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REVIEW

Cytomegalovirus immune evasion of myeloid lineage cells

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Abstract Cytomegalovirus (CMV) evades the immune system in many different ways, allowing the virus to grow and its progeny to spread in the face of an adverse environment. Mounting evidence about the antiviral role of myeloid immune cells has prompted the research of CMV immune evasion mechanisms targeting these cells. Several cells of the myeloid lineage, such as monocytes, dendritic cells and macrophages, play a role in viral control, but are also permissive for CMV and are naturally infected by it. Therefore, CMV evasion of myeloid cells involves mechanisms that qualitatively differ from the evasion of non-CMV-permissive immune cells of the lymphoid lineage. The evasion of myeloid cells includes effects in cis, where the virus modulates the immune signaling pathways within the infected myeloid cell, and those in trans, where the virus affects somatic cells targeted by cytokines released from myeloid cells. This review presents an overview of CMV strategies to modulate and evade the antiviral activity of myeloid cells in cis and in trans.

Keywords Cytomegalovirus · Immune evasion · Myeloid lineage · Monocyte · Macrophage · Dendritic cell

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Introduction

Numerous paradigms of viral immune evasion have been identified by studying cytomegalovirus (CMV). This is not surprising because a major fraction of CMV genes is devoted to the evasion of the immune system (evasins), and CMVs possess the largest known genomes among mammalian viruses. CMVs come in many flavors, from human CMV (HCMV) and other CMVs infecting primate species (rhesus CMV, chimpanzee CMV or gorilla CMV) to CMVs infecting rodents (e.g., rat CMV or mouse CMV–MCMV). All of these are characterized by strict species specificity, because they have coevolved with their host species. Since the immune system exerts a strong selection pressure, only the viruses that withstand this selection have a chance to replicate and disseminate their progeny. Therefore, through millions of years of coevolution, CMVs have familiarized themselves with the immune system of their respective host and developed exquisite immune evasion mechanisms that target and disable the most efficient immune mechanisms, those that typically control the replication and spread of less clever viruses.

A wealth of studies on the numerous mechanisms of CMV immune evasion of T cells and NK cells highlighted their relevance in the control of viral infections. More recently, mounting evidence for a critical role of dendritic cells (DC) and macrophages in immune responses to viral infections [1–3] was substantiated by data that multiple

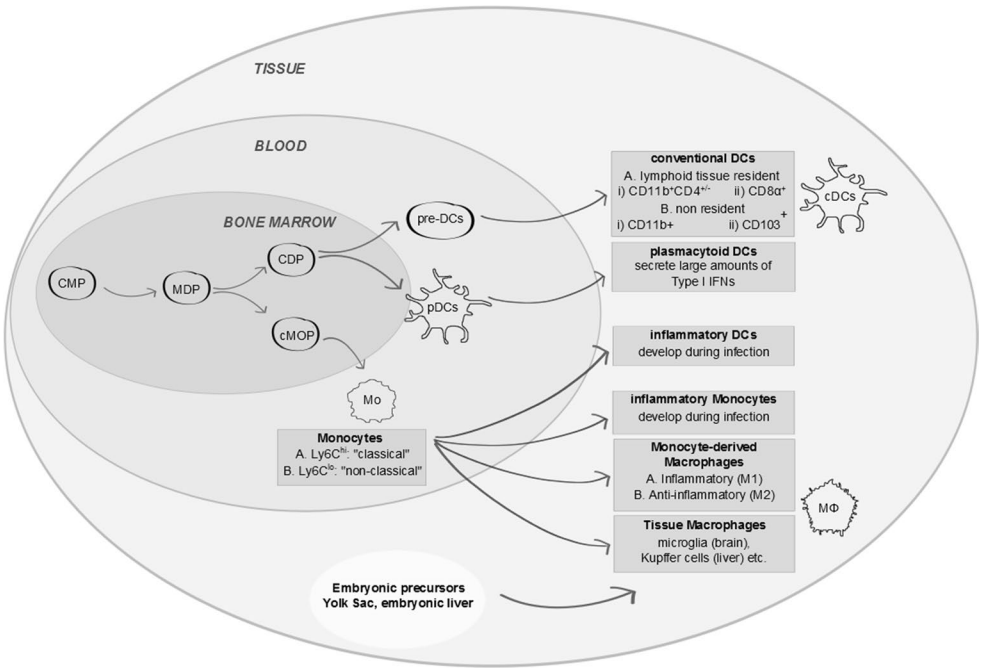

Fig. 1 Ontogenesis of monocytes, dendritic cells and macrophages. In the bone marrow, common myeloid precursors (CMP) develop to monocyte/dendritic cell precursors (MDP) from which common monocyte precursors (cMOP) or common DC progenitors (CDP) emerge. The majority of the different DC subsets originate from the CDP, which develop into the interferon type I producing plasmacytoid DC (pDC) or pre-DC, which mainly circulate in the blood. Conventional DC (cDC) develop from the pre-DC and are found in different tissues, where also pDCs can be present. The cDC can be found in lymphoid tissues expressing CD8a and/or CD4 in addition to CD11b, whereas the nonresident cDCs express CD11b and CD103. On the other hand, cMOP give rise to monocytes, which can be divided into the M1 and M2 subtype depending on the abundance of the marker Ly6C. Monocytes are mainly found in the blood and further develop into different cell types once they enter the tissue where they encounter pathogens. Depending on the environment, the monocytes can develop into highly divergent subtypes, namely inflammatory monocytes, inflammatory DCs, macrophages and tissue-resident macrophages. Moreover, tissue macrophages can originate from embryonic precursor cells that are seeded in specific tissues, such as Kupffer cells in the liver and microglia in the brain

targets of CMV evasins are cytokines or receptors in myeloid immune cells [4, 5]. This notion is particularly exciting if one considers that myeloid DC and macrophages are, besides mast cells ([6, 7], reviewed by [8] in this issue of MMI), permissive for CMV infection [1, 9–11] and play key roles in virus dissemination to distant sites [12, 13] and in virus latency [14, 15]. This review will cover the current knowledge on CMV evasion of antiviral defense mechanisms of several classes of myeloid cells including monocytes, macrophages and DC.

