NEUROSCIENCE

Synapse and genome: An elusive tête-à-tête

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Two recent papers center on the emerging intersection of DNA methylation and homeostatic plasticity. To better appreciate the context of these studies, we first briefly review the mechanistic connections between DNA methylation and plasticity before delving into the ways in which these two papers fortify the connection between synapse and nucleus but also highlight the need for studies with a broader perspective.

Activity-dependent development of the nervous system involves an ongoing conversation between the synapse and the nucleus. Connections between neurons are strengthened and weakened by multiple forms of neuronal plasticity that depend, in part, on new transcription and translation [for reviews, see (*1*, *2*)]. At the same time, the emergence of complex learned behaviors with development depends critically on epigenetic modifications in the neuronal genome. Diseases like Rett syndrome, in which impaired readout of epigenetic marks by the protein MeCP2 (methyl CpG binding protein 2) offers a prime example, is far from the only one. Diseases associated with impaired or abnormal plasticity as diverse as schizophrenia, depression, and addiction have all been linked to epigenetic mechanisms [for reviews, see (*3*–*5*)].

The study of epigenetic contributions to neuronal plasticity sits at the intersection of two highly complex, rapidly evolving, and often contentious areas of research. Both involve large networks of multifunctional proteins, one network located in the nucleus and the other at the synapse. Understanding how these two networks converse with each other is a major research goal. However, characterizing each network alone has proven to be a moving target. Considering just DNA methylation, notions of this mark have evolved from a concept of near permanence to an understanding that it is both dynamic and multifaceted, with differing functions depending on the flavor and location in the genome. At the same time, synaptic plasticity has evolved from a near-exclusive focus on Hebbian mechanisms to encompass a broader view of cellular and synaptic mechanisms operating over multiple spatial and temporal scales both to dynamically reconfigure networks and to homeostatically maintain stable circuit function.

Two recent papers (*6*, *7*) center on an emerging intersection between DNA methylation and homeostatic plasticity. Here, we first review some of the mechanistic connections between DNA methylation and plasticity. We then examine how these two papers strengthen these connections, while also highlighting the need for studies with a broader genomic perspective.

DNA methylation and Hebbian plasticity

DNA methylation has long been known to be critical for early development and cellular differentiation. However, within the last decade, there is growing appreciation for a continued role in shaping neuronal activity into adulthood. Some of the first work to link DNA methylation specifically to synaptic plasticity came from Sweatt and colleagues (*8*, *9*), who used the nucleoside analogs zebularine and 5-azacytidine to inhibit DNA methyltransferases (DNMTs) acutely in hippocampal slices. These drugs blocked long-term potentiation (LTP), without changing baseline transmission as assessed using field potential recording. At about the same time, two groups reported that LTP was also selectively impaired in slices from mice lacking the methyl DNA binding protein, MeCP2 (*10*, *11*).

Concern about a lack of specificity of drugs used to inhibit DNMT activity led Feng and colleagues (*12*) to examine mice in which genes encoding DNMTs were conditionally knocked out from forebrain neurons. DNMT1 deletion was initially reported not to affect postmitotic cerebellar or hippocampal neurons (*13*). However, double knockout of *DNMT1* and *DNMT3A* (but neither alone) reduced LTP and enhanced long-term depression (LTD) without appearing to affect baseline transmission (*12*).

These findings made sense in light of the profound learning deficits observed in patients and animals lacking normal MeCP2 function and in animals given DNMT inhibitors or lacking both brain DNMT isoforms. However, several additional studies now suggest that blockade of LTP is not a direct consequence of MeCP2 loss, but rather a secondary consequence resulting from a net reduction of excitatory synaptic transmission. Several groups found strong, cell-autonomous reductions in the frequency of miniature excitatory postsynaptic currents (mEPSCs) in cultured neurons lacking MeCP2 (*14*–*16*). Such reductions in frequency are presumed to reflect a reduction in the number of excitatory synapses or of their propensity to release vesicles of glutamate, whereas changes in the amplitude of mEPSCs are presumed to reflect changes in the postsynaptic response to individual vesicles. Because LTP induction requires sufficient postsynaptic depolarization, it can be harder to achieve when the stimulated synapses are fewer or weaker. This can be overcome by directly depolarizing the postsynaptic cell to, in essence, rescue activity. Indeed, when postsynaptic depolarization is supplied directly, normal LTP can be induced in neurons from mice lacking MeCP2 (*17*). This demonstrated that the LTP deficits described earlier were likely due to insufficient activity from weaker/fewer synapses rather than an intrinsic defect in LTP. Although this experiment has not been performed in mice lacking DNMT activity, it raises the distinct possibility that mechanisms connecting LTP to DNA methylation are secondary to other kinds of changes in synaptic strength, such as those that occur in homeostatic plasticity.

