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Focus on Molecules: Rod cGMP Phosphodiesterase Type 6

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1. Structure

Rod cGMP phosphodiesterase type 6 (rod PDE6: α, β EC 3.1.3.45; γ EC 3.1.4.17; uniprot IDs for human and mouse, respectively, for each subunit; α –P16499, P27664; β –P35913, P23440; γ –P18545, P09174; Genbank IDs for human and mouse, respectively, for each subunit; α –4585863, 31560752; β –4505668, 6679254; γ –76827070, 31982123) is the primary effector enzyme in the phototransduction cascade. The enzyme is a member of a large family of cyclic nucleotide phosphodiesterases that differentially hydrolyze cAMP and cGMP. It is a membrane-associated heterotetrameric enzyme consisting of α- and β-subunits (~99 kD) forming the catalytic core of the enzyme, and two identical inhibitory γ-subunits (~10 kD) that maintain basal activity levels in the dark. The α- and β-subunits both have homologous C-terminal catalytic domains, high affinity non-catalytic cGMP binding sites (GAF domains), and PDE6 γ-subunit binding sites. Primary post-translational modifications are N-terminal acetylation and C-terminal isoprenylation and carboxylmethylation that facilitates membrane association. Domains on the γ-subunit that mediate interaction with the catalytic subunits have been mapped to a basic amino acid rich region (aa 24–45), a 10–20 aa stretch upstream of residue 76 and the C-terminal tail (aa 77–87). More recently, a polyproline region (aa 20–28) conferring binding to Src homology type 3 (SH3) domains has been identified, and may be involved in regulating MAP kinase signaling. While a high resolution crystal structure of PDE6 is yet to be resolved, several groups have determined lower resolution structures and there is an extensive body of in vitro biochemical experiments examining subunit interactions (Cote, 2004). Molecular modeling indicates that the GAF and catalytic domains on each catalytic subunit are aligned to each other and the gamma subunits bind at the catalytic site and primarily at the N-terminal GAF domain (Kajimura et al., 2002) as illustrated in Fig. 1.

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2. Function

PDE6 is activated in response to light stimulation of the receptor in the outer segments of rod and cone cells (Koutalos et al., 1995). A visual cascade of biochemical reactions is initiated when rhodopsin (the visual pigment) is activated by the incident light. Activated rhodopsin stimulates the exchange of GDP for GTP and activates the G-protein, transducin. Transducin activates PDE6 by displacing the inhibitory γ-subunits from the active site of the enzyme, thereby greatly stimulating cGMP hydrolysis. Thus, PDE6 rapidly reduces the cytoplasmic cGMP concentration, which causes closure of cGMP-gated channels and produces a transient hyperpolarization of the rod plasma membrane leading to a reduction in glutamate release at the synapse. Membrane association appears to be regulated by a prenyl binding protein initially thought to be a fourth subunit of the enzyme. Despite numerous attempts by several investigators PDE6 has not been expressed in fully functional form. Efforts to identify possible chaperone proteins led to the identification of AIPL1 as a required protein for PDE6 expression; however, its expression with all PDE6 subunits was not sufficient for functional expression. A developmental role for PDE6 as an effector of the G-protein coupled receptor frizzled-2 mediated Wnt/Ca^{2+}/cGMP signaling pathway was recently demonstrated. The PDE6 γ-subunit has also been shown to interact with the SH3 domain-containing protein PACSIN, indicating a role in endocytosis. The γ-subunit is also expressed in several non-retinal tissues where it may regulate PDE5 function, or interact with other SH3 domain-containing proteins.

3. Disease involvement

The first animal model of retinal degeneration (*rd1*, previously known as *rodless* and *rd*) is caused by a recessive nonsense mutation in the PDE6 β-subunit [reviewed in (Farber et al., 1994)]. *rd1* mice develop normally until onset of photoreceptor outer segment elaboration at days 8–10 postnatally. Rapid photoreceptor degeneration ensues and rod photoreceptors are lost by one month. A defect in the corresponding canine PDE6 β-subunit gene causes another retinal degenerative disorder (rcd1) in Irish setters, and a defect in the PDE6 α-subunit gene in Cardigan Welsh corgi dogs (rcd3) generates a similar phenotype. Rapid and severe photoreceptor degeneration mimicking that observed in the *rd1* mouse is also seen in mice carrying a targeted deletion of the PDE6 γ gene, suggesting that functional assembly of the PDE6 complex requires at a minimum all three subunits. Several mutations have been found in both the α- and β-subunit genes in patients with autosomal recessive retinitis pigmentosa (RP); however considering the entire spectrum of RP disorders PDE6 mutations are rare. The mechanism of retinal degeneration in both the animal and human rod PDE6 disorders remains unclear; however, elevated cGMP levels are known to lead to photoreceptor toxicity.

