Virology & Retrovirology Journal

SCIENTIFIC LITERATURE

Review Article

Immunity in Adenoviral Infection; A Narrative Review on Cellular Aspect of Immune Responses

Seyyed Mohammad Amin MOUSAVI SAGHARCHI[1*], Narges KOOHI[2] and Seyyed Pedram DANESHVAR[3]

[1]Department of Microbiology, College of Basic Sciences, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran

[2]Student Research Commitment, Isfahan University of Medical Sciences, Isfahan, Iran

[3]Department of Biology, College of Basic Sciences, University of Tabriz, Tabriz, Iran

ARTICLE INFO

Received Date: December 04, 2023
Accepted Date: January 17, 2024
Published Date: January 23, 2024

KEYWORDS

Adenovirus; Intracellular pathways; Cellular immunity; Immune responses; Adenoviral infection; Immune cells; Immune factors

Citation for this article: Seyyed Mohammad Amin MOUSAVI SAGHARCHI, Narges KOOHI and Seyyed Pedram DANESHVAR. Immunity in Adenoviral Infection; A Narrative Review on Cellular Aspect of Immune Responses. Virology & Retrovirology Journal. 2024; 6(1):129

Corresponding author:
Seyyed Mohammad Amin MOUSAVI SAGHARCHI,
Department of Microbiology, College of Basic Sciences, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran
Email: aminmousavi8063@yahoo.com

ABSTRACT

Adenoviruses (AdVs) have attracted special attention for immune responses against them, particularly cellular and intracellular immunity. Mentioned viruses, for their intracellular life and destructive feature, are responsible for some cellular pathway changes. In the first step, AdV is sensed by some immune cells and factors (e.g., macrophages). Note that coordination between cells is managed and regulated by proteins (e.g., interleukins). For immune responses, some functional mechanisms in cells (immune and non-immune) will occur; these mechanisms (e.g., cellular and genetic changes) are essential for immunity to AdV. Cellular receptors are the first detectors and virus destinations to reach this goal. The Coxsackievirus and Adv receptor is the first important step for AdVs to enter host cells. In the second, AdV goes uncoating, and cell entering. Intracellular traffic will change after admission because activating of pathways and some molecules to deal with the virus and its uncoating. Our intelligent virus can escape from the immune cells, and cellular functions (e.g., phagocytosis) before and during uncoating, so host cells synthesize intracellular globulins. AdV also can deactivate the immune regulation signaling for its successful escape. During all of mentioned steps, pathways, and genes in immune and host cells undergo some changes.

INTRODUCTION

Adenoviral infection

Adenoviruses (AdVs) are able to infect different parts of the human body such as the respiratory system, mucosal organs (e.g., eyes), kidneys, and gastrointestinal tract [1]. Different epidemics and infections occurred around the world. Adenoviral epidemics occur in winter and cold seasons of year [2]. Transmission of this virus is through inhalation of droplets, fecal-oral axis, and conjunctival inoculation [3,4].

Review of the history and development of immunology

Immunology is a wild field that interacts with many other sciences (e.g., microbiology). We can find the Iranian "immunologist king" Mithridates VI, Eupator of Pontus, by reviewing immunology history. For the first time, he could use poison as an antidote by prescription of small doses, So we know him as a pioneer in the Mithridatism theory, which was a prelude to the scientific understanding of acquired immunity (goes back 120 BC). Furthermore, in 430 BC, Thucydides, who was an Athenian historian, described who recovered from the plague had developed immunity to the epidemic. In 1774, Benjamin Jesty, who was a farmer, inoculated the vaccinia virus belonging to

Poxviridae to his wife for establishing immunity against the prevalent and dangerous Poxvirus. In 1796, Edward Jenner inoculated James Phillip with Cowpox obtained from a dairy maid and could found the first vaccine for the prevalent Poxvirus disease. Luis Pasteur started his experiments on chicken cholera (in 1877) and found the main causative microorganism and called it *Pasteurella multocida*; due to this experiment, he could repeat the Jenner experiment, but by Pasteurella and its inoculation to other healthy chickens, so he observed similar results. Although we know Pasteur as the "father of immunology," Koch's role in founding "germ theory" is no less than Pasteur's efforts in immunology, by "tuberculin test" [5-9].

Pioneers in the cellular immunology: Although Metchnikoff is not famous, he discovered the unknown world of phagocytosis and its role in the immune system. He introduced cells that eat and digest pathogens. He named them "phagocytes" (meaning swallowing cells in Greek) in 1886. Paul Ehrlich is credited as the pioneer who first discovered the connection, between antibodies (Ab) and antigens (Ag). The studies of Michael Heidelberger and Elvin Kabat were a step to completing this chemical information, which made it possible for further studies, especially the recognition of the structure of Ab by Rodney Porter and Gerard Edelman in 1950. How Ags are recognized by the immune system was still unknown until Ralph Steinman answered this question in 1950 by introducing phagocytic dendrites with the ability to present Ag to the immune system. Of course, Butcher introduced adhesin molecules in 1979, and Leonard introduced chemokines in 1989. T-Helper (Th) cells and their capabilities were also discovered by Mossman and Coffman in 1986. The first time the name of cytokines was mentioned dates back to 1957 after the discovery of interferon by Issacs and Lindemann [7,10-14].

Adenovirus discovery: Adenoviruses (AdVs) which are responsible for acute respiratory infections, gastroenteritis, and ocular infection, were discovered by cancer virologist Dr. Wallace Rowe and his fantastic colleagues in 1953 when they were working on adenoid lymphatic tissue and cultured its cells [15]. Although Dr. Wallace was a cancer researcher, Dr. John Trentin described it as a carcinogenic virus in 1962. Adenoviral infection caused millions of people hired in the military in 1970. Molecular and cellular details of AdV and immune responses have been discovered by some scientists in recent decades. The International Committee on Taxonomy of Viruses (ICTV) has provided a systematic classification for AdVs based on serological properties and genome sequencing to five genera [16-18]. These viruses are double-stranded DNA (ds-DNA) viruses that have more than 100 serological types which 49 of them are infective to humans [19].

Adenovirus cellular structure

Adenovirus belongs to the family of adenoviridae. Adenovirus is a large virus (65-90nm) for large genome virus due to having a 26-45 kb pair in length [20]. A double-stranded DNA (DS-DNA) is a non-envelope icosahedral virus [21,22]. About 110 genotypes were identified that classified into seven species (A to G) [1]. Pentons, hexons, and fibers compose the viral capsomeres of icosahedral capsid [23]. Penton base carries the beta epitope, hexon carries alpha and epsilon epitopes, and fiber carries gamma epitope of antigens. All of antigens and surface proteins (e.g., hemmaglutinase) are neccecary for entrance and pathogenesis [23,24].

RESULTS

Sensing and detection in the immune system

Sensors of the host's immune system monitor each stage of viral infection to identify and destroy any pathogens. The immune system responds to the presence of AdVs according to the following steps:

A. Stimulation of systemic pro-inflammatory factors and pro-inflammatory cytokines (interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-alpha (TNFα)).

B. Induction of cytotoxic cells to the infection site for the elimination of infected cells.

C. Warning for uninfected cells adjacent to viral infection.

First step of sensing in the bloodstream

At first, the presence of the AdV is sensed by cells containing factor X (FX), neutralizing antibodies (nAbs), and complement components (C3 and C4) [25,26]. The binding of FX to capsid hexon is a stimulus to activate nuclear factor kappa B (NFκB) for transcription of IL-1β cytokine genes in the spleen [27,28]. The Ad FX complex triggers signaling pathways by stimulating toll-like receptor 4 (TLR4) and Intermediary proteins (myeloid differentiation 88 (MyD88), TNF receptor-associated factor 6 (TRAF6), and toll/interleukin-1 receptor (TIR)-domain-containing

adapter-inducing interferon-β (TRIF)). However, the AdV5 can interfere with FX binding and thus IL-1β transcription with single mutations in the T425A hexon. Furthermore McEwan et al. Introduced a receptor known as motif containing 21 (TRIM21) which has proven to be successful, in the identification of Ab AdV complexes. At first, this receptor recognizes intracellular Ab and then activates the unanchored Lys63 polyubiquitin chain, which is the starting point for the activity of Activator protein 1 (AP1) and interferon regulating factor (IRF) [29-34].

Macrophages as signaling radars

The next step is binding to plasma membrane receptors and identifying pathogens, which is done by capsid fiber proteins in the case of AdV. These primary receptors connect to specific species with their fiber knobs and finally cause the virus to enter the cell. Subsequent connections are made by Arg-Gly-Asp (RGD) rings on the capsid penton [35,36]. The RGD motif serves as an adhesion interface, for integrins including, α3β1, α5β1 αvβ1, αvβ3 and αvβ5 integrins [37,38]. Macrophages are the first responders to AdVs entering the body. Furthermore when IL 1α is released it communicates through IL 1R1. Attracts polymorphonuclear neutrophils (PMNs), to the infection sites, by means of CXCL1 and CXCL2 chemokines [39-42].

