

Chapter 2

Remodeling of Potassium Channels in Cardiac Hypertrophy

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Abstract The potassium channel is a major target of remodeling in cardiac hypertrophy. To maintain physiological cardiac function in the face of increased workloads, hypertrophied cardiac myocytes undergo downregulation of K^+ channels that results in a prolongation of action potential duration (APD) and upregulation of Ca^{2+} entry channels. Increased intracellular calcium in cardiac hypertrophy activates calcineurin/nuclear factor of activated T cell pathway to permit remodeling of the K^+ channels, resulting in a positive feedback between the K^+ channel remodeling and alteration of Ca^{2+} handling. Although the I_{to} channel is the major target of the K^+ channel remodeling in hypertrophied cardiomyocytes, alteration of other K^+ channels and/or K^+ channel regulators plays an important role in the remodeling and arrhythmogenicity. In this chapter, we list types of K^+ channels and their mRNA that undergo remodeling in cardiac hypertrophy and discuss molecular mechanisms of the remodeling.

Keywords Cardiac remodeling • Hypertrophy • Potassium channels • I_{to} channels • Gene expression • Ca^{2+} handling • Action potential prolongation • Arrhythmias

2.1 Introduction

Hypertrophic growth of the heart is an adaptive process in response to increased workloads. Hypertrophy has been shown to be associated with arrhythmias which can be caused by an alteration in cellular electrophysiology and cardiac remodeling,

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including a prolongation of the action potential duration (APD). Although changes in several ionic currents have been reported in hypertrophied cardiomyocytes, accumulated experimental data have highlighted an importance of K^+ channel remodeling in the APD prolongation in models of hypertrophy [1]. Although a reduction in the transient outward potassium current (I_{to}) is the most consistent ionic current change in cardiac hypertrophy, the target type of K^+ channels varies between species and experimental conditions for hypertrophy. Furthermore, it is believed that heterogeneous reduction, either transmurally or regionally, in I_{to} density associates with QT dispersion that accounts for a mechanism to develop arrhythmias.

Subsequent studies employing molecular biological approaches revealed that modulations of Ca^{2+} -responsive signaling pathways underlie the K^+ channel remodeling [1–3]. Recently, involvement of other pathways has been reported. These molecular mechanisms may provide possible new therapeutic targets against lethal arrhythmias and sudden death in cardiac hypertrophy.

2.2 Electrical Remodeling in Cardiac Hypertrophy

Electrical remodeling in cardiac hypertrophy is considered as a compensatory response to increased workloads. Although the activated signal mechanisms differ in experimental model, it has been reported that renin–angiotensin–aldosterone system, sympathetic nervous system, and other neurohumoral mechanism are activated in cardiac hypertrophy. Mechanical stretch on myocyte also activated signal cascades in heart tissue and cardiomyocyte. These activated signal transductions induce changes in gene expression and function of ion channels, initially to maintain cardiac function. Once these compensatory mechanisms are disrupted, the maladapted responses cause several pathological features including cardiac arrhythmias.

2.2.1 *Changes in Action Potential Duration*

The most striking feature of excitable cell is its action potential profile. The cardiac myocyte is characterized as having long APD with plateau of maintained depolarization before repolarization. Changes in APD result from alterations in the expression and function of depolarizing and repolarizing currents. Electrical remodeling in cardiac hypertrophy is primarily characterized by prolongation of APD. The prolongation of APD is a consistent finding in hypertrophy by several experimental models including pressure and/or volume overload by aortic constriction [4–13] and hypertension [14–18]. Since APD is primarily responsible for the time course of repolarization, this APD prolongation represents delays in cardiac repolarization. The prolongation of APD is not a unique phenotype in cardiac hypertrophy. Several experimental studies utilizing failing heart induced by myocardial infarction [19–21],

pacing tachycardia [22–24], and genetically modified animal model [25–28] exhibit the APD prolongation as observed in hypertrophy. In addition, myocardial infarction model has higher arrhythmogenicity [29, 30]. Thus, some of findings in failing heart are also useful to comprehend the mechanisms of remodeling in hypertrophy. Since the heart tissue consists of myocyte layers with different action potential profiles, APD varies across the myocardial wall and the region of the heart [31–34]. The regional heterogeneity in APD is enhanced by hypertrophy [35]. In addition, cardiac hypertrophy also enhanced temporal dispersion of APD. The enhanced spatial and temporal dispersions contribute to the arrhythmogenicity in hypertrophied animal models. This finding is consistent with increased dispersion of monophasic action potential duration and electrocardiographic QT intervals and increased prevalence of ventricular arrhythmia in human [36–38].

