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Review

Innate immune response and viral interference strategies developed by Human Herpesviruses

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ABSTRACT

Viruses are by far the most abundant parasites on earth and they have been found to infect animals, plants and bacteria. However, different types of viruses can only infect a limited range of hosts and many are species-specific. Herpesviruses constitute a large family of DNA viruses that cause diseases in animals, including humans and that are known to undergo lytic or latent infections. Consequently, they developed numerous strategies to counteract host antiviral responses to escape immune surveillance. Innate immune response constitutes the first line of host defence that limits the viral spread and also plays an important role in the activation of adaptive immune response. Viral components are recognized by specific host Pathogen Recognition Receptors (PRRs) which trigger the activation of IRF3, NF-κB and AP-1, three regulators of IFN-β expression. IFN-β is responsible for the induction of Interferon-Stimulated Genes (ISGs) that encode antiviral effectors important to limit the viral spread and to establish an antiviral state as well in the infected cells as in the neighbouring non-infected cells. In this review, we will summarize how host cells recognize viral components and activate downstream signalling pathways leading to the production of IFN-β and ISGs. We will also review the most recent findings in Herpesviruses-encoded proteins involved in host immune evasion.

Contents

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1. General introduction

The immune response directed to pathogens like viruses proceeds in two steps. Innate immune response, that represents the first line of defence, is rapidly activated and plays an important role in the detection of invading pathogens and in the limitation of their spread. The adaptive immunity, that represents the second line of defence, takes more time to be settled and is involved in the total clearance of pathogens.

Innate immune cells express various Pattern-Recognition Receptors (PRRs) that recognize conserved microbial molecules known as Pathogen-Associated Molecular Patterns (PAMPs) such as viral nucleic acids and bacterial components such as LPS or flagellin.

To date, three classes of PRRs have been discovered, namely (i) Toll-Like Receptors (TLRs) that are membrane-associated receptors, (ii) Retinoic acid-Inducible Gene (RIG-I)-Like Receptors (RLRs) and (iii) Nucleotide-binding Oligomerization Domain (NOD)-Like Receptors (NLRs) that are cytosolic receptors [1–4]. Recently another sensor, which localizes into the cytosol, has been identified. This new receptor has been called DNA-dependent Activator of IRFs (DAI) and recognizes both microbial and host DNA [5,6]. AIM2 (Absent in Melanoma 2), has also been identified as a DNA sensor that controls the catalytic cleavage of pro-form of the cytokine IL-1β [7,8].

Viral detection by TLRs, RLRs and DAI leads to the expression of Type I interferons (IFNs) (IFN-α/-β) and pro-inflammatory cytokines such as IL-8, RANTES and IL-1β whereas NLRs and AIM2 are involved in caspase-1-mediated maturation of IL-1β [3,7–10]. These cytokines are important for recruitment and activation of the immune effector cells (i.e. neutrophiles, B lymphocytes, T lymphocytes...). Because IFN-α and -β induce the expression of genes encoding antiviral proteins, they are considered as key players in the innate antiviral response. IFN-α and -β represent also an important link between innate and adaptive immune responses [11].

Herpesviruses are largely widespread in the environment and so far, approximately 130 of them have been identified. Nine of them are human pathogens namely, Herpes Simplex Virus type-1 (HSV-1), Herpes Simplex Virus type-2 (HSV-2), Human Cytomegalovirus (HCMV), Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV) and Human Herpesvirus type-6A, 6B, 7, and 8 (HHV-6A, HHV-6B, HHV-7, and HHV-8). According to the primary target cell and the site of latency, they have been classified in three subfamilies, (i) the *Alphaherpesvirinae*, (ii) the *Betaherpesvirinae* and (iii) the *Gammaherpesvirinae*.

Structurally, Herpesviruses are enveloped viruses with a long dsDNA genome. The replication cycle occurs in three waves. The first wave leads to the expression of the immediate-early genes (IE or α) that occurs independently of *de novo* viral protein synthesis. They encode key regulators that will allow the expression of the second wave of genes: the early genes (E or β). E proteins are involved in the viral DNA replication. During the third wave, the late genes (L or γ) are expressed. Those encode structural proteins such as capsid and tegument proteins, as well as glycoproteins. All Herpesviruses share a common feature which is the ability to establish a lifelong infection by undergoing latency in their host after primary infection. During this latency, the viral DNA is present in the infected cells but no replication is observed even if some viral proteins are expressed. Upon stimuli that are not clearly defined, the virus can reactivate and reinitiate a lytic infectious cycle. Therefore, Herpesviruses have developed mechanisms to bypass the immune responses of their host to persist in it.

In this review, we will describe how viral components are recognized by host PRRs and how Human Herpesviruses (i.e. HSV-1, VZV, HCMV and EBV) subvert their host's innate immune responses.

2. The Toll-like receptor family

The role of the TLRs in innate immunity was first described in *Drosophila melanogaster* [12]. The Toll receptor has been shown to possess homologs in humans referred to as Toll-Like Receptors. To date, 11 TLRs members have been described in humans [13–15]. They were shown to bind conserved microbial molecules known as PAMPs that are shared by many pathogens but not expressed by the host. This enables them to discriminate the "non-self" from the "self". TLRs recognize various microbial components such as bacterial lipopolysaccharide (LPS), flagellin, peptidoglycan, CpG-rich DNA but also yeast wall mannans and viral nucleic acids. The cellular localization, the ligand and the adaptor proteins of each TLR are summarized in Table 1.

TLRs are type I transmembrane proteins that share common structural features (Fig. 1). They are composed by a variable N-terminal extracellular ectodomain containing 16–28 leucine-rich repeats (LRRs) that are responsible for the detection and the interaction with PAMPs [16]. Contrary to the LRR, the C-terminal intracellular domain of the TLRs is highly conserved and similar to the intracellular region of the Drosophila Toll and IL-1 receptors [16]. This intracellular domain, known as Toll/IL-1 Receptor (TIR) domain, allows the transduction signal to the nucleus [4,13]. TLRs are expressed in innate immune cells that encounter pathogens, such as monocytes and macrophages, but also in B-lymphocytes and dendritic cells [14]. However, expression of TLRs in dendritic cells varies according to the subset of these later. Indeed, human blood dendritic cells contain two subsets: myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs). Mature mDCs express TLRs-2, -3, -4, -5, -6, -7 and -8, whereas mature pDCs only express TLRs-7 and -9 [17]. Nevertheless, TLRs expression is not restricted to these cells as they are also expressed in various cell and tissue types such as vascular endothelial cells, adipocytes, cardiac myocytes and intestinal epithelial cells [18]. TLRs are mainly expressed on the cell surface except the TLRs-3, -7, -8 and -9 that are expressed in endosomal compartments [14,19,20].

Table 1
Description of the Toll-like receptors family (adapted from [4,14]).

TLR	Localization	Ligand	Adaptor
TLR1/2	Cell surface	Triacyl lipopeptides (Bacteria and Mycobacteria)	MyD88, TIRAP
TLR2/6	Cell surface	Diacyl lipopeptides (Mycoplasma), LTA (Streptococcus), Zymosan (*Saccharomyces cerevisiae*)	MyD88, TIRAP
TLR2	Cell surface	Peptidoglycan (Gram-positive bacteria), lipoarabinomannan (Mycobacteria), Hemagglutinin (Measles virus), phospholipomannan (*Candida*), Glycosylphosphophatidyl inositol mucin (*Trypanosoma*)	MyD88, TIRAP
TLR3	Endosome	ssRNA virus (West Nile Virus), dsRNA virus, Respiratory Syncitial virus (RSV), murine cytomegalovirus (MCMV)	TRIF
TLR4	Cell surface	LPS (Gram-negative Bacteria), Mannan (*Candida*), glycoinositolphospholipids (*Trypanosoma*), enveloppe proteins (RSV and MMTV)	MyD88, TIRAP, TRAM and TRIF
TLR5	Cell surface	Flagellin (Flagellated bacteria)	MyD88
TLR7	Endosome	ssRNA viruses (VSV, Influenza virus)	MyD88
TLR8	Endosome	ssRNA from RNA virus	MyD88
TLR9	Endosome	dsDNA viruses (HSV, MCMV), CpG motifs from bacteria and viruses, hemozoin (Plasmodium)	MyD88
TLR11	Cell surface	Uropathogenic bacteria, profillin-like molecule (*Toxoplasma gndii*)	MyD88

Endosomal TLRs are mainly involved in the recognition of foreign nucleic acids that require internalization into endosomes to induce signalling [20].

2.1. TLR signalling pathways

The PAMPs recognition by TLRs induces the recruitment of adaptor proteins containing a TIR domain including MyD88, TIRAP (also known as MAL), TRIF (also known as TICAM1) and TRAM (also known as TICAM2). Upon stimulation, TLRs recruit adaptors to transduce the signal and activate transcription factors such as NF-κB, AP-1 and IRF3 that allow the expression of pro-inflammatory cytokines and IFNs [15,20,21]. Depending on the adaptor protein that is recruited, TLRs are able to activate different transcription factors to induce appropriate responses to pathogens. According to the adaptor and to the TLR, two main pathways can be activated, namely (i) MyD88-dependent and (ii) TRIF-dependent pathway (Fig. 2).

2.1.1. MyD88-dependent signalling

Upon ligand recognition, TLRs-1, -2, -4, -5, -6, -7 and -9 recruit the adaptor protein MyD88 via their respective TIR domain. This leads *in fine* to the activation of NF-κB and AP-1 [22] (Fig. 2, purple and cyan frames). Once recruited, MyD88 binds the death domain (DD) of the IL-1 Receptor-Associated Kinase 4 (IRAK4) through homotypic interactions, resulting in the activation of the downstream IRAKs such as IRAK1 and IRAK2. Once phosphorylated, IRAKs are released from MyD88 and associate with and activate TNF receptor-associated factor 6 (TRAF6). The binding to TRAF6 is important for its K63-linked polyubiquitination that, in turn, allows the recruitment of a larger complex comprising TAB2/TAB3/TAK1. This induces the phosphorylation of TAK1 which is involved in the activation of the IκB kinase (IKK) complex leading to the phosphorylation, polyubiquitination and degradation of IκBα, which permits the nuclear translocation of NF-κB [4,15,21,23,24] (Fig. 2).

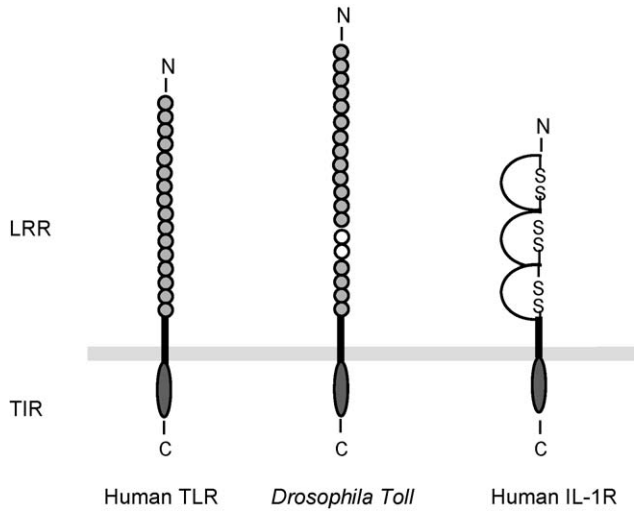

Fig. 1. Schematic representation of the protein structure of the Toll-Like Receptors. The ectodomain consists in 16–28 leucine-rich repeats that are variable among human TLRs and among different species, indicated as grey circle, and involved in the recognition of PAMPs. A cystein-rich domain (depicted as two white circles) is present in *Drosophila Toll* but missing in human TLRs. The ectodomain of the IL-1R consists in three immunoglobulin-like domains. All TLRs share an intracellular domain that is indicated as a dark grey ellipse. This TIR domain is involved in the signal transduction and is highly conserved among human TLRs and among different species.

