3 QUESTIONS ON . . .
How Your Circadian Rhythm Affects Cancer Growth & Treatment
With Amita Sehgal, PhD, Professor of Neuroscience and Director of the Chronobiology Program at Penn Medicine

BY SARAH DIGIULIO

Previous observational studies have linked chronic disruptions of circadian rhythms to increased risk of certain cancers. Now, a new study published online ahead of print in PLOS Biology has shown how circadian disruption may trigger cell proliferation, and that delivering anti-cancer treatment timed to circadian rhythm may inhibit tumor growth more effectively than untimed treatment (2019; https://doi.org/10.1371/journal.pbio.3000238).

"We suggest that chronic disruption of the normal circadian rhythm tips the balance between tumor-suppressive and tumor-progressive gene expression to favor tumor growth," senior study author Amita Sehgal, PhD, Professor of Neuroscience and Director of the Chronobiology Program at Penn Medicine, said in a statement. "Additional research will need to be done to better understand the findings and replicate them in humans. (This study was done in cultured human cancer cells and in mice.) The researchers used a hormone to replicate frequent jet lag in cultured human cancer cell models. This change accelerated cell divisions and proliferation, suggesting that frequent circadian disruptions like those experienced when people experience frequent jet lag or frequently shift their sleeping patterns do promote cancer growth."

In the second part of the study, the researchers used mouse models to evaluate how administering anti-cancer therapy timed to circadian rhythm affected cancer growth. The results suggest that the timing of treatment could help improve outcomes, when it comes to stopping that tumor growth. Again, these findings are early—and much more research will need to be done before such a strategy can be used in patients with cancer. But the research suggests that better understanding the relationship between cancer growth and circadian rhythms is important, according to Sehgal.

"Better understanding the molecular effects of jet lag, shift work, and other sources of circadian disruption may lead to strategies to minimize the increased cancer risk associated with these behaviors, as well as to better treatment strategies, including timing delivery of cancer therapy for maximum benefit," Sehgal noted.

In an interview with Oncology Times, here's what else the study author said about the research:

1. What led you to conduct this research that looks at the mechanism behind circadian rhythms and tumor growth now?
   "With all the progress made in basic mechanisms of circadian rhythms (for instance, the 2017 Nobel prize was awarded for these studies), we have been thinking more and more of how these findings apply to the clinic. It is clear that circadian disruption promotes disease, but mechanistic analysis is limited. So we sought to determine, using initially a cell culture model, how basic cellular physiology is affected by circadian disruption."

   "[This research approach] was unbiased because we did not set out to look at the link between circadian disruption and cancer. We asked how circadian disruption affects a whole range of cellular functions and found that the major effects were on cell proliferation, which then led to the relevance to cancer."

   "The key findings are: 1) A major consequence of circadian disruption is an increase in proliferation of cancer cells. Importantly, we took an unbiased approach towards this problem, so we assessed a wide range of cellular functions and found that the major change was in proliferation rate. 2) Treatment timed to the host's circadian rhythm is more beneficial, but this benefit is lost if the host's rhythm is disrupted."

   "This study actually provides a specific circadian-regulated pathway that mediates the effect on the tumor growth and the effect of the anti-cancer drug."

2. Why do you suspect that treatment timed to the host's circadian rhythm (what you refer to as "chronotherapy" in the paper) boosts the benefit of that treatment?
   "In this case, it's because the pathway targeted is rhythmic, so its activity is different at different times of day. This is also true for several other drug targets. However, chronotherapy may also work because other things in the body are cycling—for instance, your response to a drug may be different when cortisol is high versus when it's low (cortisol also cycles)."

   "In addition, we showed recently that permeability of drugs into the brain can be different at different times of day, so drugs targeting the central nervous system are subject to this additional level of control."

   "Sleep cycles can be off for several reasons (for instance dictated by a person's job) and these may not always affect the internal circadian clock. Melatonin, which cycles over the course of the day, is a good marker for determining a person's circadian timing. New assays have also been developed based on expression of clock genes, but these are in their infancy."

3. What would you say is most important for practicing oncologists, cancer care providers, and cancer researchers to know about this research and your findings?
   "They should be aware of the effects of circadian disruption, and they (and all researchers and health care providers) should take time of day into account."

   "[This organiastical work was done in mice. However, we also did experiments with cultured human cancerous cells. The drug we used is used to treat cancer and the pathway it targets is conserved in humans, so there is good reason to believe we'd see similar results in people. We need to convince cancer researchers to factor time of day into trials."

© 2019 ONCOLOGY TIMES
All Rights Reserved.

Account: 6270KC (4823)