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Dressing up artificial viral capsids self-assembled from C-terminal-modified β-annulus peptides

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Running Head: *Dressing up artificial viral capsids*

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Abstract

A variety of chemical approaches for the rational design of artificial proteins and peptides have in recent years been developed for the construction of self-assembled nanocapsules. It was previously found that a synthetic 24-mer β-annulus peptide, which participates in the formation of the dodecahedral internal skeleton of the tomato bushy stunt virus capsid, spontaneously self-assembled into artificial viral capsids with the size of 30–50 nm. The artificial viral capsids were established to encapsulate various guest molecules, such as anionic dyes, DNA, quantum dots, and His-tagged proteins. The artificial viral capsids could also be dressed up with gold nanoparticles, single-strand DNA, coiled-coil spikes, and proteins, by modifying with these molecules at the C-terminal of β-annulus peptides. Artificial viral capsids were notably stabilized by dressing up with human serum albumin, and acquired enzymatic activity by dressing up with ribonuclease.

Introduction

From the viewpoint of nanotechnology, natural protein nanocapsules, including apo-ferritin, clathrin, *Aquifex aeolicus* lumazine synthase, and spherical viral capsids (virus-like nanoparticles), are valuable organic nanomaterials exhibiting a discrete size and hollow nanospace. Owing to these advantageous characteristics, these protein nanocapsules have been employed as nano-containers, nano-carriers, and nano-reactors [1–12]. For instance, the cowpea chlorotic mottle virus capsid was utilized as a nano-reactor for the mineralization of polyoxometalates [10]. Moreover, an enzymatic reaction by horseradish peroxidase was encapsulated inside a capsid [11]. In addition to using natural protein nanocapsules, in recent years, chemical approaches for the rational

design of artificial proteins [12–22] and peptides [12, 13, 23–30] have been developed for the construction of self-assembled nanocapsules. The extension of molecular design to construct artificial protein/peptide nanocapsules would enhance the potential of such materials for application in a variety of areas and would particularly contribute to advances in the field of bio-nanotechnology. Yeates and co-workers successfully constructed a cubic structure by self-assembly of a fusion protein consisting of a dimer-forming subunit and a trimer-forming subunit [17, 18]. Furthermore, Baker and co-workers described the construction of icosahedral symmetric nanocapsules with the diameter of 25 nm by self-assembly of artificially-designed trimer proteins [19].

Compared to the research progress relating to protein nanocapsules, the construction of virus-like peptide nanocapsules by self-assembly remains largely unexplored. We have previously reported that trigonal β-sheet-forming peptide conjugates, which were designed by mimicking the self-assembly of natural spherical viral capsids, self-assembled into virus-like peptide nanocapsules [12, 13, 30]. In addition, in 2010, we found that a 24-mer β-annulus peptide, which participates in the formation of the dodecahedral internal skeleton of the tomato bushy stunt virus (TBSV) capsid, spontaneously self-assembled into hollow nanocapsules in water [12, 31]. A natural TBSV capsid structure involves an outer coat protein shell decorated on the internal skeleton consisting of a β-annulus motif. If the coat proteins were replaced with other molecules, one can envisage that “dressed up” artificial viral capsids would be constructed by the self-assembly of the β-annulus peptide connected to functional molecules. This focus review article discusses the construction of artificial viral capsids dressed up with functional molecules, including gold nanoparticles, single-stranded DNA (ssDNA), coiled-coil spikes, and proteins.

