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Inhibition of Estrogen Receptor Alpha Radiosensitizes Neuroendocrine Tumors

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BACKGROUND

The use of peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NETs) is increasing, but PRRT remains palliative at this time. Estrogen (E2) has been extensively linked to cellular proliferation and DNA repair in other cancers. Our aim is to determine whether NET cells are similarly affected by estrogen and whether inhibition of estrogen receptor alpha (ESR1) increases radiosensitivity of NET cells, which could improve PRRT response.

METHODS

Proliferation assays of three NET cell lines including QGP1 (pancreatic), GOT1 (small bowel), and NCI-H727 (lung) were performed with and without E2. ESR1 expression was measured using RT-PCR and ESR1 knockdown was established with siRNA in QGP1 cells. Viability assays combining the ESR1-inhibitor, Fulvestrant, with and without radiation (IR) (4Gy) were done in QGP1 and GOT1 cells. RT-PCR was performed to measure mRNA levels of DNA repair genes including RAD51, BRCA1, and BRCA2 following ESR1 knockdown. Using a QGP1 mouse xenograft, 5 micrograms Fulvestrant was subcutaneously injected 3 times per week, followed by 20Gy of IR, and subsequent changes in tumor volumes and cumulative survival were recorded.

RESULTS

The presence of E2 enhanced cellular proliferation, leading to significantly increased numbers of viable cells in QGP1 ($p < .001$, after 3 days of growth), GOT1 ($p < .001$, after 5 days), and NCI-H727 ($p < .001$, after 5 days) compared to those grown without E2. ESR1 mRNA levels varied across NET cell lines, with QGP1 expressing > 8-fold higher levels when compared to GOT1 and NCI-H727. Transient knockdown of ESR1 using siRNA significantly radiosensitized QGP1 cells ($p < .0001$). This effect was similarly observed in cells treated with Fulvestrant + IR compared to IR alone in QGP1 ($p < .001$) and GOT1 cells ($p < .05$). Following treatment of QGP1 with siESR1, RAD51 ($p < .001$), BRAC1 ($p < .001$), and BRCA2 ($p < .05$) mRNA levels decreased significantly, suggesting that ESR1 affects DNA repair gene transcription in NET cells. In a mouse xenograft model (n=20), treatment with Fulvestrant + IR resulted in slower tumor growth and significantly increased survival when compared to Fulvestrant or IR treated mice alone ($p < .001$).

CONCLUSIONS

Estrogen influences growth of multiple NET cell lines and inhibition of estrogen receptor alpha (ESR1) with siRNA and Fulvestrant radiosensitizes NET cells by decreasing expression of DNA repair genes. Further experiments are needed to validate these results and define the exact mechanism by which ESR1 influences DNA repair.

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