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Foreword

Retinal proteins — You can teach an old dog new tricks

Over three hundred proteins in prokaryotic and eukaryotic organisms use vitamin-A aldehyde (retinal) to carry out their biological function in response to light. These retinylidene proteins, commonly called rhodopsins, mediate such diverse processes as ion transport and phototaxis signaling in microorganisms, or various types of photosignal transduction in higher animals, most importantly vision. Retinylidene proteins are among the relatively few families of membrane proteins for which structural information is available from crystallography. Today, the possibility of using a wide range of time-resolved molecular spectroscopy assays and state-of-the art molecular dynamics simulations will help complement the now largely static view of retinal protein function with information on the conformational changes that lead to protein activation. In the end, "*… the realization of animate matter requires certain (molecular) structures upon which the higher-order structures are built, but the guiding principle (of biology) is function rather than structure.*" [Manfred Eigen, *From Strange Simplicity to Complex Familiarity: A Treatise on Matter, Information, Life and Thought*, 2013, Oxford University Press, Prolegomenon].

This issue on retinal proteins contains some of the latest discoveries in diverse aspects of retinal protein structure, function, and dynamics. These include structural, spectroscopic and theoretical studies of protein structure and dynamics, genetic, biochemical and physiological studies of protein function, signal transduction and energy transduction mechanisms, and new biotechnological applications in biomedical research.

The issue is introduced by an article on the history of microbial rhodopsin research co-authored by Mathias Grote, Martin Engelhard & Peter Hegemann. The article highlights the impact of research on retinal proteins had and still has on many aspects of biochemistry, biophysics, neuroscience, and on bioenergetics in particular. The following articles by John Spudich, Oleg Sineshchekov & Elena Govorunova, by Leonid Brown and by Keiichi Inoue, Tsukamoto Takashi & Yuki Sudo cover evolutionary aspects of the ever growing number of retinylidene proteins.

We continue with reviews on the structure and function of halobacterial retinal proteins unraveled by state-of-the-art spectroscopic studies. Antoine Gautier covers the recent progress on structural details and dynamics of retinal proteins obtained by solid-state NMR spectroscopy. The ultrafast reactions of retinal embedded in the sensory opsin of Anabaena are discussed by Igor Shapiro & Sanford Ruhman, who integrated sophisticated experimental techniques and theoretical approaches. The structural and mechanistic role of internal water molecules by FTIR spectroscopy is showcased by two comprehensive reviews co-authored by Yuji Furutani & Hideki Kandori and by Klaus Gerwert, Erik Freier & Steffen Wolf, respectively.

Proteorhodopsin and channelrhodopsin, two proteins that challenge our understanding of proton transfers in microbial rhodopsins, are addressed in three reviews that illustrate the wide range of techniques used in the field. Christian Bamann, Ernst Bamberg, Josef Wachtveitl, & Clemens Glaubitz present a comprehensive view on the structure and mechanism of the proton-pumping proteorhodopsin. Victor Lorenz-Fonfria and Joachim Heberle discuss the gating mechanism of channelrhodopsin, the latter presenting a new functionality for retinal proteins as channelrhodopsin acts as a light-gated cation channel. Coral del Val, Jose Royuela-Flor, Stefan Milenkovic, & Ana-Nicoleta Bondar used bioinformatics tools to dissect conservation motifs and homology models of channelrhodopsins.

The reviews on the structure and function of microbial rhodopsins are complemented by an overview on the usage of retinal proteins as model systems to understand folding of membrane proteins. Oznur Tastan, Arpana Dutta, Paula Booth & Judith Klein-Seetharamanhave integrated experimental and computational methods to provide a comprehensive view on the current status of retinal protein folding.

Our collection of reviews on rhodopsin concludes with a series of five papers on diverse aspects of mammalian rhodopsins, ranging from physiology to structure and function. Yasushi Imamoto & Yoshinori Shichida discuss the unique properties of cone visual pigments, the photoreceptor molecules responsible for photopic vision. Xavier Deupi builds a case on why the dim-light photoreceptor rhodopsin remains an important model system for the study of the important family of Class A (or "rhodopsin-like") G protein-coupled receptors. The next two reviews examine some of the spectroscopy techniques used to study the light-activation activation mechanism in rhodopsins: Andreyah Pope, Markus Eilers, Philip J. Reeves & Steven O. Smith describe the use of solid-state NMR spectroscopy, whereas Ulrike Alexiev and David L. Farrens summarize the basis, challenges and opportunities of fluorescence spectroscopy. Finally, Mitsumasa Koyanagi and Akihisa Terakita discuss the properties and physiology of non-visual opsin-based pigments, and their potential for optogenetic applications.

