New agent might control breast-cancer growth and spread

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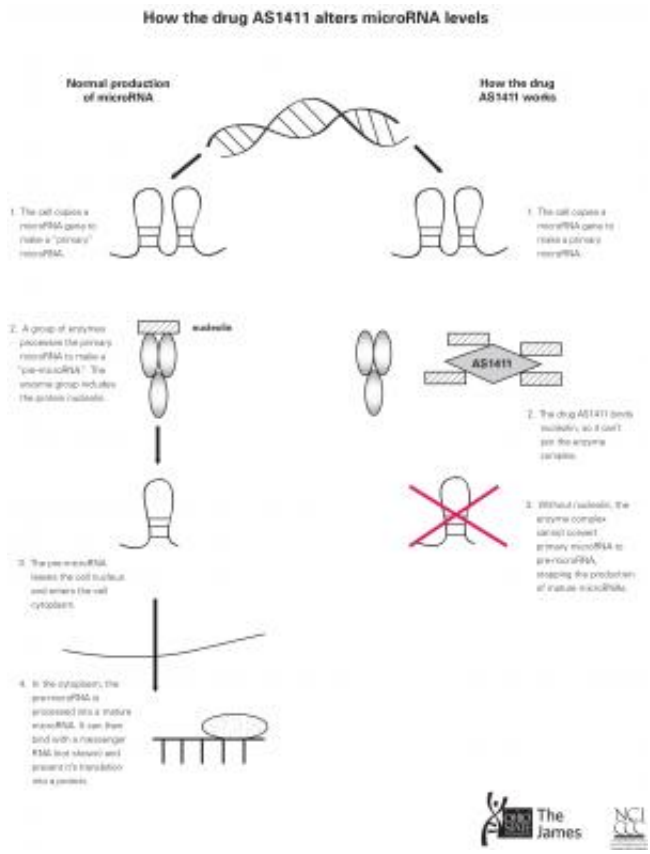

The drug AS1411 works by blocking the cell's production of regulatory molecules called microRNA, some types of which are associated with cancer. Specifically, the drug inhibits a protein called nucleolin that plays a critical role in the microRNA maturation process. Left: Steps in the microRNA maturation process. Right: How AS1411 interferes with microRNA maturation. Credit: The Ohio State University Comprehensive Cancer Center

A new study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) suggests that an unusual experimental drug can reduce breast-cancer aggressiveness, reverse resistance to the drug fulvestrant and perhaps improve the effectiveness of other breast-cancer drugs.

The findings of the laboratory and animal study, published in the *Journal of Experimental Medicine*, suggest a new strategy for treating breast cancer, the researchers say.

The drug, called AS1411, belongs to a class of agents called G-rich aptamers. The agent works by blocking the cell's production of molecules called microRNA, some types of which are associated with cancer. Specifically, the drug inhibits a protein called nucleolin that plays a critical role in the microRNA maturation process (See figure).

MicroRNA molecules help cells control the amount and kinds of proteins they make, and abnormal levels of certain microRNAs are a hallmark of many cancers.

"This study of the role of nucleolin in micro RNA regulation has clear clinical implications," 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.

"It supports a novel treatment for breast cancer that reduces cancer aggressiveness and restores drug-sensitivity by inhibiting the processing of specific microRNAs that are highly expressed in cancers."

First author Flavia Pichiorri, assistant professor of hematology, notes that nucleolin is a promising therapeutic target for microRNA

modulation in cancer cells.

"To our knowledge, this is the first large study to show a clear association between nucleolin and specific microRNAs that are causally involved in cancer," she says. "We also believe it is the first study to show that targeting nucleolin with a G-rich aptamer can control breast-cancer metastasis in an animal model through microRNA regulation."

The study's key technical findings include:

- Nucleolin is present at abnormally high levels in breast cancer cells.
- AS1411 reduces nucleolin levels and inhibits the processing of certain cancer-associated microRNAs, including miR-21, miR-103, miR-221 and miR-222, whose overexpression in breast cancer is associated with drug resistance and aggressiveness.
- AS1411 affects breast-cancer-cell motility and invasiveness by reducing the expression of several genes targeted by nucleolin-related microRNAs (e.g., PTEN);
- Impairing nucleolin in fulvestrant-resistant breast-cancer cells restores sensitivity to the drug, suggesting that agents targeting nucleolin can improve the effectiveness of conventional anti-cancer agents.

Provided by Ohio State University Medical Center

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