Sex-specific spatial reorganization of the tumour-immune interface with HLA loss

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Background and rationale
Pancreatic cancer is one of the leading cancer-related causes of death with a five-year survival rate of 10%. Immunotherapies are treatments that leverage the immune system to recognize and kill cancer cells. These treatments have transformed outcomes in several cancer types but have shown little benefit in pancreatic cancer for unknown reasons. A possible explanation is that some pancreatic tumours lose genes located in the HLA region, which are required for displaying cancer-derived protein fragments to immune cells. A loss of these genes impairs killer T cells in recognizing cancer cells in a process known as immune escape that has previously been linked to immunotherapy resistance. However, the extent to which immune-escape mechanisms occur in pancreatic cancer or how it shapes the tumour-immune system interaction is unknown.

Objective
The goal of this work is to characterize the frequency of HLA loss in pancreatic cancer and its association with patient outcomes and interaction with the immune system, including how this loss affects the physical proximity of immune cells to tumour cells and how this is modulated by patient sex.

Methods and Results
In this work we combined whole-genome sequencing, RNA sequencing, and advanced multiplexed imaging from the largest epithelium-enriched pancreatic cancer cohort to date. We then built machine learning tools to integrate these results with existing single-cell and spatial transcriptomics cohorts.

We find that 26% of patients have undergone HLA loss and that this usually occurs early during tumour development. Strikingly, we then identified a sex specific difference in the tumour-immune interface between samples with and without HLA loss.

Conclusion(s)
We identified HLA loss to be a common, early event that reshapes how tumours organize themselves relative to immune cells in a sex-specific manner, suggesting sex is an important determinant of immune system dynamics in pancreatic cancer.

Anticipated Impact
Our findings offer a clearer picture of how pancreatic tumours hide from the immune system. By identifying which patients have tumours with HLA loss and understanding how this differs between men and women this research may help stratify patients into groups more or less likely to benefit from immunotherapy, thus guiding development of better targeted treatment strategies.