The innate immune response induced by adenovirus, adenoviral vectors and other viruses

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For: Advanced Virology, VTMC 833

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ABSTRACT

When pathogens invade cells, they initiate an innate immune response to clear the pathogen. Different pathogens induce different responses in different cell types because they express different PRRs, and the most important response is the production of inflammatory cytokines and type I interferon. Which cytokines are induced is dependent on the pathogen and the signaling pathways activated by them. Pattern recognition receptors (PRRs) paly a role in the connection between the pathogen and host signaling pathways. Innate immunity helps the host clear pathogens but sometime it impacts the effect of vaccines and gene therapy. Adenoviruses (Ads) can meet the need for gene
therapy and vaccination but a major limitation to its application as a vector, is that adenoviruses induce rapid and strong innate immune response that shorten the duration of the gene therapy and vaccination. So it is very important to uncover the mechanism by which viral vectors are recognized by the host innate immune system to develop more effective transgene and vaccine vectors. This review provides a summary of current knowledge of the interactions between the innate immune system and viruses, and then I will discuss the innate immune responses specifically induced by adenoviruses.

INTRODUCTION

Adenovirus was firstly isolated from adenoid tissue in the 1950’s (1). More than 50 serotypes of human adenovirus have been found, and they can be divided into six subgroups (A-F, group B can be subdivided into B1 and B2) based on sequence homology and on their ability to agglutinate red blood cells (2). Adenovirus infection can cause a broad spectrum of illnesses in immune-compromised and immune-competent hosts. They are the cause of a large number of acute febrile respiratory syndromes among military recruits. They are also the cause of ocular, respiratory and gastrointestinal infections in the general population (3).

The structure of adenovirus

Adenovirus (Ad) virions are characterized by a nucleoprotein core containing a linear double-stranded DNA genome (~30–40 kb) surrounded by an icosahedral, non-enveloped capsid (~70 to 100 nm in diameter) (Fig 1). Human Adenovirus serotype 5, the most extensively studied Ad, contains ~36 kb genome that encodes genes that can be divided into 4 early genes (E1–E4) and five late genes (L1–L5). Early genes can be transcribed before DNA replication and they mainly express functional proteins to help virus complete the life cycle, while late genes transcribe after DNA replication and express viral structure proteins (4). Bovine Ad serotype 3, which is researched in our lab, has a 34,446 bp genome, and it can be divided into four early regions (E1-E4) and 7 late regions (L1-L7). In addition, to completing virion production, two other elements are essential. The Ad genome has inverted terminal repeats (ITR) and a packaging sequence, which are required for the replication and encapsidation of the viral DNA, respectively (5). Adenoviruses encode one or two non-encoded RNA called virus-associated RNA (VA-RNA), which can be synthesized by internal polymerase III and plays a very important role in viral replication (2).

The adenoviruses (Ads) genome can encode more than 40 proteins, however only 13 proteins have been shown to be constituents of the virus particle (6), and they play a role in infection and stabilizing the viral particle. The structural proteins can be divided into three groups, major capsid proteins, minor capsid proteins and core proteins. In the major capsid proteins group, the most abundant one is hexon, 240 trimers of hexon (pII) proteins constitute the frame of the capsid. Then 12 pentons (pIII) are fixed on the 12 capsid vertices to form a whole icosahedral structure, and one fiber (pIV) protrudes from each penton base. The fiber consists of three parts, an N-terminal tail which binds on the penton base, a C-terminal knob domain which can attach to cells in the first step of infection, and a slender rod-like shaft which connects the N-terminal tail to the C-terminal knob (7). The minor capsid proteins group: IIIa, VI, VIII and IX are associated with the capsid (8), play a role to stabilize the structure of the capsid. In the core protein
group, there are six other structural components which are located in the virus core, five of them bind the double stranded DNA genome [V, Mu, IVa2, VII and the terminal protein (TP)], pVII binds the viral DNA genome tightly and forms a nucleoprotein complex, pV links the viral DNA genome to the capsid, the last protein is the 23K virion protease which can cleave some viral proteins to make them mature proteins (4). The whole structure of adenovirus is shown in Figure 1.

