Loss of epigenetic repression of retrotransposons in Pancreatic Neuroendocrine Tumors

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BACKGROUND

- Roughly half of the human genome is derived from transposons that still pose threats to its integrity.
- Most transposons are silenced in normal cells by various epigenetic mechanisms.
- Faithful silencing of transposons is sufficiently compromised in disease contexts, especially in the cancers leading to their aberrant expression and activity.

- MEN1 (multiple endocrine neoplasia I), DAXX (death domain associated protein) and ATRX (ATRX chromatin remodeler) are the most frequently mutated genes reported in pancreatic neuroendocrine tumors (PNETs).
- All three proteins have roles in chromatin remodelling.
- ATRX/DAXX complex is essential for heterochromatin formation at retrotransposons (RTEs).
- RTEs are derived from ancient retroviruses and propagated themselves through reverse transcription of an RNA intermediate.
- RTE de-repression can play causal roles in cancer cells as they can function as promoters or enhancers leading to altered expression of oncogenes.
- They can code for proteins and splice into genes that leads to chimeric transcripts or altered protein isoforms.

OVERALL AIMS

- To examine if ATRX/DAXX loss leads to disrupted heterochromatin and increased expression of retrotransposons in PNETs.
- To examine the extent of retrotransposon expression in PNETs with functional consequences for detection and/or therapeutic targeting.

REFERENCES


RESULTS

- PNETs with ATRX/DAXX mutations exhibit increased expression of full length HERV9 loci

- Increased expression of HERV elements in ATRX-mutant PNETs. Volcano plot showing log2fold changes of HERVs in ATRX-mutant PNETs (red) as compared to ATRX WT. Each dot represents a HERV subfamily. p-value < 0.0001 by Wald’s test and log2 fold change > 1 are highlighted in red.

- HERV families expressed in ATRX-mutant PNETs. Heatmap showing HERV expression in ATRX-mutant PNETs (red shades). ATRX mutant: Mutation in ATRX or DAXX or MEN1. ATRX WT: WT for all three genes. RNA-seq data from Chan et al., 2018.

- Knockdown experiments in GQP1 cell line

- Boxplots show expression (counts per million mapped reads) of a HERV9 locus (HERV9_5p13.3a) across PNETs grouped by genotype. RNA-seq data from Scarpa et al., 2017 and ICGC (N=49)

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