Can We Treat Cancer With Circadian Rhythms?

If the timing of circadian clocks can throw the body into cancer, could circadian clocks be used to treat cancer? That's a question that scientists are investigating.

February 5, 2019 By Michael Breus, PhD

As I talked about in my previous article of this series on sleep and cancer, our circadian clocks oversee many processes that are critical for healthy cell function. In our daily circadian cycles, or rhythms, our bodies are equipped with a master regulator that keeps our cells functioning properly. When those cycles are thrown off course—by poor sleep or other factors—those key cellular functions can also go awry.

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When to treat disease

Research into the power of circadian timing as a factor in disease treatment stretches back decades, to our earliest understanding of circadian biology. The scientist who pioneered chronobiology and coined the term "circadian rhythms" – Dr. Franz Halberg – studied the daily bio rhythms of disease and healing and investigated how to time medications and treatments in order to deliver the greatest benefit and the least harm. (Halberg personally oversaw his wife's cancer treatment, and she lived well beyond initial expectations.)

And still, the importance of chronobiology in treating medical conditions remains often overlooked. Think about the medications you're currently taking. You probably know what doses you're supposed to take—how many pills, how many times a day. But do you have a sense of when the best time to take your medications are? Most patients don't. And neither do most doctors. But there really is a best time of day to treat many conditions, from arthritis to high blood pressure.

(My book, The Power of When, explores how living in sync with our natural bio rhythms can make us happier, healthier, more productive, and biologically "younger." In the book, I discuss the timing of therapy and medication for many of our most common illnesses. And you can find your chronotype—the key to your individual bio rhythms–by taking my quiz.)

In cancer therapy, chronotherapy—treatment that uses the body's natural rhythms as a tool—is gaining major steam and credibility as a therapeutic option.

Chronotherapy for cancer: how does it work?

The fundamental idea behind chronotherapy hasn't changed that much since Franz Halberg's time. Chronotherapy for cancer seeks to use the body's natural bio rhythms to enhance the effectiveness of cancer treatment, and minimize the harm inflicted by cancer treatments including chemotherapy, radiation, and surgery.

What has changed since Halberg's day? We now have an enormous body of research documenting the many ways circadian clocks and rhythms affect how our body functions, and how disease grows. The body's immune defense system, its ability to metabolize toxins, its specific responses to different medications, all fluctuate throughout the day according to circadian rhythms. So, too, does the activity of cancer cells. There are times of day when tumors grow more aggressively (often at night), and when cancer cells may be more vulnerable to the medications that seek to eradicate them.

Taking all of these factors into account, we now may be able to target cancer treatments in alignment with these bio rhythms. That's not an easy prescription: circadian rhythms are highly individualized, differing from one person to the next. (Night owls, or Wolves, have different circadian timing than early birds, or Lions.) Those differences, as well as other factors including genetics and cancer type, may have a big impact on how successfully bio rhythms can be used to improve cancer therapy and outcomes. Studies also show there may be gender-based differences in chronotherapy, with men and women responding differently to circadian-aligned treatments for cancer. Age may affect how well chronotherapy works. But there is tremendous opportunity in chronotherapy as an element of cancer treatment. Let's take a look at some of that science.

How cancer cells respond to circadian cues

A quick recap on the basic biology of circadian rhythms: There is a central circadian clock in the brain functions as a master timekeeper for peripheral circadian clocks located in cells and tissues throughout the body. This network of circadian timekeepers regulate, in a series of daily rhythmic patterns, most of the body's physiological processes, including digestion, metabolism—and sleep. Those circadian rhythms—and the clock genes that direct their activity—also regulate cellular activity.

Cancer cells are the product of abnormal cell activity and uncontrolled cell proliferation. But cancer cells, like healthy cells, also fall under the influence of circadian rhythms and clock genes. That makes them a target for chronotherapy. Today's cancer chronotherapy research is exploring several avenues: to increase the effectiveness of existing cancer treatments, specifically chemotherapy and radiation; to reduce the toxicity of those treatments; and to target the activity of the circadian system as a form of treatment all its own.

The benefits of chronotherapy in cancer treatment

Over the past few decades, several studies have shown that timing chemotherapy according to circadian rhythm activity can significantly enhance these drugs' effectiveness and also reduce their toxicity. In animal (human?) studies, scientists have found circadian-timed chemotherapy

benefits in treating breast, bladder, gynecological, colorectal and lung cancers.

The timing of radiation therapy also may increase its effectiveness. A 2014 study of treating glioblastoma in mice found that timing radiation to when daily cycles predicted tumors would be least resistant to radiation led to higher survival rates. And a 2017 study found that specific timing of radiation (in the mornings) reduced the toxicity of the treatments.

The latest science on cancer chronotherapy

Another exciting cutting-edge component of chronotherapy involves developing drugs that target the workings of the circadian system itself. New research shows it is possible to manipulate activity of circadian rhythms in order to kill cancer cells and inhibit tumor growth.

Scientists are investigating components of circadian clock machinery, proteins known as REV-ERBs. When activated, REV ERB proteins inhibit specific functions that cancer cells need to survive. In recent research, scientists found that drugs targeting these proteins killed cancer cells, while at the same time leaving healthy cells undamaged.

