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Report

Differential roles of CaMKII isoforms in phase separation with NMDA receptors and in synaptic plasticity

标题

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SUMMARY

Calcium calmodulin-dependent kinase II (CaMKII) is critical for synaptic transmission and plasticity. Two major isoforms of CaMKII, CaMKIIα and CaMKIIβ, play distinct roles in synaptic transmission and long-term potentiation (LTP) with unknown mechanisms. Here, we show that the length of the unstructured linker between the kinase domain and the oligomerizing hub determines the ability of CaMKII to rescue the basal synaptic transmission and LTP defects caused by removal of both CaMKIIα and CaMKIIβ (double knockout [DKO]). Remarkably, although CaMKIIβ binds to GluN2B with a comparable affinity as CaMKIIα does, only CaMKIIα with the short linker forms robust dense clusters with GluN2B via phase separation. Lengthening the linker of CaMKIIα with unstructured "Gly-Gly-Ser" repeats impairs its phase separation with GluN2B, and the mutant enzyme cannot rescue the basal synaptic transmission and LTP defects of DKO mice. Our results suggest that the phase separation capacity of CaMKII with GluN2B is critical for its cellular functions in the brain.

摘要

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正文常包含以下模块：

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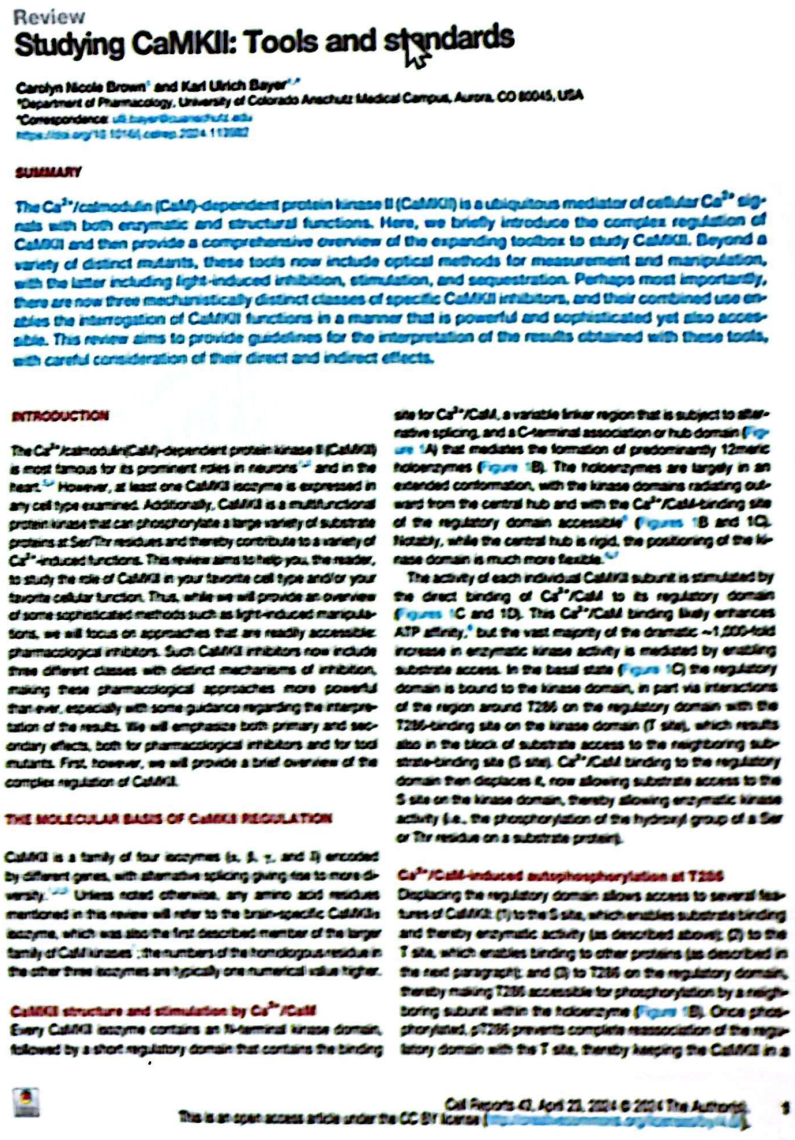

Review

Studying CaMKII: Tools and standards

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SUMMARY

The Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII) is a ubiquitous mediator of cellular Ca^{2+} signals with both enzymatic and structural functions. Here, we briefly introduce the complex regulation of CaMKII and then provide a comprehensive overview of the expanding toolbox to study CaMKII. Beyond a variety of distinct mutants, these tools now include optical methods for measurement and manipulation, with the latter including light-induced inhibition, stimulation, and sequestration. Perhaps most importantly, there are now three mechanistically distinct classes of specific CaMKII inhibitors, and their combined use enables the interrogation of CaMKII functions in a manner that is powerful and sophisticated yet also accessible. This review aims to provide guidelines for the interpretation of the results obtained with these tools, with careful consideration of their direct and indirect effects.

