Characterising the tumour microenvironment of primary pancreatic ductal adenocarcinomas and matched positive and negative mesenteric lymph nodes

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BACKGROUND:

The tumour microenvironment in PDAC is complex and often exhibits an immunosuppressive phenotype. Lymph node invasion is a poor prognostic marker and represents initiation of metastasis. We hypothesize that different cellular makeup within the tumour and proposed lymph node metastatic niche could modulate this lymphatic spread and represent a target for treatment in patients with lymphatic spread.

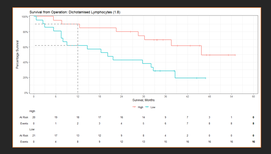
AIMS:

1. Investigate TME of primary tumors and factors that predispose to lymphatic spread.
2.Investigate the TME of positive lymph nodes and characterize the cellular heterogeneity of this proposed niche

RESULTS:

- 41 patients were included who had pancreatic resections in 2019 and 2020. Survival analysis demonstrated tumour size, tail of pancreas cancer, positive lymph nodes, positive resection margins, high post-operative CA19-9 levels and low pre-operative peripheral lymphocytes were correlated with poor survival. Negative lymph nodes, negative resection margins and high peripheral lymphocytes were correlated with longer disease-free survival.
- SpatialDecon analysis characterised the cell phenotypes within tissues. Low peripheral lymphocytes were correlated with higher spatial deconvolution signatures for macrophages, NK, mDCs and monocytes.
- Differential gene expression, single sample gene set expression analysis using linear mixed model was used to characterize the tissue types and tissues were compared between patients and clinical characteristics.

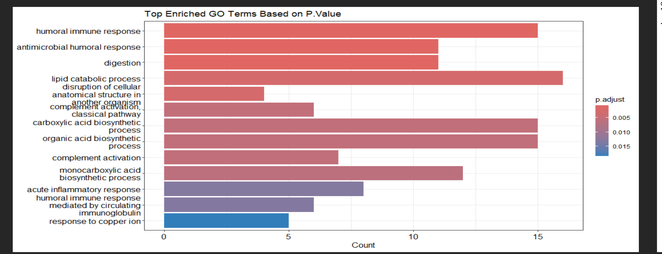
N=41
Resected
2019-2020

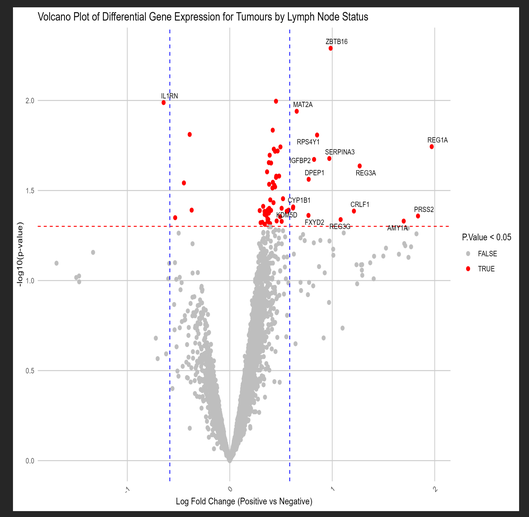


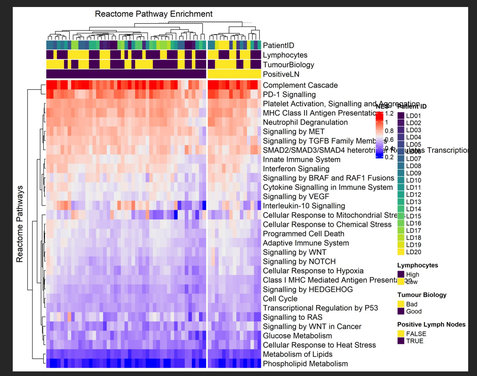
Clinical
Correlation

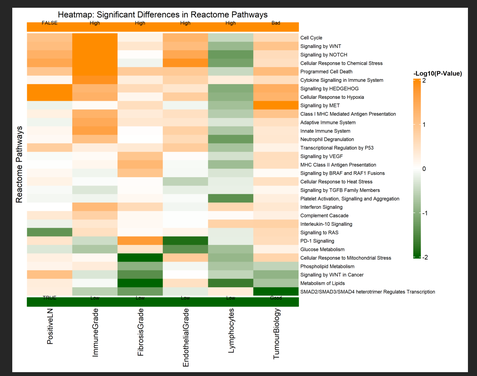
GeoMx
Whole
Transcriptome

The TME of tumour with lymphatic spread have a distinct transcriptomic profile characterized by upregulated humoral immune responses, downregulated signaling via HEDGEHOG pathway and increased signaling to RAS



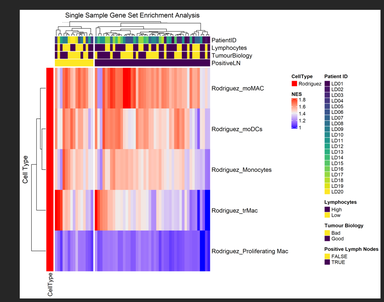






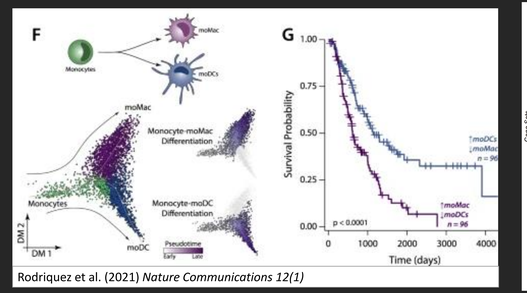
Positive Lymph Nodes from patients with poor prognosis have increased signaling via PD-1, NOTCH and WNT pathways

Transcriptomic Signatures for moMAC were upregulated in patients with low lymphocytes (poor prognosis) and in those with lymphatic spread. Correlating with survival analysis from TCGA database.



Future Directions:

- *Increase number of patients with second tissue microarray containing 21 further patients (3 tumour, 2 LNP, 1 LNN and 1 normal)*
- *Correlation of relevant differentially expressed genes to OS and DFS using TCGA and local databases.*
- *Assess for targetable pathways for pharmaceutical blockade / genetic models for proof of concept.*



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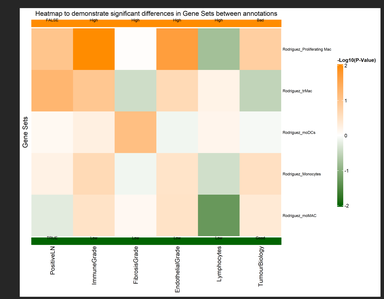

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