PHYS ORG

Missing molecule in chemical production line discovered

December 11 2013

It takes dozens of chemical reactions for a cell to make isoprenoids, a diverse class of molecules found in every type of living organism. Cholesterol, for example, an important component of the membranes of cells, is a large isoprenoid chemical. The molecule that gives oranges their citrusy smell and taste is an isoprenoid, as is the natural antimalarial drug artemisinin.

Now, researchers at the Salk Institute have discovered a missing step in the chain of reactions that some cells use to produce isoprenoids. Their findings, published December 10 in *eLife*, are not only an advance in basic science, but have immediate implications for how isoprenoids are produced for commercial use, says Joseph Noel, professor and director of Salk's Jack H. Skirball Center for Chemical Biology and Proteomics and a Howard Hughes Medical Institute Investigator.

"It turns out that not all organisms make these very important products in the way that we thought they did," says Noel, holder of Salk's Arthur and Julie Woodrow Chair and the senior author of the new paper.

All larger isoprenoids are derived from a common building block molecule called isopentenyl diphosphate (IPP), which can be made through two chemical pathways. Animal cells use the mevalonate pathway to make IPP, many bacterial cells use a pathway dubbed DXP, and plant cells use both. But scientists have struggled to understand how archaebacteria, and some bacteria, produce IPP. While many of these organisms lack proteins that are key to the DXP pathway, they're also missing the proteins that perform two final steps of the mevalonate pathway. Normally, these production steps involve first adding phosphate to the intermediate molecule, and then removing an atom of carbon.

In 2006, a team of scientists discovered that some bacteria had an enzyme called isopentenyl phosphate kinase (IPK), which could add phosphate to the precursor molecule only if the carbon had already been removed, suggesting that these two steps of the pathway could be reversed—first, a carbon removed, then, a phosphate added, rather than the other way around. But a protein that could remove the carbon—called a decarboxylase—hadn't been found to prove that the alternate pathway ending existed.

"We decided to go on what some might call a fishing expedition," says Noel. "We used bioinformatics to find all organisms with the IPK enzyme; suspecting that these would all also have the decarboxylase we were looking for."

The approach worked: in an unusual type of bacteria that live in hot springs, Noel and his colleagues pinpointed a decarboxylase that works in conjunction with IPK. First, the decarboxylase removes carbon, and then IPK adds a phosphate—the process, reversing the last two steps of the classic mevalonate pathway, still ends in IPP. Surprisingly, the decarboxylase was one that had been identified in the past, but researchers had assumed it worked in the classic version of the mevalonate pathway—removing a carbon only after phosphate had been added. Noel's team showed that the protein, however, only worked with the alternate ending of the mevalonate pathway.

"Organisms don't always do what we think they do," says Noel. "And now that we have discovered this decarboxylase, us and many other labs can start looking in more detail at all these organisms and figuring out which have unexpected wrinkles in this pathway."

For companies that produce isoprenoids—as a source of drugs, scents and flavor molecules—the discovery provides a new potential chemical pathway to make their products with. "Now, both the decarboxylase and the IPK can be put into organisms that are engineered to produce a molecule of interest," says Noel. "It may be that we can build an organism with both the conventional and alternate pathways."

Whether having both pathways working at once could boost production is unknown, but Noel's team is currently looking into it. They're also further probing the role of IPK in plant cells. The scientists discovered that many plants not only have every enzyme in the classic mevalonate pathway, but they also have a copy of IPK. Noel thinks the IPK may act as a control point to regulate the production of IPP.

"From a curiosity standpoint, we're learning something new about biology in looking at these systems," he says. "But this is also a case where these findings are immediately translatable to industry because of the economic value of these chemical products."

Provided by Salk Institute

Citation: Missing molecule in chemical production line discovered (2013, December 11) retrieved 14 August 2024 from https://phys.org/news/2013-12-molecule-chemical-production-line.html