Deacetylate to differentiate

Many progenitor cell types start differentiation by turning on transcription. But on page 577, Shen et al. show that oligodendrocytes (OLs)—the myelin-forming cells of the nervous system—require a general transcriptional shutdown for differentiation. The transcriptional slowing is due to histone deacetylation, which compacts chromatin. The authors find that histone H3 must be deacetylated for OL progenitors to start differentiating after they exit the cell cycle. Although this shuts off many genes, typical OL proteins such as myelin were only expressed after global deacetylation, which normally occurred in mice during the first two weeks after birth. This timing might coincide with reduced levels of mitogens, which inhibit deacetylation.

Delaying deacetylation with a drug called VPA similarly delayed OL maturation in mice. VPA is used to treat epilepsy, but the findings suggest that it might be harmful to young children.

In neuronal and astrocyte precursors, the promoters of their fate-inducing transcription factors are inaccessible and must therefore be opened before differentiation. In OL progenitors, in contrast, it is thought that the promoters of genes such as myelin are inactive due to the presence of transcriptional inhibitors. The overall effect of deacetylation is therefore to allow myelin transcription by turning off the expression of these inhibitors.

Deacetylation was followed by histone methylation, which more permanently silences gene expression. By starting with (reversible) deacetylation, OL progenitors probably maintain some plasticity in early stages of differentiation.

Cdk5 protects huntingtin

A cyclin-dependent kinase protects neurons from toxic fragments of huntingtin (htt), according to Luo et al. (page 647).

Htt has various neurological functions, including vesicle trafficking. Htt is a common substrate for proteases that cleave the protein into smaller fragments, although the function of this cleavage is so far unknown. Mutant versions of htt with an expanded polyglutamine tract (>38 residues) form toxic aggregate-prone fragments that kill neurons and cause Huntington’s disease (HD). The new findings show that the number of these fragments is minimized via the actions of cdk5.

The group found that cdk5 phosphorylates htt and thus protects it from cleavage by caspases. The protection might be due to the resulting charge change or a structural alteration that blocks protease accessibility. Phosphorylated, and thus uncleaved, mutant htt was much less toxic to neurons.

In contrast to full-length htt, mutant fragments interfered with cdk5’s protection. In brains of a mouse HD model, cdk5 activity was reduced. This inactivity arises because the mutant fragments interfere with the interaction of cdk5 and its activator, p35. Thus, as more fragments accumulate, less full-length htt is protected from cleavage. This positive feedback might explain the rapid neurodegeneration that occurs after HD onset. It is not yet clear what levels of mutant htt fragments are required to reduce the activity of cdk5 such that cleavage is promoted and the positive feedback loop initiated.