DNA methylation and homeostatic plasticity

Hebbian plasticity has the potential to disrupt the stability of brain networks through possible positive feedback between activity and synaptic strength: Strong synapses drive more network activity, which in turn strengthens synapses, which in turn increases activity. Luckily, there are also homeostatic mechanisms that promote network stability by globally adjusting the strength of synaptic transmission in opposition to Hebbian changes. Synaptic scaling is a form of nega-

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tive feedback that reduces synaptic strength when network activity is high and increases synaptic strength when it is low (*18*, *19*). Synaptic scaling is expressed as a change in the accumulation of surface AMPA receptors leading to a corresponding change in quantal amplitude (mEPSC amplitude). In addition to scaling of excitatory synapses, multiple other biophysical mechanisms for homeostatic plasticity have been identified. For example, under some conditions, the frequency rather than the amplitude of mEPSCs changes, reflecting changes in the probability of release or the number of release sites. Like late phases of LTP and LTD, homeostatic plasticity requires transcription.

The first evidence linking homeostatic plasticity to DNA methylation came from Nelson *et al*. (*14*), who found that treating hippocampal cultures with blockers of synaptic inhibition to raise activity levels resulted in decreased presynaptic function at excitatory synapses. This presynaptic form of homeostatic plasticity was mimicked and occluded by DNMT inhibitors. The reduction in excitatory presynaptic transmission was also seen following loss of MeCP2. Although DNMT inhibition was accompanied by demethylation of the *BDNF* promoter and reduced *BDNF* expression, this was shown not to contribute to the homeostatic plasticity. Controversy has also surrounded the question of whether or not *BDNF* is an important target of MeCP2 regulation in vivo (*20*).

Several subsequent studies have linked MeCP2 to the postsynaptic form of homeostatic plasticity, synaptic scaling. Two studies (*21*, *22*) showed that scaling down of postsynaptic strength in response to increased activity requires MeCP2 expression and phosphorylation, whereas a third (*16*) showed a cell autonomous requirement for MeCP2 for scaling up of synapses in response to reduced activity. Although scaling up and scaling down do not occur through identical mechanisms (*23*), both seem to require MeCP2. This work strongly implicates DNA methylation in synaptic scaling but leaves open the questions of where, when, and how the relevant methylation was regulated.

Other epigenetic targets and synaptic plasticity

Just as ideas about which forms of plasticity are regulated epigenetically have evolved, views of the underlying epigenetic mechanisms have also been in flux. The discovery in 2009 (*24*) that Tet proteins and 5-hydroxymethylcytosine (5hmC) play a significant role in the mammalian epigenome (*25*) invigorated many areas of research pertaining to 5mC regulation. It opened up possible mechanisms to explain regulated loss of 5mC that could alter downstream cellular processes at the synapse.

Tet proteins oxidize 5mC to produce 5hmC. This activity has primarily been investigated as a mechanism of active DNA demethylation. Two commonly cited examples of active demethylation in mammals occur (i) during zygotic reprogramming, where 5mC throughout the paternal genome is converted to 5hmC, then fully demethylated, and (ii) activity-induced, loci-specific loss of 5mC in neurons. In the years since MeCP2's initial characterization, our understanding of cytosine modification in mammals has grown to include multiple forms such as 5hmC, as well as functional distinctions at both the nucleotide level, such as mCG versus non-CpG methylation (mCH), and at the genomic level, such as promoter versus gene-body methylation. Concomitant with this expanding view of DNA methylation, the reader functions of MeCP2 have grown more complex and nuanced (*26*, *27*).

A model of 5hmC as an intermediate in active DNA demethylation suggests that it should be fairly rare and short-lived. However, surprisingly high levels of 5hmC (10 times that found in ES cells) are detected in the brain (*28*), raising the possibility that it could directly influence epigenetic readers now understood to potentially encounter this mark. For example, experiments testing the effect of 5hmC on MeCP2 DNA binding reveal a second surprise in that MeCP2 can in fact bind hydroxymethyl DNA. Although subsequent characterization has become confused among studies using different 5mC and 5hmC contexts [reviewed in (*27*)], unbiased MeCP2 genomic mapping in neurons finds broad enrichment and an association with gene bodies where 5hmC is also often enriched (*29*). Although these data do not yet provide a unified picture for MeCP2 function, they do suggest important roles outside of typical mCG islands most often found at gene promoters.