![Figure 1: The structure of adenovirus. A schematic depiction of the structure based on cryo-electron microscopy and crystallography (4).](image)

**Application of adenoviruses**

With the development of recombinant DNA technology, genomics and immunology, adenovirus has been researched more and more thoroughly. Subsequently, adenovirus vectors were used for gene therapy, vaccination and treatment of tumors because of the inherent advantages of adenoviruses.

Gene therapy is a technique for correcting defective genes responsible for disease development by introducing a new functional gene to complement or replace a defective gene in target cells. Gene therapy started by using retrovirus vector-mediated gene replacement, but the use of adenovirus for gene therapy becomes more and more prevalent because of several advantages. In 2008, the first case of gene therapy using an adenoviral vector succeeded (9). Adenovirus associated virus was used as a vector to treat Leber congenital amaurosis, a monogenetic eye disease which causes the blindness of children. After adenovirus vector mediated gene therapy, vision was significantly improved (9). This method has the potential to maintain sight if patients are treated before onset of Leber congenital amaurosis. Adenovirus associated virus vector can be used in gene therapy without adverse effects, especially for the neuronal and retinal gene, so it will be a promising method to treat nervous system diseases and eye diseases (10).

Being used as a vaccine vector is another use for adenoviruses. Traditional viral vaccines are inactivated or attenuated viruses. Inactivated viral vaccines cannot express
antigens in the cytosol, so the antigens cannot be presented to CD8 T cells to induce the cell mediated immunity. For attenuated virus vaccines, although they can induce cell mediated immunity, that is a potential risk to the recipient because of the residual pathogenicity (11). A novel vaccine method is using adenoviruses as a vaccine carrier. Adenoviruses can induce both innate and adaptive immunity, and CD4 and CD8 T cells can be induced (12). Adenovirus vectored vaccine are used widely in both animals and human against diseases, such as rabies (13), avian influenza H5N1 (14), swine influenza (15) and is also a promising method to develop vaccines against HIV (16).

Adenoviruses are also used as an antitumor agent. To do this, two methods are being used, the first is infecting and killing the tumor cells by viral replication; the second is using adenovirus as a vector to transfer siRNA to silent the genes which induce the formation of tumors. Modified adenoviruses are selected to recognize and infect cancer cells, subsequently, adenoviruses lyse the cancerous cells and come out to infect the neighboring cells until all the cancer cells are killed. But it cannot infect and lyse healthy cells (17). Adenoviruses can be adapted as a vector in RNA interference by transferring siRNA to cancer cells to control cancer cell growth. In this method, siRNAs were designed to target genes that regulate the growth of cancer cells (18). Treatment of human renal carcinoma cells (HRCCs) by this method resulted in inhibition of proliferation and induction of apoptotic cell death (19).

**Advantages and disadvantages of adenovirus for gene therapy and vaccination.**

Adenoviruses (Ads) can meet almost all the criteria of vectors used for gene therapy and vaccination, such as stability, safety and efficiency (8). They can infect a broad range of cells from different species or different organs, and cells both dividing and post-mitotic quiescent. And the vectors can be easily grown to large scale in tissue culture, making the production of vectors for gene therapy and vaccination much easier. The Adenovirus vectors can express transgenes efficiently, and it is also possible to use strong heterologous promoters to enhance transgene expression. The genome of adenoviruses can be easily manipulated, which makes the insertion of target genes into the viral genome much easier and more practicable. The adenovirus vectors are replication deficient so there is no serious threat of horizontal transmission. Their use is safe without a potential risk of insertion mutagenesis because the vector genome remains epichromosomal and does not integrate into the host genome (20).