The picture that emerges from this special issue on retinal proteins is that, despite the long history of research in the field, rhodopsins remain at the forefront of several state-of-the-art fields: Proteorhodopsins abound in the oceans and may have played a role in early photosynthesis, channelrhodopsins are at the foundation of the new field of optogenetics, and a mammalian rhodopsin helps us understand how point mutations translate to protein malfunction and disease. Progress in the understanding of retinal protein structure and function was always accompanied by methodological advances. - cryo-electron microscopy, cubic phase crystallization, QM/MM simulations, solid-state NMR and time-resolved vibrational spectroscopies (IR and Raman), to name just a few. Retinal proteins will certainly continue to play an important role in the development of time-resolved pump-probe experiments using X-ray free-electron lasers, a technique that will allow obtaining information on membrane protein activation at an unprecedented temporal and spatial resolution. As an additional example, a mammalian rhodopsin has been

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the first (and so far only) G protein-coupled receptor for which the structure of disease-related mutants has been solved, leading the way to understand how point mutations translate to protein malfunction and disease. Such developments augur a luminous future for the field of retinal protein research.

Joachim Heberle studied chemistry at the Universities of Stuttgart and Würzburg (Germany). After receiving his Diploma in Physical Chemistry from Würzburg University (1988), he moved to the Free University of Berlin to do his Ph.D. in Biophysics (1991). His postdoc work at the Hahn-Meitner-Institute in Berlin lead him to build an independent research group for Biomolecular Spectroscopy at the Research Centre Jülich (1993). He was a visiting scientist at the University of Arizona (with George Atkinson) and at the University of Göteborg (with Bo Malmström). After his Habilitation at Düsseldorf University (1998), he became Full Professor in Biophysical Chemistry at Bielefeld University (2005). In 2009, he accepted an offer from the Freie Universität Berlin to join the Faculty of Physics as a Full Professor in Experimental Molecular Biophysics. His research interests are photosensory (membrane) proteins and bioenergetics. His group develops and applies vibrational spectroscopic techniques to resolve the functional mechanism of these proteins.

Dr. Xavier Deupi is a Scientific Officer in the Condensed Matter Theory group (Research with Neutrons and Muons Department) and in the Laboratory of Biomolecular Research (Biology and Chemistry Department) of the Paul Scherrer Institute (Switzerland). He conducts research in the field of computational structural biology of G protein-coupled receptors, studying the molecular principles of ligand selectivity, efficacy and biased signaling.

Dr. Deupi graduated in Chemistry in Institut Quimic de Sarria (Barcelona, Spain; 1998), and obtained a Ph.D. in Biochemistry and Molecular Biology in Universitat Autonoma de Barcelona (Spain; 2003), studying the structure of transmembrane proteins using molecular dynamics simulations. From 2003 to 2005, Dr. Deupi was a postdoctoral fellow at Stanford University (USA) in the laboratory of Prof. Brian Kobilka, where he combined computational models with fluorescence spectroscopy data to study the activation mechanism of the beta 2 adrenergic receptor. He returned to Universitat Autonoma de Barcelona in 2005 as a junior research scientist, and in 2008 received a postdoctoral senior grant within the prestigious Ramon y Cajal Program (Ministry of Economy and Competitiveness, Spain). In 2010, Dr. Deupi moved to the Paul Scherrer Institute, where he has strengthened his ties to experimental biology, forming a group that combines computational and experimental structural biologists, and establishing close collaborations with other experimental biologists worldwide.

Prof. Gebhard Schertler is a Full Professor of Structural Biology at the Department of Biology of ETH Zürich (Switzerland) and the head of the Biology and Chemistry Department at the Paul Scherrer Institute (PSI; Switzerland), where he is a member of the Directorial Board. He is also on the Scientific Advisory Board of Heptares Therapeutics.

Prof. Schertler studied Chemistry and Biochemistry at the University of Innsbruck (Austria), and from 1984 to 1989 he did a Ph.D. at the Max-Planck Institute for Biochemistry in Munich (Germany). Then, he moved to the MRC Laboratory of Molecular Biology (Cambridge, UK), where he became a group leader in 1998. There, Schertler made major contributions to the field of structural biology of visual pigments and GPCRs using electron microscopy and X-ray diffraction methods. In his current position, Schertler has established an interdisciplinary research team on GPCRs, and is responsible for strategic biological applications at the Swiss Free Electron Laser (SwissFEL), currently being built at PSI.

Joachim Heberle

Xavier Deupi

Gebhard Schertler