Spatiotemporal delivery of epigenetic and chemotherapeutic nucleoside analogs to pancreatic cancer

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Recently, it has been shown that a potent chemical inhibitor of S-adenosylhomocysteine hydrolase, 3-deazaneplanocin A (DZNep), modulates chromatin through indirect (i.e., reducing methyl group availability) inhibition of histone methyltransferases including Enhancer of Zeste Homolog 2 (EZH2). DZNep, a carbocyclic analog of adenosine, depletes cellular levels of the Polycomb Repressive Complex 2 (PRC2) components while inhibiting the associated histone H3 at lysine 27 trimethylation (H3K27me3). While the mechanisms and effects of DZNep have been studied in numerous solid tumors and leukemia, less is known about the potential of this compound for pancreatic cancer treatment. Nevertheless, its current potential for reducing EZH2 levels, reverting epithelial-to-mesenchymal transition (EMT), and preventing tumor progression, makes it a highly promising antimetastatic agent. The therapeutic potential of DZNep in combination with other agents, such as polyphenols and histone deacetylase inhibitors, has begun to emerge with encouraging results. Since increasing evidence suggests that future cancer therapies will take advantage of the synergistic effects achieved from different combinations of epigenetic reversal and conventional antitumor agents, we evaluated the potential of an investigational 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 (HPDE) cells. Co-exposure of DZNep and gemcitabine induced cytotoxic additivity or synergism in both well- and poorly-differentiated pancreatic cell lines by increased apoptosis. 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 through the reversal of histone methylation, emphasizing the promising clinical utilities of epigenetic reversal agents’ in future pancreatic cancer combination therapies.