Review

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Bacterial microcompartments and the modular construction of microbial metabolism

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Bacterial microcompartments (BMCs) are protein-bound organelles predicted to be present across 23 bacterial phyla. BMCs facilitate carbon fixation as well as the aerobic and anaerobic catabolism of a variety of organic compounds. These functions have been linked to ecological nutrient cycling, symbiosis, pathogenesis, and cardiovascular disease. Within bacterial cells, BMCs are metabolic modules that can be further dissociated into their constituent structural and functional protein domains. Viewing BMCs as genetic, structural, functional, and evolutionary modules provides a framework for understanding both BMC-mediated metabolism and for adapting their architectures for applications in synthetic biology.

Bacterial microcompartments are specialized metabolic modules

In the past decade, genomics-enabled technologies have firmly established the concept of bacterial communities functioning as multicellular organisms consisting of specialist functional guilds [1,2] (Figure 1A). At the same time it has become apparent that eukaryotic-like division of labor likewise extends subcellularly; it is now known that some enzymes catalyzing sequential reactions are encapsulated in organelles, for example, in bacterial microcompartments (BMCs) (Figure 1B). BMCs consist of enzymes and supporting proteins enclosed by a protein shell. They include anabolic carboxysomes (Figure 1C), found in cyanobacteria and some chemoautotrophs and anoxygenic phototrophs, that function in carbon fixation [3,4]. In addition, a variety of catabolic BMCs, termed metabolosomes (Figure 1D), are found in heterotrophs; metabolosomes have been implicated in the degradation of propanediol (PDU BMC), ethanolamine (EUT BMC), ethanol (ETU BMC) [3], choline (CUT BMC) [5,6], in the fermentation of plant biomass [glycyl radical propanediol (GRP) BMC] [7,8], and aerobic degradation of algal polysaccharides [planctomycete and verrucomicrobia metabolosome (PVM) BMC] [9]. In all of these examples, BMCs play a key role in the success of the organism in its particular niche.

Although functionally distinct BMCs vary in their encapsulated enzymes, all are defined by homologous shell proteins. The first crystal structures of each of the three types of proteins constituting BMC shells came from the carboxysome: BMC-H, a hexamer of proteins containing a single PF00936 domain [10]; BMC-T, a trimer of proteins containing two PF00936 domains [11]; and BMC-P, a pentamer formed by proteins containing one PF03319 domain [12] (Figures 1B and 2A–C). Given the structural similarities between BMC shell proteins (hexagons and pentagons) and those of icosahedral viruses, a model for the BMC shell based on geometric constraints was proposed in which hexagonal BMC-H and BMC-T proteins form the facets and the pentagonal BMC-P proteins cap the vertices [10] (Figure 1B).

Although first described more than 50 years ago [13], BMCs have only recently become a prominent area of research, with several complementary advances driving the field forward in the past decade (Box 1). The first X-ray crystallographic studies [10] revealed the structure of the basic building block of the shell, how the facets are formed, and provided a hypothesis for the structural basis of the selective permeability. The structures were placed in the context of genomic sequence data, showing that, unexpectedly, many bacterial species have the potential to form carboxysome-like shells [10]. This anticipated insights from the growth of microbial (meta)genomics and bioinformatics, which amplified and extended these observations [3,14–17]. To date, evidence for BMCs has been found in 23 bacterial phyla, with 23 distinct loci identified [14] (Table 1). A third recent major advance was the demonstration that BMC proteins could be fluorescently labeled without disrupting function [18–20]; this led to studies of the cell biology of BMCs, including their spatial organization in the cell and their assembly. Collectively, the insights from these advances span a wide range of the levels of biological organization, from the genes that encode BMC-associated proteins, to their organization into loci that are frequently horizontally transferred as genetic modules, to the self-assembly of various proteins into organelles that play key roles in microbial ecology and evolution. Because of their attributes as self-assembling metabolic modules, they have

