IJC Heart & Vasculature 48 (2023) 101271

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

How does NFAT3 regulate the occurrence of cardiac hypertrophy?

Wang Hui [a,1], Su Wenhua [a,b,1], Zhang Shuojie [a], Wang Lulin [a], Zhao Panpan [a], Zhang Tongtong [a], Xie Xiaoli [a,*], Dan Juhua [a,*]

[a] Laboratory of Molecular Genetics of Aging & Tumor, Medical School, Kunming University of Science and Technology, Kunming, Yunnan, China
[b] Department of Cardiology, The First People's Hospital of Yunnan Province, Kunming, Yunnan, China

ARTICLE INFO

Keywords:
Cardiac hypertrophy
NFAT3
Nuclear translocation

ABSTRACT

Cardiac hypertrophy is initially an adaptive response to physiological and pathological stimuli. Although pathological myocardial hypertrophy is the main cause of morbidity and mortality, our understanding of its mechanism is still weak. NFAT3 (nuclear factor of activated T-cell-3) is a member of the nuclear factor of the activated T cells (NFAT) family. NFAT3 plays a critical role in regulating the expression of cardiac hypertrophy genes by inducing their transcription. Recently, accumulating evidence has indicated that NFAT3 is a potent regulator of the progression of cardiac hypertrophy. This review, for the first time, summarizes the current studies on NFAT3 in cardiac hypertrophy, including the pathophysiological processes and the underlying pathological mechanism, focusing on the nuclear translocation and transcriptional function of NFAT3. This review will provide deep insight into the pathogenesis of cardiac hypertrophy and a theoretical basis for identifying new therapeutic targets in the NFAT3 network.

Introduction

The NFAT family was first identified as a cluster of transcription factors expressed in activated but not static T cells[1]. To date, five NFAT family members have been discovered. Four members of the family, NFAT1 (NFATc2/NFATp), NFAT2 (NFATc1, NFATc), NFAT3 (NFATc4), and NFAT4 (NFATc3, NFATx), were all cloned from murine Ar-5 and human Jurkat T cells[2]. NFAT5 is a distinct NFAT family member that is involved in the cellular response to hypertonic stress[3]. NFAT protein is expressed in almost all tissues, but the expression level varies greatly. For example, NFAT1 is mainly expressed in the pancreas [4], testis, placenta, hypothalamus, hippocampus, cerebellum, olfactory bulb and frontal cortex of the brain[5,6], NFAT2 is mainly expressed in the cardiovascular system, digestive system and kidney[7], and NFAT3 is more balanced, mainly expressed in adipose tissue, myocardium, ovary, spinal cord, brain and other regions[5,8,9]. NFAT4 is mainly expressed in skeletal muscle and smooth muscle[10], as well as in the lung, hypothalamus and striatum. There are few studies on the function of NFAT1, 2, 4 and 5, but there are several studies on NFAT3 in cardiac hypertrophy pathogenesis[11–13].

Cardiac hypertrophy includes primary cardiac hypertrophy (hypertrophic cardiomyocytes) and secondary cardiac hypertrophy. Cardiac hypertrophy is a common inherited disease characterized by an increase in the thickness of the ventricular wall (≥1.5 cm) in the absence of increased afterload, and it is recognized as an important cause of sudden cardiac death among young adults and competitive athletes[14]. Secondary cardiac hypertrophy can be divided into two types: physiological and pathological. Physiological hypertrophy is usually caused by normal growth, pregnancy, or movement of cardiomyocytes. Pathological myocardial hypertrophy is the maladaptive response of the heart to various adverse pathological stimuli, such as hypertension and myocardial infarction[15]. Both physiological and pathological hypertrophy progression depends on upstream triggers and signalling mechanisms [16–18].

In previous studies, several regulatory mechanisms have been found to have positive or negative effects on cardiac hypertrophy, including cell metabolism[19], proliferation[15], miRNA[20–22], immune response[23,24], translation regulation[25], epigenetic modification [26,27] and many more. As an important marker of cardiac hypertrophy, NFAT3 caught our attention. In this review, we summarize the functional network of NFAT3 in cardiac hypertrophy, focusing on its nuclear translocation and transcriptional function.

* Corresponding authors.
E-mail addresses: 20130168@kust.edu.cn (X. Xiaoli), danjuhua@kust.edu.cn (D. Juhua).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ijcha.2023.101271
Received 10 July 2023; Received in revised form 24 August 2023; Accepted 8 September 2023
2352-9067/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. The structure of NFAT3

The protein structures of the NFAT family are homologous, including two conserved functional regions, namely, the NFAT homologous region (NHR) and Rel homologous region (RHR), and a nonconserved C-terminal domain[28]. NHR is mainly related to the transcriptional regulation of NFAT, and RHD is mainly involved in the combination of NFAT and DNA[28]. Phosphorylation/dephosphorylation is the main regulatory mode of NFAT transcriptional activity. NHR contains many conserved structural units, such as serine-rich structures SRR1 and SRR2 (serine-rich regions, SRRs) and serine-proline-rich structures SP1, SP2 and SP3 (serine-proline regions, SPs), which can be phosphorylated by NFAT kinases, such as casein kinase (CK1), glycogen synthase kinase 3 (GSK-3) and tyrosine phosphorylation regulatory kinase (DYRK)[28]. NHR also contains the binding motifs of calcineurin SPRIEIT, CK1 binding motif FSILF and a masked nuclear localization sequence (nuclear localization signal, NLS) (Fig. 1). As a member of the NFAT family, NFAT3 also has a similar domain structure. In the inactive state, serine residues of NFAT are phosphorylated to form a conformation covering the NLS. However, in the activated state, the serine of NFAT in the cytoplasm is dephosphorylated, and the NLS is exposed. Then, NFAT3 enters the nucleus to regulate the expression of target genes by cooperating with other relevant transcription factors.

2. Regulation of NFAT3 expression level and function

The expression of NFATs is specifically regulated in different organs and tissues. The involvement of NFATs in the cardiovascular system was first shown by the fact that mice lacking the NFAT2 gene have lethal defects in cardiac valve formation[29,30] and abnormalities in the cardiac septum. As early as 1998, Molkentin et al. discovered that mice expressing an activated form of NFAT3 in the heart develop cardiac hypertrophy and heart failure[31]. Later, Bushdid et al. explored its role in cardiac development; they built a mouse model with disruption of both the NFAT3 and NFAT4 genes that demonstrated embryonic lethality after embryonic Day 10.5 and thin ventricles, pericardial effusion, and a reduction in ventricular myocyte proliferation[32]. However, how the expression of NFAT3 in cardiac myocytes is regulated is unclear.

A study revealed that the inhibition of NFAT3 expression in $CD4^+$ T cells occurred largely via TBX5 deficiency-mediated downregulation of NFAT3 promoter/enhancer activity[33]. TBX5 plays important roles in cardiac function, including chamber formation, septation, and cardiomyocyte differentiation[34]. Therefore, NFAT3-mediated regulation of cardiac development might be regulated by TBX5. However, the regulatory mechanism of TBX5 in cardiomyocytes still needs to be further verified. The expression of NFAT3 is affected not only by promoter activity but also by chromatin modification of the NFAT3 gene. As the epigenetic modification of the gene, including acetylation and/or methylation of histones and/or DNA, affects transcriptional activity, further investigation is required to elucidate additional details of these modifications in the NFAT3 gene.

As a transcription factor, NFAT3 translocates into the nucleus to perform its function, and the process is precisely regulated. Studies have shown that Ca^{2+} promotes the dephosphorylation of the regulatory domain of NFAT3 by activating CaN[35]. Then, the obscured NLS sequence is released to transport NFAT3 into the nucleus. When Ca^{2+} increases in the cell, CaM binds with Ca^{2+}, exposing hydrophobic surfaces that will attach to CaN to promote its binding with Ca^{2+}. The Ca^{2+}-CaN complexes link to NFAT3 and dephosphorylate it. Consequently, the hidden NLS sequence is exposed and mediates the nuclear translocation of NFAT3. In the nucleus, NFAT3 combines with its co-factors and switches on the transcription of its target genes.

