

To study the link between stress and tumor growth in animals, researchers expose the animals to stress, then inject them with tumor cells (or vice versa) and monitor tumor growth. In such studies, researchers find a clear connection between stress and tumor growth, but it's not as simple as: More stress equals a bigger tumor. Instead, it depends on the type and timing of the stressful experiences.

For example, extreme cold appears to protect against tumor development in rats as does restraining the animal. In contrast, many other physical and psychological stresses, including handling, overcrowding and being bullied by other dominant animals, appear to promote tumor growth. Whether or not stress promotes tumor growth also depends on the type and timing of the injection of tumor cells and the type of animals used in the studies.

"These things are not simple," says Emory University psychologist Jay Weiss, PhD. "That's why the results aren't just simple and straightforward. Instead you get these interesting and unexpected courses of tumor development."

Once researchers establish a connection between stress and cancer in animals, the next question centers on what mechanism links stress to tumor development.

Psychobiologist Shamgar Ben-Eliyahu, PhD, of Tel Aviv University in Israel, has been working for the past decade on the link between stress, tumor development and a type of white blood cells called natural killer (NK) cells. Of all the immune system cells, NK cells have shown the strongest links to fighting certain forms of the disease, specifically preventing metastasis and destroying small metastases.

Ben-Eliyahu and his colleagues have found that stress--including forced swim, surgery and social confrontation--decreases NK-cell activity in rats for as little as an hour and as long as a day or two. In addition, these types of stresses also cause a two-to five-fold increase in certain types of tumors, as well as promote tumor metastasis, the researchers find.

For example, in a study published in a recent issue of the *International Journal of Cancer* (Vol. 80, p. 880_888), he and his colleagues report that the stress of abdominal surgery promotes the growth of cancerous tumors in rats. And although their study is not definitive, the study indicates that stress acts by suppressing NK-cell activity, the researchers write.

This finding may have implications for people undergoing surgery to remove tumors, they conclude. Several studies find that NK-cell activity is suppressed for days after general surgery. If that also happens when cancer patients have surgery to remove tumors, it could leave them at risk for metastasis.

Bridging stress and tumors

Meanwhile, Emory's Weiss is building the case for another connection between stress, the immune system and tumor development.

Recently he's found evidence that b-lymphocytes--the type of white blood cell that produces antibodies--are involved in fighting tumor cells in the lungs of rats (Cancer Research, Vol. 99, p. 1080_1089). This finding is exciting because b-lymphocytes are the immune cells that are most influenced by stress, says Weiss.

"We might now have a bridge linking stress to the tumor process," he says. Now that he's found the connection between b-cells and cancer, he can test whether stress influences that relationship.

Weiss believes it may be that the b-cells are somehow associated with the decrease in NK-cell activity that Ben-Eliyahu has found. Weiss's research suggests that b-cells can work on tumor cells in ways other than through their antibody system, which normally takes several days to kick in.

Instead, he and his colleagues find, these b-cells begin working just hours after tumor cells are injected into the animals. One possible explanation is that the b-cells begin to produce a substance called interleukin 12, which is known to activate NK cells. This implies that stress-induced reductions in b-cells may influence cancer by interrupting the production of interleukin 12--a hypothesis Weiss will now test.

Less clear in humans

The link between stress and cancer is much stronger in animals than it is in humans, says University of Pittsburgh psychologist Andrew Baum, PhD. Indeed, there are no clear findings in human studies--some retrospective studies find that people with cancer report more stressful life events before being diagnosed with cancer but others find no relationship. And the research itself is fraught with methodological problems, says Dana Bovbjerg, PhD, head of the biobehavioral medicine program at Mount Sinai School of Medicine's Rutenber Cancer Center.

Still, to date, the idea that stress may influence cancer development hasn't been given a fair shot, he says. It will take an extremely large, longitudinal study to tease the relationships apart. In addition, oncologists are still debating the importance of the immune system in fighting cancer--the primary mechanism investigated in the animal literature.

And while researchers such as Baum are looking at the immune system as a mechanism, they are also examining other options. He and his colleagues are replicating a 1985 study by psychologist Janet Keicolt-Glaser, PhD, and her husband, virologist Ron Glaser, PhD, which found that stress impedes cells' ability to repair DNA damage. Failure to repair DNA damage is one of the first stages of cancer development, many theories say.

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