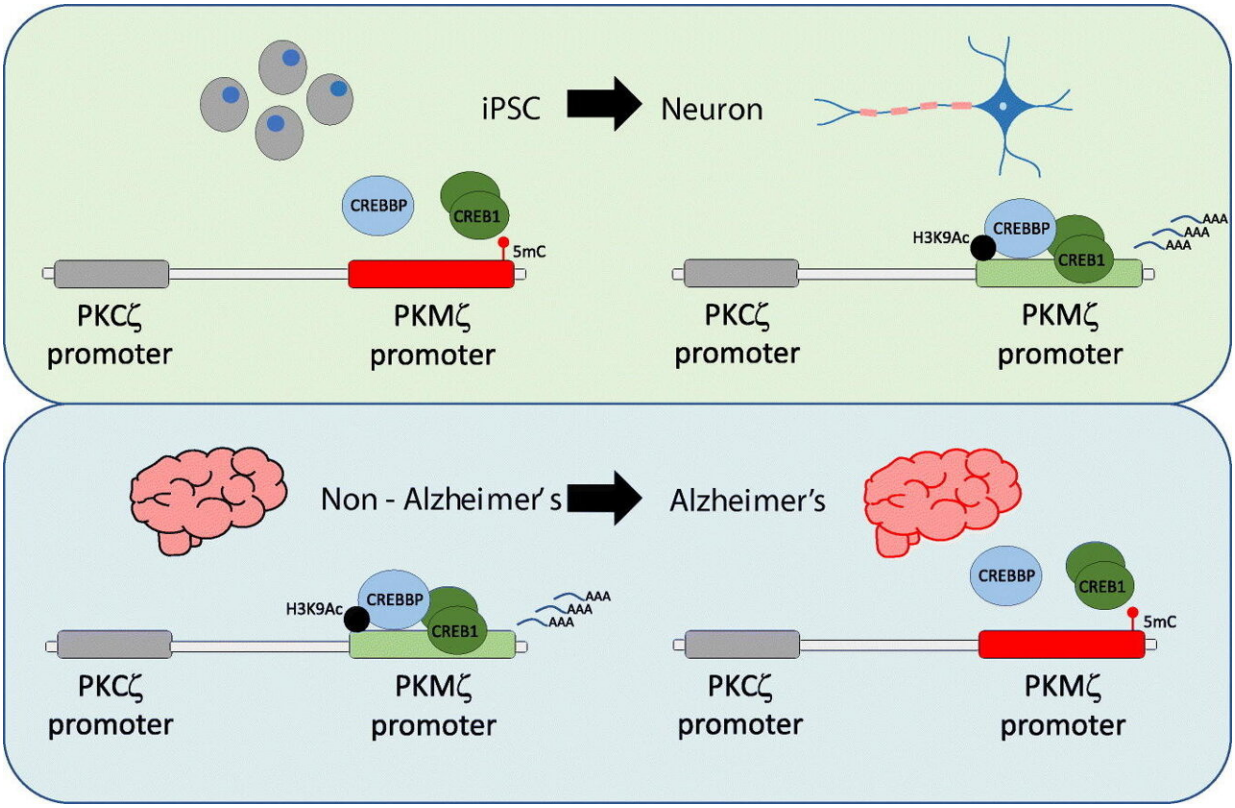
Study describes mechanism that regulates activity of memory gene

April 18 2023, by Theo Ruprecht



Graphical abstract. Credit: *Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms* (2023). DOI: 10.1016/j.bbagrm.2023.194909

The protein PKMzeta is known to be associated with long-term memory formation. Neurological disorders such Alzheimer's disease, as well as depression and aging, correlate with reduced levels of this protein in the

brain. Researchers affiliated with institutions in Brazil and the United States have now discovered a mechanism that helps explain the link and could pave the way to future medical innovations. Their study is reported in article published in the journal *Biochimica et Biophysica Acta (BBA)—Gene Regulatory Mechanisms*.

To understand the mechanism, the researchers used epigenetics, the science of how environmental stimuli activate or inhibit gene expression without altering the DNA sequence. An epigenetic technique often used by researchers is gene silencing by DNA methylation, in which methyl groups are added to a specific section of a gene to prevent its transcription. For example, methylation of the DNA sequence of a gene may turn the gene off so it does not make a protein.

In the article, the authors recall that in the central nervous system the protein CREB1 normally binds to a section of the gene PKMzeta so that it expresses the protein of the same name. The study showed, however, that hypermethylation of this piece of the gene resulted in significantly lower levels of the protein PKMzeta.

"Our analysis revealed that DNA methylation regulates expression of this gene, which plays a role in several pathologies," said Deborah Schechtman, last author of the article and a professor at the University of São Paulo's Institute of Chemistry (IQ-USP) in Brazil. "I believe that when basic science is well done it provides vital information for drug development and advanced therapies."

Inside DNA

Dimitrius Pramio, first author of the article and a Ph.D. candidate in biochemistry at IQ-USP, described the materials used in the study, some of which were obtained thanks to partnerships with Yale University and SUNY Upstate Medical University in the US. "The materials included

databases, human cells isolated from patients or modified in the laboratory, and animal cells," he said.

Several tests were conducted to see if methylation of the gene PKMzeta would lead to a drop in levels of the protein it produces, using drugs that interfere in DNA methylation and the gene-editing technique CRISPR. In this case, alterations made to the gene PKMzeta prevented proper binding of the protein CREB1. "Production of the protein PKMzeta did indeed fall as a result," Schechtman said.

The results confirmed that the gene in question requires CREB1 to trigger production of the protein PKMzeta and that DNA methylation explains the drop in levels of the protein.

The authors also analyzed the role of other genes in the central nervous system to see if they were inhibited by this process of DNA hypermethylation that prevented CREB1 binding. "We wanted to find out whether the process occurred more globally," Schechtman said.

If the expression of other genes besides PKMzeta is affected by this pattern of DNA methylation, it must be particularly relevant to brain alterations possibly associated with pathologies, and the authors showed that the mechanism is not confined to the protein PKMzeta.

Next steps

Several ways forward from this study suggested themselves. One would be to analyze other genes affected by this process of DNA methylation that inhibits CREB1 binding, with the aim of seeing what role they play in the organism, as well as their possible association with diseases.

Another possibility would be to try to understand what the protein PKMzeta actually does in the central nervous system. "We know it's

involved in memory, but how does this work in detail? That's a relevant question," Schechtman said.

For Pramio, it is also important to test the mechanism in more precise models. For example, specific brain regions could be analyzed, as could animal models of diseases such as Alzheimer's and depression. "Other studies have shown that the use of certain antidepressants in animal models of depression restores expression of the gene PKMzeta when it's inhibited, but they didn't investigate DNA methylation," he said.

Other conditions could also be examined. Schechtman, for example, is working on chronic pain, and there is a possibility that the gene PKMzeta could be involved in such conditions owing to its participation in synaptic remodeling of neurons. "Many questions and hypotheses have been raised by the study," she said.

According to Pramio, progress in these research lines could contribute in future to the development of new treatments, which would be particularly important for depression and Alzheimer's, given the challenges posed to physicians by these disorders.

More information: Dimitrius Tansini Pramio et al, DNA methylation of the promoter region at the CREB1 binding site is a mechanism for the epigenetic regulation of brain-specific PKMζ, *Biochimica et Biophysica Acta (BBA)—Gene Regulatory Mechanisms* (2023). DOI: 10.1016/j.bbagrm.2023.194909

Provided by FAPESP