Nature Reviews Drug Discovery | Published online 16 Feb 2018; doi:10.1038/nrd.2018.24

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CANCER

Reset your circadian clock

The circadian clock controls several physiological functions, such as metabolism, cell proliferation and inflammation. Now, writing in *Nature*, Sulli *et al.* report that pharmacological targeting of the circadian clock components REV-ERBα (also known as NR1D1) and REV-ERBβ (also known as NR1D2), which are nuclear hormone receptors that repress several pathways involved in tumorigenesis, can be a novel anticancer strategy.

Two recently developed REV-ERB agonists, SR9009 and SR9011, had shown activity in reducing obesity in a mouse model through changes in the expression of enzymes involved in the metabolism and transport of fatty acids. These observations led Sulli *et al.* to investigate whether enhancing the repressive function of REV-ERBs could also repress the expression of genes aberrantly activated in cancer cells. "Cancer cells thrive on an altered metabolic homeostasis," explains Satchidananda Panda, lead author of the study, "therefore, reactivating a circadian clock component could be a novel approach to deprive cancer cells of a metabolic state that fuels tumour growth."

> "This study indicates that the development of drugs targeting the circadian clock may provide effective tools for cancer treatment"

SR9009 and SR9011 induced apoptosis in a range of cancer cell lines that include melanoma, leukaemia, brain, breast and colon cancers, and in cells driven by different oncogenes, including *HRAS*, *KRAS*, *BRAF*, *CTNNB1* (encoding β-catenin) or by *PTEN* deficiency, with little toxicity to normal cells. This selectivity suggested that SR9009 and SR9011 may affect processes that are specific for cancer cell survival, such as autophagy and *de novo* lipogenesis, which are tightly regulated by REV-ERBs. "Irrespective of where or how a cancer started, all cancer cells need more nutrients and more recycled materials to build new cells," says Panda. Indeed, treatment of these cell lines with SR9009 or SR9011 reduced the number of autophagosomes and increased accumulation of lysosomes and p62 (a protein degraded by autophagy). It also reduced the expression of the lipogenic enzymes fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1).

Next, taking advantage of the fact that SR9009 can cross the blood–brain barrier and to assess whether activation of REV-ERBs might be a therapeutic approach, the authors tested SR9009 *in vivo*, in two mouse models of glioblastoma. SR9009 reduced glioblastoma growth, triggered apoptosis and downregulated the expression of autophagy genes. The efficacy of SR9009 was similar to that of temozolomide, which is the current standard treatment for glioblastoma, although it lacked toxicity.

This study indicates that the development of drugs targeting the circadian clock may provide effective tools for cancer treatment and raises the possibility of developing drugs to manipulate biological clocks for the treatment of not only cancer, but other diseases that might be related to circadian rhythm disruption.

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ORIGINAL ARTICLE Sulli, G. *et al.* Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. *Nature* **553**, 351–355 (2018)