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The Multifaceted Roles of NK Cells in the Context of Murine Cytomegalovirus and Lymphocytic Choriomeningitis Virus Infections

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Conflict of Interest
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Abbreviations
APC, Ag-presenting cell; CMV, cytomegalovirus; DC, dendritic cell; DNAM-1, DNAX accessory molecule-1; HCMV, human cytomegalovirus; IE, immediate-early; LCMV, lymphocytic choriomeningitis virus; MCMV, murine cytomegalovirus; NCR1, natural cytotoxic receptor 1; NKG2D, NK group 2, member D; TNFR2, TNF receptor 2; TRAIL, TNF-related apoptosis inducing ligand.

ABSTRACT

NK cells belong to innate lymphoid cells and able to eliminate infected cells and tumor cells. NK cells play a valuable role in controlling viral infections. Also, they have the potential to shape the adaptive immunity via a unique crosstalk with the different immune cells. Murine models are important tools for delineating the immunological phenomena in viral infection. To decipher the immunological virus-host interactions, two major infection models are being investigated in mice regarding NK cell-mediated recognition: murine cytomegalovirus (MCMV) and lymphocytic choriomeningitis virus (LCMV). In this review, we recapitulate recent findings regarding the multifaceted role of NK cells in controlling LCMV and MCMV infections and outline the exquisite interplay between NK cells and other immune cells in these two settings. Considering that, infections with MCMV and LCMV recapitulates many physiopathological characteristics of human cytomegalovirus infection and chronic virus infections respectively, this study will extend our understanding of NK cells biology in interactions between the virus and its natural host.

Keywords: NK cells; LCMV; MCMV; Viral infections

INTRODUCTION

NK cells are innate cytotoxic lymphocytes and play an integral role in combating various pathogens. NK cells act by releasing cytokines and performing cytolytic activity toward tumor cells and virally infected cells (1). Even though NK cells are key players of innate immunity for ages, they have some emerged substantial adaptive roles as well (2). Unlike T and B lymphocytes which have rearranged Ag receptors, NK cells recognize their surroundings through receptors for pro-inflammatory cytokines, and via germline-encoded inhibitory and activating receptors (1,3). NK cells contribute to defense against wide spectrum of viral infections, such as; arenaviruses (e.g., lymphocytic choriomeningitis virus [LCMV]), and herpesviruses (e.g., murine cytomegalovirus [MCMV]), primarily by cytotoxicity, and modestly by IFN-γ (4).

Certain viruses establish chronic infection in the host such as HIV, hepatitis virus (e.g., hepatitis C and B) and cytomegalovirus (CMV). To induce persistent infection, viruses

adopt different mechanisms based on their distinct biology and could be dissected into two models. The infection with DNA viruses (e.g., CMV) is characterized by low level of viremia, latency/reactivation and a ''camouflage and/or sabotage'' strategy. On other hand, infection with RNA viruses such as (HIV, hepatitis viruses and LCMV) is characterized with high level of viremia as they are highly replicating (5-7).

MCMV is a member of the genus CMV of the beta-herpesviruses and is species-specific and is targeting hematopoietic cells with a slow replicative life. MCMV is known to cause protracted infection in their hosts. After resolving the acute phase, the virus goes through a latency period, which is defined by minimal genes transcription and inert viral progeny (8,9). MCMV has been broadly used as a model for delineating the function of NK cells in viral control. Before sparking the adaptive immunity, NK cells have appreciated role in MCMV infection at early stages (10). MCMV shares more than 80% of genome similarity with human CMV (HCMV), and studying the immune response including NK cell response during MCMV infections would give meaningful insights and better understanding about the NK cell immunity in human models (11).

LCMV is an enveloped RNA virus and is a member of the Arenaviridae family. The house mouse (Mus musculus) is the natural host of LCMV and can affect humans. In addition, LCMV is extensively used in immunological research as a prototypical and generalizable model of viral infection in mice and to study the host-virus interactions for highly replicating viruses in humans such as HIV and hepatitis viruses. Many seminal and fascinating findings have been achieved due to LCMV research which has been extended to other human chronic viral infections that mimic the LCMV infections model (12,13). Using LCMV infection model is instrumental for delineating the regulatory involvement of NK cells to virus pathogenesis in humans with no direct influence on disease control.