Keating et al. reported that IRAK2, rather than IRAK1, is important for TRAF6 K63-linked polyubiquitination and subsequent activation of NF-κB upon TLR stimulation [25]. Furthermore, the complex formed by MyD88/IRAK4/IRAK2 has been recently crystallized showing how important IRAK2 is in TLR-mediated activation of NF-κB [26]. The MyD88-dependent pathway also leads to the activation of Mitogen Activated Protein (MAP) kinases (MAPKs) such as the Extracellular signal-Regulated Kinase (ERK or p44/p42), the JUN N-terminal Kinase (JNK) and p38 (Fig. 2, purple and cyan frames). These MAPKs promote the activation of the Activator Protein (AP)-1 that plays a role in the control of pro-inflammatory genes expression. Furthermore, in addition to MyD88, the TLRs-1, -2, -4 and -6 recruit another TIR-containing adaptor, the TIR-associated protein (TIRAP), which is also known as MyD88-adaptor-like (MAL) and that serves as a linker adaptor to recruit MyD88 to the TLRs [4,26,27] (Fig. 2).

In plasmacytoid dendritic cells (pDCs), TLR7- and TLR9-dependent signalling pathways require MyD88 to induce IFN-α expression (Fig. 2, grey frame). Upon stimulation with agonist, TLR7 and TLR9 recruit MyD88 that associates with Interferon-Regulatory factor (IRF-) 7 along with IRAK4, TRAF6, TRAF3, IRAK1 and IKKα. In this large complex, IRF7 is phospohrylated by IRAK1 and IKKα allowing its nuclear translocation and subsequent expression of IFN-α (Fig. 2, grey frame). The activation of IRF7 in pDCs also requires the precursor of osteopontin (OPNi) [4,20]. In addition to IRF7, TLR7 and TLR9 trigger the activation of NF-κB through a MyD88/IRAK4/IRAK2/TRAF6-dependent pathway.

2.1.2. TRIF-dependent signalling

The adaptor TIR-domain-containing adaptor inducing IFN-β (TRIF) is important in TLR3 and TLR4-dependent signalling pathways (Fig. 2, blue frame). In addition to NF-κB and AP-1, the TRIF-dependent pathway leads to the activation of the Interferon Regulatory Factor (IRF)-3. TRIF-dependent activation of NF-κB, AP-1 and IRF3 triggers the formation of an enhanceosome that permits the expression of IFN-β. Upon LPS stimulation,

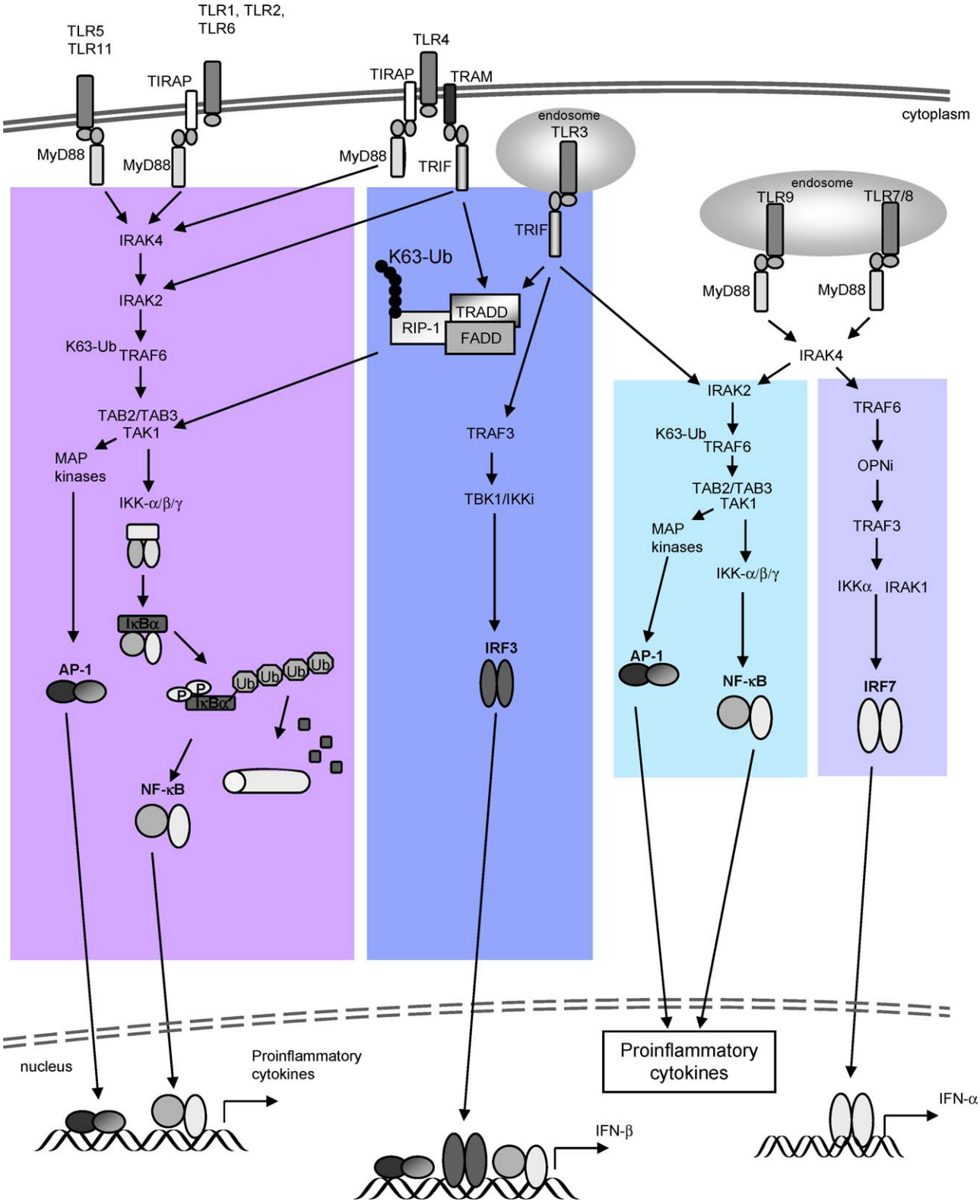

Fig. 2. TLR-mediated signalling pathways. Upon ligand stimulation, all the TLRs, except the TLR3, recruit the adaptor MyD88. In turn, MyD88 binds a protein complex composed of IRAK4, IRAK2 and TRAF6. TRAF6 self-polyubiquitinates resulting in the phosphorylation of TAK1. In turn, TAK1 activates the IKK complex that leads to the phosphorylation, ubiquitination and degradation of IκBα. This allows NF-κB to translocate into the nucleus. Simultaneously, the TAK1-containing complex activates the MAP kinase pathway triggering the activation of AP-1. Together, NF-κB and AP-1 induce the expression of pro-inflammatory cytokines. In pDCs, TLR7 and TLR9 induce the activation of NF-κB and AP-1 through the classical MyD88/IRAK4/IRAK2-dependent pathway. These TLRs also associate with MyD88 to activate IRF7. MyD88 forms a multiprotein complex with IRAK4, TRAF6, TRAF3, OPN-i, IKKα and IRAK1 that leads to the phosphorylation of IRF7. This allows its nuclear translocation and the induction of IFN-α expression. In addition to MyD88, some TLRs recruit other adaptor proteins upon stimulation. TLR4 and TLR2, in the combination with the TLR1 or the TLR6, recruit TIRAP that serves as a link adaptor for the recruitment of MyD88. Moreover, TLR4 recruits a second link adaptor named TRAM that allows the interaction with the adaptor TRIF. Upon stimulation with agonist, TLR3 recruits TRIF, an adaptor that interacts with a protein complex composed of TRADD, FADD and RIP-1 and which triggers the activation of NF-κB and AP-1. TRIF-mediated activation of NF-κB and AP-1 also occurs through an IRAK2/TRAF6-dependent pathway. Upon stimulation, TRIF also binds TRAF3, which activates TBK1 and IKK-i. TBK1, along with IKK-I, phosphorylates IRF3 and permits its homodimerization and nuclear translocation. IRF3, along with NF-κB and AP-1, cooperate to induce the expression of type I IFNs.

in addition to TIRAP and MyD88, the TLR4 binds to the TRIF-related adaptor molecule (TRAM) which allows the recruitment of the TRIF and leads to the activation of the IRF3 [27] (Fig. 2). In response to dsRNA challenge, TLR3 recruits the adaptor TRIF that interacts with a complex composed of the Receptor-Interacting Protein kinase 1 (RIP1), the Tumor necrosis factor Receptor type 1-Associated Death Domain protein (TRADD) and the FAS-Associated death domain-containing protein (FADD) (Fig. 2, blue frame). RIP1 undergoes K63-linked polyubiquitination that permits the activation of TAK1, which in turn activates NF-κB and AP-1 [28]. TRIF was also reported to recruit a large complex that comprises TRAF6/TAB2/TAB3/TAK1 (Fig. 2, cyan frame). As mentioned above, the activated TAK1 induces the activation of the downstream IKK complex and MAP kinases leading to nuclear translocation of the NF-κB and AP-1 respectively. In this pathway, the activation of NF-κB and AP-1 involves IRAK2 and TRAF6 [25] instead of IRAK1 and IRAK4 [29,30] (Fig. 2, cyan frame).

TRIF-dependent pathway also leads to the activation of IRF3. TRIF interacts with the TNF Receptor-Associated Factor 3 (TRAF3) to activate two non-canonical IKKs namely the TRAF family member-associated NF-κB activator (TANK)-Binding Kinase 1 (TBK-1, also known as NAK or T2K) and the inducible IKK (IKK-I or IKK-ε) [14,15,31,32]. These two kinases phosphorylate IRF3, leading to its homodimerization and allowing it to translocate into the nucleus (Fig. 2, blue frame).

2.2. Viral recognition by TLRs

Viral nucleic acids, such as double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), unmethylated CpG rich motif (CpG-DNA) and viral structural proteins, such as glycoproteins, are considered as PAMPs and are recognized by some TLRs. Among TLRs, only the endosomal ones, such as TLRs-3, -7, -8 and -9, are involved in the detection of viral nucleic acids [20]. Indeed, viral particles are endocytosed and degraded in late endosomes or lysosomes. Therefore, viral DNA and RNA are released into these intracellular acidic compartments, allowing viral nucleic acids to be in close contact with endosomal TLRs. Furthermore, endosomal localization of some TLRs is important to discriminate self nucleic acids from non-self ones to avoid the induction of autoimmune diseases. Only few TLRs were reported to play a role in the recognition of DNA viruses and more particularly, only TLRs-2, -3 and -9 were shown to recognize Human Herpesviruses.

