The stress and cancer link: 'Master switch' stress gene enables cancer's spread

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In an unexpected finding, scientists have linked the activation of a stress gene in immune-system cells to the spread of breast cancer to other parts of the body.

Researchers say the study suggests this gene, called ATF3, may be the crucial link between stress and cancer, including the major cause of cancer death – its spread, or metastasis. Previous public health studies have shown that stress is a risk factor for cancer.

Researchers already know that ATF3 is activated, or expressed, in response to stressful conditions in all types of cells. Under typical circumstances, turning on ATF3 can actually cause normal and benign cells to commit suicide if the cells decide that the stressors, such as irradiation and a lack of oxygen, have irrevocably damaged the cells.

This research suggests, however, that cancer cells somehow coax immune-system cells that have been recruited to the site of a tumor to express ATF3. Though it's still unclear how, ATF3 promotes the immune cells to act erratically and give cancer an escape route from a tumor to other areas of the body.

"It's like what Pogo said: 'We have met the enemy, and he is us,'" said Tsonwin Hai, professor of molecular and cellular biochemistry at The Ohio State University and senior author of the study. "If your body does not help cancer cells, they cannot spread as far. So really, the rest of the cells in the body help cancer cells to move, to set up shop at distant sites. And one of the unifying themes here is stress."

Hai and colleagues first linked the expression of the ATF3 gene in immune-system cells to worse outcomes among a sample of almost 300 breast-cancer patients. They followed with animal studies and found that mice lacking the ATF3 gene had less extensive metastasis of breast cancer to their lungs than did normal mice that could activate ATF3.

This stress gene could one day function as a drug target to combat cancer metastasis if additional studies bear out these results, Hai said. In the meantime, she said the results provide important insights into how cells in a tumor use their signaling power to coopt the rest of the body into aiding cancer's survival and movement to distant organs.

The research is published in a recent issue of the *Journal of Clinical Investigation*.

Hai, a member in the Ohio State University Comprehensive Cancer Center, has studied ATF3 in cancer cells for years. When she had a chance to examine human samples from about 300 breast-cancer patients, she was stunned to find that the expression of ATF3 gene in certain immune-system cells was associated with worse cancer outcomes in this group of patients. ATF3 in cancer cells showed no such association.

To test that clinical data, she and colleagues conducted two rounds of studies in mice. The researchers first injected breast cancer cells into two groups: normal mice and mice that cannot express ATF3 in any cells. The cancer in normal mice metastasized to the lungs far more rapidly and extensively than did cancer in the mice lacking ATF3. In the second round of experiments, they used genetically altered mice that could not express ATF3 in a group of immune system cells called myeloid cells, and the results were similar.

"The cancer cells were always the same, but we had different hosts. The primary tumors were similar in size, but only in the host that can express ATF3 – the stress gene – did the cancer cells metastasize efficiently," Hai said. "This suggests that the host stress response can help cancer to metastasize.

"If the body is in perfect balance, there isn't much of a problem. When the body gets stressed, that changes the immune system. And the immune system is a double-edged sword," she said.

In general, when cancer cells first appear, the immune system recognizes them as foreign and various immune cells travel to the site to attack them. Early on in cancer's development, this process typically works.

But as cancer cells grow and thrive in a tumor, they send out certain molecular messengers to promote a chronic wound-healing response. Cancer cells, by acting like a wound that never heals, hijack this process to help themselves survive and spread.

"ATF3 induction in immune cells is one way this probably happens. We're not saying it's the only way," Hai said.

ATF3 is a master switch type of gene: Its gene product, the ATF3 protein, turns on and off other genes. Knowing this, the researchers analyzed the genes that are controlled by ATF3 using a genome-wide global approach. Combining this set of data with another set of data from human samples, Hai and colleagues were able to identify an ATF3 gene signature that can predict whether cancer patients had a low or high risk of dying.

"Since our global gene analysis was carried out using samples from mouse models, our ability to identify a gene signature to partition patients into high risk or low risk suggests that our mouse model has relevance to human breast cancer," she said.

Though the work suggests a drug to dampen ATF3's effect could lower the risk for metastasis, Hai noted that scientists don't fully understand what the overall effects of that dampening would be.

"We have this gene for a reason. It's a gene that helps us adapt to changes. So it's a question of how and when to target ATF3," she said.

There are lots of ways to turn on ATF3 in cells, and stress signals sent out by cancer cells represent just one method to express this gene in immune-system cells and produce a chronic would-healing response. Other ways include radiation, chemotherapeutic agents, a high-fat diet, UV damage and even chronic behavioral stress.

Hai plans to test whether these other kinds of stressors also affect the immune cells through ATF3 induction, changing them from attacking cancer cells to helping cancer cells.

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