Type I interferon as a messenger

Type I interferon (IFN) forms a barrier, against viruses, in cells that have not been infected. Transcription of TLR9 by MyD88 adapter is necessary for Secretion IFNα by splenic plasmacytoid dendritic cells (pDCs). In contrast, non-pDC cells (such as Kupffer cells, conventional DCs, or peritoneal macrophages (MFs)) don't need this mechanism and produce IFNα by recognizing cytosolic DNA [29,43]. Unlike IFNα, IFNβ production in response to the AdV requires endosomal escape and direct contact with viral DNA by the cytosolic sensor cyclic GMP-AMP synthase (cGAS). These sensors have the ability to identify DNA, within cells and produce messenger molecules called cGAMP homodimers which're cyclic guanine adenine monophosphates [44]. cGAMP binds to the stimulator of interferon genes (STING) adapter and activates tank-binding kinase 1 (TBK1) and IRF3 [45,46].

Nuclear sensors function

The difference between viral and cellular DNA inside the nucleus is possible through the host DNA repair, or the MRE11/RAD50/NBS1 (MRN) complex, when large amounts of AdV double-stranded DNA (dsDNA) are produced inside the cell, and inhibit the replication of viral DNA [47,48]. The main enemy of MRNs are E1B-55K and E4-ORF3 proteins, which prevent the activation of DNA damage response. Furthermore the AdV protein VII plays a role, in regulating responses by binding and sequestering the high mobility group box 1 (HMGB1) protein within the nucleus [49-52].

Entrance gates

The surprising structure of the human AdV (HAdV) capsid has complicated how it binds to host cells. Two types of receptors are involved in these interactions:

A. High-affinity primary receptors or fiber knobs

B. The main receptors in all HAdV types such as Coxsackie and Adenovirus

receptor (CAR).

Also, the endocytosis of vesicles made of clathrin proceeds faster due to the interactions of the penton base of the Adenovirus capsid and αv integrins. Although the molecular mechanisms effective in isolating HAdV are still unknown, the hypothesis of pVI inner capsid protein for easier endosomalization has been proposed. These proteins are a license for the coating particles to enter the cell. The main structure of the N region of pI consists of a projected domain that's amphipathic α-helical. The vector transport of uncoated AdV particles is carried out with the help of dynein microtubule motors in these tubules [53-57].

Interactions of complex Fiber-CD4 and epithelial cells

Species B1, C, and E in AdVs cause some respiratory tract infections. CAR forms a tight junction between polarized epithelial cells. The relationship between CAR and fiber protein is one of the co-factors in the infectivity of HAdv endocytosis. The fiber knob of AdV-12 with the N-terminal Ig-like domain (D1) of CAR creates a strange communication ability. The CAR-binding surface loop sequences are composed of an AB loop. Although these receptors are important for the pathogenesis of serotypes such as A and C, some species such as, B, are useless, and others are used. Binding tightly to the decay-accelerating factors (DAF) receptor and transduction is the next step. Then,

the relationship between CAR and group B coxsackieviruses (CVB) changes the structure of the capsid and creates a gate for the virus to enter and release the RNA genome [58-62].

Fiber-CD4 intracellular cooperation

The fibrous knob in type B Adenoviruses cannot maintain the sequence, which requires primary receptors to infect cells. In other words, CD46 is the receptor of most B Adenoviruses and some D types of HAdVs, especially AdV. CD46 is a type of complement regulatory protein whose extracellular domain consists of three main components:

A. Four short consensus repeats (SCRs), each of which is a set of 65 to 70 amino acids.

B. The glycan-rich region attached to the hydroxyl groups of serine, threonine or proline-rich STP domain in the protein chain.

C. The small domain near the cell membrane whose function is still unresolved.

CD46 establishes a short cytoplasmic tail containing 16 to 23 amino acids by appending to the cell membrane with the aid of a single transmembrane domain on the intracellular membrane. The molecular structure of CD46 changes completely upon binding to hydroxyacyl-coenzyme A dehydrogenase (HADH) fibers compared to unbound receptors [63,64].

CD46-AdV fiber interactions were discovered when explorations was performed on the interplay of the co-crystal fiber knob in the SCR1-2 complex and CD46. So, SCR-1 and SCR-2 are critical interfaces, especially SCR-2, because the remaining glutamic acid in the SCR-2 (E63) position constructs a key interaction with arginine 280 in the fiber knob [65-67].

Virus uncoating and entry to the cellular matrix and plasma

The release of protein VI and endosomal triggering are two important events in AdV cell entry enabled by viral disassembly. Protein VI is discharged from inside the viral capsid. Exposure to the endosomal environment helps prepare protein VI for transport of Adenovirus to the nucleus. Furthermore, protein VI has a essential function as a cofactor for the viral cysteine protease during viral contamination [68,69]. During virion disassembly in the endosome, the capsids can undergo conformational changes that allow recognition of these alterations by the dynein motor proteins along cytoplasmic microtubules. This facilitates the process of transporting the virion genome to the nucleus. After alterations befall in the viral capsid, the connection between the capsid-motor protein and nuclear pore complexes (Nups) occur. Finally, the naked viral nucleic acid is exuded from the capsid after accessed the nuclear pore complex and permits the viral genome to penetrate into the nucleus. Nevertheless, nuclear smuggling associated to the last phase is not clarified, yet [56,70,71].

Rupturing of the cell membrane and the extracellular matrix

The extracellular matrix (ECM) serves as a safeguarding framework, for the cell membrane comprising a skeleton of proteins and sugars. The removal of particles, from the environment and the regulation of surface receptors, known as endocytosis has been extensively studied in the past. Specifically endocytosis can be facilitated by clathrin at the binding site of the cytosolic adapter protein 2 (AP2) complex to endocytic receptors and phosphoinositides. This interaction triggers the formation of clathrin coats around vesicles, which eventually leads to the internalization of the cargo [72]. Caveolar coats are enriched in cholesterol and sphingolipids, and they act as signaling platforms for the recruitment of specific receptors. Moreover, Lipid rafts are distinctive domains that are loaded from cholesterol and sphingolipids. They serve as signaling platforms and can mediate endocytosis independently of clathrin and caveolae [73-75].

Endocytosis; clathrin-mediated: Attracting the Hip1 Hip1 / Hip1R heterodimer by clathrin causes the formation of actin-dependent invaginations in the cellular membrane. Then, proteins passing through short endocytic sorting motifs in cytoplasmic domains are recruited into clathrin-coated pits (CCPs). Tyrosine-based motifs are the most common sorting sequence in cargo proteins [76,77].

The name Hip1 is derived from the interaction of the huntingtin protein with AP2. a heterotetramer of AP2 consists of two massive components (α and β2) and two small chains (μ2 and σ2). Recently, researchers have shown that Eps15, clathrin fragments and K44A-dynamin negatively regulate the formation of clathrin-coated pits. These constructs demonstrated that the infectious entry of Ad2 and Ad5 viruses into epithelial cells is dependent on clathrin [78-80].

Phagocytosis and related functions

Invading microorganisms are large particles that are removed by phagosomes and macropinosomes. The process of

phagocytosis starts when Fc receptors (Fc Rs) bind, to antibodies. The fusion of endoplasmic reticulum (ER) membranes with the plasma membrane can contribute to the creation of phagocytic membranes in extensive phagocytosis. Phagocytosis plays a role in the functioning of cells, epithelial, fibroblasts and certain immune cells, like neutrophils and macrophages. Researchers have identified four steps involved in zippering phagocytosis:

A. Opsonized fragments bind to Fc-Rs coated with immunoglobulins (Igs), like FcγRI (CD64), FcγRIIA (CD32), and FcγRIIIA (CD16). A threshold based on the concentration of activated kinases, such as spleen tyrosine kinase (SYK), determines the type of intracellular trafficking pathway for FcγRI receptors.

B. The cellular membrane extension (zippering) for particle engulfment without the need for actin polymerization or signaling from the cytoplasmic domain.

C. Multiple proteins, within the cytoskeleton play a role, in triggering receptor signaling pathways, including the complex known as actin-related protein 2/3 (Arp2/3) complex. This complex is responsible for nucleating new branches of actin filaments beneath the particle. These newly formed actin filaments then push against the plasma membrane, leading to its extension and reconstruction around the target. This process is referred to as pseudopod extension.

