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Innate immunity and alpha/gammaherpesviruses: first impressions last a lifetime.

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Abstract

Innate immune system is considered the first line of defense during viral invasion, with the wealth of the literature demonstrating innate immune control of diverse viruses during acute infection. What is far less clear is the role of innate immune system during chronic virus infections. This short review focuses on alpha- and gammaherpesviruses, two highly prevalent herpesvirus subfamilies that, following a brief, once in a lifetime period of acute lytic infection, establish life-long latent infection that is characterized by sporadic reactivation in an immunocompetent host. In spite of many similarities, these two viral families are characterized by distinct cellular tropism and pathogenesis. Here we focus on the published *in vivo* studies to review known interactions of these two viral subfamilies with the innate immunity of the intact host, both during acute and, particularly, chronic virus infection.

Keywords

innate immune response; gammaherpesvirus; alphaherpesvirus; EBV; KSHV; HSV; MHV68

Alphaherpesvirus and gammaherpesvirus overview.

Herpesviruses are ancient viruses that have coevolved with their hosts and, following exposure, establish a lifelong infection which is never cleared. The *Herpesviridae* family contains three subfamilies, alpha-, beta-, and gammaherpesviruses, which are all large (100–200 nm), linear double-stranded DNA (120–250 kb) viruses [1]. This review focuses on the alpha-(herpes simplex viruses (HSV-1 and HSV-2)) and gammaherpesvirus (human Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV), and murine

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gammaherpesvirus-68 (MHV68) also known as murid herpesvirus 4) subfamilies. The choice of these two subfamilies was driven, in part, by the anatomical differences in establishing chronic infection: neurotropic nature of latent alphaherpesvirus infection versus systemic distribution of the latent gammaherpesvirus reservoir. The current review is further focused on the published studies of an intact host infection that reveal the complexity of virus-host interactions that is not fully captured by *in vitro* studies.

Alphaherpesviruses.

HSV-1 and HSV-2 share 83% homology in the coding regions. HSV-1 infects approximately 55% of the U.S. population and clinically manifests as vesicular lesions, mostly of the oral mucosa. Infection of the conjunctiva leads to a recurrent keratoconjunctivitis, a leading infectious cause of blindness worldwide [2]. HSV-2 infects around 20% of the U.S. population and is the common cause of genital disease [3]. For both HSV-1 and HSV-2, latent infection is established in the ganglia innervating the site of the original inoculation, with HSV-1 typically residing in the trigeminal and HSV-2 the sacral ganglia. Reactivation from latency delivers infectious virions in proximity to the original site of inoculation, with subsequent lytic amplification and transmission to a naïve host [4]. Systemic dissemination of HSV is uncommon but can occur in immunocompromised individuals leading to high morbidity and mortality.

HSV-1 and HSV-2 have a sufficiently broad host range to allow infection of laboratory animals. While HSV infection of genetically tractable mouse models recapitulates many features of acute infection in humans, spontaneous HSV reactivation in mice happens at much lower levels than in humans, an important caveat of this animal model. Other animal models of HSV infection, such as rabbits and guinea pigs, do spontaneously reactivate HSV [5] but, unfortunately, lack the robust host genetic tools available in the murine system. Studies in mouse models utilize multiple routes of HSV infection to mimic diverse aspects of viral pathogenesis observed in humans (summarized in Table 1), with most publications focused on the first 5–7 days of HSV infection during which acute viral replication occurs at the inoculation site and the innervating ganglia [5].

Gammaherpesviruses.

EBV and KSHV are highly prevalent human gammaherpesviruses, with over 95% of adults worldwide harboring life-long infection with the former. Unlike alphaherpesviruses, gammaherpesviruses establish systemic infection of lymphoid cells and are associated with the development of cancers, including B cell lymphomas [6,7]. EBV infects naïve B cells and usurps B cell differentiation by inducing a robust germinal center response that includes both virus-infected and uninfected B cells, leading to passive expansion of the viral latent reservoir via cellular proliferation [8,9]. Subsequent B cell differentiation produces EBV-infected memory B cells, a reservoir of long-term infection, or plasma cells that reactivate the latent virus [10,11]. While KSHV infection of human B cells remains less understood, existing studies indicate that KSHV may employ similar mechanisms of B cell manipulation. Many EBV-driven B cell lymphomas are of germinal center or post germinal center origin, highlighting an unintended consequence of the infection of germinal center B cells [12,13]. Importantly, increased viral reactivation often precedes tumorigenesis [14,15].

