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Calcineurin signaling in the heart: The importance of time and place

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ABSTRACT

The calcium-activated protein phosphatase, calcineurin, lies at the intersection of protein phosphorylation and calcium signaling cascades, where it provides an essential nodal point for coordination between these two fundamental modes of intracellular communication. In excitatory cells, such as neurons and cardiomyocytes, that experience rapid and frequent changes in cytoplasmic calcium, calcineurin protein levels are exceptionally high, suggesting that these cells require high levels of calcineurin activity. Yet, it is widely recognized that excessive activation of calcineurin in the heart contributes to pathological hypertrophic remodeling and the progression to failure. How does a calcium activated enzyme function in the calcium-rich environment of the continuously contracting heart without pathological consequences? This review will discuss the wide range of calcineurin substrates relevant to cardiovascular health and the mechanisms calcineurin uses to find and act on appropriate substrates in the appropriate location while potentially avoiding others. Fundamental differences in calcineurin signaling in neonatal verses adult cardiomyocytes will be addressed as well as the importance of maintaining heterogeneity in calcineurin activity across the myocardium. Finally, we will discuss how circadian oscillations in calcineurin activity may facilitate integration with other essential but conflicting processes, allowing a healthy heart to reap the benefits of calcineurin signaling while avoiding the detrimental consequences of sustained calcineurin activity that can culminate in heart failure.

1. Introduction

It has been forty years since Claude Klee began her seminal work deciphering the structure and regulation of the calcium-activated protein phosphatase calcineurin [1–3] and almost twenty years since Jeff Molkentin and Eric Olson demonstrated that sustained activation of calcineurin in cardiomyocytes is sufficient to promote hypertrophic remodeling, decompensated failure, and arrhythmogenic death [4]. Numerous studies have subsequently verified that inhibition of calcineurin is an effective method for blunting hypertrophic growth and protecting the heart from both initial oxidative damage and subsequent pathological remodeling in response to a variety of insults [5–10]. Hundreds, if not thousands of papers have been published citing a role for calcineurin in cardiovascular disease, yet there is much we still do not understand regarding control and specificity of this enzyme that must function in the calcium-rich environment of a continually contracting heart without initiating a pathological signaling cascade. Here, we will review regulation of calcineurin and mechanisms it uses to target specific substrates within the myocardium. Key features unique to calcineurin signaling in the heart will be addressed including: fundamental differences in calcineurin signaling in neonatal verses adult

Abbreviations: AID, autoinhibitory domain of calcineurin; AKAP, A kinase anchor protein; AngII, angiotensin II; APD, action potential duration; β_1-AR, β_1-adrenergic receptors; CABIN-1, calcineurin binding protein 1; Carabin, TBC1 domain family member 10C; CHP, calcineurin homologous proteins; CIB1, Ca^{2+}-and integrin-binding protein-1; CN, calcineurin holoenzyme; CnA, catalytic subunit of calcineurin; CnB, regulatory subunit of calcineurin; CnA*, constitutively active calcineurin; CRTC, CREB-regulated transcriptional coactivators; CS1, calsarcin 1; CsA, cyclosporin A; DRP1, dynamin related protein 1; ENDO, endocardium; EPI, epicardium; FOXO1, forkhead box protein 01; FRET, fluorescence resonance energy transfer; I-1, protein phosphatase inhibitor 1; $I_{Ca,L}$, LTCC current; I_p, Na/K ATPase pump current; I_{to}, fast transient outward K^+ current; LMCD1, LIM and cysteine-rich domains 1; LTCC, voltage-activated L-type calcium channel; MLP, muscle LIM protein; MuRF1, muscle-specific RING finger 1; NCX1, sodium calcium exchanger 1; NFAT, nuclear factor of activated T cells; NHE1, Na^+/H^+ exchanger 1; OMM, outer membrane of mitochondria; PC-1, polycystin-1 PC-1; PICOT, protein kinase C-interacting cousin of thioredoxin; PKA, protein kinase A; pNPP, p-nitrophenyl phosphate; PP1, protein phosphatase 1; PLN, phospholamban; RCAN, regulator of calcineurin; Rcan1.4, exon four isoform of RCAN1; RyR2, ryanodine receptor 2; SR, sarcoplasmic reticulum; TFEB, transcription factor EB; TRPC, transient receptor potential canonical channel.

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cardiomyocytes and the importance of maintaining heterogeneity in calcineurin activity across the myocardium, particularly as it relates to ion channel activity and arrhythmogenesis. Finally, we will discuss how a circadian pattern of calcineurin activity may allow a healthy heart to reap the benefits of calcineurin signaling while avoiding the detrimental consequences of sustained calcineurin activity that can culminate in heart failure.

