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CHAPTER SIX

CUBIC MEMBRANES: THE MISSING DIMENSION OF CELL MEMBRANE ORGANIZATION

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Abstract

Biological membranes are among the most fascinating assemblies of biomolecules: a bilayer less than 10 nm thick, composed of rather small lipid molecules that are held together simply by noncovalent forces, defines the cell and discriminates between “inside” and “outside”, survival, and death. Intracellular compartmentalization—governed by biomembranes as well—is a characteristic feature of eukaryotic cells, which allows them to fulfill multiple and highly specialized anabolic and catabolic functions in strictly controlled environments. Although cellular membranes are generally visualized as flat sheets or closely folded isolated objects, multiple observations also demonstrate that membranes may fold into “unusual”, highly organized structures with 2D or 3D periodicity. The obvious correlation of highly convoluted membrane organizations with pathological cellular states, for example, as a consequence of viral infection, deserves close consideration. However, knowledge about formation and function of these highly organized 3D periodic membrane structures is scarce, primarily due to the lack of appropriate techniques for their analysis in vivo. Currently, the only direct way to characterize cellular membrane architecture is by transmission electron microscopy (TEM). However, deciphering the spatial architecture solely based on two-dimensionally projected TEM images is a challenging task and prone to artifacts. In this review, we will provide an update on the current progress in identifying and analyzing 3D membrane architectures in biological systems, with a special focus on membranes with cubic symmetry, and their potential role in physiological and pathophysiological conditions. Proteomics and lipidomics approaches in defined experimental cell systems may prove instrumental to understand formation and function of 3D membrane morphologies.

1. Introduction

Membrane-bound cell organelles are typically considered to have rather spherical topology, delineated by one phospholipid-bilayer membrane that separates the interior from the exterior. However, this simplification of organelle topology is a rule not a law, and it is well known that a large number of membrane structures exists in Nature with more complex 3D morphologies. Indeed, the topology of membrane-bound organelles is a rather unexplored area of research. This might be due to
difficulties in obtaining information about topological parameters from living or fixed cells, and the interpretation of these parameters in the cellular context. Nevertheless, the importance of topology considerations, for example, subcellular compartmentalization, transport phenomena, and sorting events that involve membrane trafficking processes is evident. Cell membrane morphology, controlled by the principles of self-assembly and/or self-organization, is likely to adopt an optimally organized structure under the influence of selective conditions. This is a dynamic process, perhaps restricted to sub-membrane domains, and short-lived, and is dependent on the lipid as well as protein components of the membrane.

As a consequence of limited in vivo technologies, knowledge about the molecular mechanisms underlying membrane morphology is scarce and largely restricted to the descriptive level. Indeed, higher order membrane topologies identified by transmission electron microscopy (TEM), are frequently reported in the literature, yet due to their very heterogeneous representations, common features are difficult to comprehend. Among these nonlamellar cell membranes, especially cubic membrane organizations attract great attention (Almsherqi et al., 2006; Hyde et al., 1996; Landh, 1995, 1996) because of their unique feature of 3D periodicity in TEM micrographs and great similarity to the bicontinuous lipidic cubic phases (Bouligand, 1990; Larsson, 1989; Larsson et al., 1980; Luzzati, 1997). Cubic membranes (Figs. 6.1 and 6.2) have therefore often been compared to self-assembled cubic lipidic phases in aqueous dispersions that are well

Figure 6.1  Cubic membrane architecture (Almsherqi et al., 2008). (A) Two-dimensional transmission electron micrograph of a mitochondrion of 10 days starved amoeba Chaos cells and (B) three-dimensional mathematical model of the same type of cubic membrane organization. Scale bar: 250 nm.
characterized in vitro, with several applications. Indeed, the efforts toward understanding formation and functional roles of cubic membranes in biological systems have been paralleled by the efforts in investigating cubic phases formation and their behavior in lipid–water systems.

2. CELL MEMBRANE ARCHITECTURE

2.1. Membrane symmetries

Biological membranes may exhibit point or line symmetry. A membrane is symmetrical if it can be nontrivially rotated, inverted, mirrored, and translated such that it is indistinguishable from its initial appearance. Symmetry of

Figure 6.2  Periodic cubic surfaces and cubic membrane. Oblique views of the unit cell of (A) Primitive, (B) Double Diamond, and (C) Gyroid cubic surfaces observed in biological systems. (D) The bilayer constellation of a 3D mathematical model of a cubic membrane. Three parallel Gyroid-based surfaces can be used to describe a biological membrane (bilayer), in which case the centered surface is the “imaginary” hydrophobic mid-bilayer surface and the two parallel surfaces are the two apolar/polar (interfacial) surfaces.
biological membranes is mainly described by rotations. Several sets of membrane arrangements exhibit symmetry such as parallel membranes and hexagonal packing of tubes. In contrast, a cubic membrane exhibits distinct morphological patterns when projected which may even be translated into unique signatures in many directions (Fig. 6.3). The patterned membrane organization of cubic membranes consists of a network arranged in a nonrandom order and is evenly spaced. Therefore, through an overall inspection of TEM micrographs, cubic membranes are recognized via perceptual cues of the patterned membrane organization (Almsherqi et al., 2006; Landh, 1996). This unique appearance of cubic membranes in TEM micrographs frequently allows for the differentiation of cubic membrane organization from other membrane arrangements such as tubulo-reticular structures (TRS) and annulate lamellae (AL) (Figs. 6.4 and 6.5).

Cubic membranes represent highly curved, 3D periodic structures that correspond to mathematically well-defined triply periodic minimal surfaces or the corresponding periodic nodal surfaces and their respective constant mean curvature or level surfaces (Fig. 6.2). Both the latter surface descriptions are approximative descriptions of surfaces parallel to the minimal or nonzero level surface (Landh, 1996). Cubic membranes have been detected

**Figure 6.3** Computer simulation of TEM images. (A) Schematic illustration of TEM data in 2D projections of a specimen with a finite thickness. A 3D object (a) is depicted and is translucent to the projection rays of an electron beam; (b) representation of one unit cell of the gyroid surface; (c) projection plane onto which the rays impinge, in analogy of the film on which the image would be recorded; (d) 2D projection map provides a corresponding template for matching the patterned membrane domain in the TEM micrograph. (B) Comparison between a 3D cubic membrane model of a gyroid-based surface and its computer simulated projections at different viewing directions. Multiple 2D projections that are generated from the same 3D structure form a library of different patterns. The bottom row corresponds to computer-simulated projections for the top row, based on a projected specimen thickness of one-half of a unit cell viewed at the [1, 0, 0] (left), [1, 1, 0] (middle), and [1, 1, 1] (right) directions. The computer-generated projection can be matched with TEM micrographs to determine the 3D structure of a cubic membrane arrangement (see section 2.4. for further details).
without any obvious restrictions or preferences in all kingdoms of life, both under physiological or pathological conditions (Table 6.1). They appear not to be limited to certain types of cells, although they may occur more frequently in some cell types. Furthermore, cubic membranes are not strictly associated with any particular organelle and can apparently evolve from almost any cytomembrane: plasma membrane, endoplasmic reticulum (ER), nuclear envelope (NE, both inner (INE) and outer (ONE)), inner mitochondrial membrane, and the Golgi complex. The smooth ER, however, seems to be the organelle most frequently associated with cubic membrane formation. So far, three surface families have been identified to exist, and these three types of cubic membranes are schematically shown in Fig. 6.2. They are designated according to their corresponding triply periodic minimal (or level) surfaces as gyroid (G), double diamond (D), and primitive (P) surfaces.

Cubic membranes often coexist with other “unusual” membrane arrangements, such as TRS, which are irregularly arranged tubes that bifurcate and reanastomose. In many cases, these tubes show a preferential

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**Figure 6.4**  Cell membrane organization. Schematic diagram depicting the likely 3D structure of annulated lamellae, tubulo-reticular structure (TRS) and the membrane folding transition. The pores of annulated lamellae may alternate in arrangement with the symmetry often being quadratic (A) or the pore face each other with the symmetry being hexagonal (B). Two examples of TRS membrane arrangements; (C) interconnected sacular (cisternae) and (D) tubular membrane organization show no global symmetry. A possible model of continuous membrane folding for the formation of double diamond (lower left) and gyroid (upper left) cubic type, hexagonal (upper right) and lamellar structures, and whorls (lower right) (E). The coexistence of these membrane organizations has been reported frequently in UT-1 and COS-7/CV-1 cells with HMG-CoA reductase and cytochrome b(5) overexpression, respectively. Panels A-D adapted from Figs. 17 and 18; Bouligand, 1991.
orientation. The main difference of TRS to cubic membranes is that TRS symmetry is usually nematic, since the layers do not show obvious periodic distribution (Fig. 6.4D). The preferential alignment along a direction may be due to an elongation process, perhaps in association with the cytoskeleton, and is not necessarily the result of a spontaneous membrane alignment. However, there are many cases in which the periphery of a perfectly preserved cubic morphology shows TRS appearance, which, therefore, may be introduced by the fixation method (Landh, 1995). Membranes of true cubic morphology are often mis-labeled as TRS in the literature, due to the convoluted image projections observed for both structures. Many of the examples listed in Table 6.1 have been designated as TRS, despite the presence of a distinct cubic symmetry (Almsherqi et al., 2005; Landh, 1996). TRS have attracted biomedical interest due to their potential use as an ultrastructural marker for pathological conditions: they occur in virus-infected and in cancer cells and have been, therefore, often regarded as an

Figure 6.5  Examples of different membrane organizations observed in UT-1 cells, 48–72 h after compactin (40 μM) treatment (Deng et al., unpublished). (A) Annulate lamellae, (B) stacked undulated lamellae that show hexagonal transition, (C) cubic, and (D) hexagonal membrane morphologies may coexist in the same cell. Membrane folding appears to originate at the nuclear envelope or the endoplasmic reticulum.
Table 6.1  Occurrence of cubic membranes in biological systems.

| Description of cells/tissue | Cognomes                        | $S^a/a$ (nm) | References                                    |
|-----------------------------|---------------------------------|--------------|-----------------------------------------------|
| **Monera**                  |                                 |              |                                               |
| Gracilicutes                |                                 |              |                                               |
| Oxyphotobacteria            |                                 |              |                                               |
| Cyanobacteria               |                                 |              |                                               |
| Thylakoid lamellae in *Anabaena* sp. |                | D/50         | Lang and Rae (1967)                           |
| Thylakoid lamellae in *Anabaena* sp. |                |              | Beams and Kessel (1977)                       |
| Thylakoid lamellae in Heterocyst of  *Anabaena azollae* | | Honeycombed lamellae | Lang (1965)                                   |
| Thylakoid in *Anabaena variabilis* infected with cyanophages | | PLB-like structure | Granhall and von Hofsten (1969)               |
| **Protista**                |                                 |              |                                               |
| Algae                       |                                 |              |                                               |
| Clorophyta                  |                                 |              |                                               |
| Chlorophyceae               |                                 |              |                                               |
| Membranes in chloroplasts of *Zygnema* |                | P^m/350      | McLean and Pessoney (1970)                     |
| Membranes in chloroplasts of *Zygnema* |                | G^m/500      | Deng and Landh (1995)                         |
| Thylakoid membranes in chloroplast of  *Chorella vulgaris*  | | Masses of prethylakoid tubules | Bryan *et al.*  (1967)                        |
| Thylakoid membranes in chloroplast of  *Protosiphon botyoides* | | Sinusoidal thylakoids | Berkaloff (1967)                              |
| Charophyceae                |                                 |              |                                               |
| Plasma membrane of *Chara coralline*,  *C. braunii* | Charasome | G/140 | Barton (1965), Franceshi and Lucas (1980, 1981), Lucas and Franceshi (1981) |
| Organism/Structure | Description                  | Code | Reference                        |
|-------------------|-------------------------------|------|----------------------------------|
| Plasma membranes of *Nitella* | Interconnected tubules | G    | Crawley (1965)                   |
| Rhodophyta        |                               |      |                                  |
| Rhodophyceae      | ER in *Erythrocystis montagnei* | Crystalline body | Tripodi and de Masi (1977)     |
| Gymnomycota (Myxomycota, slime moulds) |                       |      |                                  |
| Plasmodiogynnomycotina |                          |      |                                  |
| Myxomycetes       | Mitochondria in *Physarum polycephalum* | Regular tubular network | Daniel and Järlfors (1972a,b) |
|                   | Mitochondria in *Didymium nigripes* | Unusual tubular morphology | Schuster (1965)                |
| Mastigomycotina   |                               |      |                                  |
| Diplomastigomycotina |                        |      |                                  |
| Oomycetes         | ER in *Oedogoniomyces zoospores* | Organized lamellar system | Reichle (1972)                 |
| Protozoa          |                               |      |                                  |
| Sarcomastigophora |                               |      |                                  |
| Mastigophora      |                               |      |                                  |
| Phytomastigophora | Photosynthetic lamellae in dark-grown *Chlamydomonas reinhardtii* y-1 | Meshed network, PLB-like | Friedberg *et al.* (1971), Hoober *et al.* (1969) |
| Zoomastigophorea  | ER in *Leptomonas collosoma*  | Membrane lattice | Linder and Staehelin (1980)     |
| Rhizopoda         | Mitochondria in *C. carolinense* | D^2/150 | Pappas and Brandt (1959), Brandt and Pappas (1959), Borysko and Roslansky (1959), Daniels and Breyer (1968) |
| Amoebida          |                               |      |                                  |
| Description of cells/tissue | Cognomes | $S^a/a$ (nm) | References |
|-----------------------------|----------|-------------|------------|
| Mitochondria in *C. carolinense*<sup>a</sup> | D<sup>2</sup>, P<sup>2</sup>/130 | Deng and Mieczkowski (1998); Deng et al. (1999) |
| Mitochondria in *Chaos illinoisensis* | Complex tubular patterns D<sup>2</sup> | Daniels and Breyer (1965) |
| Pelobiontida | | |
| Intranuclear membrane in *Pelomyxa palustris* | Crystalloid | Daniels and Breyer (1967) |
| Cnidospora | | |
| Microsporidea | | |
| Membranes in sporoblast of *Nosema apis* | Honeycomb network | Youssef and Hammond (1971) |
| Ciliophora | | |
| Oligohymenophora | | |
| Hymenostomatida | | |
| Pniculina | | |
| Contractile vacuolar membranes of *Paramecium aurelia, Paramecium multimicronucleatum* | Smooth spongiome | Mckanna (1976), Allen and Fok (1988), Allen et al. (1990), Fok et al. (1995), Hausmann and Allen (1977), Ishida et al. (1993, 1996) |
| Intranuclear membrane of *Neobursardium gigas* | Crystal configuration G/160 | Nilsson (1969) |
| Tetrahymenina | | |
| Contractile vacuolar membranes of *Tetrahymena pyriformis* | Nephridial tubules | Elliott and Bak (1964) |

