Oncogenic KRAS and the Non-coding Transcriptome

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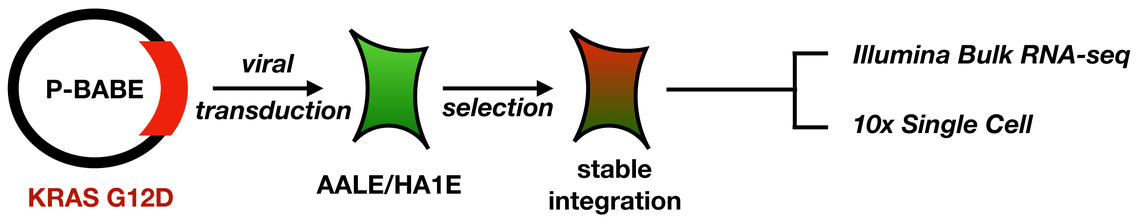
Context

- RAS genes are the most frequently mutated oncogenes in human cancer.
- We analyzed the transcriptomes of human lung and kidney cells transformed with mutant KRAS to define the landscape of RAS-regulated noncoding RNAs.

Experimental Design

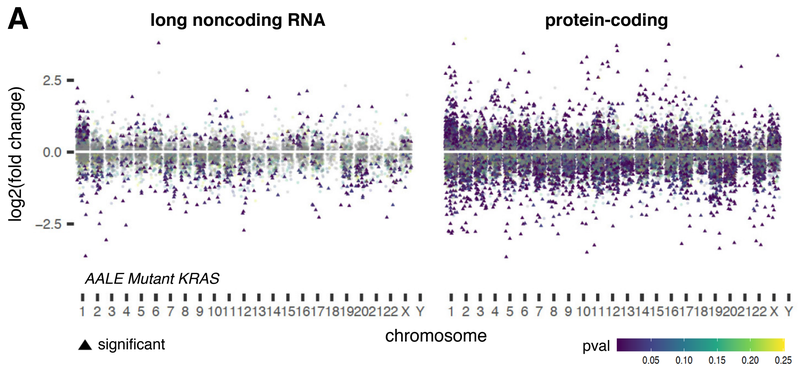
To determine the landscape of noncoding RNAs affected by oncogenic RAS signaling, we performed RNA-seq on **human lung epithelial cells (AALE)** that undergo malignant transformation upon introduction of mutant KRAS



Conclusion

- upregulated **noncoding transcripts** throughout the genome that are enriched for **transposable elements** that are preferential targets of **KRAB zinc-finger proteins**.
- KRAS-mediated reprogramming of **repetitive RNA** induces an **interferon response** that contributes to cellular transformation.

