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REVIEW

Is CaMKII a link between inflammation and hypertrophy in heart?

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Abstract Myocardial infarction is a major cause of morbidity and mortality in the developing and developed world. Although current interventions have been successful in prolonging life, they are inadequate because mortality is still high among MI patients. The multifunctional Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) plays a key role in the structure and contractility of the myocardium. CaMKII activity is increased in MI hearts and CaMKII promotes cardiac hypertrophy and inflammation, processes consistently activated by myocardial injury. Hypertrophy and inflammation are also related to neurohumoral and redox signaling which uncouple CaMKII activation from Ca^{2+}/calmodulin dependence. Thus, CaMKII may act as a nodal point for integrating hypertrophic and inflammatory signaling in myocardium.

Keywords CaMKII · Heart · Myocardium · Myocardial infarction · Heart attack · Inflammation · Hypertrophy · Toll-like receptors · Oxidative stress · ROS · AngII

Myocardial infarction (MI) is a major cause of heart failure (HF) and related death. Clinical interventions using β-blockers, angiotensin converting enzyme inhibitors, angiotensin II (AngII) receptor, and mineralocorticoid receptor antagonists have improved mortality and morbidity from HF [1]. Yet, mortality and morbidity remain alarmingly high, making cardiovascular disease the major cause of death. Clearly, additional avenues of therapy need to be explored. MI and HF are marked by increased activity of the multifunctional Ca^{2+}/calmodulin-dependent protein kinase (CaMKII), cardiac hypertrophy, increased reactive oxygen species (ROS) and inflammation. Here, we will briefly review the injury-triggered molecular signals linking CaMKII and toll-like receptor (TLR)-mediated inflammatory events. We will explore the possibility that CaMKII may connect increased ROS to maladaptive hypertrophic and proinflammatory signaling after MI. Emerging evidence suggests that upon stress and injury, cardiomyocytes sense and launch a local inflammatory response that, in conjunction with the circulating immune response, determines the outcome of the injury.

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CaMKII and myocardial injury

CaMKII occupies a central role in the physiology and pathology of cardiomyocytes. As a multifunctional serine/threonine kinase, CaMKII has both short-term signaling effects in maintaining excitation–contraction coupling [2, 3] and long-term effects on gene transcription in cardiomyocytes [4].

Inflammation and CaMKII activity and expression are increased in failing human hearts [5, 6]. MI in animal models is also associated with increased activity of CaMKII [7–9] and inflammation [4, 10–13]. Transgenic overexpression of cytosolic or nuclear isoforms of cardiac CaMKIIδ in mouse hearts results in cardiac hypertrophy [14, 15]. In contrast, inhibition of CaMKII improves myocardial contractility in failing human hearts [5]. We demonstrated that inhibition of CaMKII limits myocardial death and preserves myocardial function after MI in animal models [7, 16, 17]. Thus, increased CaMKII activity correlates with pathological changes in the mammalian heart, which can be offset by inhibiting CaMKII.

We generated genetically modified mice expressing a peptide that competitively binds to the catalytic site of CaMKII to inhibit the enzyme activity. This peptide, designated as AC3-I, is under the control of α-MHC promoter that imparts cardiac specific expression of the peptide in the transgenic AC3-I mice. These mice appear to be normal under basal conditions. However, under stress, such as pharmacologic activation of β-adrenergic receptors, Ang II receptors, and myocardial infarction, these mice, compared to WT controls, display improved cardiac performance, reduced hypertrophy and stress related apoptosis [7, 16, 17]. Knockout mice lacking functional CaMKIIδ are also resistant to the consequences of transaortic banding (TAB) surgery. TAB-operated mice lacking CaMKIIδ showed less hypertrophy [18] and reduced tendency to transition to left ventricular dilation and heart failure [19], consistent with the concept that excessive CaMKII activation promotes cardiomyopathy [20]. These findings from many laboratories support a prominent role for CaMKII in the pathophysiology of the heart in health and disease.

CaMKII and inflammation

Inflammation is an integral part of the MI-related myocardial injury. Until recently, cardiomyocytes were considered innocent bystanders without active involvement in the inflammatory response after MI, which was thought to relate exclusively to invasion by circulating immunocompetent leukocytes in response to injury [21–23]. However, it has become evident that several proinflammatory cytokines are synthesized by cardiomyocytes upon ischemic injury [21, 23, 24]. These cytokines may profoundly affect the injured myocardium.

