



LEFT VENTRICULAR HYPERTROPHY: MECHANISM OF DEVELOPMENT

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ABSTRACT

Left ventricular hypertrophy (LVH) is an enlargement of the left ventricle caused by chronically increased hemodynamic load, such as arterial hypertension or aortic stenosis. In the initial stages, LVH has a protective nature, but later it can lead to heart failure and arrhythmias. The biochemical mechanisms of hypertrophy involve complex molecular pathways regulating cell proliferation and protein synthesis. These pathways interact through cell surface receptors, transcription factors, and enzymes, leading to structural and functional changes in cardiomyocytes. Changes in the extracellular matrix, inflammatory processes, and oxidative stress play an important role in the transition of hypertrophy from adaptive to pathological stage. Various hormones, vasoactive substances, growth factors, and cytokines are involved in myocardial hypertrophy. Despite significant knowledge concerning signaling pathways related to receptor stimulation, little is still known about the mechanochemical systems that transduce physical signals into cellular responses.

Keywords: left ventricular hypertrophy, mechanisms, receptors, molecular pathways,

INTRODUCTION

Left ventricular hypertrophy (LVH) is a process of enlargement of the left ventricle, leading to an increase in its mass. It usually develops as an adaptive response to chronic hemodynamic stress in diseases with left ventricular overload, such as arterial hypertension and aortic stenosis. Although left ventricular hypertrophy initially plays a protective role, it can lead to deterioration of cardiac function with an increased risk of developing heart failure and cardiac arrhythmias [1, 2, 3].

The mechanism of left ventricular hypertrophy development involves complex molecular pathways regulating cell proliferation and protein synthesis. These pathways include cell surface receptors, transcription factors, enzymes, and other molecules that are important for the response of cardiomyocytes to stress stimuli [4, 5, 6]. As a result of the molecular interactions between these elements, cardiomyocytes undergo structural and functional changes, including an increase in cell mass, synthesis of contractile proteins, and reorganization of the cytoskeleton. At the same time, remodeling of the extracellular matrix develops, which is a part of the hypertrophy process and its transition to the pathological stage. As a result of the deposition of fibrillar collagen in the adventitia of the intramyocardial vessels and the interstitium, the structure of the myocardium changes (**Figure 1**). This, in turn, leads to changes in the mechanical and electrical properties of the myocardium [2]. Inflammation and oxidative stress are other factors contributing to myocardial damage and the development of fibrosis in the process of transition to maladaptive LV hypertrophy (**Figure 2**).

Fig. 1. Elements of the process of left ventricular hypertrophy in chronic pressure overload of the LV myocardium. The increase in myocardial mass is due to hypertrophy of individual cardiomyocytes. Cardiomyocyte hyperplasia is rare and can develop in cases of fetal and juvenile forms of hemodynamic overload in congenital heart diseases.

