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)2D3, 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)2D3. 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 BRAFV600E mutation was detected by direct DNA sequencing analysis. The interaction between BRAFV600E 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 BRAFV600E mutation (p<0.01). In thyroid cancer cells expressing BRAFV600E, CYP24A1 expression was increased by at least 3 fold when compared to those without BRAFV600E 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 BRAFV600E 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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