Membranous Organelles in Bacteria

Milton H. Saier Jr.^a Mikhail V. Bogdanov^b

^aDivision of Biological Sciences, University of California, San Diego, La Jolla, Calif., and ^bDepartment of Biochemistry and Molecular Biology, Houston Medical School, University of Texas, Houston, Tex., USA

Key Words

Intracellular membranes · Outer membrane vesicles · Chromatophores · Magnetosomes · Bacterial nuclear envelopes · Anammoxosomes · Acidocalcisomes · Organellar evolution

The traditional view of life on Earth divides the living world into two major groups, prokaryotes and eukaryotes. These two groups were originally suggested to differ in very basic respects. While eukaryotes had complex cell structures including a cytoskeleton and intracellular membrane-bounded organelles, prokaryotes were believed to lack them. In fact, numerous textbooks and current sources still note this distinction and hold it to be true. For example, in Campbell's *Biology* [Campbell, 1993, p. 515] it is stated without equivocation: 'Prokaryotic cells lack membrane-enclosed organelles.' In 'Functional Anatomy of Prokaryotic and Eukaryotic Cells' [Tortora et al., 2009, chapt. 4] it is similarly claimed that 'Prokaryotes lack membrane-enclosed organelles, specialized structures that carry on various activities'. In the current *Wikipedia*, under 'Prokaryote' the following statement can be found: 'The prokaryotes are a group of

organisms whose cells lack a cell nucleus (karyon) or any other membrane-bounded organelles'. In the same online compendium under 'Organelle', one can read: 'whilst prokaryotes do not possess organelles per se, some do contain protein-based microcompartments'. Proteinaceous microcompartments will be the subject of a forthcoming *Journal of Molecular Microbiology and Biotechnology* written symposium, but this one will show that these generalizations, suggesting a lack of subcellular compartmentalization in prokaryotes, are blatantly in error [Murat et al., 2010a].

Intracellular Membranes of *Escherichia coli* and Other Bacteria

In this written symposium on membrane-bounded organelles in bacteria, we consider many of the well-characterized intracellular and extracellular vesicular structures of known function. We begin with vesicular structures found within the bacterial workhorse, *Escherichia coli*. This organism can be induced to produce extensive intracellular membranes (ICMs) and vesicles, particularly when certain integral membrane proteins are produced

Fig. 1. Electron micrographs of thin sections of *E. coli* cells overproducing the b-subunit of the F-type ATPase. Top: 3 h after initiation of overproduction at 37°; bottom: 3 h after initiation of overproduction at 25°. Reproduced from Arechaga et al. [2000], with permission.

Fig. 2. Transmission electron micrograph of the ICM in negatively stained thin sections of a fresh *R. sphaeroides* cell. The asterisk indicates a storage granule. Reproduced with permission from Adams et al. [2011].

in large quantities [Arechaga et al., 2000, 2003] (see fig. 1 and symposium article entitled ‘Membrane invaginations in bacteria and mitochondria: common features and evolutionary scenarios’ by Arechaga). Protein overproduction using recombinant DNA technologies often results

in the formation of inclusion bodies, consisting primarily of denatured or partially denatured protein in the cell cytoplasm [Carrio and Villaverde, 2002]. The task of renaturing inclusion body polypeptides to their native structures represents a major challenge in biotechnology, but substantial success has been achieved [Baneres et al., 2011; Schlapschy and Skerra, 2011].

Some overproduced membrane proteins appear in various forms within the cell cytoplasm. These include cytoplasmic micelles (CMs) and intracellular membrane vesicles (ICVs) in addition to ICMs [Aboulwafa and Saier, 2011; Arechaga et al., 2000; Bogdanov and Dowhan, 2012] (see symposium article entitled ‘Subcellular localization of integral membrane proteins in *Escherichia coli*’ by Bogdanov et al.). Mesosomes, intracellular extensions of the plasma membrane, have been identified in both Gram-positive and Gram-negative bacteria, although they have been characterized most extensively in the former organism where they may play roles in ‘extracellular’ digestion [Cherepova et al., 1986; Greenawald and Whiteside, 1975; Li et al., 2008; Santhana Raj et al., 2007].

Mesosomes in Gram-positive bacteria appear to result from invagination of the plasma membrane, which is also thought to be the origin of the ICMs and ICVs in *E. coli* [Arechaga et al., 2000; Biriuzova et al., 1980; Hirata, 1979]. It is possible that the ICM in *E. coli* [Bogdanov and Dowhan, 2012] is of similar function, structure and origin as previously studied mesosomes in other bacteria. Moreover, chromatophorous ICMs of photosynthetic bacteria and magnetosomes of magnetotactic bacteria are also believed to have their origin in plasma membrane sites of invagination. It may be that all of these ICMs have related modes of biogenesis.

