**Prognostic Role Found for miR-21 Expression in Triple-Negative Breast Cancer**

Findings Suggest Measurement of Changes in the Tumor Microenvironment Are Important in this Heterogeneous Group, According to Study Published in *The American Journal of Pathology*

Philadelphia, PA, December 1, 2014 – “Triple-negative” breast cancer (TNBC) occurs in patients whose cells do not express receptors for estrogen, progesterone, and/or human epidermal growth factor receptor 2 (ER−/PR−/HER2−). Because of the absence of these predictive biomarkers, treatment assignment can be difficult. Now, researchers report that high levels of the microRNA miR-21 in the tumor microenvironment, but not in the tumor epithelia (cancer cells), are associated with worse clinical outcomes for patients with TNBC, thus identifying a possible TNBC prognostic biomarker, according to a study in *The American Journal of Pathology*.

TNBC accounts for 15% to 20% of breast cancer cases, and patients have shorter recurrence-free survival (RFS) and breast cancer-specific survival (CSS) relative to other major subgroups. It is likely that different subtypes of TNBCs exist, and the heterogeneity may be responsible for a wide variation in response to treatment. “Predictive biomarkers for therapeutic response prediction and novel therapeutic targets that address distinct biological features of TNBC subgroups are needed for these patients,” says Lorenzo F. Sempere, PhD, head of the Laboratory of microRNA Diagnostics and Therapeutics at Van Andel Research Institute in Grand Rapids, MI. “These findings add support to the growing importance of miRNA-based diagnostics.”

miRNAs are short, noncoding, regulatory RNAs that modulate gene expression in critical developmental, physiological, and pathological processes. In previous work by these authors and others, miR-21 was associated with poorer disease outcomes in cancers of the colon, pancreas, and breast. The goal of this study was to explore in greater detail the influence of miR-21 on TNBC outcomes, looking both at the amount and the location of miR-21 expression. The authors had reason to believe that changes in the tumor’s surrounding microenvironment (a complex of stromal cells, immune cells, extracellular matrix, and cytokines/chemokines) could be even more important than changes within the cancer cells.
Tissue samples from 901 female patients diagnosed with non-metastatic invasive breast cancer were analyzed using a fully automated, tissue slide-based in situ hybridization/immunohistochemical (ISH/IHC) assay. The tissue was acquired from the National Cancer Institute Cancer Diagnosis Program.

miR-21 expression was found in 42.8% (386) of the 901 cases. Using fluorescence microscopy, the cases were divided according to their miR-21 signal intensity, with 694 cases determined to be in the non-or low-expressing group and 207, in the high-expressing group. The authors found that the high-expressing miR-21 group exhibited significantly shorter RFS (hazard ratio (HR), 1.71; \( P < 0.001 \)) and CSS (HR, 1.96, \( P < 0.001 \)) compared to the low-expressing group in multivariate analysis after adjusting for age, tumor size, grade, and lymph node involvement. RFS and CSS were determined five years after diagnosis and during the overall follow-up period (median 10.33 years).

Looking further, the investigators assessed the contribution of tumor compartment of miR-21 expression to the risk associated with disease outcome. Twenty cases were found to have only tumor epithelia-specific expression and 187 cases, with predominant expression in the tumor stroma. They found that for patients with TNBC, outcomes were threefold worse for women with high levels of miR-21 located in the tumor stroma than for those with any other miR-21 score or location (5-year CSS: HR, 3.09, \( P = 0.017 \)). For ER+ or PR+ cases, women with high levels of miR-21 in the tumor epithelia had worse outcomes than those with other miR-21 scores or locations.

“This large retrospective study in a cohort of 901 early-stage breast cancer indicated that both expression levels and compartment-specific expression of miR-21 contain prognostic information,” says Dr. Sempere. “This knowledge could be exploited to implement tumor compartment-specific anti-miR-21–based therapies in breast cancer, especially in TNBC cases for which effective targeted therapies are still lacking.”

NOTES FOR EDITORS


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Full text of this study is available to credentialed journalists upon request; contact Eileen Leahy at 732-238-3628 or ajpmedia@elsevier.com. Journalists wishing to interview the authors may contact Beth Hinshaw Hall at 616-234-5519 or Beth.HinshawHall@vai.org.

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