

Therapeutic potential of co-targeting PRMT5 and MAT2A in MTAP-loss pancreatic cancer

Johana Luhur¹, Diego Chacon Fajardo^{1,2}, Emer Cahill¹, Henry Barraclough-Franks¹, Silvia Lombardi¹,
Yasir Mahmood¹, Braydon Meyer^{1,2}, Clare Stirzaker^{1,2}, Sean Porazinski^{1,2}, Marina Pajic^{1,2}

1 The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, New South Wales, Australia

2 St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Sydney, Australia

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with genetic and epigenetic alterations and desmoplastic stroma. Standard-of-care chemotherapies offer only modest benefit in unselected populations, highlighting the need for personalised treatments. PRMT5 (protein arginine methyltransferase 5) is a synthetic lethal target in MTAP-deleted tumours, and *CDKN2A/MTAP* co-deletion occurs in approximately 30% of PDAC [1, 2]. MAT2A (methionine adenosyltransferase 2A) further deepens this dependency [1].

Methods

Multiple MTAP-loss patient-derived xenografts were implanted subcutaneously into immunodeficient mice and treated with the MTA-cooperative PRMT5 inhibitor (MRTX-1719) [3] and/or the MAT2A inhibitor (AG-270) [4]. Patient-derived cell lines were also injected orthotopically into the pancreas and treated with MRTX-1719 alone or combined with AG-270. Tumour growth, survival, tumour histology, and metastatic colonisation of the liver and lungs were assessed.

Results

MTA-cooperative PRMT5 inhibition alone reduced tumour growth and extended survival in most MTAP-loss subcutaneous models, although one model was resistant despite confirmed target engagement. In contrast, a subcutaneously responsive model showed no response to monotherapy in the orthotopic setting, suggesting that the pancreatic microenvironment limits PRMT5 inhibitor efficacy. Combination with MAT2A inhibition significantly reduced tumour growth and prolonged survival, with increased apoptosis and decreased tumour cell proliferation. Either monotherapy or combination treatment did not prevent metastatic colonisation of the liver and lungs, despite sustained target engagement in the metastatic lesions.

Conclusion

Combined PRMT5 and MAT2A inhibition improves primary tumour control where monotherapy fails, but does not prevent metastatic spread. Whether stromal MTAP activity accounts for the reduced efficacy of MTA-cooperative inhibition *in vivo* remains to be determined.

References

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