Phase-Separated Molecular Assembly of a Nanotube Composed of Amphiphilic Polypeptides Having a Helical Hydrophobic Block

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Supporting Information

ABSTRACT: Amphiphilic block polypeptides of poly(sarcosine)-b-(L- or D-Leu-Aib)_n (SL12OMe or SD12OMe) and poly(sarcosine)-b-(L-Leu-Aib)_n (SL14OMe) were reported to self-assemble into a nanotube morphology. Herein, we tried to construct a phase-separated nanotube by sticking two different kinds of nanotubes. SD12OMe nanotubes were found to stick to SL14OMe nanotubes with a heat treatment at 50 °C, but the sticking yield was limited. The amphiphilic polypeptides were functionalized by replacement of methyl ester with aromatic groups of N-ethylcarbazole (SL12Ecz) and naphthalimide (SD12NpiTEG), but they lost the ability to form homogeneous nanotubes. A fraction of the functionalized amphiphilic polypeptides mixing in the nanotube-forming amphiphilic polypeptides, a mixture of SL12OMe and SL12Ecz (9:1) as well as a mixture of SD12OMe and SD12NpiTEG (9:1), allowed nanotube formation. These two kinds of nanotubes partly stuck together with a heat treatment at 15 °C to maintain a segregated state of two kinds of aromatic groups along the nanotube, resulting in the formation of a phase-separated nanotube.

INTRODUCTION

Phase separation of the components in molecular assemblies is generally observed in biological systems and is deeply related with the functional aspects of the molecular assemblies. For example, rafts in biological membranes are regions having a high density of cholesterol, sphingomyelin, and some proteins, which are considered to contribute to the efficient signal transduction through membranes.1 Membrane tubules are another example of phase separation as the tubules growing from a giant vesicle were composed of a liquid disordered phase, which is related with the phenomenon of lipid sorting.2 Apart from lipid membranes, however, it is still challenging to obtain molecular assemblies in water, showing chimeric morphologies constituted by a single membrane with phase separation.3 So far, we have reported a chimeric morphology of a nanoround-bottom flask shape where vesicle and tubule morphologies coexisted as a result of phase separation.3 The driving force for the phase separation was stereocomplex formation between right- and left-handed helical peptide blocks in membranes generating vesicle morphology, whereas the excessively existing helical peptides were excluded from the stereocomplex region and self-assembled into tube morphology.

On the other hand, unsymmetric membranes displaying chemically different surfaces were successfully prepared by artificial systems.4-8 In these unsymmetric membranes, two surfaces are considered to be phase-separated into two chemically different species along the membrane normal. The other type of lateral phase separation in the membrane, however, is extremely difficult to obtain with self-assembling artificial amphiphiles because two separated phases are liable to proceed to membrane fission. The nanoround-bottom flask shape molecular assembly4 is also regarded as a successful example for lateral phase separation in the membrane, however, with the help of taking different morphologies in accordance with the phase-separated regions of two different amphiphile compositions. This consideration prompted us newly to challenge a molecular assembly of a single morphology, not a chimeric morphology, composed of laterally phase-separated membrane. We herein design a phase-separated nanotube where two kinds of nanotubes stick together but without mixing the component amphiphiles. This type of preparation may be classified into an assembling strategy of inducing directional attraction between components.9-11

The nanotube having a phase separation along the long tube axis can be functionalized by incorporating different chromophores into the phase-separated regions. One example is a photovoltaic system composed of hole- and electron-transporting layers. The similar configuration can be realized...
by using the phase-separated nanotube where two regions of the nanotube contain hole and electron mediators. As a starting system aiming at a photovoltaic nanotube, N-ethylcarbazole (Ecz)\textsuperscript{12} and naphthalimide\textsuperscript{13} were chosen for hole- and electron-transporting chromophores, respectively, and were introduced to the terminal of the hydrophobic helical block of amphiphilic polypeptides (Figure 1). The two kinds of chromophores also make it possible to evaluate whether component amphiphilic polypeptides are separated in the nanotube after sticking the two kinds of nanotubes by measuring fluorescence resonance energy transfer (FRET) between them. Preparative conditions to obtain the functionalized phase-separated nanotube are studied here by transmission electron microscopy (TEM) observations and fluorescence measurements in order to deepen our knowledge on molecular assembling under an advanced geometrical control which is prerequisite for functional molecular assemblies for the next generation.