Artificial viral capsid self-assembled from a β-annulus peptide

A TBSV capsid with a diameter of 33 nm, exhibiting icosahedral symmetry, was generated by the self-assembly of 180 quasi-equivalent protein subunits containing 388 amino acids [32, 33]. A part of the sequence of the protein subunit formed a three-fold symmetric annular β-structure (β-annulus motif), which participated in the construction of a dodecahedral internal skeleton. We have previously prepared a 24-mer peptide (INHVGGTGGAIMAPVAVTRQLVG) constituting a β-annulus motif of TBSV utilizing a Fmoc solid-phase method [31]. We also established that the peptide spontaneously self-assembled into a spherical nanocapsule (artificial viral capsid) with the size of 30–50 nm in water (Fig. 1). The existence of a hollow cavity inside the assembly was confirmed by synchrotron small angle X-ray scattering and transmission electron microscopy (TEM) analyses. Intriguingly, the 24-mer β-annulus peptide from TBSV only formed a nanocapsule, and the formation of unimolecular folded structures or fiber structures was not observed. Moreover, the artificial viral capsid was formed at a concentration higher than the critical aggregation concentration (CAC = 25 μM) of the β-annulus peptide, which was established by concentration dependence using dynamic light scattering (DLS) evaluation. Thus, the process of artificial viral capsid formation can be controlled by conditions such as concentration, and is suitable for the encapsulation and release of guest molecules. The surface ζ-potential of the artificial viral capsid was determined to be dominated by the charges of the C-terminal sequence, whereas the N-terminal sequence exhibited a negligible effect [34]. This implies that the C-terminal is directed toward the outer surface, while the N-terminal is positioned toward the interior of the artificial capsids. Furthermore, the interior possesses cationic

charges at neutral pH. Consequently, we envisaged that anionic guest molecules could be encapsulated inside the artificial virus capsid, and the N-terminal modification of the β-annulus peptide would enable guest-selective encapsulation into the capsid (Fig. 1).

Encapsulation of guest molecules into artificial viral capsids

The addition of an aqueous solution of anionic dyes or the M13 phage DNA to the lyophilized powder of the β-annulus peptide afforded artificial viral capsids, which encapsulated guests via electrostatic interactions [34]. Moreover, anionic fluorescent quantum dots (CdTe nanoparticles) were also encapsulated into artificial viral capsids via electrostatic interactions, which was quantitatively evaluated by fluorescence correlation spectroscopy [35]. The obtained results showed that the CdTe quantum dots were spontaneously encapsulated into the capsid at a concentration higher than CAC (25 μM). We also reported that fluorescent ZnO nanoparticles were effectively encapsulated into artificial viral capsids self-assembled from β-annulus peptides containing a ZnO-binding sequence (HCVAHR) at the N-terminal [36]. Additionally, we successfully encapsulated selectively His-tagged GFP into the capsid self-assembled from β-annulus peptides modified with Ni-NTA at the N-terminal [37].

As mentioned above, long-chain nucleic acids, such as the M13 phage DNA, were easily encapsulated in an artificial viral capsid by electrostatic interactions; however, encapsulation of oligonucleotides utilized as nucleic acid drugs was challenging. We have recently reported that single-stranded oligonucleotides could be encapsulated into an artificial viral capsid via disulfide bonds at the N-terminal, and then released under reductive conditions [38]. Such an approach provides a novel strategy for applying artificial viral capsids as effective delivery materials for nucleic acid drugs, such as

siRNA.

Artificial viral capsid dressed up with gold nanoparticles

As mentioned above, it has been suggested that the C-terminals of the β-annulus peptides are directed toward the outer surface of artificial viral capsids [34]. Thus, we envisaged that artificial viral capsids decorated with functional molecules on the outer surface could be generated by appropriate modification of the C-terminals of the β-annulus peptides. In other words, we imagined that the outer coat proteins decorated on the internal skeleton of natural TBSV could be replaced by functional molecules to construct "dressed up" artificial viral capsids.

In the first instance, we attempted to produce artificial viral capsids dressed up with gold nanoparticles (AuNPs) (Fig. 2) [39]. A 29-mer β-annulus peptide bearing a Cys residue at the C-terminal was synthesized, and subsequently the peptide was conjugated to AuNP (5 nm) via the Cys residue at a concentration below the CAC, followed by protection with thioctic acid. After concentrating to a concentration above CAC, unmodified AuNPs were removed by dialysis. The TEM analysis demonstrated the formation of assemblies consisting of 30–60 AuNPs with similar size to that of artificial viral capsids. The ζ-potential of the AuNP assemblies at pH 4.6 was −30.5 ± 9.8 mV, reflecting charges of thioctic acid on the AuNPs, whereas that of unmodified artificial viral capsids at the same pH was 0.01 ± 9.8 mV. These results confirmed the outer surface decoration of AuNPs on the artificial viral capsids.

