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Review

Human adenoviruses: A suspect behind the outbreak of acute hepatitis in children amid the COVID-19 pandemic

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ABSTRACT

As of 10 May 2022, at least 450 cases of pediatric patients with acute hepatitis of unknown cause have been reported worldwide. Human adenoviruses (HAdVs) have been detected in at least 74 cases, including the F type HAdV41 in 18 cases, which indicates that adenoviruses may be associated with this mysterious childhood hepatitis, although other infectious agents or environmental factors cannot be excluded. In this review, we provide a brief introduction of the basic features of HAdVs and describe diseases caused by different HAdVs in humans, aiming to help understand the biology and potential risk of HAdVs and cope with the outbreak of acute child hepatitis.

1. Introduction

On April 23, 2022, the WHO announced that, as of 21 April 2022, at least 169 cases of acute hepatitis of unknown cause had been reported in 12 countries worldwide. Patients' age ranged from 1 month to 16 years old. Adenoviruses (AdVs) were detected in at least 74 cases, and of the cases with information on molecular testing, 18 cases were identified as HAdV41. SARS-CoV-2 was identified in 20 cases of those who were tested. Furthermore, 19 cases were detected with a SARS-CoV-2 and adenovirus co-infection (https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376). As of 10 May 2022, the total number of cases reported worldwide is approximately 450, including 11 deaths (https://www.ecdc.europa.eu/en/news-events/epidemiological-update-hepatitis-unknown-aetiology-children). Gastrointestinal symptoms, including diarrhea, abdominal pain and vomiting, have been reported in most cases worldwide. Gastrointestinal symptoms of childhood hepatitis include nausea, vomiting, upper abdominal distention, and diarrhea. In the past, hepatitis caused by enteric adenovirus, especially severe hepatitis, was rarely reported. Data from 1960 to 2016 show that approximately 50% of reported cases of HAdV-associated hepatitis worldwide were from liver transplant recipients (Ronan et al., 2014; Schaberg et al., 2017). Furthermore, as SARS-CoV-2 infection has also been reported in this acute hepatitis incident in children, the possibility that HAdV may be a disease co-factor should also be taken into consideration.

AdVs have been studied intensively as models of virus–cell interactions and latterly as gene vectors (Russell, 2009). AdVs are a large family of viruses composed of more than 100 known serotypes that can infect various vertebrate species, including mammals, birds, fish, reptiles, and amphibians (Davison et al., 2003). Human adenovirus (HAdV) can infect humans, causing acute respiratory disease, gastroenteritis, keratoconjunctivitis, and obesity (Flatt and Butcher, 2019). These diseases are generally self-limiting, but severe and deadly infections can occur in immunocompromised hosts (Lion, 2014a). Children are more susceptible to HAdVs infection because their immune systems are less developed. HAdVs cause a range of mild symptoms, including colds, vomiting, diarrhea, and sometimes pneumonia, but rarely hepatitis and only in immunocompromised patients. Human adenovirus-F (HAdV-F), known as enteric adenovirus (EAD), includes HAdV40 and HAdV41. The incidence of EAD in childhood diarrhea is only lower than that of rotaviruses

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and noroviruses (Ramani and Kang, 2009). Since the prevalence of EAD in general population is far below the high diagnostic rate reported in this outbreak of child hepatitis, the potential role of EAD (or its possible mutants/variants) in unknown hepatitis infection requires close attention.

2. Classification, genome structure and replication of HAdV

To date, more than 100 HAdV genotypes have been identified (http://hadvwg.gmu.edu/), which are classified into 7 species (A–G) based on their biological characteristics, tumorigenicity, and DNA homology (Chang et al., 2008).

