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REVIEW ARTICLE

A brief review on the molecular biology of human adenoviruses

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ABSTRACT

Human adenoviruses infection causes diseases worldwide in all age groups and genders, which is associated with a wide range of diseases affecting the gastrointestinal tract, respiratory tract, urinary tract, and the eye, but they are often isolated from the pharynx and stool of asymptomatic children. However, in developing countries, diarrhea is a major cause of morbidity and mortality; and after rotaviruses, human adenoviruses are considered to be the second most important cause of viral infantile diarrhea. Also, human adenoviruses cause fatal acute respiratory distress syndrome in healthy adults and are especially fatal in infants and immune-compromised individuals. This review summarizes both classical and contemporary discoveries in the study of human adenoviruses at the molecular level, with particular emphasis on viral receptors, capsid proteins, nucleic acid, and genome properties as well as the molecular interactions governing the virion assembly. In this article, we provide insightful information concerning the molecular aspects of human adenoviruses. This would develop an understanding of the virus and serve as a powerful tool in identifying new approaches for the prevention and treatment of adenoviral infection.

Keywords capsid proteins, diarrhea, human adenoviruses, molecular biology, viral replication

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INTRODUCTION

The discovery of human adenoviruses (Hadv) began over the past century, during which a cytopathogenic agent was observed when the tissue of tonsils and adenoids are extensively cultivated after the screening of children by Rowe and coworkers.[1,2] The adenoid tissue, where the virus was initially isolated, has led to the name of the virus as "adenoid degeneration virus" and described their basic habitat associated with asymptomatic persistence in the lymphoid tissue. Hadv are increasingly recognized as a serious and global public

health concern because they are implicated in a wide range of diseases affecting the population, especially in children under 5 years of age and immunocompromised individuals,[3] and mostly in developing countries.[4,5] Hadv are associated with different kinds of disorders, affecting the gastrointestinal tract,[6] respiratory tract,[7] urinary tract, and the eye depending on the viral species and serotype.[8] Based on deoxyribonucleic acid (DNA) sequence analysis, Hadv are classified into seven species (Hadv-A to G), with more than 100 genotypes.[9]

However, respiratory tract infections are associated with Hadv species B, C, and E,[5] with Hadv-F, Hadv-C, Hadv-D, and Hadv-G and A genotypes detected in case of gastroenteritis.[6,10,11] While members of the human adenovirus species D are mostly isolated from individuals with keratoconjunctivitis and conjunctivitis. Consequently, Hadv are "often also isolated from the pharynx and stool of asymptomatic children".[2]

Hadv are members of the genus Mastadenovirus of the family Adenoviridae. The Hadv genome is enclosed within an icosahedral, non-enveloped capsid that ranges between 70-90 nm in diameter made of up fiber proteins, penton, and hexon.[12] Adenoviruses are medium-sized DNA viruses with a linear double-stranded genome (dsDNA), 34-36kbp in size and large enough to encode up to ~40 proteins.[13]

The disease outcome, the interaction between the virus and the host, vaccination, and treatment of Hadv infections depend on the viral serotype responsible for the disease. Currently, only vaccines for human adenoviruses E4 and B7 are available in use.[5] Until now, there is no anti-viral treatment approved against Human adenovirus infections.[14] However, significant progress has been reported on cidofovir and ribavirin.[15] The cidofovir is an acyclic nucleoside phosphonate that acts against adenoviruses and other DNA viruses.[16] Its mechanism of action is independent of the serotype, it generally inhibits the Adv replication cycle, by acting as a nucleotide monophosphate, together with phosphylations by cellular kinases, and the compounds are activated to form 2' deoxyribonucleoside 5'-triphosphates (dNTPs) analogues. Viral DNA polymerases bind to the formed analogues, resulting in the interference with the viral replication process.[15–17] Ribavirin, similar to cidofovir, is also a nucleoside analog and its action is restricted to adenovirus species C only. The suggested mechanism by which ribavirin acts on adenovirus is by direct inhibition of its infection through depletion of intracellular guanosine triphosphate (GTP) pools as well as indirect inhibition by interference with RNA capping.[15,18] The aim of this review was to summarize both classical and contemporary discoveries in the study of human adenoviruses at the molecular level with a particular emphasis on capsid proteins, nucleic acid and genome properties, viral receptors and the molecular interaction governing the virion assembly. However, insightful information on Hadv would advance an understanding of the virus and serve as a powerful tool in identifying new approaches for the prevention and treatment of human adenoviral infections.

