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Elucidating the mechanisms of cooperative calcium-calmodulin interactions: A structural systems biology approach

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Abstract

Background: Calmodulin is an important multifunctional molecule that regulates the activities of a large number of proteins in the cell. Calcium binding induces conformational transitions in calmodulin that make it specifically active to particular target proteins. The precise mechanisms underlying calcium binding to calmodulin are still, however, quite poorly understood. Results: In this study, we adopt a structural systems biology approach and develop a mathematical model to investigate various types of cooperative calcium-calmodulin interactions. We compare the predictions of our analysis with physiological dose-response curves taken from the literature, in order to provide a quantitative comparison of the effects of different mechanisms of cooperativity on calcium-calmodulin interactions. The results of our analysis reduce the gap between current understanding of intracellular calmodulin function at the structural level and physiological calcium-dependent calmodulin target activation experiments. Conclusion: Our model predicts that the specificity and selectivity of CaM target regulation is likely to be due to the following factors: variations in the target-specific Ca2+ dissociation and cooperatively effected dissociation constants, and variations in the number of Ca2+ ions required to bind CaM for target activation.

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