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Study reveals new mechanism that might promote cancer's growth and spread in the body

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Researchers have discovered a previously unknown mechanism that promotes the growth and spread of cancer. The mechanism involves key immune cells and a new role for small regulatory molecules called microRNA. The findings suggest a new strategy for treating cancer and perhaps diseases of the immune system.

Tiny vesicles released by tumors cells are taken up by healthy immune cells, causing the immune cells to discharge chemicals that foster cancer-cell growth and spread, according to a study by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at Children's Hospital in Los Angeles.

The study uses lung cancer cells to show that the vesicles contain potent regulatory molecules called microRNA, and that the uptake of these molecules by immune cells alters their behavior. The process in humans involves a fundamental receptor of the immune system called Toll-like receptor 8 (TLR8).

The findings, published in the early edition of the *Proceedings of the National Academy of Sciences*, suggest a new strategy for treating cancer and diseases of the immune system, the researchers say, and a new role for microRNA in the body.

"This study reveals a new function of microRNA, which we show binds to a protein receptor," says principal investigator Dr. Carlo Croce, director of Ohio State's Human Cancer Genetics program and a member of the OSUCCC – James Molecular Biology and Cancer Genetics program. "This tells us that some cancer-released microRNAs can bind and activate a receptor in a hormone-like fashion, and this has not been seen before."

MicroRNAs help control the type and amount of proteins that cells make, and they typically do this by binding with the messenger-RNA that encodes a protein.

"In this study we discovered a completely new mechanism used by cancer to grow and spread, therefore we can develop new drugs that fight tumors by entering this newly identified breach in cancer's fortress," says co-corresponding author and first author Dr. Muller Fabbri, assistant professor of Pediatrics and Molecular Biology and Immunology at the Keck School of Medicine of the University of Southern California.

"Equally exciting, we show that this mechanism involves a fundamental receptor of the immune system, TLR8, suggesting that the implications of this discovery may extend to other diseases such as autoimmune and inflammatory diseases," Fabbri says.

Key findings of the study include the following:

- Lung tumor cells secrete microRNA-21 and microRNA-29a in vesicles called exosomes, and these exosomes are taken up by immune cells called macrophages located where tumor tissue abuts normal tissue.
- In human macrophages, microRNA-29a and microRNA-21 bind

with TLR8, causing the macrophages to secrete tumor-necrosis-factor alpha and interleukin-6, two cytokines that promote inflammation.

- Increased levels of the two cytokines were associated with an increase in the number of tumors per lung in an animal model, while a drop in those levels led to a drop in the number per lung, suggesting that they also play a role in metastasis.

Provided by Ohio State University Medical Center

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