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REVIEW

CMV and natural killer cells: shaping the response to vaccination

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Cytomegaloviruses (CMVs) are highly prevalent, persistent human pathogens that not only evade but also shape our immune responses. Natural killer (NK) cells play an important role in the control of CMV and CMVs have in turn developed a plethora of immunoevasion mechanisms targeting NK cells. This complex interplay can leave a long-lasting imprint on the immune system in general and affect responses toward other pathogens and vaccines. This review aims to provide an overview of NK cell biology and development, the manipulation of NK cells by CMVs and the potential impact of these evasion strategies on responses to vaccination.

Keywords: CMV · HCMV · Immune evasion · NK cells · Vaccination

Introduction

Cytomegaloviruses (CMVs) are beta-herpesviruses that establish life-long persistent infection of their hosts. After resolution of acute infection, the virus enters a state of latency during which very few genes are transcribed and no new viral progeny are being generated. Latency is interrupted by occasional reactivations of the virus and expression of genes associated with the lytic virus life-cycle [1]. The success of CMVs as pathogens is a consequence of multiple immunoevasion mechanisms such as downregulation of immunoreceptor ligands or expression of decoy molecules that they employ against every arm of the immune system, including NK cells, which play an important role in the early control of virally infected and malignant cells [2]. Individuals lacking NK cells may suffer from recurrent virus infections, most commonly caused by herpes viruses and papilloma viruses, as well as increased susceptibility to malignant tumors [3–5]. However, in other cases, there is no obvious clinical immunodeficiency associated with the absence of NK cells, indicating redundancy with other immune compartments for distinct genetic deficiencies [6, 7]. As NK cells also regulate other arms of the immune response, their modulation by CMV can have broader consequences for immunity [8]. For instance, the strength of the primary NK cell response against the virus can have a significant impact on the adaptive immune response, although the underlying mechanisms for this are not yet clear and vary according to host and virus genotypes [9, 10]. CMV infection is associated with expansion of effector memory CD8 T cell clones that are sustained for the lifetime of the host and can comprise a significant percentage of the total CD8 T cell population in aging individuals [11]. Multiple lines of evidence in experimental animals and in humans which will be discussed in this review, now indicate that CMV infection leaves a similar long-lasting imprint on NK cell phenotype and function, affecting NK cell responses to other pathogens and to vaccination.

Vaccines facilitate control and eradication of infectious diseases that have plagued humanity for centuries but new infections,

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including those with pandemic potential, continue to emerge. Understanding the different factors that can influence the response to vaccination is crucial for developing effective vaccines against these new threats. Recent evidence suggests that NK cells can contribute to both the induction and the effector phases of vaccination-induced immunity but that this is dependent upon the CMV-infection status of the vaccinated individual. Here we provide an overview of NK cell biology and development, the manipulation of NK cells by CMVs and the potential impact of CMV evasion strategies on responses to vaccination.

NK cell activity depends on a balance of signals from inhibitory and activating receptors

As first-responders among lymphocytes, NK cells must be able to react quickly to a wide variety of stimuli. They do not possess a single specific antigen receptor but, rather, they express multiple receptors and co-receptors that, synergistically, allow them to recognize potential threats and coordinate responses with other immune cells. Whether an NK cell will attack or tolerate a tumor cell or an infected target cell depends on the net balance of signals transduced by this plethora of receptors. If activating signals prevail, NK cell can kill the offending cell by lysis or induction of apoptosis and/or can secrete cytokines and chemokines to activate other arms of the immune system [12].

All NK cell receptors are germline-encoded and are often present as co-receptors on other immune cells. Some of these receptors, as well as their ligands, are stochastically expressed which results in heterogeneity in the number and type of receptors expressed by each NK cell within an individual. For example, it has recently been estimated that individual humans may possess between 6000 and 35 000 phenotypically distinct NK cell subsets [13]. Moreover, in some cases both receptors and their ligands are encoded by polygenic loci with a high degree of polymorphism in the population that leads to differences in susceptibility of hosts to infection [14].

Inhibitory NK cell receptors recognize self-molecules that are expressed on healthy cells and as such are responsible for the prevention of autoimmune responses, especially in the context of inflammation. These receptors also play a role in NK cell education and threshold-setting for future activation (reviewed in [15]). Downregulation of self-molecules can result in absence of inhibitory signals and may lead to "missing-self" recognition [16]. MHC Class I molecules (HLA Class I in humans) are the principal family of self-molecules recognised by inhibitory and activating NK cell receptors [16–18].

In humans, there are three different families of NK cell receptors for MHC I: Leukocyte Ig-like Receptor (LIR-1), CD94/NKG2 receptors and Killer-cell Immunoglobulin-like Receptors (KIRs). LIR-1 is an inhibitory receptor and recognizes all major groups of MHC Class I, although with varying specificities. CD94/NKG2 receptors can be activating (e.g. CD94/NKG2C) or inhibitory (e.g. NKG2A) but recognize only HLA-E, whereas, activating (short-tailed) and inhibitory (long-tailed) KIRs recognize all classical Class I HLA molecules (A, B and C) but in an allele-specific, and in some cases, peptide-selective manner (reviewed in [19]). In addition, there are numerous non-MHC Class I ligands for NK cells including the Clr/Ocil ligands that are recognized by inhibitory NKR-PI C-type lectin receptors [20], nectins and nectin-like molecules that are recognized by the activating receptor DNAM-1, inhibitory TIGIT and CD96 that has so far been reported to display both inhibitory (in mouse models) and activating properties [21–24]. Finally, ligands for activating NK cell receptors can include self and altered-self molecules (including MHC-I-bound peptides); induced self-ligands; foreign, virally encoded molecules; and immune complexes (immunoglobulin Fc binding to CD16) (reviewed in [15, 25]). Whilst such a wide arsenal of inhibitory and activating NK cell receptors might seem redundant, evolution of diverse receptor-mediated pathways is likely to have been driven by pathogens, including cytomegaloviruses, which have developed mechanisms to interfere with nearly all of these pathways.

