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REVIEW

Caspase-8-dependent control of NK- and T cell responses during cytomegalovirus infection

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Abstract

Caspase-8 (CASP8) impacts antiviral immunity in expected as well as unexpected ways. Mice with combined deficiency in CASP8 and RIPK3 cannot support extrinsic apoptosis or RIPK3-dependent programmed necrosis, enabling studies of CASP8 function without complications of unleashed necroptosis. These extrinsic cell death pathways are naturally targeted by murine cytomegalovirus (MCMV)-encoded cell death suppressors, showing they are key to cell-autonomous host defense. Remarkably, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$, *Ripk1*$^{-/-}$*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ and *Casp8*$^{-/-}$*Ripk3*$^{K51A/K51A}$ mice mount robust antiviral T cell responses to control MCMV infection. Studies in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice show that CASP8 restrains expansion of MCMV-specific natural killer (NK) and CD8 T cells without compromising contraction or immune memory. Infected *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ or *Casp8*$^{-/-}$*Ripk3*$^{K51A/K51A}$ mice have higher levels of virus-specific NK cells and CD8 T cells compared to matched RIPK3-deficient littermates or WT mice. CASP8, likely acting downstream of Fas death receptor, dampens proliferation of CD8 T cells during expansion. Importantly, contraction proceeds unimpaired in the absence of extrinsic death pathways owing to intact Bim-dependent (intrinsic) apoptosis. CD8 T cell memory develops in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice, but memory inflation characteristic of MCMV infection is not sustained in the absence of CASP8 function. Despite this, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice are immune to secondary challenge. Interferon (IFN)γ is recognized as a key cytokine for adaptive immune control of MCMV. *Ifngr*$^{-/-}$*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice exhibit increased lifelong persistence in salivary glands as well as lungs compared to *Ifngr*$^{-/-}$ and *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice. Thus, mice deficient in CASP8 and RIPK3 are more dependent on IFNγ mechanisms for sustained T cell immune control of MCMV. Overall, appropriate NK- and T cell immunity to MCMV is dependent on host CASP8 function independent of RIPK3-regulated pathways.

Keywords Apoptosis · Necroptosis · Cell death · Proliferation · Herpesvirus · Ripoptosome

Introduction

Cytotoxic CD8 T cells are responsible for primary control of human cytomegalovirus (HCMV) as well as murine (M) CMV (MCMV) infection [1–4]. Natural killer (NK) [5] contributes to initial control and regulate CD8 T cell response patterns [6] although both are impacted by a wide variety of virus-encoded modulatory mechanisms [1, 7, 8]. Similarities in NK [9] as well as T cell [10] responses to MCMV and HCMV [11] have been well recognized [2–4]. CMV-specific T cells are generated in two broad patterns, termed conventional (or non-inflationary) and inflationary [10] memory responses [1, 3, 12]. During acute MCMV infection, conventional epitope-specific CD8 T cells undergo rapid expansion followed by a contraction phase that parallels the clearance of viral antigen, leaving a population of memory T cells in place. Inflationary T cell proliferation continues in response to lifelong, sporadic viral antigen presentation [13–15]. Memory inflation is a shared hallmark of HCMV and MCMV infection [2–4, 12]. Though less pronounced, memory inflation is observed with other herpes simplex and some other latent/persistent pathogens [12]. Strong biological similarities with HCMV have fostered investigations of MCMV-specific CD8 T cell immunity in mice. Antiviral T

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cell response characteristics are influenced at many levels [4, 16], including through the influence of NK cell function [17] and may dictate disease pathogenesis [18], while mediating long-term protection from reinfection [7, 19].

We discovered that the mid-gestational death exhibited by *Casp8*$^{-/-}$ mice results from receptor-interacting protein (RIP) kinase (RIPK)3-dependent death, most likely unleashed programmed necrosis (necroptosis) that destroys vascular cells in the yolk sac to cut short development [20]. The viable and fertile *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice we generated carry a full complement of hematopoietic lineages and are able to control MCMV infection [21, 22]. *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice sustain robust T cell development and response characteristics. Remarkably, these mice exhibit enhanced levels of MCMV antigen-specific T cell expansion with normal contraction and CD8 T cell function, including the cytotoxic ability to kill virus-infected target cells in vivo [23, 24]. Even though caspase (CASP)8 and RIPK3 mediate potent cell-autonomous death pathways, necroptotic signaling does not contribute to other arms of the immune system. Apoptotic machinery makes a modest contribution to restraining NK and CD8 T cell proliferation during the expansion phase of the immune response. CASP8 also contributes to sustained lifelong memory inflation characteristic of CMV CD8 T cell responses.

