Scientists probe powerful molecular messaging system that goes beyond DNA

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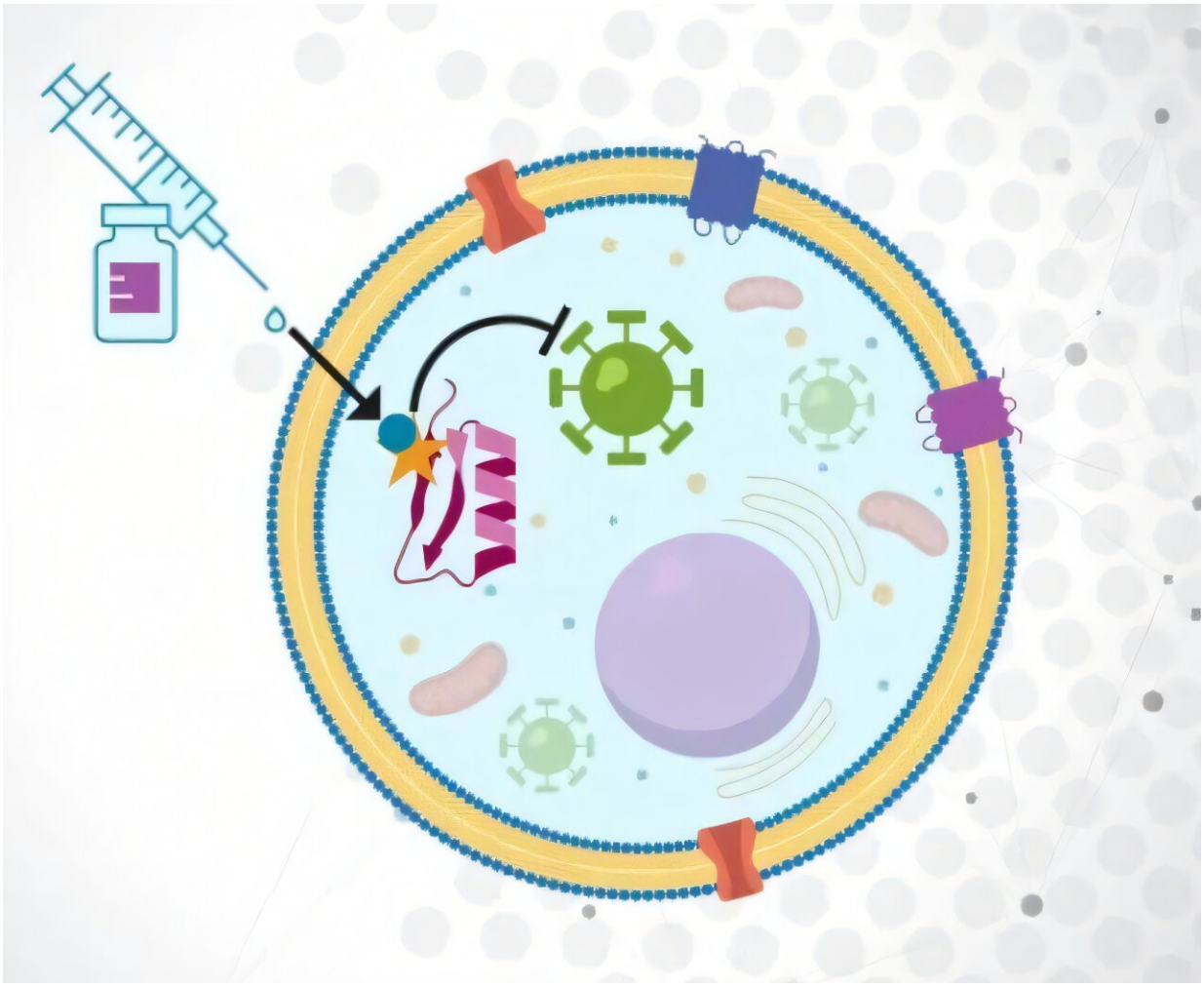


This illustration shows how post-translational modifications might be used to stop a virus. A coiled protein is shown in purple inside the left portion of a cell; the green sphere with spikes illustrates a virus. A compound, illustrated by a small blue ball, could interfere with the virus's ability to commandeer the cell's

machinery. Other parts the cell, such as mitochondria and the endoplasmic reticulum, are also shown. Credit: Stephanie King | Pacific Northwest National Laboratory

Scientists are uncovering the secrets of a fast-acting molecular messaging network that strongly influences how people and all organisms adjust and react to the world around them.

