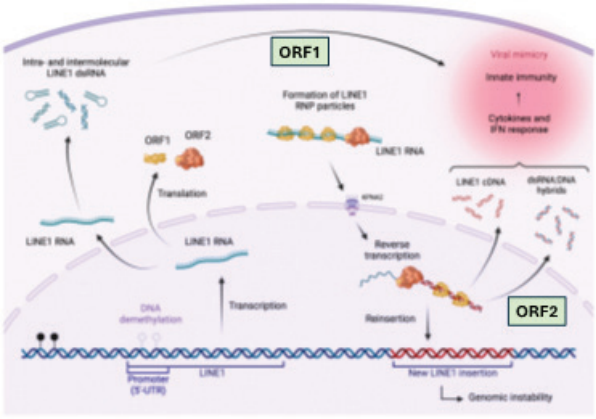

Figure 1: LINE1 retrotransposon working model. LINE1 repeat RNA expression is induced through epigenetic changes. LINE1 RNA is translated into ORF1 and ORF2 proteins, which bind and process repeat RNAs with the ability to reinsert into the genome. The balance of these repeat RNA and DNA species induces innate immune responses similar to a viral infection.

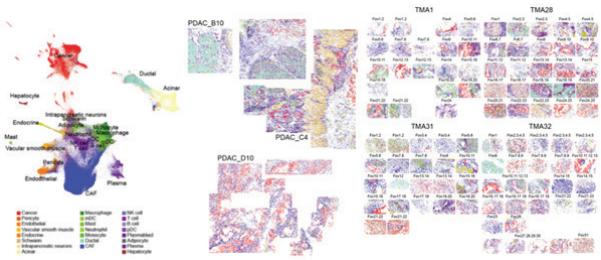

Figure 2: Spatial Molecular Imaging of LINE1 and Coding Genes in Human PDAC Left: UMAP clustering and cell annotation of 46 human PDAC samples. Right: Spatial mapping of every cell type.

Unlocking the Dark Genome: Targeting LINE1 to Activate Innate Immunity in Cancer

David Ting, MD
Associate Clinical Director of Innovation, Mass General Cancer Center; Associate Professor of Medicine, Harvard Medical School
dting1@mgh.harvard.edu

The non-coding parts of the genome, or "dark genome" is composed primarily of repeat elements, and the aberrant expression of these sequences is a common feature found in cancer, neurodegenerative disease, autoimmune disorders, and ageing. The majority of these are non-coding RNAs that have shown the ability to stimulate a viral-like innate immune response. One of these, the long interspersed nuclear element 1 (LINE1) retrotransposon is composed of ORF1, a ribonucleotide protein, and ORF2, a reverse transcriptase and endonuclease, which allow for the replication and movement of LINE1 and other repeat elements in the genome analogous to a retrovirus (Fig. 1). However, the impact of LINE1 on viral-like innate immune responses has not been well explored.

Using spatial molecular imaging (You et al. Cell 2024), we have recently characterized the expression of LINE1 RNAs in pancreatic ductal adenocarcinoma (PDAC). This revealed that LINE1 RNA expression drives cellular plasticity in tumor cells and induces dysfunction in the responding microenvironment cells (Fig. 2). This broader viral-like infection of the microenvironment suggested that targeting of LINE1 could impact tumor cells directly, as well as the immune response to them. We suppressed LINE1 ORF1 protein expression using shRNA, which led to repeat RNA mediated induction of innate immune responses. This led to significant PDAC cancer cell toxicity and alterations in the tumor microenvironment in a mouse model of PDAC (You et al. Cancer Discovery 2025). In addition, we found increased sensitivity of PDAC cell lines to conventional combination chemotherapy (FOLFIRINOX) and newer KRAS inhibitors.

Our results demonstrate a critical and previously uncharacterized role of LINE1 ORF1 as a suppressor of innate immunity and as an attractive novel immune oncology and therapeutic resistance target for PDAC. We are looking for strategic partners and investors to develop inhibitors of LINE1 ORF1 and other dark genome targets as novel cancer therapeutics.