4. Future studies

While tremendous progress has been made in the study of rod PDE6 since its discovery in the early 1970's there are still several unresolved issues that require further investigation. A high resolution structure of PDE6 remains to be determined despite significant effort. Several researchers have tried and failed to express functional PDE6 that has all of the

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properties of the native enzyme, indicating that other proteins are yet to be identified that are required for PDE6 expression and functional assembly. Therefore, other proteins directly involved in PDE6 expression, assembly and targeting will also be strong candidates for retinal disease genes. Lastly, the exact mechanism by which elevated cGMP levels lead to retinal degeneration remains to be determined.

Acknowledgements

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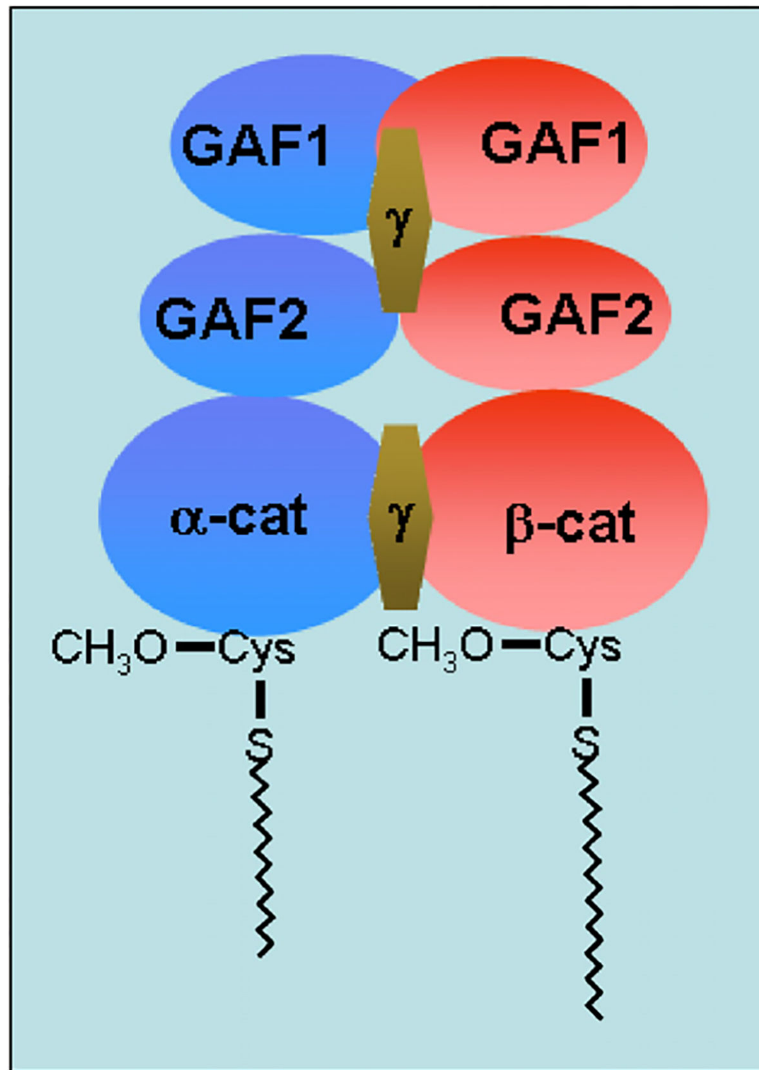

Fig. 1.

Domain structure of Rod PDE6. The structural model of PDE6 is based on electron microscopy observations of highly purified PDE6 catalytic subunits that differentiate the enzyme into three primary structural domains (Kajimura et al., 2002). Non-catalytic cGMP binding sites on the α- and β-subunits (GAF-1 and GAF-2 domains) are in proximity forming two of the domains, and the catalytic region of both subunits at the C-terminus forms the third and largest domain. One possible model favors PDE6 γ-subunit binding to the GAF and catalytic domains independently as shown. Other models suggest binding across all domains and binding of one γ-subunit to each catalytic subunit, and the most recent model for PDE6 structure suggests asymmetric binding of the γ-subunits among intertwined GAF domains (not shown). Membrane association is facilitated by farnesylation of the α-subunit and geranylgeranylation of the β-subunit at the C-terminal cysteine residue, and both cysteines are carboxylmethylated.