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European Journal of Immunology HIGHLIGHTS

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].

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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.

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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

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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.

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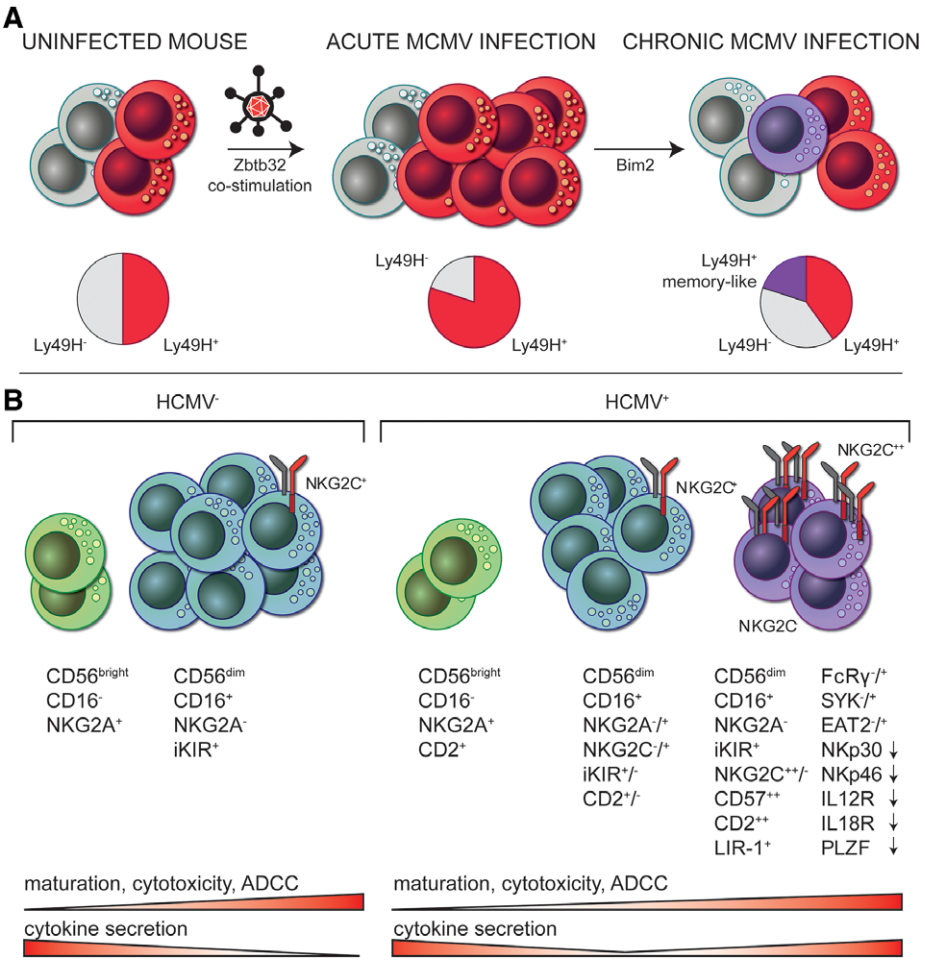

Figure 1. CMV infection induces long-lived memory-like NK cells in mice and humans. (A) Around half of all NK cells in C57BL/6 mice express Ly49H. Upon MCMV infection, they proliferate strongly and efficiently control the virus [184], even upon transfer into Ly49H- mouse strains [185]. Following viral 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],

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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

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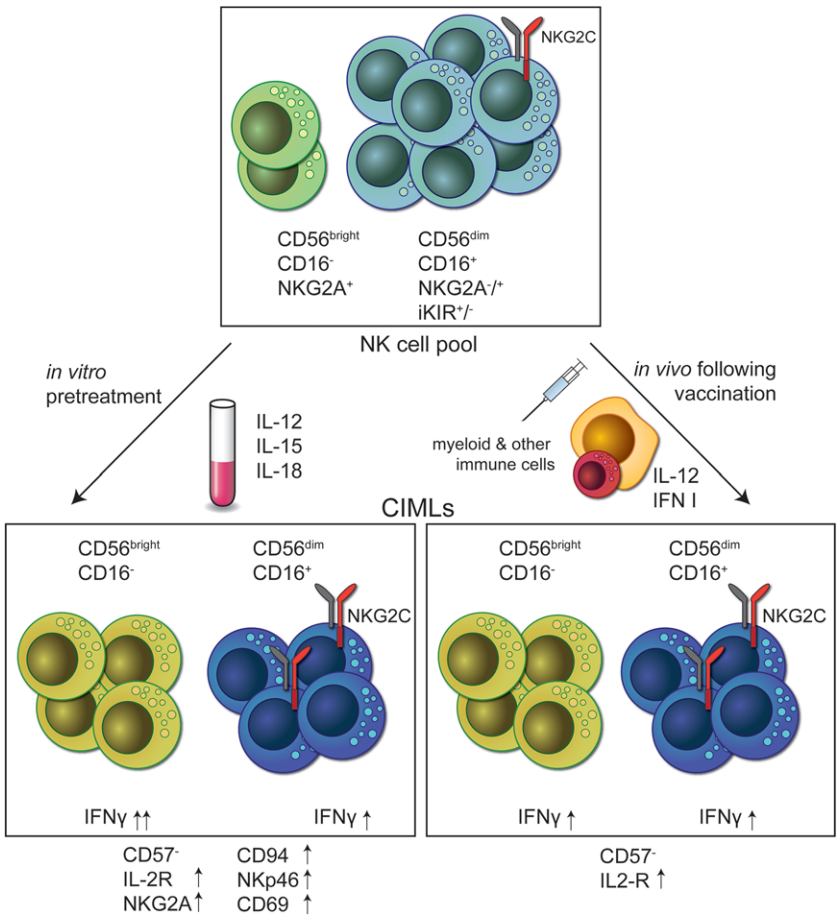

Figure 2. Human cytokine-induced memory-like NK cells. Human NK cells can differentiate into CIMLs following in vitro treatment with cytokines or after vaccination. In vitro, both CD56bright and CD56dim cells can give rise to CIMLs. CD56bright CIMLs show a greater capacity to produce IFN-γ and fail to 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,

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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

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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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References

1 **Roizman, B. and Pellett, P. E.**, The family *Herpesviridae*: a brief introduction. In Knipe, D. M., Howley, P. M., Griffin, D. E. and Lamb, R. A. (Eds.), *Fields Virology* (5 Edn.), Lippincott Williams & Wilkins, 2007, pp. 2480–2499.

2 **Jiao, Y., Huntington, N. D., Belz, G. T. and Seillet, C.**, Type 1 innate lymphoid cell biology: lessons learnt from natural killer cells. *Front Immunol* 2016. **7**: 426. eCollection 2016.

3 **Orange, J. S.**, Natural killer cell deficiency. *J. Allergy Clin. Immunol.* 2013. **132**: 515–525; quiz 526.

4 **Biron, C. A., Byron, K. S. and Sullivan, J. L.**, Severe herpesvirus infections in an adolescent without natural killer cells. *N. Engl. J. Med.* 1989. **320**: 1731–1735.

5 **Etzioni, A., Eidenschenk, C., Katz, R., Beck, R., Casanova, J. L. and Pollack, S.**, Fatal varicella associated with selective natural killer cell deficiency. *J. Pediatr.* 2005. **146**: 423–425.

6 **Parry, D. A., Holmes, T. D., Gamper, N., El-Sayed, W., Hettiarachchi, N. T., Ahmed, M., Cook, G. P. et al.**, A homozygous STIM1 mutation impairs store-operated calcium entry and natural killer cell effector function without clinical immunodeficiency. *J. Allergy Clin. Immunol.* 2016. **137**: 955–957 e958.

7 **Vely, F., Barlogis, V., Vallentin, B., Neven, B., Piperoglou, C., Ebbo, M., Perchet, T. et al.**, Evidence of innate lymphoid cell redundancy in humans. *Nat. Immunol.* 2016. **17**: 1291–1299.

