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

Zou, Minjing[1]; Alzahrani, Ali[1]; Bin Humaid, Faisal[1]; Baitei, Essa[1]; Parhar, Ranjit[1]; Al-Mohanna, Futwan[1]; Meyer, Brian[1]; Shi, Yufei[1]
[1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Background/Purpose: 1, 25$(OH)_2D_3$, 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$(OH)_2D_3$. 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 $BRAF^{V600E}$ mutation was detected by direct DNA sequencing analysis. The interaction between $BRAF^{V600E}$ 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 $BRAF^{V600E}$ mutation ($p<0.01$). In thyroid cancer cells expressing $BRAF^{V600E}$, *CYP24A1* expression was increased by at least 3 fold when compared to those without $BRAF^{V600E}$ 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 $BRAF^{V600E}$ 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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