Mini-Review

Regulation of Calcium/Calmodulin-Dependent Protein Kinase II Activation by Intramolecular and Intermolecular Interactions

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As its name implies, calcium/calmodulin-dependent protein kinase II (CaMKII) is calcium dependent. In its basal state, the activity of CaMKII is extremely low. Regulation of intracellular calcium levels allows the neuron to link activity with phosphorylation by CaMKII. This review will briefly summarize our current understanding of the intramolecular mechanisms of activity regulation and their modulation by Ca^{2+}/CaM and will then focus on the growing number of other modes of intermolecular regulation of CaMKII activity by substrate and scaffolding molecules.

Regulation of CaMKII by its autoinhibitory domain

All members of the CaMKII family (α, β, γ, and δ isozymes) share a similar domain organization (Fig. 1). In this review, amino acid (aa) positions will be given with reference to the rat αCaMKII isozyme unless otherwise stated. The catalytic domain is located at the N terminal (aa 1–272) and is followed by a regulatory region (aa 273–314). The most variable part of the kinase lies distal to the regulatory domain. In this region, there are both isozyme-specific sequences and a high degree of alternative splicing within isozymes with several hotspots for variation (for review, see Hudmon and Schulman, 2002). The C terminus of the kinase also encodes a domain responsible for assembly of the 8–14 subunit holoenzyme (aa 315–478) (Kolb et al., 1998; Shen and Meyer, 1998).

A large number of protein kinases are kept inactive by interactions with inhibitory domains that are within the same polypeptide [e.g., the pseudosubstrate domain of protein kinase C (Quest, 1996)] or within a regulatory subunit [e.g., the R subunits of protein kinase A (Taylor et al., 2004)]. The regulatory domain of CaMKII is just distal to its catalytic domain and is bipartite: N-terminal sequences (aa 282–300) are believed to interact with the catalytic domain to block both ATP (Colbran et al., 1989; Smith et al., 1992) and substrate (Mukherji and Soderling, 1995) sites, whereas the C-terminal (aa 293–310) end binds Ca^{2+}/CaM (Payne et al., 1988).

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The overlap of these subdomains is no accident. Binding of Ca^{2+}/CaM is the primary signal for release of autoinhibition. Current models of activation posit that the binding of Ca^{2+}/CaM serves to disrupt the interactions of specific residues within the autoinhibitory domain with the catalytic domain (Smith et al., 1992). Because there is no crystal structure for the catalytic and regulatory parts of CaMKII, the interaction face of these two domains has been inferred using the effects of charge-reversal mutagenesis on activity and molecular modeling (Yang and Schulman, 1999). This study confirmed the role of Arg^{297} at the P-3 position of the pseudosubstrate ligand (Mukherji and Soderling, 1995) and identified residues in the catalytic domain that may have direct interactions with the regulatory region. Some of these contacts are also important for regulation of kinase activity by other protein binding partners, as will be discussed below.

Regulation of CaMKII by autophosphorylation

In addition to relieving autoinhibition, binding of Ca^{2+}/CaM also initiates autophosphorylation of CaMKII, providing additional layers of regulation (Fig. 2). The first autophosphorylation site to be identified in the rat αCaMKII was Thr^{286}. Phosphorylation of this site occurs as an inter-subunit reaction in the holoenzyme and requires Ca^{2+}/CaM binding to both the "kinase" and "substrate" subunits (Hanson et al., 1994). This site is associated with the development by the enzyme of Ca^{2+}/CaM-independent activity (Miller et al., 1988; Schworer et al., 1988; Thiel et al., 1988; Lou and Schulman, 1989). Ca^{2+}/CaM -independent activity never reaches the level that the fully Ca^{2+}/CaM-stimulated enzyme can attain, but it can be substantial and is postulated to be important for synaptic and cellular plasticity [see the mini-review by Elgersma et al. (2004)].

