Published in final edited form as:

J Mol Med (Berl). 2011 June ; 89(6): 537–543. doi:10.1007/s00109-011-0727-5.

Is CaMKII a link between inflammation and hypertrophy in heart?

Madhu V. Singh* and

Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA 52242. USA

Mark E. Anderson

Departments of Internal Medicine and Molecular Physiology and Biophysics, Carver College of Medicine, University of Iowa, Iowa City, IA 52242. USA. mark-e-anderson@uiowa.edu

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 that 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 has 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.

*Corresponding author. madhu-singh@uiowa.edu, Phone: 319-335-8954, Fax: 319-353-5552 .

Disclosure Statement:

MVS and MEA are named inventors on a pending patent on Use of Calmodulin Kinase II to treat or prevent heart muscle inflammation. MEA is a named inventor on awarded and pending patents claiming to use CaMKII inhibition for therapeutic purposes.

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 CaMKII δ 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 CaMKII δ are also resistant to the consequences of transaortic banding (TAB) surgery. TAB operated mice lacking CaMKII δ 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 pro-inflammatory 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 pro-inflammatory 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 pro-inflammatory 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, 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 (*Cfb*) 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 pro-inflammatory genes and second, cardiomyocytes themselves express pro-inflammatory 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 classical complement pathways were selectively studied. In addition, we also demonstrated that CaMKII regulates a TLR-mediated NF- κ B inflammatory pathway.

CaMKII and NF- κ B 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 influences 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 pro-inflammatory transcription factor nuclear factor kappa B (NF- κ B) that induces the production of pro-inflammatory 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- κ B 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, pro-inflammatory responses in cardiomyocytes appear dependent on NF- κ B and CaMKII.

A major question is how CaMKII regulates the NF- κ B mediated gene expression in the cardiomyocytes. MI involves elaboration of several cytokines as well involvement of TLRs that can activate NF- κ B. The classical pathway of NF- κ B activation involves signaling-mediated phosphorylation and subsequent proteasomal degradation of I κ B inhibitor proteins. Degradation of I κ B facilitates the translocation of the NF- κ B dimers to the nucleus where they bind to target genes and activate transcription. CaMKII seems to activate NF- κ B by its action at different levels in the signaling pathway. In neuronal cells, activation of Ca²⁺ is sufficient to activate NF- κ B whereas pharmacological or inhibitory peptide mediated inhibition of CaMKII completely blocks the activation of NF- κ B in electrophoretic mobility shift assays (EMSA) (30). In T cells, CaMKII inhibition eliminated the 12-myristate 13-acetate (PMA) induced phosphorylation and degradation of I κ B but TNF- α induced I κ B 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- κ B. CaMKIV phosphorylated p65 to activate NF- κ B dependent transcription (32). In yet another study, CaMKII activated NF- κ B in T lymphocytes indirectly by phosphorylating CARMA1, a kinase that is involved in NF- κ B 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- κ B 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- κ B and cardiac hypertrophy

Activation of NF- κ B has long been thought to correlate with cardiac hypertrophy. Treatment with hypertrophic agents, such as angiotensin II (AngII), phenylephrine (PE), or endothelin (ET-1) activate NF- κ B 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- κ B 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- κ B activation by expressing a dominant negative I κ B (38). Although available data point towards a molecular correlation between NF- κ B and hypertrophic gene expression, the mechanism is not clear and does not appear to be direct. For example, an NF- κ B 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 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 pro-inflammatory 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 CaMKII δ . 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 ($\text{Ca}^{2+}/\text{CaM}$). Once activated, CaMKII can be autophosphorylated at a specific threonine residue (Thr287) (reviewed in (45)). This phosphorylation renders the kinase independent of $\text{Ca}^{2+}/\text{CaM}$ 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 $\text{Ca}^{2+}/\text{CaM}$ 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 $\text{TNF-}\alpha$ are believed to be mediated by ROS (48). Inflammation is also closely related to induced 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 ($\text{NF-}\kappa\text{B}$ pathway). Thus, CaMKII may turn out to be an attractive therapeutic target for containing hypertrophy and inflammation in the heart and elsewhere.

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 (PLN) and L-type Ca^{2+} channels (LTCC). 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 TLR4 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- κ B 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- κ B activation that may be under regulation of CaMKII. IL-1 β is a recognized inhibitor of glucose-induced insulin secretion. IL-1 β signals through MyD88 and is akin to the TLR pathway. Thus, CaMKII may be involved in IL-1 β mediated diabetes.

