Rational design and validation of an anti-protein kinase C active-state specific antibody based on conformational changes

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Protein kinase C (PKC) plays a regulatory role in key pathways in cancer. However, since phosphorylation is a step for classical PKC (cPKC) maturation and does not correlate with activation, there is a lack of tools to detect active PKC in tissue samples. Here, a structure-based rational approach was used to select a peptide to generate an antibody that distinguishes active from inactive cPKC. A peptide conserved in all cPKCs, C2Cat, was chosen since modeling studies based on a crystal structure of PKCβ showed that it is localized at the interface between the C2 and catalytic domains of cPKCs in an inactive kinase. Anti-C2Cat recognizes active cPKCs at least two-fold better than inactive kinase in ELISA and immunoprecipitation assays, and detects the temporal dynamics of cPKC activation upon receptor or phorbol stimulation. Furthermore, the antibody is able to detect active PKC in human tissue. Higher levels of active cPKC were observed in the more aggressive triple negative breast cancer tumors as compared to the less aggressive estrogen receptor positive tumors. Thus, this antibody represents a reliable, hitherto unavailable and a valuable tool to study PKC activation in cells and tissues. Similar structure-based rational design strategies can be broadly applied to obtain active-state specific antibodies for other signal transduction molecules.

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