Cytomegalovirus-encoded immunoevasins drive host evolution

Cytomegalovirus (CMV) immune evasion strategies target multiple mechanisms in every arm of the immune response, permitting successful dissemination through the population and establishment of life-long, persistent infection. Human cytomegalovirus (HCMV) infects a major portion of the world's population [26] however due to strict species specificity it cannot be used to infect experimental animals. A number of closely related animal CMVs exist that are used as models; the best established and most widely used is murine CMV (MCMV) [27] due to the availability of numerous mutant mouse and virus strains. Rhesus CMV is highly related to HCMV and shares many gene families, however it is highly prevalent in both wild and captive rhesus monkeys making it difficult and expensive to maintain seronegative animals. Additionally, rhesus monkeys are much more expensive than mice and there are significantly fewer monkey strains available [28]. Finally, CMVs on their own represent excellent model organisms and tools for manipulating the immune system due to the features discussed below.

CMVs modulate NK cell responses by engaging inhibitory and avoiding activating receptors using multiple and often polyfunctional immunoevasins with wide specificities for numerous, often unrelated, targets. Decoy molecules encoded by CMVs preserve cell surface expression of inhibitory ligands whilst engagement of activating receptors is avoided by downregulation of their ligands. Additionally, CMVs encode Fc receptors that interfere with NK-mediated antibody-dependent cell-mediated cytotoxicity(ADCC) and complement attack [29]. The plethora of HCMV and MCMV NK evasins is summarized in Table 1; details and mechanisms of their action are beyond the scope of this review but can be found elsewhere [9, 29–33].

Table 1. Human and mouse CMVs' NK cell evasion strategies. (M) denotes MCMV's genes

Immunoevasin	Target receptor	Action	References
Regulators of MHC I expression			
UL40	NKG2A, NKG2C, KIRs (?)	Provides peptide for loading and stabilization of HLA-E and UL18	[44, 150, 151]
m04 (M)	inhibitory Ly49s and Ly49P (act)	Escorts some MHC I to the cell surface, enhances interaction with inhibitory NK cell receptors	[152–155]
Virus encoded decoy molecules			
UL18	LIR-1, unknown activating receptor	Inhibition of LIR-1^+ and activation of LIR- NK cells	[156]
m12 (M)	activating and inhibitory NKR-P1	Activation or inhibition of NK cells, depending on the mouse and viral strain.	[47, 50, 157, 158]
m144 (M)	unknown inhibitory receptor	Inhibits NK cell responses	[159]
m157 (M)	Ly49H (act), Ly49C, Ly49I (inhib)	Ligand for inhibitory Ly49I/C and activating Ly49H receptors. Activation of Ly49H^+ cells in C57Bl/6 mouse strains.	[37, 38]
Prevention of activating receptor engagement			
US9	NKG2D	Proteasomal degradation of MICA008	[160]
UL16		Intracellular retention of MICB, ULBP-1, ULBP-2 and ULBP-6. UL16 with bound ligands is further targeted to lysosomal degradation by US20 family members.	[140, 161–163]
US18, US20[a)]		Lysosomal degradation of full length MICA	[164]
US12, US13 and US20		Proteasomal degradation of ULBP-2, MICB and UL16	[140]
miR-UL112		Inhibition of MICB mRNA translation	[165]
UL142		Downregulation of full-length MICA and ULBP3 from the cell surface	[166, 167]
m138 (M)		Downregulation of surface MULT-1, H60a and RAE1-ε	[168, 169]
m145 (M)		Intracellular retention of MULT-1	[170]
m152 (M)		Retention of all Rae isoforms with varying efficacy, H60a and MHC I in the ER.	[171, 172]
m155 (M)		Intracellular retention of H60a	[168, 169, 173, 174]
m154 (M)	2B4	Lysosomal and proteasomal degradation of CD48	[64]
US2[a)]	DNAM-1, CD96	Degradation of Nectin-2 and 6 α-integrins	[175]
UL141	DNAM-1, CD96	Downmodulation of surface expression of PVR and Nectin2	[175–177]
m20.1 (M)	DNAM-1	Downmodulation of surface expression of PVR	[178]
US18, US20	NKp30	Inhibition of surface expression of B7-H6	[140]
pp65	NKp30	Dissociation of ζ-chain from NKp30	[179]
UL141	TRAIL	Retention of Trail-R1 and Trail-R2 in the ER	[180, 181]
m166 (M)	TRAIL	Surface expression inhibition of TRAILR	[182]

[a)]US2 and US12 family members have been shown to target multiple membrane proteins [140, 175] whose relevance to NK cell immune evasion is not yet clear. In addition, deletion of individual US12 family members resulted in changes in NK cell reactivity toward infected cells [175] however the receptors mediating this recognition not yet known.

One of the best-described CMV decoy molecules is the MCMV-encoded MHC I-like molecule, m157. Depending on the virus and mouse strain, m157 can engage inhibitory Ly49I and C receptors [34–36] and the activating Ly49H receptor [37, 38]. It has been proposed that inhibitory Ly49 and KIR receptors predate activating counterparts [39] so it is possible that m157 evolved originally as an inhibitory Ly49 receptor decoy but virus-associated mortality subsequently drove evolution of the activating Ly49H receptor [31]. However, m157 has only a modest effect on NK cell function in vivo and only in C57BL/6-related mouse strains and it has recently been reported that wild mouse populations lacking Ly49H thrive despite the high prevalence of MCMV infection in the wild [40]. Inhibitory Ly49C is usually engaged in cis interactions with MHC I on NK cells. In cis interactions the receptor is interacting with its ligand present on the same cell and not on the target cell (trans interaction). If a receptor is engaged in cis it is not available for exploitation by m157 expressed in trans. It appears that viral evasion has "selected" inhibitory receptors that can ensure proper NK cell education and functionality in the presence of decoys by engaging in cis [35, 36, 41] (for review on cis and trans interactions of cell surface receptors see [42]). Similarly, the HCMV-encoded decoy molecule UL18 engages the inhibitory receptor LIR-1 but the availability of LIR-1 is regulated by its cis interactions with HLA molecules [43].