The target antigen expressed on the adenovirus vectors or the products of transgenes expressed can induce strong immune response when administered via different parenteral or mucosal (intranasal or oral) routes (21). Antigens of the transgene products can induce both humoral and cellular mediated response, although the mechanism is not very clear (20). The transgene products of gene therapy or vaccine vectors can induce the animals to produce antibodies (22), with antibodies of primarily the IgG2a isotype, indicating the predominance of Th1-type help (21). Adenoviral vectors can also induce strong innate immunity, which can potentiate the subsequent adaptive immune response, including cellular and humoral mediated response. Furthermore, the maturation of antigen presenting cells by adenoviral vectors can facilitate antigen presentation and prolong the duration of immunity (21).

**Disadvantages of adenovirus for gene therapy and vaccination.**
Adenoviruses have been used widely in gene therapy, vaccination and antitumor therapy because of their advantages, such as: safety, efficiency and stability. Despite these advantages, they also have limitations which hamper their use as a vector. Induction of immunity, both innate and adaptive immunity, by the vectors are the greatest problem which needs to be solved before clinical application (23). To overcome this problem, adaptive immunity has been studied extensively and minimized by deleting almost all the genome of adenovirus to make gutted (helper-dependent) vectors. But innate immunity, results in tissue damage and rapid clearance of the vector. Thus influences the therapeutic efficiency and safety, but the mechanism of innate immune action is not clear. This is a challenge for the clinical use of the adenovirus vectors (24). So it is important to understand the mechanism by which innate immunity is induced by adenovirus to support the development of more efficient and safer vectors.

Another disadvantage limiting the application of adenovirus is pre-existing immunity (25). Human adenovirus 5 is the most studied and used adenovirus. It is prevalent in the human population, which creates the situation which the effect of the vector vaccine or gene therapy is highly variable. When vectors derived from the human adenovirus 5 are injected, the pre-existing immunity will clear the vector quickly, and the efficiency will be reduced. So the efficiency of the human adenovirus derived vectors is highly variable in the human population (25). To circumvent this pre-existing immunity, several method are under investigation, including mucosal delivery of vectors (26), modification of the hexons and pentons (27) and development of novel vectors derived from nonhuman adenovirus (28).

**Cell entry of adenovirus**

The cell entry of adenovirus is a complex process and many steps are involved in the induction of innate immunity (29). Cell entry can be divided into four steps: attachment, internalization, escape and translocation (30), and different adenovirus serotypes use different receptors to enter cells.

The first step of adenovirus cell entry is attachment. The interaction between the fiber knob of adenovirus and the primary receptor of the cell is termed attachment. As mentioned above, different adenovirus types use different primary receptors, but almost all adenoviruses use Coxackie and Adenovirus Receptor (CAR) (31). Except CAR, several other primary receptors can be used by adenovirus to enter cells. Human adenovirus 3,11, 35, in human adenovirus group B, recognize and bind CD46 (32). Some adenovirus types use sialic acid as the primary receptor, such as human adenovirus 37 (33) and bovine adenovirus 3 (34). Adenovirus uses its fiber knob to bind the cell receptor in a high affinity interaction to achieve the first step in cell entry.

Once adenovirus has attached to the cell surface, it must enter the cell. Shortly after attachment, the virus initiates internalization which is via the endosome (35). In this process, the second receptor integrin is used, it can recognize and interact with RGD motifs, which are present on the each of the five loops protruding from the top of the pentameric penton base complex. Furthermore, the interaction between adenovirus penton base and the integrin will activate signaling molecules, such as PI3K, p130CAS, and small GTPases (36, 37). These signaling molecules increase cell survival (38), but they also can be used by adenovirus to facilitate its infection (39). PI3K may also have some detrimental effect on cells, because it is involved in signaling pathways that induce
the production of inflammatory cytokines (40).

