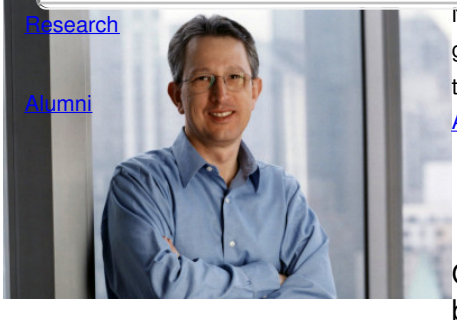
Genes Found to Play a Role in Breast Cancer's Spread to the Brain



Joan Massagué

New research led by investigators at Memorial Sloan Kettering Cancer Center (MSKCC) identifies three genes that specifically mediate the metastasis, or spread, of breast cancer to the brain and illuminates the mechanisms by which this spread occurs. The study was published online today in *Nature*. [PubMed Abstract]

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Joan Massagué, PhD, Chair of the Cancer Biology and Genetics Program at MSKCC

According to the study, COX2 and HB-EGF — genes that induce cancer cell mobility and invasiveness — were found to be genetic mediators in the spread of breast cancer to the brain. A third gene, ST6GALNAC5, was shown to provide cancer cells with the capability of exiting the blood circulation and passing through the blood-brain barrier to enter the brain tissue.

“Our research sheds light on the role these genes play in determining how breast tumor cells break free and, once mobile, how they decide where to attack,” said Joan Massagué, PhD , Chair of the Cancer Biology and Genetics Program at MSKCC and a Howard Hughes Medical Institute investigato

Breast cancer metastasis to the brain typically occurs years after removal of a breast tumor, suggesting that disseminated cancer cells initially lack the specialized functions needed to overtake the dense network of capillaries that constitute the blood-brain barrier. This barrier prevents the entry of circulating cells and regulates the transport of molecules into the brain tissue. To generate brain metastasis, circulating cancer cells must, therefore, be able to pass through the blood-brain barrier and interact with the brain microenvironment.

In the study, Dr. Massagué and his colleagues isolated cancer cells that preferentially targeted the brain from patients with advanced disease. By combining this approach with gene expression profiling, additional testing in mouse model systems, and analysis of a body of clinical data, the investigators identified certain genes and functions that selectively mediate cancer cell passage through the blood-brain barrier.

The authors observed that ST6GALNAC5, an enzyme that is normally active only in brain tissue, causes a chemical reaction that creates a coating on the surface of breast cancer cells that enhances their ability to breach the blood-brain barrier. Their findings show that breast cancer cells use this brain-specific cell-coating enzyme as a means of infiltrating the brain.

“Our results draw attention to the role of the cell surface coating as a previously unrecognized participant in brain metastasis, and to the possibility of using drugs to disrupt its interactions,” said Dr. Massagué. “Further study is necessary to explore the role of these genes in brain metastasis and their interest as therapeutic targets.”

The study authors also noted that COX2 and HB-EGF, which prime breast cancer cells for entrance into the brain, had previously been found to be involved in breast cancer’s spread to the lung. This suggests a partial sharing of genetic mediators of metastasis to both the brain and lung and may explain the association of brain and lung relapse in women with breast cancer.

Metastasis is responsible for the majority of all cancer deaths and occurs when tumor cells acquire the ability to escape their original location and invade

healthy tissue and organs elsewhere in the body. According to the National Cancer Institute , 170,000 new cases of cancer metastasis to the brain are diagnosed each year in the United States alone. The incidence of brain metastases is rising as a result of their resistance to treatments that are effective against cancer spread to other sites.

Researchers from the University of Chicago and the following institutions in The Netherlands contributed to this research: Academic Medical Center, Amsterdam; Erasmus Medical College, Rotterdam; Josephine Nefkens Institute, Rotterdam; and Cancer Genomics Centre, Rotterdam.

The work was supported by grants from the National Institutes of Health, the Alan and Sandra Gerry Metastasis Research Initiative, the Kleberg Foundation, the Hearst Foundation, and the Netherlands Genomics Initiative/Netherlands Organization for Scientific Research.