Cytogenetic and Molecular Changes Involving Rat Chromosome 10 in Experimental Endometrial Adenocarcinoma

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ABSTRACT

Endometrial adenocarcinoma (EAC) is a disease with serious impact on the human population. The etiology of EAC is known to be greatly influenced by genetic factors. Inbred BDII rat females are highly prone to spontaneously occurring EAC, thus, the BDII strain represents a suitable animal model for the genetic study of this complex disease. Deletion in the proximal part of rat chromosome 10 (RNO10) was recurrently observed in EACs developing in offspring from BDII experimental crosses.

This thesis is focused on the analysis of cytogenetic and molecular changes of RNO10 in EAC tumors. Dense microsatellite marker allelotyping was performed along RNO10 to characterize the chromosomal changes in detail. The analysis showed that there were three separate segments in the proximal part of RNO10, where allelic losses were more pronounced. Based on comparative mapping, we suggested that the *Tsc2*, *Irf1*, and *Tp53* tumor suppressor genes (TSGs), one in each of three regions of recurrent allelic loss, could be candidates with possible contribution to rat EAC development.

Using comparative mapping data, we constructed an ordered map of RNO10, by which we could expand the present evolutionary data for genetic interrelationship between RNO10 and its counterparts in humans and mice. Furthermore, applying RH mapping to RNO10 genes, we discovered that the segment of RNO10 harboring *Tp53* was absent from the rat whole genome RH panel. This may reflect a functional role for p53 in the establishment of the RH clones and the finding implies that RH mapping might be a useful tool to identify functionally active growth-regulatory genes at cellular level.

Finally, we examined the expression level and sequence integrity status of the candidate TSGs in a subset of EAC tumors. Out of 14 EACs, lowered expression of either or both *Irf1*, and *Tp53* was observed in 7 (50%), including two tumors displaying inactivating mutations in the *Tp53* gene. Moreover, aberrant *Irf1* mRNAs were detected in another three EAC tumors. Taking all data into consideration, we suggest that genetic aberrations involving RNO10 are important in EAC development, including those changes that affect the normal function of p53 and Irf1 transcription factors.

Keywords: EAC, rat chromosome 10, RNO10, RH, FISH, tumor suppressor gene, *Tp53*, *Irf1*, *Tsc2*, LOH, AI

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