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The nucleotide sequence and a first generation gene transfer vector of species B human adenovirus serotype 3

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Abstract

Human adenovirus (Ad) serotype 3 causes respiratory infections. It is considered highly virulent, accounting for about 13% of all Ad isolates. We report here the complete Ad3 DNA sequence of 35,343 base pairs (GenBank accession DQ086466). Ad3 shares 96.43% nucleotide identity with Ad7, another virulent subspecies B1 serotype, and 82.56 and 62.75% identity with the less virulent species B2 Ad11 and species C Ad5, respectively. The genomic organization of Ad3 is similar to the other human Ads comprising five early transcription units, E1A, E1B, E2, E3, and E4, two delayed early units IX and IVa2, and the major late unit, in total 39 putative and 7 hypothetical open reading frames. A recombinant E1-deleted Ad3 was generated on a bacterial artificial chromosome. This prototypic virus efficiently transduced CD46-positive rodent and human cells. Our results will help in clarifying the biology and pathology of adenoviruses and enhance therapeutic applications of viral vectors in clinical settings.
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Keywords: Human adenovirus type 3; Species B1 adenovirus; Gene transfer vector; Bacterial artificial chromosome

Introduction

Today's major Ad vectors used in clinical applications are derived from the species C serotypes Ad2 and Ad5 which efficiently infect a variety of post-mitotic cells, including specialized tissues of the upper respiratory epithelium and the gut, in addition to many tumor cells. Their biology is very well characterized (for reviews, see, Meier and Greber, 2003; Russell, 2000; Shenk, 2001). Species C entry into epithelial cells occurs after virus binding to the Coxsackie virus B Ad receptor (CAR) (Bergelson et al., 1997) followed by engagement of αv containing heterodimeric integrins as secondary receptors (Wickham et al., 1993), which facilitate viral endocytosis and signaling into target cells (Meier et al., 2002; Suomalainen et al., 1999). Although species C Ads efficiently infect a number of cells and tissues, the lack of CAR or integrin expression may limit their general usefulness for gene therapy.

Recently, recombinant species B Ads or fiber swapped Ad vectors in which the fiber protein of the commonly used Ad5 is swapped with species B Ad fibers have gained interest for gene therapy and vaccination approaches. Species B Ads are divided into B1 and B2 subspecies. The B1 group comprises of Ad3, Ad7, Ad16, Ad21, and Ad50 and predominantly infects the upper respiratory tract, whereas the B2 group serotypes Ad11, Ad14, Ad34, and Ad35 are associated with kidney and urinary tract infections (Schmitz et al., 1983; Wadell, 2000). Infections with B1 Ads are a major cause of acute febrile and severe respiratory illness among military recruits (Dudding et al., 1972). In particular, the widespread Ad3 and Ad7 account for 13% and 19.7% of all Ad isolates typed and reported to WHO (Wadell, 2000). They are considered highly virulent and have been associated with acute clinical manifestations of considerable severity, residual lung damage, and fatal outcomes in children and military recruits in the US (for recent report, see

Abbreviations: Ad, adenovirus; BAC, bacterial artificial chromosome; CAR, Coxsackie virus B and Ad receptor; ITR, inverted terminal repeat; kbp, kilo base pairs; MLP, major late promoter; MOI, multiplicity of infection; mu, map units; ORF, open reading frame.

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Ryan et al., 2002). Seventeen genome types of Ad3 have been identified (Li and Wadell, 1988). These variants have been noticed to segregate in different geographic areas, time periods, and clinical conditions.

