Title:	Deciphering the Implications of Modular Rearrangements and Circular Permutations in 1,2 -Propanediol Bacterial Microcompartment Domain Proteins
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Abstract:	Understanding the fundamental principles behind macromolecular structure-function interactions requires an understanding of their complexity and dynamics. The complex organization of a system entails diverse components interconnected in different ways. Bacterial microcompartments (BMCs) are such types of sophisticated nano-machinery that involve unique protein assemblages of thousands of protein subunits forming mega Dalton (MDa)-sized icosahedral organelle in prokaryotes. They function to provide adaptive growth advantage in special environment conditions by segregating segments of metabolic pathways which include toxic intermediates. The compartment's structural design contains a catalytic core surrounded by selectively permeable shell proteins which belong to the conserved BMC domain family. The canonical domains present are either single–domain or tandemly fused dimer domains, oligomerizing as homohexamers or pseudohexamers with a comparable conformational topology with the □/□ BMC domain fold. Over the evolution, the divergence in amino acid sequences and genetic occurrences in BMC have resulted in complicated protein fold variants. The domains are also associated with circular permutations emphasizing the structural variety of shell proteins. Thus, much diversity is embedded into them which is underexplored. My thesis strained the question of sequence and structural diversity in the shell protein domains. In this context, I have used biophysical approaches to get insights into this puzzle by exploring one of the most complex metabolosomes, 1,2 propanediol microcompartment (1,2 Pdu MCP). The outer shell of 1,2 PduMCP is a mosaic of eight different shell proteins and is encoded by a single operon. I have used two key shell proteins of the 1,2 Pdu MCP, PduA and PduB' to create synthetic shell protein variants by in vitro domain swapping. Two approaches were used, in one instance, synthetic dimer proteins were created by fusing two PduA domains to produce a PduA dimer that is circularly permuted and resembles PduB'. In this work, the potential role of domain dimerization (pseudohexamer) and therein circular permutation is addressed. Next, the PduB' dimer was broken down into constituent domains as single-domain proteins, and a circularly permuted variation of PduA was created to be compared to PduA. Apart from in-vitro studies, I have also substituted PduA protein chromosomally in-vivo with its circularly permutant variant. My research investigated the significant role and effect of structural topology and their exquisite sequence specificities. These viiinew protein variants with native sequences shed light on the evolutionary significance of various sequences, the structure of shell proteins, and how these factors relate to BMC's overall stability.
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