

Researchers closer to understanding cell-division gatekeeper enzyme

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(PhysOrg.com) -- An enzyme called Pin1 regulates the protein that initiates cell division by changing the shape of a peptide bond.

Researchers at Notre Dame and Virginia Tech have discovered how Pin1 communicates through an internal conduit between its two domains to decide whether it will open or shut the gate to cell division.

The research is reported in the early online edition of the [Proceedings of the National Academy of Sciences](#) (*PNAS*) the week of July 4 in the article, "Stereospecific gating of functional motions in Pin1," by Andrew T. Namanja, Xiaodong J. Wang, Bailing Xu, Ana Y. Mercedes-Camacho, Kimberly A. Wilson, Felicia A. Etzkorn, and Jeffrey W. Peng.

"We are trying to understand the fundamental molecular workings of how Pin1 binds cis and trans shaped [peptides](#), and how binding each shape sets up a different dynamic communication link," said Etzkorn, professor of bioorganic chemistry in the College of Science at Virginia Tech.

It has been determined that Pin1 can bind [ligands](#) (small [molecules](#)) in both domains at the same time, and that the two domains communicate across the protein. Peng, associate professor of biophysics at the University of Notre Dame, is looking at the dynamics of this communication.

"Where in the past people have taken photos – stopped action images –

Jeff Peng is in effect shooting video, capturing the protein in action," said Etzkorn.

"What we discovered is that the dynamics of Pin1 change, depending whether its partner is cis or trans shaped. It moves stiffly when bound to cis and more loosely when bound to trans," said Peng.

The researchers previously used nuclear magnetic resonance (NMR) to measure the ligand dynamics of cis and trans bound to the protein (reported in the *Journal of the American Chemical Society*, April 1, 2010).

Etzkorn explains that cis binds solely to the catalytic domain (peptidyl-prolyl isomerase), and trans binds to both the catalytic and WW (Trp-Trp) domains. "The catalytic reaction is a shape shift, which swings the gate open or closed in effect," she said.

The catalytic domain and the WW domain are both parts of Pin1. What the PNAS article reports is how the protein communicates between the two domains, and how the dynamics of Pin1 affects that communication. "We showed that the quality of communication across the interface of the two domains is different depending upon whether cis or trans is bound." said Peng.

"What we are really trying to understand is what Pin1 is doing when it is bound to its native cis or trans substrate, why there are two domains, and how they work together, essentially how the [enzyme](#) works," said Etzkorn.

Understanding the workings of Pin1 has many applications. For example, if Pin1 can be shut down, then cell death occurs, which is a good thing if the dividing cell is a cancer cell. "Understanding the dynamics of ligand binding to Pin1 will help with rational drug design,"

said Etzkorn.

"Many proteins are modular and flexible, and thus may exploit the dynamic gating strategies we've found in Pin1," said Peng.

More information: www.pnas.org/

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