The highly restricted species specificity of human EBV and KSHV has limited *in vivo* studies of the natural host to rare polymorphisms and mutations that unveil the pathogenicity of these viruses [16]. In contrast, the natural rodent gammaherpesvirus, MHV68, represents a tractable animal model of chronic gammaherpesvirus infection that has provided a wealth of information about the virus-host interactions in the intact host. MHV68 is genetically and biologically similar to EBV and KSHV, establishes latency in B cells, and drives lymphomas in immunocompromised hosts [17–19]. Intranasal and intraperitoneal are the most common routes of infection, with the spleen and peritoneal cavity representing the two sites of MHV68 latency examined in most studies. Acute MHV68 replication is cleared within 9–12 days with the peak of viral latency in the spleen observed at 16 days post infection [20].

Innate immune system of the host has traditionally been perceived as the “first line of defense” and, as such, has been almost exclusively examined in the context of acute virus replication *in vivo*. In contrast, studies of chronic virus infections place a major emphasis on defining parameters of adaptive immune responses, with innate immune factors mostly disregarded. Importantly, the few paradigm shifting studies that had examined innate immune pathways during lymphocytic choriomeningitis virus infection [21,22], have highlighted the continuing role of the host innate immunity in modifying viral control and pathogenesis in a chronically infected host. This review focuses on comparing innate immune mechanisms relevant for the control of alpha- and gammaherpesvirus infections during both acute, and, more importantly, chronic phase of infection of an intact host.

Sensing herpesvirus infection.

TLRs:

There is a myriad of virus pattern sensors whose expression and function are further modified in the cell type-dependent manner. Due to the high complexity, this review focuses on the sensors that were examined during alpha- or gammaherpesvirus infection of the intact host (Fig. 1). One such group of sensors, Toll like receptors (TLRs) [23], are present on the cell surface (TLR2) or in endosomes (TLRs 3, 7, and 9). TLR2 is a promiscuous sensor of pathogens; the exact viral moieties recognized by this sensor remain poorly understood [24]. In contrast, the ligands for the other TLRs are better defined, such as dsRNA for TLR3, ssRNA for TLR7, and CpG for TLR9 [24].

TLRs in HSV infection.

The role of TLR2 during HSV-1 infection is nuanced. In animal models, significantly fewer $TLR2^{-/-}$ mice succumbed to intraperitoneal infection with HSV-1. $TLR2^{-/-}$ mice displayed decreased systemic levels of pro-inflammatory cytokines and fewer inflammatory lesions in the brain, despite slightly increased brain HSV-1 titers [25], suggesting that TLR2 primarily mediates immunopathology during acute HSV-1 infection. Intriguingly, specific polymorphisms in intron 1 of human *TLR2* are associated with increased HSV-2 shedding and lesion frequency over a monitored 60 day period [26], indicating a role during chronic infection. Unfortunately, in what will become a trend in this review, far less is understood about the role of TLRs during chronic HSV infection of animal models.

TLR3$^{-/-}$ mice display increased disease score, including hind limb paralysis, and a significant increase in the viral titers during acute HSV-2 infection. Loss of TLR3 in astrocytes renders these more permissive to HSV-2 replication [27]. Highlighting significance of TLR3, *TLR3* deficiency in humans results in childhood HSV encephalitis [28,29]. The role of the other endosomal TLRs, TLR7 & TLR9, is less defined. Nothing is known about TLR7 during HSV infection. TLR9 restricts acute HSV-1 infection following intranasal infection [30], but has no impact on HSV-1 replication following a footpad route of inoculation [31], indicating a route of inoculation-dependent restriction of acute HSV-1 infection by TLR-9. The role of TLR7 or TLR9 in human HSV infection is not known.

TLRs in gammaherpesvirus infection.

