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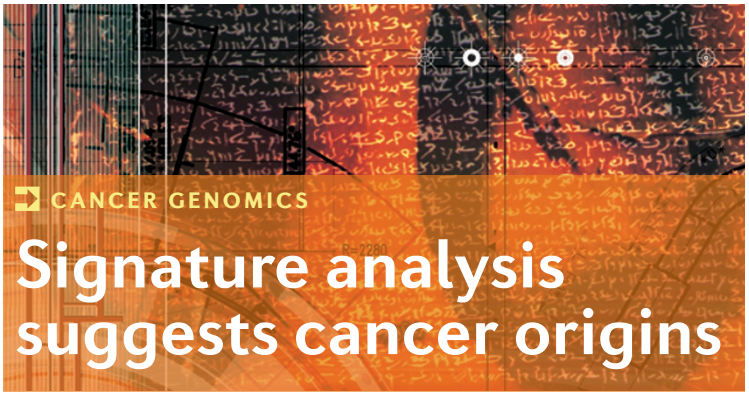

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Signature analysis suggests cancer origins

> The findings provide insights into the mechanisms that give rise to mutations in cancer

Large-scale sequencing initiatives have yielded catalogues of mutations from thousands of cancers. A newly published study uses this repository of data to uncover the mutational signatures of a wide spectrum of cancer types. The findings provide insights into the mechanisms that give rise to mutations in cancer — a crucial and largely unaddressed issue.

Alexandrov *et al.* had previously developed an algorithm to determine mutational signatures in breast cancer and have now extended this method to 30 different cancer types. They analysed nearly 5 million mutations and identified 21 mutational signatures. The authors correlated these mutation patterns with the effects of known mutagens or with the known sequence features of processes such as DNA repair.

Several signatures showed transcriptional strand bias, in which the mutations favoured either the transcribed or the untranscribed strand. DNA damage leading to mutations that show transcriptional strand bias may be repaired by transcription-coupled nucleotide excision repair (NER), as this type of DNA repair mainly operates on the transcribed strand. Signatures that exhibited transcriptional strand bias were highly prevalent in cancers that are strongly associated with tobacco smoking, such as lung and liver cancer. Tobacco carcinogens are known to cause bulky helix-distorting adducts, and NER activity may explain the high prevalence of this mutational signature in these cancer types.

Other abnormalities in DNA maintenance, including the APOBEC family of DNA- and RNA-editing enzymes, were suggested to underlie some signatures. However, APOBEC activation constitutes part of the normal immune response to viruses and these mutations may therefore be the result of damage from an innate immune response rather than from defects in the APOBEC enzymes themselves. The authors also observed a signature with microsatellite instability (MSI), which is characterized by a high number of substitutions and a high number of insertions and deletions. MSI is frequently associated with the inactivation of DNA mismatch repair genes, and the authors found that cancers with this signature, such as colorectal cancer, had a very strong correlation with the inactivation of this class of genes.

Other signatures had features that could be directly correlated with known consequences of environmental factors or mutagens, such as ultraviolet radiation, tobacco smoke or anticancer drugs.

This study also sheds light on the rate of acquiring mutations, as one signature was strongly associated with the age of patients at diagnosis, which suggests that this particular mutation pattern is acquired at a similar rate in various individuals.

Finally, the origin of several mutational signatures remains unknown and provides an avenue for future research. Further refinement of this method will reveal an even more precise definition of these mutation patterns and give deeper insights into how they and, consequently, cancers arise and develop.

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ORIGINAL RESEARCH PAPER Alexandrov, L. B. *et al.* Signatures of mutational processes in human cancer. *Nature* http://dx.doi.org/10.1038/nature12477 (2013)