**Fungi**

| | | |
|-----------------|----------|-------------|
| Amastigomycota | | |
| Ascomycotina | | |

<sup>a</sup> Not documented
| Plant                                                                 |                                                                 |                                                                 |                                                                 |
|----------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| Ascomycetes                                                          | ER in apothelial cells of *Ascobolus stercorarius*               | Lattice bodies                                                  | Anderson and Zachariah (1972), Zachariah (1970), Zachariah and Anderson (1973), Wells (1972) |
| Plant                                                                |                                                                 |                                                                 |                                                                 |
| Pteridophyta                                                         |                                                                 |                                                                 |                                                                 |
| Oocytes in *Selaginella kraussiana*                                   | Pseudocrystal                                                   |                                                                 | Robert (1969a,b)                                                |
| Plant                                                                |                                                                 |                                                                 |                                                                 |
| Spermatophyta                                                        |                                                                 |                                                                 |                                                                 |
| Angiosperms                                                          |                                                                 |                                                                 |                                                                 |
| Magnoliophyta (anthophyta)                                           |                                                                 |                                                                 |                                                                 |
| Dicotyledons                                                         |                                                                 |                                                                 |                                                                 |
| Ranunculidae                                                         |                                                                 |                                                                 |                                                                 |
| Ranunculaceae                                                        |                                                                 |                                                                 |                                                                 |
| ER of nectaries in *Helleborus foetidus*                             | Cotte de mailles                                                | P²/80                                                           | Eymé (1963, 1966), Eymé and Blance Le (1963)                     |
| ER of ovules in *Ficaria ranunculoides*                              | Cotte de mailles                                                | P                                                               | Eymé (1966, 1967)                                               |
| ER in virus-infected leaf ER complex                                  | ER complex                                                      | P²/65                                                           | Robinson (1985)                                                 |
| ER in phloem-parenchyma cells of *Helleborus niger*                  | ER complex                                                      | P²/75                                                           | Behnke (1981)                                                   |
| ER in differentiating sieve elements of *Eranthis cilicica*          | ER complex                                                      | G²/70, 145                                                      | Behnke (1981)                                                   |
| Papaveraceae                                                         |                                                                 |                                                                 |                                                                 |
| ER in ovules of *Papaver rhoeas*                                     | Cytoplasmic complex                                             | P², D²                                                          | Ponzi *et al.* (1978)                                           |
| Hamamelididae                                                        |                                                                 |                                                                 |                                                                 |
| Urticales                                                            |                                                                 |                                                                 |                                                                 |
| ER in differentiating sieve elements of *Ulmus americana*             | Complex network/maize                                           |                                                                 | Evert and Deshpande (1969)                                      |
| Description of cells/tissue          | Cognomes                      | $S''/a$ (nm) | References                                      |
|-------------------------------------|-------------------------------|-------------|------------------------------------------------|
| Caryophyllidae                      |                               |             |                                                 |
| Caryophyllales                      |                               |             |                                                 |
| ER in sieve elements of beet yellow | Convulated ER                 |             | Esau and Hoefert (1980)                         |
| vein virus infected Beta            |                               |             |                                                 |
| Dilleniidae                         |                               |             |                                                 |
| Capparales                          |                               |             |                                                 |
| ER in nectaries of _Diplotaxia erocoides_ | Cotte de mailles            | $P^2/55$    | Eymé (1966, 1967)                              |
| Malvales                            |                               |             |                                                 |
| ER in differentiating sieve elements | Convolved ER                  |             | Thorsch and Esau (1981)                        |
| _Gossypium hirsutum_                |                               |             |                                                 |
| Rosidae                             |                               |             |                                                 |
| Leguminosae                         |                               |             |                                                 |
| Plastids in bean root tips of _Phaseolus vulgaris_ | Tubular complex            |             | Newcomb (1967)                                  |
| ER in differentiating sieve element of _P. vulgaris_ | Convoluted membranes        |             | Esau and Gill (1971)                           |
| Sapindales                          |                               |             |                                                 |
| ER in differentiation sieve elements of _Acer_ | Quasi-crystalline membranes | $D^2/180$   | Wooding (1967)                                  |
| ER in differentiation sieve elements of _Acer pseudoplatanus_ | Vesicular aggregates        |             | Northcote and Wooding (1966)                    |
| Asdteridae                          |                               |             |                                                 |
| Gentianales                         |                               |             |                                                 |
| ER in differentiating sieve element of _Nymphoides peltata_ | Convulated membrane complex | $G^2/125$   | Johnson (1969), Oparka and Johnson (1978)       |
| Monocotyledons                      |                               |             |                                                 |
| Commelinidae                        |                               |             |                                                 |
| Poales                              |                               |             |                                                 |
| Poacea (Gramineae) | ER in *Triticum aestivum* infected by wheat spindle streak mosaic virus | Membranous body | G^2 | Hooper and Wiese (1972), Langenberg and Schroeder (1973) |
|-------------------|------------------------------------------------------------------|-----------------|-----|---------------------------------------------------|
| Liliidae          |                                                                  |                 |     |                                                    |
| Liliales          |                                                                  |                 |     |                                                    |
| ER of differentiating sieve elements | *Dioscorea bulbifera* | Lattice-like membrane | G/40 | Behnke (1968) |
| ER of differentiating sieve elements | *Dioscorea macroura* | Lattice-like membrane | G\(^1\), G^2/30, 140 | Behnke (1968) |
| ER of differentiating sieve elements | *Dioscorea reticulata* | Lattice-like body | G/35 | Behnke (1965, 1968) |
| ER of differentiating sieve elements | *Smilax excelsa* | Convoluted ER |     | Behnke (1973) |
| Arecales          |                                                                  |                 |     |                                                    |
| ER in differentiating sieve elements | *Cocus nucifera* | Convoluted tubular ER | G^2 | Parthasarathy (1974a,b) |
| ER in differentiating sieve elements | *Chamaedorea pulchra*, *C. oblongata*, *C. elegens*, *Elaeis guineensis* | Convoluted tubular ER |     | Parthasarathy (1974a,b) |
| Gymnosperms       |                                                                  |                 |     |                                                    |
| Coniferophyta     |                                                                  |                 |     |                                                    |
| Coniférales       |                                                                  |                 |     |                                                    |
| ER in sieve cells in *Pinus strobus* | | Lattice-like bodies |     | Murmains and Evert (1966) |
| ER in sieve cells in *Pinus pinea* | | Vesicular aggregation |     | Wooding (1966) |
| Animalia          |                                                                  |                 |     |                                                    |
| Mollusca          |                                                                  |                 |     |                                                    |
| Cephalopoda       |                                                                  |                 |     |                                                    |
| Nautiloidea       |                                                                  |                 |     |                                                    |
| Description of cells/tissue | Cognomes | $S^o/a$ (nm) | References |
|-----------------------------|----------|-------------|------------|
| **Nautilida**               |          |             |            |
| ER in retinula cells in *Nautilus macromphalus* | Tubular array of myeloid body | $P > 10^5$/550 | Barber (1967), Barber and Wright (1969) |
| Gastropoda                  |          |             |            |
| Opisthobranchia             |          |             |            |
| Nudibranchia                |          |             |            |
| ER in spermatids of *Spurilla nepolitana* | Undulating tubular body | $P^2$/130 | Eckelbarger (1982), Eckelbarger and Eyster (1981) |
| **Pulmonata**               |          |             |            |
| Helicida                    |          |             |            |
| ER in photoreceptor cells of *Helix pomatia* | Biocrystal |           | Röhlich and Török (1963) |
| Basommatophora              |          |             |            |
| ER in spermatids of *Planorbarius corneus* | Cytoplasmic crystalloid | $D^2$/50 | Starke and Nolte (1970) |
| Stylommatophora             |          |             |            |
| ER in type I photoreceptor cells of *Limax maximus* | Corrugated ER | $D^2$/195 | Eakin and Brandenburger (1975) |
| **Annelida**                |          |             |            |
| Polychaeta                  |          |             |            |
| Aphroditidae, Polynoïnae    |          |             |            |
| ER in luminous cells of *Acholoe astericola* | PER, Photosomes | $D^2$/250 | Bassot (1964, 1966), Bassot and Nicolas (1978), Bilbaut (1980), de Ceccatty *et al.* (1977) |
| ER in luminous cells of *Lagisca extenuata* | PER | $D^2$/250 | Bassot (1966) |
| ER of photoreceptor cells in *L. extenuata* | PER | $D^2$ | Bassot and Nicolas (1978) |
| Organism                          | Description                                      | Author(s)                        |
|----------------------------------|--------------------------------------------------|----------------------------------|
| ER in luminous cells of *Harmothoe lunulata* | PER                                              | Bassot (1985), Bassot and Nicolas (1987, 1995), Nicolas (1979, 1991) |
| ER of photoreceptor cells in *Arctonoe vittata* | Crystalline element                              | Singla (1975)                    |
| Syllidae                         | ER of photoreceptor cells in *Syllis amica*       | PER                              | D²/50 | Bocquet and Dhainaut-Courtois (1973) |
| Nereidae                         | ER of inner segment in photoreceptor cells in *Nereis virens* | Paracrystalline body             |      | Dorsett and Hyde (1968)             |
| Nereidae                         | ER of photoreceptor cells in *Nereis limnicola*   | Crystalloid body                  | G     | Eakin and Brandenburger (1985)      |
| Oligochaeta                       | ER in spermatids of *Eisenia foetida*             | UNDULATING TUBULAR BODY          |      | Stang-Voss (1972)                   |
| Hirudinea                        | ER in photoreceptor cells of *Hirudo medicinalis* | PER                              |      | Walz (1982)                        |
| Arthropoda                       | Mitochondria in spermatids of *Euscorpius flavicaudis* |                                |      | André (1959)                       |
| Pseudoscorpions                  | ER of spermatids in *Diplotemus sp.*             | Highly ordered membrane          |      | Bawa and Werner (1988)              |
| Description of cells/tissue | Cognomes | $S''/a$ (nm) | References |
|-----------------------------|----------|--------------|------------|
| **Crustacea**               |          |              |            |
| Copepoda                    |          |              |            |
| ER of retinula cell in *Macrocyclops albidus* | Elaborately wound membranes | | Fahrenbach (1964) |
| **Malacostraca**            |          |              |            |
| Decapoda                    |          |              |            |
| ER of spermatozoa in *Cragon septemspinosa* | Paracrystalline lattice $D^2$ | | Arsenault et al. (1979, 1980) |
| Schwann cell processes in the ventral nerve cord of *Procambarus sp.* | Anastomosing tubular inclusion | | Pappas et al. (1971) |
| Schwann cell processes in the walking limb nerves *Nephrops sp.* | Anastomosing networks | | Holtzman et al. (1970) |
| Mitochondria in oocytes of *Cambarus* and *Orconectes* | Honeycombed cristae | | Beams and Kessel (1963) |
| **Isopoda**                 |          |              |            |
| ER in bordering cells of Bellonci organ in *Sphaeroma serratum* | Annulate lamellae $G/50$ | | Chaigneau (1971) |
| **Tanaidacea**              |          |              |            |
| ER in sperm of *Tanais cavolinii* | Spongy/foamy cytoplasm | | Cotelli and Donin (1980) |
| **Insecta**                 |          |              |            |
| **Apterygota**              |          |              |            |
| Thysanura                   |          |              |            |
| ER in rectal epithelial cells of *Petrobius maritmus* | Puzzles tridimensionnels $G^2/120$ | | Fain-Maurel and Cassier (1972) |
| Mitochondria in intestinal cells of *P. maritmus* |  | $D^2/160$ | Fain-Maurel and Cassier (1973) |
| **Pterygota**               |          |              |            |
| Orthoptera                  |          |              |            |
| ER in spermatids of *Melanoplus diffentialis differentialis* | Textum $P^2/250$ | | Tahmisian and Devine (1961) |
| Animal Phylum          | Organism                                      | Mitochondria/ER Location                                           | Mitochondria Properties                          | Reference                                |
|------------------------|-----------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------|------------------------------------------|
| Hemiptera              | *Locust migratoria migratorioides*           | Mitochondria in corpus allata                                      |                                                  | Fain-Maurel and Cassier (1969)           |
| Diptera                | *Dysdercus fasciatus*                        | ER in spermatids                                                   | Sinusoidal tubules                              | Folliot and Maillet (1965)               |
|                        | *Pyrrocoris apterus*                         | ER in oocytes                                                      | PER                                              | Mays (1967)                              |
|                        | *Notonecta undulata*                         | ER in spermatogenic cells of *Notonecta undulata*                  | Anastomosing tubules                            | Tandler and Moribier (1974)              |
|                        | *P. apterus*                                  | ER in spermatogonai a and spermatocytes of *P. apterus*            | PER                                              | Wolf and Motzko (1995)                   |
| Lepidoptera            | *Calliphora erythrocephala*                  | Mitochondria in flight muscle cells of *Calliphora erythrocephala*| Regular fenestrated cristae                      | Smith (1963)                             |
|                        |                                                | ER in photoreceptor cells of vitamin A deficit *Aedes aegypti*     | Masses of membranes                             | Brammer and White (1969)                |
| Hymenoptera            | SER in scale cells of butterfly *Mitoura grynea* | Membrane-cuticle unit                                              |                                                  | Chiradella (1989, 1994)                 |
|                        |                                                | ER in secretory cells of Dufour’s gland in *Parischnogaster mellyi*| Vesicular profiles                              | Delfino *et al.* (1988)                  |
| Blattodea              | Mitochondrion in secretory cells of the spermatheca in *Periplaneta am.* |                                            |                                                  | Gupta and Smith (1969)                  |
| Chordata               | Urochordata                                   |                                                    |                                                  |                                         |
|                        | *Asciacea tethyodea*                         |                                                    |                                                  |                                         |
|                        | *Stolidobranchiata*                          |                                                    |                                                  |                                         |

