Virology 479-480 (2015) 591–599

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Review

Adenovirus membrane penetration: Tickling the tail of a sleeping dragon

Christopher M. Wiethoff [a], Glen R. Nemerow [b,*]

[a] Loyola University Chicago, 2016 S. First Avenue, Maywood, IL 60153, USA
[b] The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

ARTICLE INFO

Article history:
Received 20 December 2014
Returned to author for revisions
18 February 2015
Accepted 3 March 2015
Available online 19 March 2015

Keywords:
Adenovirus
Protein VI
Membrane destruction
Cell trafficking
Receptors
Virus structure
Innate immunity

ABSTRACT

As is the case for nearly every viral pathogen, non-enveloped viruses (NEV) must maintain their integrity under potentially harsh environmental conditions while retaining the ability to undergo rapid disassembly at the right time and right place inside host cells. NEVs generally exist in this metastable state until they encounter key cellular stimuli such as membrane receptors, decreased intracellular pH, digestion by cellular proteases, or a combination of these factors. These stimuli trigger conformational changes in the viral capsid that exposes a sequestered membrane-perturbing protein. This protein subsequently modifies the cell membrane in such a way as to allow passage of the virion and accompanying nucleic acid payload into the cell cytoplasm. Different NEVs employ variations of this general pathway for cell entry (Moyer and Nemerow, 2011, *Curr. Opin. Virol.*, 1, 44–49), however this review will focus on significant new knowledge obtained on cell entry by human adenovirus (HAdV).

Contents

Introduction

There are more than 60 different types of human adenovirus belonging to 6 distinct subgroups (A–G) (King et al., 2012; Liu et al., 2012) and many of these are associated with acute respiratory, gastrointestinal and ocular infections. Although usually self-limiting, these infections can lead to fatal disseminated infections in immunocompromised individuals (Lion, 2014). Conditionally-replicating (i.e., oncolytic) or replication-defective adenoviruses are now well known for their use in gene transfer or vaccine delivery. However, optimal targeting to specific cell types remains an unresolved goal. Thus, an understanding of complex interactions of HAdV with the host is crucial. Over the past several years, detailed knowledge of cell entry by this relatively large (150 MDa) virus has been obtained and some of its most closely held secrets have been revealed. These include the mechanism of

* Corresponding author. Tel.: +1 858 784 8072.
E-mail address: gnemerow@scripps.edu (G.R. Nemerow).

