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# How breast cancer spreads: Researchers find key to lymph node metastasis in mice

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The invasion of cancer cells into the lymph vessels that connect the breast to surrounding lymph nodes is the first step leading to the metastasis, or spread, of cancer throughout the body. Metastasis is the primary cause of breast cancer deaths. Surprisingly little is known about the control of this process and how it might be interrupted to prolong the lives of women with breast cancer. In a study to be reported Sept. 10 in the *Proceedings of the National Academy of Sciences* Online Early Edition, researchers at Johns Hopkins describe their discovery of how a protein responsible for cell survival in low oxygen can trigger the spread of cancer cells into the lymphatic system in a mouse model of breast cancer.

The researchers knew that like all solid tumor cancers, breast cancer cells can grow so densely that they end up starved for oxygen. To survive, cancer cells trigger the growth of new blood vessels by activating a protein called hypoxia-inducible factor 1, or HIF-1. "We've known that increased levels of HIF-1 are associated with increased tumor vessels and with patient mortality," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Medicine, director of the vascular program at Hopkins' Institute for Cell Engineering and a member of the McKusick-Nathans Institute of Genetic Medicine. "Now we've found that HIF-1 activity is directly responsible for the spread of breast cancer to the lymph vessels."

Working in mice injected with human breast cancer cells, which when left undisturbed grow into tumors that spread from the breast to the

lungs, Semenza's team previously found that interfering with HIF-1 in these mice reduced growth of the primary tumor and prevented metastasis through blood vessels to the lung. "So of course we wanted to see whether blocking HIF-1 could affect lymph node metastasis as well," he says.

In new experiments, they injected mice with human breast cancer cells that were genetically engineered to knock down HIF-1 protein levels and, after 24 days, examined the mouse lymph nodes to see if the human breast cancer cells had spread. They found that compared to mice whose HIF-1 levels were left undisturbed, lymph nodes with knocked-down HIF-1 contained 76 percent fewer human breast cancer cells, supporting the idea that HIF-1 is somehow involved in the spread of breast cancer to lymph nodes.

To better understand how HIF-1 triggers this to happen, Semenza's team then starved human breast cancer cells of oxygen to see which of the genes involved in the growth of lymphatic vessels might respond to HIF-1. They found that the platelet-derived growth factor B gene —PDGF-B—was five times more active when oxygen was lacking. A closer look at the DNA sequence around the PDGF-B gene showed regions of DNA known to be recognized and bound by the HIF-1 protein. They tested this in cells and found that, indeed, HIF-1 protein binds to the PDGF-B gene and turns it on.

The team then took a closer look at PDGF-B to find out how it works once the gene is turned on. They found that PDGF-B that is made by breast cancer cells is pumped out of the cell and stimulates the growth of lymph vessels.

Treating the mice with either digoxin, which blocks HIF-1 activity, or imatinib, a cancer drug, reduced tumor size by 78 percent and reduced lymph node metastasis by 94 percent, although the researchers

emphasized that more work must be done to determine whether these drugs will be effective in treating breast cancer patients.

"We're very excited by these results, having shown for the first time that HIFs are directly involved in the lymphatic metastasis of breast cancer," says Semenza. "These results provide experimental support for breast cancer clinical trials that target HIF-1 or PDGF-B." The first study of digoxin in women with breast cancer at the Johns Hopkins Oncology Center will begin later this year.

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