MHC I molecules are very efficiently downregulated during both HCMV and MCMV infection in an effort to avoid presentation of virally encoded peptides to CD8 T cells. As MHC Class I downregulation could lead to "missing-self" recognition and NK cell-mediated killing of infected cells, CMVs have developed strategies to either selectively downregulate MHC I molecules that are efficient presenters of peptide to CD8 T cells, while sparing those that are better at engaging inhibitory NK cell receptors (HCMV) [32], or return some MHC I to the cell surface (MCMV) [30]. Moreover, HCMV stabilizes the expression of HLA-E, a ligand for the inhibitory CD94/NKG2A receptor, by providing a mimetic-peptide that overcomes inhibition of peptide loading [32, 44]. However, HLA-E in HCMV infected individuals is also recognized by the activating receptor CD94/NKG2C, although the specificity is much lower and co-engagement of NKG2A and NKG2C still results in inhibition of NK cell [45]. Nevertheless, the evolutionary pressure exerted by this recognition is sufficient to select for HCMV strains with polymorphisms that abrogate recognition by NKG2C but not NKG2A [46], at least in transplant patients. The impact of these polymorphisms on the expansion of CD94/NKG2C$^+$ NK cells during HCMV infection is not yet known.

Missing self-recognition can also be mediated by non-MHC I molecules; one such example is the MCMV-encoded decoy m12 that targets the inhibitory NKR-P1B receptor [47–49], and is assumed to have driven the evolution of the related activating receptor, NKR-P1C (NK1.1), that also recognizes m12 in a mouse- and virus strain-dependent manner [50]. The SLAM family of receptors (SFR) has also been shown to aid in MHC-I-dependent missing-self recognition [51]. The ongoing evolutionary arms race between viral immunoevasins and host defenses is also evident in the evasion of activating receptor NKG2D, with CMVs encoding multiple strategies to prevent surface expression of NKG2D ligands (Table 1). Finally, *in silico* models show that CMV-like viruses that modulate NK cell ligands and downregulate MHC I, can select for genetically diverse and highly allele-specific receptor families with activating and inhibitory members, such as KIR and Ly49 [52–55].

Influence of CMV on NK cell education

Binding of self-molecules via inhibitory receptors is also required for NK cell education and modulation of effector function. Since NK cell inhibitory receptors and their ligands are encoded by distinct loci located on different chromosomes, it is possible for some NK cells to express inhibitory NK cell receptors for which there is no self-ligand. Potential autoreactivity of such cells is prevented by a mechanism termed "licensing" or "disarming": if an NK cell does not encounter a ligand for at least one inhibitory receptor during its maturation it becomes hyporesponsive toward targets with low or no MHC I (reviewed in [56]). In mouse models, NK cell responsiveness increases with each inhibitory receptor that can find its ligand during maturation [12, 57]. The tuning of NK cell responsiveness is not restricted only to the maturation stages, rather it's a continuous process depending on the availability of receptor ligands. Unlicensed cells are not redundant; the inflammatory environment can ameliorate their anergy and they can be effective against targets that express self-MHC I that would inhibit licensed cells, such as MHC I-expressing tumors or viruses such as CMV that encode NK cell inhibitory receptor decoys (reviewed in [12, 57]). Conversely, NK cells in mice that overexpress or constitutively express ligands for NKG2D or Ly49H receptor displayed tolerance against targets expressing these ligands [12, 58].

NK cell education can also be mediated by non-MHC I self-molecules [59]. For example, the SFR that have been shown to act as both inhibitory and activating receptors depending on adaptor molecules [60], can play a significant role in tuning of NK cell responsiveness although it is not yet clear whether this tuning is a consequence of their activating or inhibitory role [61, 62]. MCMV and HCMV regulate the expression of one SFR, 2B4 (Table 1) [63, 64]. It is not known whether other SFRs are targeted by CMVs however, a recent work demonstrated in mice that SFRs and their adaptor molecules are promising modulators that can enhance immune responses to vaccines [65].

Although expression of NK cell receptors is often described as stochastic, a growing body of research reveals the impact of inhibitory receptor signaling during NK cell maturation on the expression of other NK cell receptors [12]. For example, signaling from activating NK cell receptors via SLP-76 changes the expression of inhibitory Ly49A, Ly49G2 and Ly49I receptors in mice and completely abolishes acquisition of KIR2DL1, KIR2DL2/DL3, and KIR3DL1 in human NK cells and it has been proposed that this is driven by the expression of activating ligands on bone marrow stromal cells [66]. Interestingly, cytomegaloviruses have a wide cell and tissue tropism including bone marrow stromal cells, a tissue that is important for generation and maintenance of NK cells, and, in an influenza model, the bone marrow was found

to be an important site of proliferation of long-lived memory-like NK cells [67]. It will be interesting to see whether bone marrow stroma influences the generation of CMV-induced memory-like NK cells and whether latent CMV in the bone marrow modulates NK cell maturation and education.

