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CIRCULATING MIRNA PROFILES POINT TO DYSREGULATION IN TGFβ/SMAD3 TUMOR SUPPRESSOR SIGNATURE IN BRCA POSITIVE BREAST CANCER PATIENTS

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Purpose of Study Over 240,000 individuals are diagnosed with breast cancer (BrCa) of which 12,000 individuals carry BRCA germline mutations. MicroRNA dysregulation is common in malignancy and may correlate with germline mutations.

Aims:

1. Analyze microRNAs in patients with breast cancer with or without BRCA germ line mutations, with and without cancer.
2. Identify molecular BRCA mutant patients to deduct reasons for accelerated malignancy.

Methods Used We analyzed plasma miR expression from 94 br cancer patients (41 BRCA positive) relative to 24 normal controls. All samples were collected between 2010 and 2014 and survival data was known for all cancer patients. TaqMan Open Array panel was used to simultaneously run hundreds of microRNA assays in the Applied Biosystem Open array real time PCR. Using AB open array real time PCR, 756 miRNA species were detected. Two-sample t-test was used for all 2-sample comparison and ANOVA followed by Tukey HSD post-hoc test to compare the miRs mean differences. All tests were 2-tailed and results with a $p < 0.05$ were considered statistically significant.

Summary of Results BRCA+underexpressed hsa-mir-10a and hsa-mir-376c and over-expressed Hsa- mir- 326 and Hsa-mir-143 relative to BRCA-; $p < 0.05$.

Using Coremine data mining linking genes and diseases differentially expressed circulating miRs are linked to tumor suppressor TGFβ/SMAD3.

Conclusions The early onset of breast cancer in BRCA mutant patients may recapitulate the pro-oncogenic effects of TGF-β. The context dependent SMAD3 binding & tumor suppression TGF-β effects are abrogated in BRCA mutant patients. TGF-β/Smad3 tumor-suppressor signature suppresses local inflammation in the tumor microenvironment.