ticipate in local axon assembly. The fact that c-Jun regulates its expression reinforces the notion that c-Jun has an important role in "turning on" the regeneration program after injury.

c-Jun also has a role in regulating neuronal apoptosis. Initial in vitro studies found that c-Jun was activated after NGF withdrawal correlating with neuronal apoptosis. Furthermore, c-Jun overexpression induced neuronal death, whereas c-Jun suppression or dominant-negative c-Jun expression resulted in the blockade of neuronal death (see references in Herdegen et al., 1997). In line with these observations, Raivich et al. show decreased developmental cell death in the facial motor neuron pools of the *c-jun*$^{\Delta n}$ mice.

Interestingly, neuronal death is also sometimes induced by axotomy. Raivich and colleagues showed that c-Jun also plays a role in mediating axotomy-induced cell death. Neuronal loss was substantially reduced in *c-jun*$^{\Delta n}$ mice following nerve transection compared to the control mice. One tempting explanation for this seemingly counterintuitive effect is that the genetic program induced by c-Jun to promote axon growth overlaps with the genetic program mediated by c-Jun in nonneuronal cells that promotes cell proliferation (Eferl and Wagner, 2003). Attempts to reenter the cell cycle in postmitotic neurons usually lead to apoptosis (Becker and Bonni, 2004). The idea that the axon growth and cell cycle programs overlap is in line with recent findings that suppressing cell cycle repressors in neurons enhances axon growth (Konishi et al., 2004).

Although Raivich et al. provide compelling evidence for a vital role of c-Jun in the adult animal during regeneration, their study does not provide the definitive answer about the specific role of c-Jun in neurons. Previous work has shown that c-Jun is also upregulated in nonneuronal cells after axotomy (see references in Herdegen and Leah, 1998). Nestin-Cre-mediated recombination also mutates the *c-jun* gene in glial cells, which may well contribute to the regeneration phenotype seen in *c-jun*$^{\Delta n}$ mice. Furthermore, the data from Raivich et al. do not rule out the possibility that the lack of c-Jun during development may also contribute to the regeneration defect in the adult animals even though no apparent developmental abnormality is observed in the mutant mouse nervous system. Therefore, a definitive answer for the role of neuronal c-Jun in regeneration can only be obtained with a neuron-specific c-Jun knockout in adult animals. This can readily be achieved via crossing the *c-jun*$^{f/f}$ mice with a neuron-specific and inducible Cre line or by local introduction of a neuron-specific Cre-expressing vector.

Finally, in *c-jun*$^{\Delta n}$ mice, facial nerve regeneration still occurs to some degree, suggesting that multiple redundant pathways exist to promote regeneration. Indeed, another related transcription factor, ATF3, is also upregulated in response to axotomy with a similar expression pattern to that of c-Jun. Dimers of ATF3 and c-Jun or other transcription factors can recognize the cAMP response element (CRE) binding motif (see Hai and Hartman, 2001, for review). Coordination of CRE- and AP-1-regulated genes may be required to control robust axon regeneration. It would be interesting to see whether mutating both of these transcription factors causes an even more profound failure of axon regeneration than was observed in the current study.

Feng-Quan Zhou, Mark A. Walzer, and William D. Snider
Neuroscience Center
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599

Selected Reading

Becker, E.B., and Bonni, A. (2004). Prog. Neurobiol. *72*, 1–25.

Bomze, H.M., Bulsara, K.R., Iskandar, B.J., Caroni, P., and Skene, J.H. (2001). Nat. Neurosci. *4*, 7–9.

Chang, L., Jones, Y., Ellisman, M.H., Goldstein, L.S., and Karin, M. (2003). Dev. Cell *4*, 521–533.

Eferl, R., and Wagner, E.F. (2003). Nat. Rev. Cancer *3*, 859–868.

Estus, S., Zaks, W.J., Freeman, R.S., Gruda, M., Bravo, R., and Johnson, E.M., Jr. (1994). J. Cell Biol. *127*, 1717–1727.