There is a paucity of reports linking TLR polymorphisms in humans to EBV or KSHV-driven disease, thus, TLR-gammaherpesvirus interaction has been defined using the MHV68 model. While expression of TLR2 attenuates acute MHV68 replication in part by increasing type I interferon (IFN) expression [32], TLR3, in contrast to that observed for HSV, is dispensable for the control of acute MHV68 infection [33]. TLR7 expression has no impact on acute MHV68 infection [34], while TLR9 attenuates acute MHV68 infection in the route of infection-dependent manner, similar to that observed for HSV. TLR9 deficiency has no effect on acute MHV68 titers following intranasal inoculation [34,35], however, lack of TLR9 leads to increased MHV68 acute titers following intraperitoneal or intravenous inoculation. Interestingly, a combined deficiency of TLR7 and TLR9 along with the loss of host protein UNC93B, which is required for endosomal TLR signaling, results in significantly higher acute MHV68 titers in several organs.

In the context of chronic infection, loss of TLR9 results in increased MHV68 reactivation and MHV68 DNA copy number [34,35]. Similar to acute infection, while chronic MHV68 infection is well-controlled in TLR7$^{-/-}$ mice, loss of both TLR7 and TLR9 leads to an even greater increase in reactivation and viral copy numbers as compared to TLR9 deficiency alone [34], highlighting non-overlapping functions of TLR7 and TLR9. Interestingly, administration of LPS or CpG to chronically infected mice induces MHV68 reactivation [36], however, the TLR dependence of this phenotype is unknown.

IFI16 and cGAS:

Other relevant viral sensors include interferon-inducible protein 16 (IFI16), which can recognize cytosolic and nuclear DNA [37] and cyclic GMP-AMP synthase (cGAS), which senses cytosolic DNA. Activation of cGAS by cytosolic DNA produces cyclic GMP-AMP (cGAMP) that engages Stimulator of IFN Genes (STING) [38]. Both cGAS and IFI16 engage STING to induce type I IFN expression (Fig. 1).

IFI16 and cGAS in HSV infection.

While well-described in tissue culture, the *in vivo* role of IFI16 during HSV infection remains enigmatic, due to the divergence of human and mouse IFI16 orthologues. Knockdown of mouse orthologue p204 in corneal epithelium led to mild increase in the titers of HSV-1 in the cornea [39] offering some insight into the role of this sensor in the

human infection. Polymorphisms of human *IFI16* or *cGAS* have not yet been associated with HSV- or EBV/KSHV-driven disease in humans.

In contrast to IFI16, the role of cGAS is well defined in mouse models of acute HSV infection. All cGAS$^{-/-}$ mice died within 6 days of HSV-1 infection, accompanied by increased HSV-1 titers in the brain, reduced type I IFN, and severe disease, [40,41]. Intriguingly, the true extent of cGAS anti-HSV-1 activity may be masked by HSV-1 tegument protein, UL37, which deaminates cGAS, rendering it unable to sense dsDNA, [42]. Severely attenuated phenotype of HSV-1 mutant encoding catalytically dead UL37 was completely rescued in cGAS$^{-/-}$ mice, offering an elegant evidence for the physiologically relevant viral-host antagonism [42].

IFI16 and cGAS in gammaherpesvirus infection.

As mentioned in the previous section, nothing is known about the role of IFI16 during gammaherpesvirus infection of an intact host. In contrast and similar to HSV, cGAS attenuates acute MHV68 infection [43]. Interestingly, the role of MHV68 protein orf52, a homologue of KSHV cGAS antagonist [44], has not been resolved *in vivo*. As with alphaherpesvirus infection, the impact of cGAS on chronic gammaherpesvirus infection is unknown.

Inflammasome:

The inflammasome complex is assembled in the cytosol upon sensing of microbial patterns, with subsequent ASC-dependent recruitment and activation of caspase-1 or caspase-11 that mediate cleavage of pro IL-1β and pro IL-18 into their active forms [45] (Fig. 1). Relevant inflammasome associated sensors include AIM2 (cytosolic DNA) and NLRP3 (cytosolic ATP and other motifs).

Inflammasome in HSV infection.

