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Chapter

How Human Herpesviruses Subvert Dendritic Cell Biology and Function

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Abstract

In the last decades, a multitude of distinct herpesvirus-mediated immune evasion mechanisms targeting dendritic cell (DC) biology were uncovered. Within this chapter, we summarize the current knowledge how herpesviruses, especially the α-herpesviruses HSV-1, HSV-2, varicella-zoster virus (VZV), and the β-herpesvirus HCMV, shape and exploit the function of myeloid DCs in order to hamper the induction of potent antiviral immune responses. In particular, the main topics covering herpesvirus-mediated immune evasion will involve: (i) the modulation of immature DC (iDC) phenotype, (ii) modulation of iDC apoptosis, (iii) the inhibition of DC maturation, (iv) degradation of the immune-modulatory molecule CD83 in mature DCs (mDCs), (v) interference with the negative regulator of β2 integrin activity, cytohesin-1 interaction partner (CYTIP), (vi) resulting in modulation of adhesion and migration of mDCs, (vii) autophagic degradation of lamins to support productive HSV-1 replication in iDCs, (viii) the release of uninfectious L-particles with immune-modulatory potential from HSV-1-infected mDCs, and (ix) the implications of DC subversion regarding T lymphocyte activation.

Keywords: dendritic cells, HSV-1, HSV-2, VZV, HCMV, CD83, CYTIP, adhesion, migration, lamins, autophagy, H-particles, L-particles, T lymphocyte activation

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1. Introduction

Herpesviridae constitute an extremely successful virus family, evident from the considerable prevalence among the world's population [1]. During co-evolution of herpesviruses with its human host, not only the host's immune system was compelled to mount efficient antiviral defense mechanisms but also the virus has evolved a multitude of sophisticated strategies to dampen those immune responses [2–6]. Thus, herpesviral infections of men represent a tug of war, in which the host's antiviral responses are faced with the virus-mediated immune evasion mechanisms. The probably most intriguing strategy of herpesviral immune subversion is the establishment of latency in immune-privileged niches in the host, leading to lifelong persistent infections accompanied by episodes of viral reactivation [7, 8]. An additional cornerstone contributing to the success of human herpesviruses is the potent infection of a plethora of distinct cell types *in vitro* and *in vivo*, including the manipulation of vital functions of nonimmune as well as immune cells, many of them targeting dendritic cell (DCs) as described below [3, 5, 9–12].

DCs are specialized leukocytes that are highly efficient to antigen specifically activate T lymphocytes, and thus link the innate with the adaptive arm of our immune system [13–16]. In the past four decades, several groups identified DCs as being a rather heterogeneous cell population comprising distinct subsets [17–21]. Those subsets greatly differ in their expression of distinct surface markers, function, anatomical localization as well as migratory capability [22–24]. In general, two distinct DC classes can be defined: myeloid conventional/classical (cDC1—$CD141^+$ and cDC2—$CD1c^+$) and plasmacytoid DCs (pDCs) [25–27]. pDCs play a crucial role during viral infections, since they secrete high amounts of type I interferons upon toll-like receptor (TLR) activation [28–30]. The conventional/classical DCs are specialized in antigen presentation and comprise distinct DC subsets with spatial differences, i.e., blood or lymphoid as well as nonlymphoid tissues. Noteworthy, a third main group among the DC lineage, which arises from monocytes, is called monocyte-derived DCs and reflects inflammatory DCs [31]. Within this chapter, we will mainly focus on monocyte-derived DCs or conventional DCs and their interplay with distinct human herpesviruses.

Another important feature among DCs is that these cells exist in two distinct activation states. In essence, immature DCs (iDCs) reside and patrol in the vast majority of tissues under steady-state conditions, seeking for (nonhost) antigens [32]. Upon antigen uptake and antigen recognition via, e.g., engagement of pathogen recognition receptors, or the perception of "danger" signals, including inflammatory cytokines released from adjacent infected cells, DCs undergo maturation [33]. While sessile iDCs possess a strong phagocytic but low antigen-presenting capacity, mature DCs (mDCs) turn into efficient migrating and antigen-presenting cells (APCs) [32]. DC activation is characterized by an elevated production of type I and III interferons (IFNs) as well as pro-inflammatory cytokines, such as IL-6, TNF-α, or IL-12 [34–37]. Moreover, mDCs are equipped with high surface levels of MHC class I and II molecules [38, 39], and abundantly expose the co-stimulatory molecules CD80, CD86, and CD40, which are important for proper T lymphocyte activation [32]. In this regard, the interaction of DC-expressed CD40 with CD40 ligand (CD40L) expressed on T lymphocytes will result in DC-derived IL-12 production, which is an important Th1 cytokine [28].

In addition, the glycoprotein CD83 is massively expressed on the surface of mDCs, thus serving as reliable marker of mature DCs. More importantly, CD83 is crucial for T lymphocyte development as well as activation, based on its inherent potent immune-modulatory properties [40–44]. Beyond that, migration of mDCs toward T lymphocyte-rich areas in lymphoid organs is facilitated by a switch in the chemokine receptor repertoire during DC activation. In particular, the C–C chemokine receptor 7 (CCR7) is one of the driving forces that chemotactically guides mDCs toward lymphoid-expressed C–C motif chemokine 19 (CCL19) and CCL21. Once arrived in the lymph node, mDCs present their peripheral-acquired antigens to T lymphocytes, which harbor the cognate antigen receptor, to subsequently prime an adaptive immune response [45–50].

Given the pivotal role of DCs during the induction of an adaptive immune response, it is not surprising that herpesviruses efficiently infect DCs and hijack vital DC-inherent functions, such as migration and antigen presentation, to hamper the antiviral host defense. Many of the *in vitro* HSV infection studies, that have been performed, involve the analysis of murine bone marrow-derived DCs (BMDCs). Additionally, human blood monocyte-derived DCs serve as a second widely used *in vitro* model system for the elucidation of herpesviral-mediated modulations of DC biology and function. This is due to the development of appropriate settings for the generation of monocyte-derived DCs in large numbers, for their subsequent highly efficient infection with specific human herpesviruses [51–56]. Concerning *in vitro*

