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LOH in a transgenic model of breast cancer

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Introduction

The erbB2/neu gene is known to encode a tyrosine kinase transmembrane receptor of the HER family and is frequently amplified and overexpressed in human breast cancer. In these cancers other genetic modifications, such as gene amplification, deletion or mutation, are likely to contribute to the development of malignant tumors. Loss of heterozygosity (LOH) is the most common type of mutation seen in human primary breast carcinoma. To study the molecular events involved in erbB2/neu transformation several groups have studied transgenic models with erbB2/neu under control of the mouse mammary tumor virus long terminal repeat (MMTV-LTR). These mice develop mammary tumors stochastically and after a long latency peroid.

Aims

To study molecular events at the level of LOH in a wide range of chromosomal loci in order to determine which loci are important in collaboration with the activated erbB2/neu transgene.

Comments

In human breast cancer the pattern of loss of heterozygosity (LOH) is complex and both the cancer and in situ lesions can be genetically unstable. The evidence presented in this paper suggests that specific early genetic changes (in this case a transgene) co-operate with particular tumor suppressor genes. Interestingly, using a gene frequently implicated in human breast cancer, several chromosomal loci syntenic with human tumor suppressor genes (or putative loci) were identified. It may be important in human studies to subdivide tumors being studied for LOH on the basis of the known cellular phenotype such as erbB-2 status.

Methods

Transgenic mice were bred from the mouse mammary tumor virus/neu (MMTV/neu) transgenic mice line MN-10 to produce (BALB/c x C57BL/6)F1 females. These mice developed spontaneous mammary tumors after multiple pregnancies. LOH analysis was performed on mammary tumors. Eighty-six simple sequence length polymorphism markers, chosen to be evenly distributed (~20cM), were used to cover all of the somatic chromosomes. PCR was performed using a radiolabelled primer and LOH was scored on autoradiographic film by comparison with normal DNA from the kidney.

Results

Mammary tumors appeared in multiparous females between 10 and 26 months of age. A total of 62 mammary tumors were collected, with multiple tumors from individual mice collected separately and treated as independent tumors. LOH was very common with 56 of 62 tumors (90%) having at least one chromosome with LOH. The mean number of chromosomal losses was 2.1 with a median frequency of 2.4 and a maximum of 9. The average rate of loss for all chromosomes was 11% with individual chromosomes being low (5% or below - Chr 2, 3, 5, 6, 10, 11, 12, 13, 15, 17 and 18) or near the average (Chr 7, 9, 14, 16 and X). Chr 1 had a rate of loss of ~20%, but this was not significantly greater than the average. Chr 8 (21%), 4 (50%) and 19 (32) all displayed significantly greater losses and these chromosomes underwent further investigation.

Discussion

There were three chromosomes identified as being potential locations for tumor suppressor genes that are particularly linked to tumorigenesis involving erbB2/neu. Up to two independent tumor suppressor loci are present on Chr 8. One mapped close to E-cadherin and is syntenic with human chromosome 16q22.1. The other (67cM distal) is syntenic to human Chr 16q24.3. Both these regions have been implicated in human breast cancer. Chr19 losses possibly represent two loci, one of which is syntenic to human Chr 11q and the other to 10q23-25 which harbours the PTEN/MMAC1 gene. Up to five distinct loci were identified on Chr 4 with synteny to various human loci including 8q22, 9q32-34 and 9p21-23 (which harbours MTS1 and MTS2).Hence, specific LOH loci, many of which are syntenic with regions of human chromosomes that are known to harbour tumor suppressor genes, have been linked to erbB-2/neu malignant progression in these mice. Other novel loci have also been identified. A similar transgenic line has been studied byRitland*et al* (*Cancer Res* 1997, **57**:3520-3525) which shares some of the characteristic losses described here and an extra loci of loss on chromosome 3. These differences may relate to the different mouse strains used. Further study of LOH in similar animal models may help identify tumor suppressor genes linked to specific types of breast cancer.

References

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