(continued)
| Description of cells/tissue | Cognomes | $S^a/a$ (nm) | References |
|-----------------------------|----------|-------------|------------|
| Golgi of test cells in the ovary of *Styela* sp. | Honeycomb, lattice-like | | Kessel and Beams (1965) |
| Cephalochordata | | | |
| ER in Joseph’s cells of the *Branchiostoma lanceolatum* | Meandrous tubules | G$^2$/175 | Welsch (1968) |
| Vertebrata | | | |
| Agnatha; Cephalaspidomorphii | | | |
| Petromyzoniformes | | | |
| ER in retinal pigment epithelium cells of *Lampetra fluviatilis* | Undulated membrane complex | G$^4$/155 | Öhman (1974) |
| Osteichthyes | | | |
| Actinopterygii | | | |
| Salmoniformes | | | |
| ER in epithelium of the olfactory organ in *Salmo trutta trutta* | Turtuous interconnected ER | | Bertmar (1972) |
| Plasma membrane in gill epithelia cells of *Salmo salar* | Tubular system | D | Pisam *et al.* (1995) |
| ER in adrenocortical cells of *Salmo fario* | Imbricated cisternae of ER | G$^2$/200 | Jung *et al.* (1981) |
| Siluriformes | | | |
| ER of clear cells in the dendritic organ of *Plotsus anguillaris* | Tubular network | D/100 | van Lennep and Lanzing (1967) |
| Anguilliformes | | | |
| ER in “club cells” of juvenile *Anguilla rostrata* | Array of circular figures | | Leonard and Summers (1976) |
| Class        | Description                                                                 | Location                                                                 | Reference                                      |
|--------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|
| Perciformes  | ER in chloride cell of freshwater-adapted *Scophthalmus maximus*             | Membraneous tubular system                                               | Pisam *et al.* (1990)                         |
|              | Plasma membrane in gill epithelia cells of *Oreochromis niloticus*           | Tubular system                                                           | Pisam *et al.* (1995)                         |
| Dipnoi       | Lepidosireniformes                                                           | Paracrystalline inclusion                                                | Adriaensen *et al.* (1990)                    |
| Crossopterygii| ER of Neuroepithelial cell in the lung of *Protopterus aethiopicus*           | Regular arrays of tubules                                                | Locket (1973)                                 |
| Amphibia     | Anura                                                                       |                                                                          |                                               |
|              | Pipidae                                                                     | Regularly fenestrated cristae                                             | Kalt (1974)                                   |
|              | //Discglossida                                                               | Sinusoidal tubules                                                       | Hourdry (1969)                                |
|              | //Ranidae                                                                    | Crystalloid                                                              | Neuwirth *et al.* (1979)                      |
| Urodel       | Salamandridae                                                                | Annulate lamellae                                                        | Kessel (1990)                                 |
|              | //ER in oocyte of *Necturus maculosus maculos*                               |                                                                          |                                               |
|              | //ER in retinal pigment epithelium cells of *Notophtalamus viridescens*      | Fenestrated lamellae                                                     | Yorke and Dickson (1985)                      |