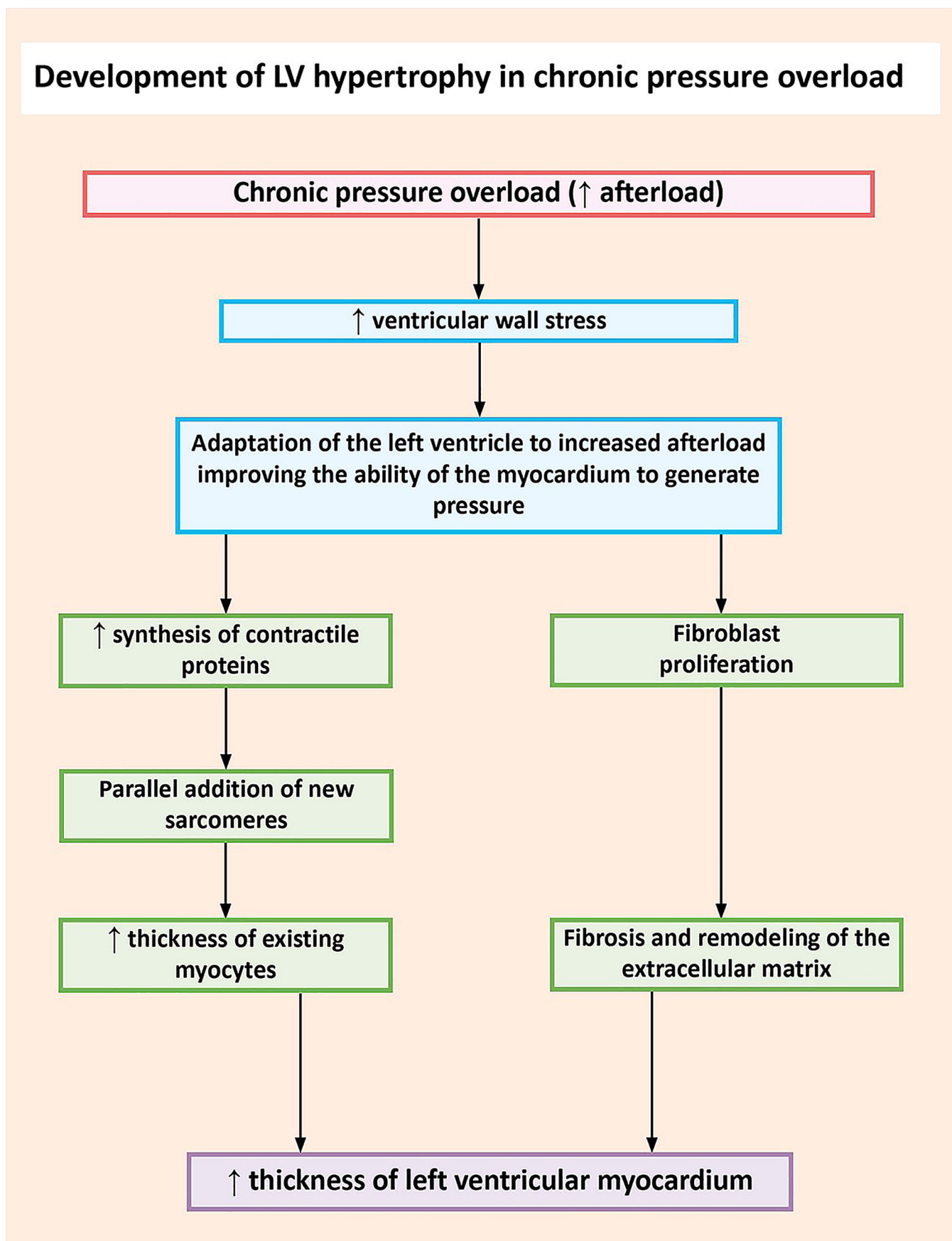
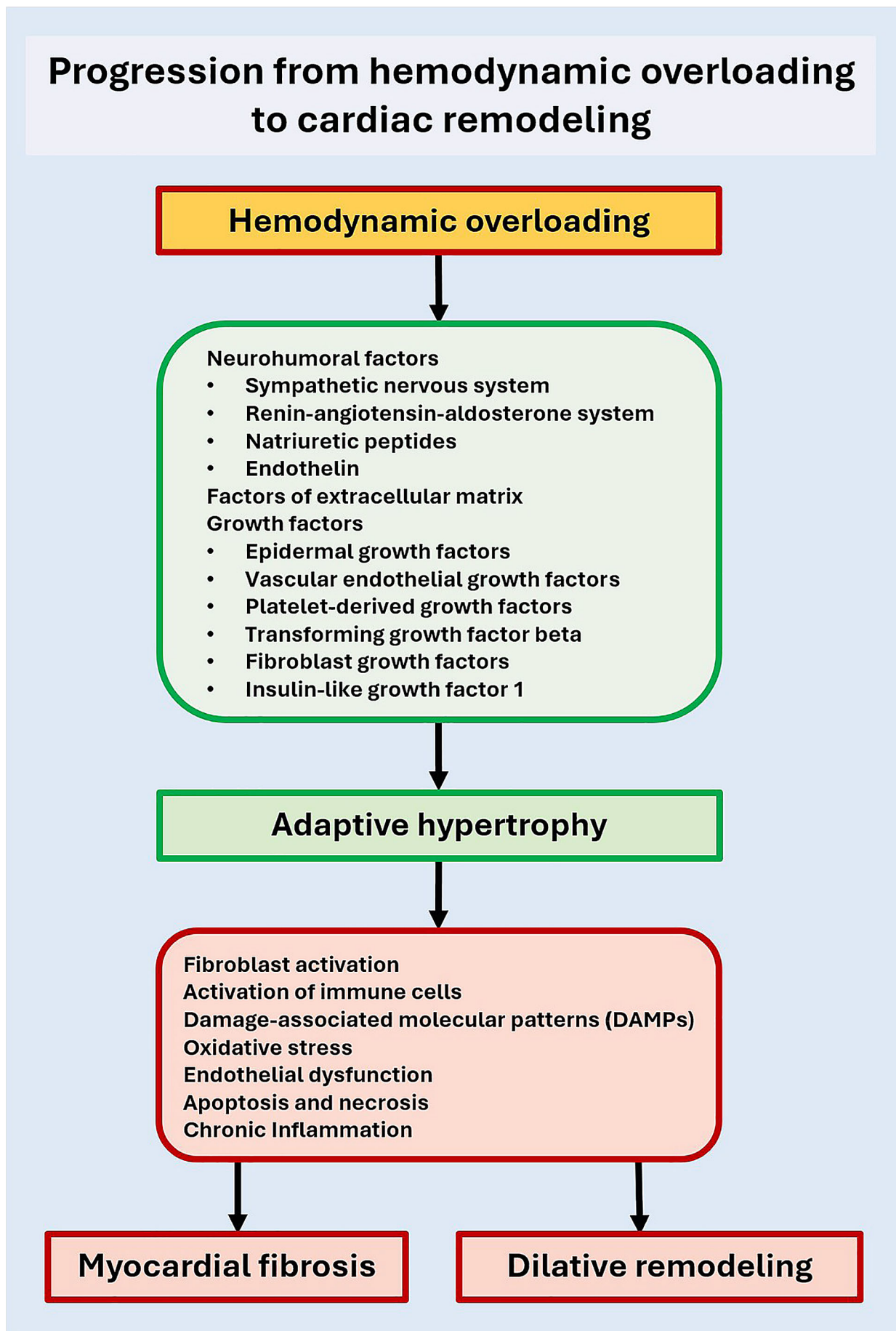


Fig. 2. Elements involved in the development of adaptive and maladaptive LV hypertrophy.



It is widely believed that the heart is an organ characterized by a fixed number of cardiomyocytes, which (in the absence of irreversible cellular damage) persist throughout life until the organism dies [7]. At any time, the myocardium should be composed primarily of a homogeneous population of cells of identical age [8]. Because of the constant number of myocytes, the primary process leading to increased left ventricular mass in LVH is hypertrophy of the myocardial cells, rather than an increase in their number (Figure 1). However, there are potential sources of new cardiomyocytes in the heart [8], and rare variants of left ventricular hypertrophy exist in which, in addition to hypertrophy, hyperplasia of cardiomyocytes is also found, for example, in hypertrophic cardiomyopathy [9, 10]. In experimental animals, a hyperplastic response was induced by left ventricular pressure overload in models of artificial juvenile aortic stenosis [11].

Etiological factors for the development of left ventricular hypertrophy

- **Hemodynamic stress.** Pressure and/or volume overload of the ventricle are the main causes of the structural and functional changes in myocardial hypertrophy.

