Conclusion Expression of TROP-2 in cervical cancer is associated with increased levels of intratumoral TILs, indicating the potential therapeutic target for TROP-2 targeted antibody-drug conjugate alone or in combination with immune checkpoint inhibitors.

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FUNCTIONAL CHARACTERIZATION OF NRIP1 IN ENDOMETRIAL CANCER; MUTATIONS ASSOCIATES WITH AGGRESSIVE FEATURES WHILE LOW EXPRESSION LEVELS PREDICT POOR SURVIVAL

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Introduction/Background NRIP1, encoding an obligate corepressor to the estrogen receptor alpha (ERα), is a significantly mutated gene in endometrial cancer (EC) with possible implications on hormone signaling and cancer development. We aimed at determining the prognostic impact of NRIP1 mutations and mRNA expression in patients with ERα-positive EC, and functionally test patient-observed mutations in vitro on ERα-dependent transcriptional activity.

Methodology Sanger sequencing of recurring NRIP1 frameshift mutations was performed on 242 EC patients enriched for ERα-positive tumors (endometrioid histology). Transcriptional profiles of 305 patients, in part overlapping with the sequenced samples, were used to investigate differentially expressed genes between NRIP1 mutated/non-mutated tumors, and to determine the relation of NRIP1 mutation status with expression and patient survival. A dual-luciferase reporter assay was used to uncover the effect of NRIP1-mutants on ERα-regulated gene transcription using COS-1 cells.

Results Hotspot NRIP1 mutations were identified in 5.4% of the samples, and associated with high FIGO-stage, deep myometrial infiltration, and positive lymph-node status. However, there was no significant difference in disease-specific survival between patients with mutated and wildtype NRIP1, and mutation status did not associate with NRIP1 expression levels. Interestingly, reporter assays showed that the repressive effect of wildtype NRIP1 was significantly abolished with NRIP1 mutants. Further, low NRIP1 expression levels were significantly associated with decreased disease-specific survival, high grade, negative ERα status and low BMI. Gene Set Enrichment Analysis revealed an increase in gene sets related to proliferation in NRIP1 mutated tumors.

Conclusion The relatively low mutation rate hampers a firm conclusion on the prognostic value of NRIP1 frameshift mutations in endometrioid EC. However, low NRIP1 expression may be a marker of poor prognosis. Our functional investigations demonstrate that frameshift mutated NRIP1, compared to wildtype NRIP1, have a significantly reduced corepressor effect on ERα-transcriptional activity, suggesting a possible effect on estrogen signaling.