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All-Trans Retinoic Acid Radiosensitizes Neuroendocrine Tumor Cells via Peptidyl-Prolyl Cis-Trans Isomerase 1 Inhibition

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) is a promising radiation-based therapy for metastatic neuroendocrine tumors (NETs) but remains palliative. Peptidyl-prolyl cis-trans isomerase (Pin1) is an evolutionally conserved enzyme that catalyzes the cis-trans isomerization of phosphorylated serine/threonine-proline motifs of its substrates and has recently been involved in DNA double strand break (DSB) repair in BRCA-proficient breast cancer cells. Here we study whether Pin1-inhibition with All-Trans Retinoic Acid (ATRA) radiosensitizes NET cells.

METHODS

The pancreatic and lung NET cell lines QGP1, BON1 and NCI-H727 were treated with 4Gy of radiation (IR) and either 50nM or 100nM of ATRA based on dose response curves. The poly (ADP-ribose) polymerase 1 inhibitor (PARPi) Talazoparib (10nM) was added to QGP1 cells to evaluate the additive vs. synergistic effects with ATRA and IR. Pin1 knockdown using siRNA, and BRCA1 and gH2AX western blot were used to determine mechanistic effects. Retinoic Acid Receptor (RAR)-alpha status was determined in cell lines using RT-PCR.

RESULTS

ATRA treatment alone showed a significant decrease in tumor cell viability in QGP1 ($p=0.013$), BON1 ($p=0.0001$), and NCI-H727 ($p=0.0003$). Combining ATRA + IR yielded further significant decrease in cell viability vs. IR alone (QGP1 ($p=0.0001$), BON1 ($p=0.0001$), NCI-H727 ($p=0.0003$)). ATRA synergized with Talazoparib and IR in QGP1 cells ($p<0.0001$). Pin1 knockdown with siRNA + IR further decreased cell viability in QGP1 ($p=0.0002$) and BON-1 ($p= 0.015$) cells when compared to IR alone, suggesting that ATRA radiosensitizes NET cells through Pin1 inhibition. ATRA also decreased BRCA1 mRNA levels in QGP1 cells after IR and increased DNA double strand breaks as evidenced by increased gH2AX mRNA and protein expression after treatment. RAR alpha was highly expressed in all 3 cells lines with an average cycle threshold (CT) value of 20.42, 21.44, and 22.90 in QGP1, BON1, and NCI-H727 respectively.

CONCLUSIONS

ATRA radiosensitizes pancreas and lung NET cells through Pin1-inhibition and decreases BRCA1 levels. This ATRA-induced BRCA1-deficient phenotype synergizes with PARP1 inhibition and IR. Further studies will focus on validating these results in animal models.

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