Disorderly protein brings order to cell division

January 26 2007

The secret to the ability of a molecule critical for cell division to throw off the protein yoke that restrains its activity is the yoke itself—a disorderly molecule that seems to have a mind of its own, say investigators at St. Jude Children's Research Hospital, Innsbruck Medical University (Austria) and Max Planck Institute (Martinsried, Germany).

The researchers showed that the disorderly protein yoke, called p27, participates in its own destruction by swinging the end of its long arm up into a key side pocket of the cell division molecule called CDK2. After the end of p27 slips into the pocket, CDK2 marks p27 for destruction by tagging it with a molecule called phosphate. The tag signals the cell's protein destruction machinery to dispose of p27, freeing CDK2 to trigger cell division.

The finding is important because it explains how CDK2 normally shrugs off p27. Once free of p27, CDK2 can participate in a specific step of cell division. The findings also explain how some abnormal enzymes cause this to occur prematurely, putting cell division into overdrive—a state that produces cancer. A report on the work appears in the January 25 issue of the journal *Cell*.

The long p27 molecule drapes itself like an arm over the shoulders and down the side of CDK2, the researchers explained. The upper arm of p27 binds tightly to the shoulders of CDK2; as the arm drops over the shoulders, the "elbow" of p27 inserts itself into a side "pocket" of the

molecule.

Meanwhile, the long, floppy forearm and hand of p27 hangs freely below CDK2. Initailly, this is where the story of p27 became puzzling: the part of p27 that CDK2 must tag is on the "hand" at the free end of the floppy arm, at a point called amino acid threonine 187 (T187). But CDK2 can tag T187 only when this part of p27 fits into the pocket of CDK2, where the elbow of p27 is already lodged.

"Previous studies produced conflicting evidence to explain how CDK2 disposes of p27," said Richard Kriwacki, Ph.D., associate member of the Department of Structural Biology at St. Jude. "We knew p27 inactivated CDK2; yet we also knew that CDK2 tags T187 with phosphate even while it still carries the p27 yoke on its shoulders. The question was, how does the pocket of CDK2 tag T187 while T187 is so far away and the pocket itself has the elbow of p27 jammed into it? What we knew about the process didn't make sense."

The key to both normal and premature tagging of p27 and its subsequent destruction is the activity of enzymes called kinases, according to Kriwacki. Kinases are enzymes that tag specific amino acids—the building blocks of proteins—with phosphate. CDK2 itself is a kinase, which is why it can tag the hand of p27 with a phosphate group.

The team showed that a specific type of kinase tags the elbow of p27 at a spot called amino acid Y88. This causes the elbow to change shape and pop out of CDK2's side pocket. The floppy end of p27 carrying T187 is then free to swing up and insert its hand into the pocket of CDK2, where T187 gets tagged by phosphate. "Our study showed that because the floppy part of p27 is so unstructured it can move around freely and swing up and into the CDK2 pocket," Kriwacki said.

Normally, p27 is removed from CDK2 only at a specific time during the

precise process that leads to cell division, Kriwacki noted. "However, some abnormal kinase enzymes, called tyrosine kinases, jump the gun and tag the elbow of p27 before CDK2 should become active," he said. "This sets CDK2 free to push the cell to divide, even when it shouldn't."

"The findings explain why the anti-cancer drug Gleevec® is effective in treating some forms of leukemia in certain individuals," said Yuefeng Wang, Ph.D., a postdoctoral student in Kriwacki's laboratory who did much of the work on this project. "Gleevec blocks the abnormal tyrosine kinase BCR-ABL and prevents it from tagging Y88," he said. "That keeps the elbow of p27 lodged in the pocket of CDK2 and prevents premature cell division. Our study suggests that other cancer-causing tyrosine kinases may also trigger premature CDK2 activity."

Results of the study suggest that blocking the CDK2 pocket after an abnormal kinase dislodges the p27 elbow might be an effective strategy for preventing cancer cell division, Kriwacki said.

Source: St. Jude Children's Research Hospital