Recently, we demonstrated that in response to MI, cardiomyocytes induce expression of multiple proinflammatory proteins including the components of the complement fixation pathway that are hardwired to the innate immune response of the body [4]. Although, increased synthesis of complements within the ischemic heart has been known [25], synthesis of complements by cardiomyocytes was unexpected.

We performed microarray-based gene expression profiling of AC3-I mice to identify the genes that are regulated by CaMKII after MI. We looked for the genes whose expression is induced in WT hearts upon MI but attenuated in AC3-I hearts where CaMKII activity was inhibited. Since, the inhibitory AC3-I peptide is expressed in cardiomyocytes, genes whose induction is attenuated in AC3-I hearts after MI would be likely to be regulated by CaMKII. Through this approach, we identified a cluster of proinflammatory genes that met our criteria of increased expression after MI in AC3-C hearts (control transgenic hearts expressing a scrambled version of an inhibitory peptide, AC3-C) and reduced expression in infarcted AC3-I hearts [4]. Unexpectedly, we found that complement factors that are predominantly expressed by liver and immune cells were expressed in cardiomyocytes. We further characterized and validated these findings to demonstrate that complement factor B (CFB), a critical component of the alternative complement fixation pathway, was induced in cardiomyocytes and that mice with genetic ablation in the functional complement factor B gene were resistant to post-MI functional remodeling of the heart and had improved post-MI survival. From these findings, two things became apparent: first, CaMKII regulates expression of proinflammatory genes and second, cardiomyocytes themselves express proinflammatory genes, including the complement factors, and expression of inflammatory genes in myocardium is triggered by injury. The demonstration that a component of the alternative complement pathway was induced in the myocardium upon injury also was novel because in earlier studies, only the classical complement pathway was selectively studied. In addition, we also demonstrated that CaMKII regulates a TLR-mediated NF-κB inflammatory pathway.

CaMKII and NF-κB in cardiomyocytes

Post-MI inflammatory response is the sum of contributions from infiltrating sentinel immune cells as well as local cardiac cells. Although inflammation evokes the notion of immune response through specialized sentinel and effector cells, cardiomyocytes actively participate in the inflammatory process by producing cytokines and complement factors, which influence the local milieu [4, 21, 26]. MI-related cell death activates the danger sensing receptors on the cardiomyocytes, such as TLRs, by releasing cytosolic contents from dying cells and by proteolysis of the extracellular matrix. These endogenous agonists activate the major proinflammatory transcription factor nuclear factor kappa B (NF-κB) that induces the production of proinflammatory cytokines and complement factors. These factors can further amplify the inflammatory response. For example, we have shown that expression of CFB in cardiomyocytes is induced by MI or lipopolysaccharide (LPS) through activation of NF-κB and is regulated by CaMKII [4]. Complement-mediated plasma membrane damage can enhance an inflammatory cascade through synthesis and release of inflammatory cytokines such as TNF-α and IL-6 [27, 28]. Complement fixation pathways also produce potent anaphylatoxins that recruit migrating immune cells to the site of injury and enhance the inflammation [29]. Thus, proinflammatory responses in cardiomyocytes appear dependent on NF-κB and CaMKII.

A major question is how CaMKII regulates the NF-κB-mediated gene expression in the cardiomyocytes. MI involves elaboration of several cytokines as well involvement of TLRs that can activate NF-κB. The classical pathway of NF-κB activation involves signaling-mediated phosphorylation and subsequent proteasomal degradation of IκB inhibitor proteins. Degradation of IκB facilitates the translocation of the NF-κB dimers to the nucleus where they bind to target genes and activate transcription. CaMKII seems to activate NF-κB by its action at different levels in the signaling pathway. In neuronal cells, activation of Ca^{2+} is sufficient to activate NF-κB whereas pharmacological or inhibitory peptide-mediated inhibition of CaMKII completely blocks the activation of NF-κB in electrophoretic mobility shift assays [30]. In T cells, CaMKII inhibition eliminated the 12-myristate 13-acetate (PMA) induced phosphorylation and degradation of IκB but TNF-α induced IκB degradation was unaffected [31]. Thus, a signaling pathway-specific role of CaMKII was proposed. Furthermore, in yeast two-hybrid analysis, another multifunctional CaM kinase, CaMKIV, associated with the p65 subunit of NF-κB. CaMKIV phosphorylated p65 to activate NF-κB-dependent transcription [32]. In yet another study, CaMKII activated NF-κB in T lymphocytes indirectly by phosphorylating CARMA1, a kinase that is involved in NF-κB activation [33].