- Diseases causing hemodynamic overload, such as arterial hypertension, aortic stenosis, and/or regurgitation (Figure 3).

- Intense physical (sports) activity. It can cause adaptive, non-pathological physiologic hypertrophy of the left ventricle.

- **Genetic factors.** Mutations in sarcomere genes and genetic variations predispose to the development of myocardial hypertrophy. Most often, their action is combined with that of other stimuli, causing hypertrophy.

- **Infiltrative diseases.** Amyloidosis, sarcoidosis, Fabry disease, hemochromatosis, glycogenoses.

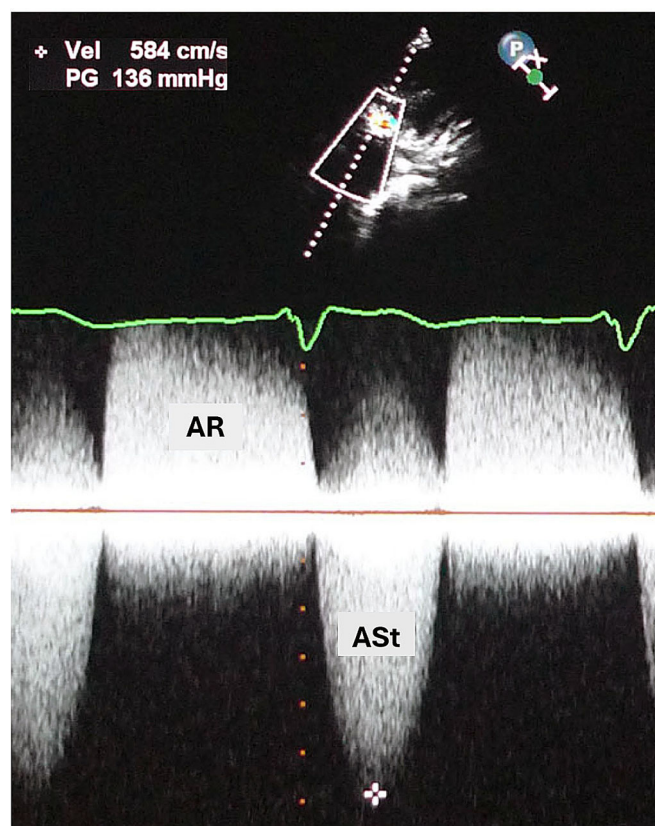
Hemodynamic stress

Hemodynamic stress is a well-known factor in the development of LVH. Volume loading leads to harmonious heart growth, in which its shape remains relatively normal, but its size increases, and an initially enlarged normal heart develops. This process resembles normal cardiac growth in response to the obligatory volume load during the growth process due to the increase in circulating blood volume and cardiac output [12]. Under pressure loading, the adaptive increase in mass shows the pattern of concentric hypertrophy with wall thickening without a volume change. The process progresses with the development of changes in the ultrastructure and contractile function of the myocardium.

Genetic factors

Two hundred thirty-two genes have been found to be dysregulated in hemodynamic stress [13]. Some of the genes associated with myocardial hypertrophy are Acta1, Myh7, Nppa, and Nppb [13]. The incidence of hypertrophic cardiomyopathy is estimated at 1:200 to 1:500, making it one of the most common genetically determined heart diseases [14].

Fig. 3. Example of a hemodynamic cause of LV hypertrophy. Continuous wave Doppler imaging of the aortic valve flow velocity in a patient with severe aortic valve disease (stenosis and regurgitation). **ASt**, systolic flow velocity in aortic stenosis; **AR**, aortic regurgitation flow velocity.



- **ACTC (cardiac α -actin gene).** The E101K mutation of the ACTC gene, leading to alterations in cardiac α -actin, is associated with apical hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular noncompaction, and septal defects [15, 16, 17].

- **MYH7 (β -myosin heavy chain gene, β -MHC).** Mutations in MYH7 are associated with various phenotypes, including left ventricular hypertrophy. In patients with familial hypertrophic cardiomyopathy, these mutations are associated with reduced sarcomere force-generating capacity [18].

- **NPPA (atrial natriuretic peptide gene).** After birth, NPPA expression is downregulated. Its activation is associated with left ventricular hypertrophy both in vitro and in vivo [19].

- **NPPB (brain natriuretic peptide gene).** It is a stress marker that plays a role in regulating blood pressure and water balance. Its expression is increased in hypertrophic hearts [20].

- **PFKP (the platelet form of phosphofructokinase gene).** During the maladaptive hypertrophy phase, PFKP is upregulated in cardiomyocytes [21].

- **CDK1 (cyclin-dependent kinase 1 gene).** It enhances cardiac fibrosis by transforming fibroblasts into myofibroblasts through the TGF- β pathway [22]. In hyper-

trophic cardiomyocytes, CDK1 expression is increased [21]. CDK1 may also exert an anti-hypertrophic effect [22].

- **COL3A1 (type III collagen gene).** The increased expression of COL3A1 in hypertrophic cells suggests its involvement in the development of pathological hypertrophy, contributing to cardiac tissue remodeling and fibrosis [21].

- **Genes for transcription factors.** Csx/Nkx2.5, GATA4, and Mef2C promote the expression of embryonic genes, such as genes for ANP, BNP, and β -MHC [23]. These transcription factors (Csx/Nkx2.5, GATA4, and Mef2C) are important in regulating cardiac function and structural changes in hypertrophy.

Infiltrative diseases

Infiltrative diseases, such as amyloidosis [24], sarcoidosis [25], Fabry disease [26], and glycogenosis [27], can be the cause of left ventricular hypertrophy.