These drugs—known as REV-ERB agonists—reduced tumor growth. They also killed a dangerous form of damaged cell known as senescent cells. Senescent cells aren't cancerous. But they can cause disease-generating problems, and make cancer growth more likely. I've seen senescent cells referred to as "zombie cells," which is a pretty apt description. Senescent cells have stopped dividing as normal cells do. But unlike normal aged or damaged cells, senescent cells don't die. They continue to be active in ways that cause problems for health. For example, research has connected the presence of senescent cells to aging, and to a number of diseases. Studies have also showed that getting rid of senescent cells can slow aging and alleviate disease. Eliminating senescent cells appears to invigorate the body's ability to repair and heal itself.

Senescent cells contribute to cancer development, in part by secreting chemicals that help tumors grow. There's also evidence that senescent cells may make cancer recurrence more likely, and may increase the negative side effects of chemotherapy and other cancer treatments.

One of the most exciting discoveries that's been made about targeting circadian rhythm function with REV-ERBs? The treatment appears to be effective for many types of cancer. Recent studies have found REV-ERB targeting worked for a wide range of cancers with different profiles and genetic triggers. What makes targeting circadian activity so broadly effective? It appears likely that this is because the therapy addresses the fundamental cellular activity that all cancer cells undergo—activity that is influenced by circadian rhythms.

Scientists have been looking at the therapeutic potential of REV-ERB proteins for several years. Previous studies in mice have shown targeting these clock proteins may be an effective way to treat metabolic disorders, including reducing obesity and lowering blood sugar. This circadian-based treatment may also help treat sleep problems, including circadian-rhythm disorders caused by shift work and jet lag.

We're now seeing some of the first studies to show the potential of directly targeting circadian rhythm mechanics in order to treat cancer. It's a tremendously exciting breakthrough, and an important new direction in cancer and chronotherapy research.

Melatonin as a cancer fighter

Melatonin is a fascinating hormone with a broad range of effects on the body. Best known as a facilitator of sleep, melatonin has other functions that make it a promising therapeutic tool for cancer. Melatonin has antioxidant and antimitotic properties—it is a powerful regulator of healthy cell function, and an inhibitor of dangerous cell proliferation. There's a strong body of research showing melatonin may protect against, and slow the growth of, several types of cancer.

Melatonin's rise and fall is closely linked to our 24-hour circadian rhythms. The sleep hormone is both regulated by circadian clocks and, at the same time, helps to keep circadian clocks in sync. Melatonin is also sometimes referred to as "the darkness hormone." Nearly all melatonin is produced at night, in response to darkness. During the day, exposure to light (sunlight, as well as artificial light) suppresses melatonin production, and hormone levels drop to almost nothing. Light exposure has a powerful, determinative effect on melatonin. This is one major reason why excessive and poorly timed light exposure is such a health concern today.

Even mild to moderate light exposure in the evenings can delay and diminish melatonin's nightly rise, interfering with sleep and throwing circadian clocks out of sync. When the nighttime window of melatonin production shortened, the body receives less of the cell-protecting, cancer-inhibiting benefits of the hormone. The disruption of melatonin's natural 24-hour rise-and-fall cycle is one important factor in nighttime light exposure being considered an emerging risk factor for cancer.

Melatonin is being explored with great interest as a potential treatment for cancer. Scientific research is demonstrating a number of ways the hormone might be deployed as a cancer therapy.

Melatonin to suppress cancer. There's a striking and growing body of research showing that melatonin can slow down the growth of tumors and reduce the risk of metastasis in a range of cancers, including both hormone-dependent and hormone-independent cancers. Hormone-dependent cancers are ones that require specific hormones to grow and spread. Many breast cancers are hormone dependent, relying on estrogen (or in some cases, progesterone). Other hormone-dependent cancers include endometrial, ovarian, prostate and colorectal cancers. Hormone-independent cancers no not need hormones to survive. Research shows melatonin may effectively suppress cancer growth in a long list of cancer types, including breast, prostate, ovarian, cervical, oral liver, gastric, pancreatic and colorectal cancers. There's also evidence of melatonin's ability to reduce cancer metastasis in breast, renal, and lung cancers, as well as other cancer types.

Melatonin to boost cancer treatment. Melatonin also can be used with other cancer treatments to boost their effectiveness, according to research. Studies show that pairing melatonin with chemotherapy drugs and radiation treatments can enhance the effectiveness of these therapies. There's also evidence showing the presence of melatonin with these treatments can reduce their

toxicity, alleviating some of their painful, harmful side effects. Particularly exciting research also indicates melatonin may help to overcome drug-resistance in cancer therapy. Studies have shown that some drug-resistant cancers become responsive to therapy when melatonin in used alongside those medications and treatments.

Interested in the broad health benefits of melatonin for sleep and health? I wrote about melatonin and its importance to healthy bio time here.

The future of cancer chronotherapy

What does the future look like for circadian-based cancer treatment? Along with other treatment strategies such as immunotherapy and genetics, chronotherapy is an exciting part of the emerging world of precision medicine, where we develop cancer treatments to align specifically with individual biology.

But in many ways, we're not there yet. We still need to develop better, more accurate methods for measuring individual circadian biology. We also need more research into chronobiology and chronotherapy, to better understand circadian rhythms and how they can be used to treat cancer—and other diseases. A 2016 study found that only a tiny fraction of scientific research was being devoted to investigating the benefits of chronobiology. Among those studies, 3.4 percent focused on cancer. We need much more attention paid toward these promising chronotherapies, and to the still-undiscovered aspects of chronobiology that may offer new hope and new treatments for cancer.

In the final installment of this series, I'll talk about how to sleep better with cancer, and the specific risks and challenges that cancer poses for sleep.

Sweet Dreams,

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