Molecular factors influencing epithelial-mesenchymal transition in breast cancer

Akademisk avhandling

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Avhandlingen är baserad på följande delarbeten:

I. **Nilsson GM**., Akhtar N., Kannius-Janson M., Baeckström D. Loss of E-cadherin expression is not a prerequisite for c-erbB2-induced epithelial-mesenchymal transition. *International Journal of Oncology.* 2014 Jul;45(1):82-94.

II. **Nilsson G**., Kannius-Janson M. Forkhead box F1 promotes breast cancer cell migration by upregulating lysyl oxidase and suppressing Smad2/3 signaling. *Manuscript.*

III. Nilsson J., **Nilsson G**., Nemes S., Kovács A., Helou K., Jirström K., Kannius-Janson M. Nuclear factor I-C2 is a powerful prognostic marker in breast cancer. *Manuscript.*

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Abstract

Epithelial-mesenchymal transition (EMT) is a developmental process defined by loss of epithelial characteristics and acquisition of mesenchymal phenotype. EMT or similar processes are also implicated in carcinoma cell invasion and the progression of breast carcinoma to metastasis. In a cell model system for mammary carcinogenesis it has previously been shown that signaling from the oncogenic receptor tyrosine kinase c-erbB2 (HER2), frequently overexpressed in mammary cancers, induces EMT. In this system, c-erbB2-induced EMT was significantly delayed by high cell-density and cell-cell-dissociation occurred before downregulation of the epithelial adhesion molecule E-cadherin. Loss of E-cadherin expression is generally viewed as a fundamental event in EMT. This thesis shows that ectopic expression of E-cadherin concomitant with c-erbB2 signaling did not hinder the progression of EMT. E-cadherin expressed in mesenchymal cells had a weaker attachment to the cytoskeleton, implicating that rearrangement of the cytoskeleton is an important mechanism in EMT-associated cell-cell-dissociation. Expression of dominant negative E-cadherin weakened cell-cell adhesion but did not enable EMT at high cell-density. These finding indicate that loss of E-cadherin is a consequence rather than a cause of EMT and that density-dependent inhibition of EMT is not mediated by E-cadherin. The expression of the transcription factor nuclear factor I-C2 (NFI-C2) is lost during mammary tumor progression and NFI-C2 has been shown to counteract EMT by repressing the transcription factor Forkhead box F1 (FoxF1). FoxF1 induces EMT and invasiveness in breast cancer cells. In this thesis, Affymetrix microarray was used to find oppositely regulated targets of NFI-C2 and FoxF1. The extracellular matrix enzyme lysyl oxidase (LOX) was found to be negatively regulated by NFI-C2 and positively regulated by FoxF1 and responsible for the increased invasiveness caused by FoxF1 overexpression. A signaling pathway was identified where FoxF1-induced upregulation of LOX activated focal adhesion kinase, subsequently suppressing Smad2 activity. In parallel, overexpression of FoxF1 activated the p38 MAPK signaling pathway. These findings give new insights into the regulation of signaling pathways known to be important during breast tumor progression. Based on the findings that NFI-C2 is lost during breast tumor progression and suppresses EMT, the prognostic value of NFI-C2 in a mixed cohort of breast cancer patients was investigated. NFI-C2 was found to be a powerful prognostic marker associated with good prognosis in breast cancer.

Keywords: breast cancer, epithelial-mesenchymal transition, c-erbB2, E-cadherin, NFI-C2, FoxF1, LOX

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