Cancer mutations occur decades before diagnosis

07.02.2020 - Researchers at EMBL's European Bioinformatics Institute (EMBL-EBI) and the Francis Crick Institute have analysed the whole genomes of over 2600 tumours from 38 different cancer types to determine the chronology of genomic changes during cancer development.

Cancer occurs as part of a lifelong process in which our genome changes over time. As we age, our cells cannot maintain the integrity of the genome after cell division without making some errors (mutations). This process can be accelerated by various genetic predispositions and environmental factors, such as smoking. Over our lifetime these mutations build up and cells may be mis-programmed, leading to cancer.

The scientists published their research in Nature as part of an international collaboration of over 1300 scientists known as the Pan-Cancer Analysis of Whole Genomes (PCAWG). The project aims to identify and catalogue the underlying patterns of mutation that give rise to many different cancer types. Access to this resource has significant implications for aiding the understanding of tumour progression, as well as opening up possibilities for early diagnosis and clinical intervention.

Calibrating cancer's molecular clock

"We can map out the point mutations arising throughout normal ageing to create a molecular clock for the human genome, akin to tracking the rings of a tree," says Moritz Gerstung, Group Leader at EMBL-EBI. "This provides us with a yardstick to estimate the age of some alterations seen in cancer, and to measure how far a tumour has progressed."

The researchers used data from the Pan-Cancer project and The Cancer Genome Atlas (ICGC) to create tumour development timelines for several cancer types including glioblastoma, and colorectal and ovarian adenocarcinoma. Their findings suggest that tumour development can span the entire lifetime of an individual, so the mutations that initiate cancer progression may arise decades before diagnosis.

"We've observed that changes in chromosome count within tumour cells typically occur late during...
tumour evolution. However, in some cases, such as in glioblastoma multiforme tumours, these changes can occur decades before diagnosis," says Stefan Dentro, Postdoctoral Fellow at EMBL-EBI. "Typically, cells don't survive for very long with an odd number of chromosomes, but somehow these cells do; possibly founding a tumour that is detected many years later."

Towards early cancer detection

"We've developed the first timelines of genetic mutations across the spectrum of cancer types," says Peter Van Loo, co-lead author and group leader in the Cancer Genomics Laboratory at the Francis Crick Institute. "For more than 30 cancers, we now know what specific genetic changes are likely to happen, and when these are likely to take place. Unlocking these patterns means it should now be possible to develop new diagnostic tests that pick up signs of cancer much earlier."

Understanding the sequence and chronology of mutations leading to cancer may help clarify the mechanisms of cancer development, which otherwise appear convoluted due to the presence of many alterations in the final cancer cells. Being able to determine whether a mutation typically occurs early or late during cancer progression may also help to guide early detection. This would make it possible to define the sets of alterations to screen for, to detect pre-cancerous cells at different stages of transformation.

"To a large extent, cancer development is an unfortunate consequence of the normal ageing of our cells," says Moritz Gerstung. "Fully understanding the molecular progression of the disease is the first step towards identifying targets for early detection and perhaps treatment. The observation that many genetic alterations were already present years before the cancer was diagnosed provides a window of opportunity to detect aberrant cells before they become fully malignant."