Chromatophores (ICMs) in Photosynthetic Bacteria

For over 60 years it has been recognized that many photosynthetic bacteria possess intracellular pigmented membrane structures (the ICM; fig. 2) that are capable of catalyzing light-driven reactions including proton motive force (pmf)-driven ATP synthesis [Schachman et al., 1952] or photophosphorylation [Pardee et al., 1952]. This intracellular photosynthetic apparatus, quantitatively different in lipid and protein composition from the cytoplasmic membranes of these organisms, assumes various morphological types, some continuous with and others discontinuous with the plasma membranes, depending on the organism under study. The biogenesis of these

photosynthetic membranes continues to be an exciting area of research with the potential of revealing novel mechanisms of membrane differentiation. In the symposium article by Drews entitled 'The intracytoplasmic membranes of purple bacteria – assembly of energy-transducing complexes', the energy-transducing complexes that are responsible for light-driven electron flow and photophosphorylation are analyzed and reviewed. This article focuses on purple α -proteobacterial species of the genus *Rhodobacter*, in which the ICMs contain the light-harvesting complexes as well as the bacteriochlorophyll-containing reaction centers where conversion of light energy into a pmf is initiated.

In the symposium article by Woronowicz et al. entitled 'Structural and functional proteomics of intracytoplasmic membrane assembly in *Rhodobacter sphaeroides*', a temporal and spatial proteomic approach is taken to the study of photosynthetic ICM structure, function and assembly. As also noted in the article by Drews, the ICMs appear to result from invagination of the plasma membrane, and these invagination sites as well as ICM vesicles have been isolated and characterized. Many of the proteins that comprise these membranes and the photosynthetic complexes they contain have been identified, and four pigmented fractions have been separated, the reaction center-light harvesting 1 (RC-LH1) core complex, the LH2 peripheral antenna and two fractions with distinct associations of LH2 with core complexes. The ratios of these different constituent complexes proved to change as ICM development proceeds. Other proteins, many of which were identified, also cofractionate with these complexes, providing functional and biogenic insight. Changes have been followed under different growth conditions showing, for example, that vesiculation of plasma membrane growth initiation sites to form vesicular ICMs is quickly arrested upon introduction of oxic conditions. The experimental approaches used to define their properties are briefly presented in the symposium article by Woronowicz et al.

Magnetosomes in Magnetotactic Bacteria

Magnetotactic bacteria and the chains of magnetosomes that allow these organisms to align in the Earth's magnetic field is the topic of discussion in the symposium articles by Lower and Bazylinski entitled 'The bacterial magnetosome: a unique prokaryotic organelle' and by Murat entitled 'Magnetosomes: how do they stay in shape?' These membrane-bounded organelles are found

in a diversity of bacteria. These bacterial cytoplasmic organelles contain Fe_3O_4 (magnetite) or in anaerobic bacteria, Fe_3S_4 (greigite), often as small cubo-octahedral crystals. Chains of magnets grow by deposition of new membrane-enclosed magnets at the ends of the chains. The mechanisms of biogenesis and coupling of magnetic field detection to a response are still under intensive study, but much information is already available (see the symposium articles by Lower and Bazylinski and by Murat).

Magnetotaxis is well documented for animals that use the Earth's magnetic field for navigation purposes. These animals are capable of sensing the Earth's magnetic field through the use of magnets linked to nerves [Frankel and Bazylinski, 2006, 2009; Jogler and Schuler, 2009; Lefevre et al., 2011, 2012]. This is true for birds (e.g. homing pigeons), bees (i.e. for foraging), fish (i.e. for migration) and sea turtles (i.e. for migration). Humans can also respond to magnetic fields. Some have an immutable sense of direction, and human tissue culture cells respond to imposed magnetic fields. Imposition of strong magnetic fields ($100\times$ that of the Earth) to the brains of epilepsy patients causes a 10-fold increase in the frequency of seizures. Furthermore, continual exposure to power lines has been reported to increase the incidence of cancer in people. Crystals of magnetite (Fe_3O_4) have been identified in human brains and the brain tissues of many animals using magnetic resonance imaging [Wiltshko and Wiltshko, 2012].