Artificial viral capsid dressed up with coiled-coil spikes

It is known that natural viruses displaying protein spikes (e.g., adenovirus) increase

cell-surface recognition and infectivity as a consequence of increased surface area. Thus, we subsequently attempted to construct artificial viral capsids with peptide spikes consisting of α-helical bundle (coiled-coil) structures on the outer surface (Fig. 3) [40]. To generate artificial viral capsids bearing protein spikes, we designed a dimeric coiled-coil-forming β-annulus peptide, which was synthesized by the native chemical ligation of a β-annulus-SBn peptide with a Cys-containing coiled-coil-B peptide. The DLS and TEM experiments demonstrated that the obtained β-annulus-coiled-coil-B peptide self-assembled into a spherical structure with the size of 30–50 nm. When the complementary coiled-coil A peptide was added to the coiled-coil B-displayed capsid, the CD spectra showed the formation of an α-helical bundle structure. The TEM image of a 4:1 mixture of the β-annulus-coiled-coil-B peptide and the coiled-coil-A peptide showed the formation of spherical assemblies with the size of 40–60 nm. Furthermore, small spheres of approximately 5 nm were attached to the surface, which corresponded to dimeric coiled-coil spikes (Fig. 3). Unfortunately, the addition of 1 equivalent of the coiled-coil-A peptide to the β-annulus-coiled-coil-B peptide induced a transformation of the spherical structure to a fibrous assembly.

Artificial viral capsid dressed up with DNA

DNA represents not only genetic material but can also be utilized as an aptamer bound to specific molecules, or as a nano-material for arranging functional molecules. We have developed β-annulus peptide conjugates bearing ssDNA (dA_{20} or dT_{20}) at the C-terminal, which were directed toward the outer surface of the capsid (Fig. 4A) [41]. The DLS and TEM experiments demonstrated that the dA_{20}-conjugated β-annulus peptides self-assembled into artificial viral capsids with sizes of 45–160 nm, despite

anionic repulsion. Addition of complementary poly-T to the artificial viral capsids dressed up with dA_{20} led to the formation of aggregates (Fig. 4B). Conversely, addition of non-complementary poly-dA did not afford such aggregates (Fig. 4C). These observations imply that dA_{20} on artificial viral capsid hybridized with the complementary DNA to form aggregates by cross-linking of capsids with polynucleotide chains.

Artificial viral capsid dressed up with human serum albumin

As described above, the TBSV capsid consists of an outer coat protein shell linked through covalent bonds to an internal skeleton encompassing a β-annulus motif. Mimicking this natural capsid structure, we designed an artificial viral capsid dressed up with other proteins [42]. Since human serum albumin (HSA) is a blood-compatible protein and is not immunogenic, an artificial viral capsid dressed up with HSA has potential for application as a biocompatible material. The β-annulus peptide-HSA conjugate was synthesized by linking the Cys residue of the β-annulus peptide at the C-terminal and the Cys residue at position 34 of HSA via a bismaleimide linker. DLS and TEM experiments demonstrated that the conjugate self-assembled into spherical structures with the size of 50–70 nm at pH 7 (Fig. 5A, B). The ζ-potential of the conjugate assemblies revealed that the HSA proteins were displayed on the outer surface of the artificial viral capsid. Remarkably, the CAC of the conjugate at pH 7 was approximately 0.01 μM (Fig. 5C), which is 1/2500 lower than that of the unmodified β-annulus peptides (25 μM). These results suggest that the artificial viral capsids were stabilized by dressing up with HSA on the outer surface.