INTRODUCTION

The Ca^{2+}/calmodulin(CaM)-dependent protein kinase II (CaMKII) is most famous for its prominent roles in neurons[1,2] and in the heart.[3] However, at least one CaMKII isozyme is expressed in any cell type examined. Additionally, CaMKII is a multifunctional protein kinase that can phosphorylate a large variety of substrate proteins at Ser/Thr residues and thereby contribute to a variety of Ca^{2+}-induced functions. This review aims to help you, the reader, to study the role of CaMKII in your favorite cell type and/or your favorite cellular function. Thus, while we will provide an overview of some sophisticated methods such as light-induced manipulations, we will focus on approaches that are readily accessible: pharmacological inhibitors. Such CaMKII inhibitors now include three different classes with distinct mechanisms of inhibition, making these pharmacological approaches more powerful than ever, especially with some guidance regarding the interpretation of the results. We will emphasize both primary and secondary effects, both for pharmacological inhibitors and for tool mutants. First, however, we will provide a brief overview of the complex regulation of CaMKII.

THE MOLECULAR BASIS OF CaMKII REGULATION

CaMKII is a family of four isozymes (α, β, γ, and δ) encoded by different genes, with alternative splicing giving rise to more diversity.[1,2,4] Unless noted otherwise, any amino acid residues mentioned in this review will refer to the brain-specific CaMKIIα isozyme, which was also the first described member of the larger family of CaM kinases[5]; the numbers of the homologous residue in the other three isozymes are typically one numerical value higher.

CaMKII structure and stimulation by Ca^{2+}/CaM

Every CaMKII isozyme contains an N-terminal kinase domain, followed by a short regulatory domain that contains the binding site for Ca^{2+}/CaM, a variable linker region that is subject to alternative splicing, and a C-terminal association or hub domain (Figure 1A) that mediates the formation of predominantly 12meric holoenzymes (Figure 1B). The holoenzymes are largely in an extended conformation, with the kinase domains radiating outward from the central hub and with the Ca^{2+}/CaM-binding site of the regulatory domain accessible[6] (Figures 1B and 1C). Notably, while the central hub is rigid, the positioning of the kinase domain is much more flexible.[6,7]

The activity of each individual CaMKII subunit is stimulated by the direct binding of Ca^{2+}/CaM to its regulatory domain (Figures 1C and 1D). This Ca^{2+}/CaM binding likely enhances ATP affinity,[8] but the vast majority of the dramatic ~1,000-fold increase in enzymatic kinase activity is mediated by enabling substrate access. In the basal state (Figure 1C) the regulatory domain is bound to the kinase domain, in part via interactions of the region around T286 on the regulatory domain with the T286-binding site on the kinase domain (T site), which results also in the block of substrate access to the neighboring substrate-binding site (S site). Ca^{2+}/CaM binding to the regulatory domain then displaces it, now allowing substrate access to the S site on the kinase domain, thereby allowing enzymatic kinase activity (i.e., the phosphorylation of the hydroxyl group of a Ser or Thr residue on a substrate protein).

Ca^{2+}/CaM-induced autophosphorylation at T286

Displacing the regulatory domain allows access to several features of CaMKII: (1) to the S site, which enables substrate binding and thereby enzymatic activity (as described above); (2) to the T site, which enables binding to other proteins (as described in the next paragraph); and (3) to T286 on the regulatory domain, thereby making T286 accessible for phosphorylation by a neighboring subunit within the holoenzyme (Figure 1B). Once phosphorylated, pT286 prevents complete reassociation of the regulatory domain with the T site, thereby keeping the CaMKII in a

