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The many different cellular functions of MYO7A in the retina

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Abstract

Mutations in *MYO7A* cause Usher syndrome type 1B, a disorder involving profound congenital deafness and progressive blindness. In the retina, most of *MYO7A* is localized in the apical region of the RPE (retinal pigmented epithelial) cells, and a small amount is associated with the ciliary and periciliary membrane of the photoreceptor cells. Its roles appear to be quite varied. Studies with *MYO7A*-null mice indicate that *MYO7A* participates in the apical localization of RPE melanosomes and in the removal of phagosomes from the apical RPE for their delivery to lysosomes in the basal RPE. In the first role, *MYO7A* competes with microtubule motors, but, in the second one, it may function cooperatively. An additional role of *MYO7A* in the RPE is indicated from its requirement for light-dependent translocation of the ER-associated, visual cycle enzyme, RPE65, and normal functioning of the visual retinoid cycle. In photoreceptor cells, lacking *MYO7A*, opsin accumulates abnormally in the transition zone of the cilium, suggesting that *MYO7A* functions in a selective barrier for membrane proteins at the distal end of the transition zone. It is likely that the progressive retinal degeneration that occurs in Usher 1B patients results from a combination of cellular defects in the RPE and photoreceptor cells.

Keywords

Myosin VIIa; retina; melanosome; phagosome; endoplasmic reticulum; cilium

INTRODUCTION

Myosin VIIa (*MYO7A*) is an unconventional myosin that is required for normal hearing and vision; mutations in the *MYO7A* gene result in Usher syndrome type 1B [1], which is characterized by congenital profound hearing loss and progressive retinal degeneration [2]. Actin-based motor activity was first demonstrated with *MYO7A*, using protein purified from mouse testes and retinas [3]. More recently, the mechanism of *MYO7A* motor activity has been the focus of biochemical and structural studies, which indicate *MYO7A* is primarily a monomer [4, 5]. As a monomer, *MYO7A* seems less likely to function in organelle or protein transport – a process better suited for a dimeric motor. However, some recent evidence suggests that *MYO7A* may be dimerized following interaction with cargo molecules [6].

Our interest concerns the function of *MYO7A* in the retina. A major approach of our studies has involved mutant phenotype analyses of *shaker1* mice, which have mutations in the orthologue of the Usher 1B gene [7]. These studies indicate that *MYO7A* function includes organelle transport, and so they have particular relevance to the general capabilities of *MYO7A*. The present brief review summarizes the results of these phenotypic studies.

LOCALIZATION OF MYO7A IN THE RETINA

Most of the *MYO7A* in the retina is present in the retinal pigment epithelium (RPE), as first shown by Hasson et al [8]. Some is also present in the photoreceptor cells, although there

has been some disagreement about its localization in these cells. The one region that has been immunolabeled [9] and associated with a mutant phenotype [10] is the connecting cilium, which is structurally similar to the transition zone of other cilia [11, 12]. Support for restriction to this region has also come from immunolocalization studies that have included null mutant retinas for controls [13], or involved overexpression following gene therapy treatment (own unpublished data). MYO7A appears to be associated with the membrane of the connecting cilium, as well as the periciliary membrane that forms a partial pocket around the connecting cilium [9, 14].

MELANOSOME MOTILITY

The most obvious defect in the retinas of shaker1 mice is that of melanosome mislocalization. In pigmented mammals, some of the melanosomes of the retinal pigment epithelium (RPE) extend into the apical processes that surround the tips of the photoreceptor outer segments. However, by microscopy, it is evident that this apical region is completely devoid of melanosomes in the RPE of shaker1 retinas, suggesting that a function of MYO7A is to move melanosomes into this region [15] (Fig. 1). In primary cultures of mouse RPE cells, melanosomes can be observed undergoing short movements. When the motility of melanosomes in wild-type cells is compared with that of shaker1 RPE cells, it is clear that the melanosomes in the mutant cells move faster and further [16].

This behavior resembles that of melanosomes in melanocytes. When MYO5A is lacking in melanocytes, melanosomes similarly move more rapidly [17]. Loss of MYO7A in the RPE or MYO5A in melanocytes allows melanosomes to travel more freely on microtubules, indicating that the role of these myosins in their respective cells is to capture the melanosomes from the microtubule motors and deliver them to the apical processes or dendrites, respectively. The comparison to MYO5A in melanocytes extends to the molecular linkage to the melanosome. Both motors require RAB27A on the melanosomes membrane, plus an exophilin protein that links the motor to RAB27A: melanophilin, in the case of MYO5A [18–21], and MYRIP, in the case of MYO7A [16, 22–25]. Interestingly, MYO5A has been demonstrated to function as a dimeric motor that progresses along actin filaments [26]. Since MYO7A and MYO5 have such comparable *in vivo* functions, it suggests that MYO7A in RPE cells may function in a mechanistically similar manner.