Monocytes, macrophages and DC

Monocytes, macrophages and DC are diverse lineages of cells that are specialized in sensing pathogens and mounting cytokine responses. Additionally, DC can present antigens to cells of the adaptive immune system. Upon pathogen encounter, these cells may get infected, and/or they take up the pathogen or pathogen components and then initiate and orchestrate immune responses.

DC, which are particularly rare and widely distributed, are of hematopoietic origin (Fig. 1). During steady state, they arise from common myeloid precursors (CMP) that give rise to monocyte/DC precursors (MDP), which further differentiate either to common monocyte precursors (cMOP) or to common DC progenitors (CDP) [16–18]. CDP differentiate into plasmacytoid DC (pDC) [19] or pre-DC. The pre-DC differentiate further into conventional DC (cDC), either the lymphoid-resident $CD11b^+CD4^{+/-}$ DC and $CD8\alpha^+$DC or the nonresident $CD11b^+$ and $CD103^+$ DC subsets [20]. Depending on their location, DC exhibit particular functions. Specialized DC subtypes mostly have a short lifespan and are constantly renewed [21]. $CD8\alpha^+Clec9A^+$ DC are particularly efficient in cross-presenting antigen and priming naïve $CD8^+$ T cells in lymphoid organs of mice [22], and the $CD141^+$(BDCA3$^+$) DC subset displays similar functions in human tonsils [23]. In recent efforts to harmonize the DC nomenclature for mouse and man, the chemokine receptor XCR1 has been identified as a cross-species marker for cross-presenting DC subsets [24]. In contrast, the subset of inflammatory DC does not

develop out of the CDP lineage and is normally not present during steady state. They develop from monocytes that infiltrate tissues as a consequence of inflammation or microbial stimulation [25] (Fig. 1).

Monocytes represent approximately 4 and 10 % of the nucleated cells in the blood of mice and humans, respectively. Currently, two major monocyte subsets are distinguished in mice: Ly6C^{hi} (classical) and Ly6C^{low} (nonclassical) cells. Their human counterparts are CD14^{+}CD16^{-} (classical) and CD14^{low}CD16^{+} (nonclassical) [26]. The identity of subsets expressing intermediate or low levels of Ly6C in mice or CD14 in humans is poorly understood. It was speculated that mouse Ly6C^{low} cells and their human CD14^{low}CD16^{+} counterparts may even be terminally differentiated into blood-resident macrophages rather than *bona fide* monocytes [27]. Classical Ly6C^{hi} or nonclassical Ly6C^{lo} monocytes differ in their migratory abilities and their secretion of pro-inflammatory cytokines and are also referred to as inflammatory monocytes (IM) or patrolling monocytes (PM), respectively (reviewed in [28]). Interestingly, the CMV chemokine MCK-2 appears to switch their behavior: It promotes the recruitment of PM to infection sites, upon which the virus infects and hijacks them to facilitate its dissemination to distal organs [29]. On the other hand, the classical Ly6C^{hi} IM are recruited to sites of infection, but do not serve as vehicles for further dissemination. Instead, they appear to regulate and dampen CD8 T cell responses against the virus in a process dependent on iNOS activity [30]. Classical monocytes have long been believed to be the precursors of basically all tissue macrophages [31], but recent evidence indicates that certain tissue macrophage populations develop from embryonic precursors under steady-state conditions (reviewed in [32], also see below).

Upon inflammation, monocytes are massively recruited into the inflamed tissue by chemoattractants and differentiate not only to inflammatory DC but also to monocyte-derived macrophages [33]. The type of immune response that such monocyte-derived cells induce is highly dependent on the local inflammatory environment that they encounter. Monocyte-derived macrophages can either promote inflammation (pro-inflammatory M1 macrophages) or contribute to its resolution (anti-inflammatory M2 macrophages) [34]. The latest evidence suggests that monocyte-derived macrophage subsets represent a spectrum of activated phenotypes rather than stable subpopulations [35]. One such example of inflammatory monocyte-derived cells are TNF and iNOS-producing DC (TIP-DC), which appear upon Listeria infection [36] and presently are regarded as inflammatory monocytes rather than macrophages [37].

Macrophage subsets show a high degree of surface marker expression overlap [38]. Therefore, they are best classified on the basis of specific gene expression profiles, morphology, proliferation, phagocytosis, and antigen presentation [39, 40]. Generally, macrophages regulate inflammation; however, they also can cause pathology [34]. More recently, it has become evident that most macrophage populations are derived from yolk sac or other embryonic precursor cells that seed the different developing tissues before birth. These tissue-resident macrophages are maintained in adulthood by self-renewal [41]. This group of tissue-resident macrophages is highly divergent, and representatives are found in nearly all tissues and are referred to as microglia (brain), alveolar macrophage (lung), Kupffer cell (liver), and others [42].

During the last decades, the functional analysis of prototype DC, monocytes and macrophages in the human system was primarily based on in vitro studies of monocyte-derived DC and macrophages. Nowadays, it is clear that such cells represent the inflammatory variants of these cells and not the organ-resident DC and macrophages found in steady state. Similar caveats apply to bone marrow-derived DC and macrophages that have extensively been studied in the mouse system [43, 44].

Pathogen recognition by myeloid cells

Monocytes, macrophages and DC express various combinations of pattern recognition receptors (PRR) that sense pathogen-associated molecular patterns (PAMP). Two main classes of PRR that play a role in antiviral defenses have been described in mammalian cells: membrane receptors such as Toll-like receptors (TLR) and cytoplasmic sensors including (but not limited to) retinoic acid-inducible gene I (RIG-I)-like receptors (RLR), NOD-like receptors [45] and a growing family of cytosolic DNA sensors [46]. PRR that are known to sense CMV are shown in Fig. 2 and detailed in the text below.

Toll-like receptors

Toll-like receptors (TLR) are type I transmembrane proteins localized at the cell surface or within endosomes [47]. So far, 10 TLR have been identified in humans and 12 in mice. TLR mediate innate signaling in response to a range of PAMPs. Viruses do not have unique structural components enclosing them, such as the bacterial cell wall; thus, sensing of viral infection is mainly dependent on recognition of aberrant nucleic acids or cellular alterations induced by viral infection.

