# Predisposition to endometrial cancer: Genetic analysis in an experimental animal model system

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## Abstract

Through research in the last few decades it has been established beyond doubt that cancer, in essence, is a disease of the genes. However, cancer is a heterogeneous disease, which in most cases depends on alterations in several genes, often in interaction with environmental factors. Consequently, identification of genes involved in predisposition to and occurrence of cancer in humans is obstructed by the fact that the human population is genetically heterogeneous and subject to a varying and uncontrollable environment.

To circumvent some of these difficulties the molecular genetic analysis of human cancer may be complemented by studies of animal models. The use of inbred animals in a reasonably constant environment will reduce problems relating to genetic heterogeneity. Females of the inbred BDII rat strain are highly predisposed to develop endometrial carcinoma (EAC). In the present thesis, BDII rats are used to model human cancer. The model was used to throw light on two different genetic aspects of cancer: (1) identification of genetic factors causing susceptibility to tumor development and (2) characterization of gene alterations during the transformation of the normal cell into a cancer cell.

To study the genetics of cancer susceptibility in the BDII strain, BDII animals were crossed to animals from two other inbred strains (BN and SPRD), which were not susceptible to EAC. Genome-wide screens with microsatellite markers were performed in progeny from intercrosses and backcrosses, and we looked for associations of specific alleles and the EAC phenotype. The genotype data obtained were subjected to different statistical tests, and significant association was detected in four different chromosome regions on rat chromosome (RNO) 1, 11, 17 and 20. Suggestive association were seen in a few other chromosomal locations. We concluded that EAC susceptibility in the BDII strain is dependent on the interaction of several genetic factors rather than one major susceptibility gene.

For the identification and characterization of molecular cytogenetic changes in the tumors a first screen was made with cytogenetics and CGH (comparative genome hybridization). More detailed analysis was performed in two chromosome regions on RNO5 and RNO10. Indications were that the proximal part of RNO10 was involved in deletions in EAC tumors, and as a step towards the characterization of these aberrations, a detailed map was constructed of the proximal part of the chromosome using FISH (fluorescence in situ hybridization) and RH (radiation hybrid) mapping. In the course of this analysis it was observed that the *Tp53* gene was absent in the RH panel. We concluded that this most likely was a reflection of *Tp53* function, and that it may be possible to use RH panels to identify other growth-inhibiting genes.

Copy number reductions were often seen in the middle part of RNO5 in EAC tumors. An analysis of allelic imbalance in cell cultures from EAC tumors using microsatellite markers showed that there was often LOH (loss of heterozygosity) in the region, but that there appeared to be no specific allele preference. FISH analysis with probes of genes in different parts of RNO5 confirmed that deletions were common in the middle of the chromosome. In a subset of the tumors (4 out of 16) preliminary FISH data suggested that there was homozygous deletion of the *Cdkn2a/2b* loci. These loci encode three proteins (p15, p16 and p19) known to be involved in tumor suppression.

**Keywords:** Allelic imbalance, BDII rat, Endometrial carcinoma, Fluorescence in situ hybridization, Genome wide scan, LOH, Radiation hybrid, RNO5, RNO10, Susceptibility genes, TP53, Transmission disequilibrium test. **ISBN 91-628-5900-5**