Chapter 53
Looking into Eyes: Rhodopsin Pathologies in *Drosophila*

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53.1 Introduction

The capacity to see the world around us is a unique experience and one of the best understood processes in biology. The small insect *Drosophila melanogaster* has played a central role in our understanding of vision. *Drosophila* was the first organism in which the process of phototransduction (PT) was subjected to genetic analysis. This revealed that many anatomical and physiological aspects of vision are conserved from insects to mammals (Wang and Montell 2007; Sanes and Zipursky 2010). In addition, the detailed analysis of RD caused by altered PT has uncovered many pathological mechanisms of retinal disease, most of which were subsequently found to operate in mammals.

RP represents a heterogeneous group of retinal dystrophies in which death of photoreceptor neurons (PNs) leads to progressive blindness. RP is caused by mutations in at least 181 genes, and is arguably the most complex genetic disorder in man (Daiger 2004; Daiger et al. 2007). Most cases of RP are autosomal dominant

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(i.e., ADRP), while a minority of cases exhibit a recessive pattern of inheritance (Daiger et al. 2007). Alterations in rhodopsin (Rho) structure and/or dynamics have emerged as central pathogenic events in RP. Thus, *Rho* mutations account for at least 25% of all RP cases; and defects in PT that involve alterations in Rho dynamics are associated with other RP mutations (Hamel 2006; Daiger et al. 2007). Here, we highlight pathogenic mechanisms linking altered Rho states to RP, with a focus on *Drosophila* studies. Excellent reviews cover the study of RP mechanisms and emerging therapies, and the utility of other systems in understanding RP (Kennan et al. 2005; Mendes et al. 2005; Hartong et al. 2006; Sancho-Pelluz et al. 2008; Rivas and Vecino 2009; Shintani et al. 2009).

53.2 The Dark Side of Rhodopsin

The *Drosophila* compound eye is composed of approx. 800 "eyes" or ommatidia. Each ommatidium contains eight PNs (R1-8) and additional nonneuronal cells that support vision. PNs are divided into six outer photoreceptors (R1-R6), sensitive to light contrast and mediating motion detection, and two inner PNs (R7-8) responsible for color detection (Cook and Desplan 2001). R1-6 PNs express a single Rho ortholog, called *Rh1*, which is encoded by the *ninaE* locus (O'Tousa et al. 1985; Zuker et al. 1985); R7-8 PNs express a combination of *Rh3-6* genes (Cook and Desplan 2001).

Rh1 is a seven-transmembrane G protein-coupled receptor that localizes to rhabdomeres – the light-sensing organelles of PNs – where it interacts with light particles. Activated Rh1 binds the G_q protein, which becomes activated and recruits the phospholipase C (NorpA). NorpA hydrolytic activity leads to the opening of TRP or TRPL Ca^{2+} channels (Fig. 53.1). Rh1 is inactivated by GPRK1-mediated phosphorylation and binding to Arrestin 2 (Arr2; Dolph et al. 1993) and via a novel dCAMTA/dFbxl4 pathway, which is poorly defined (Han et al. 2006). Arr2 is phosphorylated by Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and detaches from phosphorylated Rh1, which becomes substrate of the Ca^{2+}/CaM-dependent protein phosphatase RDGC. In contrast to vertebrate PT (involving cyclic GMP), fly PT is mediated by phosphoinositol (PI) signaling. The pool of PI 4,5-biphosphate (PIP_2) necessary for PT is continuously regenerated from diacylglycerol (DAG); the DAG kinase (RDGA) and the PI transfer protein RDGB are important for this reconversion (Wang and Montell 2007).

Abnormalities in PT are a major cause of RD in *Drosophila* and humans, and virtually all mutations that affect PT components result in severe RD in the fly (Wang and Montell 2007). A second collection of mutants are those carrying mutations in the *Rh1* gene. *Rh1* mutations were first associated with RD in the fly. Inactivation of the *Rh1* gene causes RD (O'Tousa et al. 1989; Leonard et al. 1992), and several *Rh1* gain-of-function (GOF) mutations were isolated, which induce a slow and progressive RD (Colley et al. 1995; Kurada and O'Tousa 1995; Kurada et al. 1998). Subsequently, loss-of-function (LOF) and GOF Rho mutations were

