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The endocrinological component and signaling pathways associated to cardiac hypertrophy

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ABSTRACT

Although myocardial growth corresponds to an adaptive response to maintain cardiac contractile function, the cardiac hypertrophy is a condition that occurs in many cardiovascular diseases and typically precedes the onset of heart failure. Different endocrine factors such as thyroid hormones, insulin, insulin-like growth factor 1 (IGF-1), angiotensin II (Ang II), endothelin (ET-1), catecholamines, estrogen, among others represent important stimuli to cardiomyocyte hypertrophy. Thus, numerous endocrine disorders manifested as changes in the local environment or multiple organ systems are especially important in the context of progression from cardiac hypertrophy to heart failure. Based on that information, this review summarizes experimental findings regarding the influence of such hormones upon signalling pathways associated with cardiac hypertrophy. Understanding mechanisms through which hormones differentially regulate cardiac hypertrophy could open ways to obtain therapeutic approaches that contribute to prevent or delay the onset of heart failure related to endocrine diseases.

1. Cardiac hypertrophy

Cardiovascular diseases still represent the main cause of morbidity and mortality, and estimates indicate that these diseases will be responsible for the deaths of more than 23 million people in 2030 worldwide (Laslett et al., 2012). In general, cardiovascular diseases are characterized by cardiac morphological and physiological changes that, in most cases, lead to heart failure - a clinical syndrome that results from impairment of the ability of the ventricle to fill or eject blood - and death because the heart is no longer able to maintain the oxygenated blood supply to different organs.

Although different stimuli can induce heart failure, which is considered the final common pathway of every heart disease, this condition is typically preceded by cardiac hypertrophy, which is initially characterized by an increase in volume of cardiomyocytes and, consequently, by an increase in the ventricular wall. Cardiac hypertrophy presents different phenotypes related to the way the cardiomyocytes increase in volume, which can occur with the addition of contractile units (sarcomeres) in series or in parallel, thus installing a concentric or eccentric hypertrophy, respectively. While in concentric hypertrophy, there is thickening of the ventricular wall to the detriment of the ventricular cavity, in eccentric hypertrophy, the ventricular wall is thin, with an increase in the ventricular cavity, and these different geometric arrangements leads to profound functional changes. Thus, initially, myocardial growth corresponds to an adaptive or compensatory response in an attempt to normalize ventricular wall stress and ensure the maintenance of contractile function. This condition can be maintained over time, characterizing a physiologic hypertrophy. However, depending on the stimulus and, in some cases, the intensity and/or persistence, different molecular mechanisms can be triggered, and this growth is accompanied by adverse cardiovascular events characterizing a pathological hypertrophy. From this stage, cardiac hypertrophy predisposes the heart to arrhythmic events, cell death and an increase in the number of non-muscle cells, mainly fibroblasts, resulting in contractile deficiency and heart failure (Grossman et al., 1975). In part, the arrhythmias occur due to increased expression of HCN (hyperpolarization-activated cyclic nucleotide-gated) channels in hypertrophic cardiomyocytes and end-stage failing hearts since HCN channels play critical roles in the generation and conduction of electrical impulse (Stillitamo et al., 2008).

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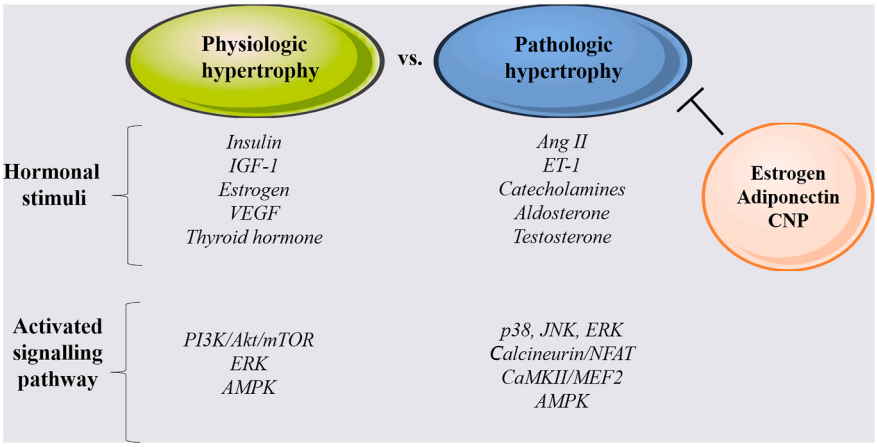

Fig. 1. A schematic of the main endocrine factors and signaling pathway involved in physiological and pathological cardiac hypertrophy. Classically, hormonal stimuli such as insulin, IGF-1, estrogen, VEGF and thyroid hormone lead to activation of PI3K/Akt/mTOR, ERK and AMPK and installation of physiological hypertrophy. On the other hand, hormones such as Ang II, ET-1, catecholamines, aldosterone and testosterone are largely associated with the activation of p38, JNK, ERK, Calcineurin/NFAT, CaMKII/MEF2 and AMPK and development of pathological hypertrophy. It is important to note that endocrine signaling is complex and there is integration and cross talk between various pathways in the development of the hypertrophic phenotype. Estrogen, adiponectin and CNP are capable to counteract the pathological response. *IGF-1:* insulin-like growth factor 1*; VEGF:* vascular endothelial growth factor receptor*; Ang II:* Angiotensin II*; ET-1:* endothelin*; CNP:* C-natriuretic peptide. *PI3K:* phosphoinositide 3-kinases*; Akt:* serine/threonine protein kinase B*; mTOR:* mammalian target of rapamycin*; ERK:* extracellular signal-related kinase*; AMPK:* AMP-activated protein kinase*; JNK:* c-Jun N-terminal kinases*; p38:* p38 mitogen-activated kinases*; NFAT:* nuclear factor of activated T cells*; CaMKII;* Ca2+-/calmodulin-dependent protein kinase*; MEF2:* myocyte enhancer factor 2.

In the past decade, a growing number of studies have suggested that previously unrecognized mechanisms, including cellular metabolism, proliferation, non-coding RNAs, immune responses, translational regulation, and epigenetic modifications, positively or negatively regulate cardiac hypertrophy (Nakuma and Sadoshima, 2018). Whatever the activating mechanisms, the initial stimuli for hypertrophic processes can be grouped into biomechanical and stretch-sensitive stimuli, in which are stimuli that lead to pressure or volume overload, and neurohumoural stimuli, which are associated with adrenergic activation or the release of cytokines, peptide growth factors or hormones (Heineke and Molkentin, 2006).

Considering the environment to which cardiomyocytes are exposed and its consequences, different endocrine factors can act directly on these cells, activating specific signalling pathways and promoting morphological and functional changes, triggering cardiac damage and heart failure, and further exacerbating the patient's condition.