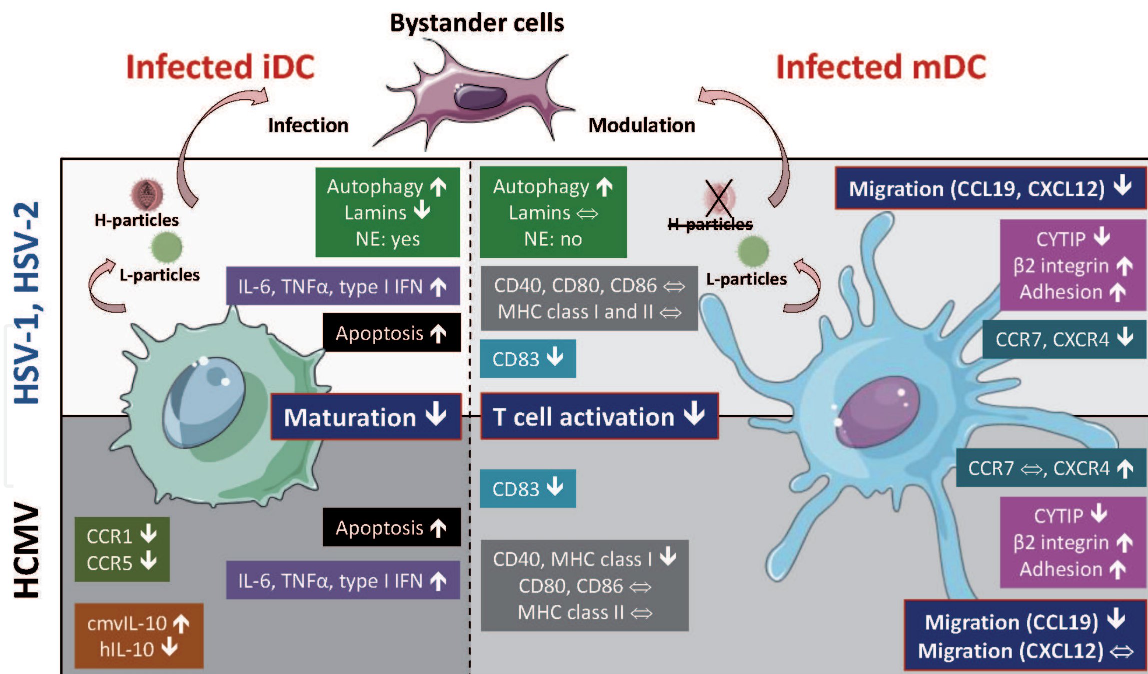

Figure 1.
Schematic summary of HSV- and HCMV-mediated immune evasion strategies targeting DCs. The upper panel depicts immune evasion mechanisms observed for HSV-1- as well as HSV-2-infected iDCs (left panel) and mDCs (right panel). The lower panel illustrates those observed for HCMV-infected iDCs (left panel) and mDCs (right panel). Abbreviations: iDC: immature dendritic cell, mDC: mature dendritic cell, H-particles: heavy (infectious) particles, L-particles: light (noninfectious) particles, NE: nuclear egress, IL-6: interleukin-6; TNFα: tumor necrosis factor α, IFN: interferon, CCR1/CCR5/CCR7: C–C chemokine receptor type 1/type 5/type 7, cmvIL-10: cytomegalovirus-encoded interleukin-10, hIL-10: human cellular IL-10, CCL19: CC-chemokine ligand 19, CXCL12: C-X-C motif chemokine ligand 12, CXCR4: C-X-C motif chemokine receptor 4, CYTIP: cytohesin-1 interacting protein. (Graphics modified from SMART: Servier Medical Art).

HCMV infection studies of DCs, the infection efficiency varies depending on the viral strain used. This is due to the absence versus presence of the genetic locus comprising UL128-UL131, which is crucial for endothelial cell- and leukotropism [57–59].

Within this chapter, we summarize how herpesviruses, especially the α-herpesviruses HSV-1, HSV-2, VZV, and the β-herpesvirus HCMV, shape and exploit the function of classical DCs (summarized in **Figure 1**).

2. Interaction of herpesviruses and immature DCs

2.1 Impediment of iDC biology by herpesviruses

Well-studied examples of functional paralysis of DCs are the herpesviral interference with the expression levels of important surface molecules on iDCs, viability of iDCs, and DC maturation when infecting myeloid iDCs. Regarding the first, complete infection with a clinical isolate of the α-herpesvirus HSV-1 (MC1) asynchronously inhibits the surface expression of CD1a, CD40, CD54 (intercellular adhesion molecule 1, ICAM-1), CD80, and CD86 on iDCs. Apart from this, CD11c, MHC class I and class II surface exposure is unaltered upon HSV-1 MC1 infection of iDCs, indicative of a selective targeting of distinct surface molecules on iDCs [60]. Inconsistent with this, a recombinant disabled infectious single-cycle (DISC)-HSV-1 strain, deleted for glycoprotein H (gH) and thus rendering viral progeny noninfectious, does, however, reduce MHC class I but induce CD86, MHC class II as well as CD1a surface expression on directly infected iDCs, when using a low MOI [61, 62]. Importantly, CD80 and CD83 are unaffected on directly infected iDCs, whereas these molecules are strongly induced on uninfected bystander cells that

additionally show an increase in MHC class I and class II, CD54, and CD86 levels [62]. Moreover, supernatants of HSV-1-infected iDCs are sufficient to trigger partial phenotypic maturation of iDCs, mirrored by an increase in MHC class II and CD86 surface levels [63]. Given the latter two observations, directly HSV-1-infected iDCs might secrete soluble factors that shape the phenotype (and function) of uninfected bystander cells, such as DCs [63].

Apart from HSV-1, HSV-2 reduces CD40, CD80, CD86, and CD83 and slightly hampers MHC class II surface expression on macaque as well as human iDCs [64]. Noteworthy, one study, conducted with murine BMDCs, revealed a serotype-dependent and age-specific regulation of MHC class I and II as well as co-stimulatory molecule expression upon an HSV-1 versus HSV-2 infection of iDCs [65].

Additionally, the β-herpesvirus HCMV significantly alters the surface protein repertoire on iDCs. In particular, HCMV-infected iDCs show reduced CD1a, CD11c, CD13, CD33, CD40, CD54, CD58, CD80, CD83, and MHC class I expression levels, whereas CD86 or MHC class II surface expression is only slightly decreased by HCMV [66, 67]. Beyond this, an HCMV infection of iDCs also dampens their migratory capacity toward CCL3 and CCL5 due to the UL18-dependent internalization of the chemokine receptors CCR1 and CCR5, without affecting CCR7 [68, 69].

Interestingly, and in sharp contrast to the abovementioned herpesviruses, the α-herpesvirus VZV does not disturb the surface expression of important immune molecules on iDCs, such as CD1a, CD40, CD86, MHC class I, and MHC class II [70].

