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Cerasomes: A New Family of Artificial Cell Membranes with Ceramic Surface

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1. Introduction

Organic-inorganic hybrid materials have attracted much attention in the field of materials science because of their great potential for use in a wide variety of applications through fusion of individual organic and inorganic properties (Schmidt, 1994; Mackenzie, 1994; Sanchez et al., 2001; Schottner, 2001). Up to the present time, various kinds of material combinations and synthetic strategies have been developed. The sol-gel method is one of the most powerful techniques to prepare hybrid materials and has provided moderate preparative conditions for the construction of inorganic oxide frameworks that are derived from hybrid materials (Sakka, 2005). In particular, the preparation of novel materials with organized nanostructures is a fascinating research subject in the field of hybrid materials (Ulman, 1996; Ozin, 2000; Dabbs & Aksay, 2000; Scott et al., 2001; van Bommel et al., 2003; Cölfen & Mann, 2003). These approaches are generally based on sol-gel techniques that utilize the presence of molecular assemblies as templates, such as rod-like micelles (Yanagisawa et al., 1990; Kresge et al., 1992; Inagaki et al., 1999), block-copolymers (Krämer et al., 1998; Melosh et al., 1999; Ryoo et al., 2000), microemulsions (Sims et al., 1998; Feng et al., 2000), organogels (Ono et al., 1998), cast films of bilayer membranes (Sakata & Kunitake, 1990) and bilayer vesicles (Hubert et al., 2000). Thus, the properties of nanohybrids depend on their nanostructures, especially the structure at the interface between the inorganic and organic components. Pre-organization by employing non-covalent interactions between an organic template and an inorganic precursor is known to be very important. However, the interface between the organic and inorganic components in these hybrids seems to be structurally ambiguous and more difficult to control at the molecular level than the individual component structures. Additionally, most of these materials are composed of inorganic components alone, and the organic portions are simply employed as templates. In contrast, a novel class of layered organic-inorganic nanocomposites composed of amphiphilic molecules with a covalent bond between the silicate and the surfactant has been developed in recent years (Huo et al., 1996; Shimojima et al., 1997; Moreau et al., 2001; Ruiz-Hitzky et al., 2002; Zhang et al., 2004). These materials offer great potential because the hybrid precursors can form three-dimensional networks during the self-assembling process, whereby inorganic layers and organic moieties are covalently linked with stable Si-C bonds. We recently developed cerasomes, a novel type of organic-inorganic nanohybrid, through a combination of sol-gel reactions and self-assembling of lipidic organotrialkoxysilanes in aqueous media to form vesicles covered with silicate surfaces (Katagiri et al., 1999). A

cerasome is composed of a spherical lipid-bilayer membrane having an internal aqueous compartment, like so-called liposomes formed with phospholipids or synthetic lipids (Torchilin & Weissig, 2003; Kunitake, 1992), but is additionally covered with a silicate, surface framework (Fig. 1). While liposomes are widely used as biomembrane models and functional nanocapsules, their morphological instability is always a serious challenge for practical applications. It is hoped that cerasomes will overcome this limitation through the existence of a surface, silicate layer. Moreover, we can say that a cerasome is a novel organic-inorganic nano hybrid having a precisely designed nanostructure. That is, the thicknesses of both the organic and inorganic layers of a cerasome are attributed to the molecular structure of the cerasome-forming lipid, and the vesicular size of a cerasome is basically controllable by applying conventional methodologies for preparing monodispersed liposomes.

In this article, we review the design and preparation of cerasomes, as well as their morphological characterization. Additionally, the potential of the cerasome as a new family of artificial cell membranes is described from the viewpoints of surface modification versatility, hierarchical integration as a multicellular model and its functions as a cell-friendly drug carrier and molecular device.

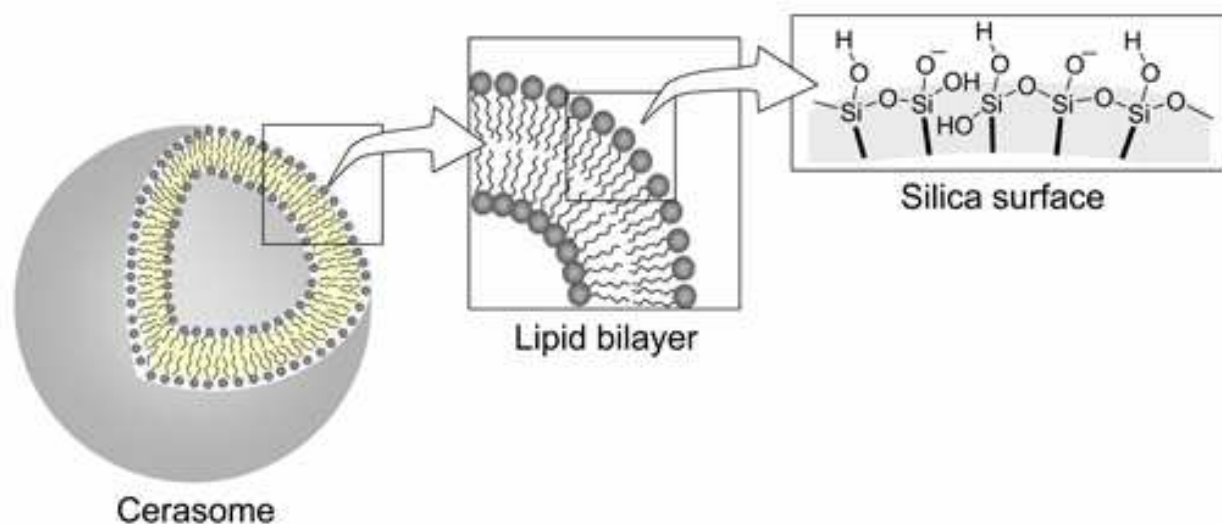


Fig. 1. Schematic drawing of a cerasome.

2. Design and preparation of cerasomes

The basic idea for designing a bilayer-forming lipid has been referred to as the concept of critical packing parameters for lipid assemblies (Israelachivili et al., 1976). Additionally, we considered the importance of a connector unit, which can form intermolecular hydrogen bonds to enhance morphological stability of the lipid assembly between the hydrophobic alkyl chains and the hydrophilic regions within a lipid molecule (Brockerhoff, 1977). We previously revealed the effect of a connector unit by systematic investigations of so-called peptide lipids, which have an amino acid or an oligopeptide moiety between the hydrophobic tail and the hydrophilic head (Murakami & Kikuchi, 1991). Our design of the cerasome-forming lipids takes these points into account, as well as the simplicity of synthesis. In addition, the silanol group as a head moiety is protected by ethoxy groups to store the synthesized lipid stably. The general molecular structure of a cerasome-forming

lipid is shown in Fig. 2. Upon hydrolysis of the triethoxysilyl group, the lipid is converted into an amphiphilic structure to form a lipid bilayer in aqueous media. Condensation among the silanol groups of the relatively hydrophobic membrane surface proceeds to develop a silica-like inorganic framework, or a siloxane network, resulting in a cerasome.

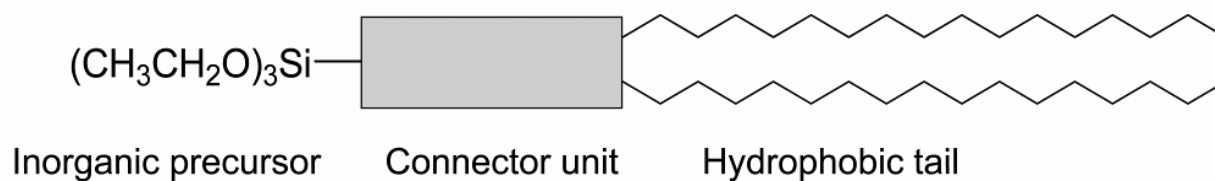


Fig. 2. General molecular structure of a cerasome-forming lipid.

