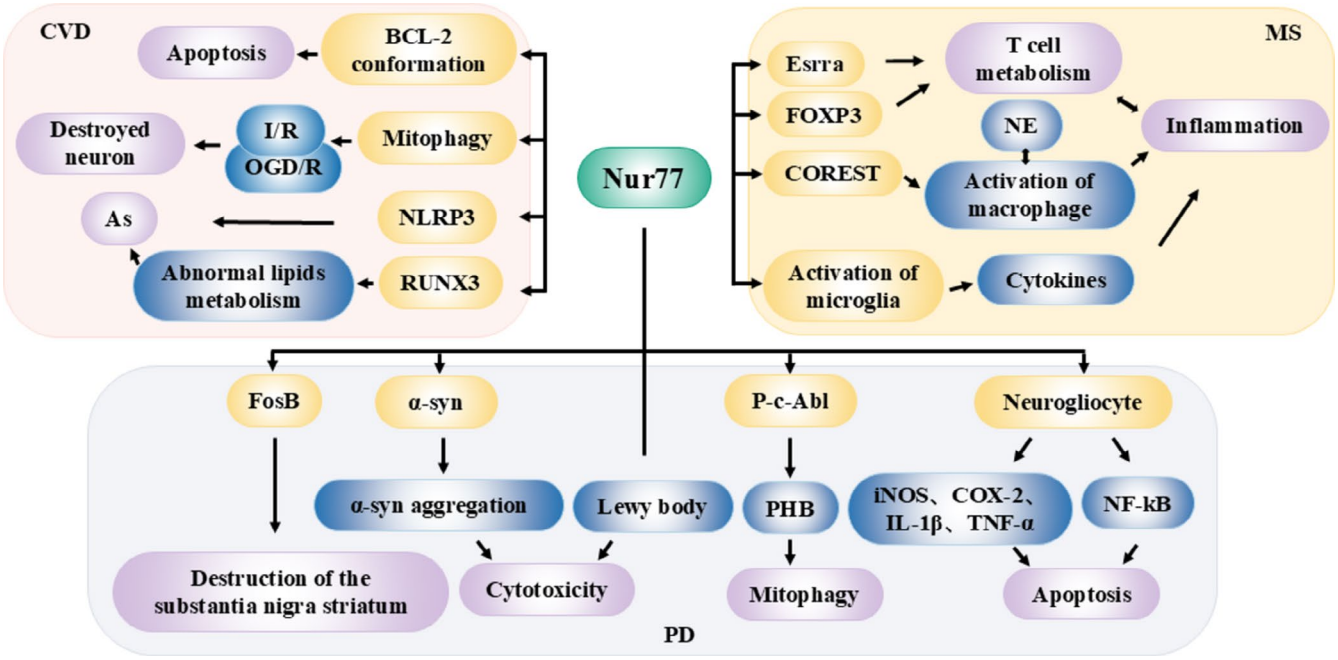

FIGURE 4 Nur77 in neurodegenerative diseases. Numerous studies have identified Nur77 as having a neuroprotective role in neurodegenerative diseases. In the PD model, Nur77 mitigates alpha-SYN toxicity, alters inclusion body morphology, prevents DA cell death, regulates mitochondrial autophagy, and reduces inflammation. In the MS model, Nur77 regulates T-cell metabolism and regulates the production of norepinephrine (NE) in macrophages, thereby limiting autoimmune encephalomyelitis (EAE). Additionally, Nur77 suppresses the spontaneous and excessive activation of microglia, thereby curtailing the inflammatory response. In the CVD model, Nur77 impedes the progression of cerebral atherosclerosis and serves as a mediator between mitochondria-mediated apoptosis and autophagy.

4.1 | Breast cancer

Breast cancer is the most common malignant tumor in females, and the research on Nur77 in breast cancer is relatively extensive, although there has been controversy about whether Nur77 inhibits or promotes breast cancer. Nur77 is a key player in inhibiting exogenous fatty acid uptake by breast cancer cells, inhibiting CD36 and FABP4 expression by recruiting SWI/SNF complexes and HDAC1 transcription, thereby hindering the development of breast cancer. However, the highly expressed nuclear receptor PPARγ interacts with Nur77 to recruit ubiquitin ligase Trim13 to target Nur77 for degradation. This effect of Nur77 is ineffective during breast cancer progression, while Csn-B treats breast cancer by disrupting Nur77-Pparγ binding, thereby enhancing Nur77's blocking of fatty acid uptake in the tumor metabolic microenvironment.[129] In vitro, hypoxia induces the expression of HIF-1α and Nur77 in breast cancer cells, while the addition of β-glucan from *Lentinus* (LNT) downregulates HIF-1α expression in oxygen-free environments, and the process is partially dependent on Nur77, involving the Nur77-mediated ubiquitin-proteasome pathway. LNT appears to inhibit breast cancer progression in part through the Nur77/HIF-1α signaling axis.[158]

Conflicting data have also been published, with Paraspeckle Component 1 (PSPC1) reported as a major regulator of the pro-cancer response, including activation of TGFβ, TGFβ-dependent epithelial–mesenchymal transition, and metastasis. Knockdown of NUR77 reduces the expression of PSPC1 in MDA-MB-231 breast cancer cells. The results of chromatin immunoprecipitation showed that Nur77 regulates PSPC1 by interacting with the Nuclear Respiratory Factor Binding Element sequence in the PSPC1 gene promoter. Nur77 antagonists inhibit breast tumor growth and downregulate PSPC1 in tumors.[17]

These studies illustrate inconsistencies in data related to the Nur77 breast cancer study. More clinical evidence and mechanistic studies are needed to clarify the role of Nur77 in breast cancer development.

4.2 | Lung cancer

The present study tends to promote lung cancer metastasis by Nur77. Orphan nuclear receptors Nur77 (NR41A and Nur77) are overexpressed in most patients with lung cancer. RNA interference knockdown of Nur77 (si Nur77) inhibits the growth of cancer cells and induces apoptosis. Nur77 promotes lung cancer cell development by inhibiting P53 and activating mTORC1.[159] Additionally, TGF-β enhances lung cancer cell invasion through the phosphorylation-dependent nuclear output of the nuclear receptor Nur77.[17]

TIAM1-RAC1 signaling promotes small-cell lung cancer cell survival through Nur77 nuclear isolation.[160]

4.3 | Liver cancer

Current studies suggest that Nur77 inhibits the occurrence and progression of liver cancer. Nur77 is downregulated in HB tumors compared with paracancer tissue and inhibits tumor cell proliferation by affecting β-catenin expression.[161] Extracellular vesicles are crucial in intercellular communication within the tumor microenvironment, and TGF-β stimulates palmitoylation of hexokinase 1 (HK1) in HSCs, promoting HK1 secretion via large extracellular vesicles in a TSG101-dependent manner. Large extracellular vesicles of HK1 are hijacked by HCC cells, accelerating glycolysis and HCC progression. Nur77 transcription activates the expression of the depalmitoylase ABHD17B to inhibit HK1 palmitoylation, reducing HK1 release. The small molecule PDNPA, which binds to Nur77 to generate steric hindrance and block Akt targeting, disrupts Akt-mediated Nur77 degradation and preserves Nur77's inhibition of HK1 release, inhibiting HCC progression.[1] Furthermore, nuclear output from Nur77 promotes apoptosis of liver cancer cells, and chemotherapy agents targeting Nur77-mediated cytoplasmic vacuolation and paratropsis may provide a promising strategy for fighting HCC, which often evades apoptosis.[162–164] Nur77 inhibits HCC development through transcriptional activation of the lncRNA WAP four-disulfide core domain 21 pseudogene (WFDC21P). WFDC21P can inhibit glycolysis by simultaneously interacting with PFKP and PKM2, two key enzymes in glycolysis.[21] Gluconeogenesis is an important metabolic process of hepatocytes and is downregulated in HCC. Nur77 inhibits HCC by reducing phosphoenolpyruvate carboxykinase SUMOylation to shift glucose metabolism to gluconeogenesis.[32]

4.4 | Colon cancer

Reportedly, high Nur77 expression promotes the apoptosis of colon cancer cells and inhibits the growth of colon tumors.[165,166] However, conflicting data show that most human colon tumors (9 out of 12) have elevated Nur77 levels compared with non-tumor tissues and are potentially induced by different colon carcinogens, including deoxycholic acid (DCA). DCA-induced Nur77 expression upregulates anti-apoptotic BRE and angiogenic vascular endothelial growth factor (VEGF), enhances the growth, colony formation, and migration of colon cancer cells, and acts as an important mediator of Wnt/β-catenin and AP-1 signaling pathways.[167,168] Beta-catenin is a potent cancer-causing protein in colorectal cancer, and hypoxic triggering of the Nur77–beta-catenin feedforward loop promotes aggressive growth of colon cancer cells.[169] Nur77 antagonists inhibit colon tumor growth, downregulate PD-L1 expression in mouse colon Mc-38-derived tumors and cells, and inhibit Nur77-dependent T-cell depletion in tumor-infiltrating lymphocyte and spleen.[170]

However, studies have shown that the effect of Nur77 on colon cancer tissue is affected by TGF-β, and differentiation inhibitor 1 (ID1) is a target gene of TGF-β and a key promoter of colon cancer progression. Nur77 enhances TGFβ/SMAD3-induced ID1 mRNA expression by blocking SMurF2-mediated Smad3 monoubiquitination, upregulating ID1 to play a pro-cancer role. In the absence of TGFβ, Nur77 disrupts the stability of ID1 protein by promoting SMURF2-mediated ID1 polyubiquitination, leading to ID1 downregulation and its anticancer effect.[34] These inconsistent reports make it difficult to clarify the role of Nur77 in colon cancer.

