REPORT

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

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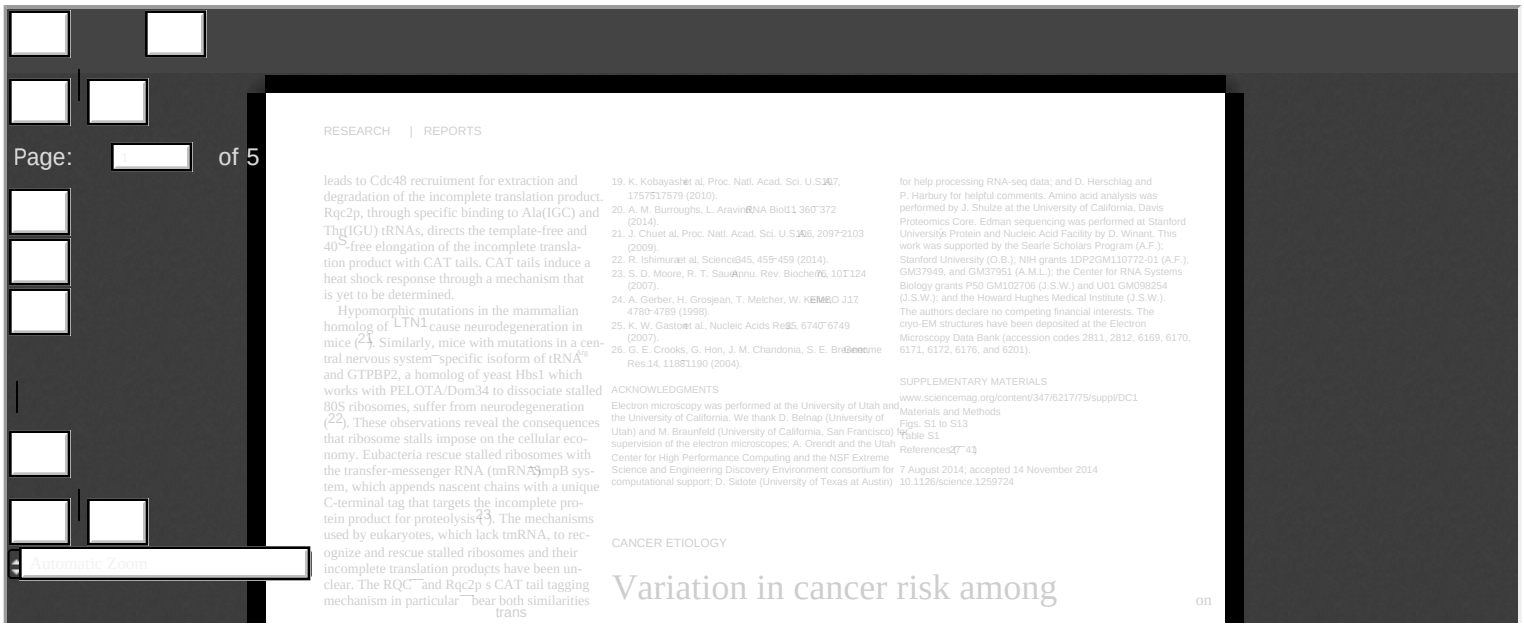

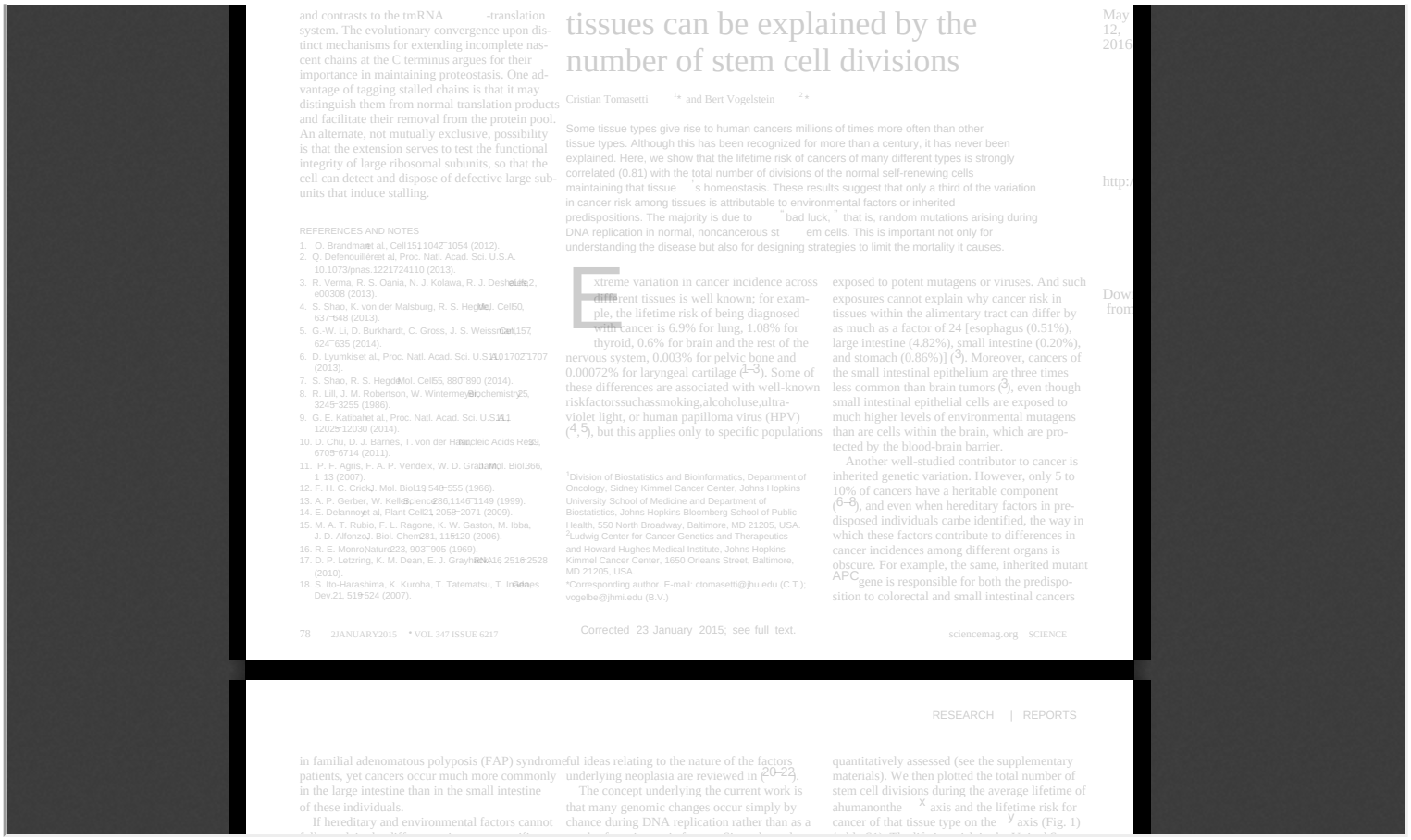

and contrasts to the tmRNA -translation system. The evolutionary convergence upon distinct mechanisms for extending incomplete nascent chains at the C terminus argues for their importance in maintaining proteostasis. One advantage of tagging stalled chains is that it may distinguish them from normal 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 ([1–3]). 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%)] ([3]). Moreover, cancers of the small intestinal epithelium are three times less common than brain tumors ([3]), 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 patients, yet cancers occur much more commonly in the large intestine than in the small intestine of these individuals.

If hereditary and environmental factors cannot

ful ideas relating to the nature of the factors 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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