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Viral channel forming proteins — How to assemble and depolarize lipid membranes in silico☆

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ABSTRACT

Viral channel forming proteins (VCPs) have been discovered in the late 70s and are found in many viruses to date. Usually they are small and have to assemble to form channels which depolarize the lipid membrane of the host cells. Structural information is just about to emerge for just some of them. Thus, computational methods play a pivotal role in generating plausible structures which can be used in the drug development process. In this review the accumulation of structural data is introduced from a historical perspective. Computational performances and their predictive power are reported guided by biological questions such as the assembly, mechanism of function and drug–protein interaction of VCPs. An outlook of how coarse grained simulations can contribute to yet unexplored issues of these proteins is given. This article is part of a Special Issue entitled: Membrane Proteins edited by J.C. Gumbart and Sergei Noskov.

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1. Introduction

Bridging computation and experiments implies that there are two independent worlds each of which delivers information by itself but mutually supports the overall investigations on a subject, here a protein. Computational results help to predict and need verification from experiments. It is the view however, that based on high quality computational developments, computational modeling should also be seen as a source for delivering of smart 'suggestions' which need to be 'matched' with experiments.

Abbreviations: AMA, amantadine; BFM, bond fluctuation method; BST-2, bone marrow stromal cell antigen 2; CD, circular dichroism; CGMD, coarse-grained molecular dynamics; ClyA, cytolysin A; DHPC, dihexanoylphosphocholine; DPC, dodecylphosphocholine; *E. coli*, *Escherichia coli*; EM, electron microscopy; ff, force field; FTIR, Fourier transform infrared; GT, genotype; HCV, hepatitis C virus; HepG2, hepatocellular carcinoma cell line 2; HIV, human immunodeficiency virus; HMA, hexamethylene amiloride; HPV, human papillomavirus; MscL, large-conductance mechanosensitive channel; MS-EVB2, multi state empirical valence bond model 2; nAChR, nicotinic acetylcholine receptor; NMR, nuclear magnetic resonance; NN-DNJ, N-nonyl-deoxynojirimycin; PDB, protein data bank; PMF, potential of mean force; REMD, replica exchange molecular dynamics; RIM, rimantadine; RMSD, root mean square deviation; RyR2, ryanodine receptor 2; SARS-CoV, sever acute respiratory syndrome coronavirus; SPPS, solid-phase peptide synthesis; ssNMR, solid state NMR; TCP, thermodynamic cycle perturbation method; TFE, trifluoroethanol; TMD, transmembrane domain; VCP, viral channel forming protein; Vpu, viral protein U.

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1.1. Historical perspective

Evidence for the existence of proteins encoded by viruses which alter membrane permeability has been reported for the first time in the late 70s [1,2]. It had been found that synthesis of host proteins in cells invaded by viruses is lowered in order to allow viral protein synthesis to occur. This finding has been called the 'shut-off phenomenon'. The cause of this phenomenon was attributed to 'coat proteins' causing an alteration of ion gradients within the infected cell which gave rise to speak about a 'membrane leakage-model': proteins must exist which form 'small pores in the lipid bilayer through which ions could diffuse freely' [1].

In the 90s, proteins which alter membrane permeability were identified for a series of viruses such as 2B and 3A of polio virus [3], 6K protein of Semliki Forest virus [4], M2 of influenza A [5,6] and Vpu of HIV-1 [7,8]. Since then the number of identified and proposed channel proteins has risen (see reviews [9–15]). Identification of altered membrane permeability by the VCPs is mostly based on in vitro experiments. An immediate correlation of protein activity within the cell is unambiguously established only for very few of them.

The outcome of most of the in vitro studies is that the channels formed by the VCPs lack sophisticated gating behavior and a high selectivity. All together it seems that some of the VCPs form pores which are, to some extent, selective similar to the host ion channels. Other VCPs show characteristics like toxins by simply enabling unselective permeability for even small molecules. Experimental data support a channel-pore dualism [16]. Based on these facts the VCPs are evidently termed

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Table 1
Timeline of the emergence of structural information of the VCPs. F = FTIR, H = hypothesized, CD = circular dichroism, N = NMR, E = EM, X = X-ray, D = drug, fl = full length protein, sgl = single TMD.

year	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
M2 TMD	H			H				CD					N		F									X		D					
																								D							
Vpu cyto											N	N	N																		
TMD				H											N/F	N												D			
P7 fl										H		H							E			E			E	N			N	N	
																													D		
sgl																										N					
2B												H																			
E5				H						F								CD													

as viroporins. Usually membrane proteins with beta barrel motif for the transmembrane domain are termed as 'porins'. However, as shown below, such a motif is not reported for any of the VCPs so far.

