

# This Week's Citation Classic

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**Cheung W Y. Calmodulin plays a pivotal role in cellular regulation.**

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The role of calcium ions ( $\text{Ca}^{2+}$ ) in cell functions is beginning to be unraveled at the molecular level as a result of recent research on calcium-binding proteins and particularly on calmodulin. These proteins interact reversibly with  $\text{Ca}^{2+}$  to form a protein- $\text{Ca}^{2+}$  complex, whose activity is regulated by a cellular flux of  $\text{Ca}^{2+}$ . Many of the effects of  $\text{Ca}^{2+}$  appear to be exerted through calmodulin-regulated enzymes. [The SCI® indicates that this paper has been cited in over 740 publications since 1980.]

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"This article originated from my postdoctoral studies at the Johnson Research Foundation, University of Pennsylvania. In 1964, after completing a doctoral dissertation in some aspect of carbohydrate metabolism of an alga under Martin Gibbs at Cornell University, I joined Britton Chance as a postdoctoral fellow. He introduced me to a fascinating phenomenon—oscillation of NADH in a cell-free extract of yeast. Chance and his colleagues had shown that cyclic AMP produces striking effects on the oscillatory profile of NADH in yeast extract. Commercial preparations of cyclic AMP at that time were rather crude; it was my job to determine its purity and to find out if the cyclic nucleotide retains effectiveness after treatment with phosphodiesterase, which degrades it to 5'-AMP. While purifying the enzyme from bovine heart, I noticed that its activity was precipitously reduced. Subsequent experiments showed that the activity of the purified, but not the crude, enzyme varied widely depending on the assay procedure used.<sup>1</sup> Since phosphodiesterase regulates the extent and duration of cyclic AMP action, I decided to pursue this observation to learn why the enzyme lost activity upon purification and what substances might be used to restore it. The loss turned out to be the result of my inadvertent

removal of an activator protein, now known as calmodulin. These early experiments with phosphodiesterase unexpectedly opened a fertile new area of research in cellular regulation.

"Despite several preliminary reports of an activator protein of phosphodiesterase,<sup>2,6</sup> and confirmation by other laboratories,<sup>7,8</sup> the finding stimulated only mild interest. At that time, much of the research on cyclic AMP was centered on adenylate cyclase, which catalyzes the synthesis of cyclic AMP.

"One aspect of calmodulin seemed especially puzzling. Although it regulates the activity of phosphodiesterase, its distribution is much wider than the enzyme's, implying additional functions. By the mid-1970s—I had moved to St. Jude Children's Research Hospital in 1967—calmodulin had been found in all eukaryotes, and workers in various laboratories began to realize that calmodulin regulates a broad spectrum of  $\text{Ca}^{2+}$ -dependent cellular processes, including the regulation of  $\text{Ca}^{2+}$  itself. Therefore, in 1978, I coined the name 'calmodulin' to denote that the protein is modulated by  $\text{Ca}^{2+}$  and that it also modulates  $\text{Ca}^{2+}$  concentration.

"The importance of calcium ion in cellular physiology has been appreciated for a century. The mechanism of its action remained unclear until the discovery and recent knowledge of calmodulin. Why is it that this ubiquitous protein, which mediates the action of  $\text{Ca}^{2+}$  in many cellular processes, remained hidden from investigators through several decades during which those processes were under intensive study? The answer lies primarily in calmodulin's ubiquity and abundance. Since it is always present, in cells and in cell extracts, it is never missed. Its role was disclosed only by its inadvertent removal from phosphodiesterase during routine purification of the enzyme.

"My article reviews the salient features of calmodulin: its discovery, its molecular mechanism of action, its central role in cellular functions, criteria for calmodulin-regulated reactions, and some future directions. This wide-ranging coverage, coming at a time when interest in calmodulin was building rapidly, may be the reason for the paper's frequent citation."

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