Actin-Binding Proteins in Cardiac Hypertrophy

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Actin participates in the formation of highly differentiated myofibrils under the regulation of actin-binding proteins (ABPs), which provides a structural basis for the contractile function and morphological change in cardiomyocytes.

actin-binding proteins cardiac hypertrophy F-actin fetal genes

1. Introduction

The microfilament cytoskeleton is mainly composed of actin and actin-binding proteins (ABPs). Actin is one of the most abundant cytoskeletal proteins in eukaryotes and is involved in cell morphology change, migration, division and other cellular processes [1][2]. Actin takes two forms in cells: actin monomers (also known as globular actin, G-actin) and actin filaments (also known as filamentous actin, F-actin). Actin dynamics are finely regulated by a variety of ABPs (**Table 1**) [3]. Actin is involved in the formation of sarcomeres in cardiomyocytes [4]. The straight and uniform sarcomeric F-actin is critical for the contractile function of muscle [5]. In addition, actin assembly is thought to be related with autophagy [6][7]. The inhibition of F-actin disassembly can suppress autophagosome formation [8]. Several studies have found that F-actin is significantly accumulated abnormally in hypertrophic cardiomyocytes [9][10][11]. The dysregulation of F-actin accumulation may lead to cardiac hypertrophy through disrupting autophagy and sarcomeric structure. The function of ABPs in the development of cardiac hypertrophy has been gradually elucidated.

Table 1. Actin-binding proteins.

Types	ABPs	Basic Function	Refs.
G-actin-binding	Profilin, thymosin β4, cofilin	Bound to G-actin	[3][12][13]
F-actin-binding	Dystrophin, tropomyosin	Bound to F-actin	[1][3][14]
Actin-nucleating	Formin, Arp2/3 complex, proteins with tandem WH2 domains, leiomodin	Nucleation to initiate actin polymerization	[3][15][16][17]
Actin-elongating	Formin, tetramers of Ena/VASP	Regulation of actin assembly	[3][16]
Actin-bundling	Fimbrin/Plastin, hhLIM, gelsolin	Causes parallel F-actin filaments to closely pack together	[18][19][20][21]

Types	ABPs	Basic Function	Refs.
Severing	ADF/cofilin, gelsolin, twinfilin, FRL-α, INF-2	Severs F-actin	[22][23][24][25][26]
Capping	Twinfilin, gelsolin, tropomodulin, CapZ, Arp2/3 complex	Caps F-actin to inhibit actin polymerization	[3][27][28][29]
Motor	Myosin	Cargo transfer	[30]

2. ABPs in Cardiac Hypertrophy

2.1. Profilin-1

Profilin is widely expressed in most eukaryotes and has a molecular weight of about 17 kDa [31]. There are various profilin isoforms expressed in different tissues. Profilin-1 is universally expressed, profilin-2 is specifically expressed in the brain and profilin-3 and profilin-4 are specifically expressed in kidney and testis, respectively [32]. Profilin accelerates the nucleotide exchange of G-actin and delivers ATP-G-actin to the growing barbed ends of F-actin through interacting with the poly-proline motifs of formin, vasodilator-stimulated phosphoprotein (VASP) and CDC42-activated Wiskott Aldrich syndrome protein (WASP)/WASP family [12][33][34][35].

