ANALYSIS OF NOVEL BIOMARKERS FOR UNFAVORABLE BREAST CANCER PROGNOSIS

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Abstract:

Breast cancer is the most common malignancy in women, and a major cause of mortality and morbidity despite the advances in diagnosis and treatment. The main challenge remains to identify novel biomarkers in order to improve existing treatment modalities. Ductal carcinoma in situ (DCIS) is considered as a direct precursor of invasive breast cancer. Therefore, it would be valuable to be familiar with the natural history of DCIS, including how it develops, and if it will progress to invasive breast carcinoma. Hence, the identification of biomarkers associated with DCIS progression may prevent the development of some invasive breast cancer tumors. The expression of S100A7 (psoriasin) has previously been identified in association with the transition from DCIS to invasive breast cancer. It has also been associated with unfavorable clinical outcomes, suggesting that psoriasin may play a role as a biomarker of aggressive malignant behavior. The first part of the thesis was conducted to investigate a potential role of psoriasin in breast cancer. We demonstrated that the reduction of intercellular adhesion molecule 1 (ICAM-1) by short hairpin RNA in mammary epithelial cells induced the expression levels of psoriasin, via the phospholipase C (PLC)-IP3 pathway, along with the oncogenic protein mucin1 (MUC1) **(Paper I).** We have shown that psoriasin contributes to the expression of vascular endothelial growth factor (VEGF) and elevated expression levels of psoriasin in mammary epithelial cells leads to increased endothelial cell proliferation in a paracrine manner through receptor for advanced glycation endproducts (RAGE) by promoting oxidative stress response **(Paper II).** In the second part of the thesis, we evaluated the expression levels of several candidate biomarkers in order to allow stratification of breast cancer tumors according to their aggressiveness. Previously, we performed analysis of gene expression in 97 primary invasive diploid breast tumors and identified molecular gene signatures associated with poor clinical outcome. In **Paper III**, *CCNB2, CDCA7, ASPM, KIAA0101,* and *SLC27A2* were selected from these gene signatures. We studied their protein levels in association to patient clinical outcome in an independent cohort of 80 primary invasive breast tumors. Our data indicated that cytoplasmic CCNB2 may serve as a novel biomarker of unfavorable clinical outcomes over short-term follow-up in breast cancer**.** In addition, in a previous study, we performed gene expression analysis in 43 axillary lymph node negative tumors and identified 51 genes whose deregulated mRNA levels were significantly associated with unfavorable clinical outcome. Four candidate biomarkers; *GGH, FAAH, PIR* and *TAF5L* were selected among the identified 51-gene signature **(Paper IV).** We investigated their clinical impact in predicting breast cancer progression in an independent cohort of 80 primary invasive breast tumors. Our data suggest that elevated protein levels of GGH were associated with unfavorable prognosis and poor outcomes in breast cancer patients.

Our findings suggest that psoriasin, CCNB2 and GGH may serve as attractive targets for cancer therapy.

Keywords: ductal carcinoma *in situ,* primary invasive breast cancer, biomarkers.
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I. Petersson S, **Shubbar E**, Yhr M, Kovacs A and Enerbäck C. Loss of ICAM-1 signaling induces psoriasin (S100A7) and MUC1 in mammary epithelial cells.

II. **Emman Shubbar**, Jenny Vegfor, Maria Carlström, Stina Petersson, Charlotta Enerbäck, Psoriasin (S100A7) increases the expression of ROS and VEGF and acts through RAGE to promote endothelial cell proliferation

III. **Emman Shubbar**, Anikó Kovács, Shahin Hajizadeh, Toshima Parris, Szilárd Nemes, Katrin Gunnarsdottir, Zakaria Einbeigi, Per Karlsson and Khalil Helou. Elevated cyclin B2 expression in invasive breast carcinoma is associated with unfavorable clinical outcome

IV. **Emman Shubbar**, Khalil Helou, Anikó Kovács, Shahin Hajizadeh, Szilárd Nemes, Charlotta Enerbäck, and Zakaria Einbeigi, High levels of γ-glutamyl hydrolase (GGH) are associated with poor prognosis and unfavorable clinical outcomes in invasive breast cancer.

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