

Functional genetic studies of Psoriasis: A potential biomarker for breast cancer with a poor prognosis

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I. Carlsson H, Yhr M, **Petersson S**, Collins N, Pollyak K, Enerbäck C. Psoriasis (S100A7) and Calgranulin-B (S100A9) Induction is Dependent on Reactive Oxygen Species and is Downregulated by Bcl-2 and Antioxidants. *Cancer Biol Ther.* 2005 Sep 23;4(9)
- II. **Petersson S**, Bylander A, Yhr M, Enerbäck C. S100A7 (Psoriasis), highly expressed in Ductal Carcinoma *In Situ* (DCIS), is regulated by IFN-gamma in mammary epithelial cells. *BMC Cancer* 2007 Nov 6;7(1):205
- III. **Petersson S**, Shubbar E, Yhr M, Kovacs A and Enerbäck C. Loss of ICAM-1 signaling induces psoriasis (S100A7) and MUC1 in mammary epithelial cells. *Under review.*
- IV. **Petersson S**, Nilsson J, Shubbar E and Enerbäck C. Psoriasis (S100A7) expression is linked to the differentiation marker CD24. *In manuscript*



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Abstract

Breast cancer is the most common malignancy in women. There is a high degree of heterogeneity in breast tumours and they can be divided into subtypes that have different expression pattern and clinical outcome. Ductal Carcinoma *in situ* (DCIS) is regarded as a precursor of invasive ductal breast cancer. Some DCIS lesions will not change in many years, while other will rapidly progress into invasive cancer. It is therefore important to be able to distinguish clinical subgroups of DCIS with a high risk of progression to invasive disease.

Aim: Psoriasin is one of the most abundant transcripts in high-grade DCIS with higher risk of local recurrence. Psoriasin has been associated with poor clinical outcome, suggesting its potential involvement in tumour progression. To date, several functions of psoriasin have been proposed, but none of these can fully explain its involvement in breast tumour progression. The aim of this thesis was to elucidate the functional relevance of psoriasin for the initiation and progression of DCIS, and to gain insight into regulatory pathways that control the expression.

Results: High-grade DCIS is characterised by a high apoptotic rate and reactive oxidant species (ROS) are known to influence this process. We report the induction of psoriasin by ROS in normal mammary epithelial cells. This induction was repressed by the anti-apoptotic protein Bcl-2 and the antioxidant NAC. Normal mammary epithelial cells with a stable retroviral overexpression of psoriasin were significantly more resistant to ROS-induced cell death. Furthermore, we demonstrate that the NF- κ B pathway is potentially involved in the induction of psoriasin expression. **(Paper I)**

IFN γ has been shown to exert anti-tumour action in breast cancer. We report the downregulation of psoriasin by IFN γ in a breast cancer cell line and the downregulation of psoriasin induced by culturing mammary epithelial cells in suspension (loss of contact to extracellular matrix). This effect was shown to be mediated by the activation of the STAT1 signalling pathway. In a mouse mammary epithelial cell line with tetracycline-induced psoriasin expression, we observed the increased viability of psoriasin-expressing cells after IFN γ treatment. **(Paper II)**

The massive induction of psoriasin in suspension culture compared to other stimuli (starvation, confluence and ROS) suggests that changes in adhesion to the extracellular matrix may contribute to the expression of psoriasin. We showed that the downregulation of intercellular adhesion molecule 1 (ICAM-1) (by short hairpin RNA) in mammary epithelial cells increased the expression of psoriasin, through the phospholipase C (PLC)-IP3 pathway, as well as the oncogenic protein mucin1 (MUC1). **(Paper III)**

The interaction between breast epithelial cells and the extracellular matrix contribute to pathological processes and to the normal development of a differentiated structure. Psoriasin has previously been related to epithelial cell differentiation in the skin. We now report that mammary epithelial cells shifted from a CD44⁺/CD24⁻ to a CD44⁻/CD24⁺ phenotype (representing differentiated luminal epithelia) when cultured in confluent and suspension conditions. Interestingly, this result was not observed when psoriasin was suppressed using short hairpin RNA. **(Paper IV)**

Conclusions: We have shown data suggesting that the high expression of psoriasin in high-grade DCIS tumours may be dependent on the production of ROS and a change in adhesion to the ECM, involving ICAM-1 and MUC1. The psoriasin expression leads to increased survival of the breast epithelial cells. Our data also reveal that psoriasin is tightly linked to the expression of CD24. Therefore, it is likely that psoriasin play a role in the differentiation of mammary epithelial cells.

Key words: Psoriasin, breast cancer, reactive oxidant species, NF- κ B, IFN γ , STAT1, ICAM-1, MUC1, CD24.