It is well established that MyD88-dependent signaling is crucial to control MCMV infection [3, 48, 49]. In several studies, the endosomally located DNA sensor TLR9 [50] was shown to be the key TLR sensor of MCMV infection [3, 48, 49]. Deficiency in TLR9 in mice leads to

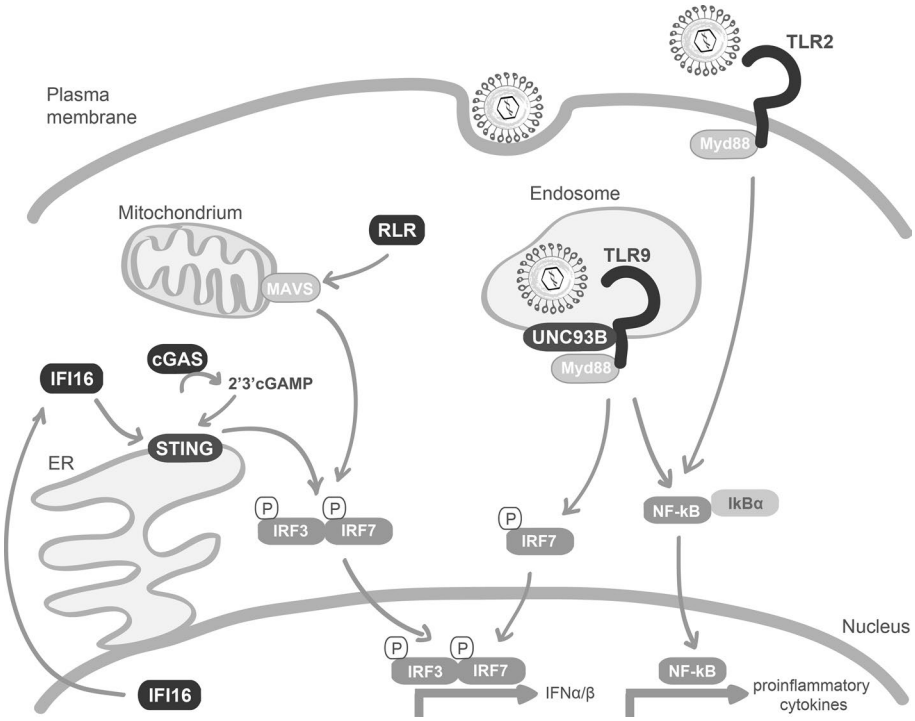

Fig. 2 Pattern recognition receptors sensing CMV in different cellular compartments. Upon ligand recognition, PRR induce distinct signaling pathways leading to activation of the transcription factors interferon regulatory factor (IRF) and NF-kB, which drive expression of proinflammatory cytokines and type I interferons. TLR9 detects CMV DNA within endosomes and is solely responsible for the type I IFN response mounted by pDCs upon infection. TLR2 seems to sense CMV at the cell surface. The ER-resident protein stimulator of interferon genes (STING) plays a crucial role for the antiviral response to CMV infection in cDCs and macrophages, but the role of DNA sensors such as cGAS and IFI16 upstream of STING still needs to be defined. The role of the RLR pathway in the context of CMV infection is not well understood so far

poor control of MCMV and reduced survival, as well as decreased levels of type I interferon (IFN) and IL12p40 in the serum, which negatively impacts NK cell activation [3, 48]. Additionally, DC derived from TLR9-deficient mice respond poorly to MCMV infection by secreting lower levels of type I IFN and pro-inflammatory cytokines. In line with these effects, deficiency in UNC93B, a membrane protein which is required for proper trafficking and functioning of endosomal TLR [51, 52], leads to increased susceptibility to MCMV infection, as well as reduced serum cytokine levels [48]. These effects show parallels to human experimental models, because IFNα secretion following pDC stimulation with HCMV was abolished in the presence of a TLR7/TLR9 inhibitor [53].

The evidence on the role of other TLR in CMV infection is more controversial. TLR3 and TLR7 appear to play only a supportive role for TLR9 in MCMV infection [54, 55], while the HCMV glycoproteins gB and gH were shown to be TLR2 agonists [56]. On the other hand, the latter effect contrasts with in vivo studies that observed no defects in MCMV control in TLR2 KO mice [49]. Furthermore, recent studies in TLR2/TLR4 KO fibroblasts show wild-type levels of NF-κB activation following MCMV infection [57]. It remains unclear whether TLR beyond TLR9 are poorly engaged because they do not encounter PAMPs in CMV infection or rather because CMV actively evades their sensing and/or downstream signaling.

Retinoic acid-inducible gene I-like receptors

The retinoic acid-inducible gene I (RIG-I)-like receptors (RLR) RIG-I (DDX58), MDA5 (IFIH1) and LGP2 (DHX58) sense cytosolic single- and double-stranded RNA and induce the production of proinflammatory cytokines and type I IFN via the adapter protein mitochondrial antiviral signaling (MAVS/Cardif/VISA). So far, there is no direct evidence that RLR play a prominent role for the type I IFN response upon MCMV [58] or HCMV infection [59]. On the other hand, two reports have described countermeasures of HCMV targeting the RLR signaling pathway [60, 61], which suggests that RLR may contribute to the recognition of CMV. This aspect will be detailed in the section on CMV evasion of PRR (see below).