2. Calcineurin structure and regulation

Calcineurin is a heterodimer composed of a 60-kDa catalytic subunit (CnA) and a 19-kDa regulatory subunit (CnB). CnA contains an N-terminal catalytic domain, a CnB binding domain, a calmodulin binding domain, and a C-terminal autoinhibitory domain (AID). CnB has four EF-hand Ca^{2+}-binding sites: two structural sites that bind Ca^{2+} with high

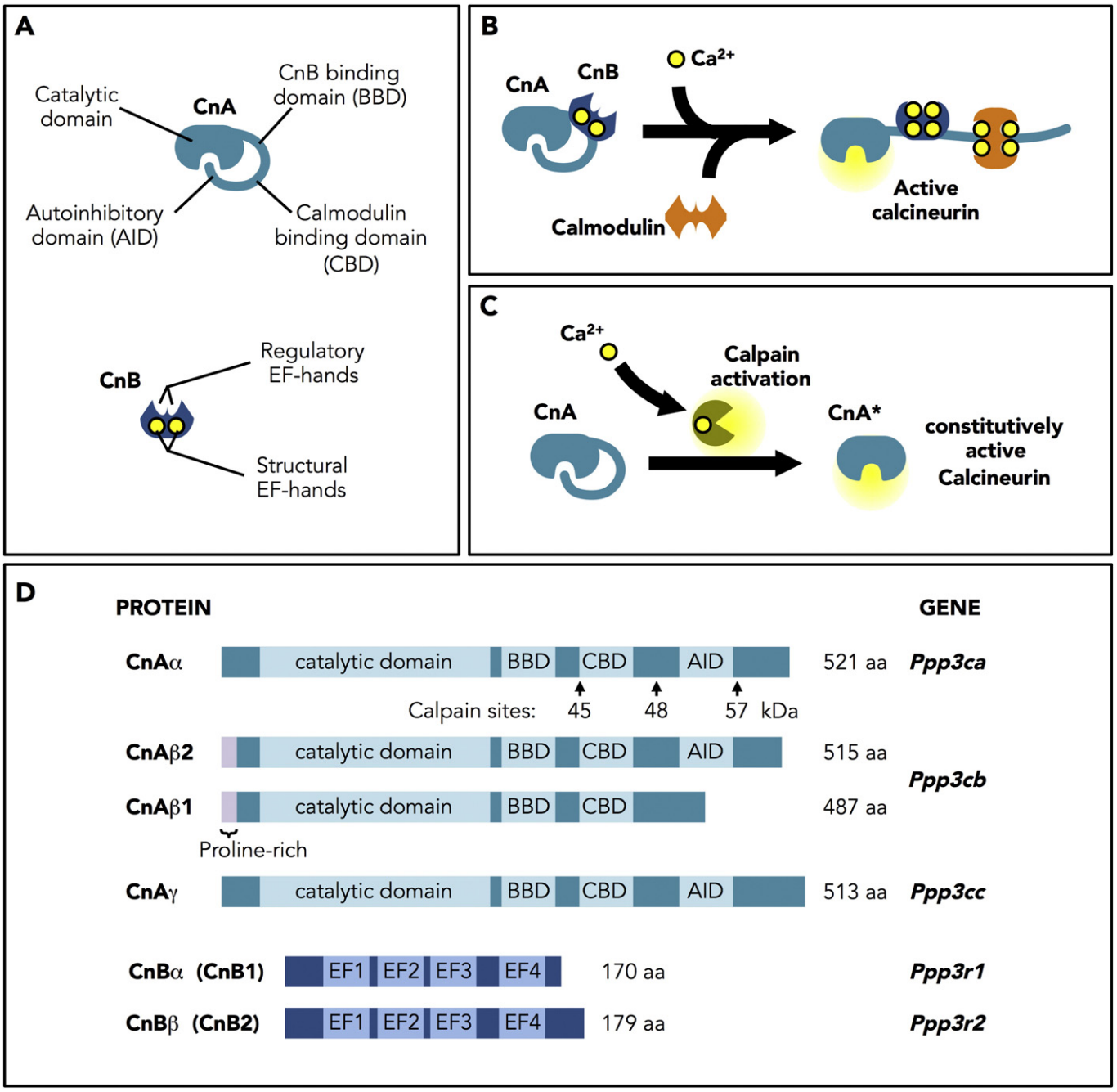

Fig. 1. Calcineurin structure, regulation and activation. A. Structure of the catalytic (CnA) and regulatory (CnB) subunits of calcineurin. CnA contains an N-terminal catalytic domain, a CnB binding domain, a calmodulin binding domain, and a C-terminal autoinhibitory domain (AID). CnB has four EF-hand Ca^{2+}-binding sites: two structural sites that bind Ca^{2+} with high affinity in the ηM range, that are always occupied, and two regulatory sites that bind in the μM range. B. Model of calcineurin activation. Binding of Ca^{2+} to the regulatory sites initiates a series of conformational changes that allow binding of a calmodulin/Ca^{2+} complex and a change in the orientation of the AID to expose the active site. C. Constitutively active calcineurin. Truncation of CnA to remove the AID yields a constitutively active phosphatase (CnA*) that no longer responds to Ca^{2+}/calmodulin. D. Calcineurin proteins and genes. In mammals, three genes encode CnA (α, β, and γ). Only CnAα (PPP3CA) and CnAβ (PPP3CB) are expressed in the heart. Of the two genes encoding the CnB regulatory subunit, only CnBα (PPP3R1) is expressed in the heart.