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Review Article

CaMKII in myocardial hypertrophy and heart failure

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ABSTRACT

Many signals have risen and fallen in the tide of investigation into mechanisms of myocardial hypertrophy and heart failure (HF). In our opinion, the multifunctional Ca and calmodulin-dependent protein kinase II (CaMKII) has emerged as a molecule to watch, in part because a solid body of accumulated data essentially satisfy Koch's postulates, showing that the CaMKII pathway is a core mechanism for promoting myocardial hypertrophy and heart failure. Multiple groups have now confirmed the following: (1) that CaMKII activity is increased in hypertrophied and failing myocardium from animal models and patients; (2) CaMKII overexpression causes myocardial hypertrophy and HF and (3) CaMKII inhibition (by drugs, inhibitory peptides and gene deletion) improves myocardial hypertrophy and HF. Patients with myocardial disease die in equal proportion from HF and arrhythmias, and a major therapeutic obstacle is that drugs designed to enhance myocardial contraction promote arrhythmias. In contrast, inhibiting the CaMKII pathway appears to reduce arrhythmias and improve myocardial responses to pathological stimuli. This brief paper will introduce the molecular physiology of CaMKII and discuss the impact of CaMKII on ion channels, Ca handling proteins and transcription in myocardium. This article is part of a special issue entitled "Key Signaling Molecules in Hypertrophy and Heart Failure".

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Contents

1. Molecular physiology of CaMKII

CaMKII is a serine–threonine kinase that exists as an elaborate holoenzyme complex consisting of a pair of hexameric stacked rings (Fig. 1). There are four CaMKII gene products (α, β, γ, δ). These CaMKII isoforms have different tissue distribution and may have subtle

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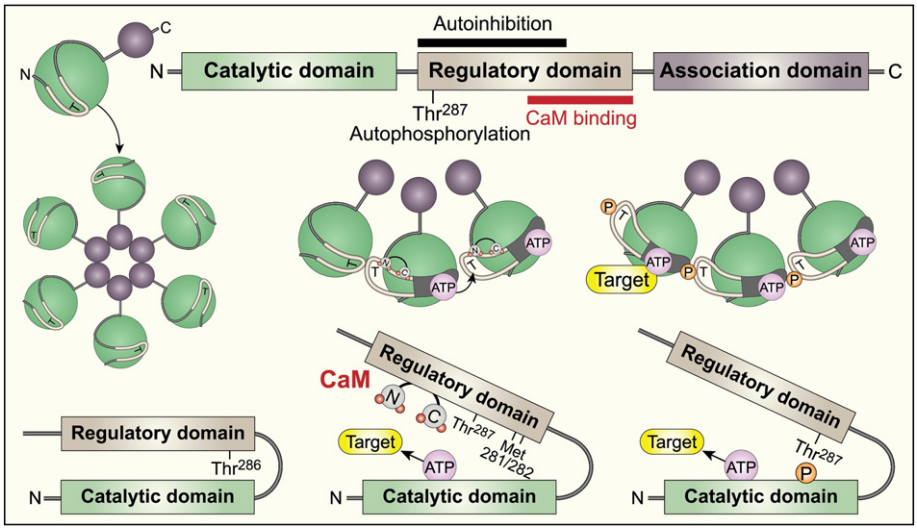

Fig. 1. CaMKII structural domains and regulation. CaMKII monomers consist of an N terminal catalytic domain and a C terminal association domain that bound a regulatory domain (top). The association domains (maroon circles) are required for assembly of the CaMKII monomers into the holoenzyme (middle panels). Under resting conditions the catalytic domain is constrained by the regulatory domain (left middle and bottom panels). After intracellular Ca^{2+} rises and complexes with calmodulin (CaM) the Ca^{2+}/CaM binds to the C terminal portion of the CaMKII regulatory domain (mid portion of the top, middle and bottom panels) to prevent autoinhibition of the regulatory domain on the catalytic domain, activating CaMKII. With sustained Ca^{2+}/CaM or increased oxidation, CaMKII transitions into a Ca^{2+}/CaM-autonomous active enzyme after autophosphorylation (at Thr 287) or oxidation (at Met281/282) of amino acids in the regulatory domain.