Opposed to the essential and direct role of NK cells in eliminating MCMV infections which is described as NK cells sensitive, NK cells have an indirect and casual role in LCMV infections control. Because NK cells are not the major defenders in LCMV infections, the latter is described as NK cell resistant. Nevertheless, depletion of NK cells has a profound impact on the modification of pathogenesis patterns and persistence of LCMV, due to the indirect effect of NK cells on LCMV, via modulating the T cell response (14). NK cells depletion experiments in murine models infected with LCMV culminate in distinct scenarios of antiviral immunity and subsequent virus clearance (14). In this review, we will pinpoint the integral role of NK cells in controlling LCMV and MCMV infections and we will shed light on the NK cells crosstalk with other immune cells in these two infections models (**Table 1**, **Fig. 1A and B**). Understanding the NK importance, role, and their cell biology in these two models would give insights about the virus host interaction and provide customized therapeutic approaches to improve host advantage during infection.

MCMV

MCMV is a member of the genus Muromegalovirus in the subfamily β-herpesvirinae. It shares characteristics with the genus CMV, including HCMV. CMVs have large double-stranded DNA genomes and can induce cytomegaly in infected cells (15). Hepesviruses including MCMV encompass both lytic (productive) and latent (non-productive) infection of the natural host (16). Both MCMV and HCMV have a specific host range. Infection of murine

Table 1. Comparison between MCMV and LCMV in terms of different features

Feature	MCMV	LCMV
Classification of virus	β-beta herpesvirinae (double-stranded DNA)	Arenaviridae (single stranded RNA)
Key immune components involved in virus control	· NK cells via IFN-γ, Ly49H, NCR1, DNAM-1, NKG2D, TNFR2, IRF4 · CD8 T cells, CD4 T cells · Proinflammatory cytokines (e.g., IL-33, IL-12, IL-18) · IFN-γ via inhibiting viral gene expression, macrophages activation, enhancing T and B cell activation	· CD8 T cells, CD4 T cells · IFN-γ
Human model	Latent viruses with low level of viremia (e.g., human CMV)	Highly replicating viruses with high level of viremia (e.g., HIV and hepatitis)
Role of NK cells in eliminating the virus	Direct (NK cell sensitive)	Indirect (NK cell resistant)
Immune evasion mechanism	· Encoding evasion proteins; m152, m04 and m06 · Downregulation of ligand for NKG2D · miRNA · Deactivation of NCRs	IFN-I

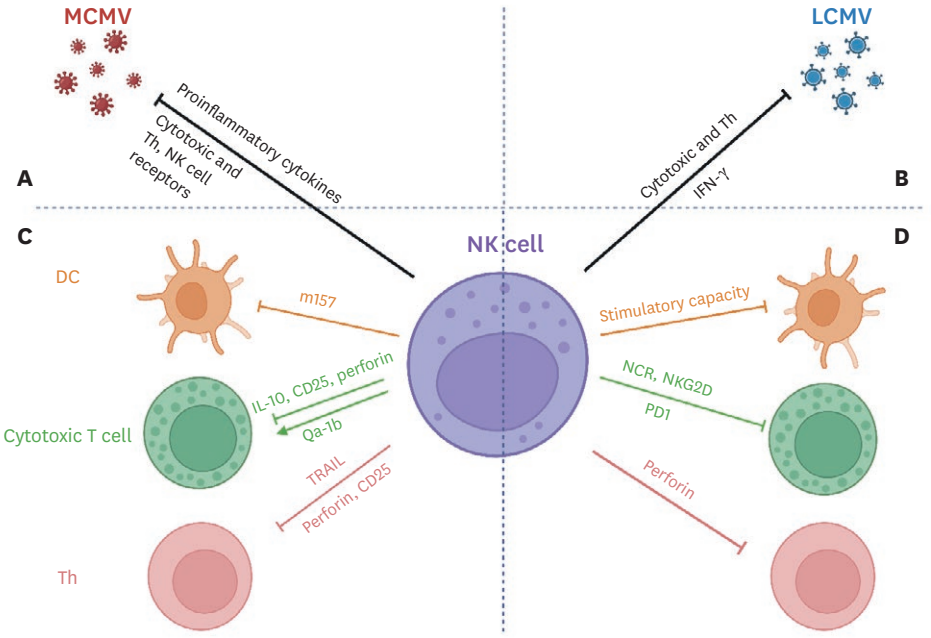

Figure 1. The role of NK cells and their crosstalk with the immune cells during MCMV and LCMV infections. Illustration of NK cell role in controlling MCMV (A) and LCMV (B) infections. (C, D) depict the crosstalk between NK cells and other immune cells in the context of MCMV and LCMV respectively (created with BioRender.ccom).

models with MCMV is used to simulate the HCMV pathogenesis due to the shared biological characteristics in their natural hosts (17-20).

