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Neuraminidase-1 and its role in multimodal therapy targeting chemotherapy resistance in pancreatic cancer

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Pancreatic cancer is a leading cause of cancer-related deaths with incidence expected to continue to rise. This lethal disease is attributed to the advent of metastatic disease that renders curative surgery possible in less than 25% of patients at the time of diagnosis. This leaves patients with the option of palliative chemotherapy, such as gemcitabine, which remains as the current golden standard, however, patients invariably develop resistance to chemotherapy and succumb to disease progression. We have previously reported that mammalian lysosomal enzyme neuraminidase-1 (Neu-1) acts to cleave α-2,3 sialic acid residues on receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR) to relieve steric hindrance and allow for receptor dimerization and downstream signaling following ligand binding. Anti-viral oseltamivir phosphate (OP) has been shown to inhibit Neu-1 activity by acting as a structural analog too α-2,3 sialic acid residues, ultimately shutting down a novel signaling paradigm implicated in multistage tumorigenesis. Recent reports have described the overlapping chemo-protective roles of anti-diabetic metformin and non-steroidal anti-inflammatory drug acetylsalicylic acid (aspirin). Sialidase assays on live PANC-1 pancreatic cancer cells stimulated with EGF treated with each of the drugs have shown a novel effect of aspirin on Neu-1 activity. Immunocytochemistry on PANC-1 cells has revealed that each drug alone alters the expression of markers of epithelial-to-mesenchymal transition (EMT) that is characteristic of metastatic cancer, suggesting that they work to prevent EMT and prevent metastasis. Collectively, this multimodal therapy works synergistically to sensitize pancreatic cancer cells to chemotherapy, prevent metastasis, angiogenesis and tumor growth.

Biography

Bessi Qorri is a trainee in Prof Dr Myron R. Szewczuk's lab. She is interested in optimizing the drug combination consisting of oseltamivir phosphate, aspirin, and metformin to target multistage tumorigenesis in pancreatic cancer. She has shown that these drugs act synergistically to inhibit malignant cell proliferation, as well as discovered a novel role of aspirin within our signaling paradigm implicated in tumorigenesis.

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