(continued)
| Description of cells/tissue                                      | Cognomes                  | $S^o/a$ (nm) | References                                |
|-----------------------------------------------------------------|---------------------------|--------------|-------------------------------------------|
| **Bufonidae**                                                   |                           |              |                                           |
| ER of cells in the parotoid gland of *Bufo alvarius*            | Crystalloid               |              | Cannon and Hostetler (1976)               |
| ER in spermatids of *Bufo arenarum*                             | Annulate lamellae         |              | Cavicchia and Moviglia (1982)             |
| **Reptilia**                                                    |                           |              |                                           |
| Lepidosauria                                                   |                           |              |                                           |
| Squamata                                                       |                           |              |                                           |
| ER in spermatids in *Anolis carolinensis*                       | Membranous body           |              | Clark (1967)                              |
| **Aves**                                                        |                           |              |                                           |
| Galliformes                                                    |                           |              |                                           |
| ER in retinal pigment epithelia cells of *Cortunix cortunix japonica* |                   |              | Ahn (1971)                                |
| ER of epithelium in uropygial gland of *Cortunix cortunix japonica* | Crystalloid               |              | Fringes and Gorgas (1993)                 |
| **Mammalia**                                                   |                           |              |                                           |
| Scandentia                                                     |                           |              |                                           |
| Tupaiidae                                                      |                           |              |                                           |
| Mitochondrias in photoreceptor cone cell of *Tupaia glis*       | Concentric whorls of cristae | $G^{10}/500$ | Samorajski et al. (1966)                  |
| SER of cells in the adrenal cortex *T. glis*                    | Crystalloid               | D            | Hostetler et al. (1976)                   |
| Mitochondria in retinal cone cell of *Tupaia belangeri*         | Peculiar whorls of cristae | $G^{12}/400$ | Foelix et al. (1987), Knabe and Kuhn (1996), Knabe et al. (1997) |
| **Chiroptera**                                                  |                           |              |                                           |
| Molossida                                                      |                           |              |                                           |
| ER of cells in sebaceous gland of *Tadarida brasiliensis*       | Crystalloid               | $D^2/105$    | Gutierrez and Aoki (1973)                 |
| Mammalia | Order | Family | Subfamily | Tissue Type | Description | Reference |
|----------|-------|--------|-----------|-------------|-------------|-----------|
| Carnivora | Felidae | | | ER of bright columnar cells in the vomeronasal organ of the cat | Hexagonal crystal-like membrane | Seifert (1971, 1972, 1973) |
| Canidae | | | | ER of follicular cells in adenohypophysis of the dog | (Tweedlike) paracrystal | Nunez and Gershon (1981) |
| | | | | ER in cutaneous histiocytoma cells of the dog | Paracrystal | Marchal et al. (1995) |
| | | | | ER in adventitial cells of the dog | Tubular aggregates | Blinzinger et al. (1972) |
| | | | | ER in mononuclear cells of dog treated with anti-dog-lymphocyte serum | Inclusion body surrounded by limiting membrane | Somogyi et al. (1971) |
| Lagomorpha | Leporidae | | | ER in ovarian steroid cells of the rabbit | | Blanchette (1966a, b) |
| | | | | ER of type II cells in taste buds of male albino rabbit | | Toyoshima and Tandler (1987) |
| | | | | ER in endothelial cells and macrophage of the New Zealand white rabbit infected with herpes simplex virus | Crystalline aggregates | Baringer and Griffith (1970) |
| Ochotonidae | | | | ER in Müller cell of Ochotona sp. | Well-developed networks of ER | Hirosawa (1992) |
| Artiodactyla | Suidae | | | ER in skin cells of pig infected with swine pox virus | Cytoplasmic inclusion | Cheville (1966) |
| Description of cells/tissue                                                                 | Cognomes                   | $S^\circ/a$ (nm) | References                                      |
|------------------------------------------------------------------------------------------|----------------------------|-----------------|------------------------------------------------|
| ER in endothelial cells of cervical cord of the pig infected with virus                    | Crystal arrays             |                 | Koestner et al. (1966)                         |
| Bovidae                                                                                  |                             |                 |                                                |
| ER of cell in preputial gland of female *Capricornus cripus*                               | Grids of SER               | G/80            | Atoji et al. (1989)                            |
| Intranuclear tubules in bovine tissue with papulosa-virus infection                       | Intranuclear tubule-like   |                 | Pospischil and Bachmann (1980)                  |
| Perissodactyla                                                                            |                             |                 |                                                |
| Equidae                                                                                  |                             |                 |                                                |
| ER in sebaceous gland of Equidae                                                          | Grids of SER               | G               | Jenkinson et al. (1985)                        |
| Rodentia                                                                                 |                             |                 |                                                |
| Muridae                                                                                  |                             |                 |                                                |
| ER in rat renal tubule cells                                                               | Fenestrated membranes      |                 | Bergeron and Thierry (1981)                    |
| ER in rat hepatocytes after hexachlorohexahydrophenanthrene in diet                        | Flattened vesicles         |                 | Norback and Allen (1969)                       |
| ER in hepatocytes of carbon tetrachloride fed rats                                        | Labyrinth tubular aggregates|                 | Reynolds and Ree (1971)                        |
| ER in rat hepatocytes after phenobarbital treatment                                        | Meshed network             |                 | Bolender and Weibel (1973)                     |
| ER in hepatomas of the rat                                                                 |                             |                 | Hruban et al. (1972)                           |
| ER in lutein cells of the rat after cycloheximide treatment                                | Crystalline tubular aggregates|               | Horvath et al. (1973)                         |
| ER in adrenal medullary cell of chlophentermine treated rat                                | Crystalloid body           |                 |                                                |
| ER in adrenal cortical cell of chlophentermine treated rat                                 | Dense body                 |                 |                                                |
| ER in meibomian glands of the rat                                                          |                             |                 |                                                |
| Mitochondria in skeletal muscle of the rat                                                |                             |                 |                                                |
| Phenomenon                                                                 | Organ/Tissue                                                                 | Reference                          |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------|
| ER in jejunal absorptive cells of rat intestine                           | Membranous body                                                             | Hatae (1990)                      |
| ER in vomeronasal epithelium in the rat                                   | Crowded elements                                                            | Garrosa and Coca (1991)           |
| ER in cell of sebaceous gland in mouse skin                               | Interconnected segments of SER                                              | Rowden (1968)                     |
| ER of neurons in the mice                                                | Network of tubules                                                           | Johnson et al. (1975)             |
| ER in testicular interstitial cells of mice                               | Tubular profiles                                                            | Christensen and Fawcett (1966)     |
| ER in Leydig cells of mice                                               | Lacy pattered ER                                                            | Russel and Burguet (1977)         |
| ER in mice retinal pigment epithelium after mild thermal exposure        | Crystalline-like body                                                        | Kuwabara (1979)                   |
| ER in hepatocytes of chlophentermine treated mice                        | Peculiar tubular structures                                                 | Lüllmann-Rauch and Reil (1973)    |
| ER in hepatocytes of mice infected with mouse hepatitis virus             | Convoluted membranous mass                                                  | Ruebner et al. (1967)             |
| ER in mice brain cells inoculated with St. Louis encephalitis virus      | Anastomosing membrane tubules                                               | Murphy et al. (1968)              |
| ER in neuron of suckling mouse infected with Semliki Forest virus         | Sinusoidal ER                                                               | Grimley and Demsey (1980, p. 151) |
| Cricetidae                                                               |                                                                              |                                   |
| ER in UT-1 cells with HMG-CoA reductase expression                       | Tubular membrane                                                            | Pathak et al. (1986)              |
| ER of CHO cells with rubella virus E1 glycoprotein expression            | Membrane complex                                                            | Hobman et al. (1992)              |
| ER in hepatocytes of the hamster after phenobarbitone treatment          | Grid of SER                                                                 | Ghadially (1988, p. 512)          |
| ER in sebaceous gland of the hamster                                     |                                                                             | Bell (1974a)                      |
| Description of cells/tissue | Cognomes                          | $S^*/a$ (nm) | References                  |
|-----------------------------|-----------------------------------|-------------|-----------------------------|
| ER in sebaceous gland of androgen treated hamster | Grids of SER | | Bell (1974b) |
| ER in smooth muscle cell of triparanol treated male hamster | Dense bodies | | Chen and Yates (1967) |
| Mitochondria in serous secretory cells of *Meriones unguiculates* | | P²/175 | Spicer *et al.* (1990) |
| Subdermal tumour in the hamster produced by inoculation of: M-1 Caviidae | Undulating tubules, UMS | | Chandra (1968) |
| ER in adrenal cortical cells of fetal guinea pig, *Cavia* sp. | | | Black (1972) |
| ER in receptor cells in the vomeronasal organ of newborn *Cavia* sp. | | | Mendoza and Kühnel (1989) |
| Primates | | | |
| Strepsirhini (Prosimii) | | | |
| ER in sebaceous gland of *Galago senegalensis* | Tubules of SER | G, P | Bell (1974a) |
| ER of interstitial cells in the antebrachial organ of *Lemur catta* | Crystalloid | G/70 | Sission and Fahrenbach (1967) |
| Haplorhini | | | |
| Tarsiiformes | | | |
| ER in sebaceous gland of *Tarsier syrichta* | Grids of SER | D² | Bell (1974a) |
| Simiiiformes | | | |
| Cercoptiteidae: ER in CV-1 cells infected with simian virus 40 | Tubular membranes network | | Kartenbeck *et al.* (1989) |
| ER in COS cells upon overexpression of msALDH | Crystalloid | | Yamamoto *et al.* (1996) |
| ER in COS-7 and CV-1 cells upon overexpression of cytochrome b(5) | Organized SER | G², D² | Snapp *et al.* (2003) |
| Tissue/Condition                                                                 | Structure Type            | Organism(s)   | Reference(s)                      |
|---------------------------------------------------------------------------------|--------------------------|---------------|----------------------------------|
| ER in Vero cells infected with SARS coronavirus                                 | Tubuloreticular structures | G             | Goldsmith et al. (2004)           |
| ER in sinusoidal endothelial cell in liver of Macaca fascicularis                | Crystalloids              |                | Tanuma (1983)                    |
| **Mulatta:** ER in sebaceous gland of *Macaca mulatta*                           | Tubules of SER           |                | Bell (1974a,b)                   |
| ER in retinal epithelium cells of *Macaca mulatta*                               | Peculiar body             |                | Ishikawa (1963)                 |
| ER in endothelial cells of the glomerular capillaries in *M. Mulatta*            | Round of hexagonal bodies |                | de Martino et al. (1969)         |
| ER in endothelial cells in liver of *M. mulatta*                                 | Cytoplasmic crystalloid   |                | Ruebner et al. (1969)            |
| **Ibidem** with nutritional cirrhosis                                            | Cytoplasmic crystalloid   |                | Ruebner et al. (1969)            |
| ER in epidermal pox disease of *M. mulatta*                                     | Crystalline inclusion     |                | Casey et al. (1967)              |
| ER in spinal/endothelia cells of *M. mulatta* after tumor induced by sarcoma virus| Honeycombed crystals      |                | Munroe et al. (1964)             |
| ER in kidney cells of *M. mulatta* infected with Tana poxvirus                   | Tubuloreticular structures|                | España et al. (1971)             |
| ER in macrophages, neutrophilic granulocytes and plasma cells of *M. mulatta* infected with SIV | Paracrystalline arrays |                | Kaup et al. (2005)               |
| ER in monkey kidney CMK cells infected with poliovirus                           | Smooth membrane vesicles  |                | Hashimoto et al. (1984)          |
| ER in endothelial cells of monkey spinal cord infected with poliovirus           | Paracrystalline arrays    |                | Blinzinger et al. (1969)         |
| ER in MA 104 cells infected with Simian rotavirus SA11                            | Crystal lattice-like structure |                | Quan and Doane (1983)            |
| ER in LLC-MK₂ infected with rubella virus                                         | Crystal lattice-like structure |                | Kim and Boatman (1967)           |

(continued)
| Description of cells/tissue | Cognomes | $S^\circ/a$ (nm) | References |
|-----------------------------|----------|----------------|------------|
| *Ceboidea*: ER in rous sarcoma virus induced tumour cells of *Saquinus* sp. | Membrane inclusion | P²/175-220 | Smith and Deinhardt (1968) |
| *Hominoiddea*: ER in hepatocytes of δ-agent inoculated *Pan trodeglas* | UMS | | Canese *et al.* (1984) |
| ER in hepatocytes of *P. trodeglas* post experimental hepatitis | | | Pfeifer *et al.* (1980) |
| ER in endothelial cells of human and chimpanzee liver infected with hepatitis virus | Tubuloreticular and paracrystalline inclusion | | Schaff *et al.* (1992) |
| *Man*: ER in villus absorptive cells in fetal small intestine of man | Convoluted membrane | | Moxey and Trier (1979) |
| ER in cells of adrenal gland in man | | | McNutt and Jones (1970) |
| ER in HEp-2 cells infected with Ilheus virus | Knotted membranes | | Tandler *et al.* (1973) |
| ER in human cancer cell lines: F-3, -9, -24, -53, No. 2117 | UMS | | Chandra (1968) |
| ER in HeLa cells | Cotte de maillet | | Franke and Scheer (1971) |
| ER in HT-29 cells infected with rotavirus | Tubuloreticular structures | | Tinari *et al.* (1996) |
| ER in cells from lymph-node culture of a patient with reticulum-cell sarcoma | Membrane inclusion with crystalline pattern | | Moore and Chandra (1968) |
| ER in B lymphocyte of a 6-month-old male infant | Tubular arrays | | Geha *et al.* (1974) |
| ER in endothelial KS cells | Paracrystalline inclusions | | Marquart (2005) |
| ER in P3-J cells | UMS | | Chandra and Stefani (1976) |
| ER in human lymphocytes | Microtrabecular lattice | | Guatelli *et al.* (1982) |
| Mitochondria in adenoma of submandibular gland of man | Reticulate cristae | | Tandler and Erlandson (1983) |
| Event                                                                 | Structure          | Reference                        |
|----------------------------------------------------------------------|--------------------|----------------------------------|
| Mitochondria in metastatic melanoma in man                            |                    | Ghadially (1988, p. 212)         |
| Lysosomes in human myxoid chondrosarcoma                              | Vesicular structure| Cameron et al. (1992)            |
| ER in human embryonic kidney cells infected with HRV                  | Micro- TRS         | Ghadially (1988, p. 496)         |
| ER in epithelial lung carcinoma of man                                | TRS                | Schaff et al. (1976)             |
| Inner nuclear membrane in parosteal sarcoma of man                    | UMS                | Murray et al. (1983)             |
| ER in bronchiogenic carcinomas                                         |                    | Ghadially (1988, p. 96)          |
| ER of endothelial cells on glomerular capillaries of nephritic man     | Crystalline bodies | de Martino et al. (1969)         |
| ER of endothelial cells in a hepatoblastoma of man                     |                    | Gonzales-Crussim and Manz (1972) |
| ER in soft tissue sarcoma of man                                       | TRS                | Szakacs et al. (1991)            |

*S*/\(a\) Indicates that the membrane (surface) morphology (\(S\)) is consistent with (\(n\)) membranes or multiple (\(m\)) membranes with a lattice size of (\(a\)).

The listed unit cell size is based on either DTC analysis or direct measurements of the 2D lattice parameters. UMS: undulating membrane structure; TRS: tubuloreticular structure; PER: paracrystalline ER; SER: smooth endoplasmic reticulum.

The table summarizes the observation of cubic membranes in normal, pathological, and experimentally manipulated cells.
indicator of infection or transformation. For example, TRS have been observed in cells infected with SARS (Almsherqi et al., 2005) and HIV (Kostianovsky et al., 1987).

In addition to TRS, annulate lamellae (AL) are another type of convoluted 3D membrane structure, and their appearance is also often correlated with that of cubic membranes. AL are frequently observed in differentiating gamates, namely in vertebrate oocytes and in spermatogonia, and appear to occur in close association with the cell nucleus (see Table 6.1). Tangential TEM sections of AL most often exhibit a hexagonal arrangement (Kessel, 1983), whereas perpendicular sections do not reveal any obvious symmetrical arrangement, even though they always exhibit an astonishingly regular organization, indicating an underlying periodic structure. Based on the apparent morphological similarities between AL and the NE, it has been suggested that AL represent a cytoplasmic NE extension that functions as a reservoir for both ER membrane components and nuclear pores (Kessel, 1983, 1992). In favor of such speculations is the fact that AL have been observed in direct continuity with the outer nuclear membrane, and that they also have been suggested to contain nuclear pore complexes (Landh, 1996). AL are assembled of superimposed pairs of membrane bilayers, which join along the pores whose distribution may vary (hexagonal, quadratic, or random). The pores present in AL are either facing each other if the membrane symmetry is hexagonal (Fig. 6.4B) or the appearance of pores alternates in a quadratic membrane arrangement (Fig. 6.4A).

2.2. Membrane polymorphisms

The coexistence of different subtypes of cubic membranes or together with other membrane organizations within the same cell organelle is quite frequent, pointing to structural or functional relationships between these membrane arrangements (Fig. 6.4E). Probably the most evident example is the ER where different membrane morphologies such as cubic membranes, lamellar and hexagonal membranes, and whorls coexist quite commonly (Landh, 1996; Snapp et al., 2003). Coexistence of at least two cubic membrane subtypes within the same organelle has also been observed in mitochondria of amoeba *Chaos carolinense* (Deng and Mieczkowski, 1998). In this organism, the relative abundance of gyroid (G) or diamond (D) and primitive (P) subtypes of cubic morphology changes during starvation, the biological significance of this polymorphic behavior, however, is currently unknown.

The ease with which cubic membranes and other membrane arrangements are interconverted can be attributed, at least in part, to the effect of weakly dimerizing ER proteins (Snapp et al., 2003). Previous work suggested that crystalloid ER biogenesis entailed a tight, zipper-like dimerization of the cytoplasmic domains of certain ER-resident proteins.
(Yamamoto et al., 1996). However, Snapp et al. (2003) found that organized smooth ER (OSER)-inducing proteins can trigger cubic membrane formation upon over-expression through low-affinity interactions between cytoplasmic domains. This observation might explain phenomena such as (a) the heterogeneity of ER membrane structures, (b) the high rate of (reversible) lamellar to cubic membrane transition, and (c) the technical difficulties and limitations in isolating intact cubic membranes from biological samples.

