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NR4A nuclear receptors in cardiac remodeling and neurohormonal regulation☆,☆☆

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A B S T R A C T

Heart failure is characterized by the constant interplay between the underlying cardiac insult, degree of myocardial dysfunction and the activity of compensatory neurohormonal mechanisms. The sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) become activated to maintain cardiac output; however, their chronic hyperactivity will eventually become deleterious. Several nuclear hormone receptors, including the mineralocorticoid receptor and estrogen receptor, are well-known to modulate cardiac disease. Recently, the subfamily of NR4A nuclear receptors i.e. Nur77, Nurr1 and NOR-1, are emerging as key players in cardiac stress responses, as well as pivotal regulators of neurohormonal mechanisms. In this review, we summarize current literature on NR4A nuclear receptors in the heart and in various components of the SNS, RAAS and immune system and discuss the functional implications for NR4As in cardiac function and disease.

Introduction

Despite advances, heart failure (HF) is one of the leading causes of death in the Western world [1] and may be caused by both acute and chronic stressors, i.e., myocardial infarction (MI) and hypertension respectively [2–4]. Adverse cardiac remodeling precedes HF and is characterized by cardiomyocyte death, hypertrophy and myocardial fibrosis. Subsequent declining pump function activates neurohormonal mechanisms, aimed at maintaining cardiac output. The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) do so by adjusting heart rate, myocardial contractility, salt and water retention and peripheral vasoconstriction [5]. Additionally, the immune system is involved in cardiac remodeling and repair to restore myocardial tissue homeostasis [6]. However, sustained activity of these initially compensatory mechanisms becomes deleterious and promotes HF progression [7].

Pharmacological agents antagonizing neurohormonal hyperactivity, such as β-blockers and angiotensin-converting enzyme inhibitors, lie at the basis of HF treatment [8,9]. However, these therapies are applied rather uniformly, and their efficacy is affected by the heterogeneity of HF patients due to different underlying causes and comorbidities [10]. Moreover, HF is characterized by the constant interplay between the underlying insult, the degree of myocardial dysfunction and neurohormonal activity. These facets are all subject to distinct regulation and are potentially novel therapeutic targets to reduce HF clinical burden and mortality.

Nuclear receptors (NRs) are master regulators of many different (patho)physiological processes. Upon binding of a specific ligand, NRs become activated, resulting in direct regulation of gene expression. Several NRs, including the mineralocorticoid receptor, are well-known to regulate cardiac disease progression (Fig. 1) and are targets of current pharmacological HF therapy [11,12]. The NR4A nuclear receptors Nur77, Nurr1 and NOR-1 form a separate subfamily within the nuclear receptor superfamily (Fig. 1). NR4A nuclear receptors are emerging as key players in cardiac stress responses and are important regulators of neurohormonal systems, and thus may be novel therapeutic targets in HF. In this review, we summarize the current knowledge on the role of NR4A nuclear receptors in the heart and in various components of the SNS and RAAS, and the impact of NR4As in cardiac function and disease will be discussed.

NR4A nuclear receptors

NR4As act as immediate-early genes and are rapidly induced by various stimuli such as growth factors, cytokines and hormones [13]. NR4As function as transcription factors or repressors by binding to NGFI-B- or Nur-response elements (NBRE or NurRE) in the DNA sequence, often found in promoter regions of genes (Fig. 2). The DNA-binding domain of Nur77, Nurr1 and NOR-1 shows extreme homology, with 94% of amino acids being identical [13–15]. Via the N-terminal domain (NTD) and ligand-binding domain (LBD), NR4As interact with and regulate the activity, stability and degradation of many other transcription fac-

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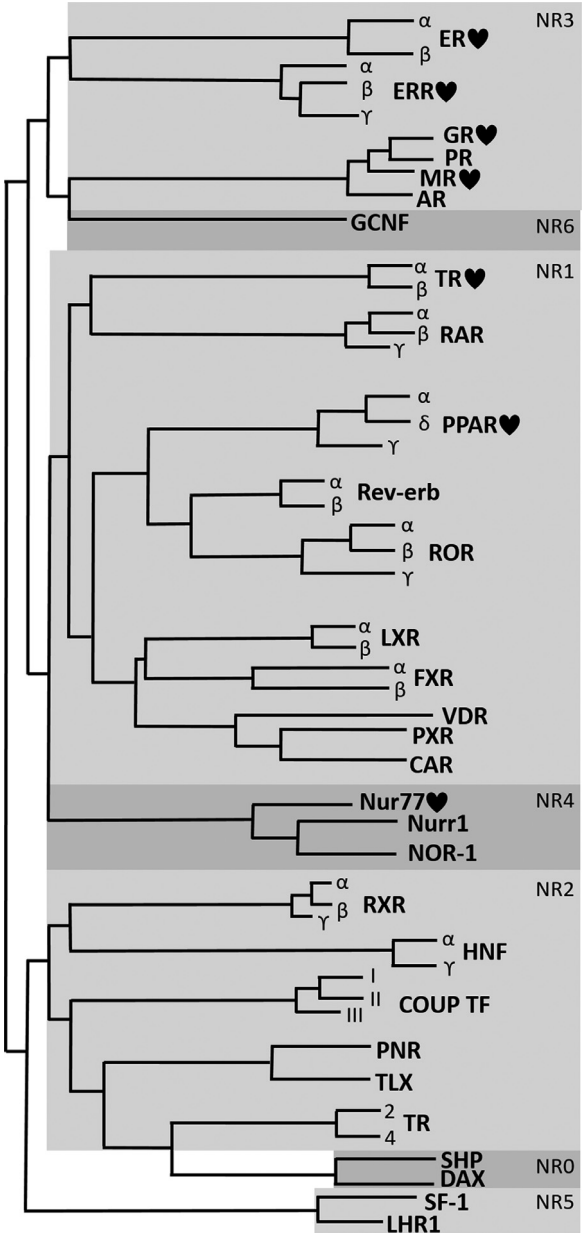

