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Epigenetic promoter alterations in GI tumour immune-editing and resistance to immune checkpoint inhibition

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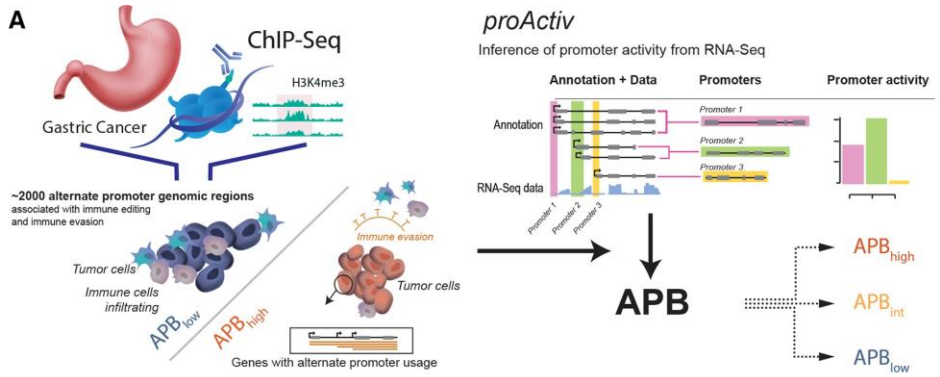
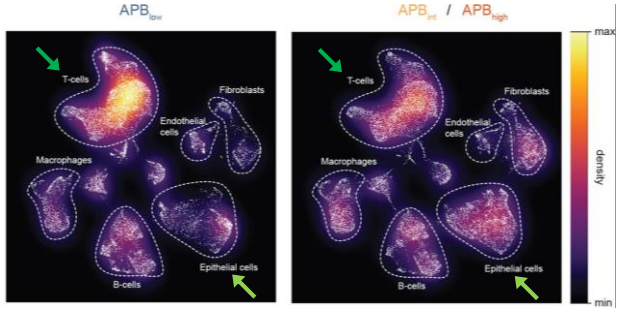
Background

- Immune escape is a key factor for tumourigenesis
- Epigenetic alterations in cancer interact with the immune microenvironment to control tumourigenesis and response to therapy
- Studies in gastric cancer have shown an association between epigenetic alternate promoters, immune-editing and immune checkpoint inhibitor (ICI) resistance



Alternate promoter burden (APB) was quantified using a novel bioinformatic algorithm (proActiv) to infer promoter activity from short-read RNA sequencing and samples categorised into APB_{high}, APB_{int} and APB_{low}



Density plot of UMap stratified by APB_{low} versus APB_{int}/APB_{high} highlighting the higher proportion of T cells in the APB_{low} tumours and epithelial cells in APB_{int}/APB_{high} tumours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Findings

- Gastric tumours with higher epigenetic promoter alterations exhibited decreased levels of T-cell cytolytic markers and expressed signatures of immune depletion
- These findings were orthogonally validated using novel technologies and platforms such as single-cell RNA sequencing and 'humanised mice'
- Multiple gastrointestinal tumour types with higher alternate promoter burden also correlated significantly with poorer survival with ICI therapy

Clinical Significance

✓ **The findings demonstrate an association between alternate promoter use and the tumour microenvironment, leading to immune evasion and immunotherapy resistance**
✓ **Alternative promoter use burden may represent a negative predictive biomarker for immunotherapy applicable to multiple gastrointestinal tumour types**

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