Stress accelerates breast cancer progression in mice: study

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Chronic stress acts as a sort of fertilizer that feeds breast cancer progression, significantly accelerating the spread of disease in animal models, researchers at UCLA's Jonsson Comprehensive Cancer Center have found.

Researchers discovered that stress is biologically reprogramming the immune cells that are trying to fight the cancer, transforming them instead from soldiers protecting the body against disease into aiders and abettors. The study found a 30-fold increase in cancer spread throughout the bodies of stressed mice compared to those that were not stressed.

It's long been thought that stress fuels cancer growth in humans. This study provides a model that not only demonstrates that stress can speed up cancer progression, but also details the pathway used to change the biology of immune cells that inadvertently promote the spread of cancer to distant organs, where it is much harder to treat.

The study appears in the Sept. 15, 2010 issue of the peer-reviewed journal Cancer Research.

"What we showed for the first time is that chronic stress causes cancer cells to escape from the primary tumor and colonize distant organs," said Erica Sloan, a Jonsson Cancer Center scientist, first author of the study and a researcher with the Cousins Center for Psychoneuroimmunology. "We not only showed that this happens, but we showed how stress talks to the tumor and helps it to spread."

In addition to documenting the effects of stress on cancer metastasis, the researchers were also able to block those effects by treating stressed animals with drugs that block the nervous system's reprogramming of the metastasis-promoting immune cells, called macrophages.

Beta blockers, used in this study to shut down the stress pathways in the mice, are currently being examined in several large breast cancer databases for their role in potential prevention of recurrence and cancer spread, said Dr. Patricia Ganz, director of cancer prevention and control research at UCLA's Jonsson Comprehensive Cancer Center. If preliminary findings indicate benefit, early phase clinical trials are being considered at the Jonsson Cancer Center testing beta blockers as a means of preventing breast cancer recurrence. Other healthy lifestyle behaviors may also influence the biological pathways described in the study, such as exercise and stress reduction techniques.

"We're going to be focusing on younger women, because they may have a multitude of things weighing on them when they're diagnosed with breast cancer. Younger women have more significant life demands and typically are under more stress," Ganz said.

Ganz said her proposed research will focus on "host factors," or things affecting the patient, that may be aiding the cancer progression and could help explain why a group of patients with the same type and stage of disease have varying rates of recurrence and cancer spread.

"This study provides evidence for a biological relationship between stress and cancer progression and identifies targets for intervention in the host environment," Ganz said. "Because of this study, we may be able to say to a patient in the future that if you follow this exercise regimen, meditative practice or take this pill every day it will help prevent recurrence of your cancer. We can now test these potential interventions in the animal model and move those that are effective into

the clinic."

In Sloan's study, mice with breast cancer were divided into two groups. One group of mice was confined in a small area for a short period of time every day for two weeks, while the other group was not. The breast cancer cells were genetically engineered to include the luciferase gene, which is the molecule that makes a firefly glow. The growth and spread of the cancer in the mice was monitored using sensitive cameras that can pick up the luciferase signal and allowed Sloan and her team to observe both the development of primary tumors and the spread of metastases throughout the body, said Steven Cole, an associate professor of hematology/oncology, a Jonsson Cancer Center researcher and senior author of the study.

What was interesting, Cole said, was that the primary tumors did not seem to be affected by stress and grew similarly in both groups of mice. However, the stressed animals showed significantly more metastases throughout the body than did the control group. The cancer, in effect, acted differently in the stressed mice.

"This study is not saying that stress causes cancer, but it does show that stress can help support cancer once it has developed," Cole said. "Stress helps the cancer climb over the fence and get out into the big, wide world of the rest of the body."

Cole said Sloan detailed the biology of the stress-induced changes in the cancer cells along every step of the pathway, providing a road map by which stress promotes cancer metastasis. Additionally, she proved that using beta blockers in stressed mice prevented the same cancer progression seen in the stressed mice that did not receive medication.

When cancer occurs, the immune system sends out macrophages to try to repair the tissue damage caused by uncontrolled growth of cancer cells.

The macrophages, in an attempt to help, turn on inflammation genes that are part of the normal immune response to injury. However, the cancer cells feed on the growth factors involved in a normal immune response. Blood vessels that are grown to aid healing instead feed the cancer the oxygen and nutrients it needs to grow and spread, and the extra cellular matrix, which provides structural support for normal cells, is attacked during the immune response, In Sloan's study, mice with breast cancer were divided into two groups. One group of mice was confined in a small area for a short period of time every day for two weeks, while the other group was not. helping the cancer cells escape from the primary tumor and spread to distant parts of the body.

"Many of the genes that promote cancer metastasis get turned on during the immune response by macrophages," Cole said. "This study shows that stress signaling from the sympathetic nervous system enhances the recruitment of macrophages into the primary tumor, and increases their expression of immune response genes that inadvertently facilitate the escape of cancer cells into other parts of the body."

Sloan showed that the beta blockers prevented the macrophages from hearing the signals sent by the sympathetic nervous system, and stopped them from infiltrating the tumor and encouraging cancer spread.

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