CaMKII has also been shown to promote an inflammatory response through cytokine production in macrophages [34]. In this study, overexpression of a constitutively active CaMKII enhanced the production of TLR-mediated IL-6 and TNF-α in RAW264.7 macrophage cells as well as in mouse peritoneal macrophages.

Thus, CaMKII appears to participate in NF-κB activation at multiple levels. Whether CaMKII acts on all these levels simultaneously or in cell specific manner, or different isoforms of CaM kinase have different targets, is not known.

NF-κB and cardiac hypertrophy

Activation of NF-κB has long been thought to correlate with cardiac hypertrophy. Treatment with hypertrophic agents, such as AngII, phenylephrine, or endothelin (ET-1) activate NF-κB transcription factor and increase mRNA levels of hypertrophy marker gene for atrial natriuretic factor (ANF) in cultured neonatal rat cardiomyocytes [35, 36]. Similarly, treatment of these cells with the inflammatory agent TNF-α induced ANF induction. These results suggest a crosstalk between the hypertrophic and inflammatory pathways. In vivo experiments have also shown that NF-κB is required for cardiac hypertrophy in a TAB rat model [37]. In a transgenic model, cardiac hypertrophy by overexpression of myotrophin in cardiomyocytes could be attenuated by preventing NF-κB activation by expressing a dominant negative IκB [38]. Although available data point towards a molecular correlation between NF-κB and hypertrophic gene expression, the mechanism is not clear and does not appear to be direct. For example, an NF-κB binding site has not been identified in the promoter for the ANF gene [36]. In addition, these studies determined the effects on gene expression at very late time points after experimental treatments. Therefore, secondary events are likely to be involved in connecting inflammation and hypertrophy. Elucidation of these mechanisms will be of considerable importance for the understanding of this pathology.

CaMKII as a link between cardiac hypertrophy and inflammation

Both, cardiac hypertrophy and inflammation are adaptive responses that attempt to preserve the cardiac function following an injury such as MI [39]. Cardiac hypertrophy constitutes a "convergent phenotype" of multiple pathways that lead to physiological or pathological hypertrophy [40]. Hypertrophy is a risk factor for HF and is commonly considered to be a mandatory precursor to HF. However, hypertrophy alone does not appear to cause HF. Despite its prevalence in heart failure of patients and animal models of heart disease, cardiac hypertrophy is not necessarily pathologic, and does not always lead to development of heart failure in all patients [41]. Since hypertrophy is also a response to physiological events such as exercise and pregnancy, its adverse effects under pathologic conditions must be associated with concomitant activation of deleterious pathways, such as inflammation.

Inflammation is an important part of HF. Clinical data suggest that chronic inflammation and heart failure are linked, because patients with chronic heart failure have increased circulating proinflammatory cytokines [22, 42]. These observations have also led to the idea that blocking the inflammatory activity should be beneficial. Anti-inflammatory therapies such as glucocorticoids [43] or TNF-α antagonists [44] have proven to be disappointing or ineffective in MI patients. Nevertheless, we reasoned that since CaMKII regulates both hypertrophy and inflammatory response following MI, CaMKII inhibition could reduce inflammation and improve HF. Evidence for this concept comes from the amelioration of post-MI cardiac dysfunction in AC3-I mice and in mice with genetically ablated CaMKIIδ. As CaMKII regulates inflammatory responses in non-cardiac tissues as well, it will be of considerable interest to investigate the effect of attenuating CaMKII activity in these tissues on the pathologic changes after injury or stress.

