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A Tale of Two Kinases in Rods and Cones

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105.1 Introduction

The G protein-coupled receptor kinase (GRK) family of serine/threonine kinases contains seven members with varying tissue localization in vertebrates. Rhodopsin kinase (GRK1) was the first member of the family identified and was shown to limit the lifetime of its substrate, rhodopsin, via phosphorylation followed by arrestin binding (Wilden and Kühn 1982; Kühn and Wilden 1987). A central role for GRK1 in retinopathies was identified when Oguchi disease, a form of stationary night blindness, was found to be due to an inactivating mutation in GRK1. Although the vision of patients with this disease is fairly normal in bright light, they have difficulty seeing in dim light. Later, individuals with similar visual problems were identified with mutations that interfere with the function of arrestin. Defects in either of these genes cause patients to suffer from an inability to properly deactivate rhodopsin, leading to problems with recovery and dark adaptation (Dryja 2000).

One question that arose from studying patients with Oguchi disease was, if GRK1 is the only GRK involved in phototransduction in rods and cones, why do Oguchi patients exhibit relatively mild defects in cone recovery (Cideciyan et al. 1998)? In contrast, mice null for GRK1 (GRK1$^{-/-}$ mice) do exhibit severe defects in cone recovery (Chen et al. 1999; Lyubarsky et al. 2000). A potential explanation would be that human cones express a second GRK that also phosphorylates the cone opsins. In 1998, the full-length cloning of GRK7 from medaka fish (Hisatomi et al. 1998) and the 13-lined ground squirrel, a cone-dominant mammal (Weiss et al. 1998), was reported. Ultimately, GRK7 was also cloned from a number of rod dominant mammals, such as human, pig, and cow, as well as additional species of fish and frog (Chen et al. 2001; Weiss et al. 2001; Shimauchi-Matsukawa et al. 2005; Wada et al. 2006; Osawa et al. 2008). These discoveries explain why Oguchi patients have only a mild defect in cone recovery; humans express both GRK1 and GRK7 in cones and when GRK1 is missing, there is partial compensation by GRK7 (Cideciyan et al. 2003).

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These genetic studies reveal an interesting heterogeneity in the expression of GRK1 and GRK7 (Table 105.1) that spans 400 million years of vertebrate evolution (Futuyama 1998). All vertebrates examined to date express GRK1 in rods. On the other hand, some vertebrates express only GRK7 in cones and others (including primates) express both GRK1 and GRK7 (Zhao et al. 1999; Weiss et al. 2001; Shimauchi-Matsukawa et al. 2005; Wada et al. 2006; Imanishi et al. 2007). Surprisingly, mice and rats have lost the gene for GRK7 and express only GRK1 in cones (Weiss et al. 2001; Caenepeel et al. 2004), also explaining why GRK1$^{-/-}$ mice have more severely impaired vision under phototopic conditions than Oguchi patients (Lyubarsky et al. 2000).

105.2 The Function of GRK7

Because cones function under a larger dynamic range of light than rods, they undergo different kinetics of deactivation and recovery (Baylor 1987; Knox and Solessio 2006). Differences in the structure, protein profile, and ionic balance between rods and cones may play a role in the distinct properties of these cells, as described in an excellent recent review by Kawamura and Tachibanaki (2008). How GRK7 might contribute to the unique properties of cones is an area of active research in several laboratories. Our laboratory determined that GRK7 phosphorylates the cone opsins in mammals (Liu et al. 2005) and Rinner et al. (2005) provided direct evidence that GRK7 is required for cone recovery in zebrafish. Information on the relative roles of GRK1 and GRK7 in humans may be derived from comparative studies of individuals with different retinopathies. For example, the visual properties of individuals with normal vision were compared with Oguchi disease patients lacking functional GRK1 and patients with Enhanced S Cone Syndrome (ESCS), whose retinas have large numbers of S cones expressing no GRK and L/M cones lacking GRK7 (Cideciyan et al. 2003). Electroretinographic studies indicate that cones lacking either GRK1 or GRK7 exhibit a reduction in normal deactivation after light exposure, but not as severe as those lacking both GRKs (Cideciyan et al. 2003). Therefore, GRK1 and GRK7 can partially compensate for each other if either one of them is missing.

The activities of GRK1 and GRK7 have been compared in several model systems. Using rods and cones isolated from carp retina, Kawamura and colleagues evaluated the rates of rod (rhodopsin) and cone opsin phosphorylation by their endogenous GRKs. They reported that GRK7 is 10 times more abundant in cones than GRK1 in rods and that the catalytic activity of GRK7 is 10 times higher than GRK1 (Tachibanaki et al. 2005). Although the absolute values were different, Fukada and coworkers came to a similar conclusion regarding the higher intrinsic activity of zebrafish GRK7 compared to GRK1 (Wada et al. 2006). In contrast, work by Horner et al. (2005) using FLAG-tagged human GRK1 and GRK7 indicated that the K_m and V_{max} values of human GRK1 and GRK7 for rhodopsin and ATP were fairly similar in vitro. Additional studies of these two kinases in vivo may further clarify their distinct or overlapping roles in cone visual signaling.

