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Poster Abstract Form

Targeting Epigenetic inhibition as a therapeutic for Pancreatic Cancer

Layla-Rose Lynam, Jason S Lee

Epigenetics and Precision Medicine Group, Frazer Institute, University of Queensland

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a tremendously high mortality rate, causing a 5-year survival rate of less than 13%[1,2]. This poor prognosis is primarily due to a lack of methods for early detection and therapeutic resistance[1,2]. Therapeutic resistance including to immunotherapies is driven by the highly complex and desmoplastic tumour microenvironment (TME) which features fibroblasts, a dense extracellular matrix, an underdeveloped vascular system, and suppressive immune cells[1,2]. Therefore, regimens that not only attenuate fibrosis but also enhance immune responses are essential. Euchromatic histone methyltransferase 2 (EHMT2), also known as G9a is frequently over expressed in various cancers[3-5]. Preclinical studies in melanoma, breast and ovarian cancer have demonstrated that inhibiting G9a enhances immune-check point inhibitor efficacy[3-5]. Furthermore, G9a inhibition has resulted in attenuated fibrosis in renal and liver cancer[6,7]. TCGA data shows that 32% of PDAC patients have EHMT2 amplification or copy number gain. Therefore, we hypothesis that G9a inhibition could attenuate the desmoplastic environment and act synergistically to enhance immunotherapies in PDAC.

Our preliminary RTqPCR data has shown increased immunostimulatory marker expression in response to G9a Inhibition in PDAC cell lines. G9a inhibition in fibroblasts has shown decreased pro-fibrotic gene and increased anti-fibrotic gene expression. To expand on these findings, we will perform co-cultures of G9a-inhibited PDAC cell lines with CAFs or PBMCs and In-vivo experiments testing the effects of G9a inhibition on immunotherapy efficacy and fibrosis.

These studies could overcome the issue of therapeutic resistance, therefore significantly improving PDAC patient outcomes.

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