PERSPECTIVES: CELL BIOLOGY

Actin' Up with Rac1

Nansi Jo Colley

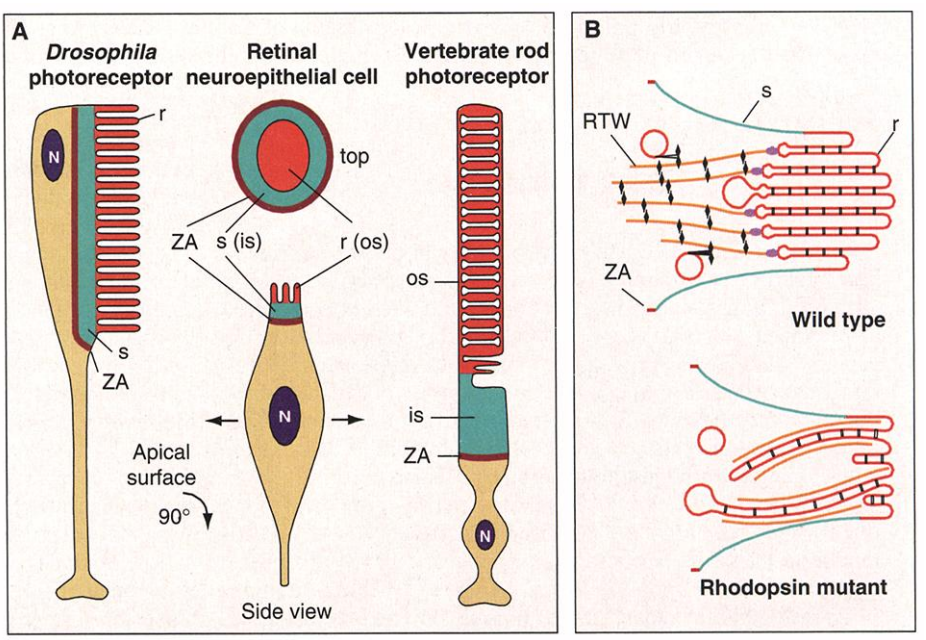
Members of the Rho family of small guanosine triphosphatases (Rho GTPases) are emerging as key regulatory molecules that couple cell surface receptors to actin cytoskeleton organization (*1, 2*). They are activated by signals emanating from a variety of receptors, including those coupled to heterotrimeric guanine nucleotide–binding proteins (G proteins), adhesion receptors, cytokine receptors, and receptor tyrosine kinases (*3*). Chang and Ready (*4*), reporting on page 1978 of this issue, now add another G protein–coupled receptor to this list—the photopigment rhodopsin found in human rod and cone photoreceptor cells and in the photoreceptor cells of the fruit fly *Drosophila*. Working with fly retina photoreceptor cells, they identified a signaling molecule, the Rho GTPase Drac1, that may be activated by rhodopsin. Together, rhodopsin and Drac1 direct morphogenesis of fly photoreceptor cells during development of the retina by regulating the organization of the cells' actin cytoskeleton.

By transducing light energy, rhodopsin activates intracellular second messengers through stimulation of G proteins in the phototransduction cascade (*5, 6*). This photopigment is also critical for the correct development and maintenance of photoreceptor cells because mutations in rhodopsin lead to retinal degeneration in fruit flies, mice, and humans (*7–9*). The photosensory area (the rhabdomere) of the fruit fly photoreceptor cell is composed of numerous precisely packed microvilli that contain rhodopsin and other components of the phototransduction cascade. The rhabdomere is equivalent to the outer segments of human rod and cone cells (see the figure).

The organization of the rhabdomere into neatly stacked membranes (microvilli) is stringently regulated. Located at the base of the rhabdomere is an actin cytoskeleton and associated proteins that are organized into the rhabdomere terminal web (RTW) (*4*). The RTW separates the rhabdomere from the cytoplasm of the photoreceptor cell and prevents the membranes from collapsing into the cytoplasm. Chang and Ready (*4*) propose that, in addition to trapping light, rhodopsin, through activation of Drac1, organizes the actin cytoskeleton into the RTW and hence is essential for correct photoreceptor cell development.