\section{RESULTS AND DISCUSSION}

\textbf{Sticking Two Kinds of Nanotubes without Chromophores.} Amphiphilic polypeptides synthesized here have a common sequence of poly(sarcosine)-\textit{b}-((L- or D-Leu-Aib))\textsubscript{\textit{n}} (\textit{l} and \textit{n} = 6; SL14OMe, \textit{d} and \textit{n} = 6; SD12OMe, \textit{l} and \textit{n} = 7; SL14OMe). N-terminals of poly(sarcosine) blocks were attached with glycolic acid, and the number-averaged molecular weights of poly(sarcosine) blocks were in the range from 21mer to 31mer. C-terminals of (Leu-Aib)\textsubscript{\textit{n}} blocks were modified with several groups of methyl ester (OMe), Ecz, 4-N,N-diethylamino-1,8-naphthalimide (Npi), and PEGylated...
naphthalimide (NpiTEG) (Figure 1). SL12OMe was previously reported to form nanotubes with a heat treatment at 90 °C for 10 min. The most-frequent nanotube length and diameter were a few hundred nanometers and ca. 80 nm, respectively, which remained as a major fraction even after heating at 90 °C for 24 h with a minor fraction of newly formed nanotubes of a doubled length. SL12OMe nanotubes therefore have a difficulty on tube elongation by further self-sticking. On the other hand, SL12OMe nanotubes were found to easily stick together with SD12OMe nanotubes at 50 °C to change the morphology into planar sheets. The driving force for the association of two kinds of nanotubes is the stereocomplex formation between right- and left-handed helical blocks of SL12OMe and SD12OMe. When a mixture of SL14OMe and SD12OMe, which have different hydrophobic helical blocks by two residues, was dispersed in water and heated at 90 °C for 24 h, nanotubes of a large diameter of 200 nm were generated. SL14OMe and SD12OMe were mixed well in the molecular assemblies owing to stereocomplex formation, but the mixture self-assembled into nanotube morphology. With the background of these previous results, we tried to find out a possible condition for SL14OMe and SD12OMe nanotubes to stick together. Both SL14OMe and SD12OMe nanotubes have similar dimensions of ca. 80 nm diameter and 300–400 nm nanotube length (Figure 2). When two kinds of nanotubes were mixed together and heated at 50 °C for 4 h, the nanotube morphology and diameter were retained but the histogram of nanotube length showed a wide distribution with a distinct fraction larger in the region of 700–1200 nm length than SL14 and SD12 nanotubes. Neither nanotube of SL14OMe nor SD12OMe showed any elongation of the nanotube length with heating at 50 °C for 4 h (Figure S13). The nanotube fraction of 700–1200 nm length is therefore considered as a result of sticking SL14OMe and SD12OMe nanotubes, even though the elongated fraction was limited. Further, when a mixture of SL14OMe and SD12OMe in ethanol was injected into a tris-buffered saline (TBS) buffer and heated at 50 °C for 4 h, a mixture of SL14OMe and SD12OMe generated nanotubes of larger diameter than 80 nm in addition to nanosheets by TEM observations (Figure S14). The nanotube fraction of 700–1200 nm with 80 nm diameter should be therefore composed of membrane without mixing SL14OMe and SD12OMe components. Taken together, SL14OMe and SD12OMe nanotubes were able to stick together to generate phase-separated nanotubes, probably because the lateral diffusion of SL14OMe and SD12OMe into the other nanotube region after sticking should be suppressed at this low temperature of 50 °C, otherwise the diameter would become larger with mixing. However, the sticking rate was limited because of the low temperature.

**Molecular Assembling of Amphiphilic Polypeptides Carrying Chromophores.** SL14 and SD12 were modified at C-terminals with N-ethylcarbazole (SL14Ecz) and 4,N,N-diethylamino-naphthalimide (SD12Npi), respectively. However, amphiphilic polypeptides of SL14Ecz and SD12Npi self-assembled into nanosheets and irregular morphologies, but any nanotubes were not observed (Figure 3a,b). The failure in nanotube formation should be due to the hydrophobic aromatic groups, making the blocks too hydrophobic. We therefore redesigned amphiphilic polypeptides SL14Ecz and SD12Npi to reduce the hydrophobic properties. Accordingly, the hydrophobic block length of SL14Ecz was shortened from 14mer to 12mer (SL12Ecz). The naphthalimide group of SD12Npi was attached with hydrophilic two chains of tri(ethylene glycol) (SD12NpiTEG).

SL12Ecz was found to self-assemble into nanosheets just after injection into a TBS buffer (Figure 3c), which were transformed into nanotubes and vesicles with heating at 90 °C for 1 h (Figure 3d). Even though nanotubes were observed partly, vesicle morphology is considered to be a thermodynamically stable assembly for SL12Ecz. Previously, poly-(sarcosine)-β-(D-Leu-Aib) was reported to self-assemble into...
curved and planar nanosheets of a few ten nanometers size, which were transformed transiently into nanotubes with ca. 80 nm diameter with heating at 90 °C for 1 h. Further heat treatment for 72 h in total caused complete transformation into vesicles of ca. 200 nm diameter. Consequently, it is considered that the helical blocks associate tightly owing to the good space filling of interdigitated isobutyl side chains from the neighbor helices. As a result, the amphiphilic polypeptide self-assembled into a curved sheet morphology, which easily changes the morphology into a nanotube morphology with temperature. However, a vesicular morphology is more thermodynamically stable than a nanotube morphology by disappearance of the hydrophobic open edges of a nanotube. In the case of SL12Ecz, vesicles therefore should be a prevailing morphology after a long period of heating. In order to obtain thermodynamically stable nanotubes, a mixture of SL12Ecz and SL12OMe was examined. A mixture of SL12Ecz and SL12OMe at 1:1 ratio was found to generate stable nanotubes with heating at 90 °C for 3 h (Figure 3e).

SD12NpiTEG also self-assembled into nanosheets and vesicles when heated at 90 °C for 1 h in a TBS buffer (Figure 3f). Similarly to the case of SL12Ecz, the mixing effect of SD12OMe on morphology was studied. A mixture of SD12NpiTEG and SD12OMe at a ratio of 1:1 self-assembled...
into nanotube-related morphologies including three-way and closed-end nanotubes (Figure 3g). Further increase of the SD12OMe content up to 1:2 ratio resulted in molecular assemblies mostly of nanotubes with heating at 90 °C for 1 h (Figure 3h). A mixture of SD12NpiTEG and SD12OMe at 1:9 molar ratio homogeneously generated nanotubes (Figure 3i).

**Sticking Two Kinds of Nanotubes Having Chromophores.** The nanotubes prepared from a mixture of SL12Ecz and SL12OMe at 1:1 molar ratio were mixed with the nanotubes prepared from a mixture of SD12NpiTEG and SD12OMe at 1:9 molar ratio. When the nanotube mixture was heated at 90 °C, fluorescence spectra showed immediate decrease of emission intensity from Ecz around 370 nm with the increase of emission intensity from NpiTEG around 520 nm (Figure 4a). The excitation spectra with monitoring the NpiTEG emission showed increase of contribution of Ecz around 350 nm upon heating, which confirmed the excited energy transfer (FRET) from Ecz to NpiTEG (Figure 4b). The same changes in the fluorescence and excitation spectra of FRET were also observed even at a lower temperature of 30 °C but required 24 h to reach those spectra at the equilibrium state with heating at 90 °C for 10 min (Figure 4c,d). It is therefore concluded that two kinds of nanotubes fused together to mix their components similarly in the temperature range from 30 to 90 °C but with different time scales.

The morphology of the reorganized molecular assemblies was analyzed by TEM observations. The TEM image after heating at 90 °C for 1 h revealed vesicle formation without any remaining nanotubes (Figure 5a). This morphology transformation is consistent with the previous result that a mixture of SL12OMe and SD12OMe generated vesicles after heating at 90 °C for 1 h. The mixing of 50% SL12Ecz and 10% SD12NpiTEG did not have any influence on tendency of vesicle formation of a mixture of SL12OMe and SD12OMe at 90 °C. It is striking however that the nanotube mixture at 30 °C for 1 h generated a certain fraction of elongated nanotubes (Figure 5b). Further heating at 30 °C for 3 h led to inhomogeneous morphologies including a small amount of vesicles (Figure 5c). Because a mixture of SL12OMe and SD12OMe nanotubes did not stick together and any vesicles were formed at 30 °C for 3 h (Figure S11), it is considered that the presences of 50% SL12Ecz and 10% SD12NpiTEG in each molecular assembly should promote the nanotube sticking and the lateral diffusion of amphiphilic polypeptide components in the fused membranes after sticking even as low as 30 °C. Probably the degree of molecular packing of helical blocks should be loosened by the bulky aromatic groups, which allows lateral diffusion of the components in membranes. The open edges of nanotubes should also be more hydrophobic because of the hydrophobic aromatic groups to promote the nanotube sticking. Even though the nanotube sticking was promoted, the number of nanotubes sticking into an elongated nanotube was limited to two or a few at most. The limitation of nanotube elongation may be related with the membrane stiffness. The amphiphilic polypeptides have large aromatic groups which loosen the molecular packing in the membrane, resulting in low elasticity. The fragile nanotubes probably cannot elongate the length further.

In the aim of reduce the lateral diffusion in membranes to obtain the phase-separated nanotubes, the content of SL12Ecz was reduced down to 10% and the incubation temperature was decreased to 15 °C. The fluorescence and excitation spectra of a mixture of nanotubes prepared from SL12Ecz/SL12OMe (1/9) and SD12NpiTEG/SD12OMe (1/9) showed nearly no change for 3 days at 15 °C (Figure 6). However, TEM observations revealed that only a mixture of the two kinds of nanotubes increased fractions of nanotube lengths in the range from 400 to 550 nm with even longer than 1 μm nanotube but individual nanotube did not (Figure 7). Two kinds of nanotubes should therefore stick together without mixing the peptide components in the sticking membrane. The two kinds of nanotubes were able to stick together at 15 °C because of the strengthened hydrophobic aromatic interaction between nanotube open edges, even though the sticking rate to generate elongated nanotubes was low. On the other hand, the diffusion of the components in membrane was suppressed because of low temperature, resulting in the generation of the phase-separated nanotube as revealed by no change in the FRET measurement.

**CONCLUSIONS**

Two kinds of nanotubes were examined on sticking together in the aim of preparation of a phase-separated nanotube. The driving force for nanotube sticking is ascribable to stabilization energy of stereocomplex formation between right- and left-handed helices. SL12OMe and SD12OMe nanotubes stuck together to convert the morphology into sheets at 50 °C, meaning that the lateral diffusion of each component in the elongated nanotube is allowed to induce change in morphology. However, SL14OMe and SD12OMe nanotubes partially grew into a phase-separated elongated nanotube,
suggesting that the lateral diffusion of each component became suppressed in the sticking nanotube membrane at 50 °C because of the difference in the helical block lengths; otherwise, the mixing of the components would change the morphology into a thick nanotube. There are two factors governing the sticking of the two nanotubes, stereocomplex formation and temperature. The stereocomplex formation leads the membrane into a homogeneous mixing state owing to a favorable association between the two components of the right- and left-handed helices. However, the mixing rate of the two components in membrane, which is in other words lateral diffusion, depends on temperature. With high temperature, the two components will be mixed so quickly and the phase-separated nanotube is not attainable. On the other hand, for sticking of the two nanotubes, the open edges of the nanotubes must be exposed to the counterpart to join, which requires a certain amount of activation energy supplied by raising temperature. In the case of the combination of SL14OMe and SD12OMe nanotubes, with a high temperature of 90 °C, they stuck together allowing lateral diffusion to afford a thick nanotube. The compromised condition of temperature was found to be 50 °C, at which the two nanotubes stuck together but without further lateral diffusion resulting in a thin nanotube.

