TUMOUR EVOLUTION

Clonal ancestry in lung cancer

Two papers published in *Science* investigated the evolution of mutational events in multiple regions of non-small-cell lung cancer (NSCLC) tumours.

de Bruin, McGranahan, Mitter, Salm, Wedge and colleagues carried out multiregion whole-exome sequencing (WES) and whole-genome sequencing (WGS) of 25 tumour samples from 7 patients with NSCLC. They identified 1,884 non-synonymous mutations, and these were classified according to whether they were ubiquitous in all tumour regions or occurred heterogeneously. Spatial intratumoural heterogeneity was observed to different extents in all patients, so the authors constructed phylogenetic trees for each tumour on the basis of the clonal (or truncal) and subclonal (or branched) mutations, and of regional copy number alterations (CNAs); branched evolution was evident in all of the tumours.

de Bruin *et al.* found that there were instances of heterogeneous occurrence of driver mutations such that some mutations were dominant only in some tumour regions from the same patient. This raises the important issue that sequencing different regions of a tumour may lead to different conclusions about driver mutations and candidate therapeutic targets. Nonetheless, driver mutations were mostly ubiquitous, indicating that these alterations occur early in tumour evolution. Analyses of CNAs indicated that they were mostly heterogeneous and therefore occur later in tumour evolution. de Bruin *et al.* also assessed the mutation spectra in the tumour samples. They found that the mutation spectra significantly changed temporally for all tumours. In particular, the proportion of C-to-A transversion mutations — which are associated with exposure to tobacco smoke — decreased as the tumours evolved, and this was confirmed using sequencing data from a larger cohort of NSCLC samples. The decrease in the proportion of C-to-A mutations was least or absent in current smokers with squamous cell carcinoma NSCLC. As the proportion of C-to-A transversions decreased, the authors noted an increase in the proportions of C-to-T and C-to-G mutations in mutation spectra that are associated with the cytidine deaminase activity of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) enzymes. APOBEC-associated mutations were mostly subclonal, indicating that APOBEC-mediated mutagenesis is involved in the progression of adenocarcinoma NSCLCs and, less clearly, of squamous cell carcinoma NSCLCs.

In a second study, Zhang and colleagues carried out WES of 48 multiregion tumour samples from 11 patients with adenocarcinoma NSCLC. They found 7,026 somatic mutations and evidence of substantial intertumoural heterogeneity. Phylogenetic trees for each tumour indicated that 76% of all mutations were detected in all regions of the same tumours, indicating that there is also intratumoural heterogeneity. Next, they mapped the known cancer-associated gene mutations on the phylogenetic trees and found that 13 of the 14 cancer-associated mutations were truncal and thus occurred early in tumour evolution. They also found that intratumoural heterogeneity of CNAs was less pronounced than that of somatic mutations. Furthermore, CNAs that targeted cancer genes were truncal, indicating that these are also early events in tumour evolution. The authors proposed that the lack of known cancer-associated mutations during diversification indicates that other unknown alterations drive tumour progression. They also found several alterations that were determined by WES to be subclonal in a region but were determined to be clonal in the same region by deep sequencing, raising concerns about how tumour heterogeneity should be evaluated.

Zhang *et al.* next looked at mutation spectra and found that never-smokers had mostly C-to-T mutations, as did some — but not all — former smokers. There was preliminary evidence that the amount of tobacco exposure and the time since smoking cessation may affect the mutation spectra, although higher numbers of patients are required to investigate this further. These authors also found evidence for APOBEC-associated mutation spectra in subclonal mutations, indicating that APOBEC-mediated mutagenesis becomes important during tumour progression.

Although based on only a few patients, these papers provide insights into the challenges presented by intratumoural and intertumoural heterogeneity. It is important to understand the key mutagenic processes that occur both during tumorigenesis and during tumour progression, and these papers provide some interesting clues about what happens during the initiation and development of NSCLC. However, identifying and understanding the changes that drive tumour progression are major challenges.

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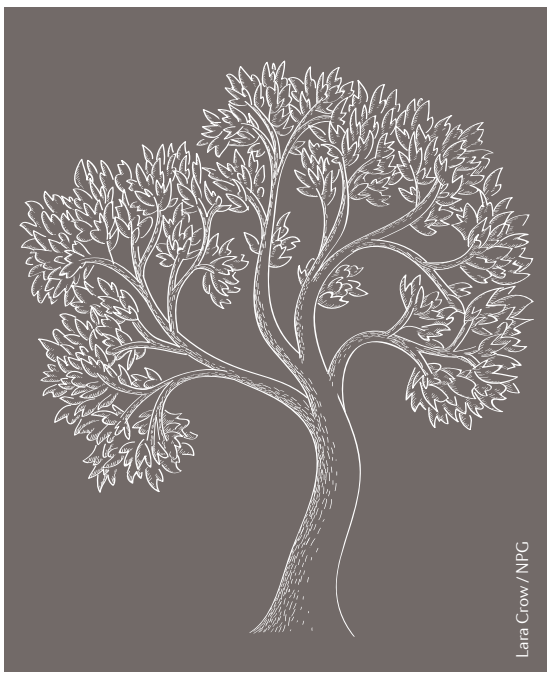
ORIGINAL RESEARCH PAPERS de Bruin, E. C. *et al.* Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. *Science* **346**, 251–256 (2014) | Zhang, J. *et al.* Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* **346**, 256–259 (2014)
FURTHER READING Westcott, P. M. K. *et al.* The mutational lanscapes of genetic and chemical models of *Kras*-driven lung cancer. *Nature* http://dx.doi.org/10.1038/nature13898 (2014)



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