Mechanisms of membrane protein insertion

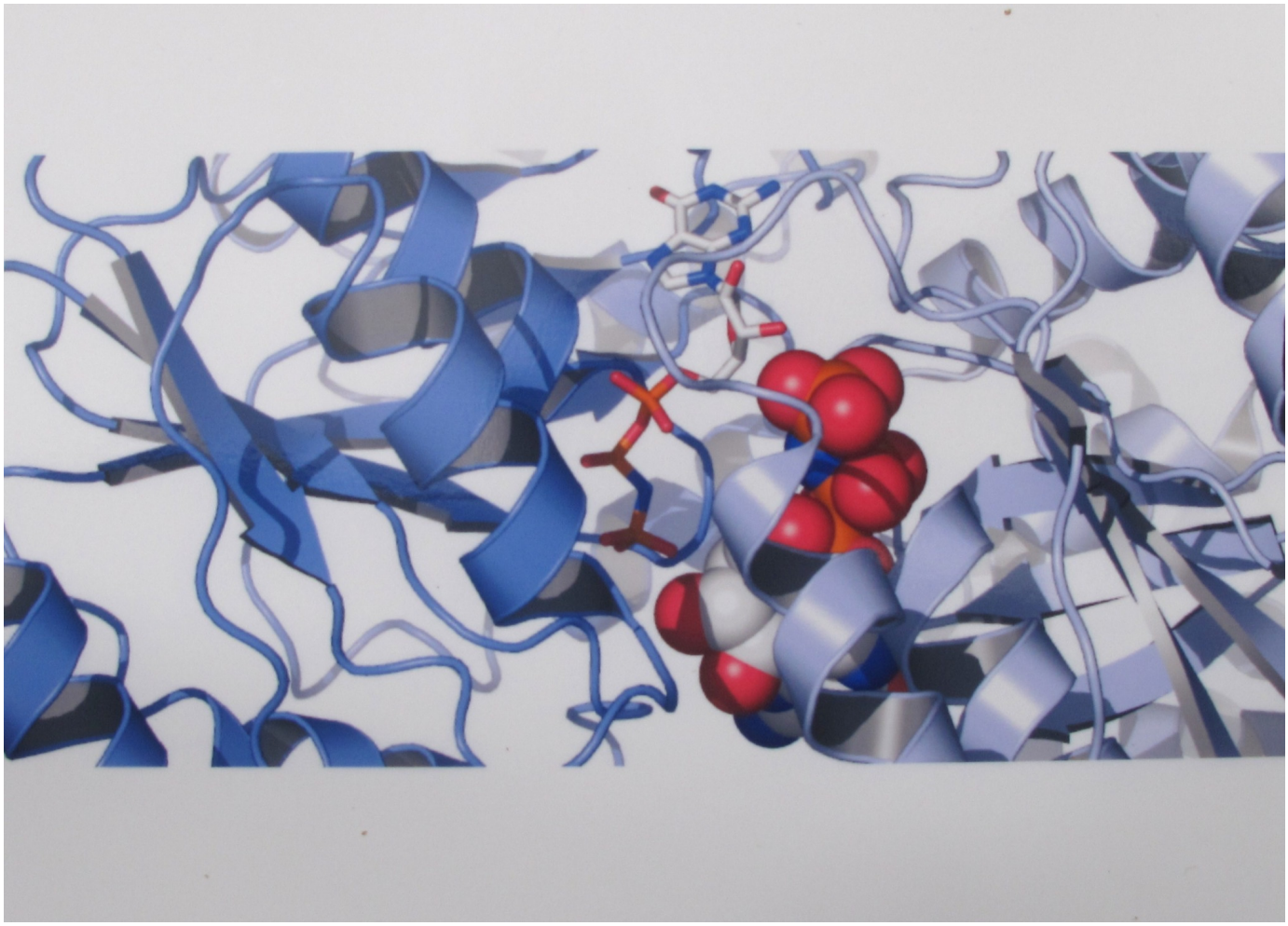
Prof. Dr. Irmgard Sinning, biochemist and structural biologist at the University of Heidelberg, will be awarded the 2014 Leibniz Prize from the German Research Foundation (DFG) for her work on the structure and function of complexes that transport different membrane proteins to the correct cellular compartments in the appropriate target membranes. Her research is primarily focussed on the co-translational SRP pathway mediated by signal recognition particles and on the GET pathway, which ensures the post-translational insertion of membrane proteins.

