MMHCC
the Mouse Models of Human Cancers Consortium

MMHCC Newsletter October 2007

MouseLine

New 'Knock-Out' Gene Model Provides Molecular Clues to Breast Cancer

CINCINNATI—New insights into the role of estrogen receptor in mammary gland development may help scientists better understand the molecular origin of breast cancer, according to new research from the University of Cincinnati (UC).

About a decade ago, U.S. scientists at the National Institutes of Health (NIH) developed a standard estrogen receptor (ER) gene knock-out mouse model to study the estrogen receptor's role in human diseases. "Unfortunately, because these mice lacked mammary glands as a consequence of genetic manipulation, using this model to study the relationship between the estrogen receptor and breast cancer proved ineffective," explains Sohaib Khan, PhD, professor of cell and cancer biology at UC.

"Knocking out the estrogen receptor gene for the entire genome, as the NIH scientists did, doesn't just affect the function of the receptor in all estrogen-responsive organs. It also creates an imbalance in the body's circulating sex hormone levels, which could affect other physiological functions," Khan adds. "An alternative model was clearly needed to study the intricacies of estrogen receptors involvement in this disease."
Estrogen receptor is a cellular protein that binds with the hormone estrogen and facilitates action in different parts of the body, including the mammary gland. Research has shown that about 70 percent of breast cancer patients have estrogen receptor-positive breast cancer, meaning their tumors will have some beneficial response to anti-estrogen drugs like tamoxifen (ta-MOX'-ee-fen, marketed as Nolvodex).

After two years of work, Khan says his team has developed a knock-out mouse model that will allow scientists to study the role of estrogen receptor in specific organs (for example, mammary glands) without affecting estrogen-signaling throughout the rest of its body.

Khan used what is called a "conditional knock-out technique" to develop a new mouse model that retains estrogen receptor in all tissues except mammary tissue, allowing scientists to study the receptor's role in breast development and breast cancer.

Using this model, Khan's team found that knocking out the gene only in mammary tissue resulted in abnormalities that compromised milk production in the nursing female. This suggests that estrogen expression is essential for normal duct development during puberty, pregnancy and lactation.

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Khan and his coworkers report the creation of this model and its potential implications in an early online edition of the *Proceedings of the National Academy of Sciences* on Sept. 4, 2007, followed by the print issue Sept. 11, 2007. The study directly refutes previous research, which suggests that estrogen receptor in epithelial cells was not essential to normal mammary gland development.

Mammary tissue is made up of two cell types—stromal cells, which give the tissue structure, and epithelial cells, which make up the lining of the mammary gland and become cancerous in the majority of breast cancers.
Unlike other organs in the body, the mammary glands develop after birth in response to increases in circulating hormones. This triggers growth of a network of branched ducts throughout the breast tissue that do not change again until a woman becomes pregnant.
"Even though the relationship between the estrogen receptor and breast cancer is well established, we still know very little about the receptor's mechanism of action," explains Khan, corresponding author of the study. "Unless we study those mechanisms more closely, improved strategies for breast cancer treatments will not be possible."
Premenopausal women with breast cancer are currently given five years of tamoxifen, a drug that blocks the estrogen receptor action in cancer cells, to prevent recurrence. Studies have shown that the drug reduces recurrence in 40 percent of the women who take it, but Khan says many women eventually develop resistance to the drug.

Using this unique mouse model, UC researchers are currently collaborating with scientists at Dana Farber Cancer Institute/Harvard Medical School to understand the relationship between estrogen-signaling and oncogene-mediated breast cancer development. Future findings from these studies could help scientists better understand the molecular origin of breast cancer and develop new drugs to more effectively treat it.

This study was funded by grants from the National Institutes of Health, U.S. Department of Defense and the UC pilot cancer grant program. Collaborators include Kay-Uwe Wagner, PhD, of the University of Nebraska, and UC colleagues Yuxin Feng and David Manka, PhD.