Hypertension and inflammation

Experimental left ventricular overload causes increased expression of pro-inflammatory 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 (ECM), 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.

Acknowledgments

This research was funded by Sandler Program for Asthma Research, Fondation Leducq Transatlantic Network, and by NIH (1R01 HL070250, R01 HL096652, HL-079031).

References

1. Krum H, Abraham WT. Heart failure. *Lancet*. 2009; 373:941–955. [PubMed: 19286093]
2. Grimm M, Brown JH. Beta-adrenergic receptor signaling in the heart: role of CaMKII. *J Mol Cell Cardiol*. 2010; 48:322–330. [PubMed: 19883653]
3. Maier LS, Bers DM. Role of Ca²⁺/calmodulin-dependent protein kinase (CaMK) in excitation-contraction coupling in the heart. *Cardiovasc Res*. 2007; 73:631–640. [PubMed: 17157285]
4. Singh MV, Kapoun A, Higgins L, Kutschke W, Thurman JM, Zhang R, Singh M, Yang J, Guan X, Lowe JS, et al. Ca²⁺/calmodulin-dependent kinase II triggers cell membrane injury by inducing complement factor B gene expression in the mouse heart. *J Clin Invest*. 2009; 119:986–996. [PubMed: 19273909]
5. Sossalla S, Fluschnik N, Schotola H, Ort KR, Neef S, Schulte T, Wittkopper K, Renner A, Schmitt JD, Gummert J, et al. Inhibition of Elevated Ca²⁺/Calmodulin-Dependent Protein Kinase II Improves Contractility in Human Failing Myocardium. *Circ Res*. 2010; 107:1150–1161. [PubMed: 20814023]
6. Kirchhefer U, Schmitz W, Scholz H, Neumann J. Activity of cAMP-dependent protein kinase and Ca²⁺/calmodulin-dependent protein kinase in failing and nonfailing human hearts. *Cardiovasc Res*. 1999; 42:254–261. [PubMed: 10435018]
7. Erickson JR, Joiner M.-I.A. Guan X, Kutschke W, Yang J, Oddis CV, Bartlett RK, Lowe JS, O'Donnell SE, Aykin-Burns N, et al. A Dynamic Pathway for Calcium-Independent Activation of CaMKII by Methionine Oxidation. *Cell*. 2008; 133:462. [PubMed: 18455987]
8. Hund TJ, Decker KF, Kanter E, Mohler PJ, Boyden PA, Schuessler RB, Yamada KA, Rudy Y. Role of activated CaMKII in abnormal calcium homeostasis and I(Na) remodeling after myocardial infarction: insights from mathematical modeling. *J Mol Cell Cardiol*. 2008; 45:420–428. [PubMed: 18639555]
9. McKinsey TA. Derepression of pathological cardiac genes by members of the CaM kinase superfamily. *Cardiovasc Res*. 2007; 73:667–677. [PubMed: 17217938]
10. Lisman KA, Stetson SJ, Koerner MM, Farmer JA, Torre-Amione G. The role of inflammation in the pathogenesis of heart failure. *Curr Cardiol Rep*. 2002; 4:200–205. [PubMed: 11960588]
11. McQueen MJ, Lonn E, Gerstein HC, Bosch J, Yusuf S. The HOPE (Heart Outcomes Prevention Evaluation) Study and its consequences. *Scand J Clin Lab Invest Suppl*. 2005; 240:143–156. [PubMed: 16112972]
12. Satoh M, Shimoda Y, Maesawa C, Akatsu T, Ishikawa Y, Minami Y, Hiramori K, Nakamura M. Activated toll-like receptor 4 in monocytes is associated with heart failure after acute myocardial infarction. *Int J Cardiol*. 2006; 109:226–234. [PubMed: 16051384]
13. Torre-Amione G. Immune activation in chronic heart failure. *Am J Cardiol*. 2005; 95:3C–8C. discussion 38C–40C.
14. Zhang T, Johnson EN, Gu Y, Morissette MR, Sah VP, Gigena MS, Belke DD, Dillmann WH, Rogers TB, Schulman H, et al. The Cardiac-specific Nuclear delta B Isoform of Ca²⁺/Calmodulin-dependent Protein Kinase II Induces Hypertrophy and Dilated Cardiomyopathy Associated with Increased Protein Phosphatase 2A Activity. *J. Biol. Chem*. 2002; 277:1261–1267. [PubMed: 11694533]
15. Maier LS, Zhang T, Chen L, DeSantiago J, Brown JH, Bers DM. Transgenic CaMKII δ C overexpression uniquely alters cardiac myocyte Ca²⁺ handling: reduced SR Ca²⁺ load and activated SR Ca²⁺ release. *Circ Res*. 2003; 92:904–911. [PubMed: 12676813]
16. Yang Y, Zhu W-Z, Joiner M.-I. Zhang R, Oddis CV, Hou Y, Yang J, Price EE, Gleaves L, Eren M, et al. Calmodulin kinase II inhibition protects against myocardial cell apoptosis in vivo. *Am J Physiol Heart Circ Physiol*. 2006; 291:H3065–3075. [PubMed: 16861697]
17. Zhang R, Khoo MS, Wu Y, Yang Y, Grueter CE, Ni G, Price EE Jr. Thiel W, Guatimosim S, Song LS, et al. Calmodulin kinase II inhibition protects against structural heart disease. *Nat. Med*. 2005; 11:409. [PubMed: 15793582]
18. Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, Grueter CE, Qi X, Richardson JA, Hill JA, et al. The delta isoform of CaM kinase II is required for pathological

