

A novel autoinhibitory function of C2-like domain of PKC θ in regulating T cell activation

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PKC θ is a major player in early TCR-induced signaling events leading to T cell activation and proliferation. Although PKC θ is believed to integrate TCR and CD28 signals, the mechanism that regulates its immunological synapse localization and activation are poorly understood. Like other novel PKC (nPKC) subfamily members, PKC θ contains a non-Ca²⁺ binding N-terminal domain similar to the Ca²⁺- and lipid-binding C2 domain of conventional PKCs (cPKCs). Nevertheless, the functional significance of this C2-like domain in PKC θ is unknown at present. In this study, we have identified the C2-like domain of PKC θ as an autoinhibitory domain. A PKC θ deletion mutant lacking the C2-like domain (Δ C2) constitutively stimulated NF- κ B, AP-1 and NF-AT activities in the absence of TCR stimulation in Jurkat T cells. A C2-PS PKC θ construct consisting of the C2-like domain and the adjacent pseudosubstrate (PS) sequence suppressed the activity of PKC θ - Δ C2, while neither C2 nor PS alone was inhibitory. In addition, the C2-PS region constitutively associated with PKC θ - Δ C2 as determined by coimmunoprecipitation and confocal imaging. However, superantigen/APC stimulation led to a dissociation of these two PKC θ regions. These results reveal a novel mechanism that regulates the activation of PKC θ by modulating an intramolecular interaction between the C2-like domain and another part of the enzyme.