Cerasome-forming lipids prepared along this design concept are shown in Fig. 3. First, we synthesized a cerasome-forming lipid (**1**) by simple condensation reactions between the three molecular components: dihexadecylamine, succinic anhydride and 3-aminopropyltriethoxysilane (Katagiri et al., 1999). Cerasome-forming lipids with a simple molecular structure having one urea group (**2**) or one amide group (**3**) in the connector unit were also prepared (Hashizume et al., 2003). The cationic cerasome-forming lipids (**4**, **5**) with a similar molecular framework of the typical peptide lipid, composed of the hydrophobic double-chain segment, quaternary ammonium head and an amino acid residue interposed between them, were developed by replacing the methyl group of the trimethylammonium head to form a 3-triethoxysilylpropyl group (Katagiri et al., 2002a; Sasaki et al., 2006). A cerasome-forming lipid with two triethoxysilyl heads (**6**) was designed to tune the siloxane network on the cerasome surface (Hashizume et al., 2004). To provide biodegradability to the cerasome, a phospholipid with a triethoxysilyl head (**7**) was also designed and synthesized.

The preparation procedure for cerasomes with a multiwalled vesicular structure is basically analogous to that of the liposomes formed with phospholipids. In general, we can adopt two kinds of preparation methods. One is the direct dispersion of the cerasome-forming lipid in aqueous media by vortex-mixing (Katagiri et al., 2007). The procedure is very simple technically; however, we should pay attention to the reaction conditions, especially the effect of pH (Ariga et al., 2000; Katagiri et al., 2001). As for the water-insoluble lipids, such as lipids (**1-3**), hydrolysis of the triethoxysilyl head group of the proamphiphile gradually proceeds to give a corresponding amphiphilic molecule. This lipid readily forms a self-assembly of the liposome-like bilayer membrane in aqueous media. In addition, condensation among the silanol groups on the relatively hydrophobic membrane surface proceeds spontaneously to develop a siloxane network. However, if the hydrolysis and subsequent condensation is much faster prior to the self-assembly, formation of the bilayer structure may be disturbed. Therefore, control of the reaction rate in the sol-gel process, especially the hydrolysis, seems to be important to cerasome formation.

For example, lipid (**1**) does not change to the corresponding amphiphilic form after prolonged vortex-mixing in aqueous media under a neutral pH condition and remains as oil droplets, primarily because of the extremely slow hydrolysis of the head group. On the other hand, a translucent solution characteristic of a liposomal dispersion is obtained under moderate acidic conditions at pH 3, where hydrolysis of the ethoxysilyl groups is gently preceded by mild acid catalysis. Under stronger acidic conditions at pH 1, however, a stable

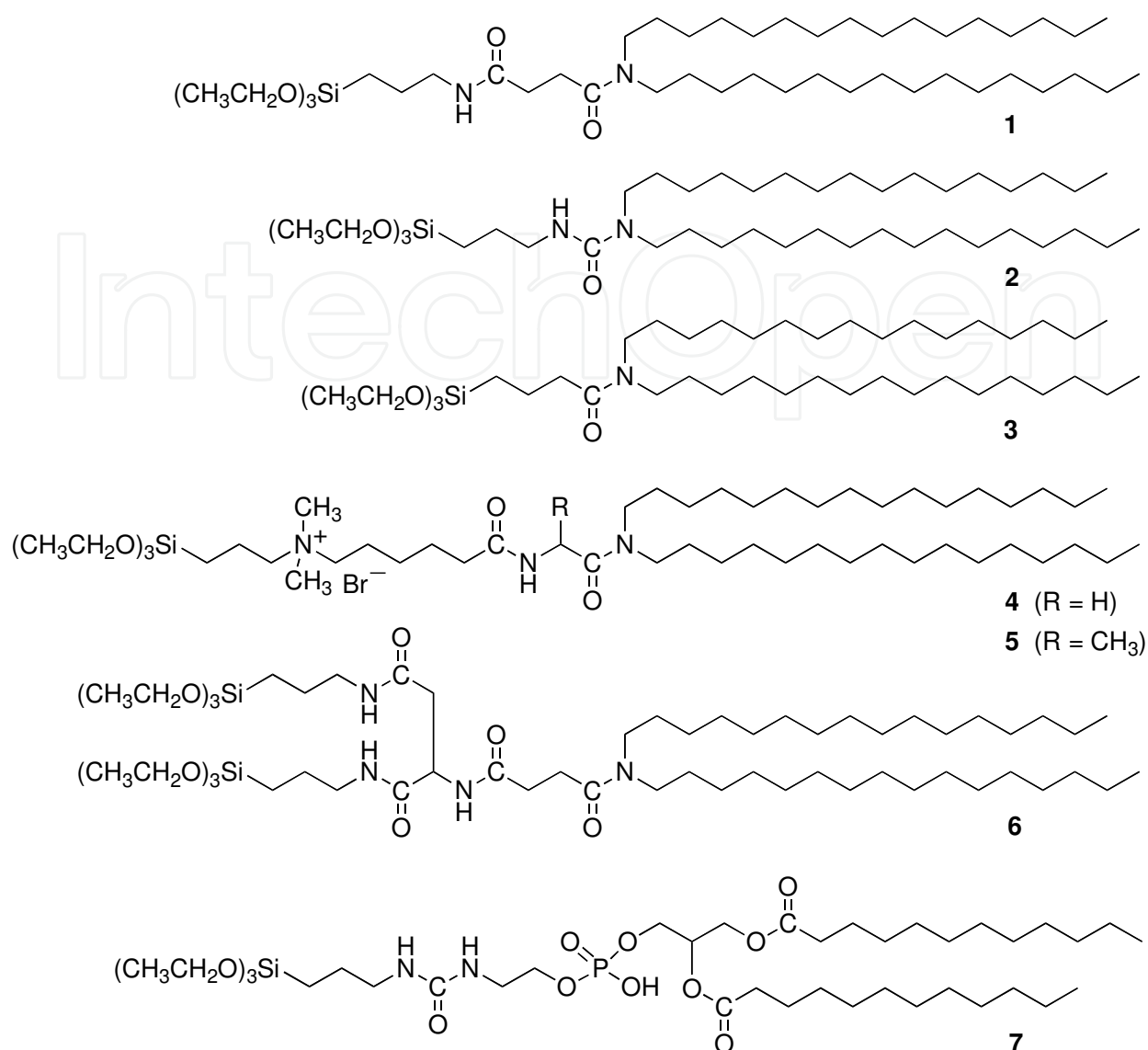


Fig. 3. Structural formulae of cerasome-forming lipids.

dispersion is not obtained, and precipitation is observed immediately. In this case, the hydrolysis and subsequent condensation reaction are so fast that the formation of the vesicular structure is prevented. At pH 12, the resulting solution is translucent, but oil droplets remain. Thus, the hydrolysis seems to proceed heterogeneously under basic conditions. The behaviors observed under the different pH conditions can be explained on the basis of a generally accepted mechanism for hydrolysis of alkoxy-silane compounds in the sol-gel process, as follows. Under acidic conditions, hydrolysis of the triethoxysilyl group continues equally for each of the proamphiphile molecules in a one-by-one manner. This process provides a suitable condition for the preparation of the lipid bilayer assembly. On the other hand, under basic conditions, particular molecules are preferentially hydrolyzed, while the other molecules remain as unreacted species. This process leads to heterogeneous hydrolysis, and various reaction stages of the lipid are observed. Thus, basic conditions seem to be unsuitable for the preparation of cerasomes. In practice, the hydrolysis behavior of cerasome-forming lipids can be monitored by ^1H NMR spectroscopy.

