Researchers describe tools to better understand CaMKII, a protein involved in brain and heart disease

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Optogenetic tools for monitoring and controlling CaMKII activation

(A) Camui is a FRET-based sensor that detects conformational changes in CaMKII upon activation. An N-terminal YFP and C-terminal CFP undergo FRET, while CaMKII is in an inactive state. A conformational change occurs upon activation by Ca\(^{2+}\)/CaM, resulting in decreased FRET. Camui is illustrated here as a...
monomer but is thought to form holoenzymes. (B) FRESCA is a FRET-based sensor of CaMKII activity that uses a modified syntide2 peptide substrate. Under basal conditions, the N-terminal CFP and C-terminal YFP undergo FRET. Upon CaMKII activation and phosphorylation of the syntide2-derived region, the phosphorylated residue binds FHA2, causing a conformational change and decreased FRET. (C) CaMKAR is a CaMKII activity reporter that consists of an N-terminal CaMKII substrate (MHRQETVDCLK) and a C-terminal phosphorylated amino acid binding domain (PAABD) connected by a circularly permuted GFP (cpGFP). This reporter is excitation ratiometric, as emission by 488-nm excitation increases upon phosphorylation of the substrate by CaMKII (and phosphorylation of the substrate), while emission by 405-nm excitation decreases or remains the same. (D) paAIP2 consists of an N-terminal LOV2-Jα domain fused to a C-terminal CaMKII-inhibitory peptide (an improved AIP-related peptide inhibitor) to generate paAIP2. Activation with 488 nm light causes undocking and unwinding of the Jα helix, resulting in exposure of the AIP2 peptide for CaMKII inhibition. (E) paCaMKII contains the light-sensitive LOV2-Jα domain inserted between the CaMKII kinase and regulatory domains. Activation with 488 nm light causes undocking and unwinding of the Jα helix, activating CaMKII, similarly as normally achieved by Ca\(^{2+}\)/CaM stimulation. Note that paCaMKII can still also be stimulated by Ca\(^{2+}\)/CaM and that either light or Ca\(^{2+}\)/CaM makes its T286 homolog accessible for autophosphorylation. The paCaMKII is illustrated here as a monomer but is likely to form dimers but not holoenzymes. (F) Light-induced clustering of CaMKII is achieved by expression and optical manipulation of three constructs: CRY2olig, CIBN-mCherry-CaMKII, and a GFP-tagged protein of interest. Activation with 488 nm light causes both CRY2olig oligomerization (tetramerization) and association of CRY2olig with CIBN, resulting in the formation of red puncta. If CaMKII interacts with the GFP-tagged protein of interest, this protein will co-cluster with the others, resulting in yellow puncta. Credit: Cell Reports (2024). DOI: 10.1016/j.celrep.2024.113982

The health impacts of a complex protein that plays a major role in the development of Alzheimer's disease and heart conditions can be lessened by three kinds of drug inhibitors, according to scientists at the University
In an overview of the protein and the inhibitors published in Cell Reports, the CU researchers discussed the best ways to use the interventions.

The protein CaMKII is ubiquitous in cells throughout the body but is perhaps best known for its prominent role in the brain and the heart. It is critical in learning and memory, but if misregulated, it can cause problems.

"The most powerful engine to drive new discoveries on CaMKII functions may lie in the availability of three distinct classes of pharmacological inhibitors," said the manuscript's senior author, Ulli Bayer, Ph.D., professor of pharmacology at the University of Colorado School of Medicine. "These inhibitors now allow a detailed first assessment of CaMKII functions in any given system in a way that is readily accessible to a broad range of scientists without specialized interest in CaMKII research."

Carolyn Nicole Brown, a graduate student working in Bayer's laboratory, co-authored the manuscript.

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Previous studies by Bayer's lab revealed that inhibiting CaMKII activity protects against some of the effects of amyloid-beta (Abeta) plaques in the brain, a hallmark of Alzheimer's disease (AD).

The researchers found one group of inhibitors, or drugs, that protected from the Abeta effects without detrimental side effects, making it potentially useful in treating a number of brain diseases.
Yet CaMKII is present in nearly every other cell. The review offers insights into the protein for those who don't study it fulltime, providing tools to fill in the gaps in knowledge about how the protein functions.

"We are experts in studying this complex protein and here we provide a guideline for non-specialists to use these new tools," Bayer said. "We are trying to make it easier for everyone."

Brown, the co-author, agreed.

"The most important advances will be filling the gaps that we don't even know about yet," she said.


Provided by CU Anschutz Medical Campus

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