Next, we will summarize the regulatory program of NFAT3 in the pathogenesis of cardiac hypertrophy.

3. Regulation of NFAT3 in the cardiac hypertrophy process

In the past decade, numerous studies have shown that the development of cardiac hypertrophy involves the activation and regulation of many signalling pathways and transcription factors[12,36,37]. Among these mechanisms, NFAT3 seems to be a very important core point. The RHR region of NFAT3 binds to the promotor region to induce the expression of hypertrophy-associated genes when stimulated by cardiac

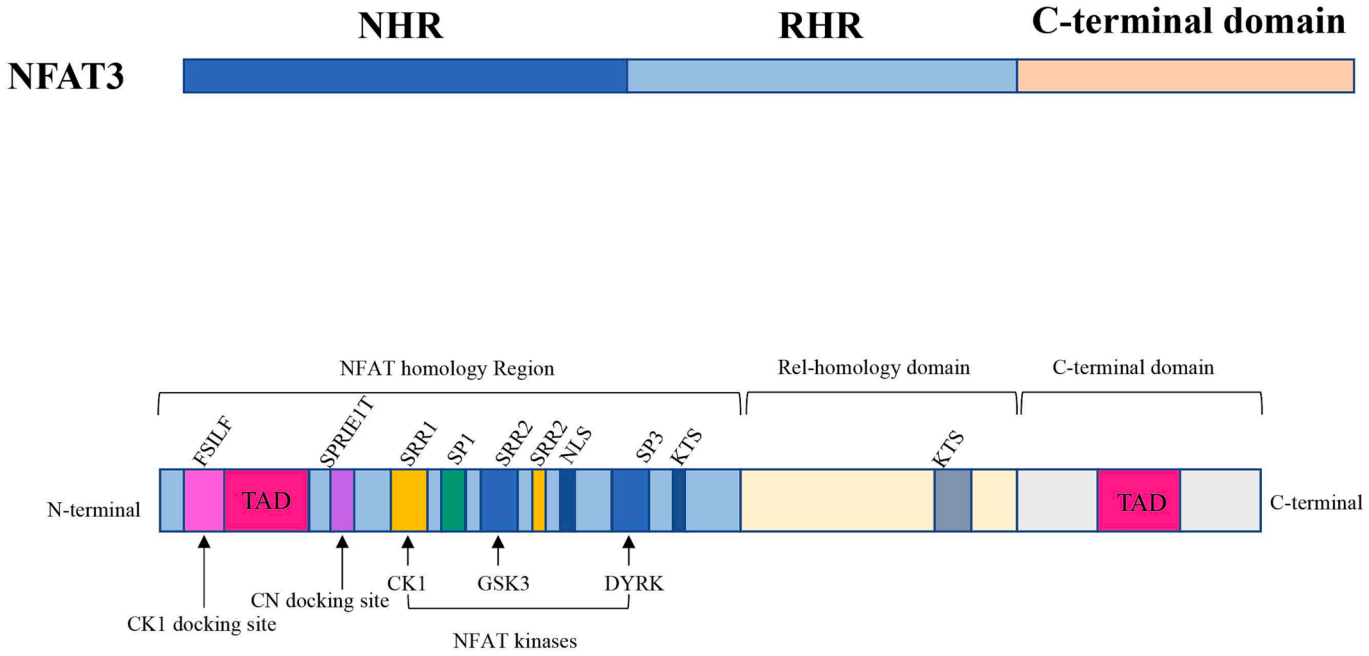

Fig. 1. General structure of the NFAT protein. NFAT proteins consist of an NHR, a DNA-binding domain (RHD) and a carboxy-terminal domain. The regulatory domain contains an N-terminal transactivation domain (TAD), as well as a docking site for casein kinase 1 (CK1), termed FSILF, and for calcineurin, termed SPRIEIT. The regulatory domain also includes multiple serine-rich motifs (SRR1, SP1, SP2, SRR2, SP3 and KTS) and a nuclear localization sequence (NLS)[28].

hypertrophic factors. However, this process is regulated by a series of complex mechanisms, including shuttling between the cytoplasm and nucleus and transcriptional activity[38]. Here, we will summarize the related research on the above regulatory mechanisms (Fig. 2).

3.1. Regulation of NFAT3 localization

NFAT3 is a very important transcription factor. Its nuclear import requires dephosphorylation by the Ca^{2+}/calmodulin-dependent phosphatase CaN, whereas its nuclear export requires rephosphorylation, which can be mediated by a variety of kinases[39–41]. We will summarize the factors and mechanisms that affect the localization of NFAT3 from its import and export to the nucleus.

3.1.1. Factors and mechanisms affect NFAT3 transport to the nucleus

As mentioned above, the nuclear import of NFAT3 is mediated by its dephosphorylation. Since many factors have been discovered to affect the phosphorylation state of NFAT3, a large number of studies have investigated the regulatory mechanisms in the pathogenesis of cardiac hypertrophy[36,42,43].

Evidence shows that hydrogen peroxide promotes myocardial hypertrophy by activating the transcription factor NFAT3[44]. Hydrogen peroxide is always stimulated by myocardial hypertrophy inducers, such as angiotensin II[44]. Angiotensin II is a polypeptide composed of eight amino acids that activates membrane-associated NADPH oxidase by binding to the cell surface receptors[45,46]. Simultaneously, oxidation products (hydrogen peroxide and ROS) contribute to angiotensin II-induced gene expression, such as the activation of a neurotrophic factor in cardiac fibroblasts[47]. Studies have shown that hydrogen peroxide can activate the PI3K and MAPK pathways[48,49]. PI3K is a kinase that regulates multiple signalling pathways, including inducing intracellular calcium release and activating CaN. A study confirmed that CaN was transiently activated when cardiomyocytes were incubated with hydrogen peroxide[50]. However, CaN is the main factor involved in NFAT3 activation. Therefore, it can be speculated that oxidants may activate NFAT3 by regulating intracellular Ca^{2+} levels.

Studies have shown that recombinant high mobility group Box 1 (HMGB1) induces cardiac hypertrophy by regulating the 14-3-3η/PI3K/Akt/NFAT3 signalling pathway[51]. HMGB1 is an inflammatory cytokine that is important in multiple organ pathologies[52]. 14-3-3 proteins are ubiquitous in all eukaryotes and play a role in the stress response of various cells. The 14-3-3 protein family includes several highly conserved acid proteins, named according to their different isoforms (β, ε, η, γ, τ, σ and ζ) detected in the cell cytoplasm and nucleus [53,54]. Studies have established that several isoforms of 14-3-3 proteins are expressed in rat cardiomyocytes, and these isoforms of 14-3-3 proteins inhibit cardiomyocyte hypertrophic responses such as a1-AR-induced hypertrophy, in which the PI3K/PKB/GSK3b and NFAT pathways are likely involved[55]. The regulation of GSK3b phosphorylation and the compartmentalization of NFAT by 14-3-3 probably contributes to this process. The 14-3-3 proteins inhibit cardiomyocyte hypertrophy by inhibiting the PI3K signalling pathway and promoting NFAT phosphorylation[55]. PI3K is activated by growth factors, and activated PI3K generates PIP3 through phosphorylation of PIP2, which activates the downstream target Akt, resulting in physiological cardiac growth [56,57]. Furthermore, a study clarified the regulation of NFAT by 14-3-3 through NFAT phosphorylation[58].

IGF-1 is a stimulator of the PI3K/Akt/mTOR signalling pathway, which can activate mTOR, thus promoting the transfer of NFAT3 from the nucleus to the cytoplasm. Rapamycin, as an inhibitor of mTOR, can eliminate the effect of IGF-1 by increasing the nuclear level of NFAT3 [59]. Thus, one target of the mTOR signalling pathway is NFAT3. However, CaN inhibition did not inhibit NFAT3 activity, suggesting that the inhibition of the mTOR signalling pathway in cardiomyocytes may be mediated by other phosphatases[59].