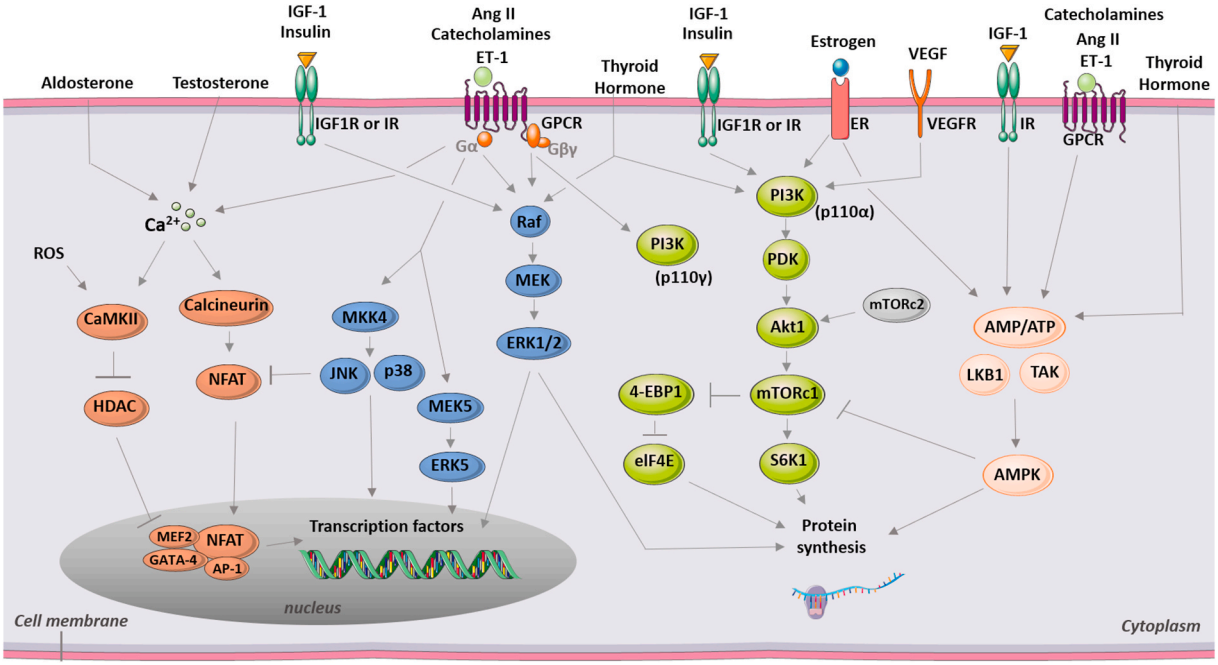

Fig. 2. Overview of the major signaling pathways involved in cardiomyocyte hypertrophy. *IGF-1:* insulin-like growth factor 1*; IGFR:* insulin-like growth factor receptor*; IR:* insulin receptor*; Ang II:* Angiotensin II*; ET-1:* endothelin*; GPCR:* G protein-coupled receptor*; ER:* estrogen receptor*; VEGF:* vascular endothelial growth factor*; VEGFR:* vascular endothelial growth factor receptor*; Ca^{2+}:* calcium*; ROS:* reactive oxygen species*; CaMKII:* Ca2+-/calmodulin-dependent protein kinase*; HDAC:* histone deacetylase*; MEF2:* myocyte enhancer factor 2*; NFAT:* nuclear factor of activated T cells*; AP-1:* activator protein-1*; MKK4:* mitogen-activated protein kinase kinase 4*; Ras:* proto-oncogene serine/threonine-protein kinase*; ERK:* extracellular signal-related kinase*; JNK:* c-Jun N-terminal kinases*; p38:* p38 mitogen-activated kinases*; PI3K:* phosphoinositide 3-kinases*; PDK:* phosphoinositide-dependent kinase*; Akt:* serine/threonine protein kinase B*; mTOR:* mammalian target of rapamycin*; 4-EBP1:* eukaryotic translation initiation factor 4E-binding protein 1*; eIF4E:* eukaryotic translation initiation factor 4E*; S6K1:* ribosomal protein p70/85 S6 kinase-1*; LKB1:* liver kinase B1*; TAK:* transforming growth factor β-activated kinase 1*; AMPK:* AMP-activated protein kinase.

Regardless of the hormonal stimuli to which the cardiomyocytes are subjected, multiple signalling pathways are then recruited. Although many of these signalling pathways can interconnect, different molecular patterns are identified according to the initial stimuli that trigger hypertrophy (Chien, 1993). This molecular signalling network results in cellular changes that affect the transcriptional pattern of cardiomyocytes to direct mechanisms that involve the regulation of intracellular calcium, protein synthesis, metabolism, autophagy, oxidative stress or even inflammation.

In addition to this complex molecular signalling network that is activated as a function of the initial stimuli, the growth of the cardiomyocytes per se can also contribute to the generation of a hypoxic environment, since, with increasing distance, the diffusion of oxygen and other substrates may be compromised, besides the increased consumption of oxygen that occurs in the hypertrophied cells (Friehs and del Nido, 2003).

There is now a growing interest in investigating the contribution of specific local stimuli in the "cardiomyocyte environment" that are responsible for the activation of certain signalling pathways and are selectively involved in the installation of physiological or pathological cardiac growth. Although the signalling pathways are complex and have many interactions between the components, some pathways are predominant and associated with the different stages of cardiac hypertrophy; thus, these pathways are targets of potential therapies. The role that some endocrine factors play in activating the signalling pathways that trigger cardiomyocyte hypertrophy will be discussed in this review.

2. Signaling pathways associated with endocrine factors-induced cardiomyocyte hypertrophy

Diverse hormones act on the heart and contribute to the pathological cardiac hypertrophy development and even the progress to heart failure. Hormones such as catecholamines, angiotensin II (Ang II) and endothelin (ET-1) are largely associated to this context. Additionally, some steroid hormones and many others endocrine factors are also known to result in similar cardiac outcome. On the other hand, thyroid hormones, insulin, insulin-like growth factor 1 (IGF-1) and estrogen generally have been associated to the physiological cardiac hypertrophy. However, it is necessary to emphasize that the signaling pathways related to the development of hypertrophy are extremely interconnected and it is not uncommon that, depending on specific conditions, which sometimes we do not even know, the pathways related to the phenotype of physiological hypertrophy are also activated in the pathological condition and vice versa. Interestingly, some factors like estrogen as well as adiponectin and C-Natriuretic Peptide (CNP) are capable to counteract the pathological response (Fig. 1).

As previously pointed out each hypertrophy phenotype can be regulated by distinct cellular signaling or by multiple interconnected signaling pathways. This review provides a brief overview of hypertrophic signaling mechanisms activated by PI3K/Akt/mTOR, MAPK, AMPK and calcium, followed by a description of the interaction between these signaling pathways and the main endocrine stimuli that lead to cardiac hypertrophy. Particularly, thyroid hormones, insulin, IGF-1, estrogen, catecholamines, Ang II and ET-1 will be addressed here, while other relevant endocrine effectors will be addressed in another time. A comprehensive figure presenting the main endocrine ligands, receptors and signaling pathways activated in the hypertrophic context is summarized in Fig. 2. In addition to the main signaling pathways associated with protein synthesis and cardiomyocyte growth, other interesting mechanisms activated during the cardiac remodeling setting will be reported. These are often involved in processes such as angiogenesis, inflammation, oxidative stress and protein degradation and, as consequence, also influence the cardiac growth.

2.1. PI3K/Akt/mTOR signalling

Phosphoinositide 3-kinases (PI3Ks) are a family of heterodimeric lipid kinases that releases inositol lipid products from the plasma membrane, mediating intracellular signalling (Toker and Cantley, 1997; Vanhaesebroeck et al., 1997). PI3K activation in cardiomyocytes is related to a wide spectrum of biological processes, particularly those that control cell growth, survival and metabolism (Ghigo et al., 2017). The three major classes of PI3K (classes I, II and III) have been described based on their molecular structure, preferred lipid substrate and catalytic domain homology (Vanhaesebroeck et al., 2001). Class I PI3Ks are heterodimeric enzymes composed of a regulatory and catalytic subunit and are subdivided into two subgroups: class I_A (p110α, β and δ catalytic and p85 or p55 regulatory subunits) and class I_B (p110γ catalytic and p101 regulatory subunits) (Vanhaesebroeck et al., 1997). The subunits that are predominantly expressed in the heart are p110α (class I_A) and p110γ (class I_B).