D. Activation of class I PI3K (p85α/p110β) leads to phagosome closure by production of PI3P lipids [81-85].

Cytosol; Good for escape

Penton base protein of Adenovirus enhances membrane permeability by binding to integrin αVβ5 in the low extracellular pH, similar to the effect of releasing small molecules around the cell. TS1 is a mutation of AdV2 with the ability to create cell entry signals. Its capsids do not dissociate upon entering the cell because they are proteolytically unprocessed. To bind the target ligand to the capsid, Ts1 binds to the CAR receptor, but cannot bind to a new ligand. The retrograde viral carrier cannot escape degradation by endosomes and lysosomes, which impairs virus dissemination. For example, the transfer of AdV to brain microcapillary cells by placing transferrin receptors (in the HI loop of the fiber knob) may be possible but ineffective overall. Therefore, precise modifications are necessary for successful targeting. Delivery of AdV5 to FcγRI (CD64) hematopoietic cells using a soluble adapter from CAR D1/D2 domains and the constant region of human IgG increases transfer efficiency and is an example of successful targeting. [86-91].

The human immune system against virus uncoating

immune cells (innate and adaptive immune cells) protect vertebrates against viruses. Mentioned cells, function related to detecting and eliminating outsider agents, releasing biochemical signals, setting off reactions of security in other immune and non-immune cells, and producing pathogen-neutralizing Abs. The defense against AdVs continues by creating long-term immune memory through acquired immunity, which can prevent the spread of recurrent and persistent infections. [92,93].

Human alpha-defensin in dealing with AdV uncoating

Antimicrobial peptides such as defensins are evolved by vertebrates against invasive pathogens. The impact of defensins, on enveloped viruses, such as Papillomaviruses and AdVs is not as extensive as it is, on enveloped viruses. However, human α-defensin 5 (αHD5) is capable of limiting non-enveloped viral infections (AdV-C5) by mechanically stabilizing the capsids during cellular entry and uncoating [94,95]. Binding of αHD5 to the penton base and fiber proteins of AdV-C5 increases the rigidity of the AdV-C5 capsid vertex region, but does not affect the two- and three-fold symmetry axes. The fact that AdV-C5 has not evolved to evade αHD5 binding suggests that αHD5 recognizes a pathogen-associated molecular pattern in AdV-C5. It may be difficult for AdV-C5 to mutate to escape αHD5 binding without compromising viral function. Binding of αHD5 could reduce adaptive immune responses and benefit the virus. This evolutionary adaptation by AdV-C5 in neutrophil-rich inflammatory environments hinders viral clearance. Specific types of defensins are produced in different locations. For instance α defensins are created within the Paneth cells of the intestine whereas β defensins are generated by epithelial cells. β-Defensin attracts neutrophils to sites of inflammation [95-99].

Complements in endosomal escape

The recognition of pathogens is an aspect of immunity and we cannot overlook the significance of the complement system in

this process. Binding of AdVs to the anti-viral Abs activates the classical complement pathway. By binding complement components (such as C1q, C3, and C4) to the Abs, the virus is opsonized [100,101]. Kupffer cells in the liver activate scavenger receptors that have activity independent of complement components and IgM, but can increase the uptake of adenovirus towards these cells. C4b deposition on AdV does not affect virus binding and endocytosis, but it prevents fiber release, exposure of VI, endosomal escape, and entry into the cytosol [102-104].

Intracellular globulins and other proteins

The TRIM21 receptor, through a high-affinity combination with the Fc region of Abs, provides another intracellular defense against adenovirus. TRIM21 captures antibodies inside the cytoplasm and plays a role in the clearance of viruses in the cytosol [105,106]. The recruitment of AAA-ATPase p97/valosin transforms TRIM21 into a K63-ubiquitinated form and provides the energy required for the degradation of viral capsids into subunits (the genome of the adenovirus and nuclear proteins) that release viral DNA to be exposed to cytoplasmic DNA sensors such as cGAS. In addition to degrading and neutralizing adenoviral particles, TRIM21 also releases immune signals to induce humoral immune responses [106-108].

The vital role of critical immune factors

The human immune system contains some types of cells and chemical compounds that, with their help, them can deal with pathogens. In Adenoviral infection, immune cells and compounds have different roles and missions. For their correct and practical functions, some connections are made between proteins and other biochemical molecules [109-111]. Macrophages, TNFs, IFNs, and ILs form a great network of cellular and molecular elements with incredible cooperation [112-114].

Macrophages

Macrophages and other cells responsible, for presenting antigens (APCs) (such as Kupffer cells and macrophages found in the spleens zone) possess receptors known as SR receptors.

These receptors can bind to patterns associated with pathogens (PAMPs) which're protein patterns discovered on viral capsids and other molecules present, on the surface and internally within pathogens, such, as proteins, polysaccharides and polyribonucleotides. Moreover they generate proteins (IFN I, IL 1α, IL 6 and TNF) that have a function in restricting infection and preventing the dissemination of AdVs [115,116]. Macrophages possess pattern recognition receptors, including TLRs, which enable them to identify patterns exhibited by adenovirus serotypes like AdV C2, AdV C5 and AdV B35. These receptors are present, on tissue macrophages such, as macrophages located in the lungs. After entering the cell adenoviruses cause the endosome membrane to break and then move into the cytosol. Their capsid proteins bind to NPC to transport the viral genome to the nucleus. During the process certain virus particles have the ability to disrupt the endosome and trigger cytosolic DNA sensors known as cGAS. This activation initiates the STING pathway leading to the generation of cytokines, like IFN I, IL 6 and IL 1α [117-119].

Inflammasome

The significance of NLRP3s involvement, in inflammation becomes clear when we observe how phorbol 12 myristate 13 acetate differentiated THP 1 cells and monocyte derived macrophages respond to AdV C5 and AdV B3 infections leading to the release of IL 1β, a cytokine. Factors such as TLR9 and cytosolic caspase inhibitors disrupt the function of NLRP3. The absence of cytosolic DNA sensors indicates that NLRP3 is indirectly activated by adenoviral DNA and involves cGAS and STING [120-122]. However this particular route operates separately from the involvement of TANK binding kinase 1 (TBK1) and I kappa B kinase epsilon (IKKε) both of which're crucial, for generating IFN I via the cGAS STING pathway. Lysosomal disruption and increased membrane permeability are features of pathways associated with STING [123-126].

Cytokines and chemokines: homeostasis of the immune system

The balance of cytokines and chemokines, in the system is crucial, for maintaining homeostasis. The importance of these responses became evident through efforts to comprehend how the immune system defends against Adenoviral threats. Cytokines and chemokines can be classified into four groups:

A. ILs: IL-1RA, IL-21, IL-31, IL-1α, IL-23, IL-4, IL-1β, IL-12p70, IL-8

B. Chemokines CXCLs: GRO-α, SDF-1α, IP-10

C. Chemokines (C-C motif) (CCLs): MIP-1α, MIP-1β, MCP-1, RANTES, eotaxin

D. Granulocyte-macrophage colony-stimulating factor (GM-CSF), also known as (CSF2)

It seems that an increased amount of cytokines, in the bloodstream might be required. In the meantime researchers have noticed a rise, in the levels of IL 1RA, IL 6 and IL 21. In the basolateral supernatant, researchers discovered a collection of interleukins (such, as IL 10, IL 4, IL 13 IL 12p70, IL 18, IL 21, IL 1RA and, IL 1α) interferons (including IFN γ) and some factors (like TNF β) along, with GM CSF [33,127-129].

Encoding cytokines and chemokines

The vital role of transcription factors Interferon regulatory factor 3 (IRF3), IRF7, and NF-kB as transcripts of cytokine and chemokine genes is revealed when the siren of AdV entry is activated and specific signals are released. IFN-I is coded by IRF7. NF κB, a transcription factor plays a role, in initiating the gene expression process for cytokines and chemokines. These include ILs such as IL 1β, IL 6, IL 8, IL 12, IL 18 as CCLs like CCL2, CCL3, CCL4 and CXCLs such, as CXCL1, CXCL2, CXCL10. The synergistic effects of NF-κB and IFN-I/STAT1 are beyond the sum of their separate effects, which are necessary to activate some chemokines, such as CXCL10 [130-133].

Achieving the transcription of IFN-I genes is possible through three different pathways. path choice depends on the answer to the question, "Which cell is infected by AdV?"

The first pathway: TLR9/MyD88 activity, starts with the release of viral dsDNA inside plasmacytoid dendritic cells. The result is the transcription of IFN-I genes with the help of IRF7 transcription.

The second pathway: is the initiation of cGAS/Stimulator of interferon genes (STING)/TBK1/IRF3 signaling by viral DNA sense within the cytoplasm. Transcription of IFN-I genes is not dependent on TLR in this pathway.

The third route involves the activation of stress activated kinases, c Jun N kinases (SAPK/JNK) and the promotion of IRF7 activity, in myeloid DC. Transcription of IFN-I genes is not dependent on TLRs or IRF3 in this pathway.

