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# Calcineurin anchoring and cell signaling

Kimberly L. Dodge and John D. Scott*

*Howard Hughes Medical Institute, Vollum Institute, Oregon Health and Sciences University, Portland, OR, USA*

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**Abstract**

The targeting of phosphatase PP2B or calcineurin toward certain substrates synchronizes a variety of physiological processes. This review emphasizes how the targeting of calcineurin through interaction with various anchoring proteins facilitates phosphatase regulation of T-cell activation, neuronal excitability and cardiac hypertrophy.


Many cellular events are dynamically regulated by protein phosphorylation. This central regulatory process is controlled by two key enzymes: protein kinases that catalyze the transfer of the gamma phosphate of ATP to the substrate and protein phosphatases that induce phosphate hydrolysis. It is important to consider how dephosphorylation is controlled as the human genome encodes of the order of 150 protein phosphatases [1,2]. Not surprisingly, the cell has evolved numerous mechanisms to control the activation status, specificity, and location of these important enzymes [3]. This review will focus on how the targeting of phosphatase PP2B or calcineurin toward selected substrates coordinates and synchronizes certain physiological processes.

Calcineurin (later called PP2B) was first identified as a major calmodulin-binding protein and later identified as a serine/threonine phosphatase [4]. The calcineurin heterodimer consists of calcineurin A and B subunits. The calcineurin A subunit contains three domains consisting of the catalytic domain, calmodulin-binding domain, and an autoinhibitory domain. Calcineurin B, the regulatory subunit, is a member of the "EF hand" family of calcium-binding proteins [4]. Activation of the enzyme occurs upon calcium/calmodulin binding, resulting in a confirmation change and the release of the autoinhibitory domain [5,6]. These aspects will be covered by other reviews in this series. Although numerous physiological processes are regulated by calcineurin-mediated dephosphorylation events, the enzyme is recognized as a modulator of T-cell activation, neuronal excitability, and cardiac hypertrophy [7–12]. The following sections emphasize how the targeting of calcineurin through interaction with various anchoring proteins facilitates the regulation of these physiological processes.

## NFAT binding to calcineurin: regulation of gene transcription

A clearly defined physiological role for calcineurin is to serve as the target for the immunosuppressive drug FK506 [8]. This compound forms a binary complex with immunophilins that specifically and potently inhibit the phosphatase [13,14]. A consequence of this inhibition in T lymphocytes is the suppression of cytokine synthesis and the immune response (Fig. 1A and [15]). The NFAT family of transcription factors are key regulators of cytokine gene transcription during the immune response and the transcriptional activity of NFAT is highly dependent on calcineurin [16]. Nuclear import, DNA-binding affinity, and gene transcription are all regulated by calcineurin activity [7]. NFAT itself is a substrate for calcineurin—a direct association between NFAT1 and calcineurin was shown using a calmodulin–Sepharose pulldown assay [7]. The phosphatase-binding domain of NFAT1 (termed the SPRIEIT motif) consists of amino acids 110–118 (Fig. 1B and [17]). Peptide-mediated disruption of this protein–protein interaction results in a

* Corresponding author. Fax: 1-503-494-0519.
*E-mail address:* scott@ohsu.edu (J.D. Scott).

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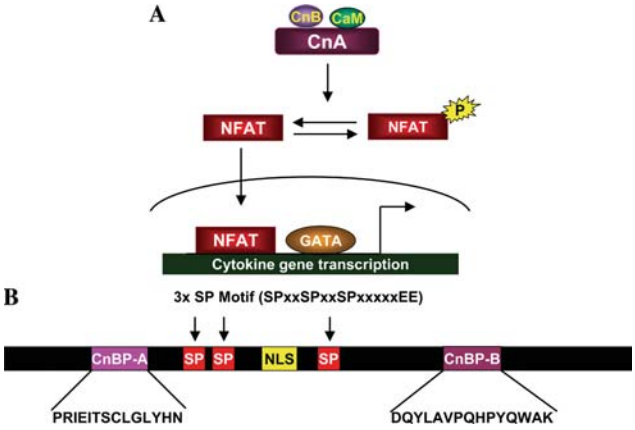