Our laboratory has elucidated mechanisms of injury- and stress-induced CaMKII activation. CaMKII is activated by displacement of its inhibitory domain by binding to the

calcified calmodulin (Ca^{2+}/CaM). Once activated, CaMKII can be autophosphorylated at a specific threonine residue (Thr287; reviewed in [45]). This phosphorylation renders the kinase independent of Ca^{2+}/CaM binding resulting in an autonomous activity. Increased β-adrenergic receptor signaling in injured or stressed heart leads to activation of CaMKII and autophosphorylation [46]. However, increased AngII production upon MI can activate CaMKII through a novel mechanism involving oxidation of dual methionine residues (M281/282) in the protein [7, 47]. This oxidation-related activity is also independent of Ca^{2+}/CaM binding of the kinase. Both, β-adrenergic and AngII signaling in post-MI hearts lead to increased autonomous CaMKII activity. In addition to the AngII signaling, stress and injury also increase the intracellular ROS that can oxidize CaMKII and augment the autonomous CaMKII activity in the stressed tissue. Thus, myocardial injury enhances CaMKII activity through increased β-adrenergic receptor activation and AngII production. CaMKII in turn plays a prominent role in MEF2-mediated hypertrophic signaling, whereby phosphorylation of inhibitory class II HDACs derepresses MEF2 transcription factor for expression of genes involved in hypertrophy. The pro-hypertrophic effects of TNF-α are believed to be mediated by ROS [48]. Inflammation is also closely related to induce ROS production. Therefore, taken together, cardiac CaMKII activity is enhanced in MI, which appears to regulate both the adaptive response arms of myocardial hypertrophy (MEF2 pathway) and inflammatory signaling (NF-κB pathway). Thus, CaMKII may turn out to be an attractive therapeutic target for containing hypertrophy and inflammation in the heart and elsewhere (Fig. 1).

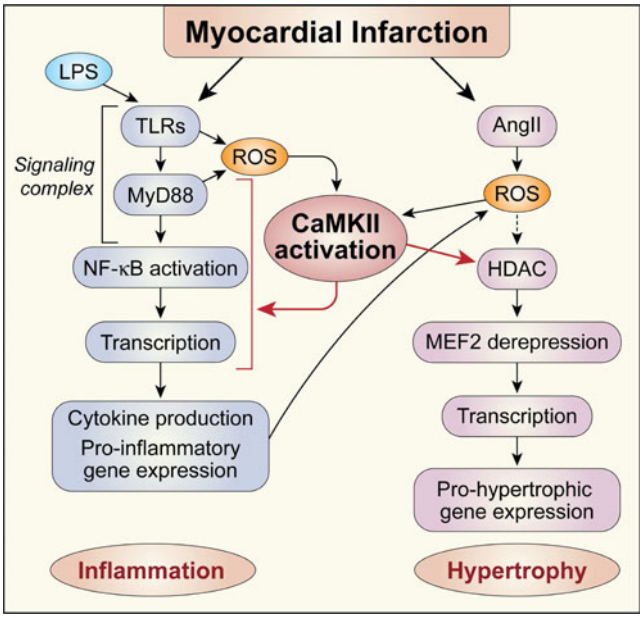

Fig. 1 CaMKII links cardiac hypertrophy and inflammation in post-MI hearts. MI induces danger sensing toll-like receptors that result in production of ROS and activation of NF-κB. NF-κB-mediated transcription of cytokines and proinflammatory molecules is the major source of inflammation at the site of injury. Inflammatory response promotes ROS production that can render CaMKII independent of Ca^{2+}-dependence, which in turn may enhance the NF-κB activity. In addition, ROS can be produced by induction of TLR and AngII receptors that also affect CaMKII. Cardiac hypertrophy is dependent upon gene expression response by MEF2 transcription factor that is phosphorylated by CaMKII for its activity. Thus, inflammatory cytokines may also induce hypertrophic gene expression. The *broken arrow* shows a possibility of ROS-mediated activation of HDAC may play a role in hypertrophic signaling

CaMKII function is dependent on Ca^{2+} homeostasis which is integral to the myocardial physiology. Not only is the activity of CaMKII regulated by Ca^{2+}, it also regulates the distribution of Ca^{2+} in various intracellular compartments. The precarious balance of intracellular Ca^{2+} is maintained by regulating Ca^{2+} entry and its removal or sequestration. CaMKII phosphorylates and regulates the activities of several Ca^{2+} handling proteins such as ryanodine receptors (RyR2), phospholamban, and L-type Ca^{2+} channels. Alterations in the function of these molecules may result in adverse cardiac outcomes, including structural and electrical changes. MI impairs myocyte function through altered CaMKII activity that regulates Ca^{2+} handling machinery in the cells [8, 49]. Thus, dysregulation of Ca^{2+} homeostasis may have profound effects on cardiac hypertrophy and inflammation.