Recently, new enhancers have been introduced for the IFN production cycle, For example, cGAS. The story is that stimulation of cGAMP production along with STING/IRF3 signaling occurs in the presence of ZCCHC3 after the recognition of adenovirus dsDNA by cytosolic cGAS. This mechanism allows the binding of hnRNAPA2B1 protein to viral DNA. Finally, it upregulates IRF3, following an increased rate of TBK1 phosphorylation. On the other hand, a series of suppressors of IFN production has been presented. For example, increased transcription of Myb-like SWIRM and MPN domains 1 (MYSM1) is an inhibitor of STING activity, so the production of IFN-I from the STING/TBK1/IRF3 pathway is disturbed despite the presence of AdV [33,134-136].

Escape plan from the immune system, genetics, and signaling changes

ISGs, also known as interferon stimulated genes play a role, in stimulating the signaling of IFN (interferon) inhibiting replication and maintaining resistance and control, over pathogens. AdVs produce a series of macromolecules and cytoplasmic signaling that bypass IFN and DNA damage responses (DDR) with their help. Consequently they cannot be detected by the system. Cells infected with AdVs, escape from the shadow of death by innate cells and TCD8, such as inhibiting interferon response, blocking TNF death ligands, Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL) [137,138]. The regions known as E3 and E1a play a role, in preventing the suppression of histocompatibility complex (MHC) class I genes. They achieve this by enhancing the binding of the repressor called chicken ovalbumin upstream promoter transcription factors (COUP TFs) and reducing the binding of NF κB. That is, they stop the transfer of MHC to the cell surface with the ER, and cancel the option of apoptosis with cytokines [139-141].

Suppression of genes responsible for interferon synthesis; a fantastic collaboration with RNA viruses for muting of related genes

Although an RNA virus cannot survive in IFN-protected cells, it can replicate in the presence of AdV. A primary gene called E1A is responsible for producing IFN-suppressing proteins, which was discovered in many studies of deletion mutations. There is a hypothesis that suggests E1A has the ability to block IFN signaling by targeting IFN stimulated gene factor 3 (ISGF3). Other effective proteins in this cycle, especially in common with cytokines, were identified by understanding IFN signaling pathways. The binding of IFN-ct/p to its receptor phosphorylates tyrosines, which are the main components of signaling and transcription activation. So basically tyrosines are enzymes that transfer phosphates specifically belonging to the

Janus kinase (JAK) family. There's this one called Jakl and another one called tyrosine kinase 2 (Tyk2). The heterodimer formed by activated signal transducer and activator of transcription (Stat) la or lb and Stat2 proteins binds to p48 and causes the formation of interferon-stimulated gene factor 3 (ISGF3). This complex travels to the nucleus to stimulate IFN signaling by binding to the IFN-a/p-stimulated response element (ISRE) of the amino-terminal DNA-binding domain of the p48 [142-146].

Ways to stop signaling

The genetic reservoir of HAdV encodes a set of genes that help viruses win the battle with the immune system. A weapon called E3 acts as a modulator of the immune system by encoding proteins such as 49K, receptor internalization and degradation α (RIDα,) RIDβ, 6.7K, and 14.7K [147-149]. The story of evading apoptosis begins with the tricking of cytotoxic T cells. Patient cells are saved from apoptosis with this method by inhibiting FasL, TNF, and TRAIL. E3 protein reduces the presentation of newly synthesized MHC by inhibiting ER trafficking. E3s utilize transporters as a means to evade detection by the system. These clever solutions enable adenoviruses to stay in the host for a long time and multiply [150-153].

E3 region: A strategy to inhibit cellular immune responses: The transcription factory of AdV produces a series of products that neutralize the antiviral properties of the immune system through the pathways of the host cell. RIDα is a protein encoded by non-pathogenic type C AdVs. Even though the interaction between RIDα and the epidermal growth factor receptor (EGFR) has been identified through region 3 (E3), still the function of this relationship between the host and pathogen deose not know. EGFR activation and signaling are facilitated through a robust pathway induced by viral entry stress that precedes viral gene expression within epithelial target cells. NF κB transcription factors, known as the defenders of the immune system, against AdVs and adenoviral vectors play a crucial role, in regulating activated EGFRs. NF-κB p65 subunit is phosphorylated by *Thr254*, which can stabilize genetic reservoirs and gene transcription through EGFR tyrosine kinase activity. The Adenoviral RIDα protein can block all these pathways in two steps:

The first step is selecting Alix as an adapter to sort activated EGFRs in secondary endosomes. The second step is the formation of a hybrid organelle independent of small guanosine triphosphate (GTPase)_ Rab7 in virus-infected cells.

RIDα expression is sufficient to reduce the activity of the EGFR/NFκB signaling cycle and EGFR activation pathway caused by TNF-α intervention. Therefore, RIDα, similar to E3, is not rescued in highly pathogenic AdVs species, which indicates a direct relationship between AdVs virulence and activated EGFR signaling [154-156].

Escape from the clutches of cell death: Sec49K is the N-terminal part released from E3-49K of AdV by proteolysis. sec49K is an enemy of activated T cells and NK cells. sec49K have tissue tropism because they stick to lymphoid cells and primary leukocytes, but they don't like to contact fibroblasts or epithelial cells. It is hypothesized that the tropism of sec49K is directly related to its immunological property. Perhaps this feature discovered is related to epidemic keratoconjunctivitis in E3-49K because it is involved in the pathogenesis of the ocular disease.

HAdVs can prevent cell apoptosis with four encoded proteins.

A. RID complex having two parts (RIDα and RIDβ proteins).

This complex is an escape map of lysosomal death with unique receptors such as Fas (CD95), and TRAIL TRAIL-R1 and TRAIL-R2.

B. 6.7K protein

C. 14.7K protein

TRAIL-R2 contributes to the function of the E3-14.7K protein (the third member of E3). Indeed, E3-14.7K reduces inflammation and apoptosis by inhibiting TNF and suppressing NF-κB transcription [157-159].

CONCLUSION

AdVs are one of many kinds of viruses that cause an immune response in the body after the entrance. the pathways and causes of this response were mentioned in this article to discuss the conceivable possibilities of the mentioned response in pathogenesis. The response that occurs by entrance of the AdV, leads to both immune and not immune related mechanisms in which are essential for immunity to AdV. Afterwards, AdV starts the procedure of uncoating and cell entering in which Intracellular traffic will change after entrance because of the activation of pathways and some molecules to deal with the virus and its uncoating.

Table 1: steps and description of Adenoviral infection and immune responses.

Steps	Key points	Description
Sensing and detection in the immune system	* Sensing in the bloodstream * Macrophages as signaling radars * Type I interferon as a messenger * Nuclear sensors function	The presence of the AdV is sensed by both nuclear and humoral sensors by cells binding to cell surface receptors which leads to the identification of pathogens by capsid fiber proteins. therefore, (IFN) creates an antiviral shield in uninfected cells.
Entrance gates	* Interactions of complex Fiber-CD4 and epithelial cells * Fiber-CD4 intracellular cooperation	Species B1, C, and E in AdVs are the cause of some respiratory tract infections The relationship between CAR and fiber protein is one of the co-factors in the infectivity of HAdv. HAdV capsid has complicated how it binds to host cells by Two types of receptors. CD46 is a type of complement regulatory protein whose extracellular domain consists of three main components. CD46 attaches to the cells layer through a transmembrane region and creates a brief sequence of 16 to 23 amino acids, within the cells interior.
Virus uncoating and entry to cellular matrix and plasma	* Rupturing of the cell membrane and the extracellular matrix * Phagocytosis and related functions * Cytosol; Good for escape	Two events that are needed for later steps in cell entry are promoted by AdV disassembly. The first one is the release of protein VI molecules located inside the viral capsid and during virion disassembly, the capsids can undergo conformational changes. The infectious entry pathway of Ad2 and Ad5 into epithelial cells is clathrin-mediated. Invading microorganisms are large particles that are removed by phagosomes and macropinosomes. First, opsonized particles bind via the conserved Fc domains of immunoglobulins. concentration of activated kinases such as spleen tyrosine kinase (SYK), determines whether the Fcγ -RI receptor is internalized by the one or the other pathway. For retargeting AdV particles to new receptors and cell types normally not affected by AdV successfully, precise activations seem to be also crucial.
Human immune system against virus uncoating	* Human alpha-defensin in dealing with AdV uncoating * Complements in endosomal escape * Intracellular globulins and other proteins	Systemic dissemination of AdV is strongly restricted by adaptive immunity and Abs. Immune cells and a range of B and T cells function is related to detection and elimination of outsider agents. This defense rises to long-living cellular and humoral immunity in the case of AdVs, which protects humans from recurring infections and also suppresses persistent infections from breaking out. Antimicrobial peptides such as defensins are evolved by vertebrates against invasive pathogens. Notably, the uncoating of AdV-C5 is restricted by human α-defensin 5 (αHD5) with stabilizing the capsids during entry. Complement is a well-conserved innate defense system when it comes to detecting pathogens. A cascade of immune signaling events is triggered by dissociation of the virion into subunits.
Vital role of important immune factors	* Macrophages * Inflammasome	In Adenoviral infection, immune cells and compounds have different roles and missions., there are some connections made of proteins and other biochemical molecules for the correct and effective function of those cells. In case of facing stress, injury, and pathogens; macrophages protect the host against them while they are functionally adapted to their tissue environment. The main sensor in the inflammasome pathway for cytoplasmic DNA is absent.
Cytokines and chemokines: homeostasis of the immune system		The immune system maintains its balance through the use of cytokines and chemokines which can be grouped into four categories.
Encoding cytokines and chemokines		The important role of transcription factors Interferon regulatory factor 3 (IRF3), IRF7, and NF-kB as transcripts of cytokine and chemokine genes is revealed when the siren of AdV entry is activated and certain signals are released. Transcription of IFN-I genes is possible through three different pathways.
Escape plan from the immune system, genetics and signaling changes	* Suppression of genes responsible for interferon synthesis * Ways to stop signaling	The story of evading apoptosis begins with the tricking of cytotoxic T cells. Although an RNA virus cannot survive in IFN-protected cells, it can replicate in the presence of AdV. Cells infected with AdVs, escape from the shadow of death by innate cells and TCD8. Interferon stimulated genes (ISGs) get activated when the IFN signaling pathway is triggered playing a role, in suppressing replication enhancing resistance and regulating pathogen control. AdVs produce a series of macromolecules and cytoplasmic signaling that bypass IFN and DNA damage responses (DDR) with their help. The genetic reservoir of HAdV encodes a set of genes that help viruses win the battle with the immune system. The transcription factory of AdV produces a series of products that neutralize the antiviral properties of the immune system through the pathways of the host cell.

