Bmi1-driven PTEN/TP53 loss promotes prostate cancer progression and treatment resistance by leveraging metabolic dependency.

Introduction and Objective: Concurrent inactivation of PTEN and TP53 is often observed in aggressive prostate cancers (PCs) that resist androgen deprivation therapy (ADT) and show poor clinical outcomes. The identification of targetable vulnerabilities that result from loss of both PTEN and TP53 is urgently needed. Here, we used transgenic, cell line and PDX models to investigate the functional roles of Bmi1-driven PTEN/TP53 loss in PC progression and treatment resistance, and potential vulnerabilities that could be targeted therapeutically.

Methods: We have established clinically relevant animal models of prostate cancer recurrence using transgenic Bmi1-CreER; PTENf/f; TP53f/f (hereafter referred to as BC-PTEN/TP53 mice) and PDX mice. A tissue recombination strategy was used to rescue transgenic BC-PTEN/TP53 mouse prostates by regeneration as grafts in SCID mice. Tumors were characterized by histology, immunohistochemistry for relevant markers, and gene expression profiling by RNA-seq. Our findings were validated using genetic and pharmacologic approaches in relevant cell lines and mouse models.

Results: Combined PTEN and TP53 deletion in Bmi1-expressing prostate cells strongly accelerated formation of prostate cancer comprising diverse phenotypes including AR-negative PCs. Notably, following castration, BC-PTEN/TP53 mice develop castration-resistant PC (CRPC) that exhibits extensive phenotypic plasticity and cellular heterogeneity. In BC-PTEN/TP53 mice, CRPC phenotype is significantly associated with enhanced cell proliferation, the loss of AR expression, and a profound decrease in the fraction of p16-mediated senescent cells. Genomic profiling analysis revealed significant enrichment of genes involved in mitochondrial and amino acid metabolism. Genetic or pharmacological inhibition of Bmi1 significantly suppressed the survival of enzalutamide-resistant PC cells lacking PTEN/TP53 with simultaneous decrease in gene sets associated with metabolic pathways. Moreover, inhibition of mitochondrial or amino acid metabolism resulted in significant growth suppression.

Conclusions: These results highlight the cooperative roles of Bmi1 with PTEN/TP53 loss in facilitating PC progression and therapeutic resistance by regulating metabolic vulnerabilities. This may provide a rational for targeted therapy to selectively eradicate PTEN/TP53-deficient tumors.