105.3 Regulation of GRK1 and GRK7 Activity Under Changing Light Conditions

GRK1 activity has been studied extensively in mammalian rods (Maeda et al. 2003) and was the first GRK family member found to be allosterically regulated by its substrate, rhodopsin, such that the light-activated form of the rhodopsin activates the kinase (Fowles et al. 1988; Palczewski et al. 1991). This has also been shown for GRK2 (Chen et al. 1993) and is likely to be true for all other GRKs (Huang et al. 2009). GRK1 is also regulated by the Ca^{2+}-sensor protein, recoverin (Kawamura 1993; Chen et al. 1995; Klenchin et al. 1995). In dim light, when Ca^{2+} levels are high, inhibition of rhodopsin phosphorylation by recoverin prolongs the lifetime of the photoreceptor (Makino et al. 2004; Chen et al. 2010). Arinobu et

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al. (2010) compared the effect of recoverin on GRK1 activity with the effect of visinin (a cone-specific paralog of recoverin in lower vertebrates) on GRK7 activity using rod and cone membranes prepared from carp retina. They reported that the K_D values for recoverin and visinin are similar for GRK1 and GRK7. However, cone opsin phosphorylation by GRK7 is inhibited by visinin to a greater extent than rhodopsin phosphorylation by GRK1 inhibited by recoverin. The authors propose that these results are due to structural differences whereby GRK7 is more sterically constrained in the binding of its substrate than GRK1.

Although cGMP is clearly the critical second messenger for phototransduction, there is evidence of a role for cAMP in photoreceptor physiology. Cyclic AMP levels are high in the dark and low in the light in photoreceptor cells (Farber et al. 1981; Cohen et al. 1992) and regulate a variety of physiological processes in a circadian fashion that involve a feedback loop between dopamine, synthesized in amacrine/interplexiform cells, and melatonin, synthesized primarily in photoreceptors (Tosini et al. 2008; Wiechmann and Summers 2008). Several substrates for cAMP-dependent protein kinase (PKA) have been identified in photoreceptors, including phosducin, arylalkylamine N-acetyltransferase (AANAT; a key enzyme in melatonin synthesis), the γ subunit of cGMP-phosphodiesterase, and several transcription factors (Bauer et al. 1992; Lee et al. 1992; Xu et al. 1998; Ganguly et al. 2001; Liu and Green 2002; Ivanova and Iuvone 2003; Yu et al. 2007). Our laboratory identified sites in the amino terminus of GRK1 and GRK7 (Ser21 and Ser36, respectively) that are phosphorylated by PKA in vitro (Horner et al. 2005). We also observed that phosphorylation by PKA reduces the ability of these kinases to phosphorylate rhodopsin. Using phosphospecific antibodies, we have determined that GRK1 and GRK7 are phosphorylated in vivo. Phosphorylation by PKA is high in the dark and low in the light, consistent with the light-dependent changes in cAMP levels (Osawa et al. 2008; Weiss et al. 2008). These experiments introduce the possibility of a novel mechanism for regulating the lifetime of rhodopsin and the cone opsins via light-dependent changes in GRK activity, resulting in higher sensitivity of the visual response under dim light and reduced sensitivity under more intense light.

It is clear from recent studies that at least one GRK is essential to deactivate the photoresponse in cones (Cideciyan et al. 1998, 2003; Lyubarsky et al. 2000), but why do many vertebrates, including humans, express two GRKs in cones? There are several possibilities: the expression of two GRKs may simply have an additive effect. This may provide a quantitative advantage for survival in specific environments where quick signal termination by higher levels of GRKs may improve visual acuity in animals that are active in daylight. Alternatively, these two kinases may have distinct biochemical properties that may differentiate their roles in cones. A better understanding of the function of these two kinases in cones will advance our knowledge of how the retina adapts to a broad range of light intensities in the natural environment.

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Table 105.1

Distribution of GRK1 and GRK7 in vertebrate photoreceptor cells

	Rods	Cones
Human	1	1, 7
Monkey	1	1, 7
Xenopus	1	1, 7
Chicken	1	1, 7[a]
Zebrafish	1A	1B, 7
Carp	1A	1B, 7
Pig	1	7
Dog	1	7
Medaka	1–1, 1–2	7
Mouse	1	1

[a]Expression of chicken GRK7 is speculative