8 **Lam, V. C. and Lanier, L. L.**, NK cells in host responses to viral infections. *Curr. Opin. Immunol.* 2016. **44**: 43–51.

9 **Babic, M., Krmpotic, A. and Jonjic, S.**, All is fair in virus-host interactions: NK cells and cytomegalovirus. *Trends Mol. Med.* 2011. **17**: 677–685. Epub 2011 Aug 1017.

10 **Mitrovic, M., Arapovic, J., Traven, L., Krmpotic, A. and Jonjic, S.**, Innate immunity regulates adaptive immune response: lessons learned from studying the interplay between NK and CD8+ T cells during MCMV infection. *Med Microbiol Immunol* 2012. **201**: 487–495. Epub 02012 Sep 00411.

11 **Blackman, M. A. and Woodland, D. L.**, The narrowing of the CD8 T cell repertoire in old age. *Curr. Opin. Immunol.* 2011. **23**: 537–542.

12 **Kadri, N., Wagner, A. K., Ganesan, S., Karre, K., Wickstrom, S., Johansson, M. H. and Hoglund, P.**, Dynamic Regulation of NK Cell Responsiveness. *Curr. Top. Microbiol. Immunol.* 2016. **395**: 95–114.

13 **Horowitz, A., Strauss-Albee, D. M., Leipold, M., Kubo, J., Nemat-Gorgani, N., Dogan, O. C., Dekker, C. L. et al.**, Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. *Sci. Transl. Med.* 2013. **5**: 208ra145.

14 **Carrillo-Bustamante, P., Kesmir, C. and de Boer, R. J.**, The evolution of natural killer cell receptors. *Immunogenetics* 2016. **68**: 3–18. Epub 02015 Sep 00221.

15 **Nash, W. T., Teoh, J., Wei, H., Gamache, A. and Brown, M. G.**, Know thyself: NK-cell inhibitory receptors prompt self-tolerance, education, and viral control. *Front. Immunol* 2014. **5**:175. eCollection 02014.

16 **Karre, K.**, Natural killer cell recognition of missing self. *Nat. Immunol.* 2008. **9**: 477–480.

17 **Augusto, D. G. and Petzl-Erler, M. L.**, KIR and HLA under pressure: evidences of coevolution across worldwide populations. *Hum. Genet.* 2015. **134**: 929–940. Epub 02015 Jun 00423.

18 **Robinson, J., Halliwell, J. A. and Marsh, S. G.**, IMGT/HLA and the Immuno Polymorphism Database. *Methods Mol. Biol.* 2014. **1184**: 109–121.

19 **Das, J. and Khakoo, S. I.**, NK cells: tuned by peptide? *Immunol. Rev.* 2015. **267**: 214–227.

20 **Kirkham, C. L. and Carlyle, J. R.**, Complexity and diversity of the NKR-P1:Clr (Klrb1:Clec2) recognition systems. *Front Immunol* 2014. **5**:214. eCollection 02014.

21 **Bernhardt, G.**, TACTILE becomes tangible: CD96 discloses its inhibitory peculiarities. *Nat. Immunol.* 2014. **15**: 406–408.

22 **Chan, C. J., Martinet, L., Gilfillan, S., Souza-Fonseca-Guimaraes, F., Chow, M. T., Town, L., Ritchie, D. S. et al.**, The receptors CD96 and

© 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

CD226 oppose each other in the regulation of natural killer cell functions. *Nat. Immunol.* 2014. **15**: 431–438. Epub 2014 Mar 1023.

23 **de Andrade, L. F., Smyth, M. J. and Martinet, L.**, DNAM-1 control of natural killer cells functions through nectin and nectin-like proteins. *Immunol. Cell Biol.* 2014. **92**: 237–244. Epub 2013 Dec 1017.

24 **Martinet, L. and Smyth, M. J.**, Balancing natural killer cell activation through paired receptors. *Nat. Rev. Immunol.* 2015. **15**: 243–254. Epub 2015 Mar 1036.

25 **Pegram, H. J., Andrews, D. M., Smyth, M. J., Darcy, P. K. and Kershaw, M. H.**, Activating and inhibitory receptors of natural killer cells. *Immunol. Cell Biol.* 2011. **89**: 216–224. Epub 2010 Jun 1022.

26 **Manicklal, S., Emery, V. C., Lazzarotto, T., Boppana, S. B. and Gupta, R. K.**, The "silent" global burden of congenital cytomegalovirus. *Clin. Microbiol. Rev.* 2013. **26**: 86–102.

27 **Cekinovic, D., Lisnic, V. J. and Jonjic, S.**, Rodent models of congenital cytomegalovirus infection. *Methods Mol. Biol.* 2014. **1119**: 289–310.

28 **Powers, C. and Fruh, K.**, Rhesus CMV: an emerging animal model for human CMV. *Med Microbiol Immunol* 2008. **197**: 109–115.

29 **Corrales-Aguilar, E., Hoffmann, K. and Hengel, H.**, CMV-encoded Fcgamma receptors: modulators at the interface of innate and adaptive immunity. *Semin Immunopathol* 2014. **36**: 627–640.

30 **Lisnic, B., Lisnic, V. J. and Jonjic, S.**, NK cell interplay with cytomegaloviruses. *Curr Opin Virol* 2015. **15**: 9–18. Epub 2015 Jul 1021.

31 **Sun, J. C. and Lanier, L. L.**, The natural selection of herpesviruses and virus-specific NK cell receptors. *Viruses* 2009. **1**: 362.

32 **Halenius, A., Gerke, C. and Hengel, H.**, Classical and non-classical MHC I molecule manipulation by human cytomegalovirus: so many targets-but how many arrows in the quiver? *Cell Mol Immunol.* 2015. **12**: 139–153. Epub 2014 Nov 1024.

33 **Zeleznjak, J., Popovic, B., Krmpotic, A., Jonjic, S. and Lisnic, V. J.**, Mouse cytomegalovirus encoded immunoevasins and evolution of Ly49 receptors - sidekicks or enemies? *Immunol. Lett.* 2017 J Immunol December 15, 2014, **193**: 6061–6069.

34 **Adams, E. J., Juo, Z. S., Venook, R. T., Boulanger, M. J., Arase, H., Lanier, L. L. and Garcia, K. C.**, Structural elucidation of the m157 mouse cytomegalovirus ligand for Ly49 natural killer cell receptors. *Proc Natl Acad Sci U S A* 2007. **104**: 10128–10133. Epub 12007 May 10130.

35 **Pyzik, M., Dumaine, A., Charbonneau, B., Fodil-Cornu, N., Jonjic, S. and Vidal, S. M.**, Viral MHC class I-like molecule allows evasion of NK cell effector responses in vivo. *J. Immunol.* 2014. **193**: 6061–6069. Epub 1402014 Nov 1401312.

36 **Corbett, A. J., Coudert, J. D., Forbes, C. A. and Scalzo, A. A.**, Functional consequences of natural sequence variation of murine cytomegalovirus m157 for Ly49 receptor specificity and NK cell activation. *J. Immunol.* 2011. **186**: 1713–1722.

37 **Arase, H., Mocarski, E. S., Campbell, A. E., Hill, A. B. and Lanier, L. L.**, Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. *Science* 2002. **296**: 1323–1326. Epub 2002 Apr 1311.

38 **Smith, H. R., Heusel, J. W., Mehta, I. K., Kim, S., Dorner, B. G., Naidenko, O. V., Iizuka, K. et al.**, Recognition of a virus-encoded ligand by a natural killer cell activation receptor. *Proc Natl Acad Sci U S A* 2002. **99**: 8826–8831. Epub 2002 Jun 8811.

39 **Abi-Rached, L. and Parham, P.**, Natural selection drives recurrent formation of activating killer cell immunoglobulin-like receptor and Ly49 from inhibitory homologues. *J. Exp. Med.* 2005. **201**: 1319–1332.

