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CANCER GENOMICS

The driving force of cancer evolution

Two novel comprehensive genomic analyses in *Cell* provide important insights into the dynamics of tumour evolution and the mutational burden of a wide range of cancer types.

Cancer develops from somatically accumulating mutations, but not all mutations drive tumorigenesis. Driver mutations have been positively selected for the growth advantage they confer. By contrast, unselected, passenger mutations have no fitness effects and thus do not contribute to cancer development.

Quantitative estimates of the number of driver mutations needed for cancer to develop were lacking. Martincorena *et al.* sought to address this issue by calculating the ratio of non-synonymous to synonymous substitutions (dN/dS) across 7,664 tumours from 29 cancer types. Quantifying positive and negative selection using molecular evolution methods allowed the authors to directly estimate any excess or deficit of mutations compared with the number expected under neutrality.

The team observed a unique pattern of selection that was universal across cancer types. In contrast to species evolution, which is characterized predominantly by negative selection, positive selection was observed to have a greater impact on cancer evolution. Using a dN/dS >1 as a marker of cancer genes under positive selection, Martincorena *et al.* identified 179 cancer genes, which were distributed heterogeneously across patients and tumour types. About 50% of the coding driver mutations were found to occur outside of known cancer genes.

Focusing on negative (purifying) selection next, the authors estimated that, on average across all analysed tumours, less than one coding substitution per tumour had been negatively selected against. The lack of negative selection on coding substitutions indicates that nearly all of these mutations are tolerated by cancer cells, which may be the result of redundancy provided by the existence of alternative pathways or two (or more) copies per gene.

Extending their analysis exome-wide, the authors estimated that the average number of driver coding substitutions per tumour ranges from around 4 to 10 mutations depending on the type of cancer. In tumours with a so-called hypermutator phenotype (up to 1,000 coding substitutions), the total number of driver mutations per tumour increased with the overall mutational burden.

The second study by Campbell *et al.* focused specifically on tumours exhibiting hypermutation (defined as ten mutations per Mb). The authors analysed 78,452 adult and 2,885 paediatric patients and determined the frequency of hypermutation between and within cancer types.

Hypermutation was observed in 5.5% and 17.0% of childhood and adult cancer genomes, respectively, and hypermutant cancers were enriched for defects in the mismatch repair pathway genes *POLE* and *POLD1*. Sequencing revealed 2,150 and 1,123 distinct variants in *POLE* and *POLD1*, respectively, although most mutations were not associated with hypermutation. Using an *in vivo* human mutagenesis screen, as the authors call it, all known and 11 novel drivers in the *POLE* and *POLD1* genes could be identified. The authors then used these data to define amino acid positions in the DNA polymerases encoded by *POLE* and *POLD1* that were particularly sensitive to mutation, or were consistently spared from mutation.

Hierarchical clustering analysis of 1,521 tumours by trinucleotide context of 217,086 mutations revealed eight major hypermutant tumour subgroups with different evolutionary dynamics and patient survival. These clusters could be distinguished by the type and order of mutagen exposure rather than the cancer histotype. That is, different cancer types exhibited striking similarities in mutational signatures, which suggests that similar forces are driving their development.

A central goal of cancer genomics is the identification of cancer genes that carry driver mutations. These two studies have yielded promising candidate genes for functional follow-up investigations. Delineating the consequences of the driver mutations identified may help elucidate the mechanisms by which biological processes are subverted in cancer development.

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> “a unique pattern of selection that was universal across cancer types”

ORIGINAL ARTICLES Martincorena, I. *et al.* Universal patterns of selection in cancer and somatic tissues. *Cell* http://dx.doi.org/10.1016/j.cell.2017.09.042 (2017) | Campbell, B. B. *et al.* Comprehensive analysis of hypermutation in human cancer. *Cell* http://dx.doi.org/10.1016/j.cell.2017.09.048 (2017)