CIRCADIAN RHYTHMS

Clocking on

Women who work at night have an increased risk of developing breast or colon cancer, which could be evidence that disruption of our circadian rhythm upsets more than just our sleep patterns. The genes that regulate the circadian clock in mammals have recently been identified, and Sigal Gery and colleagues now show that one of these genes, period 1 (*PER1*), might function as a tumour-suppressor gene.

Given the established link between circadian rhythms and the DNA-damage response, the authors investigated the response to ionizing radiation (IR) of colorectal cancer cell lines that overexpress *PER1*. The authors showed that overexpression of *PER1* induced high expression levels of p53 that were only slightly increased after treatment with IR. Despite p53 expression, these cells did not have increased expression of p21, the cyclin-dependent-kinase inhibitor that mediates p53-induced cell-cycle arrest after DNA damage. This is because, after IR, *PER1* overexpression results in the increased expression of the oncoprotein MYC, which is known to inhibit p21 expression and induce apoptosis. Therefore, cells that expressed *PER1* were less able to arrest in G2/M and had higher rates of apoptosis than control cells.

Given that *PER1* seems to be important for the cellular response to IR, does it interact with other proteins that regulate this pathway? Co-immunoprecipitation experiments showed that *PER1* can interact with the DNA-damage-response kinase, ataxia telangiectasia mutated (*ATM*), and the checkpoint protein *CHK2*. The authors propose that *PER1* might facilitate the activation of *ATM* or might function as an adaptor protein that recruits other proteins that are required for the *ATM*-mediated response to DNA damage.

Overexpression of *PER1* in various cancer cell lines inhibited clonogenic growth as well as anchorage-independent growth, which further indicates that *PER1* might function as a tumour suppressor. So the authors investigated whether *PER1* expression is altered in human cancer. Reverse transcriptase-PCR analyses showed that 70% of human non-small-cell lung cancer samples and 46% of human breast cancer samples had reduced expression levels of *PER1* compared with controls.

These results further increase our preliminary understanding of how the circadian clock regulates pathways that are crucial for the suppression of malignant growth.

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ORIGINAL RESEARCH PAPER Gery, S. *et al.* The circadian gene *Per1* plays an important role in cell growth and DNA damage control in human cancer cells. *Mol. Cell* 22 375–382 (2006)

TUMORIGENESIS

Nuclear bodies

Tumorigenesis that is driven by loss of the tumour suppressor *PTEN* is known to activate the proto-oncogene *AKT* in many human cancers. Activation of cytoplasmic *AKT* has been thought to be the most relevant. However, Pier Paolo Pandolfi and colleagues now show that additional deficiency of the tumour suppressor *PML* — which forms dynamic intranuclear structures (nuclear bodies) that are involved in apoptosis, proliferation and senescence — leads to an increase in the nuclear localization of *AKT*, which accelerates tumorigenesis.

First the authors studied the effect of *Pml* loss on *AKT* activation in *Pten*^{+/-} mice. *AKT* activation increased by 50% in normal colon and prostate cells, particularly in the nuclear compartment, and led to the development of colon and prostate cancers. To investigate whether the change in

phospho-*AKT* (pAKT) localization was an inherent feature of *Pml* loss, Pandolfi and colleagues looked at the *AKT* status of *Pml*^{+/-} and *Pml*^{-/-} mouse embryonic fibroblasts (MEFs). After the addition of serum to the cell culture, *AKT* activation — especially in the nucleus — was sustained in *Pml*^{-/-} MEFs. If *Pml* was transduced into *Pml*^{-/-} cells, *AKT* activation decreased. These findings were confirmed by confocal laser scanning microscopy.

So, does *Pml* loss increase the function of nuclear pAKT? The forkhead transcription factor *FOXO3a* is a nuclear target of pAKT, and phosphorylation of *FOXO3a* leads to its inactivation and export from the nucleus. Decreased nuclear *FOXO3a* was seen after serum stimulation in *Pml*^{-/-} MEFs compared with *Pml*^{+/-} MEFs. In addition, the *FOXO3a*

POPULATION GENETICS

Associated risk

Family history and ethnicity are known risk factors for prostate cancer, but little is known about the genetic factors behind them. Amundadottir *et al.* have now shown that a common allele is associated with prostate cancer, and that it is more common in men of African descent, who are at greater risk of prostate cancer, than in men of European descent.

Variation at microsatellite loci might have functional consequences, and can also be used to search for regions of the genome that are associated with disease risk. The authors genotyped European men with prostate cancer and found that one particular microsatellite allele, DG8S737–8, on chromosome 8q24 is associated with disease risk.

This could be because the allele itself confers risk, or because it is close to the locus that does and most individuals who carry the microsatellite allele also carry the risk allele. This would be the case if there had been little recombination between the two loci since the risk allele arose by mutation.

Significantly, the authors found that the DG8S737–8, which also increases the severity of prostate cancer, was more common in men of African descent and was also closely associated with prostate cancer risk in this population. First, this could explain why prostate cancer is more common and more severe in men of African descent; and second, it shows that the area of the chromosome in which the risk factor lies is very close to the microsatellite, as all but the closest associations would