DNA NANOSTRUCTURES

Nanocages for virus inhibition

Elaborately designed DNA icosahedral shells cage intact virions to effectively protect host cells from viral infections.

Neha Chauhan and Xing Wang

Emerging and re-emerging viral diseases present significant threats to public health, as witnessed by the ongoing COVID-19 pandemic. Viruses must first latch onto the cell membrane and disgorge their genetic instructions to infect their host cells. Virus inhibition typically relies on neutralizing or therapeutic antibodies, either produced in the host's immune system or administered exogenously, collectively wrapping around virus particles to prevent cellular entry. However, antibodies often target specific viral antigens in a one-on-one manner, resulting in weak binding strength and low antiviral efficacy, especially at low antibody levels. Importantly, current antibody-based vaccines and therapeutics face the risk of exacerbating disease severity

through antibody-dependent enhancement of infection, which 'backfires', enhancing viral replication¹. In nature, viruses exhibit multivalent binding to host cells facilitated by spatially patterned viral surface antigens. Novel strategies focusing on multivalent interaction-mediated caging of entire virus particles could significantly inhibit the virus cell binding and enhance virus inhibition capabilities. Creating macromolecular cages using protein modules is inspiring². However, the designer protein cages are much smaller than most viruses and cannot be easily functionalized with virus-binding moieties. In this issue of *Nature Materials*, Christian Sigl and colleagues report a programmable icosahedral 'canvas'-platform for the design and synthesis of DNA origami

triangular tiles that self-assemble into icosahedral shells. These structures can work as 'catcher-like' decoys to tightly trap entire virions through multivalent interactions for effective virus inhibition³.

Virus particles enclose their genetic materials in protein shells called capsids. These capsids consist of repetitive subunits that often self-assemble into an icosahedral structure, displaying polyhedral faces that determine the loci of pentamers or hexamers of protein clusters (Fig. 1a). The size and complexity of these capsids can be classified using the triangulation number (*T* number), which, according to the 'quasi-equivalence' theory by Caspar and Klug (CK-theory)⁴, can be calculated from the arrangement of pentamers and hexamers

Fig. 1 | Design principles and applications of DNA icosahedral shells. **a**, Capsid proteins conforming to an architecture with icosahedral symmetry are positioned at corners of the triangular faces, as clusters of hexamers (six dots) or pentamers (five dots). **b**, Each coloured triangle represents one of the triangular faces of the icosahedral shell displayed on the hexagonal grid. (h,k) are hexagonal coordinates that indicate where pentamers are within an icosahedral shell. $T(h,k) = h^2 + hk + k^2$. **c**, Cylindrical models of origami triangles that are assembled into corresponding shells (below), in which one of the polyhedral faces has been displaced to show the polyhedral symmetry. The bevelled edges of the triangles carry shape-complementary protrusions (light) and recesses (dark), with each combination indicated by a double-headed arrow. S_1 – S_3 number the unique edge of a triangle. **d**, Schematic of AAV2 neutralization with DNA origami half-shells and **e**, alternative uses of the shells as carriers for drug delivery, development of viral vaccines and purification of other biotherapeutic particles for therapeutics. Panel **c** adapted with permission from ref. ³, Springer Nature Ltd.

displayed on the hexagonal grid (Fig. 1b). The T number specifies the total number of unique triangular edges that form a specific icosahedron. This translates to $60T$ protein subunits, arranged onto 12 pentamers, and $10(T - 1)$ hexamers in a viral capsid of a specific T number. Inspired by the CK-theory and geometric principles^{4,5}, and combining it with multilayer DNA origami concepts⁶, Sigl and co-workers develop a programmable icosahedral ‘canvas’ for the design of pseudo-symmetric and triangular subunits that stick to each other, forming DNA icosahedral shells of different complexity. Analogous to virus capsids, each triangular edge represents a capsid protein in the cluster. The self-assembly, structure and size of each icosahedral shell is controlled by the length, the bevel angle and the shape-complementary binding pattern⁷ of its triangle components. As illustrated in Fig. 1c, the construction of a $T = 1$ DNA icosahedral shell uses a single triangular unit with three identical edges, while a $T = 3$ shell uses a single triangular unit with three different edges; higher-order shells are assembled using multiple triangular units with designer edges carrying needed shape-complementary binding patterns. Formation of each triangular unit was first examined for any structural defects by using single-particle analysis of the cryo-electron microscopy images. The defects-free units were then assembled successfully into the icosahedral shells with the desired symmetries and correct polyhedral face arrangement, confirming the robustness of DNA icosahedral design principles.

Having validated their design platform, Sigl and colleagues evolved it to enable the assembly of partial icosahedral structures with virion-sized openings for virus trapping and inhibition. The structures of these half-shell nanocages were stabilized by ultraviolet photo-crosslinking and

poly(ethylene glycol)–oligolysine/oligolysine coating, and subsequently functionalized with multiple antibodies against adeno-associated virus serotype 2 (AAV2) to test their AAV2 neutralization capability in physiological fluids and human cells. The DNA half-shells displayed an effective virus inhibition capacity, acting as physical barriers that bind and cage virions (Fig. 1d). In comparison to free anti-AAV2 antibodies, the DNA half-shells not only decreased the number of infected host cells, but also substantially lowered their AAV2 viral loads. By enclosing the antibodies, the shells shall also minimize the antibody-dependent enhancement effects without losing the antiviral activity.

The origami-based canvas of DNA shells provides excellent spatial addressability to enable precise display of multiple binders, mirroring the spatial arrangement of the target viral antigens. The resultant pattern-matching interactions, as recently demonstrated⁸ but not explored by Sigl and colleagues, should be able to further improve the shells’ viral-trapping avidity and antiviral efficacy. With the ability to economically manufacture DNA origamis that are stable under physiological conditions⁹, the work of Sigl and co-workers offers a plug-and-play platform that holds a great potential for developing clinical therapeutics to combat any emerging or re-emerging viral infections. However, there are still concerns regarding the use of DNA origami structures in a clinical setting due to their potential in vivo instability and immunogenicity. Although the poly(ethylene glycol)–oligolysine/oligolysine coating strategy¹⁰ for stabilizing the DNA shells under physiological conditions might afford a means to repress the immunogenicity of DNA origami structures, a rigorous and comprehensive safety analysis of the DNA origami shells needs to be undertaken prior to the commercial exploitation of these

shell-based therapeutics. As an alternative, virus-like particles for vaccination or drug delivery could be prepared by decorating the outer surface of a specific shell with viral antigens, whose positions conform to the polyhedral blueprints of the corresponding viral capsid. Additionally, the shells, by themselves or after being integrated into available resins, could be potentially used for the sorting and purification of other biotherapeutic particles for vaccine development and gene therapy (Fig. 1e). □

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Competing interests

The authors declare no competing interests.

SPINTRONICS

Silicon goes heavyweight

A substantial spin-orbit interaction is introduced in a purely silicon heterostructure and can be tuned through an applied gate voltage.

Christopher H. Marrows

Spintronics uses the electron spin as a state variable, and so relies on the storage and manipulation of electron spin states to record and process data.

However, there is a tension between these two functions: spin-orbit interaction enables the manipulation of spin states, but shortens spin lifetimes, because in its

presence spin is no longer a good quantum number. Now, writing in *Nature Materials*, Masashi Shiraishi and collaborators show that it is possible to realize a sizeable