CANCER GENOMICS

Tracking cancer evolution

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Understanding tumour heterogeneity and evolution is essential for the early detection of disease recurrence and the efficient treatment of cancer. Two recent studies published in *Nature* and in the *New England Journal of Medicine* prospectively tracked the evolutionary dynamics of early-stage non-small-cell lung cancer (NSCLC), providing an in-depth characterization of intratumour heterogeneity in relation to clinical outcome. Importantly, the post-operative detection of circulating tumour DNA (ctDNA) in patient plasma, as presented in the *Nature* study, was able to predict tumour recurrence.

NSCLC is the most common type of lung cancer and has a very poor prognosis. The low survival rate could be due to intratumour heterogeneity (the presence of subclonal populations within a tumour that exhibit genetic and phenotypic variation), which is frequently associated with cancer evolution and the development of drug resistance.

Abbosh *et al.* investigated ctDNA present in the blood of 100 patients participating in the Cancer Research UK-funded TRACERx (TRACKing non-small-cell lung Cancer Evolution through therapy (Rx)) study, which monitors the evolution of NSCLC from diagnosis through to death. Liquid biopsies, which are obtained using a minimally invasive procedure, have previously been shown to identify the presence of residual cancer tissue in patients with breast or colorectal cancer.

Multi-region exome sequencing of lung cancer samples obtained

during surgery was used to characterize tumour heterogeneity and reconstruct a phylogenetic tumour evolution tree with clonal (present in all cancer cells) and subclonal (present in a subset of cancer cells) variants. Information from the resulting data sets was also used to identify patient-specific single nucleotide variants (SNVs). These SNVs were then used to design PCR assay-panels for tracking the patient-specific tumour clonal variants. Blood collected from the patients before and after surgery was used to identify ctDNAs, and phylogenetic ctDNA profiling was performed, thus reconstructing the evolution of the patient-specific tumour after surgery. Where sequencing data from metastatic tissue was available, this was used to validate the tumour phylogenetic trees as well as improve the ctDNA profiling in the metastatic setting, retrospectively. This approach allowed the authors to track the evolution of tumours in patients in a non-invasive manner.

Next, the authors tested whether ctDNA profiling could detect and characterize which subclone(s) might be at the origin of NSCLC relapse. In 13 out of 14 patients, ctDNA profiling, which was performed blinded to the relapse status of the patient, identified ctDNAs prior to or at the time when clinical relapse was first detected.

Writing in the *New England Journal of Medicine*, Jamal-Hanjani *et al.* provide an in-depth characterization of the intratumour heterogeneity observed in the same patient cohort. A median of 30% of somatic mutations and 48% of copy-number alterations were identified as subclonal, although intratumour heterogeneity varied greatly between

tumours from different patients. Patients with a higher than median percentage of subclonal copy-number alterations had a higher risk of disease recurrence or death, which suggests that this patient subgroup may benefit from increased monitoring and/or early intervention. No association between clinical outcome and subclonal mutations was observed.

Intratumour heterogeneity was associated with ongoing dynamic chromosomal instability, determined in 62% of tumours, and whole-genome duplication, which was identified in 76% of tumours. The finding that genome doubling was predominantly clonal suggests that this event occurs early in cancer evolution. Notably, more than 75% of the tumours carried alterations in subclonal driver genes, which indicates that substantial subclonal diversification occurs after genome duplication.

Jamal-Hanjani *et al.* conclude that chromosomal instability could serve as a predictor of poor clinical outcome. As the study by Abbosh *et al.* shows, liquid biopsies might well serve this purpose if the reliability of detection of copy-number alterations matches that of SNVs, although considerations such as the cost of targeted ctDNA profiling are likely to also play a part. Regardless, these tools will be helpful in developing and testing new therapeutic strategies — for example, those targeting emerging subclones.

Carolina Perdigoto, Associate Editor,
Nature Communications

ORIGINAL ARTICLES Abbosh, C. *et al.* Phylogenetic ctDNA analysis depicts early stage lung cancer evolution. *Nature* <http://dx.doi.org/10.1038/nature22364> (2017) | Jamal-Hanjani, M. *et al.* Tracking the evolution of non-small-cell lung cancer. *N. Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1616288> (2017)

FURTHER READING Schwartz, R. & Schaffer, A. A. The evolution of tumour phylogenetics: principles and practice. *Nat. Rev. Genet.* **18**, 213–229 (2017)

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