In bacterial magnetosomes, magnetite or greigite (and also other sulfides such as pyrite) crystals are surrounded by a membrane of lipids similar to those of the plasma membrane but containing unique proteins. The magnetic crystals align in chains yielding large magnetic moments. Each chain has up to 100 magnetosomes per bacterium (fig. 3). They orient in the Earth's magnetic field and thereby allow the bacteria to move sideways up and down in the water column in response to geomagnetism. In the northern hemisphere, they orient northward and swim towards the south pole of a magnet. The reverse is true for those in the southern hemisphere. The two types of bacteria are not fundamentally different and interconvert at high rates relative to mutation rates [Lefevre et al., 2009; Wang et al., 2008].

Magnetotactic bacteria come from several diverse bacterial kingdoms, so magnetotaxis may be very old. In fact, ancient magnetofossils have been characterized (see the symposium article by Lower and Bazylinski). The membranes of magnetosomes apparently arise by invagination of the plasma membrane, but they contain a unique set of

Fig. 3. Low-resolution magnetosome chains (**a**) and high-resolution view of membrane-bounded magnetite crystals (**b**) in *Magnetospirillum glyphiswaldense* as revealed by transmission electron microscopy. Reproduced from Bazylinski and Schuler [2009], with permission.

proteins that biomineralize and form chains [Komeili et al., 2006; Murat et al., 2010b; Staniland et al., 2007; Tanaka et al., 2006].

As noted above, many magnetosome crystals are of similar sizes and shapes. The question is: why? If too small, they do not have the mass to overcome the energy of thermal vibration to maintain stable movement. However, magnetosome crystals are single-domain particles. If too big, individual domains orient randomly when the multidomain structures are formed (see the symposium article by Murat). These cancel each other out, yielding weak total magnetic moments. Obligate microaerophiles primarily use Fe_3O_4 (magnetite) crystals. However, some bacteria prefer to be in the oxic-anoxic transition zone, where Fe^{2+} is present in a soluble form. Fe^{3+} is largely insoluble as oxides and other ferric salts. Some of these bacteria use magnetotaxis to stay in the region of high Fe^{2+} concentration but low O_2 tension (i.e. if they go down, there is more Fe^{2+} and less O_2 , if they go up, there is more O_2 and less Fe^{2+}). Other bacteria use their magnetosomes to seek nutrient-rich sediments [Jogler and Schuler, 2009] (see also the symposium article by Lower and Bazylinski).

Anammoxosomes and Nuclear Envelopes in *Planctomycetes*

The *Planctomycetes* represent an unusual and relatively newly discovered group of organelle-containing bacteria with unique properties that are just now becoming appreciated and understood. These organisms have a complex internal cell structure. Their outermost membrane has been considered to be the cytoplasmic membrane although it may exhibit some of the properties of more typical Gram-negative bacterial outer membranes. They also have a membrane-bounded nucleoid, analogous in some respects to the nuclei of eukaryotic cells (see symposium article by Fuerst and Sagulenko entitled 'Nested bacterial boxes: nuclear and other intracellular compartments in planctomycetes'). Planctomycetes also have energy-producing, mitochondrion-like organelles referred to as anammoxosomes (anaerobic ammonium oxidation organelles) with unusually rigid lipids called 'ladderanes' because of their inflexible ladder-like structures (see symposium article by van Teeseling et al. entitled 'The anammoxosome organelle is crucial for the energy metabolism of anaerobic ammonium oxidizing bacteria'). These lipids probably contribute to energy conservation by creating a more H^+ leak-proof membrane. Such a characteristic may be important as anammoxosomes probably generate a pmf across this membrane via a quinone-dependent process analogous to and possibly mechanistically similar to the process catalyzed by the membrane cytochrome bc1 complex, present in many bacteria, and equivalent to the electron flow complex III of mitochondria. The pmf thus generated can then be used to make ATP via an F-type ATPase that has been found in association with the anammoxosome membrane. Since the anammoxosome is a separate membrane-enclosed compartment with a distinct lipid and protein composition serving a unique function, it qualifies as an intracellular organelle by any definition.

Anammoxosomes are only found in Planctomycetes, but not in all of these organisms. These organelles possibly evolved specifically to compartmentalize the enzymes catalyzing NH_4^+ oxidation and to allow energy production from the primary reaction they catalyze: anaerobic NH_4^+ oxidation. Compartmentalization may also be required because an intermediate in NH_4^+ oxidation is hydrazine ($\text{H}_2\text{N}-\text{NH}_2$), a highly reactive and toxic substance that could destroy nucleic acids if these molecules came in direct contact with them. These compelling arguments, set forth in the article by van Teeseling et al. may well pro-

vide the basis for their evolution. This logic appears to be equally applicable to the evolution of other prokaryotic organelles as well as eukaryotic organelles that probably evolved by entirely different mechanisms via very different pathways.