Artificial viral capsid dressed up with ribonuclease S

Ribonuclease S (RNase S) is a split-type enzyme, which can be reconstructed from S-protein and S-peptide with the association constant of $7 \times 10^6\ M^{-1}$ [43]. We have successfully generated an artificial viral capsid dressed up with RNase S by the self-assembly of the β-annulus-S-peptide followed by the reconstruction with S-protein (Fig. 6) [44]. The β-annulus-S-peptide was synthesized by native chemical ligation of the β-annulus-SBz peptide with the Cys-containing S-peptide (CGGGKETAAAKFERQHMDS). The β-annulus-S-peptide self-assembled into a spherical structure with the size of approximately 40 nm. The complexation of the S-protein to the S-peptide-displayed artificial viral capsid to reconstruct RNase S was confirmed by CD analysis. In the TEM image of the equimolar mixture of the β-annulus-S-peptide and S-protein, spherical assemblies with the size of 50–65 nm were observed, to which small spheres of 5–10 nm were attached on the surface (Fig. 6). The small spheres were corresponded to RNase S on the capsid surface. It was also confirmed that the ζ-potential of the RNase S-decorated artificial viral capsid reflects the surface charge of RNase S. The fluorometric assay of the RNase activity revealed that the RNase S-decorated artificial viral capsid retained 85% of ribonuclease activity compared to intact RNase S, despite the crowded surface environment. These results suggest that an artificial viral capsid exhibiting enzymatic activity was successfully constructed.

Summary

We have successfully constructed artificial viral capsids, which self-assembled from β-annulus peptides participating in the formation of the dodecahedral internal

skeleton of TBSV. The artificial viral capsids were dressed up with functional molecules, such as AuNP, ssDNA, coiled-coil peptides, HSA, and RNase S by self-assembly of C-terminal-modified β-annulus peptides. It was established that the outer protein shell of TBSV was replaced by these functional molecules in the dressed-up capsids. Understanding the self-assembly/disassembly mechanism of the dressed up artificial viral capsids by thermodynamic and kinetic analysis is important issue for the applications. We are planning these analyses using fluorescence correlation spectroscopy and isothermal titration calorimetry. The present strategy of dressing up artificial viral capsids is remarkably valuable not only to understand the physical properties of natural viral capsids but also to invest additional functionalities to natural viral capsids. Utilizing this versatile strategy, we envisage to fabricate various artificial viral capsids dressed up with envelope lipid bilayer, cell-targeting receptors, cell-penetrating peptides, and antigens. The resulting dressed-up capsids will be promising materials for application as cell-specific drug delivery carriers as well as artificial vaccine scaffolds.

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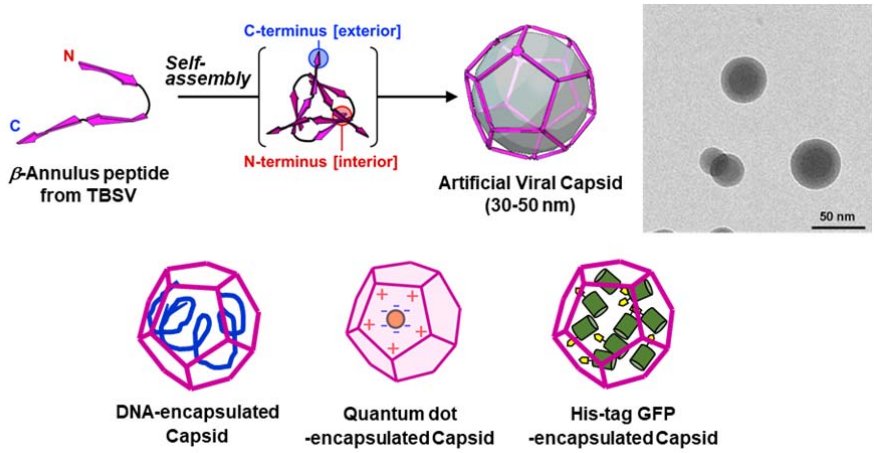

Fig. 1 Artificial viral capsids self-assembled from β-annulus peptides from TBSV and encapsulation of guest molecules into capsids.