Gdalyahu, A., Ghosh, I., Levy, T., Sapir, T., Sapoznik, S., Fishler, Y., Azoulai, D., and Reiner, O. (2004). EMBO J. *23*, 823–832.

Hai, T., and Hartman, M.G. (2001). Gene *273*, 1–11.

Herdegen, T., and Leah, J.D. (1998). Brain Res. Brain Res. Rev. *28*, 370–490.

Herdegen, T., Skene, P., and Bahr, M. (1997). Trends Neurosci. *20*, 227–231.

Huang, C., Rajfur, Z., Borchers, C., Schaller, M.D., and Jacobson, K. (2003). Nature *424*, 219–223.

Konishi, Y., Stegmuller, J., Matsuda, T., Bonni, S., and Bonni, A. (2004). Science *303*, 1026–1030.

Raivich, G., Bohatschek, M., Da Costa, C., Iwata, O., Galiano, M., Hristova, M., Nateri, A.S., Makwana, M., Riera-Sans, L., Wolfer, D.P., et al. (2004). Neuron *43*, this issue, 57–67.

Snider, W.D., Zhou, F.Q., Zhong, J., and Markus, A. (2002). Neuron *35*, 13–16.

Werner, A., Willem, M., Jones, L.L., Kreutzberg, G.W., Mayer, U., and Raivich, G. (2000). J. Neurosci. *20*, 1822–1830.

Myosin III Illuminates the Mechanism of Arrestin Translocation

Recent studies have revealed that light adaptation of both vertebrate and invertebrate photoreceptors is accompanied by massive translocations of major signaling proteins in and out of the cellular compartments where visual signal transduction takes place. In this issue of *Neuron*, Lee and Montell report a breakthrough in understanding the mechanism of arrestin translocation in *Drosophila*. They show that arrestin is carried into the light-sensitive microvilli by phosphoinositide-enriched vesicles driven by a myosin motor.

An exciting and active area in photoreceptor biology is the translocation of signaling proteins in and out of the cellular compartment where visual signal transduction takes place. This phenomenon, documented in a broad range of animal species from flies to mammals, is thought to be a major mechanism of light adaptation. Translocation allows the cell to rapidly adjust the protein composi-

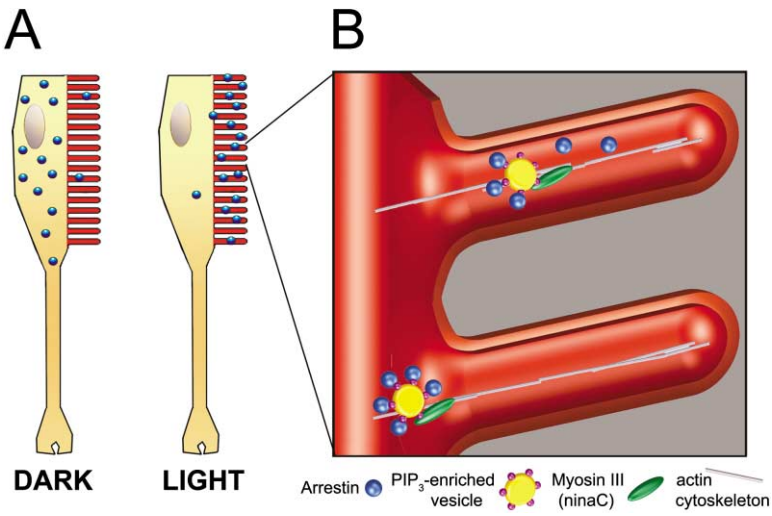

Figure 1. Light-Dependent Arrestin Translocation into the Microvilli of *Drosophila* Photoreceptors

(A) Schematic drawing of the rhabdomeric photoreceptor illustrating arrestin distribution in the dark and light. (B) Putative mechanism of arrestin translocation by myosin III. See text for details.

tion of the signaling compartments in order to optimize the sensitivity and duration of light-evoked responses as the ambient lighting conditions change dramatically during the normal diurnal cycle (see Arshavsky, 2003, and Hardie, 2003, for recent updates).

