Corrected Protein Structure Reveals Drug Targets for Cancer, Neurodegenerative Diseases

Study revises previously published structure of Protein Kinase C enzyme, proposes new strategies to turn the enzyme "on" to treat cancer or "off" to treat neurodegenerative diseases

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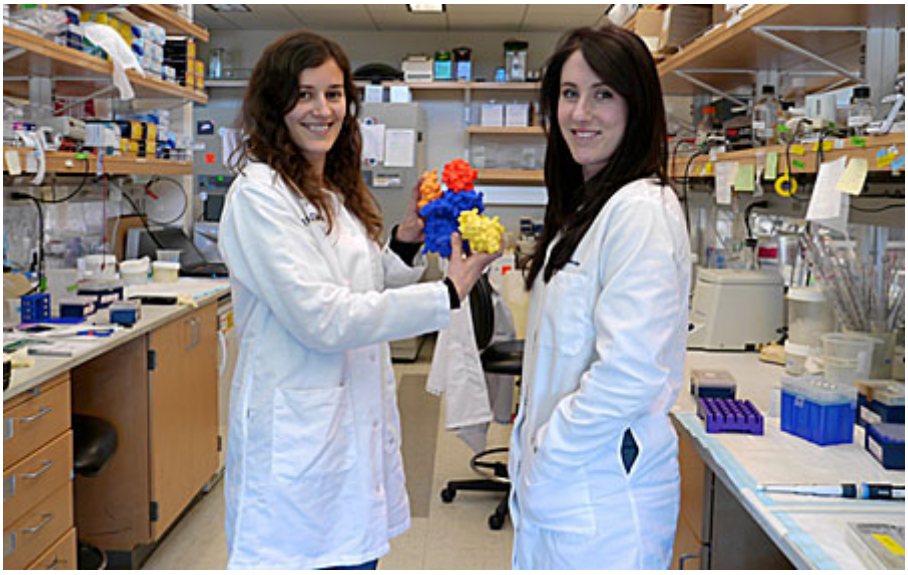
Protein Kinase C (PKC) is a family of enzymes that controls the activity of other proteins in a cell by attaching chemical tags. That simple act helps determine cell survival or death. When it goes awry, a number of diseases may result. In a study published August 13 in *Cell Reports*, researchers at University of California, San Diego School of Medicine reveal a more accurate structure of PKC, providing new targets for fine-tuning the enzyme's activity as needed to improve human health.



Study co-authors Corina Antal (left) and Julia Callender (right) holding the pieces of a new PKC model.

"By understanding how PKC clamps itself closed, we can now look for ways to wedge it open to keep it active," said Alexandra C. Newton, PhD, professor of pharmacology. "This has great potential for developing therapies for cancer, in which keeping the enzyme in its 'on' position will promote tumor cell death. We also want to do the opposite in neurodegenerative diseases, in which we need treatments that keep neurons alive."

Researchers typically use a technique called X-ray crystallography to determine the 3D structure of proteins. But sometimes they have to make assumptions in order to fit the data together as

best they can. In a 2011 study, a different research group resolved most of PKC's structure and made their best guess at how all the pieces fit together.

But that structure didn't add up with the biology of how PKC works. In collaboration with the research team of Susan Taylor, PhD, professor of pharmacology at UC San Diego School of Medicine, Newton and researchers took another look at how to connect the parts, or domains, of the enzyme. They came up with a different structure and tested it using a sophisticated cellular imaging technique to visualize whether PKC was properly packed together or not.

The researchers found that PKC's calcium-sensing (C2) domain interacts with its own tail and enzymatic domain (the part that does the chemical tagging, a process known as phosphorylation), locking the enzyme in an inactive pose. PKC begins to activate when calcium triggers the bridging of the C2 domain to the cell membrane, thus opening the enzyme for activity.

The team also validated this packing by mutating specific parts of the protein that hold the domains together, unlocking and relocking PKC between unpacked and correctly packed structures.

"Knowing the interfaces that hold PKC closed will now allow the design of small molecules that can either disrupt the interactions between PKC's domains to open up and activate the enzyme, or clamp the domains closed to prevent its activation," said first author Corina Antal, PhD, who was a graduate student in Newton's lab at the time of the study.

Co-authors of this study also include Julia A. Callender, and Alexandr P. Kornev, UC San Diego.

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Cancer

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