Deacetylate to differentiate

M any 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 glutamine 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 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.
Two VEGFs for big or branchy vessels

EGF stuck to the extracellular matrix induces branchy vessels that support tumorigenesis, but soluble VEGF prompts wider vessels that cannot provide for a tumor, as shown on page 681 by Lee et al.

VEGF directs vascular growth and patterning in developing, adult, and tumor tissues. This extracellular signaling is thought to require VEGF that is not bound to the matrix. Soluble VEGF is made by either mRNA splicing that removes the matrix attachment region, or by MMP-dependent matrix remodeling. Lee et al. now show that several MMPs also cleave VEGF directly, thus releasing it from the matrix.

Contrary to expectations, however, soluble VEGF was less effective than its matrix-bound version at supporting the vessel growth needed for tumor survival. Uncleaved VEGF induced long, thin, branchy vessels that provided the circulation needed for tumorigenesis. But soluble VEGF resulted in wide but sparse vessels that did not allow tumor growth, probably because they support very low blood pressure.

The difference in vessel growth stems from the factor’s localization. Both forms activated the same VEGF receptor, although preliminary evidence suggests they induce its phosphorylation on different residues. Soluble VEGF, which bathes the vessels, induced cell proliferation. The bound version, which is detected only at discrete sites, acted more like a chemokine—inducing filopodia and directed migration by generating a gradient. The different downstream signaling proteins that each version recruits to the receptors remain to be identified.

MMPs are provided in large quantities by inflammatory cells such as macrophages. Although inflammation is usually associated with the progression of cancer, in this case, the MMP reinforcements might combat tumor growth. In any case, the authors caution against the common practice of measuring circulating (soluble) VEGF levels to gauge tumor growth.

As most MMP knockout mice develop normally, VEGF cleavage might not be pertinent to developmental vascular patterning. There, alternative splicing seems to be the more important control mechanism. The authors plan to test this theory by creating knock-in mice that express an MMP-resistant VEGF that can still be spliced. JCB

Complexes to coordinate calcium

On page 657, Hur et al. show that signaling complexes on the plasma membrane and ER, and two different signals, unite to coordinate calcium release.

Many signaling pathways, sometimes in specific combinations, lead to calcium release from internal ER stores. In adrenal chromaffin cells, EGF alone does not cause store release unless the cells are first stimulated with bradykinin (BK), which is an inflammation-generated hormone.

Hur and colleagues show that this sensitized release requires BK’s known ability to activate PKA. PKA was found in a large complex that linked the plasma membrane and the ER. The complex also included the EGF receptor (on the plasma membrane), the calcium-release channel IP$_{3}$R1 (which was found in the ER), and a tethering protein called AKAP9.

The binding of EGF to its receptor generates IP$_3$ to open IP$_{3}$R1, but this depends on prior phosphorylation of the receptor and IP$_{3}$R1 in response to BK. IP$_{3}$R1 was phosphorylated by BK-activated PKA, and the timing of this modification correlated with the window of time in which EGF caused calcium release. The existence of the complex does not depend on BK—it was also found in unstimulated cells—but it was required for EGF-induced calcium release. Proximity of the BK and EGF pathways thus imparts the specificity.

BK alone also causes calcium store release, which in chromaffin cells triggers the exocytosis of neurohormones that stimulate heart rate and energy production. On its own, BK results in only transient neurohormone release. But by sensitizing cells to EGF, which can easily be taken up from the bloodstream, BK can produce a more lasting release. EGF does not need BK to cause calcium release in other cell types. The physiological relevance of the BK dependence in adrenal cells is unclear. JCB