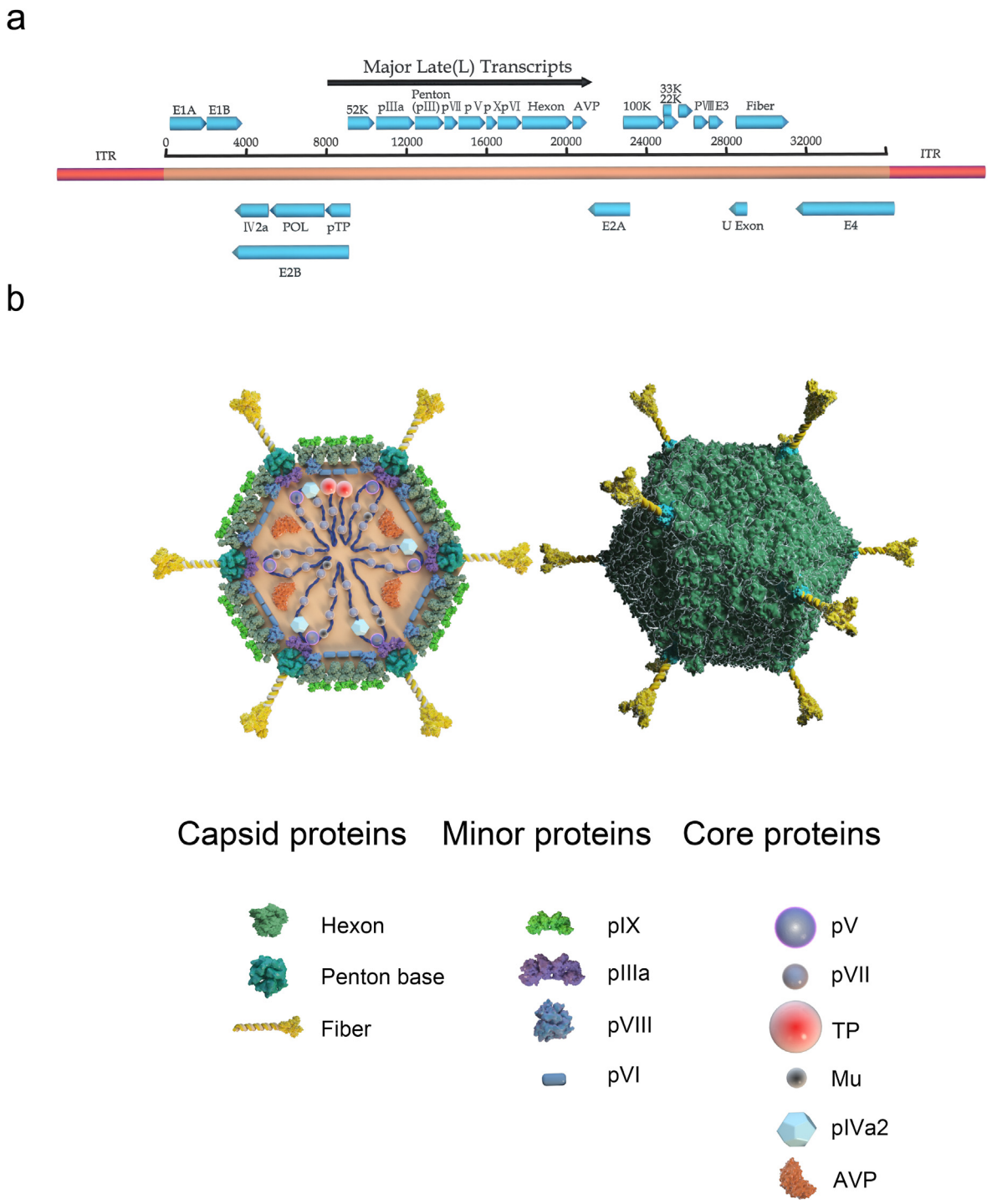

Fig. 1. The genomic map and virion structure of human adenovirus. (a) Genomic map of adenovirus adapted from (Zhang and Huang, 2019; Kulanayake and Tikoo, 2021). Regions show the production of early genes (E1A, E1B, E2A, E2B, E3, and E4), major late transcripts including 52K, IIIA, Penton, VI, V, X, VI, Hexon, AVP (adenoviral protein), POL (DNA polymerase), ITR (viral inverted terminal repeats) and so on. (b) Virion structure of human adenovirus based on crystallography and cryo-electron microscopy. Fiber, Penton base and Hexon are capsid proteins. pIX, pIIIa, pVIII and pVI are minor proteins. Core proteins contains of pV, pVII, TP, Mu, pIVa2, AVP; TP (terminal protease). The lowercase "p" refers to protein. Based on (Russell, 2009; Kulanayake and Tikoo, 2021; Giberson et al., 2012).

HAdV is a non-enveloped DNA virus of about 90 nm in diameter containing a dsDNA genome of approximately 36 kb (Davison et al., 2003; Vellinga et al., 2005). The viral genome is linked to the core protein and packed within an icosahedral capsid (Fig. 1). The major capsid protein of HAdV virion is the homotrimeric hexon, and there are 240 hexon components on the faces and edges of the capsid, with the pentons consisting of the penton bases and extended fibers on the 12 fivefold apices, while the minor capsid proteins are IIIa, VI, VIII, and IX (Russell, 2009; Vellinga et al., 2005). The major capsid proteins mediate virus entry into host cells, while minor capsid proteins affect capsid assembly, disassembly, and stability (Wiethoff et al., 2005; Wodrich et al., 2003). Fiber and hexon genes are regions where novel adenovirus recombination usually occurs, serving as the main classification basis. Here, we show the phylogenetic trees of fiber and hexon of some major HAdVs (Fig. 2). Inside the capsid, there are six core proteins, including V, VII, Mu, IVa2, the terminal protein (TP), and virion protease. The viral genome encodes several early (E1A, E1B, E2A, E2B, E3, and E4) and late (L1-5) transcriptional units that give rise to multiple mRNAs and proteins via differential processing (McConnell and Imperiale, 2004).

Adenoviruses use multiple attachment receptors, five of which have been studied structurally in the course of HAdV binding: Coxsackie and Adenovirus Receptor (CAR/CXADR), CD46, the glycans GD1a, polysialic acid (polySia), and desmoglein-2 (DSG2) (Fig. 3) (Stasiak and Stehle, 2020). CAR is a high-affinity receptor for HAdV groups A and C–F (Ortiz-Zapater et al., 2017). CD46 serves as receptor for some group B HAdVs (Cardone et al., 2011). Some HAdV-D can use sialic acid as receptor, including HAdV-37,8,19. The fiber and penton base engage host cell receptors. After the internalization of HAdV, the fiber was torn due to receptor interaction, and expose pVI. pVI destroys the vesicle membrane, resulting in the release of virus particles. After viral structural proteins enter the cytoplasm, the interaction of hexon with dynein motors transports viral particles to the nucleus through microtubules (Bremner et al., 2009; Leopold et al., 2000). Once the viral particle reaches the perinuclear microtubule tissue center, it will separate and combine with the nuclear pore complex (NPC), thus triggering the disintegration of the capsid (Strunze et al., 2011).