As with other viruses, MCMV is basically targeted by IFNs, which transduced through STAT1 (21). For instance, mice devoid of Stat1 exhibited unresponsiveness to IFNs and succumb within a few days to infection (22,23). IFNs are not only shaping the antiviral immunity via modulating the functionality of immune system cellular compartments, but also inhibit the MCMV growth by upregulation cell-intrinsic antiviral state (23).

In more details, IFNs confer antiviral state and are present in three types; types I (IFN-α, IFN-β), II (IFN-γ), and III (e.g., IFN-lambda) (24,25). Along with their broad role as immunomodulators, IFNs have unique expression patterns. For instance, almost all cells generates IFN I and III upon sensing the microbial dangers, while IFN II is produced from

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Ag-activated T lymphocytes and cytokine-activated group 1 innate lymphoid cells (ILC1) (26,27). IFN I are the key players in antiviral immunity, and their function overlaps with IFN-γ (24,28). The role of IFN-γ in establishing antiviral state is contextual in terms of virus replication cycle it inhibits (29).

During MCMV infection, IFN-γ has direct antiviral function via inhibiting viral gene expression by modulating the MCMV major immediate-early (IE) gene promoter, resulting in inhibition the IE gene transcription (30-33). Furthermore, IFN-γ has indirect immuomodulatory role in controlling MCMV infections (22). These roles include activation of macrophages and NK cells for enhanced antiviral activities (31,34,35). IFN-γ can establish the antiviral state by modulating the differentiation and maturation of T cells and B cells (36,37). Moreover, it is documented that IFN-γ has a cardinal role in T cells mediated control CMV infection via enhancement of MHC class I–dependent Ag presentation by infected cells (38).

The crucial role of NK cells in defending herpes viruses, including HCMV, is best demonstrated by the observation that people with defective NK cells are prone to these viruses (39). Human research on NK cells during CMV infections uncovers the integral characteristics of NK cell biology. Similar to NK cell lacking humans, NK cell-deficient mice are rendered vulnerable to MCMV infection with inefficient control of virus replication (40). Defects in NK cell functionality, such as diminished production of IFN-γ or cytotoxicity, also result in a case in which the mice exhibit high susceptibility to MCMV infection (40,41).

Based on the mouse strain analyzed, NK cells mount MCMV infection via various mechanisms. In the C57BL/6J background mice infected with MCMV infection, the viral protein m157, MCMV-encoded MHC I-like molecule, is sensed by the activating receptor Ly49H that induces the expansion of Ly49H+ NK cells, resulting in control of the virus and production of memory-like NK cells that resemble memory T cells (3,8,9,42). In more details, Ly49H conjugates ITAM bearing proteins, the signaling adaptor DAP 10 and DAP12, and transmits the signals to stimulates the effector function of NK cells, including degranulation and the production of IFN-γ (43,44). Another consequence of DAP12 signaling is the enhanced clonal expansion of virus specific NK cells which is further augmented by DAP10 signaling (45-47). It is noteworthy that 50% of NK cells from B6 mice show expression of Ly49H. In case of MCMV infection, Ly49H+ cell populations expand about two- to three-fold in the spleen and tenfold in the liver, in an m157-dependent manner (48). Adoptive transfer of Ly49H+ NK cells into mice deficient of Ly49H+ NK cells led to their maturation and expansion massively in the spleen and liver as demonstrated by upregulation of activation markers such as; KLRG1 and Ly6C and the leukosialin CD43 (3,47). After initial activation, NK cells gain memory like features after induction from cytokines (49). The generation of memory Ly49H+ NK cells showed independence on IL-15 (50). Other than recognition of the m157 viral glycoprotein ligand, it is well known that IL-12 promote NK cell and T lymphocytes during MCMV infections, through binding the IL-12 with their putative ligand, IL-12 receptor, which result in phosphorylation of signaling component STAT4, resulting in the translocation to the nucleus and subsequent activation of downstream targets and transcription of effector cytokine genes such as IFN-γ (51,52). However, this MCMV resistance is applied to phenotypes having Ly49H such as C57BL/6, whereas mice lacking Ly49H such as BALB/c are susceptible to MCMV infection (8,53,54).