CaMKII, inflammation, and other disease processes

Sepsis Sepsis is a special type of host inflammatory response to bacterial infection that originates from massive and widespread release of proinflammatory mediators. Bacterial endotoxins, such as LPS, are the major offending factors in sepsis that activate TLR-mediated signaling to generate inflammatory response that is amplified in a self-sustaining manner. A strong correlation between multifunctional CaM kinases and TLR-4 signaling has become apparent. CaMKII directly phosphorylates components of TLR signaling and promotes cytokine production in macrophages [34]. Complement activation is also a recognized factor in the pathogenesis of sepsis. Inhibition of the complement cascade decreases inflammation and improves mortality in animal models [50, 51]. Differentiation and survival of antigen presenting dendritic cells (DC) upon TLR-4 activation requires CaMKIV [52]. DC from CaMKIV$^{-/-}$ mice failed to survive upon LPS-mediated TLR-4 induction. However, ectopic expression of CaMKIV was able to rescue this defect. In another study, the selective inhibition of CaMKII interfered with terminal differentiation of monocyte-derived DCs by preventing up-regulation of costimulatory and MHC II molecules as well as secretion of cytokines induced by TLR-4 agonists [53]. Thus, CaM

kinases seem to play a general role in inflammatory processes.

Atrial fibrillation Changes in electrophysiology, such as hypertrophy-related electrical remodeling of the atrial myocardium, are important factors to induce atrial fibrillation (AF). AF is usually associated with cardiovascular diseases that share cardiac hypertrophy and inflammation as common features. CaMKII activity is increased in chronic AF patients [54]. Increased CaMKII activity under stress conditions is correlated with increased phosphorylation of Ca^{2+}-handling proteins that result in filling of sarcoplasmic reticulum and leaking RyR2 receptors. Excessive CamKII activation can cause AF in a mouse model of "leaky" RyR2 [55], where AF is ameliorated by inhibition of CaMKII activity.

Inflammation and fibrosis also are thought to play an important role in perturbing the electrical conduction and causing atrial fibrillation. Elevated C-reactive protein (CRP), a marker of acute phase inflammation, has been cited to associate AF with inflammation [56]. However, a role of inflammation in etiology of AF is debated. Recently, a role of myeloperoxidase (MPO) was reported to induce AF in mouse model where elimination of MPO-reduced AF [57]. Since CaMKII regulates the inflammatory response via the NF-κB pathway, it is likely to be involved in enhancing the local inflammatory response and fibrosis in atria leading to AF.

Diabetes Inflammation may play a role in the pathogenesis of diabetes. Elevated plasma levels of IL-6, CRP, and TNF-α receptor 2 have been associated with diabetes risk [58]. Type-2 diabetes is a risk factor for HF and MI [59, 60]. Inflammation may be viewed as a common mediator linking obesity to diabetes and atherosclerosis [61]. Adipose tissue in obese animals releases high amounts of TNF-α. Increased TNF-α production impairs insulin sensitivity [62, 63]. TNF-α production and its action are related to NF-κB activation that may be under regulation of CaMKII. IL-1β is a recognized inhibitor of glucose-induced insulin secretion. IL-1β signals through MyD88 and is akin to the TLR pathway. Thus, CaMKII may be involved in IL-1β-mediated diabetes.

Hypertension and inflammation Experimental left ventricular overload causes increased expression of proinflammatory cytokines in the myocardium as well as infiltration of neutrophils from the circulation. The pressure overload-related increase in inflammatory mediators correlates with cardiac hypertrophy and fibrosis [64, 65]. Whereas increased cytokine expression, proteolytic degradation of extracellular matrix, and oxidative stress are considered to be hallmark of inflammatory response, it is also believed that these stress conditions may potentially increase inflammation.

Thus, accumulating evidence suggests that CaMKII is a versatile kinase that occupies a prominent position in the normal physiology of diverse cell types, including the cardiomyocytes. In addition, this enzyme plays a crucial role in pathological processes involving cell growth, cell death, and inflammation. Consequently, identification of targets of CaMKII and elucidation of the mechanism by which CaMKII brings about these effects will be of potential therapeutic importance.

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