Myostatin, a member of the TGF-β family, is a well-established negative regulator of skeletal muscle mass[60]. Based on this, Lawrence T. Bish's group has studied the role of myostatin in the cardiac growth of neonatal cardiomyocytes. They found that myostatin blocked cardiac growth by regulating the Akt/NFAT3 signalling pathway by suppressing the dephosphorylation of NFAT3 and phosphorylation of Akt[60]. Therefore, the transfer of NFAT3 from the cytoplasm to the nucleus is suppressed[61]. This is the first report of cross-talk between the myostatin and NFAT3 pathways in cardiomyocytes. This indicates that myostatin signalling activates kinases capable of phosphorylating NFAT3, thus countering the effects of CaN, or it may be that mediators of myostatin signalling, that are further downstream, can suppress calcineurin at the transcriptional level. Further investigation is needed to

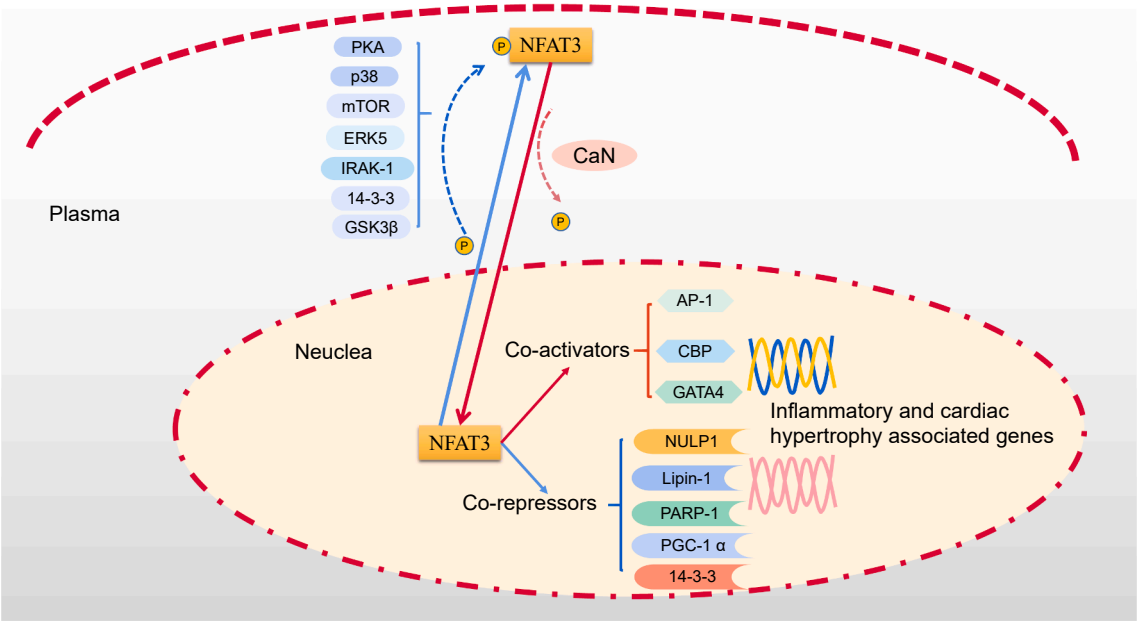

Fig. 2. Role and potential mechanism of NFAT3 and its targets in cardiac hypertrophy. CaN, p38, ERK5, IRAK-1, AP-1, CBP, GATA4, NULP1, Lipin-1, PARP-1, PGC-1α, 14-3-3, and mTOR.

identify the link between myostatin and NFAT3.

As described above, the Ca^{2+}/CaN pathway is the core point of NFAT dephosphorylation. Almost all hypertrophy stimulators promote the dephosphorylation and nuclear import of NFAT3 by increasing intracellular [Ca^{2+}] and activating CaN.

3.1.2. Factors and mechanisms affect NFAT3 export from the nucleus

NFAT3 is exported from the nucleus when it is rephosphorylated. For example, GSK3β, PKA, p38, 14-3-3 and mTOR, which promote NFAT3 phosphorylation, may influence this process.

A study reported that NFATs are targets of JNK and p38 MAP kinase phosphorylation. JNK regulates the phosphorylation of Ser^{172} in NFATc1 and $Ser^{163,165}$ in NFATc3[62,63]. P38 MAP kinase regulates the phosphorylation of Ser^{172} of NFATc1, $Ser^{163,165}$ of NFATc3 and $Ser^{168,170}$ of NFATc4[64]. Phosphorylation of NFATs by different kinases indicates that these kinases are very important for the regulation of NFAT. Among the protein kinases identified, Teddy T. C. Yang's study indicated that NFATc4 is a substrate for p38 MAP kinases[64]. Targeted disruption of the p38 MAP kinase gene may cause similar increases in the nuclear localization of NFAT3. Nuclear NFAT3 may then induce NFAT target genes and promote cell growth and differentiation. The C. Yang study further demonstrated that phosphorylation at $Ser^{168,170}$ of NFAT3 was the primary target for p38-mediated phosphorylation and subsequent activation. To explore more possible kinases that regulate the subcellular localization of NFAT3, Teddy et al. researched the role of mTOR in this process[65]. They have demonstrated that mTOR mediates basal phosphorylation and rephosphorylation of the gate-keeping residues $Ser^{168,170}$ to regulate the subcellular distribution of endogenous NFAT3. Additionally, they found that MEK5/ERK5 signalling mediated rephosphorylation at $Ser^{168,170}$ and, thus, nucleocytoplasmic shuttling of NFAT3. The series of studies by Teddy et al. identified that these kinases contribute to the phosphorylation of NFAT3 in different states, mTOR in the resting state, ERK5 upon rephosphorylation, and p38 MAPK under stress. However, another study suggested that ERK5 may not be fully responsible for the constitutive phosphorylation of NFATc4 in resting cells, and they demonstrated that IRAK-1 is a maintenance kinase responsible for phosphorylating NFATc4 in untreated resting cells[66]. They also found that IRAK-1 directly connected with NFATc4 via the N-terminal NHR region of NFATc4 and the C-terminus of IRAK-1 in the resting state of cells.

GSK3β is a downstream target of Akt, which promotes inhibitory phosphorylation of GSK3 on a serine residue near the amino terminus [67]. Thus, conditions that activate Akt concurrently inhibit GSK3, prolonging the nuclear residence of NFAT[68]. In neurons, GSK3 has been demonstrated to inhibit the transcriptional activity of the NFAT family member NFAT3[69]. Studies have shown that overexpression can promote NFAT nuclear export [69,70]. Conversely, LiCl, an inhibitor of GSK3, can slow the rate of NFAT nuclear output, thus prolonging the nuclear retention time of NFAT[71]. GSK3 is the downstream target of Akt, which inhibits the nuclear translocation of NFAT3 by phosphorylating NFAT3. Phosphorylation of serine residues near the amino terminus of GSK3 inhibits the activation of Akt[67].

The above studies have reported several kinases that are involved in regulating the nuclear concentration of NFAT3 by rephosphorylating NFAT3 at specific serine sites. Some of these processes were not confirmed to participate in the regulation of cardiac hypertrophy, and more evidence needs to be discovered.

3.2. Regulation of NFAT3 transcriptional activity

In addition to posttranslational modification, NFATc4 transcriptional activity is also modulated by interaction proteins, including coactivators and corepressors. To date, AP-1, CBP, and GATA4 have been found to activate the transcriptional activity of NFAT3. In contrast, NULP1, Lipin-1, PARP-1, PGC-1α, and 14-3-3 have been found to repress the transcriptional activity of NFAT3.