4.5 | Pancreatic cancer

Nur77 is overexpressed in human pancreatic tumors compared with non-tumor tissues. Its knockdown reduces the proliferation of pancreatic cancer cells, promotes apoptosis, and reduces anti-apoptosis gene expression (including Bcl-2 and survivin), which mediates survivin inhibition by forming the NUR77-SP1-P300 DNA-binding complex in the GC-rich region near the survivin promoter.[171] It regulates ER stress and ROS levels in pancreatic cancer cells to promote cell proliferation and survival.[172] Additionally, highly expressed Nur77 interacts with cyclin-dependent kinase inhibitor p21 to promote the proliferation of pancreatic cancer cells.[15] High expression of β1-integrin is a negative prognostic factor in patients with pancreatic cancer. Nur77 overexpression upregulates β1-integrin protein and mRNA expression, α5-integrin, and β1-integrin-dependent phosphorylated FAK expression, and promotes pancreatic cell migration and fibronectin-induced adhesion.[173]

4.6 | Leukemia

Recent studies reveal that Nur77 is a tumor suppressor gene in leukemia. Compared with wild-type mice, $Nur77^{-/-}$ mice rapidly develop acute myeloid leukemia (AML).[174–176] The main mechanism of Nur77 promotes apoptosis and differentiation of leukemia cells.[24] Ginsenoside 20 (S)-Rh2 induces apoptosis and differentiation of AML cells. It promotes the translocation of

Nur77 from the nucleus to mitochondria, enhances the interaction between Nur77 and Bcl-2, and leads to the BH3 domain exposure of Bcl-2, activating Bax. Therefore, the Nur77-mediated signaling pathway is highly involved in Ginsenoside 20 (S)-Rh2-induced apoptosis and differentiation of AML cells,[177] which represents a potential clinical application for treating this disease.

4.7 | Other cancers

Bladder cancer is the second most prevalent malignancy of the genitourinary system, and Nur77 is overexpressed in bladder tumors and cancer cells compared with non-tumor bladder tissue.[178] High Nur77 expression inhibits UM-UC-3 cell growth and cell cycle progression, and Nur77 competes with the androgen receptor to bind to Src-1, a well-known steroid coactivator, thereby inhibiting the growth of androgen-dependent bladder cancer cells.[35] Nur77 promotes the survival of melanoma cells under metabolic stress by protecting FAO, thus playing a role in promoting cancer.[38] Another study found that mitochondrial localization of Nur77 triggers apoptosis of melanoma cells.[179,180]

The function of Nur77 in tumors is complex, with varying reports showing upregulated Nur77 in melanoma, lung, bladder, colon, and pancreatic cancers, while other studies show that it is downregulated in liver and breast cancers. Moreover, its function differs across tumor types, subtypes, and different stages of development (Figure 5, Table 3). For example, Nur77 has both cancer-promoting and cancer-suppressing effects at different stages of breast and colon cancer development. The contradictory effect is attributable to the tissue-specific regulation of its activity and its interaction with different ligands or signaling pathways. For example, Nur77, through its interaction with metabolic regulators such as Sirt1 or Akt, may both enhance anti-tumor immune responses and support tumor cell metabolic adaptation. In addition, changes in the subcellular localization of Nur77, such as transfer to mitochondria or retention in the nucleus, also significantly affect its role in cancer. This bidirectional function reveals the potential challenges and opportunities for Nur77 as a therapeutic target. Future studies should further analyze its regulatory network in different tumor types to clarify the mechanisms of its cancer-promoting or cancer-suppressing effects, which would optimize its application strategies in cancer therapy.

5 | OTHER DISEASES

Additionally, Nur77 is associated with several other diseases, emphasizing its broad regulatory role in disease. Its deletion affects systemic glucose metabolism, leading to increased susceptibility to diet-induced obesity and insulin resistance in mice. HFD-induced insulin

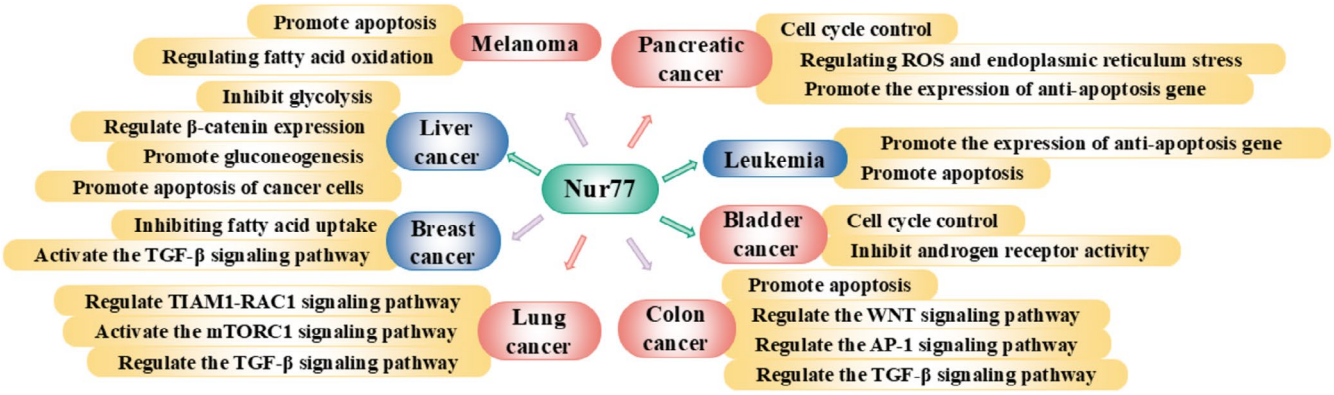

FIGURE 5 Nur77 in tumors. The multiple roles of Nur77 vary across different cancer types. In breast cancer, Nur77 has a dual role: It exerts a cancer-inhibiting effect by reducing the uptake of exogenous fatty acids in breast cancer cells and a cancer-promoting effect by activating the tumor TGF-β signaling pathway. In lung cancer, Nur77 enhances metastasis by regulating the TIAM1-RAC1, mTORC1, and TGF-β signaling pathways. In liver cancer, Nur77 acts as an anticancer agent by regulating β-catenin expression, inhibiting glycolysis, enhancing gluconeogenesis, and promoting apoptosis. In colon cancer, Nur77 exerts a cancer-inhibiting effect by promoting apoptosis of cancer cells and a cancer-promoting effect by regulating the Wnt/AP-1/TGF-β signaling pathway. Nur77 encourages pancreatic cancer development by regulating reactive oxygen species and endoplasmic reticulum stress, promoting the expression of anti-apoptotic genes, and controlling the cell cycle. Nur77 inhibits the development of leukemia by enhancing anti-apoptotic gene expression and promoting apoptosis. In bladder cancer, Nur77 suppresses tumor growth by controlling the cell cycle and inhibiting androgen receptor activity. In melanoma, Nur77 promotes cancer by regulating fatty acid oxidation and acts as an anticancer agent by promoting apoptosis. The red box indicates high Nur77 expression in the tumors relative to adjacent tumors. The blue box represents low Nur77 expression in tumors. The red arrows denote Nur77's cancer-promoting roles, green arrows indicate suppressing roles, and purple arrows highlight ongoing controversy.

TABLE 3 Nur77 in tumors.