Since NK cells of BALB/c mice are characterized by deficient Ly49H gene, these murine models control the virus at early stages of infection via generation of IFN-γ by NK cells, which

is insufficient for effective viral control. Other considerations in Inbred mice strains could affect the MCMV pathogenesis such as dendritic cells and MHC haplotypes (55,56).

NK cells express costimulatory molecules which dictate the outcome of MCMV infection. For example, DNAX accessory molecule-1 (DNAM-1; CD226) plays a key role in the differentiation of NK cells during MCMV infections. It was found that Ab targeted DNAM-1 inhibited both the proliferation of MCMV-specific Ly49H+ cells during disease and the formation of memory NK cells (57,58).

Furthermore, NK group 2, member D (NKG2D), an inducible activating receptor that is expressed mainly by all NK cells (59-61) identifies a family of stress-induced ligands present on infected and transformed cells in mice and humans (62). In murine models NKG2D exists in two isoforms: NKG2D S and NKG2D L with short and long cytoplasmic tails respectively. While NKG2D-S conjugates DAP10 and DAP12, NKG2D L binds to DAP 10 (63,64). It was found that NKG2D signaling expands Ly49H-dependent proliferation of NK cells during MCMV infections. NKG2D were reported to stimulate IFN-γ secretion from NK cells triggering NK cell-mediated cytotoxicity toward target cells expressing its ligands. (60,65,66).

Using infection model with MCMV strains with induced expression of NKG2D ligands on infected cells culminated in enhanced proliferation of Ly49H+ NK cells. Unlike the Ly49H which is adequate to expand the NK cells, NKG2D signaling is not enough alone for the expansion, possibly due to transient expression of a NKG2D-DAP12 complex (67). In contrast, NKG2D deficient NK cells were found to be more efficient in MCMV control and production IFN-γ compared to NK cell sufficient NKG2D due to the hyper reactive NK cells phenotype (68). Mechanistically, IL-15 which is induced by IFNα/β in early phase of infection improves NK cells proliferation and maturation, especially in the deficiency of NKG2D, or it is likely that NKG2D coordinates signaling of DAP10/DAP12-mediated Ly49H signaling, and thereby affects NK cells survival and proliferation (68-70). In consistent, another recent compelling study demonstrated that, NKG2D deficient mice or blocking of NKG2D signaling early during NK cell development resulted in improved reactivity of natural cytotoxic receptor 1 (NCR1) and subsequent MCMV control, and this regulatory role of NKG2D toward the NCR1 was mediated via DAP12 (71).

A recent study showed that NK cells enhanced the expression of TNF receptor 2 (TNFR2), which is linked to increased effector functions during MCMV infections. TNFR2 is induced by IL-18 enhancing their sensitivity toward TNFα, resulting in higher NK cells proliferation, activation, and glycolytic activity (72). Moreover, it was found that IRF4 expression was enhanced after activation of NK cell and in response to MCMV infections and is needed for the differentiation and proliferation of virus-specific NK cells by controlling iron uptake (73).

NCR1 (CD335/NKp46) is a murine NK cell activating marker and is a member of Ig-like transmembrane glycoproteins (74-76). Mutation of *Ncr1* leads to improved NK cell activity and efficient response to MCMV infection in two genetically distinct mouse models. For instance, the NK cells retrieved from *Noé* mice, C57BL/6J mice with-ethyl-N-nitrosourea–induced mutations, show hyperresponsiveness. This is evident upon infection with MCMV and after coculture with YAC-1 which is mouse T lymphoma cell line and is susceptible to NK cell activity. The hyperactive NK cells in *Noé* mice were due to point mutation of the *Ncr1* gene, ensuing in abolished NCR1 expression. Consistently, *Ncr1**iCre/iCre*** knock-in mice, in which NCR1 expression on the NK cells is impaired due to low levels of NCR1 transcripts,

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are tolerant to MCMV infection than WT animals. The hyperreactivity of NK cells in two independent mouse genetic models is demonstrated by less viral load and higher percentages of functional NK cells (77).

