# LIFR protein suppresses breast cancer metastasis

September 25 2012

A receptor protein suppresses local invasion and metastasis of breast cancer cells, the most lethal aspect of the disease, according to a research team headed by scientists from The University of Texas MD Anderson Cancer Center.

Reporting in *Nature Medicine*, the team described using high-throughput RNA sequencing to identify the leukemia inhibitory factor receptor (LIFR) as a novel suppressor of breast cancer metastasis, the spread of the disease to other organs.

"Based on our findings, we propose that restoring the expression or the function of key metastasis suppressors like LIFR could be used to block breast cancer metastasis," said lead investigator Li Ma, Ph.D., assistant professor in MD Anderson's Department of Experimental Radiation Oncology.

"Lack of clinically proven prognostic markers and therapeutic agents for metastasis are major barriers for eradicating breast cancer deaths," Ma said. "Although many metastasis-promoting genes have been identified, they have not been translated into clinical practice. The exceptions are the HER2- and VEGF-targeting agents, which have shown measurable but moderate benefit in the clinic."

Only a few genes have been established as metastasis suppressors, Ma said, and many researchers believe that such genes play only a minor role in metastasis.

The investigators in this study, however, found that LIFR is "highly relevant in human tumors." While 94 percent of normal human breast tissues show high LIFR expression, LIFR is downregulated or lost in a significant fraction of patients with ductal carcinoma in situ (DCIS) or invasive breast cancer, and loss of LIFR closely correlates with poor clinical outcomes.

## Protein works by activating Hippo cascade to throttle YAP

Ma said one of the major findings of the study is that LIFR suppresses both the invasion and colonization steps of metastasis by activating the Hippo kinase cascade that leads to functional inactivation of the transcriptional co-activator YAP.

"The LIFR protein is highly relevant in human cancer because it is down-regulated in about 40 percent of human breast cancers and completely lost in nearly 10 percent," Ma said. "Remarkably, in our study of approximately 1,000 patients, we found that loss of the LIFR protein in non-metastatic stages I to III breast tumors is highly associated with poor metastasis-free, recurrence-free and overall survival outcomes."

Ma noted that this work was regarded by peer reviewers as "a ground-breaking contribution" because it:

- Challenges the dogma that metastasis-suppressor genes are only a small component of metastasis compared with metastasis-promoting genes;
- Is the first report of a cell membrane receptor that activates Hippo signaling and has a critical function in cancer; and
- Might have a significant impact on clinical practice.

Ma said information about LIFR in cancer in the literature is very scarce. But some small studies have reported that LIFR is also lost in colon cancer and liver cancer through a gene-silencing mechanism called hypermethylation.

"There are many directions of research that should be pursued," Ma said. "For example, in order to develop LIFR-based methods of treatment, we must further understand the mechanism of its function and regulation of its expression."

Ma added that her group is generating LIFR conditional knockout mice to determine whether genetic deletion of LIFR in the breast will lead to tumorigenesis and metastasis.

Provided by University of Texas M. D. Anderson Cancer Center