Molecular characterization of type I endometrial carcinomas

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Abstract

Endometrial carcinoma is the most common malignancy in the female reproductive tract. In Sweden over 1300 women are diagnosed every year, and although the prognosis is favourable in the majority of cases, about 160 patients die of the disease every year. Since the clinical outcome may be quite different for patients with the same diagnosis, indications are that there may be important differences among the tumours at the molecular level. The overall goal of our research was to contribute to the understanding in the molecular biology underlying endometrioid adenocarcinomas.

In total, 124 type I endometrial carcinoma patients were included in the study. Methods such as CGH, FISH, expression array analysis and QPCR were applied to investigate molecular specificities among the tumours. In particular, we were looking for biomarkers useful in distinguishing more aggressive tumours that might require special therapy. Thus, we submitted the data to extensive statistical treatment, comparing molecular data from aggressive tumours (tumours that killed the patient, tumours that metastasized) with those less aggressive. In the CGH analysis of 98 tumours, we found that tumours from survivors on average had fewer chromosome aberrations than those from non-survivors. In fact, 33% of the non-metastatic tumours displayed no detectable aberrations, clearly a marker for good prognosis. However, we could not find any aberration that was entirely specific for non-survivors. A subset of 13 tumours was analyzed for gene amplification in a set of 15 cancer-related genes on chromosomes 2 and 7 by FISH in tumour imprints. The findings corresponded quite well with findings in inbred BDII rats, which are known to be genetically predisposed for endometrial carcinoma. These results suggest that the BDII rat provides a useful model for analyzing the genetic background of at least a subgroup of human endometrial carcinomas. The expression array analysis of 45 tumours generated a set of 218 genes that were differentially expressed between survivors and non-survivors. Using this set of 218 genes in a cross validation test 89% of the tumours were classified correctly, and in hierarchical clustering, two clusters were formed, both with over 80% homogeneity with respect to survival. In the latter analysis it was noted that five out of six stage I tumours from non-survivors, clustered in the non-survivor fraction. The gene expression analysis indicated dysfunction of the Rb/E2F pathway involved in the tumour progression. To investigate the potential involvement of this well-known pathway we aimed to characterize the protein expression of a selection of the proteins involved. Significant differences in protein expression of pRb in combination with E2F-1 were clearly related to survival. In particular, these molecular tools helped us to identify a subset of non-survivors among tumours classified as stage I tumours. If more aggressive malignancies can be identified at an early stage, the indicated adjuvant treatments may dramatically improve the disease course for these individuals. Increased knowledge about the biological differences among individual tumours will provide the basis of a more accurate prognosis. In the future extended molecular information should also contribute to the development of improved and individually tailored treatment protocols.

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I **Levan K.,** Partheen K., Österberg L., Helou K., Horvath G.

Chromosomal alterations in 98 endometrioid adenocarcinomas analyzed with comparative genomic hybridization

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II Samuelson E.*, **Levan K.*,** Adamovic T., Levan G., Horvath G.

Recurrent gene amplification in human type I endometrial adenocarcinomas detected by fluorescence in situ hybridization

Cancer Genetics and Cytogenetics, 181:25-30 (2008)

III **Levan K.,** Partheen K., Österberg L., Olsson B., Delle U., Eklind S., Horvath G.

Gene expression profiling to predict survival in patients with type I endometrial carcinoma

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IV **Levan K.,** Partheen K., Österberg L., Örndal C., Fallenius G., Eklind S., Horvath G.

Immunohistochemical characterization of cancer-related proteins in endometrioid adenocarcinomas of the uterus

Manuscript

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