Fig. 1. Nuclear hormone receptor superfamily with members involved in cardiac disease. The human nuclear receptor superfamily consists of 49 nuclear receptors distributed over 7 subfamilies. A heart indicates involvement of this member in cardiac disease regulation. AR: androgen receptor, CAR: constitutive androstane receptor, ER: estrogen receptor, ERR: estrogen-related receptor, FXR: farnesoid X receptor, GCNF: germ cell nuclear factor, GR: glucocorticoid receptor, HNF: hepatocyte nuclear factor, LHR1: liver receptor homolog 1, LXR: liver-X receptor, MR: mineralocorticoid receptor, NOR-1: neuron-derived orphan receptor 1, Nurr1: nuclear receptor-related 1, PNR: photoreceptor cell-specific nuclear receptor, PPAR: peroxisome proliferator-activated receptor, PR: progesterone receptor, PXR: pregnane X receptor, RAR: retinoic acid receptor, ROR: RAR-related orphan receptor, RXR: retinoid X receptor, SF-1: steroidogenic factor 1, SHP: small heterodimer partner, TLX: homologue of the drosophila tailless gene, TR: thyroid hormone receptor, VDR: vitamin D receptor.

tors and coregulatory proteins (Fig. 2) [13], thereby also exerting non-genomic actions. Since the physiological ligands of NR4As are yet unknown, NR4As are considered to be constitutively-active and ligand-independent, with their transcriptional activity mainly being regulated by expression levels, posttranslational modifications and protein-protein interactions [13]. Thus, NR4As may regulate disease pathology in pleiotropic ways since different molecular

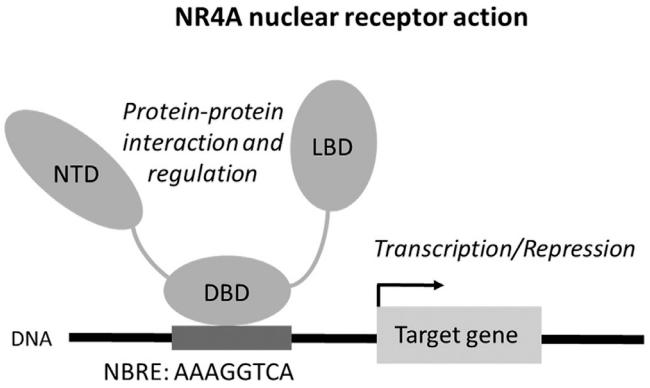

Fig. 2. NR4A nuclear receptor structure and functions. DBD: DNA-binding domain, LBD: ligand-binding domain, NBRE: NGFI-B response element, NTD: amino-terminal domain. NR4As are known for activation or repression of gene transcription by binding to their NBRE with the DBD. NR4As exert non-genomic functions by bringing together or capturing other proteins with their NTD and LBD.

signaling pathways become activated in different disease etiology, timing and co-morbidities.

NR4A nuclear receptors in neurohormonal mechanisms regulating cardiac function

The SNS

Activation of the SNS leads to the release of its effectors, the catecholamines norepinephrine and epinephrine, from post-ganglionic cardiac sympathetic neurons and from adrenal medullary chromaffin cells into the circulation [16]. Besides these classical mediators, sympathetic co-transmitters like Neuropeptide Y (NPY) are released [17]. Increased norepinephrine spillover [18] and elevated plasma NPY levels [19] have both been shown to be elevated in HF patients and are independent predictors of HF mortality.

Nur77

Norepinephrine and epinephrine are synthesized from the amino acid tyrosine and dopamine, in which tyrosine hydroxylase (TH) is the rate-limiting enzyme [20]. In the central nervous system, dopamine and norepinephrine are subject to Nur77 regulation [21]. In the brain of Nur77-knockout (KO) mice, TH mRNA expression and levels of the dopamine precursor L-DOPA are elevated compared to wild type (WT) mice, indicating enhanced TH activity [22]. Additionally, expression of the catabolizing enzyme catechol-*O*-methyltransferase (COMT) and its direct metabolites are reduced in Nur77-KO brain, suggesting that Nur77 is also involved in dopamine clearance [23]. Interestingly, Nur77 has been shown to repress TH expression in bone marrow-derived macrophages by recruiting the CoREST complex to the *th* promoter [24]. Thereby, Nur77 represses norepinephrine secretion from macrophages, which may explain why Nur77-KO mice display increased blood norepinephrine levels upon an inflammatory challenge [25]. Whether similar effects in sympathetic neurons and adrenal chromaffin cells are exerted by Nur77 remains to be elucidated.