After internalization, adenovirus is in the endosome. There are two major mechanisms to escape from the endosome, viral uncoating to make itself smaller and disruption of the endosome membrane to pass through. After entry of adenovirus into the endosome, cells acidify the endosome to respond to the infection, which can help the adenovirus uncoat. Firstly, vertex removal occurs, which is a temperature dependent course. The fiber protein and the penton base are removed in this process (41), this is followed by the removal of hexons, pVIII, pIIa, pVI and pIX (42). After the uncoating of adenovirus, it still requires endosomal membrane disruption to escape. The released protein VI plays a key role in this process. After the removal of pVI, it attaches to the endosome membrane and disrupts it, but this mechanism is not clear (43). Except the disruption of the endosome membrane, pVI is involved in the transportation of hexons from cytoplasm to nucleus (44) and activation of a 23K proteinase (45).

After escaping the endosome, partially uncoated adenovirus must inject its genome into the nucleus to replicate, but it must move to the nucleus. To achieve this, it needs to use the microtubule system to approach the nucleus (46), the cytoplasmic dynein can help the uncoated virus move to the MTOC (microtubule organizing center), which is close to the nucleus for most cells. Protein VI also plays a role in the trafficking of partially uncoated virus towards the nucleus (47). After adenovirus arrives at the MTOC, it must detach from the microtubules, then attach on the nuclear membrane. The hexons can interact with the NPC (nuclear pore complex) proteins, which mediates the dissociation of adenovirus and NPC (48). At last adenovirus will inject its genome into the nucleus to start transcription and replication. The whole process of cell entry by adenovirus is shown in Figure 2.

![Image of adenovirus cell entry](http://vir.sgmjournals.org)

**Figure 2** Cell entry of adenovirus. (a) Attachment. (b) Internalization. (c) In the endosome. (d) Escape from endosome. (e) Translocate to nucleus. (f) Genome entry the nucleus (4).

**INNATE IMMUNITY INDUCED BY VIRUSES**

When viruses infect cells, innate immunity is the first line of defense against viruses. One typical characteristic of innate immunity is the induction of inflammatory
cytokines. From the viruses attach on the cells to the expression of inflammatory cytokines, a long and complex signaling pathway occurs. The PAMPs (pathogen associated molecular patterns) of viruses can be recognized by PRRs (pattern recognition receptors), then the PRRs will recruit an adaptor protein to initiate a signaling cascade, which activates transcription factors to induce the expression of cytokine genes. The PRRs are located in different parts of cells. TLRs (Toll Like Receptors), which are the best researched PRRs are located in the endosome and on the cell surface, and other PRRs such as NLRs (NOD-like receptors) and RLRs (RIG-I-like receptors) are cytosolic receptors, located in the cytoplasm. Different PRRs recognize different pathogen and initiate different signaling pathways to induce the production of cytokines.

Adenovirus can be recognized by different PRRs. Adenoviral proteins can be detected by the cell surface TLRs, although we still do not know which TLR and proteins are involved in this process. Adenoviral DNA can be recognized by TLR9 and activate inflammasome. Type I interferon can be produced in the RIG-I pathway because of the recognition of adenoviral virus associated RNA (VA-RNAs).

Pathogen recognition by TLRs on the cell surface

TLR1, 2, 4, 5, 6, 10 are located on the cell surface, and play a key role in the recognition of bacterial and fungal antigens, such as LPS (lipopolysaccharide), bacterial flagellin, LTA (lipoteichoic acid), and lipoproteins (49). But some new studies have found that TLR2 and TLR4 can also detect viral envelope proteins (Figure 3).

