**Oncogenic KRAS and the Non-Coding Transcriptome**

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RAS genes are the most frequently mutated oncogenes in human cancer but the impacts of these mutations on the vast noncoding transcriptome are unclear. The broad impacts RAS mutations have on the genome are well characterized and thus we hypothesized these perturbations would extend to non-coding transcripts. We analyzed the transcriptomes of human lung and kidney cells transformed with mutant KRAS to define the landscape of RAS-regulated noncoding RNAs. We found that oncogenic RAS signaling upregulates noncoding transcripts throughout the genome that are enriched for transposable elements. A majority of these repetitive sequences, known as Transposable Elements (TEs), are preferential targets of KRAB zinc-finger proteins that are broadly downregulated in both mutant KRAS cells and lung adenocarcinomas. These data also revealed that this KRAS-mediated reprogramming of repetitive RNA induces an interferon response that contributes to cellular transformation. We further explored this interferon response using single cell RNA sequencing where we demonstrated a consistent correlation between the expression of TEs and interferon response genes in clusters of cells demonstrating a strong immune signal. Our results reveal the extent to which mutant KRAS remodels the noncoding transcriptome, expanding the scope of genomic elements regulated by this fundamental signaling pathway.

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