Autophagy

Major finding: Disruption of the circadian clock components reduces cancer cell viability *in vitro* and *in vivo*.

Mechanism: The REV-ERB agonists SR9009 and SR9011 block autophagy and trigger apoptosis in cancer cells.

Impact: Pharmacologic modulation of circadian clock components may be a potential anticancer therapy.

REV-ERB AGONISTS BLOCK AUTOPHAGY IN CANCER CELLS

The circadian clock coordinates diverse cellular processes including cell proliferation, metabolism, inflammation, and the DNA damage response. Consequently, circadian rhythm disruption elevates the risk of cancer, suggesting the possibility for pharmacologic modulation of circadian clock components in cancer therapy. The nuclear hormone receptors REV-ERBα and REV-ERBβ are essential circadian clock repressors, and recently two REV-ERB agonists, SR9009 and SR9011, with *in vivo* activity have been developed. These compounds allowed Sulli and colleagues to investigate the effects of circadian clock pharmacologic modulation on cancer cell viability. Both SR9009 and SR9011 induced apoptosis in a variety of cancer cell lines including brain, breast, and colon cancers, melanoma, and leukemia, and including cells driven by HRAS, KRAS, BRAF, or β-catenin, or by PTEN deficiency, with little toxicity to normal cells. Cancer cells depend on autophagy, which exhibits a circadian regulation controlled by REV-ERBα, prompting investigation of the effects of REV-ERB agonism on autophagy. Treatment with SR9009 or SR9011 reduced the number of autophagosomes and increased accumulation of lysosomes and p62 (a protein degraded by autophagy), suggesting that REV-ERB agonism inhibits autophagy. REV-ERB agonism also blocked autophagy and induced apoptosis in cells that had undergone oncogene-induced senescence. *In vivo*, SR9009 triggered apoptosis in NRAS-driven nevi, benign lesions comprised of cutaneous melanocytes that have undergone oncogene-induced senescence. Further, SR9009, which can cross the blood–brain barrier, suppressed glioblastoma growth *in vivo*. In addition to suggesting that pharmacologic modulation of circadian clock components may be a potential strategy for the treatment of patients with cancer, these findings support further investigation of REV-ERB agonists as anticancer therapeutics. ■

Sulli G, Rommel A, Wang X, Kolar MJ, Puca F, Saghatelian A, et al. Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. Nature 2018;553:351–5.

Sarcoma

Major finding: Aberrant myogenic activation in endothelial cells can drive fusion-negative rhabdomyosarcoma (FN-RMS).

Approach: Genetic fate mapping in a mouse model of mutant SMO–driven FN-RMS uncovers the cell of origin.

Impact: An endothelial cell of origin may explain the development of FN-RMS at sites devoid of skeletal muscle.

FUSION-NEGATIVE RHABDOMYOSARCOMA CAN ARISE FROM ENDOTHELIAL CELLS

Rhabdomyosarcoma (RMS) is a pediatric soft-tissue sarcoma with histologic features of embryonic skeletal muscle that is divided into two histologic subtypes—alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS). The majority of ARMS tumors harbor PAX3–FOXO1 or PAX7–FOXO1 fusion proteins, which are associated with poor outcomes, and ARMS is thought to arise from muscle progenitor cells in developing skeletal muscle. However, fusion-negative (FN) ARMS, lacking PAX3/PAX7–FOXO1, can arise in sites without skeletal muscle, suggesting the possibility that some FN-ARMS may derive from non-myogenic cells. To determine the cell of origin of FN-RMS, Drummond, Hanna, and colleagues used a previously developed mouse model of head and neck FN-RMS driven by constitutive activation of a mutant *Smo* allele (*SmoM2*) driven by *aP2-Cre*. Crossing the $Smo^{M2/+}$ mice with *aP2-Cre*;mT/mG mice harboring the $Rosa26^{mT/mG}$ reporter allele allowed for genetic fate mapping of progenitor cells. aP2-Cre labeled cells in both adipose tissue and skeletal muscle, but these tissues were unaffected by SMOM2 expression. Instead, SMOM2 expression in Cre-expressing endothelial progenitor cells in the skeletal muscle interstitium promoted myogenic transdifferentiation and RMS tumorigenesis, suggesting an endothelial cell of origin for these FN-RMS tumors. The resulting tumors expressed myogenic genes required for head and neck muscle development including *Tbx1*, *Pitx2*, *Tcf21*, and *Msc*, and also retained expression of endothelial genes including *Kdr* (also known as *Vegfr2*), *Gata2*, *Sox18*, and *Cdh5*. Activation of the hedgehog pathway induced aberrant expression of myogenic genes in *Kdr*-expressing endothelial progenitor cells, which may drive RMS tumorigenesis. Taken together, these findings suggest that FN-RMS can arise from endothelial progenitor cells with aberrant myogenic factor expression induced by mutant SMO, and may explain the genesis of FN-RMS in sites without skeletal muscle. ■

Drummond CJ, Hanna JA, Garcia MR, Devine DJ, Heyrana AJ, Finkelstein D, et al. Hedgehog pathway drives fusion-negative rhabdomyosarcoma initiated from non-myogenic endothelial progenitors. Cancer Cell 2018;33:108–24.e5.