Once the uncoating process is complete, pVII mediates the entry of the viral genome into the nucleus and then pVII interacts with histone chaperones to coordinate their removal from the HAdV genome (Lynch et al., 2019). The virus releases the core containing all the necessary information to initiate a productive infection and then the synthesis and assembly of virus particles (Flatt and Butcher, 2019). The first viral biosynthetic process is the expression of early regional protein products 1A(E1A) and 1B(E1B), which lead to the violent reorganization of cell behavior, force the static and terminally differentiated infected cells to divide, and make the cells unable to respond to the clues of apoptosis (Gallimore and Turnell, 2001). After E1A and E1B expression, early regions 2A and B (E2A and E2B) are expressed. E2A encodes the single-stranded DNA-binding protein (DBP) that involves in the synthesis of single-stranded viral DNA during genome replication; E2B encodes TP and viral DNA polymerase, which is responsible for viral DNA synthesis (De Jong and Van der Vliet, 1999; de Jong et al., 2003). Subsequently, early region 3 (E3) gene expression, whose main function is to maintain cell viability during lytic infection, may also contribute to sustained HAdV infection. Early region 4 (E4) gene encodes a variety of products, and their functions include regulating transcription, the cell cycle, cell signaling, and DNA repair (Weitzman, 2005). The late viral genes are transcribed from a common major late promoter (MLP) and are produced through different splicing mechanisms (Young, 2003). The viral mRNAs encoding structural proteins are exported to the cytoplasm for translation. Then, the late proteins are imported back into the nucleus for the later stage of virus assembly. During assembly, the core of the virion

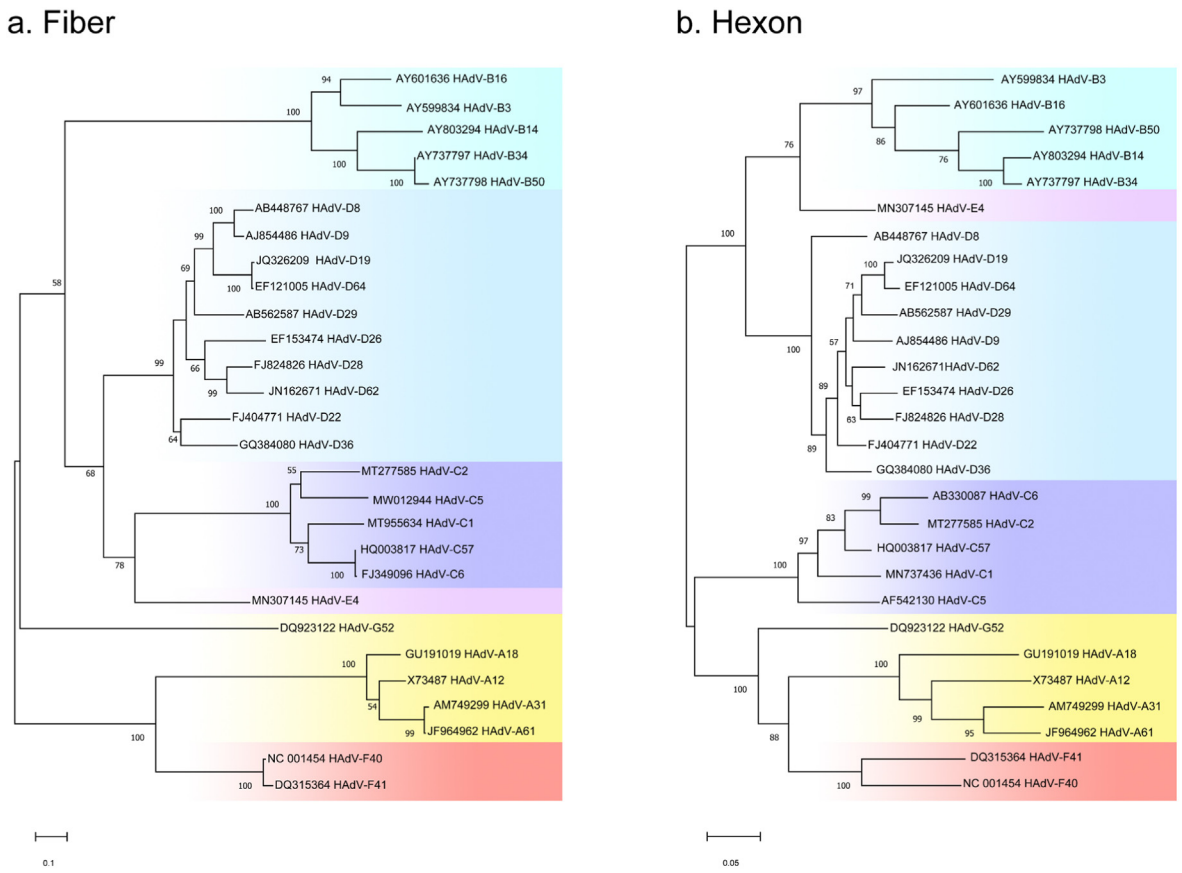

Fig. 2. Phylogenomic analysis of fiber (a) and hexon (b) of 28 representative HAdVs. A bootstrapped maximum likelihood (ML) tree with 1000 repetitions is constructed using MEGAX software and generalized time-reversible (GTR) model. More than 50% bootstrap rate is displayed on branch nodes.

