Identification of tumor-associated pathways in *MEN1/DAXX/ATRX* mutated Pancreatic Neuroendocrine Tumors (PanNETs)

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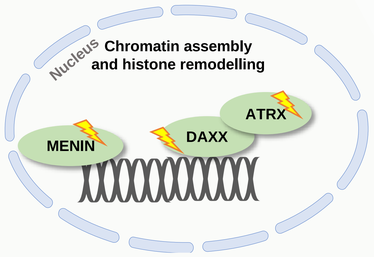
Background

- The most commonly mutated genes in PanNETs are *MEN1, DAXX* and *ATRX.*
- Menin, DAXX and ATRX are involved in chromatin remodeling and epigenetic regulation.
- Cell of origin, pathways and mechanism of progression associated with *DAXX/ATRX* mutations are still unclear.



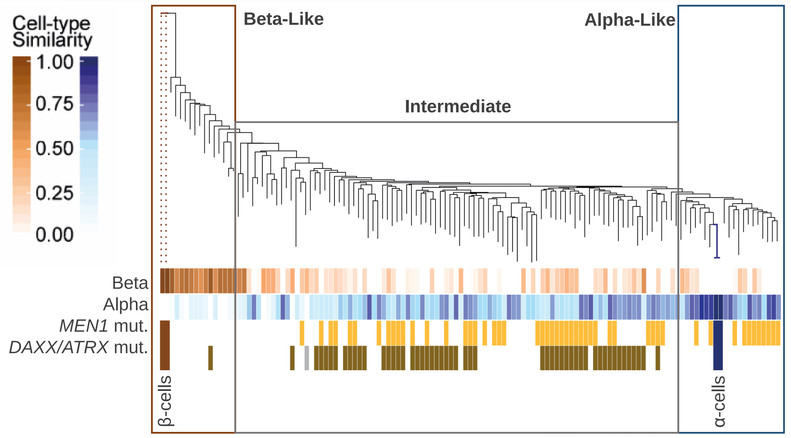
MEN1	**41%**
DAXX, ATRX	**32%**

Aims and Experimental Setup

- Does epigenetic reveal cell of origin of PanNETs? (section 1)
- Do epigenetic profiles correspond to a specific genetic background? (section1)
- Do epigenetic signatures show clinical relevance? (section 1)
- Do epigenetic signatures overlap with already published gene expression PanNET subgroups? (section 2 and 3)
- Which are the main dysregulated pathways in *DAXX/ATRX/MEN1* mutated tumors? (section 4)

DNA methylation (Illumina, 450K arrays) and gene expression (RNAseq) signatures of PanNETs and putative α-/β-cells of origin have been analyzed to answer these questions

1. DNA methylation profiles of PanNETs reveal at least 2 cells of origin and 3 PanNET epigenetic subgroups with clinical relevance



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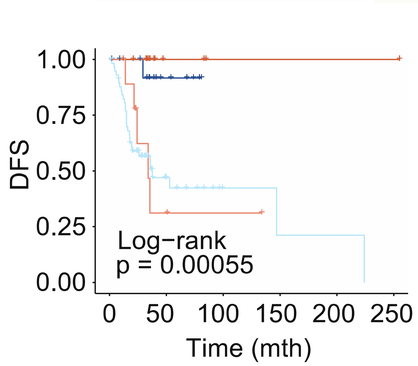
α-like: high similarity to normal α-cells; mainly *MEN1* mutated

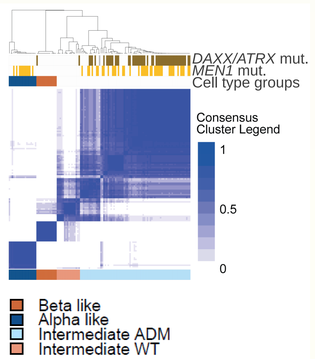
β-like: thigh similarity to normal β-cells; mainly MEN1/DAXX/ATRX wild type.

Intermediate: intermediate similarity to α- or β-cells; higher values are shown for α-cell similarity; subgroup enriched for tumors with *MEN1/DAXX/ATRX* (intermediate-ADM) mutations.