Transcriptome reprogramming by mutant KRAS

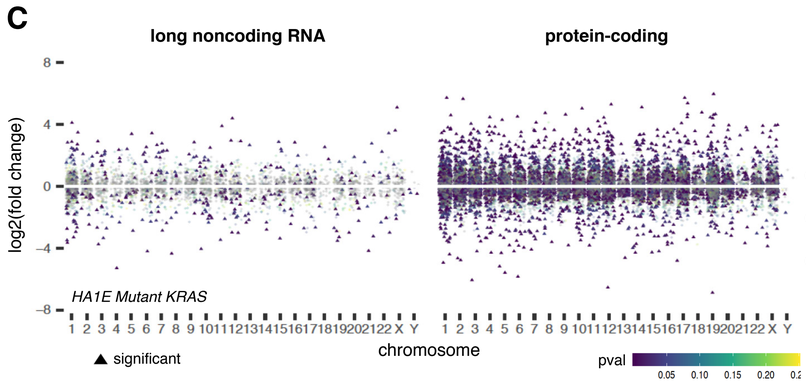


AALE

GSEA

- IFN Alpha Response ↑
- Oxidative Phosphorylation ↑
- IFN Gamma Response ↑

279 Significantly DE lncRNA



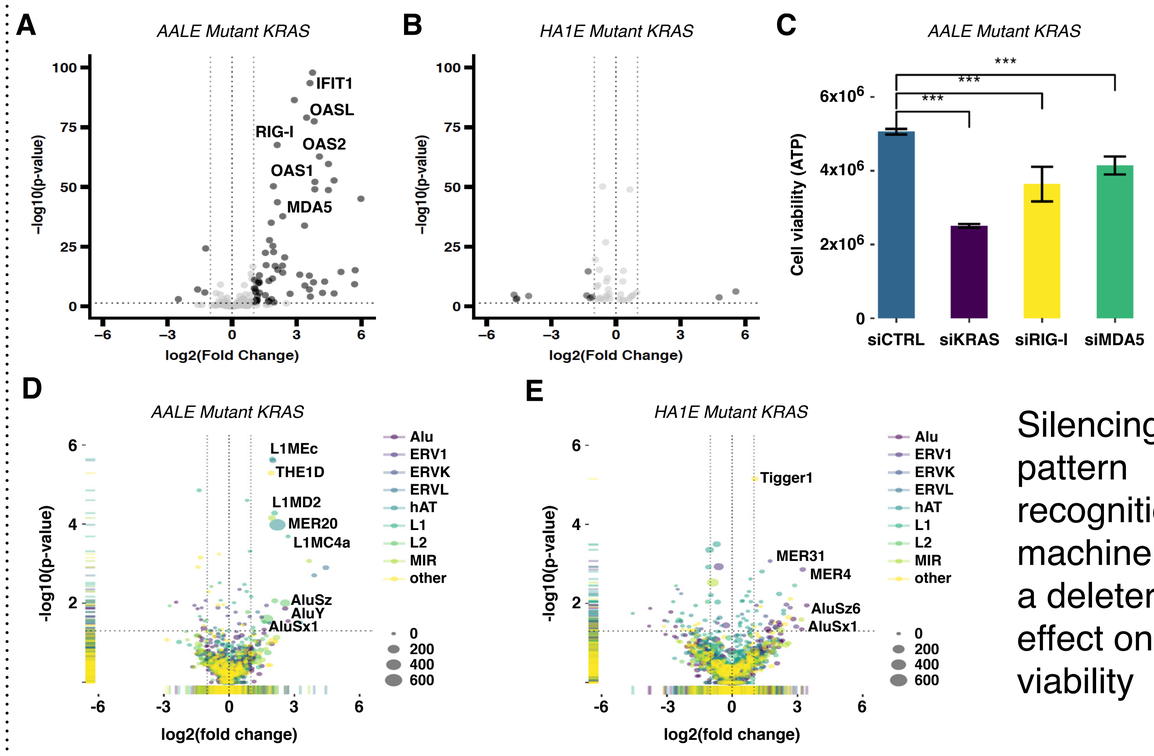
HA1E

GSEA

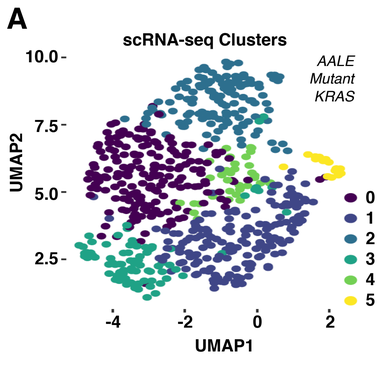
- KRAS Signaling Up ↑
- IFN Alpha Response ↓
- MYC Targets V1 ↓