Cytosolic DNA sensors

Sensing and initiation of immune signaling in response to viral infections may also occur independently of TLR or RLR [62] in case that dsDNA is detected by cytosolic DNA sensors. DAI (ZBP1) was the first identified cytosolic DNA sensor [63] and has been shown to recognize HCMV dsDNA leading to phosphorylation of IRF3 and IFNβ production in fibroblasts [59, 64]. Interestingly, DAI is not required in mice to mount adequate inflammatory responses to MCMV, although its absence leads to slightly poorer control of MCMV replication during acute infection [65]. The cyclic GMP-AMP synthase (cGAS) is the major cytosolic DNA sensor in all cell types assayed [66]. cGAS recognizes dsDNA and produces a secondary messenger molecule, cGAMP, which binds and activates the adaptor protein stimulator of interferon genes (STING) to initiate downstream signaling [66, 67]. While STING plays a key role in the induction of type I IFN response against HCMV [68], CMV sensing by cGAS has not been described as of yet. This might be due to the fact that the DNA sensor gamma-interferon-inducible protein 16 (IFI16) [69] was shown to bind HCMV DNA and trigger STING-dependent type I IFN signaling [70]. The evidence on the role of IFI16 in CMV replication is controversial, because some reports have shown that it restricts HCMV expression and replication by interacting with the SP-1 transcription factor and the IR-1 binding element [71, 72], while others have shown that IFI16 enhances CMV replication [73–75]. Either way, cytosolic DNA sensors appear to play an important role in CMV sensing by cDC, because type I IFN induction upon MCMV infection is entirely independent of TLR and RLR in this cell type [58]. On the other hand, cytosolic DNA sensors seem to be irrelevant in pDC, where the induction of type I IFN upon MCMV infection is entirely dependent upon TLR [3, 49, 58].

CMV immune evasion of pattern recognition receptors

The absence of evidence should not be interpreted as the evidence of absence. Therefore, the lack of responses of a defined PRR to CMV infection may mean that the PRR in question does not recognize the virus, but it may also be caused by active viral inhibition of the PRR in question. For instance, there is no evidence that RLR induce type I IFN responses upon HCMV infection [59], but two studies have reported HCMV-induced degradation of RIG-I protein during productive infection in human foreskin fibroblasts [60, 61], and the HCMV-encoded protein pUL37x1 impedes signaling downstream of MAVS when stably expressed in HeLa cells [76]. Therefore, it is tempting to speculate that the lack of RIG-I responses may be a result of active CMV inhibition, yet more evidence is required to understand whether RLR inhibition by CMV genes plays a biologically relevant role in the context of viral infection.

Likewise, the HCMV-encoded UL83 protein has been shown to bind and block oligomerization of the DNA sensor IFI16 in the nucleus, thereby reducing IFN signaling following HCMV infection of fibroblasts [70]. Somewhat in contradiction with this observation, it was reported that UL83 recruits IFI16 to enhance expression from the major IE promoter (MIEP) [73], whereas IFN suppresses MIEP gene expression [77, 78]. Therefore, the effects of UL83 on IFI16 signaling remain controversial.

Weekes et al. [60] have reported progressive downregulation of protein levels of IFI16, IRF3 and NF-kB by quantitative temporal proteomics during HCMV infection, arguing that CMV may encode several genes that interfere with pathogen sensing and signaling downstream of such receptors, yet M45 is the only known MCMV protein which has been identified to modulate signaling downstream of PRR sensing (Fig. 3). M45 is well established as an anti-apoptotic protein [79], but has also been shown to affect NF-κB activation via its interaction with RIP1 and RIP3 [65, 80]. More recently, tegument M45 was shown to activate NF-κB in fibroblasts within the first hours of MCMV infection, a phenotype dependent on its interaction partners NEMO and RIP1 [57]. M45 expressed during the early phase of infection sequesters NEMO and directs it for degradation, leading to inhibition of NF-κB activation and a reduction in the production of proinflammatory cytokines upon TLR stimulation [81].

Inhibition of interferons

One of the earliest responses to CMV infection is the activation of the type I IFN genes IFNα and IFNβ [82]. Type I IFNs make several indispensable contributions to herpesvirus immune control, most notably the induction of cellular resistance to viral replication by inducing gene expression of interferon-stimulated genes (ISGs), which exert broad antiviral effects [83, 84]. Mice defective in type I IFN signaling are highly susceptible to MCMV infection [85, 86]. Similarly, treatment with type I IFN or inhibition of the type I IFN response alters HCMV replication in human fibroblasts [87–89]. Type I IFN gene transcription is initiated in many cell types, which become infected or get in contact with CMV, e.g., fibroblasts, endothelial cells or epithelial cells (reviewed in [90]). However, distinct DC lineages such as pDC and cDC represent the most prominent sources for type I IFN secretion upon MCMV exposure [58]. We will describe the mechanisms by which CMV inhibits the signaling downstream of the IFN receptor in any cell type and those where the virus inhibits IFN responses in the infected myeloid cells.