The PI3K catalytic p110α subunit is coupled to receptor tyrosine kinase and is classically activated in cardiomyocytes by endocrine factors, such as thyroid hormone, insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF) and estrogen (Kenessey and Ojamaa, 2006; McMullen et al., 2004; Simoncini et al., 2000; Zhou et al., 2005). Activation of this subunit has been shown to be critical for physiological but not pathological cardiac hypertrophy (McMullen et al., 2003). In this context, transgenic mice with increased PI3K (p110α) activity presented cardiac hypertrophy with preserved cardiac function and lifespan (Shioi et al., 2000). However, p110α knockout mice were embryonically lethal (Bi et al., 1999).

On the other hand, activation of the p110γ subunit occurs through stimulation of the Gβγ subunit of the G protein-coupled receptor (GPCR) (Oudit et al., 2004). Several studies have shown p110γ subunit activation by increased levels of Ang II, catecholamines, aldosterone and endothelin (ET-1) in cardiomyocytes (Oudit et al., 2004). p110γ activation is strongly associated with the negative regulation of cardiac contractility. Hence, PI3K (p110γ) knockout mice showed increased contractile function (Crackower et al., 2002). These transgenic mice were protected from catecholamine-induced cardiac dysfunction since the p110γ subunit contributes to β-adrenergic receptor internalization (Oudit et al., 2003; Oudit and Kassiri, 2007; Pretorius et al., 2009).

Serine/threonine protein kinase B (Akt) is an important downstream target of PI3K that mediates its cellular signalling. Numerous studies have implicated the Akt family in protein synthesis stimulation, which is involved in the growth of cardiomyocytes (Shiojima and Walsh, 2006). The mammalian genome contains three Akt genes, which are located on different chromosomes and encode Akt1, Akt2 and Akt3 (Datta et al., 1999; Scheid and Woodgett, 2001). While all Akt isoforms are widely expressed in mammals, Akt1 has elevated expression in cardiac cells (Matsui and Rosenzweig, 2005).

In response to endocrine stimulation, Akt is recruited to the plasma membrane through its N-terminal PH domain. Membrane-associated Akt1 is phosphorylated by phosphoinositide-dependent kinase-1 (PDK1) and phosphoinositide-dependent kinase-2 (PDK2) at serine 473 and threonine 308, respectively, leading to its activation (Cantley, 2002). Akt activation is closely related to cardioprotection, and it has been suggested that Akt1 is required for physiological but not pathological heart growth. Hence, Akt1 knockout mice have blunted physiological hypertrophic responses to swim training but not pathological responses to pressure overload (DeBosch et al., 2006). These results are consistent with the PI3K-p110α transgenic mouse phenotype. In addition, Akt1 knockout mice developed cardiac dilation and dysfunction (DeBosch et al., 2006).

Insulin and IGF-1 are potent activators of PI3K/Akt1 in cardiomyocytes. Increased cardiac IGF-1 production in athletes was shown to be associated with physiological cardiac hypertrophy in part due to Akt activation (Neri Serneri et al., 2001). Similarly, IGF-1 overexpression in the heart induced heart growth and enhances cardiac

function besides PI3K/Akt signalling activation (McMullen et al., 2004). On the other hand, low cardiac IGF-I levels are associated with higher heart failure risk (Vasan et al., 2003). In addition, insulin receptor knockout mice due to Akt signalling suppressed showed decreased heart size and impaired contractile function (Belke et al., 2002; Shiojima et al., 2002). Thus, the circulating level of IGF-I/PI3K(p110α)/Akt1 is inversely correlated with cardiovascular disease (Ungvari and Csiszar, 2012). As a cardioprotective effect, IGF-1-Akt dramatically accelerates and amplifies the transcriptional reprogramming of fibroblasts to functional cardiomyocytes, representing a potential approach for restoring cardiac function after myocardial injury (Zhou et al., 2015). Consistent with the role of PI3K/Akt signaling, diverse studies have showed that its activation by endocrine factors is essential to improve the cardiac contractile function or even to attenuate the progression from cardiac hypertrophy to heart failure. In this context, this signaling pathway has been demonstrated to be involved with increased contractility observed in thyroid hormone-mediated cardiac hypertrophy (Diniz et al., 2009; Kenessey and Ojamaa, 2006) or after VEGF treatment (Shiojima et al., 2005; Xu et al., 2011; Zhou et al., 2005). Likewise, the G protein-coupled estrogen receptor (ERβ) attenuated Ang II- or ET-1-induced pathological cardiomyocyte hypertrophy by upregulating the PI3K/Akt signalling pathway (Gonçalves et al., 2018; Pei et al., 2019). In addition, adiponectin supressed pathological growth and fibrosis in cardiac cells through activation of Akt signalling pathway (Cao et al., 2014; Fujishima et al., 2014).

The predominant mechanism by which Akt regulates cellular trophism occurs through activation of mammalian target of rapamycin (mTOR) (Sengupta et al., 2010). mTOR is part of two distinct serine/threonine kinase complexes (mTORC1 and mTORC2), which both regulate cardiac growth under physiological stimuli. Once activated, mTORC1 stimulates protein synthesis through two different pathways: 1) activating the ribosomal protein p70/85 S6 kinase-1 (S6K1), which increases protein translation, or 2) releasing 4E-binding protein-1 (4-EBP1) from eukaryotic translation initiation factor 4E (eIF4E), stimulating the initiation of translation (Cantley, 2002; Proud, 2004). mTORC2 stimulates cardiomyocyte growth by directly phosphorylating and activating Akt, which in turn subsequently activates mTORC1 (Sarbassov et al., 2005; Shiojima and Walsh, 2006). Thus, several studies have documented mTORC1 activation in IGF-1 receptor-, insulin-, leptin- or thyroid hormone-mediated cardiomyocyte growth (Diniz et al., 2009; Kenessey and Ojamaa, 2006; Sharma et al., 2007; Sen et al., 2013; Pires et al., 2017; Zeidan et al., 2011). In accordance with these data, it was recently demonstrated that elevated testosterone concentrations initially induced increased cardiac function (Wadthaisong et al., 2019) and cardiac hypertrophy by mTORC1/S6K1 activation (Altamirano et al., 2009). In conclusion, activation of PI3K/Akt/mTOR signalling has been shown to be fundamental for cardiomyocyte growth, particularly in response to physiological stimuli.

2.2. MAPK signalling

The mitogen-activated protein kinase (MAPK) pathway is a large family of kinases that ultimately culminate in activation of either extracellular signal-regulated kinases (ERK1 and ERK2, often termed ERK1/2), c-Jun N-terminal kinases (JNK1, 2 and 3), p38 mitogen-activated kinases (p38α, β, γ and δ) or big MAP kinase (BMK or ERK5) (Rose et al., 2010; Turner and Blythe, 2019). The signalling cascade is activated in cardiomyocytes by G-protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) upon binding by ligands such as growth factors, cytokines, or hormones (Liu and Molkentin, 2016). Once activated, these kinases phosphorylate a variety of intracellular targets that include transcription factors, leading to reprogramming of gene expression involved in cell growth, differentiation, proliferation, mobility, and survival. Consequently, these subfamilies regulate mechanisms that are associated with cardiac regulation, including heart development, hypertrophy, and pathological remodeling (Wang, 2007). Even with a vast number of studies, the role of MAPK signalling in the heart has remained uncertain due to peculiar responses to activation of each subfamily in different settings of cardiac hypertrophy and heart failure.

