Short-term stress enhances anti-tumor activity in mice, study shows

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Public speaking, anyone? Or maybe a big job interview? Dry your palms and take a deep, calming breath; there may be a silver lining. Researchers at the Stanford University School of Medicine have shown that, at least in laboratory mice, bouts of relatively short-term stress can boost the immune system and protect against one type of cancer. Furthermore, the beneficial effects of this occasional angst seem to last for weeks after the stressful situation has ended. The finding is surprising because chronic stress has the opposite effect -- taxing the immune system and increasing susceptibility to disease.

"This is the first evidence that this type of short-lived stress may enhance anti-tumor activity," said Firdaus Dhabhar, PhD, associate professor of psychiatry and behavioral sciences and a member of Stanford's Cancer Center, and Institute for Immunity, Transplantation and Infection. "This is a promising new way of thinking that calls for more research. We hope that it will eventually lead to applications that help us to care for those who are ill, by maximally harnessing the body's natural defenses while also using other medical treatments."

The study will be published in a future print issue of the journal *Brain, Behavior, and Immunity*, and a review copy of the article is now available on the journal's Web site.

The researchers studied a particular type of skin cancer called squamous cell carcinoma that is known to be vulnerable to attack by the immune system.

Understanding how the intricate two-step between stress and the immune system plays out in the dance hall of diseases like cancer is important for future therapies. Certain types of stress, such as the so-called fight-or-flight response to an immediate but temporary threat, has been shown to increase the recruitment of immune cells to the surface of the skin and the surrounding lymph nodes -- presumably in preparation for imminent injury.

"Acute stress galvanizes an organism's protective systems," said Dhabhar, whose laboratory focuses on understanding the physiological effects of both acute and chronic stress. "But although it's one of nature's fundamental survival systems, thus far it's been rather underappreciated."

The researchers investigated the effect of short-term, or acute, stress on 30 laboratory mice exposed for 10 weeks to thrice-weekly doses of cancer-causing ultraviolet light. The light was non-blistering and non-burning and the mice experienced only a slight reddening of the skin after each exposure. But because the light was composed mainly of the most dangerous wavelength -- called UV-B -- starting at week 11, many of the mice went on to develop precancerous and cancerous growths similar to those seen in humans.

To stress the mice, the researchers placed them in well-ventilated plastic tubes for 2.5 hours prior to UV exposure from weeks four to six, for a total of nine bouts of stress. The mice were not squeezed or compressed, but their ability to move was restricted. Previous research showed that mice confined in such a way mount a behavioral and hormonal stress response.

Dhabhar and his colleagues compared the prevalence and tumor burden of the skin cancers in the stressed mice with that of a non-stressed, UV-exposed control group of 30 mice. They found that fewer of the mice

that had been acutely stressed developed skin cancer during weeks 11 through 21, and that those that did exhibited a lower total amount of tumors (a measurement called tumor burden) than the non-stressed mice.

The stressed mice weren't protected indefinitely. Approximately 90 percent of the mice in both groups developed cancer after week 22, though the stressed group continued to have fewer tumors until week 26.

"It's possible that the pre-tumor cells were eliminated more efficiently in the group that was stressed. There may also have been a longer-term enhancement of immunity as we have seen in our non-cancer-related studies," said Dhabhar, explaining why tumor development appeared to lag in the stressed mice. "However, acute stress did not lower tumor burden beyond week 26. We are in the process of determining why."

Other stress-induced changes lingered for weeks, however. The researchers found that, during the same time period, the skin of the stressed mice had higher levels of immune-activating genes than did the control group -- almost as if the mice were preparing for battle.

"Evolutionarily, it makes sense," said Dhabhar. "In nature, stress and immune activity are typically coupled. It's like a lion chasing and wounding a gazelle. Nature taps into this stress response to give a boost to the immune system in the face of danger." He compared the effect to how drug-makers often increase the potency of vaccines by including generic immune-activating molecules called adjuvants.

As intriguing as the results are, Dhabhar doesn't really imagine that we'll be confining human patients in straightjackets or tossing them in front of an intimidating audience as a therapeutic technique any time soon (thank goodness!). But he is convinced that acute stress may be better for us than most of us think, and that bio-behavioral interventions are worth investigating. As long as you can return to a normal, psycho-

physiological resting state within a few hours of a stressful event, you'll probably be fine.

"The key is not to let the stress response linger," he said. To understand why, Dhabhar and his colleagues are now probing more deeply into the biological basis of these protective effects of the acute stress response.

"What we want to do now is to fine-tune the stress dynamics so that we can get maximal benefits," he said. "We are working to determine what molecules and cells are involved, and when. It may be possible one day to harness these protective effects by behaviorally or pharmacologically activating the pathways involved."

Source: Stanford University Medical Center (news : web)

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