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

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Background. Pancreatic Neuroendocrine Tumors (PanNETs) are tumors of the Islets of Langerhans. Recent data on super-enhancer signatures and transcriptome profiles suggest that subgroups of PanNETs might originate from either endocrine α- or β-cells or progenitor cells. The most commonly mutated genes in PanNETs are *MEN1, DAXX* and *ATRX*, which encode for proteins involved in epigenetic regulation. *DAXX/ATRX* mutated PanNETs are globally hypomethylated and behave clinically in a more aggressive way. Cell of origin, pathways and mechanism of progression associated with *DAXX/ATRX* mutations are still unclear.

Experimental approach. We analyzed the DNAme (Illumina, 450K arrays) signatures of 157 PanNETs and we compared them to the DNAme profiles of their putative cell of origin (α- or β-cells). Subsequently, we characterized the relative changes in gene expression in 53 matching PanNETs (public available RNAseq data) focusing on specific pathways of progression dependent on *DAXX* and *ATRX* mutations.

Results. We found that PanNETs can be classified into four different epigenetic groups, which might have at least two different cells of origin: α-like, β-like, intermediate-ADM and intermediate-WT. Alpha-like and β-like tumors were mainly early stage PanNETs which showed strong epigenetic similarities to either α- or β-cells, respectively. Additionally, tumors that presented recurrent mutations in *MEN1*, *DAXX* and/or *ATRX* (intermediate-ADM) were epigenetically similar to α-cells, suggesting an α-cell origin. The epigenetic groups could be recapitulated on a transcriptional level. Intermediate-ADM tumors clustered into two further subgroups characterized by specific pathways of expression.

Conclusions. We showed that DNAme signatures define PanNETs with different cell of origin, clinical outcome and genetic background. Additionally *MEN1/DAXX/ATRX* mutated PanNETs show transcriptional heterogeneity. We have been able to identify new oncogenic pathways peculiar for these tumors, opening up new horizons for therapeutic interventions.