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Viruses and the nuclear envelope

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Viruses encounter and manipulate almost all aspects of cell structure and metabolism. The nuclear envelope (NE), with central roles in cell structure and genome function, acts and is usurped in diverse ways by different viruses. It can act as a physical barrier to infection that must be overcome, as a functional barrier that restricts infection by various mechanisms and must be counteracted or indeed as a positive niche, important or even essential for virus infection or production of progeny virions. This review summarizes virus–host interactions at the NE, highlighting progress in understanding the replication of viruses including HIV-1, Influenza, Herpes Simplex, Adenovirus and Ebola, and molecular insights into hitherto unknown functional pathways at the NE.

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Introduction

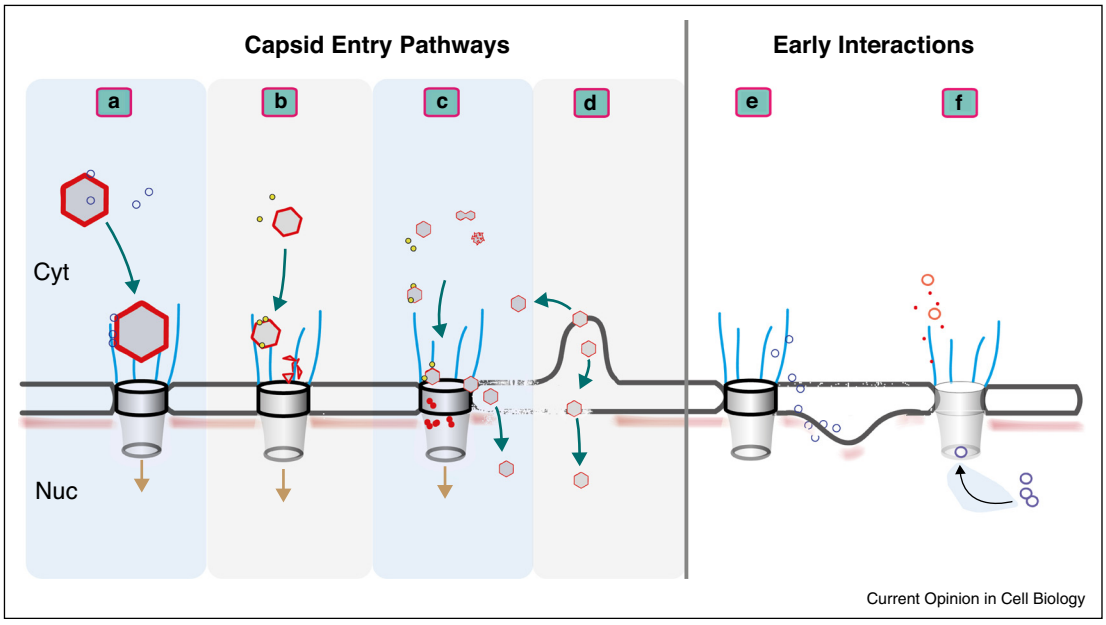
Enveloped viruses enter cells by fusion at the plasma membrane or from within vesicles after endocytosis, while non-enveloped viruses enter by physical permeation of and transport across host membranes [1]. Whether a virus is membrane-bound and where its genome is replicated within the cell are major factors that drive subsequent events, particularly those involving the NE. After cell entry, virus capsids (or nucleoprotein complexes) are transported to appropriate sites and uncoated to release the virus genome. A coordinated series of events then takes place during which the genome is replicated and new capsids are assembled. Progeny virus are released from the cell, again via complex routing pathways which, depending on the virus, can involve the NE in various ways. Virus interactions with the NE can be generally categorized based on whether they promote early events (e.g., virus entry into the nucleus) or late events (e.g., virus assembly or nuclear exit), or whether they manipulate the NE to facilitate infection at other levels (e.g., control gene expression, signalling, antiviral responses or apoptosis). Virus proteins and their interactions with specific NE proteins or structures are listed comprehensively in Table 1 (online), as context for the recent findings highlighted in this article.