40 **Abolins, S., King, E. C., Lazarou, L., Weldon, L., Hughes, L., Drescher, P., Raynes, J. G. et al.**, The comparative immunology of wild and laboratory mice, Mus musculus domesticus. *Nat Commun* 2017. **8**: 14811.

41 **Forbes, C. A., Scalzo, A. A., Degli-Esposti, M. A. and Coudert, J. D.**, Ly49C-dependent control of MCMV infection by NK cells is cis-regulated by MHC class I molecules. *PLoS Pathog.* 2014. **10**: e1004161. eCollection 1002014 May.

42 **Held, W. and Mariuzza, R. A.**, Cis-trans interactions of cell surface receptors: biological roles and structural basis. *Cell. Mol. Life Sci.* 2011. **68**: 3469–3478.

43 **Li, N. L., Fu, L., Uchtenhagen, H., Achour, A. and Burshtyn, D. N.**, Cis association of leukocyte Ig-like receptor 1 with MHC class I modulates accessibility to antibodies and HCMV UL18. *Eur. J. Immunol.* 2013. **43**: 1042–1052.

44 **Prod'homme, V., Tomasec, P., Cunningham, C., Lemberg, M. K., Stanton, R. J., McSharry, B. P., Wang, E. C. et al.**, Human cytomegalovirus UL40 signal peptide regulates cell surface expression of the NK cell ligands HLA-E and gpUL18. *J. Immunol.* 2012. **188**: 2794–2804. Epub 1102012 Feb 1102015.

45 **Beziat, V., Hervier, B., Achour, A., Boutolleau, D., Marfain-Koka, A. and Vieillard, V.**, Human NKG2A overrides NKG2C effector functions to prevent autoreactivity of NK cells. *Blood* 2011. **117**: 4394–4396.

46 **Heatley, S. L., Pietra, G., Lin, J., Widjaja, J. M., Harpur, C. M., Lester, S., Rossjohn, J. et al.**, Polymorphism in human cytomegalovirus UL40 impacts on recognition of human leukocyte antigen-E (HLA-E) by natural killer cells. *J. Biol. Chem.* 2013. **288**: 8679–8690. Epub 402013 Jan 409618.

47 **Aguilar, O. A., Mesci, A., Ma, J., Chen, P., Kirkham, C. L., Hundrieser, J., Voigt, S. et al.**, Modulation of Clr ligand expression and NKR-P1 receptor function during murine cytomegalovirus infection. *J Innate Immun* 2015. **7**: 584–600.

48 **Chen, P., Aguilar, O. A., Rahim, M. M., Allan, D. S., Fine, J. H., Kirkham, C. L., Ma, J. et al.**, Genetic investigation of MHC-independent missing-self recognition by mouse NK cells using an in vivo bone marrow transplantation model. *J. Immunol.* 2015. **194**: 2909–2918. Epub 1402015 Feb 1401513.

49 **Rahim, M. M., Chen, P., Mottashed, A. N., Mahmoud, A. B., Thomas, M. J., Zhu, Q., Brooks, C. G. et al.**, The mouse NKR-P1B:Clr-b recognition system is a negative regulator of innate immune responses. *Blood* 2015. **125**: 2217–2227. Epub 552015 Jan 556122.

50 **Aguilar, O. A., Berry, R., Rahim, M. M., Reichel, J. J., Popovic, B., Tanaka, M., Fu, Z. et al.**, A viral immunoevasin controls innate immunity by targeting the prototypical natural killer cell receptor family. *Cell* 2017. **169**: 58–71.e14.

51 **Alari-Pahissa, E., Grandclement, C., Jeevan-Raj, B., Leclercq, G., Veillette, A. and Held, W.**, Activation by SLAM family receptors contributes to NK cell mediated "missing-self" recognition. *PLoS One* 2016. **11**: e0153236. eCollection 0152016.

52 **Carrillo-Bustamante, P., Kesmir, C. and de Boer, R. J.**, Virus encoded MHC-like decoys diversify the inhibitory KIR repertoire. *PLoS Comput. Biol.* 2013. **9**: e1003264. Epub 1002013 Oct 1003210.

53 **Carrillo-Bustamante, P., Kesmir, C. and de Boer, R. J.**, Quantifying the protection of activating and inhibiting NK cell receptors during infection with a CMV-like virus. *Front Immunol.* 2014. **5**: 20. eCollection 02014.

54 **Carrillo-Bustamante, P., Kesmir, C. and de Boer, R. J.**, Can selective MHC downregulation explain the specificity and genetic diversity of NK cell receptors? *Front Immunol.* 2015. **6**: 311. eCollection 02015.

55 **Carrillo-Bustamante, P., Kesmir, C. and de Boer, R. J.**, A Coevolutionary arms race between hosts and viruses drives polymorphism and polygenicity of NK cell receptors. *Mol. Biol. Evol.* 2015. **32**: 2149–2160. Epub 2015 Apr 2123.

© 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

56 **Nash, W. T., Teoh, J., Wei, H., Gamache, A. and Brown, M. G.**, Know thyself: NK-cell inhibitory receptors prompt self-tolerance, education, and viral control. *Front Immunol* 2014. **5**: 175.

57 **Elliott, J. M. and Yokoyama, W. M.**, Unifying concepts of MHC-dependent natural killer cell education. *Trends Immunol.* 2011. **32**: 364–372.

58 **Shifrin, N., Raulet, D. H. and Ardolino, M.**, NK cell self tolerance, responsiveness and missing self recognition. *Semin. Immunol.* 2014. **26**: 138–144.

59 **He, Y. and Tian, Z.**, NK cell education via nonclassical MHC and non-MHC ligands. *Cell Mol Immunol* 2017. **14**: 321–330. Epub 2016 Jun 1036.

60 **Wu, N. and Veillette, A.**, SLAM family receptors in normal immunity and immune pathologies. *Curr. Opin. Immunol.* 2016. **38**:45–51. Epub 2015 Dec 1012.

61 **Chen, S., Yang, M., Du, J., Li, D., Li, Z., Cai, C., Ma, Y. et al.**, The self-specific activation receptor SLAM family is critical for NK cell education. *Immunity* 2016. **45**: 292–304. Epub 2016 Aug 1019.

62 **Wu, N., Zhong, M. C., Roncagalli, R., Perez-Quintero, L. A., Guo, H., Zhang, Z., Lenoir, C. et al.**, A hematopoietic cell-driven mechanism involving SLAMF6 receptor, SAP adaptors and SHP-1 phosphatase regulates NK cell education. *Nat. Immunol.* 2016. **17**: 387–396. Epub 2016 Feb 1015.

63 **Romo, N., Magri, G., Muntasell, A., Heredia, G., Baia, D., Angulo, A., Guma, M. et al.**, Natural killer cell-mediated response to human cytomegalovirus-infected macrophages is modulated by their functional polarization. *J. Leukoc. Biol.* 2011. **90**: 717–726. Epub 0312011 Jul 0311178.

64 **Zarama, A., Perez-Carmona, N., Farre, D., Tomic, A., Borst, E. M., Messerle, M., Jonjic, S. et al.**, Cytomegalovirus m154 hinders CD48 cell-surface expression and promotes viral escape from host natural killer cell control. *PLoS Pathog.* 2014. **10**: e1004000. eCollection 1002014 Mar.

65 **Aldhamen, Y. A., Rastall, D. P., Chen, W., Seregin, S. S., Pereira-Hicks, C., Godbehere, S., Kaminski, N. E. et al.**, CRACC-targeting Fc-fusion protein induces activation of NK cells and DCs and improves T cell immune responses to antigenic targets. *Vaccine* 2016. **34**: 3109–3118. Epub 2016 May 3103.

66 **Freund, J., May, R. M., Yang, E., Li, H., McCullen, M., Zhang, B., Lenvik, T. et al.**, Activating receptor signals drive receptor diversity in developing natural killer cells. *PLoS Biol.* 2016. **14**: e1002526. eCollection 1002016 Aug.

