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Summary

TUMOR-DERIVED EXOSOMAL DDX3X REPROGRAMS TUMOR-ASSOCIATED NEUTROPHILS TO DRIVE IMMUNE CHECKPOINT BLOCKADE RESISTANCE IN GASTRIC CANCER

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Tumor-derived exosomal DDX3X drives immune checkpoint blockade resistance in gastric cancer by reprogramming neutrophils to suppress CD8⁺ T cells, and targeting DDX3X with the small-molecule inhibitor RK-33 synergizes with anti–PD-1 therapy to reduce tumor burden and restore T-cell infiltration in preclinical models.

KEY POINTS

- EV/ESCRT signature scores were elevated in ICB non-responders and selectively correlated with MDSC-like and PMN-MDSC-like infiltration and T-cell exhaustion in TCGA-STAD, implicating tumor extracellular vesicle biogenesis in neutrophil-driven immune evasion.
- Intersectional TEV proteomics from gastric cancer cell lines SNU-719 and MKN-45 versus normal gastric epithelium GES-1 nominated DDX3X as a top GC-enriched cargo, with single-cell analysis localizing DDX3X expression predominantly to malignant epithelial cells.
- Multiplex immunofluorescence of patient tumors showed DDX3X-high regions harbored increased tumor-associated neutrophil infiltration alongside reduced CD8⁺ T-cell density.
- TEV-delivered DDX3X was internalized by neutrophils and reprogrammed them toward an immunosuppressive phenotype characterized by ARG1 upregulation, which in turn blunted CD8⁺ T-cell proliferation and effector cytokine production.
- In orthotopic YTN16 syngeneic gastric cancer models, the DDX3X small-molecule inhibitor RK-33 synergized with anti–PD-1 blockade, markedly reducing tumor burden and restoring intratumoral CD8⁺ T-cell infiltration and effector function compared with either monotherapy.

– Co-targeting the TEV–DDX3X–neutrophil axis represents a rational combinatorial strategy to overcome resistance and broaden clinical benefit from immune checkpoint blockade in gastric cancer.

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