Phosphorylation of Thr^{286} alters the interaction of the regulatory domain with the catalytic core, but it also alters the interaction of the kinase with Ca^{2+}/CaM, causing its off-rate to fall by over three orders of magnitude (Meyer et al., 1992). This results in a phenomenon that has been termed "CaM trapping." Peptide models of trapping have suggested that autophosphorylation induces a local conformational change that allows formation of additional, stabilizing interactions between CaM and Phe^{293} and Asn^{294} of CaMKII (Putkey and Waxham, 1996; Waxham et al., 1998). Studies using CaMKII holoenzyme confirmed this model and showed that these residues interact with specific side chains in the C-terminal domain of CaM (Singla et al., 2001). This ability

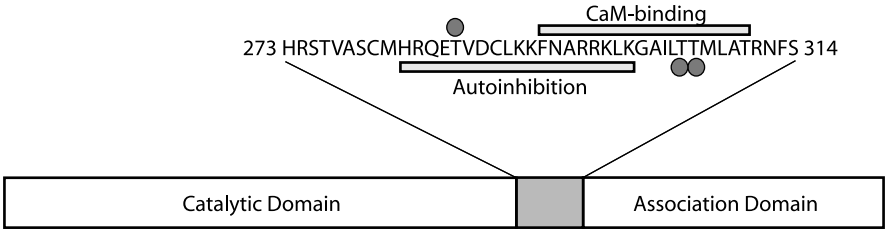

Figure 1. Schematic diagram of CaMKII domain structure. All CaMKII isozymes contain an N-terminal catalytic domain, an internal regulatory domain, and a C terminal that mediates holoenzyme formation. The regulatory domain, whose sequence is shown above the diagram, is bipartite. The proximal end (aa 282–300) contain residues that interact with the catalytic domain to inhibit phosphotransferase activity (indicated by gray bar below sequence). The distal portion of this domain (aa 293–310) binds to Ca^{2+}/CaM (indicated by gray bar above sequence). Regulatory phosphorylation sites at Thr^{286}, Thr^{305}, and Thr^{306} are indicated by gray dots.