Long-term impact of MCMV on NK cell phenotype, behavior and responses to other pathogens

Following infection or vaccination, pathogen-specific cells of the adaptive immune response undergo clonal expansion (proliferation) and differentiation followed by contraction of the effector cell pool and formation of long-lived, highly antigen-specific memory cells with the ability to mount fast and efficient recall responses. While most NK cell receptors are not antigen specific, in certain mouse strains the activating Ly49H receptor specifically recognizes MCMV m157, as described above ([37, 38] and reviewed in [68]). However, this pathogen-specific recognition is restricted only to C57BL/6 and related mice and a few laboratory strains of MCMV (e.g. most commonly used Smith and K181 strains) [33, 36, 69–72]. Furthermore, serial passage of WT MCMV in Ly49H$^+$ mice results in the accumulation of mutations that abrogate interaction between MCMV and Ly49H [69, 73], while in mixed infections (infection with 2 or more strains of MCMV) only MCMV strains that do not engage Ly49H are able to reach the salivary gland, the main dissemination place [74].

Nonetheless, Ly49H and m157 interaction results in the antigen-specific expansion of Ly49H$^+$ cells, control of the virus and generation of long-lived memory-like NK cells with capabilities similar to memory T cells (Fig. 1A) and is currently a major model for studying virus-induced memory NK cell formation. MCMV-induced memory-like NK cells are less reliant on STAT1- and STAT4-mediated signals and produce less IFN-γ in response to IL-12 with IL-18 compared to naïve or Ly49H$^-$ NK cells [75]. These cells also display inappropriate NK cell homing to infected tissues following adoptive transfer and reduced IFN-γ production during subsequent influenza or listeria infections, whilst still generating appropriate responses to MCMV m157$^+$ [75]. It appears, therefore, that expansion of CMV-specific memory-like NK cells could compromise responses to other infections, however this may be offset by increased responsiveness to antibody-mediated signals (ADCC) (see below).

HCMV infection leads to accumulation of terminally differentiated NK cells with potential long-term consequences

Human CMV infection is characterized by accumulation of highly differentiated subsets of NK cells (Fig. 1B). Over ten years ago, Guma et al. observed an expansion of mature (CD56^{dim}CD16$^-$) NK cells expressing CD94/NKG2C$^+$ in HCMV$^+$ individuals [76]. This observation has now been corroborated in HCMV-infected children [77], in adults undergoing acute HCMV infection [78] and in hematopoietic stem cell transplant patients with reactivated HCMV [79, 80], among whom HCMV reactivation is associated with significantly increased NK cell maturation rates [80–82]. As described above, CD94/NKG2C is an activating receptor for HLA-E, which is stabilized at the surface of HCMV-infected cells, suggesting that this is a host protective response to control HCMV infection and maintain latency. Moreover, many expanded, CD94/NKG2C$^+$ cells subsequently lose expression of the FcRγ adaptor molecule [83, 84]. Despite the FcRγ loss, not only is signaling through the Fc-receptor CD16 preserved (due to the ability of CD16 to transmit signals through CD3ζ) but FcRγ$^-$ cells display enhanced ADCC responses to HSV-1 [85] and influenza-infected targets [86], as well as against antibody-opsonized HCMV virions [87], especially if NKp46 [85] or CD2 are also engaged [88, 89]. HCMV-expanded NK cells are long-lived [90, 91] with stable epigenetic imprints that are transmitted to the cell progeny and that resemble those found in memory T cells [86, 92]. CD94/NKG2C$^+$ FcRγ- NK cells are thus highly adapted to combat HCMV re-infection or reactivation in seropositive individuals, although CMV infection can also prompt the expansion of NKG2C$^-$ NK cell population (discussed below).

Differences are emerging, however, in the phenotype of CMV-induced memory-like NK cells in humans and mice. Many NK cells in HCMV$^+$ individuals are deficient in the transcription factor PLZF, and many of PLZF- cells also lack the SYK, EAT-2 and FcRγ adapter molecules (Fig. 1B) as a consequence of hyper-methylation of their promoter regions. Furthermore, epigenetic modification (methylation) of the IFN-γ gene promoter explains increased secretion of this cytokine upon re-stimulation [93]. Interestingly, although NK cells in HCMV$^+$ patients display demethylation of PRDM1 and ZBTB32 genes [93] the same genes that regulate proliferative burst of Ly49H+ memory-like NK cells in mice [94], mouse memory-like NK cells are FcRγ and Syk sufficient [86]. Stable epigenetic relaxation of cytokine secretion and regulators of proliferation could be potentially dangerous, especially in cells that are highly activated by an inflammatory milieu. In the case of human CD94/NKG2C$^+$ NK cells, this danger is circumvented by downregulation of receptors for IL-12 and IL-18 [95], common NK cell activating cytokines, and by dampening of tonic signaling from activating receptors mediated by Syk, EAT-2 and FcRγ [96].

Although HCMV-expanded NK cells display a mature phenotype associated with reduced cytokine responsiveness, IFN-γ cytokine-driven responses of NKG2C$^+$CD57$^-$ NK cells in HCMV$^+$ individuals are strongly boosted by vaccination compared to their CD57^{bright} counterparts consistent with further differentiation steps occurring before these cells lose cytokine responsiveness [97]. The extent to which highly differentiated FcRγ$^-$, PLZF$^-$ adaptive NK cells participate in vaccine-induced responses has not yet been fully addressed and it is conceivable that vaccines or adjuvants relying heavily on cytokine-driven pathways may be less potent in HCMV$^+$ individuals with high frequencies of these cells.