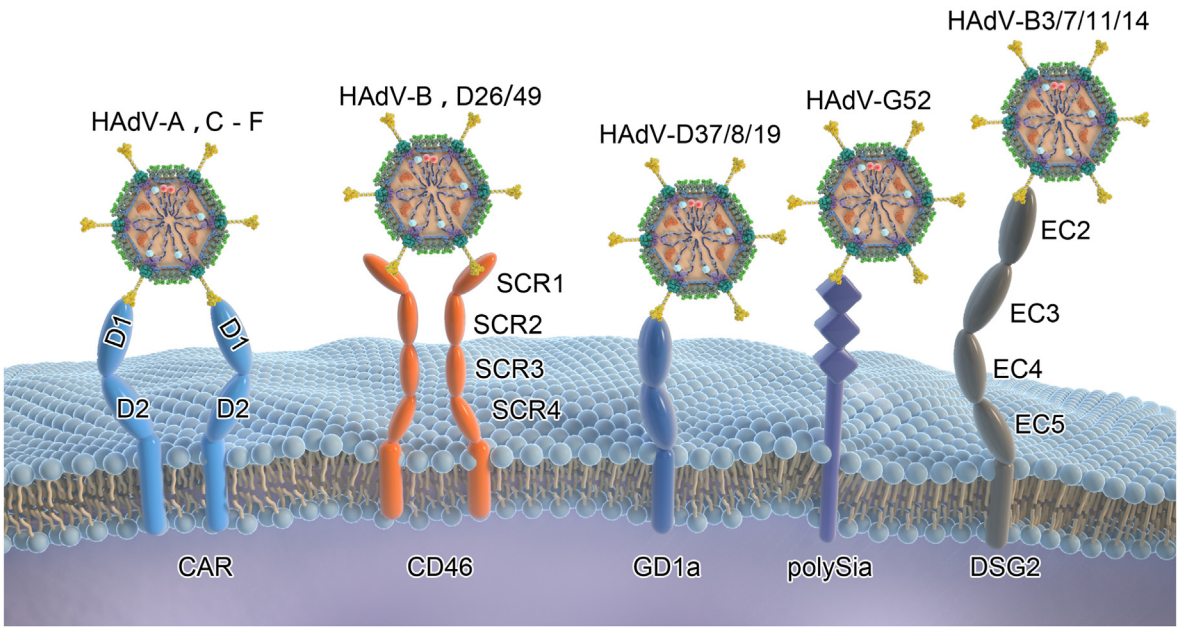

Fig. 3. The five major human adenovirus receptors and corresponding recognized HAdVs. Coxsackie and adenovirus receptor (CAR) comprises two immunoglobulin-like extracellular domains (D1-2); CD46 (human membrane cofactor protein), the extracellular part of which consists of four short consensus repeats (SCR, 1–4) and a serine, threonine and proline (STP)-rich region; Glycans: GD1a and Polysialic acid (polySia); Desmoglein-2(DSG-2) comprises five extracellular cadherin domains (EC1-5) in addition to a transmembrane segment and an intracellular domain. Based on (Stasiak and Stehle, 2020; Henaff et al., 2011; Arnberg, 2012; Persson et al., 2010; Harrison et al., 2016).