TLR2 is shown to recognize cytomegalovirus (CMV) (50). In this research, UV-inactivated CMV was used to induce the innate immune response and the result showed that UV-inactivated CMV can induce the production of IL-6 and IL-8, and CMV-induced cytokine secretion is CD14 and TLR2 dependent (50). In another study, herpes simplex virus-1 were used to induce the innate immune response of both cell lines and knockout mice (51). Chemokines levels in TLR2 deficient mice were significantly lower than in either wild-type or TLR4 deficient mice. Compared with wild-type mice, TLR2 deficient mice had reduced mortality. These results suggested that HSV-1 induced innate immunity in both cell lines and TLR2 deficient mice (51). Vaccinia virus envelope proteins were shown to induce innate immunity (52). In a study, someone proved that the vaccinia virus can induce TLR2 and MyD88 mediated production of inflammatory cytokines (52). And another study demonstrated that varicella-zoster virus (VZV) induces the production of inflammatory cytokines via TLR2 pathway (53). It also shows that VZV induced cytokine production was species specific. VZV activated NF-κB in human cell line expressing a murine TLR2, but it did not induce cytokines in murine embryonic fibroblasts (53). Some studies also demonstrated that TLR4 plays a role in recognizing viral proteins and inducing the innate immunity. Fusion protein of respiratory syncytial virus can induce PBMC to produce IL-4, IL-8 and TNF-α, in this process both TLR4 and CD14 are required (54). In another study of TLR4 recognition of antigens, mouse mammary tumor virus (MMTV) envelope protein interacted TLR4 and activated the TLR4 pathway to produce cytokines (55).

Adenovirus can also induce innate immune response by cell surface TLRs, although we still do not know which TLR and proteins are involved in this process. UV-inactivated adenovirus and empty capsid have been proved to induce the production of inflammatory cytokines from human peripheral blood mononuclear cells, and the
inflammatory cytokine levels were not diminished compared to mature adenovirus (56). This means adenoviral protein also can induce innate immune response.

Pathogen recognition by TLRs in the endosome

Many viruses enter cells via engulf enter and stay in the endosome. They can be detected by TLRs on the membrane of endosome and initiate production of inflammatory cytokines. TLR3, 7, 8 and 9 are located on the endosome membrane. TLR3, 7 and 8 can recognize RNA and initiate a signaling pathway, while TLR9 can recognize DNA (57). All of these TLRs mainly recognize viral nucleic acids. The signaling pathways are shown in Figure 3.

![Diagram of TLR signaling pathways](image)

**Figure 3** Signaling pathways initiated by TLRs on the cell surface and in endosome. TLR1, 2, 4, 5 and 6 are located on the cell surface, while TLR3, 7, 8 and 9 are in the endosome. They use different signaling pathway to induce the production of cytokines (58).

TLR3 is located in the endosome of immune cells, such as NK cells, macrophages, B-cells, and non-immune cells, including epithelial cells. TLR3 is involved in the recognition of double-strand RNA (dsRNA) of RNA virus, both the genome dsRNA and the transcribed dsRNA. When A549 and human tracheobronchial epithelial cells were challenged by RSV, the expression levels of TLR3 and PKR were enhanced, and NF-κB activity can be enhanced as well, and then induce the production of inflammatory cytokine IL-8 (59). Others demonstrated that TLR3 recognizes the double-strand RNA of West Nile virus during infection (60).

TLR7 recognizes single-strand RNA (ss-RNA), both the viral genomic ss-RNA
and the synthetic ssRNA of RNA virus (61). So TLR7 mediates the innate immune response against RNA virus infection, such as vesicular stomatitis virus (62) and influenza virus (63). TLR7 and MyD88 were required for the recognition of vesicular stomatitis virus (64). In this research, vesicular stomatitis virus was used to infect MyD88−/− bone marrow cells and was observed that the production of IFN-α was significantly reduced when compared to the wild type cells. In another experiment, vesicular stomatitis virus was used to challenge TLR7+ and TLR9+ pDCs and it was observed that TLR7+ pDCs secreted much less IFN-α than the TLR9+ pDCs. These results demonstrate that vesicular stomatitis virus is recognized by the TLR7/MyD88 pathway (62). Influenza virus is also recognized by TLR7 (63). TLR3+/−, TLR4+/− and TLR9+/− Flt3L DC can secrete normal levels of IFN-α in response to infection by influenza, but TLR7+/− Flt3L only produced background levels of IFN-α. This means the TLR7 plays an important role in the response of influenza virus infection (63).