differences in Ca/CaM sensitivity and activation kinetics, but, at present, understanding of the potentially specific roles for various CaMKII isoforms is incomplete. The predominant, though not exclusive, form in myocardium appears to be CaMKIIδ. Two major splice variants of CaMKIIδ are expressed in the adult heart, $CaMKII\delta_B$ [1,2] and $CaMKII\delta_C$ [2–4], the former containing an 11 amino acid nuclear localization sequence [5]. It appears that CaMKIIδ is functionally significant for myocardial pathology, as it was recently shown that targeted deletion of CaMKIIδ is sufficient to prevent adverse consequences of transaortic banding, a surgical model of pathological afterload augmentation [6,7] (Table 1). Each of the dozen CaMKII monomers that compose the holoenzyme consists of three domains (Fig. 1). Under basal conditions CaMKII activity is submaximal because the N-terminus catalytic domain is constrained by the pseudosubstrate region within the regulatory domain. CaMKII indirectly senses increases in intracellular Ca by binding calcified calmodulin (Ca/CaM) at the CaM-binding region in the regulatory domain, which is adjacent to the pseudosubstrate region. Ca/CaM binding reorders CaMKII so that the catalytic domain is not constrained by the pseudosubstrate domain. During brief, low frequency increases in intracellular [Ca], CaMKII deactivates after Ca/CaM unbinds from the regulatory domain.

2. CaMKII activity becomes Ca/CaM independent by autophosphorylation and oxidation

If Ca/CaM elevations are prolonged or occur at high frequency, the CaMKII monomers catalyze intersubunit phosphorylations at an autophosphorylation site (Thr 286/287, the precise numbering varies according to isoform) in the regulatory domain [8]. Thr 287 autophosphorylation reduces the likelihood of Ca/CaM unbinding by increasing the affinity by a factor of 10^5 [9], but also confers residual Ca/CaM-independent activity after Ca/CaM dissociation [10]. Ca/CaM-autonomous activity also emerges under conditions favoring oxidation of a pair of Met residues (281/282) [11] which are present on the CaMKII isoforms most relevant to myocardial biology (CaMKIIδ and γ [12]). CaMKII activation by oxidation requires initial Ca/CaM binding and does not promote the increase in Ca/CaM affinity (so-called CaM trapping) seen with autophosphorylation, presumably because CaM trapping is prevented by oxidation of a Met residue embedded in the CaM binding region (Met 308). Increased oxidation can shift the Ca dependence for CaMKII activation to low levels that may favor CaMKII activation even under ambient intracellular Ca activity [13]. CaMKII Met oxidation is reversed by methionine sulfoxide reductase A (MsrA) [11] a finding that provides potential insight into deleterious consequences of MsrA gene deletion [11,14] and the benefits of MsrA overexpression [15]. It appears that Thr autophosphorylation and Met oxidation are interactive processes, because Thr autophosphorylation is increased under circumstances of enhanced intracellular reactive oxygen species (ROS) [11]. ROS inactivates many phosphatases, so ROS could favor Thr autophosphorylation by reducing the capacity to dephosphorylate Thr 286/287. Increased Met oxidation may also lead to improved accessibility of Thr 286/287 for autophosphorylation, even in the absence of elevated Ca/CaM.

3. Ca/CaM-autonomous CaMKII activity is implicated in heart disease

The ability of CaMKII to transition between Ca/CaM-dependence and independence has important implications for physiology and

Table 1

Genotype/description	Phenotype
AC3-I/AC3-C α — MHC promoter transgenic [9,11]	Cardiomyopathy resistance to MI, isoproterenol infusion and angiotensin II.
CaMKIIN α — MHC promoter transgenic [80]	Reduced myocardial NF-κB signaling
$CaMKII\delta_B$ α — MHC promoter transgenic [1,2]	Hypertrophy and secondary cardiomyopathy
$CaMKII\delta_C$ α — MHC promoter transgenic [2–4]	Spontaneous cardiomyopathy, arrhythmias, and sudden death
CaMKIV α — MHC promoter transgenic [16]	Elevated myocardial CaMKII, hypertrophy and proarrhythmia
$CaMKII\delta^{-/-}$ Global knockout [6,7]	Resistance to aortic banding induced cardiomyopathy
$CaMKII\gamma^{-/-}$ Global knockout [12]	Reduced macrophage and endothelial cell apoptosis in response to ER stress

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