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Neuronal Chromatin Architecture Regulator CTCF Dictates Remote Memory

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Review of Kim et al.

How the brain is able to form and store memories for long periods of time is a longstanding question in neuroscience. After learning, cellular and molecular consolidation processes start in specialized brain regions, including the hippocampus and the ACC. One of the first events in memory consolidation and synaptic plasticity is gene transcription and *de novo* protein synthesis (Alberini and Kandel, 2014). Disruption of this process leads to severe long-term memory impairments in a wide range of species. This observation prompted studies of the transcriptional regulatory mechanisms required for memory formation. These include transcription factors, which control the rate of transcription, and epigenetic factors and chromatin architecture regulators, which dictate the access of transcription factors and the general transcriptional machinery to gene loci.

Because DNA is packed into chromatin and arranged in the nucleus as chromosomes, gene transcription is highly influenced by chromatin architecture. The term chromatin architecture refers to the 3D organization of chromatin, which is determined by loop formation and interactions with structural proteins. The 3D position of genes ensures a precise regulation of gene transcription. For example, chromatin loops increase or decrease proximity between promoters and transcriptional regulatory sequences (e.g., enhancers or insulators). Chromatin loops also relocate gene loci between transcriptionally active and silent domains (Medrano-Fernández and Barco, 2016).

Several studies have reported the functional importance of chromatin architecture in cognition (Rajarajan et al., 2016). For instance, interfering with chromatin loops in mouse forebrain neurons by abolishing the recruitment of chromatin-modifying complexes onto the DNA alters expression of protein-coding genes and miRNAs and results in long-term memory impairments (Jaitner et al., 2016). Similarly, acutely disrupting the configuration of transcriptionally silent chromatin domains (i.e., chromocenters) in hippocampal neurons impairs *de novo* gene transcription and leads to long-term memory impairments in adult mice (Gulmez Karaca et al., 2018). However, until now, the role of chromatin architecture regulators was investigated only in recent long-term memory (i.e., days after learning). Whether chromatin architecture controls long-term maintenance of memory remains unclear.

Remote memories, which represent experiences acquired several weeks, months, or even years ago, are believed to be formed by the transfer of recent memories from hippocampus to cortical areas. Importantly, like recent memories, remote memories require regulation of gene transcription, which raises the possibility that determinants of chromatin architecture also contribute to the formation of remote memories.

Neuronal CCCTC-binding factor (CTCF) is a well-characterized chromatin architecture regulator (Medrano-Fernández and Barco, 2016). It functions as an insulator, meaning that it recognizes a particular DNA sequence and interferes with enhancer-promoter interactions. The CTCF binding sequence is present in various regions, including enhancers, gene promoters, and gene bodies (Rajarajan et al., 2016). Recent studies have shown that CTCF binding governs the formation of chromatin loops (Guo et al., 2015), which indicates that CTCF regulates 3D-genomic architecture. However, whether CTCF-mediated chromatin architecture changes gate memory storage is still unclear.

In a study published in *The Journal of Neuroscience*, Kim et al. (2018) investigated the functions of CTCF in hippocampal-cortical networks during recent and remote memory. To do so, they knocked out CTFC selectively in excitatory or inhibitory mouse forebrain neurons and tested these mice on

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hippocampus-dependent tasks (i.e., Morris water maze) and contextual-fear conditioning either 24 h or 3 weeks after training (Kim et al., 2018). They found that recent memory did not require CTCF in either excitatory or inhibitory neuronal networks. In contrast, when tested after 3 weeks, mice lacking CTCF in excitatory neurons displayed remote memory impairments in both behavioral tasks. Eliminating CTCF in inhibitory neurons promoted remote memory deficits in Morris water maze, but not in contextual-fear conditioning. Overall, these findings suggest a specific role for CTCF in remote memory and a cell type-specific function. Specifically, CTCF in excitatory neurons regulates remote spatial and contextual-fear memory, whereas in inhibitory neurons CTCF seems to be required only for spatial memory.

To elucidate the mechanisms through which CTCF in excitatory neurons contributes to remote memory, Kim et al. (2018) recorded activity in hippocampus and ACC in brain slices from CTCF KO and WT mice. Field recordings showed that basal transmission and late LTP were impaired in ACC neurons of CTCF-deficient animals compared with WT, but no difference in basal transmission or late LTP in the hippocampus was detected. These experiments clearly demonstrate that CTCF regulates synaptic plasticity selectively in cortical neurons. According to the traditional view of systems consolidation theory, the hippocampus is required only for recent memory consolidation, whereas remote memories depend on cortical regions, such as the ACC. This could explain why CTCF KO animals have selective remote memory deficits.

Although Kim et al. (2018) uncovered the functions of CTCF in remote memory, the precise neuronal mechanisms are not clear. Given that late LTP depends on gene transcription, late LTP impairments in slices suggest that after learning, ACC neurons exhibit altered gene expression. This is supported by recent evidence that CTCF regulates learning-induced chromosomal changes in the *Arc* and *BdnfIV* gene loci, and thus dictates their transcription upon learning (Sams et al., 2016). It is tempting to speculate that knocking out CTCF in ACC neurons disrupts transcription of genes required for synaptic plasticity and memory, such as *Arc* and *BdnfIV*. In this scenario, impaired gene expression patterns could underlie the mechanism by which CTCF contributes to remote memory formation.

Several studies have shown that remote memory formation requires multiple waves of gene expression for particular genes (e.g., *Arc* and *Bdnf*) (Oliveira, 2016; Medina, 2018) several hours after the initial gene transcription event. Abolishing this delayed gene transcription leads to remote memory impairments while sparing recent memory. It is currently thought that these multiple rounds of gene transcription strengthen hippocampal-cortical connectivity during systems consolidation. Therefore, rather than regulating the initial gene transcription event, an alternative hypothesis is that CTCF regulates delayed waves of gene expression. If this is the case, then CTCF activity would be expected to occur multiple times during memory consolidation to alter chromosomal architecture at the gene loci that are transcriptionally activated at various stages of consolidation. Another possibility is that CTCF establishes different chromatin architectural changes for memories that last only several days (recent) or weeks to months (remote). In this scenario, CTCF would trigger longer-lasting architectural changes for remote memories, which in turn might render the transcriptional machinery more likely to be recruited at specific gene loci later in time. If indeed CTCF regulates multiple rounds of gene expression, this could explain the selective remote memory deficits observed by Kim et al. (2018).

In contrast to the traditional view of systems consolidation, recent studies have suggested that remote memory is not fully independent of hippocampal function (Wiltgen and Tanaka, 2013). Therefore, one cannot exclude the possibility that hippocampal CTCF is partially required for remote memory. While synaptic properties of hippocampal neurons were intact in the absence of CTCF function, these experiments lacked the temporal component (i.e., weeks) required for systems consolidation. It is possible that, over time, hippocampal CTCF is necessary to maintain the hippocampal-ACC connectivity that is required for remote memory. This possibility remains to be investigated. The strategy used by the authors of knocking out CTCF simultaneously in the hippocampus and ACC does not allow dissociating the functional roles of CTCF in both regions. This could be overcome by knocking out CTCF in the hippocampus or ACC independently and addressing recent and remote memory integrity.

Overall, Kim et al. (2018) provided compelling evidence that chromatin architecture in mature excitatory neurons, regulated by CTCF, is essential for remote memory formation. These findings highlight the role of chromatin architecture in cognitive processes and provide a new direction for further investigations into the underlying mechanisms of intellectual disability, neurodegenerative disorders, and age-associated cognitive decline, which might in turn lead to the development of new therapeutic strategies.

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