Age-related breast cancer gene expression signature with strong prognostic value

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Background: Breast cancer (BC) diagnosed at ages <40 years is known to present more aggressive tumor phenotypes and poorer clinical outcome compared to older BC patients. To gain a better understanding of the possible difference in age-related expression of BC promoting genes, we aimed to identify transcriptional alterations supporting cancer progression in BC of young women.

Methods: We studied mRNA gene expression data from METABRIC discovery (n=997), and validation cohort (n=995), and explored the transcriptional patterns associated with BC of the young. We investigated differentially expressed genes (DEGs) between primary BC for patients below and above 40 years at time of diagnosis and explored gene sets (by Gene Set Enrichment Analysis) enriched in BC of the young. Protein-protein interaction (PPI) networks were explored by the STRING database and visualized in Cytoscape software. Subclusters and hub genes were identified by MCODE and CytoHubba plugins, respectively.

Results: Oncogenic- and proliferation associated signatures were enriched in women <40 BC, including signatures reflecting KRAS, MTOR and MYC. Proliferation and cell cycle processes were the dominating enriched gene ontology categories (FDR <10%). Six hub genes presenting highest PPI network connectivity were identified. High signature score (sum of hub genes expression values) was significantly associated with high tumor size, histologic grade, lymph node metastasis, ER negativity, basal-like, and HER2 enriched subtypes (P <0.001).

The 6G signature score correlated strongly with the tumour cell proliferation signatures Oncotype Dx (p=0.90-0.91, P<0.001), a PCNA score (both p=0.96, P<0.001), and the novel Statmin proliferation score (p=0.77-0.79, P<0.001).

High expression of the 6G signature associated with shorter disease specific survival (HR =1.1, 95% CI 1.0-1.1, P< 0.001, moreover associated with shorter survival in OncotypeDx-low tumors (HR: 1.077, 95% CI: 1.034-1.122) and with reduced survival in Luminal A+B tumors (HR: 1.091, 95% CI 1.053-1.131, P<0.001).

Conclusion: The current study provides new insights into age-related gene expression alterations in BC. We demonstrate evidence of higher tumor cell proliferation in young BC patients, and identified a gene expression signature reflecting tumor proliferation, aggressive tumor features and reduced survival, also in subsets of low OncotypeDx score.

Fig.1: Associations between a high 6G score and basal-like tumors, ER negativity, age <40 years and large tumor size.

Fig.2: Protein-protein interaction networks visualized in Cytoscape representing the identified up-regulated differentially expressed genes. Subclusters detected by the Cytoscape plug in MCODE (highlighted with colors); Single nodes are shown.