CIRCADIAN RHYTHMS

Channels contribute

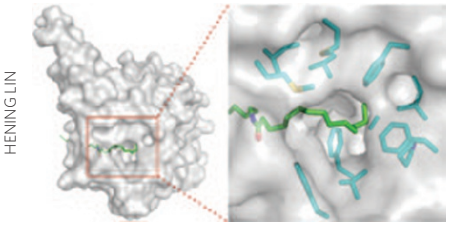
J. Neurosci. **33**, 6716–6725 (2013)

Circadian clocks are used by most animals to synchronize their behavior and physiology to the external environment. Circadian clock entrainment cues include daily light and temperature cycles. In *Drosophila*, temperature-induced synchronization of locomotive activity by central pacemaker neurons is regulated by input from peripheral tissues, but whether these pacemaker neurons can also receive direct inputs is not clear. Lee and Montell explored the possibility that the TRP family of cation channels, members of which are regulated by temperature, may act as a sensor in these neurons. They focused on *Drosophila* TrpA1 because it functions in a temperature range that matches the temperature synchronization of circadian rhythms. Whereas *TrpA1*-mutant flies responded to light cycles similarly to wild-type flies, the mutant flies had impaired temperature synchronization and were completely arrhythmic when a subset of pacemaker neurons were genetically ablated. The *TrpA1* mutants also showed erratic variation in the expression of the clock protein Period, which undergoes a predictable oscillation in wild-type pacemaker neurons. This effect was accentuated when a subset of pacemaker neurons was absent. In transgenic rescue experiments, TrpA1 expression in pacemaker neurons contributed to the temperature synchronization of locomotive activity. These results suggest that synchronization of the circadian clock does not depend exclusively on inputs from peripheral neurons and that some pacemaker neurons expressing TrpA1 contribute to temperature-controlled activity patterns. *MB*

SIRTUINS

In for the long haul

Nature **496**, 110–113 (2013)



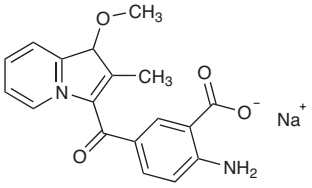
HENING LIN

Sirtuin enzymes have been classified as protein deacetylases that use a common nicotinamide adenine dinucleotide (NAD)-dependent hydrolysis mechanism. Yet many human sirtuins have only weak activity on acetyl-lysine substrates, which has prompted the search for their primary physiological targets. Jiang *et al.* now show that SIRT6 preferentially hydrolyzes long-chain fatty acyl lysine post-translational modifications. Using acylated synthetic peptides, the authors found that SIRT6 removes long-chain fatty acyl groups more efficiently than acetyl groups and does so in a sequence-independent manner. Crystallographic studies revealed that the longer acyl group of a myristoylated (C14) peptide substrate is readily accommodated by a hydrophobic pocket in SIRT6. To explore the biological role of SIRT6, the authors hypothesized that a previous link between SIRT6 and tumor necrosis factor-α (TNF-α), a protein known to have two myristoylation sites, could be explained by SIRT6 deacylation activity. A bio-orthogonal fatty acid–labeling approach was used to show that SIRT6 enhances TNF-α delipidation. Further studies in an endogenous system showed that SIRT6 mediates demyristoylation of TNF-α and that this process directly enhances TNF-α secretion. In addition to clarifying SIRT6 activity and its functional role in TNF-α mobilization, the study highlights potential connections between protein post-translational modifications and metabolism. *TLS*

ALLOSTERIC INHIBITORS

FGFR gets biased

Cancer Cell **23**, 477–488 (2013)



Receptor tyrosine kinases (RTKs) are important for cellular growth control and are therefore targets of interest for drug discovery. All known RTK inhibitors compete with either the ligand or the substrate for binding. Bono *et al.* now report the discovery and validation of an allosteric inhibitor of fibroblast growth factor receptors (FGFRs). From a high-throughput chemical screen for compounds that disrupt the interaction between a radiolabeled ligand and an extracellular domain–derived fragment of the receptor, the authors found SSR128129E (SSR). Interestingly, SSR was more potent in cellular validation assays (IC_{50} values in the nanomolar range) than in *in vitro* competitive binding assays (IC_{50} = 1.9 μM). After validating that SSR is active against multiple FGFRs, the authors investigated the mechanism underlying the differences in potencies between the *in vitro* and *in vivo* experiments. They confirmed that SSR is an allosteric inhibitor of FGFR that binds the extracellular domain at a site distinct from the ligand and inhibits activation of the kinase (by phosphorylation) but also that it shows biased antagonism of the pathways downstream of the receptor. SSR had anti-inflammatory and anti-tumor properties in FGFR-driven mouse models of arthritis and cancer, respectively. These data indicate that SSR is an allosteric, *in vivo*–active inhibitor of FGFR that can be used to understand the mechanisms of activation of FGFRs. SSR should facilitate FGFR-targeted drug discovery efforts and spark interest in the identification of allosteric inhibitors for other RTKs. *AD*

APOPTOSIS

I want you BAK

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Apoptosis, or programmed cell death, can be initiated when BAK localizes to the mitochondria, where it ruptures the mitochondrial membrane. Mitochondrial outer-membrane permeabilization (MOMP) leads to the release of cytochrome *c* and other proteins into the cytosol, which activate caspases and lead to cell death. Proapoptotic proteins, such as BAK and BAX, can be regulated directly by members of another family of proteins that contain a BH3 domain—for example, the BH3-only proteins BID and BIM. Moldoveanu *et al.* have now characterized the structural changes that take place when BID binds to BAK and explored how these changes lead to apoptosis. The authors used solution NMR spectroscopy to show that a stabilized α-helical version of BID binds to the occluded BC groove of BAK; the resulting BID-BAK complex was susceptible to calpain proteolysis in the presence of a small-micelle detergent (a proxy for BAK activation). The authors then performed mutagenesis on BID and BAK to identify which amino acids are required to generate a fully activated BAK that is capable of oligomerizing and inducing MOMP in cells. The authors concluded that the activation of BAK involves a multistep 'hit-and-run' mechanism: direct-activator BH3-only proteins interact with the BC groove of BAK, inducing several conformational changes; if biological membranes are present, the BH3-only proteins dissociate from BAK, which can then assemble into pore-forming homo-oligomers that rupture the mitochondrial membrane. *JMF*

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