Special Delivery: Outer Membrane Vesicle Trafficking in Prokaryotes

Although the observation that Gram-negative bacteria bleb off outer membrane vesicles (OMVs), releasing them into the external medium, was made over 40 years ago, their biological roles have become a focus of study only within the past few years. Recent progress in this area has revealed that bacterial OMVs are utilized for several processes including: (1) delivery of toxins to eukaryotic cells, (2) protein and DNA transfer between bacterial cells, (3) trafficking of cell-cell signals, (4) delivery of proteases and antibiotics and (5) removal of harmful incorrectly folded proteins. Some of these roles appear to be generalized among Gram-negative bacteria while others are restricted to specific bacterial species [Mashburn-Warren and Whiteley, 2006]. The symposium article by Whiteley and associates entitled 'Bacterial outer membrane vesicles in trafficking, communication and host-pathogen interactions' and the contribution by Manning and Kuehn entitled 'Functional advantages conferred by extracellular prokaryotic membrane vesicles' discuss several of these functions. Additionally, in the symposium article entitled 'The role of membrane vesicles in secretion of *Lysobacter* sp. bacteriolytic enzymes', Vasilyeva et al., present a well-characterized example of the use of these OMVs for secretion of bacteriolytic enzymes, important in microbial interactions in many environments.

Many bacteria use extracellular signals to communicate and coordinate social activities, a process referred to as quorum sensing. Some quorum signals have hydrophobic character, and how these signals are trafficked between bacteria within a population is of great interest. The opportunistic human pathogen, *Pseudomonas aeruginosa*, packages the signaling molecule, 2-heptyl-3-hydroxy-4-quinolone (*Pseudomonas* quinolone signal; PQS), into membrane vesicles that serve to traffic this molecule within a population. Removal of these vesicles from the bacterial population halts cell-cell communication and inhibits PQS-controlled group behavior.

PQS actively mediates its own packaging and the packaging of other antimicrobial quinolones produced by *P. aeruginosa* into vesicles. Thus, prokaryotes possess signal

trafficking systems with features common to those used by higher organisms. Novel mechanisms for the delivery of signals critical for coordinating group behavior have been proposed [Mashburn and Whiteley, 2005; Schertzer and Whiteley, 2012].

The extracellular matrix helps define the architecture and infrastructure of bacterial biofilms and also contributes to their resilient nature. How structural characteristics help to bridge the gap between the chemical and physical aspects of the matrix is currently under critical investigation. Schooling and Beveridge [2006] showed that OMVs are a common particulate feature of the matrix of *Pseudomonas aeruginosa* biofilms. Biofilms grown using different model systems and growth conditions contain OMVs when thin sectioned for transmission electron microscopy, and mechanically disrupted biofilms revealed OMVs in association with intercellular materials. Characterization of planktonic and biofilm-derived OMVs revealed quantitative and qualitative differences between the two and indicated functional roles, such as proteolytic activity and binding of antibiotics. The essential ubiquity of OMVs was supported by observations of biofilms from a variety of natural environments outside the laboratory and established OMVs as common biofilm constituents. They appear to be important and relatively unacknowledged particulate components of the matrix of Gram-negative or mixed bacterial biofilms [Schooling and Beveridge, 2006; Zhong, 2011].

OMVs, released by pathogenic bacteria, can transmit virulence factors to host cells [Kuehn and Kesty, 2005]. These structures are not merely a result of membrane instability and are formed by a more directed process. Kuehn and Kesty [2005] and McBroom et al. [2006] showed that only a few low-vesiculation mutants and no null mutants were recovered following screening for such mutants, suggesting that vesiculation may be a fundamental characteristic of Gram-negative bacterial growth. Gene disruptions were identified that caused differences in vesicle production ranging from a 5-fold decrease to a 200-fold increase relative to wild-type levels. These disruptions included loci governing outer membrane components and peptidoglycan synthesis and constituents of the σ^E cell envelope stress response system. Detergent sensitivity, leakiness and growth characteristics of the novel vesiculation mutant strains did not correlate with vesiculation levels, demonstrating that vesicle production is not predictive of envelope instability [McBroom et al., 2006].