67 **van Helden, M. J., de Graaf, N., Boog, C. J., Topham, D. J., Zaiss, D. M. and Sijts, A. J.**, The bone marrow functions as the central site of proliferation for long-lived NK cells. *J. Immunol.* 2012. **189**: 2333–2337. Epub 1202012 Jul 1200020.

68 **Pyzik, M., Gendron-Pontbriand, E. M. and Vidal, S. M.**, The impact of Ly49-NK cell-dependent recognition of MCMV infection on innate and adaptive immune responses. *J. Biomed. Biotechnol.* 2011. **2011**: 641702. Epub 642011 May 641722.

69 **Voigt, V., Forbes, C. A., Tonkin, J. N., Degli-Esposti, M. A., Smith, H. R., Yokoyama, W. M. and Scalzo, A. A.**, Murine cytomegalovirus m157 mutation and variation leads to immune evasion of natural killer cells. *Proc Natl Acad Sci U S A* 2003. **100**: 13483–13488.

70 **Smith, L. M., McWhorter, A. R., Masters, L. L., Shellam, G. R. and Redwood, A. J.**, Laboratory strains of murine cytomegalovirus are genetically similar to but phenotypically distinct from wild strains of virus. *J. Virol.* 2008. **82**: 6689–6696.

71 **Rodriguez, M., Sabastian, P., Clark, P. and Brown, M. G.**, Cmv1-independent antiviral role of NK cells revealed in murine cytomegalovirus-infected New Zealand White mice. *J. Immunol.* 2004. **173**: 6312–6318.

72 **Belanger, S., Tai, L. H., Anderson, S. K. and Makrigiannis, A. P.**, Ly49 cluster sequence analysis in a mouse model of diabetes: an expanded repertoire of activating receptors in the NOD genome. *Genes Immun.* 2008. **9**: 509–521.

73 **French, A. R., Pingel, J. T., Kim, S., Yang, L. and Yokoyama, W. M.**, Rapid emergence of escape mutants following infection with murine cytomegalovirus in immunodeficient mice. *Clin. Immunol.* 2005. **115**: 61–69.

74 **McWhorter, A. R., Smith, L. M., Masters, L. L., Chan, B., Shellam, G. R. and Redwood, A. J.**, Natural killer cell dependent within-host competition arises during multiple MCMV infection: consequences for viral transmission and evolution. *PLoS Pathog.* 2013. **9**: e1003111. Epub 1002013 Jan 1003113.

75 **Min-Oo, G. and Lanier, L. L.**, Cytomegalovirus generates long-lived antigen-specific NK cells with diminished bystander activation to heterologous infection. *J. Exp. Med.* 2014. **211**: 2669–2680. Epub 20142014 Nov 20141124.

76 **Guma, M., Angulo, A., Vilches, C., Gomez-Lozano, N., Malats, N. and Lopez-Botet, M.**, Imprint of human cytomegalovirus infection on the NK cell receptor repertoire. *Blood* 2004. **104**: 3664–3671. Epub 2004 Aug 3610.

77 **Monsivais-Urenda, A., Noyola-Cherpitel, D., Hernandez-Salinas, A., Garcia-Sepulveda, C., Romo, N., Baranda, L., Lopez-Botet, M. et al.**, Influence of human cytomegalovirus infection on the NK cell receptor repertoire in children. *Eur. J. Immunol.* 2010. **40**: 1418–1427.

78 **Lopez-Verges, S., Milush, J. M., Schwartz, B. S., Pando, M. J., Jarjoura, J., York, V. A., Houchins, J. P. et al.**, Expansion of a unique CD57(+)NKG2Chi natural killer cell subset during acute human cytomegalovirus infection. *Proc Natl Acad Sci U S A* 2011. **108**: 14725–14732.

79 **Foley, B., Cooley, S., Verneris, M. R., Curtsinger, J., Luo, X., Waller, E. K., Anasetti, C. et al.**, Human cytomegalovirus (CMV)-induced memory-like NKG2C(+) NK cells are transplantable and expand in vivo in response to recipient CMV antigen. *J. Immunol.* 2012. **189**: 5082–5088. Epub 1202012 Oct 1201917.

80 **Foley, B., Cooley, S., Verneris, M. R., Pitt, M., Curtsinger, J., Luo, X., Lopez-Verges, S. et al.**, Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated NKG2C+ natural killer cells with potent function. *Blood* 2012. **119**: 2665–2674.

81 **Della Chiesa, M., Falco, M., Podesta, M., Locatelli, F., Moretta, L., Frassoni, F. and Moretta, A.**, Phenotypic and functional heterogeneity of human NK cells developing after umbilical cord blood transplantation: a role for human cytomegalovirus? *Blood.* 2012. **119**: 399–410. Epub 372011 Nov 372017.

82 **Della Chiesa, M., Muccio, L. and Moretta, A.**, CMV induces rapid NK cell maturation in HSCT recipients. *Immunol. Lett.* 2013. **155**: 11–13. Epub 2013 Sep 1026.

83 **Zhang, T., Scott, J. M., Hwang, I. and Kim, S.**, Cutting edge: antibody-dependent memory-like NK cells distinguished by FcRgamma deficiency. *J. Immunol.* 2013. **190**: 1402–1406. Epub 1202013 Jan 1203023.

84 **Muntasell, A., Pupuleku, A., Cisneros, E., Vera, A., Moraru, M., Vilches, C. and Lopez-Botet, M.**, Relationship of NKG2C Copy Number with the Distribution of Distinct Cytomegalovirus-Induced Adaptive NK Cell Subsets. *J. Immunol.* 2016. **196**: 3818–3827.

85 **Wu, Z., Sinzger, C., Frascaroli, G., Reichel, J., Bayer, C., Wang, L., Schirmbeck, R. et al.**, Human cytomegalovirus-induced NKG2C(hi) CD57(hi) natural killer cells are effectors dependent on humoral antiviral immunity. *J. Virol.* 2013. **87**: 7717–7725.

86 **Lee, J., Zhang, T., Hwang, I., Kim, A., Nitschke, L., Kim, M., Scott, J. M. et al.**, Epigenetic modification and antibody-dependent expansion of

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memory-like NK cells in human cytomegalovirus-infected individuals. *Immunity* 2015. **42**: 431–442.

87 **Costa-Garcia, M., Vera, A., Moraru, M., Vilches, C., Lopez-Botet, M. and Muntasell, A.**, Antibody-mediated response of NKG2Cbright NK cells against human cytomegalovirus. *J. Immunol.* 2015. **194**: 2715–2724. Epub 1402015 Feb 1402289.

88 **Liu, L. L., Landskron, J., Ask, E. H., Enqvist, M., Sohlberg, E., Traherne, J. A., Hammer, Q. et al.**, Critical Role of CD2 Co-stimulation in Adaptive Natural Killer Cell Responses Revealed in NKG2C-Deficient Humans. *Cell Rep* 2016. **15**: 1088–1099. Epub 2016 Apr 1021.

89 **Rolle, A., Halenius, A., Ewen, E. M., Cerwenka, A., Hengel, H. and Momburg, F.**, CD2-CD58 interactions are pivotal for the activation and function of adaptive natural killer cells in human cytomegalovirus infection. *Eur. J. Immunol.* 2016. **46**: 2420–2425. Epub 201642016 Aug 201646429.

90 **Corat, M. A., Schlums, H., Wu, C., Theorell, J., Espinoza, D. A., Sellers, S. E., Townsley, D. M. et al.**, Acquired somatic mutations in PNH reveal long-term maintenance of adaptive NK cells independent of HSPCs. *Blood* 2017. **129**: 1940–1946.

91 **Schlums, H., Jung, M., Han, H., Theorell, J., Bigley, V., Chiang, S. C., Allan, D. S. et al.**, Adaptive NK cells can persist in patients with GATA2 mutation depleted of stem and progenitor cells. *Blood* 2017. **129**: 1927–1939.

92 **Schlums, H., Cichocki, F., Tesi, B., Theorell, J., Beziat, V., Holmes, T. D., Han, H. et al.**, Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function. *Immunity* 2015. **42**: 443–456.