2.2.2 *Experimental Models of Cardiac Hypertrophy*

2.2.2.1 **Experimental Models to Induce Hypertrophy**

Cardiac hypertrophy has been induced by various experimental techniques. Although the prolongation of APD is a common electrophysiological change, signals and ion currents contributing to this APD prolongation differ in each model (Table 2.1).

The pressure overload model by constriction of aorta is widely used to induce left ventricular hypertrophy (LVH). The extent of hypertrophy depends on the site and degree of aortic constriction, resulting in a variety of changes in electrical remodeling. Hypertension model is also considered as pressure and/or volume overload and is another tool to investigate electrical remodeling in hypertrophy. The hypertension model has slower progression of LVH than aortic constriction, which contributes different response of remodeling. Monocrotaline-induced pulmonary hypertension is used as a right ventricular hypertrophy (RVH) model, mostly in rats [8, 39]. Constriction of the pulmonary artery is also utilized for inducing RVH in large mammals [10].

In most of models, hypertrophy is accompanied with a variable amount of heart failure. The balance of heart failure and hypertrophy may explain the difference among several models including complete atrioventricular block [40–43], catecholamine treatment [44], and pacing-induced tachycardia model [22–24] in addition to pressure overload.

2.2.2.2 **Animal Species and Expression of Channels**

The species of animal is an important factor to understand electrical remodeling in cardiac hypertrophy. APD prolongation is observed regardless of animal species, and it is caused by alterations in K⁺ channels in most studies. However, the mechanism of APD prolongation is different between small and large mammals due to the different expression of subtype of K⁺ channel (Table 2.1).

Table 2.1 K⁺ channel remodeling in cardiac hypertrophy

Model		Currents					Comment	References
Methods	Species	APD	I_{to} (I_{to-f} , I_{to-s})	I_{K1}	I_K (I_{Kr} , I_{Ks} , I_{Kur})			
<i>Pressure/volume overload</i>								
Ao (abdominal)	Feline	↑		↔	↓	I_K slowed activation, faster deactivation	[4]	
PAC (RVH)	Feline			↑	↓	I_K slowed activation, faster deactivation	[7]	
Ao	Dog	↑	↑				[9]	
Ao	Rabbit	↑	↑	↓	↔		[5]	
Ao	Guinea pig	↑		↔	↔	$I_{Ca,L}$ ↑	[11]	
PAC (RVH)	Ferret		↓			Slowed TTP, decay and recovery	[10]	
Ao (ascending)	Rat	↑ epi	I_{to-f} ↓	↔	↔		[13]	
Ao (abdominal)	Rat	↑	↓ apex, free wall				[6]	
Ao (abdominal)	Rat	↑	↓				[12]	
DOCA/salt	Rat	↑	↓			Small negative shift gating	[15]	
DOCA/salt	Rat	↑	I_{to-f} ↓		I_{Kur} ↔		[17]	
SHR	Rat	↑	↓	↔			[14]	
RVHTN	Rat	↑	↑			Slowed I_{to} decay	[16]	
RVHTN	Rat					↓Kv4.2/4.3 mRNA, ↔Kv1.2, 1.4, 1.5, 2.1, KCNQ1	[18]	
Monocrotaline	Rat	↑ RV	↓ RV				[8]	
Monocrotaline	Rat	↑ RV > LV	↓			↓KChIP2 mRNA	[39]	
<i>AV block</i>								
	Canine	↑			I_{Ks} ↓, I_{Kr} in RV ↓	↓ KCNQ1/KCNE1 mRNA	[41, 43]	
	Rabbit	↑QT	I_{to-f} ↔	↑	I_{Ks} ↓, I_{Kr} ↓		[42]	
	Mouse	↑QT	I_{to-f} ↓			↓Kv4.2/KChIP2 mRNA	[40]	
<i>Pacing tachycardia</i>								
	Dog	↑	↓	↓			[23]	
	Rabbit	↑	↓	↔			[24]	
<i>Catecholamine treatment</i>								
Iso	Rat	↑	↓				[44]	
Iso	Rat	↑	↓ Subepi > Subendo			Indirect assessment by 4AP	[35]	

(continued)

Table 2.1 (continued)

