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Mini Review

Retinal Degeneration-3 (RD3) Protein is a Molecular Linchpin for Retinal Disease

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Received: November 15, 2018; **Published:** December 06, 2018

Abstract

Retinal degeneration 3 (RD3), is a 23 kDa protein in rod and cone photoreceptors that controls the trafficking of retinal membrane guanylyl cyclase (RetGC). RD3 binds to RetGC and promotes accumulation of RetGC in the outer segment region of photoreceptor cells. RD3 interaction with RetGC turns off its basal guanylyl cyclase enzymatic activity during the trafficking of RetGC. Mutations that disable RetGC binding to RD3 are responsible for photoreceptor degeneration in Leber Congenital Amaurosis 12 patients. In this mini review, I discuss a mechanism for how RD3 controls the trafficking of RetGC and explain why genetic mutations in RD3 and RetGC lead to retinal disease.

Keywords: *Guanylyl Cyclase; Photoreceptor; Retina; Phototransduction; Retinal Degeneration 3 (RD3)*

Abbreviations

GCAP: Guanylyl Cyclase Activating Protein; RD3: Retinal Degeneration 3; RetGC: Retinal Membrane Guanylyl Cyclase; cGMP: Cyclic Guanosine Monophosphate.

Introduction

Phototransduction in retinal rod and cone photoreceptor cells involves light-activated hydrolysis of cGMP catalyzed by phosphodiesterase PDE6 [1] (Figure 1A). The light-induced drop in cGMP level causes the closure of cGMP gated channels in photoreceptor outer segment plasma membranes that generates a neural signal [2-4]. When the light stimulus is turned off, light-activated photoreceptors convert back to the dark-adapted resting state by a process known as visual recovery [1,5]. The visual recovery process requires the rapid re-synthesis of cGMP catalyzed by the enzyme, retinal guanylyl cyclase (RetGC). This light-dependent re-synthesis of cGMP is triggered by a decrease in cytosolic Ca^{2+} concentration in light activated photoreceptor cells [3,6,7] (see Figure 1A). The Ca^{2+} sensitive RetGC enzymatic activity in photoreceptor cells is carefully regulated by two sensor proteins: (1) guanylyl cyclase activating proteins (GCAPs), which are calcium binding proteins that activate RetGC in light-activated photoreceptors [6,8], and (2) retinal degeneration 3 (RD3) protein that promotes trafficking of RetGC to the outer segment [9] (Figure 1B). RD3 is a 23-kDa protein whose deficiency causes severe photoreceptor degeneration and blindness in human patients of recessive Leber's congenital amaurosis (LCA) and in rd3 knockout mice [10]. The lack of RD3 expression in rd3 knockout mice leads to reduced levels of RetGC in photoreceptors, because RD3 is needed to control the trafficking of RetGC into the outer segment [11,12]. RD3 also acts as a potent inhibitor of RetGC enzymatic activity by binding to the enzyme with high affinity and preventing RetGC activation by GCAPs [13,14]. The ability of RD3 to bind to RetGC and suppress the cyclase activity is believed to prevent aberrant activation of RetGC by GCAPs and is critical for the survival of photoreceptors [14]. Indeed, genetic mutations in RetGC and/or RD3 are linked to many forms of retinal degeneration [9-11,15]. In this mini review, I discuss a mechanism for how RD3 controls the trafficking of RetGC and explain why genetic mutations in RD3 [9-11], GCAPs [16-18] and RetGC [19,20] each lead to retinal disease.

Discussion

The RD3 protein helps to promote the trafficking of RetGC to the outer segment disc membrane in photoreceptor cells [9-11] (Figure 1B). The membrane-bound RetGC is initially synthesized in the endoplasmic reticulum (ER), where it gets incorporated into transport vesicles. The RD3 protein binds to RetGC in transport vesicles in the inner segment and guides the trafficking of these vesicles into the outer segment. RD3 binding to RetGC is believed to stabilize the overall protein structure in the complex in order to facilitate the transfer

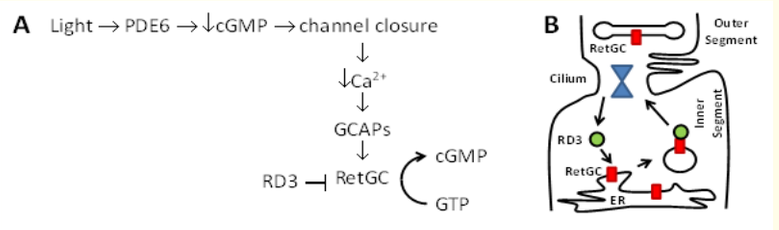

Figure 1: Physiological role of RD3 in visual phototransduction.

(A) Visual excitation pathway in retinal photoreceptor cells. Light-activated channel closure promotes a drop in cytosolic Ca^{2+} level that in turn activates RetGC, whereas RD3 binding to RetGC inhibits the cyclase activity.

(B) RD3 (green) guides the trafficking of RetGC (red) to outer segment disc membranes.

of RetGC from a transport vesicle into the outer segment disc membrane. RD3 binds to a localized site in RetGC (residues 800-851 called the dimerization domain) that also interacts with GCAP proteins [13,14]. Thus, RD3 prevents the activation of RetGC cyclase enzymatic activity by preventing the binding of GCAP proteins [14]. In essence, RD3 binding to RetGC is necessary to keep the RetGC enzymatic cyclase activity turned off during its transport to the outer segment. Otherwise, the basal RetGC cyclase activity (in the absence of RD3) would cause the synthesis of cGMP in the inner segment, which in turn could aberrantly cause apoptosis and lead to retinal degeneration [21,22]. This explains why mutations in RD3 and/or RetGC that prevent RD3 binding to RetGC are genetically linked to Leber's congenital amaurosis [11,12]. These disease causing mutations are somewhat analogous to mutations in GCAP1 that cause autosomal dominant cone dystrophy [16-18,23,24]. In particular, the Y99C mutation in GCAP1 (that weakens Ca2+ binding) causes persistent activation of RetGC that in turn leads to elevated levels of cGMP, which causes retinal degeneration. In summary, there are two types of genetic mutations that disrupt regulation of RetGC and promote retinal degeneration: (1) mutations in RD3 (or RetGC) that disable RetGC binding to RD3 and cause elevated basal cyclase activity, and (2) mutations in GCAP1 that weaken Ca2+ binding and hence cause persistent activation of RetGC. Either case leads to an increase in the basal cyclase activity in RetGC (an hence higher cGMP levels) that causes retinal degeneration. Future studies are needed to solve atomic-resolution structures of RetGC bound separately to RD3 and GCAP1 that may provide molecular insights for designing new drugs to treat retinal degeneration.

Conclusions

RD3 interaction with vesicle-bound RetGC is essential to promote its trafficking to the outer segment region of photoreceptor cells. RD3 binding to RetGC also turns off cyclase enzymatic activity during RetGC trafficking, which keeps cGMP levels low in the inner segment and prevents photoreceptor degeneration. Mutations that disable RD3 binding to RetGC therefore lead to retinal degenerative disease. Understanding the structural basis of the RD3 binding interaction may provide new insights for drug design

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Volume 10 Issue 1 January 2019