Chapter 1

Introductory Chapter: Human Adenoviruses

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1. Introduction

The date of adenoviruses' discovery is considered to be in 1953, when a cytopathogenic agent was identified during the long-term cultivation of the tissues of the tonsils and adenoids after operations in children with Rowe and coworkers [1]. This determined the name of the viruses (adenoid degeneration viruses) and outlined their basic ecology associated with asymptomatic persistence in the lymphoid tissue. Soon, adenoviruses were isolated from materials obtained from patients with acute respiratory diseases accompanied by conjunctivitis [2]. In 1954, Huebner received the new data indicating that similar viruses are also found in the secretes of patients with acute pharyngitis and conjunctivitis, and therefore they were called "adenoid-pharyngeal-conjunctival viruses" [1]. In the same year, another group of researchers, when studying the etiology of acute respiratory infections and atypical pneumonia, isolated a previously unknown virus from the US Army recruits, named RI-67. It further proved the adenoviruses' identity with the adenoid-pharyngeal-conjunctival virus [3]. In subsequent years, such viruses were isolated from patients during outbreaks of epidemic keratoconjunctivitis, although as an independent disease, it was described in the 20s of the twentieth century.

Adenoviruses are the first respiratory viruses that were isolated on tissue culture. The opportunity to grow up in vitro on synthetic media of various cells of organs and tissues of humans and animals, as well as the ability of viruses to multiply on sensitive cells to cause a cytopathic effect opened up broad prospects for the development of virology. By 1956, a large number of biologically similar but antigenically distinct strains of viruses were identified, which were decided to have a group name of adenoviruses [4]. Not less than 120 viruses that infect mammals, birds, reptiles, amphibians, and fish are described in the *Adenoviridae* family. Further study of adenoviruses, the discovery of their new serotypes made it possible to establish that this viruses cause not only respiratory diseases but also diarrhea, mesadenitis, hemorrhagic cystitis, and other pathological conditions. Only in humans, over 50 adenoviral serotypes are

known which cause a wide range of illnesses, from mild respiratory infections in young children to life-threatening multi-organ disease in immunocompromised people.

2. Adenoviruses' nomenclature

This family includes two genera designated based on genetic criteria (*Atadenovirus* and *Siadenovirus*) as well as three genera, in which adenoviruses are combined according to the type of host (*Aviadenovirus*, *Ichtadenovirus*, and *Mastadenovirus*) (https://talk.ictvonline.org/taxonomy).

Genus *Atadenovirus* presents the newly formed genus which combines adenoviruses with a high relative content of AT-pairs in genomic DNA. This genus includes also adenoviruses of snakes, possums, calves, chameleon, ducks, and lizard.

Genus *Siadenovirus* combines adenoviruses containing at the 5′ end which contains a gene of an enzyme sialidase that cuts off sialic acid residues from the surface glycoproteins of the host cells. These adenoviruses infect frogs and birds.

Genus *Aviadenovirus* includes adenoviruses of turkeys, quail, chickens, and a number of other birds. The type species causes the death of embryos and respiratory disease in quails and chickens. Other members of this genus are pathogens of the egg drop syndrome, hemorrhagic enteritis, and hepatitis.

Genus *Ichtadenovirus* has the only characterized representative which infects white sturgeon—*Sturgeon ichtadenovirus A.*

Genus *Mastadenovirus* includes various viruses of mammals: viruses of cows, sheep, deer, pigs, dogs along with all human adenoviruses.

In humans, 57 adenoviruses are known, which are divided into 7 groups (A–G).

3. Structure

Adenoviruses are non-enveloped viruses, 80–90 nm in diameter. The icosahedral capsid of adenoviruses consists of hexones carrying group-specific and type-specific antigens and pentones containing mainly group-specific antigens at each apex. From each pentone there is a fiber with a head at the end (**Figure 1**).