Until now, it has been widely assumed that rhodopsin's job in the morphogenesis of photoreceptor cells is a structural one. However, mutant fruit flies lacking 99% of their rhodopsin produce smaller but morphologically normal rhabdomeres (*10*), suggesting that rhodopsin may be more actively involved in photoreceptor cell development. The Rho GTPases are molecular switches that can convey signals from membrane receptors to the actin cytoskeleton by oscillating between inactive GDP- and active GTP-bound forms (*2*). Certain seven-transmembrane G protein–coupled receptors that have a unique amino acid motif (Asn-Pro-X-X-Tyr) in the seventh transmembrane domain can interact with Rho GTPases (*11*). *Drosophila* rhodopsin also carries the Asn-Pro-X-X-Tyr motif in its seventh transmembrane domain, indicating that it, too, may have the capacity to interact with these small G proteins.

Chang and Ready disrupted the Rho GTPase signaling pathway in fruit flies by engineering them to express a dysfunctional form of Drac1. They observed profound defects in photoreceptor cell morphogenesis (*4*) that resembled those seen in flies completely lacking rhodopsin. Dysfunctional Drac1 blocks normal development of the RTW, causing rhabdomere microvilli to collapse into the photoreceptor cell cytoplasm. In mutant flies that completely lack rhodopsin, the actin cytoskeleton is disorganized, RTW formation is defective, and microvilli also collapse into the cytoplasm. The morphological similarities between flies with dysfunctional Drac1 and those with no rhodopsin imply that rhodopsin may participate in the assembly of the actin cytoskeleton through the activity of Drac1. With immunocytochemistry, the investigators were able to pinpoint the location of Drac1 to the RTW. This further supports its involvement in organizing the actin cytoskeleton and in providing a structural constraint for photoreceptor morphogenesis. The RTW and photoreceptor defects in flies that lack rhodopsin can be abrogated if these flies are engineered



Seeing is believing. The development of fruit fly and vertebrate photoreceptor cells in the retina. (**A**) During photoreceptor cell development, there is organization of distinct membrane domains at the top of the neuroepithelial cell (center). In the fruit fly retina (left), the top (apical) surface of the neuroepithelial cell becomes rotated through 90° and expanded into closely packed microvilli, the rhabdomere (r), which contains the photopigment rhodopsin. In the vertebrate rod photoreceptor cell (right), the sensory region equivalent to the rhabdomere is called the outer segment (os). Encircling the rhabdomere or outer segment is an area—called the stalk (s) or inner segment (is), respectively—that is thought to constrain expansion of the sensory membrane. (**B**) In normal fruit flies (top), the rhabdomere terminal web (RTW) extends from the base of the rhabdomere into the cytoplasm of the photoreceptor cell. The RTW constrains the rhabdomere, preventing it from intruding into the cytoplasm. In mutant flies that completely lack rhodopsin (bottom), the RTW fails to assemble and the rhabdomere membrane collapses into the cell. N, nucleus; ZA, zonula adherens.

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to overexpress an active form of Dracl. Thus, activated Dracl is able to direct the necessary cytoskeletal organization that is otherwise lacking in the rhodopsin deficient flies (*4*). Given these observations, the authors propose that Dracl links rhodopsin to assembly of the RTW and hence to the development of photoreceptor cells. It will be intriguing to determine whether it is the rhodopsin present in the rhabdomere or the small amount of rhodopsin located in the RTW (presumably en route to the rhabdomere) that is directing Dracl activity.

Small GTPases, such as Rho, Rac, and Cdc42, are pivotal in a variety of cytoskeletal-dependent processes, including cell shape changes during embryonic development, the directed movement of the growth cone in developing neurons, formation of stress fibers and assembly of focal adhesions in the cell, progression through the cell cycle, transcriptional activation, and signaling during apoptosis. In contrast, the larger heterotrimeric G proteins typically transduce more specialized neural and endocrine signals such as those produced in response to light, odor and taste molecules, hormones, neurotransmitters, and peptides (*3, 5, 6, 12–14*). There is increasing evidence for cross talk between the various signaling pathways (*13*). Notable examples include odorant receptors that assist in the guidance of axonal projections on the olfactory bulb to generate a precise topographic map (*12*) and G protein regulation of Rho GTPases through a Rho guanine nucleotide exchange factor (*15, 16*).