Two kinds of nanotubes prepared from SL12EcZ/SL12OMe (1/1) and SD12NpiTEG/SD12OMe (1/9) fused together to change the morphology even at 30 °C, meaning that small amounts of the modified components with large aromatic groups should loosen the membrane structure to allow the lateral diffusion of components in membranes. With decreasing the content of SL12EcZ and lowering the incubation temperature down to 15 °C, however, the lateral diffusion was significantly suppressed, resulting in sticking two kinds of the nanotubes to generate a phase-separated nanotube accompanying segregation of two kinds of aromatic groups along the nanotube.

The strategy employed here for sticking nanotubes uses stereocomplex formation between the right- and left-handed helices, which leads to a membrane of homogeneous mixing of the two components resulting in disappearance of phase separation. We controlled temperature to hinder the mixing of the two components here for maintaining the phase-separated state in the sticking nanotube. We are planning newly to obtain the phase-separated nanotube with using two amphiphilic polypeptides with different hydrophilic blocks, which have a tendency to segregate each other depending on the temperature.

### EXPERIMENTAL SECTION

#### Syntheses of Amphiphilic Polypeptides.

Amphiphilic polypeptides including SL14OMe and SD12NpiTEG/SD12OMe were synthesized by the conventional liquid phase method similarly to the previous report. The synthesis of the PEGylated naphthalamide (NpiTEG, Figure 1) is described in the Supporting Information. The degrees of polymerization of poly(sarcosine) blocks were determined from 1H NMR and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (see Figures S1–S12).

#### Preparation and Sticking of Peptide Nanotubes.

Amphiphilic polypeptides were dissolved in ethanol (50 mg/mL). The peptide solution (20 μL) was injected into 10 mM TBS (pH 7.4, 1 mL), stirred at 4 °C for 30 min, and heated at 90 °C for a predetermined period to self-assemble into a nanotube morphology. In order to stick the obtained nanotubes, they were mixed and stored at 50, 30, or 15 °C. The morphology was observed by TEM. TEM images were analyzed by JEOL JEM-2000EXII at an accelerating voltage of 100 kV. The peptide solutions were applied on a carbon-coated Cu grid. The samples were negatively stained by 2% uranyl acetate, followed by suction of the excess solution with a filter paper.
**FRET Measurement.** Excitation and emission spectra were recorded by a JASCO FP-6600 fluorescence spectrophotometer. The optical path length was 1 cm, and the peptide concentration was 0.25 mg/mL. The emission spectra were measured with excitation at 330 nm. The excitation spectra were obtained by monitoring the emission from NpiTEG at 550 nm.

# ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01073.

Synthetic scheme of NpiTEG and the synthetic procedures; $^1$H NMR and MALDI-TOF-MS of amphiphilic polypeptides; TEM images and histograms of nanotube lengths of molecular assemblies of SL14OMe and SD12OMe; TEM images of molecular assemblies of SL14OMe and SD12OMe; TEM images and histograms of nanotube lengths of SL12OMe and SD12OMe nanotubes; and observation of elongated SL12OMe nanotubes by atomic force microscopy in liquid environment (PDF)

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**Notes**
The authors declare no competing financial interest.

# ACKNOWLEDGMENTS

This research was supported partially by JSPS KAKENHI grant number JP16H02279.

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