- cardiac hypertrophy and remodeling after pressure overload. *Proc Natl Acad Sci U S A*. 2009; 106:2342–2347. [PubMed: 19179290]
19. Ling H, Zhang T, Pereira L, Means CK, Cheng H, Gu Y, Dalton ND, Peterson KL, Chen J, Bers D, et al. Requirement for Ca²⁺/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. *J Clin Invest*. 2009; 119:1230–1240. [PubMed: 19381018]
 20. Anderson ME. CaMKII and a failing strategy for growth in heart. *J Clin Invest*. 2009; 119:1082–1085. [PubMed: 19422097]
 21. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res*. 2002; 53:31–47. [PubMed: 11744011]
 22. Frantz S, Bauersachs J, Ertl G. Post-infarct remodelling: contribution of wound healing and inflammation. *Cardiovasc Res*. 2008
 23. Mann DL. Stress-activated cytokines and the heart: from adaptation to maladaptation. *Annu Rev Physiol*. 2003; 65:81–101. [PubMed: 12500970]
 24. Ren G, Dewald O, Frangogiannis NG. Inflammatory mechanisms in myocardial infarction. *Curr Drug Targets Inflamm Allergy*. 2003; 2:242–256. [PubMed: 14561159]
 25. Yasojima K, Kilgore KS, Washington RA, Lucchesi BR, McGeer PL. Complement gene expression by rabbit heart: upregulation by ischemia and reperfusion. *Circ Res*. 1998; 82:1224–1230. [PubMed: 9633921]
 26. Frantz S, Ertl G, Bauersachs J. Mechanisms of disease: Toll-like receptors in cardiovascular disease. *Nat Clin Pract Cardiovasc Med*. 2007; 4:444–454. [PubMed: 17653117]
 27. Krohn CD, Reikeras O, Mollnes TE, Aasen AO. Complement activation and release of interleukin-6 and tumour necrosis factor-alpha in drained and systemic blood after major orthopaedic surgery. *Eur J Surg*. 1998; 164:103–108. [PubMed: 9537716]
 28. David S, Biancone L, Caserta C, Bussolati B, Cambi V, Camussi G. Alternative pathway complement activation induces proinflammatory activity in human proximal tubular epithelial cells. *Nephrol Dial Transplant*. 1997; 12:51–56. [PubMed: 9027773]
 29. Sjöberg AP, Trouw LA, Blom AM. Complement activation and inhibition: a delicate balance. *Trends in Immunology*. 2009; 30:83–90. [PubMed: 19144569]
 30. Meffert MK, Chang JM, Wiltgen BJ, Fanselow MS, Baltimore D. NF-kappa B functions in synaptic signaling and behavior. *Nat Neurosci*. 2003; 6:1072–1078. [PubMed: 12947408]
 31. Hughes K, Edin S, Antonsson A, Grundstrom T. Calmodulin-dependent kinase II mediates T cell receptor/CD3- and phorbol ester-induced activation of IkappaB kinase. *J Biol Chem*. 2001; 276:36008–36013. [PubMed: 11470799]
 32. Jang MK, Goo YH, Sohn YC, Kim YS, Lee SK, Kang H, Cheong J, Lee JW. Ca²⁺/calmodulin-dependent protein kinase IV stimulates nuclear factor-kappa B transactivation via phosphorylation of the p65 subunit. *J Biol Chem*. 2001; 276:20005–20010. [PubMed: 11274168]
 33. Ishiguro K, Green T, Rapley J, Wachtel H, Giallourakis C, Landry A, Cao Z, Lu N, Takafumi A, Goto H, et al. Ca²⁺/calmodulin-dependent protein kinase II is a modulator of CARMA1-mediated NF-kappaB activation. *Mol Cell Biol*. 2006; 26:5497–5508. [PubMed: 16809782]
 34. Liu X, Yao M, Li N, Wang C, Zheng Y, Cao X. CaMKII promotes TLR-triggered proinflammatory cytokine and type I interferon production by directly binding and activating TAK1 and IRF3 in macrophages. *Blood*. 2008; 112:4961–4970. [PubMed: 18818394]
 35. Smeets PJH, Teunissen BEJ, Planavila A, de Vogel-van den Bosch H, Willemsen PHM, van der Vusse GJ, van Bilsen M. Inflammatory Pathways Are Activated during Cardiomyocyte Hypertrophy and Attenuated by Peroxisome Proliferator-activated Receptors PPAR{alpha} and PPAR{delta}. *J. Biol. Chem*. 2008; 283:29109–29118. [PubMed: 18701451]
 36. Purcell NH, Tang G, Yu C, Mercurio F, DiDonato JA, Lin A. Activation of NF-kappa B is required for hypertrophic growth of primary rat neonatal ventricular cardiomyocytes. *Proc Natl Acad Sci U S A*. 2001; 98:6668–6673. [PubMed: 11381115]
 37. Li Y, Ha T, Gao X, Kelley J, Williams DL, Browder IW, Kao RL, Li C. NF-kappaB activation is required for the development of cardiac hypertrophy in vivo. *Am J Physiol Heart Circ Physiol*. 2004; 287:H1712–1720. [PubMed: 15142841]