Recently, we have shown that Nur77 represses the expression and release of sympathetic co-transmitter NPY [26] in adrenal chromaffin cells, which in Nur77-KO mice leads to elevated NPY levels in adrenal glands, plasma and the heart [27].

Nurr1

Of the NR4A nuclear receptors, Nurr1 is most well-known for regulating the expression of TH. Nurr1 is essential for the

development of midbrain dopamine neurons, which are characterized by TH expression. Homozygous Nurr1-deficient mice die within 12 hafter birth due to complete lack of TH and dopamine-expressing neurons in de midbrain [28,29]. Heterozygous Nurr1 deficiency is already sufficient to cause decreased TH expression, activity and catecholamine levels in the midbrain [29,30]. The *th* promoter has been shown to contain NBRE-like motifs, and one true NBRE DNA sequence that binds Nurr1, to directly regulate *th* transcription [31,32]. Outside the central nervous system, Nurr1 expression is reported to be high in bovine primary chromaffin progenitor cells [33]. However, TH expression and dopamine levels in the adrenal medulla were not significantly altered in homozygous Nurr1-deficient neonatal mice, suggesting organ specific regulation [29].

NOR-1

It has been reported that adipose tissue-specific NOR-1 overexpression leads to significantly decreased circulating epinephrine levels in mice [34]. In adipose tissue of these mice, expression of the catecholamine-catabolizing enzyme monoamine oxidase A (MaoA) was enhanced due to direct binding of NOR-1 to an NBRE in the *MaoA* promoter.

The RAAS

Decreasing cardiac output leads to the release of renin into the circulation by juxtaglomerular cells in the kidney. In a series of enzymatic steps, renin stimulates the production of angiotensin II (AngII). In the adrenal cortex, AngII stimulates aldosterone synthesis and release [5]. AngII can directly cause sodium retention in the proximal kidney tubule, while aldosterone increases sodium resorption in the distal kidney tubule [5], by which circulating blood volume and pressure is regulated. Furthermore, AngII is a potent vasoconstrictor and thereby regulates peripheral vascular resistance and blood pressure [5].

NR4As in aldosterone synthesis

The steroid hormone aldosterone regulates blood pressure by binding to mineralocorticoid receptors to induce sodium conservation [35]. Aldosterone synthesis is regulated by the rate-limiting enzyme aldosterone synthase, which is encoded by the *CYP11B2* gene [36]. Nur77 and Nurr1 are expressed in the adrenal cortex zona glomerulosa, both in mice [37] and in humans [38]. All three NR4A members are up-regulated by AngII in human adrenocortical tumor cells [38,39] as well as primary bovine and rat cells [40]. AngII-induced expression of Nur77, Nurr1 and NOR-1 is concomitant with enhanced *CYP11B2* expression [41]. Moreover, all three NR4A members have been shown to enhance *CYP11B2* promoter activity in H295R human adrenocortical tumor cells [41]. Two functional NBREs are present in the *CYP11B2* promoter region through which Nur77 and Nurr1 have been shown to regulate basal and AngII-induced *CYP11B2* transcription [38]. Furthermore, H295R cells expressing a dominant-negative form of Nur77, which inhibits the transcriptional activity of all NR4As, show decreased *CYP11B2* expression and reduced AngII-induced aldosterone levels [41]. The exact regulation of *CYP11B2* and aldosterone by Nur77, Nurr1 and NOR-1 and the *in vivo* consequences needs further investigation.

NR4As, AngII and hypertension

As a vasoactive peptide, AngII regulates vascular tone by inducing vascular smooth muscle cell (VSMC) contraction. However, persistent AngII stimulation due to RAAS hyperactivation induces a phenotypic switch in VSMCs, with enhanced proliferation, migration and matrix deposition, leading to hypertension [42]. AngII induces Nur77 expression in VSMCs in a PKA/CREB-dependent fashion [43,44]. Nur77 has been shown to inhibit AngII-induced VSMC phenotypic switch and vascular remodeling by down-regulation of β-catenin signaling in VSMCs [44]. Interestingly however, Nur77-KO mice do not exhibit altered systolic or mean arterial blood pressure (BP) compared to WT mice, neither under basal conditions nor upon chronic AngII-infusion [44,45].

While nothing is known thus far about the roles of Nurr1 and NOR-1 in AngII-induced vascular remodeling and hypertension, a human Nurr1 haplotype has been discovered, that is significantly associated with reduced systolic BP [46].