2.3. Cubic membranes versus cubic phases

Lipidic bicontinuous cubic phases consist of hyperbolically curved bi-layers where each monolayer is draped over a periodic cubic (minimal) surface (Fig. 6.2D). With respect to bilayer arrangements, the geometries of cubic membranes are similar to those of the cubic phases, however, two major differences exist: (i) the unit cell size and (ii) the water activity. It has been argued that the latter must control the topology of the cubic membrane (Bouligand, 1990) and hence that the cubic membrane structures must be of the inverted type rather than "normal" type (type I). All known lipid–water and lipid–protein–water systems that exhibit phases in equilibrium with excess water are of the inverted type (type II). Thus, water activity alone cannot determine the topology of cubic membranes. Inverted cubic phases have been observed with very high water activity (70–90%), in the mixtures of lipids, in lipid–protein systems, in lipid–polymer systems (Landh, 1994), and in lipid and lipopolysaccharide mixtures (Brandenburg, 1990, 1992).

Most cubic phases in lipid–water systems exhibit unit cell parameters not larger than 20 nm, while in cellular cubic membranes the lattice size is usually larger than 50 nm. However, in lipid–protein–water, lipid–poloxamer–water and lipid–cationic surfactant–water systems, cubic phases with cell parameters of the order of 50 nm have also been observed (Landh, 1996). On the other hand, the unit cell size of cubic membranes is rarely less than 50 nm (e.g., in prolamellar bodies) and the size ranges from 50 to 500 nm. Cubic membranes with large lattice size (500 nm) were frequently observed in chloroplast membranes of green algae Zygnema (Fig. 6.6).

Additionally, cubic membranes are formed under conditions corresponding to a highly regulated multiphase "equilibrium" process. This is supported by the fact that they are usually formed in close contact with different other membrane configurations. The asymmetry of biological membranes with respect to the two leaflets is likely to affect cubic membrane formation, in particular as a consequence of lipid and protein composition, and interaction with the surrounding ion milieu.
Understanding membrane morphology by transmission electron microscopy

A survey of the literature (Table 6.1) immediately unveils a multitude of “unusual” membrane organizations in various cell types. Most of these depictions were obtained by TEM of chemically fixed and thin-sectioned cells and tissues. Dependent on the thickness and orientation of the section through the specimen, relative to the coordinates of an ordered 3D structure, various types of projection patterns are observed. As a consequence, membrane ultrastructures derived from TEM images are frequently misinterpreted, in particular for the highly folded and interconnected 3D morphologies resembling cubic membranes. TEM relies on 70–90 nm thick sections through the specimens and the 2D image obtained is the result of a projection of a 3D structure. Therefore, nonlamellar biological membranes, such as inverted hexagonal or cubic structures, may yield very heterogeneous projection patterns by TEM, dependent on the orientation of the section relative to the structural axes (Fig. 6.3). Interpretation of TEM membrane patterns is further complicated if the lattice size of the observed structure is considerably smaller than that of the section thickness.

2.4. Understanding membrane morphology by transmission electron microscopy

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Serial sections or scanning EM, as well as tilting and rotation of the sample, may facilitate structure interpretation. Furthermore, TEM of multiple randomly cut sections through a specimen provides a rather simple means to reconstruct its 3D structure. More elaborate electron tomography (ET) has contributed a great deal of resolution to understanding cubic membrane organizations and their continuity with and relations to the neighbor structures (Deng et al., 1999). In ET, rather thick sections (400 nm) are imaged in multiple tilted angles (up to ±60°), yielding a large number of projections; these images are reconstructed by computational image analysis into a 3D representation of the object, which allows the 3D reconstruction of cellular structures with a resolution of 5 nm, that is, approaching the level or larger molecular assemblies (for a review see Lucic et al., 2005). EM tomography has previously been successfully applied to determine cubic membrane transition of the inner mitochondrial membrane morphology in the amoeba C. carolinense upon starvation (Deng et al., 1999). Cryo-ET from specimens in vitreous ice further improves sample preservation and membrane resolution, but obviously is not yet routinely established. Cryo-ET avoids common artifacts of conventional EM preparation techniques and is also suited for high-resolution analyses of membrane-bound organelles (Hsieh et al., 2006; Lucic et al., 2005).

Most EM experiments described in the literature that focus on biological membranes were obviously not designed to depict three-dimensionally convoluted membrane arrangements. Therefore, alternative methods have to be applied to reconstruct—potential—3D membrane morphologies from single TEM sections. Indeed, based on well-defined mathematical models of cubic membrane arrangements, projections can be calculated that simulate various section orientations and thicknesses (Fig. 6.3). Such a “direct template correlative” (DTC) matching method (Almsherqi et al., 2005, 2006; Deng and Mieczkowski, 1998; Landh, 1995, 1996) has been developed based on pattern and symmetry recognition. Through the DTC method, the electron density of the TEM image is correlated to a library of computer-simulated 2D projection maps that allows to unequivocally deduce the nature of the cubic membrane arrangement. An application of the DTC method to identify cubic membrane organization in TEM micrographs is shown in Fig. 6.7. In brief, the 2D projections (Fig. 6.7C) calculated from a mathematical 3D model (Fig. 6.7B) are matched with a selected TEM micrograph (Fig. 6.7A); consequently, a successful pattern match defines the nature of the membrane arrangement in 3D (Deng and Mieczkowski, 1998; Landh, 1995, 1996). The DTC method simplifies the experimental requirements for recording cubic membranes in biological samples, and can also be applied to examine published TEM micrographs in retrospect. The following section highlights the identification of cubic membrane structures in multiple cellular systems and subcellular organelles.
3. Cubic Membranes in Nature

3.1. Cubic membranes: From protozoa to mammals

Extensive membrane proliferations leading to unusual and highly convoluted depictions in TEM micrographs have been observed in numerous cell types from all kingdoms of life and in virtually any membrane-bound subcellular organelles, as outlined above. Table 6.1 summarizes a survey of the literature of the past six decades on cubic membrane morphologies identified in organelles, from protozoan to human cells. The occurrence of cubic membranes is listed by genera and, if applicable, the type and lattice size of the cubic membrane extracted from the published...
TEM images are presented (see also Hyde et al., 1996; Landh, 1996). Not surprisingly, due to the absence of a clear understanding of the 3D structure of the depicted membranes, many of the examples have been considered as novelties with little or no reflection on the wealth of related contributions in the literature. Hence, these morphologies appear under a large variety of nicknames, some of which are also listed in Table 6.1. Furthermore, the examples have been chosen to best represent the structural characteristics of cubic membranes, and an effort has been made to leave out those perhaps less recognizable structures such as “membraneous tubular”, “cisternal systems”, “tubular inclusions”, or “cisternal convolutions” etc. In many cases where we have chosen not to classify the cubic membrane it is mainly due to the lack of discernible details in the TEM micrographs. Interestingly, many of these undetermined cubic membrane morphologies are reported in pathological conditions in hominoidae.

3.2. Organelles with cubic membrane structure

3.2.1. Endoplasmic reticulum

The ER was found to be the most prominent target of morphological alterations because of its highly convoluted and dynamic structure and crucial functions in membrane lipid synthesis and assembly, protein synthesis and secretion, ion homeostasis, and membrane quality control. These morphologies appear under numerous nicknames in the literature, such as “undulating membranes” (Schaff et al., 1976), “cotte de mailles” (Franke and Scheer, 1971), “membrane lattice” (Linder and Staehelin, 1980), “crystalloid membranes” (Yamamoto et al., 1996), “paracrystalline ER” (Wolf and Motzko, 1995), “tubuloreticular structures (TRS)” (Grimley and Schaff, 1976), and recently, as OSER (Snapp et al., 2003).

Periodic symmetrical transitions of the ER are usually correlated with overexpression of certain ER-resident membrane proteins (Table 6.2) (see below). For example, overexpression of HMG-CoA reductase isozymes induces assembly of nuclear and cortical ER stacks with 2D symmetry, termed “karmellae” in yeast (Profant et al., 2000; Wright et al., 1988). Overexpression of this enzyme in UT-1 (Chin et al., 1982) or Chinese Hamster Ovary (CHO) cells (Jingami et al., 1987; Roitelman et al., 1992) induces formation of crystalloid ER, which houses most of the HMG-CoA reductase enzyme (Anderson et al., 1983; Orci et al., 1984). This correlation may imply a specific structure–function relationship of cubic membrane formation as a consequence of an altered protein or lipid inventory of the membrane.

The cells of the phloem in plants are involved in the long-distance transport of nutrients and are known as sieve elements. Interestingly, the ER of differentiating sieve elements is a rare example in Nature in which
Table 6.2  Occurrence of crystalloid ER membranes in cell lines overexpressing certain ER-resident membrane proteins

| Description of cells/tissue | Overexpressed proteins | Cognomes | Membrane organization | References |
|-----------------------------|-------------------------|----------|-----------------------|------------|
| UT-1 cells (Compactin resistant CHO cells) | HMG-CoA reductase | Crystalloid ER | Hexagonal, cubic ($G^2$) | Chin et al. (1982); Anderson et al. (1983); Pathak et al. (1986); Kochevar and Anderson (1987); Orci et al. (1984) |
| CHO cells | HMG-CoA reductase | Crystalloid ER | Hexagonal | Jingami et al. (1987) |
| Yeast | HMG-CoA reductase | Karmellae | Multilayer lamellar | Wright et al. (1988) |
| Yeast | Cytochrome b(5) | Karmellae | Multilayer lamellar | Vergères et al. (1993) |
| CV-1, COS-7 | Cytochrome b(5) | Organized SER | Multilayer lamellar (whorls), cubic ($D^2, G^2$) | Snapp et al. (2003) |
| COS-1 cells | msALDH | Crystalloid ER | Cubic ($G$) | Yamamoto et al. (1996) |
| COS cells | InsP$^3$ receptor | Cisternal stacks | Multilayer lamellar, whorls | Takei et al. (1994) |
| CHO cells | Unassembled rubella virus E1 glycoprotein subunits | Tubular network | Retiform | Hobman et al. (1992) |
| HEK293 cells/human Escherichia coli | Cytochrome P450 2B1 Subunit (b) of F1F0 ATP synthase | Crystalloid ER Intracellular membrane | Hexagonal | Sandig et al. (1999); Arechaga et al. (2000); Gales et al. (2002); Weiner et al. (1984) |
| E. coli | Fumarate reductase | Tubule | Hexagonal | |
two cubic membranes with the same structure but with different unit cell parameters, may coexist in the same cell (Behnke, 1965, 1968; Landh, 1996). These cells lack a nucleus and the cytoplasmic connection and exchange between vertically stacked cells is enabled through the perforated walls of the sieve elements (Behnke, 1965). Their function is to transfer the products of photosynthesis from the manufacturing site (leaves) to the storage cells (stem, roots, and seeds). The different types of cubic membranes may perhaps facilitate transport of various materials at different rates within the same cell.

3.2.2. Inner mitochondrial membranes
Numerous researchers have reported mitochondria with inner membrane configurations that resemble cubic membrane morphologies (Brandt and Pappas, 1959; Kalt, 1974; Tahmisian et al., 1956). Possibly the best-characterized cubic membrane transition was observed in the mitochondrial inner membranes of the free-living giant amoeba, *C. carolinense* (Deng and Mieczkowski, 1998). In this organism, mitochondrial inner membranes undergo dramatic changes in 3D organization upon food depletion, providing an attractive, reversible model system to investigate induced membrane reorganization. Within one day of starvation, 70% of mitochondria undergo this morphological transition, which is observed in virtually all mitochondria after 7 days of starvation (Daniels and Breyer, 1968). This structural alteration of mitochondria in *C. carolinense* has been identified by a number of laboratories; however, in several reports the inner mitochondrial membranes take the appearance of tubular-like configurations that may appear in conjunction with well defined cubic membranes (Borysko and Roslansky, 1959; Brandt and Pappas, 1959; Daniels and Breyer, 1968; Sedar and Rudzinska, 1956). Indeed, by EM tomography, we have unambiguously demonstrated that inner mitochondrial membranes in *C. carolinense* cells adopt cubic morphology under starvation conditions (Deng et al., 1999). This induced transition is accompanied by alterations in cellular oxidative stress response, which led us to speculate that cubic membrane formation may be associated with oxidative stress (Deng et al., 2002) (see also discussion below). Intriguingly, formation of cubic membranes in amoeba *Chaos* is fully reversible to wild-type tubular morphology, upon refeeding (Deng and Mieczkowski, 1998).