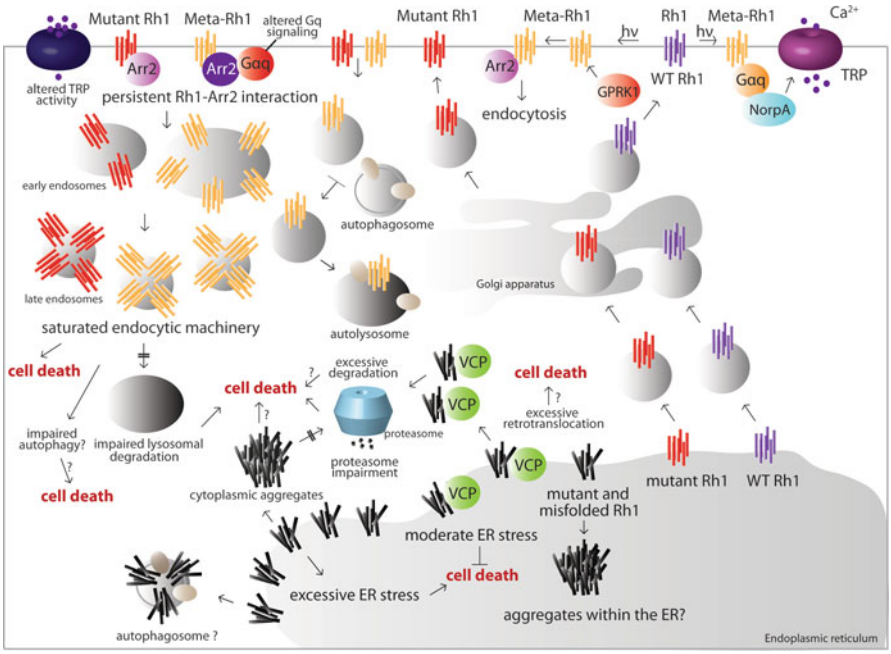

Fig. 53.1 Pathways leading to retinal degeneration in *Drosophila*. Work in *Drosophila* uncovered several pathways linking altered Rh1 states to retinal degeneration. Altered phototransduction emerged as a major contributor to cell death. Mutations in several PT cascade components (including Rh1) stabilize the interaction between Rh1 and Arr2, which in turn causes massive Rh1 endocytosis. Internalized Rh1 fails to reach the lysosomal compartment and accumulates in late endosomes, causing cell death via yet unidentified mechanisms. One potential mechanism might be autophagy impairment. Mutations that cause Rh1 misfolding lead to Rh1 retention in the ER, and to ER stress. Excessive ER stress is pro-apoptotic, while moderate ER stress appears to be protective. Interestingly, excessive Rh1 retrotranslocation and/or proteasomal degradation (mediated by VCP) appears to cause RD. It is unclear (i) whether insoluble cytosolic Rh1 aggregates are pathogenic or whether soluble Rh1 oligomers are more toxic than insoluble aggregates; (ii) how Rh1 degradation (via both ERAD and autophagy) is implemented under conditions of ER stress and how it causes RD, and (iii) whether different Rh1 folding mutants exhibit differential activation of ER stress, ERAD and autophagic machineries

discovered in patients with recessive RP and ADRP, respectively (Daiger et al. 2007). The first and most common Rho mutation to be associated with ADRP is a proline-to-histidine substitution in codon 23 (P23H; Dryja et al. 1990); remarkably, more than 120 Rho mutations have been linked to ADRP (Daiger et al. 2007). Rho mutations have been divided into at least six classes, based on their biochemical and cellular properties (Mendes et al. 2005). In *Drosophila*, dominant *Rh1* mutations causing RD affect (i) the C-terminus of the protein and do not cause Rh1 misfolding, but alter its targeting to the outer segment or (ii) the intradiscal/transmembrane domains causing Rh1 misfolding and retention within the ER.

53.3 Pathogenic Mechanisms Underlying RD in *Drosophila*

Detailed investigation of mutant flies that exhibit RD allowed the identification of several pathogenic mechanisms (Fig. 53.1). Below, we highlight some of these mechanisms, with a focus on Rh1-mediated pathologies.

53.3.1 Abnormalities in the PT Cascade

The tight regulation of Rh1 levels and activation status is critical for PN viability. Failure to uncouple activated Rh1 from the G protein leads to constitutive activation of the PT and to RD. Several mutants, such as *norpA*, *arr2*, *rdgB*, *rdgC*, or *trp* display abnormally stable Rh1-Arr2 complexes, which cause constitutive activation of PT (Alloway and Dolph 1999; Alloway et al. 2000; Kiselev et al. 2000); RD in these mutants is suppressed by vitamin A deprivation, which reduces Rh1 levels (Knust 2007). One prominent consequence of altered PT is an imbalance of Ca^{2+} levels. Thus, in *rdgA* mutants, failure to metabolize DAG leads to excessive Ca^{2+} influx through TRP channels, and *TRP LOF* mutations suppress RD (Raghu et al. 2000). Abnormally low TRP activity also causes RD, by reducing Ca^{2+} influx into PNs, which appears to stabilize the Rh1-Arr2 interaction (Wang et al. 2005). Interestingly, a constitutively active *TRP* mutant – trp^{P365} – that leads to excessive Ca^{2+} influx into PNs also exhibits RD (Yoon et al. 2000). Another defect found in PT mutants is altered G protein signaling. A novel *Rh1* mutant, $Rh1^{pp100}$, causes degeneration by increasing the binding of mutant Rh1 to Arr2 and by elevating the cytosolic levels of $G_q\alpha$; interestingly, these two processes appear to be independent (Iakhine et al. 2004). The protein TADR associates with Rh1 and loss of TADR function causes Rh1-dependent (but Arr2- and NorpA-independent) degeneration, by inhibiting the membrane detachment of G_q during light stimulation (Ni et al. 2008).