2.2.1. Role of TLR2 in Herpesvirus detection

TLR2 is expressed on the cell surface and recognizes extracellular ligands. It is able to form heterodimers with either TLR1 or TLR6 and has been shown to play a role in Herpesviruses sensing. HSV-1 was shown to interact with TLR2 and this interaction was described to be detrimental to its host. Indeed, HSV-1 recognition by TLR2 induces the expression of inflammatory cytokines in the brain that causes lethal encephalitis [33]. VZV was also demonstrated to activate the expression of proinflammatory cytokines in a TLR2-dependent manner [34]. Finally, TLR2 and CD14 were reported to be involved in the recognition of HCMV virions [35].

2.2.2. Role of TLR3 in Herpesvirus detection

Double-stranded RNA that is produced by most viruses during their replicative cycle, is often considered as a PAMP [36]. RNA viruses are important producers of dsRNA but surprisingly, only some of them induce a TLR3-dependent innate immune response. Indeed, some data have shown that, two ssRNA viruses, namely the lymphocytic choriomeningitis virus (LCMV) and the vesicular stomatitis virus (VSV), both known to produce dsRNA intermediates, did not induce any TLR3-dependent antiviral response [37].

Although no role for TLR3 was pointed out in the recognition of a DNA virus, the Murine cytomegalorvirus (MCMV) [37], TLR3 was proposed to play a role in the antiviral response against other Herpesviruses. Recent data demonstrated that TLR3 played an important role in controlling the spread of HSV-1 within the central nervous system. Indeed, Zhang et al. have described a relationship between TLR3 and Herpes Simplex Encephalitis (HSE) [38]. They observed that TLR3- and UNC-93B-deficient patients, that display an impaired activation of TLR3 signalling, were not able to produce type I IFNs upon HSV-1 infection. This led to an increased susceptibility to HSE and showed how important the TLR3 is in neuronal protection against HSE. EBV was also shown to elicit a TLR3-dependent pathway upon chronic active infection [39]. Indeed, EBV was demonstrated to produce EBV-encoded small RNA (EBER) that adopts a dsRNA-like conformation. This EBER is abundantly present in EBV-infected cells and is released during infection, which leads to the induction of type I IFNs production in a TLR3-dependent manner. These findings are consistent with those of Weber et al. who demonstrated that DNA viruses could also produce dsRNA during their replicative cycle [36].

2.2.3. Role of TLR9 in Herpesvirus detection

Like other TLRs involved in the recognition of nucleic acids, TLR9 is expressed in endosomes. CpG DNA from viral and bacterial origin, that possesses unmethylated CpG dinuclotides, is the best-characterized ligand for TLR9 [14]. Similarly to bacterial DNA, HSV DNA contains abundant CpG motifs that are responsible for TLR9 binding and subsequent IFN-α secretion [40]. It has been demonstrated that the treatment with chloroquine, an inhibitor of endosomal acidification, inhibits HSV-2 recognition by TLR9 pointing out that an intact endocytic pathway was necessary to induce TLR9-dependent signalling upon HSV-2 infection. Another study also showed that HSV-1 viral replication was not required for stimulation of TLR9/MyD88 pathway. This suggested that the interaction between HSV-1 glycoproteins and cell surface receptors may induce HSV-1 internalization and subsequent release of viral DNA in the endosomal compartment, allowing the interaction with TLR9 [41].

3. Cytoplasmic pathogen recognition receptors

As mentioned above, TLRs are involved in the recognition of either extracellular or endosomal microbial components whereas other classes of PRRs are involved in the recognition of pathogens that invade host cytosol. Among these cytosolic PRRs, the RIG-I-Like Receptors (RLRs), the NOD-Like Receptors (NLRs), the DAI and the AIM2 are the best-characterized.

3.1. RIG-I-like receptors

RLRs consist in a group of cytosolic RNA helicases that are expressed in most cell types and are involved in the recognition of viral RNA. This group encompasses three members which are Retinoic acid-Inducible Gene I (RIG-I) [42], Melanoma Differentiation-Associated gene 5 (MDA5) [43], and Laboratory of Genetics and Physiology-2 (LGP-2) [44]. RIG-I is characterized by two N-terminal Caspase-Recruitment Domains (CARDs), a DExD/H box RNA helicase domain and a C-terminal Repressor Domain (RD) (Fig. 4). The helicase and the RD domains of RIG-I are involved in the recognition of viral RNA whereas the CARDs are important for triggering the downstream signalling. In resting cells, the RD interacts with the helicase domain to mask the CARDs rendering RIG-I inactive. Upon interaction with its agonist, RIG-I undergoes conformational changes leading to CARDs exposition and activation of the downstream signalling (Fig. 4).

Like RIG-I, MDA5 contains two CARD domains and a RNA helicase domain. However it lacks the C-terminal Repressor Domain [43] (Fig. 3). In contrast, LGP-2 comprises no CARD domains and was originally found to function as a dominant-negative regulator of RIG-I/MDA5-mediated signalling [43,44] (Fig. 3). However, a recent study demonstrated that LGP-2 is required for RIG-I- and MDA5-mediated antiviral response and acts as a positive rather than a negative regulator of RIG-I/MDA5-mediated antiviral response [45]. Therefore, the role of LGP-2 in antiviral response still remains controversial.

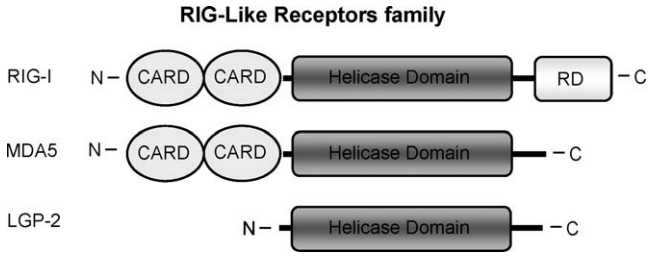

Fig. 3. Schematic representation of the protein structure of the RIG-Like Receptors family. RLRs consist in a group of cytosolic RNA helicases that comprises three members namely RIG-I, MDA5 and LGP2. RIG-I and MDA5 are composed of two amino-terminal CARD domains and a central Helicase domain. Contrary to RIG-I, MAD5 lacks the C-terminal repressor domain (RD). LGP2 only possesses the central Helicase domain.

3.1.1. RLRs signalling pathways

The activation of RLR-dependent signalling pathway leads to the activation of two important transcription factors, namely NF-κB and IRF3, that induce along with AP-1, the expression of IFN-β [15]. As TLRs do, RLRs interact with adaptor proteins such as MAVS and MITA allowing the recruitment of downstream effectors (Fig. 5).

In 2005, a new component of the RIG-I/MDA5 signalling was simultaneously discovered by four different laboratories [46–49]. This new protein named Mitochondrial Antiviral Signalling (MAVS), also termed Interferon-β Promoter Stimulator 1 (IPS-1), Virus-Induced Signalling Adaptor (VISA) or CARD adapter inducing IFN-β (Cardif), operates downstream of RIG-I/MDA5 and upstream of the IKK complex and TBK1/IKK-I. Therefore, MAVS has been characterized as an adaptor for RLRs that regulates the activation of NF-κB and IRF3 (Fig. 5). MAVS contains two TRAF binding motifs (TIM) and a N-terminal CARD-like domain allowing interaction with the TRAF proteins and the CARDs from RIG-I/MDA5 respectively [46,48]. MAVS also possesses a C-terminal mitochondrial transmembrane (TM) domain that targets the protein to the outer membrane of the mitochondria [46]. The mitochondrial localization of MAVS is essential for its function in the antiviral response since the deletion of the TM domain completely abolishes its signalling function [46].

Viral RNA recognition by RIG-I and/or MDA5 allows their CARD domains to interact with the one of MAVS and triggers the formation of two large complexes that both contain the TRADD protein. The first complex comprises TRADD, FADD and RIP-1 (Fig. 5). Altogether, these proteins form the TRADDosome that regulates the activation NF-κB [50]. When the RLRs detect viral RNA and consequently interact with MAVS, TRADD gets recruited. In turn, TRADD associates with FADD and RIP-1. This association is mediated through DD (Death Domain) homotypic interactions. Within this TRADDosome, RIP-1 is K63-linked polyubiquitinated by TRAF2 and TRAF3 that are also recruited to MAVS. This modification results in the activation of the IKK complex and subsequent activation of NF-κB [50]. FADD also interacts with caspase-8 and -10 through DED (Death Effector Domain) homotypic interactions to regulate the activation of NF-κB. In the absence of the inhibitor FLIP, caspase-8 induces cell death (Fig. 5). The second complex that is formed upon MAVS recruitment to RLRs comprises TRADD, TRAF3 and TANK (Fig. 5). This complex leads to the activation of TBK1 which in turn causes the phosphorylation of IRF3, its dimerization and its nuclear translocation [50].

In addition to MAVS, another adaptor protein was recently discovered and named Mediator of IRF3 Activation (MITA). It is also known as Stimulator of Interferon Genes (STING) or Endoplasmic Reticulum IFN Stimulator (ERIS) [51–54]. MITA was found to be essential for RIG-I-mediated signalling pathway but dispensable for MDA5-dependent immune response upon dsDNA stimulation [55]. MITA was firstly reported to be expressed at the outer membrane of mitochondria [54] but recent reports showed that MITA is rather expressed in the endoplasmic reticulum [51,52,54]. The discrepancy observed in the localization of MITA was due to its association with microsomes, a complex of continuous membranes that comprise the ER, Golgi and transport vesicles [55]. To reinforce the ER localization of MITA, co-immunoprecipitation experiments have shown that MITA associates with TRAPβ, a component of the Translocon-Associated Protein (TRAP) complex, required for protein translocation across the ER membrane following translation. MITA also interacts with SEC61β, a translocon adaptor [51]. These findings suggest that MITA could be involved in translocon function, which may facilitate the induction of type I IFNs. In

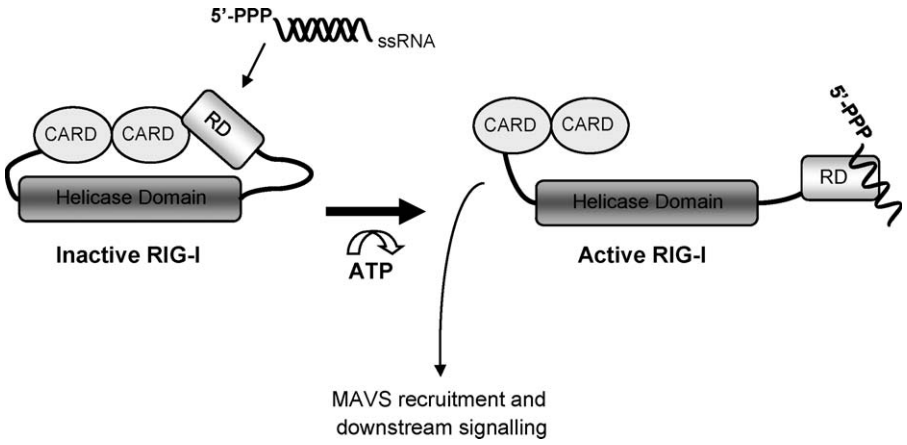

Fig. 4. Schematic representation of RIG-I activation. In resting cells, RIG-I exists as an inactive form in which the C-terminal repressor domain (RD) interacts with both CARD and Helicase domains. Upon viral infection, 5′-ppp dsRNA is produced and binds the RD domain of RIG-I which leads to a conformational change and allows the CARDs to be exposed in the presence of ATP. Therefore, RIG-I is active and the freed CARDs are able to recruit and interact with the adaptor MAVS to trigger the downstream signalling.