Model			Currents				Comment	References
Methods	Species	APD	I_{to} (I_{to-f} , I_{to-s})	I_{K1}	I_K (I_{Kr} , I_{Ks} , I_{Kur})			
<i>Genetic</i>								
Growth hormone-secreting tumor	Rat	↑	↓				[28]	
Calsequestrin	Mouse	↑	↓	↓		I_{NCX} ↑, I_{Na} ↓, $I_{Ca,L}$ ↓	[25]	
H-Ras-v12	Mouse	↑	↓			I_{NCX} ↑	[27]	
<i>Clinical</i>								
Severe HF	Human	↑	↓	↓ ↔			[100]	
Failing	Human	↑	↓ Subendo				[69]	
Failing LV	Human		I_{to-f} ↓ Subepi			I_{to-f} slowed recovery in subendo	[70]	
HF	Human					↓Kv4.3 mRNA, ↔Kv1.4, Kvβ1, Kir2.1, hERG	[46]	
HF	Human	↑	I_{to-f} ↓	↓	I_{Ks} ↓		[47]	

↑ increase, ↓ decrease, ↔ unchanged, *RVH* right ventricular hypertrophy, *AoC* aortic constriction, *PAC* pulmonary artery constriction, *TTP* time to peak, *SHR* spontaneously hypertensive rat, *DOCA* deoxycorticosterone acetate, *RVHTN* renovascular hypertension, *GH* growth hormone, *RAS* renin-angiotensin system, *Iso* isoproterenol, *HF* heart failure

Rodents (mice and rats) have shorter cardiac APD than large mammals to adapt to the extremely high heart rate (~600 bpm in mice). I_{to} is a major repolarizing current throughout this short action potential, but the contribution of delayed rectifier potassium current (I_K) and inward rectifier potassium current (I_{K1}) remains subtle. The hypertrophy model in rodents revealed reduction of I_{to} in most of the studies. I_{to} consists of two components: fast (I_{to-f}) and slow (I_{to-s}) components according to the fast and slow rates of inactivation, respectively. In rodents, I_{to-f} is considered as the major target channel rather than I_{to-s} [45]. Reduction of I_{to} is achieved by change in gating kinetics and/or the change in expression level of channels.

In large mammals, I_{to} is responsible for the initial rapid phase of action potential repolarization, representing a notch preceding plateau phase. The major contributor for repolarization is I_K (I_{Kr} and I_{Ks}). The hypertrophy model in large mammals showed reduction of I_K , but the change in I_{to} varies among experimental models.

Although data on K⁺ channel remodeling in human cardiac hypertrophy are lacking, reports using human failing heart showed downregulation of I_{to} in left and right ventricle [46] and downregulated I_{Ks} in right ventricle [47].

2.3 Remodeling of Potassium Channels

In models of hypertrophied myocardium, previous investigations have highlighted the importance of remodeling of potassium channels in the APD prolongation. The APD of cardiomyocytes is determined by a plateau phase that is controlled by a fine balance between small inward (calcium) and outward (potassium) ionic currents (Fig. 2.1). Functional downregulation of K^+ currents has consistently been observed especially in severe hypertrophy and failure regardless of species, and has been implicated as a major contributor to the APD prolongation. Distinct molecular complexes of potassium channels involve in hypertrophy depending on experimental conditions and species as described in Sect. 2.2. In this section, previous and recent publications regarding remodeling of potassium channels in channel transcript levels are summarized.

2.3.1 Transient Outward Potassium Current (I_{to})

Downregulation of I_{to} is arguably the most consistent alteration of potassium currents in hypertrophied myocardium. Because I_{to} plays an important role in the early repolarization phase of action potential in most species, it is believed that suppression of I_{to} provides an explanation of QT prolongation and QT dispersion leading to fatal ventricular arrhythmias. Exceptions are studies of some compensatory pressure overload hypertrophy models, in which there was no change or increase in I_{to} densities [16, 48, 49]. I_{to} has been classified into I_{to-f} and I_{to-s} as described in Sect. 2.2. These two components are encoded with distinct channel genes and are modulated differently and regionally in response to hypertrophic stresses.