Tumor type	Expression level (cancer/paracancer)	Biological function	Mechanism	Reference
Breast cancer	Low	Promotion and inhibition	Inhibiting fatty acid uptake; Activate the TGF-β signaling pathway	[17,158]
Lung cancer	High	Promotion	Regulate TIAM1-RAC1 signaling pathway; Activate the mTORC1 signaling pathway; Regulate the TGF-β signaling pathway	[17,159,160]
Liver cancer	Low	Inhibition	Inhibit glycolysis; Regulate β-catenin expression; Promote gluconeogenesis; Promote apoptosis of cancer cells	[1,32,162–164]
Colon cancer	High	Promotion and inhibition	Promote apoptosis; Regulate the WNT signaling pathway; Regulate the AP-1 signaling pathway; Regulate the TGF-β signaling pathway	[165–170]
Pancreatic cancer	High	Promotion	Increased GLS1 promoter methylation Cell cycle control; Regulating ROS and endoplasmic reticulum stress; Promote the expression of anti-apoptosis gene	[171–173]
Leukemia	Low	Inhibition	Promote the expression of anti-apoptosis gene; Promote apoptosis	[174–177]
Bladder cancer	High	Inhibition	Cell cycle control; Inhibit androgen receptor activity	[35,178]
Melanoma	High	Promotion and inhibition	Promote apoptosis; Regulating fatty acid oxidation	[38,179,180]

resistance is greater in the skeletal muscle and liver of Nur77-deficient mice. Loss of Nur77 expression in skeletal muscle impairs insulin signaling and reduces GLUT4 protein expression.[55,181] Gestational diabetes mellitus (GDM) is a common complication of pregnancy. Nur77 expression is abnormally upregulated in the placental tissues of GDM mice. This may be linked to Nur77's ability to enhance the insulin sensitivity of HTR-8/SVneo cells by activating the IRβ/IRS/Akt/GLUT4 pathway and regulating autophagy.[80] Leptin is an anorexic hormone in the hypothalamus that inhibits food intake and increases energy expenditure. Non-response to leptin leads to obesity. Nur77 enhances the transcriptional activity of STAT3 by recruiting acetylase p300 and HDAC1, regulating the expression of the Pomc gene in the middle and lower hypothalamus, thereby promoting the STAT3 acetylation activator. Therefore, Nur77 can be used as a leptin-driven positive regulator of hypothalamic anti-obesity.[36]

6 | DISCUSSION AND CONCLUSIONS

This paper reviewed the function of Nur77, revealing its role in nervous system regulation, mitosis, and genome integrity, cell differentiation, cell homeostasis, aging, infection and inflammation, oxidative stress, and autophagy. We summarized the current regulatory mechanisms of Nur77 and its identification as a substrate for transcription factor regulation (Table 1) and as a transcription-independent regulator through protein interactions and changes in subcellular localization (Table 2). Additionally, we examined the current role of Nur77 in neurological diseases and cancer, emphasizing its potential as a therapeutic target.

Nur77 plays an indispensable role in various physiological processes, particularly in aging. Oxidative stress, mitochondrial dysfunction, and chronic inflammation increase significantly with an increase in age, becoming the core drivers of aging and related diseases. For the first time, our research team found that Nur77 deficiency is associated with aging phenotypes in mice, including kidney, liver, and fat aging. The NUR77-deficient mice had a shorter lifespan than the wild-type mice. Nur77 is essential in multi-organ aging models. For example, the regulation of Sirt1 homeostasis by Nur77 facilitates oxidative stress and apoptosis resistance, thereby delaying organ degradation associated with aging. In renal aging, Nur77 alleviates renal fibrosis and improves function by inhibiting TGF-β/Smad signaling pathways. In addition, the

role of Nur77 in cancer and neurodegenerative diseases, such as Alzheimer's and Parkinson's, is of interest. In cancer, Nur77 exhibits bidirectional function by modulating tumor suppression and growth promotion pathways. In neurodegenerative diseases, it has shown therapeutic potential by regulating mitochondrial autophagy, inhibiting inflammation, and maintaining neuronal survival. Among them, one common regulatory mechanism of Nur77 in cancer and neurodegenerative diseases is its regulation of T-cell metabolism. In T-cell biology, Nur77 is essential for thymic cell selection and the maintenance of immune tolerance. Its dysfunction can lead to T-cell failure, impaired anti-tumor immune function, and increased susceptibility to neurodegenerative diseases such as MS, and certain infection-related diseases.

Although existing studies have shown that Nur77 plays an important role in aging and disease, its specific molecular mechanisms and interaction networks still need to be explored further. A comprehensive understanding of the regulatory role of Nur77 in cell homeostasis and pathological processes not only helps to reveal its central role in age-related diseases but also provides a solid scientific basis for therapeutic strategies targeting Nur77.

Beyond the classical transcription of the nuclear receptor family, Nur77 has other functions independent of transcription. However, with the increasing number of Nur77 substrates discovered, transcription remains its primary function for exerting its physiological and pathological effects. Additionally, Nur77 modulates the same substrate across different physiological and disease models, resulting in varied physiological changes, possibly due to microenvironment and tissue specificity (Figure 6). However, Nur77 regulates multiple substrates in the same disease, playing different or opposing roles, necessitating further in vivo studies to elucidate its mechanisms.

Furthermore, in different tumor types, subtypes, and developmental stages, Nur77 plays different roles, promoting and inhibiting cancer as a proto-oncogene and tumor suppressor gene, respectively. It is an important anti-tumor drug target, which can induce apoptosis and autophagy through Nur77 mediation and inhibit tumor growth. Screening small molecules that block or enhance the interaction between nuclear receptors and key proteins may represent a new direction for screening nuclear receptor-targeting drugs. Currently, due to the limitation of technical means, the endogenous ligand of Nur77 has not been isolated and detected. Although the discovery of agonists and antagonists in vitro facilitates the study of Nur77's function, finding and identifying its true endogenous ligand remain a challenging task. Therefore, developing new separation techniques and pioneering new detection methods is essential. Continued rapid growth in Nur77 research will enhance our understanding of the function of this protein, clarify its role in human health and disease, and promote its clinical application as a therapeutic target.

This review comprehensively explored the multifaceted functions of Nur77. The findings underscore the therapeutic potential of Nur77, particularly in neurodegenerative diseases and cancer. Its ability to modulate

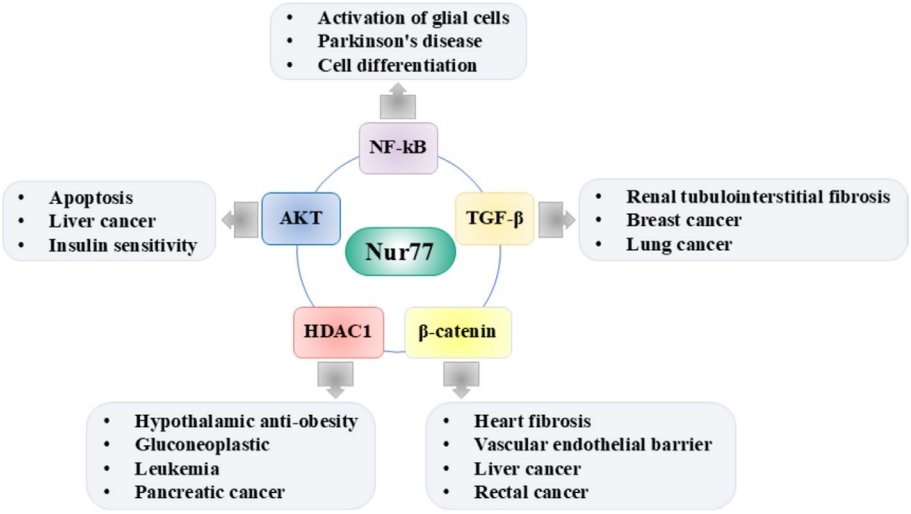

FIGURE 6 Shared substrate regulation of Nur77 in various physiological and disease processes. Nur77 is involved in the development of renal tubulointerstitial fibrosis, breast cancer, and lung cancer through the TGF-β signaling pathway. Additionally, Nur77 contributes to cardiac fibrosis, the integrity of the vascular endothelial barrier, and the development of liver and rectal cancers via the β-catenin signaling pathway. Nur77 also affects gluconeogenesis, hypothalamic anti-obesity mechanisms, and the development of pancreatic and breast cancers by binding to HDAC1. Furthermore, it influences apoptosis, insulin sensitivity, and liver cancer development through the Akt signaling pathway, and it plays a role in glial activation, Parkinson's disease, and cell differentiation through the NF-κB pathway.

critical cellular processes positions it as a promising target for drug development. However, significant gaps remain in our understanding of its mechanisms of action and translational applications. Future research should focus on elucidating such mechanisms, with an emphasis on preclinical and clinical studies to unlock its full potential as a therapeutic target across diverse diseases.

AUTHOR CONTRIBUTIONS

Yanteng Wang wrote the original draft of the manuscript; Na Li and Difei Wang reviewed the manuscript; Wenwei Guan conducted the literature review.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.jp) for English language editing. This work was supported by the Major Research Plan of the National Natural Science Foundation of China [grant number 92249305] and the Doctoral research project of Liaoning Province [2023-BSBA-334].

