TUMORIGENESIS

Turning the hands of time

Mammals exhibit oscillations in metabolism, physiology and behaviour with a near 24 h periodicity, a phenomenon known as the circadian rhythm. Changes to circadian oscillations, or phases, are associated with an increased risk of cancer and accelerated tumour progression, although why this might be remains unclear. The van der Horst laboratory now provide evidence for a link between DNA damage response (DDR) signalling and the scheduling of circadian rhythms.

The circadian rhythm is driven by the central pacemaker — or clock — in the brain, which synchronizes oscillations in peripheral tissues by modulating the activity of numerous pathways, including cell cycle and DDR signalling. As this process commonly involves feedback regulation from the periphery to the clock, Oklejewicz and colleagues asked whether DNA damage could affect the timing of circadian phases. Using a luciferase reporter gene under the control of the clock-regulated *Per2* promoter in Rat-1 fibroblasts they found that exposure to ionizing radiation (IR) advanced circadian phases in a dose-dependent manner, essentially resetting the clock. The mechanism underlying this change was unique to DNA damage and did not mimic the changes induced by other agents, such as forskolin or dexamethasone. Next, they showed that C57BL/6J mice exposed to a non-lethal dose of IR also exhibited phase advancement of circadian behaviour, indicating that exposure to IR affects the central pacemaker and not just peripheral oscillations.

So, how is the central pacemaker altered by DNA damage? The authors showed that abrogation of ataxia-telangiectasia mutated (ATM, which primarily regulates the DDR to IR) kinase activity, reduced the phase advancement in Rat-1 fibroblasts, indicating that ATM-dependent signalling can mediate clock resetting. Consistently, they also found that primary human fibroblasts derived from patients with the cancer-predisposed ataxia-telangiectasia (ATM-deficient) or Nijmegen breakage syndrome (defective for NBS (also known as nibrin), an important player in the DDR) did not exhibit phase advancement after exposure to IR. They also showed that ultraviolet irradiation (to which the kinase ataxia-telangiectasia and rad3-related (ATR) primarily responds) and oxidative DNA damage resulted in phase advancement, indicating that DDR signalling might be a regulatory input to which the central pacemaker responds. Interestingly, DNA damage-mediated phase advancement of the clock did not appear to involve the modulation of known clock genes, leaving open the question of how the DDR feeds back to the clock. However, the clock proteins PER1 and TIM1 (also known as TIMELESS) were previously shown to be targets of ATM and ATR and are promising candidates.

Defective DDR signalling is associated with increased cancer predisposition, as is reflected by the plethora of cancer-prone syndromes that are caused by mutations in DDR genes. This study now provides an interesting link that could improve our understanding of the underlying mechanisms that lead to increased tumorigenesis when circadian rhythms are altered.

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ORIGINAL RESEARCH PAPER Oklejewicz, M. *et al.* Phase resetting of the mammalian circadian clock by DNA damage. *Curr. Biol.* **18**, 286–291 (2008)
FURTHER READING Fu, L. & Lee, C. C. The circadian clock: pacemaker and tumour suppressor. *Nature Rev. Cancer* **3**, 350–361 (2003)