Correction: Genetic Instability Is Not a Requirement for Tumor Development

In the Point-Counterpoint Review article in the May 15, 2008 issue of Cancer Research (1), Drs. Jason H. Bielas and Robert A. Beckman should have been included as the second and third authors, respectively, of the Response section. The affiliation for Dr. Bielas is the Department of Pathology, University of Washington School of Medicine, Seattle, Washington and the affiliations for Dr. Beckman are Oncology Clinical Research, Merck Research Laboratories, North Wales, Pennsylvania and Simons Center for Systems Biology, Institute for Advanced Study, Princeton, New Jersey.


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Conclusions

Why are somatic mutations found in sporadic tumors in repair and related genes, such as TP53, and why is there so often chromosomal instability in sporadic cancers if the instability itself is not the primary driving force?

The answer almost certainly lies in the relation between repair or chromosomal instability, and apoptosis. Selection in tumors against apoptosis is as important, if not more so, than selection for increased growth rate (see 24). Each repair pathway seems to have a default line to apoptosis, in case the magnitude of DNA damage is excessive. This is also true for the control of chromosomal integrity during cell division. For TP53 mutations, it has become clear that a major selective effect is against apoptosis, presumably by some sort of dominant interference with the pathway from p53 to apoptosis. The same is likely to be the case for hMLH1 and hMSH2 mutations, and can be presumed to be likely for aspects of the control of chromosomal integrity, other than by p53.

Selection against apoptosis could account for the reason why only a small subset of genes involved in repair is found to be mutated somatically in tumors. Only that subset may give rise to interference with the apoptotic pathways and so to the selective advantage, initially in the heterozygote, which accounts for their presence in many cancers.

It has been claimed that the overall number of mutations seen in cancers, whether functionally relevant or not, cannot be accounted for without an increase in the mutation rate. However, based on quite reasonable assumptions about the normal mutation rate and the cell biology of cancer development, it can be shown that this is not the case (25).

The key issue is that mutations that provide a selective advantage are essential for tumorigenesis. The direct selective effects of such mutations override the secondary effects of mutations that increase genomic instability and only indirectly contribute to the somatic evolution of cancers. Genomic instability may, however, often be a byproduct of direct selective effects. It will then, in at least some cases, have important consequences for the subsequent evolutionary behavior of a cancer.

Most sporadic tumors start to grow with a normal mutation rate as they accumulate their successive advantageous mutations leading to clonal expansion. Although some tumors will acquire a mutator phenotype before they present clinically, it is not necessary to invoke an increased mutation rate to explain the development of colorectal cancer patients. Genes Chromosomes Cancer 1995;14:223–6.

References


Acknowledgments

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Response

In the accompanying article, Bodmer emphasizes the importance of selection in tumor evolution. We agree, as we believe that selection of mutator mutations increases the mutation rate, fuels further selection, and drives carcinogenesis. Competition experiments invariably show the selective advantage of mutators over nonmutators (1). Mathematical modeling shows that mutator pathways are more efficient than nonmutator pathways (2). It seems unlikely that less efficient processes would predominate in nature. Bodmer presents arguments against the mutator phenotype. First, he states that in human nonpolyposis colon cancer, mutations in the adenomatous polyposis coli (APC) gene precede loss of the wild-type mismatch repair gene. This is controversial (3) and recent data have established a role for APC in genomic stability and base excision repair (4). Second, Bodmer asserts that there are only a limited number of DNA repair mutants in tumors; however, large-scale sequencing studies have identified a high prevalence of...
mutations in DNA repair in cancer cell lines. For example, the Cancer Genome Project reports that 60% and 58% of cancer cell lines have somatic mutations in DNA repair and replication genes, respectively (5). Third, he considers models with only recessive mutator mutations when many dominant mutator sites exist. Fourth, he considers models with only two mutational events for oncogenic transformation despite epidemiologic (6) and in vitro (7) evidence for 6 to 12 events. Moreover, DNA sequencing has revealed an average of 9 (range 318) and 12 (range 423) candidate cancer gene mutations in breast and colorectal tumors, respectively (8). Last, he claims that normal mutation rates in 5,000 stem and 1,000 tumor cell generations can account for tumor diversity (7). If correct, in contradiction to experimental findings (9), much of the diversity in tumors would also be present in surrounding normal tissue. The genesis of cancer is not only of academic interest. Early genetic instability would not only produce causative mutations but also produce multiple random mutations that may be a sentinel of tumor heterogeneity and a source of drug resistance.

Lawrence A. Loeb
University of Washington School of Medicine
Seattle, Washington

References
5. Available from the Wellcome Trust Sanger Institute Cancer Genome Project web site, http://www.sanger.ac.uk/genetics/CGP.