Beyond targeting surface molecule expression on iDCs, a herpesviral infection additionally impacts the expression and release of cytokines and interferons via replication-dependent vs. -independent pathways [71, 72]. Regarding HSV-1, directly infected murine iDCs produce increased amounts of IL-12, which is dependent on viral replication [72–74]. By contrast, IL-12 levels are barely detectable or decrease upon an HSV-1 infection of human iDCs [62, 63, 72]. Moreover, IL-12 production is negatively influenced in the presence of an additional inflammatory stimulus, e.g., LPS or CD40, upon an HSV-1 infection of both murine and human origin [62, 63, 65, 73]. This reduction in IL-12 secretion during DC activation might partially explain the reduced T lymphocyte stimulatory capacity upon infection, since IL-12 is an important cytokine for Th1 responses and highly induced upon DC activation [63, 75]. Moreover, CD40 downregulation on HSV-1-infected iDCs might be involved in the impairment in IL-12 secretion during DC activation [60, 62, 76]. Furthermore, TNFα production by HSV-1-infected iDCs increases strain specifically, which is further dependent on viral replication [77], while IL-6 production is also elevated [72, 73].

Apart from directly infected iDCs, uninfected bystander iDCs, as well as iDCs treated with the supernatant derived from infected cultures, exhibit elevated levels of IL-12, but not IL-6, with or without the presence of the additional inflammatory stimulus LPS, and upregulate CD86 as well as MHC class II expression [62, 63, 74]. Regarding this bystander effect, type I IFNs, which are secreted by infected cells for paracrine perception, are one of the most important mediators [71, 78]. Notably, recombinant IFN-α is sufficient to induce partial maturation and IL-12 secretion by iDCs [78]. Type I interferons (IFN α/β) are cytokines with potent antiviral properties, which are predominantly secreted by pDCs early upon infection, but also by cDCs, and other cell types, during a second wave of innate antiviral response [79–82]. Concerning the latter, type I IFN production upon an HSV-1 infection of iDCs is independent from TLR9 signaling and viral replication, but dependent on viral entry, involving recognition of distinct viral glycoproteins, and very likely includes the sensing of virion-associated DNA [78, 81, 83]. Regarding the aforementioned findings, another study shows that HSV-1 strain KOS isolate-dependently triggers TLR2 activation, while only a minority of these substrains

as well as clinical isolates are capable of doing so [74]. In particular, this TLR2 induction upon an HSV-1 infection results in highly elevated levels of IL-6 as well as IL-12, independent of viral replication. Moreover, UV-inactivated HSV-1 isolates, possessing TLR2-activating property, induce IL-6 and IL-12 production via single and sequential TLR2- as well as TLR9-dependent mechanisms in iDCs. By contrast, replication-competent HSV-1, capable of inducing TLR2 signaling, induces IL-6 and IL-12 expression via MyD88 signaling either through TLR2- or TLR9-dependent mechanisms in iDCs. Moreover, HSV-1 subspecies that do not activate the TLR2 pathway are mostly recognized via TLR9-dependent mechanisms in iDCs. Among others, HSV-1 is recognized via specific mechanisms in iDCs involving two distinct membrane-bound TLRs, i.e., TLR2 and TLR9, whose involvement vary among different HSV-1 isolates and the presence versus absence of viral replication [74]. Also, other pathogen recognition receptors (PRRs), such as DNA sensors, contribute to the recognition of HSV-1, not only in iDCs, and corporately act to induce a potent antiviral response [4, 81, 84, 85].

Notably, the cytosolic DNA sensor DDX41 and its downstream mediator stimulator of interferon genes (STING) play an important role in mediating a type I IFN response upon HSV-1 infection of iDCs [85]. By contrast, elevated levels of pro-inflammatory cytokines and type I IFNs upon HSV-1 infection of iDCs are not triggered via RIG-I-like receptor (RLR)/mitochondrial antiviral signaling protein (MAVS)-dependent mechanisms, which sense pathogen-derived RNA species [71]. These combined observations reveal that iDCs undergo IFN signaling-dependent as well as -independent changes upon an HSV-1 infection [71].

To counteract the antiviral response of iDCs upon viral recognition, HSV-1-encoded virion host shutoff (vhs, UL41) dampens the production of type I IFN as well as TLR-independent release of pro-inflammatory cytokines (TNFα, IL-6, and IL-12) immediately upon infection of human as well as murine iDCs [71, 72, 86]. In particular, HSV-1 vhs inhibits the early replication-independent activation of NFκB, which is an essential transcription factor for IFN expression and consequent IFN signaling, leading to the induction of interferon-stimulated genes (ISGs) [71, 72]. Moreover, ICP27 additionally counteracts NFκB as well as interferon regulatory factor 3 (IRF3) activation to hamper early antiviral immune responses, as at least shown in macrophages [77]. Apart from this, a multitude of distinct viral proteins target specific steps during HSV-1 recognition, such as ICP0; however, most of these data are based on studies using cell types others than DCs [5, 87].

Also, HSV-2 shapes the production of cytokines and IFNs upon infection of iDCs. In particular, HSV-2 strongly and replication-dependently induces the production of IL-6 and TNFα by murine and human iDCs, while the latter also increases independent of viral replication [88–90]. The elevated secretion of TNFα has been connected to support a co-infection with HIV-1 and might act in trans, very likely via promoting the expression of HIV-1 co-receptor CCR5 on bystander cells [88]. Apart from this, IFNβ and IFNγ are specifically upregulated during the incubation of iDCs with UV-inactivated HSV-2, but not with replication-competent HSV-2, showing higher cytokine levels in the human system [88, 90]. Contrasting elevated amounts of IL-12 upon HSV-1 exposure of murine iDCs, HSV-2 does not influence the secretion of this cytokine in the absence of any additional stimulus [90]. However, LPS-induced IL-12 production by murine iDCs is also hampered upon exposure to HSV-2 or UV-inactivated HSV-2 virions, reminiscent of HSV-1 [65].

