Scientists produce cancer drug from rare plant in lab

September 10 2015

Mayapple (Podophyllum peltatum). Credit: Wikipedia/CC BY 3.0

Many of the drugs we take today to treat pain, fight cancer or thwart disease were originally identified in plants, some of which are endangered or hard to grow. In many cases, those plants are still the

primary source of the drug.

Now Elizabeth Sattely, an assistant professor of chemical engineering at Stanford, and her graduate student Warren Lau have isolated the machinery for making a widely used cancer-fighting drug from an endangered plant. They then put that machinery into a common, easily grown laboratory plant, which was able to produce the chemical. The technique could potentially be applied to other plants and drugs, creating a less expensive and more stable source for those drugs.

"People have been grinding up plants to find new chemicals and testing their activity for a really long time," Sattely said. "What was striking to us is that with a lot of the plant natural products currently used as drugs, we have to grow the plant, then isolate the compound, and that's what goes into humans."

In her work, published Sept. 10 in the journal *Science*, Sattely and her team used a novel technique to identify proteins that work together in a molecular assembly line to produce the cancer drug. Her group then showed that the proteins could produce the compound outside the plant - in this case, they had put the machinery in a different plant, but they hope to eventually produce the drug in yeast. Either the plant or yeast would provide a controlled laboratory environment for producing the drug.

This work could lead to new ways of modifying the natural pathways to produce derivative drugs that are safer or more effective than the natural source.

"A big promise of synthetic biology is to be able to engineer pathways that occur in nature, but if we don't know what the proteins are, then we can't even start on that endeavor," said Sattely, who is also a member of the interdisciplinary institutes Stanford Bio-X and Stanford ChEM-H.

Finding the machinery

The drug Sattely chose to focus on is produced by a leafy Himalayan plant called the mayapple. Within the plant, a series of proteins work in a step-by-step fashion to churn out a chemical defense against predators. That chemical defense, after a few modifications in the lab, becomes a widely used cancer drug called etoposide.

The starting material for this chemical defense is a harmless molecule commonly present in the leaf. When the plant senses an attack, it begins producing proteins that make up the assembly line. One by one, those proteins add a little chemical something here, subtract something there, and after a final molecular nip and tuck, the harmless starting material is transformed into a chemical defense.

The challenge was figuring out which of the many proteins found in the mayapple leaf were the ones involved in this pathway. Sattely started with the realization that the proteins she needed to find weren't always present in the leaf. "It's only when the leaf is wounded that the molecule is made," she said.

And if the molecule is only made after wounding, the proteins that make that molecule are probably also only around after a wound as well.

The question then became, "What are all the molecules that are there after wounding?" Sattely said.

It turns out that after damaging the plant leaf, 31 new proteins appeared. Sattely and her team put various combinations of those proteins together until they eventually found 10 that made up the full assembly line. They put genes that make those 10 proteins into a common laboratory plant, and that plant began producing the chemical they were seeking.

Drugs from yeast

The eventual goal is not simply moving molecular machinery from plant to plant. Now that she's proven the molecular machinery works outside the plant, Sattely wants to put the proteins in yeast, which can be grown in large vats in the lab to better provide a stable source of drugs.

Producing a drug in yeast also provides some flexibility that isn't present when isolating a drug from plants.

"We can only use what the plant gives us," Sattely said.

In yeast, scientists can modify the genes to produce proteins with slightly different functions. For example, they could nip a little more off the chemical or add a slightly bigger side chain, or subtly alter the function of the eventual drug.

It may also be possible to feed the yeast a slightly different starting product, thereby changing the chemical that the molecular assembly line churns out. These approaches would provide a way of tweaking existing drugs in an effort to improve them.

Sattely said the work is a good example of how chemistry can be applied to problems of human health, which is the goal of Stanford ChEM-H. She thinks the technique she developed to find the pathway in mayapple could be applied to a wide range of other plants and drugs.

"My interests are really identifying new molecules and pathways from plants that are important for human health," she said.

More information: "Six enzymes from Mayapple that complete the biosynthetic pathway to the etoposide aglycone," by W. Lau; E.S. Sattely, *Science*, www.sciencemag.org/lookup/doi/ …

1126/science.aac7202

Provided by Stanford University