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Elucidating the role of MUC1 in modulating pancreatic cancer cell survival by metabolomic analysis

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Abstract

MUC1, a type I transmembrane protein, is significantly overexpressed and aberrantly glycosylated in pancreatic cancer. Signaling through MUC1 cytoplasmic tail facilitates tumorigenic properties in cancer cells. Our studies have identified novel interactions between MUC1 cytoplamic tail and hypoxia-inducible factor-1 alpha (HIF-1α), a master regulator of glycolytic gene expression in solid tumors. Furthermore, MUC1 induced stabilization and activation of HIF-1α in pancreatic cancer cells. We also observed increased glucose uptake and lactate production under conditions of MUC1 expression and such effects were significantly diminished by knockdown of HIF-1α. To evaluate the entire spectrum of metabolite flux regulated by MUC1, we performed NMR-based metabolomic studies. Our 1D NMR studies indicated significant differences in the spectrum of metabolites present under conditions of MUC1 expression in pancreatic cancer cells. We then labeled MUC1 expressing or control S2-013 pancreatic cancer cells with $^{13}C_6$-glucose and performed 2D ^{1}H-^{13}C HSQC NMR experiment to identify the ^{13}C-labeled metabolites in the cell extracts. These studies identified MUC1-regulated metabolites involved in multiple metabolic pathways in pancreatic cancer. Overall, metabolites involved in glucose metabolism, amino acid metabolism and TCA cycle were regulated by overexpression of MUC1, suggesting their role in MUC1-mediated induction of cell growth and proliferation in pancreatic adenocarcinoma. Flux through pentose phosphate pathway, which contributes to nucleotide biosynthesis, is enhanced by MUC1 overexpression. Also, we observed increased levels of several amino acids, including glutamine, in MUC1 overexpressing S2-013 cells. Hence, MUC1 may provide distinct survival advantage to cancer cells under certain nutrient limiting conditions.

Biography

Pankaj Kumar Singh completed his Ph.D at the age of 26 years. He completed his postdoctoral studies from Salk Institute for Biological Studies, San Diego, California. He is currently an associate professor at Eppley Institute for Cancer Research, University of Nebraska Medical Center, Omaha, Nebraska. He has published several papers in reputed journals, including PNAS and Nature, and has obtained several national awards. His research is focused on metabolic alterations in tumors and he is utilizing metabolomic tools to investigate the mechanisms of chemoresistance in pancreatic cancer.