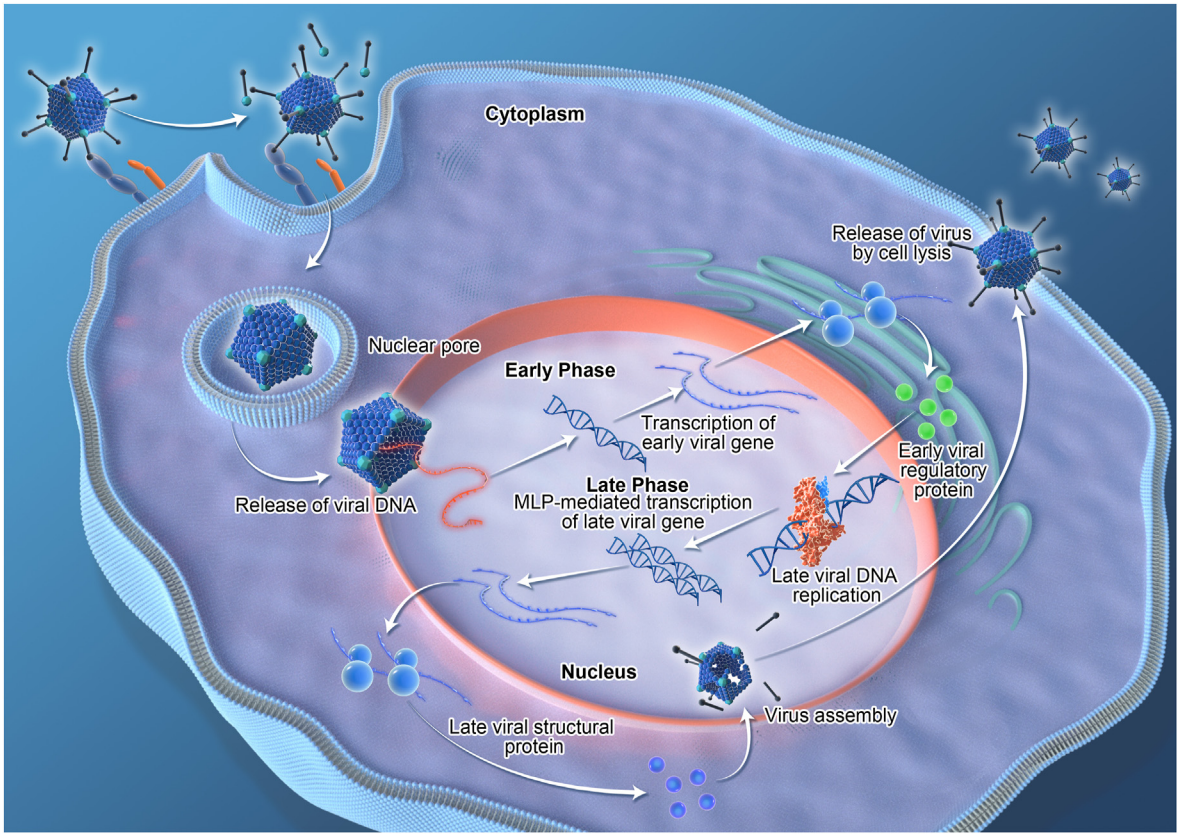

Fig. 4. The replicative cycle of human adenovirus (Dodge et al., 2021; Georgi and Greber, 2020; Charman et al., 2019). 1) HAdV virion bind to cognate receptors to mediate internalization into endosomes. 2) Virions escape from the endosome, dock on nuclear pore complex, and release genome into the nucleus. 3) Transcription of the early viral genes into mRNAs. The mRNAs are exported to the cytoplasm for translation of early viral proteins, which are imported into the nucleus. 4) Transcription of the late structural genes into mRNA from a common major late promoter (MLP). The mRNA are exported to the cytoplasm for translation of structural proteins, which are imported into the nucleus for assembly. 5) Virion assembly occurs in the nucleus. 6) Virion is released from the nucleus and then released from the cell by cytolysis.

condenses into a fluid-like unstructured state in the immature particle and then undergoes proteolytic maturation via a protein-VI-activated viral protease to produce mature infectious virions (Fig. 4) (P é rez-Bern á et al., 2015; Mangel and San Mart í n, 2014).

3. Diversity of HAdV pathogenesis

HAdVs cause multiple diseases, including gastroenteritis (HAdV-A, F, and G), pneumonia (HAdV-B, C, and E), hepatitis (HAdV-C), meningoencephalitis (HAdV-A, B, and D), cystitis (HAdV-B), and keratoconjunctivitis (HAdV-B and D) (Lion, 2014a; Robinson et al., 2011; Jones et al., 2007; Echavarr í a, 2008). HAdVs are transmitted mainly by airborne droplets. Most HAdVs can also spread through the digestive tract and close contact. People of all ages can be infected with HAdVs, but infants, the elderly, and people with low immune function are more susceptible to HAdVs infection. We summarize HAdVs and their corresponding diseases in Table 1. The basis of cell or tissue tropism of HAdVs is still not well established. Certain HAdVs have strong tissue tropisms, but the same clinical manifestations can be caused by different types and species (Lion, 2014b). As shown in Table 1, adenoviral keratoconjunctivitis are most commonly caused by representatives of HAdV-D. Gastrointestinal manifestations are mainly associated with HAdV-F40 and 41, HAdV-G52 and some members of HAdV-D. Respiratory tract manifestations are mainly associated with representatives of HAdV-B, and HAdV-E4 and some members of HAdV-C. Liver manifestations are mainly associated with representatives of HAdV-C.

The pathogenesis of adenovirus infection in host cells is not very clear. It is generally acknowledged that host innate immunity and adaptive immunity regulate adenovirus replication and pathogenesis. Among this worldwide outbreak of hepatitis of unknown cause, some cases have been identified as AdV-positive, especially human adenovirus-F (HAdV-F) type 41 (HAdV41). HAdV-F, also known as enteric adenovirus (EAD), includes HAdV40 and HAdV41 (Uhnoo et al., 1984). HAdV40 mainly infects infants under 1 year of age, while HAdV41 infects older children. Both viruses have generally been sporadic worldwide. HAdV-F has the same structure and genomic characteristics as ordinary adenoviruses and tolerates gastric acid and various digestive enzymes, which helps it replicate in the digestive tract and cause disease. Therefore, HAdV-F has thus the potential to be an excellent candidate as an oral delivery vector candidate for vaccination, such as HIV or MERS (Lu et al., 2009, 2013; Yamasaki et al., 2013; Lemiale et al., 2007; Guo et al., 2015; Mennechet et al., 2019). HAdV40 and HAdV41 were found to co-circulate, but HAdV41 was predominant (Chandra et al., 2021). HAdV40 strains were genetically conserved, whereas HAdV41 strains accumulated new mutations. HAdV41, which possesses different amounts of short and long fibers in the virion, is an important pathogenic virus, but its morphogenesis is still unclear (Song et al., 2012). The vast majority of gastroenteritis caused by HAdV-F occurs in infants under 3 years old. In general, HAdV-F does not cause infection outside the gastrointestinal tract and is mainly transmitted through fecal–oral channels, sewage, or contaminated food. It is prevalent throughout the year without obvious seasonal distribution characteristics. The incubation period is about 3–10 days. The main symptoms are intermittent diarrhea accompanied by vomiting, or fever and dehydration in some cases. SARS-CoV-2 infection has been detected in the unknown hepatitis cases from Israel and the UK (https://www.haaretz.com/israel-news/israel-examining-12-cases-of-kids-hepatitis-after-who-warning-1.10752779; https://www.gov.uk/government/publications/acute-hepatitis-technical-briefing). A new study raised a hypothesis that the unidentified child hepatitis may be related to the superantigen caused by SARS-CoV-2 (Brodin and Arditi, 2022). Staphylococcal enterotoxin B, which is similar to the superantigen motif in the spike protein of SARS-CoV-2 (Cheng et al., 2020), can cause toxic shock and hepatocyte apoptosis in mice infected with HAdV C5 (Yarovinsky et al., 2005). However, the mechanism by which HAdV41 infects the liver remains elusive, which awaits further investigation.

