MAR17-2016-020466

Abstract for an Invited Paper
for the MAR17 Meeting of
the American Physical Society

Ion transport across the biological membrane by computational protein design[1]

GEVORG GRIGORYAN, Dartmouth College

The cellular membrane is impermeable to most of the chemicals the cell needs to take in or discard to survive. Therefore, transporters—a class of transmembrane proteins tasked with shuttling cargo chemicals in and out of the cell—are essential to all cellular life. From existing crystal structures, we know transporters to be complex machines, exquisitely tuned for specificity and controllability. But how could membrane-bound life have evolved if it needed such complex machines to exist first? To shed light onto this question, we considered the task of designing a transporter de novo. As our guiding principle, we took the "alternating-access model"—a conceptual mechanism stating that transporters work by rocking between two conformations, each exposing the cargo-binding site to either the intra- or the extra-cellular environment. A computational design framework was developed to encode an anti-parallel four-helix bundle that rocked between two alternative states to orchestrate the movement of Zn(II) ions across the membrane. The ensemble nature of both states was accounted for using a free energy-based approach, and sequences were chosen based on predicted formation of the targeted topology in the membrane and bi-stability. A single sequence was prepared experimentally and shown to function as a Zn(II) transporter in lipid vesicles. Further, transport was specific to Zn(II) ions and several control peptides supported the underlying design principles. This included a mutant designed to retain all properties but with reduced rocking, which showed greatly depressed transport ability. These results suggest that early transporters could have evolved in the context of simple topologies, to be later tuned by evolution for improved properties and controllability. Our study also serves as an important advance in computational protein design, showing the feasibility of designing functional membrane proteins and of tuning conformational landscapes for desired function.

[1]Alfred P. Sloan Foundation Research Fellowship