Molecular biomarkers of solid tumors and their use in prognosis and prevention of cancer

Molekulární biomarkery solidních nádorů a jejich využití v prognóze a prevenci nádorových onemocnění

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Summary

Malignant tumors of ovary and breast are among the most widespread cancers in women. Despite improvements in diagnostics and in therapy, mortality is still very high. An important tool for early cancer detection, as well as for monitoring prognosis and preventing progression, are molecular biomarkers; biomarkers were the topic of this work.

The aim of this work was to find out (i) whether there are differences in gene expression between tumor and non-tumor tissues, and among controls (C), primary tumors (pT) and intraperitoneal metastases (iM), respectively; (ii) whether gene expression or genetic variants (single nucleotide polymorphisms, DNA methylation, germline mutations) associate with clinical data of patients, thus being potentially relevant for prognosis.

In epithelial ovarian cancer (EOC), 50 of 94 genes were deregulated in controls compared to tumors. Fifteen of 66 genes were deregulated in intraperitoneal metastases compared to primary tumors. Gene expression of ABCA7, ABCB2, ABCC3, ESR2, NH1H4 and NR1I1 was deregulated either in comparison of primary tumors and metastases, or in comparison of C – pT – iM. The most interesting findings are relationships between ABCA2/12, ABCB1, PLK1 and PRC1 gene expression, and tumor grade, stage or tumor cells proliferation. Associations between ABCA9/10, ABCC9, ABCG2 and SLC16A14 gene expression, and progression-free survival of EOC patients, which was found out either in primary tumors or in metastases, are also very important. Other interesting associations were found for polymorphisms rs908832 and rs2271862 in *ABCA2* gene, and rs2290203, rs8028856 and rs8031684 in *PRC1* gene. *ABCB1* promotor was hypermethylated in tumors compared to controls. The methylation status was influenced by neoadjuvant chemotherapy application.

In breast cancer, germline mutations in *ABCC8* and *ABCD2* genes were analyzed by methods of next generation sequencing. Forty-one and 72 variants were discovered,

respectively; 72 % were new. Six variants were *in silico* predicted to be potentially harmful or to influence binding of transciptional factors.

The greatest importance of this work is the analysis of the whole ABC transporter family in EOC tissues, and comparison of gene expression levels in controls, primary tumors and intraperitoneal EOC metastases. The results highlight genes that are important for ovarian and breast cancer patients prognosis. The possibilities of their use in preventing progression and therapy failure will be subject to future studies.