3.2.1. Coactivators of NFAT3

AP-1

In addition, hydrogen peroxide has been shown to activate ERK, and ERK appears to regulate the activation of the transcription factor AP-1 [49]. The NFAT3 binding site in the promoters of most genes contains the AP-1 binding site adjacent to the core consensus NFAT binding sequence. Thus, the hypertrophy inducers ANG II and hydrogen peroxide may activate NFAT3 in cardiomyocytes through an AP-1 transcription factor-dependent mechanism[44].

GATA4

GATA4 has been ascribed to a number of critical functions in the heart, spanning from the specification and differentiation of cardiac myocytes early in development to the regulation of the cardiac hypertrophic response in the adult. In 1998, Eric et al. found an interaction between GATA4 and NFAT3 using the yeast two-hybrid system and determined their synergistic activation in the heart to develop cardiac hypertrophy and heart failure[43]. Subsequently, a series of studies [72,73] further confirmed the synergy between these two transcription factors. In the nucleus, NFAT3 forms complexes with GATA4, leading to the activation of the transcription of genes (ANF, a-actin, b-myosin, TNFa, ET-1, Adss1, etc.) essential for cardiac development. In addition, Heineke et al. found that GATA4 and GATA6 can promote myocardial adaptation to pressure overload by enhancing cardiac angiogenesis[74].

CREB-binding protein (CBP)

Recruitment of the coactivator CREB-binding protein (CBP) to transcription factors is important for gene expression. Various regions of CBP, such as the KIX and CH3 domains, have been shown to interact with numerous transcription factors. Yang et al. demonstrated that two transactivation domains, located at the NH2 and COOH termini of NFATc4, are critical for interacting with CBP[75]. The presence of two interacting sites may allow efficient recruitment of CBP to the NFAT transcription complex. Binding of CBP potentiates NFATc4-mediated transcription activity. Removal of either NFATc4 transactivation domain abolishes CBP potentiation. Conversely, mutation of the KIX or CH3 domain prevents CBP-mediated potentiation of NFATc4 transcription activation. Furthermore, the presence of two interacting sites may allow a longer duration for transcription mediated by the NFATc4·CBP complex by retaining CBP in the vicinity of NFAT downstream target promoters. These data demonstrate that the presence of two CBP-interacting sites may promote immediate prompt downstream actions, in response to extracellular stimuli, to recruit CBP and to increase the expression of NFAT-mediated genes.

3.2.2. Corepressors of NFAT3

NULP1

NULP1, transcription factor 25, also known as nuclear localization protein 1, is a member of the helix-loop-helix transcription factor family, playing an important role in embryonic development[76]. NULP1 has been shown to modulate the activity of serum response factors. Serum reactive factor[77] is a transcription factor involved in heart development and heart disease. NULP1 also inhibits the transcriptional activity of NFAT3 by directly interacting with the topological domain of NFAT3 through its C-terminus[12]. Therefore, NULP1 can inhibit the transcriptional activity of NFAT3, further inhibiting the occurrence of cardiac hypertrophy[12].

Lipin-1

Lipin-1 is a bifunctional protein that regulates gene transcription and, as a Mg^{2+}-dependent phosphatidic acid phosphatase (PAP), is a key enzyme in the biosynthesis of phospholipids and triacylglycerol[78]. Hyun et al. have shown that Lipin-1 represses the activity of NFATc4 bound to DNA, thus expanding the role of Lipin-1 in regulating transcription factor activity[79]. In vivo, Lipin-1 represses NFATc4 transcriptional activity through protein-protein interactions, and Lipin-1 is present at the promoters of NFATc4 transcriptional targets. Catalytically active and inactive Lipin-1 can suppress NFATc4 transcriptional activity. Blocking the loss of Lipin-1-mediated repression of NFAT may lead to

treatments for inflammation.

Poly-ADP-ribose polymerase-1 (PARP-1)

Poly-ADP-ribose polymerase-1 (PARP-1) is a nuclear enzyme that accounts for the bulk of ADP ribosylation in vivo[80]. Olabisi et al. demonstrated that PARP-1 binds to and ADP-ribosylates NFAT in an activation-dependent manner[81]. Furthermore, ADP-ribosylation regulates NFAT DNA binding and IL-2 gene expression. Hence, in addition to phosphorylation, ADP-ribosylation provides another layer of regulation of NFAT-dependent gene transcription.

PGC-1α

Peroxisome proliferator–activated receptor gamma coactivator 1 alpha (PGC-1α), a coregulator that interacts with multiple cardiac transcription factors, plays a crucial role in the regulation of cardiac hypertrophy[82]. PGC-1α regulates the expression of metabolic genes associated with mitochondrial and metabolic adaptations and maintains energy balance during the transition from compensated hypertrophy to heart failure[83]. The present study revealed that PGC-1α protected cardiomyocytes from hypertrophy by suppressing the calcineurin/NFATc4 signalling pathway[37]. PGC-1α limited the expression of NFATc4, prevented its dephosphorylation and nuclear translocation by suppressing calcineurin, and repressed its binding activity and transcription activity to the BNP promoter.

14-3-3

14-3-3 proteins were first discovered in 1967 as acidic proteins found abundantly in the brain. 14-3-3 proteins have been shown to interact with an array of partners, ranging from enzymes to structural proteins. Through their interaction, 14-3-3 proteins regulate the catalytic activity of their bound enzymes, determine the subcellular localization of target proteins, or both[84]. Decreased NFAT phosphorylation caused by the calcium-stimulated phosphatase calcineurin or mutation of the PKA phosphorylation sites disrupts 14-3-3 binding and increases NFAT transcription activity[85]. In contrast, NFAT phosphorylation caused by cAMP increased 14-3-3 binding and reduced NFAT transcription activity. The regulated interaction between NFAT and 14-3-3 provides a mechanism for the integration of calcium and cAMP signalling pathways. Liao et al. evaluated the role of 14-3-3 in cardiomyocyte hypertrophy by using an adenovirus vector expressing the YFP-R18 fusion peptide (AdR18) to inhibit 14-3-3 interactions[55]. Liao et al. suggested that 14-3-3s inhibits cardiomyocyte hypertrophy through regulation of the PI3K/PKB/GSK3β and NFAT pathways[55].

Conclusions

NFATs have been well studied in immune cells and are key regulators of T-cell activation[86]. Activated NFAT interacts with other transcription factors to regulate the expression of specific genes according to different cell types and regulatory signals, including the immune response, cell cycle, and angiogenesis[87]. NFAT3 is known to be expressed in the heart and has been associated with cardiac hypertrophy [12]. NFAT3 is activated in response to various hypertrophic stimuli, such as mechanical stress[88] and neurohormonal signals[89]. NFAT3 has been implicated in regulating genes that control cell growth[90], apoptosis[59], and fibrosis in the heart[91], all of which are important components of hypertrophic remodelling. NFAT1 and NFAT4 are also expressed in the heart and are involved in the regulation of cardiac hypertrophy[31,92]. NFAT2 has been studied extensively in immune cells, but it was also reported to play a role in cardiac hypertrophy[93]. The functions of NFAT2, NFAT4 and NFAT1 can overlap with NFAT3, but they might have distinct roles as well. NFAT1 and NFAT4 have been shown to regulate genes related to hypertrophic growth and fibrosis [94,95]. NFAT4, in particular, has been associated with the foetal gene program in the heart, which is reactivated during hypertrophy[32]. In addition, crosstalk and interaction between different NFAT subtypes and other signalling pathways may regulate cardiac hypertrophy in a complicated way.

NFAT3 not only plays a role in cardiac hypertrophy but also plays roles in other heart diseases. It has been reported that the plasma level of NFAT3 is increased in patients with chronic atrial fibrillation [95], suggesting that NFAT3 may affect the occurrence and development of atrial fibrillation. However, the exact function and regulatory mechanism remain to be further studied. Regarding the role of NFAT3 in other heart diseases, we have not found any research reports.

