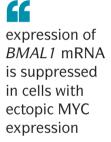
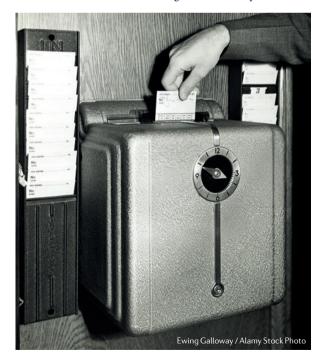
RESEARCH HIGHLIGHTS

MYC clocks on

The circadian clock and its links with systemic and cellular metabolism are fairly well characterized, but how these links are disrupted during tumour development is still being established. Dang and colleagues have found that the oncogenic protein MYC is involved in the regulation of the circadian clock and that the deregulated expression of MYC in cancer cells leads to a loss of cellular circadian rhythm.

CLOCK–BMAL1 (also known as ARNTL) and MYC–MAX are transcriptional complexes that bind to E-box sequences in the promoters of the genes that they regulate. Dang and colleagues have suggested previously that deregulated MYC expression





might result in the binding of MYC-MAX to genes that are normally regulated by CLOCK-BMAL1. Using U2OS cells that express luciferase under the control of the BMAL1 promoter, the authors showed that MYC activation suppressed the circadian rhythmicity of expression from the BMAL1 promoter, whereas this was maintained in cells expressing a transcriptionally inactive form of MYC. Quantitative PCR indicated that expression of BMAL1 mRNA is suppressed in cells with ectopic MYC expression. Similar results were evident in hepatocellular carcinoma cells established from transgenic mice with conditionally activated MYC transcription.

How does MYC suppress BMAL1 expression? The authors examined the known BMAL1 repressors, the transcription of which is regulated by promoters that contain E-boxes. Expression of MYC in U2OS cells and in mouse hepatocellular carcinoma cells resulted in increased expression of period 2 (PER2), cryptochrome 1 (CRY1), nuclear receptor subfamily 1, group D, member 1 (NR1D1; encoding REV-ERBa) and NR1D2 (encoding REV-ERB_β). Chromatin immunoprecipitation assays and promoter studies indicated that all of these genes are bound by MYC and are therefore direct targets of MYC-MAX-directed transcription. Short interfering RNA (siRNA) experiments indicated that REV-ERBα and REV-ERBβ, but not PER2 or CRY1, were required for MYCmediated suppression of BMAL1 transcription.

High NMYC expression in neuroblastoma is associated with a poor prognosis, and the authors showed that NMYC also disrupts *BMAL1* expression through the increased expression of REV-ERB proteins in neuroblastoma cell lines. In addition, low-level expression of *BMAL1* and increased expression of mRNAs encoding REV-ERB proteins correlated with a poor prognosis in two different sets of clinical samples.

What effect does suppression of BMAL1 by MYC-induced expression of REV-ERB proteins have on tumour cells? Nuclear magnetic resonance was used to look at specific metabolites and indicated that cells expressing high levels of MYC consumed glucose at a higher rate than cells with physiological MYC levels and that the circadian-associated changes in the metabolism of glucose were lost in cells expressing high levels of MYC. The use of other sources of carbon for metabolism, such as glutamine, also showed a circadian regulation in cells expressing physiological levels of MYC, but not in those expressing deregulated MYC, and similar results were evident in the expression of enzymes involved in metabolism, such as hexokinase 2.

The authors conclude that the deregulated expression of MYC and NMYC leads not only to alterations in cell proliferation rates but to perturbations in the circadian rhythm of cells, thereby disrupting cellular metabolism.

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