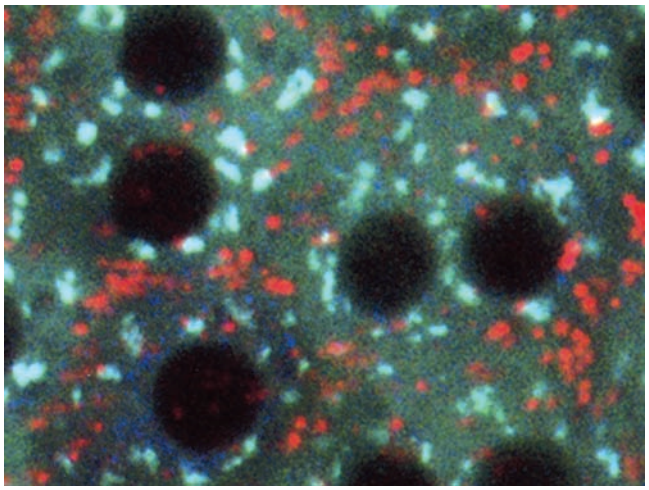
In This Issue

New structure found in plain sight

Like explorers spotting an uncharted island on the horizon, Imanishi et al. (page 373) have identified a previously unknown cellular structure that could be an entirely new organelle. The structure, located in cells of the retinal pigment epithelium, appears to be an essential waypoint in the retinoid cycle—the series of chemical reactions that regenerates 11-*cis*-retinal, the chromophore for rhodopsin, after light converts it to all-*trans*-retinal.

Isolated retinas do not survive long outside of the eye, complicating studies of retinal biology. The authors circumvented this problem by looking directly into the eyes of live mice with two-photon fluorescent microscopy. Retinol and retinyl esters show weak intrinsic fluorescence, producing high-resolution images of intact retinal cells and revealing a fence-like intracellular structure dubbed the retinyl ester storage particle, or retinosome. In wild-type mice exposed to light, retinyl ester levels in retinosomes rise, and then fall, consistent with the recycling of retinoid intermediates produced by light exposure.



Storage sites for retinyl esters called retinosomes (red) do not colocalize with organelles such as the Golgi (blue).

Retinosomes are absent in mice lacking the enzyme LRAT, which produces retinyl esters. Mice lacking RPE65, which is required for processing retinyl esters, accumulate large quantities of the esters in overgrown retinosomes. Biochemical analysis shows that retinosomes also contain adipose differentiation–related protein (ADRP).

The new structure provides a context for understanding the retinoid cycle. By compartmentalizing a portion of the cycle, the retinosome can locally enrich intermediates in the cycle to drive energetically unfavorable reactions. Just as important, sequestering the retinyl esters can prevent toxic reaction intermediates from poisoning the cell.

The retinosome's highly ordered structure suggests that it incorporates other proteins, and the authors are now trying to use ADRP as a hook to isolate pure retinosomes for further analysis. Since defects in the retinoid cycle underlie many forms of congenital blindness, the ability to observe retinosomes directly in intact eyes may also provide a powerful diagnostic tool in the clinic. ■

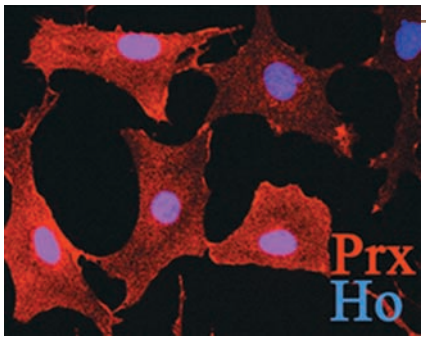
Krox-20 conducts the Schwann song

When Schwann cells begin to myelinate large-diameter axons, they stop dividing, become resistant to apoptosis, and start producing myelin proteins. How are all of these changes coordinated? On page 385, Parkinson et al. identify several new signaling interactions in Schwann cells, and show that the transcription factor Krox-20 is a master regulator of myelination.

The authors found that Krox-20 expression makes Schwann cells resistant to the mitogen NRG-1 and the apoptosis-inducing action of TGF-β. Rather than specifically targeting these signaling molecules, Krox-20 appears to act through a general mechanism, suppressing the activity of the JNK/c-Jun pathway. The data show that JNK/c-Jun signaling is required for both proliferative and apoptotic responses in Schwann cells. Krox-20 expression increases the expression of the scaffold protein JIP-1, a known inhibitor of JNK activity, and also decreases the level of c-Jun protein in the cell, providing two possible ways to inhibit JNK/c-Jun signals.

Surprisingly, expression of Krox-20 in cultured 3T3 fibroblasts, which are not related to Schwann cells, causes the fibroblasts to stop dividing, resist apoptosis, and express the myelin genes periaxin and P_0. The ability to induce so many specialized responses in a different cell type indicates that Krox-20 is a master regulator.

By turning off a single pathway that is activated by both NRG-1 and TGF-β, Krox-20 can coordinate changes in both proliferative and apoptotic activities without affecting other processes activated by growth factors. Its position as a master regulator explains why mutations in Krox-20 often lead to severe hereditary myelination disorders. Parkinson et al. are now trying to determine whether Krox-20 acts directly or indirectly to reduce c-Jun levels and induce myelin gene expression. ■



Krox-20 makes fibroblasts turn on myelin genes.