Among the β-*Herpesvirinae*, also HCMV modulates cytokine expression of iDCs upon infection. During early responses, HCMV triggers the production of the pro-inflammatory cytokines IL-6 and TNFα, chemokines, such as CCL5, CXCL10, and CXCL11, as well as the TLR3-independent production of type I IFN by infected iDCs [67, 91–93]. Consistent with the HSV-mediated suppression of

IL-12 production in the presence of LPS or CD40L by iDCs, also HCMV hampers the induction of IL-12 during DC activation [67, 92]. In addition, HCMV encodes a multitude of chemokines/cytokines and chemokine/cytokine receptors itself, thereby hijacking the host's immune responses [94, 95]. One of the best-characterized viral encoded chemokines, which has been implicated in the modulation of DC biology, is cmvIL-10 that shares functional analogy with its human IL-10 homolog [96]. Notably, HCMV-infected iDCs show a decreased production of cellular IL-10, which is an important anti-inflammatory immune dampening cytokine [91, 97]. Noteworthy, the expression of cmvIL-10 increases during the course of infection and, apart from influencing DC maturation (see also Section 2.3), it inhibits the expression of IL-6, IL-12, and TNFα, when iDCs are exposed to cmvIL-10-containing supernatants, derived from HCMV AD169-infected fibroblasts [98].

2.2 Herpesviruses modulate cell survival of iDCs

Another functional impairment of iDC biology is the enhanced apoptosis observed in HSV-1-, HSV-2-, and HCMV-infected iDCs [60, 63, 65, 90, 99, 100]. Concerning HSV-1, upon an initial anti-apoptotic phase, which is most likely important for viral replication, infected iDCs show a subsequent early increase in apoptosis concomitant with higher caspase-3 activity, which is dependent on viral gene expression [60, 63, 99, 101]. Mechanistically, HSV-1 triggers a strong decline in the cellular FLICE-inhibitory protein (c-FLIP) expression, a pro-survival protein, in a cell type-independent manner, which strongly correlates with reduced cell survival of iDCs [102]. However, differential regulation of apoptosis in iDCs versus epithelial cells, whereas in the latter, viral ICP27 plays a dominant role to prevent premature cell death [103, 104], is further associated with lower levels of anti-apoptotic latency-associated transcript (LAT) sequences in iDCs [102, 105]. Since LATs are able to block caspase-8-triggered apoptosis and can partially compensate for c-FLIP downmodulation, lower LAT abundancies in iDCs are insufficient to counterbalance HSV-1-induced apoptosis in iDCs [106, 107]. Given the temporal and cell type-dependent regulation of apoptosis, HSV-1 adopts its anti-apoptotic factors to ensure efficient viral replication in, e.g., epithelial cells, by inhibiting apoptosis, and simultaneously avoid DC-mediated antigen presentation, by promoting premature cell death of these cells.

Consistent with HSV-1, also HSV-2 strongly induces apoptosis of infected and bystander iDCs, while it is not fully clear whether viral gene expression plays an essential role during this process [64, 65, 90, 99]. In particular, HSV-2 mediates an increase in caspase-3 activity, transient induction in caspase-8 protein levels, and decrease in c-FLIP expression, which is accelerated in comparison to HSV-1 [90, 99, 102]. While HSV-1 and HSV-2 seem to dampen the presentation of viral antigens by infected iDCs via induction of premature cell death, uninfected bystander DCs are capable of cross-presenting engulfed antigens derived from apoptotic cells and to stimulate $CD8^+$ T lymphocytes (further discussed in Section 4).

Apart from HSVs, also the β-herpesvirus HCMV induces iDC apoptosis and/or necrosis early upon infection, which triggers maturation of uninfected bystander iDCs [100]. Regarding HCMV-associated apoptosis in iDCs, a viral-encoded IL-10 homolog (cmvIL-10) mediates the downregulation of c-FLIP expression upon LPS stimulation of iDCs [108]. However, cmvIL-10-triggered apoptosis is absent in unstimulated iDC cultures [109].

In sharp contrast, VZV-infected iDCs do not undergo apoptosis, suggesting that VZV benefits from viable directly infected iDCs for virus dissemination and persistence [70, 110]. In this regard, VZV selectively downregulates Fas on the surface of infected iDCs and mDCs, very likely to inhibit apoptosis of these cells [111].

2.3 Perturbation of DC maturation during herpesviral infections

Apart from directly influencing the phenotype and viability of iDCs, herpesviruses additionally evolved mechanisms to suppress DC maturation upon recognition of the virus, since this step is associated with the switch into an antigen-presenting phenotype, for efficient priming of adaptive (antiviral) immune responses. Regarding this, HSV-1 blocks the expression of important molecules, such as CD80, CD83, CD86, MHC class II, CCR7, and CXCR4, in directly infected DCs in the absence or presence of additional stimuli, i.e., LPS or pro-inflammatory cytokines [62, 73, 86, 112, 113]. Thus, HSV-1-infected iDCs are hampered in their maturation capacity and therefore unable to efficiently stimulate T lymphocytes [62, 113]. Two HSV-1-encoded proteins are known so far to be involved in the inhibition of DC maturation, i.e., the viral encoded virulence factor ICP34.5 and vhs [72, 73, 86, 113, 114].

Regarding the first, ICP34.5 is essential and sufficient to partially perturb LPS-induced DC maturation via blocking IFN-α/β secretion *in vitro* as well as *in vivo* [113]. Noteworthy, the N-terminal domain of ICP34.5 interacts with and suppresses TANK-binding kinase 1 (TBK1) to block IRF3 phosphorylation and ultimately IFN and IFN-stimulated gene induction [114, 115]. Apart from this, ICP34.5 additionally targets the IκB kinase complex to potently abrogate NFκB activation in DCs upon TLR4 stimulation. Particularly, ICP34.5 recruits protein phosphatase 1 (PP1) to dephosphorylate IκB kinase in order to tightly control NFκB activation during an HSV-1 infection of DCs [73]. Notably, inhibiting DC activation by HSV-1 ICP34.5 sufficiently promotes viral replication in a murine corneal infection model [113]. Furthermore, due to its attenuated replication efficiency and its incapability to inhibit DC maturation, an engineered HSV-1 ICP34.5 mutant induces protective immunity in a DC-dependent way upon lethal challenge in mice and thus constitutes a promising vaccination candidate [114].

In contrast to the ICP34.5-mediated inhibition of TLR-dependent DC activation, the tegument-associated viral protein vhs suppresses TLR-independent pathways that induce DC maturation upon viral recognition [72, 86]. Concerning its involvement in suppressing DC maturation, vhs exerts its inhibitory function by targeting replication-dependent and -independent cellular responses, the latter involving the blockade of NFκB activation [71, 72]. Vhs is a ribonuclease that degrades viral as well as cellular mRNAs upon infection and is thus implicated in interfering with a variety of distinct pathways [116, 117]. Since tegument proteins are directly released into the infected cell, vhs might immediately suppress DC activation prior to ICP34.5. Also, HSV-1 vhs mutant strains might possess a promising potential for vaccine development, as these strains are highly attenuated *in vivo* [118–121].