Initial response to CMV infection

Inoculation of mice with MCMV results in a cascade of events triggered by virus-infected cells (including the production of IFNβ, chemokines and other cytokines) along with important contributions of innate and adaptive immune cells that are recruited to sites of infection through the action of host and virus factors. Recruited lymphocytes kill virus-infected cells [2] and produce cytokines (including IL-2, IFNγ, IL-12 and IL-18) that contribute to the quality of antiviral immunity [25]. Recruitment is strongly influenced by the production of viral chemokine MCK-2 [26]. MCK-2 recruits patrolling/resident monocytes that support viral dissemination [27] and orchestrates inflammatory monocytes to suppress local T cell responses [16]. Conventional (c)DCs present viral antigens to T cells, mediating (1) T cell receptor (TCR) stimulation by viral epitope bound to major histocompatibility complex (MHC) class I and II, (2) co-stimulation through accessory receptors, and (3) expression of regulatory and inflammatory cytokines. By encoding proteins that suppress cDC antigen presentation and co-stimulation [2], MCMV paralyzes antigen presentation and T cell activation [28] directly from infected DCs [29]. Evidence [10, 30–33] supports contributions of CD8α^{+}CD11b^{-} cDC1 cells, possibly together with CD103^{+} DCs, in the cross-presentation of viral antigens following phagocytosis of MCMV-infected cells and cell debris. This enables cDC1 cells to bypass viral suppression mechanisms to drive robust antiviral CD8 T cell responses.

CD8 T cell response

The conventional view has been that virus infection triggers CD8 T cells to undergo an exponential expansion and differentiation into effector cells subsets [34] influenced by levels of killer cell lectin-like receptor G1 (KLRG1) and IL-7Rα (or CD127). KLRG1 was first recognized as a terminal differentiation marker on NK and activated T cells [35, 36] and later implicated in cell cycle inhibition [37]. IL-7 is a critical cytokine for CD8 T cell survival during homeostasis and following infection. CD8 T cells expressing CD127, the high-affinity α chain of IL-7 receptor, exhibit an enhanced response to this pro-survival cytokine [38]. Upon activation, KLRG1^{lo}CD127^{hi} naïve CD8 T cells downregulate CD127 to become KLRG1^{lo}CD127^{lo} early effector cells (EECs) [39, 40]. These cells have the potential to differentiate into KLRG1^{hi}CD127^{lo} short-lived effector cells (SLEC), KLRG^{lo}CD127^{hi} memory precursor effector cells (MPEC), or KLRG1^{hi}CD127^{hi} double positive effector cells (DPEC) [40, 41]. SLEC differentiation is promoted by TCR signaling in combination with proinflammatory cytokines [40, 42, 43] conferring limited differentiation plasticity and survival upon this subset [42, 44, 45]. In contrast, KLRG1^{lo}CD127^{hi} MPECs display increased survival and retain the differentiation potential to become EECs or SLECs [40]. While SLECs and MPECs both exhibit comparable cytotoxicity and IFNγ production [40, 46], the majority of SLECs undergo abrupt contraction following the peak of the acute phase, leaving MPECs to further differentiate into memory T cells [44]. Although DPECs were initially thought to be terminally differentiated [40], these cells have shown the capacity to down-regulate KLRG1 and also contribute to memory [45]. Conventionally, memory CD8 T cells are categorized as T effector memory (Tem) cells or T central memory (Tcm) cells, based on distinct features such as effector function, localization, migration and life span [47]. Tcm cells display high expression of CD62L and CCR7 but low levels of CCR5, consistent with continued residence in secondary lymphoid organs. In contrast, Tem cells express low levels of CD62L and CCR7 but high levels of CCR5, and reside in non-lymphoid tissues. Tcm cells have a high proliferation capacity and can give rise to effector cells following antigen (re)encounter; whereas, Tem cells exhibit less proliferation capacity but can mount rapid cytotoxic responses to invading pathogens [48]. Both subsets circulate and contribute to antiviral host defense during acute and chronic/persistent phases of virus infection. Tissue resident memory T (Trm) cells are potentially derived from Tem and represent another

hallmark of CMV infection, providing first-line protection from reinfection [2–4]. In contrast to circulating Tcm and Tem subsets, Trm residence in all organs enables prompt responses to reinfection or reactivation [47]. HCMV-specific CD8 Trm cells reside in diverse body sites [49] and similar to what is known about MCMV [50].

