Published in final edited form as:

AFCS Nat Mol Pages. 2011 ; 2011: . doi:10.1038/mp.a001756.01.

Phosphodiesterase 6C, cGMP-specific cone alpha'

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Abstract

Network Map States Transitions Functions Protein Classes

Sequence Interactions Pathways Domains & Motifs Protein Structure Orthologs

Sequence Interactions Pathways Domains & Motifs Protein Structure Orthologs Blast Data

Protein Function

Phosphodiesterase 6C (PDE6C) is a member of the cyclic nucleotide phosphodiesterase superfamily (Conti and Beavo 2007) that is specific for cone photoreceptor cells. It is the primary effector enzyme involved in the cone phototransduction cascade (Ebrey and Koutalos 2001; Zhang and Cote 2005; Kawamura and Tachibanaki 2008). In vertebrate cone cells, the holoenzyme is a catalytic PDE6C homodimer to which two inhibitory PDE6H subunits bind (Hamilton and Hurley 1990; Li *et al.* 1990).

Cone photoreceptors have been shown to have homologous isoforms of all of the central proteins involved in the rod visual excitation pathway, including opsins (Nathans *et al.* 1986), transducin (Lerea *et al.* 1986; Blatt *et al.* 1988; Morris and Fong 1993), PDE6 (Hurwitz *et al.* 1985; Li *et al.* 1990; Hamilton and Hurley 1990), and the cGMP-gated ion channel (Haynes and Yau 1985; Cobbs and Pugh 1985).

When light photoisomerizes 11-cis-retinal to the all-trans isomer in cone opsin, the activated visual receptor then interacts with and activates the cone-specific transducin heterotrimer. This causes exchange of GDP with GTP in the α -subunit and dissociation of the activated α -subunit from the $\beta\gamma$ subunits of transducin. The GTP-bound transducin α -subunit then interacts with cone PDE6 holoenzyme to relieve the inhibitory constraint of the PDE6H subunit thereby accelerating hydrolysis of cGMP in the active site of PDE6C. When the intracellular concentration of cGMP drops, it results in the closure of the cGMP-gated channels causing membrane hyperpolarization (Arshavsky *et al.* 2002). It should be noted that the foregoing summary is, in many respects, inferred from the extensive knowledge of the rod phototransduction pathway rather than from direct experimental evidence of the cone signaling pathway.

Regulation of Activity

Cone PDE6 exists as a catalytic homodimer of two PDE6C subunits (unlike mammalian rod PDE6, which is a heterodimer). Each PDE6C subunit consists of two, tandem GAF domains (named for their occurrence in cGMP binding PDEs, certain adenylate cyclases, and the *Escherichia coli* FhIA protein; Aravind and Ponting 1997; Zoraghi *et al.* 2004) and a catalytic domain that is highly conserved among all the Class I phosphodiesterases. Using heterologous expression of various constructs of the PDE6 regulatory domain (some as chimeric proteins containing the PDE5 catalytic domain), the PDE6C GAFa domain has been shown to contain a high-affinity, noncatalytic cGMP binding pocket (Huang *et al.* 2004; Muradov *et al.* 2004), as well as sites of interaction with the inhibitory γ -subunit (Muradov *et al.* 2004). Upon binding of cGMP to the GAFa domain of PDE6C, a considerable rearrangement of secondary structure occurs, as judged by changes in the NMR spectra (Martinez *et al.* 2008). Although cGMP occupancy of the PDE6 GAFa domain has not been reported to directly affect the enzymological properties of the enzyme (Arshavsky *et al.* 1992; D'Amours and Cote 1999; Mou and Cote 2001), direct inter-domain allosteric communication between the GAF and catalytic domains has been observed for rod PDE6 (Zhang *et al.* 2008), and presumably occurs for cone PDE6 as well.

The primary mechanism of regulation of PDE6C enzyme activity is the binding/release of the inhibitory γ -subunit (PDE6H). This 83-amino-acid protein interacts at multiple sites on the PDE6C catalytic subunit, presumably occluding the active site as has been directly shown for rod PDE6 (Granovsky *et al.* 1997). Inhibition of cone PDE6 holoenzyme is relieved upon displacement of the γ -subunit by the light-activated, GTP-bound cone transducin α -subunit, GNAT2 (Muradov *et al.* 2010). Interestingly, cone PDE6 holoenzyme is much more efficiently activated *in vitro* by transducin than rod PDE6, regardless of whether rod (GNAT1) or cone transducin α -subunit is used for these assays (Gillespie and Beavo 1988; Muradov *et al.* 2010).

Mutational analyses with chimeric constructs consisting of the PDE5 catalytic domain in which two loop regions have been substituted for their PDE6C counterparts have identified γ -subunit-interacting residues near the catalytic pocket based on biochemical results (Granovsky and Artemyev 2000; Muradov *et al.* 2004) and structural results (Barren *et al.* 2009).