HSV-1 is only one example among *Herpesviridae* that potently blocks activation of DCs upon infection, since also its family member HSV-2 aims to inhibit DC maturation [90, 112]. Similar to HSV-1, HSV-2 suppresses the activation of DCs in directly infected cells, but not in their uninfected counterparts [90]. However, the precise underlying mechanisms are yet undefined.

Also, VZV has evolved strategies to avoid the activation-driven upregulation of functionally important surface molecules on DCs upon infection [70]. In essence, VZV interferes with the NFκB signaling pathway that strongly regulates the expression levels of maturation-associated proteins in DCs. While the upstream receptors for NFκB signal perception remain unaffected, both NFκB subunits p50 and p65 are trapped in the cytoplasm of VZV-infected DCs to avoid signaling via this pathway. Moreover, the E3 ubiquitin ligase domain of ORF61 seems to inhibit IκBα degradation in DCs, as demonstrated in a TNFα-stimulated NFκB reporter assay in HEK293FT cells [122].

Notably, also the β-herpesvirus HCMV potently blocks maturation of DCs upon an inflammatory stimulus [66, 67]. Particularly, the viral encoded IL-10 homolog (cmvIL-10; UL111a) does not only induce apoptosis of iDCs or the surface exposure of DC-SIGN to promote HCMV infection but also negatively affects DC maturation via IL-10 receptor perception [98, 108, 123]. Upon cmvIL-10 stimulation of iDCs, the IL-10 signaling pathway is induced, reflected by significant activation of STAT3, an intrinsic key factor implicated in the control of DC maturation [108, 124]. Thus, cmvIL-10 functionally resembles the human IL-10 homolog and thus dampens DC-induced antiviral immune responses.

Given the distinct regulation of surface proteins, implicated in immune activation, as well as the inhibition of DC activation, it seems reasonable to assume that different herpesviral species evolved specific and independent strategies to hijack DC biology and function to support efficient replication and favor the establishment of latency.

2.4 HSV-1 manipulates autophagy in a cell type-dependent manner

Macroautophagy (henceforth autophagy) is a conserved cellular machinery that delivers intracellular constituents, such as proteins or whole cellular organelles, to lysosomal digestion, both under homeostatic or stress-related conditions. In essence, autophagy induction, upon, e.g., starvation or stress-related stimuli, provides a source of amino acids from degraded proteins for de novo protein biosynthesis. Furthermore, autophagy is also important for antigen presentation, since it represents an additional route to process cytoplasmic and nuclear antigens, e.g., during viral infections, for MHC class II-mediated presentation. Moreover, autophagy is also involved in cross-presentation of exogenous antigens via MHC class I molecules [125–127]. Thus, autophagic degradation plays an important role during antiviral defense mechanisms in infected cells. Apart from classical autophagy, a process called xenophagy is characterized by the specific autophagic sequestration of foreign pathogen-derived contents, such as whole viral particles, to limit viral replication [128–130]. However, this chapter focuses on classical autophagy as well as its modulation during herpesviral infections of DCs.

Mechanistically, mammalian autophagy involves the coordinated interplay of different autophagy-related proteins (ATG) [131, 132]. During initiation of the phagophore, i.e., the initial autophagosome membrane, a complex containing UNC-51-like kinase 1 (ULK1), focal adhesion kinase family interacting protein of 200 kDa (FIP200), ATG13, and ATG101 is formed. Subsequently, phagophore nucleation involves the activation of the PI3KC3 complex I, which among others includes Beclin 1 or class III phosphatidylinositol 3-kinase (PI3K), and a ubiquitin-like conjugation system consisting of different ATG proteins. The expansion of the autophagophore is among others characterized by lipidation of microtubule-associated protein light chain 3 (LC3)-I. In particular, the attachment of phosphatidyl-ethanolamine (PE) to LC3B-I generates LC3B-II, which is inserted into the nascent autophagosomal membrane. Thus, the LC3B-I to LC3B-II conversion indicates autophagy induction, based on the increased presence of mature autophagosomes. The final steps are the fusion of mature autophagosomes with lysosomes, and the subsequent degradation of the resulting autophagolysosomes including their cargo, by, e.g., hydrolysis [125, 133].

It is well established that autophagy is triggered in various cell types upon a herpesviral infection [134]. As a viral countermeasure, HSV-1 evolved strategies to manipulate autophagy, however, in a cell type- and infection stage-dependent way. As such, HSV-1 induces autophagy very early upon infection [135], whereas the viral encoded protein ICP34.5, classified as leaky late gene product, subsequently

suppresses autophagy via targeting Beclin 1 or dephosphorylating eIF2α, while US11, a late gene, inhibits protein kinase R (PKR) to block eIF2α phosphorylation, in, e.g., fibroblasts or neurons [136–140]. In this regard, PKR and eIF2α are two key factors, in, e.g., fibroblasts, that participate during the induction of autophagy upon an HSV-1 infection [141, 142].

Apart from this, the interplay between HSV-1 and autophagy in myeloid antigen-presenting cells, such as DCs, underlies a different regulation. Very interestingly, induction of autophagy in HSV-1-infected murine DCs follows a PKR/eIF2α-independent mechanism, which is not counteracted by ICP34.5. Particularly, in infected murine BMDCs HSV-1, genomic DNA is sensed via a STING-dependent pathway, but independent of viral replication and leads to the transient induction of autophagy [143]. Beyond this, in the context of an HSV-1 infection of murine BMDCs or a related cell line, i.e., DC2.4, ICP34.5 does not block autophagy induction, but rather blocks the maturation of autophagosomes, and in turn autophagic flux. This ICP34.5-dependent mechanism suppresses the autophagy-dependent processing of viral antigens for presentation via the MHC class I as well as class II pathway [144, 145]. More precisely, HSV-1 ICP34.5-encoded Beclin 1-binding domain is responsible for the aberrant autophagosome maturation and thus subversion of $CD4^+$ T cell stimulation in murine DCs [145].