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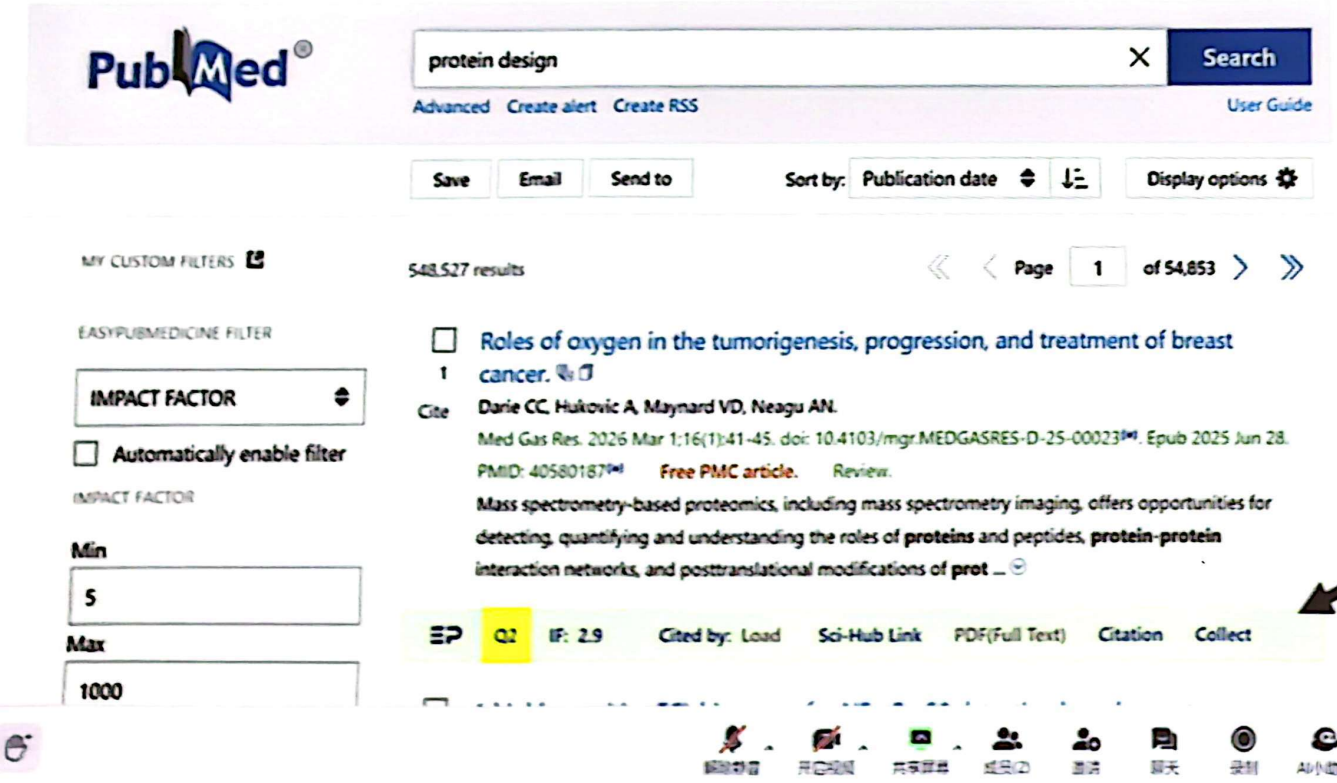

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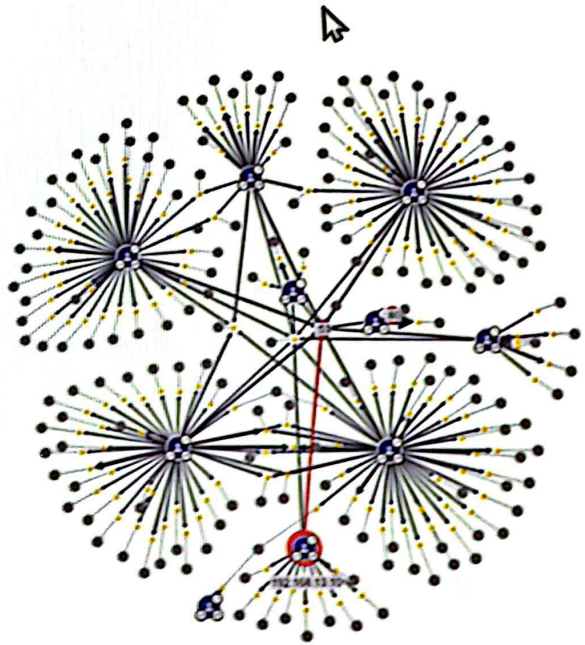

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2. 蛋白质序列设计：深度学习模型可以生成新的蛋白质序列，以实现特定的功能或结构。

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Review

Protein Design with Deep Learning

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Abstract: Computational Protein Design (CPD) has produced impressive results for engineering new proteins, resulting in a wide variety of applications. In the past few years, various efforts have aimed at replacing or improving existing design methods using Deep Learning technology to leverage the amount of publicly available protein data. Deep Learning (DL) is a very powerful tool to extract patterns from raw data, provided that data are formatted as mathematical objects and the architecture processing them is well suited to the targeted problem. In the case of protein data, specific representations are needed for both the amino acid sequence and the protein structure in order to capture respectively 1D and 3D information. As no consensus has been reached about the most suitable representations, this review describes the representations used so far, discusses their strengths and weaknesses, and details their associated DL architecture for design and related tasks.