It is well documented that NK cells have a direct contribution on the limiting of virus pathogenesis and a crossbridge role in aiding CD8 T cell responses. For instance, Robbins et al. (55), found that early control of MCMV by NK cells is accompanied with low production of plasmacytoid dendritic cells (DCs) cytokines which prevent the deletion of conventional DCs and subsequent enhancing of antiviral CD8 T cells. By the same token, NK cells are not the only warriors in controlling the MCMV. For example, CD8 T cells are required for early MCMV control in the absence of Ly49H–m157 interaction, and this role T cells is minimal in the presence of intact Ly49H. Furthermore, the proinflammatory cytokines produced from NK cells and other immune cells drive the antiviral CD8 T cells response directly, and indirectly via priming of DC (10). It is well documented that CD4 T cells are efficient drivers to control MCMV in salivary glands by means of IFN-γ secretion and not by exerting helping functions for B cells and CD8 T cells (11,78,79).

The expansion of Ly49H+ NK cells is not only mediated by activating receptors (e.g., Ly49H, NCR1 and NKG2D), costimulatory markers (e.g., DNAM 1) and cellular compartments (e.g., NK cells, cytotoxic and Th cells), but also via proinflammatory cytokines. For example, IL-33 induces ST2 signaling in NK cells, contributing to efficient expansion of Ly49H+ NK cells and efficient MCMV control via augmenting IL-12-induced IFN-γ secretion by NK cells (80). Moreover, IL18 which depend on MyD88 downstream signaling is needed for efficient expansion of NK cells and massive IFN-γ during MCMV infection, and the MyD88 expression is enhanced by IL-12 signaling through STAT4 (81).

As formerly mentioned, NK cells generate a coordinated antiviral defense against a plethora of viral infections including MCMV, culminating in virus elimination (82,83). NK cells curtail the detrimental consequences of acute MCMV infection and regulate persistent infection. This is supported by selective depletion of NK cells by administering mice with Ab to asialo GM1, a neutral glycosphingolipid expressed on NK cells. NK cell deletion substantially accelerated MCMV dissemination in NK cells depleted mice (84).

In the context of HCMV and MCMV infection, MHC I molecules are downregulated in to sidestep presentation of viral peptides to cytotoxic T cells. Besides, MHC class I down-regulation leads to “missing-self” recognition axis and NK cell-driven lysis of infected cells. To evade from the immune response, CMVs either selectively downregulate MHC I molecules that are potent presenters of peptide to CD8 T cells, while sparing those that are integral in engaging inhibitory NK cell receptors (HCMV) (85) or keep selected MHC class I to the cell surface (MCMV) (86).

MCMV are adept in developing various strategies in immune evasion, which is part of natural selection process and pathogen driven evolution These evasion strategies make the contest against infections complicated. To exemplify, MCMV uses encoded evasion proteins which are MHC I expression regulators. m152 and m06 are MHC I negative regulators that reduce the expression of MHC I. These two proteins retain MHC I molecules intracellularly and thereby avoid CD8 T cell mediated killing. Another encoded protein from MCMV called m04 is considered MHC I positive regulator as it binds to MHC I and translocate them to the cell surface and hence restoring the ‘self’ signature and allowing the binding of inhibitory

receptors Ly49, rendering them inaccessible to NK cell killing (87). Further, engagement of MHC I and m04 interfere with peptide loading or recognition by TCR (88). Moreover, MCMV downregulates the ligand for NKG2D, NK cell activating marker, and subsequently impairs the NK cell activity (89). It is reported that gp40, encoded my m152, was found inhibits RAE-1γ ligand for NKG2D and hence limiting NK cells activity (90). In addition, viruses use their miRNA (noncoding regulatory RNA) to hinder NK cell activity (91). By the same token, murine NCRs are targets for immune evasion proteins. Studies on HCMV showed that pp65, a tegument protein in HCMV, can counteract NKp30 activation (92). During evolution, immune cells including the NK cells are evolved to encounter immune evasions by choosing different pathways. It is may well be that the evasion proteins have immunodominant epitopes that are possible presented by a given MHC molecule on the surface of the MCMV-infected cell and provoke cellular immunity (93). It is also possible that some MHC alleles evolves via polymorphisms that can alter the peptide loading with peptide loading complex, a multiunit membrane complex in the endoplasmic reticulum which coordinates peptide translocation into the endoplasmic reticulum (94,95). When MCMV evade from NK cells mediated killing, this would substantiate the requirement for CD8 T cells during the early viral control to mount the MCMV infection (10). Moreover, the immune evasion of MCMV which result in deletion of MHC class I molecules in the salivary gland preclude the CD8 T cells from activation and performing their effector functions, confining the local activation to CD4 T cells (78). Nevertheless, further studies are needed to investigate the mechanism of how immune cells can overcome the evasion of virus from immunosurveillance.