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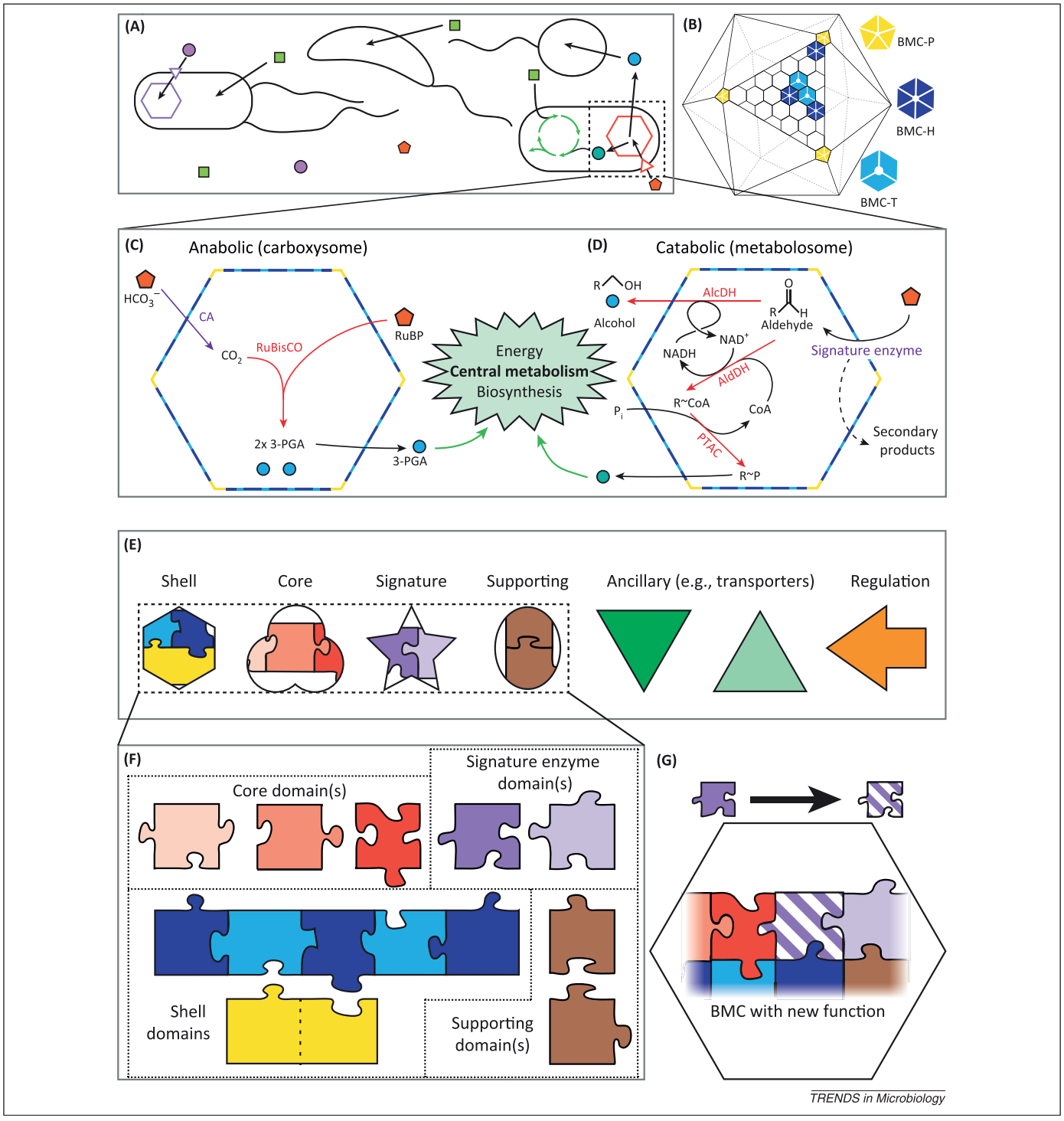

Figure 1. Bacterial microcompartments (BMCs) are metabolic modules embedded within members of bacterial communities. **(A)** Representation of a microbial consortium, each member with a distinct complement of metabolic pathways and sharing metabolites (filled in shapes). The metabolism of some members involves BMCs (open hexagons) that require metabolite-specific transporters (open triangles) and are linked to central metabolism. **(B)** Cartoon representation of an icosahedral BMC and how the three types of shell proteins fit together to form the shell. **(C, D)** Characterized metabolic models for (C) carboxysome and (D) metabolosome function, depicting the flux of specific metabolites across the shell and integration with cellular metabolism (e.g., Calvin–Benson cycle). In the carboxysome, ribulose bisphosphate is abbreviated RuBP, and 3-phosphoglyceraldehyde is abbreviated 3-PGA. **(E)** Cartoon representation of the genetic and functional modularity of the components of a BMC locus. Each symbol may represent one or more genes and/or proteins (e.g., the core module for metabolosomes consists of the AldDH, AlcDH, and PTAC enzymes). **(F)** Cartoon representation of how each genetic module is constituted of one or more protein domain(s) (shown as puzzle pieces), with each domain interacting with others either physically or through biochemical intermediates. **(G)** Potential utility of the genetic, functional, and domain-based modularity of BMC loci: a domain within the native signature enzyme could be replaced by a modified structurally similar domain with a different function. Abbreviations: AldDH, coenzyme A (CoA)-dependent aldehyde dehydrogenase; AlcDH, alcohol dehydrogenase; PTAC, phosphotransacylase.

motivated efforts by synthetic biologists and bioengineers to find ways to utilize these features with the aim of building designed organelles [21]. In this review, we will focus on these recent advances in understanding various aspects of BMC structure, function, and assembly in the context of modularity – from the protein domain to the role of the organism in the environment (Figure 1) – and how this can be applied to biotechnology.