Prof. Dr. Irmgard Sinning

"Irmgard Sinning will be awarded the 2014 Gottfried Wilhelm Leibniz Prize. Her research combines biochemistry, biophysics and structural biology at the highest level," the DFG announced in early December 2013. According to the DFG appraisal, the award, which is the most prestigious science prize in Germany, honours Sinning's significant contributions to understanding a certain critical transport process, the so-called SRP- (signal recognition particle) mediated pathway that ensures the delivery of different membrane proteins to their specific target membranes in the cellular compartments.

Combination of structure and function

Prof. Dr. Irmgard Sinning is chair of biochemistry and structural biology at the University of Heidelberg and head of structural biology at the Heidelberg University Biochemistry Center (BZH). The aim of her research is to understand the molecular mechanisms of important cellular processes on the atomic level, especially the large molecular machines that ensure the biogenesis of



GTPase complex - the functional centre of the SRP system.
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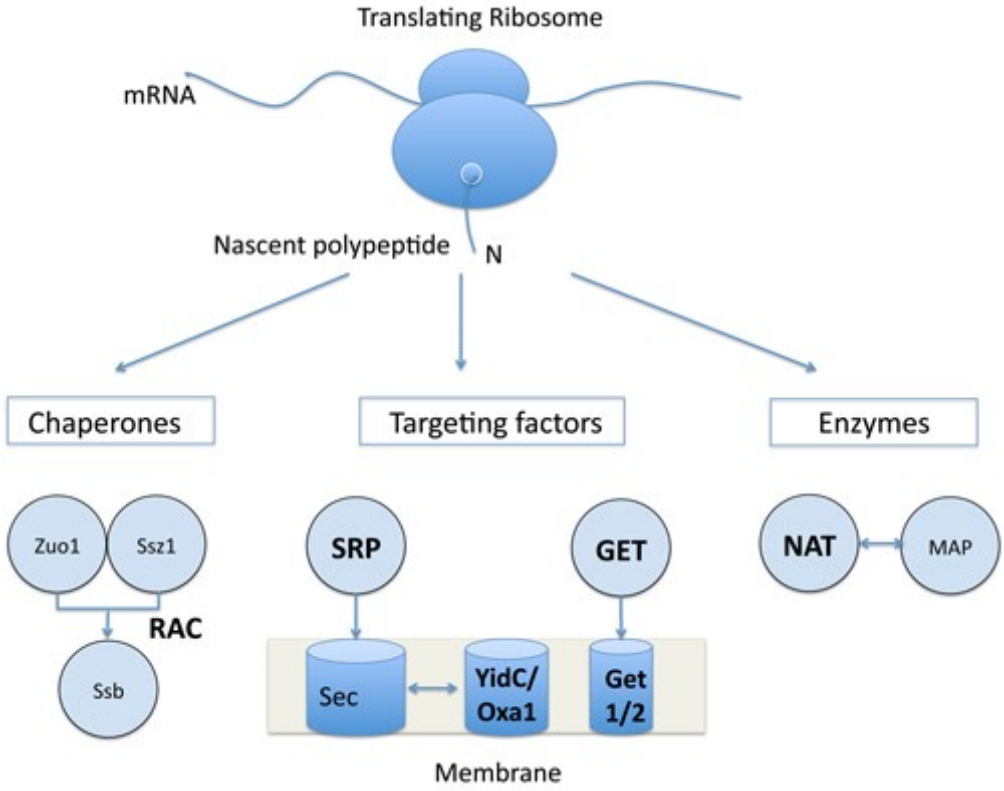
membrane proteins, the delivery of membrane proteins to and integration into specific target membranes. The mechanistic principles according to which these machines work and are regulated can be explained by the combination of biophysics and structural biology with cell and molecular biology or biochemistry, i.e. the elucidation of the three-dimensional architecture of the protein complexes along with functional analyses.

Sinning and her team use X-ray structure analysis as one of the most effective methods for determining protein structures. A key prerequisite for the successful application of the method is the purification of the components and the generation of flawless protein monocrystals. This is a labour-intensive and cumbersome process. The Heidelberg cluster of excellence "CellNetworks" and the group run by Prof. Irmgard Sinning have therefore established a high-throughput protein crystallisation platform at the BZH that enables the crystallisation of biological macromolecules at the nanoscale. The platform can also be used by researchers who are not affiliated with CellNetworks.

SRP and GET signalling pathways



Research projects of Prof. Sinning's team at the BZH.