Profilin-1 is directly associated with cardiac hypertrophy [36]. Overexpression of profilin-1 in the vascular tissues of FVB/N mice leads to vascular remodeling and hypertension by increasing actin aggregation, which provides mechanical stress for the development of cardiac hypertrophy [37][38]. It has been shown that the protein level of profilin-1 is significantly increased in mammalian hypertrophic hearts (**Figure 1**). The myocardin-related transcription factor megakaryoblastic leukemia (MKL) induces the expression of the signal transducer and activator of transcription 1 (STAT1) via its SAP-domain (SAF-A/B, acinus and PIAS protein domain) activity, which upregulates *PFN* expression [39]. Whether this is the explanation for the increased protein level of profilin in cardiac hypertrophy remains to be investigated. In cardiomyocytes, the functional abnormality of profilin-1 can change the abundance or activity of multiple proteins associated with cardiomyopathy. For example, the overexpression of profilin-1 can contribute to decreases in the phosphorylation level of endothelial nitric oxide synthases (eNOS) at Ser1177 in the hearts of spontaneous hypertensive rats [9]. Levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), skeletal muscle α-actin (α-SMA) and phosphorylated ERK1/2 (active form) were significantly increased in neonatal rat ventricular myocytes (NRVMs) following stimulation by phenylephrine or endothelin 1, which can be inhibited by siRNA-directed *PFN1* silencing [36]. Increased phosphorylation of ERK1/2 activates the mechanistic (mammalian) target of rapamycin complex 1 (mTORC1) that subsequently inhibits autophagy [40][41][42]. It may be a potential key mechanism of cardiac hypertrophy mediated by the dysregulation of profilin-1 (**Figure 1**). Additionally, the inhibition of Rho-associated coiled-coil-containing protein kinase pathway (ROCK) can suppress the upregulation of profilin-1 induced by advanced glycation end products (AEGs) in H9c2 cells [43]. By comparison, overexpression of *PFN1* results in the reactivation of fetal genes (*NPPA* and *NPPB*), an increase in F-actin in myocardium and destruction of myofibrils [36]. These processes can be reversed by inhibiting the expression of profilin-1 [9]. The inhibition of profilin-1 expression in H9c2 cells and Sprague–Dawley rats can attenuate cardiac hypertrophy induced by AEGs [43][44]. In *Drosophila*, myocyte-specific overexpression of profilin

leads to disorders in muscle fibers and sarcomeres, which result in damaged muscle ultrastructure and function [36].

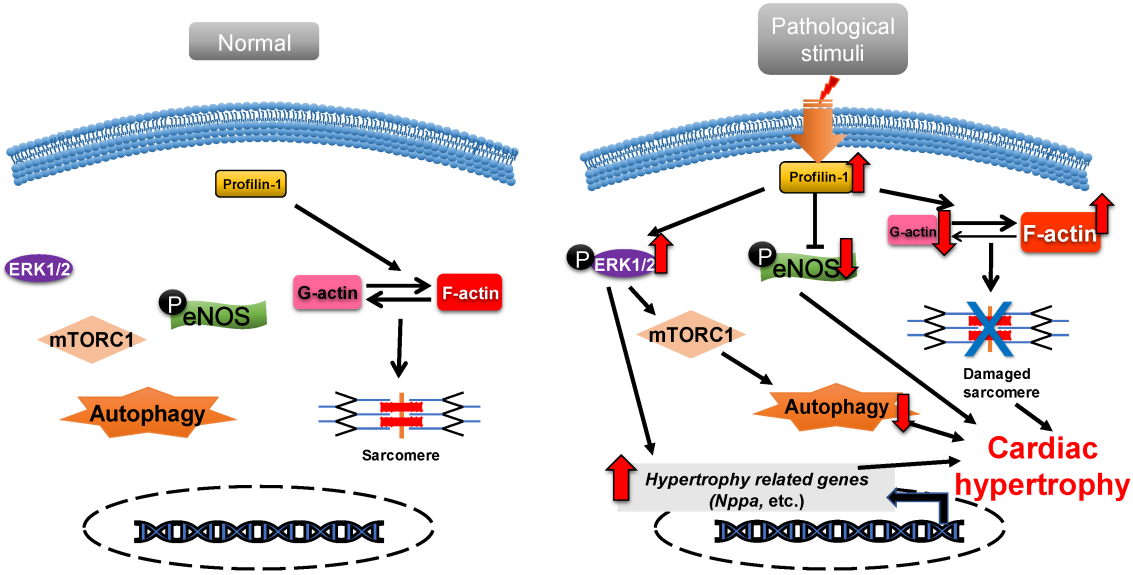

Figure 1. Profilin-1 mediates cardiac hypertrophy. In normal cardiomyocytes, profilin-1 is at a basal level and the fetal genes are not activated. Pathological stimuli increase the protein level of profilin-1, which results in ERK1/2 activation, F-actin accumulation and eNOS inhibition. This results in the reactivation of hypertrophy-related genes, inhibition of autophagy and damage to sarcomere structure and, ultimately, the development of cardiac hypertrophy.