Regarding the cerasome-forming lipids with good water solubility, such as lipids (4) and (5), the direct dispersion method was adopted for its ease and utility.

The second procedure of cerasome preparation is the ethanol sol injection method (Katagiri et al., 2003). In this method, the hydrolysis of cerasome-forming lipids is performed by incubating an acidic ethanol solution of the lipids for an appropriate time. The sol thus obtained is injected into water, and the solution is incubated for an additional 24 h. This method is useful for cerasome-forming lipids with poor water solubility.

In general, the size of the multiwalled cerasomes is in the range of sub-micrometers. Upon sonication of the aqueous dispersion of the cerasome, the multiwalled vesicles convert into the corresponding single-walled vesicles with a diameter less than 100 nm (Katagiri et al., 2007; Sasaki et al., 2006). For sonication conditions, the use of a probe-type sonicator at 30 W power above the phase transition temperature of the lipids for 3 min is generally recommended. The vesicular size can be evaluated by dynamic light scattering (DLS) measurement. Cell-sized cerasomes with a diameter larger than 1 μm can also be prepared by employing the preparation method of giant liposomes (Luisi & Walde, 1999).

3. Morphological characterization of cerasomes

3.1 Aggregate morphology

The aggregate structures of cerasomes can be evaluated by means of various microscopic measurements, such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM) and optical microscopy. For TEM measurements of cerasomes, we can use three kinds of imaging techniques (Kikuchi & Yasuhara, in press). First, negative staining with heavy metal ions is a simple and convenient technique. For example, a negatively-stained TEM image of a cerasome formed with lipid (4), using the direct dispersion method, is shown in Fig. 4 (a). An internal view of

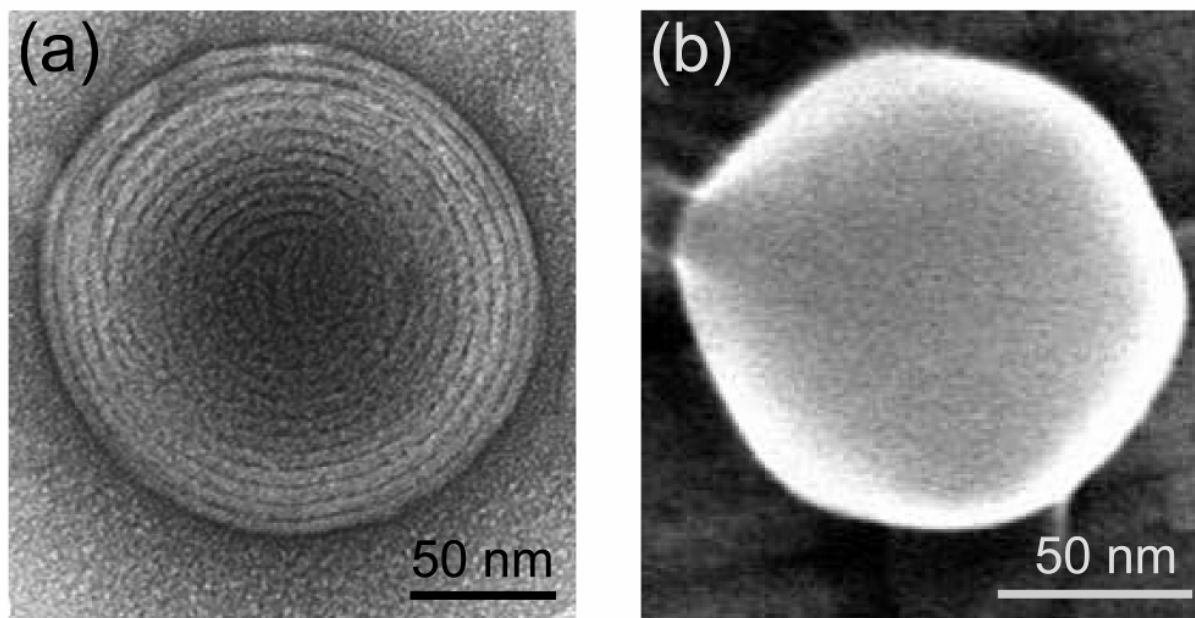


Fig. 4. Microscopic images of multiwalled cerasomes: a negatively stained TEM image of a cerasome formed with lipid (4) (a) and a SEM image of a cerasome formed with lipid (2) (b).

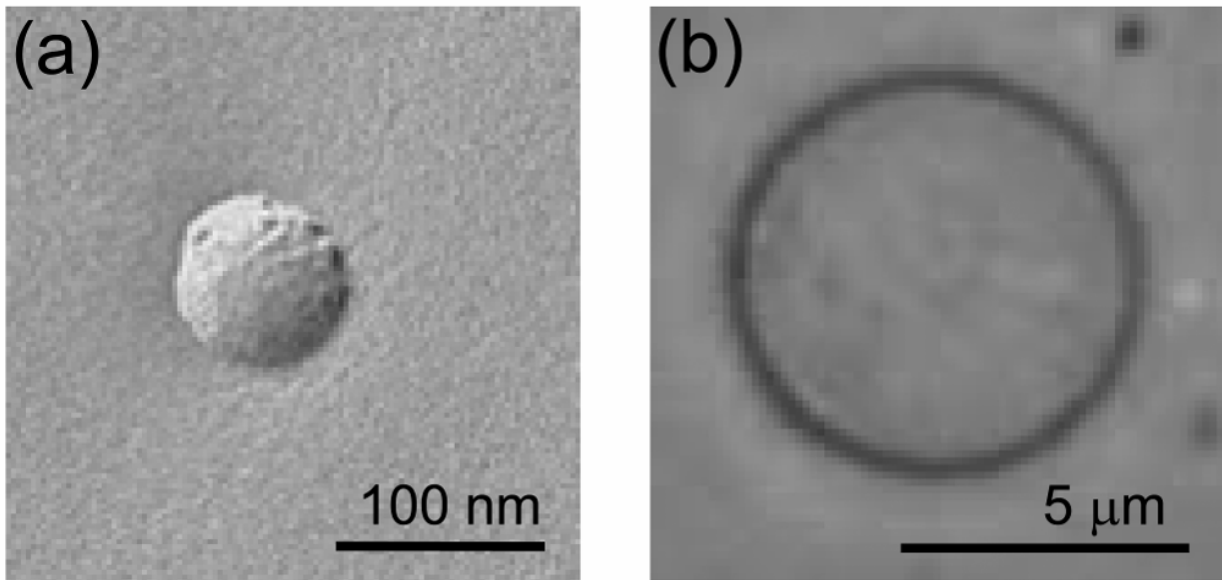


Fig. 5. Microscopic images of single-walled cerasomes: a freeze-fracture TEM image of a small cerasome formed with lipid **(5)** (a) and a phase contrast image of a giant cerasome formed with lipid **(5)** (b).

the multiwalled vesicles with a bilayer thickness of about 5 nm was clearly confirmed. A similar image was obtained by cryogenic TEM without a staining agent. On the other hand, freeze-fracture TEM imaging can provide information on the vesicular surface structure. Figure 5 (a) shows a surface image of a single-walled cerasome formed with lipid **(5)**, as observed by freeze-fracture TEM.

In general, SEM is a challenging technique for imaging conventional liposomes formed with phospholipids because of the poor structural integrity of the samples. However, cerasomes can be visualized by SEM because of their high morphological stability. An SEM image of a multiwalled cerasome formed with lipid **(2)**, using the ethanol sol injection method, is shown in Fig. 4 (b). The enhanced morphological stability of the cerasome also allows clear AFM imaging, as described later. For micrometer-sized giant cerasomes, optical microscopy is a powerful tool to provide dynamic imaging. Figure 5 (b) shows a phase contrast image of a giant cerasome formed with lipid **(5)**. By using an appropriate fluorescent probe, we can visualize the lipid layer of a cerasome and its inner aqueous phase, separately.

3.2 Surface siloxane network

One of the important characteristics of the cerasomes is the presence of a surface siloxane network. This inorganic framework provides the cerasome much higher morphological stability compared with that of a conventional liposome.

The formation of siloxane bonds on the surface of a cerasome formed with lipid **(1)** was evaluated by Fourier transform infrared spectroscopy (Katagiri et al., 2007). Stretching bands assigned to the Si-O-Si and Si-OH groups were observed around 1100 and 950 cm^{-1} , respectively. The former peak intensity was much weaker than the latter in the cerasome in the aqueous dispersion state. Thus, it is suggested that the cerasome had a silica-like surface with a siloxane framework, but the degree of polymerization was not particularly high. The detectable species of lipid oligomers in the cerasome as evaluated by matrix assisted laser

desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) spectra are listed in Table 1. Trimethylsilylation was performed for the aqueous dispersion samples of a cerasome prepared after 10 h. While the monomer, dimer and trimer species were also detected in the sample as prepared, oligomers with higher molecular weights such as tetramers and pentamers were also detected in the sample during the prolonged incubation. This implies that the siloxane network grew as the incubation time increased. From cryoscopic measurements, the number-average molecular weight was determined to be 1300 for the aqueous dispersion of the cerasome incubated for 10 h. This value corresponds to the molecular weight of the dimer species. On the other hand, the size of the cerasome did not change appreciably after the allotted incubation time, as confirmed by TEM and DLS measurements. Accordingly, the siloxane network was not so highly developed on the cerasome surface. These observations were also supported by a computer-aided molecular model study, since the length of the Si-O-Si bond was much shorter than the calculated diameter of the cross-section of the dialkyl tail.

Species	Molecular weight	
	Observed ^a	Calcd
Monomer	901.7	900.7
Dimer	1640.4	1641.0
Trimer (cyclic)	ud	2217.9
Trimer (linear)	2380.3	2380.3
Tetramer (cyclic or branched)	2957.3	2957.3
Tetramer (linear)	3117.4	3119.6
Pentamer (cyclic or branched)	3695.3	3696.7
Pentamer (linear)	ud	3859.0

^a Evaluated by MALDI-TOF-MS spectra after incubation for 10 h. ud: undetectable.

Table 1. Detectable species of lipid oligomers for a cerasome formed with lipid (**1**)

Surfactant solubilization is a useful method to evaluate morphological stability of liposomes in aqueous media. Thus, the resistance of a cerasome formed with lipid (**1**) against a nonionic surfactant, Triton X-100 (TX-100), was evaluated from the light scattering intensity of the vesicles (Katagiri et al., 2007). A liposomal membrane formed with 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) was used as a reference. When three equivalents of TX-100 were added to the DMPC liposome, the light scattering intensity was drastically decreased, indicating a collapse of the vesicles. In contrast to the DMPC liposome, the cerasome exhibited a remarkable morphological resistance toward TX-100, and the light scattering intensity of the cerasome incubated for 24 h did not change, even in the presence of 36 equivalents of TX-100. Such surprising morphological stability of the cerasome was also confirmed by the DLS measurements. Morphological stability of such a cerasome seems to be superior to that of an excellent example of the polymerized liposomes recently developed (Mueller & O'Brien, 2002). It is noteworthy that the resistance of the cerasome toward TX-100 was insufficient immediately after preparation. Thus, it is clear that the morphological stability of the cerasome comes from development of the siloxane network

on the vesicular surface. As for the cationic cerasomes prepared from lipids (4) or (5), the resistance against TX-100 was comparable to that of a conventional liposome, even after prolonged incubation. However, cationic cerasomes have an extremely high morphological stability against other kinds of surfactants, such as cetyltrimethylammonium bromide (CTAB), which completely dissolves DMPC liposomes (Sasaki et al., 2004). Accordingly, we can control the morphological stability of the vesicles through modification of the molecular design of the cerasome-forming lipids.

3.3 Phase transition and phase separation behavior

Phase transition parameters for the cerasomes were evaluated by differential scanning calorimetry (DSC). The enthalpy change from the gel to liquid-crystalline state (ΔH) and the temperature at the peak maximum (T_m) for the aqueous dispersion of a cerasome prepared from lipid (1) were 47.5 kJ mol⁻¹ and 10.5 °C, respectively. Upon sonication of the cerasome with a probe-type sonicator for 10 min at 30 W, the ΔH value decreased to 11.5 kJ mol⁻¹, whereas the T_m value did not change. For a cerasome formed with lipid (4) in the aqueous dispersion state, the ΔH and T_m values were 33.3 kJ mol⁻¹ and 25.7 °C, respectively. These phase transition parameters are comparable to those for peptide lipids previously reported (Murakami & Kikuchi, 1991). Upon sonication of the cerasome prepared from lipid (4) with a probe-type sonicator for 10 min at 30 W, the endothermic peak for the phase transition apparently disappeared. We have previously clarified that the transformation of the multiwalled vesicle to the corresponding single-walled vesicle is reflected in the decrease of both the ΔH and T_m values (Murakami & Kikuchi, 1991). Additionally, ΔH is more sensitive than T_m to such morphological changes. Since it is well known that the multiwalled vesicles formed with conventional liposomes generally transform to single-walled vesicles under the sonication conditions employed in this study, cerasome (1) is more tolerant towards morphological changes than the liposome-forming lipids. Formation of the siloxane network on the vesicular surface can prevent such morphological transformations.

Cerasomes enhance the creation of lipid domains in the vesicle (Hashizume et al., 2006a). For example, a cerasome prepared from the mixture of lipid (1) and 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylcholine (DPPC) formed a phase-separated lipid domain, as evaluated by DSC. That is, the aqueous dispersion of the homogeneous mixture of these lipids showed two phase transition peaks originating from the individual lipids. Similar phase separation behavior was observed in the cerasome formed with lipid (1), and the peptide lipid replaced the triethoxysilylpropyl group of lipid (5) as a methyl group. Such marked phase separation was not detected for the bilayer vesicle formed with DPPC and the peptide lipid. These results are mainly attributable to the polymerizable nature of the cerasome-forming lipid.

4. Surface modification of cerasomes

As mentioned, the surface of a cerasome is covered with a number of small siloxane oligomers. Since a cerasome exhibits analogous reactivity to the inorganic silica surface, we can modify a cerasome surface to give various unique organic-inorganic hybrid vesicles (Fig. 6).