Structural proteins of adenoviruses are designated by Roman numerals in descending order of molecular weight. The adenovirus capsid consists of seven structural proteins; three major capsid proteins hexon, fiber, and penton; and four minor proteins protein IIIa (pIIIa), VI, VIII, and protein IX [5]. Fibers provide binding to cellular receptors and participate in the discrimination of infected cells, causing inhibition of the synthesis of cellular macromolecules [6]. Soluble proteins of pentone cause a cytopathic effect similar to the action of infectious adenoviruses,

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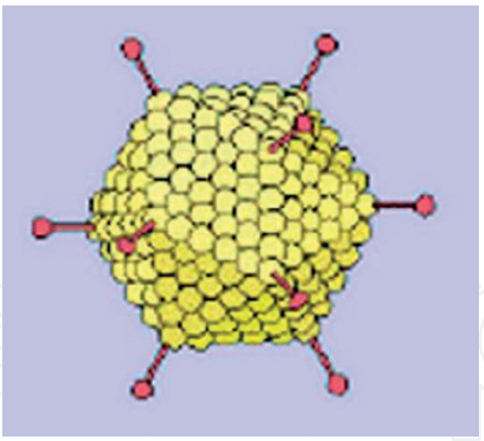

Figure 1. Adenovirus structure (from Linda Stannard, of the Department of Medical Microbiology, University of Cape Town).

but it manifests itself much faster (after 4–6 h). The pathogenetic significance of hexons is confirmed by the fact that antibodies against their epitopes demonstrated a neutralizing effect. They may be involved in the development of receptor-dependent endocytosis initiated by fibers, the main target for neutralizing antibodies [7].

A feature of adenoviral DNA is the presence of a terminal protein (TP), which is covalently linked to the 5′ end of each of the DNA strands. One of the possible functions of TP is the DNA attachment to the nuclear matrix after viral genome has entered the nucleus. Due to the interaction of TP, DNA is retained in the form of a ring structure, thus increasing the efficiency of transfection of adenoviral DNA isolated from virions [8]. The size of DNA is (20–25) 103 kDa, which corresponds to approximately 36,000 base pairs. This would be enough for about a dozen medium-sized proteins, but the information capacity of DNA is much more: adenoviruses synthesize about 40 proteins. This is achieved by reading information from both DNA strands and alternative splicing, which provides several types of mRNA based on the primary transcript of one gene. The 13 proteins are included in the mature virion, the rest belong to nonstructural components, functioning at the stage of intracellular reproduction of the virus [9].

4. Antigenic structure

Antigenic structure of *Mastadenovirus* is represented by three soluble antigens: the hexone A-antigen is common for all serotypes; pentone antigen (B-antigen) is a toxic antigen, it inhibits the action of interferon and increases the severity of associated respiratory infections; and fibril C-antigen is a type-specific which promotes the adsorption of adenoviruses on monkey or rat erythrocytes and causes their agglutination. Manifest forms of the disease cause epidemic serotypes (3, 4, 7, 14, 21) of subgroups B and E. Serotypes 1, 2, 5, and 6 subgroups C cause a latent current, contributing to the formation of chronic tonsillitis and adenoiditis. Clinical forms of adenovirus infection presented in **Table 1**.

Clinical manifestations	Serotype	Ref.
Acute respiratory diseases	1, 7, 14, 21	[10]
Viral pneumonia	1, 3, 4, 7, 55	[10–12]
Conjunctivitis	3, 7, 8, 10, 14, 19, 37	[13]
Gastroenteritis	9, 11, 31, 40, 41	[9, 14]
Meningoencephalitis	2, 6, 7, 12, 32	[15]

Table 1. Clinical forms of adenovirus infection.

The WHO have reported that data on the incidence and ramp prevalence of adenoviral infections are not exact, since in many cases, adenoviruses cause mild forms and therefore remain unregistered, according to general practitioners [16]. However, in recent years, adenoviruses caused widespread outbreaks in Asia [17–19] in which adenoviral infection was accompanied by the development of acute respiratory distress syndrome (ARDS) in Malaysia [18], China [16, 19], and South Korea [19].

