ADAM10 promotes pancreatic cancer progression and modulates the immune microenvironment

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest cancers, with a five-year survival rate below 15% [1]. New treatment options are urgently needed. ADAM10, a membrane-bound metalloprotease, is overexpressed in pancreatic tumour cells and contributes to stromal fibrosis and metastasis [2,3]. We set out to investigate the role of ADAM10 as a potential target for antibody–drug conjugate (ADC) therapy [4].

Methods

We generated ADAM10 knockout (KO) KPC lines using CRISPR-Cas9. ADAM10 KO and control cells were analysed in vitro and as subcutaneous tumours in immunocompetent C57BL/6 mice to evaluate tumour growth kinetics. Quantitative mass spectrometry was used to identify differentially shed proteins in conditioned media (the secretome) from control and KO cells and differentially expressed proteins in tumour samples. Tumour tissues were analysed by western blot/immunohistochemistry to assess expression of key markers.

Results

ADAM10 KO cells showed reduced proliferation and impaired wound-healing capacity in vitro, and analysis of the secretome identified changes in proteins involved in adhesion, ECM organisation, and other transmembrane receptor signalling. ADAM10 KO tumour growth was significantly slower in vivo, and proteomics showed changes in matrix and immune-related pathways. Notably, ADAM10 KO tumours also showed increased CD8+ T cell infiltration, and a greater response to the anti-PD1 treatment.

Conclusion

Loss of ADAM10 decreases tumour growth and enhances anti-tumour immunity by modulating ECM and immune cell activation pathways within the pancreatic cancer microenvironment. These findings highlight ADAM10 as a promising therapeutic target, with potential to improve immunotherapy responses in PDAC. We are now evaluating ADC treatment in immunocompetent models.

References

1. Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. CA: A Cancer Journal for Clinicians, 74(1), 12-49. Retrieved from https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.3322/caac.21820. doi:https://doi.org/10.3322/caac.21820
2. Gaida MM, Haag N, Günther F, Tschaharganeh DF, Schirmacher P, Friess H, et al. Expression of A disintegrin and metalloprotease 10 in pancreatic carcinoma. International journal of molecular medicine. 2010;26(2):281-8.
3. Mueller AC, Piper M, Goodspeed A, Bhuvane S, Williams JS, Bhatia S, et al. Induction of ADAM10 by Radiation Therapy Drives Fibrosis, Resistance, and Epithelial-to-Mesenchyal Transition in Pancreatic Cancer. Cancer Research. 2021;81(12):3255-69.
4. Atapattu L, Saha N, Chheang C, Eissman MF, Xu K, Vail ME, et al. An activated form of ADAM10 is tumor selective and regulates cancer stem-like cells and tumor growth. J Exp Med. 2016;213(9):1741-57.


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