2.3.1.1 The Fast Transient Outward Potassium Current (I_{to-f})

In mammalian hearts, the fast transient outward potassium current (I_{to-f}) is conducted by channels comprised of voltage-gated α -pore-forming subunits (Kv4.3 in human/canine and Kv4.2 and Kv4.3 in rodents/ferrets) and an auxiliary β -subunit (Kv channel interacting protein 2; KChIP2). Expression of Kv4 channels correlates with regional heterogeneities in I_{to-f} , which is reflected by a predominant expression in the mid-myocardium and epicardium. In many hypertrophy models, reduction of I_{to-f} density generally correlates with decreased Kv4 channel transcript levels. It is notable that hypertrophic stress induced by non-myocyte cell-conditioned growth medium or phenylephrine ablates regulated expression of I_{to} and Kv4 mRNA, which is seen during normal heart development [50].

KChIP2 has at least two functions, which are to assist transport of Kv4 channels to the plasma membrane and to regulate gating kinetics of Kv4 channels [51]. The former function is in line with no I_{to-f} functional expression in KChIP2 knockout

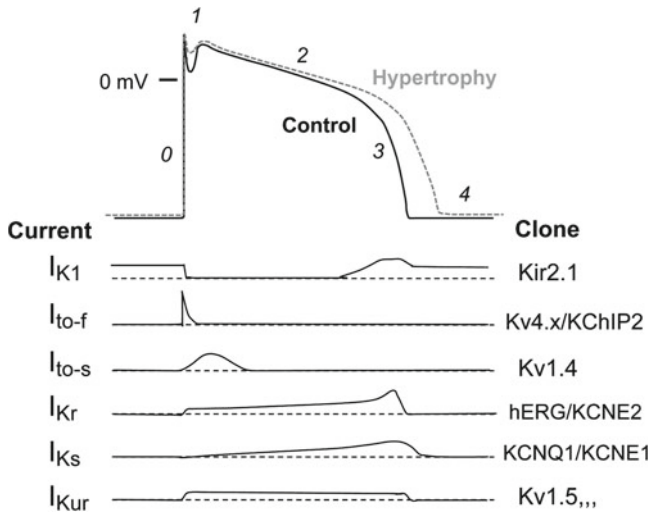


Fig. 2.1 Schematic diagram illustrating the major potassium currents that underlie the action potential in the mammalian ventricle. Top panel shows a control (solid line) and hypertrophied (gray dotted line) action potential profile. The phases of the action potential are labeled. Lower panels show schematic time courses of major K⁺ currents as well as clones that encode the currents

mice [52], and KChIP2 accelerates recovery from inactivation in the latter case [51]. Hypertrophy stimulations decrease gene expression of KChIP2 as well as Kv4 α -subunit, which results in reductions in I_{to-f} [10, 53]. Actually, recent data in hypertrophied rat neonatal cardiomyocytes suggest that decrease in KChIP2 expression controls α 1AR-induced reduction in I_{to-f} through regulation of NF- κ B [54].

2.3.1.2 The Slow Transient Outward Potassium Current (I_{to-s})

Kv1.4 is the predominant gene which encodes the voltage-gated α -pore-forming subunit of the endocardial I_{to-s} channel. In contrast to I_{to-f} , responses of I_{to-s} to hypertrophic stimulations are controversial. In LVH/RVH rats, there was no change in Kv1.4 mRNA, although Kv4.2 and Kv4.3 mRNA are the target of remodeling [8, 18, 55]. In a transgenic mouse model of hypertrophy with overexpressed L-type Ca²⁺ channels, Kv1.4 mRNA is increased, whereas Kv4.2 and Kv4.3 mRNA are reduced [56]. Interestingly, Kv1.4 mRNA levels are high at birth, increase during postnatal days (P0 to P10), and subsequently decrease to very low levels in adult rat ventricles, while Kv4.2 increase between birth and adult, becoming the predominant K⁺ channel protein [57]. Such K⁺ channel isoform switch during postnatal development is diminished by incubation with non-myocyte cell-conditioned growth medium or phenylephrine that induces cardiomyocyte hypertrophy, resulting in reversion of fetal phenotype of transient K⁺ channel currents [50].

