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**FAK suppresses antigen processing and presentation to promote immune evasion in pancreatic cancer**

Canel M, Sławińska A, Lonergan D, et al. [FAK suppresses antigen processing and presentation to promote immune evasion in pancreatic cancer.](https://gut.bmj.com/content/73/1/131) Gut 2024; 73:131-155. doi: 10.1136/gutjnl-2022-327927

Pancreatic cancer is set to become the second-leading cause of cancer mortality within the next decade. With immunotherapies having limited efficacy in this patient population, there is urgent need to identify new treatment therapies.

Studies have established focal adhesion kinase (FAK) activity is elevated in pancreatic ductal adenocarcinoma (PDAC), and FAK inhibitors in combination with immunotherapies are currently in clinical trials. Canel et al., investigated the immunoregulatory function of FAK, with particular focus on cell-intrinsic mechanisms, to identify additional targets of therapy.

Canel et al., demonstrated that FAK-/- cancer cells derived from mouse KrasG12Dp53R172H (KPC) tumours reprogrammes the cellular response to IFNγ (interferon gamma) to promote immunosurveillance. Mechanistically, this is by upregulation of class-I transcriptional co-activator NLRC5 (NLR Family CARD Domain Containing 5), which aids in expression of the immunoproteasome. Furthermore, co-depletion of FAK and STAT3 (Signal transducer and activator of transcription 3) enabled extensive infiltration of CD8 (cluster of differentiation 8) T-cells in these models. Importantly, FAK’s role in regulating antigen processing and presentation is diminished as cells differentiate towards an extreme squamous phenotype.

These findings were corroborated when undertaking proteomic analysis using human patient-derived pancreatic cancer cell lines (PDCLs). Heterogeneity was ensured in that classical and squamous cell subtypes were represented. FAK expression was deleted in PDCLs using CRISPR-Cas9 (Clustered regularly interspaced palindromic repeats-CRISPR-associated protein 9) gene editing. Further validation was obtained from dataset analysis from the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA).

PDAC is generally regarded as an immunologically ‘cold’ tumour type, devoid of CD8 T-cell infiltration and unresponsive to single-agent immunotherapy. These findings posit that targeting FAK protein degradation could bring additional therapeutic benefit.