# Stress May Awaken Dormant Cancer Cells

Study findings suggest therapeutic targets to investigate for preventing cancer relapse.

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Sometimes cancer comes back long after the original tumor has been treated and removed. This is called recurrent cancer. Cancer can recur in the same place as the original tumor or in other places in the body if the tumor cells spread. Cancerous cells can lie dormant for years. But what triggers these cells to reawaken hasn't been well understood.

Past studies have linked chronic stress with cancer progression. To investigate whether stress can awaken dormant tumor cells, a research team led by Dr. Dmitry Gabrilovich of AstraZeneca and Dr. Valerian Kagan of the University of Pittsburgh and Sechenov University developed mouse models with dormant tumors. Their study was funded in part by NIH's National Cancer Institute (NCI). Results were published on December 2, 2020 in Science Translational Medicine.

The team tested the effects of several stress hormones—including cortisol, epinephrine, norepinephrine, and serotonin—on dormant tumor cells taken from the mice. They found that neutrophils, a type of disease-fighting immune cell, were activated by the stress hormones. The neutrophils then produced inflammation-inducing proteins called S100A8 and S100A9.

Further experiments showed that these proteins were needed to reactivate the dormant tumor cells. However, they didn't directly affect dormant tumor cells. The presence of S100A8/A9 altered certain lipids (fats) and led to their accumulation in the neutrophils. These lipids interacted with the dormant tumor cells, leading to tumor cell reactivation and new tumors.

Periodically stressing mice with dormant tumors led to tumor growth. However, giving the mice a beta blocker, which blocks stress hormone, prevented tumor cell reactivation.

To determine whether humans have a similar stress-induced response, the researchers tested blood samples taken from 80 people with non-small cell lung cancer. They compared levels of norepinephrine and S100A8/A9 in those who never had a cancer recurrence or had a late recurrence with those who had an early recurrence (within 33 months). Patients who had an early recurrence showed higher levels of the molecules.

"Our data suggest that stress hormone levels should be monitored in patients recovering from

cancer and that managing stress to keep those hormones at bay would be beneficial to prolong remission," says Dr. Michela Perego of The Wistar Institute, who is first author of the paper.

There are multiple factors that come together to cause a recurrence of cancer. These results show that stress hormone levels are one that might be monitored and reduced in standard cancer treatment. The findings also suggest new therapeutic approaches to investigate for preventing cancer relapse.

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