2.5 HSV-1 exploits cellular autophagy in infected human monocyte-derived iDCs

Noteworthy, one interesting example of how herpesviruses hijack cellular autophagy to promote viral replication, i.e., nuclear egress, comes from the interplay of HSV-1 with human monocyte-derived DCs [146]. In general, after generation of nuclear progeny capsids, these viral structures have to cross the nuclear membrane [147]. However, during nuclear egress, the nuclear lamina, which is a dense meshwork inside the nucleus, represents the main barrier for nucleocapsids to get access to the inner nuclear membrane. Lamins and other membrane-associated proteins are the main constituents of the nuclear lamina. Lamins are a group of type V intermediate filament proteins and are grouped into types A, B, and C. While lamin B connects the nuclear lamina with the inner nuclear membrane, lamin A/C—products of alternative splicing—supports the stiffness of the nuclear envelope [148]. In proliferating cells, such as fibroblasts, the nuclear lamina undergoes reversible disassembly during mitosis or during the nuclear export of large messenger ribonucleoprotein (mRNP) complexes. Mechanistically, lamina disassembly is initiated by site-specific phosphorylation of lamin A/C [149–151]. During co-evolution, HSV-1 has evolved a nuclear egress complex (NEC), including viral protein kinases as well as cellular effectors, such as Pin1, to mediate a similar phosphorylation-triggered destabilization of the nuclear lamina and budding of the capsid at the nuclear envelope, a process reminiscent of the nuclear export of large mRNPs [150, 152]. This process is triggered in permissive proliferating cells, such as HFF or Vero cells, in which an HSV-1 infection results in the release of considerable amounts of HSV-1 virions [153].

In sharp contrast, human monocyte-derived mDCs only barely release infectious progeny virus into the supernatant [154], despite the efficient release of significant amounts of noninfectious light (L-) particles void of the capsid [155], further discussed in Section 3.3. By contrast, iDCs promote complete replication of HSV-1, with the final release of infectious heavy- (H-) particles into the supernatant. Notably, the nuclear egress of HSV-1 capsids in iDCs is facilitated by autophagy-dependent lamin degradation [146] and is thus fundamentally different from other cell types, such as fibroblasts. Furthermore, the loss of lamin protein expression is dependent

on viral replication, but independent from viral-encoded vhs in infected iDCs. By contrast, autophagic degradation in mDCs is hampered based on an intrinsic inhibition. In essence, elevated kinesin family member 1 B (KIF1B) and KIF2A expression levels block the fusion of autophagosomes with lysosomes, which is an essential step during autophagic degradation, and thus inhibit the nuclear egress of viral capsids due to stable lamin expression. Apart from this, HSV-1 ICP34.5 is not involved in the differential regulation of autophagic turnover in human monocyte-derived iDCs versus mDCs and does not interfere with lamin degradation [146].

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3. Herpesviruses and mature DCs

Upon DC activation, these vital immune cells undergo a phenotypic and functional switch, and thus become equipped with several functionally important molecules. Among others, molecules for (i) antigen presentation, i.e., MHC class I and II molecules, (ii) co-stimulation as well as modulation of T cell stimulation, e.g., CD40, CD80, CD83, CD86, or (iii) adhesion and migration, e.g., CCR7, CXCR4, and cytohesin-1 interaction partner (CYTIP), are highly expressed by mDCs [14, 44, 156]. However, herpesviruses aim to avoid potent induction of adaptive antiviral immune responses and thus aim to alter the expression of several of these proteins.

In essence, HSV interfere with CD83, CCR7, CXCR4, and CYTIP protein expression in mDCs [112, 157–159]. By contrast, CD40, CD80, CD86, and MHC class I as well as class II expression is mostly unaltered upon an HSV infection of mDCs [112, 154, 157]. Noteworthy, HSV-1-mediated MHC class I as well as class II evasion, however, occurs in distinct cell types others than APCs; however, this will not be further discussed within this chapter [160–163].

Regarding VZV, infected mDCs show decreased levels of CD80, CD83, CD86, and MHC class I surface expression, whereas the abundance of MHC class II surface molecules is not affected [164]. Among the β-*Herpesvirinae*, HCMV strongly hampers CD40, CD83, and MHC class I surface expression on mDCs, while only slightly affecting, if at all, CD80, CD86, or MHC class II expression, or leaving other important molecules, such as CCR7, unaffected [12, 66, 165, 166].

In the following sections, we will highlight the functional consequences of a herpesviral infection of mDC regarding the CD83 protein expression, mDC adhesion as well as migration.

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3.1 Modulation of CD83 expression in mDCs

Intensive research has proven the vital role of the glycoprotein CD83 during the development of the mammalian immune system as well as during the priming and controlling of immune responses. In this regard, several *in vitro* and *in vivo* studies revealed the immune-modulatory potential of the two known CD83 isoforms, i.e., the membrane-bound and soluble CD83 (sCD83). Particularly, the membrane-bound form of CD83 is pivotal for the thymic $CD4^+$ T lymphocyte selection, via stabilizing MHC class II surface expression on thymic epithelial cells, and essential to suppress overshooting immune responses during the development or resolution of autoimmune disorders [42, 167–169]. Apart from this, sCD83 possesses an interesting therapeutic potential in order to prevent/resolve autoimmune disorders and to inhibit transplant rejection, which is mediated via the induction of regulatory mechanisms including indoleamine 2,3-dioxygenase (IDO)-induced regulatory T lymphocytes [170–173]. Considering this, it is not surprising that herpesviruses target CD83 to combat the induction of an antiviral immune response.

One well-known example regarding the modulation of CD83 protein expression in infected mDCs is mediated by the α-herpesvirus HSV-1. Upon infection of mDCs, HSV-1 inhibits both the expression of cell membrane-bound and intracellular CD83 protein [157, 174]. In particular, the HSV-1 encoded immediate-early expressed infected cell protein 0 (ICP0) triggers the proteasome-dependent, but ubiquitin-independent degradation of CD83 in mDCs. The same is true using a HEK293T co-transfection model. Thus, ICP0 cell type-independently mediates CD83 degradation without the need of any additional viral factor [174].

Notably, an HSV-1 infection does not only hamper CD83 expression on directly infected mDCs but also on their uninfected bystander counterparts. This bystander effect is due to the release of uninfectious light (L-) particles which are void of the capsid and thus the viral genome (discussed further in Section 3.3), but contain viral proteins, including ICP0, to modulate the function of adjacent uninfected cells [155, 175]. Noteworthy, apart from the degradation of CD83 in HSV-1-infected mDCs, the infection does not provoke the release of sCD83 molecules, excluding the involvement of CD83 shedding [157]. However, the precise molecular mechanism, how HSV-1 ICP0 triggers CD83 degradation, is still under investigation.

