MiRNA-21 linked to tumor suppressor loss, herceptin resistance

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Overexpression of a specific type of microRNA can derail treatment by disabling an important molecular brake on breast cancer cell proliferation, according to evidence presented by researchers from The University of Texas M. D. Anderson Cancer Center at the American Association for Cancer Research 101st Annual Meeting 2010.

The study showed that MiRNA-21 interferes with trastuzumab (Herceptin®) therapy by blocking the phosphates and tensing homolog gene known as PTEN.

"PTEN acts as a tumor suppressor and is involved in regulating cell proliferation and death," said Sumaiyah K. Rehman, first author of the study and a graduate research assistant in the Department of Molecular and Cellular Oncology at M. D. Anderson. "When it is expressed normally, cells proliferate more slowly and senesce, or stop growing."

Mutations in the PTEN gene play a role in many types of cancer and influence both the development of breast cancers and their response to treatment.

"We know that there are signaling pathways in cancer cells that drive malignancy and progression," said senior author Dihua Yu, M.D., Ph.D., professor and deputy chair of the Department of Molecular and Cellular Oncology. "PTEN acts as a brake on those monogenic signaling pathways, and PTEN loss has been found in about 40 percent of breast cancers. So it is well-documented that PTEN loss is correlated with a

poor clinical outcome in breast cancer patients."

Interfering with a targeted therapy

MicroRNAs (MiRNA) are snippets of RNA that influence gene expression by targeting specific messenger RNAs (mRNA). mRNAs are responsible for ensuring that proteins and their products are produced correctly, and interference from miRNAs can disrupt or alter this normal protein production.

"MiRNAs are molecules that exist in our cells and regulate a variety of physiological functions," said Rehman, who also is a graduate student at The University of Texas Graduate School of Biomedical Sciences at Houston (GSBS). "MiRNA regulation is disrupted in most diseases and in all cancers." Altered expression of miRNA also has been linked to the development of resistance to chemotherapy drugs such as cisplatin.

The researchers suspected that overexpression of miRNA-21 leads to reduced levels of PTEN and, in turn, to resistance to Herceptin. Herceptin is a targeted therapy used to treat metastatic breast cancer. Like other targeted cancer treatments, Herceptin homes in on a specific abnormal gene to slow or shut down cancer growth. The target gene in Herceptin treatment is ErbB-2-also known as HER2/neu or HER2.

"Herceptin is the most successful example of targeted cancer therapy," Yu noted. "But only about one-third of patients benefit from this therapy as a single agent." PTEN loss is a key reason.

MiRNA-21's role in Herceptin resistance

The hypothesis was tested in three HER2-overexpressing breast cancer cell lines. In a series of experiments, miRNA-21 and/or a control

miRNA were introduced and expressed in the HER2-overexpressing cell lines. The cells were then treated with Herceptin. The researchers found that cells with higher levels of miRNA-21 had reduced PTEN expression and were significantly more resistant to the drug than were the control cells.

The researchers also determined that miRNA-21 reduces PTEN expression by inhibiting PTEN messenger RNA at a specific site in the PTEN transcript in breast cancer cells.

In another experiment, when the researchers downregulated miRNA-21 in high HER2-expressing cells, cellular PTEN levels rose, and the cells became more sensitive to Herceptin compared to control miRNA cells.

The researchers then sought to determine the clinical relevance of their findings by measuring levels of miRNA-21 in tumor samples from patients with HER2-positive breast cancer treated with Herceptin. They found a significant correlation between high levels of miRNA-21 and poor patient response to Herceptin, as well as a correlation between elevated miRNA-21 and disease progression.

Rehman also observed that patients with low tumor levels of miRNA-21 tend to experience either a partial response to Herceptin or stable disease.

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