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CANCER GENOMICS

The relevance of extensive editing in tumour transcriptomes

> “transcriptome diversity … that is both functionally important and clinically relevant”

Post-transcriptional editing of RNA is a widespread, conserved mechanism by which genetic diversity can be introduced without any changes to the DNA, but its role in cancer has remained unclear despite the observation that the number of editing-induced RNA mutations is comparable to the number of somatic mutations in coding regions of DNA. Now, three studies demonstrate that adenosine-to-inosine (A-to-I) RNA editing (which is the most common form) introduces transcriptome diversity in tumours from a range of cancer types; diversity that is both functionally important and clinically relevant.

Using RNA sequencing (RNA-seq) data from The Cancer Genome Atlas (TCGA), Han *et al.* and Paz-Yaacov *et al.* systematically analysed genome- and transcriptome-wide profiles of A-to-I RNA editing, respectively. They showed that levels of editing in tumour tissue differed significantly from those in matched normal tissue from the same individuals, with examples of both under-editing (for example, in chromophobe kidney cancer) and over-editing (for example, in breast tumours; a finding replicated by Fumagalli *et al.*).

Consistent with the known role of ADAR1 (adenosine deaminase acting on RNA), all three studies report a significant correlation between A-to-I RNA editing activity and *ADAR1* expression in tumour tissues. Furthermore, Fumagalli *et al.* analysed TCGA RNA-seq data from patient samples and found that levels of both *ADAR1* and A-to-I RNA editing in a range of cancer types correlate significantly with *ADAR1* copy number and with expression of *STAT1*, which they used as a marker of type I interferon signalling. The significance of the *STAT1* correlation increased for most cancer types studied when adjusting for *ADAR1* copy number, suggesting that both factors independently regulate A-to-I RNA editing in these cancers. These molecular correlates provided insight into potential regulatory mechanisms, but what are the clinical correlates of A-to-I RNA editing?

Paz-Yaacov *et al.* reported a significant correlation between A-to-I RNA editing levels and survival in patients with certain cancers; similarly, Han *et al.* identified a proportion of A-to-I RNA editing sites that correlated significantly with established clinical parameters (disease stage, patient survival or tumour subtype). However, the potential contribution of interferon signalling to these clinical correlations was not reported in these studies.

Han *et al.* then focused on sites that showed nonsynonymous RNA editing, in which editing of the transcript could be translated into changes in the resulting protein sequence. For three such editing events that were found in two or more cancer types, functional assays revealed a significant impact of A-to-I RNA editing on viability in two different cell lines. This demonstration of *in vitro* ‘driver-like’ functional effects is consistent with the *in silico* predictions of Paz-Yaacov *et al.*, which identified nonsynonymous A-to-I RNA editing events that are likely to translate into altered protein function.

Further supporting the functional importance of A-to-I RNA editing, Fumagalli *et al.* showed that reducing editing levels in several breast cancer cell lines (through *ADAR1* knockdown) significantly decreased proliferation and increased apoptosis. Notably, Han *et al.* went on to identify functional effects of clinical relevance, demonstrating that certain nonsynonymous editing events influenced the sensitivity of a mouse leukaemia cell line to the cytotoxic effects of a range of compounds, suggesting a role for A-to-I RNA editing in drug sensitivity.

Together, these three studies provide evidence that A-to-I RNA editing is a functionally important and clinically relevant source of transcriptome diversity in cancer, and they highlight the need to study its potential roles as a pathogenic mechanism, a biomarker of disease and a therapeutic target.

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ORIGINAL RESEARCH PAPERS Han, L. *et al.* The genomic landscape and clinical relevance of A-to-I RNA editing in human cancers. *Cancer Cell* **28**, 515–528 (2015) | Paz-Yaacov, N. *et al.* Elevated RNA editing activity is a major contributor to transcriptomic diversity in tumours. *Cell Reports* **13**, 267–276 (2015) | Fumagalli, D. *et al.* Principles governing A-to-I RNA editing in the breast cancer transcriptome. *Cell Reports* **13**, 277–289 (2015)