Here, we summarized the regulatory role of NFAT3 in the pathogenesis of cardiac hypertrophy from three aspects: i, the regulation of NFAT3 expression; ii, the regulation of NFAT3 localization; and iii, the regulation of NFAT3 transcript activity. Some factors affect more than one aspect; for example, the oxide induced by hypertrophic stimulators regulates NFAT3 not only by regulating its localization by upregulating the level of intracellular Ca^{2+} but also by affecting the activity of coactivator AP-1.

There is evidence that cell-specific expression of NFAT3 is mediated not only by promoter activity but also by modification of chromatin structure in the NFAT3 gene. Since epigenetic modifications of genes (histone acetylation, methylation, and DNA acetylation and methylation) affect transcriptional activity, further study of the genetic modification mechanisms in NFAT3 genes is required[33]. When stimulated, the intracellular Ca^{2+} concentration increases and binds with CaM to form an active binary complex that regulates CaN activity. Activated CaN promotes the dephosphorylation of NFAT3, which is transported to the nucleus. NFAT3 binds to other transcription factors in the nucleus to promote the expression of hypertrophy-related genes. Studies have shown that NFAT3 plays a role in a variety of cells and tissues, such as hippocampal cells[96,97], tumour cells[98–103], and lungs[104,105]. Several molecules have been shown to modulate NFAT3 in noncardiac cells; for example, cAMP inhibits Ca^{2+}-induced nuclear export of the MEF2 corepressor HDAC5 and prevents Ca^{2+}-stimulated nuclear import of the MEF2 coactivator NFAT3/c4[106]. ORP4L activated NFAT activity and thus promoted the expression of a gene cluster that supported cell proliferation. Notably, ORP4L sustained inositol-1,4,5-trisphosphate receptor 1 (IP3R1) expression at both the mRNA and protein levels via Ca^{2+}-dependent NFAT3 activation, which offered a mechanistic explanation for the role of ORP4L in intracellular Ca^{2+} homeostasis[107]. Lead induces COX-2 expression in glial cells by activating NFAT3, regulating lead-associated inflammatory neurotoxicity[108]. COX-2 induction by arsenate occurs through NFAT3-dependent and AP-1 or NF-kB-independent pathways and plays a crucial role in antagonizing arsenite-induced cell apoptosis in human bronchial epithelial Beas-2B cells[109]. However, whether or not these molecules play a role in the heart and how they do so is unclear. Therefore, the in-depth study of NFAT3 and its related targets will provide a new method for the future treatment of heart-related diseases by targeting NFAT3.

CRediT authorship contribution statement

Wang Hui: Writing – original draft. **Su Wenhua:** Supervision, Validation. **Zhang Shuojie:** Methodology. **Wang Lulin:** Methodology. **Zhao Panpan:** Visualization. **Zhang Tongtong:** Investigation. **Xie Xiaoli:** Formal analysis, Funding acquisition, Writing – review & editing. **Dan Juhua:** Formal analysis, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Funding

Contract grant sponsor: National Natural Science Foundation of China (81960065). Applied Basic Research Foundation of Yunnan Province (202001AY070001-286 , 202201AT070194).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