5. Transmission

The source of infection is a sick person in the acute stage of the disease, convalescent, or a virus carrier. Pathogens are secreted with nasopharyngeal secretions, sputum, conjunctival discharge, feces, and urine (mainly in individuals with immunosuppression). The timing of isolation of pathogens from the upper respiratory tract reaches the 25th day of illness onset and more than 1.5 months with feces. Adenoviral infections are transmitted by airborne, introducing the virus to the conjunctiva and possibly by the fecal-oral route, thus affecting not only the respiratory tract but also other organs. The widespread disease is 5–10% of all viral diseases. Incidence is recorded throughout the year with a rise in the cold season. Both sporadic cases and epidemic outbreaks are observed. The most susceptible to infection are children from 6 months to 5 years, as well as military personnel. Particularly it has a high incidence in the newly formed groups of children and adults (in the first 2–3 months). In 95% of the adult population, antibodies to the most common serotypes of the virus can be detected in the serum [20].

6. Reproduction

The deproteinization of viruses entered the cell starts in the cytoplasm and ends in the nucleus, where DNA is released with a terminal protein attached to it. Transcription of the genome and replication of viral DNA occur in the nucleus with the help of cellular enzymes [21]. First, mRNAs are synthesized, which code for the synthesis of virus-specific enzymes and then also RNAs that carry information on the synthesis of capsid proteins and strands. The assembly

of virus particles occurs in the nucleus, where crystal-like inclusions are formed. Several hundred viral particles are synthesized in each cell. The release of adenoviruses is accompanied by the destruction of the host cell. The cycle of reproduction of adenoviruses in the cell lasts 14–24 h.

Adenoviruses can multiply in different cells, including airway epithelial cells and lymphocytes. Virus-infected cells become targets for immunity effectors. However, adenoviruses impose such properties on cells that allow them to avoid destruction or at least reduce this possibility. Adenoviruses produce factors that block the synthesis and expression of HLA-I molecules on the cell surface and thereby inhibit the presentation of viral antigens attacked by CD8+T-lymphocytes. Cells infected with adenoviruses acquire increased resistance to interferons and TNF-a, a potent cytotoxic cytokine. In both cases, adenoviral proteins interfere with molecular mechanisms that determine antiviral effects. Among the products of early adenoviral genes are factors that delay the development of apoptosis. In general, this reflects a strategy aimed at improving the survival of infected cells and creating conditions for viral persistence [22].

7. Pathogenesis

From the pathogenetic point of view, adenoviruses damage the respiratory tract and belong to the "respiratory" viruses. However, adenoviruses also can cause lesions of the intestine and conjunctiva, as well as the central nervous system, bladder, and genitals. Adenoviruses multiply in the mucous membrane with a gradual, consistent involvement in the pathological process of the descending parts of the respiratory tract. Reproduction of adenoviruses also can occur in the intestinal tissue or lymph nodes which is accompanied by a multiple increase in lymph nodes. In addition to local changes, adenoviruses have a general toxic effect which appears as a fever and symptoms of general intoxication (weakness, lethargy, loss of appetite, headache, and nausea). The ability of adenoviruses to reproduce in the epithelial cells of the respiratory tract, conjunctiva, and intestine with the occurrence in some cases of hematogenous dissemination creates a wide range of clinical manifestations of this infection, including the appearance of generalized lymphadenopathy and widespread exanthema. In addition to adenoviruses in the genesis of acute pneumonia, the attachment of a secondary bacterial flora is important, which is facilitated by the suppression of the immune system [23–24].

8. Adenoviral latency

The term "adenoviruses" has an ecological coloration, reflecting the tendency to persistence in the lymphoid tissue, so that adenoviruses can be isolated from the tonsils, adenoids, appendix, and lymph nodes of practically healthy people.