2.3.2 Delayed Rectifier Potassium Current (I_K)

I_K plays an important role in cardiac repolarization process. Reduction of I_K currents in hypertrophied cardiomyocytes has been reported in different models, which may contribute to delayed repolarization in heart failure. In feline ventricular myocytes, hypertrophic stimulation has reduced I_K current density with slowed activation and accelerated deactivation, which may result in a greater predisposition to developing early after depolarization [4, 7]. In hypertrophy models in rabbits, both two components of the I_K currents, I_{Kr} and I_{Ks} , are downregulated [42]. Actually, most of the studies consistently show reduction of I_{Ks} [42, 47, 58], while I_{Kr} (or HERG) is reduced or unchanged [46, 57]. The different results of I_{Kr} changes are model specific. Reduction of I_{Ks} may be associated with alteration of transmural APD heterogeneity. In ventricles of canine failing hearts, the percentage of I_{Ks} reduction was greater in epicardial and endocardial cells than that in midmyocardial cells, which may result in elimination of the transmural I_{Ks} gradient [58].

2.3.3 Other Potassium Current

Kv1.5 reduction in hypertrophy is also observed [59–61]. Kv1.5 encodes the ultra-rapid delayed rectifier K^+ currents (I_{Kur}) which is dominantly found in atrium not in ventricles. Kv1.5 remodeling in post-MI LVH appears to be related to thyroid hormone (T3) level [61]. Because the Kv1.5 gene has a T3 responsive element in the promoter region, T3 enhances Kv1.5 expression in rat heart [62]. Downregulation of KCHIP2 also contributes to the Kv1.5 remodeling, because KCHIP2 interacts with Kv1.5 to assist cell surface expression [63]. Antisense oligodeoxynucleotides directed against Kv1.5 mRNA revealed atrial-specific Kv1.5 remodeling [64]. Thus, role of Kv1.5 remodeling may be more significant in atrial fibrillation rather than in ventricular hypertrophy [65]. There are several studies to show downregulation of I_{K1} or alteration of kinetics in heart failure [23], but several studies reported no change of Kir2.1 mRNA in failing heart compared with normal heart [46, 66].

2.4 Regional Heterogeneity of Electrical Remodeling

Regional heterogeneity of cardiac repolarization times results in the T wave in the electrocardiogram. Transmural and/or interregional heterogeneities of potassium channel expression are major contributors to the regional heterogeneity of repolarization times. The densities of I_{to-f} vary transmurally in the heart, that is, more prominent in epicardium than in endocardium [32, 67, 68]. Hypertrophic stimulation alters the transmural heterogeneity [69, 70]. In rats with LVH induced by isoprenaline [71] and aortic constriction [6], APD is predominantly prolonged in epicardial

cells resulting from greater reduction in I_{to-f} amplitude compared to endocardial cells. In rat ventricular myocytes that are remote from infarct zone, hypertrophy in epicardium reduced current densities of I_{to-f} and protein expression of Kv4.2 and Kv4.3 greater than in endocardium [72].

There is interregional heterogeneity of left ventricular repolarization [6, 73]. APD and I_{to-f} density vary gradually from apex to septum. APD is shortest in left ventricular apex, longest in septum, and intermediate in left ventricular free wall, reflecting from differential I_{to-f} amplitude [6]. Hypertrophied rat cardiomyocytes induced by abdominal aorta constriction ablate the interregional heterogeneity by greater I_{to-f} reduction in apex and free wall [6]. Myocardial infarction also eliminates the interregional heterogeneity of APD, I_{to} , and Kv4.2 expression between RV free wall and intraventricular septum [74].

2.5 Possible Mechanisms for Remodeling of Potassium Channels

The involvement of the calcineurin/NFAT pathway in reducing I_{to-f} has been reported [75–79] (Fig. 2.2). Calcineurin is a Ca²⁺/calmodulin-dependent protein phosphatase, and its activity is increased in hypertrophied hearts [80–82]. A calcineurin inhibitor cyclosporine A abolishes reduction of I_{to-f} and Kv4.2/Kv4.3 mRNA expression in hypertrophied rat ventricle [83]. In fetal rodents, calcineurin/NFAT increased I_{to-f} by transcriptional upregulation of Kv4.2 [84].

On the other hand, APD prolongation by I_{to} reduction in mice and rats leads to calcineurin activation via increase in $[Ca^{2+}]_i$ [76, 85–87]. In case of human or canine, reduction in I_{to} , I_{K1} , and I_{Ks} contributes to APD prolongation [47, 58], leading to increase in $[Ca^{2+}]_i$. But contribution of the regulation of channels to activation of calcineurin in human or canine is unclear.

