

New discoveries in circadian rhythms provide insight into cancer treatment

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Carla Finkelstein shares notes with visiting student Xianlin Zou. Credit: Virginia Tech

In a recent paper in *Science Signaling*, associate professor of cell and microbiology Carla Finkelstein, of the Department of Biological

Sciences, and her collaborators identified an alternative mechanism to control circadian rhythms in normal cells that is driven by oncoproteins.

This discovery places molecules involved in monitoring and calibrating the response of [cells](#) to genomic damage at the center of the machinery driving [circadian rhythms](#).

Anyone who has ever experienced jetlag is familiar with circadian rhythms. Various processes in the [human body](#) are governed by circadian rhythms, even down to the individual cell. These processes are tightly controlled by a variety of molecular mechanisms and [feedback loops](#) that help the body self-regulate in response to external cues like sunlight and temperature.

Researchers are now discovering that molecules usually implicated in protecting us from cancer initiation and progression are directly involved in regulating the function of our daily circadian rhythms. Not only that, but this molecular interplay seems to regulate how well our body responds to therapeutic modalities seldom delivered to treat certain diseases, such as cancer.

While [healthy cells](#) share a circadian [rhythm](#) with the rest of the body, tumors often have a different rhythm than the healthy cells surrounding them. Tumors divide differently than healthy cells and at different times. Like a person singing out of tune within a chorus, that one difference can ultimately wreck the entire melody. Or in this case, the healthy functions of cells.

"We know that our cells experience over 10,000 mutations a day," said Finkielstein. "These are usually mitigated by a repair system comprised of a host of protein interactions. However, only a handful of mutations, three to six depending on the type of cancer, are needed for malignant cells to get a foothold. And if one of these mutations occurs in the repair

system, then the chances for cancer increase dramatically."

It's obvious, then, that fine-tuning these processes is critical for maintaining normal cell functioning and that either dysregulation of circadian rhythms or alteration in oncoproteins can lead to numerous diseases and disorders. However, the good news is that the interplay among circadian molecules, oncoproteins, and tumor suppressors, as previously discovered by Finkielstein's group, can be used to tailor therapeutics in a more effective way.

Chronotherapeutics, or the application of therapeutics at times when drugs are most efficacious, have seldom been used in modern treatment plans. But the evidence is mounting that timing is truly everything when it comes to the best treatment plans. Lower and more effective doses translate to fewer side effects for patients, which is particularly relevant to cancer patients who are often given massive doses of very aggressive drugs. What has delayed the application of chronotherapeutics seems to be a lack of molecular foundation for the theory.

But all the proof needed may come from a small number of regulatory proteins that act as sensors, like the circadian protein PERIOD 2 (PER2), and integrators, like the [tumor suppressor](#) p53 and the oncoprotein MDM2. These proteins keep the division of cells regulated and timely. In the past few years, the transdisciplinary team of researchers has been patiently unwinding the crosstalk mechanisms responsible for understanding how the [circadian clock](#) and the cell division machinery coordinate processes to specifically understand how their regulation can be exploited therapeutically.

"Our findings were totally unexpected and welcome as they expanded our vision of how the circadian clock is regulated in [normal cells](#) to include components of the cell division cycle that are necessary to keep proliferation in check," said Finkielstein. "As a result, we can now test

the hypothesis of how deregulation of circadian rhythms, for example by shift work, could be associated with the etiology of cancer or how mutations in 'guardian' genes responsible for proliferative decisions lead to abnormal clocks in cancer cells, a finding of relevance when considering new therapeutic opportunities."

In the uncharted waters of chronobiological research, Finkielstein and her team are forging ahead to discover not only how [cancer](#) occurs but when and why it occurs. Their findings could help us understand when tumor cells are most treatable and deliver more effective treatments at the proper time.

More information: JingJing Liu et al. Distinct control of PERIOD2 degradation and circadian rhythms by the oncoprotein and ubiquitin ligase MDM2, *Science Signaling* (2018). [DOI: 10.1126/scisignal.aau0715](https://doi.org/10.1126/scisignal.aau0715)

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