LUNG CANCER HETEROGENEITY IN SPACE AND TIME

Lung cancer is the leading cause of cancer-related mortality worldwide. Understanding the pathogenesis and evolution of this disease might guide therapy and improve prognosis. Two articles published in *Science* elucidate the high level of intratumour heterogeneity (ITH) in lung cancer.

In the first study, Zhang *et al.* sequenced the DNA from 48 regions of 11 lung cancers and reported that 76% of mutations were present in all regions of the same tumour, but the number and type of mutations varied substantially among tumours.

In the second study, Charles Swanton's group sequenced the DNA from 25 regions across seven different lung cancers. "This approach allows us to look at ITH both in space (how different is one region from another region within a tumour) and time (how mutations differ over time; mutations present in all tumour cells occurred earlier than those present in only few regions)," explain Elza de Bruin and Nicholas McGranahan, lead authors of the study.

The researchers reported that the majority of driver mutations tend to occur early in tumourigenesis and are present in all tumour cells. "However, we also identified important mutations in a subset of cells," says de Bruin, suggesting that single-region biopsy could fail to identify all the driver mutations within the tumour.

Moreover, smoking-related genomic events represented many of the early mutations found in tumours from past and current smokers, with genome-doubling events occurring long before the development of clinical disease. Of note, the mutations that occurred later are caused by the activation of the DNA-editing protein APOBEC. As McGranahan emphasizes, "it looks like lung cancers take a long time to develop, slowly accruing mutations through smoking, until something triggers genetic mistakes." Lung cancer could stay dormant for up to 20 years and the ability to detect early events would be an important step towards an improved prognosis for this disease.

This is a small study, but "shows the complexity of lung cancer evolution," says Swanton. He concludes, "We have more to learn; the results of the UK-wide study, TRACER-x, are eagerly awaited to shed more light on the evolution of lung cancer."

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Original articles de Bruin, E. C. *et al.* Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. *Science* doi:10.1126/science.1253462 | Zhang, J. *et al.* Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* doi:10.1126/science.1256930