HSV-1 infection of NLRP3$^{-/-}$ mice results in early onset severe disease, with slightly increased viral titers [46]. Loss of AIM2 has no impact on acute HSV-1 infection, an intriguing absence of phenotype which could reflect the efficient antagonism of AIM2 by HSV-1 tegument protein VP22 [47]. The role of inflammasome in chronic HSV infection is less clear, as loss of NLRP3 resulted in greater immunopathology at 15 days post HSV-1 infection [46].

Inflammasome in gammaherpesvirus infection.

Acute MHV68 infection is not affected by combined caspase1/11 deficiency [48] or loss of AIM2[49]. Further, loss of caspase1/11 and, presumably, generation of biologically active IL-1β has no impact on chronic MHV68 infection [48]. Unexpectedly, deficiency of IL-1R1, a receptor engaged by IL-1α and IL-1β, attenuates MHV68 reactivation [50], highlighting the proviral functions of either inflammasome-independent IL-1α or non-canonical processing of IL-1β. While loss of AIM2 has no effect on chronic MHV68 infection, deficiency of NLRP3 or ASC resulted in a slight (less than 2-fold), statistically significant increase in MHV68 genome copy numbers in long-term infected spleens (60 days; [49]), a time point beyond that examined in caspase1/11 deficient mice [48]. Importantly, human

deficiency of XIAP, a multifunctional protein that also suppresses NLRP3 inflammasome [51], results in severe EBV-driven hemophagocytic lymphohistiocytosis [52]. Further, EBV and KSHV attenuate NLRP3 inflammasome activation *in vitro* [53,54], highlighting the importance of additional studies of inflammasome during chronic infection.

Connecting sensors to IFN transcription.

MyD88 and TRIF in HSV infection.

MyD88 and TRIF are important adapter proteins downstream of TLRs and contribute to the induction of type I interferons (IFN) [45] (Fig. 1). Both adapters play a relatively minor role during acute HSV infection in spite of the significant antiviral role of TLR3 during acute HSV infection. Specifically, parameters of acute HSV-1 infection in MyD88$^{-/-}$, TRIF$^{-/-}$, and MyD88$^{-/-}$TRIF$^{-/-}$ mice were either similar to that of control mice [39] or produced a minor (10%) increase in mortality [55]. The role of MyD88 and TRIF in chronic HSV-1 infection is not defined.

MyD88 and TRIF in gammaherpesvirus infection.

Similar to acute HSV infection, TLR adapters MyD88 and TRIF have minimal impact during acute MHV68 infection. While TRIF or MyD88 deficiency did not affect acute MHV68 replication following low dose inoculation [33], a 100-fold higher inoculation dose of MHV68 led to loss of viral control and reduction in type 1 IFN in the lungs of MyD88$^{-/-}$ mice [32].

Intriguingly during chronic infection, MyD88 supports the establishment of MHV68 latency, via promoting MHV68-driven germinal center response and B cell differentiation [33]. Because MyD88 participates in several signaling networks, it is not clear whether the proviral role of this adaptor during chronic MHV68 infection is exclusively due to the TLR signaling pathways.

STING in HSV and gammaherpesvirus infections.

The adapter STING, which is activated by cGAS and IFI16 to induce type I IFN, is profoundly antiviral during acute HSV-1 infection: STING expression ensures host survival, particularly following infection with neuroinvasive McKrae strain, and attenuates viral replication and disease scores [40,41,56,57]. In the context of McKrae HSV-1 infection, STING is required for the upregulation of tetherin, which impedes HSV-1 neuroinvasion [58]. Chronic HSV infection has not been explored in STING$^{-/-}$ mice. In contrast to the critical role of STING during HSV-1 infection, STING deficiency has minimal if any effect on acute MHV68 titers and no measurable effect during chronic infection [49].

Activation of IFN.

Sensing of herpesviruses converges upon activation of the transcription factors NF-κB, IFN regulatory factor (IRF) 3, and IRF7, with subsequent expression of type I IFN and inflammatory cytokines [23]. For example, engagement of STING leads to its relocalization together with TANK- binding kinase 1 (TBK-1) from endoplasmic reticulum to the Golgi

complex where TBK-1 phosphorylates IRF3 and IRF7, leading to the production of type I IFN [45] (Fig. 1).

