Reconstructing mutational histories of oesophageal cancer

Secrier, M.[1]

[1]UCL Genetics Institute, University College London, London, UK

Mutational processes contributing to the development of cancer emerge from various risk factors of the disease and impose specific imprints of somatic alterations in the genomes of cancer patients. These mutational footprints, called "signatures", can be read from the tumour sequencing data and reveal the main sources of DNA damage driving neoplastic progression. In this sense, they can be considered a form of evidence for historical mutational events that have acted during tumour evolution. I will discuss some of the insights we have obtained into the development and progression of oesophageal adenocarcinoma, an aggressive disease with limited treatment options, by tracking mutational signatures in human cancer tissues as well as 3D cell models of this malignancy. Using this strategy applied to whole-genome sequencing data from 129 cases, we have previously uncovered three subtypes of oesophageal cancer with distinct aetiologies related to DNA damage repair deficiencies, ageing and oxidative stress, and with different therapeutic options. Further, we have shown that organoids grown in vitro from patients' tumours effectively recapitulate the genomic and transcriptomic profiles of the tumours of origin, and thus constitute a suitable model for this cancer type. By tracking the evolution of mutational processes during organoid culture growth we were also able to demonstrate a dynamic clonal architecture that mimics well the extensive intratumour heterogeneity observed in this cancer. Tracing mutational signature trajectories from early to later stages of cancer development in both primary tumours and organoid systems unveils a refined picture of evolution in this cancer, with frequent bottlenecks (~60% of cases) where mutational pressures shift. Finally, we suggest that the observed genomic signatures and their specific temporal dynamics could be further exploited for patient stratification in the clinic.