The high levels and ability of MeCP2 (and most recently, the E3 ubiquitin-protein ligase UHRF2) to read 5hmC suggest that this mark might serve a regulatory role distinct from, and more significant than, simply an intermediate in active DNA demethylation (*30*). In fact, there is growing evidence that 5hmC and mCH have CNS-specific roles. Recent advances in epigenomic profiling are finding that although mCG patterns are largely consistent across cell types [reviewed in (*31*)], 5hmC and mCH increase significantly during postnatal neuronal development to establish cell-type–specific patterns. Studies tracking 5hmC over time have found that certain loci are stable over the long term, again counter to the expectation of an intermediate (*32*, *33*). Interestingly, MeCP2 expression increases in parallel with the levels of 5hmC and mCH during postnatal neuronal development (*32*, *33*).

With this stability and readability in the neuronal epigenome, it is not surprising that a role for 5hmC in transcription regulation is beginning to emerge, and some forms of learning and memory are also companied by changes in 5hmC patterns (*34*, *35*), providing the possibility that this mark on its own may regulate synaptic function.

Tet proteins join the nuclear-synaptic conversation

Two recent studies now add Tet proteins to the network of epigenetic regulators that influence the synapse alongside MeCP2 and DNMTs. Both use developing primary neurons in dissociated cultures to demonstrate that Tet levels respond to changes in neuronal activity that ultimately result in synaptic scaling. These studies are important additions to a small but growing body of literature investigating the effect of epigenetics on non-Hebbian mechanisms of plasticity. However, they follow previous studies in focusing on 5mC levels and DNA demethylation as the mechanisms of action. When taken together and in the context of 5hmC as a possible contributor, contradictions and ambiguities continue to plague this field as investigators wade through the deepening complexity.

Meadows *et al*. (*7*) begin by examining the effect of activity blockade on the expression of proteins known to regulate methylation. They find that, whereas DNMT levels are stable, Tet1, but not Tet3, expression increases. The rest of the study manipulates DNMT activity to mimic the effect of increased Tet1 expression. Inhibition of DNMTs pharmacologically or by shRNA knockdown scales up mEPSC amplitude similar to the upscaling that occurs when activity is blocked. This suggests that decreased neuronal activity up-regulates Tet1, which drives demethylation (mimicked by loss of methylation via DNMT inhibition), ultimately resulting in scaling up. However, these findings are at odds with the earlier work by Nelson *et al*. mentioned above, where a different class of

inhibitors or DNMT1/3 knockout in cultured hippocampal neurons resulted in synaptic scaling down (*14*).

Yu *et al*. (*6*) also start by examining the expression of Tet proteins after manipulating activity in neuronal cultures. Unlike Meadows *et al*., they find that Tet3 is specifically down-regulated by activity blockade with no effect on Tet1 or Tet2 levels. This replicates an earlier finding also in primary neocortical neurons (*35*). Yu *et al*. follow this up with additional manipulation of Tet protein levels and/or inhibition of base excision repair (BER) enzymes responsible for downstream steps of active DNA demethylation. The relationship found in this study is that upscaling is associated with increased 5mC and scaling down with demethylation. This is consistent with earlier work showing that DNA demethylation through Gadd45b is activity induced (*36*), as well as the earlier study by Nelson *et al*. (*14*).

A fourth recent publication (*37*) also touches on this controversy with the finding that activity deprivation in vivo by monocular deprivation results in increased DNMT1/3 expression and increased 5mC in the visual cortex. Transcriptome analysis from the cortex reveals changes in expression of many genes involved in synaptic function. Given that monocular deprivation has been shown to produce homeostatic upscaling in the visual cortex, this finding is also consistent with a relationship where increased 5mC produces upscaling.

Although the majority of studies reviewed suggest a positive correlation between 5mC levels and synaptic activity, it is possible that differences in cell type and/or experimental conditions can account for conflicting findings. This raises the potential for significant complexity in the relationship between 5mC and synaptic strength if fairly minor experimental differences can produce diametrically opposed results. Perhaps at this stage, rather than focusing on teasing out specific mechanistic nuances, it is worth taking a step back to examine the subject from a wider perspective.

When following the logic that has led to these recent studies, the spotlight is easily trained on mCG. Investigations into MeCP2 function have necessarily focused on mCG, given the only recent appreciation for contributions from other modifications. Among Tet/5hmC studies, the focus has also been on active DNA demethylation, and again on mCG levels. However, in a tissue that clearly shows unique properties and patterns of cytosine modification, it is possible that continuing this narrow focus may pull attention away from other relevant aspects of the mechanism (Fig. 1).