During infection, CD8 T cells respond to a broad spectrum of MCMV epitopes. In C57BL/6 mice, more than 26 epitopes from 18 viral proteins are recognized by CD8 T cells, driving either conventional or inflationary antiviral response patterns depending on their expression patterns within virus-infected cells [10]. Conventional epitope-specific CD8 T cells follow a classical pattern of expansion, contraction and stable memory, initially exhibiting a predominant SLEC phenotype with only modest levels of MPECs [15]. Following the peak acute response, the majority of the KLRG1^{hi} cells contract and MPECs differentiate into memory cells, most of which exhibit a Tcm phenotype (CD62L^{hi}KLRG1^{lo}CD127^{hi}). Inflationary epitope-specific cells mostly display CD62L^{lo}KLRG1^{hi}CD127^{lo} Tem phenotype. Although they may initially expand similar to conventional cells, inflationary cells exhibit hallmark continuous expansion over the course of lifelong infection by recruiting from either naïve or Tcm pools. In healthy adult humans [11] or mice [10], 30% or more of total peripheral blood CD8 T cells may recognize CMV-specific epitopes without classical signs of T cell exhaustion [3]. Percentages vary owing to MHC class I antigen presentation of different epitopes recognized in individual humans or inbred strains of mice.

CD8 T cell immunity has long been recognized as crucial for control of CMV infection, despite viral subversion of MHC class I-dependent antigen presentation. Conventional as well as inflationary CD8 T cell responses exhibit distinct requirements for antigen presentation. cDC1-dependent cross-presentation drives antiviral CD8 T cell expansion during the acute phase to avoid viral subversion, but this does not seem to contribute to memory inflation where infected non-hematopoietic cells drive proliferation and differentiation of inflationary populations during long-term infection [31, 33, 51], potentially through spontaneous reactivation of infected sinusoidal and vascular endothelial cells [14, 52], sites consistent with DNA deposition in MCMV-infected mice [53]. With MCMV, different sites or states of latency may contribute to the observed patterns [54]. Any comparison to HCMV remains complicated because myeloid progenitors are predominant sites of latency [55], so a lot more information is needed. Inflationary epitopes tend to be derived from viral antigens expressed immediately after reactivation in a pattern that suggests they manage to avoid the consequences of MHC class I downregulation. Consistent with this notion, the magnitude of memory inflation correlates with inoculum dose [30, 31, 56], requires systemic infection [31], and is enhanced by repeated challenge [57]. The extent to which antigen processing depends on the immunoproteasome also dictates the type of response observed [58]. In any event, memory inflation appears to depend on latency and reactivation cycles and to involve CD8 T cells that provide crucial host defense in maintenance of latency [2–4]. Only virus antigen-specific CD8 T cells undergo memory inflation. Consistent with long-established data showing that an inflationary epitope-specific vaccine confers protection against MCMV challenge [59], adoptive transfer of epitope-specific inflationary CD8 T cells suffices to control infection [13]. In striking contrast, epitope-specific conventional CD8 T cells fail to protect mice due to the impact of MHC class I downmodulation reducing levels of antigen on infected cells below the threshold for cytotoxic T cell recognition [60]. Two-photon confocal microscopy studies have reinforced the impact of CD8 T cell collaboration as necessary to override MHC-I downregulation to effectively kill MCMV-infected cells [61].

Dendritic cell function

Antigen presentation by cDC1 during acute infection as well as by nonhematopoietic cells during long-term infection is dependent on co-stimulation which contributes to the magnitude and patterns of MCMV-specific CD8 T cell responses. Interactions between costimulatory receptors CD80/86 and CD28 are required for robust expansion of both conventional and inflationary CD8 T cell subsets during the acute phase but are dispensable for memory inflation [62]. Interactions between CD27 and receptor CD70 [63] as well as 4-1BBL and 4-1BB [64] also support the conventional and inflationary response patterns. Interestingly, elimination of 4-1BB enhances CD8 T cell levels during the acute phase but decreases memory inflation. In contrast, OX40L engagement of costimulatory receptor OX40 does not impact the acute response magnitude during the acute phase but is required for optimal inflationary CD8 T cell response persistence [65]. These data together support the contribution of co-stimulation to the magnitude and pattern of MCMV-specific CD8 T cell responses.

Finally, both the cytokine milieu and consequent transcriptional patterns influence the patterns of MCMV-specific CD8 T cells. IL-12 has long been recognized for promoting MCMV-specific CD8 T cell responses [66]; whereas, IL-10 and IL-33 suppress the adaptive immune response [67, 68]. IL-2 promotes T cell proliferation and thereby supports a robust MCMV-specific CD8 T cell response during both acute and latent phases [69]. The pro-survival cytokine IL-15 is more important than IL-7 in maintaining T cell levels during latency [70]. CD8 T cell differentiation depends on distinct transcriptional factors that emerged from studies on lymphocytic choriomeningitis virus (LCMV) [34] where

the ratio of transcription factors T-bet, supporting SLEC differentiation, and eomesodermin (EOMES), supporting MPEC differentiation, is crucial for lineage determination. Elimination of transcription factor FOXO1 undermines the generation of MCMV-specific CD8 T due to an increase in cell death rather than defective proliferation [71]. MCMV-specific *Foxo1*$^{-/-}$ T cells show impaired Tcm phenotypes similar to observations with LCMV [72]. Notably, loss of FOXO1 alters the T-bet:EOMES ratio in CD8 T cells following MCMV infection, suggesting a similar level of importance of these two transcriptional factors for MCMV as observed in LCMV.