Source: http://healthnews.uc.edu/news/?/5431/

Publication:
Feng Y, Manka D, Wagner KU, Khan SA.
Estrogen receptor-{alpha} expression in the mammary epithelium is required for ductal and alveolar morphogenesis in mice.
Proc Natl Acad Sci U S A. 2007 Sep 11;104(37):14718-23. Epub 2007 Sep 4.
PMID: 17785410

Selected Meetings

October 17 – 18, 2007
CHI's 2nd International: Exploring Next Generation Sequencing: Applications and Case Studies
Providence, Rhode Island
Meeting Information: https://chidb.com/register/2007/sqe/reg.asp

October 17 - 20, 2007
AACR-Advances in Breast Cancer Research: Genetics, Biology and Clinical Applications
San Diego, California
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/advances-in-breast-cancer-research.aspx

October 22 – 26, 2007
AACR-NCI-EORTC International Conference
Molecular Targets and Cancer Therapeutics: Discovery, Biology and Clinical Applications
San Francisco, California
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/molecular-targets-and-cancer-therapeutics.aspx

October 23 – 27, 2007
The American Society of Human Genetics (ASHG) – 57th Annual Meeting: The Bridge Between Research and Practice
San Diego, California
Meeting Information: http://www.ashg.org/genetics/ashg/menu-annmeet.shtml

October 28 – November 1, 2007
21st International Mammalian Genome Conference
Kyoto, Japan
Meeting Information: http://www.imgc2007.com/

October 30 – November 3, 2007
Workshop on Surgical Techniques in the Laboratory Mouse
Bar Harbor, Maine
Meeting Information: http://www.jax.org/courses/events/coursedetails.do?id=454&detail=scope

Selected Meetings cont.

October 31 – November, 3, 2007
AACR-The Role of Non-Coding RNAs in Cancer
Cambridge, Massachusetts
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/the-role-of-non-coding-rnas-in-cancer.aspx

November 4 – 8, 2007
AACR-Centennial Conference: Translational Cancer Medicine: Technologies To Treatment
Singapore, Singapore
Meeting Information: http://www.pwevent.com/AACR2007/index.html

November 4 – 9, 2007
Workshop on Surgical Techniques in the Laboratory Mouse
Bar Harbor, Maine
Meeting Information: http://www.jax.org/courses/events/coursedetails.do?id=454&detail-scope

November 6 – 10, 2007
Chemotherapy Foundation Symposium XXV: Innovative Cancer Therapy for Tomorrow
New York City, New York
Meeting Information: http://www.chemotherapyfoundation.org/professional_education/index.html

November 14 – 16, 2007
Phacilitate Oncology Leaders' Forum 2007
Boston, Massachusetts
Meeting Information: http://www.phacilitate.co.uk/pages/oncology/index.html

November 14 – 17, 2007
AACR-Advances in Colon Cancer Research
Cambridge, Massachusetts
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/advances-in-colon-cancer-research.aspx

For additional meetings and information see http://emice.nci.nih.gov/emice/communication/calendar

Notices and Funding Opportunities

Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)
NOT-OD-07-088
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html

Advanced Genomic Data Analysis and Visualization Methods for the Cancer Genome Atlas (TCGA) Data (R21)
RFA-CA-08-005
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-005.html

Tools for Germplasm Cryopreservation (SBIR [R43/R44] and STTR [R41/R42])
RFA-RR-07-007 and RFA-RR-07-008
National Center for Research Resources
National Institute of Child Health and Human Development
National Institute of Environmental Health Sciences
http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-07-007.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-07-008.html

NIA Intervention Testing Program Solicits Proposals for Compounds to Test for Anti-Aging Activity in Mice
NOT-AG-07-009
National Institute on Aging
http://grants.nih.gov/grants/guide/notice-files/NOT-AG-07-009.html

Research on Malignancies in the Context of HIV/AIDS (R21 and R01)
PA-07-454 and PA-07-455
National Cancer Institute
National Institute of Dental and Craniofacial Research
http://grants.nih.gov/grants/guide/pa-files/PA-07-454.html
http://grants.nih.gov/grants/guide/pa-files/PA-07-455.html

Multidisciplinary Fellowships in Cancer Nanotechnology Research (F32 and F33)
RFA-CA-08-003
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-003.html

Bioinformatics

NCI Releases New Tool for Finding Cancer-Related Proteins

NCI recently released the Computational Proteomics Analysis System (CPAS), a new software tool for the cancer Biomedical Informatics Grid (caBIG™) that enables cancer proteomics researchers to store, analyze, and share clinical proteomics data, thus driving the discovery of cancer-related proteins for developing new diagnostic tools and therapies.

LabKey Software, in collaboration with the Fred Hutchinson Cancer Research Center, developed CPAS with funding from the NCI Clinical Proteomic Technologies Initiative for Cancer, which was launched in 2006 to help build the foundation of analytical systems, technologies, data, reagents, standards, and infrastructure to advance the understanding of protein biology in cancer and accelerate discovery research and clinical applications.

Researchers can obtain the CPAS software at https://cabig.nci.nih.gov/tools

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