93 **Luetke-Eversloh, M., Hammer, Q., Durek, P., Nordstrom, K., Gasparoni, G., Pink, M., Hamann, A. et al.**, Human cytomegalovirus drives epigenetic imprinting of the IFNG locus in NKG2Chi natural killer cells. *PLoS Pathog.* 2014. **10**: e1004441.

94 **Beaulieu, A. M., Zawislak, C. L., Nakayama, T. and Sun, J. C.**, The transcription factor Zbtb32 controls the proliferative burst of virus-specific natural killer cells responding to infection. *Nat. Immunol.* 2014. **15**: 546–553. Epub 2014 Apr 1020.

95 **Nielsen, C. M., White, M. J., Bottomley, C., Lusa, C., Rodriguez-Galan, A., Turner, S. E., Goodier, M. R. et al.**, Impaired NK Cell Responses to Pertussis and H1N1 Influenza Vaccine Antigens in Human Cytomegalovirus-Infected Individuals. *J. Immunol.* 2015. **194**: 4657–4667. Epub 1402015 Apr 1403088.

96 **Schlums, H., Cichocki, F., Tesi, B., Theorell, J., Beziat, V., Holmes, T. D., Han, H. et al.**, Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function. *Immunity* 2015. **42**: 443–456.

97 **Darboe, A., Danso, E., Clarke, E., Umesi, A., Touray, E., Wegmuller, R., Moore, S. E. et al.**, Enhancement of cytokine-driven NK cell IFN-gamma production after vaccination of HCMV infected Africans. *Eur. J. Immunol.* 2017. **6**: 201746974.

98 **O'Sullivan, T. E. and Sun, J. C.**, Generation of Natural Killer Cell Memory during Viral Infection. *J Innate Immun* 2015. **7**: 557–562. Epub 000372015 Mar 000375424.

99 **Della Chiesa, M., Sivori, S., Carlomagno, S., Moretta, L. and Moretta, A.**, Activating KIRs and NKG2C in viral infections: toward NK cell memory? *Front Immunol* 2015. **6**: 573.

100 **Guma, M., Budt, M., Saez, A., Brckalo, T., Hengel, H., Angulo, A. and Lopez-Botet, M.**, Expansion of CD94/NKG2C+ NK cells in response to human cytomegalovirus-infected fibroblasts. *Blood* 2006. **107**: 3624–3631. Epub 2005 Dec 3629.

101 **Kaiser, B. K., Pizarro, J. C., Kerns, J. and Strong, R. K.**, Structural basis for NKG2A/CD94 recognition of HLA-E. *Proc Natl Acad Sci U S A* 2008. **105**: 6696–6701. Epub 0802732008 Apr 0802736130.

102 **Rolle, A., Pollmann, J., Ewen, E. M., Le, V. T., Halenius, A., Hengel, H. and Cerwenka, A.**, IL-12-producing monocytes and HLA-E control HCMV-driven NKG2C+ NK cell expansion. *J. Clin. Invest.* 2014. **124**: 5305–5316. Epub 72014 Nov 77410.

103 **Muntasell, A., Lopez-Montanes, M., Vera, A., Heredia, G., Romo, N., Penafiel, J., Moraru, M. et al.**, NKG2C zygosity influences CD94/NKG2C receptor function and the NK-cell compartment redistribution in response to human cytomegalovirus. *Eur. J. Immunol.* 2013. **43**: 3268–3278. Epub 201342013 Oct 201343779.

104 **Goodier, M. R., White, M. J., Darboe, A., Nielsen, C. M., Goncalves, A., Bottomley, C., Moore, S. E. et al.**, Rapid NK cell differentiation in a population with near-universal human cytomegalovirus infection is attenuated by NKG2C deletions. *Blood* 2014. **124**: 2213–2222.

105 **Noyola, D. E., Fortuny, C., Muntasell, A., Noguera-Julian, A., Munoz-Almagro, C., Alarcon, A., Juncosa, T. et al.**, Influence of congenital human cytomegalovirus infection and the NKG2C genotype on NK-cell subset distribution in children. *Eur. J. Immunol.* 2012. **42**: 3256–3266. Epub 201242012 Oct 201242725.

106 **Makwana, N. B., Foley, B., Lee, S., Fernandez, S., Irish, A. B. and Price, P.**, Asymptomatic CMV infections in long-term renal transplant recipients are associated with the loss of FcRgamma from LIR-1+ NK cells. *Eur. J. Immunol.* 2016. **46**: 2597–2608. Epub 201642016 Sep 201646426.

107 **Newhook, N., Fudge, N. and Grant, M.**, NK cells generate memory-type responses to human cytomegalovirus-infected fibroblasts. *Eur. J. Immunol.* 2017. **47**: 1032–1039.

108 **Beziat, V., Liu, L. L., Malmberg, J. A., Ivarsson, M. A., Sohlberg, E., Bjorklund, A. T., Retiere, C. et al.**, NK cell responses to cytomegalovirus infection lead to stable imprints in the human KIR repertoire and involve activating KIRs. *Blood* 2013. **121**: 2678–2688. Epub 452013 Jan 459516.

109 **Della Chiesa, M., Falco, M., Bertaina, A., Muccio, L., Alicata, C., Frassoni, F., Locatelli, F. et al.**, Human cytomegalovirus infection promotes rapid maturation of NK cells expressing activating killer Ig-like receptor in patients transplanted with NKG2C-/- umbilical cord blood. *J. Immunol.* 2014. **192**: 1471–1479. Epub 1302014 Jan 1302017.

110 **Berrien-Elliott, M. M., Wagner, J. A. and Fehniger, T. A.**, Human Cytokine-Induced Memory-Like Natural Killer Cells. *J Innate Immun* 2015. **7**: 563–571.

111 **Cooper, M. A., Elliott, J. M., Keyel, P. A., Yang, L., Carrero, J. A. and Yokoyama, W. M.**, Cytokine-induced memory-like natural killer cells. *Proc Natl Acad Sci U S A.* 2009. **106**: 1915–1919. Epub 0813192009 Jan 0813192130.

112 **Keppel, M. P., Yang, L. and Cooper, M. A.**, Murine NK cell intrinsic cytokine-induced memory-like responses are maintained following homeostatic proliferation. *J. Immunol.* 2013. **190**: 4754–4762.

113 **Leong, J. W., Chase, J. M., Romee, R., Schneider, S. E., Sullivan, R. P., Cooper, M. A. and Fehniger, T. A.**, Preactivation with IL-12, IL-15, and IL-18 induces CD25 and a functional high-affinity IL-2 receptor on human cytokine-induced memory-like natural killer cells. *Biol. Blood Marrow Transplant.* 2014. **20**: 463–473.

114 **Romee, R., Schneider, S. E., Leong, J. W., Chase, J. M., Keppel, C. R., Sullivan, R. P., Cooper, M. A. et al.**, Cytokine activation induces human memory-like NK cells. *Blood.* 2012. **120**: 4751–4760. Epub 412012 Sep 419214.

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115 **Nabekura, T. and Lanier, L. L.**, Tracking the fate of antigen-specific versus cytokine-activated natural killer cells after cytomegalovirus infection. *J. Exp. Med.* 2016. **213**: 2745–2758. Epub 2016 Oct 2724.

116 **Lee, S. H., Fragoso, M. F. and Biron, C. A.**, Cutting edge: a novel mechanism bridging innate and adaptive immunity: IL-12 induction of CD25 to form high-affinity IL-2 receptors on NK cells. *J. Immunol.* 2012. **189**: 2712–2716.

117 **He, X. S., Draghi, M., Mahmood, K., Holmes, T. H., Kemble, G. W., Dekker, C. L., Arvin, A. M. et al.**, T cell-dependent production of IFN-gamma by NK cells in response to influenza A virus. *J. Clin. Invest.* 2004. **114**: 1812–1819.

