PKC EFFECTS ON VASCULAR FUNCTIONS AND TUMOR GROWTH OF HUMAN PROSTATE CANCER

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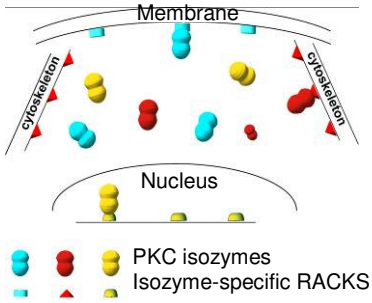
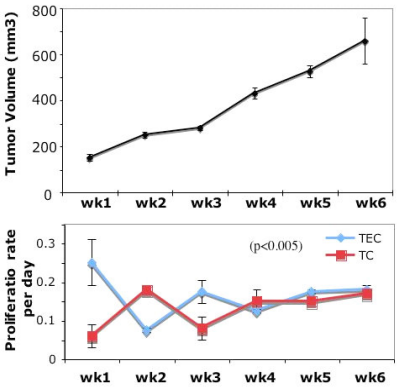


Protein kinase C (PKC) is a family of highly homologous isozymes involved in a variety of normal signaling events and in diseases. Research into the role of individual isozymes was affected by the lack of isozyme-selective pharmacological inhibitors and activators. We have taken a rational approach to identify such pharmacological tools, based on our observation that within the same cell, different PKC isozymes are localized to unique subcellular sites (Scheme below) and that location of the activated isozymes is mediated, in part, by their anchoring to isozyme-selective anchoring proteins or receptors, termed collectively RACKs, for receptors for activated C-Kinase. We reasoned [1] and subsequently demonstrated [2] that inhibitors and activators of localization of individual isozymes can be generated. These are short peptides that induce or inhibit protein-protein interactions between each isozyme and its RACK. These peptide regulators were found to be highly effective (with full biological activities exerted at 500ng/Kg), selective and well tolerated when delivered in a sustained fashion. Here, we applied these peptides to determine the role of PKC in prostate cancer growth and angiogenesis. PKC has been implicated in mediating tumor progression and angiogenesis. However, conflicting reports exist on the role of individual PKC isozymes in different types of tumors. Using a xenograft model of PC3 human prostate tumor cells, we found that the proliferation rate of the tumor endothelial cells (TEC) and tumor cells (TC) are different during growth phase (figure). We then found that several PKC isozymes are activated in this cell line. Next, using PKC-selective regulators, we found that a peptide inhibitor selective for PKCβII, βIIV5-3 at 3.6 or 36mg/Kg/day, reduced final tumor weight by 70%. βIIV5-3 significantly decreased the proliferation rate of TEC and TC at week 3 (p=0.008 and p=0.06, respectively) and further decreased tumor cell proliferation rate as measured at week 6. This anti-tumorigenic effect was more evident with higher dose of βIIV5-3. These data support a pro-angiogenic as well as tumor-promoting role for PKCβII in prostate cancer and suggest that delivery of βIIV5-3 may provide a novel therapy for this chemo-resistant type of human cancer.



References: 1. Mochly-Rosen D. (1995) Science, 1995. 268: 247-251.
2. Souroujon, MC and Mochly-Rosen D. (1988) Nature Biotechnol, 16: 919-924s.