STRUCTURE OF VIRAL SYMMETRY

A mature form of adenoviruses (virion) is made up of more than 7200 polypeptides (proteins) molecules, with a cumulative mass of ≈150×106 kilo Dalton (kDa).[19] The symmetry of adenoviruses consists of three major capsid proteins, with the hexon emerging as the biggest and most numerous of the structural proteins that make up the capsid.[20] The hexon in adenoviral virion is composed of 720 monomers that form 240 hexon homotrimers, which in turn form 20 capsid facets, each comprises of 12 hexon homotrimers.[21] The other two major capsid proteins are fibre and penton base that forms the penton complexes made up of three subunits of protein IV and five subunits of protein IIIa is located at the icosahedral edges, and hexamers of protein VI (PVI) are located under the penton base.[22,23] The 240 hexons fill the facets and the 12 pentons are the vertices of the icosahedron on the vertices are also the characteristics fibres (62 kDA), that range from 10 to 30nm in distinctive serotypes and act as attachment structures (one per cell).[24]

Viral structural proteins

Human adenoviruses structural proteins are classified in to three types; minor capsid proteins, major capsid proteins and core proteins (Figure 1).[23]

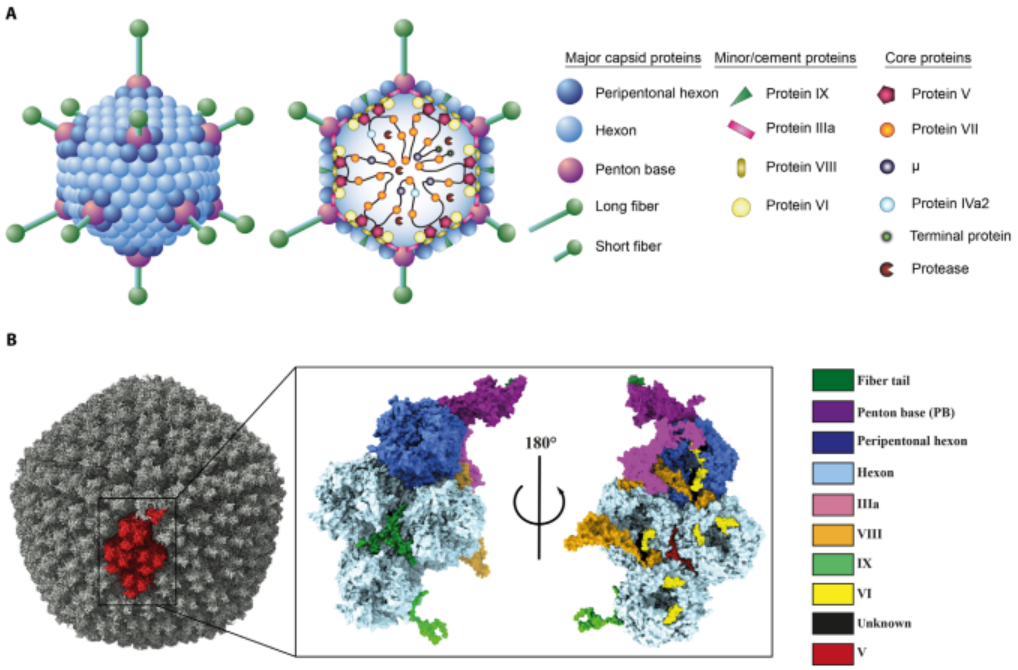

Figure 1 Structure of adenovirus A) Schematic representation of adenovirus structure and the cross-sectional structure of adenovirus showing the capsid proteins, B) "Surface representation of the adenovirus electron density with one asymmetric unit (ASU) highlighted in red (left) and a surface representation of the ASU atomic model viewed from the virion outside (middle) and inside (right)". Adopted from Rafie *et al.* (2021).[23]