118 **White, M. J., Nielsen, C. M., McGregor, R. H., Riley, E. H. and Goodier, M. R.**, Differential activation of CD57-defined natural killer cell subsets during recall responses to vaccine antigens. *Immunology* 2014. **142**: 140–150.

119 **Goodier, M. R., Rodriguez-Galan, A., Lusa, C., Nielsen, C. M., Darboe, A., Moldoveanu, A. L., White, M. J. et al.**, Influenza Vaccination Generates Cytokine-Induced Memory-like NK Cells: Impact of Human Cytomegalovirus Infection. *J. Immunol.* 2016. **197**: 313–325. Epub 1502016 May 1502027.

120 **Horowitz, A., Behrens, R. H., Okell, L., Fooks, A. R. and Riley, E. M.**, NK cells as effectors of acquired immune responses: effector CD4+ T cell-dependent activation of NK cells following vaccination. *J. Immunol.* 2010. **185**: 2808–2818. Epub 1002010 Aug 1000842.

121 **Horowitz, A., Hafalla, J. C., King, E., Lusingu, J., Dekker, D., Leach, A., Moris, P. et al.**, Antigen-specific IL-2 secretion correlates with NK cell responses after immunization of Tanzanian children with the RTS,S/AS01 malaria vaccine. *J. Immunol.* 2012. **188**: 5054–5062. Epub 1102012 Apr 1102713.

122 **Jost, S., Quillay, H., Reardon, J., Peterson, E., Simmons, R. P., Parry, B. A., Bryant, N. N. et al.**, Changes in cytokine levels and NK cell activation associated with influenza. *PLoS One* 2011. **6**: e25060. Epub 0022011 Sep 0025023.

123 **Jost, S., Tomezsko, P. J., Rands, K., Toth, I., Lichterfeld, M., Gandhi, R. T. and Altfeld, M.**, CD4+ T-cell help enhances NK cell function following therapeutic HIV-1 vaccination. *J. Virol.* 2014. **88**: 8349–8354. Epub 02014 May 00914.

124 **Suliman, S., Geldenhuys, H., Johnson, J. L., Hughes, J. E., Smit, E., Murphy, M., Toefy, A. et al.**, Bacillus Calmette-Guerin (BCG) revaccination of adults with latent Mycobacterium tuberculosis infection induces long-lived bcg-reactive NK cell responses. *J. Immunol.* 2016. **197**: 1100–1110. Epub 1502016 Jul 1501913.

125 **Goodier, M. R., Lusa, C., Sherratt, S., Rodriguez-Galan, A., Behrens, R. and Riley, E. M.**, Sustained immune complex-mediated reduction in CD16 expression after vaccination regulates NK cell function. *Front Immunol* 2016. **7**: 384. eCollection 2016.

126 **Leong, J. W., Chase, J. M., Romee, R., Schneider, S. E., Sullivan, R. P., Cooper, M. A. and Fehniger, T. A.**, Preactivation with IL-12, IL-15, and IL-18 induces CD25 and a functional high-affinity IL-2 receptor on human cytokine-induced memory-like natural killer cells. *Biol. Blood Marrow Transplant.* 2014. **20**: 463–473. Epub 2014 Jan 1013.

127 **Marquardt, N., Ivarsson, M. A., Blom, K., Gonzalez, V. D., Braun, M., Falconer, K., Gustafsson, R. et al.**, The human NK cell response to yellow fever virus 17D is primarily governed by NK cell differentiation independently of NK cell education. *J. Immunol.* 2015. **195**: 3262–3272. Epub 1402015 Aug 1401817.

128 **Moro-Garcia, M. A., Alonso-Arias, R., Lopez-Vazquez, A., Suarez-Garcia, F. M., Solano-Jaurrieta, J. J., Baltar, J. and Lopez-Larrea, C.**, Relationship between functional ability in older people, immune system status, and intensity of response to CMV. *Age (Dordr)* 2012. **34**: 479–495. Epub 12011 Apr 11313.

129 **Trzonkowski, P., Mysliwska, J., Szmit, E., Wieckiewicz, J., Lukaszuk, K., Brydak, L. B., Machala, M. et al.**, Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination–an impact of immunosenescence. *Vaccine* 2003. **21**: 3826–3836.

130 **Turner, J. E., Campbell, J. P., Edwards, K. M., Howarth, L. J., Pawelec, G., Aldred, S., Moss, P. et al.**, Rudimentary signs of immunosenescence in Cytomegalovirus-seropositive healthy young adults. *Age (Dordr)* 2014. **36**: 287–297. Epub 12013 Jul 11312.

131 **Wald, A., Selke, S., Magaret, A. and Boeckh, M.**, Impact of human cytomegalovirus (CMV) infection on immune response to pandemic 2009 H1N1 influenza vaccine in healthy adults. *J. Med. Virol.* 2013. **85**: 1557–1560.

132 **Furman, D., Jojic, V., Sharma, S., Shen-Orr, S. S., Angel, C. J., Onengut-Gumuscu, S., Kidd, B. A. et al.**, Cytomegalovirus infection enhances the immune response to influenza. *Sci. Transl. Med.* 2015. **7**: 281ra243.

133 **Mwaanza, N., Chilukutu, L., Tembo, J., Kabwe, M., Musonda, K., Kapasa, M., Chabala, C. et al.**, High rates of congenital cytomegalovirus infection linked with maternal HIV infection among neonatal admissions at a large referral center in sub-Saharan Africa. *Clin. Infect. Dis.* 2014. **58**: 728–735.

134 **Tembo, J., Kabwe, M., Chilukutu, L., Chilufya, M., Mwaanza, N., Chabala, C., Zumla, A. et al.**, Prevalence and risk factors for betaherpesvirus DNAemia in children >3 weeks and <2 years of age admitted to a large referral hospital in sub-Saharan Africa. *Clin. Infect. Dis.* 2015. **60**: 423–431.

135 **Pawelec, G.**, Immunosenenescence: role of cytomegalovirus. *Exp. Gerontol.* 2014. **54**: 1–5.

136 **Bjorkstrom, N. K., Riese, P., Heuts, F., Andersson, S., Fauriat, C., Ivarsson, M. A., Bjorklund, A. T. et al.**, Expression patterns of NKG2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. *Blood* 2010. **116**: 3853–3864. Epub 282010 Aug 281679.

137 **Lopez-Verges, S., Milush, J. M., Pandey, S., York, V. A., Arakawa-Hoyt, J., Pircher, H., Norris, P. J. et al.**, CD57 defines a functionally distinct population of mature NK cells in the human CD56dimCD16+ NK-cell subset. *Blood* 2010. **116**: 3865–3874. Epub 282010 Aug 282323.

138 **Nabekura, T., Kanaya, M., Shibuya, A., Fu, G., Gascoigne, N. R. and Lanier, L. L.**, Costimulatory molecule DNAM-1 is essential for optimal differentiation of memory natural killer cells during mouse cytomegalovirus infection. *Immunity* 2014. **40**: 225–234. Epub 2014 Jan 1016.

139 **Draghi, M., Pashine, A., Sanjanwala, B., Gendzekhadze, K., Cantoni, C., Cosman, D., Moretta, A. et al.**, NKp46 and NKG2D recognition of infected dendritic cells is necessary for NK cell activation in the human response to influenza infection. *J. Immunol.* 2007. **178**: 2688–2698.

140 **Fielding, C. A., Weekes, M. P., Nobre, L. V., Ruckova, E., Wilkie, G. S., Paulo, J. A., Chang, C. et al.**, Control of immune ligands by members of a cytomegalovirus gene expansion suppresses natural killer cell activation. *Elife* 2017. **6**: e22206.

141 **Bigley, A. B., Rezvani, K., Shah, N., Sekine, T., Balneger, N., Pistillo, M., Agha, N. et al.**, Latent cytomegalovirus infection enhances anti-tumour cytotoxicity through accumulation of NKG2C+ NK cells in healthy humans. *Clin. Exp. Immunol.* 2016. **185**: 239–251.

