Cell Cycle 13:4, 507–507; February 15, 2014; © 2014 Landes Bioscience

An imPERfect link to cancer?

Comment on: Antoch MP, et al. Cell Cycle 2013; 12:3673–80; PMID:24091726; http://dx.doi.org/10.4161/cc.26614

Hema M Kopalle[1] and Carrie L Partch[1,2,*]; [1]Department of Chemistry and Biochemistry; University of California, Santa Cruz; Santa Cruz, CA USA; [2]Center for Chronobiology; University of California, San Diego; San Diego, CA USA; *Email: cpartch@ucsc.edu; http://dx.doi.org/10.4161/cc.27862

The molecular links between circadian disruption and cancer have been subject to much scrutiny, because environmental perturbations (shift work, jet lag) that disrupt internal circadian rhythms in humans are linked to increased risk of cancer.[1] Components of the molecular circadian clock not only work together to create daily rhythms, but may also regulate pathways for genomic surveillance and cellular proliferation independently of each other. The circadian transcriptional repressor *Period* (*Per*) has been shown to elicit changes in tumor cell proliferation and sensitivity to radiation or chemotherapy drugs, suggesting that it may be a bona fide tumor suppressor. However, Antoch and colleagues present work, in the December 1, 2013 issue, showing that *Per* genes do not influence tumorigenesis when confounding genetic background effects are removed.[2]

The notion of PER proteins as tumor suppressors was first proposed through a series of mouse model studies initiated over a decade ago, causing an explosion in circadian/cancer research. *Per2* deficiency was reported to increase tumor development in irradiated and untreated mice, and subsequent experiments linked deregulation of PER1 expression with increased cellular proliferation in cancer cell lines.[3,4] Whereas prior studies used mouse models or cell lines with diverse genetic backgrounds, Antoch and colleagues used mice from a pure genetic C57BL/6J background for their study. In this context, loss of *Per* genes (*Per1*$^{-/-}$ or *Per2*$^{-/-}$) did not show a significant effect on spontaneous tumor onset in non-irradiated mice or after whole-body irradiation, although the authors noted intriguing, gender-specific differences in cancer in *Per1*$^{-/-}$ mice. Both *Per1*$^{-/-}$ and *Per2*$^{-/-}$ mice developed pathological conditions over the course of the experiment that strongly resembled accelerated aging. However, accelerated aging phenotypes have been seen before with deletion of other circadian clock genes, so it is still unclear whether this is due specifically to loss of *Per* or disruption of circadian timing per se.[5]

These data bring new insight to the study of *Per* genes and the clock in aging and cancer, and could allow for better integration of the conflicting data already present in the field. Given that the circadian clock is driven by a transcriptional feedback loop, disruption of the clock by removing positive or negative elements of the loop has a dramatically different transcriptional signature and could be expected to result in opposing phenotypes. However, deletion of the other major circadian transcriptional repressor Cryptochrome (*Cry*), which forms a complex with *Per*, increases lifespan and causes cells to become more resistant to cancer.[6] Therefore, while there appears to be a definite link between disruption of the circadian cycle and cancer, the molecular links between the two have yet to be completely explored. Experimental models that disrupt circadian rhythms with altered lighting schedules to induce chronic jetlag show increased incidence of cancer[7] and may be the best paradigm for mimicking clock disruption in the human population. The work presented by Antoch and colleagues here provides conclusive evidence that the role of *Per* may not be well-suited to a definition as a conventional tumor suppressor.

References

1. Schernhammer ES, et al. J Natl Cancer Inst 2001; 93:1563-8; PMID:11604480; http://dx.doi.org/10.1093/jnci/93.20.1563
2. Antoch MP, et al. Cell Cycle 2013; 12:3673-80; PMID:24091726; http://dx.doi.org/10.4161/cc.26614
3. Fu L, et al. Cell 2002; 111:41-50; PMID:12372299; http://dx.doi.org/10.1016/S0092-8674(02)00961-3
4. Gery S, et al. Mol Cell 2006; 22:375-82; PMID:16678109; http://dx.doi.org/10.1016/j.molcel.2006.03.038
5. Yu EA, et al. Aging (Albany NY) 2011; 3:479-93; PMID:21566258
6. Ozturk N, et al. Proc Natl Acad Sci U S A 2009; 106:2841-6; PMID:19188586; http://dx.doi.org/10.1073/pnas.0813028106
7. Filipski E, et al. Mutat Res 2009; 680:95-105; PMID:19833225; http://dx.doi.org/10.1016/j.mrgentox.2009.10.002