Mechanisms of immune escape associated with immunotherapy targets in a subset of pancreatic neuroendocrine tumours

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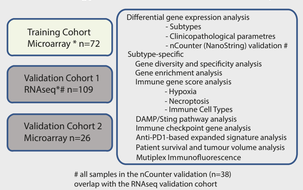
Background

- In recent years, there have been significant advances in our understanding of the molecular features of PanNETs.
- We defined, for the first time, four transcriptomic (gene and microRNA) subtypes of patient PanNETs: metastasis-like primary (MLP)-1 (28%) and MLP-2 (15%), insulinoma-like (22%) and intermediate (35%; Sadanandam et al., Cancer Discovery 2015).
- Despite our improved understanding of the molecular nature of PanNETs, novel therapeutic approaches for patients remain elusive. Moreover, little is known about the immune landscape of PanNETs to date.
- Thus, in this study (Young et al., Gut 2020), we performed detailed profiling of immune genes to understand the landscape of immune cell types in patient PanNETs, mechanisms and its potential to aid immunotherapy choices.

Methods and Results

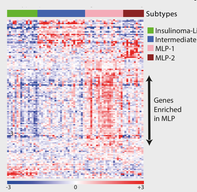
Strategies, subtype-specific immune genes and overall survival in PanNETs

Strategy to delineate immune landscape

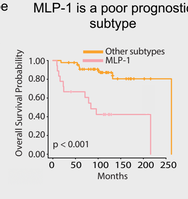


all samples in the nCounter validation (n=38) overlap with the RNAseq validation cohort

Immune enrichment in MLP-1 subtype



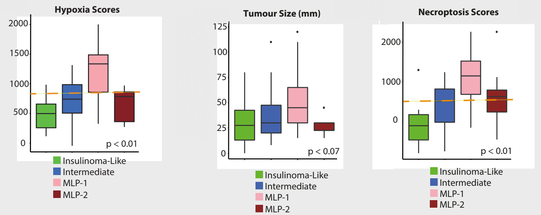
MLP-1 is a poor prognostic subtype



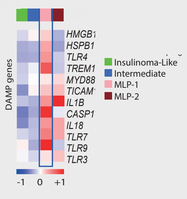
Results

Cascade of changes in MLP-1 from hypoxia to damage associated molecular patterns (DAMP)

Increased hypoxia scores, tumour size and necroptosis scores in MLP-1 subtype

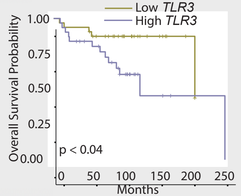


Increased expression of DAMP genes in MLP-1 subtypes

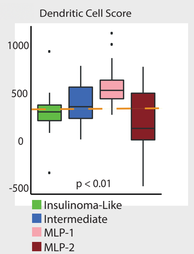


Dendritic cells, related genes, pathways and antigen presenting machineries in MLP-1 subtype

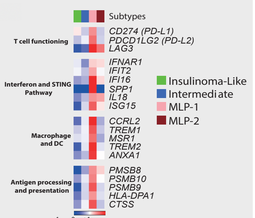
Increased expression of TLR3 gene in MLP-1 subtype



Increased dendritic scores in MLP-1 subtype



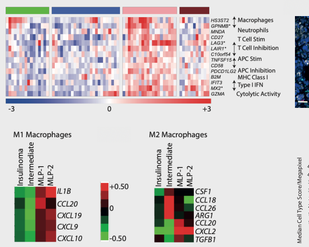
MLP-1 specific change in immune genes, cell types, pathways and antigen presenting machineries



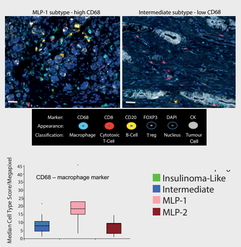
Results

MLP-1-specific immune changes; spatial profiling and drug response signature

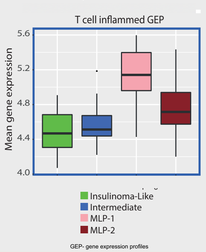
MLP-1 specific changes in immune cell types



Spatial profiling validating the immune cell type changes in MLP-1



Ribas signature showing potential response to immune checkpoint inhibitor



Conclusions

What are the new findings?

- The current study demonstrates differential immune-related gene expression in PanNETs and identified a molecular subtype, metastasis-like primary (MLP)-1, with enriched immune gene expression profiles (GEPs).
- Our data suggest this enrichment is related to MLP-1 subtype characteristics (poor prognosis and increased tumour size) and GEPs associated with increased hypoxia, necroptosis, viral mimicry and stimulator of interferon gene pathway (STING), resulting in activation of immune suppressive microenvironment via the damage-associated molecular pattern pathway (DAMP).

How might it impact on clinical practice in the foreseeable future?

- This study provides novel data regarding the immune microenvironment of PanNETs with potential therapeutic implications. The MLP-1 PanNET subtype identifies tumours with enriched immune suppressive GEPs. This study poses the basis for potential clinical trials according to PanNET molecular subtypes to aid the development of precision immunotherapy in this rare disease.

We have developed gene expression diagnostics assays with prognostic significance. Sadanandam et al., ENETS 2019.

References

1. Young and Sadanandam, et al., Immune landscape, evolution, hypoxia-mediated viral mimicry pathways and therapeutic potential in molecular subtypes of pancreatic neuroendocrine tumours. *Gut* 2020: doi:10.1136/gutjnl-2020-32101
2. Sadanandam A, *et al.* A Cross-Species Analysis in Pancreatic Neuroendocrine Tumors Reveals Molecular Subtypes with Distinctive Clinical, Metastatic, Developmental, and Metabolic Characteristics. *Cancer Discovery* 2015: 5(12); 1296–313.
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Acknowledgments

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