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Integration Of Epigenomics And Metabolomics Reveals New Signaling In Aggressive Thyroid Cancer

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Although genetic mutations are causal in human cancers, the contribution of chromatin changes to cancer onset and progression remains less well understood. Multi-omics profiling of human tumors can provide insight into how alterations in chromatin structure are propagated through the pathway of gene expression to result in cancer signaling. We applied multi-omics profiling of 36 human thyroid cancer primary tumors, metastases, and patient-matched normal tissue. Over 80% of the tumors harbored BRAFV600E mutations, and the remaining tumors mostly had activating mutations in the MAPK pathway. Through quantification of chromatin accessibility associated with active transcription units and global protein expression, we identify local enhancers that are highly correlated with coordinated RNA and protein expression. The enhancers are predicted to be actively bound by MAPK transcription factor, indicating they are under MAPK control. These cancer-specific enhancers associated with upregulation of lysosomal peptidase expression and dipeptide abundance in tumors. We show that upregulated dipeptides stimulate MAPK activity, and BRAF inhibition results in loss of lysosomal function in mutants. Perturbation of lysosomal peptidases and dipeptide abundance decreases MAPK activity only in mutant cells compared to wildtype. These analyses suggest that BRAF thyroid tumors integrate MAPK-driven epigenetic regulation with lysosomal metabolite signaling in a positive feedback circuit. Using local cancer-specific epigenetic features, we isolated key cancer signaling, making way for potential targets for cancer therapeutics.

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