The two key proteins undergoing massive translocation in photoreceptors of both vertebrates and invertebrates are the G proteins, transducin and G_q, respectively, and arrestin. G proteins mediate signals from rhodopsins to their downstream targets. Upon illumination, large fractions of transducin and G_q exit the light-sensitive compartments, resulting in a lower sensitivity of the photoresponses, which is required for the prevention of "blinding" the cell with bright light (see Sokolov et al., 2002, Kosloff et al., 2003, and references within). Arrestin is responsible for terminating the light signal by binding to photoexcited rhodopsin. In light, arrestin translocates in the direction opposite to G protein as more and more rhodopsin becomes photoexcited and more and more arrestin is needed to quench it (see Peet et al., 2004, Peterson et al., 2003, Lee et al., 2003, and references within). While the functional role of protein translocation is beginning to be revealed, the cellular mechanisms governing this phenomenon remain far from understood.

The power of *Drosophila* genetics has been particularly useful for unveiling the cellular mechanisms responsible for protein translocation, most importantly in the case of arrestin. A schematic of a *Drosophila* photoreceptor is illustrated in Figure 1. Visual transduction takes place in the rhabdomere, a rod-shaped cellular compartment composed of tightly packed microvilli located on the side of the photoreceptor (see Hardie and Raghu, 2001, for a recent review). The light-dependent translocation of the prevalent form of *Drosophila* visual arrestin (Arr2) from the cell cytoplasm to the rhabdomeres was first described by Kiselev et al. (2000). The functional role of this process in visual transduction was recently reported by Lee et al. (2003) who found that arrestin translocation correlates with the onset of accelerated photoresponse recovery. They also found that introducing specific mutations into arrestin resulted in a striking slowdown of both arrestin translocation and the onset of accelerated response recovery in the mutant flies. Based on this evidence, the authors concluded that photoresponse duration in the rhabdomeres is regulated by the amount of arrestin present. Having a small amount of arrestin in dim light allows rhodopsin to stay active longer and to generate long sensitive responses that are most useful in detecting individual photons encountered under these conditions. On the contrary, as more light stimulates the cell during a sunny day, the increased arrestin content in rhabdomeres allows rapid rhodopsin quenching. This yields less-sensitive responses and helps the cell to avoid signal saturation under these conditions.

Another interesting observation by Lee et al. (2003) was that the mutations impairing arrestin translocation also impaired the ability of arrestin to bind to phosphoinositides, in particular to PIP_3. Furthermore, other mutations affecting the enzymes responsible for phosphoinositide turnover affected arrestin translocation as well. These data strongly suggested that translocation is dependent upon phosphoinositides, but what is the mechanism involved? A breakthrough in addressing this question is reported by Lee and Montell in this issue of *Neuron* (Lee and Montell, 2004). They demonstrate that arrestin translocation in *Drosophila* requires the presence of a type III myosin motor (also called NINAC in *Drosophila*) enriched in the eye. They further show that arrestin and myosin III can be coprecipitated in the presence of phosphoinositides and that each of them interacts with phosphoinositides directly, yet there is no direct protein-protein interaction between the two.

These findings have led the authors to put forward the hypothesis summarized in Figure 1. They propose that photoreceptor illumination results in the formation of PIP_3 within the lipid vesicles located in the cell body. These vesicles can then bind multiple molecules of arrestin and employ a myosin III motor that carries them into the rhabdomere along an actin cytoskeletal path. As the vesicles enter the microvilli, arrestin becomes available to terminate rhodopsin signaling. Yet, the mechanism responsible for arrestin exchange between the vesicles and rhodopsin remains to be elucidated. Perhaps, the release of arrestin requires dephosphorylation of PIP_3.

Interestingly, myosin III in *Drosophila* comes in two splice isoforms, p132 and p174, detected exclusively in the cell bodies and rhabdomeres, respectively. While the lack of both isoforms results in complete abolishment of arrestin translocation, the selective expression of either p132 or p174 has different consequences. Flies containing only p132 have no obvious phenotype. To the contrary, arrestin translocation is severely slowed (although not eliminated) in flies containing only p174. Given the pattern of subcellular distribution of these proteins, it is tempting to speculate that moving the arrestin-containing vesicles toward the rhabdomere is more important for translocation overall than moving these vesicles through the microvilli.