AdV is able to escape from the immune cells and cellular functions before and during the uncoating. Therefore, it is known as an Intelligent virus that makes the host cells synthesize intracellular globulins. Moreover, AdV also can deactivate the immune regulation signaling for its successful escape. Immune and host cells undergo some changes during all of mentioned steps, pathways, and genes. Hence, knowing these striking changes and significant factors can lead to two beneficial consequences:

A: Helps the medical staff in treatment of diseases that are caused by the above-mentioned virus like the respiratory infection.

B: Improves the future pharmaceutical medicines that are made to cure respiratory infections and other diseases caused by this intelligent virus.

It is predictable that the AdV will change its infectivity and functions to infect cells in the near future, cellular pathways and immune responses will change due to behavior and features of the AdV. For this, we should monitor the changes in cellular and molecular scale, constantly.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Greber UF. (2020). Adenoviruses - Infection, pathogenesis and therapy. FEBS letters. 594: 1818-1827.
2. Mitchell LS, Taylor B, Reimels W, Barrett FF, Devincenzo JP. (2000). Adenovirus 7a: a community-acquired outbreak in a children's hospital. The Pediatric infectious disease journal. 19: 996-1000.
3. Lynch JP, Fishbein M, Echavarria M. (2011). Adenovirus. Seminars in respiratory and critical care medicine. ©Thieme Medical Publishers.
4. Ison MG. (2006). Adenovirus infections in transplant recipients. Clinical infectious diseases. 43: 331-339.
5. Doan T, Melvold R, Waltenbaugh C. (2005). Concise medical immunology: Lippincott Williams & Wilkins.
6. Kaufmann SH. (2019). Immunology's coming of age. Frontiers in immunology. 10: 684.
7. Silverstein AM. A history of immunology: Academic Press; 2009.
8. Spoel SH, Dong X. (2012). How do plants achieve immunity? Defence without specialized immune cells. Nature reviews immunology. 12: 89-100.
9. Márió G, Payam B. (2020). Introductory Chapter: Cytokines-The Diamonds and Pearls of Biological Systems.
10. Gajdács M, Behzadi P. (2020). Introductory chapter: cytokines-the diamonds and pearls of biological systems. Cytokines. 1.
11. Jafari R, Ranjbar AR, Hosseini RF. (2019). A biographical history of some Iranian pioneers in medical immunology and allergy. Archives of Iranian Medicine. 22: 344-352.
12. James DG. (2010). Pioneers of Immunology. Journal of Medical Biography. 18: 182.
13. Schmalstieg Jr FC, Goldman AS. (2010). Birth of the science of immunology. Journal of Medical Biography. 18: 88-98.
14. Brent L. (1996). A history of transplantation immunology: Academic Press.
15. Ginsberg HS. (1999). The life and times of adenoviruses. Advances in virus research. 54: 1-13.
16. A Short History of Adenovirus. Human Adenoviruses. p. 1-13.
17. Carter BJ. (2004). Adeno-associated virus and the development of adeno-associated virus vectors: a historical perspective. Molecular therapy. 10: 981-989.
18. Shah M, Ashraf A, Khan M, Rahman M, Habib M, et al. (2017). Fowl adenovirus: history, emergence, biology and development of a vaccine against hydropericardium syndrome. Archives of virology. 162: 1833-1843.
19. Usman N, Suarez M. (2023). Adenoviruses. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.
20. Kajon AE, Weinberg JB, Spindler KR. (2019). Adenoviruses☆. Reference Module in Biomedical Sciences: Elsevier.
21. Kulanayake S, Tikoo SK. (2021). Adenovirus Core Proteins: Structure and Function. Viruses. 13.
22. Russell W. (2009). Adenoviruses: update on structure and function. Journal of General Virology. 90: 1-20.
23. Norrby E. (1969). The structural and functional diversity of adenovirus capsid components. Journal of General Virology. 5: 221-236.

24. Boudin M-L, Boulanger P. (1982). Assembly of adenovirus penton base and fiber. Virology. 116: 589-604.
25. Khare R, Hillestad ML, Xu Z, Byrnes AP, Barry MA. (2013). Circulating antibodies and macrophages as modulators of adenovirus pharmacology. Journal of virology. 87: 3678-3686.
26. McEwan WA, Tam JC, Watkinson RE, Bidgood SR, Mallery DL, et al. (2013). Intracellular antibody-bound pathogens stimulate immune signaling via the Fc receptor TRIM21. Nature immunology. 14: 327-336.
27. Doronin K, Flatt JW, Di Paolo NC, Khare R, Kalyuzhniy O, et al. (2012). Coagulation factor X activates innate immunity to human species C adenovirus. Science. 338: 795-798.
28. Wang W-C, Sayedahmed EE, Mittal SK. (2022). Significance of Preexisting Vector Immunity and Activation of Innate Responses for Adenoviral Vector-Based Therapy. Viruses. 14: 2727.
29. Atasheva S, Shayakhmetov DM. (2016). Adenovirus sensing by the immune system. Current opinion in virology. 21: 109-113.
30. Grossman Z, Mendelson E, Brok-Simoni F, Mileguir F, Leitner Y, et al. (1992). Detection of adeno-associated virus type 2 in human peripheral blood cells. Journal of general virology. 73: 961-966.
31. Kapur R, Semple JW. (2016). Platelets as immune-sensing cells. Blood Advances. 1: 10-14.
32. Pulendran B, Palucka K, Banchereau J. (2001). Sensing pathogens and tuning immune responses. Science. 293: 253-256.
33. Atasheva S, Shayakhmetov DM. (2022). Cytokine responses to adenovirus and adenovirus vectors. Viruses. 14: 888.
34. Lyons M, Onion D, Green NK, Aslan K, Rajaratnam R, et al. (2006). Adenovirus type 5 interactions with human blood cells may compromise systemic delivery. Molecular Therapy. 14: 118-128.
35. Di Paolo NC, Miao EA, Iwakura Y, Murali-Krishna K, Aderem A, et al. (2009). Virus binding to a plasma membrane receptor triggers interleukin-1α-mediated proinflammatory macrophage response in vivo. Immunity. 31: 110-121.
36. Koizumi N, Kawabata K, Sakurai F, Watanabe Y, Hayakawa T, et al. (2006). Modified Adenoviral Vectors Ablated for Coxsackievirus–Adenovirus Receptor, α v Integrin, and Heparan Sulfate Binding Reduce In Vivo Tissue Transduction and Toxicity. Human gene therapy. 17: 264-279.
37. Hesse A, Kosmides D, Kontermann RE, Nettelbeck DM. (2007). Tropism modification of adenovirus vectors by peptide ligand insertion into various positions of the adenovirus serotype 41 short-fiber knob domain. Journal of virology. 81: 2688-2699.
38. Kurachi S, Koizumi N, Sakurai F, Kawabata K, Sakurai H, et al. (2007). Characterization of capsid-modified adenovirus vectors containing heterologous peptides in the fiber knob, protein IX, or hexon. Gene therapy. 14: 266-274.
39. Cerullo V, Pesonen S, Diaconu I, Escutenaire S, Arstila PT, et al. (2010). Oncolytic adenovirus coding for granulocyte macrophage colony-stimulating factor induces antitumoral immunity in cancer patients. Cancer research. 70: 4297-4309.
40. Kluth DC, Ainslie CV, Pearce WP, Finlay S, Clarke D, et al. (2001). Macrophages transfected with adenovirus to express IL-4 reduce inflammation in experimental glomerulonephritis. The Journal of Immunology. 166: 4728-4736.
41. Shashkova EV, Doronin K, Senac JS, Barry MA. (2008). Macrophage depletion combined with anticoagulant therapy increases therapeutic window of systemic treatment with oncolytic adenovirus. Cancer research. 68: 5896-5904.
42. Zsengellér Z, Otake K, Hossain S-A, Berclaz P-Y, Trapnell BC. (2000). Internalization of adenovirus by alveolar macrophages initiates early proinflammatory signaling during acute respiratory tract infection. Journal of virology. 74: 9655-9667.
43. De Pascalis R, Rossi AP, Mittereder L, Takeda K, Akue A, et al. (2020). Production of IFN-γ by splenic dendritic cells during innate immune responses against Francisella tularensis LVS depends on MyD88, but not TLR2, TLR4, or TLR9. Plos one. 15: e0237034.

