Researchers decode targets for hundreds of signaling enzymes

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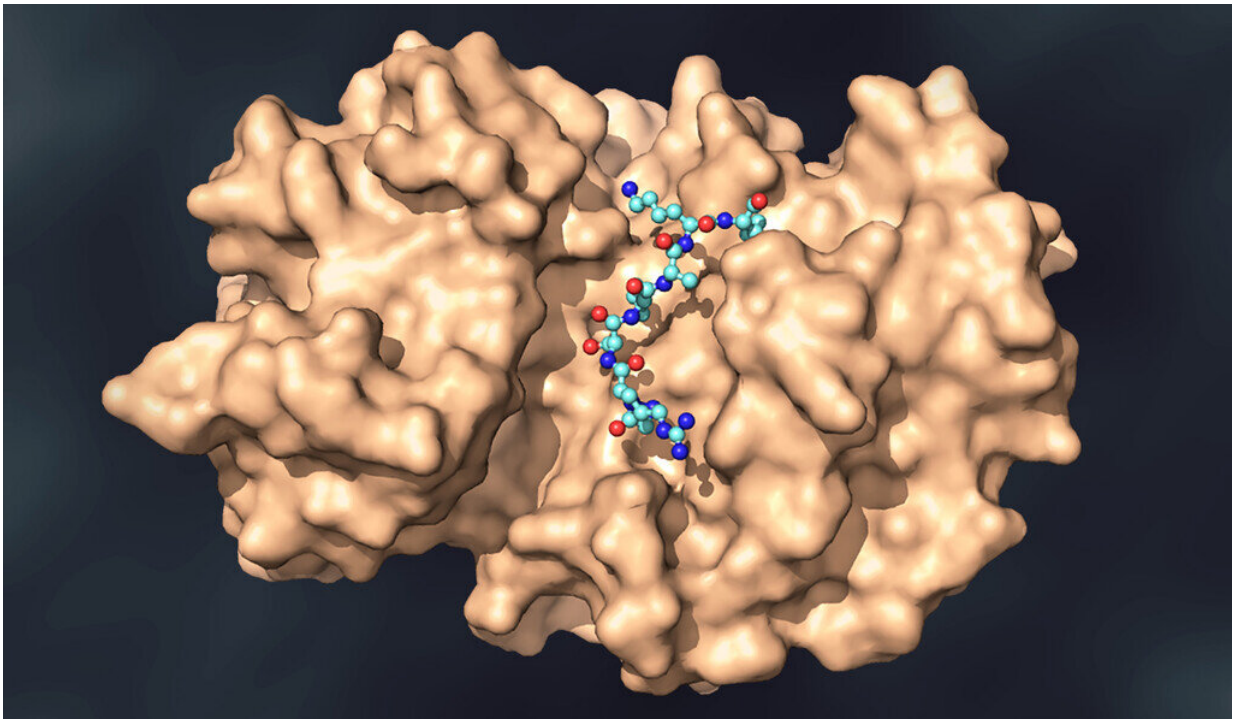

A kinase bound to an amino acid chain. Credit: Turk lab

When cells in the human body sense a change in the environment, molecules known as kinases can help them respond: these specialized enzymes activate proteins, propagating signals within a cell that ultimately alter its function. Yet if scientists want to understand the role of a specific kinase—and there are hundreds of them—they must first

understand which protein it targets. In most cases, this is not known.

In a new analysis of more than 300 kinases in the human body, Yale researchers revealed new insights into which proteins these enzymes are more likely to target. What they found, they say, will lead to a deeper understanding of human biology and identify targets for disease treatment.

The findings were published in *Nature*.

Kinases are enzymes that facilitate a process called phosphorylation. Essentially, a kinase recruits a little piece of a molecule called a phosphate group, which consists of a phosphorus atom and four oxygen atoms, and helps attach it to a specific area of a protein known as a phosphorylation site.

"When a protein gets phosphorylated by a kinase, that flips a switch that can change the protein's activity or where it goes in the cell. It can change the protein's function in any number of ways," said Benjamin Turk, an associate professor of pharmacology at Yale School of Medicine and co-senior author of the study. Other co-senior authors are Michael Yaffe at Massachusetts Institute of Technology and Lewis Cantley at Weill Cornell Medicine.

There are more than 500 kinases in the human body that act on hundreds of thousands of phosphorylation sites. That variety, Turk said, speaks to how essential phosphorylation is to cellular processes.

"But not knowing which kinases go with which phosphorylation sites is a huge gap in knowledge," he added.

To fill that gap, Turk and his colleagues focused on how kinases recognize their targets. Proteins are made up of amino acids, of which

there are 20; kinases recognize short strings of amino acids that surround the phosphorylation site. For the study, the researchers put together different amino acid strings, using all of the possible amino acid combinations, and measured how quickly different kinases phosphorylated each of the amino acid strings.

"By looking at which chains are phosphorylated fastest and slowest, it tells you which sequences of amino acids are favored or disfavored by a particular kinase," said Turk.

In an interesting finding, Turk said, the researchers discovered that some phosphorylation sites scored poorly for their known kinases. But they scored much worse for the other kinases.

"We think in cases like this it's possible the phosphorylation site evolved to evade the wrong kinases rather than to increase recognition by the right kinase," he said. "This tells us more about how specificity arises in these systems."

The new study yielded an online resource that can now be used by other researchers. Those who want to know what their kinase of interest might phosphorylate—or what kinase their protein of interest is phosphorylated by—can use a search engine that produces a ranked list of possible options based on the study's findings.

The results have also informed another project in Turk's lab in which researchers are exploring a small group of kinases called mitogen-activated protein kinases, or MAP kinases. Each of these kinases has a very different role in the human body despite being quite similar to each other molecularly.

In a second study published in *Science Signaling*, Turk and his colleagues—including lead author Guangda Shi, who conducted the

research as a graduate student in Turk's lab and is now at the University of Pennsylvania—describe how different MAP kinases target their proteins and their varied effects. The work, they say, helps clarify how signaling pathways in cells can be as specific as they are and could have implications for understanding and treating diseases like cancer.

"Certain MAP kinases are frequently hyperactivated in cancer and they have become drug targets for treatment," Turk explained. "Understanding how and where kinases act will help us understand their signaling pathways more deeply. And that will give us insight into all sorts of biological functions and where they go wrong in disease."

More information: Jared L. Johnson et al, An atlas of substrate specificities for the human serine/threonine kinome, *Nature* (2023). DOI: 10.1038/s41586-022-05575-3

Guangda Shi et al, Proteome-wide screening for mitogen-activated protein kinase docking motifs and interactors, *Science Signaling* (2023). DOI: 10.1126/scisignal.abm5518

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