News & views

Medical research

Molecular portraits of lung cancer evolution

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Assessing the genetic and cellular changes that underlie human lung cancer as it evolves could aid the development of treatments. The TRACERx project reports data from studies tracking the disease. **See p.525, p.534, p.543, p.553 & p.563**

Profiles of human lung cancers captured over time can shed light on how individual tumours change as they progress, and such insights might help efforts to provide effective therapies. Five studies[1–5] in this issue report analyses of lung cancer in the clinic, examined as part of the TRACERx – tracking cancer evolution through therapy (Rx) – project.

Lung cancer is the leading cause of cancer-related mortality worldwide[6]. There are two subtypes: non-small cell lung cancer (NSCLC), which represents 85% of cases, and small cell lung cancer, which accounts for the remaining 15% (ref. 7). NSCLC can occur as one of three subtypes, classified on the basis of cellular appearance under the microscope (histological assessment). The three groupings are lung adenocarcinoma, lung squamous cell carcinoma and large cell carcinoma.

Lung adenocarcinoma, the most common NSCLC, harbours multiple mutations that offer clinical targets, whereas lung squamous cell carcinoma and large cell carcinoma have fewer targetable mutations[7]. For lung adenocarcinoma, advances in DNA sequencing have driven the ability to classify treatments on the basis of targetable mutations (such as those in the genes *EGFR*, *MET* and *ALK*) and the development of small-molecule inhibitors that target pathways affected by these mutations[8]. People with NSCLC have also benefited from the use of immunotherapy approaches, which harness immune cells to target tumours[7]. Although targeted treatments and immunotherapies have improved the overall survival times for subsets of patients, there are still opportunities to introduce new approaches that could further extend the lives of people with lung cancer.

Progress in genomics has improved our understanding of the DNA landscape of lung cancers and other tumours. However, such techniques have typically been used to examine samples from a single biopsy, giving only a snapshot of a portion of a tumour and its microenvironment. Sampling of distinct tumour regions has shown that a tumour can have various genomic landscapes, representing genetically different populations of cells[9]. This phenomenon is referred to as intratumour heterogeneity, and it can change over time as the tumour evolves[10]. Studies evaluating genomic heterogeneity have observed this type of complexity in various cancers, including those of the kidney, pancreas, brain, prostate, breast and lung, as well as leukaemias[11–18]. These studies suggest that intratumour heterogeneity might drive cancer progression and so should influence the choice of treatment strategies.

The ongoing lung TRACERx study[19] has followed human lung cancers over time, and the latest results provide the most comprehensive description of the natural history of NSCLC so far, including detailed clinical annotations and extensive genomic characterization of multiple regions of tumours (Fig. 1). A total of 421 individuals with NSCLC in the United Kingdom were profiled, for genomic analysis of 1,644 tumour regions. Also presented is a study[3] examining tumour DNA in the bloodstream, which is known as circulating tumour DNA (ctDNA), and another study that looked at the role of immune cells in targeting lung cancer[5]. TRACERx provides a framework for sample collection over time and location in the body – from diagnosis to relapse after treatment failure, comprising both primary tumours and tumours that have spread to distant sites (metastases).

TRACERx's main objective was to determine the relationships between intratumour heterogeneity and clinical outcome (as measured by

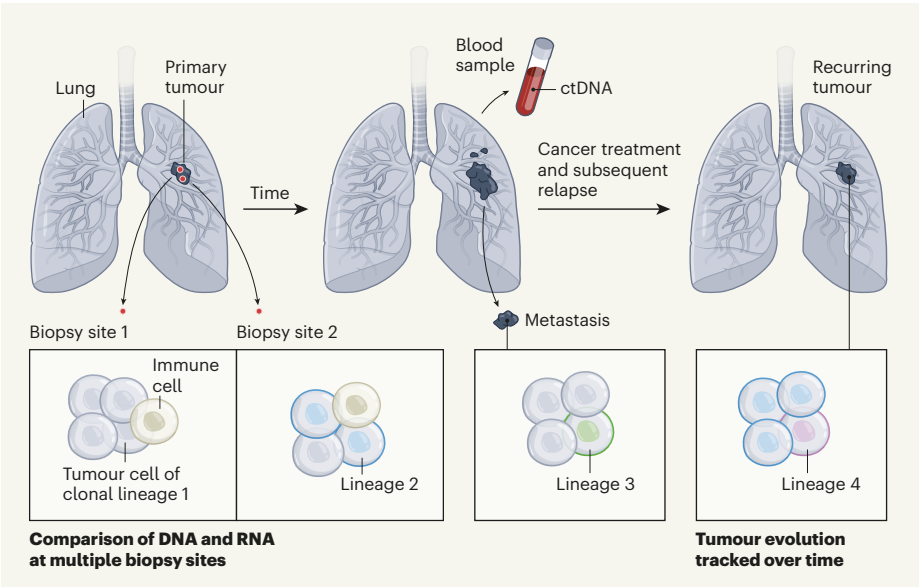

Figure 1 | Tracking genetic and cellular changes as lung cancer arises and is treated. A series of papers from the TRACERx project[1–5] report an analysis of data examining various aspects of lung cancer. This project monitored the evolution of such cancers over time by examining the patterns of cellular lineages (clones) of tumour cells present in biopsies. The work assessed RNA to clarify gene expression, investigated immune cells associated with tumours, and analysed tumour cells that had spread (metastasized) to distant sites. The authors examined the use of tumour DNA shed into the bloodstream, called circulating tumour DNA (ctDNA), as a way of monitoring the disease.

