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DDR1 inhibition as a strategy enhancing chemoresponse in pancreatic cancer

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The extracellular matrix (ECM), a principal component of pancreatic ductal adenocarcinoma (PDA), is rich in fibrillar collagens that facilitate tumor cell survival and chemoresistance. Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase that specifically binds fibrillar collagens and has been implicated in promoting cell proliferation, invasion, ECM remodeling, response to growth factors and epithelial-mesenchymal transition (EMT). We found that collagen-induced activation of DDR1 stimulated pro-tumorigenic signaling through protein tyrosine kinase 2 (PYK2) and pseudopodium-enriched atypical kinase 1 (PEAK1) in pancreatic cancer cells. Pharmacologic inhibition of DDR1 with an ATP competitive orally available small molecule kinase inhibitor (7rh) abrogated collagen-induced DDR1 signaling in pancreatic tumor cells and consequently reduced colony formation and migration. Furthermore, the inhibition of DDR1 with 7rh showed striking efficacy in combination with chemotherapy in orthotopic xenografts and autochthonous pancreatic tumors where it significantly reduced DDR1 activation and downstream signaling, reduced primary tumor burden, and improved chemoresponse. These data demonstrate that targeting collagen-signaling in conjunction with conventional cytotoxic chemotherapy has the potential to improve outcome for pancreatic cancer patients.

Biography

Huocong Huang has completed his MD degree from Sun Yat-sen University, China and PhD degree from Dr. Keith Johnson's Lab at University of Nebreska Medical Center. He is now a Post-doctoral Researcher from Dr. Rolf Brekken's lab at UT Southwestern Medical Center. He has been dedicated to studying pancreatic cancer microenvironment ever since his PhD study. He was involved in pancreatic cancer SPORE projects and tumor microenvironment network projects focusing on matrix-driven epithelial-mesenchymal transition in pancreatic cancer, and now he is developing many novel therapeutic strategies for the disease by targeting the tumor stroma and cancer-matrix interaction.

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