Fragmented sleep accelerates cancer growth

By John Easton
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Poor-quality sleep marked by frequent awakenings can speed cancer growth, increase tumor aggressiveness and dampen the immune system's ability to control or eradicate early cancers, according to a new study published online Jan. 21 in the journal *Cancer Research.*

The study is the first to demonstrate, in an animal model, the direct effects of fragmented sleep on tumor growth and invasiveness, and it points to a biological mechanism that could serve as a potential target for therapy.

"It's not the tumor, it's the immune system," said study director David Gozal, chairman of pediatrics at the University of Chicago Comer Children's Hospital. "Fragmented sleep changes how the immune system deals with cancer in ways that make the disease more aggressive."

"Fortunately, our study also points to a potential drug target," he said. "Toll-like receptor 4, a biological messenger, helps control activation of the innate immune system. It appears to be a lynchpin for the cancer-promoting effects of sleep loss. The effects of fragmented sleep that we focused on were not seen in mice that lacked this protein."

Gozal, an authority on the consequences of sleep apnea, was struck by two recent studies linking apnea to increased cancer mortality. So he and colleagues from the University of Chicago and the University of Louisville devised a series of experiments to measure the effects of disrupted sleep on cancer.

They used mice, housed in small groups. During the day—when mice normally sleep—a quiet, motorized brush moved through half of the cages every two minutes, forcing those mice to wake up and then go back to sleep. The rest of the mice were not disturbed.

After seven days in this setting, both groups of mice were injected with cells from one of two tumor types (TC-1 or 3LLC). All mice developed palpable tumors within 9 to 12 days. Four weeks after inoculation the researchers evaluated the tumors.

They found that tumors from mice with fragmented sleep were twice as large, for both tumor types, as those from mice that had slept normally. A follow-up experiment found that when tumor cells were implanted in the thigh muscle, which should help contain growth, the tumors were much more aggressive and invaded surrounding tissues in mice with disrupted sleep.

"In that setting, tumors are usually encased by a capsule of surrounding tissue, like a scar," Gozal said. "They form little spheres, with nice demarcation between cancerous and normal tissue. But in the fragmented-sleep mice, the tumors were much more invasive. They pushed through the capsule. They went into the muscle, into the bone. It was a mess."

The difference appeared to be driven by cells from the immune system, called tumor-associated macrophages (TAMs), which cluster at the site of tumors. TAMs are a hallmark of the immune system's response to cancer, but they can respond in a variety of ways, depending on chemical signals they receive. Some, labelled M1, promote a strong immune response and can eliminate tumors cells. Others, known as M2, suppress the immune response and instead promote the growth of new blood vessels—which encourages tumor growth.

Well-rested mice had primarily M1-type TAMs, concentrated in the core of the tumors. Sleep-fragmented mice had primarily M2-type TAMs. These were abundant, especially around the

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periphery of the tumors. The sleep-disrupted mice also had high levels of toll-like receptor 4 (TLR4).

Three key molecules are part of the signaling pathway that appeared to be tilting macrophages toward M2: TLR4 and two downstream signals called MYD88 and TRIF. So the researchers injected tumor cells into a series of mice that were unable to produce one of these three proteins and subjected them to fragmented sleep. Tumor growth was slightly reduced in mice lacking MYD88 or TRIF, but in mice lacking TLR4, tumor growth was no greater than in mice with undisturbed sleep.

Taking TLR4 out of the picture resulted in major curtailment of tumor growth. “When we injected tumor cells into mice that lacked TLR4,” Gozal said, “the differences between undisturbed and sleep-fragmented mice disappeared.”

“This study offers biological plausibility to the epidemiological associations between perturbed sleep and cancer outcomes,” Gozal said. “The take home message is to take care of your sleep quality and quantity like you take care of your bank account.”

The Centers for Disease Control and Prevention estimate that about 70 million Americans suffer from chronic sleep problems. “Considering the high prevalence of both sleep disorders and cancer in middle age or older populations,” the authors wrote, “there are far-reaching implications.” Their next step is to determine whether sleep affects metastasis or resistance to cancer chemotherapy.

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TAGS

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