

## INCREASED CYP24A1 GENE EXPRESSION IS ASSOCIATED WITH BRAFV600E MUTATION AND ADVANCED DISEASE STAGE IN PAPILLARY THYROID CARCINOMA

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**Background/Purpose:** 1, 25(OH)<sub>2</sub>D<sub>3</sub>, the active form of vitamin D, has been shown to exert antiproliferative effects in many cancers. Overexpression of *CYP24A1*, the primary vitamin D-inactivating enzyme, is also observed in a variety of human cancers, thus potentially neutralizing the antitumor effect of 1, 25(OH)<sub>2</sub>D<sub>3</sub>. The expression of *CYP24A1* has not been systematically studied in thyroid cancer. In the present study, we investigated 57 papillary thyroid carcinoma (PTC) specimens for *CYP24A1* expression, and its association with *BRAF* mutation and disease progression.

**Methods:** *CYP24A1* expression was measured by qPCR and *BRAF*<sup>V600E</sup> mutation was detected by direct DNA sequencing analysis. The interaction between *BRAF*<sup>V600E</sup> and *CYP24A1* expression was determined by Western blot and real-time RT-PCR.

**Results:** *CYP24A1* expression was increased in PTC as compared to benign multinodular goiter. The expression is further increased in stage III and IV tumors. There is a strong association between *CYP24A1* overexpression and *BRAF*<sup>V600E</sup> mutation (p<0.01). In thyroid cancer cells expressing *BRAF*<sup>V600E</sup>, *CYP24A1* expression was increased by at least 3 fold when compared to those without *BRAF*<sup>V600E</sup> expression. Furthermore, *BRAF* inhibitor PLX4720 can significantly reduce *CYP24A1* expression and enhance the antiproliferative effects of calcitriol in thyroid cancer cell lines.

**Discussion & Conclusion:** *CYP24A1* overexpression is a poor prognostic indicator for PTC and may reflect *BRAF*<sup>V600E</sup> mutation and MARK activation. The cross-talk between vitamin D and MAPK signaling pathways may result in resistance to calcitriol mediated anti-tumor effects and the resistance can be reversed by *BRAF* inhibitor PLX4720.

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