TLR9 can recognize unmethylated-CpG-motif-containing viral or bacterial DNA, and then initiate a signaling pathway to induce the production of type I interferon and anti-viral responses (64, 65). Many DNA virus can be recognized by TLR9, including varicella-zoster virus (VZV) (66), murine cytomegalovirus (MCMV)(67), herpes simplex virus (HSV)(68), Epstein-Barr virus (EBV) (69) and adenovirus (70). In one study, adenovirus were used to challenge MyD88+/− and TRIF+/− pDCs to check which adaptor protein is involved in this signaling pathway, and the results showed the IFN-α production by MyD88+/− pDCs was abolished, while TRIF−/− pDCs was not affected (70). This proved the MyD88 is involved in this signaling pathway. Then they investigated which TLR was involved and used TLR7+/−, TLR8+/−, and TLR9+/− pDCs infected by adenovirus. The results showed that IFN-α produced by TLR9+/− pDCs is decreased significantly, while the production of IFN-α by TLR7+/− and TLR8+/− pDCs was not affected (70). These observations demonstrate that adenovirus can be recognize by TLR9 in the endosome, TLR9 then recruits MyD88 to initiate the signaling pathway to produce INF-α.

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TLRs can use different signaling pathway to induce the production of inflammatory cytokines, because they use different adaptor proteins to initiate the signaling pathways. Most PRRs use MyD88 as the adaptor proteins, some of them use the MyD88 pathway to induce the production of cytokines (71). Other PRRs, like TLR3 and 4, use TIR containing adaptor inducing IFN-β (TRIF) as adaptor protein, so they use TRIF pathway to induce the production of cytokines (71). In the MyD88 pathway, after the PRRs recognize and associate with the pathogens, the adaptor protein MyD88 will be recruited. Then MyD88 will recruit and activate IRAK (IL-1 receptor-associated kinase), like IRAK1, IRAK2 and IRAK4, and they will bind and activate TRAF6 (TNF receptor-associated factor 6) to form a complex including E2 ubiquitin-conjugating enzymes. TRAF6 will be polyubiquitinated, and the polyubiquitinated TRAF6 will activate TAK (transforming growth factor-β-activated kinase 1) and TABs (TAK1-binding proteins). Activated TAK and TABs will activate NF-κB (nuclear factor κB) and AP-1 (activator protein-1). Activated NF-κB and AP-1 can directly interact with the cytokine genes promoter to regulate they express (72). The other pathway is dependent on TRIF, and in this pathway many cytokines and type I interferon are induced. PRRs will activate TRAF6 after binding the adaptor protein TRIF, and the TBK1 (TANK binding kinase 1) and IKKi (IkB kinase) will be activated by TRAF6. TANK (TRAF family member-
NF-κB activator) and NAP1 (NAK-associated protein 1) can recognize and bind with TBK1 and IKKi, the IRF3 (interferon regulation factor 3) and IRF7 will be activated and transported into the nucleus to induce the expression of type I interferon genes (73) (Figure 3).

**Pathogen recognition by TLRs in the cytoplasm**

As well as the PRRs in the endosome and on the cell surface, there are some soluble PRRs in the cytosol including NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs). These receptors can also recognize bacterial and viral pathogens and induce innate immune response against the viral infection.

