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Poster Abstract Form

Targeting Copper in combination with standard-of-care chemotherapy reduces fibrosis and metastasis in PDAC

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal survival outcome which has seen limited improvement in the past decades, mainly due to the dense, collagen-rich stroma that infiltrates and encapsulates the tumour. This stroma is known to diminish chemotherapy efficacy. Recently, studies have proposed copper depletion approaches in cancer due to the observation that excess copper is linked to cancer progression and metastasis. Copper is an essential trace element in several fundamental biochemical processes including mitochondrial respiration and extracellular matrix formation. Copper chelators such as Ammonium tetrathiomolybdate (ATTM) are already approved for use in copper accumulation diseases and are under investigation in other forms of cancer. However to date, they have not been investigated in PDAC.

Methods

We aimed to explore the effect of ATTM in PDAC in combination with standard-of-care chemotherapy, in both 3D physiologically relevant *in vitro* and orthotopic *in vivo* models of PDAC.

Results

Our data shows that ATTM inhibits the activity of lysyl oxidases, the major cuproenzyme family responsible for fibrillar collagen biogenesis, in cancer cells and cancer-associated fibroblasts. Additionally, ATTM significantly reduces the metabolic activities of both stromal and cancer compartments through inhibiting key intracellular cuproenzymes. When used in combination with chemotherapy, ATTM reduces fibrosis and liver metastasis *in vivo* compared to chemotherapy alone in an immunocompetent orthotopic model.

Conclusion

Our data present strong evidence for repurposing an approved copper chelator to target both intracellular and extracellular copper-dependent metalloenzymes in combination with chemotherapy in difficult-to-treat solid tumours such as PDAC.