PHAGOSOME MOTILITY

Studies with *Dictyostelium* found that myosin VII was required for the initial stages of particle adhesion during phagocytosis [27]. Given the importance of phagocytosis of photoreceptor outer segment disk membranes by the RPE [28], as part of the turnover of the disk membranes [29], it was thus considered that a phagocytic defect might underlie the retinal pathology associated with Usher syndrome. However, in studies of shaker1 mice, the ingestion of disk membranes by the RPE appeared to be normal. Nevertheless, the disposal of the phagosomes was found to be defective. The phagosomes took longer to be cleared from the apical RPE to the basal RPE, and their digestion is slower [30]. The delivery of phagosomes from the apical to the basal RPE has been shown very vividly in the opossum retina, which has an RPE that is up to 100 μm deep. Colchicine blocks this delivery [31], suggesting the involvement of microtubule motors. A plausible role for MYO7A is that it transports phagosomes through the apical actin meshwork until they can be coupled to microtubule motors, as illustrated in Fig. 1. In this manner, MYO7A would be functioning cooperatively with microtubule motors – in contrast to the competitive nature of its role in capturing melanosomes from microtubule motor activity. Alternatively, in a less direct role, MYO7A might transport lysosomes to the apical RPE, so that lysosomes could fuse with the

phagosomes, somehow enabling their release from the apical region. Support for this second hypothesis comes from the finding that some MYO7A is associated with lysosomes [32].

THE VISUAL CYCLE

Shaker1 retinas have been reported to have a mild electrophysiological defect [33], and a greater resistance to acute light damage [34]. The latter has been linked to a defect in the visual retinoid cycle. Following the absorption of a photon of light, the visual pigment becomes bleached. Regeneration of the visual pigment occurs through a series of reactions, known as the visual retinoid cycle [35–38]. A key step in this cycle is the reisomerization of the retinoid chromophore, a reaction that is catalyzed by the enzyme RPE65 [39–41]. RPE65 undergoes a light-dependent translocation within the RPE cells [34]. In shaker1 retinas, RPE65 does not undergo this translocation, and the visual cycle is inhibited, which, in turn, most likely affords the protection against acute light damage [34].

RPE65 associates with smooth ER in the RPE, suggesting that MYO7A might translocate the enzyme by transporting smooth ER tubules and vesicles. Interestingly, MYO5 has been shown to associate with and move ER membrane in a variety of systems, such as squid axon [42], budding yeast [43], and dendrites of Purkinje cells [44–47]. Perhaps MYO7A is comparable to MYO5 in an additional function (other than melanosome transport) – namely, ER membrane transport. ER tubules are also moved along microtubules by microtubule motors [48], so that if MYO7A proves to be an actin-based motor for ER in the RPE, its function is likely to be linked to that of microtubule motors, as appears to be the case in melanosomes and phagosome motility (Fig. 1).

OPsin DELIVERY

The localization of MYO7A in the connecting cilium of photoreceptor cells suggests that it might participate in moving proteins along this connection between the inner and outer segments. Consistent with this suggestion, immunogold labeling of opsin of shaker1 retinas shows that, in the absence of functional MYO7A, abnormally high levels of opsin accumulate in the connecting cilium [10]. However, this phenotype could arise from a less direct link to opsin transport. Transport along cilia appears to be a highly regulated process, and proteins involved in this regulation, such as in the maintenance of a diffusion barrier [49], would be required for the normal distribution of proteins within the structure. Kinesin-2 motors seem to be the primary motors required for the transport of opsin along the connecting cilium – their absence has a much more severe effect on opsin delivery to the outer segment [50]. MYO7A's role is more likely to be an auxiliary one.

CONCLUSION

Analyses of MYO7A-deficient mice indicate that MYO7A has a variety of roles in the RPE and photoreceptor cells of the mammalian retina. In the RPE at least, the roles appear to involve organelle transport. Each of the mutant phenotypes resulting from lack of MYO7A is likely to compromise the health of the retina, suggesting that retinal degeneration in Usher 1B patients results from a combination of different cellular defects.