**Pathogen recognition by NLRs**

A study showed that a plasmid DNA vaccine could induce both innate and adaptive immune response, but the TLR9 and MyD88 pathway was not involved. This means there are other PRRs involved in the recognition of plasmids DNA (74). The NLRs are likely to induce the innate immune response, because they can recognize viral DNA. NLRs can be divided into two subfamilies, NOD-subfamily and NALP-subfamily (75). NOD-subfamily has NOD1 and NOD2, and they can recognize peptidoglycan (PGN) and muramyl dipeptide (MDP), respectively. Both of these two molecules are present on Gram-negative and Gram-positive bacteria (76). The NALP-subfamily, form a protein complex termed inflammasome by binding two other proteins, ASC and caspase-1 (77). The inflammasome has three types, NALP3, NALP1 and IPAF, but only NALP3 can recognize viral pathogens. It can recognize viral DNA and RNA from many different kinds of virus (77). NALP3 uses its adaptor protein ASC to recruit caspase-1 to form the inflammasome complex. Caspase-1 can be activated in the inflammasome, so it will process pro-IL-1β and pro-IL-18 to their mature forms IL-1β and IL-18, respectively (78). Adenovirus can induce production of inflammatory cytokines by the NALP3 pathway (79).

The inflammasome can be activated by adenoviral DNA, to induce the maturation of the pro-IL-1β (79). Cells from NALP3−/− and ASC−/− mice show reduced inflammatory responses to adenovirus particles. Bacterial, viral and mammalian (host) DNA can also induces the activation of inflammasome, but in this pathway ASC is involved and NALP3 is not (79). The signaling pathway of the inflammasome is shown in Figure 4.

**Figure 4** Signaling pathway NALP3 used to process pro-IL-1β and pro-IL-18 to their mature forms. NALP3 pathway promotes the maturation of caspase-1. Then the activated caspase-1 catalyzes pro-IL-1β and pro-IL-18 to their mature forms (80).
Pathogen recognition by RLRs

The RIG-I-like receptors (RLRs) family is another PRR family in the cytoplasm which recognizes and binds nucleic acids. This family has two PRRs, Mda5 and RIG-I, both of which can recognize viral RNA (Figure 5). The only difference is that Mda5 recognizes dsRNA, while RIG-I recognizes 5′-triphosphate ssRNA (81). RIG-I mainly acts on RNA viruses, like Newcastle-disease virus (NDV) and influenza virus (82), and flaviviruses, like Japanese encephalitis virus (JEV) and hepatitis C virus (HCV) (82). Mda5 mainly recognizes NDV, IV and JEV, and they can also induce the production of type I IFNs and inflammatory cytokines against picornaviruses, like Theiler’s virus and Mengo virus (83). In the pathway of RIRs, Mda5 and RIG-I use CARD (caspase recruitment domain) to bind the CARD of the adaptor protein to recruit it, these two sensors use the same adaptor protein IPS-1 (IFN-β promoter stimulator-1) (84). Then the FADD (Fas-associated death domain) protein will associate with caspase 8 and caspase 10 and form a complex with IPS-1. The newly formed complex will activate NF-κB (84).

Research found that RIG-I can recognize molecules from DNA virus such as adenovirus (85). Type I interferon can be produced in the RIG-I pathway because of the recognition of VA-RNAs which are small non-encoding RNAs, and the adaptor protein IPS-I is essential for the induction of type I interferon in a cell line MEFs. While in
another cell line GM-DCs, production of inflammatory Cytokines and Type I IFN is by both IPS-I-dependent and independent pathways (85).

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, immune cells detect viral antigens through PRRs on the cell surface, in the endosome and in cytoplasm. All these PRRs can initiate a signaling pathway to induce the production of inflammatory cytokines and type I interferon against the viruses. For viruses, both their nucleic acids and structural proteins can induce innate immune responses. But only several viral proteins have been to be recognized by PRRs. Work should be carried on to detect if other viral proteins are involved in the induction of innate immunity, especially by adenovirus which can be used as a vector for gene therapy and vaccination. The adenovirus empty capsid has been proved to induce innate immune response, and work should be carried on to determine which protein and which domain of this protein is involved in the induction of innate immunity. Then the innate immunity induced domain can be deleted to reduce the innate immunity. This may be result in a more efficient vector with fewer side effects.

REFERENCE


