

## tenacious memory

Vivienne Baillie Gerritsen

We need to remember. Yet there are things we would like to forget. They just hang on in there regardless of feeling and time. What is it that keeps a memory alive inside us? What is it that makes a sort of indelible imprint on our brain while other memories slip away? We probably imagine memory as something with a fuzzy border that is impossible to grasp – a little like a piece of cloud. In the past years, however, scientists have demonstrated that our ability to remember things in a lasting fashion is in the hands of several biological molecules that are found in the hippocampus, the part of our brain where memories are formed. When a memory stirs and is chosen to be long-lasting, new proteins are synthesized and synaptic connections begin to grow. One molecule that is proving to have a central role in this process is a protein known as CPE-binding protein 3, or CPEB3 – a protein which, surprisingly, also has prion-like properties.



sketch by Honoré Daumier

(1808-1879)

About twenty years ago, scientists noticed that *Xenopus* oocytes were full of mRNAs that carried a short sequence in their untranslated 3' regions, each of which had a role in controlling cytoplasmic polyadenylation and mRNA translation during development. It was named cytoplasmic polyadenylation element, or CPE, and turned out to be the binding platform for a protein coined CPE-binding protein, or CPEB, which triggered off mRNA polyadenylation and its subsequent translation. Over the years, four

different kinds of CPEB – 1, 2, 3 & 4 – have been identified both in vertebrates and invertebrates; each reacts with different RNA motifs and has a unique molecular function. Concomitantly, it became apparent that, besides germ-cell development, CPEB is able to mediate many other mechanisms one of which is synaptic plasticity.

Synaptic plasticity is the ability synapses have to undergo biochemical and morphological changes in response to neural stimulation. It is at the heart of a brain's capacity to learn and memorize – two faculties that are both intangible and hugely intriguing. What is it in our brain that gives us the ability to remember our mother's face, the way to walk home, or remember our date of birth? Scientists have divided memory into two overlapping phases: short-term memory and long-term memory, both of which involve different molecular activities. Short-term memory is a memory that doesn't last and is brought about by the covalent modification of pre-existing proteins in pre-existing synaptic connections. Long-term memory, however, or what is also known as the persistence of memory, requires the synthesis of novel proteins as well as the growth of new synaptic connections. And this is where CPEB comes in.

CPEB – and more specifically CPEB3 – is found in the hippocampus, and belongs to the limbic system which deals with short-term and long-term memory as well as with spatial

navigation. What is the link between CPEB3 and memory on the molecular level? As mentioned, long-term memory requires the growth of new and lasting synaptic connections which themselves depend upon the local translation of specific mRNAs. This is achieved with the help of CPEB3. How? In a nutshell, upon synaptic stimulation, the level of CPEB3 is increased, promoting the aggregation of CPEB3. Now activated, the protein then binds to the CPEs of specific mRNAs, causing their polyadenylation and subsequent translation. Novel proteins are hence synthesized and literally fuel the growth of new synaptic connections – thus forming the basis upon which long-term memory is formed.

It may sound straightforward but every stage – from CPEB3 activation to synaptic growth – is complex. CPEB3 has turned out to be a protein with a prion-like nature: upon stimulation, it creates aggregates much like prions would, and it is in this form that the protein becomes functional. For this, CPEB3 carries a prion formation region which itself is divided into three parts: a central domain that is thought to interact with the cell's actin cytoskeleton, and two flanking domains involved in promoting aggregation. Upon synaptic stimulation, CPEB3 levels rise, subsequently triggering off aggregation, while the actin-binding domain interacts with the cell's cytoskeleton no doubt to stabilize the forming aggregates.

Meanwhile, it is in this aggregated form that CPEB3 springs to life and binds to the CPE domains of mRNAs to stimulate their translation. It does not do this on its own,

however, but associates with several other factors. The role of CPEB3 in human memory has actually been funnelled down to what is known as human episodic memory, i.e. the memory of autobiographical events which occur at a given time and place. With this in mind, it is not difficult to understand that severe neurological disorders are bound to arise if the normal regulatory control of CPEB3 is hindered. Uncontrolled aggregation of CPEB3 could indeed be at the heart of prion diseases in the brain.

CPEB family proteins have come a long way. First thought to be required only for germ-cell development, they now appear to also have a central role in the persistence of memory. What is more, CPEB3 and its prion-like nature proves yet again that prions are not necessarily bad but can be of biological importance. However, as the years go by, there is growing evidence that prion-like mechanisms – no doubt caused by 'dysfunctional prions' so to speak – are at the heart of neurodegenerative disorders such as Alzheimer's, Huntington's disease and Parkinson's disease. The rule seems to be that pathological prions are of a stochastic nature, while 'healthy' prions depend upon tight regulation and are induced by physiological stimuli. It is always a little perturbing to narrow down the talent we have of remembering to a mere interplay of molecules. Yet without that interplay, we would have no memories. We know today that CPEB3 is needed to solidify memory. What would be intriguing to find out now is what traces the contours of memory itself.

---

## Cross-references to UniProt

Cytoplasmic polyadenylation element-binding protein 3, *Homo sapiens* (Human) : Q8NE35

## References

1. Fioriti L., Myers C., Huang Y.-Y., Stephan J.S., Trifilieff P., Colnaghi L., Kosmidis S., Drisaldi B., Pavlopoulos E., Kandel E.R.  
The persistence of hippocampal-based memory requires protein synthesis mediated by the prion-like protein CPEB3  
Neuron 86:1433-1448(2015)  
PMID:
2. Richter J.D.  
CPEB: A life in translation  
TRENDS in Biochemical Sciences 32:279-285(2007)  
PMID: