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[BioChemistry] Vaccinia A27 Protein Structure is Revealed to Regulate Virus and Host Cell Membrane Fusion

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([Chinese Version])

Academia Sinica Newsletter (2013/08/27) Two research teams in Academia Sinica, Dr. Andrew H.-J. WANG at the Institute of Biological Chemistry and Dr. Wen CHANG at the Institute of Molecular Biology, have joined the effort to solve the crystal structure of a vaccinia envelope A27 protein and showed that the A27 protein trimer is the structural unit critical for vaccinia virus egress as well as controlling viral fusion suppressor complex formation. The findings shed light on the viral fusion regulation mechanism of vaccinia virus, a member of poxvirus family that also contains variola virus, the etiological disease of smallpox disease. Revelation of viral membrane protein structure will aid in design of improved vaccine in the future. The research was published in PLoS Pathogens on August 23, 2013.

Poxvirus family contains many pathogenic members such as mousepox, sheepox and monkeypox viruses that are present in our society whereas vaccinia virus, as the prototypic member of this family, is considered safe to be used for induction of protective immune responses in humans. Researches now are focused on understanding vaccinia virus structure proteins in order to improve the future vaccine design.

Vaccinia mature virus has more than 20 envelope proteins, including the A27 protein, which is conserved in pathogenic poxviruses such as variola and monkey poxivuses. A27 protein has multiple functions in the virus life cycle. During virus entry, A27 mediates the attachment of mature vaccinia virus to cell surface heparan sulfate. A27 also tethers a viral fusion suppressor protein, A26, to mature virions. During virion morphogenesis, A27 mediates mature virus transport in infected cells.

Dr. Andrew H.-J. WANG's lab used X-ray crystallography to determine the structure of A27 protein, which forms a novel hexamer consisting of four parallel strands and two anti-parallel strands. Hexamerization depends on the coiled-coiled domain from L47 to L82 within each A27 strand, and mutational analysis revealed that amino acid residues within the coiled-coiled domain are critical for A27 self-assembly in vitro. Based on the crystal structure, Dr. Wen CHANG's lab generated a series of mutant vaccinia viruses that interrupt A27 protein-protein contact interface resulting in attenuation of virus egress and virus spreading in cells. Furthermore, CHANG's lab also demonstrated that A27 protein complex formation through the coiled-coiled domain is crucial to its biological activity in vivo, and revealed how A27 regulates virus-induced membrane fusion through its ability to form complexes with A26 protein. Since A27 is a critical target of neutralizing antibodies against pathogenic poxvirus infection in humans, our findings provide a structural basis for the development of anti-pox drugs and vaccines.

Related Website:
http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1003563

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