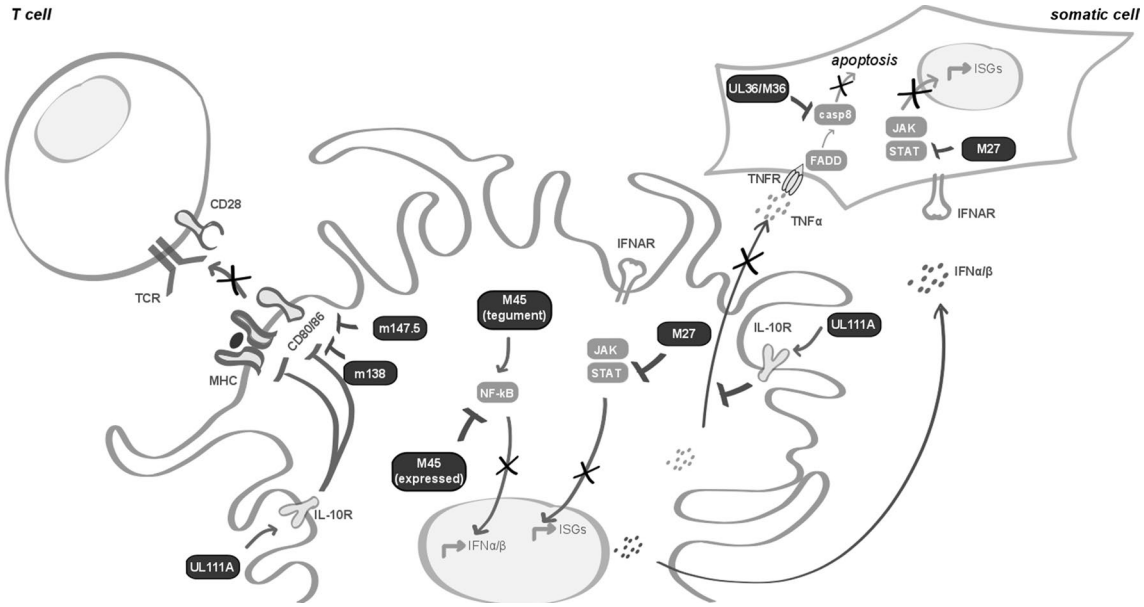

Fig. 3 Cytomegalovirus evasion strategies affecting the function of myeloid cells. Cytomegalovirus proteins expressed in myeloid cells or in somatic target cells are shown as *dark ovals*, and their target genes are indicated in *light gray boxes*. Please note that M45 acts on NFκB signaling both as an agonist or an antagonist, depending on its presence in the viral tegument or upon expression within the cell. Also, please note that M27 acts both in the infected myeloid cell or in their targets, suppressing IFN secretion and its downstream signaling, respectively

CMV inhibition of interferon signaling

Released IFNα and IFNβ molecules bind to a common receptor on the plasma membrane expressed by all cells, the IFNα/β receptor (IFNAR). Like many other cytokine receptors, IFNAR is pre-associated with Janus family tyrosine kinases (JAK) Jak1 and Tyk2 through which it signals by inducing inter- and intramolecular phosphorylation. Phosphorylation of cytoplasmic sites of IFNAR results in docking sites for signal transducer and activator of transcription (STAT) 1 and 2 molecules. Phosphorylated STAT dimers rapidly enter the nucleus and bind to their target DNA sequences within enhancer elements of ISGs to recruit the molecular machinery of gene transcription. IFNAR triggering results in the formation of STAT1/STAT2 heterodimers and STAT1 homodimers, the former recruit IRF9 which leads to the heterotrimeric ISGF3 transcription factor that translocates into the nucleus and induces the expression of ISGs.

The M27 protein of MCMV is the best-characterized CMV-encoded modulator of the signaling cascade downstream of the IFNAR [4, 82, 91–93]. The 79 kDa M27 protein was shown to disrupt IFNAR signaling (Fig. 3). This effect is achieved by recruiting DNA-damage DNA-binding protein 1 (DDB1), an adaptor of the Cul4A-RocA ubiquitin ligase, to STAT2, which targets the latter for proteasomal degradation [92]. While M27 is not required for MCMV replication in unstimulated fibroblasts, it becomes essential in IFN-treated cells, in which DDB1 represents a conditional essential factor for MCMV replication. Accordingly, M27-deficient MCMV exhibited a dramatically attenuated replication phenotype in vivo [4, 94]. In clear contrast to cDC and macrophages, M27 efficiently controls IFNAR signaling in fibroblasts but does not influence type I IFN induction in this cell type [82].

We recently showed that IFNβ is sufficient to repress MCMV transcription at the immediate-early level in endothelial cells and in vivo and that this repression is entirely reversible once IFN is removed [78]. Therefore, IFNAR signaling induces a state that is consistent with the formal definition of viral latency. The suppression of viral replication depended on IFN-mediated induction of ND10-resident proteins, including DAXX, Sp100 and PML [78]. The MCMV gene *ie1* and the HCMV-encoded *pp71* disrupt ND10 bodies, arguing that these functions are critical for CMV evasion of IFN-induced effector genes [95]. In light of this, it is not surprising that viral gene expression is suppressed only if the cells are pretreated with IFNβ prior to infection, before viral genes are expressed. Interestingly, we observed that longer exposure to IFNβ improves the repression of viral gene expression [96] (Fig. 4). Finally, the reversible inhibition of CMV transcription in the presence of IFN prompts us to propose that CMV latency may be understood as a viral evasion mechanism of strong IFN responses.