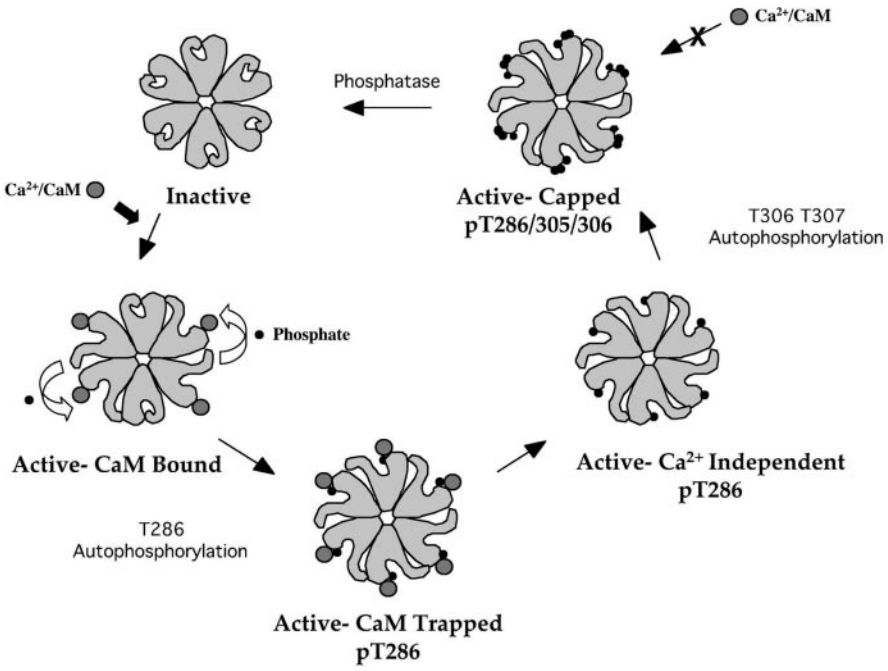

Figure 2. Regulation of CaMKII by autophosphorylation. Autophosphorylation within the regulatory domain of CaMKII defines several activity states for the kinase. In the absence of Ca^{2+}/CaM and autophosphorylation, CaMKII is inactive (Inactive). Binding of Ca^{2+}/CaM activates the kinase for substrate phosphorylation, bringing it to 100% of its maximal activity (CaM Bound). Binding of two Ca^{2+}/CaMs to adjacent subunits stimulates inter-subunit phosphorylation of Thr^{286}. The off-rate of Ca^{2+}/CaM from $pThr^{286}$ CaMKII is decreased by >1000-fold, resulting in an enzyme that remains at 100% of its maximal Ca^{2+}/CaM-stimulated activity even as calcium falls in the cell (CaM Trapped). Once Ca^{2+}/CaM dissociates, the enzyme remains active but at a lower level than with saturating Ca^{2+}/CaM, having between 20 and 80% of its maximal Ca^{2+}/CaM-stimulated activity (Ca^{2+} Independent). The dissociation of Ca^{2+}/CaM also uncovers additional sites in the regulatory domain (Thr^{305} and Thr^{306}), which rapidly become autophosphorylated. The $pThr^{286}$/$pThr^{305}$/$pThr^{306}$ CaMKII remains active at 20 – 80% of maximal activity because of $pThr^{286}$ but is incapable of binding Ca^{2+}/CaM (Capped). Phosphatase activity is required to reset the kinase to its basal state, and theoretically these sites could be individually regulated by dephosphorylation to produce $pThr^{286}$ or $pThr^{305}$/$pThr^{306}$ states of the kinase from the triple-phosphorylated form. The $pThr^{305}$/$pThr^{306}$ state of the kinase would be completely inactive and unresponsive to Ca^{2+}/CaM.

of CaMKII to hang onto CaM long after calcium levels have fallen is integral to its ability to act as a neuronal frequency detector (DeKoninck and Schulman, 1998; Eshete and Fields, 2001).

Eventually, if calcium levels are low for long enough, Ca^{2+}/CaM will dissociate from the kinase. Dissociation makes additional autophosphorylation sites in the regulatory domain available. Thr^{305} and Thr^{306}, which are protected by bound Ca^{2+}/CaM (Meador et al., 1993), can now undergo autophosphorylation if the kinase is still in its active, $pThr^{286}$, state. Phosphorylation of these additional sites prevents rebinding of Ca^{2+}/CaM and maximal activation of the kinase. Thr^{305}/Thr^{306} have been called "inhibitory" sites, but, for the kinase as studied *in vitro*, this is somewhat of a misnomer because only kinase that is constitutively active as a result of Thr^{286} phosphorylation can become phosphorylated at these sites at a high rate. Slow basal phosphorylation of Thr^{306} occurs in the absence of kinase activation, presumably because of the proximity of this residue to the catalytic site (Hanson and Schulman, 1992; Colbran, 1993) producing an enzyme that cannot be activated. As will be discussed below, there is an additional mechanism involving a CaMKII-binding protein that can rapidly mediate phosphorylation of these sites, in the absence of $pThr^{286}$, to produce an inhibited kinase that requires phosphatase to regain its ability to be stimulated by Ca^{2+}/CaM.

Regulation of CaMKII by proteins with domains homologous to the CaMKII autoinhibitory domain

In the last several years, it has become apparent that CaMKII activity is not just a function of global cell calcium levels. Neurons are complex cells with many distinct subcellular compartments that can be regulated separately, and localization of signaling molecules is clearly important for their specificity of action both in terms of local levels of activators and the range of available substrates. For CaMKII, there has been an avalanche of papers in the last few years identifying new binding partners, many of which are also substrates (Griffith et al., 2003; Colbran, 2004a). A number of these interactions were found to be activity dependent, either requiring the presence of Ca^{2+}/CaM or the phosphorylation of Thr^{286} for binding. As will be detailed below, this dependence on activation has implications for the regulation of CaMKII by these binding partners and suggests a general mechanism for activity-dependent docking of CaMKII to these proteins.

The first example of a CaMKII binding partner that was capable of regulating the activity of the enzyme is the NR2B subunit of the NMDA receptor (NMDAR). Binding of CaMKII to various subunits of the NMDAR had been recognized for several years, and multiple binding sites had been identified (for details, see Colbran, 2004a). One site on NR2B stood out as interesting because of its homology to the autoinhibitory domain of CaMKII (Fig. 3*A*). Interaction with this site required the activation of CaMKII, by either binding of Ca^{2+}/CaM or Thr^{286} phosphorylation (Bayer et al., 2001). Once bound, the kinase remained attached even when Ca^{2+}/CaM was dissociated. Phosphorylation of Thr^{286} was not required for maintenance. A similar interaction was subsequently characterized for the C terminal of the *Drosophila* ether-a-go-go (Eag) potassium channel (Sun et al., 2004), which also features a CaMKII-binding domain with homology to

the autoinhibitory domain of the kinase (Fig. 3*A*). Both the NR2B and Eag CaMKII-binding domains were centered over a phosphorylation site (Ser[1303] and Thr[787], respectively) that was within a CaMKII consensus sequence similar to that found in the autoinhibitory domain of the kinase at Thr[286].

