Ca\textsuperscript{2+}-dependent Cell Signaling through Calmodulin-activated Protein Phosphatase and Protein Kinases Minireview Series*

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James T. Stull†
From the Department of Physiology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9040

Over 100 years ago Sydney Ringer first showed that extracellular Ca\textsuperscript{2+} was necessary for muscle contractions (1). Research during the past 50 years has revealed that intracellular Ca\textsuperscript{2+} mediates a large number of cellular responses with the high affinity and specificity required for a regulatory second messenger. The identification and biochemical characterization of Ca\textsuperscript{2+}-dependent signaling pathways were stimulated by the pioneering proposal that Ca\textsuperscript{2+} acts by binding to specific intracellular proteins, which may be considered Ca\textsuperscript{2+} receptors (2). The class of proteins that binds Ca\textsuperscript{2+} with high affinity and specificity now includes hundreds of members (3). Nevertheless, a large proportion of studies focused on calmodulin because it was recognized as a regulator of many different target enzymes (4). Calmodulin interactions with proteins are categorized into six distinct classes based on Ca\textsuperscript{2+}-independent and -dependent modes of binding and regulation (5). Complementary structural features in both calmodulin and respective target proteins allow diverse and discrete modes of effector regulation.

Biophysical studies of Ca\textsuperscript{2+} binding to calmodulin and Ca\textsuperscript{2+}/calmodulin binding to peptide targets from Ca\textsuperscript{2+}/calmodulin-dependent protein kinases have provided insights into how calmodulin functions (5, 6). Calmodulin has four Ca\textsuperscript{2+}-binding sites with two in a globular N-terminal domain separated by a flexible a-helix from a C-terminal globular domain containing the other two Ca\textsuperscript{2+} binding sites. In the presence of Ca\textsuperscript{2+} each domain adopts an open conformation exposing a hydrophobic pocket that renders calmodulin functional for binding to target sequences. The process of complex formation includes sequential interactions between the C-terminal hydrophobic pocket with a hydrophobic residue in the target N-terminal sequence followed by interactions between the N-terminal globular domain with the C-terminal sequence of the calmodulin-binding domain. Calmodulin thus collapses and wraps around the peptide, resulting in the formation of a high affinity complex. The high affinity binding of calmodulin to a target sequence is only partly responsible for enzyme activation as surface residues on calmodulin may subsequently interact with other areas of the enzyme (7–9).

Based upon biophysical and biochemical studies with target enzymes, models of Ca\textsuperscript{2+}/calmodulin-dependent cellular responses have been proposed and tested, employing the integrative powers of genetic, cell biological, and physiological approaches. Much of our understanding of Ca\textsuperscript{2+}/calmodulin regulation of biological processes comes from the wealth of information on calmodulin-dependent protein kinases I, II, IV, and myosin light chain kinases, in addition to the calmodulin-dependent protein phosphatase, calcineurin.

Protein phosphatases play dynamic roles in diverse cellular processes. Protein phosphatase IIB, or calcineurin, is a serine/threonine protein phosphatase activated by Ca\textsuperscript{2+}/calmodulin and, thus, couples Ca\textsuperscript{2+} signals to specific cellular responses via protein dephosphorylation (10). Calcineurin was initially identified in neuronal tissues, but it was quickly recognized that it had a broad tissue distribution and a highly conserved structure from yeast to man. The immunosuppressive drugs, cyclosporin A and FK506, were initially used to discover the essential role of calcineurin in T cell activation (11), and these pharmacological inhibitors have provided tools to explore the roles of calcineurin in diverse Ca\textsuperscript{2+}-dependent signaling pathways (12). Calcineurin has been implicated in a wide variety of biological responses involving transcriptional mechanisms, and in the first minireview in this series ("Calcium, Calcineurin, and the Control of Transcription") Gerald R. Crabtree will review its role in regulating transcription during development via dephosphorylation of the NF-AT transcription complex. Ca\textsuperscript{2+} also regulates transcription through phosphorylation of several transcription factors, including CREB and MEF2, by a Ca\textsuperscript{2+}/calmodulin-independent protein kinase cascade involving three distinct kinases. Ca\textsuperscript{2+}/calmodulin-dependent protein kinases I and IV have broad but overlapping substrate specificities and similar mechanisms of activation. Both kinases are phosphorylated by a third kinase, which enhances Ca\textsuperscript{2+}/calmodulin-dependent activity. In the second minireview ("Defining Ca\textsuperscript{2+}/CaM-dependent Protein Kinase Cascades in Transcriptional Regulation") Ethan E. Corcoran and Anthony R. Means will review the biochemical properties of this cascade and its physiological role in mediating Ca\textsuperscript{2+} regulation of specific transcriptional processes.

Another ubiquitous effector of Ca\textsuperscript{2+} signaling is the multifunctional Ca\textsuperscript{2+}/calmodulin-dependent protein kinase II, which has broad substrate specificity with substrates found in nuclear, cytoskeletal, and membrane compartments of cells (13). Much of the early work focused on understanding its biochemical properties, including the autophosphorylation mechanism that results in the trapping of calmodulin on the kinase and conversion of the enzyme to a Ca\textsuperscript{2+}-independent form. The dynamic and spatial aspects of autophosphorylation are an important element of regulation, allowing it to respond to transient cellular Ca\textsuperscript{2+} oscillations. The third minireview ("Cellular Signaling through Multifunctional Ca\textsuperscript{2+}/Calmodulin-dependent Protein Kinase II" by Thomas R. Soderling, Bill Chang, and Debra Brickey) will focus on the role of Ca\textsuperscript{2+}/calmodulin-dependent protein kinase II in the neuronal synapse where its translocation and activation regulate a number of proteins in the postsynaptic cell.

In contrast to the Ca\textsuperscript{2+}/calmodulin-dependent protein kinases and calcineurin that have broad substrate specificities, myosin light chain kinases are dedicated protein kinases for which the only known physiological substrate is the regulatory light chain of myosin II. Early studies focused on its biochemical properties, including the mechanism of activation by Ca\textsuperscript{2+}/calmodulin, with an emphasis on its role in muscle tissues (14, 15). However, the discovery in nonmuscle cells of other conventional myosin IIIs with diverse functions such as cell spreading and migration, cytokinesis, cell adhesion, secretion, and cytoskeletal arrangements that affect plasma membrane ion movements has broadened our perspective on the functional importance of this enzyme (16–18). Recent interest has also been stimulated by its involvement in pathophysiological processes. In the fourth minireview ("Dedicated Myosin Light Chain Kinases with Diverse Cellular Functions") Kristine E. Kamm and James T. Stull will review the family members of the dedicated myosin light chain kinases and how they participate in regulating diverse cellular functions.

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