OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference on
Biomarkers & Clinical Research

July 15-17, 2013 Courtyard by Marriott Philadelphia Downtown, USA

Differential processing of let-7a precursors as a biomarker for chemoresistance in pancreatic cancer

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Abstract

Overexpression of ribonucleotide reductase subunit M2 (RRM2), involved in deoxyribonucleotide synthesis, predominantly drives the chemoresistance of pancreatic cancer to nucleoside analogs (e.g., gemcitabine). While silencing RRM2 by synthetic means has shown promise in reducing chemoresistance, targeting endogenous molecules, especially microRNAs (miRNAs), to advance chemotherapeutic outcomes has been poorly explored. Based on computational predictions, we hypothesized that the let-7 tumor suppressor miRNAs will inhibit RRM2-mediated gemcitabine chemoresistance in pancreatic cancer. Reduced expression of the majority of let-7 miRNAs with an inverse relationship to RRM2 expression was identified in innately gemcitabine-resistant pancreatic cancer cell lines. Direct binding of let-7 miRNAs to the 3' UTR of RRM2 transcripts identified post-transcriptional regulation of RRM2 influencing gemcitabine chemosensitivity. Intriguingly, overexpression of human precursor-let-7 miRNAs led to differential RRM2 expression and chemosensitivity responses in a poorly differentiated pancreatic cancer cell line, MIA PaCa-2. Defective processing of let-7a precursors to mature forms explained the discrepancies observed with let-7a expressional outcomes. Consistently, the ratios of mature to precursor let-7a were progressively reduced in gemcitabine-sensitive L3.6pl and Capan-1 cell lines induced to acquire gemcitabine resistance. Besides known regulators of let-7 biogenesis (e.g., LIN-28), short hairpin RNA library screening identified several novel RNA binding proteins, including the SET oncoprotein, to differentially impact let-7 biogenesis and chemosensitivity in gemcitabine-sensitive versus -resistant pancreatic cancer cells. Further, LIN-28 and SET knockdown in the cells led to profound reductions in cellular proliferation and colony-formation capacities. Finally, defective processing of let-7a precursors with a positive correlation to RRM2 overexpression was identified in patient-derived pancreatic ductal adenocarcinoma (PDAC) tissues. These data demonstrate an intricate post-transcriptional regulation of RRM2 and chemosensitivity by let-7a and that the accumulation of let-7a precursors as a favorable biomarker for judging chemoresistance in pancreatic cancer.

Biography

Raj Govindarajan received a PhD in Biochemistry and Molecular Biology at the University of Nebraska Medical Center and postdoctoral training in Pharmaceutical Sciences at the University of Washington. Currently, he is a Faculty member in the Center for Drug Discovery and the Department of Pharmaceutical and Biomedical Sciences at the University of Georgia. He is an Editorial Board Member for American Journal for Cancer Research, Expert Opinion for Emerging Drugs, Frontiers in Drug Metabolism and Transport, and Journal of Pharmacogenomics and Pharmacoproteomics. His research involves novel therapeutics for pancreatic cancer and he receives grant support from NCI.