1. Kopie Internetseite Nature (Link: http://www.nature.com/nm/journal/v12/n8/abs/nm1447.html)

2. Kopie Internetseite Universität von Texas (Link: http://www.mdanderson.org/departments/newsroom/display.cfm?id=C7DCFA78-2762-4C92-8381B0EAC873E500&method=displayFull&pn=9cd50d60-76be-11d4-aec300508bdcce3a)

3. Kopie Internetseite Universität von Texas (Link: http://www.cancerwise.org/september_2006/display.cfm?id=946DFEE0-5759-4410-860A464596909DC4&method=displayFull&color=red)

Letter *Nature Medicine* - **12**, 939 - 944 (2006)
Published online: 23 July 2006; | doi:10.1038/nm1447

1. Kopie Internetseite Nature

Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma

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Stress can alter immunological, neurochemical and endocrinological functions, but its role in cancer progression is not well understood. Here, we show that chronic behavioral stress results in higher levels of tissue catecholamines, greater tumor burden and more invasive growth of ovarian carcinoma cells in an orthotopic mouse model. These effects are mediated primarily through activation of the tumor cell cyclic AMP (cAMP)–protein kinase A (PKA) signaling pathway by the β$_2$ adrenergic receptor (encoded by *ADRB2*). Tumors in stressed animals showed markedly increased vascularization and enhanced expression of VEGF, MMP2 and MMP9, and we found that angiogenic processes mediated the effects of stress on tumor growth *in vivo*. These data identify β-adrenergic activation of the cAMP–PKA signaling pathway as a major mechanism by which behavioral stress can enhance tumor angiogenesis *in vivo* and thereby promote malignant cell growth. These data also suggest that blocking ADRB-mediated angiogenesis could have therapeutic implications for the management of ovarian cancer.

2. Kopie Internetseite Universität von Texas

Preclinical Study Shows Chronic Stress Agitates Ovarian Cancer; Reducing Stress Slows Tumor Growth

M. D. Anderson News Release 07/23/06

When mice with ovarian cancer are stressed, their tumors grow and spread more quickly, but that effect can be blocked using a medication commonly prescribed for heart disease, according to a preclinical study by researchers at The University of Texas M. D. Anderson Cancer Center.

The finding, published in the journal Nature Medicine, now available on-line, provides the first measurable link between psychological stress and the biological processes that make ovarian tumors grow and spread. Specifically, the researchers showed that stress hormones bind to receptors directly on tumor cells and, in turn, stimulate new blood vessel growth and other factors that lead to faster and more aggressive tumors.

“This study provides a new understanding of how chronic stress and stress factors drive tumor growth,” says Anil Sood, M.D., associate professor of gynecologic oncology and cancer biology and director of ovarian cancer research.

In fact, when the researchers blocked the stress hormone receptors in their experimental system using a heart disease drug called propranolol, also known as a “beta blocker,” they were able to stop the negative effects of stress on tumor growth. The researchers used the beta blocker because the same hormone receptors, called beta adrenergic receptors, are found in the heart and normally work to maintain blood flow.

“The concept of stress hormone receptors directly driving cancer growth is very new,” says Sood, the study’s senior author. “Not much had been known about how often these receptors are expressed in cancer, and more importantly, whether they had any functional significance. Our research opens a new area of investigation.”

The research began when Sood and his colleague Susan Lutgendorf found an association between ovarian cancer patients who reported high levels of stress in their lives and an increase in a factor that stimulates blood vessel growth in tumors. By contrast, patients who had more social support in their lives had lower levels of this factor. Sood wondered if hormones associated with chronic stress might affect how cancers grow.

Sood’s research team, led by investigators Premal Thaker, M.D., Liz Han, M.D., and Aparna Kamat, M.D., in the Department of Gynecologic Oncology, developed a mouse model of ovarian cancer to study the link. In their experiments, the researchers confined the mice in a small space for zero, two or six hours during the day.

The confinement caused the mice to produce the same stress hormones as humans produce when they are under stress. These beta adrenergic hormones are sometimes called the “fight-or-flight” hormones because they are released when people are fearful or threatened, and are also responsible for causing the heart to beat harder and faster.

Sood and his colleagues found that, surprisingly, cancer cells make receptors for these hormones on their surface and that when these receptors are activated they set in motion a chain of events that leads to formation

of new blood vessels that feed tumors, a process called angiogenesis. New blood vessel formation is known to allow tumors to grow and spread more rapidly.

“We were quite surprised to find these beta adrenergic receptors on ovarian cancer cells,” says Sood. “In fact, we found them in 17 of 19 ovarian cancer cell lines we tested.”