142 **Waggoner, S. N., Cornberg, M., Selin, L. K. and Welsh, R. M.**, Natural killer cells act as rheostats modulating antiviral T cells. *Nature* 2011. **481**: 394–398.

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143 **Xu, G., Smith, T., Grey, F. and Hill, A. B.**, Cytomegalovirus-based cancer vaccines expressing TRP2 induce rejection of melanoma in mice. *Biochem. Biophys. Res. Commun.* 2013. **437**: 287–291.

144 **Slavuljica, I., Busche, A., Babic, M., Mitrovic, M., Gasparovic, I., Cekinovic, D., Markova Car, E. et al.**, Recombinant mouse cytomegalovirus expressing a ligand for the NKG2D receptor is attenuated and has improved vaccine properties. *J. Clin. Invest.* 2010. **120**: 4532–4545.

145 **Trsan, T., Busche, A., Abram, M., Wensveen, F. M., Lemmermann, N. A., Arapovic, M., Babic, M. et al.**, Superior induction and maintenance of protective CD8 T cells in mice infected with mouse cytomegalovirus vector expressing RAE-1gamma. *Proc Natl Acad Sci U S A* 2013. **110**: 16550–16555.

146 **Quinn, M., Erkes, D. A. and Snyder, C. M.**, Cytomegalovirus and immunotherapy: opportunistic pathogen, novel target for cancer and a promising vaccine vector. *Immunotherapy* 2016. **8**: 211–221.

147 **Hansen, S. G., Sacha, J. B., Hughes, C. M., Ford, J. C., Burwitz, B. J., Scholz, I., Gilbride, R. M. et al.**, Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. *Science* 2013. **340**: 1237874.

148 **Hansen, S. G., Ford, J. C., Lewis, M. S., Ventura, A. B., Hughes, C. M., Coyne-Johnson, L., Whizin, N. et al.**, Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature* 2011. **473**: 523–527.

149 **Tomic, A., Varanasi, P. R., Golemac, M., Malic, S., Riese, P., Borst, E. M., Mischak-Weissinger, E. et al.**, Activation of innate and adaptive immunity by a recombinant human cytomegalovirus strain expressing an NKG2D ligand. *PLoS Pathog.* 2016. **12**: e1006015.

150 **Tomasec, P., Braud, V. M., Rickards, C., Powell, M. B., McSharry, B. P., Gadola, S., Cerundolo, V. et al.**, Surface expression of HLA-E, an inhibitor of natural killer cells, enhanced by human cytomegalovirus gpUL40. *Science* 2000. **287**: 1031.

151 **Ulbrecht, M., Martinozzi, S., Grzeschik, M., Hengel, H., Ellwart, J. W., Pla, M. and Weiss, E. H.**, Cutting edge: the human cytomegalovirus UL40 gene product contains a ligand for HLA-E and prevents NK cell-mediated lysis. *J. Immunol.* 2000. **164**: 5019–5022.

152 **Kavanagh, D. G., Koszinowski, U. H. and Hill, A. B.**, The murine cytomegalovirus immune evasion protein m4/gp34 forms biochemically distinct complexes with class I MHC at the cell surface and in a pre-Golgi compartment. *J. Immunol.* 2001. **167**: 3894–3902.

153 **Kielczewska, A., Pyzik, M., Sun, T., Krmpotic, A., Lodoen, M. B., Munks, M. W., Babic, M. et al.**, Ly49P recognition of cytomegalovirus-infected cells expressing H2-Dk and CMV-encoded m04 correlates with the NK cell antiviral response. *J. Exp. Med.* 2009. **206**: 515–523. Epub 20082009 Mar 20080952.

154 **Kleijnen, M. F., Huppa, J. B., Lucin, P., Mukherjee, S., Farrell, H., Campbell, A. E., Koszinowski, U. H. et al.**, A mouse cytomegalovirus glycoprotein, gp34, forms a complex with folded class I MHC molecules in the ER which is not retained but is transported to the cell surface. *EMBO J.* 1997. **16**: 685–694.

155 **Pyzik, M., Charbonneau, B., Gendron-Pontbriand, E. M., Babic, M., Krmpotic, A., Jonjic, S. and Vidal, S. M.**, Distinct MHC class I-dependent NK cell-activating receptors control cytomegalovirus infection in different mouse strains. *J. Exp. Med.* 2011. **208**: 1105–1117. Epub 20102011 Apr 20101825.

156 **Prod'homme, V., Griffin, C., Aicheler, R. J., Wang, E. C., McSharry, B. P., Rickards, C. R., Stanton, R. J. et al.**, The human cytomegalovirus MHC class I homolog UL18 inhibits LIR-1+ but activates LIR-1- NK cells. *J. Immunol.* 2007. **178**: 4473–4481.

157 **Carlyle, J. R., Jamieson, A. M., Gasser, S., Clingan, C. S., Arase, H. and Raulet, D. H.**, Missing self-recognition of Ocil/Clr-b by inhibitory NKR-P1 natural killer cell receptors. *Proc Natl Acad Sci U S A* 2004. **101**: 3527–3532. Epub 2004 Feb 3527.

158 **Rahim, M. M., Wight, A., Mahmoud, A. B., Aguilar, O. A., Lee, S. H., Vidal, S. M., Carlyle, J. R. et al.**, Expansion and protection by a virus-specific NK cell subset lacking expression of the inhibitory NKR-P1B receptor during murine cytomegalovirus infection. *J. Immunol.* 2016. **197**: 2325–2337. Epub 1602016 Aug 1600710.

159 **Farrell, H. E., Vally, H., Lynch, D. M., Fleming, P., Shellam, G. R., Scalzo, A. A. and Davis-Poynter, N. J.**, Inhibition of natural killer cells by a cytomegalovirus MHC class I homologue in vivo. *Nature* 1997. **386**: 510–514.

160 **Seidel, E., Le, V. T., Bar-On, Y., Tsukerman, P., Enk, J., Yamin, R., Stein, N. et al.**, Dynamic co-evolution of host and pathogen: HCMV downregulates the prevalent allele MICA 008 to escape elimination by NK cells. *Cell Rep* 2015. **12**: 00054–00056.

161 **Cosman, D., Mullberg, J., Sutherland, C. L., Chin, W., Armitage, R., Fanslow, W., Kubin, M. et al.**, ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. *Immunity* 2001. **14**: 123–133.

162 **Dunn, C., Chalupny, N. J., Sutherland, C. L., Dosch, S., Sivakumar, P. V., Johnson, D. C. and Cosman, D.**, Human cytomegalovirus glycoprotein UL16 causes intracellular sequestration of NKG2D ligands, protecting against natural killer cell cytotoxicity. *J. Exp. Med.* 2003. **197**: 1427–1439.

163 **Eagle, R. A., Traherne, J. A., Hair, J. R., Jafferji, I. and Trowsdale, J.**, ULBP6/RAET1L is an additional human NKG2D ligand. *Eur. J. Immunol.* 2009. **39**: 3207–3216.

164 **Fielding, C. A., Aicheler, R., Stanton, R. J., Wang, E. C., Han, S., Seirafian, S., Davies, J. et al.**, Two novel human cytomegalovirus NK cell evasion functions target MICA for lysosomal degradation. *PLoS Pathog.* 2014. **10**: e1004058. eCollection 1002014 May.

165 **Stern-Ginossar, N., Elefant, N., Zimmermann, A., Wolf, D. G., Saleh, N., Biton, M., Horwitz, E. et al.**, Host immune system gene targeting by a viral miRNA. *Science* 2007. **317**: 376–381.

166 **Ashiru, O., Bennett, N. J., Boyle, L. H., Thomas, M., Trowsdale, J. and Wills, M. R.**, NKG2D ligand MICA is retained in the cis-Golgi apparatus by human cytomegalovirus protein UL142. *J. Virol.* 2009. **83**: 12345–12354. Epub 12009 Sep 12330.

167 **Chalupny, N. J., Rein-Weston, A., Dosch, S. and Cosman, D.**, Down-regulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142. *Biochem. Biophys. Res. Commun.* 2006. **346**: 175–181. Epub 2006 May 2024.

