Targeting Thyroid Hormone Mediated Cancer Stem Cell Expansion, Treatment Resistance in ER+ Breast Cancer Patients

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\textbf{ABSTRACT}

Thyroid hormone (TH) treatment increases anti-estrogen resistance in HER2-negative breast cancer (BC) patients. Here we show that TH treatment also increases the expansion of a resistant subpopulation of BC cells. In ER+ BC cells TH reduced Tam mediated growth inhibition, whereas ICI treatment was mildly inhibitory. IHC staining revealed that the increase in Ki67+ cells was associated with a significant decrease in HR expression. The ESR1 gene was downregulated in TH treated cells, whereas THBS1 and FOS were upregulated. The individual expression of THBS1 and FOS were not significantly correlated with Ki67 expression. Gene set enrichment analysis revealed a significant enrichment of cell cycle regulatory genes and proteins only in ER+ BC cells, indicating a major role for these receptors in cross-talk of TH and E2. These results confirm our hypothesis, that TH can independently target a subpopulation of ER+ BC cells that were resistant to anti-estrogen treatment. Moreover, TH induced a significant increase of ALDH+ cells, implicating a role for TH in cancer stem cell expansion in ER+ BC cells. This is the first study to show that TH treatment increases ER+ BC cell proliferation, and suggests a strategy of TH treatment together with anti-estrogen treatment to target a resistant subpopulation of ER+ BC cells.

\textbf{RESULTS}

Figures 1-5 show representative images from the experiments described in the results section. The figures include graphs and images depicting the effects of TH and anti-estrogen treatment on cell proliferation, Ki67 expression, and ALDH+ cell expansion in ER+ BC cells.

\textbf{CONCLUSIONS}

1. TH treatment increases ER+ BC cell proliferation by targeting a subpopulation of cells that are resistant to anti-estrogen treatment.
2. TH induced a significant increase of ALDH+ cells, implicating a role for TH in cancer stem cell expansion in ER+ BC cells.

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