Bicomponent MACPF pore-forming proteins: a new subgroup in the MACPF superfamily?

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Recent advances in the resolution of MACPF (membrane attack complex/perforin) protein structures have caused changes in structural definition and classification of the MACPF domain-containing pore-forming toxins (PFTs). A study by (Gilbert et al., 2012) has disproved the original concept of a four-domain structure of cholesterol-dependent cytolysins (CDCs) as they have shown that domains 1 and 3 should be seen as a single functional MACPF domain. These results additionally supported the joint assignment of CDC and MACPF protein families to the MACPF/CDC superfamily.
Through our re-investigation of a fungal aegerolysin, ostreolysin A (OlyA) we have found it to be a crucial component of a bicomponent PFT, acting in concert with a MACPF protein, pleurotolysin B (PlyB). Sequence analysis, 3D structural modeling, proteins' membrane binding, oligomerization, and permeabilization characteristics and EM membrane pore visualization have enabled us to propose a new model of bicomponent MACPF protein pore formation.
In contrast to other metazoan cytolytic proteins with the MACPF domain, the PlyB C-terminal domain seems to be designed to interact specifically with membrane-bound OlyA. This interaction is prerequisite for PlyB attachment and structural rearrangement of the MACPF domain to create a transmembrane □-barrel pore. We have confirmed that the all-beta structured OlyA exhibits the traits of the C-terminus of other MACPF proteins and targets PlyB to the membrane.
We propose that, based on the bicomponent nature of fungal MACPF proteins the C-terminal domain, analogous to the domain 4 in other MACPF/CDC pore-forming protein, should be supplemented with a separate aegereolysin superfamily protein. This renders the bicomponent fungal MACPF proteins to be a distinct protein family within a MACPF superfamily of PFTs. However, the structural information supporting our claims is still lacking as crystal structures of the monomeric and/or pore structure of both proteins have not yet been solved.

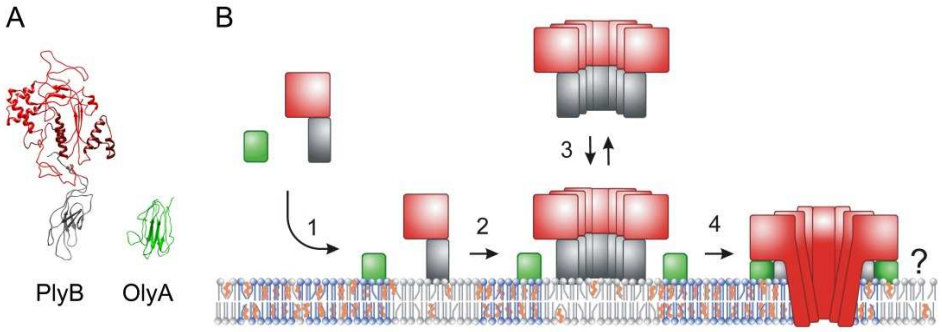

Figure: A. 3D models of PlyB and OlyA. **B.** Hypothetical model of pore formation by PlyB and OlyA: Step 1**.** Monomeric OlyA (green) and monomeric PlyB, depicted with the MACPF domain (red) and C-terminal region (grey) bind to the membrane. Step 2. PlyB oligomerizes to form the presumed pre-pore complex. Step 3. The oligomerised PlyB complex can dissociate from the surface of the bilayer or associate with OlyA in step 4, to form the transmembrane pore-complex. The location and number of OlyA monomers in the final complex is not certain.

Gilbert, R. J., Mikelj, M., Dalla Serra, M., Froelich, C. J. and Anderluh, G. 2012. Effects of MACPF/CDC proteins on lipid membranes. Cell Mol Life Sci.