How does arrestin return back to the cell body once the light is turned off? No evidence for cytoskeletal involvement was revealed by Lee and Montell (2004), suggesting that arrestin simply diffuses from the microvilli in the dark. This explanation fits with the fact that the microvilli make up only a tiny fraction of the total photoreceptor cytoplasm. Thus, the motors would only be needed for transporting arrestin against its concentration gradient.

Another important question raised by Lee and Montell (2004) is whether the mechanism similar to that illustrated in Figure 1 may take place in vertebrate photoreceptors. The authors point out that mammalian visual arrestin binds to inositol phosphates (Palczewski et al., 1991) and that two mammalian homologs of fly myosin III, Myo3A and Myo3B, are expressed in the retina with the former enriched in both rods and cones (Dosé et al., 2003). Yet, no vesicular structures have been reported in the cilium, the structure connecting the outer segment, a cellular compartment where visual transduction occurs in vertebrates, to the rest of the photoreceptor cell body. In addition, there is no conservation of the lysine residues responsible for binding PIP_3 by *Drosophila* arrestin in the molecule of vertebrate visual arrestin. However, little is known about the mechanisms governing arrestin translocation in vertebrates, which leaves open the possibility of the existence of a broader analogy. For example, one may suggest that myosin motors carry arrestin as a direct cargo or help arrestin to reach the base of the connecting cilium. It is also possible that the mechanism revealed in *Drosophila* may function in other vertebrate cell types where other arrestin isoforms are active.

In summary, the studies of arrestin transport in the fly set the stage for understanding the mechanisms that govern the light-dependent translocation of signaling proteins in both vertebrate and invertebrate photoreceptors. This area of research is particularly exciting because it has just gained momentum during the past two years and it holds promise in revealing the most general principles of how individual proteins become highly compartmentalized in polarized neurons.

Katherine J. Strissel and Vadim Y. Arshavsky
Howe Laboratory of Ophthalmology
Harvard Medical School
Boston, Massachusetts 02114

Selected Reading

Arshavsky, V.Y. (2003). Sci. STKE. E43.

Dosé, A.C., Hillman, D.W., Wong, C., Sohlberg, L., Lin-Jones, J., and Burnside, B. (2003). Mol. Biol. Cell *14*, 1058–1073.

Hardie, R.C. (2003). Curr. Biol. *13*, R775–R777.

Hardie, R.C., and Raghu, P. (2001). Nature *413*, 186–193.

Kiselev, A., Socolich, M., Vinos, J., Hardy, R.W., Zuker, C.S., and Ranganathan, R. (2000). Neuron *28*, 139–152.

Kosloff, M., Elia, N., Joel-Almagor, T., Timberg, R., Zars, T.D., Hyde, D.R., Minke, B., and Selinger, Z. (2003). EMBO J. *22*, 459–468.

Lee, S.-J., and Montell, C. (2004). Neuron *43*, this issue, 95–103.

Lee, S.-J., Xu, H., Kang, L.W., Amzel, L.M., and Montell, C. (2003). Neuron *39*, 121–132.

Palczewski, K., Pulvermüller, A., Buczylko, J., Gutmann, C., and Hofmann, K.P. (1991). FEBS Lett. *295*, 195–199.

Peet, J.A., Bragin, A., Calvert, P.D., Nikonov, S.S., Mani, S., Zhao, X., Besharse, J.C., Pierce, E.A., Knox, B.E., and Pugh, E.N., Jr. (2004). J. Cell Sci. *117*, 3049–3059.

Peterson, J.J., Tam, B.M., Moritz, O.L., Shelamer, C.L., Dugger, D.R., McDowell, J.H., Hargrave, P.A., Papermaster, D.S., and Smith, W.C. (2003). Exp. Eye Res. *76*, 553–563.

Sokolov, M., Lyubarsky, A.L., Strissel, K.J., Savchenko, A.B., Govardovskii, V.I., Pugh, E.N., Jr., and Arshavsky, V.Y. (2002). Neuron *34*, 95–106.