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Transgenic oncogenes induce oncogene-independent cancers with individual karyotypes and phenotypes

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Received: February 11, 2010; Received in revised form: March 24, 2010; Accepted: April 1, 2010;

DOI: http://dx.doi.org/10.1016/j.cancergencyto.2010.04.008

Abstract

Cancers are clones of autonomous cells defined by individual karyotypes, much like species. Despite such karyotypic evidence for causality, three to six synergistic mutations, termed *oncogenes,* are generally thought to cause cancer. To test single oncogenes, they are artificially activated with heterologous promoters and spliced into the germ line of mice to initiate cancers with collaborating spontaneous oncogenes. Because such cancers are studied as models for the treatment of natural cancers with related oncogenes, the following must be answered: 1) which oncogenes collaborate with the transgenes in cancers; 2) how do single transgenic oncogenes induce diverse cancers and hyperplasias; 3) what maintains cancers that lose initiating transgenes; 4) why are cancers aneuploid, over- and underexpressing thousands of normal genes? Here we try to answer these questions with the theory that carcinogenesis is a form of speciation. We postulate that transgenic oncogenes initiate carcinogenesis by inducing aneuploidy. Aneuploidy destabilizes the karyotype by unbalancing teams of mitosis genes. This instability thus catalyzes the evolution of new cancer species with individual karyotypes. Depending on their degree of aneuploidy, these cancers then evolve new subspecies. To test this theory, we have analyzed the karyotypes and phenotypes of mammary carcinomas of mice with transgenic SV40 tumor virus– and hepatitis B virus–derived oncogenes. We found that (1) a given transgene induced diverse carcinomas with individual karyotypes and phenotypes; (2) these karyotypes coevolved with newly acquired phenotypes such as drug resistance; (3) 8 of 12 carcinomas were transgene negative. Having found one-to-one correlations between individual karyotypes and phenotypes and consistent coevolutions of karyotypes and phenotypes, we conclude that carcinogenesis is a form of speciation and that individual karyotypes maintain cancers as they maintain species. Because activated oncogenes destabilize karyotypes and are dispensable in cancers, we conclude that they function indirectly, like carcinogens. Such oncogenes would thus not be valid models for the treatment of cancers.

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