Activation of ERK1/2, frequently termed ERK as a singular noun, mediates both physiological and pathological cardiac hypertrophies. Besides, ERK1/2 activation is correlated with the maturation and hypertrophy of fetal cardiomyocytes (Chattergoon et al., 2012). Transgenic mice with specific activation of MEK1-ERK1/2 signaling in the heart developed concentric hypertrophy that lacked signs of interstitial fibrosis, increased cardiac function and resistance to apoptosis, demonstrating a phenotype consistent with physiological hypertrophy (Bueno et al., 2000). In fact, in addition to role of ERK1/2 in coordinating mechanisms that facilitate concentric hypertrophy, its activation also prevented eccentric growth in response to hormonal stimuli (Kehat et al., 2011). Then, some authors have described the influence of distinct endocrine factors on ERK activation and demonstrated a slight, rapid increase in phosphorylated ERK1/2 levels in cardiomyocytes that were stimulated with insulin and IGF-1 (Clerk et al., 2006), as well as in adult murine models stimulated with thyroid hormone (Araujo et al., 2010; Elnakish et al., 2012; Fernandes et al., 2011).

However, although ERK1/2 activity has been associated with cardiac physiological growth, its role also was demonstrated to be involved in response to hormones that induce pathological heart growth, such as leptin, aldosterone, Ang II, ET-1 and catecholamines (Archer et al., 2017; Chen et al., 2014; Clerk et al., 2006; Lee et al., 2019; Liu et al., 2019; Rajapurohitam et al., 2012; Ren et al., 2010). In response to agonists associated to GPCR such as Ang II, ET-1 and catecholamines, several studies have demonstrated that ERK1/2 activation is directly subject to redox regulation. In this sense, NADPH oxidase corresponds to a key system responsible for production of reactive oxygen species (ROS), which in turn activate ERK1/2 in mediating downstream molecular mechanisms that regulate pro-hypertrophic genes (Cheng et al., 2005; Santos et al., 2011; Shih et al., 2001; Sirker et al., 2007; Xiao et al., 2002). Another mechanism by which ERK1/2 signaling stimulates the hypertrophic growth in cardiomyocytes is that related to phosphorylation and activation of the GATA4-cardiac transcription factor. GATA4 is a regulator of many cardiac structural genes, as well as genes activated in response to phenylephrine, ET-1, Ang II (Liang et al., 2001; Tang et al., 2011) and other hormones associated with cardiac remodeling.

Thus, considering the broad involvement of ERK1/2 in different settings of cardiac hypertrophy, it has been proposed that this MAPK pathway contributes to hypertrophic responses via two distinct mechanisms. The mechanism that may be responsible for driving physiological hypertrophy involves the Gα subunit of Gq activating the classical MAPK signalling cascade (Raf/MEK/ERK), which results in phosphorylation of the threonine and tyrosine residues of ERK1/2 by MEK1/2 (Anderson et al., 1990; Robbins et al., 1993), leading to protein synthesis and cell growth (Bernardo et al., 2010). In contrast, autophosphorylation of ERK1/2 at residue Thr188 results from the association of Gβγ subunits with the Raf/MEK/ERK complex, directing ERK1/2 to the nucleus to control factors that initiate the transcription of genes associated with pathological forms of hypertrophy (Lorenz et al., 2009; Vidal et al., 2012).

Additionally, some hormones act by interfering with the effects of ERK activation associated with hypertrophy. For example, C-type natriuretic peptide (CNP) has an inhibitory action on the ET-1-induced phosphorylation of ERK, accompanied with the suppression of the ET-1-stimulated activity of GATA-4 and the expression of molecular markers of cardiac hypertrophy such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and alpha skeletal muscle isoform of actin (Tokudome et al., 2004). Notably, Ang II-induced ERK activation is associated with cardiac hypertrophy and interstitial fibrosis in female mice, but these effects were inhibited by estrogen via ERβ, demonstrating another protective mechanism by counteracting pro-hypertrophic signalling pathway (Pedram et al., 2008).

The JNK and p38 branches of the MAPK cascade are collectively known as stress-activated MAPKs due to their specific responses to physical, chemical and physiological stressors (Kyriakis and Avruch, 2012). On cardiac tissue, studies are inconsistent on whether JNK and p38 are implicated in beneficial or deleterious mechanisms associated with hypertrophy. Loss-of-function studies demonstrated that p38 and JNK have crucial roles as negative regulators of cardiac hypertrophy (Liang and Molkentin, 2003; Maillet et al., 2013). In this context, the use of a specific p38 inhibitor compound enhanced IGF-1–induced physiological cardiomyocyte hypertrophy, as observed by increase in protein synthesis without ANP promoter activation (Taniike et al., 2008). Supporting that finding, cardiac-specific suppression of p38 or JNK1/2 dominant-negative transgenic mice displayed increased interstitial fibrosis, cardiomyocyte apoptosis and cardiac hypertrophy in response to pressure overload (Liang et al., 2003; Nishida et al., 2004; Zhang et al., 2003a). There is also exacerbation of cardiac hypertrophy and cardiomyocyte apoptosis in mice with a cardiac-specific deletion of MKK4 (the upstream kinase that activates JNK and p38) in response to pressure overload and β-adrenergic stimulation with isoproterenol (Liu et al., 2009). Interestingly, a mechanism involving JNK antagonizing the pathological growth response through crosstalk with calcineurin/nuclear factor of activated T cells (NFAT) signalling was suggested (Liang et al., 2003; Liu et al., 2009).

In particular, the physiological hypertrophy resulting from thyroid hormone did not alter the expression of either phosphorylated p38 or JNK levels in the myocardium (Araujo et al., 2010; Elnakish et al., 2012; Teixeira et al., 2018). On the other hand, JNK is upregulated in human hearts with hypertrophic cardiomyopathy, in pressure overload-induced hypertrophic mouse hearts and in aldosterone-treated cardiomyocytes (Ma et al., 2018; Okoshi et al., 2004). Both JNK and p38 are stimulated in cardiomyocytes by hormones that act on pathological heart growth, such as ET-1, Ang II and phenylephrine (Bogoyevitch et al., 1995; Ma et al., 2018; Okoshi et al., 2004; Rajapurohitam et al., 2012), but only p38 is required for ANP expression and morphological changes observed during the development of myocyte hypertrophy (Nemoto et al., 1998). Consistent with that, p38 activation mediates ET-1-induced GATA4 binding to BNP gene (Kerkelä et al., 2002). The pharmacological inhibition of p38 MAPK blunted hypertension and cardiac hypertrophy in response to Ang II (Bao et al., 2007) and blocked protein synthesis and the stimulation of other hypertrophic responses in cardiomyocytes treated with the same Ang II or ET-1 agonist (Kerkelä et al., 2002; Rajapurohitam et al., 2012). The last study demonstrated that Ang II and ET-1 stimulate leptin production in cultured neonatal myocytes via p38 activation. Consequently, p38 MAPK has also been shown to mediate the hypertrophic effects of leptin in human and rat ventricular cardiomyocytes as well as mechanisms associated with myocardial matrix remodeling, such as collagen content and matrix metalloproteinase-2 activity (Madani et al., 2006; Rajapurohitam et al., 2003). Together, these findings suggest that sustained p38 or JNK activation are also involved in the pathogenesis of hypertrophy and heart failure (Bernardo et al., 2010; Maillet et al., 2013).

