New research finds trigger for breast cancer spread

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Research led by Shyamal Desai, PhD, Assistant Professor of Biochemistry and Molecular Biology at LSU Health Sciences Center New Orleans, has discovered a key change in the body's defense system that increases the potential for breast cancer to spread to other parts of the body. The results, reported for the first time, are featured in the January 2012 issue of *Experimental Biology and Medicine*.

For cancer cells shape matters. All cells contain a protein cytoskeleton that acts as a scaffold determining overall shape and function, the position of the cell within an organ or tissue, and the ability of the cell to communicate with its neighbors to prevent the uncontrolled growth typical of cancer cells. However, cell transformations that result in cancer disrupt the genetic programs of the cell and alter the cytoskeleton, leading to changes in shape, function, and cell communication that produce uncontrolled growth and metastatic spreading of the tumor. Understanding these changes to the normal genetic program of a cell and the consequences that ultimately lead to cancer have been major challenges to cancer biologists.

This research, funded by the National Institutes of Health, found that a cellular defense system called the ISG15 pathway, which is normally involved in fighting bacterial and viral infection, is triggered in breast cancer to disrupt normal cytoskeletal function and increase the possibility that the cancer cells will metastasize, or spread.

"Our findings, for the first time, causally link an alteration in the ISG15

pathway during transformation with metastatic potential," notes Dr. Shyamal Desai, Assistant Professor of Biochemistry and Molecular Biology at LSU Health Sciences Center New Orleans, "thus providing a novel therapeutic target for future drug discovery."

Cells contain a protein quality control pathway termed the Proteasome that breaks down damaged and unneeded proteins to their component amino acids for recycling. Such proteins are marked for degradation by flagging them with a small protein called Ubiquitin, which is then recognized by the Proteasome. Alterations in the genetic program that controls the Ubiquitin/Proteasome system have been known for some time to cause cell transformation and cancer. More recently, Dr. Desai and her colleagues have demonstrated that, unlike normal cells, transformed cancer cells produce increased amounts of a related control system that marks proteins with another small protein called ISG15.

Previous research reports that the amount of ISG15 is increased in high-grade compared with low-grade cancers. The ISG15 system is normally activated by interferon and is part of an ancient cellular immune response designed to counter bacterial and viral infection. By a still unidentified mechanism, cancer cell transformation activates the ISG15 pathway. Dr. Desai and colleagues have previously reported that activation of the ISG15 system interferes with function of the Ubiquitin/Proteasome pathway. In their latest work, Dr. Desai and colleagues show that several key proteins that regulate cell movement, invasion, and metastasis are blocked from Proteasome degradation by the ISG15 system and that genetic manipulation to inhibit this pathway reverses cancer cell transformation, suggesting an approach to blocking cancer progression.

Arthur Haas, PhD, the Roland Coulson Professor and Chairman of Biochemistry and Molecular Biology at LSU Health Sciences Center New Orleans, discovered the ISG15 pathway and co-discovered the

Ubiquitin/Proteasome system that was awarded the 2004 Nobel Prize in Chemistry. "These results provide a functional link between the Ubiquitin and ISG15 pathways that reveals how small cell alterations can yield large overall consequences for cell transformation."

The research team also included Arthur Haas, PhD, and Dr. Desai's lab members Ryan Reed, Surendran Sankar, PhD, and Julian Burks in the LSUHSC Department of Biochemistry and Molecular Biology, Jerome Breslin, PhD, in the LSUHSC Department of Physiology, and Ashok Pullikuth, PhD, in the LSUHSC Department Pharmacology, as well as scientists at the UMDNJ-Robert Wood Johnson Medical School in New Jersey, and the University of Pennsylvania School of Medicine in Philadelphia.

"Although this current project focused on breast cancer, ISG15 is also elevated in a variety of cancers," concludes Dr. Desai. "Therefore, this discovery has important implications in other cancers as well."

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