Binding of CaMKII to the Eag or NR2B C termini, or to peptides encompassing the NR2B 1209–1310 binding site, was associated with an increase in the calcium-independent activity of the kinase. The activity of the bound form did not require Thr[286] phosphorylation, suggesting that it was a consequence of binding of the autoinhibitory-like domains of NR2B and Eag to the kinase in a manner that blocked autoinhibition but not substrate access. Alignment of the sequences revealed substantial similarity to the CaMKII autoinhibitory domain, including conservation of residues in this domain (Fig. 3*A*, indicated by dots over the alignment) that had been shown to make contacts with the catalytic region (Yang and Schulman, 1999). This suggested that these binding partners may form interactions with the CaMKII catalytic domain via these side chains.

Site-directed mutagenesis of NR2B demonstrated that several of these conserved residues (Lys[1292], Arg[1300], and Ser[1303]) did indeed participate in CaMKII binding (Strack et al., 2000). Interestingly, additional residues in the NR2B sequence (Leu[1298], Arg[1299], and Gln[1301]), which were not predicted from the CaMKII study by Yang and Schulman (1999), were found to be critical for binding. Residues distal to the Ser[1303] phosphorylation site were not studied. These point mutant studies suggests that NR2B makes contacts with the CaMKII catalytic domain that are not identical to those made by the autoinhibitory peptide of the kinase.