The least studied subfamily, ERK5, also plays a role in regulating cardiac growth in vitro and in vivo. Adenoviral-mediated expression of constitutively activated MEK5 (a specific upstream kinase of ERK5) showed that the MEK5–ERK5 pathway controls the addition of sarcomeres in series within cardiomyocytes, inducing these cells to assume a highly elongated morphology (Nicol et al., 2001). The same study also demonstrated that transgenic mice that overexpressed MEK5 in the heart developed a pronounced and fatal decompensating eccentric cardiac hypertrophy. Compared to other MAPKs, the ERK5 signalling branch is less well characterized for specific hormone-induced cardiac hypertrophy contributions. However, it has been demonstrated that ERK5 is activated in phenylephrine-treated cardiomyocytes, contributing to the upregulation of cardiomyocyte foetal gene expression (ANP, BNP and alpha skeletal muscle isoform of actin) (Nicol et al., 2001). Additionally, aldosterone (Araujo et al., 2016), ET-1 (Chu et al., 2011) and Ang II stimulate ERK5 in cardiomyocytes, with Ang II receptor type 1 (AT1)-mediated Ang II-induced ERK5 phosphorylation (Zhao et al., 2010). Interestingly, Ang II-induced cardiac hypertrophy associated with ERK5 activation is attenuated in androgen receptor knockout male mice (Ikeda et al., 2005), indicating the influence of sex hormones on left ventricle mass.

Due to the diverse components of the MAPK signalling pathway, additional mechanistic studies on hormonal-specific responses associated with distinct isoforms of the subfamilies and their interactions with other signalling cascades are required to determine the appropriate therapy for cardiac hypertrophy and heart diseases.

2.3. AMPK

Heart growth is a process that results from coordinated increase in cardiomyocytes size associated with changes in metabolism of these cells (Tham et al., 2015). In this context, AMP-activated protein kinase (AMPK) is a heterotrimeric complex containing one catalytic α subunit (either α1 or α2) and two regulatory subunits (β and γ) that acts as an energy sensor to detect the intracellular ratio of AMP/ATP to maintain cellular energy homeostasis. After AMP binds to the AMPK γ subunit, the allosteric change in the kinase structure allows AMPK phosphorylation by upstream kinases, such as liver kinase B1 (LKB1), Ca^{2+}-/calmodulin-dependent protein kinase β (CaMKKβ) or transforming growth factor β-activated kinase 1 (TAK1). The activity of AMPK is mainly determined by the phosphorylation of threonine 172 (Thr172) on its catalytic α subunit, which is consistently used as an indicator of the activation state of the kinase. Once activated, AMPK primarily modulates cardiac metabolism but also plays an essential role in a variety of non-metabolic biological processes in the heart, including the regulation of protein synthesis, transcriptional activity and cardiac fibrosis in response to hypertrophic stimuli (Li et al., 2017).

Some studies propose that long-term inhibition of AMPK exacerbates pathological hypertrophy, leading to heart failure, whereas intermittent AMPK activation has a cardioprotective role (Lipovka and Konhilas, 2015; Maillet et al., 2013). Thus, previous data demonstrated that thyroid hormone rapidly activates AMPK signalling both in isolated cardiomyocytes cultures (Takano et al., 2013) and in the cardiac tissue of T3-treated rats (Tavares et al., 2013). Additionally, gain/loss of function experiments confirmed the important contribution of AMPK in controlling protein synthesis and, consequently, thyroid hormone-induced cardiomyocyte hypertrophy (Takano et al., 2013). Likewise, the use of nucleoside 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), an analogue of AMP that is capable of stimulating AMPK, suppressed the IGF-1 and insulin-induced increase in cardiomyocyte surface area (Kim et al., 2008).

The effects of other pro-hypertrophic stimuli are blunted by treatment with different pharmacologic agents that activate AMPK. Treatment with AICAR or metformin attenuated the increases in both protein synthesis and cell surface area associated with phenylephrine- and Ang II-induced cardiomyocyte hypertrophy (Chan et al., 2004; Hernández et al., 2014; Pang et al., 2010; Stuck et al., 2008). Interestingly, resveratrol treatment reduced oxidative stress, prevented the increase in systolic blood pressure and counteracted cardiac hypertrophy in Ang II-infused mice through AMPK signalling (Dolinsky et al., 2013, 2015). Corroborating such findings, the use of pterostilbene and gnetol, which are analogues of resveratrol, suppressed ET-1-induced cardiomyocyte hypertrophy in vitro, suggesting AMPK is a potential mediator of these cardioprotective compounds (Akinwumi et al., 2017).

In further studies, metformin treatment attenuated cardiac hypertrophy and dysfunction in mice that were subjected to transverse aortic constriction (Fu et al., 2011; Xu et al., 2014), which represents a widely used model of pressure overload associated with catecholamine excess (Schneider et al., 2011). Conversely, AMPKα2 knockout mice are more susceptible to developing cardiac hypertrophy than wild-type animals in the context of pressure overload and isoproterenol injections

(Zarrinpashneh et al., 2008; Zhang et al., 2008). Associated to such findings, it was demonstrated that AMPK signaling contributes to the inhibitory effects of adiponectin on myocardium hypertrophy after in vivo pressure overload model and as well as in vitro cultured cardiomyocytes stimulated by Ang II and α-adrenergic receptor agonist (Shibata et al., 2004). Estrogen-mediated cardiomyocyte protection in Ang II-induced hypertrophy and cardiac injury is due to the upregulation of Sirtuin 1 and also the activation of AMPK (Shen et al., 2014).

These findings demonstrate that AMPK is a critical negative regulator of physiological and pathological cardiac growth in response to different stimuli and confers actions related to reducing protein synthesis. In light of this, AMPK counteracts protein synthesis and cell growth via inhibition of pathways such as the eukaryotic elongation factor-2 (eEF2)–eEF2 kinase axis and the mTOR–p70 ribosomal S6 protein kinase (p70S6K) pathway (Chan and Dyck, 2005; Zhang et al., 2008).

It is important to note that the protective effects of AMPK related to cardiac hypertrophy and heart failure also include anti-proliferative and anti-fibrotic effects (Beauloye et al., 2011). Such findings have been shown in studies in which AMPKα2 knockout mice were subjected to pressure overload models (Zhang et al., 2008, 2018) or isoproterenol injection (Wang et al., 2016) and showed exacerbated myocardial fibrosis in the absence of AMPK. Additionally, isoproterenol-induced cardiac fibrosis was reduced by exercise training via AMPK activation (Ma et al., 2015). Interestingly, AMPK activation by metformin treatment alleviates isoproterenol-induced cardiac fibrosis in both young and old mice (Wang et al., 2016). The protective effect of estrogen via ERβ signalling, preventing mechanisms involved with the fibrotic process in response to Ang II and ET-1 is mediated by AMPK (Pedram et al., 2016). The increased phosphorylation of AMPK is also a key mechanism stimulated by CNP that contributes to abolish atrial fibrosis and dysregulation of gap junctional proteins such as connexin (Cx40 and Cx43) induced by Ang II (Ding et al., 2019).

