Abstract C16: Biomarkers of proliferation, survival, and migration of human breast tumor cells: Future perspectives

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Abstract

Background: Despite recent major advance in the understanding of the mechanisms of breast cancer (BC) progression and in the development of novel therapeutic modalities, BC remains the second leading cause of mortality among women. Mortality is almost invariably due to metastasis. The different histological subtypes of BC and molecular maker expression (ER, PR and HER2) have strong prognostic and predictive values but are not enough to prevent that BC patients (BCP) develop a relapse and metastasis. So the aim of this work was the simultaneous evaluation of the expression of biomarkers related to BC progression and metastasis (OPG, TRAIL, TRAIL receptors (R) [R1, R2, R3 y R4], RANKL, RANK (RANKL-R), SDF-1, CXCR-4 (SDF-1-R), IL-6, IL-6-R, MCSF and M-CSF-R in BC cells together with the study of classic prognostic parameters (age, ER, PR, HER2, tumor size and histological grade) in BCP. Regarding the expression of these biomarkers in BC cells, the results are contradictory.

Material and methods: This was a prospective cohort study. We included surgical biopsy samples from 19 BCP with primary infiltrative ductal carcinoma, early clinical stage (I-II) and sentinel lymph node negative. Moreover, non-malignant breast tissues (10) were analysed and used as a control. The biomarkers were evaluated by immunohistochemistry on biopsy of breast tissues. Clinicopathological information was retrieved from pathology and medical records. Statistical analysis: Fisher's Exact Test was used to analyze associations between categorical variables in BCP and controls. Kappa coefficients were used to evaluate the degree of concordance between two categorical variables measured in the same individuals (biomarkers and classical parameters). Mann-Whitney test was used to determine differences in continuous or at least ordinal variables (biomarkers and classical parameters) between the two groups. Software: InfoStat and SPSS 18.0. The threshold for significance was set at $p=0.05$

Results: BC samples exhibited significant higher prevalence of the expression of R3, R4, RANK, IL-6, CXCR4 and SDF-1 than non-malignant breast tissues ($p=0.0002$, $p=0.0003$, $p=0.0239$, $p=0.0087$, $p=0.0019$ and $p=0.0403$, respectively). On the other hand, R2, found in 65% of BC samples (3/19), was associated with age ($p=0.0451$). R2 expression was positive in BCP with age mean of 71.5y (range 55-81y). R1, R2 and MCSF expression in BC samples was associated with HER2 [Kappa coefficients: -0.253(-0.445;-0.061); 0.354(0.036;0.672) and -0.354(-0.578;-0.129), respectively]. No statistically significant association was found between the rest of non-classical biomarkers and clinicopathological parameters.

Discussion: In conclusion, R3, R4, RANK, IL-6, CXCR4 and SDF-1 expression could clearly distinguish between women with malignant and non-malignant breast tissue. R3 and R4 expression in BC cells could produce the TRAIL resistance, suggesting an anti-apoptotic effect. RANK and CXCR4 expression in BC cells suggest that they have the ability to migrate to bone through the

action of RANKL and SDF-1 released by stromal cells of the tumor microenvironment. R1, R2 and M-CSF expression in BC cells were associated with worse classic prognostic parameter HER2. Since these ligands and their receptors are implicated in the regulation of proliferation, survival, migration and future bone metastasis during breast tumor progression, assessment of these biomarkers and it association with classic prognostic parameters in tumor biopsies of BCP could be useful in identifying patients with more aggressive tumors that are also at risk of bone metastasis, which may thus improve the available options for therapeutic intervention.

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