Tumors alone may be linked to cancer patients' cognitive problems

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New research suggests that both tumors and chemotherapy could be linked to the cognitive problems experienced by cancer patients because each affects the circadian clock, throwing off cellular processes related to behavior and memory.

Scientists found that mice with breast cancer tumors were less likely than healthy mice to stick to a normal exercise pattern, even with cues from a consistent light and dark cycle—a sign that their circadian circuitry was disrupted. The tumor's presence also flattened the release of a key hormone that is needed to give humans and animals a burst of energy when they wake up.

Removing the tumor returned the affected mice to near-normal conditions.

The researchers also found that chemotherapy appeared to lengthen the circadian clock in treated animals, which was evident in their longer pattern of exercise when compared to untreated mice. The mice on chemo had poorer memory overall, but there was no impact on the rhythm of their hormone release.

"We know that cancer patients frequently have a lot of issues with attention and memory capabilities during the course of their treatments, and sometimes these problems can last weeks, months or even years post-remission," said Kyle Sullivan, a Graduate Pelotonia Fellow in the Neuroscience Graduate Program at The Ohio State University who led the study.

"Which aspect of going through cancer is causing what's been called the 'chemo brain' phenomenon? Is it the biology of having a tumor? Chemotherapy treatments? Or stress related to the diagnosis? We're trying to establish a more causative role in how these attention and memory deficits arise."

Sullivan presented the research Wednesday, Oct. 23, at the Society for Neuroscience meeting in Chicago.

Virtually all cells in the body are controlled by 24-hour circadian

rhythms linked to the Earth's rotation, and these rhythms are present in all vertebrates, including humans.

Mice make a good model for circadian rhythm studies because they reliably run on an exercise wheel at the times they are most active—at night.

When the researchers compared running habits of mice with breast cancer tumors to healthy mice, they found that the mice with cancer "weren't as good at figuring out when it was time to get up and get on the wheel," said Sullivan, whose work is based in Ohio State's Institute for Behavioral Medicine Research. "They started to have more activity when you'd expect the mice to be inactive or less active. When we took out that tumor, they looked more like normal, healthy mice."

The tumor also evened out the release of a hormone called corticosterone, the mouse equivalent to cortisol in humans. While cortisol is often associated with stress, it also is released in the morning to get the body going after a prolonged period of sleep. Previous research has connected a flatter cortisol rhythm with poorer memory outcomes in cancer patients.

In contrast to the tumor findings, treating mice with paclitaxel—a common chemotherapy drug—did not change the rhythm of their circulating levels of corticosterone. And though a fear-based test showed the chemo interfered with memory controlled by the hippocampus in the brain, the memory of treated mice remained better during specific times of day—a finding consistent with normal circulation of corticosterone.

The chemo did have a different effect on the circadian master clock. When untreated and treated mice were all placed in constant darkness—losing cues from an alternating light-and-dark schedule—the mice with chemo extended their wheel-running routine after the

treatment was over. Rather than functioning on a natural 23.75-hour rhythm like the normal mice, the chemo-treated mice had a rhythm closer to 24 hours.

"'Chemo brain' is really a misnomer, because cognitive impairments can be seen prior to chemo treatments," Sullivan said. "Our findings suggest the circadian clock is affected in distinct ways by cancer alone and cancer treatment alone."

Future research will zero in on rhythm effects on cells not only in the body, but in the master clock in the brain. The work could someday lead to treatments aimed at resetting the disrupted circadian clock in cancer survivors.

"Our lab uses breast cancer models because the behavioral issues these patients have are well established by previous studies," said Leah Pyter, assistant professor of psychiatry and behavioral health, senior author on the study and a member of the Cancer Control Research Program at Ohio State's Comprehensive Cancer Center. "There are so many breast cancer patients, and fortunately, so many of them survive. Survivorship issues are germane to their quality of life."

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