Capsid with a Twist: Structure of Pleomorphic Poxvirus Scaffold

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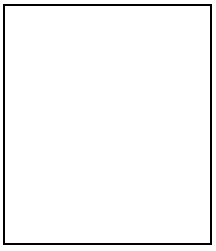
Poxviruses are large, enveloped double-stranded DNA viruses that are widely known for devastating smallpox disease that claimed millions of lives throughout the history. Despite the eradication of smallpox in 1980, frequent zoonotic outbreaks of smallpox-like diseases threaten human health, as exemplified by recent spread of monkeypox[1]. Therefore, detailed molecular understanding of poxvirus replication cycle is necessary for the development of prevention and treatment strategies.

Assembly of immature poxvirus particles is driven by the self-assembly of multiple copies of scaffolding protein on viral membrane, which results in the formation of spherical, capsid-like shell. The scaffold determines the overall shape and size of the virus particles, and hence critical for subsequent virus maturation[2]. In order to understand molecular mechanism that governs the scaffold assembly, we utilized scaffold protein D13 from vaccinia virus, a prototypal poxvirus, for in vitro assembly into various multimers. The resulting assembly products were studied using cryo-electron microscopy (cryo-EM) and electron tomography (cryo-ET) for detailed structural investigation.

D13 trimers interact mainly via electrostatic interactions to form loosely connected hexagonal lattice or twisted connections of the hexameric rings of D13 trimers. Most notable feature of the assembly structures is the short N-terminal α-helix, of which the dislocation from its hydrophobic binding pocket induces inter-trimeric interaction[3]. The intactness of the N-terminal helix determines whether the assembly proceeds to spherical scaffold shell that resembles authentic virus particle, or into twisted hexameric rings. We propose that these assembly structures are the keys to understand the regulation mechanism of poxvirus scaffold assembly, and that the development of peptide that irreversibly attaches to the binding pocket of N-terminal α-helix could permanently impair scaffold formation.

References

[1] Kozlov, M. *Nature.* **2022**, *608*, 655-656.
[2] Hyun, J. *Appl. Microsc.* **2022**, *52:11*
[3] Hyun, J.; Matsunami, H.; Kim, T.G.; Wolf, M. *Nat. Comm.* **2022**, *13,* 1704



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