Nur77 in adverse cardiac remodeling and heart failure

In healthy humans, basal Nur77 mRNA expression is most pronounced in the heart compared to other metabolic tissues [47]. Nur77 uses two alternative non-coding exons differentially in ventricular myocardial tissue from hypertrophic cardiomyopathy patients, compared to Nur77 in healthy myocardial tissue [39], indicating that there is a preference for distinct promoter sequences of Nur77 in either healthy or hypertrophic hearts.

In the adult mouse heart, the expression of Nur77 is most abundant of the three NR4A receptors [47,48]. Distinct experimental models have revealed that cardiac Nur77 protein expression is rapidly upregulated by various stressors, including β-adrenergic stimulation via isoproterenol (ISO) [49], chronic AngII infusion [50], transverse aortic constriction (TAC) [51], ischemia/reperfusion (I/R) injury [52] and MI [53]. Furthermore, even without a pathological stimulus, Nur77 knockdown leads to hypertrophy in neonatal rat cardiomyocytes (NRCMs). Moreover, global- and cardiomyocyte specific Nur77 deficiency in mice leads to overt elevation of diastolic $[Ca^{2+}]_i$ in cardiomyocytes [47,54]. Together, these reports substantiate the importance of Nur77 in regulating cardiac function and remodeling in a wide variety of cardiac pathologies.

Nur77 in β-adrenergic overstimulation-induced cardiac remodeling

The SNS increases cardiac contractility through the binding of norepinephrine and epinephrine to β-adrenergic receptors on cardiomyocytes. However, SNS hyperactivity leads to β-adrenergic overstimulation, causing cardiomyocyte $[Ca^{2+}]_i$ overload and hypertrophy, cardiomyocyte death and ultimately reducing cardiac pump function [5,55].

Nur77 expression is rapidly and transiently induced in cultured NRCMs in response to β-adrenergic agonist ISO, most likely via $[Ca^{2+}]_i$ and protein kinase A signaling [47,56]. Already within 1 h, expression of both mRNA and nuclear Nur77 protein are significantly upregulated in NRCMs [47,57]. Rapid Nur77 induction is also observed in whole mouse hearts *in vivo* after a single i.p. ISO injection [49]. Furthermore, short-term β-adrenergic stimulation with either ISO or epinephrine in induced pluripotent stem cell-derived (iPSC) cardiomyocytes from healthy human subjects results in higher Nur77 expression [58]. Moreover, Nur77 is significantly higher in ISO-stimulated iPSC cardiomyocytes derived from Takotsubo cardiomyopathy patients, a condition believed to involve enhanced β-adrenergic signaling and higher sensitivity to catecholamine-induced cardiomyocyte toxicity [58].

Two independent research groups demonstrated that Nur77 protects against adverse cardiac remodeling induced by chronic β-adrenergic stimulation [47,57]. In line with these observations, siRNA-mediated Nur77 silencing promotes ISO-induced NRCM hypertrophy [47,57]. Additionally, Nur77-KO mice show decreased survival, enhanced cardiomyocyte hypertrophy and more cardiac fibrosis upon chronic ISO infusion [47]. In accordance, intramyocardial injection of a Nur77-encoding adenovirus in mice leads to reduced cardiac hypertrophy, fibrosis and to improved ejection fraction upon chronic ISO infusion [57]. Nur77 is thought

Table 1
Pleiotropic functions of NR4A nuclear receptors in neurohormonal mechanisms and the heart. $[Ca^{2+}]_i$: intracellular calcium concentration; AngII: angiotensin II; CCR2: c-c chemokine receptor type 2; COMT: catechol-O-methyltransferase; CoREST: REST corepressor 1; CYP11B2: aldosterone synthase; I/R: ischemia/reperfusion; LAD: left anterior descending coronary; MaoA: monoamine oxidase A; mTORC1: mammalian target of rapamycin complex 1; NAD+: nicotinamide adenine dinucleotide; NFATc3: nuclear factor of activated T-cells, cytoplasmic 3; NPY: neuropeptide Y; O-GlcNAc: O-linked N-acetylglucosamine; PARP-1: Poly [ADP-ribose] polymerase 1; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system; TAC: transverse aortic constriction; TH: tyrosine hydroxylase; TSC2: tuberous sclerosis complex 2.