References

[1] M. Rincón, R.A. Flavell, Transcription mediated by NFAT is highly inducible in effector CD4+ T helper 2 (Th2) cells but not in Th1 cells, Mol. Cell. Biol. 17 (3) (1997) 1522–1534.
[2] J.P. Viola, L.D. Carvalho, B.P. Fonseca, L.K. Teixeira, NFAT transcription factors: from cell cycle to tumor development. Brazilian J. Med. Biol. Res. = Revista brasileira de pesquisas medicas e biologicas. 38 (3) (2005) 335–344.
[3] C. Lopez-Rodríguez, J. Aramburu, A.S. Rakeman, A. Rao, NFAT5, a constitutively nuclear NFAT protein that does not cooperate with Fos and Jun, Proc. Nat. Acad. Sci. USA 96 (13) (1999) 7214–7219.
[4] S. Baumgart, E. Glesel, G. Singh, N.M. Chen, K. Reutlinger, J. Zhang, et al., Restricted heterochromatin formation links NFATc2 repressor activity with growth promotion in pancreatic cancer, Gastroenterology 142 (2) (2012).
[5] E.O. Hernández-Ochoa, P. Robison, M. Contreras, T. Shen, Z. Zhao, M. F. Schneider, Elevated extracellular glucose and uncontrolled type 1 diabetes enhance NFAT5 signaling and disrupt the transverse tubular network in mouse skeletal muscle, Exp. Biol. Med. (Maywood) 237 (9) (2012) 1068–1083.
[6] S.E. Plyte, M. Boncristiano, E. Fattori, F. Galvagni, S.R. Paccani, M.B. Majolini, et al., Identification and Characterization of a Novel Nuclear Factor of Activated T-cells-1 Isoform Expressed in Mouse Brain* 276 (2001) 14350–14358.
[7] R. Li, L. Zhang, W. Shi, B. Zhang, X. Liang, S. Liu, et al., NFAT2 mediates high glucose-induced glomerular podocyte apoptosis through increased Bax expression, Exp. Cell Res. 319 (7) (2013) 992–1000.
[8] R.D. Groth, L.G. Coicou, P.G. Mermelstein, V.S. Seybold, Neurotrophin activation of NFAT-dependent transcription contributes to the regulation of pro-nociceptive genes, J. Neurochem. 102 (4) (2007) 1162–1174.
[9] A.B. Benedito, M. Lehtinen, R. Massol, U.G. Lopes, T. Kirchhausen, A. Rao, et al., The transcription factor NFAT3 mediates neuronal survival, J. Biol. Chem. 280 (4) (2005) 2818–2825.
[10] T.T. Phuong, Y.H. Yun, S.J. Kim, T.M. Kang, Positive feedback control between STIM1 and NFATc3 is required for C2C12 myoblast differentiation, Biochem. Biophys. Res. Commun. 430 (2) (2013) 722–728.
[11] W. Su, Q. Huo, H. Wu, L. Wang, X. Ding, L. Liang, et al., The function of LncRNA-H19 in cardiac hypertrophy, Cell Biosci. 11 (1) (2021) 153.
[12] X. Zhang, F. Lei, X.M. Wang, K.Q. Deng, Y.X. Ji, Y. Zhang, et al., NULP1 Alleviates Cardiac Hypertrophy by Suppressing NFAT3 Transcriptional Activity, J. Am. Heart Assoc. 9 (16) (2020) e016419.
[13] J.D. Molkentin, Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs, Cardiovasc. Res. 63 (3) (2004) 467–475.
[14] B.J. Maron, J.J. Doerer, T.S. Haas, D.M. Tierney, F.O. Mueller, Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006, Circulation 119 (8) (2009) 1085–1092.
[15] M. Nakamura, J. Sadoshima, Mechanisms of physiological and pathological cardiac hypertrophy, Nat. Rev. Cardiol. 15 (7) (2018) 387–407.
[16] M. Maillet, J.H. van Berlo, J.D. Molkentin, Molecular basis of physiological heart growth: fundamental concepts and new players, Nat. Rev. Mol. Cell Biol. 14 (1) (2013) 38–48.
[17] Y.K. Tham, B.C. Bernardo, J.Y. Ooi, K.L. Weeks, J.R. McMullen, Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets, Arch. Toxicol. 89 (9) (2015) 1401–1438.
[18] I. Shimizu, T. Minamino, Physiological and pathological cardiac hypertrophy, J. Mol. Cell. Cardiol. 97 (2016) 245–262.
[19] J. Ritterhoff, S. Young, O. Villet, D. Shao, F.C. Neto, L.F. Bettcher, et al., Metabolic Remodeling Promotes Cardiac Hypertrophy by Directing Glucose to Aspartate Biosynthesis, Circ. Res. 126 (2) (2020) 182–196.
[20] M. Harada, X. Luo, T. Murohara, B. Yang, D. Dobrev, S. Nattel, MicroRNA regulation and cardiac calcium signaling: role in cardiac disease and therapeutic potential, Circ. Res. 114 (4) (2014) 689–705.
[21] H. Seok, H. Lee, S. Lee, S.H. Ahn, H.S. Lee, G.D. Kim, et al., Position-specific oxidation of miR-1 encodes cardiac hypertrophy, Nature 584 (7820) (2020) 279–285.
[22] A. Robson, Oxidation of miRNAs by ROS leads to cardiac hypertrophy, Nat. Rev. Cardiol. 17 (11) (2020) 678.
[23] R.A. Frieler, R.M. Mortensen, Immune cell and other noncardiomyocyte regulation of cardiac hypertrophy and remodeling, Circulation 131 (11) (2015) 1019–1030.
[24] Y. Zhang, Z. Huang, H. Li, Insights into innate immune signalling in controlling cardiac remodelling, Cardiovasc. Res. 113 (13) (2017) 1538–1550.
[25] M.J. Zeitz, J.W. Smyth, Translating Translation to Mechanisms of Cardiac Hypertrophy, J. Cardiovascular Dev. Disease 7 (1) (2020).
[26] C.M. Greco, G. Condorelli, Epigenetic modifications and noncoding RNAs in cardiac hypertrophy and failure, Nat. Rev. Cardiol. 12 (8) (2015) 488–497.
[27] Z. Wang, X.J. Zhang, Y.X. Ji, P. Zhang, K.Q. Deng, J. Gong, et al., The long noncoding RNA Chaer defines an epigenetic checkpoint in cardiac hypertrophy, Nat. Med. 22 (10) (2016) 1131–1139.
[28] M.R. Müller, A. Rao, NFAT, immunity and cancer: a transcription factor comes of age, Nat. Rev. Immunol. 10 (9) (2010) 645–656.
[29] A.M. Ranger, M.J. Grusby, M.R. Hodge, E.M. Gravallese, F.C. de la Brousse, T. Hoey, et al., The transcription factor NF-ATc is essential for cardiac valve formation, Nature 392 (6672) (1998) 186–190.
[30] J.L. de la Pompa, L.A. Timmerman, H. Takimoto, H. Yoshida, A.J. Elia, E. Samper, et al., Role of the NF-ATc transcription factor in morphogenesis of cardiac valves and septum, Nature 392 (6672) (1998) 182–186.
[31] M. Bourajjaj, A.S. Armand, P.A. da Costa Martins, B. Weijts, R. van der Nagel, S. Heeneman, et al., NFATc2 is a necessary mediator of calcineurin-dependent cardiac hypertrophy and heart failure, J. Biol. Chem. 283 (32) (2008) 22295–22303.
[32] P.B. Bushdid, H. Osinska, R.R. Waclaw, J.D. Molkentin, K.E. Yutzey, NFATc3 and NFATc4 are required for cardiac development and mitochondrial function, Circ. Res. 92 (12) (2003) 1305–1313.
[33] O. Kaminuma, N. Kitamura, Y. Nishito, S. Nemoto, H. Tatsumi, A. Mori, et al., Downregulation of NFAT3 Due to Lack of T-Box Transcription Factor TBX5 Is Crucial for Cytokine Expression in T Cells, J. Immunol. (Baltimore, Md: 1950) 200 (1) (2018) 92–100.
[34] F. Greulich, C. Rudat, A. Kispert, Mechanisms of T-box gene function in the developing heart, Cardiovasc. Res. 91 (2) (2011) 212–222.
[35] C. Wang, J.F. Li, L. Zhao, J. Liu, J. Wan, Y.X. Wang, et al., Inhibition of SOC/Ca2+/NFAT pathway is involved in the anti-proliferative effect of sildenafil on pulmonary artery smooth muscle cells, Respir. Res. 10 (2009) 123.
[36] M. Horiba, T. Muto, N. Ueda, T. Opthof, K. Miwa, M. Hojo, et al., T-type Ca2+ channel blockers prevent cardiac cell hypertrophy through an inhibition of calcineurin-NFAT3 activation as well as L-type Ca2+ channel blockers, Life Sci. 82 (11–12) (2008) 554–560.
[37] X.P. Liu, H. Gao, X.Y. Huang, Y.F. Chen, X.J. Feng, Y.H. He, et al., Peroxisome proliferator-activated receptor gamma coactivator 1 alpha protects cardiomyocytes from hypertrophy by suppressing calcineurin-nuclear factor of activated T cells c4 signaling pathway, Trans. Res.: J. Lab. Clin. Med. 166 (5) (2015) 459.
[38] B. Fiedler, K.C. Wollert, Interference of antihypertrophic molecules and signaling pathways with the Ca2+-calcineurin-NFAT cascade in cardiac myocytes, Cardiovasc. Res. 63 (3) (2004) 450–457.
[39] Y. Kalkan, L. Tümkaya, H. Bostan, Y. Tomak, A. Yılmaz, Effects of sugammadex on immunoreactivity of calcineurin in rat testes cells after neuromuscular block: a pilot study, J. Mol. Histol. 43 (2) (2012) 235–241.
[40] F. Rusnak, P. Mertz, Calcineurin: form and function, Physiol. Rev. 80 (4) (2000) 1483–1521.
[41] M. Zayzafoon, Calcium/calmodulin signaling controls osteoblast growth and differentiation, J. Cell. Biochem. 97 (1) (2006) 56–70.
[42] M. Lu, H. Wang, J. Wang, J. Zhang, J. Yang, L. Liang, et al., Astragaloside IV protects against cardiac hypertrophy via inhibiting the Ca2+/CaN signaling pathway, Planta Med. 80 (1) (2014) 63–69.
[43] J.D. Molkentin, J.R. Lu, C.L. Antos, B. Markham, J. Richardson, J. Robbins, et al., A calcineurin-dependent transcriptional pathway for cardiac hypertrophy, Cell 93 (2) (1998) 215–228.
[44] V.C. Tu, H. Sun, G.T. Bowden, Q.M. Chen, Involvement of oxidants and AP-1 in angiotensin II-activated NFAT3 transcription factor, Am. J. Physiol. Cell Physiol. 292 (4) (2007) C1248–C1255.
[45] K.K. Griendling, D. Sorescu, M. Ushio-Fukai, NAD(P)H oxidase: role in cardiovascular biology and disease, Circ. Res. 86 (5) (2000) 494–501.
[46] K.K. Griendling, M. Ushio-Fukai, Reactive oxygen species as mediators of angiotensin II signaling, Regul. Pept. 91 (1–3) (2000) 21–27.
[47] T. Fujii, N. Onohara, Y. Maruyama, S. Tanabe, H. Kobayashi, M. Fukutomi, et al., Galpha12/13-mediated production of reactive oxygen species is critical for angiotensin receptor-induced NFAT activation in cardiac fibroblasts, J. Biol. Chem. 280 (24) (2005) 23041–23047.
[48] V.C. Tu, J.J. Bahl, Q.M. Chen, Signals of oxidant-induced cardiomyocyte hypertrophy: key activation of p70 S6 kinase-1 and phosphoinositide 3-kinase, J. Pharmacol. Exp. Ther. 300 (3) (2002) 1101–1110.
[49] V.C. Tu, J.J. Bahl, Q.M. Chen, Distinct roles of p42/p44(ERK) and p38 MAPK in oxidant-induced AP-1 activation and cardiomyocyte hypertrophy, Cardiovasc. Toxicol. 3 (2) (2003) 119–133.
[50] J. Coronella-Wood, J. Terrand, H. Sun, Q.M. Chen, c-Fos phosphorylation induced by H2O2 prevents proteasomal degradation of c-Fos in cardiomyocytes, J. Biol. Chem. 279 (32) (2004) 33567–33574.

[51] F. Su, M. Shi, J. Zhang, Y. Li, J. Tian, Recombinant high-mobility group box 1 induces cardiomyocyte hypertrophy by regulating the 14-3-3η, PI3K and nuclear factor of activated T cells signaling pathways, Mol. Med. Rep. 23 (3) (2021).

