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Introduction to the Special Issue on viral channel forming proteins

Cells have developed a special type of membrane proteins which enables the flux of ions across the lipid membrane. The proteins oligomerize and form pores, which lower the energy barrier for ions to pass the hydrophobic barrier imposed by the lipid membrane. Substrate flux does not consume any energy and is therefore in contrast with protein induced "transport" processes. The mode of action of channel proteins can be either triggered by gradients, ligands or mechanical stress within the membrane.

Viruses hijack the cell and modulate the interior of the cell to replicate their genomes. Similar to the host cells barriers such as the lipid membrane have to be overcome so that ions can flow across to support the cellular life cycle of the virus. Consequently the same type of proteins needs to be developed by the viruses, or the host channel proteins have to be used and manipulated adequately. Since the discovery of a channel that conducts protons in the genome of influenza A viruses, the proton channel M2, similar proteins have been proposed and detected in other viruses. It has also been shown that some of the channel proteins also conduct larger molecules or substrates. After almost 30 years of research on these proteins still some open questions remain. So far for most of the viruses we do not know why and also at which stage during the cellular life cycle they need ion or substrate channeling. Claiming to be a substrate channel, it is interesting to know whether these channels are specific for certain substrates or even classes of substrates. The known channel proteins are reported to be up to 100 amino acids in length, with one exceptions of being 274 amino acids in length. Is there a relation between specificity and size, and if so, then what structural feature is responsible for this? What triggers channel activity? There is not yet a single channel resolved in its entire length by X-ray crystallography or NMR spectroscopy. However, parts of the proton channel have now been reported on the atomic level ensemble within the lipid membrane and even in the presence of drugs by both of the two techniques mentioned.

For many viruses channel proteins are essential. Combating influenza, its M2 proton channel has been one of the first targets for antiviral therapy. Interestingly, binding sites of drugs have been reported to be within and outside the channel. However, not very many drugs have been reported up to date targeting these channel proteins. This may have two reasons. Firstly, targeting a membrane protein, which is relatively small, with small molecules is a challenge even for modern drug development. Secondly in many cases these proteins are not that essential or have not yet been described as such. Because of these reasons, other targets, usually the globular viral proteins are on the top of the list being the target. With increasing spread of retroviral diseases in combination with the enormous mutation rate, viral channel proteins, called "soft targets," may sooner or later move into the focus either as single target, in case they are found to be essential for the viral life cycle, or as a peripheral target in a drug cocktail.

This special issue aims to present a summary of the state of the art on viral channel proteins written by experts in the field. A general overview of how many channels exist is reported. Contributions cover (K⁺-channels) channels encoded by plant viruses, a newly discovered protein Sa from SARS-Co, which is found to exhibit channel activity, and two proteins encoded by HIV-1 and HCV, Vpu and p7, respectively, focusing on structural discoveries. In another contribution a link between sequence homology and structural features of Vpu with known and structurally resolved host channels is presented. The proton channel M2 from influenza A is discussed intensively in this special issue. This especially since the discovery of structural features within the lipid membrane on an atomic level by two groups using different techniques has sparked exciting discussions about the mechanism of function of this channel and its interaction with the known antiviral drugs amantadine and its derivatives. Novel antiviral drugs against M2 are reported and computer simulations of drug-protein interactions of M2 are presented.

We wish to thank all researchers for their outstanding contributions and also the team of Biochimica and Biophysica Acta–Biomembranes for their generous support which made this special issue reality.

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Dr. Wolfgang B. Fischer obtained his doctorate in chemistry at the Heidelberg University, Germany. During his postdoctoral years at Boston University, MA, USA, and TU Dresden, Germany, he moved into the field of membrane proteins. He discovered structurally active water molecules in the light driven proton pump bacteriorhodopsin and structural features in the nicotinic acetylcholine receptor using FTIR spectroscopy. At Oxford University he developed into molecular dynamics (MD) simulations on viral channel forming proteins. He proposed the assembly state of Vpu from HIV-1 and generated the first computational model of p7 from HCV. Now at National Yang-Ming University (www.ym.edu.tw/~wfischer) he has published the first computational model of 3a from SARS-CoV. The major areas of research are self-assembly, ion and substrate flux in constrained geometries and folding at the membrane surface. The techniques applied are docking approaches, classical and ab initio MD simulations.