Discovery of new plant protein fold may be seed for anti-cancer drugs

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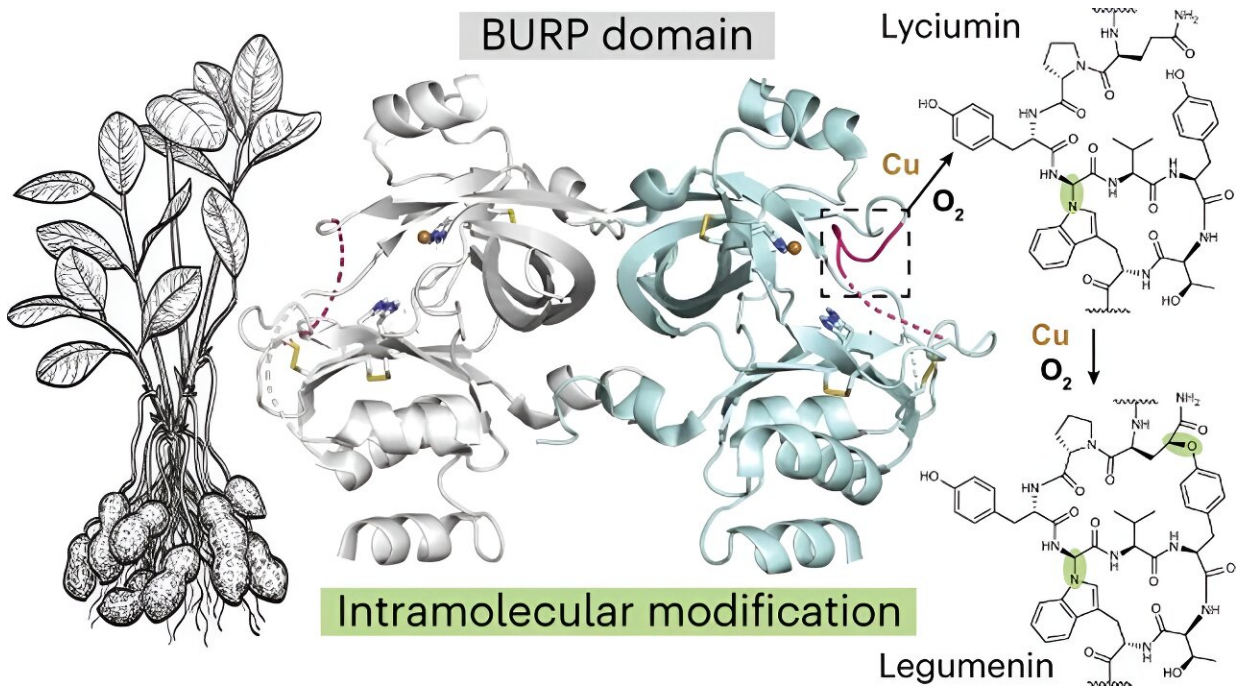

The new protein fold from AhyBURP is found in the roots of the peanut plant. The protein uses copper and oxygen to form cyclic peptides. We can investigate how this chemistry occurs more thoroughly now that we know what the protein structure looks like. Credit: *Nature Chemical Biology* (2024). DOI: 10.1038/s41589-024-01552-1

University of Michigan researchers are celebrating their discovery of a new plant biochemistry and its unusual ability to form cyclic

peptides—molecules that hold promise in pharmaceuticals as they can bind to challenging drug targets.

Cyclic peptides are an emerging and promising area of drug research.

The new study, led by U-M College of Pharmacy researchers Lisa Mydy and Roland Kersten, revealed a mechanism by which plants generate cyclic peptides. The research is published in the journal *Nature Chemical Biology*.

Mydy identified the new plant protein fold and its novel chemistry, which she said had never been seen before. The protein can generate cyclic peptides, one of which holds potential as an anti-cancer drug.

"It's extremely exciting," said Mydy, a postdoctoral research fellow in the Department of Medicinal Chemistry. "This type of discovery doesn't happen too often."

Mydy and colleagues studied the biosynthesis of a class of macrocyclic peptides found in plants and known for their potential use as therapeutic drugs. They identified a "fascinating new protein fold that has a really unusual mechanism to form cyclic peptides. It is a new biochemistry that we have not seen before," Mydy said.

The researchers also examined peptide cyclase, a protein called AhyBURP found in the roots of the peanut plant, a representative of the founding Unknown Seed Protein, or USP-type, which in turn is part of the BURP-domain protein family.

"There was no experimental information on our protein AhyBURP," Mydy said. "The only hint we had for function was that the protein needed copper to cyclize a peptide."

The research team studied the protein structures with X-ray crystallography and used the Advanced Photon Source at Argonne National Laboratory. In the process, they found that the "protein AhyBURP uses copper and oxygen in a unique way that we're still investigating," Mydy said.

"Most cyclic peptides need another enzyme to come in and do the cyclization chemistry," she said. "However, AhyBURP can do it within the same protein on itself. Other copper-dependent proteins function by attaching oxygen somewhere on the peptide. We don't observe that, and we want to know why. I see this as the first example of this type of chemistry that can happen with copper and oxygen within a protein."

The discovery of the new protein grew from ongoing work in Kersten's lab. As part of the U-M Natural Product Discovery Initiative, the Kersten lab aims to discover and research new plant-based chemicals that can become drugs and ultimately cure human diseases.

"We use a modern approach where we screen the genetic sequences of plants, searching for genes connected to new chemistry," said Kersten, assistant professor of medicinal chemistry at the College of Pharmacy. "That's how we identified the cyclic peptide products and their underlying proteins as a target of interest."

This class of peptides is of interest because their cyclization properties make them more structured and stable, increasing their potential to be used as drugs.

Many drugs, including chemicals derived from living organisms, are cyclic, meaning that they can bind drug targets and remain intact in a patient for a desired time. Nature has evolved many biochemical solutions to produce such cyclic molecules.

Kersten has isolated other compounds made by the same protein family that have been shown to have suppressing effects on lung cancer cells in lab tests, so there is growing hope that this discovery will have potential as a future anti-cancer agent.

"Now that we know what the protein looks like for one of the BURP-domain proteins, we can test more ideas about how the protein may influence the chemical reaction between the peptide, copper and oxygen to form cyclic peptides," said Mydy, a structural biologist and enzymologist by training.

"It is a fantastic and challenging puzzle to figure out why this is happening and understand the structure. It's extremely exciting to be part of this type of discovery that may eventually lead to effective pharmaceutical therapeutics."

More information: Lisa S. Mydy et al, An intramolecular macrocyclase in plant ribosomal peptide biosynthesis, *Nature Chemical Biology* (2024). DOI: 10.1038/s41589-024-01552-1

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