FoxM1 upregulation correlates with worse recurrence-free survival in breast cancer

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Introduction

Breast cancer is a leading cause of cancer-related death among women in the United States[1]. Most deaths from breast cancer are due to the metastasis of recurrent, drug-resistant disease. Metastatic breast cancer is incurable, with only one of four women surviving 5 years from diagnosis[1,2].

Breast cancers harbor intrinsic molecular heterogeneity, allowing stratification into distinct subtypes[3]. Basal-like breast cancer is a particularly aggressive subtype with a high rate of metastasis and poor overall survival rate[4]. Most basal-like breast cancers lack estrogen receptor, progesterone receptor, and human epidermal growth factor 2 receptor expression, and are thus referred to as triple negative[5]. Due to a poor understanding of the molecular drivers of basal like or triple negative breast cancer, few therapeutic options currently exist for these patient subpopulations.

Increased expression of the transcription factor forkhead box protein M1 (FoxM1) occurs in many tumor types, including breast cancer[6,7]. FoxM1 regulates the expression of key proteins involved in mitotic progression, genomic stability and epithelial mesenchymal transition. Upregulation of FoxM1 is associated with drug resistance and metastasis in preclinical models of breast cancer[6,7]. However, the clinical implications of FoxM1 upregulation in breast cancer, including in basal like and triple negative breast cancer, remain unclear.

We hypothesize that upregulation of FoxM1 is associated with worse clinical outcome in breast cancer patients. We tested this hypothesis using publicly accessible cancer genomics datasets. The specific aims of the current study were to: (1) compare FoxM1 expression in breast cancer and normal breast tissue samples, and (2) correlate FoxM1 expression with clinical outcome.

Methods

Oncomine Analysis:
We searched the Oncomine Cancer Database (8) at https://www.oncomine.org/resource/main.html using search query ”FoxM1”. In the gene summary view, the number “8” under ”Cancer vs Normal Analysis” for ”Breast Cancer”. The datasets that reported FoxM1 as a significant transcription factor in the studies were analyzed independently. Additional data filters, such as “mRNA” when specifying for data type and “Clinical Specimen” when specifying for “Sample Type”, were added to the analysis by typing into the “Search” box and selecting each independently.

KM Plotter Analysis:
We searched the Kaplan-Meier Plotter Breast Cancer database (9) at http://kmplot.com/analysis/index.php?p=service using search query “FoxM1” under the “mRNA gene chip”- Affy id/Gene Symbol” options. Clinical outcomes corresponding to “survival” was selected, with recurrence-free survival (RFS).

Results

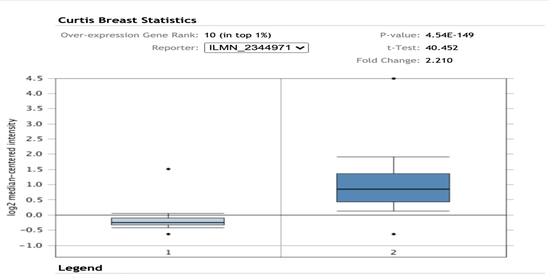

Figure 1: **FoxM1 is more highly expressed in invasive ductal breast cancer vs normal breast tissues.** Oncomine database search for FoxM1 expression in invasive ductal breast carcinoma. FoxM1 is significantly **(P=4.54E-149)** overexpressed in breast carcinoma vs. normal breast tissue samples.

Results

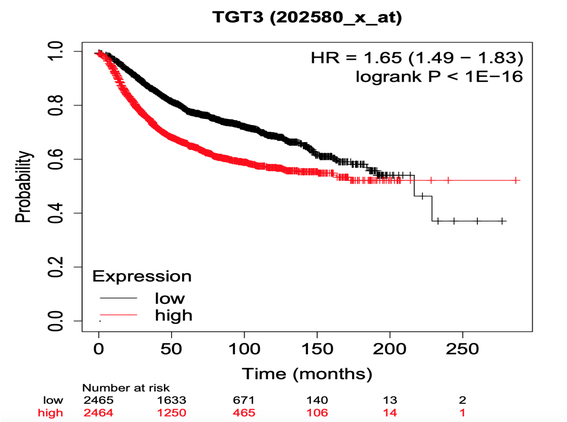

Figure 2: Recurrence-free survival rate is lower in breast cancer cases with high FoxM1 expression. Kaplan-Meier plots for recurrence-free survival in patients with breast cancer (N=4929) stratified by FoxM1 expression. Recurrence-free survival was significantly lower (**P<1E-16**) in patients with high FoxM1 expression.

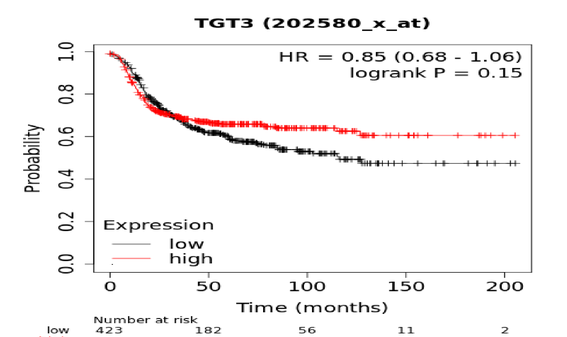

Figure 3: Recurrence-free survival rate is not significantly different in patients with basal-like breast cancer who have high vs low FoxM1 expression. Kaplan-Meier plots for recurrence-free survival in patients with basal-like breast cancer (n=846) stratified by FoxM1 expression. FoxM1 expression was not significantly associated with recurrence-free survival in patients with basal-like breast cancer.

Discussion

FoxM1 overexpression is linked with metastasis and chemoresistance in breast cancer[10]. We performed database analyses of FoxM1 expression in cancer genomics datasets from patients with breast cancer. Our results indicate that FoxM1 is overexpressed in breast cancer compared with normal breast tissue. Further, the results indicate that FoxM1 upregulation is significantly associated with worse recurrence-free survival rates in breast cancer patients. FoxM1 has been associated with worse prognosis in triple breast cancer[12]. However, in our analysis, we found no significant correlation between FoxM1 and recurrence-free survival in patients with basal-like breast cancer. Future studies will determine mechanisms regulating FoxM1 expression, biological effects of FoxM1 upregulation, and whether FoxM1 suppression alters breast cancer progression.

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Acknowledgements

Thank you to Mercer University.