IRFs in HSV infection.

Of the nine IRFs, IRF3 and IRF7 are the primary mediators of type I IFN expression downstream of multiple viral sensors. Interestingly, while IRF3 expression was dispensable for the control of HSV-1 replication in the cornea, IRF3 played a critical role in limiting HSV-1 spread through the central nervous system (CNS), with increased mortality, HSV-1 titers, and a significant drop in type I IFN expression within the CNS of $IRF3^{-/-}$ mice [55,59,60]. In contrast, IRF7 expression was important for the control of both peripheral and CNS HSV-1 infection. All $IRF7^{-/-}$ mice succumbed to infection accompanied by severe disease and significantly higher viral titers in the serum, cornea, trigeminal ganglia, and CNS when compared to $IRF3^{-/-}$ and control mice [60]. Combined deficiency of IRF-3 and IRF-7 revealed overlapping functions of these transcription factors in the control of HSV-1 infection [60].

Unfortunately, as with many other aspects of the innate immune system, the role of IRF3 and IRF7 is entirely unexplored in chronic HSV infection.

IRFs in gammaherpesvirus infection.

Similar to HSV-1, increased MHV68 acute titers were found in the lungs of $IRF3^{-/-}$ and $IRF7^{-/-}$ mice [61]. Interestingly, another member of the IRF family, IRF1, which is dispensable for expression of type I IFN during MHV68 infection [61,62], also attenuated acute MHV68 replication.

While the roles of IRF3 and IRF7 in chronic MHV68 infection are unknown, global loss of IRF1 showed that IRF1 is critical for the attenuation of chronic MHV68 infection and MHV68- but not LCMV-driven germinal center response [63]. Further, IRF1 protein levels are selectively decreased in EBV positive post transplant lymphoproliferative disease, suggesting that IRF1 may act as a tumor suppressor during EBV lymphomagenesis [63]. Surprisingly, while investigating the cell-type-dependent roles of IRF1, we have recently shown that B cell-intrinsic IRF-1 expression supports the establishment of MHV68 latency and MHV68-driven germinal center response, in part by increasing levels of activated tyrosine phosphatase SHP1, which plays a B cell-intrinsic proviral function during MHV68 infection [64,65]. These exciting results highlight pleiotropic, cell type-dependent roles of IRF1 during chronic gammaherpesvirus infection. Finally, another IRF family member, IRF2, was shown to directly suppress MHV68 latent gene expression [66].

Type I IFN signaling.

The culmination of viral sensing by the innate immune system is the release of type I IFN and its engagement of the type I IFN receptor (IFNAR). Activation of IFNAR leads to the assembly of the STAT1-STAT2-IRF-9 complex and transcription of hundreds of IFN stimulated genes (ISGs), with only a handful of ISGs attenuating replication of any particular virus, based on high throughput screens of antiviral activity [67] (Fig. 1).

IFNAR and STAT1 in HSV infection.

The STAT1-containing complex downstream of IFNAR is critical for the expression of ISGs. *STAT1* deficiency in humans leads to disseminated HSV-1 infection and recurrent encephalitis [68]. Not surprisingly, IFNAR$^{-/-}$ mice manifested increased HSV-1 titers in the cornea and trigeminal ganglia [69,70]. Interestingly, while loss of type II IFN signaling (that also engages STAT1) had no impact on acute HSV-1 titers, combined type I and II IFN signaling deficiency resulted in high mortality and systemic HSV-1 dissemination, indicating that type II IFN signaling is needed for the control of systemic HSV-1 spread in the absence of IFNAR [70]. Similarly, loss of STAT1 led to significantly higher HSV titers, disease scores, and decreased survival [71]. Mice with neuronal-specific STAT1 deficiency rapidly succumbed to HSV-1 corneal infection, indicating that IFN-mediated control of HSV replication in peripheral tissues is not enough to ensure host survival [72].

