A new 5-genes Signature predictive of Risk of Relapse in Early Breast Cancer

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Abstract

Background

Gene Signatures can be used to assist in making treatment decisions in breast cancer. They are expensive and time consuming. We were interested in looking for the "core" genes of published signatures in order to find a less expensive tool.

Materials & Methods

To select the candidate genes we used data of NBG Gene Expression Omnibus including 408 breast cancers. Quantitative reverse transcribe PCR was done on a set of 261 consecutive breast cancer cases with minimum follow up of 5 years (paraffin embedded issue). Raw intensity data of Affymetrix Hu133A and Hu133B arrays of the two datasets (GSE1456 and GSE3494) were preprocessed using R/Bioconductor, using the supercomputer Michelangelo. The candidate genes were selected from the -70-gene signature\(^{1,2}\), the "recurrence-score\(^{3}\), the "two-gene-ratio model\(^{4}\) and the "Insulin Resistance signature\(^{5}\), for a total of 98 genes. We evaluated the 50 mRNA more significantly related to DFS by embedded sections, split into a training (n 137) and a validation set (n 124).

Results

The signature was developed on the training set and a multivariate stepwise Cox analysis selected 5 genes independently associated with DFS: FGF18 (HR=1.13, p=0.05), BCL2 (HR=0.57, p=0.001), PRC1 (HR=1.51, p=0.001), MMP9 (HR=1.11, p=0.08), SERF1a (HR=0.83, p=0.007). These five genes were combined into a linear score weighted according to the coefficients of the Cox model, as: 

$$
\text{Score} = 0.125 \times \text{FGF18} - 0.560 \times \text{BCL2} + 0.409 \times \text{PRC1} + 0.104 \times \text{MMP9} - 0.188 \times \text{SERF1a}
$$

The linear score was highly associated with DFS in the training set (HR=2.7, 95CI=1.9-4.0, p<0.001). The signature was then evaluated on the validation set assessing the discrimination ability by a Kaplan Meier analysis, using the same cut off classifications patients at low, medium or high risk of relapse as defined on the training set. The score resulted highly associated with DFS also in the validation set (p<0.001).

Patients Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF18</td>
<td>8.6</td>
<td>10.8</td>
<td>16.0</td>
</tr>
<tr>
<td>BCL2</td>
<td>8.4</td>
<td>9.1</td>
<td>11.0</td>
</tr>
<tr>
<td>PRC1</td>
<td>8.6</td>
<td>10.8</td>
<td>11.0</td>
</tr>
<tr>
<td>MMP9</td>
<td>8.6</td>
<td>10.8</td>
<td>11.0</td>
</tr>
<tr>
<td>SERF1a</td>
<td>8.6</td>
<td>10.8</td>
<td>11.0</td>
</tr>
</tbody>
</table>

% DFS according to 5-gene Signature

Discussion

5-gene Signature: possible role in Breast Cancer

Overexpression of "BCL2" and "SERF1a" is related to a higher risk of relapse. Overexpression of "FGF18" and "MMP9" is related to a better prognosis.

5 gene-Signature: "FGF18" overexpressed in tumours affects tumour and microenvironment.

"Self-sufficiency in growth signal"

"BCL2" overexpressed also in BC, negative prognostic role

"PRC1": correlate with the mitotic spindle, crucial role in the completion of cytokinesis, overregulated by p53, expressed in p53 defective cells

"MMP9": overregulated in tumour microenvironment, influences extracellular matrix, cell adhesion, cell survival, receptor expression, impairs activity of growth factors and chemokines

"Tissue invasion and metastasis"

"SERF1a": function still unknown but reported to be related to a worse prognosis.

Conclusions

Overexpression of "BCL2" and "SERF1a" is related to a higher risk of relapse.

Overexpression of "FGF18" and "MMP9" is related to a better prognosis.

References