Newly characterized follicular thyroid carcinoma cell lines demonstrate antitumor synergy in response to combined MEK and Akt inhibitors

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ABSTRACT

Follicular thyroid carcinoma (FTC) is a well-differentiated cancer that encompasses 15-20% of all thyroid cancers and invasion is frequently seen in the vascular structures within the thyroid gland and neck. FTC is associated with up to 40% of all thyroid cancer related deaths with no curative treatments beyond surgery and 131Iodine. We report three new authenticated FTC cell lines (SDAR1, SDAR2, SDAR3) from a patient diagnosed with metastatic FTC to a lymph node and neck mass. A fourth FTC cell line (THJ-306T) was derived from another FTC patient, all of which had features of radiiodine insensitive tumors. Short tandem repeat (STR) analysis validated that the cell lines were derived from patient tumor tissues. Interestingly, the SDAR cell lines were not mutated for retinoblastoma (Rb), KRas, HRas, PI3K, BRAFV600E or PAX8/PPARgamma. However, the primary tumor cell line, SDAR1, was mutant for p53. Expression of Pax8 and TSHR mRNA were present while PDS, DIO2, TPO and NIS were absent. For the FTC cell line, THJ-306T, contained Rb and NRas codon 61 mutations and expressed TTF1 and Pax8 mRNA. With respect to oncogenic signaling pathways, pERK and pAkt were elevated in all four cell lines. Based upon these findings we tested and demonstrated antitumor proliferative synergy using a MEK inhibitor (GSK-1120212) combined with an Akt inhibitor (MK-2206). Using IC50 concentrations and fixed ratio drug concentrations, CI values for combinatorial therapy were 0.071, 0.29, 0.24 and 0.29 respectively for SDAR1, SDAR2, SDAR3 and THJ-306T. Progymiod iodide measurement of cell death revealed synergy of the combinatorial therapy. Thus, inhibiting these two oncogenic pathways in four new FTC cell lines demonstrated strong antitumor synergy. We are currently examining the role of Rb/hp which may play a role in the observed synergy. Moreover, with the recent discovery that inhibition of the Akt pathway leads to NIS re-expression and radiiodide uptake, we are exploring whether these cells when exposed to combinatorial therapy respond to iodide uptake and retention.

INTRODUCTION

Follicular thyroid carcinoma (FTC) accounts for ~15-20% of all thyroid cancers and invasion is frequent in vascular structures within the thyroid gland and neck. FTC is associated with up to 40% of all thyroid cancer related deaths with no curative treatments beyond surgery and 131Iodine. We report three new authenticated FTC cell lines (SDAR1, SDAR2, SDAR3) from a patient diagnosed with metastatic FTC to a lymph node and neck mass. A fourth FTC cell line (THJ-306T) was derived from another FTC patient, all of which had features of radiiodine insensitive tumors. Short tandem repeat (STR) analysis validated that the cell lines were derived from patient tumor tissues. Interestingly, the SDAR cell lines were not mutated for retinoblastoma (Rb), KRas, HRas, PI3K, BRAFV600E or PAX8/PPARgamma. However, the primary tumor cell line, SDAR1, was mutant for p53. Expression of Pax8 and TSHR mRNA were present while PDS, DIO2, TPO and NIS were absent. For the FTC cell line, THJ-306T, contained Rb and NRas codon 61 mutations and expressed TTF1 and Pax8 mRNA. With respect to oncogenic signaling pathways, pERK and pAkt were elevated in all four cell lines. Based upon these findings we tested and demonstrated antitumor proliferative synergy using a MEK inhibitor (GSK-1120212) combined with an Akt inhibitor (MK-2206). Using IC50 concentrations and fixed ratio drug concentrations, CI values for combinatorial therapy were 0.071, 0.29, 0.24 and 0.29 respectively for SDAR1, SDAR2, SDAR3 and THJ-306T. Progymiod iodide measurement of cell death revealed synergy of the combinatorial therapy. Thus, inhibiting these two oncogenic pathways in four new FTC cell lines demonstrated strong antitumor synergy. We are currently examining the role of Rb/hp which may play a role in the observed synergy. Moreover, with the recent discovery that inhibition of the Akt pathway leads to NIS re-expression and radiiodide uptake, we are exploring whether these cells when exposed to combinatorial therapy respond to iodide uptake and retention.

RESULTS

Characterization of Four New Follicular Thyroid Cancer Cell Lines

Oncogenic Signaling Identified in FTC Cell Lines

MEK & Akt Inhibitors Inhibit Cell Proliferation

Antitumor Synergy of Combinatorial MEK & Akt Inhibitors

1. We have developed and characterized four new human FTC cell lines, matching genetic and molecular characteristics to that of the parental tumor tissues.

2. We observe over-expression of specific oncogenic pathways (pAkt and pERK) and have demonstrated that targeting these molecular pathways results in antitumor synergy.

Results & Summary

1. Four new FTC cell lines have been added to the small pool of authenticated FTC-derived cell lines thereby expanding the resources currently available for FTC research.

2. These cell lines are sufficiently characterized allowing one to track genetic drift over time and to always be certain of its origin.

3. Screening for oncogenic signaling pathways such as pAkt and pERK in patient tissue microarrays (TMA) will determine the incidence of oncogene overexpression and may provide predictive value for combinational molecular targeted therapy.

4. The ability to derive cell lines from patient tumors, identify the oncogenic pathway involved, and evaluate available therapies, allows for a personalized treatment regimen in the near future, particularly for those cases with recurrent/metastatic disease unresponsive to routinely used therapies.

In Impact and Future Directions

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