GENETICS

Signatures of mutational processes in cancer—a big step closer

The complexity and diversity of somatic mutations that occur in human cancer genomes is revealed for the first time, thanks to an extremely thorough assessment of mutational patterns of human cancers in a study published in *Nature*. All cancers are caused by alterations and mutations in DNA, but our knowledge of the processes that generate these mutations has so far been remarkably limited. Recent advances in sequencing technology have advanced the field of cancer genetics—it is now possible for thousands of somatic mutations to be identified from a single cancer sample. In the present study, Michael Stratton and his extensive team of collaborators developed an algorithm to extract mutational signatures from somatic mutations across a spectrum of human cancers.

As cancers develop, each mutation leaves an ‘imprint’ or evidence of that mutational process behind, which is what the researchers assessed to understand the carcinogenesis process. Stratton provides some context about our knowledge of these processes: “What is remarkable is how little we know about the processes that are causing the mutations in many cancers.” Previously, Stratton’s group developed a computational method that allowed signatures of mutational processes to be deciphered from the genomes of 21 breast cancers. Now, using mathematical concepts to extract information to help determine what has gone wrong during cancer, the researchers extended their analysis to a dataset that included 7,042 samples from 30 different cancer types. The researchers assessed how these signatures contribute to mutations across cancer types, providing new insights into the way cancer develops. Critically, this latest research has potential implications for how cancer might be prevented and treated in the future.

Stratton’s team analysed almost 5 million mutations from over 7,000 cancers to

extract over 20 distinct signatures. In all cases, they also compared the DNA of cancer cells with that of healthy cells from the same patients, to serve as controls for discovery of the mutational processes that occur during malignancy. The researchers uncovered a diverse range of distinct signatures, some of which are present in many cancer types, whereas others are specific to individual tumour types.

The prevalence of somatic mutations was highly variable ranging between 0.001 per megabase (Mb) of DNA to more than 400 per Mb. Perhaps not surprisingly, the investigators observed that certain childhood cancers carried the fewest mutations. Conversely, cancers related to chronic mutagenic exposure, such as lung cancer (tobacco exposure) and malignant melanoma (UV exposure) exhibited the highest prevalence of mutations. Each of the cancer types had at least two mutational signatures, while other cancers, such as those of the liver or uterus, had up to six distinct mutational processes. Known signatures associated with lung cancer and smoking, UV exposure and skin cancer, and DNA mismatch repair (such as *BRCA* mutations in breast cancer) were revealed, but the researchers also uncovered multiple mutational signatures that had not been previously identified.

The 21 mutational signatures varied according to cancer types. One or two signatures were surprisingly extremely common across half of the cancer types. In particular, one mutational signature previously found in breast cancers was also identified in 16 other cancer types, and was very common—it was present in around 20% of the dataset. The researchers

believe that this signature is due to the activity of the APOBEC family of cytidine deaminases, which are known to prevent viruses from replicating in human cells. But, APOBEC activation is a double-edged sword. Although it serves as part of the immune response to viruses, it is possible that this defence process also unleashes collateral mutational damage to the genome that eventually contributes to the oncogenic process.

The significance of this work is summarized by Stratton in an online podcast: “This is the largest analysis, to date, of cancer genomes, with over 7,000 cancer genomes aggregated together for analysis. This study is the first comprehensive overview of the mutational signatures that are operative in human cancer.” Ludmil Alexandrov, first author of the study, further elaborates on the significance of this work. “We have revealed more than 20 distinct mutational processes, and have provided the next step towards a better understanding of cancer biology. Furthermore, our findings could have far-reaching implications for both cancer treatment and prevention.”

Undoubtedly, this latest research provides a better understanding of the processes that lead to cancer, which in turn will enable more-effective prevention as well as targeted treatment approaches to help reduce the effect of the mutational processes in cancer.

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