Mapping Pathways From Stress to Cancer Progression

By Karen Ross

Using in vitro, animal, and human clinical approaches, researchers are beginning to understand the relationship between psychological stress and cancer progression at the biochemical and molecular levels.

The focus of many of these studies is basic biology—the experience of stress and changes in gene expression that may be associated with tumor progression. “We’re very much interested in taking an incremental approach and elucidating potential biological processes that might be involved,” said Paige McDonald, Ph.D., chief of the National Cancer Institute’s Basic and Biobehavioral Research Branch, which funds research on stress and cancer.

“Our goal is to support very sophisticated mechanistic studies, with the eventual goal of using those basic science data to develop effective interventions.”

Earlier studies on stress and cancer often looked for associations between chronic psychological stress, such as depression, anxiety, or loneliness, and the incidence or course of cancer in humans. The results of these studies have been “mixed and moderately controversial,” said Susan Lutgendorf, Ph.D., who is studying relationships between stress hormones and ovarian cancer at the University of Iowa in Iowa City.

Currently, there is no good evidence that stress causes cancer. “Where the evidence is stronger is for disease progression.”

African American women get breast cancer at a younger average age and often in a more aggressive and lethal form than do white women. Although inherited differences in breast cancer–related genes might explain some of the disparity, most breast cancers are not hereditary, said Sarah Gehlert, Ph.D., principal investigator of CIHDR. She and her colleagues are testing the idea that psychosocial factors play a role.

Using Sprague–Dawley rats, a strain genetically predisposed to develop mammary tumors, CIHDR investigator Martha McClintock, Ph.D., found that social stress can influence cancer dynamics. The rats, which normally live in groups, were housed alone, producing behavioral and physiologic changes indicative of stress. Unlike group-housed rats, which will actively explore a new object placed in their cage, the isolated rats exhibited what is known as vigilant behavior, standing in one place and looking around constantly. “Although it is difficult to assess feelings in rodents, what they are experiencing appears similar to the vegetative symptoms of human depression,” Gehlert said. Also, the isolated rats had altered glucocorticoid responses to stress that are similar to changes seen in stressed humans. The isolated rats developed mammary tumors at a much higher rate than did their group-housed counterparts, and their tumors were larger and more aggressive and occurred at younger ages.

Another CIHDR group, led by Suzanne Conzen, M.D., has discovered a mechanism that may explain how excessive exposure to glucocorticoids can aid breast tumor growth. They found that glucocorticoids inhibited apoptosis, or programmed cell death, of cultured human mammary cells. Now they are working to understand the molecular pathway that leads from a glucocorticoid signal outside the cell to changes in gene expression that promote cell survival.

With the animal and cell culture results as a guide, Gehlert and her CIHDR colleague Funmi Olopade, M.D., have launched a study to see whether social isolation is associated with the development of highly aggressive tumors in human breast cancer patients. The study participants are African American women from Chicago’s South Side who are newly diagnosed with breast cancer. Gehlert is assessing the degree of their social isolation through
extensive interviews with the women and through neighborhood data, such as crime statistics. She accounts for the women’s socioeconomic status by collecting information on their income; education; professional status; and ownership of a home, car, and other durable goods. To evaluate access to health care, another important variable in health outcomes, Gehlert is taking a thorough health history for each woman and determining what health care resources are located in the women’s immediate neighborhoods. To monitor stress physiologically, Gehlert is analyzing glucocorticoid levels in saliva samples from the women at several times during the study. In keeping with the animal experiments, Gehlert has found that the daily cycling of glucocorticoid levels is abnormal in highly socially isolated women. Olopade has collected tumor samples from each woman and will examine them for changes in expression of genes such as BRCA1 that influence the aggressiveness of breast cancers.

The CIHDR projects, Gehlert said, aim to unravel the mechanisms by which “the social environment gets under the skin to change gene expression.” This endeavor could help elucidate whether one’s social environment could affect the course of breast cancer.