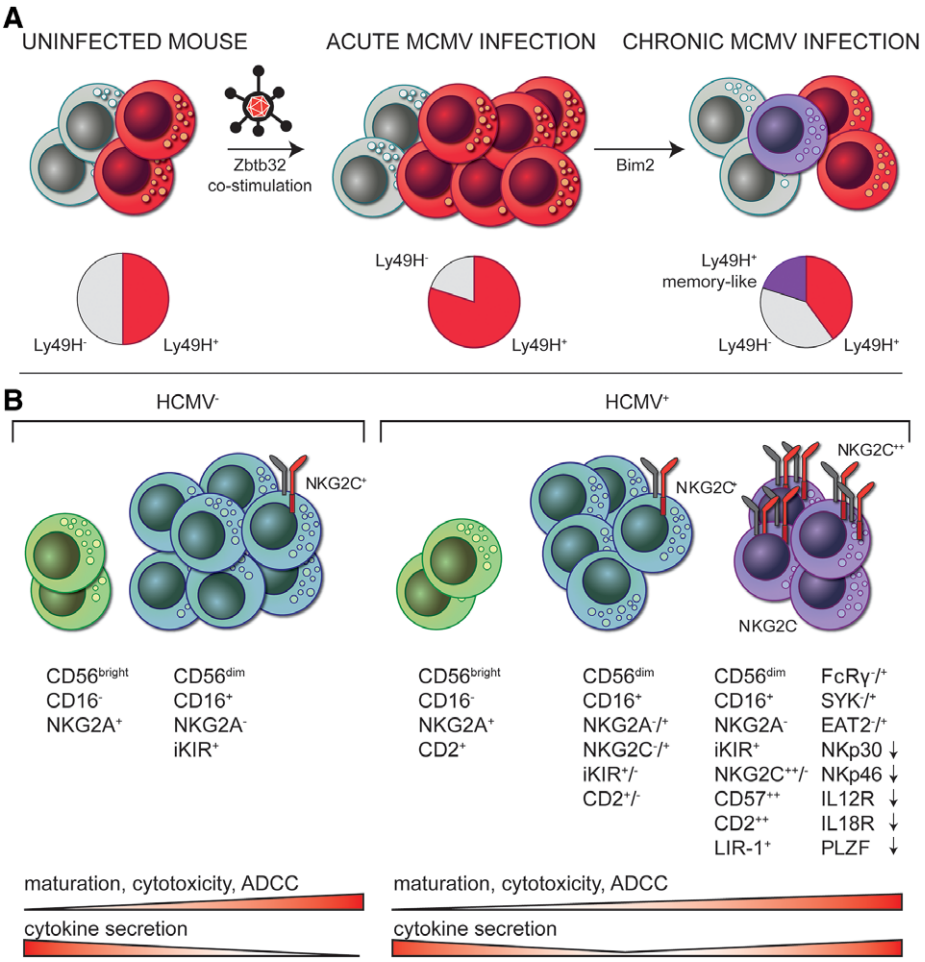

Figure 1. CMV infection induces long-lived memory-like NK cells in mice and humans. (A) Around half of all NK cells in C57BL/6 mice express Ly49H. Upon MCMV infection, they proliferate strongly and efficiently control the virus [184], even upon transfer into Ly49H- mouse strains [185]. Following viral clearance, the expanded pool of Ly49H+ cell contracts leaving a small proportion of long lived NK cells (detected up to 70 days PI) with recall ability reminiscent of memory T cells and with diminished ability to respond to other pathogens or MCMV lacking m157 [74]. Like T cells, memory-like NK cells require pro-apoptotic Bim-signaling for efficient contraction and memory formation [186], as well as co-stimulation via other co-stimulatory receptors such as DNAM-1 and Ly49D [114, 187] (not shown). (B) In physiological conditions, two subsets of human NK cells exist. Functionally competent but immature CD56brightCD16- NK cells that mostly reside in secondary lymphoid organs, express inhibitory NKG2A, are excellent cytokine producers but poor killers give rise to the fully mature and cytotoxic, major NK cell population in the blood characterized as CD56dimCD16+NKG2A-/+ inhibitory KIR+ cells [188, 189]. Upon HCMV infection, a new subset appears among the fully mature CD56dimCD16+ population that is characterized by increased levels of NKG2C compared to NKG2C+ cells in HCMV- patients [77] (although not all expanded cells are NKG2C+), high levels of LIR-1 and, in many cases, CD57 (marker of fully mature cells) [77], perforin and granzyme expression, and the increased ability to secrete IFN-γ and TNFα. These cells often express at least one inhibitory self-binding KIR that allows licensing of these cells [80, 95, 107, 190]. Expanded NKG2C+ NK cells in HCMV+ TAP-deficient patients express polyclonal KIRs and are unresponsive toward HLA I negative targets [191]. Furthermore, most of these cells are deficient for adaptor molecule FcRγ and, consequently, express lower levels of those receptors that depend on FcRγ for signal transmission such as NKp30 and NKp46 [82, 84, 86], while there are no changes in the expression of DNAM-1 and 2B4. Some also lose signaling molecules SYK and EAT-2 [92].

The molecular mechanisms behind expansion of the CD94/NKG2C$^+$ subset of NK cells are not yet completely clear. Although CD94/NKG2C$^+$ NK cells expand only in HCMV infected individuals [98], the rate and extent of the expansion varies greatly among HCMV$^+$ individuals (reviewed in [99]). CD94/NKG2C$^+$ NK cells can expand in vitro when co-cultivated with fibroblasts undergoing productive HCMV replication. HLA Class I regulators encoded by the US2-11 gene region are required for this expansion but, despite the demonstration of weak interactions between NKG2C and UL18 [100, 101] neither UL16 nor UL18 are required. Interaction of NKG2C with HLA-E, and IL-12 secretion by monocytes, has also been identified as prerequisites for the expansion of NK cells in this context [102]. The proportion of CD94/NKG2C+ NK cells increases with age in different populations and surface levels of NKG2C correlate with the copy number of *KLRC2,* the gene encoding NKG2C [84, 103–105]. Among congenitally infected children, symptomatic HCMV infection was associated with higher proportions of CD94/NKG2C$^+$ NK cells [105],

suggesting that their expansion is ligand-driven. Among African children, anti-HCMV antibody titres were higher in *KLRC2*$^{-}$ heterozygous and homozygous null individuals than in homozygous *KLRC2*$^{+}$ children suggesting that lack of *KLRC2* impairs control of the virus [104], but this was not seen in adults in the same community or in congenitally infected children [105]. A recent finding showing earlier accumulation of effector memory CD45RA^{+} CD8 T cells in *KLRC2*$^{-/-}$ individuals provides a possible explanation for this discrepancy [88].