44. Ablasser A, Goldeck M, Cavlar T, Deimling T, Witte G, et al. (2013). cGAS produces a 2′-5′-linked cyclic dinucleotide second messenger that activates STING. Nature. 498: 380-384.
45. Minamitani T, Iwakiri D, Takada K. (2011). Adenovirus virus-associated RNAs induce type I interferon expression through a RIG-I-mediated pathway. Journal of virology. 85: 4035-4040.
46. Yamaguchi T, Kawabata K, Kouyama E, Ishii KJ, Katayama K, et al. (2010). Induction of type I interferon by adenovirus-encoded small RNAs. Proceedings of the National Academy of Sciences. 107: 17286-17291.
47. Avgousti DC, Herrmann C, Kulej K, Pancholi NJ, Sekulic N, et al. (2016). A core viral protein binds host nucleosomes to sequester immune danger signals. Nature. 535: 173-177.
48. Shah GA, O'Shea CC. Viral and cellular genomes activate distinct DNA damage responses. Cell. 2015;162(5):987-1002.
49. Karen KA, Hoey PJ, Young C, Hearing P. (2009). Temporal regulation of the Mre11-Rad50-Nbs1 complex during adenovirus infection. Journal of virology. 83: 4565-4573.
50. Ryan EL, Hollingworth R, Grand RJ. (2016). Activation of the DNA damage response by RNA viruses. Biomolecules. 6: 2.
51. Syed A, Tainer JA. (2018). The MRE11–RAD50–NBS1 complex conducts the orchestration of damage signaling and outcomes to stress in DNA replication and repair. Annual review of biochemistry. 87: 263-294.
52. Ahi YS, Mittal SK. (2016). Components of adenovirus genome packaging. Frontiers in microbiology. 7: 1503.
53. Bewley MC, Springer K, Zhang Y-B, Freimuth P, Flanagan JM. (1999). Structural analysis of the mechanism of adenovirus binding to its human cellular receptor, CAR. Science. 286: 1579-1583.
54. Coyne CB, Bergelson JM. (2005). CAR: a virus receptor within the tight junction. Advanced drug delivery reviews. 57: 869-882.
55. Meier O, Boucke K, Hammer SV, Keller S, Stidwill RP, et al. (2002). Adenovirus triggers macropinocytosis and endosomal leakage together with its clathrin-mediated uptake. The Journal of cell biology. 158: 1119-1131.
56. Greber UF, Flatt JW. (2019). Adenovirus entry: from infection to immunity. Annual review of virology. 6: 177-197.
57. Nemerow GR. (2000). Cell receptors involved in adenovirus entry. Virology. 274: 1-4.
58. Hewitt RJ, Lloyd CM. (2021). Regulation of immune responses by the airway epithelial cell landscape. Nature Reviews Immunology. 21: 347-362.
59. Persson BD, Lenman A, Frängsmyr L, Schmid M, Ahlm C, et al. (2020). Lactoferrin-hexon interactions mediate CAR-independent adenovirus infection of human respiratory cells. Journal of virology. 94: e00542-20.
60. Cohen CJ, Shieh JT, Pickles RJ, Okegawa T, Hsieh J-T, et al. (2001). The coxsackievirus and adenovirus receptor is a transmembrane component of the tight junction. Proceedings of the National Academy of Sciences. 98: 15191-15196.
61. Fejer G, Freudenberg M, Greber U, Gyory I. (2011). Adenovirus-triggered innate signalling pathways. European Journal of Microbiology and Immunology. 1: 279-288.
62. Milstone AM, Petrella J, Sanchez MD, Mahmud M, Whitbeck JC, et al. (2005). Interaction with coxsackievirus and adenovirus receptor, but not with decay-accelerating factor (DAF), induces A-particle formation in a DAF-binding coxsackievirus B3 isolate. Journal of virology. 79: 655-660.
63. Fleischli C, Verhaagh S, Havenga M, Sirena D, Schaffner W, et al. (2005). The distal short consensus repeats 1 and 2 of the membrane cofactor protein CD46 and their distance from the cell membrane determine productive entry of species B adenovirus serotype 35. Journal of virology. 79: 10013-10022.
64. Sirena D, Lilienfeld B, Eisenhut M, Kälin S, Boucke K, et al. (2004). The human membrane cofactor CD46 is a receptor for species B adenovirus serotype 3. Journal of virology. 78: 4454-4462.
65. Chen CZ, Gorham RD, Gaieb Z, Morikis D. (2015). Electrostatic interactions between complement regulator CD46 (SCR1-2) and adenovirus Ad11/Ad21 fiber protein knob. Molecular Biology International. 2015.

66. Persson BD, Reiter DM, Marttila M, Mei Y-F, Casasnovas JM, et al. (2007). Adenovirus type 11 binding alters the conformation of its receptor CD46. Nature structural & molecular biology. 14: 164-166.
67. Wang H, Liaw Y-C, Stone D, Kalyuzhniy O, Amiraslanov I, et al. (2007). Identification of CD46 binding sites within the adenovirus serotype 35 fiber knob. Journal of virology. 81: 12785-12792.
68. Kilcher S, Mercer J. (2015). DNA virus uncoating. Virology. 479-480:578-590.
69. Wiethoff CM, Wodrich H, Gerace L, Nemerow GR. (2005). Adenovirus protein VI mediates membrane disruption following capsid disassembly. Journal of virology. 79: 1992-2000.
70. Nemerow GR, Stewart PL. (2016). Insights into adenovirus uncoating from interactions with integrins and mediators of host immunity. Viruses. 8: 337.
71. Nestić D, Božinović K, Pehar I, Wallace R, Parker AL, et al. (2021). The revolving door of adenovirus cell entry: not all pathways are equal. Pharmaceutics. 13: 1585.
72. Kadlecova Z, Spielman SJ, Loerke D, Mohanakrishnan A, Reed DK, et al. (2017). Regulation of clathrin-mediated endocytosis by hierarchical allosteric activation of AP2. Journal of Cell Biology. 216: 167-179.
73. Medina-Kauwe LK. (2003). Endocytosis of adenovirus and adenovirus capsid proteins. Advanced drug delivery reviews. 55: 1485-1496.
74. Meier O, Gastaldelli M, Boucke K, Hemmi S, Greber UF. (2005). Early steps of clathrin-mediated endocytosis involved in phagosomal escape of Fcγ receptor-targeted adenovirus. Journal of virology. 79: 2604-2613.
75. Meier O, Greber UF. (2004). Adenovirus endocytosis. The Journal of Gene Medicine: A cross-disciplinary journal for research on the science of gene transfer and its clinical applications. 6: S152-S163.
76. Kirchhausen T, Owen D, Harrison SC. (2014). Molecular structure, function, and dynamics of clathrin-mediated membrane traffic. Cold Spring Harbor perspectives in biology. 6: a016725.
77. Manna PT, Gadelha C, Puttick AE, Field MC. (2015). ENTH and ANTH domain proteins participate in AP2-independent clathrin-mediated endocytosis. Journal of Cell Science. 128: 2130-2142.
78. Carroll RC, Beattie EC, Xia H, Lüscher C, Altschuler Y, et al. (1999). Dynamin-dependent endocytosis of ionotropic glutamate receptors. Proceedings of the National Academy of Sciences. 96: 14112-14117.
79. Traub LM. (2005). Common principles in clathrin-mediated sorting at the Golgi and the plasma membrane. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 1744: 415-437.
80. Wang L, Shao YY, Ballock RT. (2006). Peroxisome proliferator-activated receptor-γ promotes adipogenic changes in growth plate chondrocytes in vitro. PPAR research. 2006. 67297.
81. Al Assaf E. (2020). Signalling pathways involved in cancer cell migration towards CXCL8 and CXCL10: University of East Anglia.
82. Biglari A, Southgate TD, Fairbairn LJ, Gilham DE. (2006). Human monocytes expressing a CEA-specific chimeric CD64 receptor specifically target CEA-expressing tumour cells in vitro and in vivo. Gene Therapy. 13: 602-610.
83. Ebbinghaus C, Al-Jaibaji A, Operschall E, Schöffel A, Peter I, et al. (2001). Functional and selective targeting of adenovirus to high-affinity Fcγ receptor I-positive cells by using a bispecific hybrid adapter. Journal of Virology. 75: 480-489.
84. Ivanov AI. (2008). Actin motors that drive formation and disassembly of epithelial apical junctions. Frontiers in Bioscience-Landmark. 13: 6662-6681.
85. Schmitt M, Metzger M, Gradl D, Davidson G, Orian-Rousseau V. (2015). CD44 functions in Wnt signaling by regulating LRP6 localization and activation. Cell Death & Differentiation. 22: 677-689.
86. Leopold PL, Crystal RG. (2007). Intracellular trafficking of adenovirus: many means to many ends. Advanced drug delivery reviews. 59: 810-821.
87. Lindert S, Silvestry M, Mullen T-M, Nemerow GR, Stewart PL. (2009). Cryo-electron microscopy structure of an adenovirus-integrin complex indicates conformational changes in both penton base and integrin. Journal of virology. 83: 11491-11501.

