In This Issue

Stressed cells dance on a bright stage

While studying the stress response of yeast cells, Jacquet et al. (page 497) discovered a new type of oscillatory process that can control gene expression. In addition to creating a computational model that should help to direct future studies of cell stress, the authors identified a sort of biological Heisenberg effect, in which the process of observing certain cells under the microscope could significantly influence their physiology.

In the yeast *Saccharomyces cerevisiae*, two related transactivators, Msn2 and Msn4, translocate from the cytoplasm to the nucleus in response to a wide variety of stresses. Using high resolution time-lapse video microscopy, Jacquet et al. examined the translocation of an Msn2-GFP hybrid protein in single cells. Under the bright light of the fluorescence microscope, Msn2 migrates to the nucleus, indicating that light generates a stress response in GFP-expressing cells.

Rather than simply translocating to the nucleus, Msn2 and Msn4 display an unexpected oscillatory pattern in the light-exposed cells, synchronously shuttling into and out of the nucleus with a periodicity of a few minutes. The oscillations only occur at intermediate stress levels; high stress causes Msn2 and Msn4 to remain in the nucleus, whereas at low stress levels the proteins remain in the cytoplasm. The oscillatory behavior varies between individual cells and does not require new protein synthesis.

Cut protein to boost fibers

In a new analysis of melanosome biogenesis, Berson et al. (page 521) demonstrate that the proteolytic cleavage of a glycoprotein drives the formation of the characteristic fibrous striations seen in these organelles. The work uncovers a general mechanism that may regulate the development of lysosome-related organelles in a variety of cell types, and also shows a striking parallel between the experimentally tractable melanocyte system and the complex pathogenesis of amyloid diseases.

Melanosomes, specialized organelles that store melanin pigments, develop intraluminal fibrils superficially similar to those seen in amyloid diseases, but little is known about how these fibrils form. Previous work identified an apparent paradox, suggesting that the melanosome fibrils do not contain membrane, but do contain the integral membrane glycoprotein Pmel17.

The new work resolves this issue, showing that Pmel17 must be cleaved by proprotein convertases to initiate fibril formation. A cleavage product is eventually released into the lumen of the melanosome and incorporated into fibrils. Since many cell types develop specialized lysosome-related organelles, proprotein convertases or other proteases may be general initiators of similar morphogenetic processes for a wide range of organelles.

Besides illuminating a previously obscure aspect of organelle biogenesis, the work suggests a strong similarity between normal melanosome fibril formation and the pathogenic fibril formation that occurs in amyloid diseases. Some pathogenic amyloid proteins are specifically cleaved by proprotein convertases, and proteolytic processing is also a general feature of Alzheimer’s disease and prion diseases. Berson et al. propose that proteolytic maturation is a normal step in lysosome-related organelle biogenesis, and pathogenic variations in the process may drive inherited organelle defects as well as amyloid diseases. The authors are now trying to reproduce melanosome fibril formation in vitro, and hope to use the system as a model for understanding both normal and pathogenic fibril formation.