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Protein kinase C-delta inactivation inhibits the proliferation and survival of cancer stem cells in culture and *in vivo*

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Abstract

Background: A subpopulation of tumor cells with distinct stem-like properties (cancer stem-like cells, CSCs) may be responsible for tumor initiation, invasive growth, and possibly dissemination to distant organ sites. CSCs exhibit a spectrum of biological, biochemical, and molecular features that are consistent with a stem-like phenotype, including growth as non-adherent spheres (clonogenic potential), ability to form a new tumor in xenograft assays, unlimited self-renewal, and the capacity for multipotency and lineage-specific differentiation. PKCδ is a novel class serine/threonine kinase of the PKC family, and functions in a number of cellular activities including cell proliferation, survival or apoptosis. PKCδ has previously been validated as a synthetic lethal target in cancer cells of multiple types with aberrant activation of Ras signaling, using both genetic (shRNA and dominant-negative PKCδ mutants) and small molecule inhibitors. In contrast, PKCδ is not required for the proliferation or survival of normal cells, suggesting the potential tumor-specificity of a PKCδ-targeted approach.

Methods: shRNA knockdown was used validate PKCδ as a target in primary cancer stem cell lines and stem-like cells derived from human tumor cell lines, including breast, pancreatic, prostate and melanoma tumor cells. Novel and potent small molecule PKCδ inhibitors were employed in assays monitoring apoptosis, proliferation and clonogenic capacity of these cancer stem-like populations. Significant differences among data sets were determined using two-tailed Student's t tests or ANOVA.

Results: We demonstrate that CSC-like populations derived from multiple types of human primary tumors, from human cancer cell lines, and from transformed human cells, require PKCδ activity and are susceptible to agents which deplete PKCδ protein or activity. Inhibition of PKCδ by specific genetic strategies (shRNA) or by novel small molecule inhibitors is growth inhibitory and cytotoxic to multiple types of human CSCs in culture. PKCδ inhibition efficiently prevents tumor sphere outgrowth from tumor cell cultures, with exposure times as short as six hours. Small-molecule PKCδ inhibitors also inhibit human CSC growth *in vivo* in a mouse xenograft model.

Conclusions: These findings suggest that the novel PKC isozyme PKCδ may represent a new molecular target for cancer stem cell populations.

Keywords: Protein Kinase C isozymes, Synthetic lethal interaction, Cancer-initiating cell, Xenograft tumor model

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