		Nur77	Nurr1 or NOR-1
SNS	Brain	Suppresses TH expression	Nurr1 enhances midbrain TH expression and dopamine
		Enhances COMT expression	Enhances midbrain catecholamine levels
		Limits dopamine synthesis and clearance	
	Adrenal medulla	Suppresses NPY expression and secretion	For Nurr1, no effect on TH expression and dopamine levels
		Limits circulating NPY levels	
		Limits NPY-induced cardiomyocyte hypertrophy	
	Macrophages	Suppresses TH gene expression via CoREST	
		Limits circulating norepinephrine levels	
	Adipose tissue		NOR-1 enhances MaoA expression by binding NBRE
			Attenuates circulating epinephrine levels
RAAS	Adrenal cortex	Binds NBRE in CYP11B2 promoter	Nurr1 or NOR-1 both bind NBRE in CYP11B2 promoter
		Enhances CYP11B2 expression	Enhances CYP11B2 expression
		Enhances aldosterone levels	Enhances aldosterone levels
Heart	Knockdown or overexpression, no insult	Attenuates cardiomyocyte hypertrophy	NOR-1 enhances cardiomyocyte hypertrophy
		Limits action potential duration	
		Enhances cardiomyocyte protein O-GlcNAcylation	
		Blunts store-operated Ca^{2+} entry	
		Blunts Ca^{2+}-driven contractility	
	β-adrenergic-induced remodeling	Limits cardiomyocyte $[Ca^{2+}]_i$	NOR-1 functionally interacts with PARP-1
		Limits calcineurin activity	Enhances PARP-1 acetylation and activation
		Functionally interacts with NFATc3 and GATA4	Enhances cardiomyocyte NAD+ depletion
		Suppresses cardiomyocyte NPY-receptor 1 signaling	Enhances cardiomyocyte hypertrophy
		Prevents cardiomyocyte hypertrophy	
		Decreases fibrosis	
		Improves ejection fraction	
	AngII-induced remodeling	Enhances TSC2 proteasomal degradation, mTORC1 activity	
		Enhances cardiomyocyte hypertrophy and apoptosis	
		Enhances cardiac fibrosis	
	TAC-induced remodeling	Enhances cardiomyocyte hypertrophy	
		Enhances cardiac perivascular fibrosis	
	I/R injury and oxidative stress	Mitochondrial translocation	
		Enhances cytochrome C release	
		Enhances mitochondrial structural degradation	
		Enhances cardiomyocyte apoptosis	
		Enhances contractile dysfunction	
	LAD ligation-induced remodeling	Limits CCR2 expression and infiltration of monocytes	
		Limits inflammatory phenotype of infiltrating monocytes	
		Attenuates scar size	
		Improves scar density	
		Enhances cardiac pump function	