165 Significantly DE lncRNA

Mutant KRAS activates IFN-related genes and transposable elements

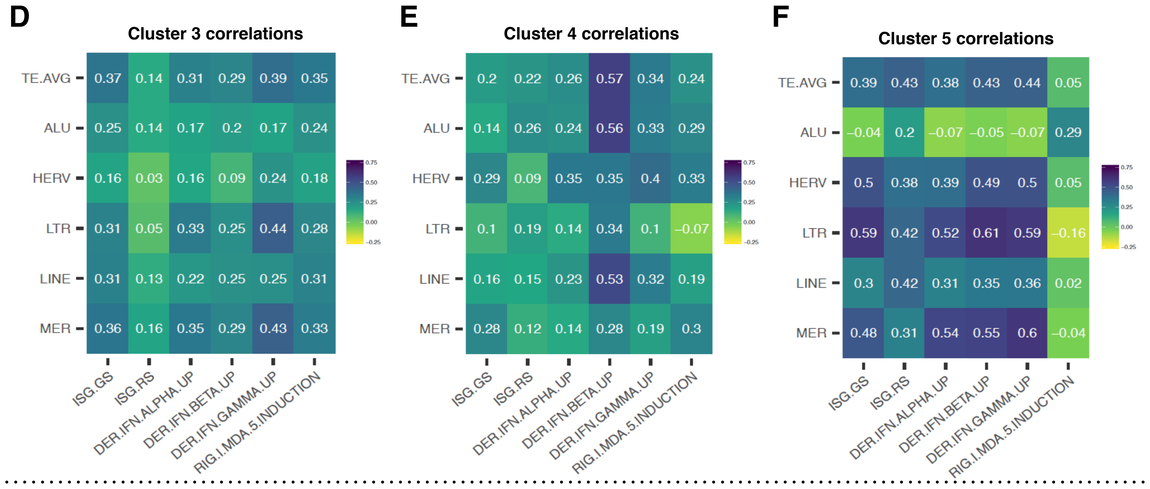


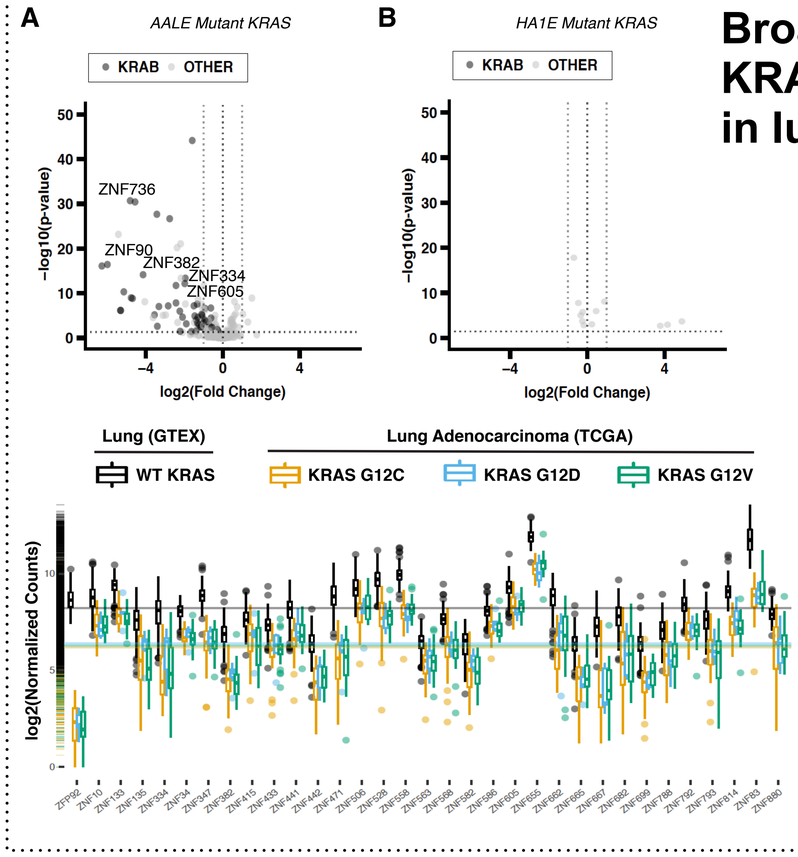
Silencing RNA pattern recognition machinery has a deleterious effect on cell viability



Coordinated regulation of IFN-related genes and transposable elements

Single Cell data clustered weakly but aggregating signal into gene sets reveals coordination between TE expression and IFN signaling in select subpopulations





Broad suppression of KRAB zinc finger proteins in lung cancer cells

Global down regulation of ZNF mRNA is unique to AALE and reflected in TCGA and GTEx datasets. ChIP-seq data indicated these ZNFs bind to upregulated TE sequences (Trono, *et al*)