disease-free survival; that is, the length of time after treatment for which the person survives without symptoms of the cancer). Tumour heterogeneity was assessed by sequencing the protein-coding regions of the cancer genome (whole-exome sequencing) or by whole-genome sequencing. Secondary objectives included understanding the effects of chemotherapy with platinum-based drugs, assessing intratumour heterogeneity as a predictive biomarker tool, understanding cancer spread, and tracking the dynamics of mutational intratumour heterogeneity in people with relapses. The TRACERx studies seek to understand the genetic changes and development of lineages of tumour cells that underlie disease and relapse after targeted therapy, as a way of categorizing individualized treatments.

In the study by Frankell *et al.*[1] (page 525), the TRACERx consortium combined genomic profiling with radiology scans and histological assessments to elucidate patterns of intratumour heterogeneity. The team also developed methods to allow effective discrimination between different types of genomic change — truncal and subclonal events, and whole-genome doublings. Truncal events are genetic changes that occur early and that are often present in all cellular lineages (clones) of a tumour, whereas a subclonal event occurs later and is found in only a subset of cancer cells. Interestingly, genomic alterations in a subset of genes, including those in the *MYC* and receptor tyrosine kinase pathways, were associated with truncal events, whereas alterations in other genes, such as *STK11*, *TP53* and *KRAS*, were linked to subclonal events. The authors found that both subclonal whole-genome doubling (a duplication of the nuclear DNA content) and large-scale expansion of specific subclones were associated with a decrease in disease-free survival time.

In rare cases, the authors observed lung tumours that had two distinct genomic origins — these 'collision tumours' consist of two tumours that converge on the same space in the lung. The authors also report that some individuals with a history of heavy smoking can nevertheless have lung adenocarcinomas with mutations typical of those found in cancers in non-smokers.

The TRACERx study is ideally designed to assess the genomic path from initial tumour (primary lung cancer) to metastasis. Al Bakir *et al.*[2] (page 534) sought to understand the underlying mechanisms that drive metastasis by comparing the genomes of primary tumours with those of their metastases, using a multiple-sampling strategy. The data hinted at distinct types of metastasis, which the authors defined as either early divergence, for those found before 'clonal sweeps' (in which one tumour clone becomes dominant throughout the primary tumour), or late divergence (those after clonal sweeps). Clones that give rise to metastases were more likely to have undergone outgrowths (growth of cells associated with subclonal events) than were non-metastatic clones. Furthermore, the metastases could be associated with either one clone (monoclonal) or more than one clone (polyclonal).

To detect and assess the state of metastasis, Abbosh and colleagues[3] (page 553) harnessed new technology for the detection of ctDNA. Monitoring ctDNA can allow early detection, as well as providing a method for assessing relapse. The authors developed a computational tool called ECLIPSE that enables subclones at low levels of ctDNA to be tracked non-invasively. This method could identify individuals with polyclonal metastatic dissemination, which is associated with poor clinical outcomes. ctDNA analysis has the potential to help select patients for clinical trials of adjuvant drug therapy (further treatment after surgery) or neo-adjuvant therapy (before surgical treatment). It can also predict the metastatic potential of tumours and aid the development of biomarkers for diagnosing or tracking tumours.

"The ongoing lung TRACERx study has followed human lung cancers over time."

Given that heterogeneous tumours will vary in their abundance of RNA as well as in DNA alterations, Martínez-Ruiz *et al.*[4] (page 543) searched for connections between intratumour heterogeneity and diversity in the messenger RNA molecules expressed, or in changes in gene expression. The authors found that positive mutational selection, as measured by the outgrowth of a clone containing a particular mutation, occurs most often in the most highly expressed genes. In addition, assessing different versions (alleles) of the same gene permitted the authors to observe both copy-number-dependent and copy-number-independent events that modulate preferential expression of a particular allele. Copy-number-independent events were associated with changes to regulators of DNA and histone proteins (epigenetic regulators), including mutations resulting in regulator-gene inactivation.

Treatment strategies also affect tumour heterogeneity, and might result in the emergence of treatment-resistant dominant subclones. Al Bakir *et al.* noted that chemotherapy with platinum-based agents contributed to tumour evolution and heterogeneity that were linked to platinum-induced mutations. Tumour heterogeneity also includes the immune microenvironment, in which T cells and B cells of the immune system have a prominent role in antitumour defences. Ng *et al.*[5] (page 563) observed that antitumour B-cell responses, found locally or throughout the body, contributed to antitumour immunity by producing tumour-binding antibodies.

This latest update to the TRACERx studies raises questions over the role of genomic variation in the development of distinct clonal patterns and metastases, the potential for harnessing the results to target metastatic clones that grow after adjuvant therapy, and the benefits of regular assessment of tumours. Future studies should consider incorporating such strategies to better understand the complexities associated with a tumour and its microenvironment.

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