

## Oncogenic c- and N-Myc Disrupt Circadian Rhythm

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Circadian rhythms are regulated by feedback loops comprising a network of factors that regulate Clock-associated genes. Chronotherapy seeks to take advantage of altered circadian rhythms in some cancers to better time administration of treatments to increase efficacy and reduce toxicity. Taking advantage of cancers that have substantially different circadian rhythms, or are ‘out of phase’, with normal tissues, could open a wide therapeutic window to make them vulnerable to chemotherapy or targeted drugs at different times than normal tissue. However, there is currently no basis to identify which cancers have disrupted circadian rhythms and would be amenable to chronotherapy. c- and N-Myc are oncogenic transcription factors translocated or amplified in many cancers. While the role of Myc in circadian rhythm is currently unknown, it may affect circadian rhythm by binding to the same E-box promoter regions used by the central regulators of circadian rhythm, Clock/Bmal1. Thus, we hypothesized that Myc may disrupt circadian rhythm through inappropriate engagement of E-box promoters.

Here we show in neuroblastoma, osteosarcoma, and hepatocellular carcinoma cells that overexpressed Myc specifically upregulated the negative circadian regulator Rev-erba, which in turn decreased expression of Bmal1. Importantly, Myc-expressing cells showed dramatically disrupted circadian oscillations, which could be partially rescued by inhibiting expression of Rev-erba. Together, these data suggest that Myc-driven cancers have altered circadian oscillation due to upregulation of Rev-erba, and that cancers driven by Myc may thus be good candidates for chronotherapy.

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