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Abbreviations

RPE	retinal pigmented epithelium
ER	endoplasmic reticulum

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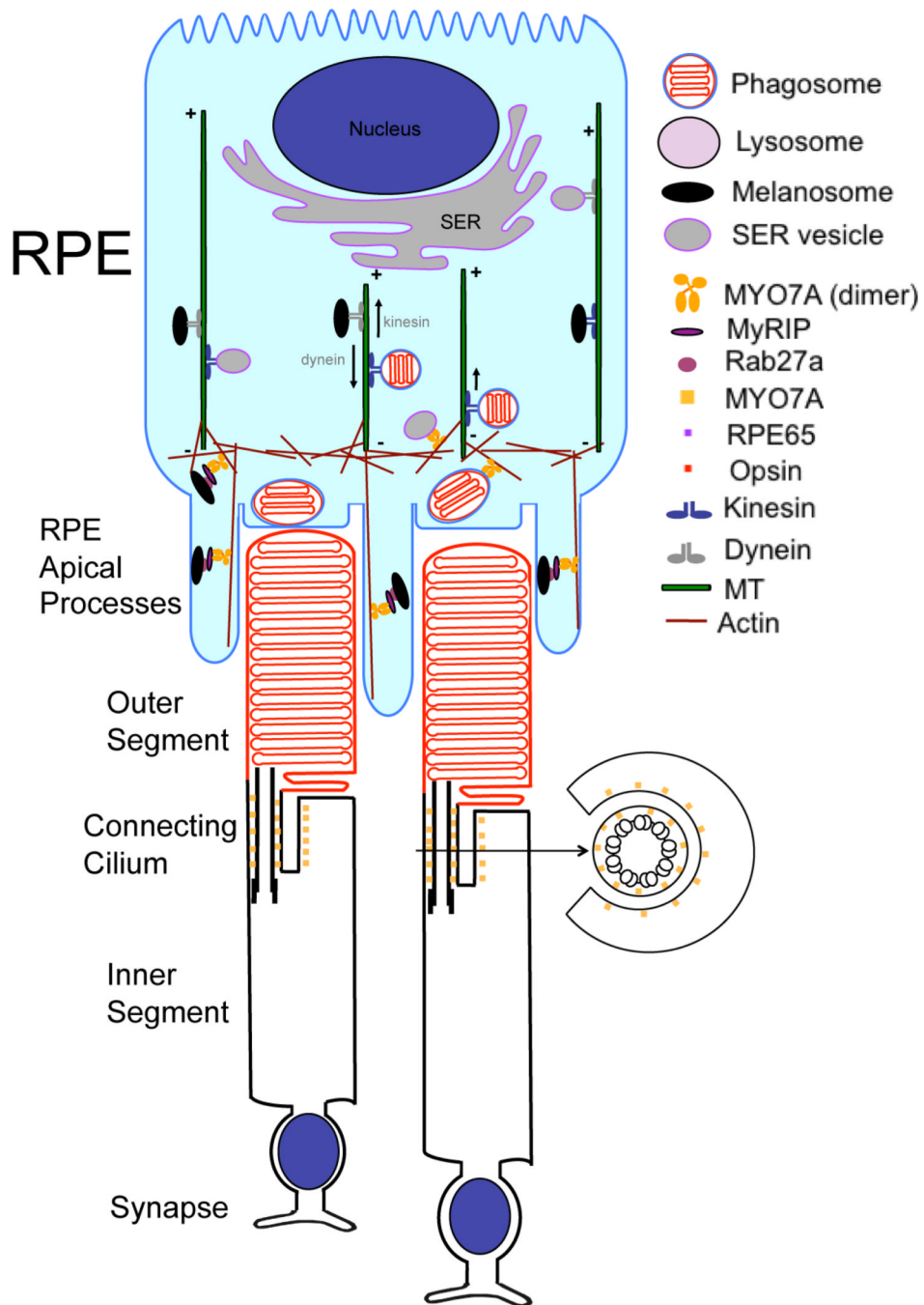


Figure 1. Illustration of MYO7A functions in an RPE cell and its localization in photoreceptor cells. MYO7A is present in the apical RPE where it is involved in the transport of melanosomes, phagosomes and smooth ER vesicles, in conjunction with microtubule motors. In photoreceptor cells, MYO7A is associated with the ciliary and periciliary plasma membranes.