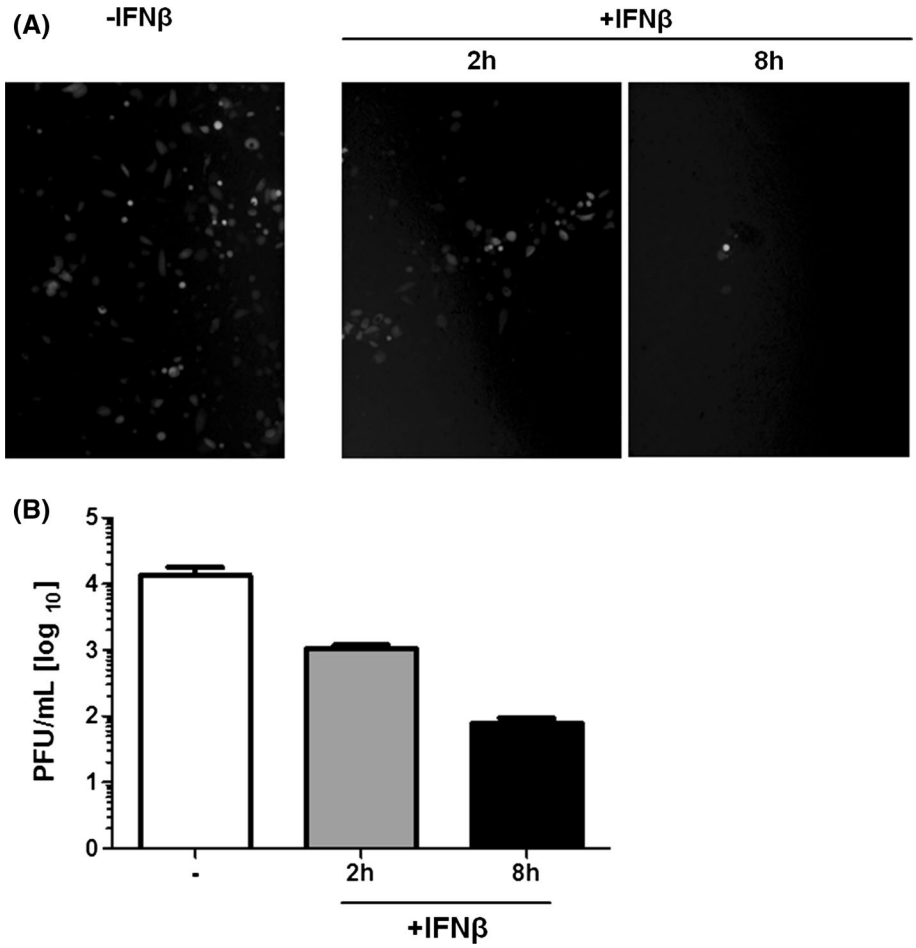

Fig. 4 Sufficient pretreatment time blocks MCMV replication. Liver sinusoidal endothelial cells (LSECs) stimulated with IFNβ (100 U/mL) for 2 or 8 h, or left unstimulated (-IFNβ), were infected (MOI = 0.1) with a reporter MCMV that expresses the enhanced yellow fluorescent protein (EYFP) gene under the control of the ie1/3 promoter [155]. **a** 6 Days post-infection, EYFP expression was evaluated and representative fluorescent images from two independent experiments are shown. **b** Infectious virus titers in supernatants of infected cells at 6 days post-infection. Shown are means + SD from biological triplicates

CMV inhibition of interferon response

We have addressed pathogen sensing in the various cell types that are triggered by CMV to produce antiviral type I IFN responses. We generated pDC, cDC and macrophages from mouse bone marrow, stimulated them with MCMV and (in line with previous reports) observed that a high percentage of cDC and macrophages were infected, whereas pDC were largely resistant [1, 3]. On the other hand, pDC mounted the highest IFN responses followed by cDC and macrophages. UV inactivation of the virus did not affect the magnitude of IFN responses mounted by pDC, whereas the IFN responses of cDC and macrophages were significantly enhanced. These results implied that CMV may actively block the induction of IFN responses in cDC and macrophages, but not in pDC [58]. Since previous studies indicated that the CMV-encoded STAT2 antagonist M27 inhibits IFNAR signaling [4] and that positive feedback reinforces IFN secretion in cDC and macrophages [97], we argued that M27 might inhibit the IFNAR feedback in these cells. To test this hypothesis, we infected these cells with CMV deficient for M27 (CMVΔM27). Interestingly, CMVΔM27 induced similar IFN responses as WT virus in pDC, whereas IFN responses were strongly enhanced in cDC and moderately in macrophages infected with the same virus.

These results indicated that M27 inhibits the IFN induction in cDC very efficiently, whereas additional factors were needed in macrophages. Thus, available data argue that CMV has developed cell type-specific evasion strategies that do not affect IFN responses of pDC and that significantly down-modulate IFN responses of cDC and macrophages [58]. The resistance of pDC to M27 is explained by the fact that pDC are not permissive for MCMV, which means that viral immune evasins are not expressed and cannot dampen the immune response. pDC responding with type I IFN production to CMV might be triggered by apoptotic bodies and exosomes derived from infected cells or by incoming virions that are unable to initiate viral gene expression, but evidence distinguishing between these scenarios is currently lacking. The fact that M27-deficient MCMV as well as inactivated virions induced a much stronger IFNα and IFNβ response in cDC and to a lesser extent in macrophages indicates that MCMV-encoded factors must actively suppress type I IFN synthesis in those cells [58], substantiating earlier observations in

macrophages [82]. Two hypotheses could explain this M27 phenotype: First, M27 could have an additional STAT2-independent function emerging in macrophages and cDC but unapparent in fibroblasts, perhaps related to signaling downstream of the PRR present in the myeloid cells. Alternatively, STAT2 is required for an autocrine IFNAR-dependent feedback loop that potentiates type I IFN production in myeloid cells other than pDC (Fig. 3). Further experiments analyzing cDC and macrophages derived from STAT2-deficient mice will resolve this issue.

Interference of CMV with co-stimulation, cytokine production and adherence of myeloid cells

Conventional DC do not only participate in immediate responses to infection, but also play a central role in connecting innate and adaptive immunity by priming antigen-specific T cells. DC provide three types of signals that activate antiviral T cells. The signal 1 relies on the presentation of antigenic viral peptides by MHC molecules to T cell receptors (TCR) found on CD4 or CD8 T cells. Signal 2 engages the TCR-associated co-receptors by proteins upregulated on the DC surface upon sensing of PAMPs, whereas signal 3 is mediated by secreted cytokines promoting T cell differentiation and proliferation. Besides the well-known inhibition of antigen presentation by MHC molecules, CMVs also block the other two signals, resulting in severe functional impairment of infected DC [10, 98–101]. We observed that MCMV-infected DC are initially activated, but subsequently the co-stimulatory molecules CD80 and CD86 are strongly downregulated [10]. While early in infection DC could stimulate autologous T cells, this capacity was completely lost 2 days post-infection (dpi).

Screening a library of deletion mutants led us to identify an MCMV gene, m147.5, responsible for diminished surface expression of CD86 [5]. Another viral protein, m138, targets the co-stimulatory molecule CD80 [102] (Fig. 3). Co-stimulation via the CD80/CD86-CD28 axis turned out to be important as significantly lower numbers of T cells were detected early after infection in B7-($CD80^{-}CD86^{-}$) and CD28-negative mice, and this was associated with increased virus titers [103, 104]. Moreover, infection of mice with an MCMV mutant lacking the genes m138 and m147.5 induced a stronger CD4 T cell response with lower viral titers in liver and salivary glands [105], suggesting physiologic relevance of these immunomodulatory genes. However, as pointed out in a recent review [106], the interplay between different immune cells in vivo is highly complex, potentially compensating for viral immune modulation. In fact, a strong cellular immune response is mounted in MCMV-infected mice, perfectly able to terminate acute infection, although it cannot prevent latency. We and others investigated therefore how priming of T cells can occur in the presence of functional CMV immune evasins [11, 107–111]. Early after intraperitoneal infection with MCMV, we found no infected $CD8\alpha^{+}$ DC and only a small number of infected $CD8\alpha^{-}$ DC in the spleen [11]. The majority of the infected splenocytes were probably stromal cells [112]. Dalod et al. [1] estimated that less than 5 % of $CD8\alpha^{+}$ DC and less than 1 % of $CD11b^{+}$ DC in the spleen are infected. In view of these data, it was surprising that $CD8\alpha^{+}$ DC turned out to be the DC subset, which stimulated T cell proliferation [11]. In addition, we observed that T cells were preferentially generated against antigens that can be cross-presented but not to antigens that are only directly presented. We concluded that cross-presentation is the dominant mechanism that drives priming of MCMV-specific T cells in acute infection. Consistent results were obtained by colleagues who used different approaches to address this question, e.g., replication-deficient mutants [108] or Batf3 knockout mice which lack cross-presenting $CD8\alpha^{+}$ and $CD107^{+}$ DC [110].

