CANCER GENOMICS

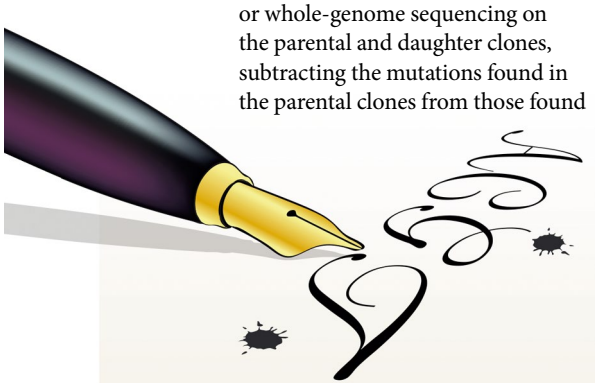
Switching APOBEC mutation signatures

> APOBEC activity is not a constant feature of tumours but can be switched on at variable stages

Accumulating evidence from cancer sequencing studies shows that endogenous and exogenous mutagenic processes leave diverse signatures within cancer genomes. Two recent studies report substantial temporal and spatial variability in mutagenic signatures caused by APOBEC cytidine deaminases.

Petljak et al. focused on characterizing mutagenic signatures in experimentally tractable systems, by analysing exome sequencing data from 1,001 human cancer cell lines and 577 patient-derived xenografts representing diverse tissue types. The signatures largely mirrored those obtained from primary tumour samples and were consistent with known clinical annotations, such as signatures of tobacco exposure in smoking-associated cancers, signatures of ultraviolet (UV) light exposure in melanoma or signatures of different types of known DNA repair defect.

The authors focused on the temporal aspects of mutation signatures; they took 28 of the cell lines, representing a broad spectrum of cancer types and mutation signatures, generated one or more subclones of each line (termed the 'parental' clones) and cultured these lines for up to 161 days followed by a second subcloning stage (generating the 'daughter' clones). They then carried out whole-exome or whole-genome sequencing on the parental and daughter clones, subtracting the mutations found in the parental clones from those found in the daughter clones to reveal the mutations that occurred during propagation in culture.



Credit: P. Morgan/Springer Nature Limited

Accumulation of mutation signatures was largely as expected: for signatures caused by exogenous mutagens, such as tobacco smoke or UV light, to which the cells were no longer exposed, the signatures did not accumulate in culture, unlike the continued accumulation of signatures caused by ongoing endogenous processes such as defective DNA repair mechanisms.

One notable result was the high variability of APOBEC-mediated cytidine deamination signatures, with substantial differences found even between daughter clones of the same cell line. This clone-to-clone variability was confirmed in a further four cell lines that were sampled serially throughout the culturing time course; this finer-scale temporal sampling showed that APOBEC-mediated mutagenesis can occur in bursts of rapid mutation accumulation ('episodic mutagenesis') followed by longer periods with little mutation accumulation.

The authors investigated the possible molecular triggers of this APOBEC-mediated mutagenesis. RNA sequencing (RNA-seq) showed no clear-cut relationship between the expression levels of the likely causative enzymes (APOBEC3A and/or APOBEC3B) and mutagenesis, although it remains possible that short bursts of APOBEC3A or APOBEC3B upregulation are functionally relevant but not captured at the specific timepoints of the RNA-seq experiments. The strongest correlate of APOBEC signatures identified by the authors was the culture-induced mobilization of LINE-1 transposable elements; APOBEC3 enzymes have been implicated in an innate immunity response to restrict the transposition of these elements.

In a separate study, Roper et al. characterized the genomes, transcriptomes and proteomes of multiple metastases from five patients with lung adenocarcinoma or thymic carcinoma. In three of the patients, APOBEC mutagenesis was among the most prominent signatures. Interestingly, the APOBEC signatures were variable within each of the patients: absent in the primary diagnosis samples and of greatly differing prominence among the multiple resulting metastases. This observation is further support for a model whereby APOBEC activity is not a constant feature of tumours but can be switched on at variable stages.

Also analysing immune interactions, Roper et al. reported a correlation between APOBEC signatures and upregulation of interferon signalling genes, and further showed that treatment of cell lines with interferon-γ led to *APOBEC3B* upregulation. Whether the induction of interferon signalling is linked to the LINE-1 mobilization suggested by Petljak et al. remains to be determined.

These studies emphasize the complexities of APOBEC-mediated mutagenesis in human cancer and highlight that the presence or absence of APOBEC signatures in a cancer sample will not necessarily represent the mutation status at a different tumour site or timepoint. It will be interesting to further investigate whether these signatures can be leveraged for therapeutic opportunities, such as immunotherapy strategies.

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ORIGINAL ARTICLES Petljak, M. et al. Characterizing mutational signatures in human cancer cell lines reveals episodic APOBEC mutagenesis. *Cell* **176**, 1282–1294.e20 (2019) | Roper, N. et al. APOBEC mutagenesis and copy-number alterations are drivers of proteogenomic tumor evolution and heterogeneity in metastatic thoracic tumors. *Cell Rep* **26**, 2651–2666.e6 (2019)