As previously mentioned, NK cells have indispensable role in elimination the MCMV infection, by means of cytotoxicity and IFN-γ secretion (4). Studies on humans with NK cells deficiency reveal their vulnerability to herpesviruses including HCMV (96,97). Similarly, NK cells-depleted mice by Abs exhibited enhanced viral synthesis and pathogenesis (84).

LCMV

LCMV belongs to Arenaviridae family of viruses (98). Morphologically, LCMV has ribosomes resemble “sandy” when visualized by electron microscopy (hence their name) (99). The non-cytopathic LCMV is replicating in rodents, the principle reservoir and can afflict humans as well, where it can cause disease ranging from asymptomatic to severe neurological complications (100). LCMV was identified by Charles Armstrong over eighty years ago in patients with aseptic encephalitis in St. Louis (101).

LCMV is considered an experimental model to address the virus-host immunity interaction including the pathogenesis and persistence. It is noteworthy that, LCMV interaction with the host is largely dependent on the strain and dose of LCMV (102).

LCMV is an enveloped virus with single stranded RNA and arranged in bi-segmented ambisense, (L and S) that encode three major structural proteins: the nucleoprotein, NP and two mature virion glycoproteins, GP-1 and GP-2 (103-105).

LCMV enters the host via binding of their glycoprotein to αDG-expressing cells such as DCs, macrophages, and fibroblastic reticular cells (106,107). Upon attachment of LCMV to the target, the viral membrane unites with the cell membrane and become internalized in the vesicle where it delivers the genetic material in cytoplasm (108).

Various LCMV strains were isolated, and studies were focused on three main strains; the Armstrong strain and is referred to neurotropic, the Traub strain and the WE strain. Traub and WE strain are described as viscerotropic (102). Further, LCMV variants were generated from these 3 main isolates; Docile strains are derivatives of WE strain, and clone 13 is a derivative of Armstrong with a difference in two point mutations present in RNA polymerase and glycoprotein (109,110). Moreover, the infectivity and tropism of clone 13 strain was shown to be higher compared to the WE strain, due to higher affinity of clone 13 strain to bind α-DG (7,111). Upon infection, LCMV can elicit distinct patterns of immune response based on the strain. For instance, Armstrong and WE cause an acute infection in mice, in which the virus is resolved in a few days. Clone 13 and docile strain can lead to chronic infection defined by T cell exhaustion and high virus load.

As a part of innate immunity, NK cells act in immediate action during early viral infection and in proximity to T cell activation sites and precede T cell response, but the responses can be concurrent, especially when the virus persists (112,113).

During viral infection, engagement of Toll-like receptor to germs or proinflammatory cytokines secreted from DCs drive the NK cells to be stimulated (114,115). Importantly, IFN-I is essential proinflammatory cytokine that activates NK cell (116). In addition, NK cells recognize foreign substances via germline-encoded inhibitory and activating receptors through a variety of activating and inhibitory receptors, which affects the cytotoxicity against virally infected cells with involvement in disease progression (117).

In contrary to the integral and direct role of NK cells in control of herpesvirus infection, NK cells are unable to curb the LCMV replication in murine models (118), despite the deficiency of adaptive cellular compartments (119). Thus, LCMV infection is utilized as a powerful experimental tool for addressing the regulatory role of NK cell in shaping the disease pathogenesis (120). During LCMV infection, NK cells were profoundly activated and accumulated dramatically in the liver due to proliferation (121,122). While NK cells are dispensable for control of LCMV, NK cells have the potential to shape adaptive immunity by regulating T cell responses (123-125).

