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Multiple calcium binding sites make calmodulin multifunctional

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Abstract

Protein-protein or protein-ion interactions with multisite proteins are essential to the regulation of intracellular and extracellular events. There is, however, limited understanding of how ligand-multisite protein interactions selectively regulate the activities of multiple protein targets. In this paper, we focus on the important calcium (Ca^{2+}) binding protein calmodulin (CaM), which has four Ca^{2+} ion binding sites and regulates the activity of over 30 other proteins. Recent progress in structural studies has led to significant improvements in the understanding of Ca^{2+}-CaM-dependent regulation mechanisms. However, no quantitative model is currently available that can fully explain how the structural diversity of protein interaction surfaces leads to selective activation of protein targets. In this paper, we analyze the multisite protein-ligand binding mechanism using mathematical modelling and experimental data for Ca^{2+}-CaM-dependent protein targets. Our study suggests a potential mechanism for selective and differential activation of Ca^{2+}-CaM targets by the same CaM molecules, which are involved in a variety of intracellular functions. The close agreement between model predictions and experimental dose-response curves for CaM targets available in the literature suggests that such activation is due to the selective activity of CaM conformations in complexes with variable numbers of Ca^{2+} ions. Although the paper focuses on the Ca^{2+}-CaM pair as a particularly data rich example, the proposed model predictions are quite general and can easily be extended to other multisite proteins. The results of the study may therefore be proposed as a general explanation for multifunctional target regulation by multisite proteins.

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