[52] F. Biscetti, A. Flex, S. Alivernini, B. Tolusso, E. Gremese, G. Ferraccioli, The Role of High-Mobility Group Box-1 and Its Crosstalk with Microbiome in Rheumatoid Arthritis, Mediators Inflamm. 2017 (2017) 5230374.

[53] H. Jia, Z. Liang, X. Zhang, J. Wang, W. Xu, H. Qian, 14-3-3 proteins: an important regulator of autophagy in diseases, Am. J. Transl. Res. 9 (11) (2017) 4738–4746.

[54] V. Obsilova, M. Kopecka, D. Kosek, M. Kacirova, S. Kylarova, L. Rezabkova, et al., Mechanisms of the 14-3-3 protein function: regulation of protein function through conformational modulation, Physiol. Res. 63 (Suppl 1) (2014) S155–S164.

[55] W. Liao, S. Wang, C. Han, Y. Zhang, 14-3-3 proteins regulate glycogen synthase 3beta phosphorylation and inhibit cardiomyocyte hypertrophy, FEBS J. 272 (8) (2005) 1845–1854.

[56] B. DeBosch, I. Treskov, T.S. Lupu, C. Weinheimer, A. Kovacs, M. Courtois, et al., Akt1 is required for physiological cardiac growth, Circulation 113 (17) (2006) 2097–2104.

[57] B.T. O'Neill, J. Kim, A.R. Wende, H.A. Theobald, J. Tuinei, J. Buchanan, et al., A conserved role for phosphatidylinositol 3-kinase but not Akt signaling in mitochondrial adaptations that accompany physiological cardiac hypertrophy, Cell Metab. 6 (4) (2007) 294–306.

[58] S. Chhabra, P. Fischer, K. Takeuchi, A. Dubey, J.J. Ziarek, A. Boeszoermenyi, et al., 15N detection harnesses the slow relaxation property of nitrogen: Delivering enhanced resolution for intrinsically disordered proteins, Proc. Nat. Acad. Sci. USA 115 (8) (2018), E1710-e9.

[59] A.A. Shati, Doxorubicin-induces NFAT/Fas/FasL cardiac apoptosis in rats through activation of calcineurin and P38 MAPK and inhibition of mTOR signalling pathways, Clin. Exp. Pharmacol. Physiol. 47 (4) (2020) 660–676.

[60] L.T. Bish, K.J. Morine, M.M. Sleeper, H.L. Sweeney, Myostatin is upregulated following stress in an Erk-dependent manner and negatively regulates cardiomyocyte growth in culture and in a mouse model, PLoS One 5 (4) (2010) e10230.

[61] S.J. Lee, Regulation of muscle mass by myostatin, Annu. Rev. Cell Dev. Biol. 20 (2004) 61–86.

[62] C.W. Chow, C. Dong, R.A. Flavell, R.J. Davis, c-Jun NH(2)-terminal kinase inhibits targeting of the protein phosphatase calcineurin to NFATc1, Mol. Cell. Biol. 20 (14) (2000) 5227–5234.

[63] C.W. Chow, M. Rincón, J. Cavanagh, M. Dickens, R.J. Davis, Nuclear accumulation of NFAT4 opposed by the JNK signal transduction pathway, Science (New York, N.Y.) 278 (5343) (1997) 1638–1641.

[64] T.T. Yang, Q. Xiong, H. Enslen, R.J. Davis, C.W. Chow, Phosphorylation of NFATc4 by p38 mitogen-activated protein kinases, Mol. Cell. Biol. 22 (11) (2002) 3892–3904.

[65] T.T.C. Yang, R.Y.L. Yu, A. Agadir, G.J. Gao, R. Campos-Gonzalez, C. Tournier, et al., Integration of protein kinases mTOR and extracellular signal-regulated kinase 5 in regulating nucleocytoplasmic localization of NFATc4, Mol. Cell. Biol. 28 (10) (2008) 3489–3501.

[66] D.M. Wang, S. Fasciano, L.W. Li, The interleukin-1 receptor associated kinase 1 contributes to the regulation of NFAT, Mol. Immunol. 45 (15) (2008) 3902–3908.

[67] D.A. Cross, D.R. Alessi, P. Cohen, M. Andjelkovich, B.A. Hemmings, Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B, Nature 378 (6559) (1995) 785–789.

[68] M. Diehn, A.A. Alizadeh, O.J. Rando, C.L. Liu, K. Stankunas, D. Botstein, et al., Genomic expression programs and the integration of the CD28 costimulatory signal in T cell activation, Proc. Nat. Acad. Sci. USA 99 (18) (2002) 11796–11801.

[69] I.A. Graef, P.G. Mermelstein, K. Stankunas, J.R. Neilson, K. Deisseroth, R. W. Tsien, et al., L-type calcium channels and GSK-3 regulate the activity of NF-ATc4 in hippocampal neurons, Nature 401 (6754) (1999) 703–708.

[70] C.R. Beals, C.M. Sheridan, C.W. Turck, P. Gardner, G.R. Crabtree, Nuclear export of NF-ATc enhanced by glycogen synthase kinase-3, Science (New York, N.Y.) 275 (5308) (1997) 1930–1934.

[71] J.D. Klemm, C.R. Beals, G.R. Crabtree, Rapid targeting of nuclear proteins to the cytoplasm, Curr. Biol. 7 (9) (1997) 638–644.

[72] T. Oka, M. Maillet, A.J. Watt, R.J. Schwartz, B.J. Aronow, S.A. Duncan, et al., Cardiac-specific deletion of Gata4 reveals its requirement for hypertrophy, compensation, and myocyte viability, Circ. Res. 98 (6) (2006) 837–845.

[73] T. Oka, Y.S. Dai, J.D. Molkentin, Regulation of calcineurin through transcriptional induction of the calcineurin A beta promoter in vitro and in vivo, Mol. Cell. Biol. 25 (15) (2005) 6649–6659.

[74] G.M. Dittrich, N. Froese, X. Wang, H. Kroeger, H. Wang, M. Szaroszyk, et al., Fibroblast GATA-4 and GATA-6 promote myocardial adaptation to pressure overload by enhancing cardiac angiogenesis, Basic Res. Cardiol. 116 (1) (2021) 26.

[75] T. Yang, R.J. Davis, C.W. Chow, Requirement of two NFATc4 transactivation domains for CBP potentiation, J. Biol. Chem. 276 (43) (2001) 39569–39576.

[76] H. Steen, D. Lindholm, Nuclear localized protein-1 (Nulp1) increases cell death of human osteosarcoma cells and binds the X-linked inhibitor of apoptosis protein, Biochem. Biophys. Res. Commun. 366 (2) (2008) 432–437.

[77] Z. Cai, Y. Wang, W. Yu, J. Xiao, Y. Li, L. Liu, et al., hnulp1, a basic helix-loop-helix protein with a novel transcriptional repressive domain, inhibits transcriptional activity of serum response factor, Biochem. Biophys. Res. Commun. 343 (3) (2006) 973–981.

[78] G.S. Han, S. Siniossoglou, G.M. Carman, The cellular functions of the yeast lipin homolog PAH1p are dependent on its phosphatidate phosphatase activity, J. Biol. Chem. 282 (51) (2007) 37026–37035.

[79] H.B. Kim, A. Kumar, L. Wang, G.H. Liu, S.R. Keller, J.C. Lawrence Jr, et al., Lipin 1 represses NFATc4 transcriptional activity in adipocytes to inhibit secretion of inflammatory factors, Mol. Cell. Biol. 30 (12) (2010) 3126–3139.

[80] W.M. Shieh, J.C. Ame, M.V. Wilson, Z.Q. Wang, D.W. Koh, M.K. Jacobson, et al., Poly(ADP-ribose) polymerase null mouse cells synthesize ADP-ribose polymers, J. Biol. Chem. 273 (46) (1998) 30069–30072.

[81] O.A. Olabisi, N. Soto-Nieves, E. Nieves, T.T. Yang, X. Yang, R.Y. Yu, et al., Regulation of transcription factor NFAT by ADP-ribosylation, Mol. Cell. Biol. 28 (9) (2008) 2860–2871.

