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Optimized DZNep exposure presensitizes pancreatic cancer cells to anticancer nucleoside analogs: Utilization of novel drug delivery

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Abstract

We evaluated the potential of a histone methylation reversal agent 3-deazaneplanocin A (DZNep) in improving the chemosensitivity of pancreatic cancer to nucleoside analogs (i.e., gemcitabine). DZNep brought delayed but selective cytotoxicity to pancreatic cancer cells without affecting normal human pancreatic ductal epithelial cells. Coexposure of DZNep and gemcitabine induced cytotoxic additivity or synergism in both well- and poorly-differentiated pancreatic cell lines. In contrast, DZNep exerted antagonism with gemcitabine against HPDE cells with significant reduction in cytotoxicity compared with the gemcitabine-alone regimen. DZNep marginally depended on purine nucleoside transporters for its cytotoxicity, but the transport dependence was circumvented by acyl derivatization. Drug exposure studies revealed that a short priming with DZNep followed by gemcitabine treatment rather than co-treatment of both agents to produce a maximal chemosensitization response in both gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer cells. DZNep rapidly and reversibly decreased trimethylation of histone H3 lysine 27 but increased trimethylation of lysine 9 in an EZH2- and JMJD1A/2C-dependent manner, respectively. However, DZNep potentiation of nucleoside analog chemosensitization was found to be temporally coupled to trimethylation changes in lysine 27 and not lysine 9. Polymeric nanoparticles engineered to chronologically release DZNep followed by gemcitabine produced pronounced chemosensitization and dose-lowering effects. Together, our results identify that an optimized DZNep exposure can presensitize pancreatic cancer cells to anticancer nucleoside analogs and emphasize the promising clinical utilities of histone methylation reversal agents' and engineered nanoparticle approaches in future pancreatic cancer combination therapies.

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.