4.1 Tuning of the siloxane network

Development of the siloxane network on a cerasome surface can be tuned when the cerasome is prepared by the ethanol sol injection method in the presence of

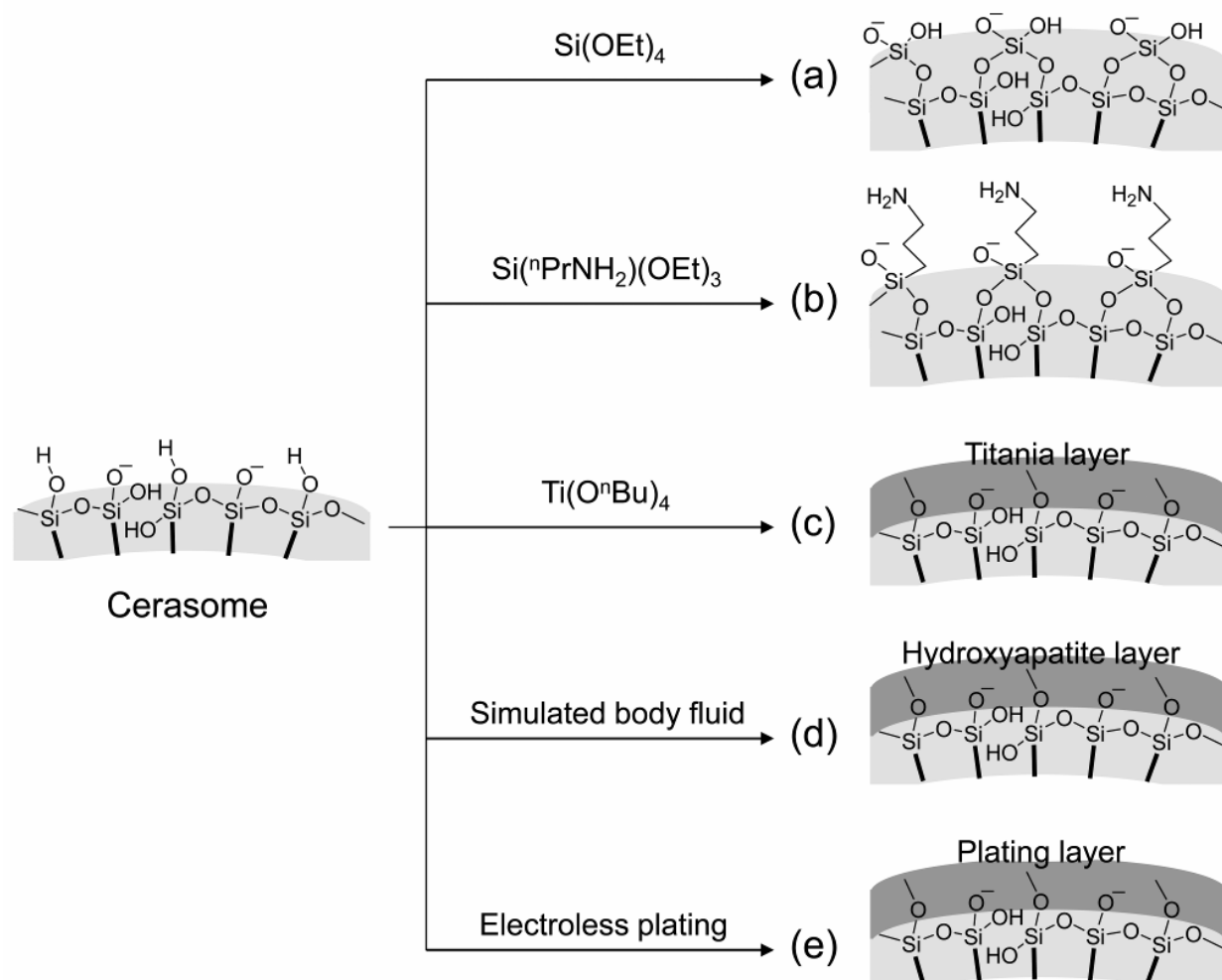


Fig. 6. Modification of the cerasome surface: development of a siloxane network (a), introduction of an organic functional group (b), coating with titania (c), hydroxyapatite (d) and a metallic nanolayer (e).

tetraethoxysilane (TEOS) (Katagiri et al., 2003). As such, when the sol prepared from lipid (1) with TEOS after 12 h incubation was injected into an aqueous solution under various pH conditions, the monodispersed and stable aggregates of the cerasome were formed. The hydrodynamic diameter and polydispersity index evaluated from the DLS measurements were 250–270 nm and 0.05– 0.13, respectively. Formation of the cerasomes with a diameter of 150–300 nm was observed for all the samples with and without a surface modification by TEOS, as confirmed by TEM. The values were in well agreement with those obtained from the DLS measurements.

Differences in the development of the siloxane network can be evaluated from a pH dependence of the zeta-potential of the cerasomes. For the cerasome without a surface modification, the zeta-potentials were in a range of +10 to -70 mV. The isoelectric point of the cerasome appeared at 4.3. Thus, the present cerasome possessed large negative charges under neutral and basic conditions, reflecting deprotonation of the silanol groups on the cerasome surface. For the cerasome modified with TEOS, a lower shift of the isoelectric point to 3.2 was observed. It has been reported that the isoelectric point of the typical silica particles derived from the sol-gel method lies in the range of 2–3, and the zeta-potentials for

the particles are ranged from +20 to -80 mV in the analogous pH region (Nishimori et al., 1996). These results indicate that the surface electrical state of the cerasome modified with TEOS resembled that of the silica particles rather than that of the cerasome without surface modification. Thus, lipid (**1**) and TEOS were effectively co-polymerized to form the cerasome with a well-developed siloxane network.

4.2 Coating with functional layers

Surface modification of a cerasome with functional amino groups is readily achieved in a similar manner by replacing TEOS with 3-aminopropyltriethoxysilane (APS) (Katagiri et al., 2003). For a cerasome formed with lipid (**1**) in the presence of APS, the hydrodynamic diameter and polydispersity index were 210–220 nm and 0.19–0.25, respectively. The isoelectric point evaluated from the pH dependence of the zeta-potential was shifted to 10.0 for the APS-modified cerasome. In the pH range lower than 10, the zeta-potential of the cerasome increased with a decrease of pH to reach +100 mV at pH 6. The value is considerably higher than the corresponding maximal value of the cerasome derived from lipid (**1**) alone. Such a difference is attributable to an effective introduction of the amino group of APS on the former cerasome surface. Thus, in the physiological pH region, the cerasome prepared from lipid (**1**) without modification was present as a polyanionic vesicular particle, whereas the cerasome modified with APS was polycationic. Additionally, it may be possible to control the isoelectric point of the cerasome to a desired value by changing the molar ratio of lipid (**1**) and APS. Accordingly, we can prepare functionalized cerasomes modified with various alkoxysilane compounds by adopting this technique.

Using the ethanol sol injection method for cerasome preparation in the presence of titanium alkoxide, we can create a titania-coated cerasome (Hashizume et al., 2006b). Specifically, the cerasome-forming lipid (**1**) and titanium tetrabutoxide, $\text{Ti}(\text{O}^n\text{Bu})_4$, were incubated in acidic aqueous ethanol in the presence of acetylacetone as a co-catalyst. The sol was injected into the aqueous media and followed photo-irradiation to produce a cerasome with a diameter of c.a. 150 nm. The zeta-potential of the titania-coated cerasome changed from +30 to -40 mV, depending on the medium pH, and the isoelectric point was 4.8, which is comparable to that of colloidal titania, ranging between 5–7. The photocatalytic activity of the titania-coated cerasome was confirmed by photolysis of methylene blue in aqueous media by means of electronic absorption spectroscopy.

Biomimetic mineralization of supramolecular scaffolds consisting of biomolecules or their analogues has received much attention with regard to the creation of novel biomaterials. Likewise, we applied biomimetic deposition of hydroxyapatite (HAp) onto cerasomes (Hashizume et al., 2010). When a cerasome formed with lipid (**1**) was immersed into a solution having 1.5 times higher ion concentration than that of simulated body fluid (SBF), the cerasome induced heterogeneous nucleation of HAp, as evaluated by means of SEM, energy-dispersive X-ray spectroscopy and X-ray diffraction. The HAp deposition was further accelerated when dicarboxylic and monocarboxylic acid groups were displayed on the cerasome surface. These carboxylic acid groups were expected to enhance calcium ion binding to the cerasome surface, causing an increase of HAp nucleation sites. At lower surface concentrations on the cerasome surface, the dicarboxylic acid group is apparently more effective for HAp deposition than the monocarboxylic acid group. The HAp-coated cerasome is useful as a biocompatible material having unique properties deriving from the lipid bilayer structure of the cerasome.

