ABSTRACT

Endometrial cancer is a common gynecological malignancy in the industrialized world. It is the 4th most common cancer in female and the 8th most common cause of cancer death in women in the US. In Sweden, endometrial cancer represents 5.6% of all cases of diagnosed cancers and is the third most common cancer in women after breast and colon cancer. Complex disorders like cancer are genetically heterogeneous entities, in the sense when a set of tumors appear clinically identical, they manifest substantial individual differences at the cytogenetic and molecular levels. This complexity is derived from inherent genetic heterogeneity of the human population, as well as from differences in environment and life style of each patient. This heterogeneity make the results from genetic analysis of human cancer difficult and sometimes impossible to interpret. Inbred animal models are unique experimental genetic tools, providing the potential to reduce genetic heterogeneity, facilitating the identification of the important steps. Female rats of the inbred BDII strain are genetically predisposed to endometrial cancer, thus, virgin BDII rats spontaneously develop EAC in incidences up to 90% before the age of 24 months. Females of the inbred BDII rat strain were crossed to males from two inbred rat strains with very low incidence of EAC. Intercrossing F1 rats or backcrossing to BDII rats produced segregating F2 and N1 populations. Subsets of these populations were found to be affected by spontaneous EAC. A genome-wide screening method, comparative genomic hybridization (CGH), was applied to the tumor material in order determine if any copy number abnormalities were present. The CGH study was combined with karyotype analysis. Although there was a complex pattern of chromosomal aberrations involving changes in several chromosomes, recurrent aberrations were seen in eight distinct regions situated in six different chromosomes, occurred repeatedly in EAC tumors within our model. Among the most common aberrations detected by CGH were gain/amplification in the long arm and/or loss in the short arm of RNO15 and loss in the middle part of RNO5.

The involvement of RNO15 was further analyzed by FISH in a subset of the tumors. We detected aberrations at the DNA level, particularly those leading to amplification in small DNA segments. These aberrations were often cryptic, i e undetectable by ordinary cytogenetic analysis. Subsequently, we subjected a larger series of EAC tumors to LoH with polymorphic microsatellite markers covering the entire length of RNO15. We found that allelic imbalance and/or loss of heterozygosity (AI/LOH) was common in these tumors and that four different well-defined regions along the chromosome were selectively affected.
Molecular cytogenetic analysis of RNO5 revealed that there were frequent rearrangements of this chromosome in rat EACs. These aberrations often lead to homozygous microdeletions eliminating the *Cdkn2a* gene, which encodes important tumor suppressor proteins.

To facilitate the connection between cytogenetic and molecular data in the rat we have also constructed detailed banded ideograms of the rat chromosomes. The ideograms were based on actual microscopic images of normal prometaphase chromosomes and describes the location of a total of 535 bands. It was shown that the linear correlation was excellent between ideograms based on cytogenetic measurements and the underlying sequenced DNA molecules.

Key words: cancer, animal model, BDII rat, endometrial cancer, RNO15, RNO6, molecular cytogenetic analysis, CGH, allelic imbalance, FISH, ideogram, *Cdkn2a*

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