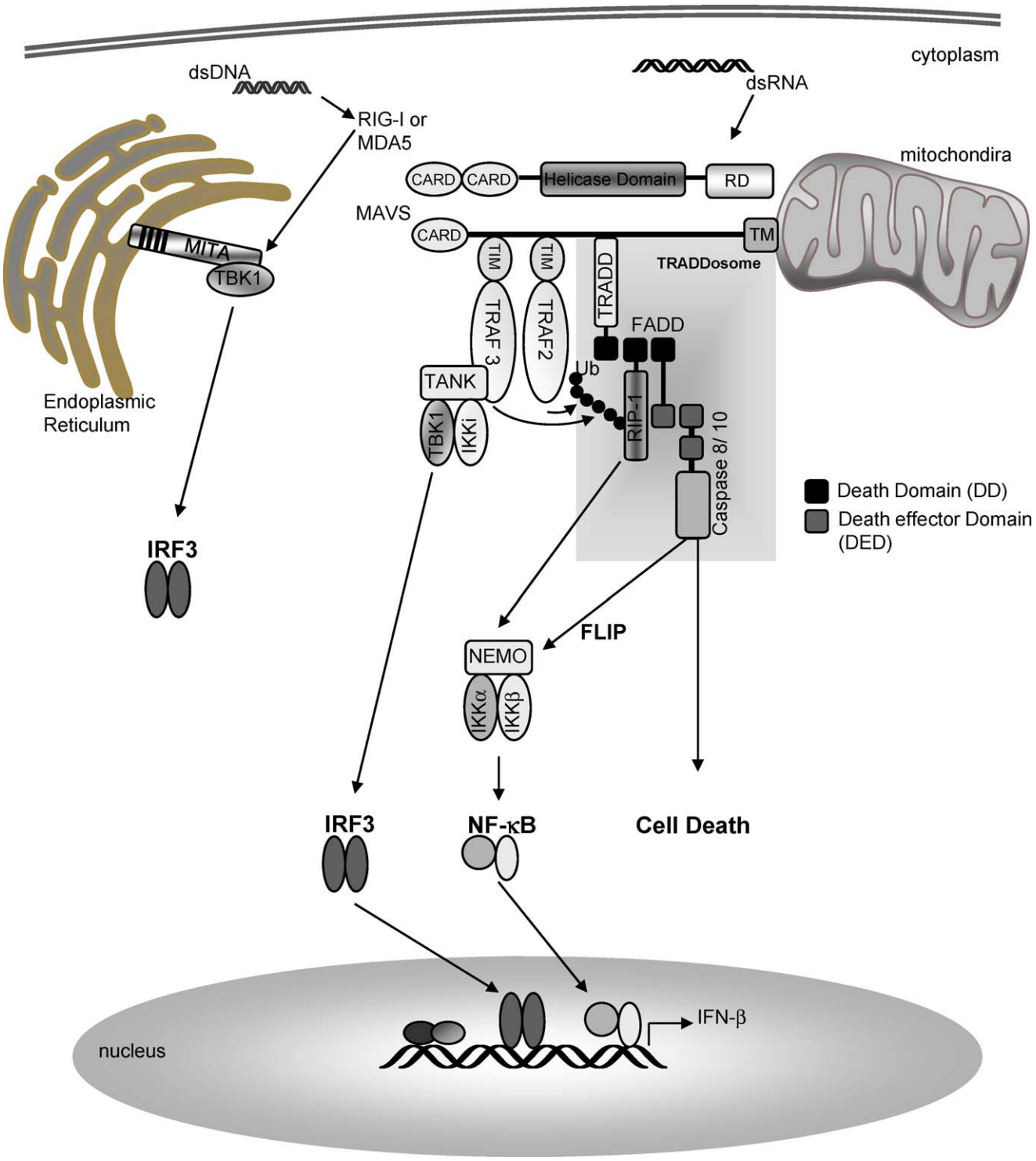

Fig. 5. RLRs-mediated signalling pathway. Upon infection, viral RNA binds RIG-I or MDA-5 which in turn recruits the adaptor protein MAVS via CARD homotypic interactions. Then, MAVS associates with, TRAF2, TRAF3 and also with TRADD leading to the formation of a large complex called the TRADDosomes. In this complex, TRADD associates with FADD and RIP-1. Ubiquitination of RIP-1 by TRAF2 and TRAF3 whithin the TRADDosome induces the activation of NF-κB which is also controlled by caspases-8 and -10 in the presence of FLIP. TRADD also associates with TRAF3 and TANK controlling the activation of IRF3. Upon dsDNA stimulation, MITA, which is expressed in the ER, interacts with both RIG-I and TBK1 allowing the activation of IRF3 activation.

addition, MITA was also found in association with RIG-I and TBK1 (Fig. 5). So, MITA might allow RIG-I-mediated detection of viral trancripts as well as dsDNA at the intersection of ribosome/ER translocon [51]. Furthermore, phosphorylation of MITA at Ser358 by TBK1 has been shown to constitute a critical step for subsequent virus-triggered activation of IRF3 [54].

Recently, the role of the DEAD-box helicase, DDX3 (also known as DDX3X) in the activation of IFN-β has been pointed out [56,57]. DDX3 was shown to interact with IKKε upon viral infection [57] but it was also found to be a substrate of TBK1. Indeed, TBK1-dependent phosphorylation induces DDX3 nuclear translocation and binding on target promoter where it activates the expression

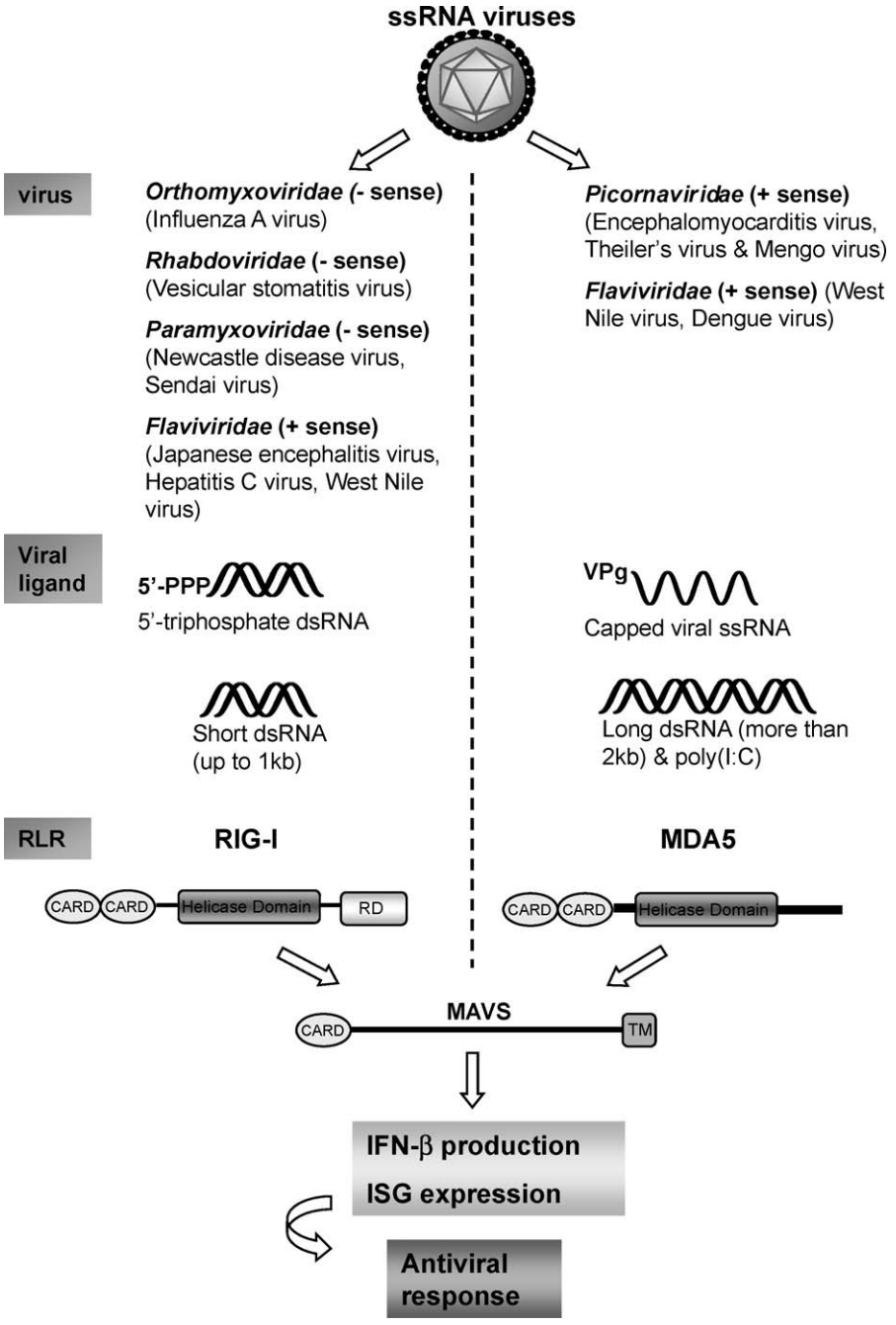

Fig. 6. Schematic overview of the RIG-I/MDA-5 discrimination among viral ligands. RIG-I is preferentially involved in the detection of viral 5′-ppp dsRNA and short dsRNA whereas MDA-5 is more sensitive to capped viral ssRNA and long dsRNA. Moreover, RIG-I and MDA-5 recognize different ssRNA viruses to induce appropriate innate immune responses.

of IFN-β [56]. In addition, DDX3 was also shown to bind stem-loop RNA of viral origin but also the CARD of MAVS and the RD of RIG-I through its C-terminal domain [58]. It was suggested that DDX3 may be required for initial sensing of viral RNA and facilitates MAVS-dependent signalling [58]. Taken together, these new findings suggest that DDX3 acts as an enhancer IFN-β expression upon RLRs stimulation.

3.1.2. Viral recognition by RLRs

As mentioned above, RIG-I and MDA5 are able to activate similar pathways. Interestingly, recent studies have shown that these two RLRs recognize different ssRNA viruses, pointing out that RIG-I and MDA5 can discriminate among different ligands to induce an appropriate innate immune response to RNA viruses (Fig. 6).

RIG-I was demonstrated to be important for the recognition of *in vitro* transcribed RNA [59]. Independently, two groups reported that viral ssRNA bearing a 5′-triphosphate (5′-PPP) end was a ligand for RIG-I [60,61] but recent studies opposed that *in vitro* transcribed RNA bearing only a 5′-triphosphate moiety was not sufficient to induce the activation of RIG-I. It was proven that only stem-loop RNA species bearing a 5′-triphosphate end stimulated the immune system [62,63]. In addition, it was published that the viral genome of the Sendai and Influenza A viruses rather than their transcripts, could activate type I IFN response through a RIG-I-dependent pathway [64]. This suggests that the single-stranded

genome from RNA viruses such as these two viruses could adopt a "panhandle" conformation by pairing of complementary 5′ and 3′ ends, allowing the activation of RIG-I. Altogether, these new findings suggest that RNA secondary structures with the combination of a 5′-triphosphate end seem to be sufficient to induce RIG-I activation and subsequent induction of type I IFNs expression.

