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Cancerous tumors deliver pro-metastatic information in secreted vesicles

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Cancer researchers have known for well over a century that different tumor types spread only to specific, preferred organs. But no one has been able to determine the mechanisms of organ specific metastasis, the so-called "soil and seed" theory of 1889. New details that could help shed light on this hypothesis have been provided by a team of researchers from Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center, and their collaborators, proposing a new mechanism controlling cancer metastasis that offers fresh diagnostic and treatment potential.

The findings, recently published online by *Nature Medicine*, show how melanoma cancer cells release small "exosome" vesicles (microscopic particles like "bubbles" filled with many different molecules such as proteins and nucleic acids) that travel to the bone, liver, lung and brain. This cellular material fuses with these organs and establishes an environment ripe for spreading tumor cells.

These dangerous cancer exosomes have many effects, the researchers say, such as triggering inflammation, promoting leaky blood vessels and "educating" bone marrow progenitor cells to participate in the metastatic cascade soon to come.

The fact that these exosomes circulate in the blood -- and thus are readily measurable as well as accessible -- could provide an advantage to cancer diagnoses, prognoses and treatment, the researchers say.

"The exosome profile could be useful in a number of ways -- to help detect cancer early, to predict the aggressiveness of a patient's tumor and response to chemotherapy or other treatments, and to understand the risk of cancer recurrence or spread before traditional methods would be able to," says Dr. David C. Lyden, the Stavros S. Niarchos Associate Professor in Pediatric Cardiology, associate professor of Pediatrics and Cell and Developmental Biology at Weill Cornell Medical College and a pediatric neuro-oncologist at Memorial Sloan-Kettering Cancer Center.

"We believe each tumor type will have its own exosomal protein profile that will represent each tumor subtype," says Dr. Jacqueline F. Bromberg, an associate attending physician at Memorial Sloan-Kettering Cancer Center and associate professor of Medicine at Weill Cornell, who studies breast cancer. "The exosomal proteins will be useful for prognosis in predicting which patients, including those who develop disease decades after their original diagnosis, will likely be at risk for future metastatic disease."

Dr. Lyden and Dr. Bromberg are the study's co-senior authors.

The study's lead author, Dr. Hector Peinado, instructor of molecular biology in the Department of Pediatrics at Weill Cornell Medical College, says the study suggests that effective cancer treatment must be multi-layered. "If, in the future, we were able to find a way to control the 'education' of bone marrow cells, as well as the release and content of tumor exosomes in cancer patients, we would be able to curtail and reduce the spread of cancer, and improve the patient's quality of life and survival," he says.

Not Just Trash Bags

Dr. Lyden and his colleagues have long been trying to decode the biochemical processes that produce the "pre-metastatic niche" -- the

sites in distant organs that are primed to provide a nurturing home for cells that spread from a primary tumor. He and his colleagues were first to identify that bone marrow-derived cells (BMDCs) were found to be crucial to formation of this niche. In this study they sought to understand the signals that prompt BMDCs to do their work at the niche. They looked at exosomes, microvesicles secreted by all cells, which were long thought to be just cellular trash bags to dump used proteins. Recently, however, exosomes were found to contain RNA, including nucleic acids found in cancer cells. Interest in exosomes increased due to their obvious diagnostic potential.

The researchers were interested to see if the exosomes budding off of melanoma actually participated in the course of the cancer -- and they found that they do, and to a great extent.

"Upon their release from the primary tumor, exosomes derived from melanoma cells fuse with cells in distant metastatic organs and lymph nodes, mediating vascular leakiness and inflammation, thereby promoting the formation of pre-metastatic niches that enhance future metastatic growth," Dr. Lyden says.

According to Dr. Peinado, a number of exosomal proteins are transferred by the exosomes to BMDCs where they can reprogram or "educate" the cells to participate in the metastatic cascade. "We found an oncogenic protein, called MET, that is produced by highly metastatic tumors and packaged into pro-metastatic exosomes. The tumor exosomes circulate, fuse and transfer their information, including the MET oncoprotein, to many cells, such as bone marrow cells, which in turn promote a pro-metastatic phenotype," he says.

They also discovered that the education of BMDCs by exosomes is long-lasting, and this may explain how a tumor dormant for decades suddenly develops metastatic disease. These findings are crucial, says Dr.

Bromberg, because "educated bone marrow is the key in disease recurrence and may even foster a future secondary cancer."

Examining human blood samples, the scientists found a distinct signature of exosomal proteins (including MET) in patients with stage IV, widely metastatic melanoma that was not found in blood exosomes from patients with non-metastatic melanoma.

They say this protein signature could be used to predict which patients with stage III disease and local lymph node metastasis would then go on to develop distant metastatic disease. "Treatment modalities could be initiated earlier in these high-risk patients to prevent disease progression," Dr. Lyden says. "Our results demonstrated that MET oncoprotein expression, which can be easily analyzed in a simple blood test, could be used as a new marker of metastatic disease in melanoma patients."

The researchers then discovered two ways to reduce exosomal-induced metastasis. One way was to target the protein, Rab27a, responsible for production of exosomes. Another was to proactively educate BMDCs using exosomes spawned from melanoma cells that rarely metastasize.

"We have found that less or non-metastatic exosomal proteins may educate bone marrow cells not to avoid partaking in the metastatic process," says Dr. Lyden. "We are working on determining which particular exosomal proteins may be responsible for preventing metastatic participation.

"This concept may one day be applied to the clinic, where non-metastatic exosome proteins may help prevent the acceleration of tumor growth and metastatic disease, allowing patients with cancer to live longer lives," he says.

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