2.2. ADF/Cofilin

Actin-depolymerizing factor (ADF)/cofilin consists of a single ADF homologous domain and has a molecular weight of about 15 kDa. The ADF/cofilin family contains ADF (also known as destrin, mainly expressed in endothelial and epithelial cells) and two cofilin isoforms (cofilin-1 is universal and cofilin-2 is cardio-specific) [45][46]. ADF/cofilin can bind to both G-actin and F-actin and can sever and depolymerize F-actin in regulating actin dynamics, which contributes to the cell contractility power [47]. The activity of cofilin is regulated by phosphorylation primarily from the ROCK/Lin-11, Isl1 and MEC-3 domain kinase (LIMK)/cofilin signaling pathway (**Figure 2**) [48][49]. Cofilin is inactivated via phosphorylation.

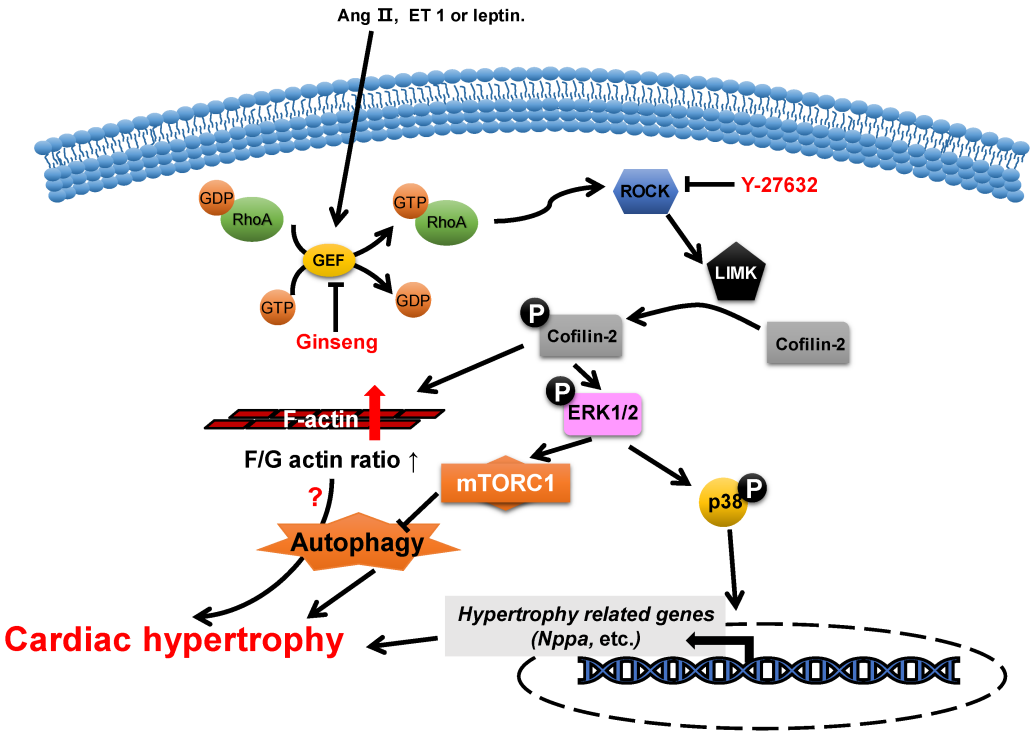

Figure 2. Proposed roles of cofilin-2 in cardiac hypertrophy. Neurohumoral factors (e.g., Ang II, ET 1 and leptin) lead to cofilin-2 phosphorylation through the RhoA/ROCK/LIMK signaling pathway. Phosphorylated cofilin-2 can lead to F-actin accumulation, which may subsequently contribute to cardiac hypertrophy through disrupting autophagy. In addition, it promotes the activation of ERK1/2 and p38, which contributes to the inhibition of autophagy and the reactivation of hypertrophy-related genes, which subsequently cause cardiac hypertrophy.

The abundance change in cofilin-2 does not play a role in the morphogenesis of neonatal rat cardiomyocytes [50], while its activity is closely associated with the development of cardiac hypertrophy. The levels of phosphorylated cofilin-2 are increased in myocardial hypertrophy through the activation of LIM-kinase (LIMK) by ROCK, which is induced by multiple neurohumoral factors, such as angiotensin II [51][52], endothelin 1 [11] and leptin [10][53]. In hypertrophic cardiomyocytes, the increase in levels of phosphorylated cofilin-2 results in an increase in F-actin/G-actin ratios and the levels of phosphorylated ERK1/2 and p38 [11][53][54][55][56]. Y-27632 [11], an inhibitor of ROCK, can reduce the levels of phosphorylated cofilin-2 through the inhibition of ROCK activity, which attenuates endothelin-1-induced neonatal cardiomyocyte hypertrophy, whereas this is achieved in ginseng (*Panax quinquefolius*) [54] through inhibition of p115Rho guanine nucleotide exchange factor (GEF) activity, which inhibits leptin-induced cardiac hypertrophy. In addition, WD-repeat domain 1 (WDR1), a major cofactor of the ADF/cofilin, has been reported to protect myocardium from myocardial hypertrophic stimuli [5].