DISCLOSURES

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Yanteng Wang https://orcid.org/0000-0001-6807-2041
Na Li https://orcid.org/0009-0003-9650-4755
Wenwei Guan https://orcid.org/0009-0004-0306-4103
Difei Wang https://orcid.org/0000-0002-1118-658X

REFERENCES

1. Chen QT, Zhang ZY, Huang QL, et al. HK1 from hepatic stellate cell-derived extracellular vesicles promotes progression of hepatocellular carcinoma. *Nat Metab*. 2022;4(10):1306-1321.
2. Song KH. Orphan nuclear receptor Nur77 participates in human apolipoprotein A5 gene expression. *Biochem Biophys Res Commun*. 2010;392(1):63-66.
3. Ding R, Sun X, Yi B, et al. Nur77 attenuates inflammasome activation by inhibiting Caspase-1 expression in pulmonary vascular endothelial cells. *Am J Respir Cell Mol Biol*. 2021;65(3):288-299.
4. Li X, Wei W, Huynh H, Zuo H, Wang X, Wan Y. Nur77 prevents excessive osteoclastogenesis by inducing ubiquitin ligase Cbl-b to mediate NFATc1 self-limitation. *elife*. 2015;4:e07217.
5. Pu ZQ, Liu D, Lobo Mouguegue HP, et al. NR4A1 counteracts JNK activation incurred by ER stress or ROS in pancreatic β-cells for protection. *J Cell Mol Med*. 2020;24(24):14171-14183.
6. Cui C, Wang X, Zheng Y, et al. Nur77 as a novel regulator of Paneth cell differentiation and function. *Mucosal Immunol*. 2024;17(4):752-767.
7. Geng N, Chen T, Chen L, et al. Nuclear receptor Nur77 protects against oxidative stress by maintaining mitochondrial homeostasis via regulating mitochondrial fission and mitophagy in smooth muscle cell. *J Mol Cell Cardiol*. 2022;170:22-33.
8. Fassett MS, Jiang W, D'Alise AM, Mathis D, Benoist C. Nuclear receptor Nr4a1 modulates both regulatory T-cell (Treg) differentiation and clonal deletion. *Proc Natl Acad Sci USA*. 2012;109(10):3891-3896.
9. Liebmann M, Hucke S, Koch K, et al. Nur77 serves as a molecular brake of the metabolic switch during T cell activation to restrict autoimmunity. *Proc Natl Acad Sci USA*. 2018;115(34):E8017-E8026.
10. Shiozaki Y, Miyazaki-Anzai S, Keenan AL, Miyazaki M. MEF2D-NR4A1-FAM134B2-mediated reticulophagy contributes to amino acid homeostasis. *Autophagy*. 2022;18(5):1049-1061.
11. Chao LC, Zhang Z, Pei L, Saito T, Tontonoz P, Pilch PF. Nur77 coordinately regulates expression of genes linked to glucose metabolism in skeletal muscle. *Mol Endocrinol*. 2007;21(9):2152-2163.
12. Yang Y, Xie F, Qin D, et al. The orphan nuclear receptor NR4A1 attenuates oxidative stress-induced β cells apoptosis via up-regulation of glutathione peroxidase 1. *Life Sci*. 2018;203:225-232.
13. Shen J, Zhu X, Zhang M, et al. Nur77 promotes embryo adhesion by transcriptionally regulating HOXA10 expression. *Syst Biol Reprod Med*. 2020;66(1):50-58.
14. Yu Y, Song X, Wang X, et al. Oxidative stress impairs the Nur77-Sirt1 axis resulting in a decline in organism homeostasis during aging. *Aging Cell*. 2023;22(5):e13812.
15. Lee SO, Chintharlapalli S, Liu S, et al. p21 expression is induced by activation of nuclear nerve growth factor-induced Balpha (Nur77) in pancreatic cancer cells. *Mol Cancer Res*. 2009;7(7):1169-1178.
16. Li XC, Yin XJ, Hong W, et al. The orphan nuclear receptor NUR77 promotes trophoblast invasion at early pregnancy through paracrine placental growth factor. *J Mol Med (Berl)*. 2019;97(9):1359-1373.
17. Mohankumar KR, Shrestha R. Safe, nuclear receptor 4A1 (NR4A1) antagonists target paraspeckle component 1 (PSPC1) in cancer cells. *Mol Carcinog*. 2022;61(1):73-84.
18. You X, Guo ZF, Cheng F, et al. Transcriptional up-regulation of relaxin-3 by Nur77 attenuates β-adrenergic agonist-induced apoptosis in cardiomyocytes. *J Biol Chem*. 2018;293(36):14001-14011.
19. Lu L, Jang S, Zhu J, Qin Q, Sun L, Sun J. Nur77 mitigates endothelial dysfunction through activation of both nitric oxide production and anti-oxidant pathways. *Redox Biol*. 2024;70:103056.
20. Chen F, Yu Y, Tian H, et al. Nur77 is involved in the regulation of obesity-related lower muscle mass by promoting Pten degradation. *FASEB J*. 2023;37(8):e23083.
21. Guan YF, Huang QL, Ai YL, et al. Nur77-activated lncRNA WFDC21P attenuates hepatocarcinogenesis via modulating glycolysis. *Oncogene*. 2020;39(11):2408-2423.
22. Banta KL, Wang X, Das P, Winoto A. B cell lymphoma 2 (Bcl-2) residues essential for Bcl-2's apoptosis-inducing interaction with Nur77/Nor-1 orphan steroid receptors. *J Biol Chem*. 2018;293(13):4724-4734.
23. Jacobs CM, Boldingh KA, Slagsvold HH, Thoresen GH, Paulsen RE. ERK2 prohibits apoptosis-induced subcellular