A similar cubic architecture of inner mitochondrial membranes was identified in a TEM ultrastructural study (Kalt, 1974) that describes mitochondrial pleomorphism in supporting (sustentacular) cells in testis of African clawed frog, *Xenopus laevis*. The mitochondrial membrane constellation in the mature stage of Sertoli sustentacular cells exhibits the D subtype of cubic membrane morphology.

The mitochondria in the inner segment of the retinal cones of tree shrew species, *Scandentia*, the common tree shrew (*Tupaia glis*), and the northern
tree shrew (*Tupaia belangeri*) (Foelix *et al.*, 1987; Knabe and Kuhn, 1996; Knabe *et al.*, 1997) are unique in size and ultrastructural arrangement of their inner membranes (Samorajski *et al.*, 1966). These unusually large, patterned mitochondria exhibit one of the most complicated cubic membrane architectures known to date, with the highest possible symmetry (G subtype) of up to 12 layers of three-dimensionally folded membranes (see discussion below) (Fig. 6.7).

### 3.2.3. Plasma membrane

Convoluted invaginations of the plasma membrane that are associated with the “smooth spongiome,” which is part of the contractile vacuole complex in *Paramecium multimicronucleatum*, have been proposed to be of the G subtype of cubic membrane organization (Allen, 2000; Landh, 1996; Patterson, 1980). *Paramecium* cells are able to maintain an almost constant intracellular osmolarity regardless of the environmental osmolarity. The complex regulation of the cell volume and osmotic gradient is primarily established by the smooth spongiome, which exhibits cubic membrane organization. Therefore, cubic membranes have been suggested to play roles in water segregation and intracellular volume and osmolarity control (Landh, 1996).

“Honeycomb” structures of the T-tubular system in skeletal muscles have been observed in numerous diseased as well as in experimentally induced cases. Such structures were shown to be in continuity with the extra-cellular space and can thus be regarded as extensions of plasma membrane invaginations. The significance of honeycomb t-tubules is, however, unknown (Mastaglia and Walton, 1992), and surprisingly few studies deal with their 3D organization. Despite the elegant study of Ishikawa (1968), the 3D structure of these “honeycombs” was resolved only 30 years after their first discovery (Landh, 1996) and unambiguously demonstrated to be of cubic membrane morphology of the gyroid (G) subtype.

### 3.2.4. Photosynthesis-associated cubic membranes

The structure of photosynthetic membranes and their assembly during development have been extensively studied (Gunning, 1965; Gunning and Jagoe, 1967; Gunning and Steer, 1975). In bacteria, several publications report lattice-like membrane morphologies as a variation of the more common multilamellar (thylakoid) configuration. In vegetative, photosynthetically active cyanobacteria, *Anabaena sp.*, Lang and Rae (1967) reported a “prolamellar-like lattice”, which was formed through continuous foldings of the photosynthetic thylakoid membranes. This cubic membrane bears a close resemblance to the prolamellar body (PLB) in higher plants, with the important difference that PLB are formed in the absence of light, whereas
Cubic membranes in *Anabaena sp.* were observed in fully illuminated cultures. The analysis of micrographs (Lang, 1965) of developing heterocysts (cells involved in nitrogen fixation) of *Anabaena azollae* clearly revealed several TEM projections of more or less developed cubic membranes (Landh, 1996). Although heterocysts lack the photosynthetic apparatus, these cubic membranes appear to arise by continuous folding of the thylakoid membranes.

### 3.2.4.1. Chloroplasts of green algae *Zygnema*

In certain green algae species the chloroplast membrane(s) tend to form more complex morphologies than the simple “lamellar-like” structures. Chloroplasts of the green alga *Zygnema* transform to G-type cubic membrane (Fig. 6.6) during the log phase of cell culture (Deng and Landh, 1995). An analysis of previously reported electron micrographs by McLean and Pessoney (1970), which described “lamellar lattices” in *Zygnema* chloroplasts, indeed revealed a primitive (P) subtype of cubic membrane (Landh, 1996). This particular structure represents a continuous cubic membrane organization that is composed of several, mostly parallel, lipid bilayers (Deng, 1998).

### 3.2.4.2. Prolamellar body

The fine structure of the PLB has been extensively studied by electron microscopy (Gunning, 1965; Gunning and Jagoe, 1967; Gunning and Steer, 1975; Israelachvili and Wolfe, 1980; Menke, 1962, 1963; Murakami et al., 1985; Osumi et al., 1984; Wehrmeyer, 1965a, b,c). Three basic space-lattice structures of the PLB have been proposed: (i) a primitive cubic lattice in which the fundamental unit is a hexapode (Granick, 1961; Gunning, 1965; Gunning and Jagoe, 1967), (ii) a diamond-based face-centered cubic lattice in which the fundamental unit is a tetrapode (Gunning and Steer, 1975; Murakami et al., 1985; Osumi et al., 1984; Wehrmeyer, 1965b), and (iii) a hexagonal Wurtzite-type of lattice (Ikeda, 1968; Wehrmeyer, 1965c; Weier and Brown, 1970). The double diamond-type cubic lattice is presumably the most common cubic structure of the PLB (Landh, 1996).

### 3.2.5. Inner nuclear membrane

The formation of cubic membranes in the NE is not confined to the cytoplasmic side (i.e., the nuclear ER), but may also occur at intranuclear sites. This may appear surprising, however, formation of cubic membranes within nuclei could be realized by invaginations of a proliferating inner nuclear membrane. Intranuclear cubic or tubular membrane organizations usually develop in fast replicating neoplastic (tumor) cells (Babai et al., 1969; Karasaki, 1970) or non-neoplastic cells such as oocytes (Kessel and Beams, 1968; Miller, 1966). Their presence might play a role in mitotic activity or in facilitating nuclear-cytoplasmic communication. In human cells, intranuclear tubular (hexagonal or cubic) membrane organization was demonstrated in the endometrium during the secretory phase of the menstrual
cycle (Bourgeois and Hubert, 1988; Ghadially, 1988). Progesterone and medroxyprogesterone can induce tubular structure formation in human endometrium (Kohorn et al., 1972), which suggests a role of an extrinsic hormonal factor in cell membrane organization.

4. Biogenesis of Cubic Membranes

An extensive review of the literature reveals that virtually all membranes are capable of forming cubic structures. Their origin thus seems to be strongly coupled to the mechanisms of membrane biogenesis in general and, therefore, cubic membranes are to be considered as a defined configuration of cytomembranes. The formation and growth of cubic membranes may be a selective process to fulfill a specialized purpose under ever changing intracellular conditions. Thus, understanding the underlying rules(s) for the physiological selection between the different membrane morphologies is key. It is now well established that proteins may induce phase transition in lipid membranes resulting in new structures not observed in pure lipid–water systems (Bouligand, 1990). However, in principle, any amphiphilic molecule may be able to induce cubic membrane structures. Depending on the structure and nature of the proteins, their interactions with lipid bilayers can be manifested in very different ways. On the other hand, evidence from in vitro studies clearly differentiates membrane-forming lipids for their propensity to form nonlamellar structures, according to the molecular shape concept. The important structural role of membrane lipids in promoting cubic membrane formation in vivo is undisputed; however, only very recent evidence obtained from amoeba Chaos cells has correlated specific alterations of membrane lipids to cubic membrane formation in vivo (Deng et al., submitted). Although lipids extracted from these cells may assemble to cubic phases also in vitro (Fig. 6.8), marked differences in lattice size clearly indicate that additional factors—presumably proteins—exist in vivo that determine the overall 3D appearance of these structures. Induction of cubic membranes in Chaos cells upon starvation represents one rare example to experimentally address the molecular mechanisms leading to their formation in the biological context.

From a topological point of view, cubic membranes appear to be formed from a structural “template” (the precursor of a cubic membrane), such as invaginations of a membrane. After initiation, further accumulation of membrane lipids may lead to intersection-free highly convoluted invaginations. During the folding process, the membrane must remain a continuous fluid structure that grows and interconnects without losing its polarity and integrity. Thus, the topology of the cubic membrane depends on the topology of its precursor structure. If one isolated invagination process
triggers the membrane folding process, the topology will be that of a sphere, as is the case for vesicle formation during endocytosis or secretion. If more than one invagination takes place, it requires points of fusion to achieve a three-dimensionally interconnected membrane. Perhaps it is this symmetry that is the driving force for fusion; if fusion did not occur one would expect several independent cubic membrane systems to form, which would not necessarily bear any spatio-temporal correlation between each other or the periodicity of the template.

4.1. Role of membrane-resident proteins in cubic membrane formation

Cubic membrane formation is frequently associated with the overexpression of certain ER-resident proteins and, to a lesser extent, with overexpression of some inner mitochondrial membrane proteins. Table 6.2 lists major membrane proteins that have been shown to induce cubic membrane formation upon experimental dys-regulation.

4.1.1. ER proteins

HMG-CoA reductase is an ER-resident protein that is anchored to the membrane by seven membrane-spanning domains in its N-terminal part and has its catalytic domain extending to the cytoplasmic side. Elevated expression of HMG-CoA reductase is often associated with structural membrane alterations. The transmembrane region is indeed required to form crystalloid membrane structures of hexagonal (Fig. 6.5D) or cubic
(Fig. 6.5C) morphologies, upon overexpression. Deletion of two of the seven membrane spanning regions or a truncated protein did not result in crystalloid ER formation, and the protein localized to disordered sheets rather than packed membrane tubules under these conditions. High expression levels of the soluble fragment of HMG-CoA reductase did not induce any crystalloid ER, again indicating that it is the transmembrane domain of HMG-CoA reductase that plays an important role in determining the structure of crystalloid ER (Jingami et al., 1987; Yamamoto et al., 1996).

Crystalloid ER is frequently observed in CHO cells upon overexpression of the HMG-CoA reductase gene, or in UT-1 cells, which are a mutant variant of CHO cells that overexpress this gene by 500 fold (Fig. 6.5; Chin et al., 1982). Notably, despite the presence of elevated levels of HMG-CoA reductase, which is the key enzyme of sterol biosynthesis, the membrane of the crystalloid ER appears to have very little cholesterol. Upon addition of cholesterol to UT-1 cells, which intercalates into the ER membrane, HMG-CoA reductase was subsequently degraded and the crystalloid ER disappeared (Jingami et al., 1987); sterol supplementation drastically reduced the rate of HMG-CoA reductase synthesis and also prevented the formation of new crystalloid ER. It was therefore speculated that the cubic membrane is an alteration in the feedback control of cholesterol synthesis, for the production of sterols and the biogenesis of smooth ER. Interestingly, administration of compactin, which is an HMG-CoA reductase inhibitor, also leads to HMG-CoA reductase overexpression, and induces the formation of stacked and aggregated structures, which were termed “karmellae” in yeast (Wright et al., 1988).

The expression of msALDH in COS-1 cells also leads to alterations of the ER structure. Both HMG-CoA reductase and msALDH proteins possess large domains exposed on the cytoplasmic surface of the ER membrane, similar to the ER-resident protein, cytochrome P450. This led to the hypothesis that the formation of crystalloid membranes may require the expression of ER-resident proteins with large cytoplasmic domains (Sandig et al., 1999; Snapp et al., 2003; Yamamoto et al., 1996).

Overexpression of specific ER-resident proteins such as cytochrome b (5) in COS-7 cells also triggers the formation of “whorls and crystalloid OSER structures” (Snapp et al., 2003). It was proposed that the biogenesis of OSER structures involves weak homotypic interactions between cytoplasmic domains of proteins and may underlie the formation of other stacked membrane structures within the cells as well. Time-lapse imaging of OSER biogenesis revealed that these structures formed rather quickly once a threshold level of OSER-inducing proteins was exceeded; OSER-formation also involved gross remodeling of surrounding tubular ER.
In this system, the attachment to the cytoplasmic domain of different ER-resident membrane proteins of green fluorescent protein (GFP) that is capable of low affinity, head-to-tail dimerization was sufficient to induce OSER formation upon overexpression in living cells. Homotypic low affinity interactions between cytoplasmic domains of proteins thus can differentiate tubular ER into stacked lamellae or crystalloid structures; such a mechanism may underlie the reorganization of other organelles into stacked structures as well (Snapp et al., 2003), and provides an intriguing model system to investigate the cellular and molecular requirements for cubic membrane formation.