Although most studies have demonstrated a beneficial effect of AMPK on the heart, the role of AMPK activation during the progression of cardiac hypertrophy and remodeling remains contentious, since it stimulates either adaptive or maladaptive responses, depending on the nature and the duration of action of the stimuli (Lipovka and Konhilas, 2015). For example, Hattori et al. (2006) found increased cardiac hypertrophy in response to Ang II + AICAR treatment compared with that of rats that were treated with Ang II alone, and AICAR enhanced cell proliferation and collagen synthesis induced by Ang II in cardiac fibroblasts (Hattori et al., 2006). These findings suggest that such effects of AICAR might be associated with the concomitant activation of AMPK and the ERK-proliferative pathway. Moreover, Ang II induced similar cardiac hypertrophy in AMPKa2-knockout and wild-type mice, and phosphorylation of AMPKa-Thr172 contributed to in vivo thyroxine-induced cardiac hypertrophy (Jiang et al., 2010).

Considering the existence of some discordant findings, further investigation is required to determine the appropriate roles of AMPK within the heart. However, most of the emerging evidence has indicated that AMPK signalling pathway is associated with cardioprotective functions and may be considered as an attractive therapeutic target for treating cardiac hypertrophy and remodeling observed in cardiovascular diseases associated with hormonal influence.

2.4. Calcium-activated signalling pathway

Calcium is an important second messenger for GPCRs and biomechanical stress and plays a central role in controlling contractile function and heart growth (Frey et al., 2000; Sugden, 2001). In cardiomyocytes, two major calcium-dependent signalling pathways are involved in the control of cardiac hypertrophy: 1) the calcineurin/NFAT signalling pathway and 2) the calmodulin-dependent protein kinase II (CaMKII)/myocyte enhancer factor 2 (MEF2) signalling pathway. Calcineurin is a serine/threonine protein-phosphatase composed of a catalytic subunit (CnA) and a regulatory subunit (CnB) (Klee et al., 1979). Increased calcium levels promote calcineurin activation by the calcium-binding adaptor protein calmodulin (Wilkins et al., 2004). In addition, calcineurin activation is also affected by the redox state of cardiomyocytes. The best-characterized target of calcineurin is NFAT. When activated, calcineurin dephosphorylates cytoplasmic NFAT in conserved serine residues in the N-terminal domain, promoting nuclear translocation (Okamura et al., 2000). In the nucleus, NFAT interacts with transcription factors such as GATA-4, activator protein-1 (AP-1) (c-Jus/c-Fos) and MEF2, increasing NFAT-DNA interactions and subsequent gene transcription, which is involved in the development of the heart and postnatal cardiac growth (Wilkins et al., 2004).

In 1998, Molkentin and colleagues demonstrated for the first time the role of calcineurin in the development of cardiac hypertrophy. Calcineurin overactivation in transgenic mice led to pathological cardiac hypertrophy, fibrosis, congestive heart failure and sudden death (Molkentin et al., 1998). Furthermore, calcineurin activity was increased in patients with cardiac hypertrophy and heart failure (Haq et al., 2001), and inhibition of this protein mitigated heart growth in mice (Sussman et al., 1998). Classically, GPCR stimulation by Ang II, ET-1 and catecholamines or stimulation by mineralocorticoid leads to calcineurin activation in cardiomyocytes, and treatment with calcineurin inhibitor (cyclosporin A or FK506) attenuates hypertrophic growth in response to these hormones (Li et al., 2005; Khalilimeybodi et al., 2018; Molkentin et al., 1998; Takeda et al., 2002; Taigen et al., 2000). More specifically, Lin and collaborators (2009) have shown that isoproterenol and aldosterone stimulate heart hypertrophy in vivo and in vitro by activation of miR-23a-mediated NFATc3. On the other hand, CNP inhibit phenylephrine-, Ang II- or ET-1-induced cardiomyocyte hypertrophy by suppressing the calcineurin/NFAT pathway (Kilic et al., 2010). Calcineurin/NFAT activation is also essential for the pathological growth of the testosterone-stimulated heart. Testosterone-induced cardiac hypertrophy and increased NFAT-luciferase activity was blocked by the calcineurin inhibitors FK506 and cyclosporin A (Duran et al., 2016). In addition, leptin-induced cardiomyocyte growth is associated with functional impairment via calcineurin-mediated pathway (Jong et al., 2019).

Considering the set of results presented above, it seems clear that the calcineurin/NFAT signalling pathway is involved in the pathological development of cardiac hypertrophy. In accordance with this idea, some studies have demonstrated that physiological stimulation with IGF-1 did not alter calcineurin/NFAT signalling (Carrasco et al., 2014; Wilkins et al., 2004). Additionally, estrogen attenuated pathological hypertrophy by calcineurin/NFAT repression (Donaldson et al., 2009; Qin et al., 2008; Wu et al., 2005). However, although involved in the pathological hypertrophy in response to different endocrine molecules, genetic deletion of calcineurin results in embryonic lethality, indicating that this protein is also necessary for normal postnatal physiological growth of the heart (Schaeffer et al., 2009). In this context, acute stimulation with thyroid hormone resulted in nuclear accumulation of NFAT in cardiac cells in vivo and in vitro (Senger et al., 2018; Takano et al., 2017).

Regarding serine/threonine CaMKII, four isoforms encoded by different genes (CaMKIIα, CaMKIIβ, CaMKIIγ and CaMKIIδ) have been described. The isoform that is predominantly expressed in adult cardiomyocytes is CaMKIIδ, which has two variant isoforms: $CaMKII\delta_B$ (preferentially located in the nucleus) and $CaMKII\delta_C$ (preferentially located in the cytosol) (Edman and Schulman, 1994; Srinivasan et al., 1994). Under basal conditions, the catalytic domain of CaMKIIδ is limited by the regulatory domain, which blocks the catalytic activity of CaMKII. Increased levels of calcium stimulate calmodulin binding to the regulatory domain, which generates a conformational shift that releases the association between the regulatory and catalytic domains and allows its phosphorylation (Rostas and Dunkley, 1992). Another alternative approach to activating CaMKII is through cellular enhancement of reactive oxygen species in the absence of the calcium-calmodulin complex (Erickson et al., 2008; Luczak and Anderson, 2014). When activated

in cardiomyocytes, CaMKIIδ actives MEF2 by phosphorylating class II histone deacetylases (HDACs) (Gordon et al., 2009).

Growing evidence correlates the activation of CaMKIIδ and cardiac growth by different endocrine stimuli. Upregulation of CaMKIIδ in transgenic mice leads to cardiac hypertrophy and heart failure development (Zhang et al., 2003b), while its inhibition blocks ET-1-induced cardiomyocyte growth and mitigates heart failure (Bossuyt et al., 2008). In this sense, $G\alpha_{q11}$-knockout-mice prevented pressure overload-induced cardiac dysfunction and heart growth by suppressing CaMKIIδ (Westenbrink et al., 2015). Furthermore, G protein activation by high levels of norepinephrine, phenylephrine, ET-1 or Ang II directly induces cardiac hypertrophy via CaMKII signalling (Li et al., 2011). Similarly, Ca^{2+}/CaMKIIδ pathway regulates IGF-1-, testosterone-, and aldosterone-induced cardiac myocyte hypertrophy (Chen et al., 2019; Duran et al., 2017; Mhatre et al., 2018; Rouet-Benzineb et al., 2018). On the other hand, CNP attenuates ET-1-induced cardiac myocyte hypertrophy via a Ca^{2+}/CaMKII-associated mechanism (Tokudome et al., 2004).