38. Young D, Popovic ZB, Jones WK, Gupta S. Blockade of NFkappaB using IkappaB alpha dominant-negative mice ameliorates cardiac hypertrophy in myotrophin-overexpressed transgenic mice. *J Mol Biol.* 2008; 381:559–568. [PubMed: 18620706]
39. Medzhitov R. Origin and physiological roles of inflammation. *Nature.* 2008; 454:428–435. [PubMed: 18650913]
40. Dorn GW 2nd, Force T. Protein kinase cascades in the regulation of cardiac hypertrophy. *J Clin Invest.* 2005; 115:527–537. [PubMed: 15765134]
41. Anderson ME. CaMKII and a failing strategy for growth in heart. *The Journal of Clinical Investigation.* 2009; 119:1082. [PubMed: 19422097]
42. Heymans S, Hirsch E, Anker SD, Aukrust P, Balligand JL, Cohen-Tervaert JW, Drexler H, Filippatos G, Felix SB, Gullestad L, et al. Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2009; 11:119–129. [PubMed: 19168509]
43. Madias JE, Hood WB Jr. Effects of methylprednisolone on the ischemic damage in patients with acute myocardial infarction. *Circulation.* 1982; 65:1106–1113. [PubMed: 7042110]
44. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation.* 2004; 109:1594–1602. [PubMed: 15023878]
45. Couchonnal LF, Anderson ME. The role of calmodulin kinase II in myocardial physiology and disease. *Physiology (Bethesda).* 2008; 23:151–159. [PubMed: 18556468]
46. Yoo B, Lemaire A, Mangmool S, Wolf MJ, Curcio A, Mao L, Rockman HA. Beta1-adrenergic receptors stimulate cardiac contractility and CaMKII activation in vivo and enhance cardiac dysfunction following myocardial infarction. *Am J Physiol Heart Circ Physiol.* 2009; 297:H1377–1386. [PubMed: 19633206]
47. Christensen MD, Dun W, Boyden PA, Anderson ME, Mohler PJ, Hund TJ. Oxidized calmodulin kinase II regulates conduction following myocardial infarction: a computational analysis. *PLoS Comput Biol.* 2009; 5:e1000583. [PubMed: 19997488]
48. Higuchi Y, Otsu K, Nishida K, Hirotsu S, Nakayama H, Yamaguchi O, Matsumura Y, Ueno H, Tada M, Hori M. Involvement of reactive oxygen species-mediated NF-kappa B activation in TNF-alpha-induced cardiomyocyte hypertrophy. *J Mol Cell Cardiol.* 2002; 34:233–240. [PubMed: 11851362]
49. Zhang XQ, Musch TI, Zelis R, Cheung JY. Effects of impaired Ca2+ homeostasis on contraction in postinfarction myocytes. *J Appl Physiol.* 1999; 86:943–950. [PubMed: 10066709]
50. Huber-Lang MS, Riedeman NC, Sarma JV, Younkin EM, McGuire SR, Laudes IJ, Lu KT, Guo RF, Neff TA, Padgaonkar VA, et al. Protection of innate immunity by C5aR antagonist in septic mice. *FASEB J.* 2002; 16:1567–1574. [PubMed: 12374779]
51. Riedemann NC, Guo RF, Neff TA, Laudes IJ, Keller KA, Sarma VJ, Markiewski MM, Mastellos D, Strey CW, Pierson CL, et al. Increased C5a receptor expression in sepsis. *J Clin Invest.* 2002; 110:101–108. [PubMed: 12093893]
52. Illario M, Giardino-Torchia ML, Sankar U, Ribar TJ, Galgani M, Vitiello L, Masci AM, Bertani FR, Ciaglia E, Astone D, et al. Calmodulin-dependent kinase IV links Toll-like receptor 4 signaling with survival pathway of activated dendritic cells. *Blood.* 2008; 111:723–731. [PubMed: 17909078]
53. Herrmann TL, Morita CT, Lee K, Kusner DJ. Calmodulin kinase II regulates the maturation and antigen presentation of human dendritic cells. *J Leukoc Biol.* 2005; 78:1397–1407. [PubMed: 16204647]
54. Tessier S, Karczewski P, Krause EG, Pansard Y, Acar C, Lang-Lazdunski M, Mercadier JJ, Hatem SN. Regulation of the transient outward K(+) current by Ca(2+)/calmodulin-dependent protein kinases II in human atrial myocytes. *Circ Res.* 1999; 85:810–819. [PubMed: 10532949]
55. Chelu MG, Sarma S, Sood S, Wang S, van Oort RJ, Skapura DG, Li N, Santonastasi M, Muller FU, Schmitz W, et al. Calmodulin kinase II-mediated sarcoplasmic reticulum Ca2+ leak promotes atrial fibrillation in mice. *J Clin Invest.* 2009; 119:1940–1951. [PubMed: 19603549]

