Synergy of Anti-Cancer Drugs to Induce Cell Death in Pancreatic Cancer Cells

Summary

BRD4770 is a novel S-adenosylmethionine mimetic inhibitor of histone methyl transferase (HMT) G9a that promotes senescence in PANC-1 pancreatic cancer cells (which lack functional p53 and p16). Biolog PMM MicroPlates™ containing established anti-cancer agents were seeded with PANC-1 cells in pairwise combination with BRD4770 at different concentrations. Of four compounds which enhanced BRD4770-induced PANC-1 cell death, gossypol was found to be effective in acting synergistically to induce autophagy and cell death (1).

Results

Cellular metabolism and susceptibility to toxic chemicals was measured as previously described (2) using Biolog Phenotype MicroArray plates precoated with 92 different anti-cancer compounds, each at four different titrated concentrations. An example of one such plate (PM-M13) is depicted in Figure 1. For the assay, PANC-1 and hHPNE cells were resuspended in an RPMI-1640 based medium containing BRD4770 at 3 different concentrations and DMSO only (DMSO, 1.25uM, 2.5uM, and 5.0uM BRD4770), and seeded at 30,000 cells per well. After 48 hr incubation, Biolog Redox Dye Mix MB was added to each well, and cells were incubated in an OmniLog® 50-plate incubator/reader for automated measurement of the kinetics of cell metabolism over 24 hrs.

Four compounds enhanced cell death, as measured by decreased metabolic dye reduction (Figure 2). None of these “hit” compounds enhanced cell death in hHPNE, which expresses relatively low levels of HMT G9a. Additional testing showed that gossypol (wells D9-12) was most effective in synergizing with BRD4770 to kill PANC-1 cells. The natural product and putative BH3 mimetic, gossypol, enhanced the cytotoxicity of BRD4770 in a synergistic manner in p53-mutant PANC-1 cells but not in immortalized nontumorigenic pancreatic cells. Other data further suggested that these compounds act together to induce autophagy-related cell death in pancreatic cancer cells.

Conclusions

The Biolog Phenotype MicroArray system provides a simple format to enable discovery of potential synergistic killing of cancer cells by combining two effective anticancer agents. In this study, a novel small molecule inhibitor with activity against pancreatic cells was found to synergize with gossypol (Biolog PM-M13 MicroPlate). This unexpected synergy suggests new lines of mode-of-killing experiments and perhaps also novel approaches to treatment of pancreatic cancer.

References:
