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Outer membrane protein design

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Membrane proteins are the gateway to the cell. These proteins are also a control center of the cell, as information from the outside is passed through membrane proteins as signals to the cellular machinery. The design of membrane proteins seeks to harness the power of these gateways and signal carriers. This review will focus on the design of the membrane proteins that are in the outer membrane, a membrane which only exists for gram negative bacteria, mitochondria, and chloroplasts. Unlike other membrane proteins, outer membrane proteins are uniquely shaped as β-barrels. Herein, I describe most known examples of membrane β-barrel design to date, focusing particularly on categorizing designs as: Firstly, structural deconstruction; secondly, structural changes; thirdly, chemical function design; and finally, the creation of new folds.

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Introduction

Membrane proteins are classified by backbone configuration, which determines their function and location. In a quirk of biology, due to the mechanisms of their respective insertions through the Sec translocon [1,2], native inner membrane proteins are all α-helical, and outer membrane proteins are almost [3] all β-sheets.

The field of helical (inner) membrane protein design is much more developed than that of its β-barrel (outer) membrane protein counterpart. This is evident in the comprehensive reviews of membrane protein design that focus exclusively on helical membrane protein design [4–8]. However, there is growing interest in *o*uter *m*embrane *p*roteins (OMPs) because of their role in antibiotic resistance, their potential applications as biosensors, and their location which makes them accessible to the exterior of the cell.

OMP anatomy

The anatomy of OMPs is fundamental to their design. The known anatomic patterns of these proteins are illustrated by the ~100 non-homologous structures of OMPs in the PDB. β-Barrel strands are amphipathic and are generally oriented antiparallel to each other. The architecture of the strands which are hydrogen bound through the backbone causes the side chains to alternate in direction between those facing the pore and those facing the membrane. Loops connect the strands, with larger loops in the extracellular space and smaller turns in the periplasmic space. The loops sometimes create plugs in the barrels before connecting to the next strand (Figure 1).

Most structurally characterized outer membrane β-barrels are monomeric, with one chain making up one barrel. However, some of the barrels oligomerize. When they do it is most often as trimers, although dimers are seen in some cases. More complicated topologies also exist where multiple protein chains contribute strands to a single barrel (Figure 2). One such multi-chain barrel is α-hemolysin, which is included in this review because it is a membrane barrel despite the fact that it is known to insert into the plasma membrane.

This review focuses on how amino acids create OMP conformations. Synthetic modifications of OMPs are not within the scope of this review.

Outer membrane protein design

There are four types of protein design: Firstly, structural deconstruction — removing parts of proteins to see if structural or functional elements can be maintained; secondly, structural transformation — intentionally changing a structural characteristic of a protein; thirdly, chemical function design — adding a new chemical feature to a protein; and finally, creating a new fold — making a fold topology that has not yet been found in nature.

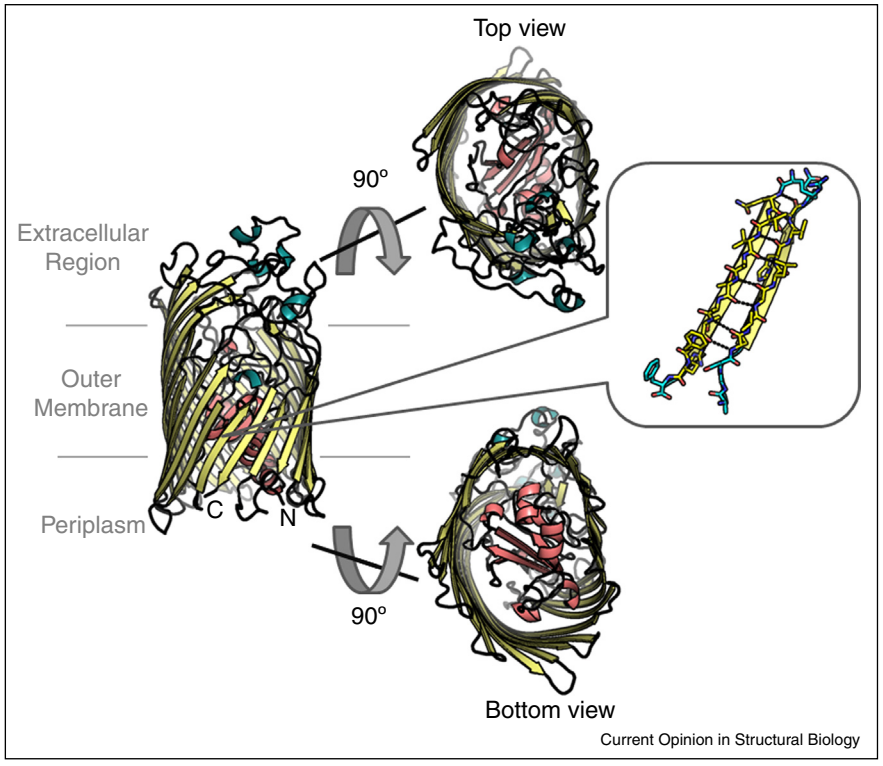
Structural deconstruction

A primary stage of protein design is determining the relationship of the protein's anatomy to its structure, function, and stability. To do this, protein designers have determined the extent to which strand-strand interactions, loops, and sequence content can be altered before changing the protein's function or stability.

Strand-strand interactions

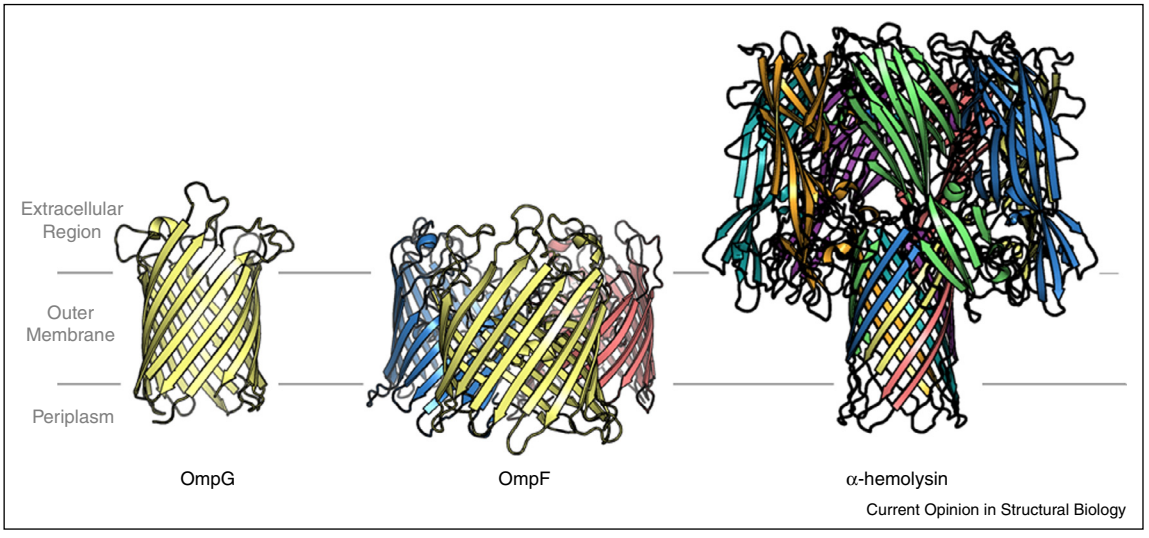
In β-barrels, side chains do not point towards each other but rather alternately point towards the interior of the

Figure 1



Anatomy of an outer membrane protein using FhuA [9] for illustration. Strands shown in yellow. Longer extracellular loops and shorter periplasmic turns shown in teal/black. The plug domain is shown in pink. Side view at left, top view and bottom view in the center, and strand view at right.

Figure 2



The three oligomeric configurations of membrane barrels. Each chain is colored differently. On the left is a single chain making a single barrel, OmpG [10]. In the center are three chains making three barrels, OmpF [11]. On the right are seven chains making one barrel, α-hemolysin [12].