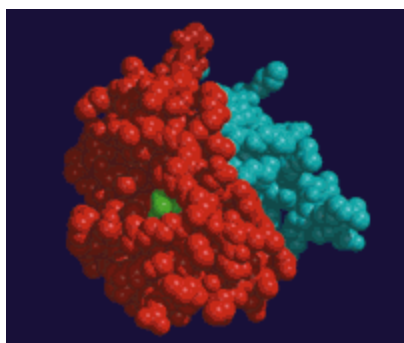


CELL BIOLOGY:

Pinning Down Cell Division

Gretchen Vogel

The events in the cell just before it divides are some of the most dramatic in biology. The chromosomes condense, the nuclear membrane disappears, and the cell starts to build its mitotic spindle--a set of fibers that will eventually pull the chromosomes to the opposite poles of the dividing cell. How the cell choreographs these complex changes is unclear, but on [page 1957](#), molecular biologist Kun Ping Lu of Beth Israel Deaconess Medical Center in Boston and Harvard University and his colleagues report evidence for a new mechanism that may play a key role.



Twister. The **Pin1** protein may help regulate mitosis by binding to phosphorylated proteins. The bright green region at left is the phosphate binding site.

LU ET AL.

Cell biologists have long known that the cell's progress toward division is controlled by a group of kinases, enzymes that add phosphate groups to a variety of cell proteins. For the most part, though, they've had few clues to what those phosphate additions actually do. That's where the Lu team's work comes in. It suggests that the phosphates serve as a sort of tag for attracting an enzyme called **Pin1**, which may cause the phosphorylated proteins to change their shapes. Researchers don't yet know exactly what this accomplishes, although they point to several possibilities, such as turning off an active enzyme, directing a protein to a new place in the cell, or targeting a protein for degradation. Whatever the precise result, however, the work provides "a new function for phosphorylation," says molecular biologist Tony Hunter of the Salk Institute in La Jolla, California.

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Lu and Hunter first discovered **Pin1** 2 years ago as a protein that interacts with and inhibits another critical cell regulator, called NIMA, which helps turn on mitosis. **Pin1** itself is an isomerase enzyme that changes the configuration of the peptide bond preceding proline, an amino acid that is an important determinant of protein structure because it can put kinks into a protein chain. Previous studies also showed that **Pin1** is crucial for both yeast and human cells to divide properly. Without it, for example, cells can't complete mitosis. But its precise role in the cell remained a mystery.

Researchers got a clue earlier this year, however, when Joseph Noel of the Salk Institute solved **Pin1**'s three-dimensional structure. It showed that the enzyme has a pocket for binding phosphate next to the site where it binds its proline target, says molecular biologist Lewis Cantley of Harvard, a co-author on the *Science* paper. That suggested **Pin1** might bind phosphorylated proteins.

To confirm that hunch, the team searched through a library of protein fragments for peptides that bind to the enzyme. Sure enough, says Cantley, **Pin1** preferentially picked out peptides that have a phosphate attached to an amino acid adjacent to a proline. With some sequences, in fact, the phosphorylated version bound thousands of times better than the unphosphorylated peptide.

Other unpublished work suggests that **Pin1** might help orchestrate cell division by interacting with other proteins involved in mitosis. When members of Lu's team went "fishing" through the contents of ruptured cells for proteins that bind to **Pin1**, they landed at least a dozen that are also targeted by an antibody, called MPM-2, that binds to proteins involved in mitosis in a wide range of cells. These proteins, too, contain a proline and an adjacent phosphate.

Taken together, say Lu and his colleagues, the experiments suggest that **Pin1** helps regulate a two-step process that governs cell division. Adding phosphates to proteins involved in mitosis creates binding sites for **Pin1**, which can then latch onto them and twist the peptide bond next to the prolines it contacts. That might, in turn, change the shape of the whole protein, perhaps altering its ability to interact with still other proteins, its location in the cell, or its life-span.

Whatever the binding does, Cantley suggests that it might enable **Pin1** to serve as a sort of checkpoint on the way to cell division. He notes that while cells lacking the protein can't divide--indeed, they die instead--manipulations that increase **Pin1** production delay the onset of mitosis. Based on that, he proposes that by binding to phosphorylated proteins, **Pin1** may slow down the activity of any proteins that are getting ahead of the rest of the cell. Hunter agrees. The properties of the protein suggest it might work as "some sort of threshold device," he says, preventing premature functioning of certain proteins. If so, cells lacking the protein may die, because events get so out of order that they go into mitotic arrest.

Other researchers aren't convinced that the story is that straightforward, however. Cancer pharmacologists Sally Kornbluth and Tony Means of Duke University have evidence that **Pin1** can bind to NIMA without the help of phosphate, and that it binds to other proteins that do not bind MPM-2. "The mechanisms that govern the effects of **Pin1** in the cell ... have yet to be defined," Means says.

Indeed, Cantley cautions that no one has yet pinned down exactly what the protein does when it binds: "We have no proof that isomerization is what's required for physiological function." It is possible, he says, that simply binding to a protein is enough to slow it down. Because researchers can now identify **Pin1**'s partners, they hope they will soon be able to sort out its role.

But even before that happens, the protein is attracting drug companies' interest. Because blocking the enzyme kills cells as they attempt to divide, drugs that inhibit the enzyme should target fast-dividing cancer cells without affecting the majority of cells in the body that divide only occasionally. "At least three or four

companies are interested in looking for inhibitors," Lu says.

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