translocation of orphan nuclear receptor NGFI-B/TR3. *J Biol Chem*. 2004;279(48):50097-50101.
24. Yu Z, Li L, Wang C, et al. Cantharidin induces apoptosis and promotes differentiation of AML cells through nuclear receptor Nur77-mediated signaling pathway. *Front Pharmacol*. 2020;11:1321.
25. Yin S, Shen M, Zhang Y, et al. Nur77 increases mitophagy and decreases aggregation of α-synuclein by modulating the p-c-Abl/p-PHB2 Y121 in α-synuclein PFF SH-SY5Y cells and mice. *Eur J Med Chem*. 2024;268:116251.
26. Chen L, Liang B, Xia S, et al. Emodin promotes hepatic stellate cell senescence and alleviates liver fibrosis via a nuclear receptor (Nur77)-mediated epigenetic regulation of glutaminase 1. *Br J Pharmacol*. 2023;180(19):2577-2598.
27. Wu H, Li XM, Wang JR, et al. NUR77 exerts a protective effect against inflammatory bowel disease by negatively regulating the TRAF6/TLR-IL-1R signalling axis. *J Pathol*. 2016;238(3):457-469.
28. Yan G, Zhu N, Huang S, et al. Orphan nuclear receptor Nur77 inhibits cardiac hypertrophic response to beta-adrenergic stimulation. *Mol Cell Biol*. 2015;35(19):3312-3323.
29. Ye T, Peng J, Liu X, et al. Orphan nuclear receptor TR3/Nur77 differentially regulates the expression of integrins in angiogenesis. *Microvasc Res*. 2019;122:22-33.
30. Peng SZ, Chen XH, Chen SJ, et al. Phase separation of Nur77 mediates celastrol-induced mitophagy by promoting the liquidity of p62/SQSTM1 condensates. *Nat Commun*. 2021;12(1):5989.
31. Shi Z, To SK, Zhang S, et al. Hypoxia-induced Nur77 activates PI3K/Akt signaling via suppression of Dicer/let-7i-5p to induce epithelial-to-mesenchymal transition. *Theranostics*. 2021;11(7):3376-3391.
32. Bian XL, Chen HZ, Yang PB, et al. Nur77 suppresses hepatocellular carcinoma via switching glucose metabolism toward gluconeogenesis through attenuating phosphoenolpyruvate carboxykinase sumoylation. *Nat Commun*. 2017;8:14420.
33. Kim BY, Kim H, Cho EJ, Youn HD. Nur77 upregulates HIF-alpha by inhibiting pVHL-mediated degradation. *Exp Mol Med*. 2008;40(1):71-83.
34. Niu B, Liu J, Lv B, et al. Interplay between transforming growth factor-β and Nur77 in dual regulations of inhibitor of differentiation 1 for colonic tumorigenesis. *Nat Commun*. 2021;12(1):2809.
35. Wu J, Liu J, Jia R, Song H. Nur77 inhibits androgen-induced bladder cancer growth. *Cancer Investig*. 2013;31(10):654-660.
36. Chen Y, Wu R, Chen HZ, et al. Enhancement of hypothalamic STAT3 acetylation by nuclear receptor Nur77 dictates leptin sensitivity. *Diabetes*. 2015;64(6):2069-2081.
37. Liu Y, Zhang J, Yi B, et al. Nur77 suppresses pulmonary artery smooth muscle cell proliferation through inhibition of the STAT3/Pim-1/NFAT pathway. *Am J Respir Cell Mol Biol*. 2014;50(2):379-388.
38. Li XX, Wang ZJ, Zheng Y, et al. Nuclear receptor Nur77 facilitates melanoma cell survival under metabolic stress by protecting fatty acid oxidation. *Mol Cell*. 2018;69(3):480-492.e7.
39. Li XM, Zhang S, He XS, et al. Nur77-mediated TRAF6 signalling protects against LPS-induced sepsis in mice. *J Inflamm Lond*. 2016;13:4.
40. Chen HZ, Wen Q, Wang WJ, He JP, Wu Q. The orphan nuclear receptor TR3/Nur77 regulates ER stress and induces apoptosis via interaction with TRAPγ. *Int J Biochem Cell Biol*. 2013;45(8):1600-1609.
41. Bian H, Liang X, Lu D, et al. In silico discovery of stapled peptide inhibitor targeting the Nur77-PPARγ interaction and its anti-breast-cancer efficacy. *Adv Sci Weinh*. 2024;11(26):e2308435.
42. Cui M, Cai Z, Chu S, et al. Orphan nuclear receptor Nur77 inhibits angiotensin II-induced vascular remodeling via down-regulation of β-catenin. *Hypertension*. 2016;67(1):153-162.
43. Zhang Y, Pang Y, Feng W, et al. miR-124 regulates early isolation-induced social abnormalities via inhibiting myelinogenesis in the medial prefrontal cortex. *Cell Mol Life Sci*. 2022;79(9):507.
44. Zhang W, Zhu X, Liu Y, et al. Nur77 was essential for neurite outgrowth and involved in Schwann cell differentiation after sciatic nerve injury. *J Mol Neurosci*. 2015;57(1):38-47.
45. Volakakis N, Kadkhodaei B, Joodmardi E, et al. NR4A orphan nuclear receptors as mediators of CREB-dependent neuroprotection. *Proc Natl Acad Sci USA*. 2010;107(27):12317-12322.
46. Shiga H, Yamane Y, Kubo M, Sakurai Y, Asou H, Ito E. Differentiation of immature oligodendrocytes is regulated by phosphorylation of cyclic AMP-response element binding protein by a protein kinase C signaling cascade. *J Neurosci Res*. 2005;80(6):767-776.
47. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature*. 2010;468(7321):253-262.
48. Rothe T, Ipseiz N, Faas M, et al. The nuclear receptor Nr4a1 acts as a microglia rheostat and serves as a therapeutic target in autoimmune-driven central nervous system inflammation. *J Immunol*. 2017;198(10):3878-3885.
49. Liu TY, Yang XY, Zheng LT, Wang GH, Zhen XC. Activation of Nur77 in microglia attenuates proinflammatory mediators production and protects dopaminergic neurons from inflammation-induced cell death. *J Neurochem*. 2017;140(4):589-604.
50. Huang HY, Chang HF, Tsai MJ, Chen JS, Wang MJ. 6-Mercaptopurine attenuates tumor necrosis factor-α production in microglia through Nur77-mediated transrepression and PI3K/Akt/mTOR signaling-mediated translational regulation. *J Neuroinflammation*. 2016;13(1):78.
51. Gordon GR, Choi HB, Rungta RL, Ellis-Davies GC, MacVicar BA. Brain metabolism dictates the polarity of astrocyte control over arterioles. *Nature*. 2008;456(7223):745-749.
52. Jimenez-Blasco D, Busquets-Garcia A, Hebert-Chatelain E, et al. Glucose metabolism links astroglial mitochondria to cannabinoid effects. *Nature*. 2020;583(7817):603-608.
53. Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. *J Neurosci*. 1996;16(3):877-885.
54. Hung AC, Huang HM, Tsay HJ, Lin TN, Kuo JS, Sun SH. ATP-stimulated c-fos and zif268 mRNA expression is inhibited by chemical hypoxia in a rat brain-derived type 2 astrocyte cell line, RBA-2. *J Cell Biochem*. 2000;77(2):323-332.
55. Chao LC, Wroblewski K, Zhang Z, et al. Insulin resistance and altered systemic glucose metabolism in mice lacking Nur77. *Diabetes*. 2009;58(12):2788-2796.
56. Popichak KA, Hammond SL, Moreno JA, et al. Compensatory expression of Nur77 and Nurr1 regulates NF-κB-dependent inflammatory signaling in astrocytes. *Mol Pharmacol*. 2018;94(4):1174-1186.
57. Wang D, Yin Y, Wang S, et al. FGF1(ΔHBS) prevents diabetic cardiomyopathy by maintaining mitochondrial homeostasis and reducing oxidative stress via AMPK/Nur77 suppression. *Signal Transduct Target Ther*. 2021;6(1):133.