DNA methylation signatures of the epigenetic subtypes show relevance in relapse prognostication and separate intermediate tumors in:

- PanNETs with *MEN1/DAXX/ATRX* mutations (intermediate-ADM)
- PanNETs *MEN1/DAXX/ATRX* wild type (intermediate-WT)





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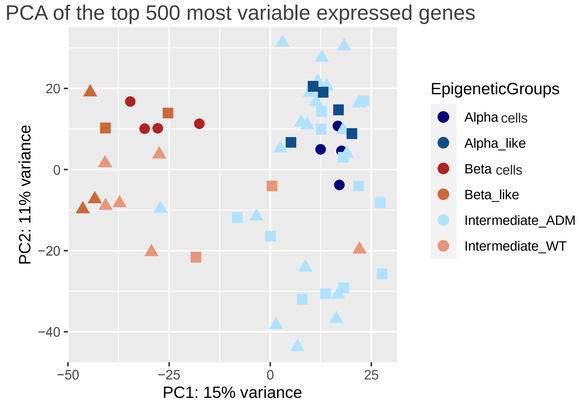
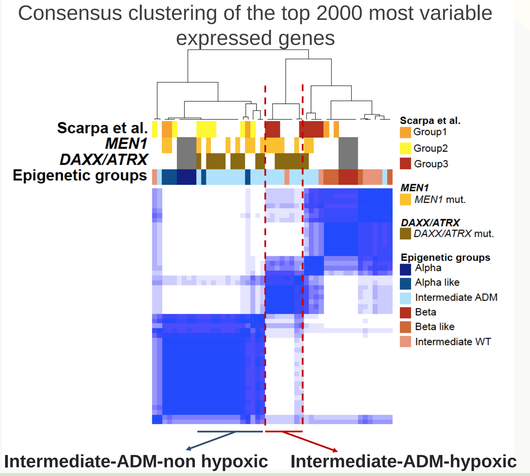
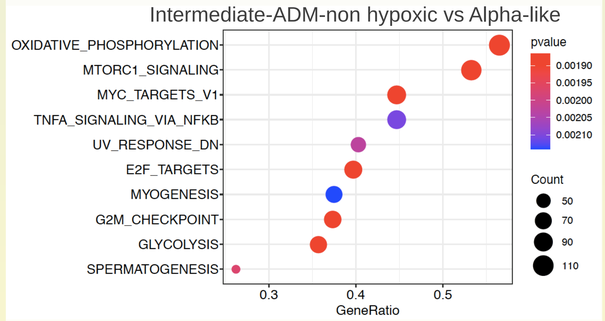
2. Gene expression signatures partially recapitulate the epigenetic groups.

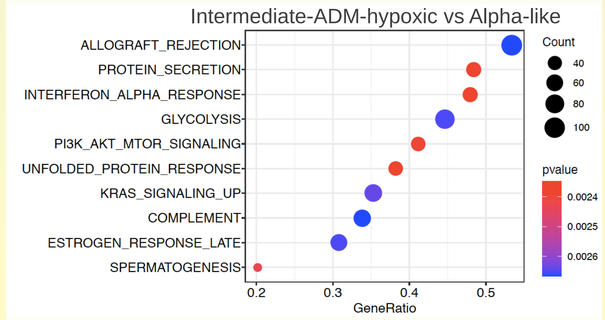


3. A subset of Intermediate-ADM PanNETs share the hypoxia signature (group 3) described by Scarpa *et al*.



4. GSEA for Intermediate-ADM-hypoxic and Intermediate-ADM-non hypoxic PanNETs shows new distinct oncogenic pathways DAXX/ATRX depedent





Conclusion

- DNA methylation signatures define PanNETs with:
  - Distinct cell of origin
  - Specific genetic background
  - Different clinical outcome
- Gene expression signatures partially overlap with the epigenetic subgroups
- Intermediate-ADM PanNETs show transcriptional heterogeneity.
- New oncogenic pathways for intermediate-ADM tumors could be identified.

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