4.1.2. Mitochondrial proteins

Only a few mitochondrial proteins have been reported to induce and maintain tubular inner membrane morphology upon overexpression (Mannella, 2006), however, none of them was correlated with well-defined cubic membrane formation. Mitofillin, F1F0-ATPsynthase, and fission-fusion proteins may induce tubular or stacked lamellar and whorl-type membrane structures upon experimental overexpression. F1F0-ATPsynthase is an essential enzymatic complex of the mitochondrial inner membrane, which couples the proton electrochemical gradient generated by the respiratory chain to ATP synthesis. Various studies have shown that this complex is strongly implicated in the curvature of the inner mitochondrial membrane (reviewed by Voeltz and Prinz, 2007). Dimerization of the complex drives tubulation of the cristae (Dudkina et al., 2005; Strauss et al., 2008), while further oligomerization of these dimers is responsible for the formation and/or stabilization of inner membrane tubules. Mitofillin is a mitochondrial inner membrane protein, which assembles into a large multimeric protein complex. siRNA knockdown of mitofillin in HeLa cells yielded mitochondria with disorganized mitochondrial inner membranes: they failed to form tubular or vesicular cristae and appeared as intermittently fused, closely packed stacks of membrane sheets, resulting in a complex maze of membraneous networks (John et al., 2005). Mitofillin thus appears to be a key organizer of mitochondrial cristae morphology (John et al., 2005). The role of mitochondrial proteins in cubic membrane formation in starved amoeba Chaos, which is a suitable model for analyzing reversible cubic membrane formation, is currently under investigation in the authors’ laboratories.

4.1.3. Morphogenic proteins

Recently a class of membrane proteins known as morphogenic proteins was identified to shape the tubular ER in yeast and mammalian cells. These proteins are highly enriched in the tubular portions of the ER and virtually excluded from other regions. The study by Voeltz and coworkers (2006)
illustrated the role of Rtn4a/NogoA, a member of the ubiquitous reticulon protein family that share a conserved C-terminal reticulon domain. Over-expression of Rtn4a/NogoA in mammalian cells, promoted the formation of ER tubules; membrane tubule formation in vitro, on the other hand, was prevented by anti-Rtn4a/NogoA antibodies. Similar results were observed in the yeast *Saccharomyces cerevisiae*, in which overexpression of Rtn1 (the yeast ortholog of Rtn4a/NogoA in mammals) also enhanced tubular ER formation. Yeast mutants lacking both Yop1 (an Rtn1 paralog) and Rtn1 showed a disrupted tubular ER, underscoring the important function of these proteins in shaping membrane structures. Reticulons contain long, hydrophobic domains that are inserted into the outer leaflet of the lipid bilayer. Since the hydrophobic domains are longer than required for spanning a bilayer membrane, it is believed that they promote a hairpin-like insertion into the lipid bilayer and give the overall appearance of a wedge-like protein. Thus, a local concentration of reticulons might induce and stabilize a high, positive membrane curvature.

Although morphogenic proteins are believed to induce membrane curvature and shape spherical or tubular morphology, to date, none of them has been reported to induce highly organized membrane structures such as hexagonal or cubic membranes in vivo. One exception to the rule is the observation of a t-tubular system in skeletal muscles (Ishikawa, 1968), in which cubic membrane organization has been associated with caveolin-3 expression (Parton *et al.*, 1997). Caveolin is synthesized in the ER but mostly resides in certain domains of the plasma membrane. Caveolins are known to play a role in inducing and maintaining membrane curvature. Individual caveolin molecules are cotranslationally integrated into the bilayer of the ER. Similar to reticulons, caveolins form a hairpin-loop within the bilayer, and tend to form hexa- or heptamers. These oligomers may leave from the ER and are transported via the Golgi apparatus to the plasma membrane, where, by a yet unknown mechanism, they induce localized sites of membrane curvature, known as caveolae (Bauer and Pelkmans, 2006; Voeltz and Prinz, 2007).

### 4.2. Role of lipids in cubic membrane formation

Up to date, cubic membrane formation is mainly associated with over-expression of certain membrane-resident proteins. Although cubic phases are formed by “nonlamellar” lipids in vitro, only very few data directly correlate cubic membrane formation with cellular lipid profiles in vivo (Ryberg *et al.*, 1983). In this study it was shown that the molar ratio of monogalactosyl diacylglycerol to digalactosyl diacylglycerol was higher in the PLB fraction that exhibits cubic membrane morphology, than in the prothylakoid fraction. Also, the content of glycolipids and protochlorophyllides was increased in the PLB fraction (Ryberg *et al.*, 1983).
Lipid analyses of fed and starved amoeba (*C. carolinense*) recently performed in the authors’ laboratory (Deng et al., submitted) may provide a first clue towards understanding the role of membrane lipids in determining cell membrane architecture. Detailed lipid analysis of amoeba *Chaos* exhibiting cubic membrane organization in their mitochondria, revealed an unusually high concentration of highly polyunsaturated fatty acids (C22:5; docosapentaenoic acid, DPA). Three predominant lipid species, namely plasmalogen PE (C16:0p/C22:5), plasmalogen PC (C16:0p/C22:5), and diacyl-PI (C22:5/C22:5), were identified in amoeba *Chaos* lipid extracts (Fig. 6.9), and their relative amounts increased up to 2.5-fold under starvation stress conditions (Deng et al., submitted). A rich body of data (for review see Nagan and Zoeller, 2001) suggests that plasmalogens—which are also present in mammalian cell membranes—may serve as mediators of membrane dynamics due to their high propensity to form inverted hexagonal structures. This property has also suggested a potential role for plasmalogens in facilitating membrane fusion processes (for review see Brites et al., 2004). Biophysical studies have also shown that the presence of plasmalogen PE lowers the lamellar to hexagonal-phase transition temperature (Lohner, 1996). Interestingly, CHO cells, which display massive membrane rearrangements upon HMG–CoA reductase overexpression (Fig. 6.5), are also rich

![Chemical structures of three major lipids found in membrane lipids extracted from amoeba *C. carolinense*: plasmalogen PC (16:0p/22:5), plasmalogen PE (16:0p/22:5), and diacyl PI (22:5/22:5).](image-url)
in plasmalogen lipids (up to 11% of their total phospholipids), especially plasmalogen PE (Nagan et al., 1998).

4.3. Electrostatic effects on cubic membrane organization

The observation that weak molecular interactions, for example, by membrane proteins, may lead to cubic membrane transformation also suggests that electrostatic interactions play an important role in that process (Masum et al., 2005, Snapp et al., 2003). In a recent experimental study on the effects of divalent cations in the isolation buffers for mitochondria, we were able to demonstrate that the presence of EDTA up to 10 mM preserved mitochondrial cubic membranes in vitro (Fig. 6.10) (manuscript in preparation). Thus, pH and the nature of the electrolytes in the cellular milieu are likely to be important factors affecting cubic membrane morphology and integrity.

In vitro studies using monoolein membranes containing negatively-charged dioleoylphosphatidic acid have shown that the electrostatic interactions caused by surface charge of the membranes (Li et al., 2001), charged short peptides such as poly-L-lysine (Masum et al., 2005), Ca$^{2+}$ concentration (Awad et al., 2005), and low pH (Okamoto et al., 2008) play an important role in the phase transition between lamellar and cubic phases as well as on the stability of cubic phases. As a consequence of altered electrostatic interactions at the membrane interface, induced either by the

Figure 6.10  Electrostatic effects on cubic membrane organization (Deng, unpublished). Mitochondria of amoeba Chaos exhibiting cubic membrane arrangements were isolated in a buffer media containing (A) 50 $\mu$M, (B) 1 mM, or (C) 10 mM EDTA. Increasing the concentration of EDTA stabilized mitochondria with cubic morphology, suggesting a modulatory function of divalent cations in cubic membrane formation.
increase in surface charge density of the membrane or by a decrease in salt concentration, the lipid membrane phase may change from the lamellar to the cubic phase. Such cubic phases may not only form to adopt the altered membrane proteins or charge distribution, but may also provide the means to rapidly adjust cellular physiology to the changing environmental conditions, such as fluctuations of (local) intracellular Ca\textsuperscript{2+} levels. The “breathing” of cubic membranes, that is, the changes in lattice size as demonstrated \textit{in vitro} (de Campo \textit{et al.}, 2004), may represent an immediate biophysical response, which may allow for a rapid adaptation to the water content and ion concentration or charge distribution in a given membrane compartment also \textit{in vivo}.

5. Cubic Membranes: Indicators of Cellular Stress and Disease?

Notably, cubic membrane morphologies are often associated with deregulated protein synthesis, cellular stress, or more severe pathological conditions. This view, however, is perhaps somewhat biased since morphological abnormalities are typically investigated for diseased cells rather than for “wild type” conditions. Nevertheless, the correlation of specific membrane alterations in the course of acute or chronic cellular stresses needs closer consideration.

5.1. Virus-infected cells

Virus–induced membrane transitions, generally referred to as cytomembranous inclusions, are a hallmark in experimental and pathological samples (Almsherqi \textit{et al.}, 2005). However, due to the absence of a clear view of the 3D nature of these membrane structures, they appear under numerous nicknames in the literature, such as “tubulocristalline inclusions” in HCV infected liver (Schaff \textit{et al.}, 1992), “convoluted membraneous mass” in viral St. Louis Encephalitis (Murphy \textit{et al.}, 1968), and “TRS” in SIV (Kaup \textit{et al.}, 2005) and SARS-virus infected Vero cells (Goldsmith \textit{et al.}, 2004).

The unexplained mechanism behind the formation of convoluted cubic membranes upon viral infection starts to unfold based on the structural similarity to crystalloid ER membranes induced by overexpression of HMG–CoA reductase in UT-1, or the parental CHO cells (Fig. 6.5), as well as in A-431 (human epidermal carcinoma) cells. Some evidence suggests that virus infection and deregulation of HMG–CoA reductase are mechanistically linked, resulting in similar membrane phenotypes. For example, West Nile Virus infection is associated with local cholesterol alterations of the plasma membrane of the host cell that leads to a sequestration of membraneous sites of viral replication (Mackenzie \textit{et al.}, 2007). Depletion
of cholesterol in the plasma membrane triggers HMG-CoA reductase upregulation and consequently leads to the formation of a crystalloid (cubic or hexagonal) ER membrane. The virus-induced convoluted membrane was reported to be essential for viral replication and survival: administration of cholesterol that reverses the HMG-CoA reductase-induced convoluted membrane formation in the infected cells significantly suppresses viral replication (Mackenzie et al., 2007). A recent study has also shown that virus-induced membrane complexes might provide partial protection against the host immune response (Hoenen et al., 2007) and hence offer a site for efficient viral replication (Mackenzie et al., 2007) or facilitate nucleo-cytoplasmic transport of genetic material (Almsherqi et al., 2008).

5.2. Neoplasia

Cubic membranes (often labeled as TRS) have been reported to occur in the cytoplasm of breast carcinoma (Seman et al., 1971), subcutaneous myxoma (Stoebner et al., 1972), malignant lymphoma (Uzman et al., 1971), in the nucleus of human osteosarcoma cells (Murray et al., 1983), alveolar cell carcinoma (Ghadially et al., 1985), and gastric adenocarcinoma (Caruso, 1991). Since viral infections frequently lead to cubic membrane formation, it would not be surprising to observe cubic membrane structures also in cases of virus-related tumors, such as leukemias, lymphomas, and in virus-induced hepatocellular carcinoma (Uzman et al., 1971). TRS appear to be nonspecific to tumor differentiation or malignancy as they develop in highly replicative undifferentiated cells as well as in differentiated tumor cells. Therefore, due to the limited number of reported cases of cubic membrane structure in neoplastic cells, they currently are not yet diagnostically useful in the classification of tumors or in clinical prognosis. However, TRS could be used as a marker for viral-induced neoplasia, for example, hairy cell leukemia (Mantovani et al., 1986).