The CD94/NKG2C^{+} NK cell population is not the only NK cell population that proliferates in response to HCMV infection. CD57^{hi}NKG2A^{-}NKG2C^{-} expanded populations have been observed in both NKG2C sufficient and deficient subjects; a recent study identified expansion of FcRγ^{-}LIR-1^{+} cells in both NKG2C^{+} and NKG2C^{-} NK cell populations among CMV^{+} renal transplant patients, irrespective of their *KLRC2* genotype, although the FcRγ^{-}LIR-1^{+} NKG2C^{-} cells displayed greater ADCC against anti-CMV antibody-coated targets than did the FcRγ^{-}LIR-1^{+} NKG2C^{+} population [106]. A recent report analyzing expansion of NK cells against HCMV-infected targets in vitro demonstrated expansion of NK cells independently of NKG2C expression [107]. It is not yet clear what drives the expansion of these CD94/NKG2C- NK cells. Although it was originally associated with the presence of activating KIR receptors of KIR B haplotype [108, 109], a later study found no difference between overall frequencies of activating KIRs between NKG2C- and NKG2C^{+} memory-like NK cells [88]. Both NKG2C- and NKG2C^{+} memory-like NK cells showed enhanced ADCC responses, higher levels of DNAM-1 and CD2 and demethylation of the *IFNG* promoter but were poorly responsive to IL12/IL18 and expressed lower levels of NKp46 [88].

Cytokine-induced memory-like NK cells in CMV infection and vaccination

In addition to CMV-induced memory-like NK cells, cytokine-induced memory-like NK cells (CIML) have been reported in mice and in humans [110]. Pre-activation of mouse NK cells with a cocktail of IL-12, IL-18 and low dose IL-15 gave rise to cells that secreted increased levels of IFN-γ following activation through activating receptor engagement or following cytokine-stimulation up to 3 weeks later [111]. The strength of the subsequent response depended on the duration of pre-activation and enhanced responsiveness was maintained after homeostatic proliferation, indicating heritable epigenetic modification [112]. However, in contrast to virus-induced memory-like NK cells, CIML NK cells did not show enhanced cytotoxicity and enhanced cytokine production was lost by week 12. The upregulation of IL-2R (CD25) plays a key role in the maintenance of human CIMLs which mount strong secondary responses in presence of picomolar concentrations of IL-2 [113]. Murine CIML also rely on common-γ chain cytokine signaling for their long term maintenance [112]. Similar observations have been made for human NK cells pretreated in vitro with various combinations of IL-12, IL-15 and IL-18 [114] (Fig. 2) and it is thus feasible that the inflammatory environment associated with acute viral infection, including CMV infection, may contribute to the formation of memory-like NK cells in vivo in humans and in mice. Indeed, induction of long-lived CIMLs in parallel with Ly49H^{+} memory-like NK cells has recently been reported in mice [115] and another study has shown that IL-12 (but not Ly49H-m157) is required for induction of IL-2R during MCMV infection [116]. In the context of tumors, however, CIMLs are generated to a much lower extent and their responses—against the tumor itself or after engagement of NK1.1 or NKG2D ligands—are much weaker than those of MCMV-induced Ly49H^{+} memory-like NKs [115]. However, when transferred into the MCMV-free environment, CIMLs showed better survival and persistence than their virally induced counterparts.

This recent appreciation of the possibility of enhancing or modifying NK cell responsiveness by pre-activation with cytokines or exposure to viruses, opens up the potential for new prophylactic and therapeutic interventions (designed to generate memory-like NK cells) for combatting infection or malignancy (Fig. 2). In humans, in vitro stimulation of peripheral blood mononuclear cells (PBMC) with vaccine antigens leads to the bystander activation of NK cells in individuals naturally exposed to, or previously vaccinated against, the corresponding pathogens (Fig. 2, [95, 117, 118]). Active vaccination (with rabies, malaria RTS,S, influenza TIV and LAIV, BCG and therapeutic HIV gp120 vaccines) has been shown to induce vaccine antigen-specific CD4^{+} T cell and IL-2 dependent NK cell responses to the vaccinating antigens (Table 2) [119–124]. As for CIMLs, cell surface expression of CD25, forming the high affinity interleukin-2 receptor (IL-2R) and thereby increasing sensitivity to antigen-induced IL-2, has been shown to be an important feature of vaccine-induced NK cell responses [119, 122, 123, 125, 126]. Whole organism vaccines including influenza, yellow fever, BCG and DTPiP (which encode pathogen associated molecular patterns, PAMPS) are potent inducers of myeloid cell-derived IL-12 and type I interferons which not only synergise with IL-2 to activate NK cells after vaccination [119, 122, 124] but also induce CIMLs [97, 119, 124, 127]. In sharp contrast to CMV infection, however, vaccination and cytokine-mediated pre-activation lead to a temporary expansion (or redistribution) of less differentiated CD56^{bright} and CD57- CD56^{dim} NK cell subsets [97, 119, 124, 125, 127] but these eventually revert to pre-vaccination levels. For example, the elevated cytokine driven response observed after influenza or yellow fever 17D vaccination of Europeans persisted for up 3 months [104, 127], the response to influenza or DTPiP vaccination of Gambians lasted for up to 6 months and the response to BCG vaccination in South Africans lasted for up to 1 year [97, 124].