Moreover, as can be seen in the phylogenomic analysis of the fibers and hexons of 28 representative HAdVs in Fig. 2, HAdV-Fs are closely related to HAdV-As, but not so closely related to other major HAdVs. We further checked the expression levels of CXADR, CD46, and DSG2 (three proteins of the major HAdV receptors) in normal human tissues in the Human Protein Atlas database. As shown in Fig. 5, the mRNA or protein expression levels of CXADR, CD46, and DSG2 are relatively high in liver tissue, especially CXADR, the receptor of HAdV41. This might explain why human adenoviruses sometimes cause hepatitis, which requires further investigation.

However, with little evidence, whether HAdV is the direct cause of unidentified hepatitis is not clear at this stage. To date, the whole-genome sequence of HAdV41 from the hepatitis cases is not yet available. Thus, whether HAdV41 has undergone important genetic mutations or recombination with other adenoviruses or beyond, including SARS-CoV-2, to acquire hepatic pathogenesis, requires further investigation. There are some unconfirmed etiological hypotheses regarding the unidentified hepatitis: (1) Inoculation of the SARS-CoV-2 mRNA vaccine may cause T-cell-based autoimmune hepatitis (Boettler et al., 2022), however, most of the reported children with acute hepatitis were unvaccinated; (2) It may be caused by new mutations or the recombination of HAdVs with other viruses, including SARS-CoV-2 (Zhu et al., 2020), but chance of recombination between a DNA virus and a RNA virus is extremely low; (3) A consequence of adenovirus infection with intestinal trophism in children previously infected by SARS-CoV-2 and carrying viral reservoirs (Brodin and Arditi, 2022); (4) Alternatively, it may be caused by drugs; toxins; environmental exposure; or new, unknown pathogens. According to the WHO, the number of cases of unexplained hepatitis in children is likely to continue to increase in the future. Countries should prepare in advance to develop targeted prevention and control measures.

4. Vaccines for HAdVs

At present, HAdV vaccines mainly include live attenuated vaccines (LAVs), recombinant vaccines and influenza vector vaccines. LAVs have been used by the American military to combat adenovirus infection. The infection rate of adenovirus increased after the military stopped using these vaccines in 1999, so they resumed using them in 2011 (Hoke and Snyder, 2013). However, LAVs contain live strains which may increase the risk of vaccine strain recombination, resulting in more violent and pathogenic viruses. In recent years, the use of genetic engineering technology to develop new HAdV vaccine is being actively explored. There are usually two strategies for producing recombinant adenovirus vaccines: (1) changing the highly variable region (HVR) to construct a recombinant hexon protein; (2) expressing hexon in the E3 region of another HAdV genome (Liu et al., 2018). However, the cancer cells used in the production process are not qualified for vaccine production. Whether the process can be reproduced and meet the production needs after replacement with Vero cells or human diploid cells remains to be further investigated. Moreover, two repeats of the neutralizing epitope of HAdV hexon protein were inserted into NA gene of influenza, and the packaged recombinant virus could produce better humoral immune response after intranasal immunization in mice (Yang et al., 2015). But further clinical research is also needed. In addition, there are a few reports on nucleic acid vaccine and subunit vaccine. Both forms of vaccines depend on the choice of immunogens, and mRNA vaccines also depend on efficient delivery systems (Zeng et al., 2020).

5. Clinical use of HAdV vectors

HAdV vectors have the advantages of easy construction, high efficiency, high titers, low pathogenicity, and no risk of inserting mutations to activate oncogenes. Therefore, recombinant vaccines based on HAdV vectors have been widely used in gene therapy of cancer, genetic diseases, and infectious diseases, such as the recombinant adenovirus type-5

Table 1
Diversity of HAdV pathogenesis.

