

Stromal precision targeting sensitizes mouse pancreatic cancer to immune checkpoint inhibition

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is largely resistant to immunotherapy. Dense extracellular matrix (ECM) and dysfunctional blood vessels restrict immune access. We investigated whether targeted stromal remodelling could alleviate immunosuppression, induce tertiary lymphoid structures (TLS) and improve responses to anti-PD-1 therapy.

Methods

Vascular and ECM targeting were assessed in autochthonous KPC tumours, orthotopic KPC tumours co-implanted with syngeneic cancer-associated fibroblasts, and resected human PDAC tissue ex vivo. Tumour-bearing mice received vascular-targeted LIGHT (LIGHT-VTP), alone or with anti-PD-1. In established orthotopic tumours, low-dose ECM-targeted TNF α (TNF α -CSG) was administered before combination therapy. Peptide binding, perfusion, hypoxia, TLS organisation, immune infiltration, tumour growth and survival were evaluated.

Results

VTP and CSG selectively bound tumour vessels and ECM, respectively, in mouse and human PDAC. LIGHT-VTP increased the proportion of perfused vessels from approximately 15% to 40–50%, reduced hypoxia and induced TLS. Adding anti-PD-1 increased centrally located TLS and CD21/CD35-positive follicular structures consistent with TLS maturation, and prolonged survival compared with LIGHT-VTP alone. TNF α -CSG priming relieved vascular compression and increased VTP binding from approximately 40% to 60%. In established tumours, triple therapy enhanced T- and B-cell infiltration, reduced tumour growth and further prolonged survival compared with dual treatment with LIGHT-VTP plus anti-PD-1.

Conclusion

Co-targeting tumour vessels and ECM enables TLS induction and improves checkpoint therapy efficacy in preclinical PDAC. These findings support further translational development of stromal priming strategies, including evaluation in a neoadjuvant setting.