The obvious importance of CD83 during the induction of an antiviral immune response becomes even more evident from the fact that also other α-herpesviruses, i.e., HSV-2 and varicella-zoster virus (VZV) mediate a strong reduction of CD83 protein expression in infected mDCs [112, 164]. Regarding VZV, CD83 is trapped inside discrete cytoplasmic compartments and fails to get transported to the cell surface in infected mDCs [164]. Thus, VZV shapes the surface molecule repertoire of infected mDCs to efficiently spread inside the host and to avoid proper T cell activation [164, 176]. Also, HSV-2 strongly inhibits CD83 surface expression upon infection of mDCs via a proteasome-dependent degradation of CD83, reminiscent of its family member HSV-1 [112]. The nature of VZV- and HSV-2-triggered CD83 modulation is currently unclear and requires further investigations.

Strikingly, apart from CD83 degradation upon human α-herpesvirus infections of mDCs, also the β-herpesvirus human cytomegalovirus (HCMV) significantly hampers CD83 protein expression by mDCs [165, 166]. In this respect, the HCMV-mediated reduction of CD83 expression by mDCs is dependent on the major immediate early protein 2 (IE2)-triggered proteasomal degradation and closely resembles the HSV-1 ICP0-dependent degradation of CD83 [157, 165, 174]. Contrasting findings were reported regarding the sCD83 levels upon an HCMV infection of mDCs. While there is evidence for increased levels of sCD83 in the supernatants of HCMV Bob-U/Bob-B-infected mDC cultures [166], concomitant with an impaired T lymphocyte-stimulatory capacity of these mDCs [166], mDC infection with HCMV TB40E does not increase the release of sCD83 into the supernatant [165].

Since different herpesviral members have independently evolved mechanisms to suppress CD83 expression by mDCs, it is reasonable to assume that CD83 possess a vital role in controlling (persistent) viral infections based on its inherent modulatory role during T lymphocyte activation.

3.2 Herpesviruses differentially modulate the migratory capacity of mDCs

During the initiation of an adaptive antiviral immune response, APCs, such as DCs, must present their acquired antigens to cognate T lymphocytes. To do so, DCs undergo a maturation process and are chemotactically guided toward T lymphocyte-rich areas inside lymph nodes. As a prerequisite for directed migration, mDCs loosen their adhesive forces and express specific chemokine receptors, i.e., CCR7 and CXCR4, which perceive the lymphoid-expressed chemokines

CCL19/CCL21 and CXCL12, respectively [32, 45, 46, 177]. These chemotactic cues, among migration-promoting signals, trigger intracellular signal transduction pathways for cell polarization [178].

Importantly, leukocytes, and especially mDCs, possess a fundamentally different regulation of their three-dimensional migration mode compared to other cell types. In general, while their two-dimensional migration is dependent on adhesive contacts mediated by integrins, their three-dimensional migration follows the "amoeboid" adhesion-independent paradigm [179–183]. Thus, mDCs can switch between their dependence on integrin-mediated adhesive contacts with specific integrin ligands versus the rapid migration along chemokine gradients without the need of preformed integrin ligand tracks. Considering this, integrin-mediated adhesive contacts require a very tight regulation to avoid aberrant adhesion, and thus immobilization, of mDCs in two- as well as three-dimensional environments [182, 184, 185].

Noteworthy, DCs are vital for efficient priming of adaptive anti-HSV-1 immune responses [186, 187]. Thus, HSV-1 evolved sophisticated strategies to hamper the migration of directly infected DCs toward draining lymph nodes, in order to hamper antigen presentation by these cells and delay the immune response. In particular, HSV-1 can efficiently infect DCs not only *in vitro* but also *in vivo* which is mirrored by the presence of HSV-1-infected DCs in primary skin lesions. However, these infected DCs do not migrate to the draining lymph nodes. By contrast, uninfected bystander skin-derived DCs acquire viral antigens and transport them to lymph node resident cells [188–192].

Based on several *in vitro* studies using human monocyte-derived mDCs, HSV-mediated mechanisms have been discovered that aim to suppress mDC migration. Concerning this, HSV-1- or HSV-2-infected mDCs reveal a rapid and very strong inhibition of their migratory capacity toward CCL19 and CXCL12 chemokine gradients, in transwell assays as well as in three-dimensional collagen matrices [112, 158, 159]. One important countermeasure of HSV-1 and also HSV-2 to hamper mDC migration is the downregulation of CCR7 surface expression [112, 158]. Considering that CCR7 orchestrates cell migration along CCL19 chemokine gradients, essential for directed migration toward T lymphocyte-rich zones in draining lymph nodes, downmodulation of this receptor constitutes an important strategy to subvert chemokine-mediated DC migration to draining lymph nodes [47, 48]. Apart from this, HSV-1 additionally hampers CXCR4 protein expression levels on mDCs, to inhibit the perception of CXCL12, a chemokine also expressed in lymphoid organs or the bone marrow [193].

However, since the inhibition of chemokine receptor expression is timely delayed in respect to the inhibited migration of HSV-infected mDCs, an additional mechanism has been suggested. Indeed, HSV-1 and HSV-2 additionally induce the adhesion of infected mDCs via amplifying the activity of β2 integrins, especially lymphocyte function-associated antigen 1 (LFA-1), despite unaffected expression levels of the respective integrin subunits [112, 159]. Compared to other integrin families, β2 integrins are the predominant integrin family expressed on leukocytes and thus possess an exceptional role in regulating mDC adhesion [194–196]. Furthermore, integrin activity and thus the ligand binding status rely on bi-directional regulatory mechanisms, i.e., inside-out and outside-in signaling events [197, 198].

In this section, we will focus on the regulation of β2 integrin activity via inside-out signaling in mDCs. This includes the direct intracellular binding of either of two specific proteins, i.e., talin or cytohesin-1, to the CD18 chain, which is common to all β2 integrins [196, 199–201]. In contrast to talin, cytohesin-1 specifically regulates β2 integrin activity and, upon CD18 binding, promotes the conformational switch into

its ligand-binding high-affinity state, thus mediating cell adhesion [196, 202, 203]. To avoid an overshoot in β2 integrin activity, the CYTIP abrogates the cytohesin-1-mediated β2 integrin activation by regulating its intracellular localization [204]. This becomes evident from an siRNA-mediated approach in which CYTIP expression was ablated in mDCs, which causes the induction of adhesion and inhibition of migration [156, 159]. Considering this inverse regulation of β2 integrin activity by cytohesin-1 and CYTIP, HSV-1 and HSV-2 have evolved an elaborate strategy to potently enhance β2 integrin activity via mediating the rapid proteasome- and ubiquitin-dependent degradation of CYTIP. Functionally, this leads to increased adhesion with subsequently inhibited DC migration and thus very likely to an impaired antiviral T lymphocyte stimulation [112, 159].

