Unraveling the Dynamics of Antibody-Antigen Interaction by DNA Origami

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Abstract To investigate the dynamic interaction between antibody and antigen, Fan *et al.* rationally designed a triangular DNA origami framework to spatially organize the antigenic epitopes at the nanoscale and thus to monitor the transient binding kinetics of the dynamic antigen-antibody complexes at room temperature. This study provides a straightforward, designable and programmable strategy to investigate the transition kinetics of antibody-antigen interaction at a single-molecule level and improve the understanding toward the design of the next-generation antibodies and vaccines for various biomedical applications. This work has been published online in *Nature Communications* on June 19, 2020.

The recognition of pathogenic antigens by antibodies is an important natural defense strategy in the mammalian adaptive immune system^[1]. The avidity of the antibody is mainly determined by the antibody structure and the spatial presentation of antigenic epitopes on the surface of a viral particle^[2]. However, it remains difficult to explore the dynamic anti-body-antigen interaction with high spatiotemporal resolution. Recently, Fan *et al.*^[3] have developed an elegant DNA origami-based strategy to probe the transient binding of the antibody to the antigen at a

single-molecule level. Exploiting the excellent addressability and programmability of DNA self-assembly, the authors successfully fabricated a triangular DNA origami framework to spatially organize the artificial epitopes at the nanoscale, namely, DNA origami epitopes(DOE). The designed DOEs site-specifically anchored six pairs of artificial epitope molecules on the prescribed positions with tailored lateral distances between each epitope pair, ranging from 3 nm to 20 nm [Fig.1(A)]. The rigidity of DOEs allows room-temperature

Fig.1 Schematic illustration of epitope spikes on the surface of a viral particle and DOEs for IgG capture and binding(A), peak force-AFM image for DOEs-captured IgGs(B), schematic of the three-stage binding process(left) and corresponding HS-AFM images(right)(C), and distinct conformations of single IgG captured by DOEs with designed distances, and schematic illustration(left) and snapshot HS-AFM images(right)(D)^[3]

(B) Scale bar, 20 nm; (C) scale bar, 10 nm; (D) scale bar, 10 nm.

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freezing of captured immunoglobulin G proteins(IgG) for high-resolution imaging of transient binding conformations. Using atomic force microscopy(AFM), they illustrated that DOEs-captured IgG at the single-molecule level, which is composed of a central fragment crystallizable(Fc) arm and two stationary antigen-binding fragments(Fab) arms on DOEs[Fig.1(B)].

The epitope distance-dependent avidity of IgG has physiologically or pathologically relevance to early immune response, and viruses may evolve tunable spatial distribution of epitope spik to escape antibody-neutralization and clearance^[4,5]. The single-molecular analysis and dynamic processing of antibody-antigen interaction are essential for designing antibody and vaccine development^[6]. In this study^[3], Fan *et al.* successfully programmed the stretched state of IgG by tuning the distance between the bivalent epitopes. The authors used high-speed AFM(HS-AFM) to image the temporal evolution of the three-stage binding process of IgG, from (i) wandering to (ii) monovalent binding, then (iii) bivalent binding states, on the epitopes with different distances[Fig.1(C)]. The flexibility of the two Fab arms of the IgG enables the binding conformations ranging from highly compact to far stretched in response to short-to-long epitope distances. The epitope distance of *ca.* 10 nm led to the highest kinetics and efficiency for bivalent IgG binding on DOEs with the most favorable binding energy

[Fig.1(D)].

In summary, Fan *et al.* provide a straightforward, designable and programmable DOEs platform to imitate the geometric distribution of surface antigen epitopes on virus particles. The DOEs strategy can be used to evaluate the avidity of different IgGs by exploring the dynamics of the IgG-binding process on their cognate antigen on the epitope distance-engineered DOEs. The development of DOEs is potentially beneficial to the rational design of next-generation vaccines and recombinant antibodies in various immunological applications, such as virus-neutralization, pathogen diagnosis and cancer immunotherapy.

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