The other system that highlights advantages of cerasomes is an asymmetric bilayer coating of monodispersed colloidal silica particles (Katagiri et al., 2004a). The particles were first coated with a cerasome-forming lipid and then coated with a bilayer-forming lipid to form an asymmetric lipid bilayer structure, which is usually seen in biological systems, but difficult to reconstitute by conventional techniques.

4.3 Coating with metallic nanolayers

Novel liposomal membranes having a metallic surface, so called metallosomes, are prepared by electroless plating of cerasomes (Gu et al., 2008). The electroless plating of a cerasome formed with lipid (5) was performed by first binding palladium tetrachloride ions (PdCl_4^{2-}) onto the cationic membrane surface through electrostatic interactions, then subsequently reducing this precursor catalyst to Pd(0) and finally depositing a layer of metal onto the cerasome surface using an appropriate plating bath. While the metallosome coated with an ultrathin Ni layer was successfully prepared by electroless Ni plating of the cerasome, it was not possible to derive the Ni-coated vesicle formed with the corresponding peptide lipid under similar plating conditions. Such results reflect the difference in the morphological stability of these vesicles. The characterization of the Ni-metallosomes was performed using various physical measurements, such as SEM, TEM, energy-dispersive X-ray spectroscopy, electron energy-loss spectroscopy and TEM tomography. The Ni layer thickness was controllable on the nanometer scale by changing the plating time. The gel to liquid-crystalline phase transition behavior of the Ni-metallosomes was observed by DSC, indicating that the metallosomes maintained the nature of the lipid bilayer membrane. Ni-metallosomes with various sizes were prepared from the corresponding cerasomes in a diameter range of 50–5000 nm. Metallosomes with an Au layer were also successfully obtained by electroless Ni/Au substitution plating of Ni-metallosomes.

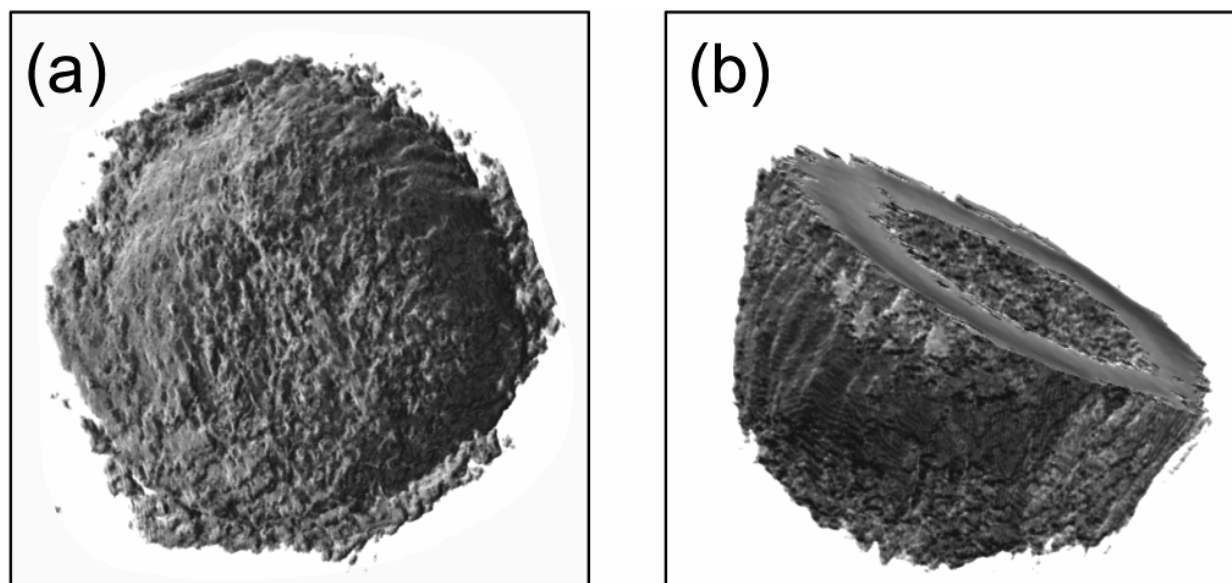


Fig. 7. Three-dimensional reconstitution of TEM images of a magnetic cerasome formed with lipid (2): the whole image (a) and the sliced image (b).

A magnetic cerasome, an artificial cell membrane having ultrathin magnetic metallic layers on the surface, was prepared through electroless plating of a magnetic metal alloy onto a cerasome (Minamida et al., 2008). Figure 7 shows three-dimensional images of a magnetic cerasome derived from lipid (2), as observed by TEM tomography. High morphological stability in the cerasome was important for constructing the magnetic lipid vesicle, and insertion of an alkylated metal ligand into the cerasome was essential for the magnetic metal alloy deposition on the cerasome surface. The magnetic property was evaluated by means of vibrating sample magnetometry. The magnetic field–magnetism hysteresis loop for the magnetic cerasome at different temperatures revealed that the magnetic cerasomes exhibited ferromagnetism, reflecting the nature of the plated magnetic metal alloy. Additionally, fluorescence microscopic observations revealed that the magnetic cerasomes were collected reversibly on the slide glass surface and manipulated by an external magnetic field.

5. Hierarchical integration of cerasomes

5.1 Three-dimensional integration on a substrate

Lipid bilayer vesicles with an inner aqueous compartment have been extensively employed as biomembrane models. Thus, it would be important to develop a new methodology to form hierarchically integrated vesicular assemblies, since the multicellular bodies in biological systems can create highly organized architectures and exhibit more functions than unicellular bodies can. Three-dimensional integration of the cerasomes on a substrate is successfully achieved by employing a layer-by-layer assembling method. As such, an anionic cerasome formed with lipid (1) was assembled on a substrate covered with oppositely charged polycations (Katagiri et al., 2002b). AFM images of the anionic cerasome layer and the cationic polymer layer are shown in Fig. 8 (a). The integration process was monitored by measuring the absorption mass changes on a quartz crystal microbalance. A similar three-dimensional assembly was created with an APS-modified cationic cerasome derived from lipid (1) and an anionic polymer on a substrate (Katagiri et al., 2004b). The alternate layer-by-layer assembly of two types of vesicles was obtained by employing the combination of an anionic cerasome formed with lipid (1) and a cationic cerasome formed with lipid (4) as shown in Fig. 8 (b) (Katagiri et al., 2002a). Notably, three-dimensional integration of lipid vesicles on a substrate can be achieved by use of morphologically stable cerasomes, but not by conventional bilayer-forming lipids.

5.2 Integration on DNA templates

In general, the interactions of ionic lipid vesicles with oppositely charged polymers induce morphological changes of the vesicles. However, the vesicular structure of cerasomes is much more stable than that of conventional liposomes. Thus, we can expect to create multicellular models by employing multipoint electrostatic interactions of the cerasomes with ionic polymers in aqueous media. In fact, we observed that cationic cerasomes formed with lipid (5) assembled on the DNA templates, as shown in Fig. 9 (Matsui et al., 2007; Hashizume et al., 2008). Under similar conditions, cationic peptide lipid in which the triethoxysilylpropyl group of lipid (5) was replaced by a methyl group, could not maintain the vesicular shape to support fusion of the vesicles.