Membrane proteins comprise more than 25% of the cellular proteome and their function depends on insertion into the correct target membrane. Most membrane proteins possess an N-terminal signal sequence that governs them to the endoplasmic reticulum (ER) and their specific cellular target membrane. Günter Blobel from Rockefeller University in New York was awarded with the Nobel Prize in 1999 for these discoveries. This signal sequence is recognised by the signal recognition particle (SRP, a ribonucleoprotein complex) of a newly synthesised peptide as it emerges from the ribosome. The SRP, along with the emerging protein and the ribosome, interacts with the SRP receptor that is located in close proximity to the translocon, a protein-conducting channel in the ER. The nascent peptide chain is inserted into the translocon channel where it enters into the ER and SRP is released from the ribosome and used again. This process, which is referred to as co-translational targeting, is controlled by specific GTP-binding proteins. Research into the structural characteristics and molecular mechanisms of the components of the multi-stage, complex SRP signalling pathway is one of the major priorities of the BZH's Department of Structural Biology. A smaller number of membrane proteins lack a hydrophobic N-terminal signal sequence. Instead, they carry their signal sequence at their C-terminus and are therefore termed tail-anchored (TA) proteins. These proteins are targeted to the ER post-translationally by the recently discovered GET (guided entry of tail-anchored proteins) pathway. This group involves proteins involved in important physiological processes ranging from intracellular trafficking to protein degradation and apoptosis (programmed cell death). The identification of components of the GET system seems complete and Sinning and her colleagues are therefore specifically focussed on elucidating the molecular and structural framework of this pathway.

Other research projects

Sinning and her team's other research projects deal with ribosome biogenesis and ribosome-associated chaperones and enzymes amongst other things. Certain membrane proteins, for example those that play a role in cellular respiration and energy transfer in bacteria, chloroplasts and

mitochondria, are integrated into the membrane by way of special membrane insertases (YidC/Oxa1/Alb3) rather than by using the membrane channel of the translocon as in the SRP pathway. However, research into the underlying molecular mechanisms is still in its infancy.

Sinning's work has shown that the biogenesis and transport of membrane proteins are much more complex than initially thought. Many aspects are still poorly understood, for example, the role of membrane lipids and the role of SRP RNA in the regulation of the SRP receptor and insertion of the proteins into the membrane. With the award of the Leibniz Prize, which is endowed with 2.5 million euros, Irmgard Sinning is able to pursue research endeavours that focus on obtaining detailed insights into the structure-function relationship of molecular machines during the co- and post-translational targeting of membrane proteins.

About

Irmgard Sinning was born in Höchstädt an der Donau in Bavaria. She studied food chemistry at the Ludwig Maximilian University in Munich (LMU) and did her PhD in the laboratory of Hartmut Michel at the Max Planck Institute of Biochemistry in Martinsried. Her PhD thesis dealt with the electron acceptor complex in the photosynthetic reaction centre of the purple bacterium Rhodopseudomonas viridis. [Hartmut Michel, along with Robert Huber and Johann Deisenhofer, were jointly awarded the Nobel Prize in Chemistry in 1988 for the determination of the three-dimensional structure of this photosynthetic reaction centre.] Sinning followed her supervisor to the Max Planck Institute of Biophysics in Frankfurt/M before completing her doctoral thesis at the LMU in 1989. She continued her post-doctoral studies on the Rhodopseudomonas membrane protein complex at the Max Planck Institute in Frankfurt. In 1991, Sinning joined T. Alwyn Jones at the Biomedical Centre of the University of Uppsala in order to broaden her knowledge about X-ray structure analysis of proteins. Jones is an internationally renowned protein crystallography expert and pioneered the development of methods that enable the interpretation of diffraction images of X-rays and the preparation of models of biological macromolecules using computer graphics. Sinning stayed with Jones for three years. From 1994 to 2001, Sinning was group leader in the Structural Biology Programme at the European Molecular Biology Laboratory (EMBL) in Heidelberg. In 2000, she was offered a position at the University of Heidelberg and is the chair of structural biology at the BZH. From 2006 to 2010, Professor Sinning was managing director of the Heidelberg University Biochemistry Center. In 2010, Sinning was awarded the "Heidelberg Molecular Life Sciences Investigator Award".

She is member of the German National Academy of Sciences Leopoldina and the European Molecular Biology Organisation (EMBO). She is also a member of the board of the Society for Biochemistry and Molecular Biology and was the society's first president from 2011 to 2013. Moreover, she is review board member of the German Research Foundation and chairperson of the biochemistry/biophysics panel, a member of the Senate Commission of the Helmholtz Association and is active in Minerva-FemmeNet, a women's mentoring programme run by the Max Planck Society.

Article

13-Jan-2014
EJ
BioRN

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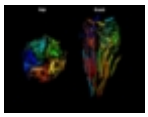

Membrane proteins

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