2.5. Other signaling

In addition to the commonly described signaling pathways involved in the development of cardiac hypertrophy, other parallel pathways can be recruited, cooperating with such outcome or even with the development of heart failure. These signaling are activated during the cardiac remodeling setting and associated with critical processes such as angiogenesis, inflammation and oxidative stress.

In this context, the cardiomyocyte growth without parallel blood vessel growth might lead to negative effects upon heart function. Then, angiogenesis is promoted during cardiac remodeling to compensate the increased distances between capillaries and cardiomyocytes. Thyroid hormone as well as insulin and IGF-1 have proangiogenic action throughout the cardiac hypertrophy development (Luidens et al., 2010; Iliadis et al., 2011; Su et al., 2003). However, the inadequate oxygen and nutrient supply in the face of the increased metabolic demand of the hypertrophic myocardium may lead to a hypoxia environment, which has been suggested to be involved in the transition from compensated to decompensated cardiac hypertrophy. Hypoxia-inducible factor 1α (HIF1α) is the central mediator of hypoxic response and has the VEGF as one of the primary target genes (Ramakrishnan et al., 2014). HIF-1α/VEGF signaling pathway is increased by thyroid hormone, which is associated to physiological growth response (Anjos-Ramos et al., 2006; Luidens et al., 2010). In contrast, this signaling is down-regulated in long term cardiac hypertrophy resulted by pressure-overload model (Tian et al., 2020; Zeriouh et al., 2019) and by stimulation with Ang II (Guan et al., 2013), endorsing the cardiac angiogenesis impairment along with the pathological hypertrophy.

Factors secreted by endothelial cells have emerged as potential molecules that may impact the morphology and function of cardiac myocyte and non-myocyte cells. In this line, the nitric oxide (NO), that is primarily involved in vasodilation, might be expressed within myocardium, and modulated by hormones in the context of cardiac hypertrophy. The physiological hypertrophy promoted by thyroid hormones and IGF-1 stimulates NO production (Da Silva et al., 2018; Burgos et al., 2017). Estrogen also stimulates the expression of NOS isoforms in both neonatal and adult cardiac myocytes (Nuedling et al., 1999), suggesting that the protective mechanism of estrogen in cardiac hypertrophy and other cardiovascular consequences may be partially attributed to NO signaling (Bhuiyan et al., 2007). On the other hand, in relation to pathological hypertrophy models as that induced by Ang II, cardiomyocyte growth is accompanied by reduced NO synthase (NOS) activity and NO production (Jiang et al., 2018). However, when NO signaling is activated by treatment with nebivolol (a third-generation beta-blocker) occurs the reduction of cardiomyocyte hypertrophy stimulated by isoprenaline or Ang II in neonatal cardiomyocytes, evidencing the important role of NO for the prevention of pathological hypertrophy growth (Ozakca, 2019). Other studies also reinforce the contribution of NO signaling to counter-regulatory the cardiac hypertrophy induced by Ang II and neurohormonal stimuli as isoproterenol and phenylephrine (Belge et al., 2014; Jesus et al., 2018). Then, NO signaling has emerged as a cardioprotective target to be considered in the scenario of cardiac hypertrophy and heart failure.

Cardiac hypoxia and impaired NO signaling have been associated with stress oxidative and inflammatory responses. The nuclear factor kappa B (NF-κB) represents a key transcription factor that regulates such responses and growing evidence have also demonstrated the contribution of NF-κB signaling pathway in both in vivo and in vitro cardiac hypertrophy. NF-κB activation is required for hypertrophic growth of cardiomyocytes stimulated by several hypertrophic agonists, including thyroid hormone, phenylephrine, ET-1 and Ang II (Purcell et al., 2001; Rajapurohitam et al., 2012; Takano et al., 2017, 2018). Insulin can also activate NF-κB in cardiac myoblasts (Madonna et al., 2014). The pharmacological blockage or cardiomyocyte-specific NF-κB inhibition has been shown to attenuate Ang II, ET-1, and thyroid hormone-induced hypertrophy (Rajapurohitam et al., 2012; Takano et al., 2017). In contrast, NF-κB inhibition accelerates the progression of cardiac remodeling with increased cardiomyocyte apoptosis stimulated by Ang II-dependent genetic heart failure model (Zelarayan et al., 2009). These findings reveal that the exact role of NF-κB in cardiac hypertrophy is controversial in different contexts of physiological and pathological cardiac hypertrophy and additional studies are still necessaries to clarify its function.

Of note, growing evidence suggest the vast field of signaling pathways that may contribute to cellular responses that culminate in cardiac hypertrophy. The hormonal influence on these signaling and possible interventions in order to blockade or delay the prejudicial responses associated to these mechanisms remains to be further explored.

2.6. Ubiquitin-proteasome system (UPS) in cardiac hypertrophy

The balance between protein synthesis and degradation is one key process of cardiac hypertrophy development, which involves an adaptation in protein turnover. In this context, in addition to the signaling pathways linked to protein synthesis, as already described in this review, processes related to protein degradation have also been reported participants in cardiac growth.

The ubiquitin-proteasome system (UPS) is the main non-lysosomal pathway for intracellular protein degradation in the heart (Ciechanover et al., 1978). The UPS is responsible for several biological processes by controlling protein quality and removing misfolded, damaged and oxidized proteins in the cytoplasm and nucleus (Hirsch et al., 2004). Regarding cardiac hypertrophy, emerging evidence suggest that the UPS also favours protein synthesis by degrading proteins that suppress this process, which contributes to heart growth (Shukla and Rafiq, 2018). In general, activation of the UPS and increased expression of proteasome subunits have been described in different models of cardiac hypertrophy (Drews et al., 2010; Lee et al., 2016; Li et al., 2015; Meiners et al., 2008).

In this context, proteasomal inhibition affects cardiomyocyte growth under both physiological and pathological stimuli (Cacciapuoti, 2014). Then, proteasome inhibition prevented isoproterenol-induced cardiac hypertrophy by blocking NF-κB activation (Stansfield et al., 2008) and mTOR signaling pathway (Zhang et al., 2015). Similarly, the proteasome inhibitor MG132 reduced cardiomyocyte growth and improved cardiac function by regulating the ERK1/2 and JNK1 signalling pathways (Chen et al., 2010). In accordance with these data, proteasome inhibition supresses Ang-II-induced cardiac hypertrophy and remodeling by regulating multiple downstream mediators (Akt, ERK 1/2, p38, STAT3, TGF-β, NF-κB and Smad) (Li et al., 2015; Ma et al., 2013; Shu et al., 2018). On the other hand, acute administration of proteasome inhibitor MG-262 stimulated calcineurin-NFAT transactivation and promoted left ventricle dilatation and functional decompensation (Tang et al., 2010).

Lino et al. (2019) recently showed activation of cardiac UPS in

Table 1
Relationship of some signaling gain/loss of function studies and cardiac hypertrophy outcome.

