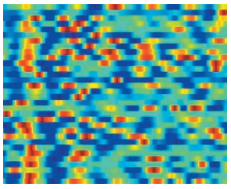
SYNTHETIC BIOLOGY

Return to sender

Genes Dev. **31**, 524–535 (2017)



GENES DEV.

Temporal control of gene expression is critical for cellular function and fate determination. Some genes, such as the Notch effector Hes1, exhibit an oscillating pattern of gene expression, marked by rapid mRNA synthesis and degradation due to negative feedback. Optogenetic approaches have enabled the generation of artificial oscillations with rapid spatial–temporal precision, whereas the use of bioluminescent or fluorescent reporters allows detection of oscillations at the single-cell level. However, it is not clear whether this oscillatory information can be transferred to neighboring cells. Isomura *et al.* developed a combined optogenetic and bioluminescence approach to investigate whether oscillatory information could be communicated between cells. In photosensitive, signal-sending cells, they used a modified version of the LightOn–GAVPO system consisting of the light–oxygen–voltage (LOV) domain protein Vivid (VVD), which forms an active homodimer with the p65 transactivation domain upon blue-light exposure. This complex binds to the upstream activating sequence, driving short-lived expression of the Notch ligand Delta. Delta interacts with the Notch receptor on the neighboring photo-insensitive cell, which contains a destabilized bioluminescent *Hes1* reporter and a native oscillator circuit of Hes1. Periodic blue-light exposure of the GAVPO-expressing cells produced *Hes1* oscillations in the neighboring cells that were dependent on the length of exposure. Overall, this optogenetic bioluminescence system enables detection of cell–cell communication with spatiotemporal resolution. *GM*

INFECTIOUS DISEASE

A lethal sugar fix

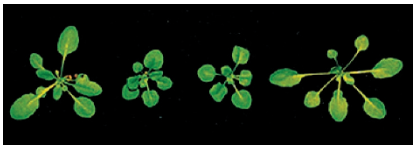
Science **355**, 1416–1420 (2017)

Trypanosomes cause substantial disease in both humans and livestock, yet the few treatments available are frequently toxic or not curative. Dawidowski *et al.* sought to identify new drugs that kill these parasites by inhibiting transport of trypanosomal enzymes into glycosomes, essential organelles required for glucose metabolism in the parasite. The interaction of the N termini of trypanosomal peroxins PEX5 and PEX14 is required for both glycosome biogenesis and import of glycolytic enzymes from the parasite cytoplasm, and silencing PEX14 has been shown to be lethal to *Trypanosoma brucei*. The researchers solved the NMR structure of the PEX14 N terminus to screen *in silico* for pharmacophores that mimicked its interaction with the WxxxF peptide motif of PEX5. Optimization of one of the hits containing a pyrazolo-[4,3-*c*] pyridine scaffold led to compounds with two aromatic ring systems that are shown to bind PEX14 through hydrophobic interactions in X-ray structures. The derivatives caused mislocalization of glycosomal enzymes and were toxic against *Trypanosoma* species *in vitro*. One of the molecules was twice as potent against *Trypanosoma cruzi* as benznidazole, which is approved for the treatment of Chagas disease in humans. Another derivative, with improved plasma properties, restricted parasitemia in *T. brucei*–infected mice without causing adverse side effects, suggesting that inhibitors of PEX5–PEX14 interactions may generate clinical candidates for treating trypanosomiases. *AF*

PLANT DEVELOPMENT

Get lit on steroids

Dev. Cell **41**, 47–58 (2017)



ELSEVIER

Brassinosteroids (BRs) are plant steroids that control development via a signaling cascade that includes a plasma membrane receptor kinase, BRASSINOSTEROID INSENSITIVE 1 (BRI1), and the transcription factors BRI1-EMS-SUPPRESSOR 1 (BES1) and BRASSINAZOLE-RESISTANT 1 (BZR1). A process called photomorphogenesis incorporates light signals to regulate plant development, but the mechanisms of the light–brassinosteroid interaction are not well understood. The stability and phosphorylation states of BES1 and BZR1 are known to be important during BR signaling. To better understand the role of BES1 and BZR1 stability, Yang *et al.* identified and explored the function of BES1- and BZR1-binding proteins. A two-hybrid screen identified several *Arapbidopsis thaliana* RING finger E3 ubiquitin ligases, SINAT1–SINAT5, that bound more specifically to dephosphorylated BES1 than to the phosphorylated form. *In vitro* ubiquitination assays, RNAi, overexpression, and degradation assays confirmed that BES1 interacts with SINATs, causing BES1 degradation and diminished BR signaling, ultimately resulting in effects on plant growth and morphology. Further RNAi experiments showed that BES1 is genetically epistatic to SINATs, consistent with SINAT regulation of BES1. Finally, the authors showed that SINAT levels are increased by light through a mechanism dependent on their own E3 ligase activity, thereby explaining the light-induced destabilization of dephosphorylated BES1. *MB*

ENZYMOLOGY

Radical ring resizing

Nature **544**, 322–326 (2017)

The biosynthesis of oxetanocin A, a nucleoside analog that has antitumor, antiviral, and antibacterial activity, requires the function of two enzymes (OxsA and OxsB) to rearrange a purine nucleoside co-opted from primary metabolism. Bridwell-Rabb *et al.* have now biochemically and structurally characterized OxsB, a cobalamin (Cbl)-dependent radical *S*-adenosylmethionine (SAM) enzyme, and found that not only is it responsible for catalyzing the formation of the natural product's oxetane ring, but it also catalyzes a reaction that is unusual for this family of enzymes. Compared to both canonical radical SAM enzymes and traditional Cbl-dependent enzymes, the structure of OxsB (the first for this superfamily) reveals an unprecedented mode of Cbl binding and an expanded radical SAM fold that, in part, functions to tether the [4Fe–4S] cluster, the SAM co-substrate, and the Cbl cofactor close together within the enzyme. As the name of this enzyme family suggests, the OxsB-catalyzed reaction proceeds through a radical intermediate. However, OxsB is the first characterized Cbl-dependent radical SAM enzyme not catalyzing a C-methylation reaction; instead, it catalyzes a thermodynamically unfavorable carbon-ring contraction. While the exact catalytic role of the Cbl cofactor remains to be elucidated, the novel structural and mechanistic features of OxsB further expand the growing collection of diverse functions for enzymes in this superfamily. *CD*

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