CANCER

High fat deals a low blow

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Senescent cells, or those that are no longer dividing, produce the senescence-associated secretory phenotype (SASP), marked by a cocktail of cytokines, chemokines and enzymes that has been linked to cancer risk in obesity. To understand the basis for this link, Yoshimoto *et al*. studied the impact of diet on cancer in mice and found that cancer-prone mice consuming a high-fat diet, but not a normal diet, developed hepatocellular carcinoma. The authors did find evidence of senescent cells in the liver, and mice lacking IL-1β, an upstream regulator of SASP induction, had smaller numbers and sizes of tumors compared to wild-type mice. As intestinal microbiota have been linked to obesity, the authors then demonstrated that antibiotic treatment led to decreased populations of senescent cells and carcinoma. The authors searched for a possible mediator of this interaction, identifying a single molecule—deoxycholic acid—as highly present in the serum metabolites of mice fed with high-fat but not a normal diet. Decreasing deoxycholic acid concentrations blocked formation of carcinomas and senescent cells, and, reciprocally, treatment with this molecule increased cancer formation in mice on a high-fat diet. These data led to a model where high fat consumption initiates deoxycholic acid production, which induces formation of senescent cells, with subsequent SASP inducing cancer. *CG*

BIOSYNTHESIS

Deciphering dehydrophos

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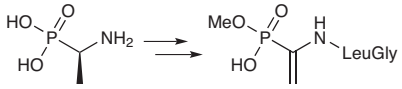

Dehydrophos is a broad-spectrum antibiotic produced by *Streptomyces luridus* that contains an aminophosphonate analog of dehydroalanine (ΔAla(P)). Cleavage of this phosphonotripeptide natural product by cellular peptidases releases methyl acetylphosphonate, which is a potent inhibitor of pyruvate dehydrogenase. Bougioukou *et al.* now report that the previously proposed mechanism for dehydrophos biosynthesis is incorrect. Analysis of the biosynthetic gene cluster suggested that it contains two putative 2-oxoglutarate/Fe(II)-dependent oxygenases, two putative alcohol dehydrogenases, two pyridoxal 5′-phosphate–dependent enzymes and two putative nonribosomal peptidyl transferases. The authors reconstituted and biochemically characterized several of these enzymes, and their experiments led them to propose a revised biosynthetic pathway with three phases. The first steps involve the formation of the C-P bond, a decarboxylation reaction and the reduction of phosphonoacetaldehyde to 2-hydroxyethylphosphonate, enzymatic reactions that have been observed in the biosynthetic pathways of other phosphonates. In the second part of the biosynthetic pathway, several enzymes convert 2-hydroxyethylphosphonate to L-Ala(P). The final phase involves two amide bond–forming reactions, monomethylation of the terminal phosphonic acid and the conversion of the C-C single bond adjacent to the phosphonate to a C-C double bond. Additional work is needed to uncover exactly how these enzymes efficiently catalyze such unusual biochemical transformations. *JMF*

PHOTOSWITCHES

Ready for red

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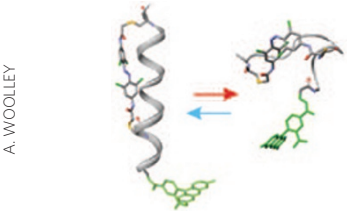

A. WOOLLEY

Photochemical tools allow scientists to use light to control the on and off state of a molecule. For *in vivo* application of these tools, switchable compounds must be responsive to red light; this requirement has limited applications of the popular azobenzene scaffold, for which no red light–activated derivatives are known. Samanta *et al.* now report a series of red light–activated azobenzenes and demonstrate their photoswitching properties *in vivo*. The authors showed that tetra-*ortho*-methoxy–substituted azobenzene can drive helix-to-coil transitions in FK-11, a peptide known to switch between conformations in response to isomerization of azobenzenes, and in other peptides in response to red light *in vitro*. In cells, azobenzene derivatives are also subject to reduction by glutathione, and the tetra-*ortho*-methoxy azobenzenes suffered from this weakness. The authors identified a tetra-*ortho*-chloro azobenzene that underwent stable *cis-trans* isomerization in response to red light and was resistant to reduction by glutathione. When linked to a fluorescent reporter peptide, this azobenzene yielded red light–mediated photocontrol in zebrafish embryos. Although it remains to be shown that these tools can be applied to interrogate a biological system *in vivo*, the development of red light–dependent, glutathione-resistant photochemical tools that can be readily derivatized makes these experiments possible. *AD*

NEUROSCIENCE

Along came a long RNA

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The mechanisms underlying neuropathic pain include abnormal spontaneous activity in neurons of the dorsal root ganglion (DRG). Upon peripheral nerve injury, the expression of voltage-dependent potassium (Kv) channels is downregulated in the injured DRG neurons, which may help induce neuropathic pain. To understand the mechanism by which Kv channel downregulation contributes to development of pain, Zhao *et al.* asked whether long noncoding RNAs (lncRNAs), whose expression has recently been associated with disease, were at play. Searching a database of expressed sequence tags, the authors found one that represented the antisense sequence of the Kv1.2 channel transcript. This lncRNA was expressed in rat DRG neurons, with expressing neurons showing small amounts of Kv1.2 protein. Two types of nerve injury downregulated Kv1.2 mRNA and protein but upregulated the levels of lncRNA in the injured DRG neurons. This upregulation was attributed to nerve injury–induced increases in the expression of the transcriptional activator MZF1 and its binding to the promoter region of the lncRNA. Upregulating lncRNA downregulated Kv1.2 expression, reduced total Kv current and excitability in DRG neurons and produced neuropathic pain symptoms. Blocking nerve injury–induced increase in DRG lncRNA expression rescued nerve injury–evoked downregulation of DRG Kv1.2 and attenuated neuropathic pain. This discovery suggests that lncRNAs are potential targets in prevention and/or treatment of neuropathic pain. *MB*

Written by Mirella Bucci, Amy Donner, Joshua M. Finkelstein, Catherine Goodman & Terry L. Sheppard