MDA5 was shown to be more sensitive to synthetic dsRNA such as poly(I:C) [59,65]. Furthermore, a recent study provided evidences for discrimination of dsRNA by RLRs based on the length of these dsRNA [66]. So, RIG-I was found to be more sensitive to short dsRNA whereas MDA5 especially recognizes long dsRNA.

In addition to RNA viruses, RLRs have also shown to be involved in the recognition of DNA viruses. Previous studies proved that HSV-1 induced type I IFNs expression through a mechanism dependent both on RIG-I and the adaptor MAVS [67,68]. Furthermore, it has been reported that MITA induced a robust expression of type I IFNs upon DNA stimulation or HSV-1 infection [51,55]. A new report has demonstrated that viral dsDNA serves as a template for RNA polymerase III (POL3) which converts DNA into RNA bearing a 5′-triphosphate moiety which is able to stimulate RIG-I [69]. It has been reported that HSV-1-induced expression of IFN-β was impaired upon treatment with a specific inhibitor or siRNA against POL3. These new findings suggest that POL3 could act as a DNA sensor leading to the expression of IFN-β in a RIG-I-dependent manner upon HSV-1 infection [69]. Epstein-Barr virus (EBV) was also found to induce a POL3/RIG-I-dependent signalling pathway. As already mentioned, EBV encodes EBERs that are noncoding and nonpolyadenylated RNAs able to form stem-loop structure leading to the formation of dsRNA molecules [70]. Similarly, EBER1 and EBER2 are transcribed by RNA polymerase III that synthesizes RNAs containing a 5′-triphosphate end that are therefore, able to activate RIG-I-dependent signalling pathways.

3.2. NLRs

Nucleotide Oligomerization Domain (NOD)-like receptors (NLRs) are cytoplasmic PRRs that recognize PAMPs able to induce innate immune responses. The human NLR family comprises more than 20 members that are divided in two main subfamilies according to their N-terminal domain (Fig. 7). NLRs share a central NACHT Nucelotide-Binding Domain (NBD) and a C-terminal LRR domain involved in the recognition of pathogens. However, they differ from each other in their N-terminal domains that can be either a CARD or a Pyrin Domain (PYD) [71,72]. Therefore, NLRs that contain a CARD are part of the NLRC subfamily, whereas NLRs that possess a PYD form the NLRP subfamily (also known as NALP). While the NLRC subfamily comprises five members, the NLRP subfamily constitutes a large group of 14 members. The best-described NLRP members are NLRP1 (also known as NALP1) and NLRP3 (also known as NALP3). Similarly, the best-characterized NLRC members are NOD1 (also known as NLRC1), NOD2 (also known as NLRC2) and NLRC4 (Fig. 7). NLRP3 is essentially involved in the activation of the inflammasome. By contrast, NOD2 rather plays a role in the activation of NF-κB and MAP kinase pathways. The production of IL-1β by macrophages and monocytes plays also an important role in the innate immune response during the viral infection. Expression of mature IL-1β results from the cleavage of pro-IL-1β by caspase-1 which is preliminary activated by a multiprotein complex called inflammasome and regulated by NLRs [73].

3.2.1. NLR-mediated inflammasome

To date, among the NLR family, only NLRP1, NLRP3 and NLRC4 are known to activate the inflammasome that leads to the cleavage of pro-form of the IL-1β in response to microbes [71,74].

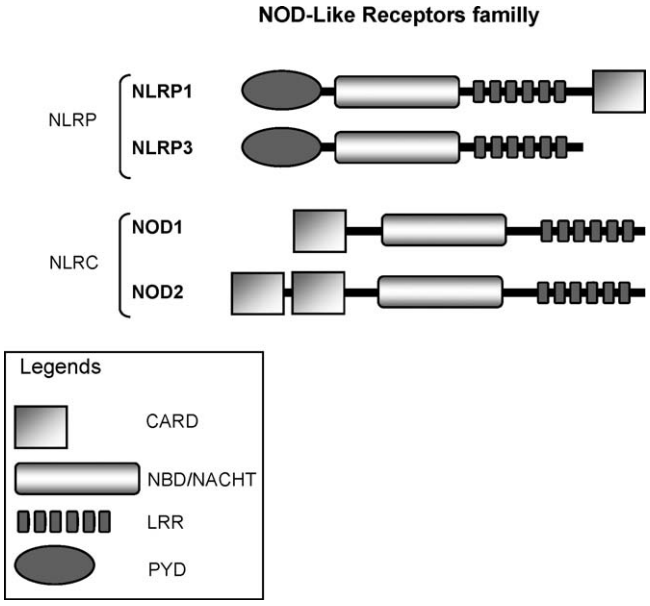

Fig. 7. Schematic representation of the protein structure of the NOD-Like Receptors family. NLR are composed of a central NACHT Nucelotide-Binding Domain (NBD) and a C-terminal LRR domain involved in the recognition of pathogens. Their N-terminal domain can be either a CARD or a PYD domain. The NLRP subfamily constitutes the largest group among the NLR family and is characterized by an N-terminal PYD domain. The best-described NLRP members are NLRP1 and NLRP3 which play an essential role in the inflammasome. The NLRC subfamily comprises only five members and is characterized by an N-terminal CARD domain. NOD1 and NOD2 are the best-described members within NLRC subfamily.

The well-described NLRP3 inflammasome is activated by many stimuli from both bacterial and viral origin and requires two signals to induce the production of mature IL-1β [72] (Fig. 8). The first signal comes from microbial PAMPs such as LPS, bacterial and viral RNA, dsRNA, dsDNA and MDP, each recognized by its specific receptor which in turn induces the production of pro-IL-1β. The second signal is the result of the presence of a wide range of Danger Associated Molecular Patterns (DAMPs) including (i) pore formation, (ii) ROS production as well as (iii) lysosome damages [71,74,75]. In response to these DAMPs, NLRP3 recruits the adaptor Apoptosis-associated Speck-like protein containing a CARD (ASC) via PYD homotypic interactions. In turn, ASC recruits the pro-caspase-1 through its CARD domain. Once matured by a catalytic process, caspase-1 homodimerizes and induces the processing of the pro-IL-1β into biologically active IL-1β that is secreted outside the cell where it induces inflammatory responses.

3.2.2. Viral recognition by NLRs

Although NLRs were initially described to play a role in innate immunity against bacteria [75,76], they have been recently involved in immune response to viral infection. There are several evidences showing that infection with Adenovirus, Influenza A virus and Modified Vaccinia Ankara (MVA) induces the activation of NLRP3-dependent inflammasome [9,77–80]. Similarly, in addition to its role in the detection of bacterial muramyl dipeptide (MDP), NOD2 was shown to induce a MAVS/IRF3-dependent signalling upon infection with the Respiratory Syncitial Virus (RSV) [81,82].

3.3. AIM2

In 2009, two teams independently discovered a new receptor for DNA that was called AIM2 (Absent In Melanoma 2) and that belongs to the interferon-inducible (IFI) family. AIM2 binds

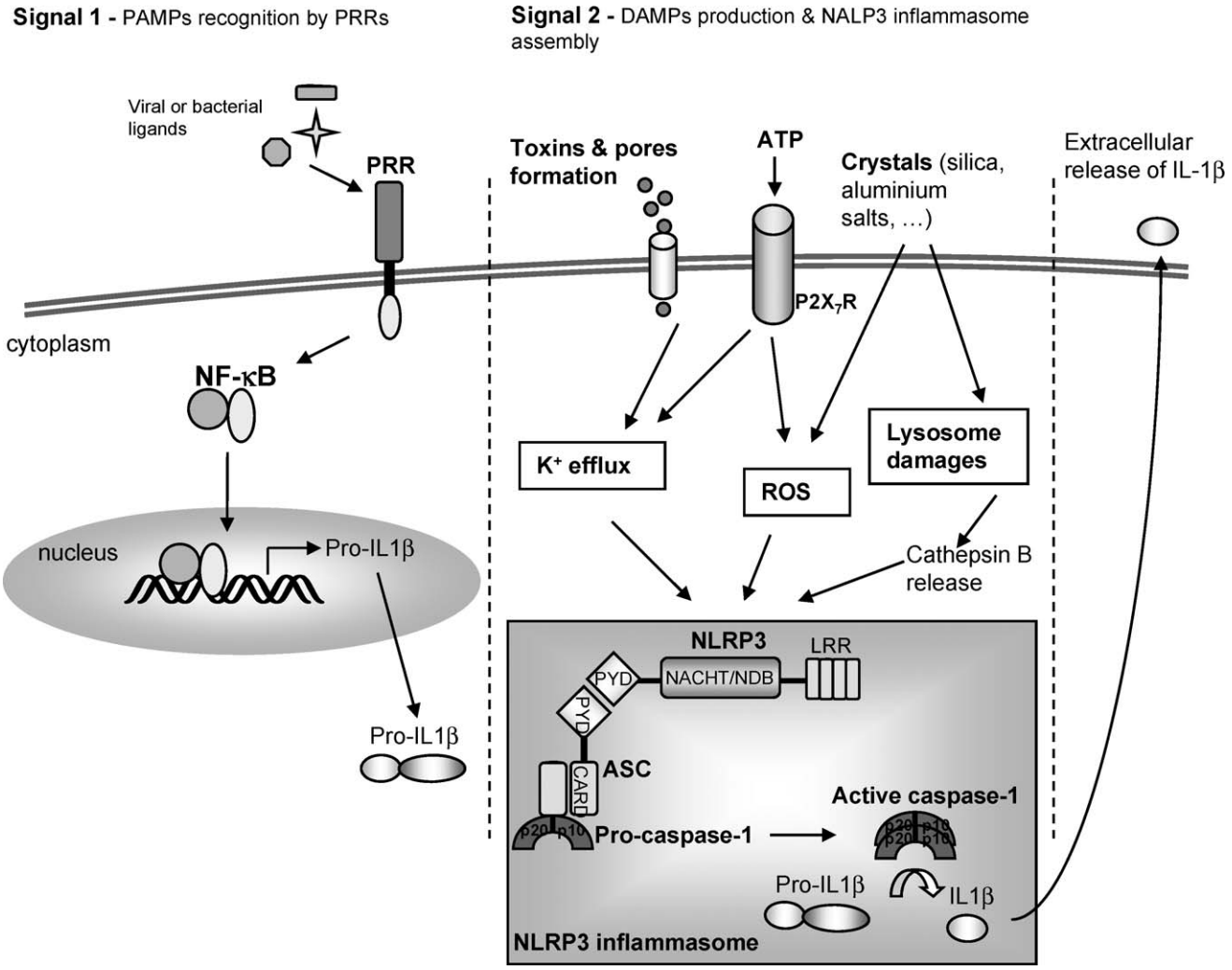

Fig. 8. Schematic overview of the NLRP3-mediated inflammasome. Some NLRs can form a multiprotein complex called inflammasome. NLRP3-mediated inflammasome is the best-characterized and its activation requires two signals. The first signal comes from a PAMP recognized by a specific PRR that triggers the activation of NF-κB and therefore allows Pro-IL-1β synthesis. The second signal is induced by DAMPs such as K^+ efflux, ROS production and lysosome damages that are produced during the infection. These DAMPs are then recognized by NLRP3, which, in turn, recruits the adaptor ASC through PYD homotypic interaction. ASC interacts with the pro-caspsase-1 which becomes activated and allows the cleavage of pro-IL-1β into biologically active IL-1β that is released outside the cell.

cytosolic dsDNA via its HIN domain, whereas its PYD domain can form homotypic interactions with the adaptor ASC. This forms a new inflammasome complex that activates caspase-1 and subsequent cleavage of pro-IL-1β into IL-1β [7,8] (Fig. 9).