In the context of LCMV infection, NK cells are effectively stimulated by a panel of inflammatory cytokine such as IFN-I, culminating in downregulation of LCMV-triggered CD4 and CD8T cell immunity as well as DCs function (122,126-129). Whereas NK cell–intrinsic IFN-I signaling enhances NK cell in terms of proliferation and effector functions (130,131), expression of IFNAR1 on antiviral T cells has been reported to protect them from NK cell–mediated lysis (132,133). Consistently, blockade of IFN-I signaling in NK cells improves helper and cytotoxic T cell responses, promotes humoral immune responses, and thereby enhances the control of persistent virus infection (134). Further, NK cell-mediated lysis of T and B cells could prevent detrimental immune-mediated liver pathology (126) and expedite viral dissemination during chronic LCMV infection (122,126,128,129). Similar regulatory functions of NK cells during acute LCMV infection attributed to reduced virus-specific memory T-cell and B-cell responses (135). Moreover, TNF-related apoptosis inducing ligand (TRAIL) expressed by immune cells enhances IL-15 signaling-induced granzyme B generation in NK cells, resulting in improved NK cell-mediated T cell killing (136). A recent study showed that LCMV specific T cells mainly Th cells and T follicular helper cells is mediated by B cells intrinsic IL-27 resulting in purging the host from the virus (137).

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Infection with LCMV leads to distinct scenarios of anti-viral T cell immunity and viral clearance. For instance, murine models given WE or Armstrong develop acute infection with robust T cell response and subsequent effective viral control (138,139). While infection with clone 13 or docile variants establishes chronic infection and impairs the anti-viral T cell function and enabling the viral persistence and associated eventually with T cells exhaustion driven by high viral dissemination (7,140). Further, the NK cells were reported to be more active in chronic infection compared to the acute one (128). In more details, mice inculcated with low doses of LCMV clone 13 developed a robust effector CD8 T cell response and viral elimination. Using intermediate dose of clone 13, mice developed partial T cell exhaustion and fulminant immunopathology and partial T cell exhaustion. Whereas infection with high dose led to a scenario in which; the T cell is exhausted with minimal liver damage and the virus persisted (141-143).

THE CROSSTALK BETWEEN NK CELLS AND OTHER IMMUNE CELLS

Following infection, NK cells become activated and can involve to host immunity by direct killing the infected cells and synthesizing antiviral cytokines such as IFN-γ, resulting in direct elimination of virus or induction subsequent immune response, or a combination of these events. Nevertheless, NK cells influence adaptive immunity via a plethora of mechanisms. For example, NK cells affect T cell response by releasing cytokines which lead to T cell immunity activation (e.g., IFN-γ) or down modulation (e.g., IL-10) (144). Another mechanism is competing NK cells with T cells for the availability of cytokines such as IL-12 (145). Further, direct engagement of NK cells with T cells lead to inhibition of NK cells (112). NK cells have unique bidirectional cross talk with distinct immune cells including T cells during MCMV and LCMV, resulting in modulation of T cell responses positively or negatively and directly or indirectly (**Fig. 1C and D**).

The role of NK cells in positive regulation of T cell response is mainly mediated by IFN-γ as demonstrated by substantial studies on human and murine models. Upon infection with viral infection including MCMV and LCMV, NK cells are activated in timely manner and become a potent producer for IFN-γ, leading to virus control and enhance the expansion of primary and memory helper and cytotoxic T cells (146-148). It is documented that IFN-γ from NK cells induce DC maturation leading to T lymphocytes activation either by increased Ag presentation or by means of proinflammatory cytokines production (149-151).

During MCMV infections, NK cells have an indispensable and direct role in eliminating the virus at the early phases along with their exquisite role in modulating other immune cells. For instance, following MCMV infection, MCMV-infected DCs are a major source of infectious viral progeny, and immature DCs are a principal target of MCMV virus (152). NK cells were reported to attack and clear m157 expressing infected DCs in direct manner. The low quantity of DC numbers led to suboptimal T cell induction, and subsequent elevated viral dissemination (153). In addition, NK cells can increase the expression of CD25 during MCMV infection with high affinity to IL-2, resulting in potential competition with T cells for the presence of low levels of IL-2 (154).