2.3. Formin

Formin is a type of multidomain protein consisting of 7 subfamilies and 15 members in human genes. Formins are characterized by the presence of two conserved domains: formin homology 1 (FH1) and FH2. FH1 binds to the profilin–actin complex via poly-proline sequences and brings the G-actin to FH2, which promotes actin nucleation and polymerization [3][57].

2.4. CapZ

CapZ, a type of capping protein, anchors F-actin to the Z disc and regulates actin turnover, which contributes to sarcomere structural changes [58][59]. PIP2, a downstream effector of RAC1, can promote the dissociation of CapZ from F-actin by weakening their binding affinity [60][61][62].

Overexpression of CapZ in transgenic mice can lead to fatal cardiac hypertrophy [59]. It has been shown that hypertrophic agonists, phenylephrine or endothelin can reduce the binding affinity between CapZ and F-actin via PIP2-dependent pathways in NRVMs [63]. This may result in sarcomere remodeling, which induces cardiac hypertrophy. The cyclic mechanical strain activates downstream focal adhesion kinase (FAK) via the mechanotransduction of integrin, which then activates phosphatidylinositol 4-phosphate 5-kinase (PIP5K) through the RhoA/ROCK pathway. PIP5K phosphorylates phosphatidylinositol 4-phosphate (PI4P) in order to produce PIP2, which reduces the affinity of CapZ and F-actin binding, which contributes to the dysregulation of F-actin assembly and cardiac hypertrophy (**Figure 3**) [62][64][65][66].

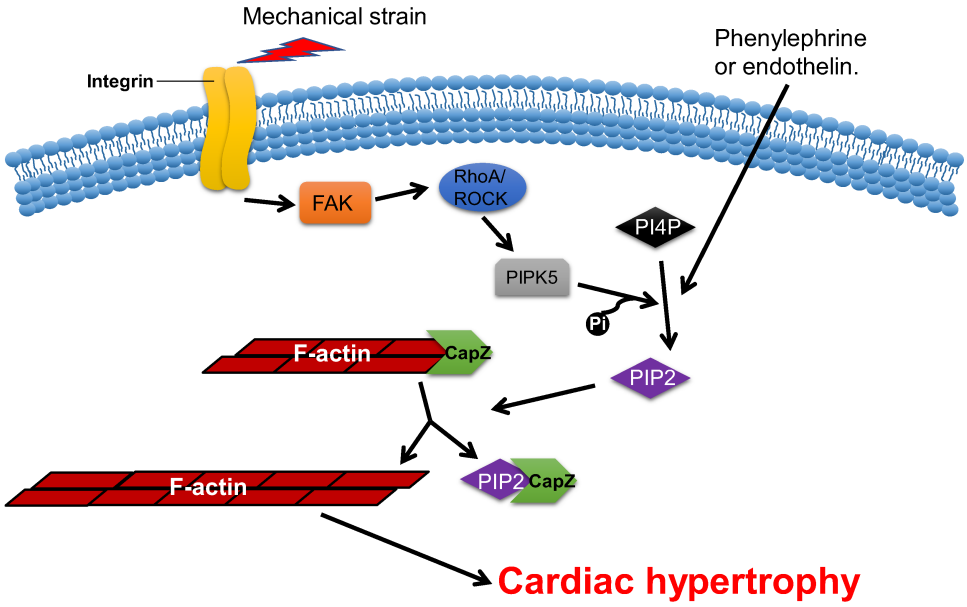

Figure 3. CapZ regulates cardiac hypertrophy. Mechanotransduction leads to the activation of RhoA/Rho-kinase pathway through integrins, which reduce the binding affinity of CapZ and F-actin. It subsequently causes cardiac hypertrophy.

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