A major difference between the species C and the species B Ads is the receptor usage, which might help the species B Ads to overcome host restrictions, as suggested in early studies (Defer et al., 1990; Di Guilmi et al., 1995; Gall et al., 1996; Roelvink et al., 1998; Stevenson et al., 1995). Using different approaches, several groups have recently identified the membrane cofactor CD46 as an attachment receptor for species B serotypes, including Ad11 (Segerman et al., 2003), Ad35 (Gaggar et al., 2003), and Ad3 (Sirena et al., 2004). Most of the downstream steps of productive virus infection are, however, unknown. It is for example unclear if integrins or other proteins act as secondary receptors for virus uptake (Mathias et al., 1994; Shayakhmetov et al., 2000) or if virus attachment to CD46 is sufficient for uptake as CD46 is apparently internalized by multiple endocytic pathways in noninfected cells, including macropinocytosis and clathrin-mediated endocytosis (Crimeen-Irwin et al., 2003). Despite this shortage of knowledge, recombinant species B-based replication defective vectors have been developed for Ad35 (Gao et al., 2003; Sakurai et al., 2003; Seshidhar Reddy et al., 2003; Vogels et al., 2003) and Ad11 (Holterman et al., 2004; Stone et al., 2005). Interestingly, these vectors show an extended tropism compared to species C vectors and infect hematopoietic and dendritic cells. Similarly, replication-competent or replication-defective viral vectors derived from Ad7 have been used for vaccine strategies (Abrahamsen et al., 1997; Lubeck et al., 1989; Nan et al., 2003). An extended tropism was also demonstrated for fiber swapped Ad vectors containing fibers of species B viruses such as Ad3 (Kanerva et al., 2002; Stevenson et al., 1997; Von Seggern et al., 2000), Ad11 (Stecher et al., 2001), and Ad35 (Havenga et al., 2001; Havenga et al., 2002; Knaan-Shanzer et al., 2001; Rea et al., 2001; Shayakhmetov et al., 2000; Yotnda et al., 2001). To generate a tool for characterization of host cell–Ad3 interactions, we constructed a recombinant E1-deleted Ad3 vector expressing eGFP using the bacterial artificial chromosome (BAC) strategy, and we report here the complete nucleotide sequence of serotype Ad3 (GB) (GenBank accession no. DQ086466). This information will serve as a reference for further characterization of this prototype species B virus strain and facilitate the development of genome-based molecular diagnostic tools of Ad infections.

Results and discussion

Nucleotide sequence and genome organization

Based on primers deduced from partial Ad3 sequences (Table 1), the full genomic sequence of Ad3 prototype GB with an overall size of 35,343 base pairs was determined by sequencing both strands using the progressive specific primer method (GenBank accession no. DQ086466). Sequence

Table 1
Previously published human adenovirus 3 sequences used for primer design

Sequence origin	GenBank Accession No.	Reference	% Homology compared to the discussed sequence (number of differences)	Region (bp)
Ad3 complete sequence	DQ086466	This publication		1–35,342
Ad3 left end fragment containing ITR, E1A		(Cogan et al., 1992)	99.24 (12/1572)	1–1569
Ad3 ITR, left end	J01960	(Tolun et al., 1979)	99.4 (1/158)	3–160
Ad3 ITR, left end	J01963	(Kosturko et al., 1982)	95.8 (32/770)	12–762
Ad3 E1A 9S protein, E1A 13S protein, and E1A 12S protein genes, complete cds	AF492352	(Avvakumov et al., 2002)	100	576–1455
Ad3 E1A protein gene, partial cds	AY380316	Lin et al., 2003, unpublished	99.3 (3/430)	704–1134
Ad3 polypeptide IX gene, complete cds	J01962	(Engler, 1981)	100	3413–3965
Ad3 DNA polymerase gene, partial cds	AY780207	Chmielewicz et al., 2004, unpublished	100	5398–5646
Ad3 virus-associated RNA, pre-terminal protein and 52/55-kDa protein genes, partial cds	U52534	Ma et al., 1996, unpublished	98.3 (10/582)	10,305–10,890
Ad3 virus-associated RNA I and RNA II genes	U10680	(Kidd et al., 1995)	99.7 (1/450)	10,399–10,849
Ad3 gene for pIIIa, pVII and penton base protein	Z29487	(Cuzange et al., 1994)	99.8 (3/1986) (penton 100% identical)	13,686–15,668 (13,905–15,540)
Ad3 hexon gene	X76549	(Pring-Akerblom et al., 1995)	99.6 (10/2835) (hexon 3 aa differences)	18,417–21,251
Ad3 hexon gene, partial cds (nonfunctional)	AY380317	Lin et al., 2003, unpublished	97.7 (18/778)	18,524–19,295
Ad3 hexon gene, partial cds	AY684873	Ju et al., 2004, unpublished	98.7 (5/397)	19,010–19,406
Ad3 L3–23-kDa gene for chymotrypsin-like endoprotease	X13271	(Houde and Weber, 1988)	99.8 (2/1273)	20,917–22,190
Ad3 E3 region	M15952	(Signas et al., 1986)	99.9 (3/4379)	26,993–31,372
Ad3 fiber polypeptide gene	X01998	(Signas et al., 1985)	100	31,118–32,447
Ad3 fiber protein gene, partial cds	AY380318	Lin et al., 2003, unpublished	98.7 (9/673)	31,406–32,079
Ad3 ITR, right end	J01961	(Tolun et al., 1979)	99.4 (1/158)	35,183–35,340

Cds, coding sequence; ITR, inverted terminal repeat; aa, amino acid residue.

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