Fig. 1. (A) Schematic diagram demonstrating the activation of the transcription factor NFAT. Activated calcineurin binds to and dephosphorylates NFAT. Dephosphorylation of NFAT promotes the translocation of the transcription factor into the nucleus, where it can bind DNA and stimulate gene transcription. (B) Schematic representation of the NFAT-binding domains. Calcineurin-binding domains (A and B) are highlighted as well as the SP-motif (serine–proline repeat). Expansion brackets show the amino acid sequences of the calcineurin-binding domain, in single letter code.

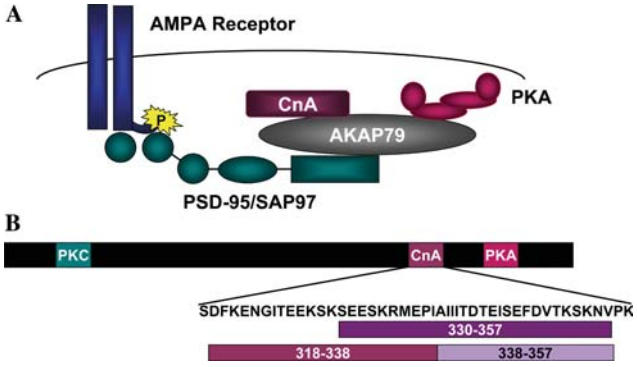


Fig. 2. (A) Schematic description of AKAP79-mediated regulation of AMPA receptor phosphorylation. AKAP79 is linked to the GluR1 subunit of the AMPA receptor via interaction with SAP97. This association positions PKA and calcineurin in close proximity to the receptor, allowing for spatiotemporal control of receptor phosphorylation. (B) Schematic description of AKAP79-binding domains. AKAP79-binding domains for PKC, calcineurin, and PKA are depicted. Expansion brackets show the amino acid sequences of the calcineurin-binding domain, in single letter code.

lack of translocation of the transcription factor to the nucleus during ionomycin-stimulation. Interestingly, peptides mimicking the SPRIEIT motif selectively disrupt the calcineurin/NFAT association and not other calcineurin substrates such as the PKA regulatory subunit or the neuronal protein Tau [17]. A second site of interaction between calcineurin and NFAT was found using truncated fragments of NFAT attached to glutathione beads [18]. Thus, calcineurin/NFAT interaction involves multiple sites of interaction and may be subjected to regulation by a number of factors.

## Calcineurin association with AKAP79: control of AMPA receptor phosphorylation

Bi-directional control of AMPA receptor phosphorylation at excitatory synapses is a delicate balance of kinase and phosphatase activity [19]. Protein kinase A (PKA) phosphorylates Serine 845 on the cytoplasmic tail of the GluR1 subunit of the AMPA receptor. Dephosphorylation by several phosphatases including calcineurin has been implicated in the downregulation of AMPA receptors and long-term depression (LTD)—a model for information storage [20,21]. Recent studies have suggested that a multifunctional anchoring protein called AKAP79 orchestrates the phosphorylation state of the GluR1 subunit [22–24]. In fact, AKAP79 binds to the PKA holoenzyme, thereby optimally positioning PKA for preferential phosphorylation of Serine 845 on GluR1 when sufficient levels of the second messenger cAMP are generated to activate the enzyme (Fig. 2A). AKAP79 also binds calcineurin and PKC, thereby forming a signaling complex of three second messenger regulated signaling enzymes [25]. This notion has been supported by biochemical and electrophysiological studies demonstrating that peptide-mediated disruption of PKA binding hampers the phosphorylation of the channel and favors the down-regulation of channel activity by calcineurin (reviewed in [26]).