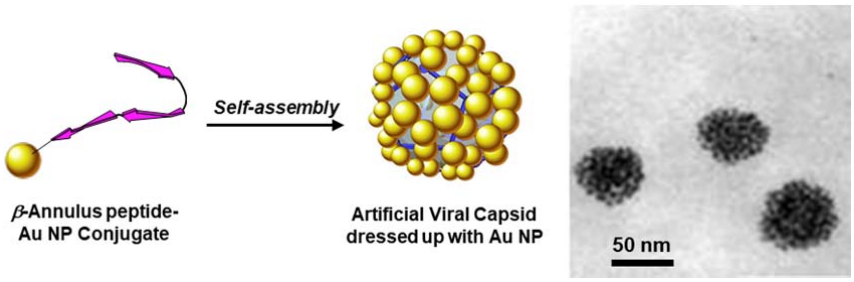

Fig. 2 Schematic illustration of the formation of artificial viral capsids dressed up with AuNPs and their TEM image.

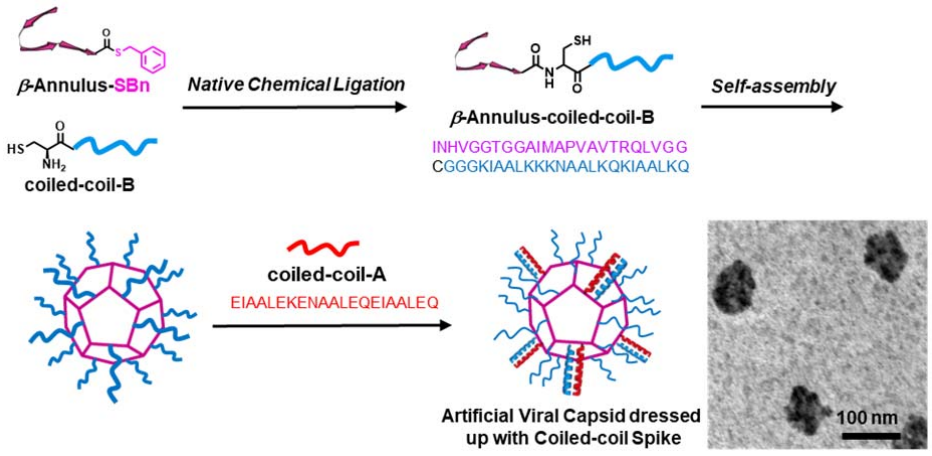

Fig. 3 Schematic illustration of the formation of artificial viral capsids dressed up with coiled-coil spikes and their TEM image.

