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Epigenetic MTAP Loss Expands the Therapeutic Window of PRMT5 Inhibition in Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), particularly small bowel NETs (sbNETs) and pancreatic NETs (pNETs), are increasingly diagnosed yet remain biologically underdefined and therapeutically challenging in patients with advanced disease. Their low mutational burden and immune-excluded biology limit current targeted and immunotherapy options. One emerging vulnerability centers on MTAP, the rate-limiting enzyme of the methionine salvage pathway. MTAP loss leads to methylthioadenosine (MTA) accumulation, partial PRMT5 suppression, and dependence on MAT2A-mediated S-adenosylmethionine availability, supporting PRMT5/MAT2A inhibition as a synthetic-lethal strategy in MTAP-deficient cancers. MTAP loss in most cancers arises from 9p21.3 co-deletion with CDKN2A, whereas well-differentiated GEP-NETs, particularly sbNETs, silence MTAP epigenetically while retaining an intact genomic locus. We investigated whether epigenetic MTAP loss is common in GEP-NETs and serves as a biomarker for therapeutic vulnerability.

METHODS

We assembled two GEP-NET cohorts (17 sbNETs, 20 pNETs; primary and metastatic) and assessed MTAP protein by IHC with paired copy number analysis of the MTAP locus. Mechanistic studies used QGP1 and NECT2 cell lines and patient-derived organoid models, including doxycycline (Dox)-inducible genetically modified PDOs (GM-PDOs) recapitulating features of parental G1/G2 tumors in the Dox-off state. MTAP protein was measured by western blot, and epigenetic regulation was tested with decitabine. The MTAP-PRMT5 axis was functionally assessed by MTA accumulation and global symmetric dimethylarginine (SDMA) level, a pharmacodynamic readout of PRMT5 activity. CRISPR-mediated MTAP knockout models tested causal sensitivity to PRMT5/MAT2A inhibitors.

RESULTS

Near-complete MTAP protein loss by IHC occurred in 13 of 17 sbNETs (76.5%) and 5 of 20 primary pNETs (25.0%). Copy number analysis showed retention of the MTAP locus in sbNET tumors with MTAP protein loss and their matched PDOs, indicating that MTAP loss is predominantly epigenetic rather than genomic. MTAP protein was similarly reduced across GM-PDOs and GEP-NET cell lines relative to MTAP-proficient controls despite an intact locus, and decitabine restored MTAP expression in both models, supporting epigenetic regulation. CRISPR-mediated MTAP knockout recapitulated the metabolic and signaling consequences of MTAP loss, increasing MTA accumulation, reducing global SDMA levels, and sensitizing GM-PDO and cell-line models to PRMT5/MAT2A inhibition.

CONCLUSIONS

These findings identify epigenetic MTAP loss as a frequent, functionally meaningful event in GEP-NETs, especially sbNETs. Despite an intact locus, epigenetic MTAP loss drives the MTA accumulation, PRMT5 suppression, and inhibitor sensitivity classically associated with genomic MTAP deletion, extending the MTAP-PRMT5 synthetic-lethal strategy beyond genomically deleted cancers to epigenetically silenced NETs and informing biomarker-driven therapy in other tumors with epigenetic MTAP loss.

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