http://dx.doi.org/10.1016/j.virol.2015.03.006
0042-6822/

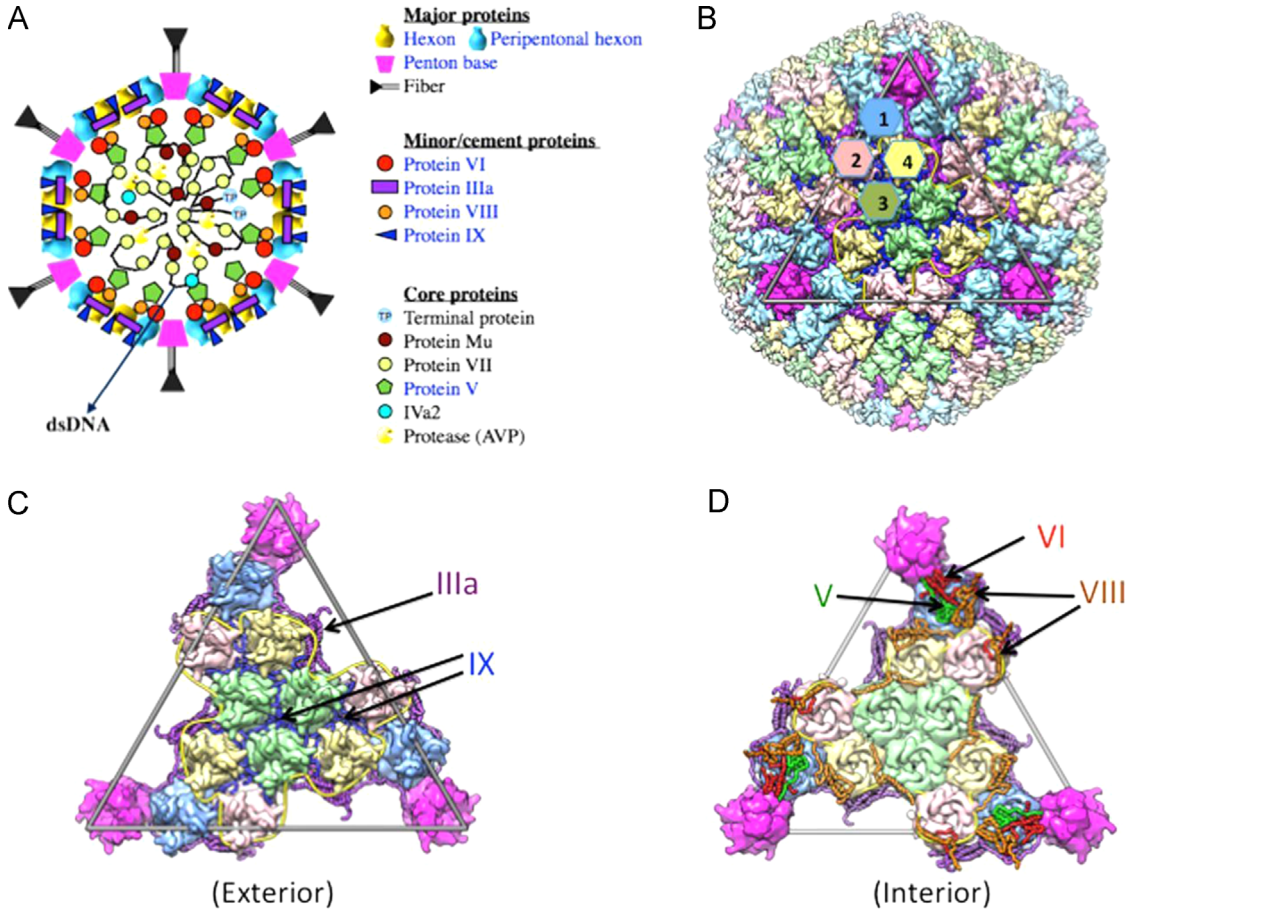

Fig. 1. Structure and organization of human adenovirus. (A) A schematic illustration of the organization of capsid and core proteins in human adenovirus. The locations of various proteins are represented by different-colored symbols and the corresponding names are shown (*Right*). The indicated locations of the core proteins are approximate. Shown in blue-colored lettering are the proteins whose structures have been identified in this study. (B) Overall organization of hexon and penton base subunits exhibiting pseudo-T=25 icosahedral symmetry. Structurally unique hexons (1–4) are color-coded in light blue, pink, green, and khaki, respectively. Penton vertices are shown in magenta. Outer cement proteins IIIa and IX are shown in purple and blue, respectively. Fiber molecules associated with the penton base are disordered. The outline of the triangular icosahedral facet is shown as a gray triangle, whereas the border of the GON hexons is indicated by yellow-colored rope. (C) An exterior view of the triangular icosahedral facet that comprises 12 hexons along with penton base vertices shown in magenta. Color representations are the same as in *B*. (*D*) An interior view of the facet in C, with three minor proteins, V (green), VI (red), and VIII (orange). It is noteworthy that a copy of V, VI, and VIII forms a ternary complex beneath the vertices, whereas VIII (orange) molecules are arranged as staples along the border (yellow-colored rope) of the GON hexons. Reddy V S, and Nemerow G R. PNAS 2014;111:11715–11720.

virus internalization, the location and structure of the virus membrane lytic protein inside the virus capsid, as well as the host immune and cellular responses triggered by HAdV cell entry.

Receptor-mediated virus attachment and internalization

Due to its size and complexity, HAdV presents significant challenges for studying its mode of cell entry. This naked virus is ~90 nm in diameter and contains a 36-KB dsDNA genome encoding 13 distinct structural proteins including a cysteine protease whose activity is required for capsid maturation (Fig. 1). Each of the 12 vertices of the virus possess two major outer capsid proteins known as the fiber (van Raaij et al., 1999) and penton base (Zubieta et al., 2005; Wickham et al., 1993) that serve as attachment and internalization receptor binding proteins, respectively. Attachment of most HAdV types is mediated by a cell receptor known as the Coxsackie and Adenovirus Receptor (CAR), a member of the Ig superfamily (Bergelson et al., 1997). CAR plays a role in maintaining the integrity of tight junctions in polarized epithelial cells and is normally sequestered on the basolateral surface of these cells (Walters et al., 2002). This situation has hindered the use of Ad gene delivery for treatment of human airway diseases (Zabner et al., 1997; Walters et al., 1999). However, a single isoform of HCAR, designated CAR^{Ex8}, appears to traffic to the apical surface of airway epithelial cells and allows a modest level of HAdV infection from this location (Excoffon et al., 2010). Interestingly, on certain cell types such as motor neurons, CAR can serve as both an attachment receptor as well as an internalization to promote virus uptake (Salinas et al., 2009; Salinas et al., 2014).

As noted above, not all species of HAdV use CAR as their primary receptor. For example, the fiber proteins of certain subgroup B adenoviruses including types 3, 7, 11 and 14 use desmoglein-2 (DSG-2) as a high affinity attachment receptor (Wang et al., 2011). DSG-2 ligation can regulate access to epithelial cell junctions and thus the use of type B Ad vectors that recognize this receptor may prove useful for targeting oncolytic HAdV to tumor cells. The fiber proteins of other subgroup B viruses including Ad types 35 and 16, have been shown to use CD46, a complement regulatory protein family member, for cell attachment (Gaggar et al., 2003). Virus types such as Ad19 and Ad37 associated with epidemic keratoconjunctivitis, a serious ocular disease, bind to α2,3-linked sialic acid (Arnberg et al., 2000; Nilsson et al., 2011) or CD46 (Wu et al., 2004). These cell receptors are widely distributed on various cell types in vivo, and thus their presence on certain tissues does not readily explain adenovirus tropism. Nonetheless, significant progress has been made in elucidating the structural basis of Ad fiber interactions with CAR