Calcineurin binding to AKAP79 was identified by the yeast two-hybrid system in 1995 [27] although earlier reports had detected the co-purification of the phosphatase with PKA [28,29]. In a screen to determine AKAP79-binding partners, a clone for the calcineurin A subunit was found to specifically interact with the anchoring protein [27]. This interaction was confirmed when AKAP79 was found to co-precipitate with calcineurin purified from bovine brain. Interestingly, recombinant AKAP79 inhibited calcineurin activity in a non-competitive manner with an inhibition constant of $4.2 \pm 18$ mM. Subsequent mapping experiments demonstrated that calcineurin bound the C-terminal two-thirds of AKAP79 and fluorescence resonance energy transfer has been used to demonstrate the formation of a ternary complex between PKA, AKAP79, and calcineurin inside COS7 cells [30,31]. Recently, we have used immunocytochemistry and co-immunoprecipitation experiments to narrow the binding site down to a region of 30 amino acids between residues 315 and 360 of the anchoring protein [32]. Peptides spanning this region inhibit phosphatase activity with micromolar inhibition constants of $3.2 \pm 18$ to $1.5 \pm 0.2$ mM and block AMPA channel rundown in cell lines and neurons (Fig. 2B). Furthermore, introduction of the AKAP79–calcineurin binding peptide to the patch pipet resulted in a loss of the AKAP79 dependent run down, consistent with the

disruption of calcineurin from AKAP79 [32]. While these data demonstrate the importance of calcineurin binding to AKAP79 as a means to precisely regulate channel function we currently do not know how the channel is activated when bound to AKAP79 or if the phosphatase has to be transiently released from anchored signaling complex at synapses.

## MCIP1 binding to calcineurin: implications for cardiac function

Cardiac hypertrophy is defined as the adaptive enlargement of the myocardium due to the growth of individual cardiac myocytes and the re-expression of fetal genes. Several key experiments have implicated the involvement of calcineurin in cardiac hypertrophy. Treatment of cardiomyocytes with the calcineurin inhibitory agents cyclosporin A or FK506 blocked agonist-induced hypertrophy [33]. Introduction of activated calcineurin via adenoviral gene transfer also induced hypertrophy in neonatal cardiac myocytes [11,12]. Finally, transgenic mice over-expressing activated calcineurin displayed profound hypertrophic hearts that rapidly progressed into heart failure [33]. These data suggest an important role for calcineurin in cardiac physiology and a role for phosphatase signaling in certain pathological states.

Targeting of calcineurin in heart cells is mediated by another set of phosphatase-binding proteins. Modulatory calcineurin-interacting proteins (MCIPs) are a family of three small, structurally related proteins expressed in cardiac and skeletal muscle as well as the brain and are potent inhibitors of calcineurin both in vitro and in vivo [34,35]. These proteins bind directly to the calcineurin A subunit and this binding neither requires nor prevents the binding of the B subunit or calmodulin (Fig. 3A and [34]). A strikingly conserved sequence in these proteins, termed the SP repeat, consists of a stretch of 31 amino acids that are similar to the serine–proline region of NFAT [35,36]. A peptide mimicking this sequence was shown to act as a competitive inhibitor of phosphatase activity, demonstrating a $K_i$ of 91.5 μM (Fig. 3B and [36]). However, other regions of the protein are likely to contribute to calcineurin inhibition. A detailed investigation into the regions of both N- and C-termini to the SP repeat demonstrated multiple sites of contact corresponding to inhibition of calcineurin activity, suggesting that multiple regions of the protein contribute to binding and inhibition [36]. The functional consequence of MCIP in the regulation of calcineurin in the heart was demonstrated in transgenic mice [34]. Expression of the transgene resulted in a 10% decrease in unstressed hearts compared to wild-type littermates. Importantly, cardiac hypertrophy and the re-induction of fetal gene expression were inhibited in these mice under stimulated conditions.