Due to the critical role of type I IFN signaling during acute infection, the studies of chronic infection are limited to either low inoculum dose that leads to some survivors (for global genetic deficiency) or genetic models of cell type-specific deficiencies. Interestingly, and in contrast to the phenotypes observed during acute HSV-1 infection, mice with neuron-specific STAT1 deficiency had similar levels of latent HSV-1 genomes in the trigeminal ganglia with decreased viral reactivation upon *ex vivo* culture. This unexpected proviral phenotype was attributed to increased neuronal death in the absence of STAT1 [73].

IFNAR and STAT1 in gammaherpesvirus infection.

Similar to acute HSV infection, increasing doses of MHV68 inoculum led to decreased survival of IFNAR$^{-/-}$ mice with corresponding increase in acute viral titers in multiple organs [74,75]. Further, STAT1$^{-/-}$ mice were profoundly susceptible to acute MHV68 infection, as inoculation with 100 PFU of MHV68 resulted in all STAT1$^{-/-}$ mice succumbing to infection, as compared to 50% survival of IFNAR$^{-/-}$ animals under the same conditions [75].

Chronically infected IFNAR$^{-/-}$ mice display a dramatic increase in the levels of persistent MHV68 replication which is not fully controlled in survivors until day 21–28 post infection [66,75]. Importantly, MHV68 reactivation was increased in IFNAR$^{-/-}$ mice at 28 days post infection, and depletion of type I IFN in wild type mice at 21–28 days post infection stimulated MHV68 reactivation [75], indicating an important and sustained role of type I IFN in the suppression of chronic gammaherpesvirus infection. Of interest, MHV68 has evolved STAT1 binding elements in the promoter of RTA, a lytic switch protein; direct, STAT1-mediated repression of RTA and subsequent lytic replication is likely to play a role during both acute and chronic infection [76].

Conclusions and future perspectives.

We hope that, in addition to the literature discussion, this review highlights important issues to be explored in the future studies. Foremost of those is the traditional perception of innate immune responses being limited to the acute phase of virus infection. In contrast, emerging studies of herpesvirus and other chronic virus infections indicate that innate immune factors

continue to exert their influence beyond the initial encounter with the virus. The role of classical innate immune system during chronic herpesvirus infection is an exciting and grossly understudied aspect of the antiviral immune response that calls for much more attention than it has been given. The interaction between classical innate immunity and viruses may be much more nuanced during chronic infection, as evidenced by the observation that neuron-specific deficiency of STAT1 decreases the efficiency of HSV-1 reactivation [73]. This observation and reports of proviral IFN function during chronic LCMV infection [21,22,77] raise an intriguing possibility that herpesviruses may usurp innate immune factors to facilitate aspects of chronic infection and regulate disease development. Finally, innate immune responses have to be fine-tuned in the context of individual virus infection. It is clear that, even for related alpha- and gammaherpesviruses, a unique combination of innate immune mechanisms controls the individual infection, a combination that is further modified by the infectious dose, route of infection, tissue- and cell type-specific immunological milieu, and myriad of other host and viral factors that have not been considered. Thus, one size does not fit all when it comes to predicting the effects of a given innate immune mechanism on acute and chronic virus infection.

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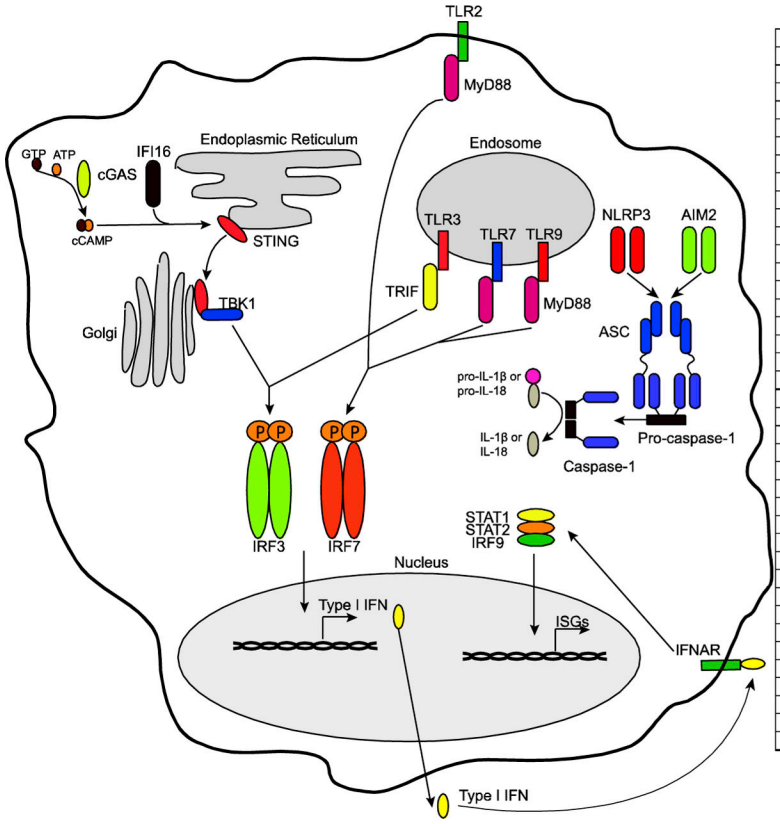