Virus entry and the nuclear envelope

Most studies of virus engagement with the NE have focused on the mechanisms of virus entry through the nuclear pore complex (NPC) [2–5], with notable exceptions (discussed below) involving viruses that cross the NE itself. With one exception (the poxvirus family) all DNA viruses (e.g., herpesviruses, adenoviruses, hepatitis B virus [HBV], parvoviruses, polyomaviruses) must deposit and replicate their genomes within the nucleus. Nuclear entry is also essential for the replication of retroviruses including HIV and certain RNA viruses (e.g., orthomyxoviruses, such as influenza virus). Interestingly certain viruses that replicate outside the nucleus, discussed below, can also modify or perturb the NE and NPC to promote virus replication. Thus, depending upon their class and size, different viruses display several variations on the theme of NPC/NE engagement and genome transport [5–8,9••,10••,11–13], four of which are illustrated in Figure 1. Herpesviruses (Figure 1a) are recruited as intact capsids to the NPC and remain largely intact as the genome exits the capsid for transport through the NPC [14••,15–17]. Adenoviruses (Figure 1b) are transported through the cytoplasm after partial disruption and release from the endosome and at the NPC major disassembly occurs coupled with genome transport [18,19••]. Other entities including DNA virus capsids (HBV, parvoviruses), nucleoprotein complexes (HIV) [20,21] or ribonucleoprotein complexes (influenza) [22–24] are also recruited to the NPC through diverse mechanisms (Figure 1c). Interestingly polyomaviruses, in addition to entering via NPCs, are also proposed to enter by stealth via the shared lumenal space of the ER and NE (Figure 1d). Viruses that enter through NPCs may do so either by binding specific NPC proteins ('nucleoporins') or by recruiting soluble nuclear import receptors (importins/karyopherins; Figure 1, see online Table 1). For many viruses, identifying the specific virus and host proteins that mediate nuclear entry, and the mechanisms of entry remain important goals.

For some viruses, a small set of candidate proteins have been identified (e.g., herpesvirus VP1-2 and pUL25) that may promote NPC engagement [25•,26–28] but the critical entry mechanisms remain unknown. For other viruses such as HIV, nearly every component of the preintegration

Figure 1



Examples of mechanisms used by viruses to achieve capsid/genome entry into the nucleus **(a,b,c,d)**, or to disrupt the NE **(e)** or NPCs **(f)** at early stages of infection. (a) Pathway used by herpesviruses, in which the capsid remains intact during genome exit. (b) Pathway used by adenoviruses; the capsid is disrupted during genome exit. (c) Pathway used by HBV, parvoviruses, influenza and retroviridae, all of which traffic to the NPC; parvovirus entry also involves NE disruption. (d) Pathway(s) used by polyoma viruses, with two potentially distinct routes involving either direct access from shared ER/NE lumen across the INM, or release into the cytoplasm ('Cyt') followed by import via NPCs. Small open circles in cytoplasm indicate nuclear import receptors ('importins'). (e) Early disruptions of the NE and lamina, as induced by reovirus. (f) Early disruption of NPCs that disrupts nuclear import and export, as induced by picornaviruses. Virus proteins and complexes are indicated by large open or coloured circles. Specific examples are discussed in the text.

complex (PIC) — including Vpr, matrix, integrase and even DNA intermediates produced by reverse transcriptase — have reported roles in recruitment to the NPC [13,29–34]. Influenza virus ribonucleoprotein complexes (RNPs) interact with importin α [22–24], and differential use of specific isoforms (e.g., importin α3 and α7) may contribute to infection and pathogenesis [35••]. At least one other importin (β1), as well as Nup153 and Nup98, appear to be required for influenza replication [36], although their precise roles remain unknown [36].

Adenovirus provides one of the best-understood models of virus nuclear entry (Figure 1b) [4,5]. Adenovirus 2 capsids are partially dissociated during endosome-mediated entry into the cytoplasm; they then recruit the host molecular motors, dynein and kinesin-1, and move toward the NE and NPCs by the predominant activity of the minus end-directed motor complex, dynein/dynactin [19••]. Capsids then engage in multivalent interactions linking them simultaneously to the NPC (via hexon binding to Nup214) and to kinesin (via pIX binding to kinesin light chain Klc1/2). Nup214 is also bound to the filament nucleoporin Nup358, which itself interacts with the heavy chain Kif5c. Kinesin-1 then, while attached to the capsid, attempts to motor away from the NPC. Since the capsid is also attached to the NPC the result effectively rips the capsid apart. This action also dislocates Nup358/Nup214 and Nup62 from the central NPC channel [19••]. This remarkable combination of events facilitates adenoviral DNA entry into the nucleus. Further interactions with host proteins are reported to be involved in adenovirus genome entry at the NPC. For example, at least for certain adenovirus subtypes, histone H1 binds to capsids stably docked at the NPC and then recruits import factors importin 7 and importin β, to the H1-capsid complex, promoting core disruption and genome import [37]. Other adenovirus proteins (e.g., protein VII) also bind multiple importins; protein VII is specifically proposed to act as an adaptor for the nuclear import of the adenovirus DNA itself [38]. These examples showcase the potential complexity of NPC engagement by other viruses about which much less is known.

Other DNA viruses that replicate in the nucleus, such as HBV, also use their own structural proteins to engage soluble nuclear import receptors that mediate passage through the NPC [11]. However in contrast to larger DNA viruses such as adenovirus and herpesviruses, HBV is thought to be physically small enough to traverse the NPC intact [39]. Indeed HBV capsids appear to traverse