58. Williams GT, Lau LF. Activation of the inducible orphan receptor gene nur77 by serum growth factors: dissociation of immediate-early and delayed-early responses. *Mol Cell Biol*. 1993;13(10):6124-6136.
59. Zhao S, Zhou L, Niu G, Li Y, Zhao D, Zeng H. Differential regulation of orphan nuclear receptor TR3 transcript variants by novel vascular growth factor signaling pathways. *FASEB J*. 2014;28(10):4524-4533.
60. Hu YW, Zheng L, Wang Q, et al. Vascular endothelial growth factor downregulates apolipoprotein M expression by inhibiting Foxa2 in a Nur77-dependent manner. *Rejuvenation Res*. 2012;15(4):423-434.
61. Kolluri SK, Bruey-Sedano N, Cao X, et al. Mitogenic effect of orphan receptor TR3 and its regulation by MEKK1 in lung cancer cells. *Mol Cell Biol*. 2003;23(23):8651-8667.
62. Lee YR, Kang GS, Oh T, Jo HJ, Park HJ, Ahn G. DNA-dependent protein kinase catalytic subunit (DNA-PKcs): beyond the DNA double-strand break repair. *Mol Cells*. 2023;46(4):200-205.
63. Qi H, Jiang Z, Wang C, et al. Sensitization of tamoxifen-resistant breast cancer cells by Z-ligustilide through inhibiting autophagy and accumulating DNA damages. *Oncotarget*. 2017;8(17):29300-29317.
64. Zhu Y, Han XQ, Sun XJ, Yang R, Ma WQ, Liu NF. Lactate accelerates vascular calcification through NR4A1-regulated mitochondrial fission and BNIP3-related mitophagy. *Apoptosis*. 2020;25(5–6):321-340.
65. Berti M, Cortez D, Lopes M. The plasticity of DNA replication forks in response to clinically relevant genotoxic stress. *Nat Rev Mol Cell Biol*. 2020;21(10):633-651.
66. Goto M, Sasaki M, Kobayashi T. The S-phase cyclin Clb5 promotes rRNA gene (rDNA) stability by maintaining replication initiation efficiency in rDNA. *Mol Cell Biol*. 2021;41(5):e00324-20.
67. Zeman MK, Cimprich KA. Causes and consequences of replication stress. *Nat Cell Biol*. 2014;16(1):2-9.
68. Guo H, Golczer G, Wittner BS, et al. NR4A1 regulates expression of immediate early genes, suppressing replication stress in cancer. *Mol Cell*. 2021;81(19):4041-4058.e15.
69. Cortez-Toledo O, Schnair C, Sangngern P, Metzger D, Chao LC. Nur77 deletion impairs muscle growth during developmental myogenesis and muscle regeneration in mice. *PLoS One*. 2017;12(2):e0171268.
70. Chao LC, Bensinger SJ, Villanueva CJ, Wroblewski K, Tontonoz P. Inhibition of adipocyte differentiation by Nur77, Nurr1, and Nor1. *Mol Endocrinol*. 2008;22(12):2596-2608.
71. Tian H, Chen F, Wang Y, et al. Nur77 prevents osteoporosis by inhibiting the NF-κB signalling pathway and osteoclast differentiation. *J Cell Mol Med*. 2022;26(8):2163-2176.
72. Pierre A, Gautier M, Callebaut I, et al. Atypical structure and phylogenomic evolution of the new eutherian oocyte- and embryo-expressed KHDC1/DPPA5/ECAT1/OOEP gene family. *Genomics*. 2007;90(5):583-594.
73. Stachowiak EK, Fang X, Myers J, Dunham S, Stachowiak MK. cAMP-induced differentiation of human neuronal progenitor cells is mediated by nuclear fibroblast growth factor receptor-1 (FGFR1). *J Neurochem*. 2003;84(6):1296-1312.
74. Stachowiak MK, Fang X, Myers JM, et al. Integrative nuclear FGFR1 signaling (INFS) as a part of a universal "feed-forward-and-gate" signaling module that controls cell growth and differentiation. *J Cell Biochem*. 2003;90(4):662-691.
75. Lee YW, Terranova C, Birkaya B, et al. A novel nuclear FGF Receptor-1 partnership with retinoid and Nur receptors during developmental gene programming of embryonic stem cells. *J Cell Biochem*. 2012;113(9):2920-2936.
76. Hawkins K, Joy S, McKay T. Cell signalling pathways underlying induced pluripotent stem cell reprogramming. *World J Stem Cells*. 2014;6(5):620-628.
77. Sunil VR, Vayas KN, Radbel J, et al. Impaired energy metabolism and altered functional activity of alveolar type II epithelial cells following exposure of rats to nitrogen mustard. *Toxicol Appl Pharmacol*. 2022;456:116257.
78. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. *Nat Rev Endocrinol*. 2017;13(10):572-587.
79. Yin TC, Van Vranken JG, Srivastava D, et al. Insulin sensitization by small molecules enhancing GLUT4 translocation. *Cell Chem Biol*. 2023;30(8):933-942.e6.
80. Li L, Bai Y, Du R, Tang L, Li L. Orphan nuclear receptor NUR77 relieves insulin resistance in HTR-8/SVneo trophoblast cells through activation of autophagy and insulin signaling. *J Physiol Biochem*. 2022;78(4):777-791.
81. Ahuja P, Bi X, Ng CF, et al. Src homology 3 domain binding kinase 1 protects against hepatic steatosis and insulin resistance through the Nur77-FGF21 pathway. *Hepatology*. 2023;77(1):213-229.
82. Zhan YY, Chen Y, Zhang Q, et al. The orphan nuclear receptor Nur77 regulates LKB1 localization and activates AMPK. *Nat Chem Biol*. 2012;8(11):897-904.
83. Fu Y, Luo L, Luo N, Zhu X, Garvey WT. NR4A orphan nuclear receptors modulate insulin action and the glucose transport system: potential role in insulin resistance. *J Biol Chem*. 2007;282(43):31525-31533.
84. Yan J, Huang J, Wu J, et al. Nur77 attenuates inflammatory responses and oxidative stress by inhibiting phosphorylated IκB-α in Parkinson's disease cell model. *Aging (Albany NY)*. 2020;12(9):8107-8119.
85. Wang B, Jin Y, Liu J, et al. EP1 activation inhibits doxorubicin-cardiomyocyte ferroptosis via Nrf2. *Redox Biol*. 2023;65:102825.
86. Lane DJ, Metselaar B, Greenough M, Bush AI, Ayton SJ. Ferroptosis and NRF2: an emerging battlefield in the neurodegeneration of Alzheimer's disease. *Essays Biochem*. 2021;65(7):925-940.
87. Wen RJ, Dong X, Zhuang HW, et al. Baicalin induces ferroptosis in osteosarcomas through a novel Nrf2/xCT/GPX4 regulatory axis. *Phytomedicine*. 2023;116:154881.
88. Chen GH, Song CC, Pantopoulos K, Wei XL, Zheng H, Luo Z. Mitochondrial oxidative stress mediated Fe-induced ferroptosis via the NRF2-ARE pathway. *Free Radic Biol Med*. 2022;180:95-107.
89. Yao D, Bao L, Wang S, et al. Isoliquiritigenin alleviates myocardial ischemia-reperfusion injury by regulating the Nrf2/HO-1/SLC7a11/GPX4 axis in mice. *Free Radic Biol Med*. 2024;221:1-12.
90. Wei R, Zhao Y, Wang J, et al. Tagitinin C induces ferroptosis through PERK-Nrf2-HO-1 signaling pathway in colorectal cancer cells. *Int J Biol Sci*. 2021;17(11):2703-2717.
91. Zhang T, Ma R, Li Z, et al. Nur77 alleviates cardiac fibrosis by upregulating GSK-3β transcription during aging. *Eur J Pharmacol*. 2024;965:176290.
92. Ma G, Chen F, Liu Y, et al. Nur77 ameliorates age-related renal tubulointerstitial fibrosis by suppressing the TGF-β/Smads signaling pathway. *FASEB J*. 2022;36(2):e22124.

