

WISTAR RESEARCHERS IDENTIFY GENE THAT REGULATES BREAST CANCER METASTASIS

Available on-line at http://www.wistar.org/news_info/pressreleases/pr_10.05.09.htm

PHILADELPHIA – (October 5, 2009) – Researchers at The Wistar Institute have identified a key gene (KLF17) involved in the spread of breast cancer throughout the body. They also demonstrated that expression of KLF17 together with another gene (Id1) known to regulate breast cancer metastasis accurately predicts whether the disease will spread to the lymph nodes. Previously, the function of KLF17 had been unknown.

Deaths of most breast-cancer patients are the result of metastasis, a complex, multi-step, and poorly understood process. “Identifying the gene that suppresses the spread of tumor cells and the mechanisms by which this suppression occurs can lead to the discovery of new markers of metastasis and potential targets for cancer prevention and treatment,” says Qihong Huang, M.D., Ph.D., assistant professor at The Wistar Institute and senior author of the study.

In this study, which appears in the October on-line issue of *Nature Cell Biology*, Huang and colleagues introduced a genetic screen targeting 40,000 mouse genes into mammary tumor cells that do not usually spread, and then transplanted those cells to the mammary fat pads in mice where they would be expected to remain. Through RNA interference (RNAi) technology, they then reduced the expression of a metastasis-suppressor gene in five mice, one of which developed lung metastases in seven weeks. RNA retrieved from the metastasized cells corresponded to KLF17.

To determine whether KLF17 played a similar role in human breast-cancer metastasis, the researchers knocked down KLF17 expression in a tagged human-breast-cancer cell line and then transplanted these cells—along with a control group still expressing KLF17—into mammary fat pads of mice. Within eight to 10 weeks, lung metastases developed in the KLF17-deficient cells, whereas the control cell set did not metastasize, demonstrating that knockdown of KLF17 expression also promotes the spread of human breast-cancer cells.

The researchers also were interested specifically in genes whose expression were increased in KLF17 knockdown cells but decreased in KLF17 overexpressing cells or vice versa. In collaboration with Professor Louise C. Showe, Ph.D. at the Wistar Institute, they found the significant genes that met these criteria. Among them, the gene Id1 was found to be up-regulated in KLF17 knockdown cells and down-regulated in KLF17 overexpressing cells. Recent findings suggest that Id1 is deregulated in various types of cancers and is important in the development of embryonic stem cell-like phenotypes in cancer cells.

To further investigate the interactions of KLF17 and Id1, the Huang lab scanned a DNA segment of mouse Id1 and found two potential KLF17 binding sites. To examine the effect of Id1 upregulation in tumor metastasis in vivo, the team generated tagged mouse and human cell lines expressing mouse or human Id1, respectively. Following transplantation back into the mice, lung metastasis developed from Id1-upregulated cells but not in controls, demonstrating that Id1 expression promotes tumor metastasis in vivo.

Further characterization of KLF17 is an ongoing subject of study for Wistar researchers. “We are continuing to examine ways to activate KLF17 and the methods by which that process slows or prevents cancer metastasis,” Huang says.

The lead author on the study is Wistar’s Kiranmai Gumireddy, Ph.D. Study investigators also included Professor Louise C. Showe, Ph.D.; and Anping Li, from the Wistar Institute; Andres J. Klein-Szanto, M.D.; from Fox Chase Cancer Center; and Phyllis A. Gimotty, Ph.D., Dionyssios Katsaros, M.D., Ph.D.; George Coukos, M.D., Ph.D.; and Lin Zhang, M.D.; from the University of Pennsylvania.

The project was supported by the Breast Cancer Alliance, Pardee Foundation, V Foundation, Commonwealth Universal Research Foundation of the Pennsylvania Department of Health, the National Cancer Institute, and the Mary Kay Ash Charitable Foundation.

The Wistar Institute is an international leader in biomedical research with special expertise in cancer research and vaccine development. Founded in 1892 as the first independent nonprofit biomedical research institute in the country, Wistar has long held the prestigious Cancer Center designation from the National Cancer Institute. The Institute works actively to ensure that research advances move from the laboratory to the clinic as quickly as possible. The Wistar Institute: Today’s Discoveries – Tomorrow’s Cures. On the Web at www.wistar.org.

CONTACT: Susan Finkelstein at (215) 898-3943 or sfinkelstein@wistar.org.