Minor capsid proteins

Minor capsid proteins present in Hadv are protein IX, protein IIIa, protein VIII and protein VI (abbreviated as PIX, PIIIa, PVIII and PVI).[25,26]

Protein IIIa: The 63.5kDa protein IIIa is generated from its 67kDa precursor by the cleavage of the protein IIIa precursors at its N terminus during maturation of the virion. Protein IIIa is positioned at the surface of the particle and its alteration may alter the viral tropism, it is also involves in virion assembly.[20]

Protein VI: Protein VI at its late stage of development is 22 kDa and is generated by detachment from a larger precursor (PVI). Protein VI is positioned interior to the capsid, presumably adjacent to the hexons.[26] The main function of protein VI is to facilitate nuclear importation of hexon proteins.[20]

Protein VIII: The protein VIII is not well studied compared to its counterpart minor capsid proteins. Its 15.3 kDa is located at the inner surface of the triangular facets as dimmers and interplays with hexons of adjacent facets. Protein VIII plays a role in the virion's structural stability.[27]

Protein IX: Protein IX is 14.3 kDa and it is the smallest among the minor capsid proteins.[26] It is unique to the Mastadenoviruses and is absent in the other adenovirus genera. Twelve molecules of protein IX are positioned at each of the 20 facets of the icosahedral capsid.[28] The central part of every facets of the icosahedral capsid is formed by the groups-of-nine hexons (GONs).[28] Furthermore, modification of protein IX affects the DNA-packaging capacity of human adenovirus, and it also affects transcriptional activity of several promoters.[28]

Core capsid proteins

Polypeptides V and VII are the principal core capsid proteins in adenoviruses which account for about 10% of the protein mass of the virion, other core proteins are protein μ (mu), protein IXa2, terminal protein and protease.[23]

Polypeptide VII: Polypeptide VII precursor is longer than polypeptide VII (pVII) with an additional 23 amino acid at its N terminus.[29] The precursor is cleaved off by a viral protease within the virion capsid to form PVII during the late steps of viral maturation. Polypeptide VII is the most common among adenoviral core proteins with an estimated molecular weight of 19.4 kDa.[26] The Adenovirus polypeptide VII protects the viral genome from a DNA damage response immediately after infecting the host.[29]

Polypeptide V: This is slightly basic and has an estimated molecular weight of 41.7 kDa which is represented in the virus particle as 180 molecules of polypeptide V. It differs from polypeptide VII in that; the later mature without proteolytic trimming and it appears to be

less tightly bound to the DNA than protein VII.[30]

Mu: The core also contains the small, basic L2 encoded 19 amino acid DNA-binding peptide (mu) and it's associated with adenovirus DNA condensation and charge.[23,31]

Terminal proteins: The E2 encoded terminal protein (TP) is attached covalently to each 5' termini of the viral genome and is involved in the initiation of replication.[30]

Major capsid proteins

The major proteins of Hadv constitute the icosahedral capsid of the virus particle, which contains a 35kb long dsDNA.[23] At each of the 12 corners of the virus particle, a penton is present, which constitutes the penton base with a protruding fibre. A fibre knob is situated at the end of each fibre. The icosahedral structure of Adenoviruses and the major capsid proteins were discovered in 1959.[31] Each hexon is surrounded by six neighbouring hexons, and each penton base is surrounded by five hexons. The hexon is a major component of the capsid, whereas the fibre is responsible for attachment to cells and the penton base is responsible for the internalization of adenoviruses into the susceptible host cells.[32]