3.3.1. Viral recognition by AIM2

Evidences showed that AIM2 induces caspase-1 activation and IL-1β production in response to dsDNA from both bacterial and viral origin such as vaccinia virus and murine cytomegalovirus [83,84].

3.4. DAI

During infection, nucleic acids, such as DNA derived from pathogens and/or damaged host cells are released and can meet sensors in the cytosol. This triggers the activation of innate immune responses. In addition to TLR9 that recognizes CpG DNA from both bacterial and viral origin, a new cytosolic receptor termed DAI (also known as ZBP-1) was found to bind B-form dsDNA leading to the activation of IRF3 which participates in the induction of IFN-β expression [5]. Additionally, B-form dsDNA was reported to stimulate immune response. Intracellular administration of B-form dsDNA, but not Z-form dsDNA, triggers the induction of type I IFNs in a MAVS/TBK1/IRF3-rather than in a TLR-dependent pathway [85]. Additional works showed that DAI directly interacted with DNA through its D3 region followed by oligomerization of DAI. Once oligomerized, DAI is able to recruit TBK1 and IRF3 leading to the activation of downstream signalling pathway [86]. There are accumulating data demonstrating that additional cytosolic DNA sensor(s) may exist(s) since DAI knockdown by RNAi abrogates type I IFNs expression upon B-form dsDNA stimulation in L929 and RAW264.7 cell lines but not in MEFs cells. This suggests that another DNA sensor exists in this cell line [5,86].

3.4.1. Viral recognition by DAI

DAI was found to contribute in mounting an innate immune response during infection with DNA viruses such as HSV-1 but not with ssRNA viruses such as the Newcastle disease virus (NDV) [5]. A more recent study also demonstrated that DAI was essential for the activation of IRF3 and so for the expression of IFN-β in the context of HCMV infection [87]. In addition, it has been shown that DAI-dependent activation of IRF3 required the adaptor MITA following HCMV infection [87].

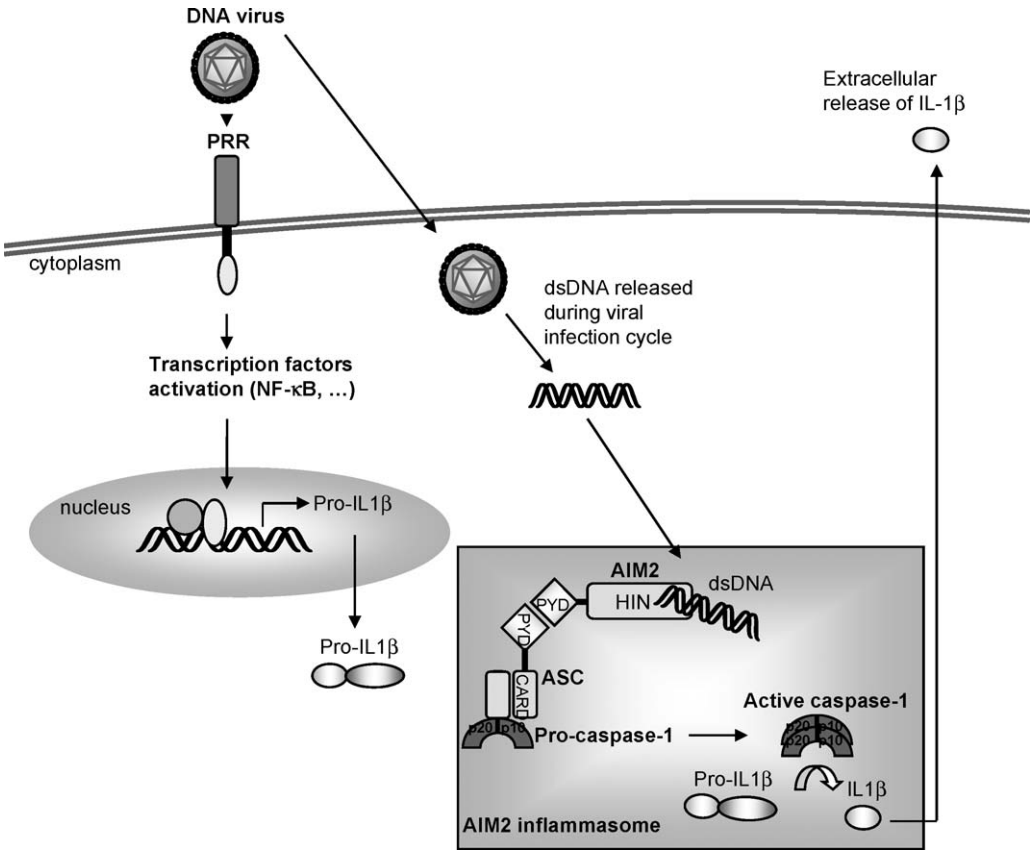

Fig. 9. Schematic representation of the AIM2-dependent inflammasome. AIM2 binds dsDNA from bacterial and viral origin but also host dsDNA. AIM2-dependent inflammasome requires two signals. The first signal comes from the pathogen (virus or bacteria) that triggers PRR-dependent signalling pathway and allows pro-IL-1β production. During the infection, dsDNA is released and gets in close contact with AIM2 in the cytosol. AIM2 then recruits the adaptor ASC through their respective PYD domain. ASC, in turn, interacts with pro-caspase-1, which is then cleaved and becomes active allowing the processing of pro-IL-1β into mature IL-1β.

In conclusion, innate immune response against viruses and other pathogens occurs in two waves. Type I IFNs production in response to PAMPs detection by host PRRs constitutes the the first wave of genes to be expressed. Type I IFNs expression is responsible for the induction of the second wave of genes, the Interferon-Stimulated Genes (ISGs) that encode antiviral effectors which allow the clearance of pathogens.

4. Type I interferon-dependent signalling pathway and antiviral actions

Interferons were first discovered by Isaacs and Lindemann in 1957 [88,89]. They found that IFNs are secreted by virally-infected cells and induce an antiviral state able to limit the propagation of the virus. Moreover, it was shown that IFNs have both autocrine and paracrine effects which enable the induction of an antiviral state both in the infected cell and in the neighbouring non-infected cells [89–92]. IFNs are classified in three types: (i) Type I IFNs include IFN-α and IFN-β. They are directly induced in response to viral infection and produced by innate immune cells such as dendritic cells and macrophages but they can also be encountered in fibroblasts. (ii) Type II IFN only comprises IFN-γ member that is produced by NK cells and by activated T cells. (iii) Type III IFNs were more recently described and include IFN-λ1, -λ2, -λ3 also known as IL-29, IL-28A and IL-28B, respectively [90]. Type III IFNs are directly produced in response to viral infection.

Type I IFNs (IFN-α/-β) play a key role in the activation of the antiviral response. They are responsible for the activation of the Jak/STAT pathway that leads to the expression of ISGs that encode antiviral effectors.

4.1. Type I IFN signalling pathway

In response to PAMPs, host PRRs activate NF-κB, AP-1, IRF3. These transcription factors then cooperate to induce the expression of type I IFNs. IFN-α and -β are released in the extracellular medium and bind to their cognate receptors which are composed of two subunits, namely the Interferon-Alpha/Beta Receptors (IFNAR) 1 and 2 (Fig. 10). The binding leads to the induction of the antiviral response through the initiation of the Jak/STAT pathway. Thus, IFN binding to IFNAR1 and IFNAR2 allows the activation of the receptor-associated kinases Jak-1 and Tyk-2 that are respectively associated to IFNAR2 and IFNAR1 (Fig. 10). Subsequently, Jak-1 and Tyk-2 respectively phosphorylate STAT1 and STAT2 that can heterodimerize and associate with an additional protein, p48 (also known as IRF9). This complex, named interferon-stimulated gene factor 3 (ISGF-3), then translocates into the nucleus where it can activate the expression of ISGs possessing a *cis*-acting DNA element termed ISRE in their promoter [89–91]. Among the ISG proteins, the best-characterized are PKR, ISG15, Mx proteins and OAS1. By targeting different cellular processes, such as the messenger RNA transcription and the protein translation and by inducing the degradation of viral products, ISGs inhibit the assembly of virions therefore limiting the viral spread [88].

5. Strategies used by Human Herpesviruses to subvert the innate immune response

Viruses are considered as obligate parasites that exploit their host's cellular machinery for their own benefit. Therefore, it is important for them to develop strategies to escape antiviral responses activated by their host. Since IFNs are key players in the