Altogether, there is little doubt that cross-priming does occur in MCMV infection, particularly when abundant viral antigen is present. The question is, however, whether the viral immune evasins prevent direct priming. Nopora et al. [111] confirmed the requirement for $CD8\alpha^{+}$ DC, yet, in CD11c-Rac mice—severely deficient in cross-presentation—the T cell response was not affected, arguing for direct priming. Similar results were recently obtained when T cell immunity to MCMV was studied in mice in which cross-presentation was abrogated by treatment with the TLR9 agonist CpG [113]. Remarkably, the loss of MHC I surface expression by CMV-encoded evasins (reviewed in [114]) is considerably less efficient in macrophages [115, 116] and cDC [99, 117] than in other cell types. Taken together, the evidence argues that direct peptide presentation is largely intact, resulting in efficient T cell effector responses [107, 115, 116] and that interference with T cell priming provides CMV only with a minor advantage during primary infection. Most likely, this allows the virus to establish latent infection at increased levels and thus to improve the chance for subsequent reactivation and transmission, as suggested by the results of Böhm et al. [118].

IL10 is a key anti-inflammatory cytokine that influences the function of various immune cells, including DC [119]. IL10 suppresses the surface expression of MHC II and co-stimulatory molecules on the cell surface of DC and represses inflammatory cytokine responses, thus regulating their immune response [120]. Numerous viruses express IL10 homologs to exploit this effect and repress the immune response [121], and the UL111A gene encodes the viral IL10 homolog (vIL10) of HCMV.

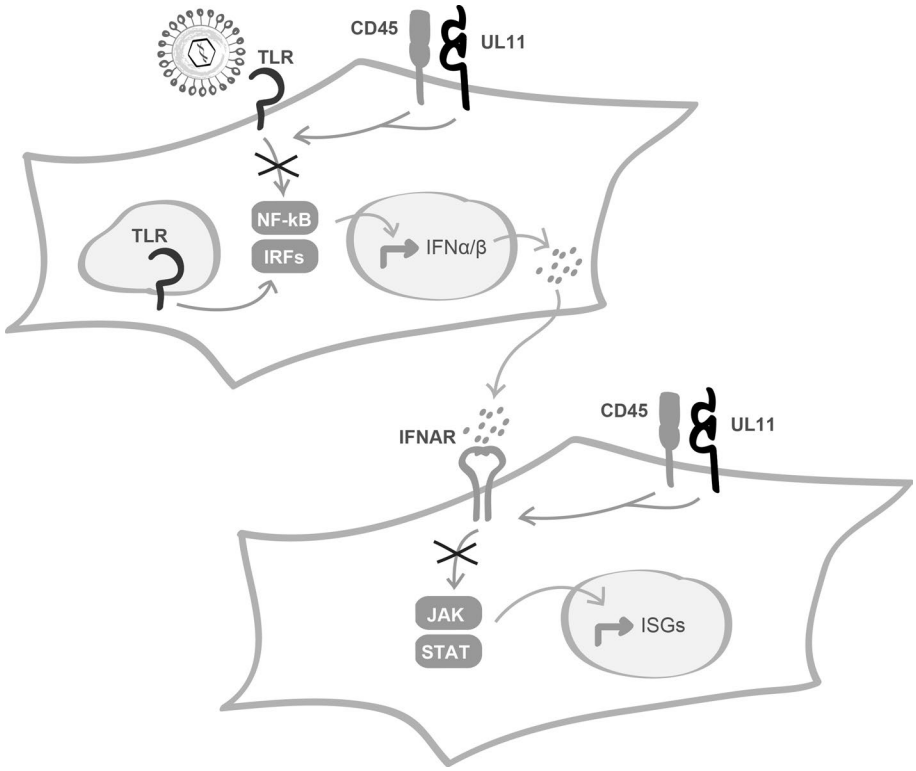

Fig. 5 Putative functions of the HCMV protein UL11 in myeloid cells. Modification of adapter proteins involved in Toll-like receptor signaling by UL11-recruited CD45 can modulate cytokine production. Similarly, CD45 dampens Jak-STAT signaling by dephosphorylating Jak kinases

UL111A is expressed during natural and experimental latency [122, 123], and it has a strong modulatory effect on different immune cells, including DC, monocytes and macrophages [124–130]. It inhibits in vitro maturation of monocytes into cDC [131] by reducing the secretion of pro-inflammatory cytokines [125] and influences the maturation of monocytes into macrophages by favoring the development of M2, rather than M1 macrophages [130]. Exposure of mature cDC to vIL10 induces apoptosis due to the suppression of anti-apoptotic genes such as bcl-2 [132] or c-FLIP$_L$ [126]. In pDC, the vIL10 suppresses the expression of IFNα [133].

Interestingly, vIL10 stimulates the antigen uptake in cDC [126], although it represses antigen presentation. vIL10 consists of two splice variants, cmvIL10 and LAcmvIL10 [134, 135], which exert different functions. While cmvIL10 reduces the expression of co-stimulatory molecules CD80 and CD86 [126, 127] and of pro-inflammatory cytokines [127], the LAcmvIL10 splice variant suppresses MHC II expression. Taken together, these effects decrease the ability of DC to stimulate T cell responses [126].