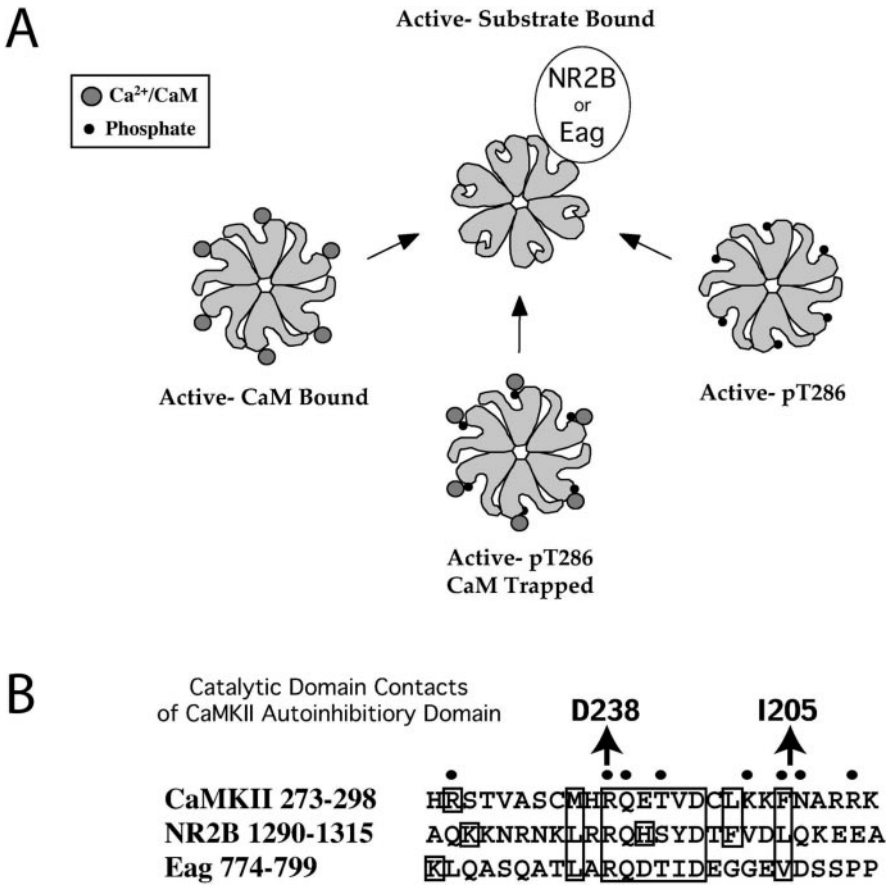

Figure 3. Regulation of CaMKII by binding interactions. Binding of CaMKII to exogenous proteins can regulate its activity. *A*, Proteins with domains that resemble the autoinhibitory domain of the kinase can bind to CaMKII in an activity-dependent manner. Activation of the kinase, by Ca^{2+}/CaM binding or Thr[286] autophosphorylation, causes a conformational change that reveals an interaction face on the catalytic domain. This interaction domain is blocked by the CaMKII autoinhibitory domain in the inactive state of the kinase. Interaction persists even in the absence of pThr[286] or Ca^{2+}/CaM and serves to block reassociation of the autoinhibitory domain with the catalytic site, thus rendering the kinase calcium independent. *B*, An alignment of the CaMKII autoinhibitory domain, NR2B, and Eag. Dots above the CaMKII sequence indicate residues of the autoinhibitory domain that were shown to contact the catalytic domain (Yang and Schulman, 1999). Catalytic domain contacts for selected residues are shown above the alignment. R283 is believed to contact D238, whereas F293 and N294 are believed to contact I205 in the catalytic domain. For a complete list of contacts, see Yang and Schulman (1999).

Mutagenesis of the Eag CaMKII-binding domain produced an even more complex picture (Sun et al., 2004). Only one conserved residue that was predicted by homology to the autoinhibitory domain to contact the catalytic domain (Arg[784]) was required for Eag binding to the kinase. Other residues (Lys[774], Thr[787], and Val[794]), which by homology would be thought to contact the catalytic domain, did not appear to be required for binding. One double mutant, G792K/E793K, which made the Eag sequence more similar to that of the CaMKII autoinhibitory domain, actually decreased CaMKII binding. Residues that were not conserved in the CaMKII alignment (Ala[783], Glu[790], Gly[792], and Glu[793]) were important for Eag binding as well as some residues (Leu[782], Gln[785], and Asp[789]) that were conserved but not identified in the study by Yang and Schulman (1999) as being important for contact with the catalytic domain. These data reinforce the idea that the contacts made by autoinhibitory-like domains with the catalytic binding face are not identical to those made by the autoinhibitory sequence of the kinase.

If these CaMKII-binding proteins are indeed interacting with the catalytic domain, it would be expected that some of the mutations in the catalytic domain that disturb autoinhibitory domain function might also perturb NR2B and Eag binding. Bayer et al. (2001) showed that I205K CaMKII failed to bind NR2B and also failed to translocate to synaptic sites in neurons. The homologous mutant of *Drosophila* CaMKII, I206K (note that the *Drosophila* CaMKII numbering is shifted by one residue), did not bind to Eag. Another mutation in fly CaMKII that would be predicted to disrupt autoinhibitory–catalytic interactions by virtue of its interaction with the P-3 residue of the phosphorylation site is Asp[239]. Mutation of this residue did not block Eag binding. This result suggests that Arg[784] in Eag, although required for Eag/CaMKII interaction, does not play a role equivalent to Arg[284] in the *Drosophila* CaMKII autoinhibitory domain: they make different contacts.

Three important conclusions can be drawn from these studies. First, the ability of autoinhibitory-like ligands to bind to CaMKII is activity dependent because of the requirement for exposure of a binding site that is normally blocked by the intramolecular interactions of the catalytic and autoinhibitory domains. Second, the molecular contacts made between CaMKII

and these ligand proteins are not identical to the intramolecular contacts made by the autoinhibitory domain of the kinase. Even residues that are conserved between the ligand protein and the CaMKII autoinhibitory domain may make different contacts. Third, the effect of autoinhibitory domain-like ligands on kinase activity depends critically on the exact nature of the contacts the ligand makes with the catalytic domain. The two examples cited here, the mammalian NR2B subunit of the NMDAR and Eag, a voltage-gated *Drosophila* potassium channel, can both activate CaMKII. This is likely attributable to their inability under the conditions studied to mimic the ATP-blocking and pseudosubstrate functions of the endogenous autoinhibitory domain. It is plausible that additional classes of activity-dependent autoinhibitory-like ligands exist that could have different effects on activity: either suppressing activity or allowing it to remain Ca^{2+}/CaM regulated. Comparisons between different classes of ligands will shed light on the structural mechanism of CaMKII activity regulation.

