Memory

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Unlocking the epigenetic secrets of memory

Oriane Mauger & Elisabeth B. Binder

The epigenetic underpinnings of memory are still poorly understood. A study provides a causal link between the epigenetic dynamics of a single genomic locus in engram cells and memory formation, achieved by the development of a reversible epigenetic editing tool.

Learning and memory are vital cognitive functions for our survival and identity. These processes are believed to be stored in so-called engram cells[1]. These are a sparse population of cells activated during an experience and reactivated upon memory recall. The plasticity of these engram ensembles is a process widely thought to be controlled by epigenetic programs and activity-dependent transcription. Although previous studies have shown correlations between epigenetic changes and memory and the formation of engram cells, proof using experiments that address causality has been lacking[2]. In this issue of *Nature Genetics*, Coda et al.[3] provide direct evidence of a functional link between epigenetic regulation at a specific genomic locus in engram cells and memory performance. The authors developed an innovative molecular tool to manipulate chromatin at specific loci in engram cells. This tool enables reversible epigenetic editing (epi-edi) of the *Arc* promoter, providing the proof of a causal link between transient epigenetic regulation of gene expression and memory formation.

This CRISPR-based epi-edi tool relies on a clever combination of a Tet-Off and floxed systems in FOS-TRAP2 and FOS-tTa mouse lines, allowing precise spatiotemporal induction of an epigenetic editing complex in FOS-positive cells, which serve as proxies for engram cells (Fig. 1). By manipulating the epigenetic landscape at the *Arc* promoter in engram cells activated during learning, the authors demonstrated significant effects on memory recall. The effects were reversible, providing direct evidence that altering a single locus in engram cells is sufficient to bidirectionally and reversibly regulate memory performance.

