IDENTIFICATION AND CHARACTERIZATION OF CANCER GENES IN HORMONE-DEPENDENT TUMORS

Molecular Genetic Analysis in Rat Models of Endometrial and Mammary Cancer

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ABSTRACT

Genetic heterogeneity among patients often makes it difficult to identify the important genetic changes in human cancer. In contrast, model systems of inbred rat strains are genetically highly homogeneous, facilitating genetic analysis. In the present investigation, comprehensive cytogenetic and molecular analysis was undertaken in rat models of endometrial and mammary cancer with the overall aim to increase our understanding of the molecular basis of tumorigenesis.

Animals of the BDII inbred rat strain are genetically predisposed to hormone-dependent endometrial adenocarcinoma (EAC) and serves as a suitable model for the study of hereditary EAC. In order to dissect out the genetic components behind these tumors, crosses between BDII females and rats from two other strains that are nonsusceptible (BN and SPRD) to EAC were made. The chromosomal changes in the developing tumors were studied using comparative genomic hybridization (CGH) and cytogenetic analysis. Specific chromosomal regions exhibiting recurrent gains/amplifications or losses/deletions were detected. Gain/amplification affecting the proximal part of rat chromosome (RNO) 6 was one of the most common aberrations found. Detailed molecular analysis revealed that one group of tumors displayed large RNO6-derived HSRs in addition to several normal or near-normal RNO6 chromosomes. Another group of tumors (two of which also had HSRs) exhibited selective increase of the RNO6q11-q16 segment, sometimes in conjunction with moderate amplification of one or a few genes, possibly representing an intermediate step in the gene amplification process. Most commonly the amplification affected the region centered around band 6q16 including the genes Mycn, Daks1 and Rrm2. A second region, centered around band 6q12 (including the Ste8a1 and Xdh genes), was also affected by gene amplification but to a lesser extent. The study clearly showed that genes in the proximal part of RNO6 must contribute to the development of this hormone-dependent tumor. Another common aberration detected by CGH in rat EACs was loss affecting the middle part of RNO5. Characterization with molecular cytogenetic analysis of RNO5 revealed that frequent rearrangements of this chromosome occur in a subgroup of rat EACs, causing extensive loss of heterozygosity and homozygous microdeletions. Our findings point to a major role of the Cdkn2a gene, which encodes important tumor suppressor proteins.

Females of the ACI inbred rat strain are uniquely susceptible to E2-induced mammary cancers. We studied tumors arising in ACI rats and in F1 progeny from ACI animals crossed to animals from two nonsusceptible inbred rat strains (COP and BN). In addition, tumors from ACI.BN-Emca8 congenic rats were analyzed. These rats were developed by introgressing an 85 cM segment from the BN rat strain into an ACI background. CGH analysis was performed as the first step in identifying genetic changes in these mammary tumors. The analysis lead to the identification of clear difference in the specific pattern of chromosomal changes between tumors occurring in the different crosses. Whole chromosomal losses affecting RNO5 and RNO20 were very common, in many cases occurring together. Gain proximally and loss distally in RNO6 was another frequent aberration, possibly representing an alternative pathway in carcinogenesis. Thus, the nonrandom pattern of chromosome aberrations detected in the E2-induced mammary tumors suggests that there were indications of at least two distinct pathways in tumor development.

Identification and characterization of cancer genes in experimental models could lead to a significantly improved understanding of tumorigenesis in humans. In addition, detailed knowledge of different pathways in cancer biology is a prerequisite for development of tumor-specific therapy.

Key words: rat, endometrial adenocarcinoma, mammary cancer, congenic rats, CGH, molecular cytogenetic analysis, RNO5, RNO6, RNO20, gene amplification, Mycn, homozygous deletion, Cdkn2a

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