Broader effects of HCMV exposure on vaccination outcomes

A broader influence of HCMV infection on vaccine induced immunity has been inferred from several studies comparing naturally occurring or vaccine-induced antibody levels or T cell responses

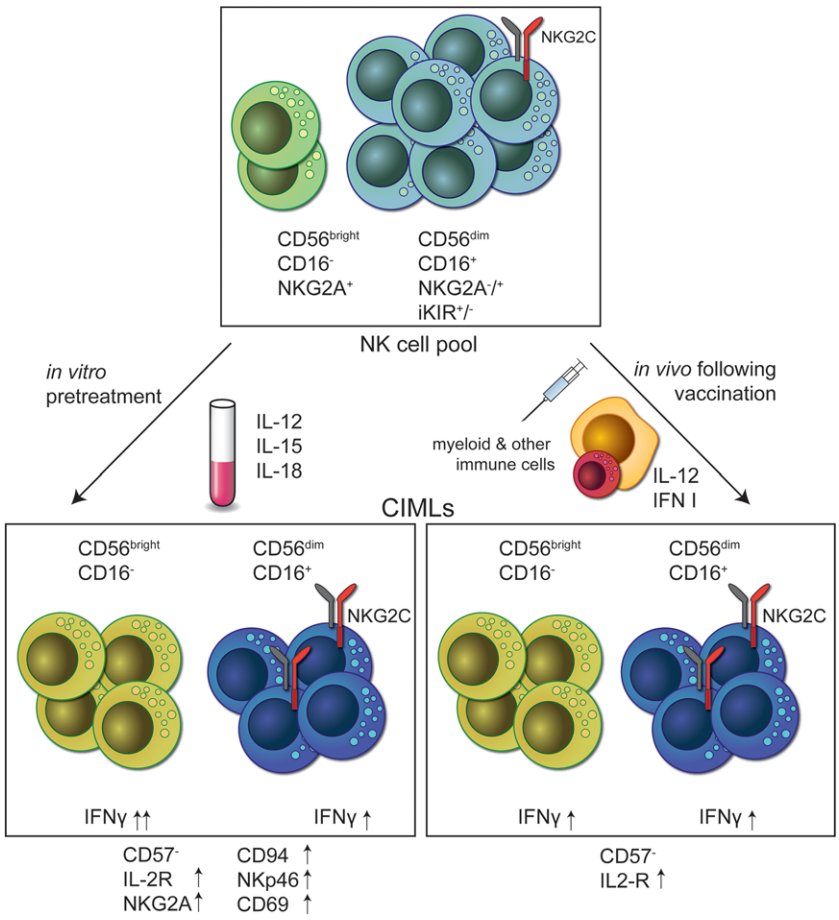

Figure 2. Human cytokine-induced memory-like NK cells. Human NK cells can differentiate into CIMLs following in vitro treatment with cytokines or after vaccination. In vitro, both CD56bright and CD56dim cells can give rise to CIMLs. CD56bright CIMLs show a greater capacity to produce IFN-γ and fail to differentiate into CD56dimNK cells. Unlike virus-induced memory-like NK cells, human CIMLs are characterized by lack of CD57 and increased surface expression of NKG2A, CD94, NKp46 and CD69, which correlate with their ability to secrete IFN-γ. CIMLs that develop after vaccination are similar to in vitro generated cells in terms of increased IFN-γ secretion, enrichment for CD57- cells and induction of IL-2R [118, 121, 122, 124, 125].

against distinct pathogens in HCMV$^+$ to HCMV- individuals. For anti-influenza responses, the impact of HCMV infection can be positive or negative depending on age and the immune readout. Poor overall health indicators have been associated with higher HCMV antibody titres, higher NK cell frequencies and lower B cell frequencies in the elderly [128] and inverse correlations have been reported between anti-HCMV IgG titres and vaccination-induced antibodies to influenza in the elderly [128] and in healthy young adults [129, 130]. Other studies have demonstrated either higher [131] or lower [132] antibody responses to influenza vaccination in HCMV- compared to HCMV$^+$ young adults, suggesting that the duration of HCMV infection (acute versus longstanding) may affect the response to vaccination. In support of this hypothesis, young mice with recently established MCMV infection displayed better IFN-γ–dependent control of influenza infection and increased frequencies of influenza antigen-specific CD8$^+$ T cells compared to older mice with chronic, latent MCMV infection [132]. If confirmed in larger studies, CMV-induced enhancement of anti-viral immunity in the recently infected may confer a survival advantage in early or mid-life but CMV-mediated immune senescence would reduce longevity in later life. This dynamic might therefore prove beneficial to children in many low-income countries with extremely high HCMV seroprevalence despite evidence of potentially deleterious effects in older populations in industrial nations [26, 104, 133–135].

The impact of HCMV infection on NK cell responses to vaccine antigens

The impact of HCMV infection on vaccine antigen or cytokine-driven response pathways can be profound. In vitro NK cell IFN-γ responses to several previously encountered vaccine antigens, including Influenza, whole cell pertussis and DTPiP (alone or co-stimulated with low concentrations of IL-12 and IL-18) are impaired in HCMV$^+$ individuals [95, 97, 119]. This effect is consistent with the well-documented impairment of NK cell IFN-γ and CD25 responses to exogenous cytokines among HCMV$^+$ individuals [95, 118, 119, 136, 137], and suggests that HCMV infection impairs the NK cell response to vaccine antigen-induced IL-2 [95, 119]. As demonstrated for CIML, post-vaccination, NK cells appear to be reliant on cytokine-driven induction of CD25 for their maintenance and function, raising the possibility that production of, or responses to, the costimulatory cytokines (type I IFNs, IL-12 or IL-18) that are required for CD25 induction may be reduced in HCMV$^+$ individuals [113, 119]. This is consistent with the impaired NK cell responses of HCMV$^+$ individuals reflecting, in part, their low frequencies of less-differentiated CD56^{bright} and CD56^{dim}CD57- NK cells, which are intrinsically more cytokine responsive [95, 119]. However, chronic HCMV infection reduces the cytokine responsiveness of all NK cell subsets [95, 119], indicating that HCMV infection has much broader effects on NK cells,

Table 2. NK cell responses after active vaccination and accessory cytokine requirements

