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BPTF role in melanoma progression and BRAF resistance therapy

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Bromodomain PHD finger transcription factor (BPTF) plays an important role in chromatin remodeling, but its functional role in tumor progression is incompletely understood. Here we reveal new pro-oncogenic roles for BPTF in promoting tumor cell proliferation and resistance to targeted therapies. shRNA-mediated BPTF silencing suppressed the proliferative capacity (by 65.5%) and metastatic potential (by 66.4%) of melanoma cells. Elevated *BPTF* copy number (mean $\geq$ 3) was observed in 28 of 77 (36.4%) melanomas. BPTF overexpression predicted poor survival in a cohort of 311 melanoma patients (distant metastasis-free survival, p=0.03, and disease-specific survival p=0.008), and promoted resistance to BRAF inhibitors in melanoma cell lines. Metastatic melanoma tumors progressing on BRAF inhibitors contained low BPTF-expressing, apoptotic tumor cell sub-clones, indicating the continued presence of drug-responsive sub-clones within tumors demonstrating overall resistance to anti-BRAF agents. These studies demonstrate multiple pro-tumorigenic functions for BPTF, and identify it as a novel target for anti-cancer therapy. They also suggest the combination of BPTF targeting with BRAF inhibitors as a novel therapeutic strategy for melanomas with mutant BRAF.