93. Jing X, Sui WH, Wang S, et al. HDAC7 ubiquitination by the E3 ligase CBX4 is involved in contextual fear conditioning memory formation. *J Neurosci*. 2017;37(14):3848-3863.
94. Palomares O, Elewaut D, Irving PM, Jaumont X, Tassinari P. Regulatory T cells and immunoglobulin E: a new therapeutic link for autoimmunity? *Allergy*. 2022;77(11):3293-3308.
95. Lory NC, Nawrocki M, Corazza M, et al. TRPM2 is not required for T-cell activation and differentiation. *Front Immunol*. 2021;12:778916.
96. Birari P, Mal S, Majumder D, et al. Nur77 influences immunometabolism to regulate the release of proinflammatory cytokines and the formation of lipid bodies during *Mycobacterium tuberculosis* infection of macrophages. *Pathog Dis*. 2023;81:ftad033. doi:10.1093/femspd/ftad033
97. O'Brien VP, Lewis AL, Gilbert NM. Bladder exposure to gardnerella activates host pathways necessary for *Escherichia coli* recurrent UTI. *Front Cell Infect Microbiol*. 2021;11:788229.
98. Lee JM, Lee KH, Weidner M, Osborne BA, Hayward SD. Epstein-Barr virus EBNA2 blocks Nur77-mediated apoptosis. *Proc Natl Acad Sci USA*. 2002;99(18):11878-11883.
99. Lee MO, Kang HJ, Cho H, Shin EC, Park JH, Kim SJ. Hepatitis B virus X protein induced expression of the Nur77 gene. *Biochem Biophys Res Commun*. 2001;288(5):1162-1168.
100. Li L, Liu Y, Chen HZ, et al. Impeding the interaction between Nur77 and p38 reduces LPS-induced inflammation. *Nat Chem Biol*. 2015;11(5):339-346.
101. Lv Q, Lv Q, Yang A, et al. Calcipotriol and iBRD9 reduce obesity in Nur77 knockout mice by regulating the gut microbiota, improving intestinal mucosal barrier function. *Int J Obes Lond*. 2020;44(5):1052-1061.
102. Zhu F, Ma J, Li W, et al. The orphan receptor Nur77 binds cytoplasmic LPS to activate the non-canonical NLRP3 inflammasome. *Immunity*. 2023;56(4):753-767.e8.
103. Bordon Y. Nur77 senses LPS and dsDNA for non-canonical inflammasome activation. *Nat Rev Immunol*. 2023;23(5):271.
104. Zhu N, Zhang GX, Yi B, et al. Nur77 limits endothelial barrier disruption to LPS in the mouse lung. *Am J Physiol Lung Cell Mol Physiol*. 2019;317(5):L615-l624.
105. Fang H, Li M, Wang X, et al. Discovery of new DHA ethanolamine derivatives as potential anti-inflammatory agents targeting Nur77. *Bioorg Chem*. 2023;141:106887.
106. Ao M, Zhang J, Qian Y, et al. Design and synthesis of adamantyl-substituted flavonoid derivatives as anti-inflammatory Nur77 modulators: compound B7 targets Nur77 and improves LPS-induced inflammation in vitro and in vivo. *Bioorg Chem*. 2022;120:105645.
107. Hu M, Luo Q, Alitongbieke G, et al. Celastrol-induced Nur77 interaction with TRAF2 alleviates inflammation by promoting mitochondrial ubiquitination and autophagy. *Mol Cell*. 2017;66(1):141-153.e6.
108. Zárraga-Granados G, Muciño-Hernández G, Sánchez-Carbente MR, et al. The nuclear receptor NR4A1 is regulated by SUMO modification to induce autophagic cell death. *PLoS One*. 2020;15(3):e0222072.
109. Zhou H, Du W, Li YE, et al. Effects of melatonin on fatty liver disease: the role of NR4A1/DNA-PKcs/p53 pathway, mitochondrial fission, and mitophagy. *J Pineal Res*. 2018;64(1):e12450.
110. Sheng J, Li H, Dai Q, et al. NR4A1 promotes diabetic nephropathy by activating Mff-mediated mitochondrial fission and suppressing parkin-mediated mitophagy. *Cell Physiol Biochem*. 2018;48(4):1675-1693.
111. Kang JS, Kim MJ, Kwon ES, et al. Identification of novel genes associated with exercise and calorie restriction effects in skeletal muscle. *Aging (Albany NY)*. 2023;15(11):4667-4684.
112. Dai W, Dierschke SK, Toro AL, Dennis MD. Consumption of a high fat diet promotes protein O-GlcNAcylation in mouse retina via NR4A1-dependent GFAT2 expression. *Biochim Biophys Acta Mol basis Dis*. 2018;1864(12):3568-3576.
113. Cai X, Jiang Y, Cao Z, et al. Mst1-mediated phosphorylation of Nur77 improves the endometrial receptivity in human and mice. *EBioMedicine*. 2023;88:104433.
114. Yao LM, He JP, Chen HZ, et al. Orphan receptor TR3 participates in cisplatin-induced apoptosis via Chk2 phosphorylation to repress intestinal tumorigenesis. *Carcinogenesis*. 2012;33(2):301-311.
115. Liu B, Wu JF, Zhan YY, Chen HZ, Zhang XY, Wu Q. Regulation of the orphan receptor TR3 nuclear functions by c-Jun N terminal kinase phosphorylation. *Endocrinology*. 2007;148(1):34-44.
116. Chen HZ, Li L, Wang WJ, et al. Prolyl isomerase Pin1 stabilizes and activates orphan nuclear receptor TR3 to promote mitogenesis. *Oncogene*. 2012;31(23):2876-2887.
117. Chen HZ, Liu QF, Li L, et al. The orphan receptor TR3 suppresses intestinal tumorigenesis in mice by downregulating Wnt signalling. *Gut*. 2012;61(5):714-724.
118. Shrestha R, Mohankumar K, Safe S. Bis-indole derived nuclear receptor 4A1 (NR4A1) antagonists inhibit TGFβ-induced invasion of embryonal rhabdomyosarcoma cells. *Am J Cancer Res*. 2020;10(8):2495-2509.
119. Hedrick E, Safe S. Transforming growth factor β/NR4A1-inducible breast cancer cell migration and epithelial-to-mesenchymal transition is p38α (mitogen-activated protein kinase 14) dependent. *Mol Cell Biol*. 2017;37(18):e00306-17.
120. Wang A. Phosphorylation of Nur77 by the MEK-ERK-RSK cascade induces mitochondrial translocation and apoptosis in T cells. *J Immunol*. 2009;183(5):3268-3277.
121. Chen HZ, Zhao BX, Zhao WX, Li L, Zhang B, Wu Q. Akt phosphorylates the TR3 orphan receptor and blocks its targeting to the mitochondria. *Carcinogenesis*. 2008;29(11):2078-2088.
122. Wang WJ, Wang Y, Hou PP, et al. Induction of autophagic death in cancer cells by agonizing TR3 and attenuating Akt2 activity. *Chem Biol*. 2015;22(8):1040-1051.
123. Ji JJ, Qian LL, Zhu Y, et al. Kallistatin/Serpina3c inhibits cardiac fibrosis after myocardial infarction by regulating glycolysis via Nr4a1 activation. *Biochim Biophys Acta Mol basis Dis*. 2022;1868(9):166441.
124. Go S, Masuda H, Tsuru M, Inden M, Hozumi I, Kurita H. Exposure to a low concentration of methylmercury in neural differentiation downregulates NR4A1 expression with altered epigenetic modifications and inhibits neuronal spike activity in vitro. *Toxicol Lett*. 2023;374:68-76.
125. Kang SA, Na H, Kang HJ, Kim SH, Lee MH, Lee MO. Regulation of Nur77 protein turnover through acetylation and deacetylation induced by p300 and HDAC1. *Biochem Pharmacol*. 2010;80(6):867-873.
126. Song H, Wu H, Dong J, Huang S, Ye J, Liu R. Ellagic acid alleviates rheumatoid arthritis in rats through inhibiting MTA1/HDAC1-mediated Nur77 deacetylation. *Mediat Inflamm*. 2021;2021:6359652. doi:10.1155/2021/6359652

127. Bridi MS, Hawk JD, Chatterjee S, Safe S, Abel T. Pharmacological activators of the NR4A nuclear receptors enhance LTP in a CREB/CBP-dependent manner. *Neuropsychopharmacology*. 2017;42(6):1243-1253.
128. 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. *Biochim Biophys Acta, Mol Cell Res*. 2021;1868(2):118908.
129. Yang PB, Hou PP, Liu FY, et al. Blocking PPARγ interaction facilitates Nur77 interdiction of fatty acid uptake and suppresses breast cancer progression. *Proc Natl Acad Sci USA*. 2020;117(44):27412-27422.
130. Huang B, Pei HZ, Chang HW, Baek SH. The E3 ubiquitin ligase Trim13 regulates Nur77 stability via casein kinase 2α. *Sci Rep*. 2018;8(1):13895.
131. Lin H, Lin Q, Liu M, et al. PKA/Smurf1 signaling-mediated stabilization of Nur77 is required for anticancer drug cisplatin-induced apoptosis. *Oncogene*. 2014;33(13):1629-1639.
132. Koeglsperger T, Rumpf SL, Schließer P, et al. Neuropathology of incidental Lewy body & prodromal Parkinson's disease. *Mol Neurodegener*. 2023;18(1):32.
133. Rouillard C, Baillargeon J, Paquet B, et al. Genetic disruption of the nuclear receptor Nur77 (Nr4a1) in rat reduces dopamine cell loss and l-Dopa-induced dyskinesia in experimental Parkinson's disease. *Exp Neurol*. 2018;304:143-153.
134. Mount MP, Zhang Y, Amini M, et al. Perturbation of transcription factor Nur77 expression mediated by myocyte enhancer factor 2D (MEF2D) regulates dopaminergic neuron loss in response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *J Biol Chem*. 2013;288(20):14362-14371.
135. Dickey CA, Loring JF, Montgomery J, Gordon MN, Eastman PS, Morgan D. Selectively reduced expression of synaptic plasticity-related genes in amyloid precursor protein + presenilin-1 transgenic mice. *J Neurosci*. 2003;23(12):5219-5226.
136. Dickey CA, Gordon MN, Mason JE, et al. Amyloid suppresses induction of genes critical for memory consolidation in APP + PS1 transgenic mice. *J Neurochem*. 2004;88(2):434-442.
137. Zhao Y, Liu Y, Zheng D. Alpha 1-antichymotrypsin/SerpinA3 is a novel target of orphan nuclear receptor Nur77. *FEBS J*. 2008;275(5):1025-1038.
138. Montarolo F, Perga S, Martire S, et al. Altered NR4A subfamily gene expression level in peripheral blood of Parkinson's and Alzheimer's disease patients. *Neurotox Res*. 2016;30(3):338-344.
139. Zhao LG, Tang Y, Tan JZ, Wang JW, Chen GJ, Zhu BL. The effect of NR4A1 on APP metabolism and tau phosphorylation. *Genes Dis*. 2018;5(4):342-348.
140. Bar-Or A, Li R. Cellular immunology of relapsing multiple sclerosis: interactions, checks, and balances. *Lancet Neurol*. 2021;20(6):470-483.
141. Cappelletti C, Eriksson A, Brorson IS, et al. Quantitative proteomics reveals protein dysregulation during T cell activation in multiple sclerosis patients compared to healthy controls. *Clin Proteomics*. 2022;19(1):23.
142. Won HY, Hwang ES. Transcriptional modulation of regulatory T cell development by novel regulators NR4As. *Arch Pharm Res*. 2016;39(11):1530-1536.
143. Yu HZ, Zhu BQ, Zhu L, Li S, Wang LM. NR4A1 agonist cytosporone B attenuates neuroinflammation in a mouse model of multiple sclerosis. *Neural Regen Res*. 2022;17(12):2765-2770.
144. Wang LM, Zhang Y, Li X, et al. Nr4a1 plays a crucial modulatory role in Th1/Th17 cell responses and CNS autoimmunity. *Brain Behav Immun*. 2018;68:44-55.
145. Shaked I, Hanna RN, Shaked H, et al. Transcription factor Nr4a1 couples sympathetic and inflammatory cues in CNS-recruited macrophages to limit neuroinflammation. *Nat Immunol*. 2015;16(12):1228-1234.
146. Montarolo F, Martire S, Marnetto F, et al. The selective agonist for Sphingosine-1-phosphate receptors siponimod increases the expression level of NR4A genes in microglia cell line. *Curr Issues Mol Biol*. 2022;44(3):1247-1256.
147. Yuan F, Wei J, Cheng Y, et al. SLAMF7 promotes foam cell formation of macrophage by suppressing NR4A1 expression during carotid atherosclerosis. *Inflammation*. 2024;47(2):530-542.
148. Hanna RN, Shaked I, Hubbeling HG, et al. NR4A1 (Nur77) deletion polarizes macrophages toward an inflammatory phenotype and increases atherosclerosis. *Circ Res*. 2012;110(3):416-427.
149. Xu S, Wei W, Zhang F, et al. Transcriptomic profiling of intracranial arteries in adult patients with Moyamoya disease reveals novel insights into its pathogenesis. *Front Mol Neurosci*. 2022;15:881954.
150. Yuan R, Zhang W, Nie P, et al. Nur77 deficiency exacerbates macrophage NLRP3 inflammasome-mediated inflammation and accelerates atherosclerosis. *Oxidative Med Cell Longev*. 2022;2022:2017815.
151. Dai Y, Zhang W, Sun Q, et al. Nuclear receptor nur77 promotes cerebral cell apoptosis and induces early brain injury after experimental subarachnoid hemorrhage in rats. *J Neurosci Res*. 2014;92(9):1110-1121.
152. Johansson IM, Wester P, Háková M, Gu W, Seckl JR, Olsson T. Early and delayed induction of immediate early gene expression in a novel focal cerebral ischemia model in the rat. *Eur J Neurosci*. 2000;12(10):3615-3625.
153. Zhang YJ, Song JR, Zhao MJ. NR4A1 regulates cerebral ischemia-induced brain injury by regulating neuroinflammation through interaction with NF-κB/p65. *Biochem Biophys Res Commun*. 2019;518(1):59-65.
154. Zhang Z, Yu J. NR4A1 promotes cerebral ischemia reperfusion injury by repressing Mfn2-mediated mitophagy and inactivating the MAPK-ERK-CREB signaling pathway. *Neurochem Res*. 2018;43(10):1963-1977.
155. Ping F, Zhang C, Wang X, et al. Cx32 inhibits the autophagic effect of Nur77 in SH-SY5Y cells and rat brain with ischemic stroke. *Aging (Albany NY)*. 2021;13(18):22188-22207.
156. Nakayama T, Hirano F, Okushi Y, et al. Orphan nuclear receptor nr4a1 regulates winter depression-like behavior in medaka. *Neurosci Lett*. 2023;814:137469.
157. Mahajan GJ, Vallender EJ, Garrett MR, et al. Altered neuroinflammatory gene expression in hippocampus in major depressive disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2018;82:177-186.
158. Zhang X, Li T, Liu S, et al. β-Glucan from Lentinus edodes inhibits breast cancer progression via the Nur77/HIF-1α axis. *Biosci Rep*. 2020;40(12):BSR20201006. doi:10.1042/BSR20201006
159. Lee SO, Andey T, Jin UH, Kim K, Sachdeva M, Safe S. The nuclear receptor TR3 regulates mTORC1 signaling in lung cancer cells expressing wild-type p53. *Oncogene*. 2012;31(27):3265-3276.
160. Payapilly A, Guilbert R, Descamps T, et al. TIAM1-RAC1 promote small-cell lung cancer cell survival through antagonizing

