SFB 35 Colloquia in Membrane Transport

23.04.2010, 15.00: Leseraum Pharmakologie

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"Molecular modelling: connecting protein structure to function using in silico methods"

Molecular modelling is gaining importance in studying protein function as its application spectrum in-creases. More importantly, improved predictive capability now allows for thorough experimental scru-tiny and validation of obtained results. An overview of methods (homology modelling and simulations) will be given and their application will be discussed. Analyses of the function of proteins by experimental techniques provide us with a large body of data that highlight e.g. the importance of amino acids, their accessibility and changes in distances. A full understanding of the function of proteins at the molecular level requires knowledge about relevant con-formations and structural changes. Although the number of protein crystal structures increases expo-nentially (presently above 50.000), only about 200 unique membrane protein structures have been sol-ved. Structures of bacterial homologs of the ABC and the NSS transporter subfamilies have become available, while the structures of the human counterparts remain elusive. Molecular modelling techniques can be used to predict the structure of these human transporters if a suitable template is available. The models created by homology modelling allow to project biochemical information onto the transporter structure. Hypotheses about the molecular details of protein function can be elaborated. Validated models can serve as a catalyst for the design of biochemical experi-ments. This is highlighted by the example of its application to the ABC transporter P-glycoprotein. Even if the structure of the human membrane transporter will become available, the crystal structure represents a single snapshot that still might not reveal the functionally relevant conformational changes. Molecular dynamics simulations are an in silico method that allows to explore the accessible phase space (accessible conformations) while fulfilling the laws of physics. Dynamics and involved conformational transitions of membrane inserted proteins can be studied at atomic resolution. Examples of applications to ABC transporters will be discussed.