In direct manner, NK cell secretes IL-10 upon infection with MCMV and results in a curtailed CD8+ T cell response and a camouflage from liver pathology (144). In depletion experiments

during MCMV infections of immunocompetent mice, it was found that, the deficiency of NK cells led to enhanced CD4 and CD8 T cell IFN-γ production, and in the case of CD8 T cells, increased BrdU incorporation and cell expansion (155). This inhibitory effect of NK cells against T cells could be due to perforin, as NK cells express perforin and have been shown to kill a variety of hematopoietic cells including T and B cell progenitors and Ag-presenting cell (APC) such as members monocyte/macrophage and DC lineages (156,157). Another complementary study showed that NK cells specifically eliminated activated CD4+ T cells in the salivary gland during MCMV infections. This was dependent on TRAIL expression by NK cells (158).

During LCMV infection, NK cells can negatively modulate the T cell immunity collaterally via interaction with DCs. In more detail, NK cells alter T cell immunity by reducing the availability of APCs. For instance, NK cell depletion experiments during chronic LCMV showed improved priming of cytotoxic T cells by Ag presenting cells in primary phase of response and this effect was not due to alteration in functionality or amount of DCs, indicating the specific elimination of virally induced APCs (128).

In a direct manner, NK cells can also restrain anti-viral T cell responses by recognizing and eliminating activated T cells as demonstrated in various human and mice settings upon infection with LCMV (159). For example, LCMV induced T cell express NKG2D ligand that engage NKG2D receptor on NK cells, and led to NK cell mediated lysis of T cells by means of perforin (122,160,161). Similarly, LCMV infected mice with depleted NK cells at early time points were more able to mount the virus by limiting the elimination of Th cells which assist the cytotoxic T cell activation (126). Moreover, depletion of NK cells mitigates the virus-induced liver injury due to effective T cell response, imparting the acute signature for the chronic LCMV infection (122,126). Recent study reported the inhibitory role of liver NK cells against hepatic antiviral CD8 T cells via PD-1-PD-L1 axis in LCMV infections (121). Another recent study showed that Qa-1b expression is primarily increased on B cells following LCMV infection. Ablation of Qa-1b leads to enhanced NK cell mediated regulation of LCMV-specific T lymphocytes (162).

As previously mentioned, using different inocula of LCMV virus infection gives insights into distinct patterns of anti-viral T cell immunity and virus control, and NK cell depletion experiments impart contextual changes for T cell response and virus clearance. For example, deletion of NK cells in mice infected with high dose of LCMV can enhance T cell immunity and subsequent viral control infection (122,126). In the setting where intermediate dose of LCMV is used, NK cells restrain the number of anti-viral T cells and thereby facilitates the viral dissemination. The liver injury in this setting is nuanced as the viral titer is inadequate to cause T cell exhaustion, culminating in a situation in which functional T cells are encountered by massive amount of infected cells and leading to fatal liver damage. Ablation of NK cells in this setting results in hyperproliferative T cell response with more ability to clear the infection, and hence impeding the liver pathology (122). Nevertheless, the influence of NK cells on calibrating T cell responses is not always prejudicial for the host. In the context of infections with high virus load, NK cells are deemed helpful by hampering T cell immunity, exacerbating the viral dissemination and T cell exhaustion, and hence limiting T cell mediated immunopathology (122).

To evade from NK cell killing, T cells benefit from expression of inhibitory receptor 2B4 on NK cells, since NK cells lacking 2B4 attack and eliminate T cells in LCMV infection (127). Another evolving strategy is type I IFN, which is reported to safeguard T cells from NK cells lysis via perforin and NCR1 expression as well as through altering the expression of inhibitory receptors

on NK cell (132,133). A recent study showed that LCMV docile strain evade from the host immunity via establishing a state of slow virus propagation due to reduced PRR activation and subsequent IFN-I production resulting in downregulated innate and adaptive immunity (163).

CONCLUDING REMARKS

In this review, we have sought to address the role of NK cells in viral control and their interplay with immune cells during MCMV and LCMV infections in murine models. It is obviously apparent that the role of NK cells is complex and context dependent. More specifically, the role of NK cells is central in eliminating the MCMV, which is used to model HCMV. On other hand, NK cells have a casual role in controlling LCMV via affecting other immune cells which can impact the outcome of disease. To conclude, uncovering the key aspects of NK cells roles toward infections remains a key avenue of upcoming research necessary for the establishment of future NK cell-targeted therapies.

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