While DNA and the genes it encodes get widespread attention, how those instructions are brought to life is an elaborate process that depends on several lesser-known molecular actions. For every factor in the environment—heat, cold, danger, pathogenic threat, hunger—an organism relies on a network of molecular signals that determine how the genetic code plays out.

Tong Zhang and other scientists at the Department of Energy's Pacific Northwest National Laboratory are part of a research effort, the Predictive Phenomics Initiative, to understand and control these processes—to figure out how factors beyond the genetic code determine the traits of people, plants and all living things. The research holds promise for the bioeconomy, human health and other areas.

Much of the action takes place through molecular events called post-translational modifications, or PTMs. These are rapid chemical signals sent to proteins—the molecular workhorses that are the ultimate product of the genetic code—that enable an organism to respond to conditions in the environment. It's a biological version of instant messaging, providing constant tweaks to keep an organism safe and healthy in a constantly changing world.

The signals can spell the difference between health and disease, or

between mighty microbial manufacturing or poor production. Zhang is studying their role in the industrial production of common everyday products and in how we fight off viruses.

Single proteins, many functions

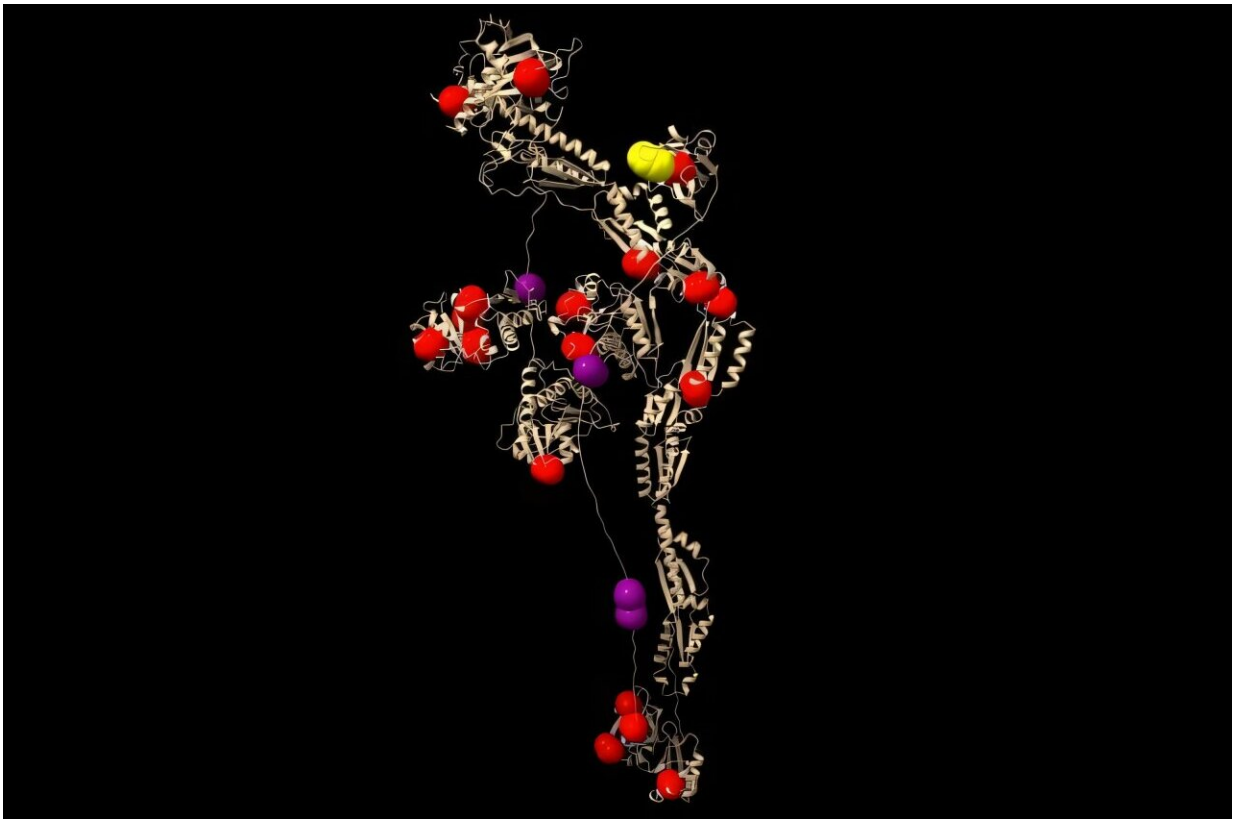
The system endows an organism with extraordinary flexibility, far beyond what its DNA calls for. While the body ultimately produces one protein from a stretch of DNA, that single protein can be modified to do many different things. A tiny chemical alteration can change what a protein is doing, how often, or when and where. That gives some organisms, like people, a vast number of specialized molecular tools —customized proteins—at their disposal.