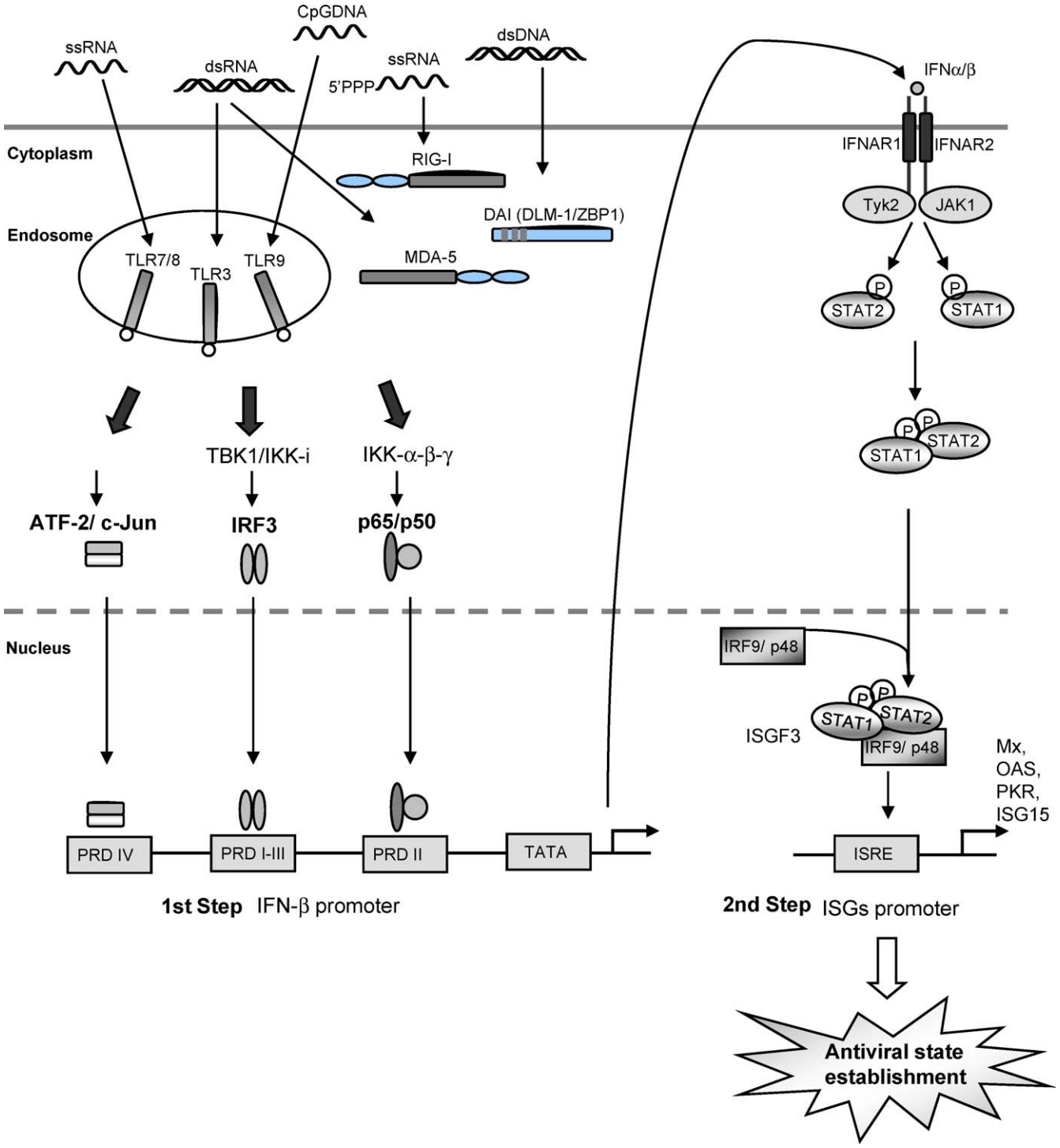

Fig. 10. Schematic representation of PRRs and type I IFN pathways. During viral infection, a two-wave antiviral response takes place. During the first wave, PRRs recognize viral PAMPs such as dsRNA, dsDNA, ssRNA and 5′-ppp ssRNA and trigger signalling pathways that activate the three main transcription factors namely, NF-κB, IRF3 and AP-1. Those transcription factors cooperate to induce the expression of IFNβ that is secreted. In response to TLR7 and TLR9 stimulation, IRF7 can also be activated which leads to the expression and the release of IFN-α. During the second wave, IFN-α/-β bind their cognate receptors composed of the subunits IFNAR1 and IFNAR2. Following the binding, the signal is transduced to the associated-receptor kinases Jak1 and Tyk2 that respectively phosphorylate STAT1 and STAT2. Phosphorylated STAT1 and STAT2 heterodimerize and associate with p48 (also known as IRF9) to form a complex called ISGF-3. This complex translocates into the nucleus to induce the expression of ISGs encoding antiviral effectors such as ISG15, PKR, Mx proteins and OAS1 and allow the establishment of an antiviral state in the infected cells as well as in neighbouring non-infected cells.

activation of antiviral responses, most viruses have elaborated a wide range of molecular mechanisms targeting the PRRs- and IFN-dependent signalling pathways, so that they can reduce the expression of IFNs and ISGs, respectively. In this last chapter, we will describe strategies used by Human Herpesviruses (i.e. HSV-1, VZV, HCMV and EBV) to subvert innate immune responses. These later are summarized in Table 2 and depicted in Fig. 11.

5.1. The Alphaherpsevirinae

5.1.1. Herpes simplex virus 1 (HSV-1)

During the primary infection, HSV-1 productively infects mucoepithelial cells. After this, it establishes a lifelong latency in its host's neurons and many years later, in response to stress, UV exposition or immune weakness, the virus can reactivate from

Table 2
Herpesvirus-encoded proteins involved in viral interference.

Herpesvirus	Viral proteins	Cellular targets	Effects
HSV-1	ICP34.5	eIF-2α	Induces eIF-2α dephosphorylation
	ICP34.5	TBK1	Prevents IRF3 activation and subsequent expression of type I IFNs
	ICP0	IRF3	Inhibtis IRF3 nuclear accumulation and subsequent induction of type I IFN
	ICP27	STAT-1α	Inhibits STAT-1α phosphorylation and the subsequent nuclear translocation and ISGs expression
	Us11	OAS	Prevents the production of 2′,5′-oligoadenylate and the subsequent activation of latent RNase L
	Vhs	mRNA	Induces the degradation of cellular and viral mRNA
VZV	?	Jak2, STAT-1α	Induces the degradation of Jak2, STAT-1α and subsequent downregulation of MHC II expression
	?	Golgi-Cell surface trafficking	Induces a downregulation of MHC I expression at the cell surface
	?	NF-κB pathway	Downregulates of pro-inflammatory cytokines expression
	Unknown viral secreted factor?	IFNα production	Impairs the establishment of the antiviral state
HCMV	pp65 (ppUL83) (still controversial?)	IRF3	Affects the phosphorylation of IRF3 and the subsequent nuclear translocation and IFN-β expression
	Immediate-early protein 2 IE86	NF-κB	Blocks NF-κB binding activity to DNA and the subsequent production of IFN-β
	?	Jak1, p48	Donwregulates MHC I expression, disrupts the ISGF3 complex and inhibits the expression of ISGs
EBV	BZLF-1	IRF7	IFN-α4, IFN-β, Tap2 downrexpression
	LF2	IRF7	Prevents IRF7 dimerization and subsequent inhibition of target genes expression
	BGLF4	IRF3	Prevents IRF3 from IFN-β binding to the promoter
	BRLF1	IRF3, IRF7	Decreases the level of IRF3 and IRF7, leading to an inhibition of IFN-β expression
	LMP2A/LMP2B	IFN receptors	Downregulates type I/II interferon receptors (IFNRs)-mediated signalling

latency, characterized by outbreaks. In addition, HSV-1 infection can also be associated with severe encephalitis. Although HSV-1 rapidly elicits an innate immune response through the activation of IRF3 [93], it has developed various mechanisms to escape its host innate immune responses and increased its capacity to replicate and to persist. Numerous studies demonstrated that HSV-1 encodes proteins that target the IRF3 pathway, IFN production and downstream signalling [94–96] (Fig. 11). Among these proteins, ICP34.5, ICP0, ICP27, Us11 and Vhs, have antiviral functions.

5.1.1.1. ICP34.5. ICP34.5 is referred to as a late gene which is already detected during the early phase and whose expression significantly increases during later phase of the viral infection. Thanks to its ability to interact with PP1α, ICP34.5 was first described to dephosphorylate eIF-2α whose phospohrylation is induced by PKR in response to HSV-1 infection, thus sustaining protein synthesis [97–99]. ICP34.5-mediated dephosphorylation of eIF-2α also leads to the inhibition of autophagy and other cellular stress responses [98]. Moreover, ICP34.5 has been recently demonstrated to form a complex with TBK1 thereby disrupting the interaction between TBK1 and IRF3 and the subsequent induction of IFN-β expression [100].

5.1.1.2. ICP0. ICP0 is an immediate-early protein which plays an important role during HSV-1 replication, latency and reactivation. It is characterized by a RING-finger domain that does not bind DNA but rather acts as an E3 ubiquitin-like ligase required for the degradation of target proteins. It was previously demonstrated that the expression of ICP0 during HSV-1 infection inhibits the induction of ISGs by targeting IRF3 activation [101]. While this inhibition is thought to require a functional RING-finger domain and proteosomal activity [101], no degradation of known components of the IRF3 pathway protagonists such as TBK1, IKKε, IRF3 and CBP has ever been observed [101,102]. In a coinfection model, the IFN-β production mediated by the Sendai Virus was demonstrated to be abrogated upon HSV-1 infection [103]. In this model, ICP0 was also found to accelerate the IRF3 degradation upon activation, thereby affecting its nuclear accumulation [103]. Another study revealed that ICP0 rapidly sequesters the activated IRF3 and CBP/p300, forming nuclear ICP0-containing foci visible by confocal microscopy. This keeps them away from activating IFN-β gene transcription [104]. More recently, the cytoplasmic localization of ICP0 has been reported to inhibit the activation of IRF3 [105]. In this context, it was shown that the inhibitory effects of ICP0 did not require its E3 ubiquitin ligase activity. Therefore it appears that, upon HSV-1 infection ICP0 inhibits the nuclear accumulation of IRF3 and that the inhibitory effect of ICP0 does not require the E3 ubiquitin ligase activity.

5.1.1.3. ICP27. ICP27 is an immediate early protein which exerts an important role in the induction of viral gene expression and in the export of viral mRNA [97]. It was also described as an antagonist of the antiviral response. Indeed, Melchjorsen and colleagues demonstrated that ICP27-null infected macrophages produced higher amounts of IFNs and other cytokines compared to wt-infected ones [106]. Similarly, macrophages infected with the IC27-mutant resulted in a stronger activation of IRF3 and NF-κB than those infected with the wt virus [106]. ICP27 was also reported to inhibit STAT-1 phosphorylation and nuclear accumulation upon IFN-α treatment during HSV-1 infection. Thereby it is able to inhibit IFNα-dependent signalling [107]. Recently, ICP27 expression has been demonstrated to induce the secretion of a soluble factor. This factor acts by inhibiting STAT-1 nuclear translocation upon IFN-α treatment and so, it prevents the subsequent expression of ISGs [108].

5.1.1.4. Us11. Us11 is a late protein able to interfere with the antiviral response due to HSV-1 infection. Indeed, Cassady and colleagues showed that the expression of Us11 earlier in the lytic cycle and prior the HSV-1-mediated PKR phosphorylation, allows the binding of Us11 to PKR. This prevents the phosphorylation of eIF-2α and thereby precludes the inhibition of viral transcripts translation [109]. More recently, Us11 has been reported to block the activation of oligoadenylate synthase (OAS) impairing the production of 2′,5′-oligoadenylate and the subsequent activation of the latent RNase L [110]. Consequently, Us11 was found to counteract the host defence by inhibiting the virus-induced RNA degradation.

5.1.1.5. Vhs. The virion host shutoff protein (vhs) is encoded by the UL41 gene and has an endoribonuclease activity. Vhs is expressed during the late phase of the lytic cycle and incorporated into the virion. It possesses the ability to shutoff cellular proteins synthesis