Regulation of CaMKII by directed autophosphorylation in the CaM-binding domain

CaMKII-binding proteins with domains similar to the kinase autoinhibitory domain regulate CaMKII by directly binding to the kinase. CaMKII can also be regulated by altering its pattern of autophosphorylation. Recently, a *Drosophila* MAGUK (membrane-associated guanylate kinase) protein called Camguk has been shown to selectively stimulate inhibitory autophosphorylation of CaMKII at low calcium levels to render it calcium insensitive (Lu et al., 2003).

Camguk is the *Drosophila* homolog of mammalian CASK (Hata et al., 1996) and *Caenorhabditis elegans* Lin-2 (Baines, 1996). It has a prototypical MAGUK structure, including a single PDZ (postsynaptic density 95/discs large/zona occludens 1), an SH3 (Src homology 3) and a GUK (guanylate kinase) domain at its C terminus. The N-terminal of Camguk contains a region highly homologous to the catalytic and regulatory domains of CaMKII. Camguk and CaMKII coimmunoprecipitate from fly heads and are present both presynaptically and postsynaptically at the third instar larval neuromuscular junction. Investigation of the interaction mechanism of these two proteins *in vitro* revealed that, in the presence of a nonhydrolyzable ATP analog or in the presence of ATP plus Ca^{2+}/CaM, the two proteins formed a very stable complex. Removal of Ca^{2+}/CaM in the presence of a hydrolysable nucleotide triphosphate led to a rapid dissociation. Dissociation was accompanied by a loss of CaMKII activity and a loss of the ability of the kinase to bind Ca^{2+}/CaM.

ATP-dependent loss of CaM binding is associated with the autophosphorylation of Thr^{305}/Thr^{306} in mammalian CaMKII (Colbran and Soderling, 1990). In the case of pure CaMKII, phosphorylation of these residues only occurs in the context of an enzyme previously made calcium independent by phosphorylation of Thr^{286}. Phosphorylation of Thr^{305}/Thr^{306} blocks Ca^{2+}/CaM binding, but the enzyme still has residual activity attributable to $pThr^{286}$. In the case of CaMKII that has been bound to Camguk, dissociated enzyme was completely dead, suggesting that it was not phosphorylated at Thr^{287} (the fly equivalent of Thr^{286}). Indeed, T287A CaMKII, which is incapable of becoming constitutively active, can bind to Camguk and become inactivated in the absence of Ca^{2+}/CaM. This property distinguishes Camguk-stimulated autophosphorylation of the CaM-binding domain from that seen with purified kinase and puts it in the same functional group of regulatory events as the slow "basal" phosphorylation seen by Colbran (1993). Association of CaMKII with Camguk can result in a completely inactive kinase.

The importance of phosphorylation in the CaM-binding domain has been highlighted by experiments in mouse hippocampus in which the association of CaMKII with the synapse, and synaptic function, were compromised in animals that were not able to normally regulate these sites (Elgersma et al., 2002). In *Drosophila,* the amount of $pThr^{306}$ in neuronal tissue is almost completely a function of Camguk levels; it is nearly undetectable in animals null for the *cmg* gene (Lu et al., 2003), suggesting that phosphorylation of these sites by the constitutively active form of the kinase *in vivo* is negligible. The ability to selectively cause the autophosphorylation of sites in the CaM-binding domain of the kinase in the absence of constitutive activity implies that the Camguk interaction could provide a mechanism by which the calcium-stimulable pool of CaMKII is downregulated when levels of Ca^{2+}/CaM are low. This model is supported by experiments at the *Drosophila* larval neuromuscular junction: active synapses have less phosphorylation of Thr^{306}, whereas inactive synapses have higher levels of $pThr^{306}$, as detected by a phospho-specific antibody (Lu et al., 2003). These studies link the phosphorylation of the native CaMKII to the level of activity at the synapse. This regulatory pathway may be important for differentiation of active and inactive synapses and suggests that phosphatase activity could, in this situation, be an important regulator of CaMKII activity [see the mini-review by Colbran (2004b)].