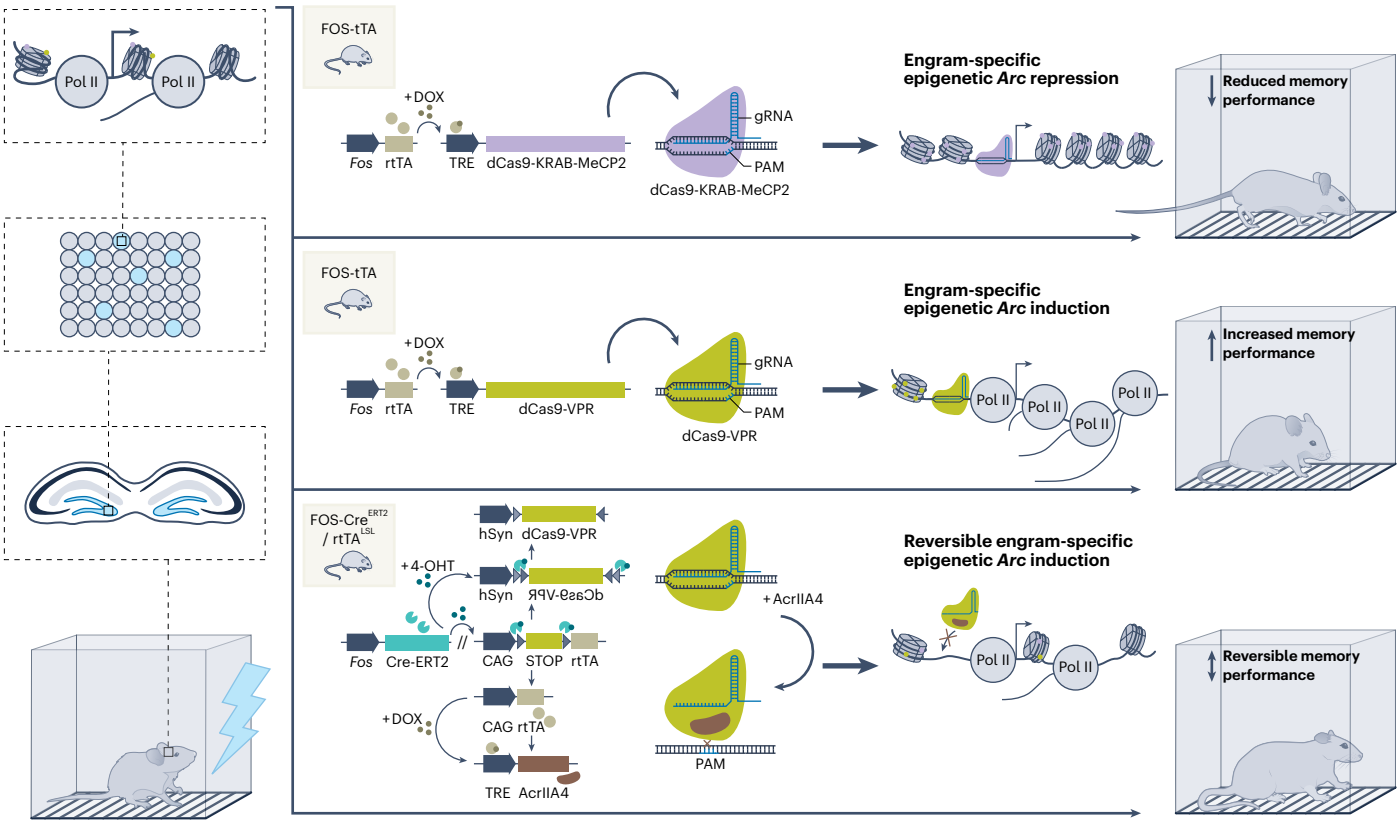

Fig. 1 | Epigenetic editing for memory manipulation. Spatiotemporal expression of a CRISPR-based repressor (dCas9-KRAB-MeCP2, top) or an activator (dCas9-VPR, middle), with AcrIIA4-dependent blockage (bottom), enables reversible control of the epigenetic landscape of the *Arc* promoter, which is sufficient for memory performance modulation. 4-OHT, 4-hydroxytamoxifen; DOX, doxycycline; Pol II, RNA polymerase II; rtTA, reverse tetracycline-controlled transactivator; TRE, tetracycline-responsive element.

Beyond linking a single epigenetic locus to memory processes, the epi-edi tools offer unprecedented opportunities to explore the molecular basis of memory and plasticity events in engram cells. The focus on *Arc* is particularly relevant as it encodes a multimodal protein long known to have various roles in synaptic plasticity, including long-term potentiation, long-term depression and homeostatic scaling. However, the specific plasticity events occurring in engram cells during learning have remained unclear[4]. The here presented epi-edi tool will help to unravel these events taking place specifically in engram cells upon epigenetic *Arc* regulation.

The authors' work[3] also enables a deeper look into the timing of *Arc* regulation. A recent study revealed that *Arc* undergoes several consecutive rounds of activity-dependent transcription[5]. As the expression of the epi-edi tool is based on the initial activation of the *Fos* promoter, it is unlikely to alter the first round of *Arc* activity-dependent transcription. This suggests that the observed effects on memory result from the manipulation of a later round of transcription, adding physiological relevance to the finding.

Arc here serves as a prototype, but many other genes are also regulated by chromatin modifications and activity-dependent transcription upon experience. It is widely believed that the activity-dependent induction of these genes contributes to memory, and although there is abundant indirect evidence, direct proof has been scarce[6]. The epi-edi tool will finally provide a way to decipher the acute plasticity events controlled by individual activity-dependent genes.

The second key advantage of the epi-edi method is its superior cellular and spatial resolution. As it relies on viral strategies, it is possible to target specific brain regions. In this study[3], the authors targeted the dentate gyrus, a key region for memory processes. Beyond the classical brain regions, recent research suggests that nearly all sub-brain regions activated during learning may have roles in memory[7]. It will therefore be interesting to assess the functional specificity of the same activity-dependent gene in different brain regions. Additionally, evidence suggests that different subsets of engrams exist within the same brain region, each with unique functions[8,9]. It is intriguing to hypothesize that the same activity-dependent gene could harbor different functions in distinct sub-engrams.

Third, the reversible and temporal capabilities of the tool are a game-changer. This system will be invaluable for dissecting the molecular programs that govern different memory stages, from initial consolidation to extinction and reconsolidation. Recent findings suggest that even during synaptic and systems consolidation, engrams are not static but undergo substantial reorganization[10]. Although the molecular basis of this engram plasticity remains unknown, it is a possibility that activity-dependent genes are involved. The epi-edi tool offers a powerful new way to test this hypothesis and explore the precise contribution of individual activity-dependent epigenetic regulation to memory dynamics.

Ultimately, in addition to providing a causal relationship between epigenetic regulation of a specific locus and memory, the developed tools open new possibilities for exploring the mechanisms of maladaptive memories and their context dependency and priming. In fact, exposure to early-life stress has been shown to reduce ARC-positive neurons associated with memory formation[11]. Understanding whether there are convergent epigenetic mechanisms between early-life stress and memory formation is crucial, as exposure to childhood adversity is an important risk factor for the development of post-traumatic stress disorder, wherein maladaptive memory processes are key symptoms[12]. Similarly, maladaptive memories are key processes underlying addiction[13], and understanding how initial drug exposure imprints cells with persistent plasticity could have therapeutic relevance[14]. Finally, a better understanding of the epigenetic regulation in engram cells and memory processes could inform therapeutic approaches for a number of psychiatric disorders, potentially enabling more targeted combinations of epigenetically active medication and psychotherapy.

Oriane Mauger[1] & Elisabeth B. Binder[2]
[1]Max Planck Institute of Psychiatry, Munich, Germany. [2]Department Genes and Environment, Max Planck Institute of Psychiatry, Munich, Germany.
e-mail: binder@psych.mpg.de

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Competing interests

The authors declare no competing interests.