Reversing the paradigm: protein kinase C as a tumor suppressor
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The serine/threonine protein kinase C (PKC) family has been intensely investigated in the context of cancer since the discovery that it serves as a receptor for the tumor-promoting phorbol esters. This led to the dogma that activation of PKC by phorbol esters promotes carcinogen-induced tumorigenesis, yet targeting PKC in cancer has been unsuccessful. Analysis of approximately 10% of the >500 mutations identified in human cancers reveals that the majority are loss-of-function and none are activating. Loss-of-function mutations occur in all PKC subgroups and by diverse mechanisms: they impede second messenger binding, prevent phosphorylation, or inhibit catalysis. Genome-editing to correct a PKC mutation in a colon cancer cell line reveals that PKC is haploinsufficient and that mutations are dominant negative with respect to the global PKC signaling output in cells. These data establish that PKC isozymes generally function as tumor suppressors, indicating that therapies should focus on restoring, not inhibiting, PKC activity.