Hexon: This is the most abundant of the capsid proteins in a typical adenovirus particle, every adenovirus particle (virion) posse's 240 hexon trimers that consist of both variable and conserved regions.[31,32] On top of each hexon-monomer, there are seven flexible type-specific loops: the hypervariable regions (HVRs).[21] The HVRs provide the adenovirus genotypes with their specific antigenicity, as different HVRs bind to different receptors, antibodies, or cells.[21,33]

Fibre: The attachment of the virus to the primary cellular receptor is mediated by the fibre; it consists of three monomers (a trimer). One of these trimers is situated at each corner of the adenovirus particle.[33] Most Hadv types have only one fibre, with the exception of Ad40 and Ad41 which have two different fibres (one long and one short). The following three domains make up a single fibre monomer: the N-terminal domain that binds to the penton base, a middle shaft which is characterized by "slight flexibility". The shaft is composed of repeats of an approximately 15-residue long motif. Different types of Hadv have different numbers of repeats, from six (Adv3) to 22 (Adv2 and Adv5), as well as the third domain specifically called as C-terminal domain that binds to the primary cellular receptor.[34]

Penton base: The penton base is a pentameric protein where each monomer contains conserved RG (arg-gly-asp)-motifs.[23] These motifs bind to secondary cellular receptors during the internalization of the adenovirus particle. The pentameric penton base and the trimetric fibre form a complex to form a penton at each corner of the virion.[34] The RGD-motif is conserved in all Ads except in species F Ads (Ad40 and Ad41).[32]

Non-structural proteins

Adenoviral non-structural proteins have been described, in which almost all of them function in the adenoviral life cycle by having catalytic and regulatory functions.[35] The DNA binding protein (DBP) is an E2-encoded which varies in size between the serotypes (473-529 amino acids, aa).[36] It has multiple functions and is involved mainly in DNA replication and other viral DNA metabolic processes.[13] Other E2-encoded proteins involved in DNA replication are the viral DNA polymerase and the terminal protein (TP).[37] The L3 region encoded 23kDa cysteine protease is a non-structural protein that is crucial for viral capsid assembly as well as for the uncoating of the viral particle at the nuclear membrane during the viral entry process.[37] It has been estimated that adenovirion contains about 10-30 protease molecules.[36] The activity of the protease is increased by the presence of adenoviral DNA and by the cleavage of pVI, specifically by the 11 amino acid peptide cleavage product pVIc.[25,36]

GENOMIC ORGANIZATION

Members of the family Adenoviridae possess linear, double-stranded DNA (dsDNA), with inverted terminal repeats ITRs.[13] An inverted terminal repeat which is a viral-encoded terminal protein (TP), is connected by a covalent bond to the 5'- end of each DNA strand.[38] The size of the Hadv genome ranges between 30,288 to 36,521 base pairs (bp) which is smaller compared to the genome in other adenoviruses from the genus aviadenoviruses. The length of an inverted terminal repeat in human adenoviruses is 36-371 bp. However, the amount of guanine + cytosine (G+C) among the adenoviruses differs between 33.7% and 63.8% depending on the genus. Consequently, G+C content present in Human adenoviruses ranges between 40.8% and 63.8%.[38,39]

However, in the Hadv genome, the middle part of the genome and the DNA sequences that encode the majority of virion structural proteins, and the proteins that are involved in the replication of the viral DNA and assembly of virion are highly conserved among all human adenoviruses, but the two ends show huge variations in length and content.[39] The genome consists of several repeats of cis-acting packaging sequence between the left terminal repeat and the first protein-coding region.[40] The variation in the content of E3 region is what differentiates the genomic organization in Hadv from other adenoviruses.[41] The E3 region differs in the number and entity of genes even among human adenoviruses serotypes.[39] The E2 region which is positioned between E1 and E3 is conserved throughout the members of the family Adenoviridae, while the length and content of E1, E3 and E4 have great variability, even within the genera.[39,42] The intermediate and late gene products of the replication cycle, which are L1 to L5, are involved in the assembly and maturation of the virion.[41]