88. Lyle C, McCormick F. (2010). Integrin αvβ5 is a primary receptor for adenovirus in CAR-negative cells. Virology journal. 7: 1-13.
89. Mathias P, Galleno M, Nemerow GR. (1998). Interactions of soluble recombinant integrin αvβ5 with human adenoviruses. Journal of virology. 72: 8669-8675.
90. Miyazawa N, Crystal RG, Leopold PL. (2001). Adenovirus serotype 7 retention in a late endosomal compartment prior to cytosol escape is modulated by fiber protein. Journal of virology. 75: 1387-1400.
91. Nakano M, Boucke K, Suomalainen M, Stidwill R, Greber U. (2000). The first step of adenovirus type 2 disassembly occurs at the cell surface, independently of endocytosis and escape to the cytosol. Journal of virology. 74: 7085-7095.
92. Lodoen MB, Lanier LL. (2006). Natural killer cells as an initial defense against pathogens. Current opinion in immunology. 18: 391-398.
93. Vujanovic L, Ballard W, Thorne SH, Vujanovic NL, Butterfield LH. (2012). Adenovirus-engineered human dendritic cells induce natural killer cell chemotaxis via CXCL8/IL-8 and CXCL10/IP-10. Oncoimmunology. 1: 448-457.
94. Flatt JW, Kim R, Smith JG, Nemerow GR, Stewart PL. (2013). An intrinsically disordered region of the adenovirus capsid is implicated in neutralization by human alpha defensin 5. PloS one. 8: e61571.
95. Smith JG, Nemerow GR. (2008). Mechanism of adenovirus neutralization by human α-defensins. Cell host & microbe. 3: 11-19.
96. Flint SJ, Nemerow GR. (2016). Human adenoviruses: from villains to vectors: World Scientific.
97. Nguyen EK, Nemerow GR, Smith JG. (2010). Direct evidence from single-cell analysis that human α-defensins block adenovirus uncoating to neutralize infection. Journal of virology. 84: 4041-4049.
98. Snijder J, Reddy VS, May ER, Roos WH, Nemerow GR, et al. (2013). Integrin and defensin modulate the mechanical properties of adenovirus. Journal of virology. 87: 2756-2766.
99. Lehrer RI, Lu W. (2012). α-Defensins in human innate immunity. Immunological reviews. 245: 84-112.
100. Cotter MJ, Zaiss AK, Muruve DA. (2005). Neutrophils interact with adenovirus vectors via Fc receptors and complement receptor 1. Journal of virology. 79: 14622-14631.
101. Tsai V, Varghese R, Ravindran S, Ralston R, Vellekamp G. (2008). Complement component C1q and anti-hexon antibody mediate adenovirus infection of a CAR-negative cell line. Viral immunology. 21: 469-476.
102. Janeway Jr CA, Travers P, Walport M, Shlomchik MJ. (2001). The complement system and innate immunity. Immunobiology: The Immune System in Health and Disease 5th edition: Garland Science.
103. Maier O, Marvin SA, Wodrich H, Campbell EM, Wiethoff CM. (2012). Spatiotemporal dynamics of adenovirus membrane rupture and endosomal escape. Journal of virology. 86: 10821-10828.
104. Sawtell K. (2020). Understanding the mechanism of Adenovirus endosomal escape: University of Oxford.
105. Fletcher AJ, Mallery DL, Watkinson RE, Dickson CF, James LC. (2015). Sequential ubiquitination and deubiquitination enzymes synchronize the dual sensor and effector functions of TRIM21. Proceedings of the National Academy of Sciences. 112: 10014-10019.
106. Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, et al. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). Proceedings of the National Academy of Sciences. 107: 19985-19990.
107. Deshane J, Siegal GP, Wang M, Wright M, Bucy RP, et al. (1997). Transductional efficacy and safety of an intraperitoneally delivered adenovirus encoding an anti-erbB-2 intracellular single-chain antibody for ovarian cancer gene therapy. Gynecologic oncology. 64: 378-385.
108. Hauler F, Mallery DL, McEwan WA, Bidgood SR, James LC. (2012). AAA ATPase p97/VCP is essential for TRIM21-mediated virus neutralization. Proceedings of the National Academy of Sciences. 109: 19733-19738.

109. Daly JM, Reynolds J, Sigal RK, Shou J, Liberman MD. (1990). Effect of dietary protein and amino acids on immune function. Critical care medicine. 18: S86-S93.

110. Li P, Yin YL, Li D, Kim SW, Wu G. (2007). Amino acids and immune function. The British journal of nutrition. 98: 237-252.

111. Wintergerst ES, Maggini S, Hornig DH. (2007). Contribution of selected vitamins and trace elements to immune function. Annals of nutrition & metabolism. 51: 301-323.

112. Elias K, Siegel R, O'Shea JJ. (2008). Molecular and Cellular Basis of Immunity and Immunological Diseases. Primer on the Rheumatic Diseases. 94-107.

113. Liu J, Cao X. (2016). Cellular and molecular regulation of innate inflammatory responses. Cellular & molecular immunology. 13: 711-721.

114. O'Shea J, Kehrl J. (1997). Molecular and cellular basis of immunity. Primer on the Rheumatic Diseases Atlanta, GA: Arthritis Foundation. 68-75.

115. Carvajal-Gonzalez JM, Gravotta D, Mattera R, Diaz F, Perez Bay A, et al. (2012). Basolateral sorting of the coxsackie and adenovirus receptor through interaction of a canonical YXXΦ motif with the clathrin adaptors AP-1A and AP-1B. Proceedings of the National Academy of Sciences. 109: 3820-3825.

116. Lütschg V, Boucke K, Hemmi S, Greber UF. (2011). Chemotactic antiviral cytokines promote infectious apical entry of human adenovirus into polarized epithelial cells. Nature communications. 2: 391.

117. Kotha PL, Sharma P, Kolawole AO, Yan R, Alghamri MS, et al. (2015). Adenovirus entry from the apical surface of polarized epithelia is facilitated by the host innate immune response. PLoS pathogens. 11: e1004696.

118. Sosa RA, Forsthuber TG. (2011). The critical role of antigen-presentation-induced cytokine crosstalk in the central nervous system in multiple sclerosis and experimental autoimmune encephalomyelitis. Journal of Interferon & Cytokine Research. 31: 753-768.

119. Gorki A-D, Symmank D, Zahalka S, Lakovits K, Hladik A, et al. (2022). Murine ex vivo cultured alveolar macrophages provide a novel tool to study tissue-resident macrophage behavior and function. American Journal of Respiratory Cell and Molecular Biology. 66: 64-75.

120. Giambelluca S, Ochs M, Lopez-Rodriguez E. (2022). Resting time after phorbol 12-myristate 13-acetate in THP-1 derived macrophages provides a non-biased model for the study of NLRP3 inflammasome. Frontiers in Immunology. 13: 7889.