Recently, we observed that the HCMV protein UL11 interacts with the cellular protein tyrosine phosphatase CD45 [136]. In view of the well-known function of CD45 in T cells [137], we hypothesized that surface-expressed UL11 may protect CMV-infected cells against cytotoxic T lymphocytes (CTL) by trans-inhibition of CD45 signaling in T cells. However, more extensive studies showed that UL11 is weakly expressed on the surface of infected cells and we did not find evidence for UL11-mediated inhibition of T cell responses [138].

Currently, we are analyzing which other CD45 functions may be influenced by UL11 in cis, that is, within the infected cell. In macrophages, CD45 limits the activity of Src kinases, which are induced upon integrin clustering. CD45-negative macrophages initially adhere more strongly to surfaces than normal macrophages, but are not able to sustain adhesion [139, 140]. Such macrophages are less mobile. Dissemination of CMV requires the release of phagocytic cells from infected tissues and later re-attachment in other organs. Therefore, the regulation of the phosphatase activity of CD45 or altering of its spatial distribution could be a mechanism by which UL11 influences this process.

On the other hand, integrin-mediated adhesion of myeloid cells is required for immunologic activation, and CD45 is involved in regulating the cytokine response. Interestingly, strong CD45 activity inhibits the secretion of TNF and IL6 [141], whereas synthesis of type I IFN is promoted [142]. This dichotomy appears to be regulated by CD45, and its differential impact on cytokine production is determined by MyD88-dependent or MyD88-independent signaling downstream of TLR (Fig. 5) [143]. Furthermore, CD45 dampens Jak-STAT signaling downstream of cytokine receptors by dephosphorylating Jak kinases (Fig. 5) [144]. Taken together, by interacting with CD45,

the CMV protein UL11 targets a key protein in several signaling pathways and thus may influence the complex networks involved in pathogen sensing and in the initiation of cytokine responses.

Apoptosis inhibition as viral defense against macrophages in cis and in trans

CMVs have evolved numerous strategies of apoptosis inhibition, targeting both the cell-intrinsic apoptosis and the extrinsic apoptosis pathway, initiated by ligands binding to death receptors on the cell surface, such as the tumor necrosis factor (TNF) receptor 1, FAS and TNF-associated apoptosis-inducing ligand (TRAIL) receptors 1 and 2. Since these strategies have been well covered by previous reviews, we will focus our attention on the effects of death receptor inhibition as a strategy to protect the virus from the antiviral activity of macrophages.

The HCMV gene UL36 and its MCMV counterpart M36 both encode proteins that bind to caspase-8 and thus block death receptor apoptosis at a step where death receptor pathways have converged [145, 146]. Initial reports described this effect as a determinant of viral tropism for macrophages, because the replication of mutants lacking the M36/UL36 gene was not affected in fibroblasts [146, 147], but was severely impaired in macrophages [146, 148]. The growth of M36-deficient mutants (ΔM36 MCMV) could be restored by the pan-caspase inhibitor ZVAD-fmk [148, 149], demonstrating that viral fitness in macrophages depends on the inhibition of caspase signaling by M36/UL36 and not on some unrelated function of these genes. MCMV recombinants expressing a dominant negative variant of the FADD gene ($FADD^{DN}$) instead of M36 (ΔM36 $FADD^{DN}$ MCMV) grow well in macrophage cultures, arguing that the block of death receptor apoptosis in cis, within the virus-infected macrophage, is crucial for viral growth [149].

M36 is highly biologically relevant for MCMV, because ΔM36 MCMV grows poorly in vivo [149, 150] and immunodeficient mice withstand ΔM36 MCMV infection [151]. Viral growth and virulence were restored in ΔM36 $FADD^{DN}$ MCMV infection, showing that the inhibition of death receptor apoptosis is critical for in vivo fitness [149, 151]. This implied that viral replication in macrophages may be a critical bottleneck for MCMV in vivo or that M36 is important for viral replication in cells beyond macrophages, although it was dispensable during in vitro replication in fibroblasts or endothelial cells [146]. This conundrum was resolved by depleting macrophages in vivo, which increased ΔM36 MCMV titers, rather than decreasing the titers of wild-type MCMV [151]. This curious effect was finally explained by coculture of fibroblasts and macrophages, which showed that M36 is important for viral replication in the presence of macrophages, because it protects the virus-infected cells from antiviral cytokines secreted by activated macrophages and in particular from TNF [151]. Therefore, M36 protects the virus-infected cells from macrophages in trans, rather than in cis (Fig. 3), because it inhibits the signaling downstream of the receptors triggered by macrophage-released cytokines [151].

It is important to note, however, that this does not exclude that M36 may also protect the virus-infected cells from other immune cells that induce apoptosis in their target cells, like T cells or NK cells, yet such ideas remain speculative in absence of direct evidence.

IE1 is another viral gene that displays a similar dichotomy in cis and trans protection from myeloid cells. Besides its ability to disrupt the intranuclear defense complex ND10 and thus protect infected cells from myeloid cell-secreted interferon in trans, IE1 was shown to act in the myeloid cells in cis, by reducing the secretion of pro-inflammatory cytokines and in particular TNF [152]. Interestingly, MCMV ΔIE1 has in vitro growth defects in macrophages and not in fibroblasts [152], which fits to the observed in vivo phenotype of this mutant [153]. The IE1-dependent reduction in the pro-inflammatory cytokine TNF has been observed in the in vitro-infected macrophages and in vivo [152]. Since TNF reduces viral titers in vitro [154], but the ablation of TNF or the TNF receptor does not rescue the growth of MCMV ΔIE1, it is feasible that redundant host factors may complement the deficiency in TNF signaling [152].

Synopsis and outlook

In conclusion, cytomegaloviruses have developed numerous strategies of viral immune evasion, blocking the antiviral activity of monocytes, DC and macrophages at multiple checkpoints. The evasion occurs both in cis, within the infected myeloid cell, and in trans, by affecting other cells which are the target of antiviral actions exerted by myeloid cells. The multitude of these evasion strategies is a testament to the relevance of myeloid cells in antiviral control, yet we may have just scratched the surface of viral immune evasion strategies within these cells. Therefore, the study of interactions between CMV and myeloid cells is a highly dynamic research field that is likely to reveal numerous novel and unexpected mechanisms of antiviral activity.

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