"DNA codes for just one protein," said Zhang, "but the body can modify and control it to do many different things. A person has roughly 20,000 genes that may code for 20,000 proteins, but with many ways to accessorize and modify that protein, there are millions of possible protein forms and functions. This gives the body remarkable flexibility for dealing with an ever-changing environment."

Zhang is creating new ways to listen in on this signaling network, now at more than 600 different types of modifications and counting. The messages are so rapid and transient that they've been difficult to detect and study. Zhang has developed new ways to preserve and measure these events, giving scientists new tools to go beyond the string of chemical bases that make up DNA and to understand how they're implemented.

His tools include careful laboratory protocols so that as many changes as possible are retained for analysis. The use of automated laboratory tools to speed processing and analysis is becoming more common. He has developed ways to measure more than one type of change—both phosphorylation and oxidation—during the same experiment, and he can

detect tens of thousands of modifications in a single experiment.



This image demonstrates how a single protein can have multiple post-translational modifications or PTMs simultaneously. Here, the red particles illustrate sites of cysteine oxidation; the purple—serine, threonine or tyrosine phosphorylation; and the yellow, lysine acetylation. Credit: Doo Nam Kim | Pacific Northwest National Laboratory

The most important tool is mass spectrometry, which yields a measurement known as a molecule's mass to charge ratio. Mass spec is the most accurate method scientists use today to detect these modifications. The technique is remarkably sensitive; that's a necessity because the mass of a typical molecular modification is far less than one

trillionth of one billionth of a single gram. That is tiny even in the microscopic world—it's like being able to detect and pinpoint the mass of a single brick on the entire Earth's surface.

"These processes have been difficult to study because there has been a lack of analytical tools," said Zhang. "Many labs have very mature technologies to study DNA or messenger RNA, but there are few labs that have the capacity to measure and characterize these protein modifications."

As better tools reveal more molecular signals, the challenge for Zhang and others will be to understand how they all fit together and which ones are most influential.

From yeast to viruses: Modifications for bioproduction, better health

Zhang and his colleagues have been exploring the phenomenon in yeast. In a paper published online July 21 in the journal *Biotechnology for Biofuels and Bioproducts*, they provide new leads for improving yield in a kind of yeast utilized to produce chemicals used in skincare products, food production and bioplastics.

The team studied Rhodotorula toruloides, a red yeast used to produce substances called oleochemicals. Scientists use a process known as nitrogen limitation to control the yeast, rerouting their resources to create additional fatty molecules called lipids that have many uses in industry.

Zhang and colleagues analyzed the organism's molecular activity in response to nitrogen limitation. The team found shifts in two types of modifications, redox modifications and phosphorylation, in many

protein pathways. It's the first time that redox modifications have been demonstrated in this yeast.

"Perhaps there is something we can do on the PTM level so that the organism channels more of its energy into what you want the cells to make," said Zhang. "We're studying that now."

Zhang's team is also looking at the role of the process in people. In a recent review paper published in the journal *Frontiers in Immunology*, Zhang's team explored the role of the process in how the body responds to viral infection.

PTMs might help a person turn off cells' ability to make copies of a viral invader or could activate immune cells to fight the virus. They could act as a gatekeeper altogether, preventing a virus from entering a cell. On the flip side, viruses can turn the process to their advantage, exploiting the host's signaling machinery to boost their own attack.

"The role of PTMs in viral attack is an emerging field," said Zhang. "There are some anti-viral drugs that work through this mechanism, but not a lot is known about how they actually work. We're hoping to learn more about these mechanisms as a way to identify new candidates for antiviral drugs."

More information: Austin Gluth et al, Nitrogen limitation causes a seismic shift in redox state and phosphorylation of proteins implicated in carbon flux and lipidome remodeling in Rhodotorula toruloides, *Biotechnology for Biofuels and Bioproducts* (2025). DOI: 10.1186/s13068-025-02657-y

Xiaolu Li et al, Proteome-wide characterization of PTMs reveals host cell responses to viral infection and identifies putative antiviral drug targets, *Frontiers in Immunology* (2025). DOI:

10.3389/fimmu.2025.1587106