121. Barlan A, Griffin T, McGuire K, Wiethoff C. (2011). Adenovirus membrane penetration activates the NLRP3 inflammasome. Journal of virology. 85: 146-155.

122. McGuire KA, Barlan AU, Griffin TM, Wiethoff CM. (2011). Adenovirus type 5 rupture of lysosomes leads to cathepsin B-dependent mitochondrial stress and production of reactive oxygen species. Journal of virology. 85: 10806-10813.

123. Chaly Y, Fu Y, Marinov A, Hostager B, Yan W, et al. (2014). Follistatin-like protein 1 enhances NLRP3 inflammasome-mediated IL-1β secretion from monocytes and macrophages. European journal of immunology. 44: 1467-1479.

124. Davis BK, Wen H, Ting JP-Y. (2011). The inflammasome NLRs in immunity, inflammation, and associated diseases. Annual review of immunology. 29: 707-735.

125. He D-K, Chen J-F, Shao Y-R, Zhou F-Q, Shen J. (2018). Adenovirus-delivered angiopoietin-1 ameliorates phosgene-induced acute lung injury via inhibition of NLRP3 inflammasome activation. Inhalation toxicology. 30: 187-194.

126. Liu F, Niu Q, Fan X, Liu C, Zhang J, et al. (2017). Priming and activation of inflammasome by canarypox virus vector ALVAC via the cGAS/IFI16–STING–type I IFN pathway and AIM2 sensor. The Journal of Immunology. 199: 3293-3305.

127. Chen D, Murphy B, Sung R, Bromberg J. (2003). Adaptive and innate immune responses to gene transfer vectors: role of cytokines and chemokines in vector function. Gene therapy. 10: 991-998.

128. Molloy CT, Andonian JS, Seltzer HM, Procario MC, Watson Jr ME, et al. (2017). Contributions of CD8 T cells to the pathogenesis of mouse adenovirus type 1 respiratory infection. Virology. 507: 64-74.

129. Sokol CL, Luster AD. (2015). The chemokine system in innate immunity. Cold Spring Harbor perspectives in biology. 7: a016303.

130. Burke SJ, Goff MR, Lu D, Proud D, Karlstad MD, et al. (2013). Synergistic expression of the CXCL10 gene in response to IL-1β and IFN-γ involves NF-κB, phosphorylation of STAT1 at Tyr701, and acetylation of histones H3 and H4. The Journal of Immunology. 191: 323-336.

131. Dai X, Sayama K, Tohyama M, Shirakata Y, Yang L, et al. (2008). The NF-κB, p38 MAPK and STAT1 pathways differentially regulate the dsRNA-mediated innate immune responses of epidermal keratinocytes. International immunology. 20: 901-909.

132. Spurrell E, Gangeswaran R, Wang P, Cao F, Gao D, et al. (2014). STAT1 interaction with E3-14.7 K in monocytes affects the efficacy of oncolytic adenovirus. Journal of virology. 88: 2291-2300.

133. Yarilina A, Park-Min K-H, Antoniv T, Hu X, Ivashkiv LB. (2008). TNF activates an IRF1-dependent autocrine loop leading to sustained expression of chemokines and STAT1-dependent type I interferon–response genes. Nature immunology. 9: 378-387.

134. Cheng W-Y, He X-B, Jia H-J, Chen G-H, Jin Q-W, et al. (2018). The cGas–STING signaling pathway is required for the innate immune response against ectromelia virus. Frontiers in immunology. 9: 1297.

135. Lam E, Falck-Pedersen E. (2014). Unabated adenovirus replication following activation of the cGAS/STING-dependent antiviral response in human cells. Journal of virology. 88: 14426-14439.

136. Li Z, Cai S, Sun Y, Li L, Ding S, et al. (2020). When STING meets viruses: sensing, trafficking and response. Frontiers in immunology. 11: 2064.

137. Schneider WM, Chevillotte MD, Rice CM. (2014). Interferon-stimulated genes: a complex web of host defenses. Annual review of immunology. 32: 513-545.

138. Sohn SY, Hearing P. (2019). Adenoviral strategies to overcome innate cellular responses to infection. FEBS letters. 593: 3484-3495.

139. Fu J, Li L, Bouvier M. (2011). Adenovirus E3-19K proteins of different serotypes and subgroups have similar, yet distinct, immunomodulatory functions toward major histocompatibility class I molecules. Journal of Biological Chemistry. 286: 17631-17639.

140. Kushner DB, Pereira DS, Liu X, Graham FL, Ricciardi RP. (1996). The first exon of Ad12 E1A excluding the transactivation domain mediates differential binding of COUP-TF and NF-kappa B to the MHC class I enhancer in transformed cells. Oncogene. 12: 143-151.

141. Li L, Santarsiero BD, Bouvier M. (2016). Structure of the Adenovirus Type 4 (Species E) E3-19K/HLA-A2 Complex Reveals Species-Specific Features in MHC Class I Recognition. The Journal of Immunology. 197: 1399-1407.

142. Clarke PA, Mathews MB. (1995). Interactions between the double-stranded RNA binding motif and RNA: definition of the binding site for the interferon-induced protein kinase DAI (PKR) on adenovirus VA RNA. Rna. 1: 7-20.

143. GALABRU J, KATZE MG, ROBERT N, HOVANESSIAN AG. (1989). The binding of double-stranded RNA and adenovirus VAI RNA to the interferon-induced protein kinase. European journal of biochemistry. 178: 581-589.

144. García-Sastre A. (2017). Ten strategies of interferon evasion by viruses. Cell host & microbe. 22: 176-184.

145. HOVANESSIAN AG. (1991). Interferon-induced and double-stranded RNA-activated enzymes: a specific protein kinase and 2′, 5′-oligoadenylate synthetases. Journal of interferon research. 11: 199-205.

146. Kitajewski J, Schneider RJ, Safer B, Munemitsu SM, Samuel CE, et al. (1986). Adenovirus VAI RNA antagonizes the antiviral action of interferon by preventing activation of the interferon-induced eIF-2α kinase. Cell. 45: 195-200.

147. Horwitz MS. (2004). Function of adenovirus E3 proteins and their interactions with immunoregulatory cell proteins. The Journal of Gene Medicine: A cross-disciplinary journal for research on the science of gene transfer and its clinical applications. 6: S172-S183.

148. Lichtenstein DL, Toth K, Doronin K, Tollefson AE, Wold WS. (2004). Functions and mechanisms of action of the adenovirus E3 proteins. International reviews of immunology. 23: 75-111.

149. Oliveira ER, Bouvier M. (2019). Immune evasion by adenoviruses: a window into host–virus adaptation. FEBS letters. 593: 3496-3503.

150. Burgert H-G, Kvist S. (1987). The E3/19K protein of adenovirus type 2 binds to the domains of histocompatibility antigens required for CTL recognition. The EMBO Journal. 6: 2019-2026.

151. Kitagawa M, Takasawa S, Kikuchi N, Itoh T, Teraoka H, et al. (1991). rig encodes ribosomal protein S15 The primary structure of mammalian ribosomal protein S15. FEBS letters. 283: 210-214.

152. Mahr JA, Boss JM, Gooding LR. (2003). The adenovirus e3 promoter is sensitive to activation signals in human T cells. Journal of virology. 77: 1112-1119.

153. Shisler J, Yang C, Walter B, Ware CF, Gooding LR. (1997). The adenovirus E3-10.4 K/14.5 K complex mediates loss of cell surface Fas (CD95) and resistance to Fas-induced apoptosis. Journal of virology. 71: 8299-8306.

154. Linné T. (1992). Differences in the E3 regions of the canine adenovirus type 1 and type 2. Virus research. 23: 119-133.

155. Wold WS, Gooding LR. (1991). Region E3 of adenovirus: a cassette of genes involved in host immunosurveillance and virus-cell interactions. Virology. 184: 1-8.

156. Yu D-C, Chen Y, Seng M, Dilley J, Henderson DR. (1999). The addition of adenovirus type 5 region E3 enables calydon virus 787 to eliminate distant prostate tumor xenografts. Cancer research. 59: 4200-4203.

157. Jiang H, White EJ, Ríos-Vicil CI, Xu J, Gomez-Manzano C, et al. (2011). Human adenovirus type 5 induces cell lysis through autophagy and autophagy-triggered caspase activity. Journal of virology. 85: 4720-4729.

158. Windheim M, Southcombe JH, Kremmer E, Chaplin L, Urlaub D, et al. (2013). A unique secreted adenovirus E3 protein binds to the leukocyte common antigen CD45 and modulates leukocyte functions. Proceedings of the National Academy of Sciences. 110: E4884-E4893.

159. Arnberg N. (2013). Adenovirus E3 protein modulates leukocyte functions. Proceedings of the National Academy of Sciences. 110: 19976-19977.