Amyloidosis. The hypertrophy in amyloidosis is typically diffuse. However, rare cases of asymmetric septal hypertrophy and left ventricular outflow tract obstruction have been reported [28].

Sarcoidosis is an infiltrative, granulomatous inflammatory disease that can affect the myocardium [29]. One of its presentations (septal myocardial hypertrophy) is similar to hypertrophic cardiomyopathy, and there are rare reports of isolated cardiac sarcoidosis hemodynamically mimicking hypertrophic obstructive cardiomyopathy [25]. In most cases of cardiac involvement in sarcoidosis, however, the thickness of the myocardium is not increased.

Fabry disease. Fabry disease is an X-linked lysosomal storage disorder resulting in attenuated activity or absence (in most males) of the enzyme α -galactosidase A (β -Gal A) [30]. According to data from Kampmann et al., at the initial examination, 48.6% of the male patients and 36.4% of the female patients with Fabry disease had left ventricular hypertrophy. The cumulative prevalence of LVH peaked at age 40 in men and 60 in women [31].

Pathogenetic factors in the development of myocardial hypertrophy

The main participants involved in the process of hypertrophy include neurohumoral factors, growth factors [32-36], extracellular matrix components [37, 38], cellular receptors [39], intracellular mediators and effectors (intracellular signaling pathways and transcription factors) [40, 41, 42].

Neurohumoral factors in left ventricular hypertrophy

Renin-angiotensin-aldosterone system

Plasma levels of angiotensin II, angiotensin-converting enzyme, and renin correlate with left ventricular mass regardless of blood pressure level [43]. Of these, the most pronounced is the correlation with the level of angiotensin II, which also shows a significant effect on the development of myocardial fibrosis. The myocardial hypertrophy and interstitial fibrosis development under the influence of angiotensin II are mediated by activation of MAPK-dependent pathways (see below) [44]. In addition, it mediates the development of cardiomyocyte hypertrophy indirectly, by stimulating the release of norepinephrine from

endings of the cardiac nerves and endothelin from endothelial cells. Another action of angiotensin II is the induction of proliferation of cardiac fibroblasts, the synthesis and secretion of adhesion molecules and proteins of the extracellular matrix, as well as the expression of integrin adhesion receptors [44]. Under its influence, fibroblast adhesion to extracellular matrix (ECM) components is also enhanced.

Sympathetic nervous system

The role of adrenergic stimulation in LVH is discussed below.

Natriuretic peptides

Natriuretic peptides are hormones that play an essential role in regulating blood pressure and body fluid volume. Their role in LVH is also discussed below.

Endothelin

Endothelin-1 (ET-1) is a potent vasoconstrictor produced by endothelial cells. ET-1 induces hypertrophic signals through G-protein-coupled receptors and promotes cell growth and hypertrophy [45].

Components of the extracellular matrix

The main components of the ECM are the following:

- **Structural proteins**

- **Collagen fibers.** These fibers are organized into three interconnected layers [46], i.e., endomysium (a fine network of collagen fibers in a proteoglycan matrix surrounding myocytes), perimysium (network-forming bundles throughout the myocardium), and epimysium (enveloping the myocardium).

- **Elastin fibers** (important for elastic properties).

- **Nonstructural proteins**

- **Proteoglycans** (such as versican [47], syndecan [48], biglycan [49]) contribute to the plasticity of the ECM and interact with growth factors.

- **Glycoproteins** (such as fibronectin [50] and laminin [51]) with a role in cell adhesion, migration, and tissue organization.

- **Glycosaminoglycans (GAGs)** (such as hyaluronic acid and chondroitin sulfate), involved in water content regulation, providing friction reduction and affecting cellular transmission of signals.

- **Matrix metalloproteinases (MMPs).** Enzymes involved in the remodeling and renewal of the ECM.

- **Growth factors**, such as transforming growth factor-beta (TGF- β) and insulin-like growth factor (IGF), modulate cellular behavior, tissue repair, and remodeling.

- **Cell adhesion molecules (CAMs).** They play a role in interactions between cells and ECM. These include integrins [52] and cadherins [53, 54].

Osteopontin

Osteopontin is an extracellular matrix glycoprotein that plays a key role in cardiac remodeling. Its expression is increased by stress, hypoxia, and exposure to angiotensin II. In patients with dilated cardiomyopathy, a significant correlation was found between increased osteopontin immunoreactivity and both impaired left ventricular function and cardiomyocyte hypertrophy [37].

Syndecans

Syndecan-4 is a transmembrane proteoglycan involved in cardiac adaptation after injury [48]. Syndecan-4 is essential for compensatory hypertrophy in the heart with pressure overload by affecting the calcineurin-NFAT-dependent pathway in cardiomyocytes [48]. Under pressure load, the phosphorylation of syndecan-4 is reduced, and the binding between syndecan-4, calcineurin, and its coactivator calmodulin is increased [55].

Fibronectin

Fibronectin is one of the main components of the extracellular matrix. Its action is mediated by direct interaction with integrin receptors on the cell surface [50]. The interaction between fibronectin and integrins initiates a process involving conformational activation of fibronectin in the extracellular space and organization of the actin cytoskeleton in the intracellular space [50]. Fibronectin contributes to pathological hypertrophy of cardiomyocytes *in vitro* and *in vivo* by activating the nuclear factor of activated T cells (NFAT) [38].

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) can both promote and prevent the development of myocardial hypertrophy. Euler et al. detected mRNA for MMP-1, MMP-2, MMP-3, MMP-9, and MMP-14, as well as protein expression of MMP-2, MMP-9, and MMP-14 in cardiomyocytes [56]. Prohypertrophic stimuli decreased MMP expression, suggesting that downregulation of MMPs may favor the hypertrophy process. The MMP inhibitors TAPI-0 and TIMP-2, as well as ARP-100 (selective for MMP-2), stimulated hypertrophy.

