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REPORT

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

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leads to Cdc48 recruitment for extraction and degradation of the incomplete translation product. Rqc2p, through specific binding to Ala(IGC) and Thg(IGU) tRNAs, directs the template-free and 40S-free elongation of the incomplete translation product with CAT tails. CAT tails induce a heat shock response through a mechanism that is yet to be determined.

Hypomorphic mutations in the mammalian homolog of LTN1 cause neurodegeneration in mice (2). Similarly, mice with mutations in a central nervous system-specific isoform of tRNA^{Ala} and GTPBP2, a homolog of yeast Hbs1 which works with PELOTA/Dom34 to dissociate stalled 80S ribosomes, suffer from neurodegeneration (22). These observations reveal the consequences that ribosome stalls impose on the cellular economy. Eubacteria rescue stalled ribosomes with the transfer-messenger RNA (tmRNA) system, which appends nascent chains with a unique C-terminal tag that targets the incomplete protein product for proteolysis (23). The mechanisms used by eukaryotes, which lack tmRNA, to recognize and rescue stalled ribosomes and their incomplete translation products have been unclear. The RQC⁺ and Rqc2p s CAT tail tagging mechanism in particular bear both similarities

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SUPPLEMENTARY MATERIALS

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Materials and Methods

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CANCER ETIOLOGY

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and contrasts to the tmRNA -translation system. The evolutionary convergence upon distinct mechanisms for extending incomplete nascent chains at the C terminus argues for their importance in maintaining proteostasis. One advantage of tagging stalled chains is that it may distinguish them from normal translation products and facilitate their removal from the protein pool. An alternate, not mutually exclusive, possibility is that the extension serves to test the functional integrity of large ribosomal subunits, so that the cell can detect and dispose of defective large subunits that induce stalling.

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tissues can be explained by the number of stem cell divisions

Cristian Tomasetti^{1*} and Bert Vogelstein^{2,*}

Some tissue types give rise to human cancers millions of times more often than other tissue types. Although this has been recognized for more than a century, it has never been explained. Here, we show that the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis. These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

Extreme variation in cancer incidence across different tissues is well known; for example, the lifetime risk of being diagnosed with cancer is 6.9% for lung, 1.08% for thyroid, 0.6% for brain and the rest of the nervous system, 0.003% for pelvic bone and 0.00072% for laryngeal cartilage (¹⁻⁵). Some of these differences are associated with well-known risk factors such as smoking, alcohol use, ultraviolet light, or human papilloma virus (HPV) (^{4,5}), but this applies only to specific populations

exposed to potent mutagens or viruses. And such exposures cannot explain why cancer risk in tissues within the alimentary tract can differ by as much as a factor of 24 [esophagus (0.51%), large intestine (4.82%), small intestine (0.20%), and stomach (0.86%)] (⁶). Moreover, cancers of the small intestinal epithelium are three times less common than brain tumors (⁵), even though small intestinal epithelial cells are exposed to much higher levels of environmental mutagens than are cells within the brain, which are protected by the blood-brain barrier.

Another well-studied contributor to cancer is inherited genetic variation. However, only 5 to 10% of cancers have a heritable component (⁶⁻⁸), and even when hereditary factors in predisposed individuals can be identified, the way in which these factors contribute to differences in cancer incidences among different organs is obscure. For example, the same, inherited mutant APC gene is responsible for both the predisposition to colorectal and small intestinal cancers

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in familial adenomatous polyposis (FAP) syndrome. In the large intestine than in the small intestine of these individuals.

If hereditary and environmental factors cannot

underlying neoplasia are reviewed in ²⁰⁻²².

The concept underlying the current work is that many genomic changes occur simply by chance during DNA replication rather than as a

quantitatively assessed (see the supplementary materials). We then plotted the total number of stem cell divisions during the average lifetime of a human on the x axis and the lifetime risk for cancer of that tissue type on the y axis (Fig. 1)

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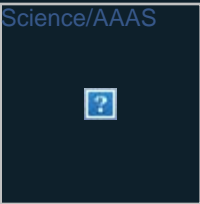
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