53.3.2 Altered Rh1 Endocytosis and Autophagy

A consequence of the prolonged interaction between Rh1 and Arr2 is the rapid internalization of Rh1-Arr2 complexes by receptor-mediated endocytosis. Increased Rh1 endocytosis leads to PN desensitization via a novel Gq-mediated, Arr2-independent and tetraspanin-dependent mechanism (Han et al. 2007). Excessive Rh1 endocytosis leads to RD in several mutants, including *rdgB*, *rdgC*, *arr1*/*2,* and *norpA*, (Knust 2007; Wang and Montell 2007). A remarkable finding is the noncell autonomous regulation of Rh1-Arr2 interaction by the secreted enzyme ceramidase (CDase; which is involved in sphingolipid metabolism; Acharya et al. 2008). The Rh1-Arr2 complex is further regulated by the endocytic adaptor AP-2, which interacts with Arr2 and promotes Rh1-Arr2 internalization; inhibition of AP-2 function

suppressed cell death caused by excessive endocytosis in *norpA* mutants (Orem et al. 2006). A primary cause of PN degeneration in *norpA* and other mutants exhibiting Rh1 pathogenic endocytosis was suggested to be the failure of lysosomal degradation of Rh1, which instead accumulates in late endosomes (Chinchore et al. 2009). Accumulation of Rh1 in late endosomes might also result from impaired lysosome-mediated autophagy. Thus, autophagy inhibition caused Rh1 accumulation in late endosomes and RD in wild-type (WT) PNs, and Rab7 overexpression (which promotes Rh1 trafficking from late endosomes to lysosomes) rescued this effect (Midorikawa et al. 2010). Remarkably, autophagy induction (by overexpressing the mediators TSC1/2 or Atg1) suppressed RD in *norpA* flies, by stimulating the clearance of Rh1-Arr2 complexes; however, autophagy stimulation did not suppress RD in $ninaE^{RH27}$ flies (Wang et al. 2009). Therefore, autophagy stimulation might represent a new therapeutic strategy for a subset of *Rho*-linked RP (see also Mendes and Cheetham 2008).

53.3.3 Impaired Rh1 Maturation, Trafficking, and Proteasomal Clearance

Impairment of Rho biogenesis and transport causes RD in both flies and humans. In *Drosophila*, Rh1 requires the chaperones NinaA (Colley et al. 1991; Stamnes et al. 1991) and Calnexin (Rosenbaum et al. 2006) but also 3-hydroxyretinal (Ahmad et al. 2006) to mature. The GTP-binding protein Rab1 mediates Rh1 transport between ER and the Golgi complex (Satoh et al. 1997); Rab6 mediates Rh1 trafficking within the Golgi and post-Golgi compartments (Shetty et al. 1998); and Rab11 facilitates Rh1 transport from the post-Golgi compartment to rhabdomeres (Satoh et al. 2005). The helix 8 in the C-terminal region of Rh1 is critical for its rhabdomeric localization (Kock et al. 2009).

How do defects in Rh1 maturation and transport cause RD? One possible mechanism is the absence of WT Rh1 from rhabdomeres, as seen in *Rh1* LOF mutants. Thus, besides its critical role in PT, Rh1 is essential for rhabdomere morphogenesis. Rh1 activates the Rho GTPase Drac1 to control cytoskeleton organization in rhabdomeres (Chang and Ready 2000).

