

Rev-erb α Modulates Myc-Driven Cancer Cell Growth and Altered Metabolism

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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. While many cancers have perturbed expression of core circadian rhythm genes, the molecular basis underlying these perturbations and their functional implications in oncogenesis are still poorly understood, and so it is impossible to predict which cancers have altered circadian rhythms and would best benefit from chronotherapy. We have observed in cancer cell models of osteosarcoma, hepatocellular carcinoma, and neuroblastoma that the c-Myc and N-Myc oncogenic transcription factors disrupt oscillation of the circadian clock by specifically upregulating the circadian rhythm gene and nuclear hormone receptor *NR1D1* (Rev-erb α). Interestingly, while Rev-erb α has not been previously recognized as an oncogene, data from The Cancer Genome Atlas revealed that it is amplified in many forms of human cancer, and we also observed that Rev-erb α was upregulated in primary human neuroblastoma and associated with poor prognosis. Therefore, we hypothesized that Rev-erb α is a novel oncogene downstream of Myc and is important for cancer cell growth.

Here we show that Rev-erb α is specifically essential for the growth of Myc-driven hepatocellular carcinoma cells, as the related protein Rev-erb β did not strongly influence growth. While knockdown of Rev-erb α expression by siRNA slowed growth, it did not cause cell death or canonical cell cycle arrest. Rev-erb α modulates circadian rhythm by downregulating the central circadian regulatory protein Bmal1, but this pathway did not play a central role in Rev-erb α control of cell growth. Additionally, while Rev-erb α has a well-described role in heme metabolism and subsequent support of mitochondria respiration, this pathway was not directly altered in Myc-driven liver cancer cells. Rather, knockdown of Rev-erb α was associated with decreased glycolytic activity characterized by a decrease in intracellular lactate and extracellular lactate production as well as an increase in certain glycolytic intermediates. In addition to these glycolytic changes, the maximum respiratory capacity of cells lacking Rev-erb α increased, as measured by oxygen consumption. These data suggest a novel role for Rev-erb α in promoting the growth of cancer cells through modulation of glucose metabolism and a shift towards increased respiration, and imply that cancers with upregulated Myc and Rev-erb α may be good candidates for chronotherapy.

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