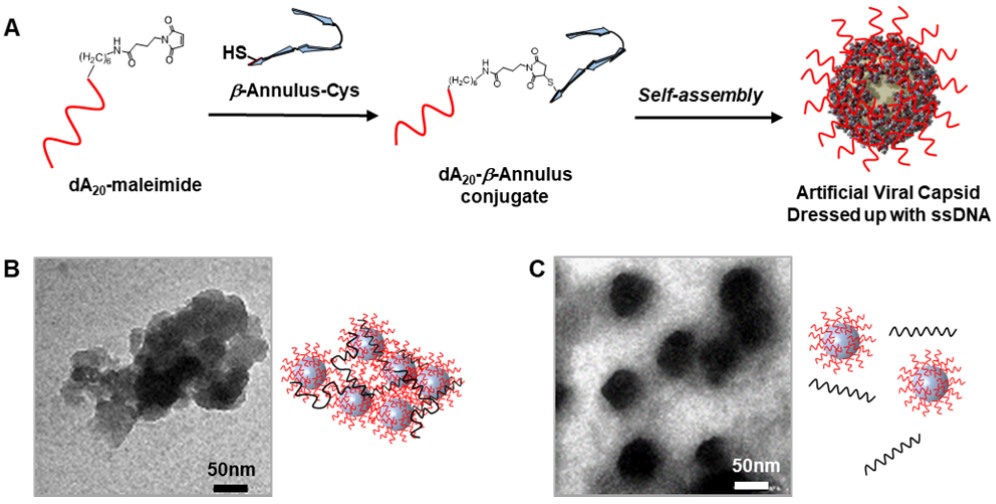

Fig. 4 (A) Schematic illustration of the formation of artificial viral capsids dressed up with ssDNA. (B, C) TEM images of dA_{20}-decorated capsids in the presence of poly-T (B) and poly-dA (C).

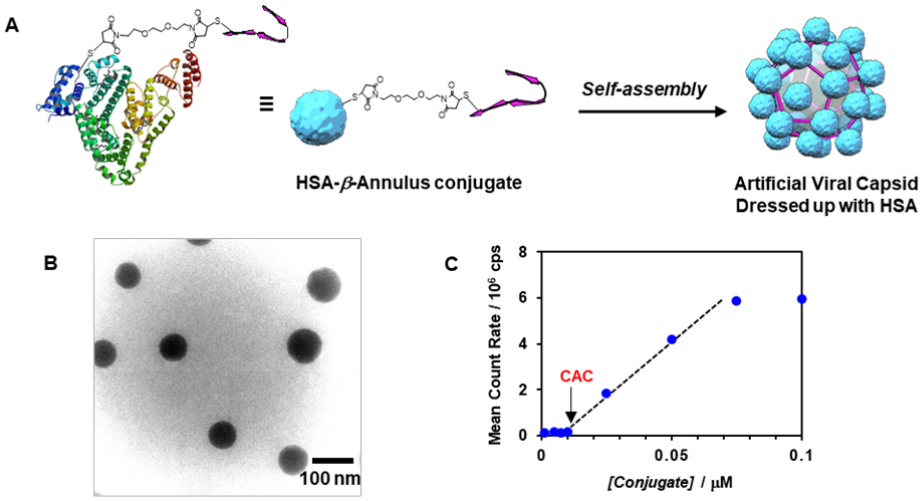

Fig. 5 (A) Schematic illustration of the formation of artificial viral capsids dressed up with HSA. (B) TEM image and (C) concentration dependence on scattering intensity of the HSA-decorated capsids.

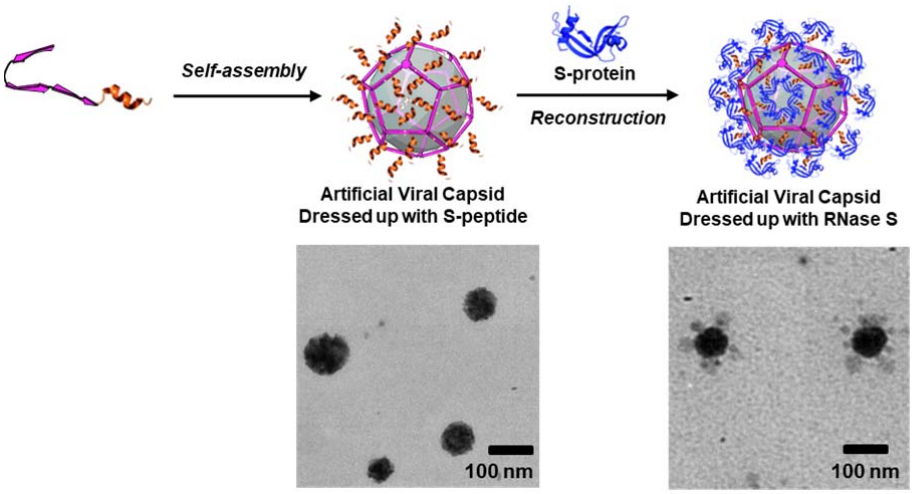

Fig. 6 Schematic illustration of the formation of artificial viral capsids dressed up with S-peptide and RNase S and their TEM images.

Graphical Abstract