Conclusions: Non basal-like triple-negative breast cancers differ from basal-like triple-negative breast cancers in several aspects, and have a lower malignant phenotype. Therefore, this subgroup of triple-negative breast cancers is important to distinguish from the basal-like triple-negative breast cancers.

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VEGF-C in association with VEGFR-3 promotes nodal metastases but does not stimulate peritumoral lymph vessel growth in breast cancer with extensive intraductal component

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One of the assumed mechanisms of lymphatic dissemination in breast cancer is lymphangiogenesis. Although the underlying molecular mechanisms in animal in vitro and in vivo studies have been clarified, controversies in clinical breast cancer studies do exist. By performing immunohistochemistry stainings on breast cancer with extensive intraductal component (N = 46), we try to clarify existing controversies. We studied breast cancer with extensive intraductal component (EIC) because it is a representative of early disease, also the assumed mechanism of intratumoral lymph vessel collapse due to high pressure does not take place.

We found a significant correlation between vascular endothelial growth factor receptor-3 (VEGFR-3) positive vessel density and lymph node metastases (P = 0.007). Lymph node status also correlated with CD34 positive blood vessels (P = 0.027). Only vascular endothelial growth factor-C (VEGF-C) cell expression in the invasive component correlated with lymph node dissemination (P = 0.047). However combining expression of VEGF-C or D with strong VEGFR-3 vessel density, which is in fact the assumed lymphangiogenesis pathway, VEGF-C both in the in situ and invasive as well VEGF-D in the invasive component correlated with lymph vessel metastases. All LYVE-1 positive lymph vessels were located peritumorally and LYVE-1 vessel density did not correlate with lymph node metastasis neither with any clinicopathological factor or growth factor.

In this study with a rather limited number of patients with EIC we could not prove that lymphangiogenesis is a mechanism of tumor spread in early disease. We did not see intratumoral lymph vessels, not even in the in situ component but we stained with the LYVE-1 antibody only. While VEGF-C and VEGFR-3 and also VEGF-D in combination with its receptor VEGFR-3 correlated with lymph node metastatic spread, peritumoral lymph vessel density did not correlate with lymph node metastases. Therefore we conclude that lymphangiogenesis based on the VEGF-C/D VEGFR-3 pathway is not solely responsible for lymph node dissemination.

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Common expression of estrogen receptor type A and its gene targets in proliferating breast epithelial cells

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Introduction: It is supported that estrogen receptor type a (ERa) exerts estrogen's mitogenic activity through induction of expression of genes that control cell proliferation, i.e. cyclinD1, c-Myc and stromal growth factor-1 (SDF-1). Failure to detect co-expression of ERα and proliferation 'markers' such as Ki67 in human mammary epithelium led to the proposal that estradiol acts indirectly in this tissue by stimulating ER-positive epithelial cells to release unknown mitogens that then trigger proliferation in neighboring ER-negative epithelium (model of paracrine breast estrogenic action).

To evaluate co-expression of ERa and proliferating marker Ki67 in normal breast epithelial cells under short-term estrogenic stimulus and increased proliferation. The simultaneous with ERα expression of estrogen-induced target proteins SDF-1, MYC and cyclin D1, that are involved in the proliferation of breast epithelial cells.

Methods: Immunohistochemistry was used on mammary tissue sections from short-term estrogen treated women to investigate co-expression of ERα and the proliferation antigen Ki67. Using the same methods, we investigated the cell localization of proteins involved in estrogen-induced proliferation, including cyclin D1, stromal cell-derived factor (SDF)-1, and MYC. To determine the percentage of double-labeled mammary epithelial cells, an observer scored 500 to 1,000 cells for each combination of antibodies (number of women used: 4).

Immunohistochemistry results:

- 23±10% of mammary epithelial cells was positive for ERa and Ki67 antigens.
- Co-expression of ERa and SDF-1 antigens was found in ~25% of cells, while co-expression of ERa and Myc was found in ~26% of cells.
- Most positive for SDF-1 cells were also positive for Myc.

Results: ERα is expressed in proliferating mammary epithelial cells together with the estrogen-induced proteins MYC, cyclin D1 and SDF-1, consistent with a direct mitogenic action by estrogen in mammary epithelium.

Conclusion: These observations obviate the need to invoke unknown paracrine mediators of estrogen action in the mammary gland.

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SPARC in breast tumors of different histological types: defined its role in patients' outcome and nodal status

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Background: to characterize the immunohistochemical distribution of secreted protein acidic and rich in cystein (SPARC) in a series of breast tumors of different histological types, and to define its role in malignant transformation and association with patients' outcome.

Materials and Methods: A total of 268 Samples of different histopathological benign and malignant breast lesions were retrieved from National Taiwan University Hospital (NTUH) between 1994 and 2005. Up to 11 year's clinical follow-up data were available for 185 infiltration ductal carcinoma (IDC) cases. Immunohistochemistry staining with SPARC were performed in tissue microarray (TMA) or whole section. The association of expression of SPARC and cumulative overall survival of IDC patients were analyzed using Kaplan–Meier survival analysis and the Cox Proportion analysis.

Results: SPARC was expressed only in benign breast phylloides of all benign lesions, in 16% IDC, 85% Metaplastic carcinoma of the breast (MCB) and all malignant breast phylloides. SPARC was strongly expressed in mesenchymal component of MCB and different expression level in epithelial component. The correlation of positive expression of SPARC and poor long-term survival is significant (p = 0.004). The result also showed strongly statistically significant association between SPARC expression and nodal status by using Chi-Square test (p = 0.037).

Conclusions: SPARC plays a crucial role in the process of epithelial-mesenchymal transition and its expression correlates with poor overall survival in IDC.

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Insulin like binding protein 7 – evidence for a possible paracrine protective effect in human breast cancer

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Background: Insulin like growth factor (IGF) has a well recognised pro-neoplastic role in various human malignancies. This study examined paired mRNA expression of Insulin like growth factor binding protein (IGFBP) 3 and 7 genes in malignant breast tissue and associated 'adjacent non cancerous tissue' (ANCT) correlating this with various prognostic parameters.

Materials and Methods: Prospectively collected breast cancer/ANCT pairs were analysed for levels of IGFBP 3 and 7 mRNA using real time Q-PCR. mRNA levels were analysed against tumour grade, nodal status, Nottingham prognostic index (NPI) stage, size, recurrence and disease free survival (DFS). Full ethical approval was obtained.

Results: Non parametric analysis was performed throughout. The number of validated results were, BP7anct = 90, BP7tumour = 84, BP3anct = 57, BP3tumour = 58. When ANCT IGFBP7 was correlated with NPI, significantly more binding protein was expressed adjacent to favourable prognostic tumours (NPI 1) when compared with poor prognostic tumours (NPI 3), (p = 0.016). This trend repeated for tumour grade, with greater expression adjacent to low grade tumours (Grade 1) compared to high grade tumours (Grade 3) (p = 0.047) and for recurrence, with significantly greater expression adjacent to tumours who remained recurrence free (p = 0.006). Survival analysis using Kaplan–Meier curves also revealed improved DFS associated with high ANCT IGFBP7 levels, which was statistically significant (p = 0.004).

Conclusions: Our data suggests that IGFBP7 may act to limit progression of the malignant phenotype in a paracrine fashion. This needs to be evaluated further with larger studies.