INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. While many patients with more differentiated thyroid cancer (DTC) respond well to therapy, anaplastic thyroid cancer (ATC) presents with a very poor prognosis and a median survival of 3-5 months. Thioredoxin interacting protein (TXNIP) is a known tumor suppressor in other cancer cell lines. ATC cells down regulate TXNIP compared to DTC [1]. It has previously been shown that genetic upregulation of TXNIP in ATC cell lines leads to decreased growth and glucose uptake, as well as attenuated tumor growth and decreased metastasis in an orthotopic thyroid cancer model [1]. Finding therapeutic agents that result in increased TXNIP expression could help improve the treatment of ATCs.

Epigenetic modification of cancer cells offers therapeutic potential. Histone deacetylase (HDAC) inhibitors, such as suberoylanilide hydroxamic acid (SAHA), show promise in regulation of different cancers. HDAC inhibitors cause DNA to be less densely packed, leading to increased transcription of certain genes [2]. HDAC inhibitors may not increase TXNIP through the same mechanism. HDAC inhibitors help improve the treatment of ATCs.

METHODS

Three anaplastic thyroid cancer cell lines Hth74, C643, and 8505c were used in these experiments. The cells were incubated with vehicle or control for the times indicated. Cells were scraped and whole cell lysates were examined for TXNIP and acetylated lysine. Cellular TXNIP and acetylated protein levels were evaluated as a loading control. Cell growth was quantitated by Vicell counting.

RESULTS

SAHA Inhibits growth of Hth74 ATC cells and increases TXNIP

Figure 3. 7 day growth curve of SAHA treated Hth74 cells. Day 7 whole cell lysates were evaluated for TXNIP expression.

SAHA Decreases 8505c ATC Cell Growth in a Dose Dependent Manner

Figure 4. 8505c cells were incubated for 3 days with increasing SAHA concentrations. Cell growth was normalized to DMSO treated 8505c cells.

SAHA Increases TXNIP in a Dose Dependent Manner

Figure 5. A. TXNIP expression after 24hrs of exposure with the concentration SAHA shown. B. Immunoprecipitation for TXNIP from Hth74 cells.

CONCLUSIONS

SAHA and VPA increase TXNIP in ATC cell lines.

8505c cell lines have a modest, but inconsistent increase in TXNIP with HDAC inhibitors.

HDAC inhibitors may not increase TXNIP through the same mechanism.

SAHA is a potential therapeutic agent for advanced thyroid cancers.

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REFERENCES