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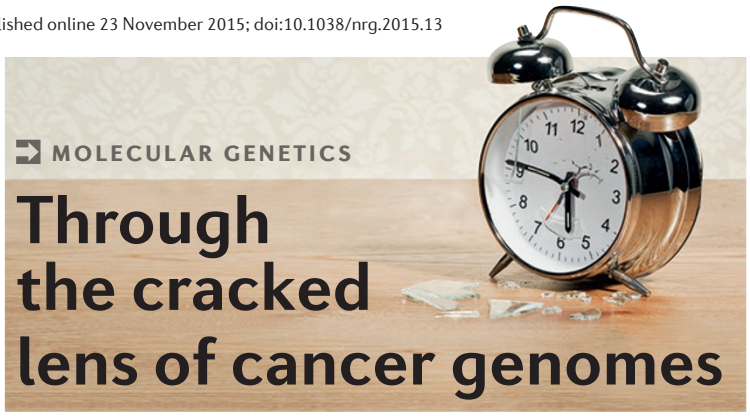

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MOLECULAR GENETICS

Through the cracked lens of cancer genomes

> The ability to track the mutational 'age' of cells might one day inform a diversity of areas, including ageing, oncogenesis and metastasis

An analysis of 10,250 genomes from 36 different human cancer types has identified evidence for the operation of clock-like mutational processes in somatic cells.

The mutational load of somatic cells comprises mutations derived from relatively constant (or 'clock-like') processes, and those occurring in 'bursts', usually as a result of environmental exposures. The action of various processes that generate different kinds of mutation produces mutational signatures — combinations of mutation types that are characteristic of the particular processes that created them.

To identify mutational signatures with clock-like features, the authors took advantage of the clonal nature of cancer cell populations. In this context, the mutations that are shared among a population are likely to have been present in the original progenitor cell. Modelling confirmed that mutations acquired after neoplastic transformation were unlikely to substantially obscure detection of clock-like processes operating in normal somatic cells. A signature exhibiting clock-like features, then, would show a correlation between the number of mutations present and age at diagnosis of the patient that the tissue was sourced from.

Previous work established mathematical and computational approaches for extracting mutational signatures from human cancer genomes. In the present study, the authors developed a method for pooling the data in order to derive consensus signatures across different cancers. Of the 33 distinct signatures that were detected from the 36 cancer types studied, 2 showed strong evidence of being the product of clock-like mutational processes.

The first, signature 1, was predominantly composed of C>T mutations, probably caused by deamination of 5-methylcytosine at CpG dinucleotides. This signature was also prominent in cancer types derived from epithelial cells that have a high turnover, such as stomach cancer and colorectal cancer, suggesting that the processes underlying signature 1 might be related to cell proliferation rate. The factors generating the second signature, signature 5, were less clear, but the cancer types with a strong signature 5 component led the authors to speculate that constant exposure to a metabolic mutagen might underlie this signature. Alternatively, signature 5 might also be related to processes specific to neoplastic transformation. Finally, although the contributions of the two clock-like signatures varied considerably between cancer types, 33 of the 36 types showed evidence for the presence of at least one of these signatures.

The ability to track the mutational 'age' of cells might one day inform a diversity of areas, including ageing, oncogenesis and metastasis. Ultimately, given that cancer can affect mutation rates, viewing these processes through the 'cracked lens' of cancer genomics can only go so far. As such, the refinement of these signatures and, potentially, the detection of additional somatic clock-like processes, will rely on future work using single-cell sequencing of normal cells.

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Nature Reviews Disease Primers

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