Examining a wider cross section of cytosine modification may bring clarity to conflicting findings from seemingly similar studies as well as reduce the number of caveats around interpretation of data such as these. For example, unappreciated differences in the mechanisms of action of different DNMT inhibitors could explain seemingly opposing results. We do not know whether different types or genomic locations of 5mC turn over at different rates, and, given that 5hmC is the product of 5mC, DNMT inhibitors may also effect this mark. Combine this with studies that use complex experimental designs involving combinations of drugs and genetic manipulations that inhibit or promote different aspects of these pathways, but have not been fully vetted regarding their effects on the epigenome in neurons, and confident interpretation becomes incredibly difficult. For example, in a cell type with high basal levels of 5hmC, does inhibiting BER increase 5mC levels due to a lack of demethylation, or could 5mC levels actually decrease due to Tet-mediated conversion to 5hmC? Without measurement of these marks using methods that can distinguish 5mC from 5hmC (*38*), it is difficult to attribute the observed scaling to one epigenetic mechanism versus another. In the case of the neuronal epigenome, there are simply still too many unknowns to predict with certainty which marks change under what conditions and, more importantly, which of those changes are critical for observed biophysical changes.

There is little doubt that active DNA demethylation in neurons is an important mechanism, and these recent studies reinforce the importance of cytosine modification while bringing to light a key role for Tet proteins in synaptic plasticity. However, understanding the role of Tet proteins, and cytosine modification more generally, will likely require an unbiased look at both 5mC and 5hmC. With advances in genomic technologies, it is now possible to specifically map both marks throughout the neuronal genome (*31*, *35*). This type of unbiased look in the context of manipulations of specific components of the pathway should provide answers to many of the fundamental questions plaguing interpretation of current studies. In addition, it will allow identifica-

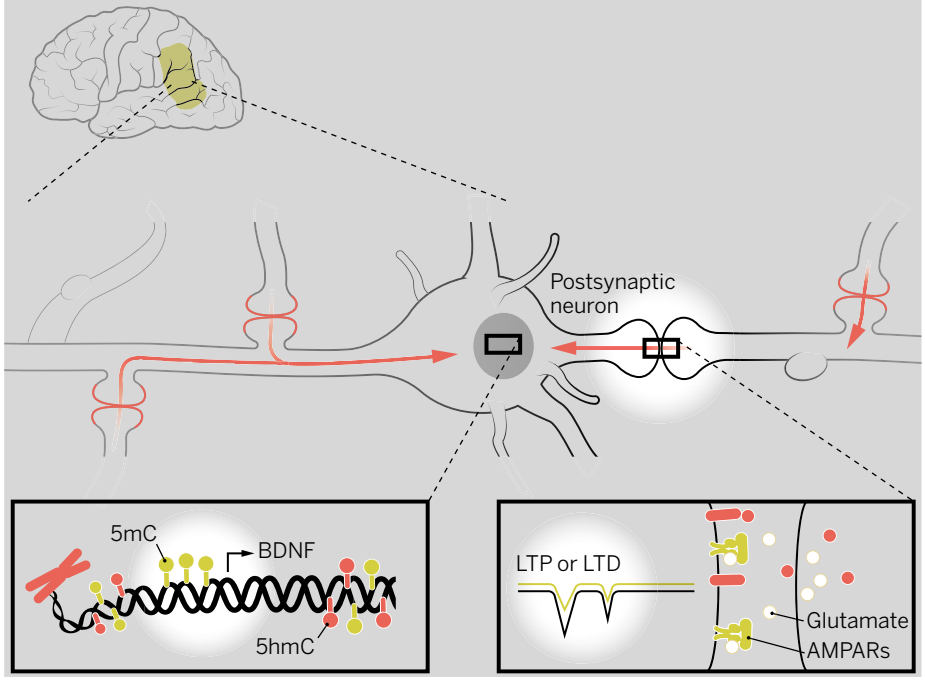

Fig. 1. LTP/LTD and mCG have been in the spotlight for so long that researchers may be missing contributions from other important factors, such as non-Hebbian plasticity mechanisms and 5hmC. Notably, LTP/LTD readouts provide synapse-specific information, but homeostatic mechanisms alter the cell more widely in keeping with the likely effects of changes in transcription. For the most part, *BDNF* expression has been the main genomic target used to assess plasticity, but there are likely many other important genes worthy of inclusion under a wider spotlight.

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tion of critical loci and gene targets. Finding more, and possibly better, representatives beyond the *BNDF* locus should facilitate a more complete study of the factors that regulate cytosine modification in response to neuronal activity, as well as those that contribute most to synaptic plasticity. Epigenetics is full of examples of context-specific function, and the genome is a big place. Until the parameters governing 5mC and 5hmC are more clearly defined both in terms of how these marks are written and erased, as well as read and interpreted, their response to, and influence, on the synapse will remain elusive.

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