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Triple-negative breast cancer subtypes identified using microRNA

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A new, large-scale study of triple-negative breast cancer shows that small molecules called microRNA can be used to define four subtypes of this aggressive malignancy.

The findings, by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) working with collaborators in Italy, could lead to new screening methods, prognostic markers and perhaps new targeted treatments for this aggressive and often-fatal form of breast cancer.

The study is published in the journal PLOS ONE.

"The treatment of women with triple-negative breast cancer is challenging because this malignancy can be very different genetically from one patient to another," says co-senior investigator Dr. Charles Shapiro, director of Breast Medical Oncology and professor of internal medicine at the OSUCCC – James.

"We believe these microRNA signatures define novel sub-sets of triple-negative breast cancer and offer new insights into the biology of the disease and better ways to treat these patients," Shapiro says.

The microRNAs that compose the signatures are involved in regulating cell growth, proliferation and survival, and in cell movement and migration.

"These findings strongly suggest that microRNAs play an important role in triple-negative breast cancer and might be used to better identify the most effective treatment for a patient's tumor," says co-senior investigator and researcher Dr. Kay Huebner, professor of molecular virology, immunology and medical genetics at Ohio State.

"Several of the deregulated microRNAs we found in the cancer samples are involved in chemo-resistance or radio-resistance. MicroRNA profiles can help us to improve and personalize therapies for individual patients," she says.

Triple-negative breast cancer accounts for about 15 percent of all breast cancers. It is characterized by cancer cells that lack estrogen, progesterone and HER2 receptors. For this reason, these tumors do not respond to hormone therapies or HER2-targeted treatments.

MicroRNAs help regulate the kind and amount of proteins that cells make. They do this by binding with messenger RNA (mRNA), molecular copies of genes that are translated into proteins. When microRNA is bound to an mRNA, the messenger molecule cannot be translated into a protein. Instead, it is either temporarily stored or destroyed.

This study investigated associations between microRNA expression levels, mRNA expression levels and overall survival and distant-disease-free survival in women with triple-negative breast cancer.

Shapiro, Huebner and their colleagues evaluated 59 normal, 165 tumor and 54 metastatic matched tissue samples, obtained through The Stefanie Spielman Fund for Breast Cancer Research at the OSUCCC – James.

The researchers ran a complete microRNA profile and a cancer-focused panel of genes for each sample. They then generated microRNA

signatures represented by certain prognostic microRNAs that, when deregulated, indicate odds of survival.

"This was a large cohort of triple-negative breast cancer cases and a major analysis effort that we believe makes this work extremely valuable," Huebner says.

To stratify the cancers, the researchers determined microRNA and mRNA expression profiles in tumor, adjacent-normal tissue and lymph-node metastatic tissue from 173 women with the triple-negative breast cancer.

"We identified microRNAs and mRNAs that uniquely represent primary and metastatic tumors, and that are specifically deregulated in that stage of the disease, says co-author Dr. Pierluigi Gasparini, a postdoctoral researcher in Huebner's laboratory.

The results define microRNA expression signatures that characterize and contribute to the differences between primary and metastatic tumors.

"We now want to learn which of these deregulated microRNAs might represent early biomarkers for cancer or metastasis detection," Gasparini says.

The study's key technical findings include:

- The microRNA signatures correlated with prognosis and were correlated with changes in mRNA expression;
- Two microRNA signatures were predictive of overall survival and distant disease-free survival, respectively, in patients 50 years of age or younger;
- mRNA expression profiling resulted in clustering of triple-

negative breast cancer into four molecular subclasses with different expression signatures.

"We believe these findings will be a reference point not only for our lab but also for many other research teams that might not have access to large patient populations, and hope that they will accelerate even more research on triple-negative breast cancer," Huebner says.

More information: www.plosone.org/article/info:d … journal.pone.0055910

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