**Catecholamines**

Another series of experiments using a mouse model of ovarian cancer has studied the associations between the sympathetic nervous system and its messenger hormones—norepinephrine and other catecholamines—and cancer progression. Anil Sood, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston, in collaboration with Cole and Lutgendorf, injected human ovarian cancer cells into the abdominal cavities of mice and then stressed the animals by confining them to a small space. The researchers chose to stress the animals by confinement, Sood said, because this approach activates both pathways that are relevant for human stress—the HPA axis and the sympathetic nervous system. Confinement also induced behavioral and physiologic symptoms of stress, including reduced interest in exploring new environments, enlargement of the adrenal glands, and weight loss, Cole said. The confined animals had elevated levels of both glucocorticoids and catecholamines, and their tumors grew faster. When the researchers prevented catecholamine signaling, either with an inhibitory drug or by using cancer cells that lacked catecholamine receptors, stress no longer affected tumor growth.

Cell culture studies revealed that catecholamine stimulation of cancer cells led to increased production of vascular endothelial growth factor (VEGF), an important mediator of blood vessel growth in tumors, Sood said. These results were borne out in their animal model. Tumor tissue from the stressed mice had higher levels of VEGF and a higher density of blood vessels than tumors of unstressed animals. The researchers concluded that stress leads to increased catecholamine release by the sympathetic nervous system, which in turn leads to increased VEGF production by tumor cells. VEGF feeds tumor growth, by promoting expansion of the tumor’s blood supply.

Now the challenge is to determine whether the same mechanisms operate in humans. The early results are intriguing, Lutgendorf said. So far, they have found that ovarian cancer patients with low levels of social support, a risk factor for chronic stress, have elevated levels of VEGF. That finding supports other results that stress influences human ovarian tumors via the sympathetic nervous system. In a report soon to be published in *Brain, Behavior, and Immunity*, these researchers report that ovarian tumor samples taken from patients with symptoms of depression and low levels of social support contain higher levels of catecholamines than do tumors from less stressed patients. Tumors from patients who are highly stressed also showed elevated expression of genes known to be responsive to the sympathetic nervous system. “There seems to be a gene expression fingerprint of stress in the tumor itself,” Cole said.

This team is also investigating another proangiogenic factor, interleukin 6, levels of which are elevated in ovarian cancer patients with low levels of social support. One of their studies, examining the relationships among interleukin 6, glucocorticoids, and depression in ovarian cancer patients, will appear soon in the *Journal of Clinical Oncology*, Lutgendorf said.

The connection between cancer and the brain appears to be bidirectional. On one hand, molecules produced by the brain under stress can apparently influence tumor growth; on the other hand, proinflammatory cytokines released by some tumors and by the immune cells that respond to tumors can affect the brain to induce symptoms of fatigue and depression, Cole said.

This phenomenon complicates the interpretation of human studies of stress and cancer. “It is difficult to tease this apart in a clinical sample,” Lutgendorf said. However, she added, animal studies, in which one can control the level of external stress, make it possible to distinguish the two pathways. Sood’s work in mice clearly demonstrated that animals subjected to stressful conditions experienced greater tumor growth than did nonstressed animals. Future work in her lab will investigate the reverse pathway in an animal model to determine whether tumor growth can induce depressive symptoms.

**Intervention**

If the hypothesis that stress has a growth-promoting influence on tumors proves correct, researchers may investigate how best to intervene and counteract its effects. One approach is to use behavioral therapy to reduce stress in cancer patients. In a study conducted by Barbara Andersen, Ph.D., and colleagues at Ohio State University in Columbus, a group of patients with newly diagnosed breast cancer participated in a program in which they learned techniques for reducing stress and for increasing cancer treatment adherence. They also discussed ways to improve physical health through diet, exercise, and quitting smoking. Compared with a control group, the treated patients were less distressed, had fewer side effects from chemotherapy, and had better general health 1 year later. The ongoing study will also evaluate the effect of the intervention on cancer recurrence and survival.

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Cole is excited about the possibility of using medications to protect cancer patients from the negative effects of stress. For example, he said, beta blockers, which inhibit catecholamine signaling, were effective at preventing stress-induced tumor growth in their mouse model. Beta blockers are already widely prescribed to treat high blood pressure. “They’ve been around for 30 years,” Cole said. “We know they’re fairly safe; they’re inexpensive. It’s a great opportunity to block stress effects systemically and see if there are any effects on the disease process.”

For the future, Lutgendorf said, continuing to integrate the efforts of basic and clinical scientists will be important “because in vitro and animal models help us understand the mechanisms underlying the phenomena we observe in clinical patients. This gives us a more complete picture of effects of stress physiology on cancer growth.”

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