Conditions that impair protein folding in the Gram-negative bacterial envelope cause stress. The destabilizing effects of various types of stress in this compartment are

Fig. 4. An acidocalcisome in an intact cell of *Agrobacterium tumefaciens*. Reproduced with permission from Docampo and Moreno [2011].

recognized and countered by a number of signal transduction mechanisms [Baumgarten et al., 2012]. Data presented by McBroom and Kuehn [2007] revealed that a bacterial stress response includes release of OMVs. Native vesicles are composed of outer membrane and periplasmic materials, and they are released from the bacterial surface without loss of membrane integrity.

The quantity of vesicle release correlates directly with the level of protein accumulation in the cell envelope. Accumulation of material occurs under stress, and is exacerbated upon impairment of the normal housekeeping and stress-responsive mechanisms of the cell. Mutations that cause increased vesiculation enhance bacterial survival upon challenge with stressing agents or accumulation of toxic misfolded proteins. Preferential packaging of a misfolded protein into vesicles for removal indicates that the vesiculation process can selectively eliminate unwanted material. Production of bacterial OMVs is thus an independent, general, envelope stress response [Manning and Kuehn, 2011; McBroom and Kuehn, 2007].

Acidocalcisomes and the Evolution of Intracellular Compartmentalization

Acidocalcisomes are calcium/polyphosphate-rich acidic membrane-enclosed organelles that are found in organisms belonging to the three domains of life (fig. 4) [Docampo and Moreno, 2011; Ramos et al., 2010]. Their membranes may contain a variety of transport systems including aquaporins, ion-pumping ATPases, cation exchangers and H^+ -pumping pyrophosphatases [Rohloff et al., 2011; Seufferheld et al., 2011]. Their functions include storage of cations and polyphosphates, osmo-, pH- and

Ca^{2+} -homeostasis, and energy metabolism [Docampo et al., 2005]. They superficially resemble eukaryotic lysosomes in their sizes, acidic properties and contents [Moreno and Docampo, 2009].

The two symposium articles by Caetano-Anollés and Seufferheld are entitled ‘The coevolutionary roots of biochemistry and cellular organization challenge the RNA world paradigm’ and ‘Phylogenomics supports a cellularly structured urancestor’. In the first of these two articles, these authors examine the origins and evolution of complex cellular structures by using phylogenomic approaches among others. These studies suggest to the authors that the last common universal ancestor of all extant living organisms on Earth, the urancestor, already had complex intracellular structures. They argue for the gradual coevolution of nucleic acids and proteins and discard the notion of an ancient RNA world. In their second article, the authors discuss intracellular and extracellular compartments including acidocalcisomes and mitochondria. They consider the channeling of redox energy to satisfy the metabolic needs of Earth’s earliest inhabitants. Thus, it is argued that the urancestor was relatively complex. The authors present molecular and microfossil evidence to support their claims. They extrapolate back 3.4 billion years, suggesting that primordial microbial communities were already in existence at that time. They thus suggest that cellular compartmentalization and energy interconversion mechanisms were early inventions.

Concluding Remarks

The compendium of articles presented in this *Journal of Molecular Microbiology and Biotechnology* written symposium reveals the near ubiquity of intracellular and extracellular membrane-bounded structures that serve unique functions in prokaryotes. Recent research in *E. coli* and other bacteria suggests that ICMs may occur in a large range of bacteria that had previously been thought to lack such structures. Similarly, recognition that OMVs in Gram-negative bacteria serve a plethora of interesting functions provides novel impetus to study these structures in much greater detail. The recent conclusion that ICMs in *E. coli*, photosynthetic bacteria and magnetotactic bacteria may all derive from the plasma membrane by invagination leads to the exciting possibility that chromatophore and magnetosome biogenesis may share mechanistic features with ICM formation in *E. coli*. This unifying consideration leads to the proposal that studies

in the prokaryotic workhorse, *E. coli*, may prove to be applicable to organellar phenomena in other prokaryotes as well as eukaryotes.

The recent discovery of prokaryotic organelles similar to those in eukaryotes (i.e. nuclear envelopes, anammoxosomes and acidocalcisomes) has led some investigators to propose that the urancestor of the three domains of life

possessed some types of organelles. Whether true or not, the presence of these structures has far-reaching implications for our understanding of prokaryotic complexity. It also suggests new approaches to the study of organellar biology. Intracellular membrane differentiation in bacteria is likely to reveal novel unifying principles applicable to all forms of life on Earth.

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