Molecular Alterations in Secondary Breast Cancers

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Methods

- Breast cancer in patients with a prior history of malignancy (SBC) is associated with decreased survival compared to patients with primary breast cancer (PBC).
- Genomic and epigenomic alterations may predict prognosis and response to treatment but no such evaluation has been performed on SBCs.
- The aim of this study is to identify transcriptomic and epigenomic signatures in patients with infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC) SBCs.

Results

IDC cohort (n=36)

- 727 significantly (P<0.05) differentially expressed genes
  - 434 upregulated genes, 105 also hypomethylated
  - 293 downregulated genes, 73 also hypermethylated

ILC cohort (n=40)

- 261 significantly (P<0.05) differentially expressed genes
  - 108 upregulated genes, 17 also hypomethylated
  - 153 downregulated genes, 46 also hypermethylated

Only 1.51% of significantly differentially expressed genes overlap between the IDC and ILC cohorts.

Background

- ER+/PR+/HER2- IDC and ILC tumors were identified in the Cancer Genome Atlas (TCGA).
- Cases of SBCs were matched 1:1 to PBC controls by age, histology, and stage.
- Differentially expressed genes were identified using RNA next-generation sequencing (RNA-seq) data.
- Genome-wide DNA methylation profiles were normalized.
- Wilcoxon rank sum test (P-value <0.01) followed by a nearest Shrunken Centroid classification algorithm was used to identify differentially methylated genomic regions with classification potential.
- DNA methylation and gene expression signatures were integrated.

Results

IDC cohort

- Upregulated and hypomethylated genes included ESR1 (estrogen receptor alpha) and TET2, involved in tumor initiation and refractory disease progression.
- Downregulated and hypermethylated genes included HLA-E, HLA-DMa, and HLA-DRB5, IRF8 (interferon signaling), and RELA (NF-κB response).

ILC cohort

- Upregulated and hypomethylated genes included DAD1 and TRIM8 (anti-apoptotic genes), and TRIM41 and UBTD1 (tags proteins for degradation).
- Downregulated and hypermethylated genes included key differentiation breast factors such as CD44 antigen.

Conclusions

- Differential gene expression and DNA methylation signatures are seen in IDC and ILC SBC.
- Genes identified in each cohort are relevant to tumor growth and proliferation.
- Differences in gene expression signatures are specific to each histological subtype, emphasizing the importance of performing disease subtype-specific evaluations of molecular alterations.
- Further studies are needed to validate these findings in a larger cohort of patients and to evaluate the impact of molecular alterations on survival.