Tissue inhibitors of matrix metalloproteinases

Extracellular matrix remodeling by MMPs under pressure overload is mainly regulated by their tissue inhibitors – TIMPs [57]. Increased levels of TIMPs are thought to lead to extracellular matrix fibrosis [58]. In mice with TIMP2 deficiency, infusion of angiotensin II leads to myocardial hypertrophy without fibrosis, while in TIMP3 deficiency, the effect is the development of fibrosis without hypertrophy [59].

Integrins

Integrins are a class of membrane receptors that are noncovalently linked heterodimers composed of α - and β -subunits [60]. They are essential in transmitting mechanical force across the cell membrane and sensing mechanical stress signals in cardiomyocytes. Integrins and several associated cytoskeletal proteins connect the sarcomeric contractile apparatus to the extracellular matrix across the cell membrane and operate as a trigger element activating the signaling pathways that activate the cardiomyocyte hypertrophy program [61].

Growth factors

Growth factors play an essential role in myocardial hypertrophy, leading to cellular responses related to cardiac growth, inflammation, angiogenesis, and hypertrophy.

• **EGFs (epidermal growth factors).** Activation of EGF receptors leads to receptor autophosphorylation and stimulation of intracellular signaling pathways, including the MAPK/ERK pathway. According to Fujino et al., EGF

may play an essential role in the early development of left ventricular hypertrophy and fibrosis [62].

• **VEGFs (vascular endothelial growth factors)** represent a superfamily of growth factors with a key role in angiogenesis. The VEGF superfamily includes the following representatives: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF (Placental Growth Factor) [35]. According to data from Xu et al., in left ventricular hypertrophy due to aortic stenosis, VEGF has a protective effect against the transition from compensatory hypertrophy to heart failure, and this effect is mediated through mitochondrial-mediated apoptosis and cardiomyocyte proliferation [63]. In a study of 179 patients with arterial hypertension and 169 healthy controls, Lanchini et al. found that the VEGF-A gene polymorphism was associated with left ventricular mass and systolic function [64]. Overexpression of VEGF-B under pressure overloading resulted in severe cardiac fibrosis and inhibition of genes responsible for lipid and glucose uptake, metabolic regulation, and mitochondrial function [65]. Overexpression of PlGF in cardiac tissues is associated with increased endothelial release of NO, stimulating cardiomyocyte hypertrophy through activation of the Akt/mTORC1 pathway [66].

• **PDGFs (platelet-derived growth factors).** The PDGF family includes four ligands (PDGF-A, PDGF-B, PDGF-C, and PDGF-D) that bind to the α - or β -isoforms of PDGF receptors (PDGFRs). PDGF-A, PDGF-B, and PDGF-C bind to the α -isoform of the receptor. These receptors have tyrosine kinase activity, i.e., they phosphorylate tyrosine residues in proteins. PDGF-B and PDGF-D bind to the β -isoform [67]. PDGFR- β is essential for the response of cardiomyocytes to stress, including angiogenesis and cardiac tissue remodeling [36]. In general, PDGFR- α expression in cardiac tissues is lower. PDGFs influence cell migration, growth and proliferation by binding to their specific tyrosine kinase (RTK) class receptors. Upon activation of PDGF receptors, signaling cascades, including the PI3K/Akt and MAPK pathways, are activated, resulting in cell proliferation and the synthesis of extracellular matrix components. In the context of myocardial hypertrophy, PDGF receptors contribute to increased cell mass and remodeling of cardiac tissue while simultaneously stimulating angiogenesis and the inflammatory response in the myocardium under increased mechanical load.

