



Original Article

Genetic Alterations during Colorectal-Tumor Development

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Abstract

Because most colorectal carcinomas appear to arise from adenomas, studies of different stages of colorectal neoplasia may shed light on the genetic alterations involved in tumor progression. We looked for four genetic alterations (*ras*-gene mutations and allelic deletions of chromosomes 5, 17, and 18) in 172 colorectal-tumor specimens representing various stages of neoplastic development. The specimens consisted of 40 predominantly early-stage adenomas from 7 patients with familial adenomatous polyposis, 40 adenomas (19 without associated foci of carcinoma and 21 with such foci) from 33 patients without familial polyposis, and 92 carcinomas resected from 89 patients.

We found that *ras*-gene mutations occurred in 58 percent of adenomas larger than 1 cm and in 47 percent of carcinomas. However, *ras* mutations were found in only 9 percent of adenomas under 1 cm in size. Sequences on chromosome 5 that are linked to the gene for familial adenomatous polyposis were not lost in adenomas from the patients with polyposis but were lost in 29 to 35 percent of adenomas and carcinomas, respectively, from other patients. A specific region of chromosome 18 was deleted frequently in carcinomas (73 percent) and in advanced adenomas (47 percent) but only occasionally in earlierstage adenomas (11 to 13 percent). Chromosome 17p sequences were usually lost only in carcinomas (75 percent). The four molecular alterations accumulated in a fashion that paralleled the clinical progression of tumors.

These results are consistent with a model of colorectal tumorigenesis in which the steps required for the development of cancer often involve the mutational activation of an oncogene coupled with the loss of several genes that normally suppress tumorigenesis. (N Engl J Med 1988; 319:525–32.)

Reference

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