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Membrane Proteins and Their Involvement in Infectious Diseases

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Protein-membrane interactions and protein-protein recognition within the membrane milieu are of fundamental importance to fully comprehend a wide range of cellular processes in all organisms. About 40% of all genes in the mammalian genome transcribe for membrane proteins. The paucity in 3D structures for most membrane proteins, the high complexity of the forces involved, and the technical difficulties present challenging obstacles to overcome before fully understanding biological events within membranes. Using a multidisciplinary approach, including cell molecular biology (cells and viruses), biophysics and biochemistry, we study the mode of action of membrane proteins, particularly those involved in infectious diseases. The principle underlying our approach is the dissection of the proteins to small fragments, which are studied for their structure, function, their ability to interfere with the function of the parental intact proteins, and network of peptide-peptide recognition within the membrane milieu. These studies led us to discover and refine mechanisms of action of membrane proteins involved in microbial and viral infections, as well as to derive general rules on the forces involved in protein-membrane interaction and protein-protein recognition within the membrane milieu.

From Innate Immunity to De-Novo Designed Antimicrobial and Anticancer Peptides: The Underlying Parameters Involved in Target Recognition by Cell-Lytic Peptides

Living organisms of all types including plants and humans have been shown to produce a large repertoire of gene-encoded lytic peptides that serve as part of their innate immunity to microbial invasion. They are considered as future antibiotics due to the increasing resistance of bacteria to available antibiotics. We established the 'carpet' mechanism as an efficient model describing action of antimicrobial peptides. Based on this mechanism we developed a novel repertoire of D,L amino-acid containing lytic peptides with potential therapeutic applications. Further in depth studies on their mode of action allowed the de-novo designed of antibacterial, antifungal and anticancer peptides.

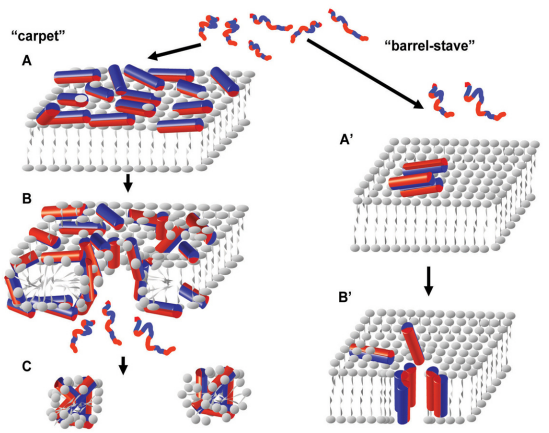

Fig. 1 *The barrel-stave and the carpet models suggested for membrane permeation. In the carpet model the peptides interact only with the lipid head groups, whereas in the barrel-stave model peptides insert into the lipid core.*

Viral infections –How do Viral Envelope Proteins Catalyze Viral-Cell Membrane Fusion?

The mechanism by which specific viral envelope proteins catalyze mixing of two membranes (membrane fusion) is still an open question. We focused on gp41 and F, the envelope glycoproteins from HIV (retrovirus) and Sendai virus (paramyxovirus), respectively. We showed that: (i) distant viral families share conserved fusion mechanisms, (ii) membrane interaction induces drastic conformational changes in the fusion proteins. These studies led us to propose the "umbrella" mechanism for virus-cell fusion. (iii) Synthetic peptides derived from envelope proteins

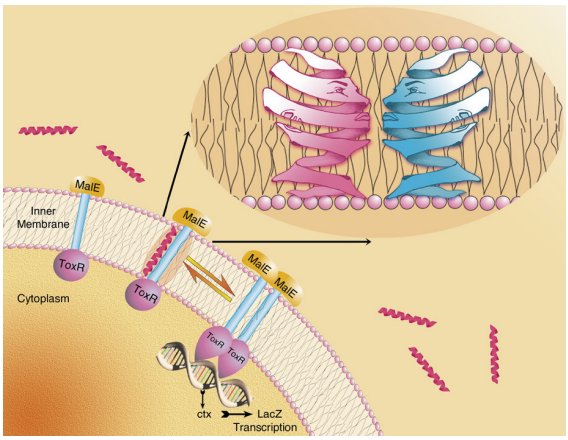

Fig. 2 *An all-D amino acid containing peptide (Red helices) that is a mirror image of the Glycophorin A transmembrane domain can recognize the wild type transmembrane domain (blue helices) in vivo*

specifically inhibit viral infection at different stages, making them ideal tools for mechanism studies, as well as promising therapeutic agents.

General Aspects on Protein-Membrane and Protein-Protein Interactions within the Membrane

We studied self- and hetero-assembly of membrane proteins within the membrane milieu. In contrast to recognition in solution, we found that the chirality of trans-membrane (TM) domains does not affect protein-protein recognition in the membrane. Furthermore, we developed a new approach that enables *in vivo* detection of hetero-association between TM domains within the membrane milieu. Based on this approach, we found that synthetic peptides composed of D- and L-amino acids, corresponding to TM domains of T-cell receptor and TAR receptors, interfere with the function of the intact proteins *in vivo*. Besides giving us important basic information, these findings serve as new tools for the design of novel compounds to interfere with membrane proteins involved in various diseases

Selected Publications

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