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Thyroid

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mTOR Signaling is Associated with Regulation of Mitochondrial Respiration in Thyroid Cancer

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Background: Thyroid cancers (TC) are divided into BRAF-like and RAS-like tumors based on their molecular signature. The mTOR (mammalian target of rapamycin) signaling pathway is commonly activated in RAS-like tumors. Oncogene-driven signaling pathways are involved in the regulation of intracellular metabolism, including glycolysis and oxidative phosphorylation (OXPHOS). There is inadequate information on the role of mTOR signaling in the regulation of TC metabolism. The purpose of this study was to determine the association between mTOR signaling and mitochondrial respiration in TC.

Methods: We conducted an in vitro study using 4 TC cell lines (2 BRAF-like, 2 RAS-like) characterized by variable activation of mTOR signaling pathway, as documented by immunoblotting to quantify a ratio of p-mTOR/mTOR. OXPHOS was measured through oxygen consumption rate (OCR) of TC cells by the Seahorse XF Cell Mito Stress Test Assay. Standard MTT assay was performed to evaluate cell proliferation. A specific mTOR inhibitor (rapamycin) as well as an mTOR activator (leucine) were used for functional studies. The association between OCR and p-mTOR/mTOR was calculated by Pearson correlation coefficient (r). The one-way Anova or Kruskal-Wallis test were used for between group comparisons, as appropriate. P-values of ≤ 0.05 were considered statistically significant.

Results: The baseline activation of mTOR signaling in TC cells correlated with baseline (r=0.75, p=0.04) and maximum OCR (r=0.91, p=0.01). In addition, the RAS-like cell lines with the highest activation of mTOR showed considerable response after inhibition of mTOR with rapamycin by inhibiting baseline OCR (FTC133: 6320 ± 1531 vs 3368 ± 651 pmol/min/mg, p=0.01; THJ29T: 4484 ± 514 vs 3067 ± 620 pmol/min/mg, p=0.047), while the TC cell lines with minimal baseline mTOR activation did not show change in mTOR phosphorylation status nor basal OCR after rapamycin treatment (TPC1: 1817 ± 201 vs 1974 ± 336 pmol/min/mg, p>0.99, BCPAP: 1051 ± 162 vs 1130 ± 228 pmol/min/mg, p>0.99). Treatment with rapamycin significantly reduced cell proliferation rates in all examined cells. On the other hand, treatment with the mTOR activator leucine increased both mTOR phosphorylation and basal OCR in TC cell lines characterized by minimal baseline mTOR activation (TPC1: 1778 ± 280 vs 2372 ± 249 pmol/min/mg, p=0.004, BCPAP: 1581 ± 603 vs 2064 ± 560 pmol/min/mg, p=0.04), but did not significantly increase OCR further in cell lines with high baseline mTOR activation and OXPHOS rate (FTC133: 4512 ± 683 vs 5355 ± 870 pmol/min/mg, p=0.27; THJ29T: 3881 ± 880 vs 4764 ± 1273 pmol/min/mg, p=0.14).

Conclusion: mTOR signaling is associated with the regulation of mitochondrial respiration as its inhibition decreases OXPHOS rate, while its activation results in increased mitochondrial respiration. The change in mitochondrial respiration might be one of the mechanisms of the growth inhibition caused by medications targeting mTOR signaling in TC.

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