Type	Including	Disease	Brief	Reference
A	Types 12,18,31,61	Gastrointestinal tract infection, Induced tumor	HAdV-A12 can induce tumor formation in newborn rodents (Trentin et al., 1962). HAdV-A31 is used for vaccination because it can escape the immune surveillance of the host (Hofmayer et al., 2009).	(Trentin et al., 1962; Hofmayer et al., 2009)
B	Types 3,7,11,14,16,21,34,35,50,55	Acute respiratory infection, pneumonia, acute febrile pharyngitis, keratoconjunctivitis, acute hemorrhagic cystitis, associated renal and urinary tract infections	Type B HAdV is divided into type B1 (B3, B7, B16, B21 and B50) and type B2 (B11, B14, B34, B35 and B55). Most members of B1 cause respiratory tract infections, while B2 is mainly related to renal and urinary tract infections (Sakurai et al., 2007). B35 is used in preclinical trials against HIV, Ebola, malaria, tuberculosis or respiratory syncytial virus (Keefer et al., 2012).	(Sakurai et al., 2007; Keefer et al., 2012)
C	Types 1,2,5,6,57	Pneumonia, acute respiratory infection, acute fever, pharyngitis, hepatitis	C1, C2, C5, C6 and C57 are the most common types. This adenovirus accounts for a large proportion of children with acute respiratory infections (Garnett et al., 2002). HAdV-C5 vector is currently used as a vaccine platform in many countries, mainly for preclinical research of HIV (Lhomme et al., 2016), malaria (Fonseca et al., 2016), Ebola virus (Li et al., 2017), influenza virus (Van Kampen et al., 2005), tuberculosis (Shen et al., 2016) or Zika virus (Guo et al., 2018), Clostridium botulinum (Chen et al., 2013).	(Garnett et al., 2002; Lhomme et al., 2016; Li et al., 2017; Van Kampen et al., 2005; Shen et al., 2016; Guo et al., 2018; Chen et al., 2013)
D	Including, but not limited to types 8,9,10,13,15,17,19,20,22,23,24,25, 26,27,28,29,30,32,33,36,37,38,39,42,43,44,45,46,47,48,49,51, 53,54,56	Epidemic keratoconjunctivitis, gastrointestinal tract infection, moderate or asymptomatic disease	This is the largest group of the seven subtypes. Most types cause conjunctivitis, while some types also cause gastrointestinal tract infection (Matsushima et al., 2013). D26 was used in large-scale human vaccination trials against HIV and Ebola virus (Milligan et al., 2016). D24 (Colloca et al., 2012), D28 (Johnson et al., 2014), D43 (Belousova et al., 2016), D48 (Farrow et al., 2016), D49 (Thorner et al., 2006), and most recently D56 (Duffy et al., 2018) or D64 (Zhou et al., 2012) are also recommended or used in preclinical vaccination studies.	(Milligan et al., 2016; Colloca et al., 2012; Johnson et al., 2014; Belousova et al., 2016; Farrow et al., 2016; Thorner et al., 2006; Duffy et al., 2018; Zhou et al., 2012)
E	Type 4	Acute respiratory infection	HAdV-E4 is the only member of this virus and is usually associated with outbreaks in military training camps (Gray et al., 1999). It has been tested as a candidate vaccine vector for other infectious diseases, such as hepatitis B (Lubeck et al., 1989) and respiratory syncytial virus (Weaver, 2014).	(Gray et al., 1999; Lubeck et al., 1989; Weaver, 2014)
F	Types 40,41	Gastroenteritis	HAdV-F40 and F41 are only associated with gastrointestinal diseases (Cukor and Blacklow, 1984). These types have been proposed as oral vector candidates for inoculation with HIV (Lemiale et al., 2007), Middle East respiratory syndrome coronavirus (Guo et al., 2015) or induction of	(Yamasaki et al., 2013; Lemiale et al., 2007; Guo et al., 2015; Cukor and Blacklow, 1984)

(*continued on next page*)

Table 1 (*continued*)

Type	Including	Disease	Brief	Reference
			allergen specific intestinal mucosal tolerance (Yamasaki et al., 2013).	
G	Type 52	Gastrointestinal tract infection	Polysialic acid is the cellular receptor of G52 type adenovirus (Lenman et al., 2018).	Lenman et al. (2018)

(Ad5) or type-26 (Ad26) vectored COVID-19 vaccine expressing the spike glycoprotein of SARS-CoV-2, and Ad-26-Vectored Ebola Vaccine Ad26.ZEBOV (Zhu et al., 2020; Milligan et al., 2016). Furthermore, comparing to other natural oncolytic viruses adenoviral vectors have a good oncolytic effect and are commonly used as an oncolytic virus vector for cancer therapy (Atasheva et al., 2020). In addition, The HAdV vector can be inoculated through mucosal surfaces such as the mouth, nose, and trachea to obtain comprehensive immunity, including mucosal immunity, humoral immunity, and cellular immunity (Douglas, 2007). It worth noting that acute hepatotoxicity has been observed in the clinical applications of AdVs in immunocompromised patients (Atasheva et al., 2020; Yilmazer et al., 2013; Wang and Zhang, 2021; Shimizu et al., 2021), which requires caution in use and further improvement of the safety of AdV vectors.

Adeno-associated virus (AAV) is a small, nonenveloped, defective virus that packages a linear single-stranded DNA genome (Daya and Berns, 2008). AAV vectors are currently among the most frequently used viral vectors for gene therapy. Alipogene tiparvovec is an adeno-associated virus serotype 1-based gene therapy for adult patients with familial lipoprotein lipase (LPL) deficiency. Alipogene Tiparvovec uses an adenovirus vector (AAV1) to integrate the active LPL gene (LPLS47X) into the DNA of muscle cells, so that these muscle cells can produce normal amounts of LPL, which realized the purpose of treating diseases by replacing defective genes with exogenous normal genes (Scott, 2015).

