Analyses of Rat Tumor Models for DMBA-induced Fibrosarcoma and Spontaneous Endometrial Carcinoma

Akademisk Avhandling

som för avläggande av Filosofie Doktorsexamen vid Institutionen för Cell och Molekylärbiologi, Naturvetenskapliga Fakulteten vid Götborgs Universitet, kommer att offentligen försvaras i Hörsal Arvid Carlsson, Medicinaregatan 3
torsdagen den 20 november 2008 kl 9.00.
Fakultetsopponent: Professor Nils Mandahl, Lunds Universitet.
Examinator: Professor Peter Carlsson

Avhandlingen baseras på föjlande arbeten:

I. Hamta A*, Adamovic T*, **Samuelson E**, Helou K, Behboudi A and Levan G. Chromosome ideograms of the laboratory rat (*Rattus norvegicus*) based on high-resolution banding, and anchoring of the cytogenetic map to the DNA sequence by FISH in sample chromosomes. *Cytogenetics and Genome Research*. 2006;115(2):158-68.

II. Sjöling Å, Lindholm H, **Samuelson E**, Yamasaki Y, Watanabe TK, Tanigami A, Levan G. Analysis of chromosomal aberrations involving chromosome 1q31-->q53 in a DMBA-induced rat fibrosarcoma cell line: amplification and overexpression of *Jak2*. *Cytogenetics and Cell Genetics*. 2001;95(3-4):202-9.

III. Sjöling Å, **Samuelson E**, Adamovic T, Behboudi A, Röhme D, Levan G. Recurrent allelic imbalance at the rat *Pten* locus in DMBA-induced fibrosarcomas. *Genes Chromosomes, and Cancer*. 2003 Jan;36(1):70-9.

IV. **Samuelson E**, Hedberg C, Nilsson S and Behboudi A. Molecular classification of spontaneous endometrial adenocarcinomas in BDII rats. 2008. *Submitted*.

V. **Samuelson E***, Levan K*, Adamovic T, Levan G and Horvath G. Recurrent gene amplifications in human type I endometrial adenocarcinoma detected by *in situ* hybridization. *Cancer Genetics and cytogenetics*. 2008;181:25-30.

UNIVERSITY OF GOTHENBURG

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Emma Samuelson
Department of Cell and Molecular Biology - Genetics
Lundberg Institute, Faculty of Science,
University of Gothenburg
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Abstract

Cancer is a disease of genes. Uncontrolled cell growth is the outcome from genetic as well as epigenetic alterations, resulting in a tumor cell mass that harbors a cancer genome. During progression, the tumor acquires self-dependence and the ability to invade other tissues and metastasize. Genetic predisposition and environmental factors such as life style, diet and exposure to carcinogenetic compounds promote initiation of tumors. The laboratory rat (*Rattus norvegicus*) has been used as an animal model in medical research for over 150 years. By using a genetically well-defined rat model in a controlled environment, we have studied two cancer models for DMBA-induced fibrosarcoma and spontaneous endometrial cancer. In the fibrosarcoma model an F1 progeny from two inbred rat strains, BN and LE, was used and tumors were induced by a single injection of the carcinogenic agent DMBA. The tumors were used for Allelic Imbalance analysis as well as identifying putative candidate genes on RNO1 displaying a region with gene amplification. We could successfully identify *Jak2* as a candidate gene for the amplification at the distal part of RNO1 in one of the fibrosarcoma cell lines. Adjacent to this region on RNO1, the Allelic Imbalance analysis displayed a LOH in the *Pten* locus. No mutation was found in the remaining allele, suggesting that *Pten* is contributing to the fibrosarcoma development in these DMBA-induced tumors by a haploinsufficient mechanism.

The endometrial tumor model is composed of the BDII rat strain, predisposed to spontaneously develop endometrial cancer. Tumors obtained from progeny from intercrosses and backcrosses between the BDII strain and two strains not prone to develop EC, were used to classify and characterize the BDII tumors according to the human classification system. We could conclude that the BDII tumors resemble the human hormone dependent type I tumors, best. This conclusion was confirmed when we tested some of our result from the BDII model on human type I tumors in a FISH study for amplification of specific genes located on HSA2p and HSA7q. In summary, we found similar patterns of amplification in the human type I tumors as was previously found in the BDII rat tumors.

In addition, we were able to improve the rat ideogram and anchor DNA sequences (*i.e.* genes) to the physical rat gene map.

The molecular profiling of tumors at different levels, *i.e.* DNA, RNA and epigenetic, has provided an efficient tool for identifying and characterizing cancer related genes. Furthermore, the use of animal tumor models provides an important route to identify molecular biomarkers for prognosis as well as new targets for drug discovery in cancer treatment.

Key words: Rat models, fibrosarcoma, endometrial carcinoma, ideogram, cancer.

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