Transcriptomic profiling of parathyroid tumors reveals distinctive molecular characteristics of carcinoma and adenoma

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Abstract

Parathyroid carcinoma is a rare malignancy which remains as a clinical unmet need lacking effective therapeutic intervention. In this study, we compared mutational profile of parathyroid carcinoma, adenoma, and normal parathyroid tissue using RNA-Seq based transcriptomics analysis and whole-exome sequencing. A total of 50 parathyroid specimens [parathyroid carcinoma (n=12), adenoma (n=28), and normal tissue incidentally obtained from thyroidectomy for various reasons (n=10)] from 50 individuals (women n=41, 80%) were analyzed. CDC73 mutation was found in 7 of 12 carcinoma specimens, which harbored germline mutation in 6 of them.

Transcriptional profiling revealed 647 carcinoma-specific differentially expressed genes (DEGs) compared to adenoma and normal tissues. Hierarchical clustering with carcinoma-specific DEGs detected two distinctive clusters (carcinoma clusters vs. normal and adenoma clusters). Carcinoma-specific DEGs include upregulation of WT1, SLC17A8, ANGPTL4, PRUNE2, MYC and downregulation of PIK3C2G. Carcinoma-specific DEGs were associated with MYC targets, G2M check point, and epithelial mesenchymal transition pathway by gene set enrichment analysis. Among carcinomas, $CDC73^{Mut}$ and $CDC73^{WT}$ differ by 393 DEGs, which revealed association of $CDC73^{Mut}$ with MYC targets whereas $CDC73^{WT}$ was associated with epithelial mesenchymal transition. (Immunohistochemistry staining of FFPE samples revealed relatively high WT1 expression in carcinoma compared to adenoma and normal tissues.)

We did not find any germline/somatic mutated gene other than CDC73, and confirmed a significantly high mutational burden in the CDC73 mutated carcinoma group. Furthermore, we found a significant allelic imbalance in CDC73 by combining allele frequency information of germline/somatic mutations in the CDC73 region and copy number status of the region, which suggests that there is a selective pressure that favors the CDC73-null environment in parathyroid carcinoma.

In summary, parathyroid carcinoma had distinctive transcriptional profiles compared to normal parathyroid tissue and parathyroid adenoma, which might provide additional diagnostic value.