After three weeks, the researchers measured the number and size of tumors in the mice. The number of tumors was 2.5 times greater in the mice that had been in the 2-hour stress group and 3.6 times greater in the 6-hour stress group compared to the mice with no stress. In addition, tumor growth was confined in the no-stress mice, but had spread to the liver or spleen in half of the stressed mice.

In additional experiments, the researchers gave the stressed mice propranolol, which blocked the effect of stress hormones. The medication completely neutralized the effect of stress on tumor growth,” says Sood.

“Beta blockers have been shown to be protective against cardiac disease,” he says. “No one has studied their effect on chronic stress as it relates to cancer in humans. There is a lot of interest now in this area of combining behavioral interventions to reduce stress, as well as using beta blockers in cancer patients.”

In follow-up studies, Sood and his team are in the process of further refining the role of stress in cancer using animal models and examining the hormone receptor status of cancers besides ovarian cancer.

Other members of the research team included Chunhua Lu, M.D., Nicholas Jennings, Guillermo Armaiz-Pena, James Bankson, Ph.D., Murali Ravoori, Ph.D., William Merritt, M.D., Yvonne Lin, M.D., Selanere Mangala, Ph.D., Tae Jin Kim, M.D., Robert Coleman, M.D., Charles Landen, M.D., Yang Li, Edward Felix, Robert Newman, Ph.D. Mary Lloyd, David Gershenson, M.D., Vikas Kundra, M.D., Ph.D., Gabriel Lopez-Bernstein, M.D., of M. D. Anderson, and Steven Cole, Ph.D., Jesusa Arevalo, Rie Takahashi, of UCLA, and Susan Lutgendorf of the University of Iowa. The research was funded by grants from the National Institutes of Health, the M. D. Anderson Ovarian Cancer SPORE, a Program Project Development Grant from the Ovarian Cancer Research Fund, Inc., and a Donna Marie Cimitile-Fotheringham Award for Ovarian Cancer Research.

3. Kopie Internetseite Universität von Texas

CANCER NEWSLINE

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Chronic Stress Agitates Ovarian Cancer in Mice

Reducing Stress Seems to Slow Tumor Growth

When mice with ovarian cancer are stressed, their tumors grow and spread more quickly, but that effect can be blocked using a common heart disease medication, according to new laboratory study results.

Significance of results

The findings, published online July 23 in the journal *Nature Medicine*, provide the first measurable link between psychological stress and the biological processes that make ovarian tumors grow and spread, says the study’s principal investigator Anil Sood, M.D., associate professor in M. D. Anderson’s Department of Gynecologic Oncology and Department of Cancer Biology.

Research methods

Sood’s research team created a stressful environment for mice infected with ovarian cancer by confining them to a small space for zero, two or six hours during the day.


Anil Sood, M.D.

The confinement caused the mice to produce the same stress hormones as humans produce. These "fight-or-flight" hormones are released when people are fearful or threatened and also are responsible for causing the heart to beat harder and faster.

Primary results

Sood and his colleagues found that, surprisingly, cancer cells make receptors for these stress hormones on their surface and that when these receptors are activated, they help form new blood vessels that feed tumors. This process, called angiogenesis, is known to allow tumors to grow and spread more rapidly.

After three weeks, the researchers measured the number and size of tumors in the mice.

The size of tumors was:

- The same in mice who spent no time in the confined space
- 2.5 times greater in the mice confined for two hours
- 3.6 times greater in mice confined for six hours

In addition, tumors spread to the liver or spleen in half of the confined mice but did not spread in mice who spent no time in the confined space.

Additional results

The researchers also gave the stressed mice a heart drug called propranolol, also known as a "beta blocker," which completely neutralized the effect of stress on tumor growth, says Sood, M. D. Anderson's director of ovarian cancer research in the Department of Gynecologic Oncology.

"The concept of stress hormone receptors directly driving cancer growth is very new," Sood says. "Our research opens a new area of investigation."

Also, no one has studied the effect of beta blockers on chronic stress as it relates to cancer in humans, Sood adds. "There is a lot of interest now in this area of combining behavioral interventions to reduce stress, as well as using beta blockers in cancer patients."

What's next?

Sood and his team are in the process, in follow-up studies, of further refining the role of stress in cancer by examining the hormone receptor status of cancers other than ovarian cancer.

– From staff reports

Resources:

Ovarian cancer (M. D. Anderson)

Anil Sood, M.D.

Department of Gynecologic Oncology

Department of Cancer Biology

Gynecologic Oncology Center