The ubiquitous transcriptional factor NFAT has four reported isoforms, which are designated as NFAT1, NFAT2, NFAT3, and NFAT4. Unlike NFAT1, –2, or –4 in immune tissues, NFAT3 is the prominent isoform in the heart. Ca²⁺-dependent activation of calcineurin induces NFAT dephosphorylation and NFAT translocation to the nucleus where it can interact with GATA4 to activate transcription of hypertrophic responsive genes [88]. Cardiac K⁺ channel genes (Kv1.5, Kv2.1, Kv4.2, Kv4.3, and KChIP2) which have putative NFAT binding sites in the promoter regions are downregulated through NFAT3 pathways after myocardial infarction [89]. Among these K⁺ channel genes, downregulation of Kv4.2 is the most sensitive to increase in NFAT3 activity compared with other genes (Kv1.5, Kv2.1, Kv4.3, and KChIP2) which require robust increase in NFAT3 activity [78]. Magnitudes of NFAT3 activation vary among hypertrophic models, which can partly explain why some studies do not show downregulation of Kv1.5 and Kv2.1. In a murine hypertrophic model, activation of NFAT3 by calcineurin transduces variations in $[Ca^{2+}]_i$ into differences in I_{to} density in endocardial and epicardial myocytes [89]. $[Ca^{2+}]_i$ and calcineurin/NFAT3

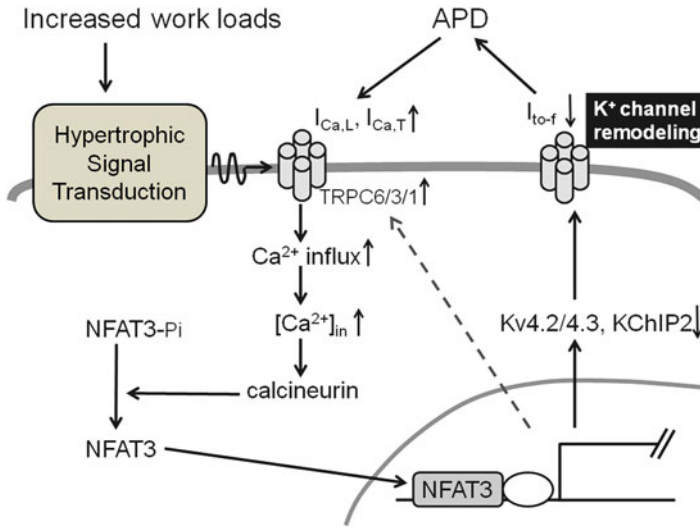


Fig. 2.2 Potential positive feedback between increased Ca^{2+} influx and K^{+} channel remodeling

activity is higher in endocardium than in epicardial myocytes, resulting in lower Kv4.2 expression and $I_{\text{to-f}}$ density in endocardial cells, at least in mice [90, 91]. This hypothesis is supported by the finding that suppression of Kv4 expression and I_{to} density in post-myocardial infarction hypertrophy is abolished by calcineurin inhibitor cyclosporine A in a rat model [83] and NFAT knockout mice [89].

Involvement of signaling pathways other than the calcineurin/NFAT pathway in K^{+} channel remodeling has been also reported. Oxidative stress through an Rac-dependent NADPH oxidase activation and superoxide production is involved in decreases in Kv4.3 mRNA [92, 93]. Kv4.2 and Kv1.4 mRNA expression is also regulated by endogenous oxidoreductase systems [72, 94, 95]. Involvement of NF- κB signaling in downregulation of $I_{\text{to-f}}$ through control of KChIP2 and Kv4.2 expression has been reported [54]. Downregulation of $I_{\text{to-f}}$ by either $\alpha 1$ adrenergic receptor or $\text{TNF-}\alpha$ stimulation may require NF- κB signaling-dependent decreases KChIP2 expression [54]. Mitogen-activated protein kinase (MAPK)/MEK and CaMK II are also involved in reduction of KChIP2 mRNA expression [53, 96]. One can speculate that TRPC6 may affect K^{+} channel remodeling by increase in pathological calcineurin/NFAT signaling [97].

2.6 Conclusions

Interruption of the Ca^{2+} -dependent positive feedback loop is a potential new therapeutic target against arrhythmias in cardiac hypertrophy [1, 98]. Considerable progress has been made in understanding the molecular mechanisms of cardiac

remodeling of K⁺ channels. We now realize that these mechanisms are highly complex reflecting the crosstalk between a variety of regulatory proteins, which can be altered in diseased hearts [99]. Clearly, future research is still needed to understand the clinical relevance of these regulatory proteins.

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