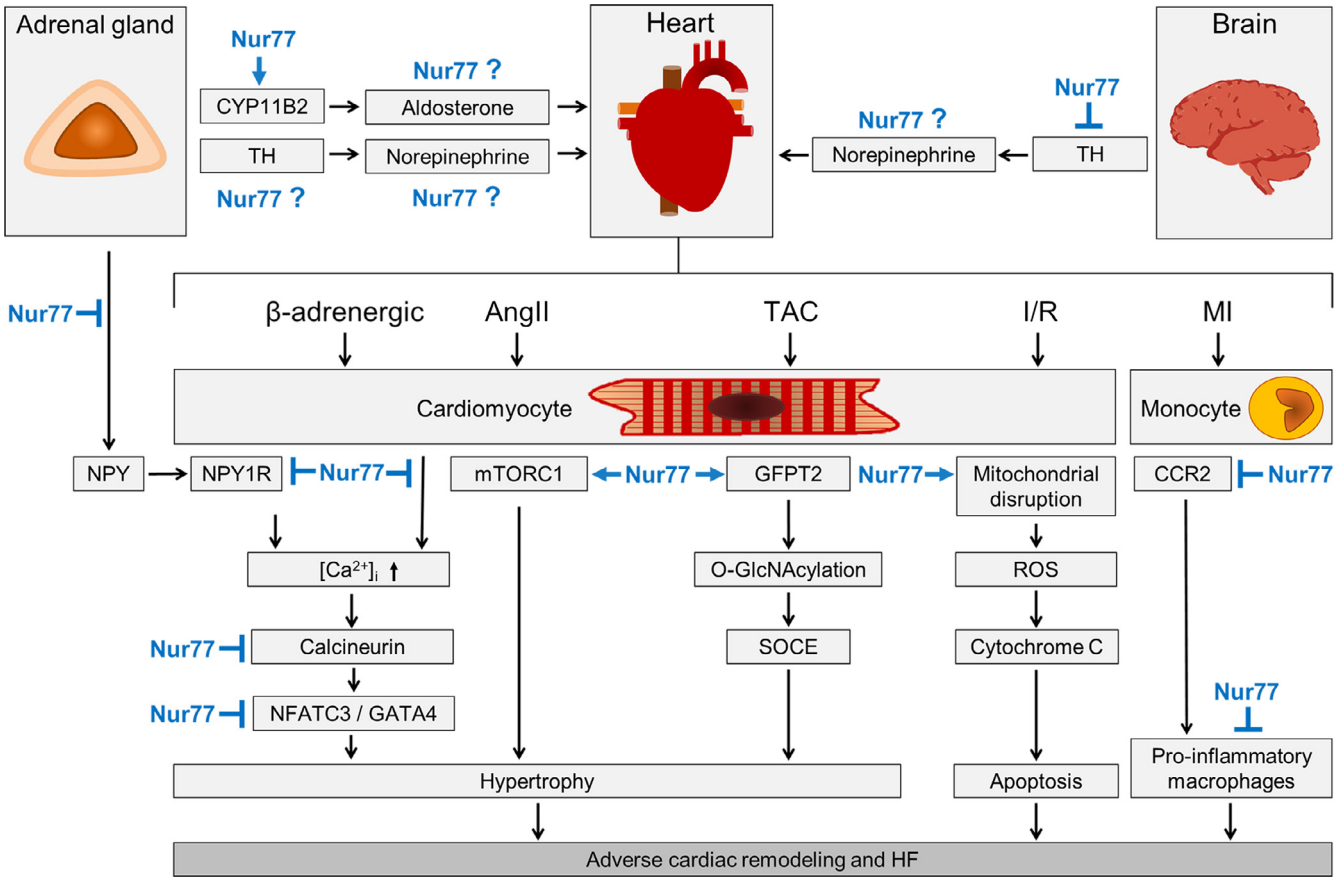

Fig. 3. Multi-level regulation of cardiac function and disease by Nur77. AngII: angiotensin II, CCR2: C-C chemokine receptor 2, CYP11B2: aldosterone synthase, GFPT2: glucosamine-fructose-6-phosphate aminotransferase, MI: myocardial infarction, mTORC 1: mammalian target of rapamycin complex 1, NPY: neuropeptide Y, NPY1R: neuropeptide Y type 1 receptor, ROS: reactive oxygen species, SOCE: store-operated calcium entry, TAC: transverse aortic constriction, TH: tyrosine hydroxylase.

to act anti-hypertrophic by functionally interacting with NFATc3 and GATA4 [57], which are key transcriptional regulators essential for developing cardiac hypertrophy [59], and thereby inhibiting their transcriptional activity. Intracellular Ca^{2+} is a critical regulator of NFATc3 nuclear import and activity through activation of the phosphatase calcineurin [60]. Cardiomyocytes isolated from Nur77-KO mice have elevated baseline diastolic and systolic $[Ca^{2+}]_i$ compared to WT mice. Accordingly, baseline cardiac calcineurin activity is higher in Nur77-KO mice [47]. Together Nur77 may not only dampen cardiac hypertrophy by inhibiting NFATc3 as a transcriptional co-repressor, but also increase the initiation threshold of the Ca^{2+}/calcineurin/NFAT signaling pathway by lowering cardiomyocyte $[Ca^{2+}]_i$. Finally, Nur77-KO cardiomyocytes exhibit altered electrophysiological properties with prolonged action potential and early-after depolarization [47], which may be explained by elevated cardiomyocyte $[Ca^{2+}]_i$, suggesting an anti-arrhythmogenic role for Nur77.

Nur77 in NPY-induced cardiac remodeling

The sympathetic co-transmitter NPY is known to raise cardiomyocyte $[Ca^{2+}]_i$ [61] and induce cardiomyocyte- and cardiac hypertrophy [62,63]. Nur77 controls cardiomyocyte hypertrophy in a paracrine manner via NPY. Conditioned medium from Nur77-silenced adrenal chromaffin cells and serum from Nur77-KO mice induce enhanced NRCM hypertrophy, which is inhibited by NPY type 1 receptor (NPY1R) antagonism [54]. Furthermore, cardiomyocyte $[Ca^{2+}]_i$ in Nur77-KO mice is partially mediated by enhanced NPY1R signaling. Accordingly, enhanced calcineurin activity and ISO-induced cardiac hypertrophy and fibrosis were attenuated by NPY1R antagonism in full-body Nur77-KO mice, but not in WT or cardiomyocyte-specific Nur77-deficient mice, revealing the influence of hormonal NPY on cardiac remodeling [54].

Nur77 in cardiac pressure overload

Persistent RAAS activity leads to increased filling pressure and afterload in the left ventricle [64]. These hemodynamic changes elevate cardiac wall stress, inducing adverse cardiac remodeling and impairment of pump function.[5] Cardiac pressure overload by transverse aortic constriction (TAC) results in enhanced Nur77 expression in murine hearts [65], more specifically in cardiomyocytes [53]. Compared to WT mice, Nur77-KO mice exhibit less cardiomyocyte hypertrophy and perivascular fibrosis after TAC [47]. It has been demonstrated that a proteolytic fragment of histone deacetylase 4 (HDAC4-NT) represses TAC-induced Nur77 expression via inhibition of the MEF2 transcription factor [65]. Concomitantly, HDAC4-NT attenuates TAC-induced cardiac protein O-GlcNAcylation and protects against TAC-induced cardiac remodeling in mice. It is thought that Nur77 mediates TAC-induced cardiac dysfunction by enhancing the expression of *gfpt2*, the rate-limiting enzyme of the hexosamine biosynthesis pathway in a non-genomic fashion [65]. As such, Nur77 overexpression in NRCMs leads to increased protein O-GlcNAcylation and among these proteins is the store-operated Ca^{2+} entry (SOCE) regulator Stim1. Nur77-mediated O-GlcNAcylation of Stim1 impairs its function, thereby blunting SOCE and impairing Ca^{2+}-driven contractility in engineered heart tissue [65]. It remains to be determined whether altered O-GlcNAcylation and SOCE underlies the attenuated TAC-induced cardiac remodeling in Nur77-KO mice [47].

