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Overview of the Role of Actin in the Intracellular Transport of Baculovirus

Sainan Li*, Huanhuan Jiang, Tian Gan, Yina Lv, Linqi Huang, Lipeng Cui

Laboratory of Microbial Resources Exploitation and Application, Department of Biology, Zhaoqing University, Zhaoqing, China

***Corresponding Author:** Sainan Li, Laboratory of Microbial Resources Exploitation and Application, Department of Biology, Zhaoqing University, Zhaoqing, China

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Abstract

Baculoviruses are a family of rod-shaped, enveloped, double-stranded DNA viruses which are specifically pathogenic to arthropod species. Baculoviruses infect their host cells, causing the rearrangement of actin in host cells, and then using actin to complete their intracellular infection process. Baculoviruses encode multiple proteins involved in regulating the rearrangement of intracellular actin network. This review summarizes the life cycle of baculoviruses, and examines the recent progress regarding the role of actin in the targeted transport of baculovirus nucleocapsids. The baculovirus proteins that interact with actin and are related to actin rearrangement are also described briefly. This information should aid in understanding the molecular biology of baculoviruses especially for gene expression and biological control.

Keywords: Baculovirus, Actin, Rearrangement, Nucleocapsid transport

Introduction

Baculoviruses are a large group of rod-shaped, enveloped, circular, double-stranded DNA viruses, which are specifically pathogenic to arthropod [1]. The sizes of baculovirus genomes vary from approximately 80 to 180 kb, which encode 89 to 183 genes [2]. Baculoviruses ubiquitously exist in the environment and have been isolated from more than 600 host insect species, which predominantly belong to the orders Lepidoptera, Hymenoptera, and Diptera [3]. Autographa californica multiple nucleopolyhedrovirus (AcMNPV), the prototype of the *Baculoviridae* family, is the first baculovirus to be sequenced [4]. So far, more than 80 baculoviruses have been sequenced. They are divided into four genera, *Alphabaculovirus, Betabaculovirus, Gammabaculovirus,* and *Deltabaculovirus* [5]. On the basis of molecular phylogenetic analysis of the *polyhedrin (polh)* gene, the members of the *Alphabaculovirus* genus can be further subdivided into group I and II NPVs [6].

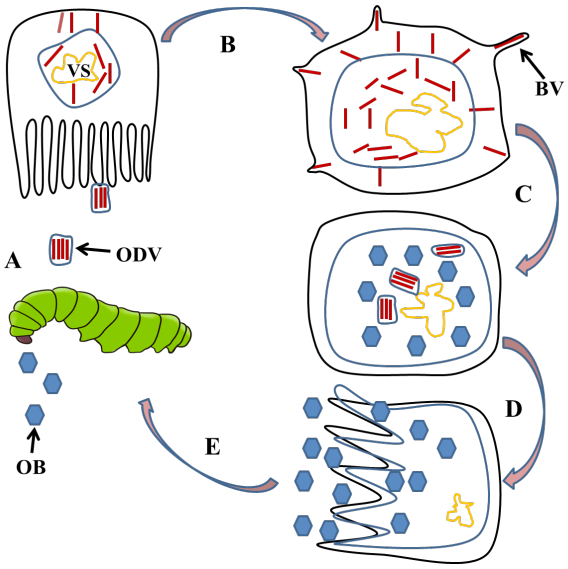
The unique life cycle of baculoviruses is that baculoviruses produce two types of virions during the infection, one is the occlusion-derived virus (ODV), and the other is the budded virus (BV). ODV and BV have similar nucleocapsid structure, but the origin and composition of their envelopes are different. The main envelope protein of BV is GP64. GP64 can mediate budding, attachment, and entry of BVs, which resulted in the system infection. The ODV envelope contains many associated and integral viral proteins. ODV is responsible for spreading infection among insects [3,7].

Actin is one of the most abundant proteins in eukaryotes and exists in the whole cell. Actin is widely involved in the construction of cytoskeleton, maintenance of cell morphology, muscle cell contraction and cell motility, phagocytosis, regulation of cell division, secretion, intracellular material transport and signal transduction. Actin exists in two forms: monomeric globular actin (G-actin) and filamentous actin (F-actin). F-actin and G-actin can be converted into each other under certain conditions, so as to maintain the dynamic balance of intracellular actin, which is the basis for the movement and replication of many pathogenic microorganisms in host cells, including baculoviruses. This review will focus on the recent advances and summarize the function of actin in the baculovirus infection and the regulation of baculovirus on intracellular actin rearrangement.

Infection cycle of baculovirus

The infection cycle of baculovirus can be divided into two stages: primary infection and systemic infection (Figure 1). Upon oral ingestion, the occlusion bodies (OBs) are dissolved in the insect midgut, releasing ODVs embedded in OBs. ODVs penetrate the peritrophic matrix of insect midgut, and then ODV envelopes fuse with microvillar membranes, releasing virus nucleocapsids into the midgut epithelial cells, initiating primary infection. In the early infection stage, newly assembled nucleocapsids egress from the nucleus, migrate across the cytoplasm, and bud from the plasma membrane to form BVs. Then, BVs spread throughout

the organism, resulting in systemic infection [3]. In the later stage of virus infection, the nucleocapsids remain in the infected nucleus, and obtain envelopes which may be derived from nuclear membranes to form ODVs [1]. The ODVs are further packaged into OBs. Upon the death and disintegration of the insect, OBs are released into the natural environment, thus starting the next infection cycle.



Figue 1: The infection cycle of baculovirus. (A) Occlusion bodies (OBs) ingested by an insect dissolve in the alkaline midgut lumen and release ODVs. Then, ODVs infect midgut epithelial cells, initiating primary infection. (B) The virions bud out from the basement membrane of the cells, initiating a systemic infection. Early in the systemic infection, more newly assembled nucleocapsids bud from the plasma membrane to form budded viruses (BVs), which spread the infection throughout the organism. (C) Late in the virus infection, the nucleocapsids remained in the infected nucleus obtain envelopes to form ODVs, which are further packaged into OBs. (D) Upon the death of the cells, OBs are released. (E) OBs enter into the natural environment, thus starting the next infection cycle. VS, virogenic stroma.

The relation of baculovirus infection and actin network rearrangement

It has been found that baculovirus infection can cause multiple sequential rearrangements of actin network in host cells [8,9]. After the viruses enter into cells, early cables are formed within the cytoplasm of infected cells, and a single nucleocapsid is at an end of most cables, suggesting that nucleocapsids or nucleocapsid-associated proteins of viruses induce the polymerization or bundling of actin [8,9]. With the expression of early viral gene, the second rearrangement of actin occurs in cells, and the F-actin cables gather near the plasma membrane [9]. Actin rearrangement-inducing factor 1 was found to be able to induce actin rearrangement and colocalize with F-actin at the plasma membrane. The various deletion mutants showed a loss of actin concentration at the plasma membrane [10,11]. At the late stage of virus infection, actin accumulates in the nucleus to form F-actin, which distributes in the ring zone surrounding the virogenic stroma (VS) [8,9]. Although G-actin and F-actin also exist in the nuclei of uninfected cells [12] and participate in many nuclear activities [13], baculovirus can cause a large number of G-actin aggregation in the nucleus and form F-actin [9]. The F-actin in the nucleus is very important for the morphogenesis of nucleocapsid. In the presence of either Cytochalasin D or Latrunculin A, two actin-binding agents that interfere with F-actin-dependent processes, the proper intranuclear assembly of viral nucleocapsids and the production of infectious progeny are prevented, showing that intranuclear F-actin is essential for baculovirus to produce progeny [14-17]. It has been reported that AcMNPV *ie-1, pe38, ac4, he65, ac102,* and *ac152*, known as the nuclear localization of actin (NLA) genes, may be required for mediating nuclear localization of G-actin [18,19]. Further studies showed that among the six NLA genes, only *ac102* is required in the nuclear localization of G-actin, and the other five NLA genes are not necessary for this process [20].

The role of actin in the transport of nucleocapsid in cells

After the nucleocapsid is released into the cytoplasm, it is transported into the nucleus via the nuclear pore complex to start the cascade expression of baculovirus genes. In general, the transport of viruses in cells requires the assistance of microtubule [21], while the transport of bacteria relies on microfilament [22]. Some viruses, such as vaccinia virus, use both microtubules and actin filaments for intracellular movement and egress [23]. Studies have found that baculovirus uses microfilament to mediate the activity of nucleocapsid in cells, and the microtubule depolymerization has no effect on the movement of nucleocapsid in cells [24,25]. In addition, nucleocapsids of AcMNPV have been found to interact with actin as soon as they enter the cytoplasm, suggesting that the nucleocapsids may use microfilament to move in cells [8,26]. Inhibition of actin entry into nucleus can delay the start of viral gene expression, suggesting that actin movement facilitates the entry of viruses into the nucleus [27]. The visualization of AcMNPV movements in cells showed that nucleocapsids of AcMNPV undergo intracellular motility driven by actin polymerization [24].

Electron tomography showed that baculovirus is propelled by a fishbone-like array of actin filaments constructed from subsets linked by branch junctions, with an average of four filaments pushing the virus by their fast polymerizing ends at any one time [28]. Using a stochastic mathematical model, the simulations of actin comet tail organization as well as the tracks adopted by baculovirus inside cells showed that the actin filaments are continuously tethered to the virus surface as they grow, branch,

and push [28,29]. Therefore, F-actin is necessary for the directional transport of baculovirus nucleocapsid in cells [27,30].

The baculovirus protein that interacted with actin

At the late stage of baculovirus infection, six viral actin-interacting proteins are synthesized, which are P78/83, BV/ODV-C42, VP39, VP80, Ac102 and Ac34 [31-35]. VP80 is associated with the nucleocapsid of both BVs and ODVs, typically at one end of the nucleocapsids. VP80 has sequence motifs with homology to invertebrate paramyosin proteins, and VP80 is entirely localized in nuclei, adjacent to the virus-triggered F-actin scaffold [32]. Although deletion of the AcMNPV *vp80* does not affect assembly of nucleocapsids, these nucleocapsids cannot migrate from the VS to the nuclear periphery to form viral progeny, showing VP80 is involved in the process of nucleocapsid egress from the VS toward the nuclear periphery along F-actin [36-39]. VP39 is the major capsid protein of baculovirus. VP39 can bind both G-actin and F-actin, but shows higher affinity for G-actin [40]. However, the function of VP39 binding G-actin is still unclear. Ac34 distributes in both the cytoplasm and the nuclei of infected cells but was not a viral structural protein [41]. The potential C3H zinc finger in Ac34 is required for its nuclear localization and optimal virus multiplication [42]. Ac34 can bind to the actin-related protein complex (Arp2/3) subunits of Sf9 cells, P40, P34, and P20, which is essential for Ac34 to relocate Arp2/3 subunits to the nucleus [33]. The subcellular distribution of Arp2/3 under steady-state conditions is controlled by chromosomal maintenance 1 (CRM1)-dependent nuclear export. Upon AcMNPV infection, Ac34 inhibits CRM1 pathway and leads to Arp2/3 retention in the nucleus to assist in virus replication [34].

P78/83 is a Wiskott-Aldrich syndrome protein (WASP)-like protein, also known as nucleation promoting factors (NPFs), locates at one end of nucleocapsid, and is involved in nuclear actin assembly during the baculovirus infection [43]. The main substrate of WASP is Arp2/3 complex, which is the most direct and important activator of F-actin formation in cells [44]. The purified Arp2/3 complex has no activity, but it can be activated by NPFs to promote the polymerization of G-actin [1,43-45].

NPFs contain two domains, the C-terminal conserved output domain (VCA domain) and the N-terminal diverse regulatory domain. The C-terminal VCA domain includes a verprolin homology motif or V, an amphipathic connector region or C, and an acidic peptide or A. V domain can bind G-actin and CA domain is responsible for binding Arp2/3 complex [46,47]. The N-terminal regulatory region of WASP contains a GTPase-binding domain, which binds to the C-terminal VCA domain through intramolecular interaction, making WASP in an inactive state [48]. Under the external stimulation, GTPase Cdc42 can competitively bind to the GTPase-binding domain, and the intramolecular interaction disintegrates subsequently to release the VCA domain, then WASP is activated to direct Arp2/3 complex to initiate G-actin polymerization to form F-actin [48]. However, the N-terminal region of P78/83 does not show similarity with any identified NPFs, there is a unique multifunctional regulatory sequence (MRS) located near the N terminus of P78/83 [49]. MRS can serve as a degron to mediate P78/83 degradation in a proteasome-dependent manner. In AcMNPV-infected Sf9 cells, MRS can bind to BV/ODV-C42, which modulates the P78/83-Arp2/3 interaction to orchestrate actin polymerization [49]. In addition, nucleocapsids are found to be able to nucleate actin polymerization in a concentration-dependent manner in vitro, and P78/83 is found to bind actin directly [40]. In conclusion, P78/83-Arp2/3 complex plays a key role in baculovirus nucleocapsid transport.

BV/ODV-C42, a nucleocapsid structural protein, is capable of directly interacting with the viral proteins P78/83 and ODV-EC27 to form a complex [50]. BV/ODV-C42 contains a nuclear localization signal (NLS) motif at the C terminus. During AcMNPV infection, BV/ODV-C42 binds to P78/83 in the cytoplasm to form a protein complex and cotransports to the nucleus under the direction of the NLS motif of BV/ODV-C42 [51]. In addition, studies have shown that BV/ODV-C42 plays a key role in the nuclear actin polymerization process, besides its role in recruiting P78/83 to the nucleus [52]. In the absence of BV/ODV-C42, even if P78/83 was tagged with a NLS, polymerized F-actin filaments could not be found in the nuclei of virus-transfected cells, despite other actin polymerization elements (i.e., G-actin, P78/83, and Arp2/3 complex) are present [52]. Furthermore, both the kinetics of pyrene-actin polymerization and F-actin-specific staining by phalloidin indicated that anti-BV/ODV-C42 can significantly attenuate the efficiency of F-actin formation [52]. Therefore, BV/ODV-C42 is directly involved in the formation of F-actin in vivo and in vitro. One possible hypothesis is that BV/ODV-C42 not only mediates the entry of P78/83 into the nucleus, but also maintains the stability of P78/83 via its interaction with P78/83, thus indirectly participates in the formation of F-actin.

In addition, it is interesting that BV/ODV-C42 was found to contain a putative pocket protein binding site (PPBS), which may be involved in the interaction with pocket proteins of host cells, such as retinoblastoma protein (pRB), p130 and p107 [50], subsequently regulate other cell activities via pRB. Tyrosine kinase activity of nuclear c-Abl is regulated in the cell cycle through a specific interaction with pRB [53]. c-Abl can phosphorylate neural WASP (N-WASP) to regulate actin comet tail formation [54]. There are two molecular masses of 78 and 83 kDa P78/83 synthesized late in baculovirus infection, and the 83-kDa protein was a phosphorylated derivative of the 78-kDa protein [55]. Therefore, it is possible that there is a c-Abl homolog exists in insect cells to phosphorylate P78/83. Studies showed that elimination of the interaction between BV/ODV-C42 and pRB resulted in the separation of c-Abl homolog from P78/83,

and the hypo phosphorylated P78/83 cannot effectively activate the Arp2/3 complex to initiate actin polymerization [52]. Hence, BV/ODV-C42 may serve as a scaffold protein that provides a molecular platform for c-Abl homolog to phosphorylate P78/83 to regulate the activity of Arp2/3 complex, and ultimately regulate the polymerization of F-actin. Recently, Ac102 was found to be a component of the P78/83-C42-EC27-Ac102 protein complex [31], and be involved in modulating BV/ODV-C42 ubiquitination and consequently ensures P78/83 activity as an NPF to initiate actin polymerization [35].

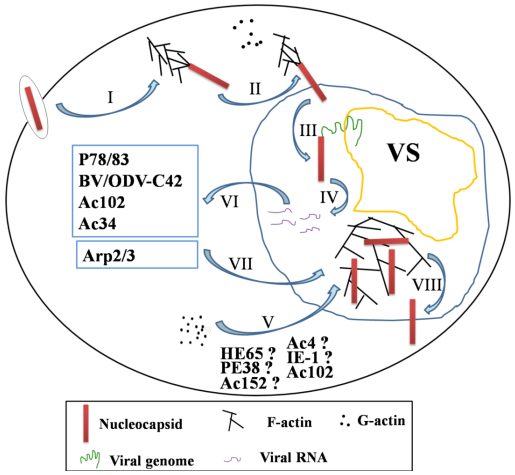


Figure 2: The possible roles of actin in the transportation of nucleocapsids in host cells. (I) Shortly after the baculovirus nucleocapsids enter into the host cytoplasm, cytoplasmic G-actin is induced to polymerize to form F-actin cable, propelling the nucleocapsids to migrate to the nuclear membrane. (II) At the nuclear membrane, induced actin polymerization is ended, the nucleocapsid is detached from the F-actin tail, then the nucleocapsid enters the nucleus via the nuclear pore complex. (III) The viral genome is released to the virogenic stroma (VS). (IV) The viral genes are replicated and transcripted. (V) With production of early viral proteins, G-actin in cytoplasm is recruited into nucleus. (VI) At the late stage of infection, P78/83, BV/ODV-C42, Ac102, VP80 and Ac34 are produced. (VII) P78/83 and Arp2/3 complex are transported into the nucleus, initiating the nucleus G-actin polymerization to form F-actin. (VIII) Nucleocapsids are assembled and egresses from the nucleus along F-actin.

In conclusion, the possible roles of actin in the transportation of nucleocapsids in host cells are as follows (Figure 2). Shortly after the baculovirus nucleocapsid is released from the endocytosis into the host cytoplasm, cytoplasmic G-actin is induced by P78/83 to polymerize to form F-actin cable, propelling the nucleocapsid to migrate to the nuclear membrane. At the nuclear membrane, P78/83 is degraded, P78/83-induced actin polymerization is ended, and the nucleocapsid is detached from the F-actin tail, then the nucleocapsid enters the nucleus via the nuclear pore complex, releasing the viral genome to the VS, subsequently initiating the replication and transcription of viral genes. With production of early viral proteins, G-actin in cytoplasm is recruited into nucleus. At the late stage of infection, P78/83, BV/ODV-C42, Ac102, VP80 and Ac34 are produced, P78/83 and Arp2/3 complex are transported into the nucleus, initiating the nucleus G-actin polymerization to form F-actin. Then nucleocapsid is assembled and egresses from the nucleus along F-actin under the interaction of VP80 and myosin. Progeny virus is produced, one replication cycle is complete. A recent study showed that the host microtubule transport system is also involved in the nucleocapsid transport from nucleus to plasma membrane to produce BV [56].

Conclusion and future direction

Viruses are non-cellular organisms that must parasitize and propagate in host cells. Viruses have no metabolic mechanism and enzyme system, they use the material and energy in the host cells to complete their replication cycle. Cytoskeleton has been used by almost all viruses to complete the key process of infection in cells, including virus localization, virus replication and gene transcription. The *Baculoviridae* family is widely used in both biotechnology and biological control, and potentially hides a treasure trove of genes and molecules that could lead to innovative biotechnology [57]. Baculovirus infection can induce G-actin to accumulate in the nucleus to form F-actin, which is unique among all pathogens. The studies on the interaction between baculovirus and actin are helpful to further uncover the transport mechanism of viral nucleocapsid and the role of actin played in the nucleus of virus infection cell. At present, more and more attention has been paid to the role of nuclear actin in cell life activities, and baculovirus infection can be used as a useful tool to reveal the function of nuclear actin and study the role of different motor proteins played in cells, which will be beneficial to promote the progress of the whole life science.

On the other hand, the specific mechanism of actin in the process of baculovirus infection is still unclear. The entry, polymerization, and depolymerization of actin are regulated by a variety of cellular signals. To date, these signal pathways, and the virus or host proteins involved in them are little known. One important reason is that, unlike mammalian systems, there are relatively little studies on the actin polymerization and depolymerization in insect systems, and many important genes involved in actin regulation have not been cloned and studied. With the elucidation of the specific mechanism of interaction between baculovirus proteins and actin in the future, the mechanism of actin rearrangement in baculovirus infected cells will be clearer understood, which will promote the understand on the baculovirus molecular biology and the interaction between baculovirus and actin network.

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