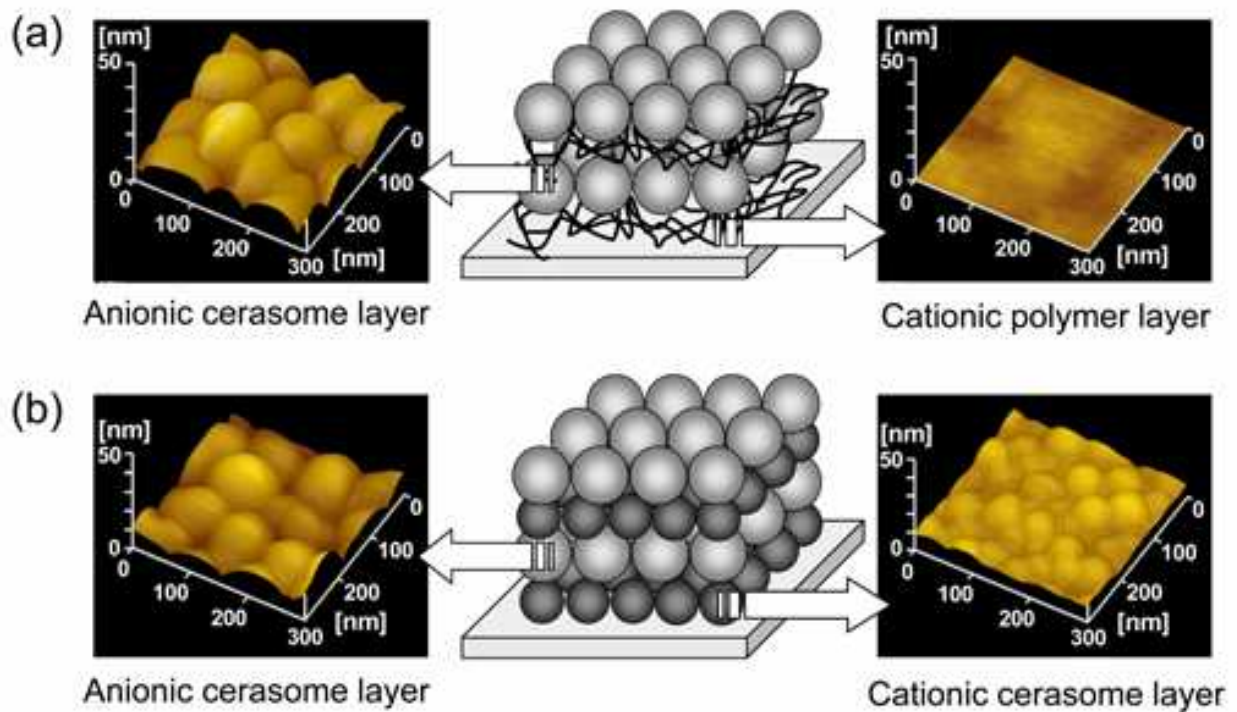


Fig. 8. AFM images of three-dimensional self-assemblies of cerasomes on a mica substrate: layer-by-layer assembly of an anionic cerasome (1) with a cationic polymer (a) and a cationic cerasome (4) (b).

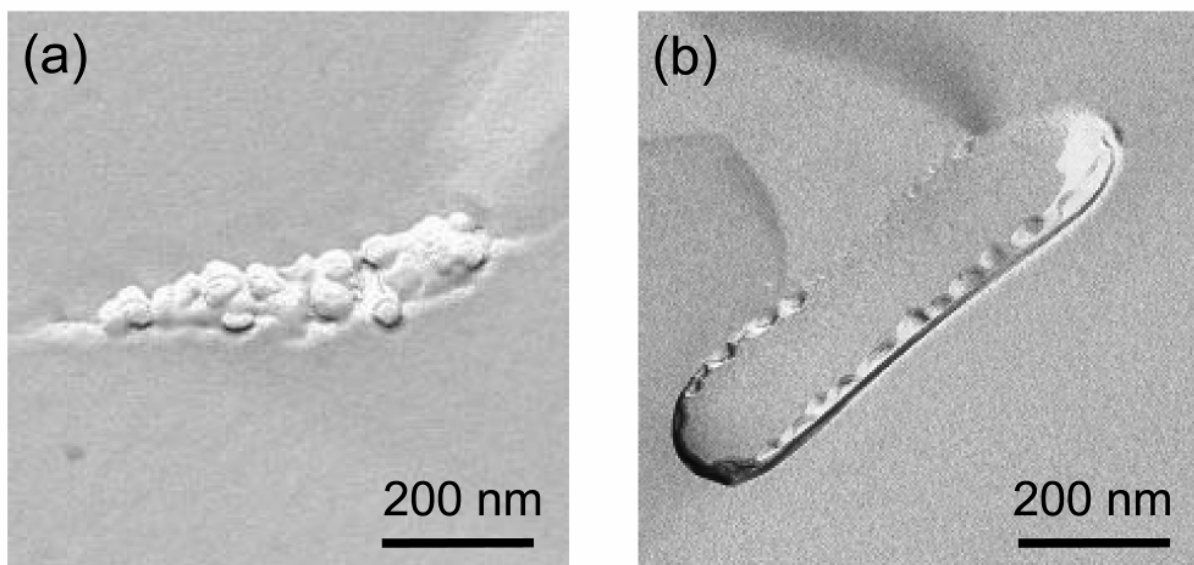


Fig. 9. Freeze-fracture TEM images of the self-assemblies of cationic cerasomes on DNA templates: assemblies of a cationic cerasome (5) on double-stranded DNA (a) and plasmid DNA (b).

6. Functionalization of Cerasomes

6.1 Potent drug carriers

Since the discovery of lipofection (Felgner et al., 1987), cationic lipids have been widely used as transfection agents in gene delivery (Behr, 1993; Kabanov & Kabanov, 1995; Mintzer & Simanek, 2009). They form cationic liposomes, to which anionic DNAs are electrostatically bound, to form complexes (or lipoplexes) that are taken in the cells via endocytosis. This is, however, an oversimplified picture. Liposomes are by no means rigid or robust. They are potentially fusible with cell membranes and therefore, toxic. They also easily undergo DNA-induced fusion to give larger particles that have lower endocytosis susceptibility and poorer vascular mobility. Additionally, serum components can interfere with fragile liposome-DNA complexes. Size instability, cytotoxicity and serum incompatibility, which are actually interrelated, are thus major problems in the current lipofection technology.

Recently, we developed an excellent transfection system using a cationic cerasome as a gene carrier (Matsui et al., 2006; Sasaki et al., 2006). We found that the cerasome formed with lipid (5) was infusible. The monomeric cerasome complex of plasmid DNA in a viral size (~70 nm) indeed exhibited a remarkable transfection performance, such as high activity, minimized toxicity and serum-compatibility, toward uterine HeLa and hepatic HepG2 cells (Fig. 10). This was in marked contrast to the non-silylated reference lipid, which forms fused, huge particles with significantly lower activity, by a factor of 10^2 - 10^3 and exhibited more pronounced toxicity. A couple of potential generalities of the present cerasome strategies with respect to nucleic acids to be delivered and cationic lipids as carriers are worth mentioning. The cerasome-plasmid complexation is strong and efficient, even at a stoichiometric lipid/nucleotide ratio. In this context, the cerasome could also be used as a size-regulated carrier for diverse types of functional nucleic acids, such as aptamers and siRNAs (Matsui et al., 2007). On the other hand, cerasomes encapsulating [70]fullerene also act as good carriers, exhibiting efficient photodynamic activity in HeLa cells (Ikeda et al., 2009).

