

Emerging roles for epigenetic modifications and chromatin remodeling in the nervous system provide the focal point for this issue's Neurobiology Select. Recent evidence shows that changes in chromatin structure are critical to the reconsolidation of fear memories. Other new papers characterize the regulation of neural stem cells by histone acetylation and establish roles for epigenetic modifications and chromatin remodeling in the formation of dendrites and synapses.

## A Frightful Change in Chromatin Behavior

It is ironic that the process of retrieving a memory puts the memory's very existence in jeopardy. This is due to the fact that retrieval of a long-term memory must be paired with a process called reconsolidation or the memory is lost. Recent work by Lubin and Sweatt (2007) now shows that activity-dependent changes in chromatin structure following the recall of a fear memory facilitate the process of reconsolidation in rats. The authors examined NF- $\kappa$ B signaling in hippocampal neurons of rats trained to associate a particular chamber with an electric shock. Following this type of fear conditioning, rats exhibit freezing behavior when placed in the training chamber, even when a shock is not applied. Remarkably, freezing behavior could be markedly reduced if rats were injected with the NF- $\kappa$ B pathway inhibitor diethylthiocarbamate (DDTC) immediately after reexposure to the chamber where they had received the shock during the training period. This impairment in reconsolidation of the fear memory was not observed immediately but became apparent the day after drug administration. Indeed, when the rats were tested within 4 hr of the initial reexposure (and DDTC injection), they retained their learned freezing behavior, suggesting that short-term memory was not impaired by the drug. The authors then showed that the NF- $\kappa$ B pathway is activated when the rats are reexposed to the chamber and that activation of the pathway triggers changes in chromatin structure, as evidenced by altered phosphorylation and acetylation of histone H3. Moreover, the effects of DDTC on memory reconsolidation could be reversed by administration of sodium butyrate, a histone deacetylase (HDAC) inhibitor that presumably restores the changes in chromatin structure that facilitate reconsolidation. Gene-promoter regions that were affected by the NF- $\kappa$ B pathway include *I $\kappa$ B $\alpha$*  and the immediate-early gene *Zif268*. Future work should determine whether these or other specific changes in gene transcription are critical factors in memory reconsolidation.

*F.D. Lubin and J.D. Sweatt (2007). Neuron 55, 942–957.*



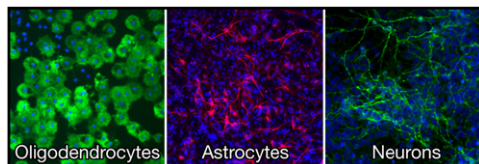
Epigenetic regulation of memory reconsolidation. Painting by J.D. Sweatt.

## An Orphan Pairs Up with HDACs in Neural Stem Cells

An orphan nuclear receptor called TLX has been shown to support the maintenance of neural stem cells. New findings reported by Sun et al. (2007) now show that HDACs partner with TLX to regulate its activity. The authors discovered that TLX binds to the histone deacetylases HDAC3 and HDAC5 and recruits these enzymes to the promoters of TLX target genes. This leads to the transcriptional repression of target genes, including the cyclin-dependent protein kinase inhibitor *p21* and the tumor suppressor *pten*, thereby promoting the proliferation of the neural stem cells. Sun et al. then mapped the region of TLX that interacts with HDAC5. Expression of a peptide from TLX based upon this region disrupts the interaction between TLX and HDAC5, which enhances the transcription of *p21* and *pten* to suppress proliferation of neural stem cells. Likewise, treating neural stem cells with valproic acid, an HDAC inhibitor, had similar consequences. These findings establish HDACs as TLX transcriptional corepressors. Future efforts may uncover the existence of TLX coactivators or the identity of a TLX ligand that may have the potential to restrain the proliferation of neural stem cells in vivo.

*G. Sun et al. (2007). Proc. Natl. Acad. Sci. USA 104, 15,282–15,287.*

## Glial Precursors Break Their Commitment



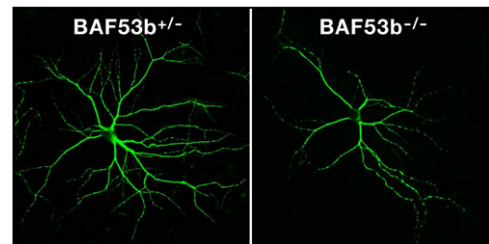
Lineage-restricted oligodendrocyte precursors exhibit the potential for multipotent differentiation upon exposure to histone deacetylase inhibitors, generating oligodendrocytes, astrocytes, and neurons. Images courtesy of C.A. Lyssiotis.