It has been proposed that the two ends of the genome (E1 and E4 regions) are transcribed first, leading to an opening and subsequent transcription of the central core of the genome structure.[37] The genome is characterized by several RNA polymerase II dependent tran-

scription units, the five early (E1A, E1B, E2, E3, E4), the delayed early units (IX, IVa2, and E2 late) as well as major late transcriptional units (MLTU).[43] The large MLTU transcript is further processed by polyadenylation and alternative splicing, creating 5 to 6 different mRNAs (L1-L5/L6).[43] The genome also encodes one or two small virus-associated RNAs (VA RNA I and II) transcribed by RNA polymerase III.[44]

VIRAL STABILITY

In terms of stability, adenoviruses are stable at -70°C and are not sensitive to lipid solvents.[2,41] Adenoviruses are relatively acid-stable.[34,45] Heat sensitivity varies among members of different genera of the family adenoviridae. Members of the genera Mastadenoviruses are sensitive to heating at a temperature above 50° C for some minutes.[2,46] Adenoviruses are moderately affected by chemical disinfectants.[46,47] Adenovirus serotypes possess an unusually variable spectrum of sensitivity to chemical biocides, especially to peroxygen compounds and iodophors.[48,49] Human adenovirus serotypes 1, 8 and 29 are sensitive to 0.05-2.5% liposomal povidone-iodine, while serotypes 2, 23, 25, 37, and 44, are resistant to inactivation by 0.05-2.5% liposomal povidone-iodine at exposure times of 5, 30, and 60 min respectively.[48] Adenoviruses lack an envelope, a suggested reason for the different sensitivities is the differences in the viral capsid proteins.[48] Adenoviruses have been shown to be up to 60 times more resistant to UV irradiation than RNA viruses such as hepatitis A virus.[49]

VIRAL RECEPTORS AND REPLICATION

Adenovirus attachment to the host cell is mediated by the interaction between the viral fibre protein and a specific receptor on the target cell. The majority of adenoviruses used the coxsackie-adenovirus receptor (CAR) as their receptor for entry into the host cell,[50,51] species B viruses are excluded, which specifically use CD46 membrane co-factor protein,[52,53] and also species D serotype 37, employed the use of sialic acid rather than CAR on target cells for attachment.[54–56] The replication of adenoviruses occurs in three phases: an immediate-early phase, a delayed-early phase which precedes viral DNA replication and a late phase which is characterized by the expression of the structural proteins of the viral capsid.[57] However, replication in adenoviruses takes place in the nucleus of the host cell and it is semi-conservative, with each strand being elongated "continuously" without Okazaki intermediates.[57] The early mRNAs appear during the first 8 to 10 hours, but they continue to be generated throughout the infection cycle.[42] Furthermore, the assembly of adenovirus particles occurs in the nuclei of infected cells and the replication cycle takes 32 to 36 hours.[45] Although fibre-deficient mutants of adenovirus seem to have an altered viral morphogenesis, a study by San Martın (2019)[20] has reported that; the fiber plays a role in capsid stabilization, rather than in capsid assembly. Three different types of infection are caused by

adenoviruses: a productive lytic infection predominantly in epithelial cells, and latent or persistent infections that occur in the lymphoid mucosal tissue which may infrequently produce virus, or transformation predominantly in an animal model.[52] In adenoviruses, lytic cycle is far more efficient then lysogenic, because in lytic huge number of virion are produce after a single replication cycle, with 1-5% being infectious.[45]