The finding that Rho GTPases are involved in the organization of the actin cytoskeleton in photoreceptor cells may shed light on some forms of the inherited neurodegenerative blinding disorder retinitis pigmentosa (RP) (*17*). This devastating group of genetic diseases is characterized by loss of rod photoreceptor cell function, often leading to a progressive decrease in peripheral vision and eventual blindness. About 30% of cases of autosomal dominant RP are caused by mutations in rhodopsin; thus far, 23 additional genetic loci have been identified in RP patients (*7–9*).

The actin cytoskeleton is essential for the correct development of outer segment disks in mammalian rod cells (*18*). Mutations in the cytoskeletal molecule myosin VIIA have been identified in patients with a form of RP called Usher syndrome type 1B (*19*). Human rhodopsin carries the Asn-Pro-X-X-Tyr motif implying that it, too, may interact with Rho GTPases (*11*). So, as Chang and Ready point out, there are several striking parallels between development of the retina in humans and fruit flies, including the conservation of molecules that regulate the actin cytoskeleton. These parallels imply that human rhodopsin may also regulate the photoreceptor actin cytoskeleton and that defects in this process could underlie some forms of RP (*4*).

The Chang and Ready findings demonstrate the startling likelihood that rhodopsin has another job besides its day (or night) job. This versatile photopigment is not only a phototransducing receptor, it also directs the actin cytoskeleton to orchestrate the formation of the elegant architecture of the photoreceptor cell.

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PERSPECTIVES: COMPUTING

Screen Savers of the World Unite!

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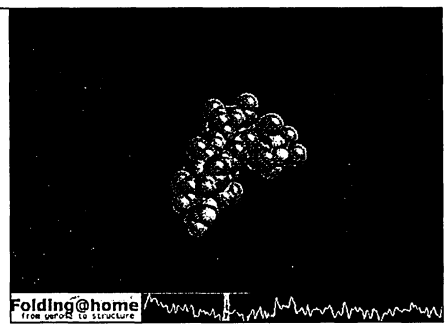
Recently, a new computing paradigm has emerged: a worldwide distributed computing environment consisting of thousands or even millions of heterogeneous processors, frequently volunteered by private citizens across the globe (*1*). This large number of processors dwarfs even the largest modern supercomputers. In addition to the scientific possibilities suggested by such enormous computing resources, the involvement of hundreds of thousands of nonscientists in research opens the door to new means of science education and outreach, in which the public becomes an active participant.

A handful of projects have already demonstrated how such large-scale distributed computing power can be utilized. For example, SETI@home has totaled over 400,000 years of single-processor CPU time in about 3 years in its search for alien life (*2*). Similarly, distributed.net has used the power of this huge computational resource for the brute-force cracking of DES-56 cryptography codes.

Virtually any other computationally intensive project could be aided by distributed computing, from the simulation of nuclear reactions or star clusters to atomic-scale modeling in material science. Perhaps the most exciting possibility, however, is in the biological realm. In the last few years, the huge amount of raw scientific data generated by molecular biology, structural biology, and genomics has outstripped the analytical capabilities of modern computers. Novel methods, algorithms, and computational resources are needed to process this wealth of raw information. For example, we need to compute the structure, thermodynamics, dynamics, and folding of protein molecules, the binding ability of drugs, and the causal events in biochemical pathways. Many of the newest distributed applications have thus focused on biological systems.



Merging research and education. The Folding@home screen saver shows a graphical representation of the protein and its potential energy as it is folding, making the research more visually accessible to the public contributing to the project.

Both SETI@home and distributed.net tackle so-called "embarrassingly parallel" problems, in which the desired calculation can easily be divided between many computers. For example, SETI@home looks for alien life by Fourier-transforming radio telescope data from different parts of the sky. These chunks can easily be assigned to different computers to be processed. However, not all problems are so easily broken down into independent parts ("parallelized"). Just as having 1000 assistants

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