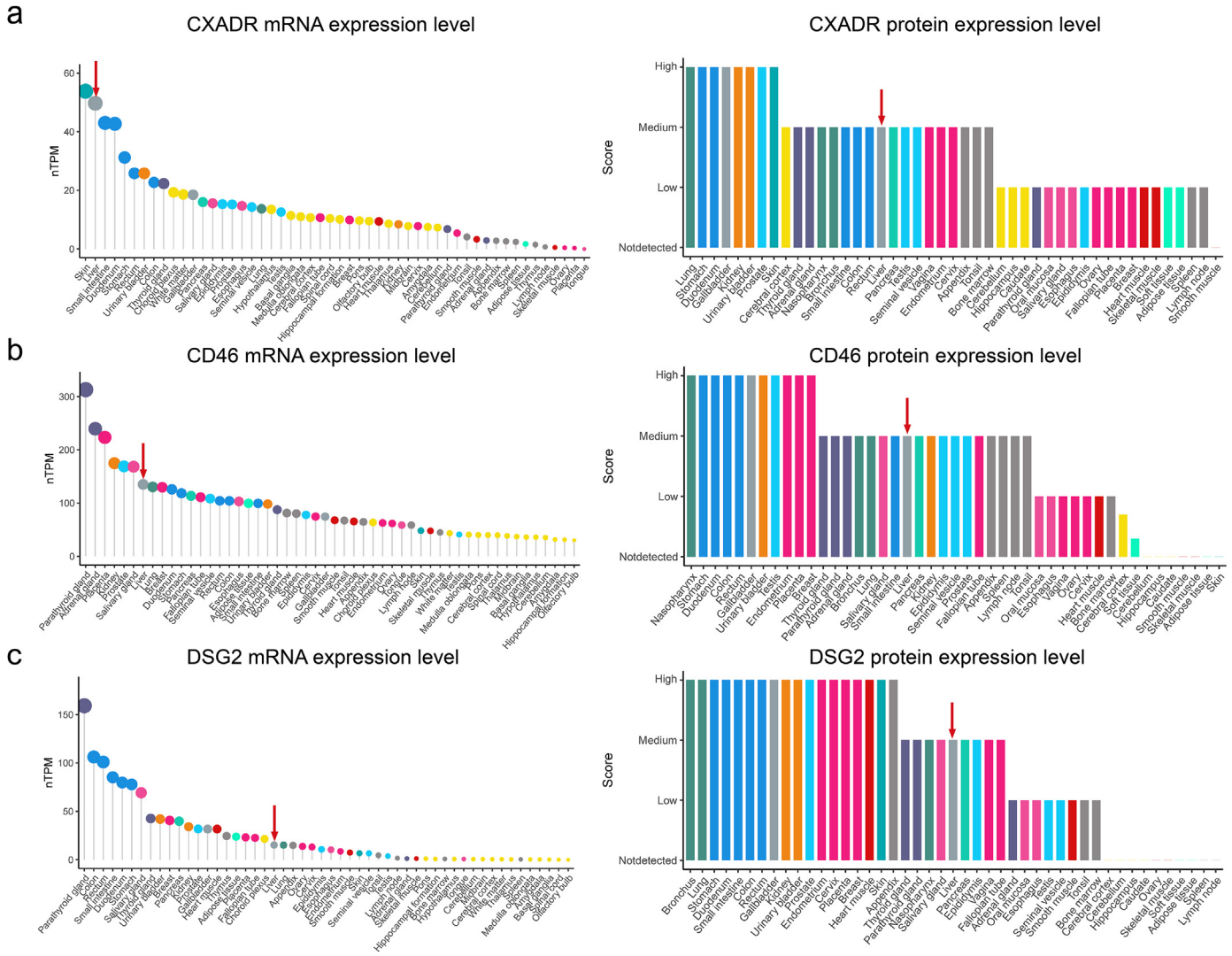

Fig. 5. The mRNA and protein expression of CXADR (a), CD46 (b) and DSG2 (c) in human normal tissues in Human Protein Atlas (HPA) database (https://www.proteinatlas.org/). RNA expression (left) was plotted as nTPM (normalized protein-coding transcripts per million), corresponding to mean values of the different individual samples from each tissue. Protein expression data (right) is shown for the tissues. Color-coding is based on tissue groups, each consisting of tissues with functional features in common.

6. Treatment and prevention

To date, there are no approved, specific antiviral therapies for HAdVs. Treatment of severe HAdVs infection revolves around broad-spectrum antivirals such as cidofovir, ganciclovir, and ribavirin (Kuwatsuka et al., 2020; Lenaerts et al., 2008). Alternative therapeutic approaches have also recently emerged. Adoptive T-cell therapy is used to combat severe HAdVs infection (Abraham et al., 2019). In addition, there are some new antiviral strategies for HAdVs, such as the inhibition of virus entry, inhibition of virus replication, interference with HAdV gene expression, and epigenetic-regulator-based inhibition (Dodge et al., 2021). Further research is urgently needed to understand HAdV pathogenesis and find effective targeted treatments and prevention methods.

7. Prospect

The pathogenesis of this acute hepatitis in children amid the COVID-19 pandemic is not completely clear. Whether HAdVs is involved in the unknown hepatitis requires further investigation. The epidemic situation of HAdVs infection remains serious. New types of HAdVs generated by gene recombination suggest the need for systematic molecular epidemiological studies of HAdVs. Further research on all aspects of HAdVs will contribute to the development of better clinical anti-HAdVs drugs and treatment, as well as the design of safer and more effective HAdVs vector vaccines.

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