A second mechanism linking Rh1 maturation defects to RD is the accumulation of high levels of Rh1 in the ER, which causes toxicity. Several dominant Rh1 alleles were isolated in *Drosophila* and found to cause light-dependent RD (Colley et al. 1995; Kurada and O'Tousa 1995). In flies carrying these alleles, mutant Rh1 localizes to the endoplasmic reticulum (ER) and impairs the maturation of the endogenous WT Rh1; intriguingly, the presence of both mutant and WT Rh1 is required for toxicity (Colley et al. 1995; Kurada and O'Tousa 1995; Kurada et al. 1998). This suggests that both conformers interact to cause toxicity in PNs (see also Griciuc et al. 2010b). More recently, Giangrande and colleagues generated transgenic flies in which the most common RP-linked *Rho* mutation, Rho^{P23H} (its equivalent in flies is $Rh1^{P37H}$), was expressed in R1-6 PNs, under the control of a promoter identical to

the endogenous Rh1 promoter; these flies underwent light- and age-dependent RD (Galy et al. 2005). The use of a small hsv tag allowed the differential analysis of mutant and WT Rh1 conformers, and revealed that Rh1^{P37H} exhibited a dual localization – being present both in rhabdomeres and the ER – while it did not interfere with the maturation of its endogenous WT counterpart. This suggests that RD in *Rh1^{P37H}* flies is due to a toxic (GOF) effect caused by Rh1^{P37H} accumulation in the ER, rather than absence of WT Rh1 from rhabdomeres (dominant negative [DN] effect). The presence of misfolded Rh1 in the ER causes ER stress, both in *Drosophila* (Ryoo et al. 2007) and mammals (Lin et al. 2007). Interestingly, moderate ER stress protects against RD in the fly (Mendes et al. 2009). To understand how ER-based Rh1^{P37H} leads to RD, we inactivated the ER-associated degradation (ERAD) effector VCP/ter94, an ATP-dependent chaperone that mediates Rho^{P23H} extraction from the ER and proteasomal degradation in mammalian cell cultures (Griciuc et al. 2010a). VCP inactivation increased the levels of misfolded Rh1^{P37H}, indicating that VCP is required for Rh1^{P37H} degradation in vivo. VCP ablation also activated the Ire1/Xbp1 ER stress pathway but, remarkably, strongly suppressed Rh1^{P37H}-induced RD; moreover, treatment of *Rh1^{P37H}* flies with VCP/ERAD or proteasome inhibitors potently suppressed RD (Griciuc et al. 2010b). These results suggest that (i) excessive retrotranslocation and/or degradation of Rh1^{P37H} represents a new pathway to cell death in the *Rh1^{P37H}* retina and (ii) partial inhibition of ERAD might be neuroprotective. Working with another Rh1 mutant (*ninaE^{G69D}*), Kang and Ryoo (2009) found that enhancement of ERAD function (by overexpression of ERAD components Hrd1 or EDEM2) rescued the loss of mature Rh1 and RD; interestingly, ERAD inhibition (by Hrd1 or EDEM2 RNAi) also rescued the loss of Rh1, but the effects on RD have not been investigated (Kang and Ryoo 2009). Collectively, these results suggest that early induction of ERAD might protect against RD by clearing the mutant Rh1 from the ER, while chronic ERAD is pro-apoptotic. It remains to be determined whether different Rh1 mutations lead to different levels of ER stress and ERAD activity and whether they cause RD via a GOF or DN mechanism, or both. It is therefore possible that, similar to autophagy, the effects of ERAD manipulation on RD might depend on the Rh1 mutation being investigated.

53.3.4 Pathways to Cell Death in RD

A major pathway to RD has been found to be the programmed cell death (PCD or apoptosis), which is promoted by the activation of *reaper*, *hid,* or *grim* genes and inhibited by *Diap1* or the caspase inhibitor *P35* (Steller 2008). This pathway appears to mediate RD in several mutants, including *rdgC*, *ninaE^{RH27}* (Davidson and Steller 1998), and *Rh1^{P37H}* (Galy et al. 2005). However, RD in the *norpA* mutant (Hsu et al. 2004) appears to be PCD-independent. Further studies in RD mutants will reveal the similarities and differences in the initiation and implementation of cell death programs as well as their underlying biochemical interactions.

53.4 Conclusions

The use of *Drosophila* to study Rho pathologies has greatly advanced our understanding of RD and its underlying mechanisms. It is remarkable to see how often the mechanisms of disease in *Drosophila* resemble those in mammals, despite differences in anatomy and physiology between these species. These pathological processes are likely to be central events in retinal disease, given their evolutionary conservation. Further genetic and proteomic investigations are required to dissect the intricate network of biochemical interactions that link alterations in Rh1 function to PN cell death. It is important to determine whether the various Rh1 altered states (e.g., caused by different Rh1 mutations) lead to distinct molecular pathologies or whether distinct sets of pathological pathways are shared between these altered cellular environments. Many secrets of visual physiology and pathology still remain hidden in the tiny eyes of *Drosophila*. These secrets will undoubtedly passionate the existing and future scholars of retinal dystrophies and could bring valuable clues about how to fight retinal disease in humans.

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