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The prognostic impact of Plasminogen Activator Inhibitor Type1 (PAI-I) and Urokinase-type Plasminogen Aktivator (uPA) concentrations in axillary lymph node metastasis in patients with primary breast cancer

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Background: Components of the plasminogen activator system play a key role in tumor invasion and metastasis. Tumor tissue levels of urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1 showed a strong prognostic impact in node-negative and node-positive primary BC. uPA/PAI-1 were the first novel prognostic factors in primary BC reaching the highest level of evidence for their clinical utility and they have recently been recommended by ASCO for clinical decision making.

Material and Methods: For the first time, correlations between uPA and PAI-1 concentrations in 73 primary tumor tissues and corresponding axillary lymphnodes (ALN) in node-negative (pN0) and node-positive (pN+) BC (1991–98) and their prognostic impact on disease-free (DFS) and overall survival (OS) were evaluated.

Results: Median follow-up was 56 months. Overall, PAI-I ($p = 0.014$) and uPA concentrations ($p < 0.001$) were significantly higher in tumour tissue than in the corresponding ALN. There was no significant difference of PAI-1 in primary tumor tissue between pN0 and pN+ disease. In involved ALN (pN+), concentrations of PAI-1 but not of uPA, were significantly higher than in pN0 ($p < 0.001$). Moreover, patients with higher PAI-1 concentrations in the corresponding ALN than in their primary tumor had a significantly shorter DFS ($p < 0.001$) and OS ($p = 0.005$).

Conclusions: Our clinical findings support the basic research data implicating uPA and PAI-1 as key proteolytic factors in metastasis-asociated processes such as adhesion, angiogenesis, invasion, proliferation and migration. For the first time, we are able to demonstrate that particularly PAI-1 seems to be involved in tumor metastasis in primary breast cancer with its concentrations being higher in involved ALN than in the primary tumor. Besides uPA/PAI-1 being validated and clinically useful prognostic factors, interference with the uPA/PAI-1 system thus promises to be an interesting therapeutic concept in BC. In 2008, a first phase II trial in metastatic breast cancer interfering with the uPA/PAI-1 system will start recruitment.

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Maintenance of breast cell lines with malignant phenotype and progenitor cells properties

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Background: Recent studies have associated some subtypes of breast cancer with it's origin from progenitor somatic cells. These properties have been studied in patented cell lines but their access is difficult in our country.

The aim of this study is to define the morpho and functional features of cell lines isolated from breast cancer specimens; to identify the possible associations between these cells and somatic progenitor cells; to maintain these cells as stable lineages.

Methods: Fresh tissues from 7 breast tumors (4 lobular and 3 ductal carcinomas) were processed and the cells obtained were cultured in Ham's F10 TC medium plus bovine fetal serum. Five stable lineages were obtained and observed by scanning (JEOL JMS 5800 LV) and transmission (LEO 906) electronic microscopes and by imunohistochemistry assays (CK5 and CK8/18).

Results: Successful isolation was obtained in three lineages. Cellular heterogeneity, loss of contact inhibition and domus aspect were compatible with malignant neoplasia. Cells come from ductal carcinomas tend to exhibit epithelial phenotype and cells from lobular carcinomas are fibroblast like. Electronic microscopy revealed special structures like dark cells, intracitoplasmatic lumen, bizarre pleomorphic nucleus with membrane invagination and a profusion of nucleoli. Additionally the smooth surface, blebs and microvilosities observed were basically different from the control culture MCF7. Anchorage independence, like side population cells, occurred in one lineage, after the 12th passage, and will be investigated for progenitor's cells markers.

Conclusions: the cultured cells tend to reproduce in vitro the properties of the original tissue, as soon as the stable alterations occurred around the carcinogenesis, but they must not be stimulated by cellular differentiation factors applied to the system. The scarce number of mitochondria also suggests deep energetic alterations in these cells, which will deserve future investigations.

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Breast cancer histological grade is associated with estrogen receptor (ER), progesterone receptor (PR), and HER2 expression

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Background: Breast cancer histological grade is independent of certain prognostic factors that are related to the degree of cancer extension, including tumor diameter and lymph node metastasis. Histological grade is one of the indicators of cancer cell's biological characteristics. It has often been reported that the histological grade is correlated with the prognosis. ER, PR, and HER2 expressions are also correlated with the prognosis.

The aim of the present study was to clarify whether breast cancer histological grade is associated with ER, PR, and HER2 expressions.

Patients and Methods: In a retrospective review, the pathological characteristics of 266 patients with breast cancer were examined. Subsequently, the relationships between the histological grade and ER, PR, and HER2 expressions were statistically analyzed. In addition, the differences among the groups of ER and/or PR positive with HER2 positive, ER and/or PR positive with HER2 negative, ER and PR both negative with HER2 positive, and ER and PR both negative with HER2 negative (Triple Negative) were also analyzed. The histological grades 1 and 2 were categorized as the grade low, and the grade 3 as the grade high. Immunohistochemical techniques were used to determine ER and PR status. All cases that stained on ER and PR immunohistochemistry, regardless of the intensity, were considered positive. HER2 staining was also performed; the patients were divided into HER2 negative (0, +1 and +2 with FISH negative) or positive (+2 with FISH positive and +3).

Results: The histological grade was significantly higher in ER negative than in ER positive ($p < 0.0001$). Furthermore, the histological grade was significantly higher in PR negative than in PR positive ($p < 0.0001$). However, the histological grade was significantly lower in HER2 negative than in HER2 positive ($p = 0.0127$). For the ER and PR both negative group with HER2 positive and the Triple Negative group, the histological grade was significantly higher than other groups ($p < 0.0001$).

Conclusion: Breast cancer tumors with a high histological grade are more likely to be ER negative, PR negative, and HER2 positive. On the other hand, not only ER and PR both negative with HER2 positive patients but also Triple Negative patients tend to have high histological grade tumors. These results suggest that, in patients with breast cancer, the tumor's histological grade is associated with ER, PR and HER2 expressions. Furthermore, the histological grade may be a prognostic factor.