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Crucial molecule that involved in spread of breast cancer found

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Researchers at Albert Einstein College of Medicine of Yeshiva University have identified a key player in the spread of breast cancer. The findings, published today in the online edition of Nature, identify a critical molecule that helps cancer spread beyond the primary tumor. The research highlights a potential new strategy against metastatic disease. The study's senior author is Jeffrey Pollard, Ph.D., professor of developmental and molecular biology and of obstetrics & gynecology and women's health at Einstein. He also holds the Louis Goldstein Swan Chair in Women's Cancer Research and is the deputy director of the Albert Einstein Cancer Center.

People rarely die from their primary (original) tumor. Instead, most cancer deaths occur because the cancer has spread, or metastasized, to other parts of the body. "By focusing on sites where cancer had spread, we were able to detect a molecule that stimulates metastasis," said Dr. Pollard. "This raises the possibility that metastasis could be kept from progressing – or even prevented – if the stimulating molecule could be blocked. This we achieved in mouse models of breast cancer."

Metastasis begins when cells break away from the primary tumor and gain the ability to move on their own. These cells invade nearby blood vessels (a process known as intravasation) and are carried by the bloodstream to other parts of the body. The bloodborne tumor cells then escape from vessels in a process known as extravasation. Once these tumor cells escape from the vessels, they seed new and deadly tumors that grow in these distant locations.

In previous studies, Dr. Pollard and his research team have shown that macrophages – immune system cells whose functions include fighting infections – actually promote the spread of cancer. His research has shown that macrophages not only assist tumor cells during both intravasation and extravasation but also help those wayward cells take root in their new locations and grow into metastatic tumors. In the current study, Dr. Pollard and colleagues investigated the process by which these macrophages are recruited to metastatic sites and subsequently promote tumor-cell extravasation, seeding and tumor growth.

Using models of human and mouse breast cancer, the researchers demonstrated that when breast tumor cells travel to the lung, these cells secrete CCL2, a chemokine molecule (i.e., one that attracts cells). CCL2 attracts immune cells called inflammatory monocytes -- in particular, those bearing receptors for CCL2, which then develop into macrophages. The monocytes and macrophages "invited" by CCL2 signaling then facilitate extravasation – the critical step in metastasis in which bloodborne tumor cells cross the vessel wall and implant in nearby tissue. One way monocytes help tumor cells escape from blood vessels and cause metastasis, the Einstein researchers found, is by secreting vascular endothelial growth factor, or VEGF, a substance that makes blood vessels leaky at the site where tumor cells exit from them.

Once the tumor cells are seeded, inflammatory monocytes continue to flock to the metastatic site – now attracted by CCL2 secreted not only by the tumor cells but also by nearby lung tissue that the tumor cells have targeted. In turn, these continuously recruited monocytes and the resultant macrophages promote the growth of the emerging metastatic tumor.

To confirm their findings, the researchers used anti-CCL2 antibodies to suppress CCL2 signaling in a mouse model of human metastasis – with

striking results. In lungs challenged with metastatic tumor cells, the anti-CCL2 antibodies inhibited the influx of inflammatory monocotyes and macrophages to the metastatic sites, and the number of metastatic sites that developed in the lungs was markedly reduced. In addition, the mice lived much longer when CCL2 signaling was blocked.

"These findings have potential implications for therapy, since in human breast cancer we know that CCL2 expression and macrophage infiltration are associated with poor prognosis and metastatic disease," said Dr. Pollard. "If we can develop ways to inhibit these processes, we might be able to slow or stop breast cancer from spreading."

More information: "CCL2 recruits inflammatory monocytes to facilitate breast tumor metastasis" *Nature* (2011).

Provided by Albert Einstein College of Medicine