5.3. Muscular dystrophy

Several muscular and neuromuscular diseases are associated with periodic membrane transformation of t-tubules of striated muscles, usually referred to as honeycomb structures. T-tubular morphological membrane transformation has been described in denervated muscles (Gori, 1972; Madaram et al., 1986; Miledi and Slater, 1969; Pellegrino and Franzini, 1963), in the muscles with induced experimental myopathy (Macdonald and Engel, 1970), bupivacaine-induced myonecrosis (Huxley and Taylor, 1958), and in tenotomized muscles of the rat (Andreev and Wassilev, 1994). They have also been observed in various human muscles as a consequence of muscular diseases (Borg et al., 1989; Cornog and Gonatas, 1967; Engel and Dale, 1968; Engel and Macdonald, 1970; Gori, 1972; Iorio Di et al., 1989;
Miike et al., 1984). The fact that cubic membrane organization appears under pathological conditions of myopathy support the notion that they may be formed in response to stress conditions, such as a decrease in cell volume in the case of muscular dystrophy. Thus, it could be speculated that the potential function of cubic membrane structures is to maintain cellular integrity by regulating the volume of the cell (organelle) and/or to accommodate stress-induced membrane-resident proteins. Interestingly, induced formation of honeycomb t-tubules may also be part of a developmental program as these membrane structures are also observed in tadpole tail muscles that spontaneously degenerate during metamorphosis (Sasaki et al., 1985). Frequent transformation of t-tubules into G-type cubic membrane (honeycomb) organization in regenerating muscle fibers post pathological or experimentally induced muscular dystrophy may reflect the adaptive reorganization of the membrane system in the regenerating cell.

5.4. Autoimmune disease
Cubic membranes (including those labeled as TRS) have been frequently reported to occur under conditions and in cell types with an immunological background, for instance in diseases in which autoantibody production is a main factor in the pathogenesis. These include diffuse connective tissue diseases such as systemic and discoid lupus erythematosus (Grimley and Schaff, 1976) and Sjögren syndrome (Nakamura, 1974) or organ limited diseases, such as thyroiditis, gastritis, myasthenia gravis, and celiac disease (Helder and Feltkamp-Vroom, 1974). TRS are also reported in autoimmune diseases characterized by deposition of immune complexes or factors, which are discrete in comparison to the diffuse connective tissue diseases like rheumatoid arthritis, nephritis, and amyloidosis (Helder and Feltkamp-Vroom, 1974). Indeed, cubic membrane organization is frequently reported in immune deficiency diseases such as HIV (Kaup et al., 2005). Such ultrastructural membrane alterations are often reported in endothelial cells and in lymphocytes; therefore, TRS should be regarded as potential markers of autoimmune diseases that are of a systemic nature.

6. Cubic Membranes: Specific Functions or Innocent Bystanders?

The frequent appearance of cubic membranes in several specialized cell types, in response to environmental conditions, stress or infection, poses the intriguing question as to their specific functions. It is possible that cubic membranes are but an inevitable self-assembled product of the complex molecular mixture of lipids and proteins, the result of “simple” molecular packing considerations and inter-molecular interactions. Even though this is
appealing to the long and unresolved debate about “nonlamellar” lipids in conjunction with cell membranes, an increasing body of evidence suggests that these structural organizations might have to fulfill a purpose and their formation cannot be rationalized solely by spontaneous molecular packing. It is important to stress that the proposed functions of cubic membranes in the following discussion are hypothetical, although recent experimental data provide support to some of these hypotheses.

6.1. Cell space organization and subvolume regulation

Continuous hyperbolic layers, as represented by cubic membranes, partition space into discrete and unconnected subvolumes. By definition, a multi-membraneous structure consisting of \( n \) membranes, partitions space into \( (n + 1) \) physically distinct, intertwined, but separate subspaces. The identity of each space itself is not a consequence of the existence of a cubic membrane; rather it is an effect of a topologically invariant membrane morphogenesis. Although an intracellular space maintains its identity as long as membrane continuity is preserved, it is only by means of a hyperbolic membrane structure that such spatial relations can be rigorously defined. The identification of cubic membranes in multiple cell types and tissues clearly demonstrates that continuous intracellular membranes are much more frequently adopted than generally acknowledged.

6.2. Inter- and intracellular trafficking

Intracellular and inter-organelle trafficking of macromolecules and communication are active areas of research, yet no unified model exists. To what extent intracellular trafficking depends on or can be optimized through specific types of membrane organization, for example, as continuous 3D space partitioners or networks, is unknown. In the three dimensions of a cell, the partitioning of the intracellular space into subvolumes—leading to an interpenetrated pipeline system—could in principle be orchestrated by membrane organization, which ultimately controls spatio-temporal activities, including intracellular trafficking and transportation, and fast response to physiological alterations such as changing temperature, osmolarity or pH. Recognition of the existence of topologically distinct spaces through the formation of cubic membranes implies that cell space is restricted and predetermined to maintain distinct but interconnected subcellular domains. Cubic membranes may induce enrichment—or exclusion—of certain lipids and proteins, as a prerequisite for vesicle-mediated subcellular trafficking. They may also function as partitioners within a membrane, to create subdomains of specific molecular composition and function. It has been repeatedly noted that the stage of cell division and differentiation has a strong influence on the formation of cubic membranes. Cells that undergo rapid cell division and
differentiation, such as the differentiating sieve elements, cells during spermatogenesis, or tumor cells are well over-represented in the collection of cubic-membrane forming cells (Table 6.1). Obviously, during cell division and differentiation events, there is a greater need for regulated spatio-temporal transport, as well as cellular communication, which is particularly well illustrated during spermatogenesis (Table 6.1). In the case of differentiating sieve elements, cubic membranes might have a particular role in the assimilated transport process. Finally, it is of interest to note that aggregates of “synaptic vesicles” often resemble cubic membranes. This can be taken as an indication of a possible on-off mechanism of membrane continuity, which might account for a regulative capacity for the controlled release of transmitter substances.

6.3. Specific structure-function relationships

Several more general functionalities are under consideration for cubic membranes. In particular, a cubic bilayer arrangement could serve as a regulator of chemical or physical potentials across the membrane surface. This is indicated in several cases in which cubic membranes have been found to be sensitive to the growth medium. An osmo-regulative capacity of a plasma membrane-associated cubic membrane can be envisioned, which might serve to allow rapid adjustment to osmotic changes. Such a function is, for instance, consistent with the presence of cubic membranes in a variety of epithelial cells (Table 6.1). Cubic membranes may also be involved in curvature-controlled activation and regulation of membrane enzyme activities. For instance, diacylglycerols, which may function as second messengers to activate protein kinase C (PKC), display a strong propensity to form negatively curved membrane structures. The activity of PKC, however, is not specifically dependent on lipids that induce reverse hexagonal phases (Senisterra and Epand, 1993), and thus, reversed cubic phases. In view of the ubiquitous occurrence of cubic membranes it would be of interest to investigate the influence of PKC on cubic phases, and vice versa, to eventually correlate the geometry of the environment to protein activity.

Certain cubic membrane structures are apparently strongly linked to specific functions, such as the cubic structure found in the PLB of photosynthetic cells in higher plants. A physical role has been proposed for the selection of D-surface geometry (Guo et al., 1995), based on theoretical considerations on how the geometry of crystals controls the emission or absorption of certain wavelengths of light through the existence of photonic band-gaps (Babin et al., 2002). Although the D-surface is isotropic, its geometry is such that it may potentially trap photons. The absorbed energy could then be used by certain molecules that are positioned along a particular lattice direction, and, for instance, trigger conformational changes to revert PLB into an active thylakoid membrane geometry. A similar structural role can be considered for the selection of different subtypes of cubic
membrane architecture (photosome) in bioluminescent scaleworms (Bassot, 1964, 1966). Interestingly, the photosome membrane organization has a D subtype cubic membrane in the resting (unstimulated) state, however, upon electrical or optical stimulation the membrane configuration changes and acquires P subtype. Do different cubic membrane subtypes manipulate different wavelengths? Does the function of the cubic membrane change with the specific alteration of its geometrical configuration? The answers to these questions clearly deserve further investigations. In addition, several other photoactive cell types exist that contain cubic membranes. Mitochondria in the retinal cone of the tree shrew (Tupaia glis) (Foelix et al., 1987) may adopt an isotropic membrane structure that allows efficient capture of the incoming light; in an alternative model, this multilayer G-surface cubic arrangement of the mitochondrial membrane (Fig. 6.7) may preferentially reflect UV light before reaching the outer segment of the retina, thus representing a specialized optical filter system.

7. APPLICATIONS OF CUBIC MEMBRANES

Although the specific functions of cubic membranes in biological systems are still to be uncovered, recent studies on the physical properties of such highly ordered membrane structures have suggested a range of potential applications, beyond conventional liposome technologies. Dispersed liquid crystalline phases such as bicontinuous cubic dispersions (known as Cubosomes®) have been the focus of recent studies as potential drug delivery agents (Barauskas et al., 2005). Lipids forming cubic phases in vitro are also well-established matrices, for example, for membrane protein crystallization (Seddon et al., 2004), but are not considered here in the context of cubic membranes.

7.1. DNA transfection

Cubic membrane function is potentially linked to intracellular trafficking processes for macromolecules. Indeed, isolated mitochondria with cubic membrane organization from starved amoeba cells (see above) have recently been shown to incorporate and retain short oligonucleotides (ODN) with high efficiency (Fig. 6.11) (Almsherqi et al., 2008). Although the molecular basis for the high affinity of ODN to cubic membranes has not been uncovered yet, it is reasonable to assume that it is strongly promoted by electrostatic interactions with the highly curved and extended membrane surface. Furthermore, delivery of ODN-cubic membrane complexes to mammalian cells in culture appears to be very effective and might, therefore, provide an attractive alternative to currently employed cationic
lipoplexes and promises high efficacy and reduced cytotoxicity. Use of cubic membranes of biological origin as a carrier for DNA transfection or delivery of other nucleic acids, such as small interfering RNA and/or short hairpin RNA is currently under active investigation (Almsherqi et al., 2008).

7.2. Do cubic membranes have optical properties?

The photonic properties of bi- or multicontinuous cubic phases based on triply periodic level surfaces (G, D, and P) have been extensively studied in materials science (Babin et al., 2002; Maldovan et al., 2002; Urbas et al., 2002). In general, the lattice size of the photonic crystal has to be of the same magnitude as the wavelength range it controls. Photonic crystals based on triply periodic surfaces with the largest photonic band gaps known are of type D and G cubic morphology (Babin et al., 2002). Similar G-surfaces describe

Figure 6.11 Cubic membrane organization and DNA uptake (Almsherqi et al., 2008). (A) Low and (B) high magnification TEM images of mitochondria containing cubic membrane structure isolated from 10 d starved Chaos cells before (A and B) and after (C and D) incubation with ODNs. Multiple electron-dense intra-mitochondrial inclusions (D) may represent cubic membrane-mediated ODN interactions. The multiple pores (B) at the surface of mitochondria with cubic membrane organization may play an important role in facilitating passive uptake of ODNs.
the cubic membrane organization of the inner mitochondrial membranes (Fig. 6.7) in the tree shrew’s (*Tupaia belangeri*) retina (Foelix et al., 1987) and photosynthesis-related membranes in prolamellar bodies of higher plants and chloroplasts of the green algae *Zygnema* (Fig. 6.6) (Deng, 1998; Deng and Landh, 1995). Based on these similar cubic geometries and relevant lattice sizes, it is tempting to speculate that perhaps *Tupaia* mitochondrial membranes and cubic membranes in *Zygnema* chloroplasts and PLB of higher plants may function as photonic crystals. The 12-layered cubic membrane organization of the mitochondria in retinal cones of tree shrew *Tupaia* and multilayer grana of photosynthetic membranes may thus enable these membranes to amplify, refract, or absorb certain wavelengths of light. Whether such an elaborate membrane arrangement is a protective response or whether it provides a specialized reaction center for embedded proteins awaits detailed analysis.

### 8. Concluding Remarks

The frequent appearance of nonlamellar membrane arrangements such as cubic membranes in cells under stressed or pathological conditions points to an intrinsic cellular response mechanisms. The extensive generation of membrane surfaces to facilitate exchange reactions between two (or more) sub-volumes, or the sequestration of specific lipids or proteins into membrane domains of nonlamellar morphology may provide a physiological advantage to cope with various stress phenomena. Current analyses of nonlamellar membrane arrangements are largely restricted to the descriptive level; the identification of inducible membrane systems, such as in virus-infected cells or the reversible transition of mitochondrial inner membranes of amoeba *Chaos* to cubic morphology upon starvation, however, opens new avenues for understanding the molecular mechanisms and cellular requirements underlying these membrane arrangements. Lipidomics and proteomics techniques on the one hand, and cryo-electron tomography on the other, hold great promise to uncover the mysteries of cubic membranes in living cells, in healthy and diseased states.

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