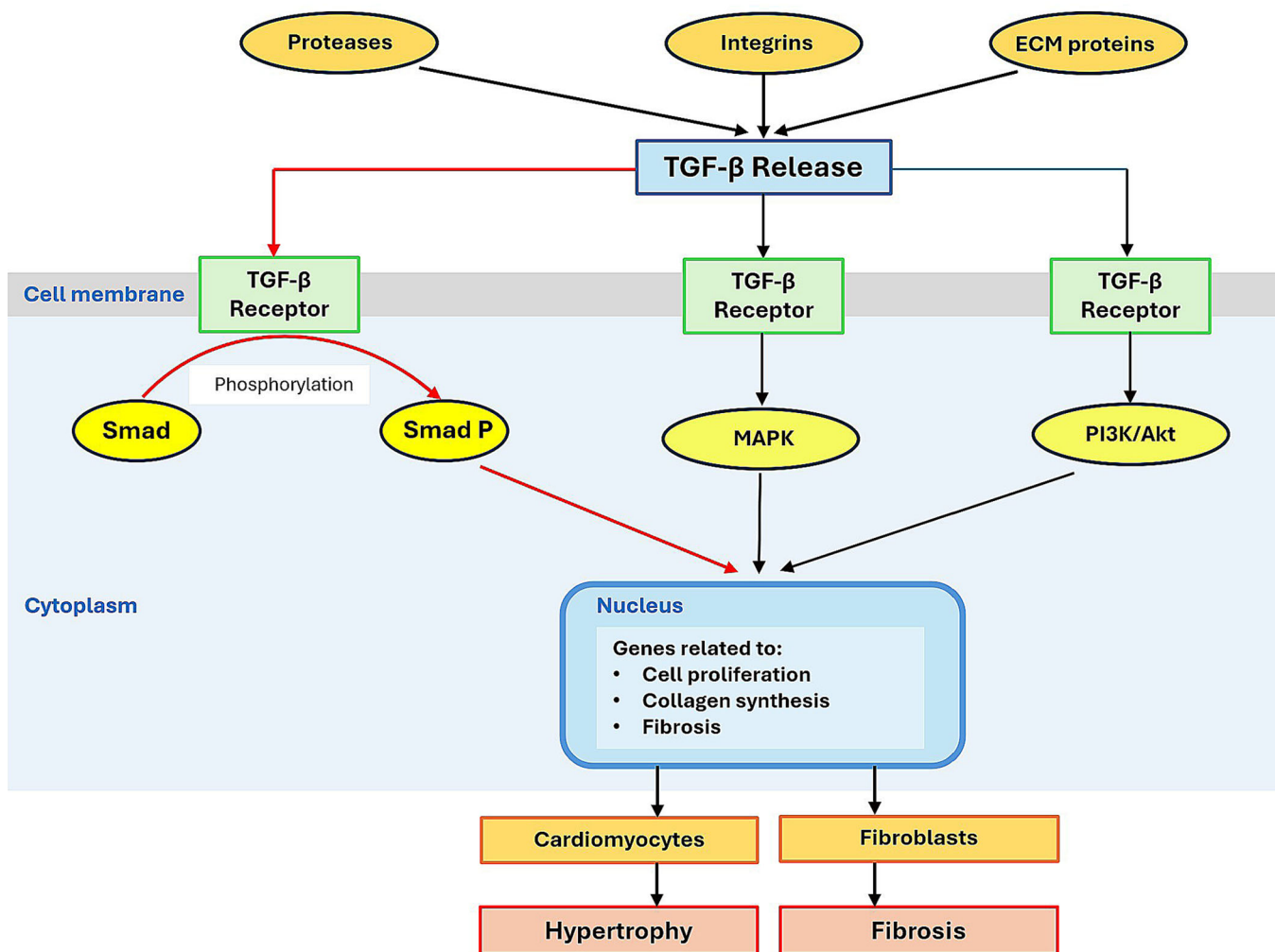
• **TGF- β (transforming growth factor beta).** Upon activation of TGF- β receptors (belonging to the family of serine/threonine kinases), a signaling cascade involving Smad proteins is triggered [68]. These proteins are phosphorylated and transported to the nucleus, where they regulate the transcription of genes related to cell proliferation, collagen synthesis, and fibrosis (Figure 4). Its overexpression in the hearts of experimental animals is associated with fibrosis and hypertrophy [33]. The release of TGF- β in myocardial injury is triggered by proteases, integrins, and specialized extracellular matrix proteins. Under pressure overloading, TGF- β initially preserves the integrity of the extracellular matrix but later favors fibrosis and ventricular dysfunction. Its excessive and prolonged effect contributes to remodeling and cardiac dysfunction [32]. In the atria, TGF-

β -mediated fibrosis may contribute to the pathogenetic substrate causing atrial fibrillation [32]. The effects of TGF- β on fibroblasts include myofibroblast transdifferentiation, expression of extracellular matrix proteins, induction of tis-

sue inhibitors of matrix metalloproteinases (TIMPs), upregulation of plasminogen activator inhibitor-1 (PAI-1), and in cardiomyocytes TGF- β causes hypertrophic response [33].

Fig. 4. Mechanism of TGF- β effect on myocardial hypertrophy and fibrosis. Smad phosphorylation is a main mechanism of action of TGF- β . **ECM**, extracellular matrix; **Smad**, Smad proteins; **Smad P**, phosphorylated Smad proteins; **MAPK**, mitogen-activated protein kinase; **PI3K/Akt**, phosphatidylinositol 3-kinase / protein kinase B.

TGF- β in the development of LV hypertrophy and fibrosis



• **FGFs (fibroblast growth factors).** The fibroblast growth factor 2 influences growth and differentiation in several tissues and is required for cardiac hypertrophy [69]. It stimulates the proliferation and differentiation of cardiomyocytes. FGF2 has been shown to influence cell survival and growth through MAPK and PI3K/Akt pathways [69, 70]. FGF is involved in extracellular matrix remodeling, which is important for the structure and function of hypertrophied myocardium [71], and also stimulates angiogenesis [72].

• **IGF-1 (insulin-like growth factor-1).** IGF-1 activates signaling pathways such as PI3K/Akt and MAPK. In patients with arterial hypertension, increased levels of in-

ulin and IGF-1 in circulation are associated with LV hypertrophy and abnormal LV geometry [34]. Local levels of IGF-1 in the left ventricle are of greater importance for the development of LVH than blood levels of IGF-1 [73].

Main membrane receptors and channels in the development of LVH

G-protein coupled receptors

Beta-adrenergic receptors (β 1 and β 2). Activation of these receptors leads to activation of adenylate cyclase in the cell membrane, resulting in an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP) and the activation of protein kinases (e.g., PKA). In chronic stimulation, such as in arterial hypertension,

these receptors can initiate pathological myocardial remodeling. Their prolonged activation has adverse consequences, the ultimate result being the development of heart failure [39]. The effect of β -adrenergic agonists on cardiomyocytes leads to the activation of STAT3 (signal transducer and activator of transcription 3), which has a dynamic role in integrating multiple cytokine signaling pathways [39].

Alpha-adrenergic receptors. Alpha-receptors are also G-protein coupled receptors [74]. Their stimulation leads to the activation of phospholipase C. Phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂), and two secondary messengers are produced – diacylglycerol (DAG), which activates protein kinase C and promotes cell growth and hypertrophy, and inositol 1,4,5-triphosphate (IP₃), which increases intracellular calcium concentration (affecting the coupling of excitation and contraction) and induces signaling pathways for hypertrophy. Alpha-adrenergic receptors can be divided into two main types – α 1 (α 1A, α 1B, α 1D) and α 2 (α 2A, α 2B, α 2C) [75, 76]. Alpha-1 receptors are found mainly in smooth muscle cells, including in the vascular bed, where they have vasoconstrictor effects. Alpha-2 receptors are located mainly in the nervous system and, to a lesser extent, in the smooth muscle cells.