Future perspectives

The control of CaMKII activity by Ca^{2+}/CaM, the first activator identified for this enzyme, is relatively well understood. In the last few years, additional protein regulators of CaMKII have been identified. The picture that emerges is one of diverse local regulation; proteins that physically interact with CaMKII and affect its subcellular localization may also regulate its kinase activity. Understanding of how these regulators function will require structural information about CaMKII and CaMKII complexes. Investigation of the roles of these proteins will help us understand how this very abundant protein kinase can have specific effects in so many different cellular contexts.

References

Baines AJ (1996) *Caenorhabditis elegans* LIN-2A and mammalian neuronal CASK are prototypical members of a subfamily of MAGUKs (membrane-associated guanylate kinases) characterized by a common kinase-like domain and a guanylate kinase domain predicted to bind ATP. Biochem J 320:694–696.

Bayer KU, De Koninck P, Leonard AS, Hell JW, Schulman H (2001) Interaction with the NMDA receptor locks CaMKII in an active conformation. Nature 411:801–805.

Colbran RJ (1993) Inactivation of Ca^{2+}/calmodulin-dependent protein kinase II by basal autophosphorylation. J Biol Chem 268:7163–7170.

Colbran RJ (2004a) Targeting of calcium/calmodulin-dependent protein kinase II. Biochem J 378:1–16.

Colbran RJ (2004b) Protein phosphatases and calcium/calmodulin-dependent protein kinase II-dependent synaptic plasticity. J Neurosci 24:8404–8409.

Colbran RJ, Soderling TR (1990) Calcium/calmodulin-independent autophosphorylation sites of calcium/calmodulin-dependent protein kinase II. J Biol Chem 265:11213–11219.

Colbran RJ, Smith MK, Schworer CM, Fong YL, Soderling TR (1989) Regulatory domain of calcium/calmodulin-dependent protein kinase II. Mechanism of inhibition and regulation by phosphorylation. J Biol Chem 264:4800–4804.

DeKoninck P, Schulman H (1998) Sensitivity of CaM kinase II to the frequency of Ca^{2+} oscillations. Science 279:227–230.

Elgersma Y, Fedorov NB, Ikonen S, Choi ES, Elgersma M, Carvalho OM,

Giese KP, Silva AJ (2002) Inhibitory autophosphorylation of CaMKII controls PSD association, plasticity, and learning. Neuron 36:493–505.

Elgersma Y, Sweatt JD, Giese KP (2004) Mouse genetic approaches to investigating calcium/calmodulin-dependent protein kinase II function in plasticity and cognition. J Neurosci 24:8410–8415.

Eshete F, Fields RD (2001) Spike frequency decoding and autonomous activation of Ca^{2+}-calmodulin-dependent protein kinase II in dorsal root ganglion neurons. J Neurosci 21:6694–6705.

Griffith LC, Lu CS, Sun XX (2003) CaMKII, an enzyme on the move: regulation of temporospatial localization. Mol Interv 3:386–403.

Hanson PI, Schulman H (1992) Inhibitory autophosphorylation of multifunctional Ca^{2+}/calmodulin-dependent protein kinase analyzed by site-directed mutagenesis. J Biol Chem 267:17216–17224.

Hanson PI, Meyer T, Stryer L, Schulman H (1994) Dual role of calmodulin in autophosphorylation of multifunctional CaM kinase may underlie decoding of calcium signals. Neuron 12:943–956.

Hata Y, Butz S, Sudhof TC (1996) CASK: a novel dlg/PSD95 homolog with an N-terminal calmodulin-dependent protein kinase domain identified by interaction with neurexins. J Neurosci 16:2488–2494.

Hudmon A, Schulman H (2002) Neuronal Ca^{2+}/calmodulin-dependent protein kinase II: the role of structure and autoregulation in cellular function. Annu Rev Biochem 71:473–510.

Kolb SJ, Hudmon A, Ginsberg TR, Waxham MN (1998) Identification of domains essential for the assembly of calcium/calmodulin-dependent protein kinase II holoenzymes. J Biol Chem 273:31555–31564.

