Nature Reviews Cancer | Published online 5 May 2017; doi:10.1038/nrc.2017.33

TUMORIGENESIS

Cancer as a symptom of evolution?

In 2015, Tomasetti and Vogelstein sparked debate about the influence of exogenous, inherited and 'other' sources of DNA mutation that lead to tumour initiation. Now, another paper in *Science* by Tomasetti, Li and Vogelstein develops their model further and explores how different sources of DNA mutation influence different cancer types.

It is widely accepted that inherited genetic alterations and exogenously induced mutations can cause cancer. But, there is a proportion of cancers — which varies by cancer type — that cannot be explained by these two sources of DNA mutation. So what causes them? Tomasetti *et al.* propose that the missing factor is endogenous mutagenesis: random DNA replication errors that occur in stem cells (because they are the only long-lived cells that divide) and thus also exist in their progeny. The existence of endogenous mutagenesis is widely accepted, as error-free DNA replication is incompatible with evolution.

Previously, Tomasetti and Vogelstein demonstrated a strong correlation between the number of stem cell divisions and cancer incidence rates in the United States. Now, Tomasetti *et al.* report an analysis of cancer incidence in 4.8 billion people from 69 countries. They analysed 17 different types of cancer for which data on stem cell divisions are available for their tissue of origin and again demonstrated a strong correlation between the lifetime risk of cancer in a tissue and stem cell divisions in that tissue.

> 'other' sources of DNA mutation that lead to tumour initiation

Next, they developed a method to estimate the sources of the mutations in different cancers. Epidemiological studies suggest that ~90% of lung adenocarcinoma cases can be prevented through avoidance of exogenous mutagens (such as tobacco smoke); there is no evidence to date of inherited mutations in lung adenocarcinoma. Using epidemiological and genome-wide DNA sequencing data from hundreds of patients with lung adenocarcinoma they found that driver mutations in 90% of the patients were at least partially due to exogenous sources, while driver mutations in 10% of the patients were not attributable to exogenous sources at all. Therefore, the authors calculated that 35% of the driver mutations among all patients with lung adenocarcinoma are not due to exogenous (or inherited) sources and were proposed to be due to endogenous mutagenesis.

There is limited evidence of environmental factors increasing the risk of developing pancreatic ductal adenocarcinoma (PDAC), with ~37% of PDAC cases considered preventable. Using exome DNA sequencing data from PDACs the authors calculated that 18% of driver gene mutations were due to exogenous sources, 5% were inherited and 77% were due to neither. Prostate, bone and brain cancers were also calculated to have a high proportion of mutations derived from non-exogenous and non-inherited sources. Furthermore, they calculated the influence of exogenous, hereditary and 'neither' sources of mutation in 32 types of cancer using data from Cancer Research UK and found considerable variation in the influence of each source for different cancer types. When they normalized the data for cancer type incidence in the UK, they found that 40–66% of mutations were due to neither exogenous nor inherited factors and were proposed to be due to endogenous mutagenesis.

Importantly, finding that a proportion of driver mutations are not influenced by exogenous sources does not mean that a cancer cannot be prevented. Most cancers require the accumulation of several mutations in one cell to initiate tumorigenesis, but if endogenous sources provide fewer than the number of mutations required for transformation and exogenous sources supply the additional mutations then tumorigenesis can still be prevented by reducing the accumulation of mutations. So, calculations of aetiology and preventability are not the same.

Assuming that the non-exogenous and non-inherited source of mutation in cancer is attributable to DNA replication error, Tomasetti *et al.* propose that these mutations may be derived from base pairing errors, DNA polymerase errors, base deamination and endogenous damage (for example, from reactive oxygen species). This model provides much food for thought and will likely stimulate further debate, and hopefully more research on tumour causation that could lead to improved prevention.

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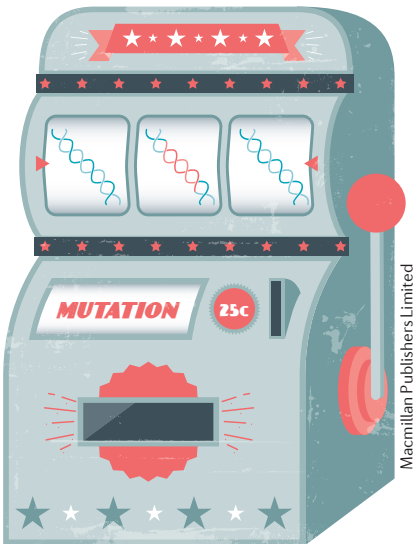
ORIGINAL ARTICLE Tomasetti, C. *et al.* Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* **355**, 1330–1334 (2017)
FURTHER READING Tomasetti, C. & Vogelstein, B. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* **347**, 78–81 (2015)



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