In This Issue

Getting lamin B1 processed and organized

Lamins are the building blocks of the nuclear lamina, a complex polymer attached to the nuclear envelope that is thought to be important for nuclear stability, chromatin organization, and gene expression. On page 1223, Maske et al. identify the protease responsible for processing lamin B1, demonstrate the existence of a nuclear receptor specific for carboxymethylated lamin B1, and show that posttranslational processing may control the localization of this lamin into subdomains within the nuclear envelope.

After being farnesylated, the COOH-terminal CAAX domain of lamin B1 is cleaved by an endoprotease, and the new COOH terminus of the protein is then methylated by the enzyme Icmt. Using a monoclonal antibody that distinguishes proteolyzed from unproteolyzed lamin B1, the authors determined that proteolysis specifically requires the CAAX endoprotease Rce1. Separate pools of farnesylated but unproteolyzed and proteolyzed but unmethylated lamin B1 appear in the nucleus, but retention of the protein’s COOH terminus in the nuclear envelope requires carboxymethylation, indicating that a nuclear receptor specifically recognizes the fully processed form of the protein. When farnesylation is inhibited, the residual mature form occupies defined subdomains of the nuclear lamina, and the authors have preliminary evidence that these subdomains are also present in untreated cells.

The results suggest that methylation of lamin B1 is a novel mechanism controlling the higher order organization of the nucleus. Lamin B1 interacts with chromatin, so the protein’s controlled localization to subdomains of the lamina might organize interacting chromatin into similar domains. The authors are now trying to identify the nuclear receptor for carboxymethylated lamin B1.

Since the well-known oncogene ras also requires processing of its CAAX domain, CAAX endoproteases, including Rce1, are popular targets for a new generation of experimental anticancer drugs. It was initially thought that CAAX processing was unnecessary in nondividing cells, but the new findings show that interfering with lamin B1 processing disrupts the integrity of the nuclear envelope, highlighting the potential for unforeseen side effects with the new drugs.

How to block botox

From both chemical weapons inspectors and plastic surgeons, botulinum toxins are the focus of intense interest. But how do these incredibly toxic proteins get into cells? On page 1293, Dong et al. demonstrate that botulinum neurotoxin B (BoNT/B) uses the vesicle proteins synaptotagmin I and synaptotagmin II as cellular receptors, and that a fragment of synaptotagmin II can inhibit the toxin’s effects in animals.

Of the seven known neurotoxins expressed by Clostridium botulinum, BoNT/A, B, and E are the most common causes of botulism in humans and the major choices for both bioterrorist and pharmaceutical uses. In previous work, researchers identified several cellular proteins that can bind to these toxins, but there were conflicting data about which, if any, of the candidate receptors actually mediate cellular entry. Once inside neurons, the toxins act as proteases to block exocytosis, ultimately leading to paralysis and death.

Using both loss-of-function and gain-of-function approaches, Dong et al. show that synaptotagmin I or synaptotagmin II can act as a receptor to internalize BoNT/B into PC-12 cells. Fusion of synaptic vesicles with the plasma membrane, and thus display of vesicle proteins on the cell surface, occurs during excitation. Indeed, BoNT internalization is dependent on electrical activity in two different cell types. Fragments of synaptotagmin II effectively block the binding of BoNT/B to cultured cells and inhibit the activity of the toxin in mice, providing strong evidence that the interaction is biologically relevant.

In the mouse experiments, an injection of synaptotagmin II fragments partially protected the animals against a subsequent challenge with BoNT/B. This is the first demonstration that a fragment from a bacterial toxin receptor can antagonize the toxin in animals. The authors are now defining the precise requirements for BoNT/B–synaptotagmin II interactions, and are also trying to identify the receptors for other Clostridium neurotoxins.