Acute Infection		
Host Factor	**Alphaherpesviruses**	**Gammaherpesviruses**
TLR2	Restricts (H, M)	Restricts
TLR3	Restricts (H, M)	Dispensable
TLR7	Unknown	Restricts (with TLR9)
TLR9	Restricts/Dispensable	Restricts/Dispensable
IFI16	Restricts	Unknown
cGAS	Restricts	Restricts
AIM2	Dispensable	Dispensable
NLRP3	Restricts	Dispensable
MyD88	Dispensable	Restricts (high inoculum)
TRIF	Dispensable	Dispensable
STING	Restricts	Dispensable
Global IRF1	Unknown	Restricts
B cell-intrinsic IRF1	Unknown	Unknown
IRF3	Restricts	Restricts
IRF7	Restricts	Restricts
IFNAR	Restricts	Restricts
Neuronal STAT1	Restricts	Not applicable
STAT1	Restricts (H, M)	Restricts
Chronic Infection		
Host Factor	**Alphaherpesviruses**	**Gammaherpesviruses**
TLR2	Restricts	Unknown
TLR3	Unknown	Unknown
TLR7	Unknown	Restricts (with TLR9)
TLR9	Unknown	Restricts
IFI16	Unknown	Unknown
cGAS	Unknown	Unknown
AIM2	Unknown	Dispensable
NLRP3	Restricts	Restricts
MyD88	Unknown	Promotes
TRIF	Unknown	Dispensable
STING	Unknown	Dispensable
Global IRF1	Unknown	Restricts
B cell-intrinsic IRF1	Unknown	Promotes
IRF3	Unknown	Unknown
IRF7	Unknown	Unknown
IFNAR	Restricts	Restricts
Neuronal STAT1	Promotes	Not applicable
STAT1	Unknown	Restricts

Figure 1. Innate immune mechanisms modifying alpha- and gammaherpesvirus infections of the intact host.

Table represents changes in viral parameters of infection observed in animal models of global or cell type-specific host factor deficiency. H, M indicates that the same viral phenotypes were observed in human genetic deficiencies and animal models.

Table.1

Virus	Rout of infection	Dosages (pfu)	Publication
HSV-1	Corneal	(10^3, 10M, 10^6, 2×10^6)/eye	37, 38, 44, 56, 57, 58, 67, 68
HSV-1	Footpad injection	2×10^6	29
HSV-1	Intracranial	10^2, 10^4, 10^5	45, 55, 57
HSV-1	Intranasal	10^6	28
HSV-1	Intraperitoneal	5×10^7, 10^9	23,40
HSV-1	Intravenous	10^7	39, 53, 54, 55
HSV-2	Intravaginal	2×10^3, 6.7×10^4	25, 37,
MHV68	Intranasal	10^2, 5×10^2, 10^3, 4×10^3, 5×10^4, 10^5, 2×10^5, 4×10^5, 10^2, 2×10^6, 4×10^6	30–33, 46, 47, 60–62, 72, 73
MHV68	Intraperitoneal	5×10^5, 10^6	33,41
MHV68	Intravenous	2×10^6	32