Oligodendrocytes are glial cells that form the protective myelin sheath that surrounds nerve cells. They arise from committed oligodendrocyte precursor cells, which are derived from multipotent neural stem cells. Inspired by previous reports indicating that oligodendrocyte precursors can be returned to a neural stem cell-like state by exposure to bone morphogenetic proteins (BMPs), Lyssiotis et al. (2007) conducted a high-throughput chemical screen to identify compounds that would similarly reverse the lineage restriction of oligodendrocyte precursor cells. They first identified compounds that would activate expression of a green fluorescent protein reporter under the control of the Sox2 promoter. Sox2 is

a transcription factor that promotes the maintenance of neural stem cells but is not expressed in committed progenitors. Compounds that triggered Sox2 reactivation in oligodendrocyte precursor cells (~200 of 40,000 compounds tested) were then screened in a secondary assay for their ability to promote neurogenesis of oligodendrocyte precursors that had been expanded in an aggregate cell culture. The four compounds that passed this test (sodium butyrate, trichostatin A, MS-275, and Apicidin) are all known HDAC inhibitors. Subsequent genome-wide analyses of transcription revealed that treatment of oligodendrocyte precursor cells with trichostatin A induced a similar set of changes as treatment of the cells with BMP-2, suggesting that both the growth factor and the HDAC inhibitor ultimately trigger similar changes in chromatin structure that facilitate a neural stem cell-like state. C.A. Lyssiotis et al. (2007). *Proc. Natl. Acad. Sci. USA* **104**, 14,982–14,987.

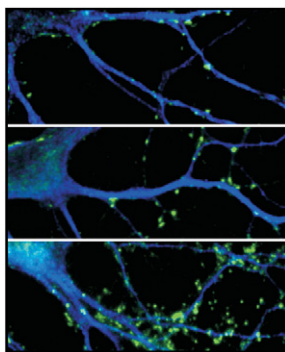
## The BAFfling Diversity of Dendrite Morphology

Previous work has shown that self-renewal and proliferation of neural stem cells is supported by the ATP-dependent chromatin-remodeling complex BAF. As neural progenitors exit the cell cycle and commit to neural differentiation, some individual subunits of this complex are replaced by different (albeit homologous) subunits. Wu et al. (2007) have now examined neurons from mice that lack one of these replacement subunits, BAF53b, which is only expressed in postmitotic neurons. The authors demonstrate that *BAF53b* deficiency leads to alterations in dendrite growth characterized by shorter dendrites with less complex arbors than those of wild-type neurons. Interestingly, this effect is dependent on neuronal activity, suggesting that chromatin remodeling by neuron-specific BAF complexes may be critical to the activity-dependent changes in dendrite patterning that occur during development. Consistent with this notion, loss of BAF53b decreased the occupancy of BAF complexes at the promoters of genes important for neurite outgrowth, such as *GAP43* and *Ephexin1*, resulting in changes in their transcription. The authors further show that BAF interacts with CREST, a calcium-responsive transcriptional activator, providing a link between activity-dependent  $Ca^{2+}$  signaling and chromatin remodeling by neuron-specific BAF complexes. These findings establish a signaling pathway that regulates activity-dependent chromatin remodeling in developing neurons. Future work may determine whether this signaling cascade also regulates chromatin remodeling in adulthood to facilitate processes associated with learning and memory. J.I. Wu et al. (2007). *Neuron* **56**, 94–108.



Dendrites are shorter and less complex in neurons lacking BAF53b (right) than in BAF53b<sup>+/-</sup> heterozygous neurons (left). Images courtesy of G. R. Crabtree.

## Synapse Number Counts on MeCP2



The density of glutamatergic synapses (green) is diminished in the absence of MeCP2 (top) and enhanced when MeCP2 expression is doubled (bottom) compared to wild-type (middle).

Loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) cause Rett syndrome, an X-linked disorder of postnatal neurodevelopment that has some features also found in autism. Duplication of the *MECP2* gene, which leads to an increase in MeCP2 protein, is also detrimental leading to mental retardation, suggesting that the activity and level of the MeCP2 protein needs to be very tightly controlled for neurodevelopment to proceed normally. Chao et al. (2007) examined mice that either lack MeCP2 or have double the normal amount to gain insight into the physiological consequences of MeCP2 misregulation. They report that the magnitude of evoked excitatory postsynaptic currents from glutamatergic neurons of the hippocampus are controlled by the amount of MeCP2 that is present. Although the level of MeCP2 does not alter probability of synaptic vesicle release, changes in MeCP2 expression do alter the size of the readily releasable pool of synaptic vesicles. In probing the underlying defect that accounts for these observations, they show that MeCP2 regulates the average number of glutamatergic synapses per neuron. Thus, this work provides a direct link between MeCP2 and the control of synaptic density. Future efforts may identify the genes regulated by MeCP2 that control synapse number, which could reveal new potential targets for the treatment of Rett syndrome and other neurodevelopmental disorders. H.-T. Chao et al. (2007). *Neuron* **56**, 58–65.

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