After acute infections, many serotypes are not eliminated from the body for a long time. Most of the latent viruses belong to subgroups B2 and C. They can persist for years in the lymphoid tissue of the pharyngeal ring and, apparently, other localizations (e.g., in the mesenteric lymph

nodes). Once in the intestine, adenoviruses asymptomatically replicate in the epithelial cells and/or Peyer's patches, periodically evolving from feces.

Latency creates the possibility of endogenous recurrences of acute infection and chronic hyperplasia (in fact, chronic inflammation) of infected lymphoid tissue. The possibility of activating a viral infection in the tonsils (chronic tonsillitis), mesenteric lymph nodes, and appendix is not excluded. Adenoviruses can be activated on the background of immunosuppressive therapy in AIDS patients. A number of new serotypes (serotypes 43–47 of subgroup D) were first isolated from AIDS patients (from feces), allowing to believe that a persistent infection creates favorable conditions for the evolution of adenoviruses [25].

The mechanism of persistence of adenoviruses in the lymphoid tissue still remains unclear. Most likely, this is due to the low content of sensitive (permissive) cells and very slow replication of the virus in lymphocytes, that is, with severely limited productive infection. It is significant that in the experiments of W. Rowe et al., who discovered adenoviruses in 1953, it took several weeks for the degeneration of a culture of adenoid tissue associated with the reproduction of latent adenoviruses. The possibility of integrative virogeny with partial expression of the viral genome is not excluded. In approximately 50% of the tonsils in adults, it was possible to detect adenoviral antigens in the absence of an infectious virus.

9. Antiadenovirals

As mentioned above, adenoviruses are unsusceptible to interferons. The acyclic nucleoside phosphonates HPMPC (cidofovir) [26] exhibit antiadenoviral activity. However, these substances are toxic, so they are applied locally in the form of ointments or by injection directly into the affected organ. The target of HPMPC is adenoviral DNA polymerase. The mechanism of the antiviral effect of this compound is based on its phosphorylation by cell kinases and in the synthesis of DNA by competition with conventional nucleosides. At consecutive inclusion in a thread of two molecules of HPMPC, elongation is blocked. The targeted effect of NM on infected cells is provided by a higher affinity of HPMPC diphosphate for viral DNA polymerase than for host DNA polymerase.

10. Adenovirus vaccines

Adenovirus infection is perhaps the only respiratory disease other than influenza, against which specific prevention methods have been developed. Military contingents in the United States since 1971 are vaccinated with live oral adenovirus vaccine against serotypes 7 and 4 which were isolated in the 1950s [27]. Live oral adenovirus vaccine has proven to be safe and highly effective in numerous clinical trials, as well as in clinical observations of acute respiratory infections among US military personnel. However, live oral adenoviral vaccine types 4 and 7 are approved only for use in military teams for adults 17–50 years old. To avoid the virus being thrown into the upper respiratory tract, it is recommended to swallow the tablets whole, without chewing. Adenovirus is extremely stable under natural conditions, and there is the possibility of being

released into the environment through excreta. Therefore, a vaccine containing live strains of adenovirus is not recommended for use in children or the general population. Despite the long-term stability of the adenovirus genome, which is confirmed by the efficacy of ongoing vaccination among the US military, random mutations or homologous recombination events, which can lead to changes in the antigenicity of adenovirus, are not excluded. In addition, over time, the epidemic types of adenovirus have changed, and in recent years, highly pathogenic serotypes 14 and 55 have been distributed throughout the world. Finally, the circulation of the types of adenoviruses can vary geographically; for example, in China, the most common types associated with acute respiratory infections (ARI) are types 3, 7, and 55 [28]. Therefore, attention should be paid to developing new adenoviral vaccines based on currently circulating adenovirus strains.