Transmembrane calcium ion channels

Increased calcium ion influx through Ca²⁺ channels in the cardiomyocyte membrane can cause increased intracellular calcium load and subsequent hypertrophy [77]. Increased intracellular Ca²⁺ levels activate intracellular signaling systems, including calmodulin and Ca²⁺ / calmodulin-dependent protein kinase (CaMKII), which have prohypertrophic effects and are responsible for myocardial remodeling.

TRPM cation channels

TRPM (transient receptor potential) channels (TRPM1 to TRPM8) are cation channels essential for multiple cellular functions [78, 79]. Studies by Guo et al. indicate that TRPM4 channels are an important element of the mechanosensory signaling pathway that induces left ventricular hypertrophy in response to pressure overload [80].

Angiotensin II and endothelin 1 receptors

They are discussed above in the text under the relevant humoral factors.

Intracellular signalling pathways

The two main signaling pathways involved in the cellular response to hemodynamic stress are the MAPK and PI3K/Akt pathways (Figure 5).

Mitogen-activated protein kinase (MAPK) pathway

This pathway is activated by various cell surface receptors, such as those for angiotensin II and catecholamines. The MAPK pathway is of critical importance in the regulation of the process of cardiac hypertrophy and remodeling in response to increased workload

[81]. The MAPK pathway is also known as the RAS-RAF-MEK-ERK pathway. The MAPK family includes several subfamilies, the most prominent of which is the ERK (extracellular signal-regulated kinase) pathway. The MAPK pathway is a major signaling cascade that can be activated by receptor tyrosine kinases upon binding to extracellular mitogenic ligands, as well as by G-protein-coupled receptors. RAS (rat sarcoma virus) proteins are small GTP-binding proteins (small GTPases) activated downstream of receptor tyrosine kinases. They hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP). They are a critical component of the system for transmitting signals from the cell membrane to the nucleus [82]. JNK (c-Jun N-terminal kinases) and p38 kinases, classified as stress-activated protein kinases, are two important branches of the larger MAPK signaling cascade [83]. Inhibition of p38 kinases and JNK promotes myocardial hypertrophy [81].

Phosphatidylinositol 3-kinase / protein kinase B (PI3K/Akt)

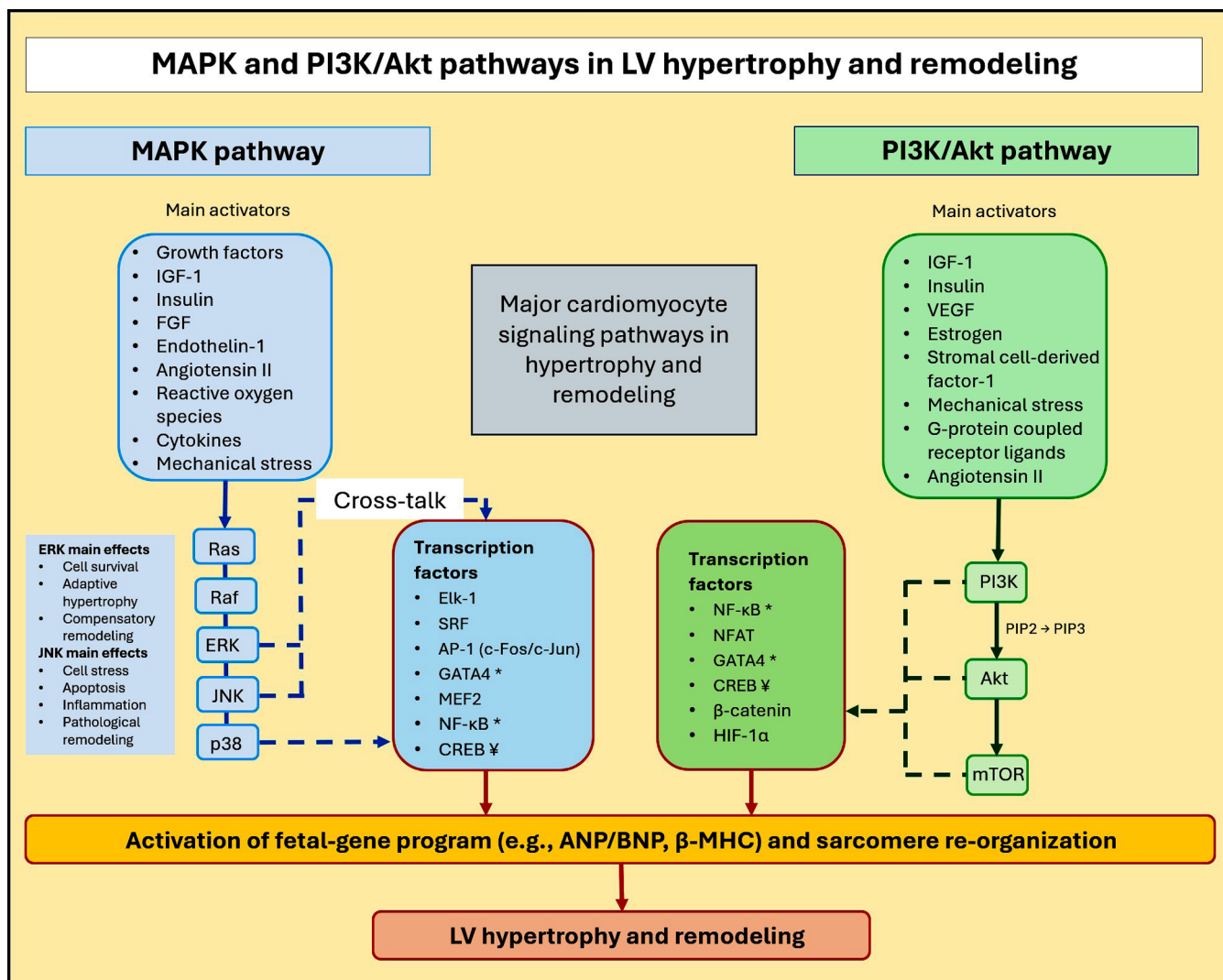
The PI3K/Akt pathway is another major signaling pathway closely related to the development of left ventricular hypertrophy. The main components of the PI3K/Akt pathway are (Figure 5):