Lou LL, Schulman H (1989) Distinct autophosphorylation sites sequentially produce autonomy and inhibition of the multifunctional Ca^{2+}/calmodulin-dependent protein kinase. J Neurosci 9:2020–2032.

Lu CS, Hodge JJ, Mehren J, Sun XX, Griffith LC (2003) Regulation of the Ca^{2+}/CaM-responsive pool of CaMKII by scaffold-dependent autophosphorylation. Neuron 40:1185–1197.

Meador WE, Means AR, Quicho FA (1993) Modulation of calmodulin plasticity in molecular recognition on the basis of X-ray structures. Science 262:1718–1721.

Meyer T, Hanson PI, Stryer L, Schulman H (1992) Calmodulin trapping by calcium-calmodulin-dependent protein kinase. Science 256:1199–1202.

Miller SG, Patton BL, Kennedy MB (1988) Sequences of autophosphorylation sites in neuronal type II CaM kinase that control Ca^{2+}-independent activity. Neuron 1:593–604.

Mukherji S, Soderling TR (1995) Mutational analysis of Ca^{2+}-independent autophosphorylation of calcium/calmodulin-dependent protein kinase II. J Biol Chem 270:14062–14067.

Payne ME, Fong YL, Ono T, Colbran RJ, Kemp BE, Soderling TR, Means AR (1988) Calcium/calmodulin-dependent protein kinase II. Characterization of distinct calmodulin binding and inhibitory domains. J Biol Chem 263:7190–7195.

Putkey JA, Waxham MN (1996) A peptide model for calmodulin trapping by calcium/calmodulin-dependent protein kinase II. J Biol Chem 271:29619–29623.

Quest AF (1996) Regulation of protein kinase C: a tale of lipids and proteins. Enzyme Protein 49:231–261.

Schworer CM, Colbran RJ, Keefer JR, Soderling TR (1988) Ca^{2+}/calmodulin-dependent protein kinase II: identification of a regulatory autophosphorylation site adjacent to the inhibitory and calmodulin-binding domains. J Biol Chem 263:13486–13489.

Shen K, Meyer T (1998) In vivo and in vitro characterization of the sequence requirement for oligomer formation of Ca^{2+}/calmodulin-dependent protein kinase II alpha. J Neurochem 70:96–104.

Singla SI, Hudmon A, Goldberg JM, Smith JL, Schulman H (2001) Molecular characterization of calmodulin trapping by calcium/calmodulin-dependent protein kinase II. J Biol Chem 276:29353–29360.

Smith MK, Colbran RJ, Brickey DA, Soderling TR (1992) Functional determinants in the autoinhibitory domain of calcium/calmodulin-dependent protein kinase II. J Biol Chem 267:1761–1768.

Strack S, McNeill RB, Colbran RJ (2000) Mechanism and regulation of calcium/calmodulin-dependent protein kinase II targeting to the NR2B subunit of the *N*-methyl-D-aspartate receptor. J Biol Chem 275:23798–23806.

Sun XX, Hodge JJ, Zhou Y, Nguyen M, Griffith LC (2004) The eag potassium channel binds and locally activates calcium/calmodulin-dependent protein kinase II. J Biol Chem 279:10206–10214.

Taylor SS, Yang J, Wu J, Haste NM, Radzio-Andzelm E, Anand G (2004) PKA: a portrait of protein kinase dynamics. Biochim Biophys Acta 1697:259–269.

Thiel G, Czernik AJ, Gorelick F, Nairn AC, Greengard P (1988) Ca^{2+}/calmodulin-dependent protein kinase II: identification of threonine-286 as the autophosphorylation site in the a subunit associated with the generation of Ca^{2+}-independent activity. Proc Natl Acad Sci USA 85:6337–6341.

Waxham MN, Tsai AL, Putkey JA (1998) A mechanism for calmodulin (CaM) trapping by CaM-kinase II defined by a family of CaM-binding peptides. J Biol Chem 273:17579–17584.

Yang E, Schulman H (1999) Structural examination of autoregulation of multifunctional calcium/calmodulin-dependent protein kinase II. J Biol Chem 274:26199–26208.