used for this purpose. The objective of this study was to test the ability of intraoperative touch imprint cytology (IC) to predict metastatic disease on SLN.

Design: SLN were received fresh and examined grossly, when less than 0.5 cm in size were bisected and when more than 0.5 cm in size were serially sectioned at 2 mm intervals along the long axis. Each surface of the sections were touched on the glass slide, stained by H&E. Results of IC were compared with results of section permanents, wich were analyzed with 10 serial levels stained with H&E and one level stained with cytokeratin AE1/AE3. Sensitivity (Se), specificity (Sp), positive and negative predictive value (PPV & NPV) and accuracy were calculated for all metastases (macro & micrometastases), micrometastases, macrometastases. False negatives were rescreened.

Results: We analyzed 179 SLN from 110 patients. The comparison between IC and definitive results of the SLN (including macro & micrometastases) showed 139 (77.65%) true negative imprints, 28 (15.64%) true positive imprints. There were not false positive imprints, there were 12 (6.70%) false negative imprints. False negative imprints were 6 macrometastases (mean size metastases 5 mm, range 3–7 mm), 3 micrometastases (mean size metastases 1.6 mm, range 2–1.5 mm) and 3 isolated tumour cells. Rescreening of the false negative imprints showed 10 negative imprints, one imprint with two diagnostic groups of cells and one imprint with multiple diagnostic groups of cells. Se, Sp, PPV, NPV, Acc for all metastases, micrometastases, macrometastases are shown in the table.

	Se	NPV	Sp	PPV	Acc
All metastases	70%	92.05%	100%	100%	93.29%
Micrometastases	73.60%	93.37%	100%	100%	94.41%
Macrometastases	82.35%	96.02%	100%	100%	96.64%

Conclusions: The majority of macrometastases can be detected by IC however IC fails to detect most micrometastases. False negative imprints for macrometastases are mainly due to sampling error. The high Sp, PPV and preservation of the arquitecture of the lymph node for histopathologic examination are the major advantages of IC for intraoperative evaluation of SLN.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Tumour biology and immunology

267 Poster

Bex2 identifies a novel subtype of breast cancer associated with estrogen-response and NGF/NF-KB pathway

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Background: Heterogeneity of breast cancer is a significant challenge in diagnosis and therapy of the disease. Despite advancements in the molecular profiling of breast cancer, there are still only three known molecular subtypes which can be used as classifiers; ER+, ER−, and ERBB2+. Better molecular classification of breast cancer can improve our understanding of the disease and potentially lead to the discovery of novel therapies.

Methods: In this study we performed microarray expression analysis of 135 breast tumors to identify novel classifiers in breast cancer. In addition, we evaluated clinical and biological relevance of our findings.

Results: We identified Bex1 and 2 genes as novel classifiers of breast cancer. Overexpression of these genes was present in 15% of samples and was associated with estrogen-response and apoptotic function. We showed Bex2 expression is necessary and sufficient for NGF anti-apoptotic activity. Moreover, Bex2 induction is mediated through p75NTR and located upstream of NF-κB. Furthermore, estrogen induces Bex2 in a time and dose dependent fashion and Bex2 is necessary for estrogen mediated anti-apoptotic activity. We also found cases with Bex2 overexpression responded better to tamoxifen therapy and proved the interaction between Bex2 and tamoxifen activity in breast cancer cells.

Conclusion: Although the importance of NGF/Bex3/NF-κB pathway is well known in neural tissues, NGF has recently been implicated in pathogenesis of breast cancer as well. Importantly, the function of Bex1 and 2 remains virtually unknown to date. Here, we show Bex1 and 2 classify a novel subtype of ER positive breast tumors which respond better to tamoxifen therapy. We demonstrate Bex2 is part of estrogen response and NGF/NF-κB pathways with anti-apoptotic function in breast cancer. NF-κB activity has recently gained much attention in the development of hormone refractory breast cancer and Bex2 can potentially be applied as an activity marker or therapeutic target within this pathway. The findings reported here show Bex1 and 2 are novel breast cancer-related genes and significantly advance our understanding of NGF/NF-κB pathway with potential clinical implications.

268 Poster

The prognostic significance of inflammation in invasive carcinoma of the breast

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The prognostic significance of inflammation in invasive carcinoma of the breast is controversial with previous studies producing conflicting results. The predominant pattern of inflammation is a diffuse infiltrate of T cells and macrophages in the stroma between carcinoma cells. Perivascular and perilobular clusters of B and T cells are less prominent. The cells necessary for a cell-mediated immune response are often present, but there is evidence that their function is impaired. Inflammatory cells may also stimulate tumour growth by release of proleolytic enzymes or angiogenic factors. 1599 patients aged less than 71 years with operable invasive carcinomas, diagnosed from 1974 to 1988, with median follow up 9.4 years were studied. No patient received adjuvant systemic treatment. An overall assessment of the intensity of lympho-histiocytic inflammation was made on haematoxylin and eosin sections by one observer. Inflammation was associated with higher grade, ductal and medullary histological types, tumour size and inversely with patient age. On univariate analysis patients with tumours with marked or moderate inflammation had a better survival than patients with tumours with absent or mild inflammation ($P = 0.04$). On multivariate analysis survival was associated with inflammation (relative risk 0.61 (95% confidence intervals 0.47 to 0.79), $P = 0.0002$) in addition to lymph node stage, histological grade, tumour size, vascular invasion and tumour type; survival was not related to patient age or oestrogen receptor status. This study suggests that the anti-tumour effects of inflammation predominate over the pro-tumour effects. Critical review of previous large studies with assessment of histological grade and multivariate analysis shows that the majority find prominent inflammation is associated with a better prognosis, consistent with the present study. These results support further studies trying to harness the immune response in the treatment of breast cancer.

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Identification of cell-of-origin subtypes and a wound healing response signature in inflammatory breast cancer

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Introduction: Recently, gene expression studies demonstrated the significance of different biological breast cancer subtypes with regard to prognosis and treatment. In this study we tested to what extent these subtypes contribute to the specific inflammatory breast cancer phenotype (IBC).

Materials and Methods: The presence of different cell-of-origin subtypes (Perou et al.) and of a wound healing signature (Chang et al.) was analyzed in gene expression data sets from 16 IBC and 18 nIBC specimens. A set was compiled of genes being part of respectively the intrinsic gene set (Perou et al.) and the wound healing response signature (Chang et al.) which were also present on the cDNA microarrays used to compare IBC and nIBC specimens (Van Laere et al). 144 and 98 genes were selected from both gene lists. These gene lists were then tested for performance in the original data sets. Next, centroids for each cell-of-origin subtype and for the quiescent and activated fibroblast signature were calculated. These centroids were than used to classify our specimens. For the cell-of-origin subtype classification, the robustness of the taxonomy was confirmed using an alternative data set of 141 genes related to the cell-of-origin subtypes. Contribution of each of the cell-of-origin subtypes to the IBC phenotype was tested by principle component analysis (PCA).

Results: The performance of the selected data sets was 84% and 100%, respectively. 8/16 IBC specimens belonged to the combined Basal-like and ErbB2-overexpressing cluster, compared to only 3/18 nIBC specimens