Structural information about the VCPs is gradually emerging due to the fact that they are small and embedded within the lipid membrane [12] (Table 1). Spear headers in respect to availability of structural information are M2 of influenza A and Vpu of HIV-1 most recently followed by p7 of hepatitis C virus. This feature is in line with the importance of the VCPs being potential drug targets. Nevertheless most of the structural information is limited to the TMDs of the VCPs and in the case of Vpu it includes also solely the cytoplasmic domain. Most recently a synthetic peptide corresponding to the extramembrane N terminal side of M2 has been crystallized in contact with a monoclonal antibody [17]. The structure can be regarded as a good approximation to the 'in vivo' structure of M2.

For many of the VCPs, channel function is reported to be non-essential [15]. In the case of Vpu it is not even identified whether a channel function is needed at all in the infectivity cycle of the virus [18].

As a drug target, the VCPs are just emerging as potential candidates since for many viruses they are not essential for survival. Therefore most of these proteins are classified as 'auxiliary' proteins. M2 from influenza A, the first VCP to be detected, has also been the target for the very first ever developed antivirals. At this moment only a hand full of other drugs are tested against VCPs. One drug is explored in clinical trials to combat HCV/HIV-1 targeting p7/Vpu. Difficulties in getting structure information, an essential prerequisite for effective drug development, foster the low attractiveness in drug development.

Another facet in the function of these viral channel forming proteins is the fact that, starting with Vpu of HIV, host factors are identified, with which the VCPs interact to steer the cells towards improved viral replication [19]. Recently a VCP of human papillomavirus, E5, has entered the league of VCPs [20]. Until then E5 had been identified as to interact with a series of host factors. Also p7 of HCV is proposed to interact with host proteins whereas experimental data identify large scale interactions with other membrane proteins of its own genome. At this moment these interactions may open a route for the development of conceptually novel drugs targeting the VCPs [21].

Low selectivity together with dual functionality, as VCP and steering molecule, supports the rather obscure characterization of these types of biomolecules being plastic and highly dynamic multi-tasking membrane proteins.

A solution to the bottle neck imposed by structural virology and the fuzziness of their mechanical behavior is to enroll into computational approaches which help to answer academic questions and support the drug development process. The intention of this review is to focus on computational modeling as the source of information.

1.2. Structural information from experimental techniques — a survey

At this stage it is the intention to survey and illuminate the structural (Table 2) and computational research on the VCPs. For more detailed information about the molecular biological features the reader may be referred to excellent reviews available in the literature, e.g. [13,15]. Structural information forms the cradle of computational modeling.

The very first structural information about a VCP was given for a synthetic peptide corresponding to the TMD of M2 of influenza A using CD spectroscopy [22] (Table 1). A helical motif has been identified. Solid state NMR spectroscopic experiments, also based on synthetic peptides corresponding to the TMD of M2, proposed a defined tilt of the peptide and left-handedness of the putative tetrameric bundle [23]. Also FTIR spectroscopic measurements on similar peptides supported the tetrameric assembly [24]. In a series of solid state NMR spectroscopic investigations using synthetic constructs [25] or expressed peptides [26,27] precise orientations of side chains of tryptophan and the essential histidines were obtained and an elaborate model of the mechanics of proton movement was established [25–27].

The M2 protein in its tetrameric state was also identified using solution NMR spectroscopy [28] (Fig. 1). At the same time X-ray spectroscopic data were available [29] (Fig. 1). All data sets reveal the left-handed nature of the helical assembly and also support the notation that the TMDs can form the assembly independent of the extramembrane domains. And following up on this, a full protein structure of M2 neither in its monomeric nor in its tetrameric form is available.

In a series of structural experiments the location of drugs such as amantadine [30] (2KQT), [29] (3C9J) and rimantadine [28] (2RLF), [31] (2LJC) and other drugs, e.g. amantadine derivatives [32] (2LY0), and [33] (2MUV) has been investigated.

The next VCP in line is Vpu of HIV-1 for which structural information has become available. Its cytoplasmic domain has been expressed in *E. coli* [34] or synthesized [35,36] and used in CD spectroscopic and solution NMR experiments. Later the structure was refined by expressed *E. coli* protein reconstituted into detergent micelles of DPC [37] (Fig. 1). The structure represents an improvement since in the studies reported earlier the VCPs have been resolved either in TFE containing solution [35,36] or in buffer of high salt concentration (500 mM sodium sulfate) [34]. What all structural studies have

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