Nur77-induced BCL2 conformational change. *Cell Rep*. 2021;37(6):109979.
161. Zhou J, Liu X, Yin H, et al. Nur77 inhibition of β-catenin expression mediates hepatoblastoma progression and enhances cisplatin's therapeutic effect. *Gene*. 2024;908:148292.
162. Yang H, Nie Y, Li Y, Wan YJ. ERK1/2 deactivation enhances cytoplasmic Nur77 expression level and improves the apoptotic effect of fenretinide in human liver cancer cells. *Biochem Pharmacol*. 2011;81(7):910-916.
163. Li B, Huang J, Liu J, et al. Discovery of a Nur77-mediated cytoplasmic vacuolation and paraptosis inducer (4-PQBH) for the treatment of hepatocellular carcinoma. *Bioorg Chem*. 2022;121:105651.
164. Luo J, Wang J, Zhang J, et al. Orphan nuclear receptor Nur77 mediates the lethal endoplasmic reticulum stress and therapeutic efficacy of cryptomeridiol in hepatocellular carcinoma. *Cells*. 2022;11(23):3870. doi:10.3390/cells11233870
165. Hu Y, French SW, Chau T, et al. RARβ acts as both an upstream regulator and downstream effector of miR-22, which epigenetically regulates NUR77 to induce apoptosis of colon cancer cells. *FASEB J*. 2019;33(2):2314-2326.
166. Wilson AJ, Arango D, Mariadason JM, Heerdt BG, Augenlicht LH. TR3/Nur77 in colon cancer cell apoptosis. *Cancer Res*. 2003;63(17):5401-5407.
167. Wu H, Lin Y, Li W, et al. Regulation of Nur77 expression by β-catenin and its mitogenic effect in colon cancer cells. *FASEB J*. 2011;25(1):192-205.
168. Cho SD, Yoon K, Chintharlapalli S, et al. Nur77 agonists induce proapoptotic genes and responses in colon cancer cells through nuclear receptor-dependent and nuclear receptor-independent pathways. *Cancer Res*. 2007;67(2):674-683.
169. To SK, Zeng WJ, Zeng JZ, Wong AS. Hypoxia triggers a Nur77-β-catenin feed-forward loop to promote the invasive growth of colon cancer cells. *Br J Cancer*. 2014;110(4):935-945.
170. Mohankumar K, Wright G, Kumaravel S, et al. Bis-indole-derived NR4A1 antagonists inhibit colon tumor and splenic growth and T-cell exhaustion. *Cancer Immunol Immunother*. 2023;72(12):3985-3999.
171. Lee SO, Abdelrahim M, Yoon K, et al. Inactivation of the orphan nuclear receptor TR3/Nur77 inhibits pancreatic cancer cell and tumor growth. *Cancer Res*. 2010;70(17):6824-6836.
172. Lee SO, Jin UH, Kang JH, et al. The orphan nuclear receptor NR4A1 (Nur77) regulates oxidative and endoplasmic reticulum stress in pancreatic cancer cells. *Mol Cancer Res*. 2014;12(4):527-538.
173. Hedrick E, Lee SO, Safe S. The nuclear orphan receptor NR4A1 regulates β1-integrin expression in pancreatic and colon cancer cells and can be targeted by NR4A1 antagonists. *Mol Carcinog*. 2017;56(9):2066-2075.
174. Zhou L, Ruvolo VR, McQueen T, et al. HDAC inhibition by SNDX-275 (Entinostat) restores expression of silenced leukemia-associated transcription factors Nur77 and Nor1 and of key pro-apoptotic proteins in AML. *Leukemia*. 2013;27(6):1358-1368.
175. Wenzl K, Troppan K, Neumeister P, Deutsch AJ. The nuclear orphan receptor NR4A1 and NR4A3 as tumor suppressors in hematologic neoplasms. *Curr Drug Targets*. 2015;16(1):38-46.
176. Mullican SE, Zhang S, Konopleva M, et al. Abrogation of nuclear receptors Nr4a3 and Nr4a1 leads to development of acute myeloid leukemia. *Nat Med*. 2007;13(6):730-735.
177. Wang C, He H, Dou G, et al. Ginsenoside 20(S)-Rh2 induces apoptosis and differentiation of acute myeloid leukemia cells: role of orphan nuclear receptor Nur77. *J Agric Food Chem*. 2017;65(35):7687-7697.
178. Cho SD, Lee SO, Chintharlapalli S, et al. Activation of nerve growth factor-induced B alpha by methylene-substituted diindolylmethanes in bladder cancer cells induces apoptosis and inhibits tumor growth. *Mol Pharmacol*. 2010;77(3):396-404.
179. Niu T, Wei Z, Fu J, et al. Venlafaxine, an anti-depressant drug, induces apoptosis in MV3 human melanoma cells through JNK1/2-Nur77 signaling pathway. *Front Pharmacol*. 2022;13:1080412.
180. Yu H, Kumar SM, Fang D, Acs G, Xu X. Nuclear orphan receptor TR3/Nur77 mediates melanoma cell apoptosis. *Cancer Biol Ther*. 2007;6(3):405-412.
181. Kanzleiter T, Preston E, Wilks D, et al. Overexpression of the orphan receptor Nur77 alters glucose metabolism in rat muscle cells and rat muscle in vivo. *Diabetologia*. 2010;53(6):1174-1183.

How to cite this article: Wang Y, Li N, Guan W, Wang D. Controversy and multiple roles of the solitary nucleus receptor Nur77 in disease and physiology. *The FASEB Journal*. 2025;39:e70468. doi:10.1096/fj.202402775RR