Vaccine	Composition/adjuvant	NK cell response	Accessory cytokine requirement or association	References
BCG (Bacillus Calmette–Guérin)	Attenuated whole organism	IFN-γ	IL-2, IL-12, IL-18	[124]
BCG	Attenuated whole organism	IFN-γ (ex-vivo)		[183]
HIV	Therapeutic subunit gp120/nef/tat vaccine	IFN-γ	IL-2, IL-12	[123]
Influenza	Intramuscular or Intradermal Trivalent inactivated (TIV) or Live attenuated (LAIV)	IFN-γ, CD25, CD107a	IL-2, IFN-α	[119]
Influenza	TIV or seasonal infection	CD69, CD25 (ex-vivo)		[122]
Influenza	TIV	IFN-γ		[184]
Influenza	TIV	IFN-γ, CD25, CD107a		[97]
DTPiP (diphtheria, tetanus, pertussis, inactivated poliovirus)	Subunit	IFN-γ		[97]
Malaria RTS,S	Conjugate	IFN-γ, CD69,	IL-2	[121]
Rabies	Inactivated whole organism	IFN-γ, CD69 CD107a, perforin	IL-2, IL-12, IL-18	[120]
Yellow Fever	Live attenuated whole organism	Ki67, CD69	IFN Type I/III	[127]

either by affecting their differentiation or licensing or by reducing the costimulatory capacity of accessory cells.

Remarkably, although vaccination results in limited boosting of vaccine antigen driven responses, several vaccines boost the responses to higher concentrations of cytokines predominantly in $HCMV^+$ individuals where these responses are down-regulated. Influenza vaccination preferentially boosts IL-12 and IL-18 stimulated NK cell IFN-γ, CD25 and CD107a expression in $HCMV^+$ Europeans, while both TIV (Trivalent Influenza Vaccine) and DTPiP have this effect in African populations where HCMV infection is near universal [97, 119]. The similar boosting of NK cell IFN-γ responses to cytokines after Yellow fever vaccination in Europeans or BCG vaccinated South African populations, although not explicitly investigated according to HCMV exposure, is also likely to involve $HCMV^+$ subjects [124]. The boosting of cytokine-driven responses in all of these studies preferentially expands or activates less differentiated subpopulations of NK cells.

Receptor-mediated activation and ADCC in the context of CMV infection and vaccination

Whilst CMV infection negatively influences vaccine-driven responses that are reliant on accessory cytokines, NK cell activation via other pathways can also be adversely affected by CMV infection. For example, murine $Ly49H^+$ 'memory-like' NK cells rely on co-stimulation via DNAM-1 and its induced ligands on macrophages and dendritic cells [138]; CMV-mediated down regulation of these ligands may have consequences for responses to infection or vaccination. Similarly, in humans, reduced expression of NKp46, and reduced NKp46 signalling capacity in adaptively expanded NK cells in HCMV+ individuals [92, 136, 137], could compromise responses to influenza virus by inhibiting the costimulatory interaction between NKp46 and viral haemaglutinin [139]. Moreover, US12-mediated down regulation of B7-H6 (a key ligand for NKp30) on HCMV-infected fibroblasts can lead to reduced NK cell degranulation [140]. However, $CD94/NKG2C^+$ NK cells show enhanced cytotoxic activity against a range of tumour cell lines which vary greatly in their expression of HLA-E, indicating that there may be conserved expression of receptors for other activating ligands [141]. Indeed, HCMV-expanded NK cells rely on signalling via accessory receptors including CD2 and its ligand, CD58, on accessory cells [88, 89]. On the other hand, HCMV-expanded, "adaptive", $CD94/NKG2C^+CD57^+$NK cells express high levels of CD16, signal very effectively via CD3ζ and possess epigenetic modifications leading to enhanced receptor-mediated cytotoxicity and IFN-γ production [92, 93]. Together these modifications lead to greatly enhanced capacity for CD16-mediated ADCC, which may compensate for their loss of cytokine responsiveness [83, 86, 87, 92]. Interestingly, HCMV-expanded memory-like NK cells do not appear to target autologous CD4+ T cells [96], a regulatory feature of NK cells described in murine models of virus-induced immune responses [142]. Such preservation of pathogen or vaccine-specific CD4+ T cells is likely to be important for the maintenance of both vaccine induced CIML and HCMV-associated, adaptive NK cell expansions.

Conclusion

Although it is clear that cytomegaloviruses are major drivers of cellular immune differentiation, affecting NK cells as well as T cells, the full impact of CMV on infection, vaccination and healthy life

span is still unclear. In the case of NK cells, the gradual differentiation away from cytokine-dependent signalling pathways towards antibody dependent or other receptor-mediated responses could be beneficial in the long-run, with cytokine-dependent activation on primary exposure to any given pathogen giving way to antibody-mediated activation during subsequent infections. The timing of HCMV infection, and the rate of subsequent cytokine-driven expansion of "adaptive" NK cells, together with host genetic background, will determine the relative costs and benefits of this process. Whilst CMV immune evasins may have evolved to promote persistence of virus in the host, further research is needed to establish which of the affected pathways are critical for immune defence against other pathogens. One as yet unconsidered aspect of this interaction between CMV and the cellular immune system is the potential use of CMVs as vaccine vectors [143–149]. CMV can induce long-term expansion of antigen-specific CD8 T cell clones, which could be highly beneficial in a vaccine. Simultaneous deletion of the NK cell imunoevasins has proven to be a good strategy for virus attenuation without compromising CD8 T cell responses. The concurrent potential of CMV-vectored vaccines to mature NK cells toward potent antibody-dependent effector cells should however also be explored.

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Abbreviations: **ADCC**: antibody-dependent cell-mediated cytotoxicity · **CMV**: cytomegalovirus · **KIR**: killer-cell immunoglobulin-like receptor · **LIR**: leukocyte Ig-like receptor · **TIV**: trivalent influenza vaccine

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