11. The mutagenic effect

Representatives of the genus *Mastadenovirus* served as objects of research in the field of molecular biology. The intrigue around the pathogenetic function of adenoviruses aggravated after their tumorigenic properties, the ability to induce malignant tumors in animals (newborn hamsters), was recorded. In 1962, Trentin et al. described the first case of the induction of a malignant tumor in animals by the human pathogenic virus—adenovirus-12, which caused tumors in rodents [29]. The oncogenic potential of adenoviruses has served as a stimulus for their careful study, which has proved useful for studying the mechanisms of viral infection and molecular processes in eukaryotic cells. On the model of adenovirus infection, splicing, adenylation, and capturing of matrix RNA, sequence and expression regulation of viral genes, their integration with cellular chromosomes, etc. were first studied with human tumors. In a series of works [30, 31], it was shown that high-oncogenic type 12 adenoviruses and type 18 adenoviruses induce chromosomal aberrations in nonpermissive cells for them. The mutagenic effect at the chromosomal level has been demonstrated for human type 2 adenoviruses and type 5 in rat cells [32], as well as for bovine adenovirus type 3 in Chinese hamster cells [33]. In humans, despite intensive research, the association of malignant tumors with adenoviruses has not been identified.

12. The use of adenoviruses as vectors for gene therapy

The promise of using adenoviruses as vectors is due to the fact that a relatively large fragment can be inserted into their linear DNA. With the advent of second-generation vectors, it became possible to embed foreign DNA sequences up to 35 kb in the adenovirus genome, while maintaining only inverted repeats and packaging site. In addition, adenovirus receptors (e.g., termination of the fibers) can be genetically modified in such a way as to increase the tropism of the virus in relation to the tumor tissue. As a product of the transgene, which allows to destroy a tumor, you can use the herpes virus thymidine kinase (family *Herpesviridae*) or the chicken anemia virus apoptin (family *Circoviridae*). In the first case, the patient is prescribed of acyclovir; in the second case, the tumor is destroyed as a result of vector-induced apoptosis. Unfortunately, genetically engineered constructions based on adenoviral vectors have not yet found clinical

application, since due to the use of multiple mechanisms by the virus for penetration into target cells, it is not possible to achieve selective delivery of vectors to cancer cells [34, 35].

13. Adenovirus vectors vaccines

Adenovirus vectors first appear in the 1980s. They have received great attention as gene delivery systems for vaccine antigens and were extensively tested in several preclinical and clinical studies. Adenovirus-based vector vaccines have been developed and are being studied against a variety of infectious diseases, including influenza, measles, hepatitis B, rabies, anthrax, Ebola, severe acute respiratory syndrome (SARS), human immunodeficiency virus 1 (HIV-1), malaria, tuberculosis [36–40]. A study of an oral tableted vaccine based on a non-replicative recombinant adenovirus-5 serotype carries DNA that encodes the hemagglutinin of A/California/04/2009 (H1N1) pdm with an adjuvant added in the form of double-stranded RNA (dsRNA) [41] showed that after a single immunization, significant systemic and local immunity occurs. Seroconversions of anti-hemagglutinating antibodies to A/H1N1 pandemic influenza viruses were detected in 92% of participants [41].

The advantages of adenoviral vectors are that they efficiently transfer genes to both dividing and nondividing cells, do not integrate into the genome, and provide high titers of recombinant virus and high expression levels of the introduced genes. Although currently used adenoviral vectors may cause nonspecific inflammation and antiviral cellular response [42]; this problem still needs to be solved.

14. Conclusions

The study of human and animal adenoviruses allows not only to explore the molecular relationship with the host organism but also to solve specific problems of medicine. In the practical field, on the one hand, new antiviral vaccines and chemotherapy drugs have been developed, implemented, or are awaiting introduction; on the other hand, there is a perspective on the therapeutic use of viruses, such as oncolytic viruses or viral vectors. These and other problems associated with adenoviruses and adenoviral infections will be covered in more detail in subsequent chapters of this book.

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