Novel biomarkers predicting long-term survival in breast cancer

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Ivarsson, Medicinaregatan 3B, fredagen den 5 juni 2009 kl. 13.00

av

Elin Karlsson

Fakultetsopponent: associate professor Bassem Haddad
Lombardi comprehensive cancer centre, Georgetown University

Avhandlingen baseras på följande arbeten:

I **Karlsson E.**, Danielsson A., Delle U., Olsson B., Karlsson P., Helou K. Chromosomal changes associated with clinical outcome in lymph node-negative breast cancer
Cancer Genetics and Cytogenetics 2007;172(2):139-46

II **Karlsson E.**, Delle U., Danielsson A., Parris T., Olsson B., Karlsson P., Helou K.
High-resolution genomic profiling to predict 10-year survival in node-negative breast cancer
Manuscript 2009

III **Karlsson E.**, Delle U., Danielsson A., Olsson B., Abel F., Karlsson P., Helou K.
Gene expression variation to predict 10-year survival in lymph-node-negative breast cancer
BMC Cancer, 2008;8(1):254

IV **Karlsson E.**, Kovács A., Delle U., Lövgren K., Danielsson A., Parris T., Brennan D., Jirström K., Karlsson P., Helou K.
Up-regulation of cell cycle arrest protein BTG2 correlates with increased survival in breast cancer
Manuscript 2009

UNIVERSITY OF GOTHENBURG

Novel biomarkers predicting long-term survival in breast cancer

Elin Karlsson
Department of Oncology, Institute of Clinical Sciences,
The Sahlgrenska academy at University of Gothenburg, Sweden

ABSTRACT

Breast cancer is the most common malignancy among women, affecting over a million women worldwide every year. During the last decades, there has been a dramatic increase in the survival rates due to earlier detection and improved treatment. Breast cancer treatment today is getting more and more targeted, but still, many patients are being overtreated, and some undertreated. Therefore, the need for additional complementary prognostic markers is urgent. In this thesis, molecular differences in tumours from breast cancer survivors and deceased patients have been explored on the DNA, RNA and protein levels. The major findings include differences on the genomic level between lymph node-negative 10-year survivors and deceased patients; gains at 4q, 5q31-5qter, 6q12-6q16 and 12q14-12q22 and losses at 8p21.2-8p21.3, 8p23.1-8p23.2, 17p, 18p, Xp21.3, Xp22.31-Xp22.33 and Xq were significantly more frequent in tumours from deceased patients compared to tumours from 10-year survivors. Gains at 1q25.2-1q25.3 and 1q31.3-1q41 were more common in tumours from 10-year survivors. In addition, a gene signature consisting of 51 genes was generated. The expression profile of these 51 genes predicted clinical outcome in our material of node-negative patients as well as in an external tumour material with good accuracy. The protein expression of four genes (*ADIPOR1*, *ADORA1*, *BTG2* and *CD46*) that differed between the survival groups, both in DNA copy number alterations and in gene expression, was explored in a larger independent cohort of breast cancer patients. The protein expression of BTG2 significantly more frequent in tumours from 5-year survivors compared to tumours from deceased patients. This finding indicates expression of BTG2 as a possible prognostic biomarker. Furthermore, the prognostic biomarkers found in this work, may in the future facilitate the prognosis as well as predict course of treatment for breast cancer patients, following extensive validation.

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