PATHOGENESIS

The pathogenesis of Hadv differs depending on the species, serotype, and organ specificity and disease patterns appear to occur within particular serotypes.[42] Adenovirus infections are divided into either localized to a single organ or can affect numerous organ systems, which may lead to disseminated disease, with especially high morbidity and mortality rate.[45] The incubation period for Adenoviruses infection ranges from 2 to 21 days with an average of 7 to 13 days and the primary site of replication is the epithelial cells of the host gastrointestinal (GI) tract, respiratory tract, eyes, and urinary bladder.[57] Human adenoviruses cause either lytic infection in epithelial cells or latent infection which takes place within the lymphoid cells (Ghebremedhin, 2014; Murali et al., 2014).[58,59] The lytic infection which is also called as viral reproduction cycle occurs when the Hadv enters the cells via ~120-nM clathrin-coated "pits and vesicles". Once in the cells, post internalization disruption of the early endosome occurs, favouring the virion to escape from the cytoplasm to the nucleus before destruction by lysosomal proteases. It then replicates inside the nucleus of the host cell (human epithelial cells).[57,60] The virus can inhibit the macromolecular synthesis and transport of messenger RNA (mRNA) from the nucleus to the cytoplasm of the host cell, thus facilitating host cellular death and cell lysis. After the virus actively replicates inside the host cell, it causes cellular death and cell lysis. Furthermore, the production of virions results in a host inflammatory response. Hadv can persist in susceptible cells in a latent state for long after lytic infection.[60–62] In the latent mode of infection, human adenoviruses generally remain in lymphoid organs, such as adenoids, tonsils, or Peyer's patches.[57,60,63] The virus-mediated tissue damage results from direct cytotoxicity of the virus, but it can also occur due to the inflammatory cell infiltrate.[64] These latent virus particles can eventually "re-activate, re-infect", and replicate in epithelial cells, causing disease symptoms again.[60]

HOST IMMUNE RESPONSE

The host immunological responses to infection caused by adenoviruses completely rely on certain factors such as the site of infection (e.g. eye, gastrointestinal tract, and respiratory tract), viral serotype, and the immunological status of the host.[66,67] Several mechanisms are "adopted" by Hadv to bypass host immune responses, which include the inhibition of intrinsic cellular apoptosis in infected cells, inhibition of responses to interferon and tumor necrosis factor (TNF), and the prevention of MHC class I expression on cell surfaces.[68]

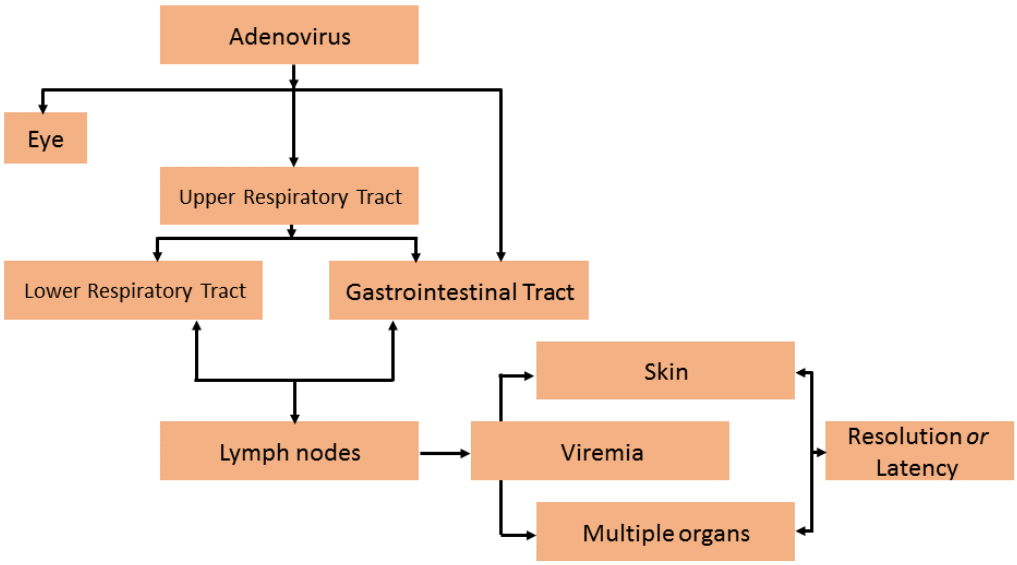

Figure 2 **Schematic representation of adenovirus pathogenesis.** [65]

