DIABETES

Relayed by a kiss

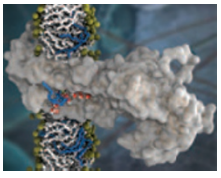
Cell Metab. **19**, 667–681 (2014)

Elevated pancreatic glucagon secretion by pancreatic α cells precedes impairment of glucose-stimulated insulin secretion (GSIS) from β cells in type 2 diabetes, but whether there is a direct connection between these two events has not been clear. To search for a connection, Song *et al.* developed a mouse model that selectively mimics the effects of elevated glucagon signaling in the liver—an organ that is known to respond to the activity of pancreatic α and β cells—and found evidence for a serum factor that suppressed GSIS *in vitro*. In comparative microarray analyses, transcripts encoding the hepatic peptide kisspeptin1 were more abundant in the model than in wild-type mice. In cultured hepatocytes and in mice, glucagon treatment led to elevated kisspeptin1 production only if glucagon receptor was expressed on hepatocytes. A synthetic version of kisspeptin1 suppressed GSIS in wild-type mice but not in mice with a pancreas-specific deletion of the kisspeptin receptor, indicating that the hepatic peptide acts on cells in the pancreas. In mice fed a high-fat diet, shRNA-mediated knockdown of kisspeptin1 in the liver or selective knockout of the kisspeptin1 receptor in the pancreas increased GSIS and improved glucose tolerance compared with scrambled shRNA or no knockout, respectively. Taken together, the findings define an α cell–liver–β cell endocrine circuit based on the peptide kisspeptin1 that causally links dysregulated glucagon secretion with impaired GSIS in diabetes. *AD*

MEMBRANE TRANSPORT

A phospholipid path

Proc. Natl. Acad. Sci. USA **111**, E1334–E1343 (2014)



PNAS

Flippases transport phospholipids between leaflets of the plasma membrane bilayer to establish and maintain appropriate membrane asymmetry. How flippases are able to move such large substrates is not well understood. The flippase ATP8A2 is a P-type ATPase that has not been structurally characterized but is thought to resemble both in structure and in catalytic cycle the structurally characterized P-type ATPase cation pumps, containing a transmembrane domain with ten helices (M1–M10). As the M4 segment of the cation-transporting ATPases and, specifically, a glutamate within the segment have been implicated in substrate binding, Vestergaard *et al.* focused on this segment within ATP8A2 to gain new insights into the flippase mechanism. They began by mutating the position equivalent to the glutamate, I364, and residues adjacent to it. Among six I364 mutations, the authors saw a direct correlation between the apparent affinity for the substrate phosphatidylserine and ATPase activity levels. Another M4 mutant, N359A, significantly affected ATPase activity and apparent substrate affinity. Homology models refined by molecular dynamics revealed a groove bordered by M1, M2, M4 and M6 that is substantially larger than that in the cation-transporting ATPases. The groove contained a substantial amount of water filling in two distinct pockets, which were differentially placed in the two modeled conformations. Further mutagenesis of a hydrophobic cluster of residues in this region including I115 and F88 suggest that the groove forms a path for lipid head group transport from the exoplasm to a cytoplasmic site in the bilayer, with I364 playing a part in the release of the phospholipid during its transfer. *MB*

SYNTHESIS

A plethora of polyenes

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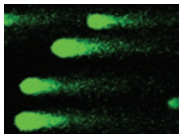
Most natural product syntheses begin with a full retrosynthetic analysis to break the molecule down into convenient starting points, with each new compound class deconstructed in different ways. Woerly *et al.* now suggest this practice has limited the reach of organic synthesis. To encourage general strategies and accessibility by nonexperts, the authors suggest a modular strategy akin to that employed in peptide and oligonucleotide synthesis. To demonstrate the approach, the authors focused on polyene structures, as these functional groups are both common in natural products and amenable to synthesis via *N*-methyliminodiacetic acid (MIDA) boronates as stable and commercially available reagents. A query of the *Dictionary of Natural Products* yielded nearly 3,000 compounds derived from all major biosynthetic classes containing polyenes, a retrosynthetic analysis of which revealed that more than 75% of the polyene motifs within these compounds could be constructed using only 12 MIDA boronate blocks. Preparation of the 12 blocks and preliminary coupling experiments demonstrated that although the MIDA precursors were stable, some of the deprotected intermediates were not. Revision of the reaction conditions to generate stable boronate esters by reacting with pinacol, along with exploration of possible solvents and reagents, led to a general synthetic strategy applicable to all cross-coupling experiments. The authors then used their methodology to synthesize 15 examples of polyene motifs and complete the first total synthesis of 3 natural products. *CG*

CANCER THERAPEUTICS

Cleaning the nucleotide pool

Nature **508**, 215–221 (2014)
Nature **508**, 222–227 (2014)



NATURE

High levels of reactive oxygen species cause cellular damage in many ways, including oxidative damage to chemical components such as nucleotide triphosphate pools. However, cancer cells are quite resilient to this damage owing to the activity of the 7,8-dihydro-8-oxoguanine triphosphatase MTH1, which prevents incorporation of these oxidized nucleotides into DNA, avoiding genetic instability and cell death. Gad *et al.* and Huber *et al.* knocked down MTH1 expression in cancer cells and observed increased oxidized dNTP incorporation, DNA damage and apoptosis, whereas normal cells were unresponsive, suggesting that chemical inhibitors of MTH1 could be useful cancer therapeutics. Gad *et al.* screened compound libraries and identified two compounds, TH287 and TH588, which selectively bound the active site of MTH1, whereas Huber *et al.* identified MTH1 as the cellular target of the small molecule SCH51344, which blocked RAS-dependent anchorage. In addition, Huber *et al.* performed additional screening and identified the (*S*) enantiomer of the dual c-MET/ALK inhibitor crizotinib as an MTH1 inhibitor that exhibited improved pharmacokinetic properties and potency compared to SCH51344. In both studies, treatment of cancer cells and mouse tumor models with TH287, TH588 or (*S*)-crizotinib resembled MTH1 knockdown with an increase of oxidized dNTP incorporation into DNA, producing more DNA strand breaks and resulting in decreased tumor growth. Overall, these findings suggest an intriguing new approach to target cancer cells. *GM*

Written by Mirella Bucci, Amy Donner, Catherine Goodman, Grant Miura and Terry L. Sheppard