METABOLIC REGULATION

Sugar high

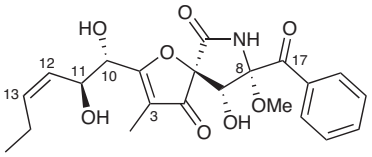
Nature **511**, 94–98 (2014)

One potential strategy to maintain insulin levels in type 2 diabetes patients is to block the activity of insulin-degrading enzyme (IDE), a zinc protease. To characterize the effect of slowing insulin degradation on glucose tolerance in animals, Maianti *et al.* identified the potent and highly selective IDE inhibitor 6bK by performing a selection on a DNA-templated macrocycle library for molecules that bind IDE. A crystal structure revealed that 6bK bound an allosteric site 11 Å away from the catalytic site, explaining its high selectivity. Treatment of lean and obese mice with 6bK produced different effects on glucose homeostasis depending on the method of glucose infusion: 6bK followed by oral glucose administration, which mimics meal intake, improved glucose tolerance, whereas 6bK followed by injection of glucose impaired glucose tolerance. Regardless of glucose delivery method, 6bK treatment in mice lacking IDE had no effect, suggesting that the different effects of 6bK may arise from the ability of IDE to degrade additional glucose-regulating hormones beyond insulin. The researchers indeed discovered that IDE regulates both glucagon and amylin in addition to insulin. The cause of 6bK-induced hyperglycemia in injected glucose tolerance tests could therefore be attributed to elevated glucagon levels, and administration of 6bK in glucagon receptor–deficient mice followed by glucose injection led to no hyperglycemic effect. These findings validate IDE inhibition as a new therapeutic strategy for the treatment of type 2 diabetes and suggest that a combination of treatments including an IDE inhibitor may be an especially effective strategy. *GM*

NATURAL PRODUCT BIOSYNTHESIS

It takes two

Angew. Chem. Int. Ed. Engl. doi:10.1002/anie.201404804



The pseurotins are a family of secondary metabolites from *Aspergillus* that have an unusual spiro-ring structure. Tsunematsu *et al.* have used several different approaches, including targeted gene deletion and *in vitro* enzymological assays, to probe the physiological functions of four enzymes in the pseurotin biosynthetic gene cluster from *Aspergillus fumigatus*. Bioinformatic analysis suggested that PsoF contains two domains, one of which is homologous to methyltransferases (MTs) and the other of which is homologous to FAD-containing monooxygenases (FMOs). Follow-up experiments indicated that the MT-like domain catalyzes the attachment of a methyl group to the C3 position of the pseurotin scaffold and that the FMO-like domain forms a 10,11-epoxide that is nonenzymatically converted to the 10,11-diol found in pseurotin A. The substrate specificity of the two domains of PsoF indicates that these two catalytic transformations occur at nonconsecutive steps in the biosynthetic pathway: the C3 position is methylated by the MT-like domain several steps before the 10,11-epoxide is formed by the FMO-like domain. Additional experiments suggested that PsoC methylates the hydroxyl group at the C8 position, that PsoD forms the ketone group at the C17 position and that PsoE isomerizes the C12-C13 olefin from *trans* to *cis*. More work is needed to reveal the exact mechanisms by which these enzymes carry out these transformations. *JMF*

PROTEINS

True to form

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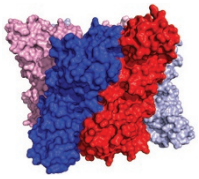

SUM CHAN

The inefficient enzyme RuBisCO fixes CO_2, enabling life, but improvements of its catalytic activity would facilitate applications in carbon capture and metabolic engineering. Structures are available for the open (apo) and closed (ligand-bound) states of two of the three known forms (I and III), but only an open structure exists for form II of the homolog from *Rhodospirillum rubrum*. Satagopan *et al.* now report the closed structure of a form II RuBisCO from *Rhodopseudomonas palustris* with a transition state analog. This RuBisCO, which forms a hexamer, unlike the dimeric *R. rubrum* homolog, cants at a different angle compared to the form I and III oligomers, creating a distinct subunit interface. Mutations to nonconserved amino acids neighboring the active site such as I165A were generally deleterious, indicating roles in enzyme function even if not directly in catalysis. The C terminus, representing a second point of divergence between the three forms, could not be exchanged between forms, though adding a C-terminal extension derived from the *R. rubrum* enzyme enhanced the activity of the *R. palustris* enzyme substantially. Finally, the slow reactivation of the I165A mutant after inhibition suggested that accessory proteins needed for regulation of the eukaryotic and cyanobacterial enzymes may not be required for *R. palustris*. These results highlight similarities and differences in enzyme structure and function that may lead to new mechanistic understanding of this important family of enzymes. *CG*

TRANSPOSON SILENCING

Vice Vasa

Cell **157**, 1698–1711 (2014)

Piwi-interacting RNAs (piRNAs) act with the Piwi class of Argonaute (Ago) proteins to suppress transposons in germline cells. Primary piRNAs are derived from genomic piRNA clusters and direct Piwi endonuclease activity to expressed transposons. The anti-transposon response is amplified by the 'ping-pong' mechanism, which uses sliced transposon RNA as guides to generate secondary piRNAs. Xiol *et al.* now identify key components of the piRNA amplifier complex (PAC) that mediates the ping-pong cycle. Comparative transcriptomic analysis of silkworms, flies and mice identified Vasa, a conserved DEAD-box RNA helicase, as a likely component of the PAC. Proteomics using a DQAD mutant of Vasa, which lacks ATPase activity, revealed that the two Agos, Siwi and Ago3, and Qin/Kumo, a Tudor domain–containing protein, interact with Vasa to form the PAC, which is localized in cytoplasmic granules called nuage. Immunoprecipitation and deep sequencing showed that the PAC also contains antisense piRNA intermediates normally associated with Siwi as well as sense transposon RNA. On the basis of surface plasmon resonance characterization of Vasa-RNA binding and crystallographic analysis of the Vasa DQAD mutant, the authors propose a model in which Vasa acts as an ATP-dependent clamp that captures Siwi–piRNA–transposon complexes, induces PAC assembly by recruiting Ago3 and Qin/Kumo and facilitates RNA intermediate transfer from Siwi to Ago3 in an ATP hydrolysis–dependent step. Taken together, this molecular proposal for strand transfer offers a useful model for future investigations of piRNA amplification mechanisms. *TLS*