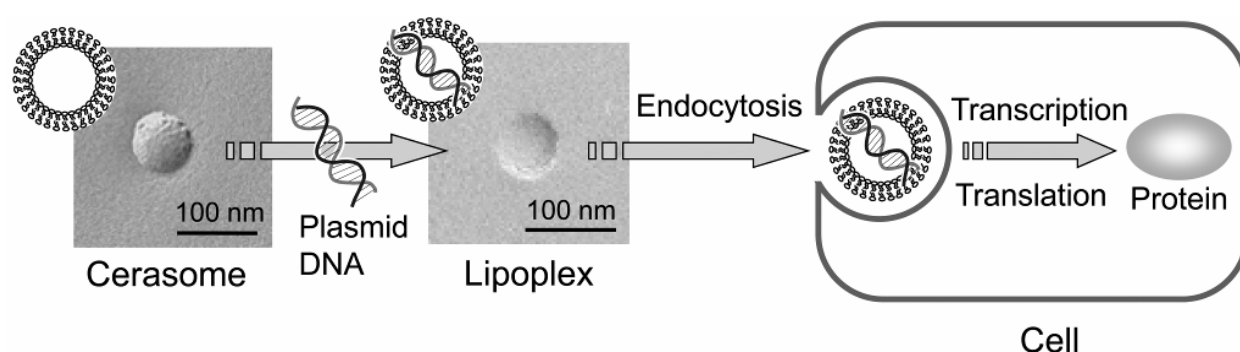


Fig. 10. Schematic representation of the transfection of a lipoplex formed with a cationic cerasome (5) and a plasmid DNA: images of the cerasome and its lipoplex were taken by freeze-fracture TEM.

6.2 Molecular devices for information processing

Signal transduction using molecules as information carriers is ingeniously designed in biological systems. Receptors and enzymes play leading roles for such information

processing; however, biomembranes are also essential to provide a platform for the performance of these functional biomolecules. On these grounds, we have developed a biomimetic signal transduction system as a molecular device on artificial cell membranes (Kikuchi et al., 1999; Tian et al., 2005). When a molecular communication system was constructed on a cerasome formed with lipid (4), its signal transduction efficiency was much more effective than that created on the corresponding peptide lipid vesicle (Sasaki et al., 2004). The system contained a synthetic steroidal receptor and NADH-dependent lactate dehydrogenase, both embedded in the membrane through noncovalent interactions, as schematically shown in Fig. 11. A biologically important molecule, pyridoxal 5'-phosphate, acted as an input signal and was specifically recognized by the artificial receptor to form a signal-receptor complex on the membrane surface. The information from the molecular recognition was then transmitted to the enzyme by a copper(II) ion, as a mediator, which increased the enzymatic activity. We found that the efficiency of the molecular information processing in the cerasome was much higher than that in the peptide lipid vesicle. The former advantage comes from an enhanced phase separation of the steroidal receptor in the cerasome than in the peptide lipid membrane, which promotes the formation of a ternary complex of the receptor, signal and mediator species. Energy transfer is another important phenomenon in molecular information processing. Indeed, efficient fluorescence energy transfer between cyanine dyes was achieved with a cerasome formed with lipid (5) (Dai et al., 2009).

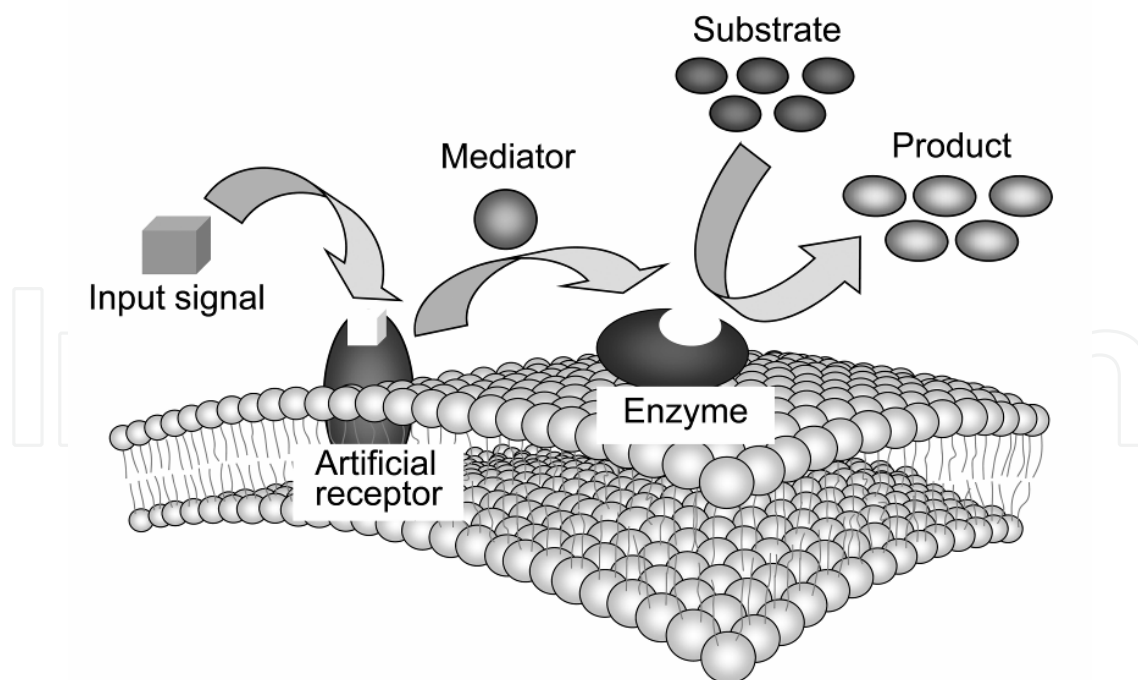


Fig. 11. Schematic representation of molecular information processing on a cerasome.

7. Conclusion

One of the useful guideposts in the creation of intelligent biomimetic materials is the hybridization of the functional building blocks of biological and artificial molecular components (Kikuchi et al., 2004). Cerasomes have been developed as a nanohybrid of membrane-forming lipids and ceramics along this line. Specifically, cerasomes behave as biomembrane models, as well as phospholipid liposomes and synthetic organic lipid vesicles. Owing to the enhanced morphological stability of the cerasome siloxane network on the vesicular surface, the hybrid performs as a superior vesicle in various applications as compared with conventional lipid vesicles. Moreover, cerasomes combine the structural and chemical characteristics of silica particles. Therefore, cerasomes have potential for application in a wide variety of novel functional fields, in which conventional lipid vesicles cannot be employed.

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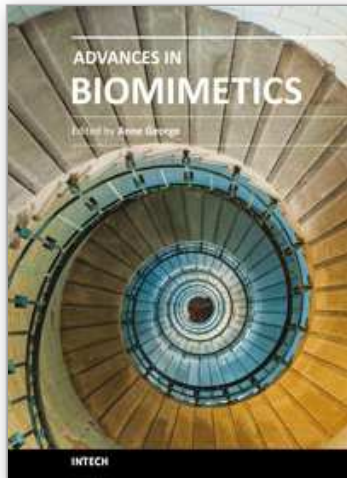
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Advances in Biomimetics

Edited by Prof. Marko Cavrak

ISBN 978-953-307-191-6

Hard cover, 522 pages

Publisher InTech

Published online 26, April, 2011

Published in print edition April, 2011

The interaction between cells, tissues and biomaterial surfaces are the highlights of the book "Advances in Biomimetics". In this regard the effect of nanostructures and nanotopographies and their effect on the development of a new generation of biomaterials including advanced multifunctional scaffolds for tissue engineering are discussed. The 2 volumes contain articles that cover a wide spectrum of subject matter such as different aspects of the development of scaffolds and coatings with enhanced performance and bioactivity, including investigations of material surface-cell interactions.

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