PS5 Late breaking

New insights into molecular differences in early versus late metastases and identification of key genes involved in breast carcinogenesis: gene-expression profiling of 144 node-negative tumours

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Background: Node negative breast cancer outcome can be predicted by the 70-gene-signature which clinical use will be further investigated in the large Mindact clinical trial. The present study, performed on pan-genomic arrays (44 K), aimed at providing further insight on the occurrence of early vs. late metastases and at identifying key genes and pathways involved in breast tumor carcinogenesis through differential expression analysis of tumours versus normal tissue.

Material and methods: Untreated consecutive node negative breast cancer patients (pts.) With available tumour samples were selected based on their outcome in two different French cancer centres: pts who did not relapse (NR) after min. 10 years (y) of follow-up, pts with a local relapse (LR), pts with distant metastasis before 5 y (M1), pts with metastasis between 5 and 10 y (M2), pts with metastasis after 10 y (M3). Gene expression profiling was performed using agilent pangenomic microarrays (44,000 probes). Molecular profiles of tumours were compared between the different groups based on outcome by repeated random validation. Additionally, the gene expression of all tumours was further compared with normal breast tissue RNA (Clontech) to allow identification of genes involved in breast carcinogenesis. Correlation with CGH status of the genes was also performed using CGH oligo arrays.

Results: A total of 144 patients were included in the present analysis: 60 NR, 37 LR, 29 M1, 12 M2 and 6 M3. A 141 gene-profile was identified that could significantly distinguish M1 versus M2+M3 tumours. Functional analysis revealed relevant genes involved in important pathways such as kinase activity, cell cycle regulation, cell maintenance or adhesion.

The comparison of all 144 tumours with normal breast tissue further identified 666 genes differentially expressed in at least 90% of tumours (435 annotations found in GeneOntology). The top 15 genes with highest expression fold change, were upregulated in 98% of the tumours and consisted of 12 identified genes as well as 3 currently unknown genes.

Discussion: Molecular profiling allows significant discrimination between early (<5 y) and late (>5 y) metastases in untreated node negative breast cancer tumours, and insight on relevant biological pathways. Comparison of tumours versus normal breast tissue allows identification of 666 genes with significant differential expression potentially associated with tumour carcinogenesis.