[82] I.S. Patten, Z. Arany, PGC-1 coactivators in the cardiovascular system, Trends Endocrinol Metab: TEM 23 (2) (2012) 90–97.

[83] Y. Chen, Y. Wang, J. Chen, X. Chen, W. Cao, S. Chen, et al., Roles of transcriptional corepressor RIP140 and coactivator PGC-1alpha in energy state of chronically infarcted rat hearts and mitochondrial function of cardiomyocytes, Mol. Cell. Endocrinol. 362 (1–2) (2012) 11–18.

[84] G. Tzivion, J. Avruch, 14-3-3 proteins: active cofactors in cellular regulation by serine/threonine phosphorylation, J. Biol. Chem. 277 (5) (2002) 3061–3064.

[85] C.W. Chow, R.J. Davis, Integration of calcium and cyclic AMP signaling pathways by 14-3-3, Mol. Cell. Biol. 20 (2) (2000) 702–712.

[86] G.J. Martinez, R.M. Pereira, T. Äijö, E.Y. Kim, F. Marangoni, M.E. Pipkin, et al., The transcription factor NFAT promotes exhaustion of activated $CD8^+$ T cells, Immunity 42 (2) (2015) 265–278.

[87] P.G. Hogan, L. Chen, J. Nardone, A. Rao, Transcriptional regulation by calcium, calcineurin, and NFAT, Genes Dev. 17 (18) (2003) 2205–2232.

[88] D. Yang, S. Ma, Y. Tan, D. Li, B. Tang, J. Chen, et al., Adrenergic receptor blockade-induced regression of pressure-overload cardiac hypertrophy is associated with inhibition of the calcineurin/NFAT3/GATA4 pathway, Mol. Med. Rep. 3 (3) (2010) 497–501.

[89] W.K. Chen, Y.L. Yeh, Y.M. Lin, J.Y. Lin, B.S. Tzang, J.A. Lin, et al., Cardiac hypertrophy-related pathways in obesity, Chin. J. Physiol. 57 (3) (2014) 111–120.

[90] S. Bai, T.K. Kerppola, Opposing roles of FoxP1 and Nfat3 in transcriptional control of cardiomyocyte hypertrophy, Mol. Cell. Biol. 31 (14) (2011) 3068–3080.

[91] J. Wang, Y. Wang, W. Zhang, X. Zhao, X. Chen, W. Xiao, et al., Phenylephrine promotes cardiac fibroblast proliferation through calcineurin-NFAT pathway, Front. Biosci. (Landmark edition) 21 (3) (2016) 502–513.

[92] B.J. Wilkins, L.J. De Windt, O.F. Bueno, J.C. Braz, B.J. Glascock, T.F. Kimball, et al., Targeted disruption of NFATc3, but not NFATc4, reveals an intrinsic defect in calcineurin-mediated cardiac hypertrophic growth, Mol. Cell. Biol. 22 (21) (2002) 7603–7613.

[93] L. Xiao, Y. Gu, L. Gao, J. Shangguan, Y. Chen, Y. Zhang, et al., Sanggenon C protects against pressure overload-induced cardiac hypertrophy via the calcineurin/NFAT2 pathway, Mol. Med. Rep. 16 (4) (2017) 5338–5346.

[94] Q. Lou, L. Li, G. Liu, T. Li, L. Zhang, Y. Zang, et al., Vericiguat reduces electrical and structural remodeling in a rabbit model of atrial fibrillation, J. Cardiovasc. Pharmacol. Ther. 28 (2023).

[95] L. Ni, S.K. Lahiri, J. Nie, X. Pan, I. Abu-Taha, J.O. Reynolds, et al., Genetic inhibition of nuclear factor of activated T-cell c2 prevents atrial fibrillation in CREM transgenic mice, Cardiovasc. Res. 118 (13) (2022) 2805–2818.

[96] M. Xu, Q. Fan, J. Zhang, Y. Chen, R. Xu, L. Chen, et al., NFAT3/c4-mediated excitotoxicity in hippocampal apoptosis during radiation-induced brain injury, J. Radiat. Res. 58 (6) (2017) 827–833.

[97] J.P.A. Dos Santos, A.F. Vizuete, C.A. Gonçalves, Calcineurin-Mediated Hippocampal Inflammatory Alterations in Streptozotocin-Induced Model of Dementia, Mol. Neurobiol. 57 (1) (2020) 502–512.

[98] T. Xiao, J.J. Zhu, S. Huang, C. Peng, S. He, J. Du, et al., Phosphorylation of NFAT3 by CDK3 induces cell transformation and promotes tumor growth in skin cancer, Oncogene 36 (20) (2017) 2835–2845.

[99] L.C.B. de Camargo, F. Guaddachi, D. Bergerat, N. Ourari, L. Coillard, V. Parietti, et al., Extracellular vesicles produced by NFAT3-expressing cells hinder tumor growth and metastatic dissemination, Sci. Rep. 10 (1) (2020) 8964.

[100] M. Fougère, B. Gaudineau, J. Barbier, F. Guaddachi, J.P. Feugeas, D. Auboeuf, et al., NFAT3 transcription factor inhibits breast cancer cell motility by targeting the Lipocalin 2 gene, Oncogene 29 (15) (2010) 2292–2301.

[101] H. Zhang, X. Xie, X. Zhu, J. Zhu, C. Hao, Q. Lu, et al., Stimulatory cross-talk between NFAT3 and estrogen receptor in breast cancer cells, J. Biol. Chem. 280 (52) (2005) 43188–43197.

[102] B.M. Ram, J. Dolpady, R. Kulkarni, R. Usha, U. Bhoria, U.R. Poli, et al., Human papillomavirus (HPV) oncoprotein E6 facilitates Calcineurin-Nuclear factor for activated T cells 2 (NFAT2) signaling to promote cellular proliferation in cervical cell carcinoma, Exp. Cell Res. 362 (1) (2018) 132–141.

[103] H. Lu, C. Huan, Transcription factor NFAT, its role in cancer development, and as a potential target for chemoprevention, Curr. Cancer Drug Targets 7 (4) (2007) 343–353.

[104] A. Yaghi, S.M. Sims, Constrictor-induced translocation of NFAT3 in human and rat pulmonary artery smooth muscle, Am. J. Physiol. Lung Cell. Mol. Physiol. 289 (6) (2005) L1061–L1074.

[105] J. Ma, R. Du, Y. Huang, W. Zhong, H. Gui, C. Mao, et al., Expression, Prognosis and Gene Regulation Network of NFAT Transcription Factors in Non-Small Cell Lung Cancer, Pathology oncology research: POR. 27 (2021), 529240.

[106] J.L. Belfield, C. Whittaker, M.Z. Cader, S. Chawla, Differential effects of Ca2+ and cAMP on transcription mediated by MEF2D and cAMP-response element-binding protein in hippocampal neurons, J. Biol. Chem. 281 (38) (2006) 27724–27732.

[107] J.W. Li, Y.L. Xiao, C.F. Lai, N. Lou, H.L. Ma, B.Y. Zhu, et al., Oxysterol-binding protein-related protein 4L promotes cell proliferation by sustaining intracellular

Ca2+ homeostasis in cervical carcinoma cell lines, Oncotarget 7 (40) (2016) 65849–65861.

[108] J. Wei, K. Du, Q. Cai, L. Ma, Z. Jiao, J. Tan, et al., Lead induces COX-2 expression in glial cells in a NFAT-dependent, AP-1/NFκB-independent manner, Toxicology 325 (2014) 67–73.

[109] J. Ding, J. Li, C. Xue, K. Wu, W. Ouyang, D. Zhang, et al., Cyclooxygenase-2 induction by arsenite is through a nuclear factor of activated T-cell-dependent pathway and plays an antiapoptotic role in Beas-2B cells, J. Biol. Chem. 281 (34) (2006) 24405–24413.