- **PI3K (phosphatidylinositol 3-kinase).** Activation of this pathway begins with stimulation of cell surface receptors (including angiotensin II or catecholamine receptors). PI3K catalyzes the production of PIP₃ [Phosphatidylinositol (3,4,5)-trisphosphate] from phosphatidylinositol bisphosphate (PIP₂).

- **Akt (protein kinase B):** PIP₃ activates protein kinase B (Akt), a member of the AGC-kinase family (serine/threonine kinases), which includes over 60 kinases classified into 14 families [84]. Alterations in the Akt signaling pathway are essential in pathological processes such as atherosclerosis, hypertrophy, and vascular remodeling [85].

- **mTOR (mechanistic target of rapamycin).** The activity of mTOR can be induced by Akt. mTOR is an atypical serine/threonine kinase belonging to the PIKK (phosphoinositide kinase-related kinase) family and is a main regulator of critical cellular processes such as protein synthesis, cell growth, proliferation, autophagy, lysosomal function, and cellular metabolism [86]. mTOR interacts with specific proteins to form two multiprotein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is critical for the development of adaptive myocardial hypertrophy in response to mechanical stress. Its complete absence disturbs the process of compensatory hypertrophy development, resulting in dilated cardiomyopathy. Furthermore, its partial and selective inhibition may have a cardioprotective effect in aging and during cardiac stress. mTORC2 is required for normal cardiac physiology and helps cardiomyocyte survival under pressure overload [86].

Fig. 5. MAPK and PI3K/Akt pathways in left ventricular hypertrophy and remodeling.



* , Phosphorylated by both ERK (or JNK/p38) and Akt.

¥ , Primary activation by Akt and secondary modulation by p38.

Interaction between MAPK and PI3K/Akt pathways

MAPK and Akt can act synergistically to activate transcription factors and molecules that induce hypertrophy. They may also have independent but complementary effects on cell proliferation, protein synthesis, and cell survival. Although both pathways are important for normal myocardial growth, excessive activation or dysregulation of either may have pathological effects. For example, dysregulation of the MAPK pathway can lead to premature cellular senescence [41, 87, 88], while dysfunction of the PI3K/Akt pathway can lead to ineffective hypertrophy, pathological remodeling after myocardial infarction, deterioration of myocardial contractility, and development of heart failure [42, 89].

Calcium-calmodulin-dependent kinases (CaMKII)

CaMKII is a calcium-dependent protein kinase that plays a crucial role in cell signaling in cardiomyocytes, regulating both cardiac contraction and myocardial hypertrophy. Increased intracellular calcium activates CaMKII, which can

lead to pathological changes in cardiac function [90, 91].

Wnt/β-catenin signaling

The Wnt/β-catenin pathway is important for the regulation of cell proliferation and differentiation [92]. Dysregulation of this signaling pathway is important in myocardial infarction, arrhythmias, arrhythmogenic cardiomyopathy, diabetic cardiomyopathy, and myocardial hypertrophy [93].

Transcription factors in left ventricular hypertrophy

The main transcription factors involved in left ventricular hypertrophy include NF-βB, AP-1, GATA4, MEF2, YAP/TAZ, Hand1/2, β-catenin, and STAT3.

MEF2 is one of the main effectors of morphological changes in the hypertensive heart as a part of a complex network of molecular signaling pathways controlling cardiac gene expression [94]. Changes in myocardial gene expression in the process of myocardial hypertrophy require transcription factors from the MEF2 family and the nuclear lysine acetyltransferase p300 [13]. Acetylation of MEF2 is required for the development and maintenance of myocardial hypertrophy [13]. MEF2 is activated by increased intracellular calcium levels and interaction with CaMKII, resulting in the activation of genes involved in myocardial

hypertrophy and cardiac growth.

STAT3 is a signaling molecule and transcription factor with important cardioprotective functions [95]. It is a critical transcriptional regulator in β -adrenoceptor-mediated cardiac adaptation to stress, pathological remodeling, and heart failure [39]. As a transcription factor, STAT3 induces expression of antioxidant, antiapoptotic, and proangiogenic genes, and can also suppress expression of genes with anti-inflammatory and antifibrotic roles. STAT3 contributes to cardioprotection against myocardial infarction, hypertrophy, diabetic cardiomyopathy, and peripartum cardiomyopathy [95]. In hearts with no STAT3 function, pronounced

cardiomyocyte hypertrophy, cell death, and subsequent fibrosis development are observed [39].

CONCLUSION

Cardiac hypertrophy is a complex process regulated by multiple molecular signaling pathways and transcription factors. These factors play a key role in controlling gene expression related to cell growth, proliferation, adaptation, and cardioprotection. Understanding the mechanisms of action and interactions may help develop new strategies for the treatment of cardiac diseases with hypertrophy and pathological remodeling.

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Please cite this article as: Ivanov A, Levunlieva E, Manov E, Najdenov S, Runev N, Left Ventricular Hypertrophy: Mechanism of Development. *J of IMAB*. 2026 Apr-Jun;32(2):6779-6791. [Crossref - <https://doi.org/10.5272/jimab.2026322.6779>]

Received: 14/08/2025; Published online: 02/04/2026



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