Mechanism of Virus Capsid Assembly

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1. Abstract

Many possible intermediates exist on the assembly path from hepatitis B capsid protein dimers to 120-dimer capsid. If every intermediate were tested, the assembly would often get stuck for entropic reasons, and essentially, every capsid would follow a unique assembly path. Yet, capsids assemble rapidly with minimal trapped intermediates. To understand the fundamental mechanisms of capsid assembly, it is critical to resolve the early stages of the reaction. We used time-resolved Small Angle X-ray Scattering to observe assembly, which is sensitive to solute size and shape and has millisecond temporal resolution. Scattering curves were fit to a thermodynamically curated library of assembly intermediates, using a maximum information entropy approach to provide a physical rationale for selecting intermediates. We found that capsid assembly was controlled by the supersaturation state of the system at the onset of assembly, dictating the intermediate structures during the early stages of the reaction. With the mildest conditions tested, we observed a nearly two-state reaction from dimer to capsid with a small number of dimers-of-dimers and trimers-of-dimers. We observed a decamer-of-dimers and a 90-dimer species in slightly more aggressive conditions. In conditions where there is measurable kinetic trapping, we found a greater diversity of early intermediates, accumulated within a fraction of a second and propagated into long-lived kinetically trapped states (>90-mer). Intermediates>30 and <90 subunits did not accumulate in all cases. These results indicate the presence of low-barrier paths that connect intermediates that can direct the ultimate assembly path to late intermediates where assembly can be paused.