Interestingly, and in contrast to the observations for HSV-infected mDCs, VZV, another member among α-*Herpesvirinae*, does not interfere with mDC migration, but hijacks mDCs to successfully disseminate inside the host and to hide from immune recognition. By using mDCs as trojan horses, VZV facilitates its access into lymphoid organs for subsequent infection of T lymphocytes, which are strongly modulated and finally used as ferries for further viral spread, which ultimately facilitates the establishment of latency [70, 176, 205–207].

Beyond this, also the β-herpesvirus HCMV differentially shapes the migration capacity of mDCs. In this respect, HCMV-infected mDCs are inhibited in their CCL19- but not CXCL12-dependent migratory capacity, despite unaltered surface expression of CCR7 but transient induction of CXCR4 surface expression levels [12]. Hence, apart from solely inhibiting the upregulation of CCR7 expression during maturation, as observed for infected iDCs [67], HCMV reduces mDC migration via a distinct mechanism, beyond CCR7-targeting. Accordingly, also HCMV triggers an increased mDC adhesion via the induction of β2 integrin activity, which is mechanistically mediated by the proteasomal degradation of CYTIP, reminiscent of the scenario observed for HSV-infected mDCs [12, 112].

Regarding the upregulation of CXCR4 surface expression, it is known that HCMV encodes a variety of chemokines and chemokine receptor homologs [9, 95], while four of them differentially modulate CXCR4 signaling, i.e., pUS27, pUS28, pUL33, and pUL78. It is likely that HCMV-encoded CXCR4 chemokine receptor homologs regulate CXCR4 expression as well as its signaling axis in a cell type-dependent manner [12, 208, 209]. Since the cognate chemokine CXCL12 is not only expressed in the lymph node but also abundantly produced by osteoblasts in the bone marrow [193], HCMV appears to shape migration of infected mDCs to an ecological niche, the bone marrow, which is highly populated with potential target cells for the establishment of latency [210]. Furthermore, since HCMV can reactivate during differentiation/maturation into mDCs [211], HCMV-positive monocytes as well as mDCs might constitute important vehicles for viral dissemination *in vivo* [66, 212].

Given the differential regulation of mDC migration by distinct herpesviruses, it highlights the importance to hijack this vital function during infection in order to establish latency or to delay the antiviral immune response.

3.3 Abortive replication of HSV-1 in mDCs accompanied by the generation of noninfectious light (L-) particles

As mentioned earlier, HSV-1-infected iDCs release considerable amounts of infectious progeny virus into the culture supernatants [60, 146], whereas HSV-1-infected mDCs do not promote productive replication of HSV-1 [146, 154]. Apart from the successful initiation of the viral tripartite gene expression cascade both in iDCs and mDCs [112, 213], these apparent contrary findings—concerning the

replication outcome—can be explained by the inhibition of HSV-1 nuclear egress in mDCs only [146]. This is based on the scarce autophagic degradation of nuclear lamins in mDCs, which facilitates the nuclear egress of HSV-1 and thus the generation of infectious virions in iDCs.

However, and noteworthy, HSV-1-infected mDCs release significant amounts of light (L-) particles which are void of the capsid and thus noninfectious [155]. Beyond this, L-particles contain virion-associated tegument constituents and the glycoprotein-scattered envelope. Furthermore, these virion-like structures are suggested to share similar maturation steps and might hijack the same cellular entry receptors for attachment and fusion as their infectious counterparts do [175, 214–216]. It has indeed been shown that L-particles can efficiently deliver their viral content toward bystander target cells. Thus, L-particles might foster HSV-1 infectivity, via, e.g., shaping surrounding cells to increase their permissiveness, complementing functional defective virions, or modulating the cellular micro-environment for immune evasion [175, 214, 217, 218]. Regarding the latter, L-particles derived from HSV-1-infected BHK21 cells as well as mDCs are able to decrease CD83 surface expression on mDCs and therefore modulate uninfected adjacent cells during an infection in benefit of the virus. Based on the fact that a whole variety of viral proteins is incorporated into L-particles, such as ICP0 which is sufficient to mediate CD83 downregulation in mDCs, these viral structures transmit important viral components to uninfected bystander cells and modulate their functions [155].

Beyond this, the generation of noninfectious particles is not unique to HSV-1 but also observed for other herpesviruses, such as HSV-2, HCMV ("dense bodies"), or VZV, and also for other distinct viruses, such as hepatitis B virus ("subviral particles"), when infecting different host cell types [214, 219–223]. Thus, herpesvirus-derived noninfectious particles possess one or more important functions to modulate antiviral immune responses and thereby foster viral replication and spread.

4. Conclusions and implications of herpesviral-mediated modulations of DC biology for T lymphocyte activation

The entire spectrum of herpesviral-mediated modulations of DC biology and function aims to delay/hamper the proper activation of T lymphocytes, which would otherwise generate a potent antiviral immune response to eliminate the virus and avoid the establishment of latency. In general, the virally induced inhibition of iDC maturation, suppression of surface expression of co-stimulatory or antigen-presentation molecules on mDCs, interference with cytokine release, or the inhibition of DC migration constitute efficient immune evasion strategies [224, 225]. On the other hand, the host counteracts these strategies and mounts an adaptive antiviral immune response, mirrored by the generation of antigen-specific $CD4^+$ and $CD8^+$ T lymphocytes as well as the production of antibodies [3, 225–227]. Regarding HSV and HCMV infections, DC-dependent cross-presentation of viral antigens represents, among others, a crucial way to induce cytotoxic T lymphocyte (CTL) responses [228–231]. Moreover, there is strong evidence that bystander migratory submucosal and lymph node-resident DCs sequentially (cross-)present HSV-derived antigens in the lymph node. By contrast, directly infected DCs are most likely not involved in the activation of $CD4^+$ and $CD8^+$ T lymphocytes [188, 189, 191, 231–234].

In summary, it is obvious that herpesviruses, including HSV-1, HSV-2, HCMV, and VZV manipulate the function of infected DCs, which are the most potent APCs, for immune evasion and subversion of antiviral immune responses [3, 176, 186].

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Conflict of interest

The authors declare no conflict of interest.

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