Secretory immunoglobulin A (SIgA) is mainly the antibody against adenovirus and can be found in the upper respiratory tract of the infected individual within 3 days of infection. But antibodies can be detected in serum and nasal secretions approximately 7 days post-infection containing both secretory IgA and IgG.[44,69] Antibodies are directed against the viral hexon, which is the alpha component of the viral capsid, containing an antigenic component that is conserved in all Mastadenoviruses.[69] Neutralizing antibodies specific to different adenovirus genotypes are produced in response to another hexon component as well as viral fibre antigen.[69]

Human adenoviruses interact with the host cell in three different possible phases; Lytic infection (epithelial cells): which is the phase whereby the virus completes its multiplication cycle, producing cellular death and releasing new viruses of which up to 5% are infectious, latent infection (lymphoid cells): in this phase of interaction, little quantity of virus are released, and the cellular death rate is offset by normal multiplication as well as oncogenic transformation; the third phase of interaction, in this phase, Human adenoviruses genome (DNA) is included in the cellular genetic material and replicates inside it without producing new infectious virus.[70]

An *in vivo* study of adenoviral ''pulmonary infection'' revealed pathological changes by histological investigation, that can be divided into two phases: The first phase, with predominantly monocyte and macrophage infiltrates typical of non-specific, cytokine-mediated inflammation, whereas the second phase is characterized by predominantly T-lymphocyte infiltration.[71–73] T-cell-mediated immunity seems to be important for recovery after acute Hadv infection since immuno-compromised individuals who lack effective cellular immunity are at a much higher risk of adenoviral infection.[71,74]

A number of researchers have reported that; both clinical and laboratory features of adenovirus infections are consistent with Th1 cell responses (production of TNF and interferon γ by T-cells).[44,73] CD4+ lymphocytes specific to adenovirus can recognize conserved antigens across different adenovirus serotypes, like-wise infection with one serotype can therefore produce T-cell-mediated immunity to infection with different serotypes. However, the neutralizing antibodies against Hadv are serotype-dependent.[69,70] The presence of adenovirus-specific CD4+ T-cells in most asymptomatic adults showed that adenovirus-specific cellular responses are long-lived.[66]

CONCLUSIONS

The high worldwide prevalence of adenoviral infections coupled with non-specific vaccine and therapeutic options available for the prevention and treatment of adenoviral infection have generated considerable interest in understanding human adenoviruses at molecular level elucidating the molecular mechanisms that underlie the development of infection caused by adenoviruses, that develop an understanding of the virus and serve as a powerful tool in identifying new approaches for the prevention and treatment of diseases caused by human adenoviruses.

ABBREVIATIONS

AdVs, adenoviruses; bp, base pair; CAR, Coxsackie adenovirus receptor; DBP, DNA binding protein; DNA, deoxyribonucleic acid, dsDNA, double stranded DNA; GONs, groups-of-nine hexons; γ, gamma; HAdVs, human adenoviruses; HVR, hypervariable region; ITR, Inverted terminal repeats; IgA, immunoglobulin A; IgG, immunoglobulin G; kDa, kiloDalton; MLTU, major late transcriptional units; MHC, major histocompatibility complex; mRNA, messenger RNA; NAb, Neutralising antibodies; RGD, Arg-Gly-Asp sequence; RNA, ribonucleic acid; SIgA, secretory immunoglobulin; TNF, tumour necrosis factor; TP, terminal protein, ts, temperature-sensitive; UV, ultraviolet; ^{o}C, degree celsius.

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DECLARATIONS

Authors' contributions

Conceptualization, resources, validation, and visualization: BS, UU, AT. Writing-original draft: BS & UU. Writing-review & editing: BS, UU, AT.

Conflict of interest

The authors declared no conflict of interest.

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