The enzymatic properties of cone PDE6 are quite similar to those of the rod PDE6 enzyme, with K_M values for cGMP of $\sim 20 \mu\text{M}$ and k_{cat} values of $\sim 4000\text{--}5000 \text{ cGMP/s/PDE6 dimer}$ (Hurwitz *et al.* 1985; Gillespie and Beavo 1988; Zhang *et al.* 2003; Huang *et al.* 2004; Muradov *et al.* 2010). cAMP is a very poor substrate for cone PDE6, with a K_M value about 30-fold higher than for cGMP (Huang *et al.* 2004). Efficient catalysis by cone PDE6 depends on the presence of Mg (Gillespie and Beavo 1988).

Interactions with Ligands and Other Proteins

Cone PDE6 holoenzyme interacts with a number of other ligands and proteins to carry out its signal transduction role in cone phototransduction. Compared with the rod PDE6 enzyme, relatively little biochemical characterization has been carried out with cone PDE6

holoenzyme due to difficulties in purifying the protein, and the inability to express a functional form of cone PDE6 in a heterologous expression system.

As is true for all Class I PDEs, PDE6C exists as a dimer, more specifically a homodimer, of two catalytic subunits (Gillespie and Beavo 1988; Muradov *et al.* 2010). Although the isolated GAFa domain of PDE6C is intrinsically monomeric (Martinez *et al.* 2008), evidence from rod PDE6 (Kamení *et al.* 2001; Muradov *et al.* 2003) as well as from other GAF-containing PDEs all points to the GAFa domain being a major determinant of dimerization with additional stabilization provided by the GAFb domain (for review, see Heikaus *et al.* 2009).

Cone PDE6C presumably binds divalent cations to the active site of the enzyme, as is the case for all other phosphodiesterase families (Ke and Wang 2007). It is likely that zinc occupies one metal ion binding site, while the other site may bind magnesium under physiological conditions, consistent with biochemical evidence for the rod PDE6 enzyme (Srivastava *et al.* 1995; He *et al.* 2000), and structural determination of a PDE5/6 chimeric catalytic domain (Barren *et al.* 2009).

The regulation of cone PDE6C catalytic activity is primarily controlled by binding of its inhibitory γ -subunit (PDE6H) with a stoichiometry of one γ -subunit per catalytic subunit. Initial characterization of the binding affinity of cone PDE6 for rod and cone inhibitory subunits suggested that PDE6C has a lower affinity for the γ -subunit than that exhibited by rod PDE6 (Hamilton *et al.* 1993). Recently, expression of human PDE6C in transgenic frog rod photoreceptors allowed evaluation of the inhibition constant (K_i) for cone and rod γ -subunits; the cone γ -subunit showed a slight preference for PDE6C ($K_i = 78$ pM) over the rod PDE6 dimer ($K_i = 155$ pM) (Muradov *et al.* 2009). In this study, rod PDE6 catalytic dimer had similarly high affinities for cone γ -subunit ($K_i = 140$ pM) and rod γ -subunit ($K_i = 105$ pM) (Muradov *et al.* 2009). The sites of interaction of the inhibitory γ -subunit with PDE6C are not well defined in comparison to the more thorough investigations performed with the rod PDE6 holoenzyme. Information from chimeric PDE5/PDE6 constructs provide evidence for stabilizing interactions of the γ -subunit with the GAFa domain of PDE6C (Muradov *et al.* 2002; Muradov *et al.* 2004).

Allosteric modulation of catalytic function could in theory result from binding of cGMP to noncatalytic binding sites of cone PDE6 (Gillespie *et al.* 1989), in analogy to the direct allosteric activation observed for PDE5 (Rybalkin *et al.* 2003); however, this mechanism has not been experimentally observed for PDE6 to date (see "Regulation of Activity" section). The GAFa domain of chicken PDE6C was expressed in recombinant form in bacteria and found to possess the high-affinity binding site for cGMP, similar in affinity to that of the purified cone PDE6 holoenzyme (Huang *et al.* 2004). Structural studies of the chicken cone PDE6 GAFa domain (PDB:3DBA; Martinez *et al.* 2008) reveal structural details of the cGMP binding pocket that complement earlier site-directed mutagenesis research to define the binding determinants for cGMP in the GAFa domain (Muradov *et al.* 2004; Huang *et al.* 2004). NMR studies reveal significant structural alterations of the GAFa domain upon binding of cyclic GMP (Martinez *et al.* 2008). An approximate stoichiometry of cGMP

binding for cone PDE6 is 1.9 mol cGMP/mol of PDE6 dimer, and the binding affinity is relatively high ($K_d = 11$ nM; Gillespie and Beavo 1988).