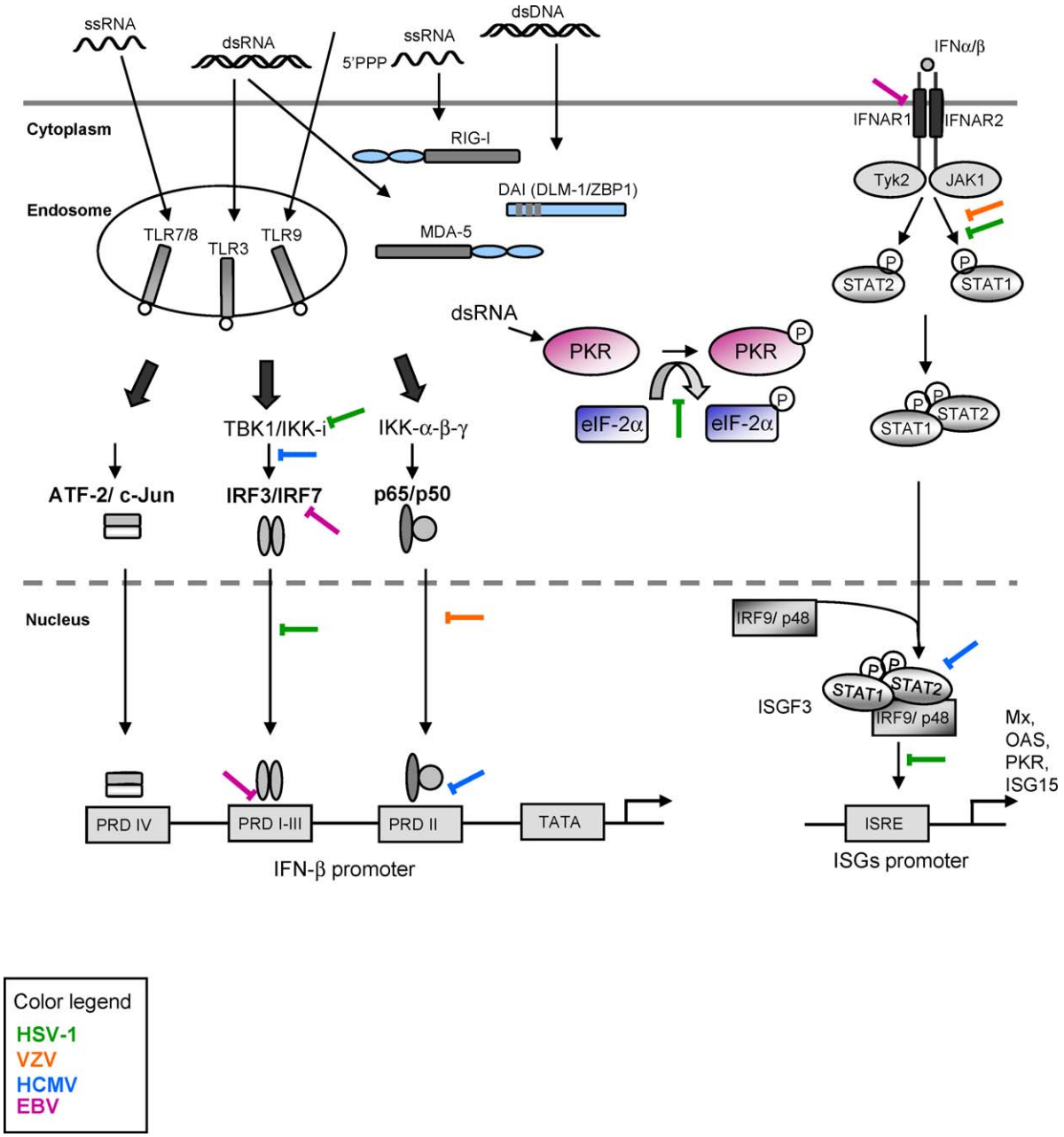

Fig. 11. Schematic overview of herpesviruses interference with the immune response. Herpesviruses encode proteins that interfere with both PRRs- and type I IFNs signalling pathways. The cellular targets are depicted with colored bars. HSV-1 interference is represented as green bars, VZV as orange bars, HCMV as bleu bars and EBV as purple bars.

by degrading mRNA from host or viral origin [111,112]. Vhs has been described to interfere with both type I and type II IFN-dependent signalling pathways by accelerating degradation of ISGs mRNAs [97].

5.1.2. Varicella-zoster virus (VZV)

VZV is a common virus responsible for two well known diseases: varicella and zoster. Varicella (i.e. chicken pox) is the disease resulting from the primary infection in skin whereas Zoster (i.e. shingles) occurs when the virus reactivates from its latency in the dorsal root ganglia. Although, to date little is known about the activation of IRFs by VZV and the subsequent induction of type I IFNs, VZV was also described to possess mechanisms to avoid immune surveillance (Fig. 11). It has been for example demonstrated to downregulate class I and II MHC protein expression [113,114]. Indeed, VZV induces the retention of class I MHC molecules in the Golgi apparatus, leading to a decrease of the cell-surface expression [114] and it reduces the level of Jak2 and STAT-1α proteins, thereby inhibiting the expression of class II MHC molecules at the cell surface [113]. Additional studies revealed that VZV inhibits NF-κB activation during viral infection [115,116]. Since it induces a very transient translocation of p65/p50 NF-κB heterodimers into the nucleus, it was shown that p65 and p50 are rapidly resequestered in the cytoplasm by IκBα whose expression is stabilized during VZV infection [115]. Therefore, by trapping NF-κB, stabilized IκBα prevents the nuclear accumulation of NF-κB heterodimers and limits the expression of target genes and the subsequent innate immune response activation. In addition, our team recently demonstrated that VZV inhibits the expression of ICAM-1 in response to TNFα treatment [116]. We showed that this down-regulation is due to an inhibition of NF-κB activation. We observed that the nuclear translocation of the p50 but not p65

NF-κB subunit upon TNFα treatment is inhibited following VZV infection. This leads to a disruption of the p65/p50 heterodimers that, consequently, cannot bind their target promoters anymore such as this of *icam-1* [116]. Therefore, by modulating the recruitment of NF-κB on selected cellular promoters, VZV is able to interfere with the innate immune response mediated by this transcription factor. A recent study in primary plasmacytoid dendritic cells (pDCs) revealed that these cells are impaired in IFN-α production following VZV infection [117]. Furthermore, the authors observed that the mixed culture of VZV-infected and non-infected pDCs avoid IFN-α expression by non-infected pDCs upon stimulation with ODN2216 [117]. This suggests the existence of a secreted factor by the VZV-infected cells that could impair the non-infected cells in producing IFN-α, consequently this indicates that VZV inhibits the capacity of pDCs to express this host defence cytokine.

5.2. The Betaherpesvirinae

5.2.1. Human cytomegalovirus (HCMV)

HCMV is a ubiquitous pathogen that causes significant morbidity and mortality in humans. It is considered as life-threatening for immunocompromised patients such as those suffering from AIDS, organ transplant recipients or neonates. During primary infection, HCMV productively infects monocytes, lymphocytes and epithelial cells. After primary infection, As other members of its family, HCMV enters in latency that occurs in monocytes and lymphocytes. Similarly to HSV-1, HCMV infection rapidly induces the activation of IRF3 and leads to the expression of IFNs and ISGs [93,118,119]. In this context, HCMV-mediated activation of IRF3 was shown to be dependent on the glycoprotein gB-mediated fusion with the cell membrane, rather than on *de novo* synthesis of viral proteins [118]. Although HCMV was found to rapidly induce the activation of IRF3, the virus rapidly abrogated host's immune responses (Fig. 11).

5.2.1.1. pp65. Abate and colleagues identified the major viral structural protein pp65 encoded by the UL83 gene as a protein able to counteract the antiviral response activated upon virus binding and penetration [120]. Although pp65 was firstly reported to dephosphorylate IRF3 affecting its subsequent nuclear translocation [120], the role of pp65 in the inhibition of IRF3 activation still remains ambiguous. Indeed, it was shown that infection with a deletion mutant virus for the UL83 gene (ΔUL83 virus) induced a strong accumulation of IFN-β mRNA whereas infection with a virus possessing a stop codon in the UL83 gene (UL83Stop virus) completely blocked the induction of IFN-β as the wt virus did [121]. It appeared that the deletion of the entire UL83 gene alters the expression of the pp71 protein, an important regulator of immediate-early gene expression. This alteration induced a delay in the expression of IE86 which is responsible for the inhibition of IFN-β expression [121]. Consequently, IE86 rather than pp65, is responsible for HCMV's immune evasion.

5.2.1.2. IE86. HCMV's viral protein IE86 is encoded by the immediate-early 2 (IE2) gene that, as described above, acts as an IFN-β antagonist. Although IE86 expression was not shown to alter the phosphorylation nor the dimerization and nuclear translocation of IRF3 [122], IE86 expression was reported to block the expression of chemokines such as RANTES, MIP-1α and IL-8 by inhibiting NF-κB activation [121,123]. Consequently, this suggested that the down-regulation of IFN-β expression by IE86 upon HCMV infection may be rather due to the inhibition of NF-κB than IRF3.

5.2.1.3. Disruption of IFN-α signal transduction pathway by HCMV. It has been shown that HCMV induced the downregulation of the IFNγ-mediated induction of class II MHC expression by decreasing the level of the Jak kinase [124]. It has also been demonstrated that HCMV interfered with the IFN-α-dependent signalling pathway in order to escape its host's innate immune response [125]. Indeed, in response to IFN-α, HCMV infection leads to a decreased expression of some components of the Jak/STAT pathway such as Jak1 and p48. Consequently, the ISGF-3 complex is disrupted and the expression of IFN-dependent genes such as 2′,5′-OAS, MxA and class I MHC are downregulated [125].

5.3. The Gammaherpesvirinae

5.3.1. Epstein-barr virus (EBV)

EBV productively infects epithelial cells and B-lymphocytes. It is a widespread virus known to cause infectious mononucleosis and to be associated with Burkitt's lymphoma. After primary infection, it enters latency in B-lymphocytes. During the first step of viral infection, EBV activates both IRF7 and IRF3 [126,127]. However, this activation is rapidly inhibited upon expression of *de novo* viral proteins (Fig. 11). A candidate EBV gene for the inhibition of IRF7 activation is *BZLF-1*. The *BZLF1* gene product, also known as Z, Zebra, Zta or EB1, is an immediate-early protein interacting with IRF7 to downregulate the expression of IRF7-dependent genes such as IFN-α4, IFN-β and Tap2 [126]. In addition, the viral tegument protein, LF2, was reported to bind the IRF association domain (IAD) of IRF7 thus, preventing its dimerization and the later IFN-α production [128]. The viral UL kinase BGLF4 was also described to inhibit host innate immune response [127]. It was demonstrated that the viral kinase BGLF4 interacted with IRF3 and provocated its phosphorylation. While the interaction with BGLF4 did not alter neither IRF3 dimerization nor nuclear translocation and CBP recruitment, it prevents IRF3 from binding to responsive promoters [127]. LMP2A and LMP2B were also demonstrated to induce the IFN receptors degradation to counteract the antiviral response [129]. The viral protein BRLF1, also known as Rta, was reported to downregulate the transcription of IRF3 and IRF7 [130]. Consequently, their mRNA levels, and thereby their protein expression, are decreased resulting in an inhibition of IFN-β expression [130].

6. Concluding remarks

The activation of the innate immune response occurs in two waves. During the first wave, invading pathogens are recognized by the host's PRRs. Those trigger the activation of several transcription factors such as NF-κB and IRF3 which are, along with AP-1, key regulators of IFN-β expression. During the second wave, released IFN-β binds its cognate receptors which induce the activation of the Jak/STAT pathway and so, leads to the activation of the ISGs, which encode antiviral effectors such as the PKR, 2′,5′-OAS, ISG15 and Mx proteins. These effectors are important for the establishment of the antiviral response as well in the infected cells as in the neighbouring non-infected cells preventing them from viral invasion. Since PRRs- and type I IFNs-triggering pathways are critical for the induction of the antiviral response, viruses have developed numerous strategies to inhibit these pathways, so that they can evade their host's innate immune response and persist.

Herpesviruses are widespread throughout the world and cause diseases in animals including humans. Furthermore, they are known for their ability to establish a lifelong latency in their host. Consequently, they set up numerous strategies to counteract antiviral responses and to evade immune surveillance. In this review, we described that *de novo* synthesis of viral proteins during Herpesvirus lytic cycle renders them able to overcome their host's immune defences. These viral proteins often target the activation of either IRF3 or the Jak/STAT signalling pathway. The viral proteins

presented in this review do not constitute an exhaustive list. Further studies would be necessary to better understand how Herpesviruses escape the immune responses.

Finally, these viral mechanisms are important to understand the virus–host interaction mechanisms and to develop appropriate therapies against Herpesvirus infection.

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