168 **Arapovic, J., Lenac Rovis, T., Reddy, A. B., Krmpotic, A. and Jonjic, S.**, Promiscuity of MCMV immunoevasin of NKG2D: m138/fcr-1 down-modulates RAE-1epsilon in addition to MULT-1 and H60. *Mol. Immunol.* 2009. **47**: 114–122. Epub 2009 Mar 1017.

169 **Lenac, T., Budt, M., Arapovic, J., Hasan, M., Zimmermann, A., Simic, H., Krmpotic, A. et al.**, The herpesviral Fc receptor fcr-1 down-regulates the NKG2D ligands MULT-1 and H60. *J. Exp. Med.* 2006. **203**: 1843–1850. Epub 2006 Jul 1810.

170 **Krmpotic, A., Hasan, M., Loewendorf, A., Saulig, T., Halenius, A., Lenac, T., Polic, B. et al.**, NK cell activation through the NKG2D ligand MULT-1 is selectively prevented by the glycoprotein encoded by mouse cytomegalovirus gene m145. *J. Exp. Med.* 2005. **201**: 211–220. Epub 2005 Jan 2010.

171 **Arapovic, J., Lenac, T., Antulov, R., Polic, B., Ruzsics, Z., Carayannopoulos, L. N., Koszinowski, U. H. et al.**, Differential susceptibility of RAE-1 isoforms to mouse cytomegalovirus. *J. Virol.* 2009. **83**: 8198–8207. Epub 02009 Jun 02543.

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172 **Lodoen, M.**, **Ogasawara, K.**, **Hamerman, J. A.**, **Arase, H.**, **Houchins, J. P.**, **Mocarski, E. S. and Lanier, L. L.**, NKG2D-mediated natural killer cell protection against cytomegalovirus is impaired by viral gp40 modulation of retinoic acid early inducible 1 gene molecules. *J. Exp. Med.* 2003. **197**: 1245–1253.

173 **Hasan, M.**, **Krmpotic, A.**, **Ruzsics, Z.**, **Bubic, I.**, **Lenac, T.**, **Halenius, A.**, **Loewendorf, A. et al.**, Selective down-regulation of the NKG2D ligand H60 by mouse cytomegalovirus m155 glycoprotein. *J. Virol.* 2005. **79**: 2920–2930.

174 **Lodoen, M. B.**, **Abenes, G.**, **Umamoto, S.**, **Houchins, J. P.**, **Liu, F. and Lanier, L. L.**, The cytomegalovirus m155 gene product subverts natural killer cell antiviral protection by disruption of H60-NKG2D interactions. *J. Exp. Med.* 2004. **200**: 1075–1081. Epub 2004 Oct 1011.

175 **Hsu, J. L.**, **van den Boomen, D. J.**, **Tomasec, P.**, **Weekes, M. P.**, **Antrobus, R.**, **Stanton, R. J.**, **Ruckova, E. et al.**, Plasma membrane profiling defines an expanded class of cell surface proteins selectively targeted for degradation by HCMV US2 in cooperation with UL141. *PLoS Pathog.* 2015. **11**: e1004811. eCollection 1002015 Apr.

176 **Stanietsky, N. and Mandelboim, O.**, Paired NK cell receptors controlling NK cytotoxicity. *FEBS Lett.* 2010. **584**: 4895–4900. Epub 2010 Sep 4897.

177 **Tomasec, P.**, **Wang, E. C.**, **Davison, A. J.**, **Vojtesek, B.**, **Armstrong, M.**, **Griffin, C.**, **McSharry, B. P. et al.**, Downregulation of natural killer cell-activating ligand CD155 by human cytomegalovirus UL141. *Nat. Immunol.* 2005. **6**: 181–188. Epub 2005 Jan 2009.

178 **Lenac Rovis, T.**, **Kucan Brlic, P.**, **Kaynan, N.**, **Juranic Lisnic, V.**, **Brizic, I.**, **Jordan, S.**, **Tomic, A. et al.**, Inflammatory monocytes and NK cells play a crucial role in DNAM-1-dependent control of cytomegalovirus infection. *J. Exp. Med.* 2016. **213**: 1835–1850. Epub 20152016 Aug 20151898.

179 **Arnon, T. I.**, **Achdout, H.**, **Levi, O.**, **Markel, G.**, **Saleh, N.**, **Katz, G.**, **Gazit, R. et al.**, Inhibition of the NKp30 activating receptor by pp65 of human cytomegalovirus. *Nat. Immunol.* 2005. **6**: 515–523. Epub 2005 Apr 2010.

180 **Nemcovicova, I.**, **Benedict, C. A. and Zajonc, D. M.**, Structure of human cytomegalovirus UL141 binding to TRAIL-R2 reveals novel, non-canonical death receptor interactions. *PLoS Pathog.* 2013. **9**: e1003224. Epub 1002013 Mar 1003221.

181 **Smith, W.**, **Tomasec, P.**, **Aicheler, R.**, **Loewendorf, A.**, **Nemcovicova, I.**, **Wang, E. C.**, **Stanton, R. J. et al.**, Human cytomegalovirus glycoprotein UL141 targets the TRAIL death receptors to thwart host innate antiviral defenses. *Cell Host Microbe* 2013. **13**: 324–335.

182 **Verma, S.**, **Loewendorf, A.**, **Wang, Q.**, **McDonald, B.**, **Redwood, A. and Benedict, C. A.**, Inhibition of the TRAIL death receptor by CMV reveals its importance in NK cell-mediated antiviral defense. *PLoS Pathog.* 2014. **10**: e1004268. eCollection 1002014 Aug.

183 **Zufferey, C.**, **Germano, S.**, **Dutta, B.**, **Ritz, N. and Curtis, N.**, The contribution of non-conventional T cells and NK cells in the mycobacterial-specific IFNgamma response in Bacille Calmette-Guerin (BCG)-immunized infants. *PLoS One* 2013. **8**: e77334. eCollection 0072013.

184 **Dou, Y.**, **Fu, B.**, **Sun, R.**, **Li, W.**, **Hu, W.**, **Tian, Z. and Wei, H.**, Influenza vaccine induces intracellular immune memory of human NK cells. *PLoS One* 2015. **10**: e0121258. eCollection 0122015.

185 **Sun, J. C.**, **Beilke, J. N. and Lanier, L. L.**, Adaptive immune features of natural killer cells. *Nature* 2009. **457**: 557–561.

186 **Min-Oo, G.**, **Bezman, N. A.**, **Madera, S.**, **Sun, J. C. and Lanier, L. L.**, Proapoptotic Bim regulates antigen-specific NK cell contraction and the generation of the memory NK cell pool after cytomegalovirus infection. *J. Exp. Med.* 2014. **211**: 1289–1296.

187 **Nabekura, T. and Lanier, L. L.**, Activating Receptors for Self-MHC Class I Enhance Effector Functions and Memory Differentiation of NK Cells during Mouse Cytomegalovirus Infection. *Immunity* 2016. **45**: 74–82.

188 **Caligiuri, M. A.**, Human natural killer cells. *Blood* 2008. **112**: 461–469.

189 **Lugli, E.**, **Marcenaro, E. and Mavilio, D.**, NK Cell Subset Redistribution during the Course of Viral Infections. *Front Immunol* 2014. **5**: 390.

190 **Foley, B.**, **Cooley, S.**, **Verneris, M. R.**, **Pitt, M.**, **Curtsinger, J.**, **Luo, X.**, **Lopez-Verges, S. et al.**, Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated NKG2C+ natural killer cells with potent function. *Blood* 2012. **119**: 2665–2674.

191 **Beziat, V.**, **Sleiman, M.**, **Goodridge, J. P.**, **Kaarbo, M.**, **Liu, L. L.**, **Rollag, H.**, **Ljunggren, H. G. et al.**, Polyclonal Expansion of NKG2C(+) NK Cells in TAP-Deficient Patients. *Front Immunol* 2015. **6**: 507.

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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