Transcriptomic Analysis of PanNET progression from microtumor to metastasis in MEN1 Patients

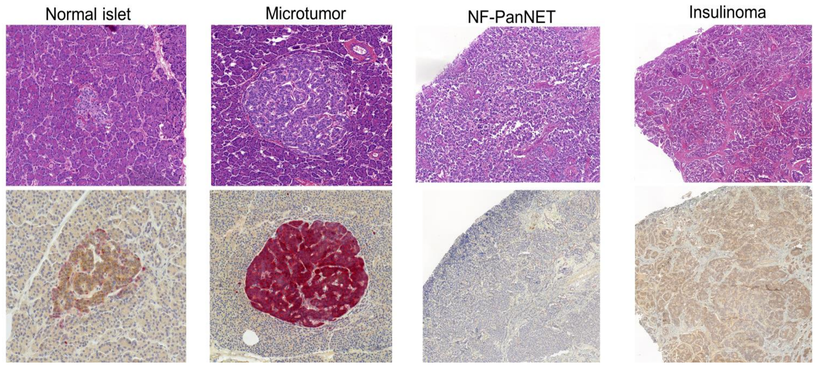
Aziz Chouchane, Philipp Kirchner, Renaud Maire, Marco Schiavo Lena, Massimo Falconi, Stefano Partelli, Detlef Bartsch, Martin Sadowski, Ilaria Marinoni and Aurel Perren

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

u^b IGMP Institut für Gewebemedizin und Pathologie

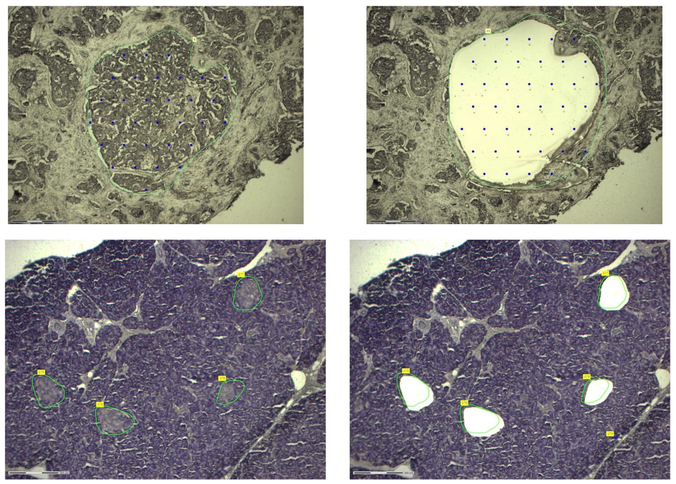
Background/Objectives:

- Microadenomatosis is the presence of several neuroendocrine microtumors within the pancreas, and it is a histological hallmark feature of MEN1.
- Microtumors are also present in 10% of the normal population
- Our objective is to explore the mechanisms of tumor progression in MEN1.



Methods:

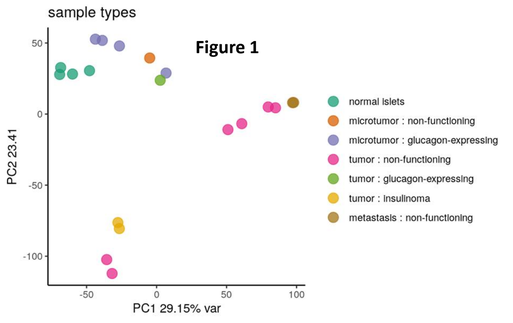
- A cohort of 5 diagnosed MEN1 patients was collected
- 4 NF-PanNETs, 1 Insulinoma, 7 microtumors, and normal islets were fixed in PAXgene (PreAnalytix, 765312), isolated and dissected for RNA extraction using laser microdissection (Zeiss PALM Beam).

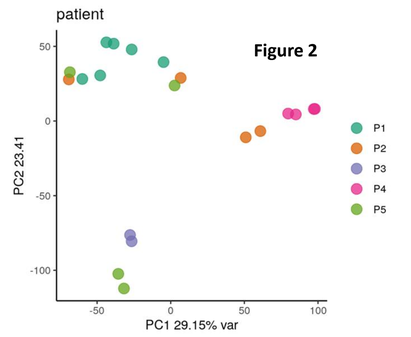


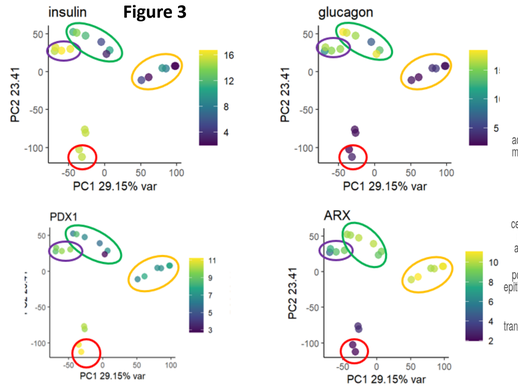
Laser Microdissection of PanNET tumor cells. Many normal pancreatic islets were dissected and pooled together by patient.

It has been established that pancreatic neuroendocrine microtumors exhibit a loss of heterozygosity of the MEN1 gene. The small percentage of microtumors that develop into PanNETs provides further evidence that the 'double-hit' of the MEN1 gene is not the main driving factor in the development of PanNETs in MEN1 patients. Our findings indicate that substantial differences in transcriptional patterns characterize the distinct stages of PanNET progression in the MEN1 setting, with microtumors exhibiting a much more similar differential gene expression to normal pancreatic islets as compared to the larger tumors, hinting at the fact that regulation mechanisms such as epigenetics are playing an important role in early PanNET progression in the MEN1 setting. Additional investigation into these differences in gene expression and pathways may not only shed light on the development of PanNET tumors in MEN1 patients, but also may identify novel therapeutic targets

Results/Graphs/Data:







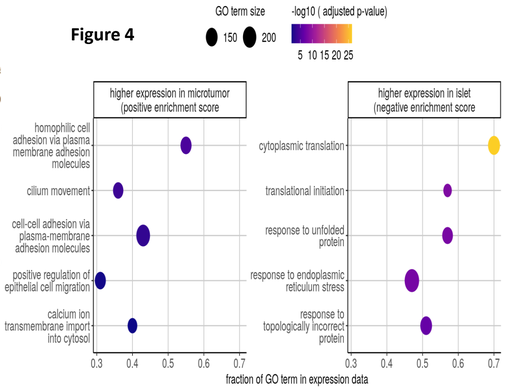


Figure Legends:

Figure 1 and 2 show a PCA cluster analysis based on the differential gene expression of the samples. Interestingly the microtumors are much more similar on their differential gene expression to normal islets than they are to large tumors. The large tumors cluster into 2 different groups, an ARX-high(PDX-1 low) group and a PDX1-high (ARX-low) group, as shown in **Figure 3. Figure 4** Gene set enrichment analysis shows the five most differentiately expressed pathways in microtumors as compared to islets

Future Directions for Research:

- Deeper exploration the pathways with differential expression in order to identify the genes of outmost significance and the mechanism by which the are regulated.
- The mechanism of phenotypic plasticity through which glucagon expressing microtumors transform into insulin secreting tumors and non-functioning tumors remains mainly unknown. Additional investigation into the transcriptional differences that exist between insulinomas, NF-PanNETs (Non-Functioning) and microtumors could provide valuable insights into this process.