Nur77 in AngII-induced cardiac remodeling

AngII may induce cardiac hypertrophy and fibrosis by directly acting on cardiomyocyte and cardiac fibroblast angiotensin receptors [66]. Chronic AngII infusion in mice increases the Nur77 protein level in the heart, while Nur77 mRNA levels remain the same in AngII treated NRCMs, as well as Nur77 transcriptional activity in H9C2 cardiac myoblasts. Actually, AngII was shown to extend Nur77 protein half-life [50]. siRNA-mediated Nur77 knockdown protects NRCMs against AngII-induced hypertrophy. Accordingly, chronic AngII infusion in Nur77-KO mice results in attenuated cardiac hypertrophy, fibrosis and apoptosis and improved left ventricular function compared to WT controls [50]. A similar phenotype is observed in rats that were treated with intramyocardial injections of lentiviral Nur77 siRNA. Of note, the differences in cardiac remodeling did not originate from altered blood pressure upon AngII infusion between WT and Nur77-KO mice [50].

In cardiac myoblasts, NRCMs and mouse hearts, Nur77 enhances AngII-induced activity of the mammalian target of rapamycin complex 1 (mTORC1) [50]. This complex promotes cardiac hypertrophy due to the capacity of mTOR to regulate cell growth [67,68]. Activity of mTORC1 is inhibited by the GTPase TSC2 [69]. In the absence of Nur77, AngII-mediated TSC2 degradation is blunted. Via its ligand-binding domain Nur77 binds TSC2 and thereby triggers TSC2 proteasomal degradation via the ubiquitination pathway. It is hypothesized that the enhanced degradation of TSC2 by Nur77 subsequently leads to enhanced mTORC1 activity and therefore may be an important pathway in AngII-induced cardiac hypertrophy [50]. Interestingly, in hypertrophic human hearts, Nur77 protein levels are higher than in control hearts and are accompanied by corresponding lower levels of TSC2 [50].

Nur77 in cardiac ischemia/reperfusion injury

Ischemia/reperfusion (I/R) injury occurs upon reoxygenation of ischemic myocardium [70]. Several pathological pathways converge during I/R injury, among which, oxidative stress-mediated opening of the mitochondrial permeability transition pore (MPTP), resulting in a total collapse of the mitochondrial membrane potential, initiating apoptosis [71]. Reperfusion after an ischemic period induces Nur77 expression in mouse hearts. Already after 1 h, Nur77 mRNA expression is even further enhanced compared to ischemic, non-reperfused hearts [72]. Nur77 is the top-upregulated gene in dog hearts upon I/R injury [52]. Functionally, I/R injury causes less contractile dysfunction in Nur77-KO than WT mice [72], presumably because of reduced cardiac cell death. Under normal conditions, Nur77 is localized predominantly in the nucleus of cardiomyocytes [53]. As soon as 15 min after reperfusion, I/R injury in mice leads to co-localization of Nur77 with the mitochondrial marker HSP60 in cardiomyocytes, which is accompanied by reactive oxygen species and DNA damage [53]. In dog hearts, I/R-induced Nur77 cytoplasmic translocation is associated with mitochondrial morphological degradation in the I/R region [52].

Given that oxidative stress mediates I/R injury, an H_2O_2 challenge in NRCMs and adult mouse cardiomyocytes also induces co-localization of Nur77 with the mitochondrial marker HSP60. A Nur77 mutant lacking its nuclear localization signals, is permanently localized at mitochondria and induces cytochrome *C* release, TUNEL reactivity and typical morphological features of apoptosis such as DNA fragmentation and chromatin condensation in cardiomyocytes [53]. An H_2O_2 challenge in NRCMs leads to decreased mitochondrial membrane potential with concomitant mitochondrial translocation of Nur77, without affecting its overall expression [73]. Accordingly, such an H_2O_2 challenge caused significantly less apoptosis in NRCMs transfected with Nur77-targeting siRNA [53].

Nur77 in immune-related cardiac remodeling

The immune system is yet another important regulator of cardiac function and remodeling, especially in ischemic heart disease with dramatic infiltration of granulocytes and monocytes/macrophages. But also during chronic heart failure, the immune system exerts its effect in the remodeling heart [6,74].

Nur77 expression is upregulated in borderzone cardiomyocytes after MI in mice [53]. But also, immune cells infiltrating the infarcted myocardium show high Nur77 expression [75]. In the absence of Nur77, infiltrating Ly-6C^{high} monocytes exhibit enhanced expression of CCR2 chemokine receptor and subsequently differentiate into pro-inflammatory macrophages with elevated expression of IL-1β, IL-6 and TNF-α. This results in diminished healing of the infarcted area, causing larger and less dense scars and reduced left ventricular function [76]. Thus, Nur77 is an important regulator of immune-related remodeling in the infarcted heart by inhibiting invasion of inflammatory monocytes as well as limiting expression of pro-inflammatory factors in monocyte-derived macrophages.

