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Targeted Therapy for Pancreatic Cancer. Kathryn Leake, Sharad S. Singhal, Sanjay Awasthi. Beckman Research Institute, City of Hope, Duarte, CA.

Pancreatic cancer is a highly aggressive and lethal neoplasm, generally resistant to chemotherapy and radiation. In-vitro studies have indicated a role of PI3K/AKT as mechanisms of apoptosis resistance in pancreatic cancer. RLIP76 is a multi-functional cell membrane protein that functions as a major mercapturic acid pathway transporter as well as key regulator of receptor-ligand complexes through regulation of the rate of clathrin-dependent endocytosis. Inhibition of RLIP76 has been shown to antagonize both PI3K and AKT in other cancers. Present studies were undertaken to determine whether targeted depletion of RLIP76 can be an effective antineoplastic therapy that overcomes chemo-radio-resistance in pancreatic cancer, and whether the PI3K/Akt signaling pathway is affected. Cell survival was assessed by MTT and colony forming assays. Cellular levels of proteins and phosphorylation was determined by Western blot analyses. The impact on apoptosis was determined by TUNEL assay. The anti-cancer effects of RLIP76 targeted interventions in vivo were determined using mice xenograft model of the pancreatic cancer. Doxorubicin transport was measured using 14C-DOX, and radiation sensitivity was determined by colony forming assays, respectively. RLIP76 depletion caused marked and sustained regression of established human BxPC-3 pancreatic cancer tumors in nude mouse xenograft model. The ability of RLIP76 to mediate drug and radiation resistance was confirmed. Results of signaling studies are consistent with an encompassing model for the role of RLIP76 in regulating the levels of fundamental proteins like PI3K, Akt, E-cadherin, CDK4, Bcl2 and PCNA. These studies show that RLIP76 represents a mechanistically significant target for developing effective interventions drug and radiation-resistant pancreatic cancers. (Supported by USPHS-NIH R01-CA77495 to SA)