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How early breast tumors become deadly: A small group of molecules might hold the answer

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Researchers have discovered a restricted pattern of molecules that differentiate early-stage breast tumors from invasive, life-threatening cancer. They also found a similar molecular signature that correlated with the aggressiveness of invasive tumors, and with the time to metastasis and overall survival.

Investigators at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) who led the study say the findings could offer new strategies for treating breast cancer by blocking progression to life-threatening invasive cancer.

The researchers investigated a common type of early-stage breast cancer called ductal carcinoma in situ (DCIS). DCIS tumors are confined to the milk duct, and, though small, they are detectable by mammography. They can sometimes grow and spread beyond the milk duct into surrounding healthy tissue, a stage called invasive ductal carcinoma.

The study, reported in the *Proceedings of the National Academy of Sciences*, compared the pattern of molecules called microRNAs in DCIS to the pattern present in invasive ductal cancer. It identified nine microRNAs that distinguished invasive cancer from DCIS.

"The transition from DCIS to invasive ductal cancer is a key event in

breast cancer progression, but it remains poorly understood," says principal investigator Dr. Carlo M. Croce, director of Ohio State's Human Cancer Genetics program and a member of the OSUCCC – James Molecular Biology and Cancer Genetics program.

"These findings suggest that this 'micro-signature' might be used to identify DCIS tumors that are at high-risk for becoming invasive cancer."

MicroRNAs are a class of molecules that help control the types and quantity of proteins cells make. Work by Croce and others has shown that microRNAs are often dysregulated during cancer development, and it has suggested that the molecules offer new biomarkers of disease, and that restoring key microRNAs to normal levels might offer a new approach to cancer treatment.

First author and cancer researcher Dr. Stefano Volinia notes that high expression of one of those molecules, called miR-210, correlates with tumor aggressiveness and with time to metastasis and overall survival.

"If we could inhibit the few miRNAs associated with tumor invasiveness, perhaps we could arrest tumor progression at the harmless, pre-invasive state," says Volinia, an assistant professor of molecular virology, immunology and medical genetics and of biomedical informatics.

For this study, Croce, Volinia and their colleagues studied microRNA profiles from data collected using whole-genome deep sequencing. They examined 80 cases of invasive ductal carcinoma, eight of DCIS, and six of normal breast biopsies.

Comparing DCIS and invasive cancer samples showed nine microRNAs that formed an "invasiveness micro-signature." Three of these miRNAs

(let-7d, miR-210, and -221) showed the most extreme changes in expression levels. Relative to their levels in normal breast tissue, the three were down-regulated in DCIS, then up-regulated in invasive cancer.

"That told us that progression from in-situ ductal cancer to invasive cancer involves a reversal of miRNA expression," Croce says.

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