Targeting STAT3 with novel liposome-incorporated antisense oligonucleotide technology enhances the efficacy of paclitaxel (taxol) and 5-fluorouracil (5-FU) in breast and ovarian cancer cells

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Background: STAT3 is a transcription factor that regulates various tumorigenic processes, such as tumor proliferation, metastasis, and drug resistance. Its overexpression and aberrant activation characterize many cancers (including breast, lung, ovarian, liver and colon cancer). Metastasis and drug resistance are two main causes of patient mortality. Activation of the JAK-STAT3 and the FGFR1-STAT3 pathways in breast and ovarian cancer cells promotes tumor initiation, migration, and taxol resistance. STAT3 also contributes to epithelial-mesenchymal transition and promotes 5-FU resistance in colorectal cancer cells. Its role in numerous malignancies has made STAT3 an ideal cancer therapeutic target. BP1003 is a neutral DOPC liposome incorporated with a nuclease-resistant P-ethoxy antisense oligodeoxynucleotide targeting STAT3 mRNA. Here we determine the effects of BP1003 in combination with taxol and 5-FU on breast and ovarian cancer cells.

Methods: Western blots determined the extent by which BP1003 reduced STAT3 protein levels. The effect of sequential taxol or 5-FU (5 h pre-treatment) and BP1003 treatments (96 h) on cell viability was analyzed with r*esazurin-based* assays. Migration and colony formation assays were performed to assess the metastatic potential of treated cells. Cells pre-treated with BP1003 (96 h) and taxol (2 h) were placed in chemotaxis chambers and allowed to migrate for 5-18 h before quantification. Colony formation involved the treatment of a low number of cells with chemotherapeutic drugs for 24 h prior to the addition of BP1003 for 10-14 days. Tumor spheroids were used to mimic in vivo solid tumor growth. Three days after formation, spheroids were treated with chemotherapeutic drugs for 1 day before being treated with BP1003 for 3 additional days.

Results: Treatment of BT549, SK-Br-3 and SK-Ov-3 cells with 250 μg/ml of BP1003 resulted in a 30%-50% decrease in STAT3 expression. Cell viability decreased by 20-35% with 200 μg/ml of BP1003 and by 45-60% in combination with taxol or 5-FU. BP1003 in combination with taxol also decreased the colony formation potential of BT549 cells by 20%. Migration of BT549 cells was reduced by 30% with 200 μg/ml BP1003 alone and by 50% in combination with taxol. The area of BT549 and SK-Ov-3 spheroids under BP1003 and taxol combination treatments was 40%-50% smaller than control spheroids and 20%-30% smaller than taxol mono-treatment.

Conclusions: BP1003 efficiently reduces STAT3 expression and enhances the sensitivity of breast and ovarian cancer cells to taxol and 5-FU. These results are in line with previous work in which BP1003 + gemcitabine displayed enhanced anti-tumor activity in pancreatic ductal adenocarcinoma. Together these results strongly suggest that BP1003 combination therapy is a novel strategy for patients with advanced solid tumors.

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