Next to the innate immune system, Nur77 may also affect the adaptive immune system involved cardiac disease. In a rat model of cardiac transplantation, high Nur77 expression was observed in T-cells infiltrating the cardiac allograft. Here, Nur77 co-localized with Htr2/omi, an apoptotic effector protease concomitant with activated caspase-3 in these cells [77]. It was proposed that Nur77 mediates apoptosis of graft-infiltrating T-cells during acute cardiac graft rejection by HtrA2/Omi release from mitochondria, however functional studies need to be performed to substantiate this hypothesis.

Nurr1 and NOR-1 in adverse cardiac remodeling

Compared to Nur77, much less is known about the functional roles of Nurr1 and NOR-1 in cardiac function and remodeling. Nurr1 mRNA expression is upregulated by β-adrenergic stimulation with ISO in mouse hearts [49] and NRCMs [47], however the functional implications for Nurr1 in cardiac hypertrophy and HF deserve further elucidation. NOR-1 mRNA is expressed in healthy porcine, murine and human hearts [49,78,79]. In myocardial tissue from hypertrophic cardiomyopathy patients, the usage of a NOR-1 alternative non-coding exon was higher than in healthy hearts, suggesting that, similar as for Nur77, alternative promoter usage in healthy and hypertrophic heart [39]. Furthermore, decreased NOR-1 transcript expression was observed in atrial appendages of patients suffering from atrial fibrillation with underlying mitral valve dysfunction or coronary artery disease, compared to controls [80]. While these reports suggest a role for NOR-1 in the pathophysiology of cardiac hypertrophy and HF, functionally not much is known thus far. NOR-1 mRNA and protein are rapidly upregulated by β-adrenergic stimulation via ISO in the mouse heart [49] and NRCMs [47,81]. ISO-induced NRCM hypertrophy is attenuated by siRNA-mediated NOR-1 silencing, while NOR-1 overexpression alone already enhances NRCM hypertrophy [82]. NOR-1 does so by binding poly-ADP-ribose-polymerase 1 (PARP-1), thereby promoting its acetylation and activation [82]. Excessive PARP-1 activation depletes cellular NAD^+, resulting in functional impairment and progression of cardiac hypertrophy and heart failure [83]. Taken together, further studies are needed to elucidate the functional importance of Nurr1 and NOR-1 in cardiac remodeling and HF.

Future perspectives: focus on Nur77

Here, we summarize the current knowledge on NR4A nuclear receptor function in the heart and in cardiac neurohormonal regulation mechanisms (Table 1). NR4As exert multi-level regulation of cardiac function and disease. In neurohormonal control, Nur77 and

Nurr1 affect the rate-limiting steps in both SNS and RAAS activity. In the heart itself, Nur77 especially is emerging as a key player in adverse cardiac remodeling.

Future research must focus on coupling NR4A-mediated regulatory mechanisms in the SNS and RAAS to cardiac function, adverse cardiac remodeling and HF. To achieve this, delineation of the cell-type specific effects of NR4As in neurohormonal and cardiac function will be key (Fig. 3). For instance, in cardiomyocytes, Nur77 mediates opposing remodeling outcomes upon differential pathological stimuli, i.e., β-adrenergic overstimulation versus chronic AngII infusion. In neurohormonal regulation mechanisms, Nur77 seems to dampen catecholamine synthesis via TH in multiple cell types in the SNS, but also seems to enhance aldosterone synthesis via *CYP11B2* regulation in the RAAS. Since the SNS, RAAS and immune system all become activated to a certain degree upon declining heart function, the dominant role of either will determine if Nur77-agonists or antagonists would improve HF outcome.

It seems that there is no one-drug-fits-all approach feasible in HF patients. Nur77 clearly illustrates that it makes a difference to know the underlying cause and pathophysiology of HF to become successful with a therapeutic strategy, because of the interplay between the heart and neurohormonal mechanisms. Therefore Nur77 may be interesting as a novel drug target in cardiac remodeling and HF, however it is crucial to improve HF patient characterization to delineate at what stage of disease it would be beneficial to enhance or inhibit Nur77 activity to prevent HF progression. In this line of thinking, it may be worthwhile considering Nur77 as a genetic disease marker, next to a therapeutic target. Single nucleotide polymorphisms (SNPs) have proven to be informative genetic markers for HF risk, and drug response [84,85]. Several SNPs in the human Nur77 gene have been found to associate with various diseases and seem to mimic phenotypes observed in Nur77-KO mice [86,87]. We hypothesize that such a loss-of-function Nur77 SNP could identify a patient who is more sensitive to the detrimental effects of sympathetic hyperactivity on cardiac function and hypertrophy due to elevated cardiomyocyte $[Ca^{2+}]_{i,}$ and who does not benefit from β-blocker therapy optimally due to enhanced NPY-NPY1R signaling.

In conclusion, although at present not all functions of Nur77 in regulating cardiac (patho)physiology have been unraveled, Nur77 seems to be a promising target in future HF characterization and therapy. Therefore, it's role deserves to be further elucidated beyond biochemical and animal-experimental studies, shifting research into the human context.

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