Although it is assumed that PDE6C is geranylgeranylated based on comparisons with rod PDE6, the sequence of the C-terminal isoprenylation motif, and its ability to bind the prenyl binding protein δ (PDE6D) (Florio *et al.* 1996; Gillespie *et al.* 1989), no experimental confirmation of this post-translational modification has been reported. Zhang *et al.* (2007) reported that knockout of the PDE6D gene greatly lowered expression of PDE6C in cone inner and outer segments, emphasizing the importance of isoprenylation of PDE6C for its proper localization and function.

The active site of PDE6C shows a very similar selectivity to the rod PDE6 enzyme for inhibition of catalysis by phosphodiesterase inhibitors (Gillespie and Beavo 1989; Zhang *et al.* 2004; Zhang *et al.* 2005).

Regulation of Concentration

Little is known about the cellular concentration of cone PDE6 in the cone outer segment. Published work relies on estimates of cone PDE6 content in retinal extracts of species containing cone-dominant retinas, such as the eastern chipmunk where the ratio of cone opsin to cone PDE6 was estimated to be 68:1 (Zhang *et al.* 2003).

Subcellular Localization

In cone photoreceptor cells, PDE6C is primarily localized to the signal-transducing outer segment organelle (Zhang *et al.* 2007). However, protein synthesis occurs in the inner segment and it has been observed that ectopically expressed PDE6C is transported from the inner segment to its final destination in the cone outer segment (Muradov *et al.* 2009). Trafficking of cone outer segment proteins appears to be dependent on kinesin-II (Avasthi *et al.* 2009) and guanylate cyclase I (Karan *et al.* 2010).

PDE6C contains a carboxyl-terminal CaaX sequence motif that is predicted to direct this protein to undergo sequential posttranslational processing. The first step is the addition of a prenyl moiety on the cysteine residue that is four amino acids from the C-terminus. Next, an endoproteolytic cleavage removes the last three amino acid residues and the prenylated cysteine becomes carboxymethylated. All mammalian PDE6C proteins contain a terminal leucine residue within the CaaX motif making it the preferred substrate for geranylgeranyl transferase (GGTase-I; Zhang and Casey 1996). After biosynthesis, prenylated phototransduction proteins such as PDE6C dock to the endoplasmic reticulum and are trafficked by vesicular transport to the outer segments where they are associated with the membrane (Karan *et al.* 2008).

Major Sites of Expression

Compared with most of the other vertebrate PDE families, PDE6 has more restricted expression. PDE6C is predominantly found in the outer segments of the cone photoreceptor cells in the retina and to a lesser extent in the pineal gland (Morin *et al.* 2001) and retina-

derived tumors (Hurwitz *et al.* 1990; Di Polo and Farber 1995; Blackshaw and Snyder 1997; Holthues and Vollrath 2004). With one exception (Ahumada *et al.* 2002), expression of PDE6C is not observed in mammalian tissues other than retina, pineal gland, and retina-derived tumors.

Expression of recombinant cone PDE6 in a heterologous expression system has been largely unsuccessful, with failure of the PDE6C protein to be expressed with significant catalytic activity in prokaryotic or eukaryotic cells (Granovsky *et al.* 1998; Piriev *et al.* 2003; White *et al.* 2004; Zhang *et al.* 2004). One notable exception is the ability of human PDE6C to be expressed ectopically in *Xenopus laevis* rods (Muradov *et al.* 2009).

Phenotypes

In humans, although an early report failed to link retinal disease with mutations in PDE6C (Gao *et al.* 1999), more recent work has identified mutations in the PDE6C gene that correlate with diseases such as cone dystrophy and achromatopsia (Thiadens *et al.* 2009; Chang *et al.* 2009; MIM # 613093 and 600827).

The cone photoreceptor function loss (cpfl1) mouse lacks cone function and shows rapid degeneration of cone photoreceptors resulting from a 116-bp insertion and a 1-bp deletion in the *PDE6C* gene (Chang *et al.* 2009).

In zebrafish, a mutation in the *PDE6C* gene results in a developmental progression of retinal degeneration similar to that of the rd1 mouse model (a model for rod photoreceptor degenerative diseases; Stearns *et al.* 2007).

Defective transport of prenylated proteins (including PDE6C) is observed in mice that lack the prenyl binding protein- δ (PrBP/ δ ; *PDE6D*) gene, resulting in altered photoreceptor physiology and slowly progressing cone dystrophy (Zhang *et al.* 2007). Proper localization of cone PDE6 to cone outer segments is also disrupted in mice lacking the Gucy2e gene, which encodes guanylate cyclase 1 (GC1; see Karan *et al.* 2008 for review).

Splice Variants

No splice variants have been experimentally verified for the *PDE6C* gene.

Antibodies

A PDE6C-specific polyclonal anti-peptide (human PDE6C a.a. 16–29) antibody is commercially available (PA1-721; ThermoFisher).

PDE6C-specific antibodies have been generated by individual laboratories and reported in the literature, including the rabbit polyclonal BC18 antibody (Piriev *et al.* 2003) and the sheep anti-PDE6 α ' antibody (Granovsky *et al.* 1998).

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