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Rationale-driven identification of novel gemcitabine sensitivity genes as biomarkers of outcome in pancreatic cancer patients by exploiting the replication stress response

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Abstract

Pancreatic adenocarcinoma (PAC) is notorious for its devastating disease course and prognosis. Gemcitabine, which inhibits DNA replication, is a widely used regimen for PAC treatment but lack of response and resistance often limits its effectiveness. The Replication Stress Response (RSR) is a signaling network that recognizes challenges to DNA replication and mobilizes diverse activities to maintain genome integrity. The RSR is critical for the prevention of pancreatic cancer by acting as a cancer barrier. Mutations in the RSR promote the proliferation of genetically unstable cells ultimately resulting in cancer but also weaken the ability of cancer cells to respond to treatment by compromising repair pathways. We utilized a rationale-driven approach to identify novel biomarkers for outcome in patients with early-stage resected PAC treated with adjuvant gemcitabine by exploiting dysregulated RSR pathways in PAC. We completed a synthetic lethal screen to identify genetic determinants of gemcitabine sensitivity in human pancreatic cancer cells. Gemcitabine sensitivity genes were assessed for their potential as biomarkers by determining their dysregulation and differential expression in pancreatic cancer tissues. Novel gemcitabine sensitivity genes, dysregulated and differentially expressed in PAC, were analyzed as biomarkers by correlating their expression by immunohistochemistry of tumor tissue from PAC patients who underwent resection with clinical outcome. The identification of novel gemcitabine sensitivity gene biomarkers may be utilized to personalize therapy for PAC patients.

Biography

Dr. Yu is an Assistant Professor and Georgia Cancer Coalition Distinguished Cancer Clinician and Scientist in the Department of Radiation Oncology at Emory University School of Medicine. Dr. Yu has studied genome maintenance for 15+ years. Dr. Yu is actively engaged in both clinical and basic science research. He is interested in understanding how cells respond to replication stress and how we can utilize this knowledge for improvements in cancer diagnosis and treatment. The ultimate goal of Dr. Yu's work is to translate insights gained from his interactions with his patients and the laboratory to innovative therapies to improve the quality of care for patients with cancer. Dr. Yu is a member of the ASTRO Radiation and Cancer Biology Committee Research Council and ASTRO Research Evaluation Committee Research Council among others.