GAIN OF FUNCTION STUDIES			
Animal model or pharmacological intervention	Hypertrophic stimuli	Effects in cardiac hypertrophy context	References
Transgenic mice with increased PI3K (p110α)	N/A	Develops cardiac hypertrophy with preserved cardiac function and lifespan	Shioi et al. (2000)
Transgenic mice with cardiac specific activation of MEK1-ERK1/2 and MEK1 adenovirus-infected cardiomyocytes	N/A	Develops concentric hypertrophy without interstitial fibrosis, increased cardiac function and cardiomyocyte resistance to apoptosis	Bueno et al. (2000)
Transgenic mice with overexpression of MEK5 in the heart and constitutively activated MEK5 in cardiomyocytes	N/A	Develops elongated morphology of cardiomyocytes, eccentric hypertrophy and dilated cardiomyopathy	Nicol et al. (2001)
Pharmacological activation of AMPK (AICAR or metformin) in cardiomyocytes	IGF-1, insulin, thyroid hormone, phenylephrine and Ang II	Attenuates protein synthesis and increase in cardiomyocyte surface area	Chan et al. (2004) Hernández et al. (2014) Kim et al. (2008) Pang et al. (2010) Takano et al. (2013) Stuck et al. (2008)
Transgenic mice with increased Calcineurin	N/A	Leads to pathological cardiac hypertrophy, fibrosis, congestive heart failure and sudden death	Molkentin et al. (1998)
Transgenic mice with upregulation of CaMKIIδ	N/A	Leads to cardiac hypertrophy and heart failure development	Zhang et al. (2003)
LOSS OF FUNCTION STUDIES			
Animal model or pharmacological intervention	**Hypertrophic stimuli**	**Effects in cardiac hypertrophy context**	**References**
PI3K (p110γ) knockout mice	catecholamine	Induces protection of cardiac dysfunction	Oudit et al. (2003) Oudit and Kassiri (2007) Pretorius et al. (2009) Crackower et al. (2002)
Akt1 knockout mice	IGF-1	Blunts physiological hypertrophic responses, but not pathological responses, and develops cardiac dilation and dysfunction	DeBosch et al. (2006)
p38 inhibition with SB203580 in cardiomyocytes	IGF-1	Enhances physiological cardiomyocyte hypertrophy, with increased protein synthesis that is not accompanied by ANF promoter activation	Taniike et al. (2008)
p38 inhibition with SB203580 in vivo	Ang II, ET-1	Attenuates hypertension and cardiomyocyte hypertrophy	Bao et al. (2007) Kerkelä et al. (2002) Rajapurohitam et al. (2012)
Cardiac-specific deletion of MKK4 (upstream kinase of JNK and p38)	Pressure overload and isoproterenol	Exacerbates cardiac hypertrophy and cardiomyocyte apoptosis	Liu et al. (2009)
AMPKα2 knockout mice	Pressure overload and isoproterenol	Augments the cardiac hypertrophy and fibrosis	Zarrinpashneh et al. (2008) Zhang et al. (2008) Zhang et al. (2018) Wang et al., 2016
AMPKα2 knockout mice	Thyroid hormone	Alleviates cardiac hypertrophy	Jiang et al. (2010)
Calcineurin inhibition with cyclosporin A or FK506	Ang II, ET-1, catecholamines, testosterone and mineralocorticoid	Attenuates cardiomyocyte hypertrophic growth in vivo and in vitro	Duran et al. (2016) Li et al. (2005) Khalilimeybodi et al. (2018) Molkentin et al. (1998) Takeda et al. (2002) Taigen et al. (2000)
Genetic deletion of calcineurin	N/A	Results in embryonic lethality	Schaeffer et al. (2009)
CaMKIIδ inhibition with KN93	ET-1	Blocks cardiomyocyte growth and improves heart failure	Bossuyt et al. (2008)
Proteasome inhibition with PS-519, PS-341 and MG132	Isoproterenol, Ang II and pressure overload	Prevents cardiac hypertrophy and attenuates collagen synthesis	Stansfield et al. (2008) Chen (2010) Ma et al. (2013)
Proteasome inhibition with acute dose of MG-262	Pressure overload	Contributed to left ventricle dilatation and functional decompensation.	Tang et al. (2010)
Immunoproteasome inhibition with ONX 0914	Isoproterenol	Attenuates cardiac hypertrophy	Zhang et al. (2015)
Inhibition of key component of the proteasome - UBA1 protein	Ang II	Supresses cardiac hypertrophy and remodeling	Shu et al. (2018)
Pharmacological blockage or cardiomyocyte-specific NF-κB inhibition	Ang II, ET-1 and thyroid hormone	Prevents cardiomyocyte hypertrophic response in vivo and in vitro	Rajapurohitam et al. (2012) Takano et al. (2017)

N/A = not examined/assessed.
PI3K: phosphoinositide 3-kinases*; ERK:* extracellular signal-related kinase*; AMPK:* AMP-activated protein kinase*; IGF-1:* insulin-like growth factor 1*; Ang II:* Angiotensin II*; CaMKIIδ:* Ca2+-/calmodulin-dependent protein kinase *δ; Akt:* serine/threonine protein kinase B*; p38:* p38 mitogen-activated kinases*; JNK:* c-Jun N-terminal kinases*; ET-1:* endothelin*; NF-κB:* nuclear factor kappa B.

thyroid hormone-induced cardiac hypertrophy, which possibly contributes to the maintenance of protein quality and cardiomyocyte growth, although the levels of polyubiquitinated proteins were not unaltered (Lino et al., 2019). Additionally, high levels of E3-ligase muscle-specific ring finger-1 (MURF1) inhibit thyroid hormone-induced cardiac hypertrophy by thyroid hormone receptor (Trα) inactivation (Kristine et al., 2016). In the same context, the activation of MURF1 and E3-ligase muscle atrophy F-box (MAFbx/Atrogin-1) also inhibited physiological cardiomyocyte growth mediated by IGF-1 factor via c-Jun in vivo (Skurk et al., 2005; Wadosky et al., 2014).

Together, these findings show that, although there are few studies that address the role of UPS in the growing heart, dynamic changes in protein degradation occur during the development of myocardial hypertrophy and may provide new possibilities for therapeutic targets (Drews et al., 2010). A list of the main studies of gain or loss of function in the setting of signaling pathways associated to cardiac hypertrophy was summarized in Table 1.

3. Conclusion

Human and animal studies and even experimental approaches using isolated cell cultures have indicated that some endocrine molecules activate signalling pathways that trigger physiological and pathological hypertrophy in cardiomyocytes and the entire heart. This is especially important in the context of various endocrine diseases in which the heart is not the main target organ affected but indirectly contributes to the worsening of the patient's clinical condition. The molecular mechanisms that contribute to the development of cardiac hypertrophy are extraordinarily complex and many key processes remain to be explored. Here, we addressed some endocrine factors and their signalling pathways primarily responsible for physiologic hypertrophic growth (such as insulin, IGF-1, estrogen, VEGF, thyroid hormone, PI3K/Akt/mTOR and ERK) compared to hormone ligands and downstream signaling pathways which result in predominantly pathologic cardiac hypertrophy (such as Ang II, ET-1, catecholamines, aldosterone, testosterone, FGF23, p38, JNK and calcium-activated signalling pathway). Considering that pathological cardiac hypertrophy is an independent risk factor for heart failure in patients and physiological hypertrophy is indispensable for normal function, a better understanding of the mechanisms by which hormones differentially regulate cardiac hypertrophy may pave the way for future therapeutic strategies in the endocrine disease setting.

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Declaration of competing interest

The authors have nothing to disclose.

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