56. Liu T, Li G, Li L, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *J Am Coll Cardiol*. 2007; 49:1642–1648. [PubMed: 17433956]
57. Rudolph V, Andrie RP, Rudolph TK, Friedrichs K, Klinke A, Hirsch-Hoffmann B, Schwoerer AP, Lau D, Fu X, Klingel K, et al. Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. *Nat Med*. 2010; 16:470–474. [PubMed: 20305660]
58. Liu S, Tinker L, Song Y, Rifai N, Bonds DE, Cook NR, Heiss G, Howard BV, Hotamisligil GS, Hu FB, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. *Arch Intern Med*. 2007; 167:1676–1685. [PubMed: 17698692]
59. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, Mandelzweig L, Adler Y, Sherer Y, Behar S. Functional class in patients with heart failure is associated with the development of diabetes. *Am J Med*. 2003; 114:271–275. [PubMed: 12681453]
60. Mozaffarian D, Marfisi R, Levantesi G, Silletta MG, Tavazzi L, Tognoni G, Valagussa F, Marchioli R. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. *Lancet*. 2007; 370:667–675. [PubMed: 17720018]
61. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006; 116:1793–1801. [PubMed: 16823477]
62. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science*. 1993; 259:87–91. [PubMed: 7678183]
63. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF- α function. *Nature*. 1997; 389:610–614. [PubMed: 9335502]
64. Smeets PJ, Teunissen BE, Willemsen PH, van Nieuwenhoven FA, Brouns AE, Janssen BJ, Cleutjens JP, Staels B, van der Vusse GJ, van Bilsen M. Cardiac hypertrophy is enhanced in PPAR α -/- mice in response to chronic pressure overload. *Cardiovasc Res*. 2008; 78:79–89. [PubMed: 18187461]
65. Kai H, Mori T, Tokuda K, Takayama N, Tahara N, Takemiya K, Kudo H, Sugi Y, Fukui D, Yasukawa H, et al. Pressure overload-induced transient oxidative stress mediates perivascular inflammation and cardiac fibrosis through angiotensin II. *Hypertens Res*. 2006; 29:711–718. [PubMed: 17249527]

Figure 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- κ B. NF- κ B mediated transcription of cytokines and pro-inflammatory molecules is the major source of inflammation at the site of injury. Inflammatory response promotes ROS production that can render CaMKII independent of Ca²⁺-dependence, which in turn may enhance the NF- κ B 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.