

MEETING ABSTRACT

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Asymmetric properties of rod cGMP Phosphodiesterase 6 (PDE6): structural and functional analysis

Bilal M Qureshi^{1*†}, Elmar Behrmann^{1,5†}, Johannes Schöneberg^{2,6}, Justus Loerke¹, Jörg Bürger¹, Thorsten Mielke^{1,3}, Jan Giesebrecht^{1,7}, Frank Noé², Klaus Peter Hofmann^{1,4}, Christian M T Spahn¹, Martin Heck¹

From 7th International Conference on cGMP Generators, Effectors and Therapeutic Implications Trier, Germany. 19-21 June 2015

Photoreceptor cGMP Phosphodiesterase 6 (PDE6) is the effector molecule of visual signal transduction and mediates fast response of light signals. The rod holo-PDE6 comprises catalytic (α , β ; each ~ 90 kDa) and two identical inhibitory (γ ; ~ 10 kDa) subunits. The catalytic subunits comprise N-terminal tandem GAF domains followed by C-terminal catalytic domains and isoprenylations for membrane-association. Contrary to activation of other tandem GAF comprising PDEs, PDE6 activation does not occur via cGMP-induced concerted conformational changes. Rather two copies of the α -subunit of retinal G-Protein ($G\alpha^*$), transducin, activate PDE6 by partially displacing the inhibitory subunits. The activation of PDE6 has therefore been described as a “de-inhibition”. The affinity of $G\alpha^*$ to PDE6 and the enzymatic activity of the intermediary 1:1 complex is highly disputed, therefore a conclusive activation model is lacking so far.

Our combined structural, enzymatic and computational investigations deal with the activation-mechanism of PDE6. Our cryo electron microscopy (EM) structure of PDE $\alpha\beta$ catalytic core shows an elongated bell-shaped structure with symmetric side-by-side arrangement of the two subunits with flexible membrane-binding domains. A comparison with nearly full-length inactive PDE2A structure [1] suggests that less compaction of both subunits and higher degree of conformational freedom of the catalytic domains result in constitutive activation of PDE6 $\alpha\beta$, which is kept inactive by the

inhibitory γ subunits. Furthermore, the structure of PDE6 suggests $G\alpha^*$ binding-sites pointing to opposing faces. The enzymatic characterization using $G\alpha^*$ titration of the PDE6 however reveal striking asymmetry of the two catalytic subunits with a high and a low affinity binding site for $G\alpha^*$. Occupancy of the PDE6 with one $G\alpha^*$ induces negligible activity, whereas occupancy with two copies of $G\alpha^*$ leads to full enzyme activity. Such an activation mechanism constitutes a “coincidence switch” that allows noise filtering (i.e., spontaneously produced $G\alpha^*$ do not activate PDE6). Our spatiotemporal simulation work indeed confirms that spontaneously generated $G\alpha^*$ lead to the formation of singly occupied PDE6 and only a high local concentration of $G\alpha^*$, as produced by an active receptor (rhodopsin), leads to doubly $G\alpha^*$ occupied effector complex. Therefore the localized large concentration of $G\alpha^*$ combined with the asymmetric properties of PDE6 constitutes a “density switch” that allows suppression effector level noise and reliable reporting of single quantum events in rod photoreceptor cells.

Authors' details

¹Biophysics and Medical Physics, Charité – Universitätsmedizin Berlin, 10117 Berlin, Germany. ²Department of Mathematics, Computer Science and Bioinformatics, Freie Universität Berlin, 14195 Berlin, Germany. ³Microscopy & Cryo Electron Microscopy Group, Max-Planck Institut für Molekulare Genetik, 14195 Berlin, Germany. ⁴Zentrum für Biophysik und Bioinformatik, Humboldt-Universität zu Berlin, 10115 Berlin, Germany. ⁵Present address: Research Group Structural Dynamics of Proteins, Center of Advanced European Studies and Research (caesar), 53175 Bonn, Germany. ⁶Present address: Department of Molecular & Cell Biology, University of California at Berkeley, Berkeley, CA 94720, USA. ⁷Present address: FEI VSG (Visualization Science Group), Zuse Institut Berlin, 14195 Berlin, Germany.

Published: 2 September 2015

* Correspondence: bilal.qureshi@charite.de

† Contributed equally

¹Biophysics and Medical Physics, Charité – Universitätsmedizin Berlin, 10117 Berlin, Germany

Full list of author information is available at the end of the article

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doi:10.1186/2050-6511-16-S1-A76

Cite this article as: Qureshi et al.: Asymmetric properties of rod cGMP Phosphodiesterase 6 (PDE6): structural and functional analysis. *BMC Pharmacology and Toxicology* 2015 **16**(Suppl 1):A76.

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