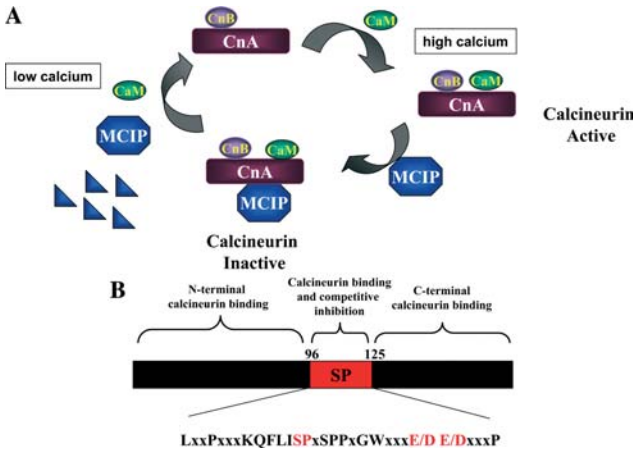


Fig. 3. (A) Schematic diagram depicting MCIP regulation of calcineurin. Calcium influx stimulates the interaction of calmodulin (CaM) with the phosphatase heterodimer. MCIP binds to the heterodimer, resulting in the inhibition of phosphatase activity. Decreases in the calcium concentration allow for the dissociation and subsequent degradation of MCIP, and calcineurin becomes active again. (B) Schematic depiction of MCIP1-binding domains for calcineurin. The SP-motif is highlighted. Expansion brackets show the amino acid sequences of the calcineurin-binding domain, in single letter code.

Two additional studies have used other calcineurin inhibitors to genetically demonstrate the importance of calcineurin-binding proteins in the regulation of phosphatase activity in the heart. Using adenoviral-mediated gene transfer, Taigen et al. [11] introduced two distinct, non-competitive peptide inhibitors of calcineurin (the calcineurin-binding domains of both Cain and AKAP79 into cardiomyocytes). The expression of the transgenes attenuated hypertrophy and fetal gene expression under hormonal-stimulation. De Windt et al. [12] provided additional evidence for the importance of calcineurin-binding proteins. In this study, transgenic mice were generated to express the same non-competitive peptides used in the previous example. Again, the expression of the transgenes resulted in reduced calcineurin activity in the heart as well as a reduced response to the hypertrophic agent catecholamine. These studies demonstrate the physiological importance of regulating calcineurin activity in the heart and furthermore show that disruption of phosphatase binding and regulation results in impaired cardiac responses.

## Conclusion and future directions

Calcineurin is a broad specificity calcium/calmodulin dependent phosphatase that coordinates a variety of cellular processes. Although the cellular role of this enzyme was primarily deduced through the use of specific inhibitors such as FK506 and cyclosporin A, these drugs

do not evaluate the contribution of compartmentalization as a determinant for substrate specificity. Anchoring proteins such as NFAT, AKAP79, and MCIP provide a spatial component to calcineurin signaling as they direct the enzyme to particular substrates [3]. Although not formally proven, it is likely that each anchoring protein may use a similar mechanism to target the phosphatase as they all contain a "PIxIxIT" motif (proline–isoleucine–Xaa–isoleucine–Xaa–isoleucine–threonine). This motif is reminiscent of the K/R–V–X–F sequence that is a defining characteristic of type 1 phosphatase targeting subunits and binds to a cleft that is distal to the active site of the enzyme [37]. Structural studies will be necessary to establish whether the "PIxPIxIxIT" motif is a primary determinant of calcineurin anchoring and if other regions of these anchoring proteins participate in the compartmentalization of the phosphatase.

An equally important function for calcineurin anchoring proteins may be to segregate signaling events by generating highly localized pools of the enzyme. Localized diffusion of the enzyme within this microenvironment may ensure that only a few phosphoproteins are dephosphorylated. Alternatively, the enzyme may remain tightly anchored with one phosphoprotein in a stoichiometry of one to one. This later scenario may well be the situation at synapses where the local concentration of calcineurin is sufficiently high to permit targeting of individual phosphatase holoenzymes with AMPA receptors, NMDA receptors, or M currents. Sophisticated cell imaging techniques and proteomic approaches may be useful in resolving the complexity of calcineurin–substrate interactions and the dynamics of phosphatase activation upon the elevation of synaptic calcium levels.

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