CD4 T cell response

Following MCMV infection, CD4 T cells also make contributions to the antiviral immune response—(1) as helper cells for antibody (Ab) production, (2) in support of CD8 T cell function, and (3) in the tissue-specific control of infection. In contrast to a dramatic inflationary response pattern of MCMV-specific CD8 T cells, most CD4 T cells follow a conventional pattern, with the noted exception of the m09 epitope-specific CD4 T cells in C57BL/6 mice [73]. MCMV-specific CD4 T cells produce IL-2, IFNγ, and TNF that likely contribute to the behavior of CD8 T cells. CD4 T cells contribute to memory inflation through secreting IL-2 and through engagement of 4-1BBL and 4-1BB [64, 69] and improve Ab production from B cells through CD28–CD80/86 interactions [74]. The most well-established immune function of CD4 T cells is their contribution to control of MCMV infection of salivary glands (SG) [75], a major site of MCMV shedding for transmission where IFNγ production by CD4 T cells appears to be crucial [76]. MCMV infection in most organs is typically brought under control within two to three weeks, with the exception of SG where active virus replication persists for more than a month. A recent study defines the SG-resident CD4 and CD8 Trm cells in response to MCMV infection [77] as being recruited from the circulating Tem pools [77]. Further studies are needed to understand the mechanism of Trm cell formation as well as function in this tissue.

NK cell response

NK cells are type 1 innate lymphoid cells (ILCs) [25] playing an important role in virus infections and tumor immunosurveillance through the rapid production of cytokines and cytotoxic elimination of target cells [9]. The NK cell response occurs as a result of signaling from germline-encoded activating receptors in balance with inhibitory receptors that together survey the overall stress levels on potential targets, particularly virus-infected and tumor cells. Activating receptors recognize stress-induced ligands as well as reduced levels (down-regulation) of MHC class I molecules (i.e., "missing self") that occurs with infection and cancer. Inhibitory receptors recognize MHC class I molecules (i.e., "self"). This dual sensing system allows NK cells to directly recognize and eliminate diseased cells. Inhibitory receptors that recognize MHC class I as well as non-MHC class I ligands [78] belong to different superfamilies—the killer cell immunoglobulin-like receptor (KIR) family specific to humans and leukocyte immunoglobulin-like receptors (LIRs) and CD94/NKG2A in humans and mice, and C-type lectin-like domain superfamily Ly49 specific to mice. These receptors all possess common cytosolic signaling motifs, either an immunoreceptor tyrosine-based inhibitory motif (ITIM) or an immunoreceptor tyrosine-based activation motif (ITAM) that dictates outcome of ligand engagement [78]. Receptor ligation results in tyrosine phosphorylation of ITIM to inhibit or ITAM to activate and recruit phosphatases and adaptors that mediate consequent signaling cascades [9]. NK cell activation occurs when positive signals override negative signals. NK cell activating receptors recognize a wide array of ligands that are either constitutively (e.g., HLA-E) or transiently (e.g., stress-induced MHC-like ligands) expressed on target cells. DAP12 is a transmembrane-anchored signaling subunit that contains ITAM. DAP12 associates with activating receptors, such as NKG2C/CD94, Ly49H and Ly49D, NK1.1 and CD16 [9]. Thus, the mouse Ly49 receptor family includes both inhibitory receptors and activating receptors (e.g., Ly49H that recognizes MCMV-encoded m157 protein). Inhibitory Ly49 receptors transduce a suppressive signal via an ITIM; whereas, activating Ly49 receptors lack ITIMs and associate with the ITAM-containing DAP12 [79]. Activating receptors recruit ZAP70 and Syk, subsequently activating PLC-γ and NFAT, NF-κB and MAP kinases [78], and, similar to T cells, this can result in the formation of a CARMA–MALT1–BCL10 complex [80, 81]. Cytokine production triggered by NK1.1 and Ly49H is compromised in NK cells from *Bcl10*$^{-/-}$, *Malt1*$^{-/-}$, *Carma*$^{-/-}$ or *Card9*$^{-/-}$ mice [80]. Thus, T cell and NK cell activation induces a similar signaling cascade upon engaging viral antigen. Although NK cells function as innate immune cells, evidence has shown that they influence adaptive T cell response parameters [6] and possess some adaptive immune features themselves, including education during development, antigen-specific clonal expansion in response to virus infection, and a sort of immunological memory [9]. NK cells develop mainly in bone marrow independent of the thymus as well as in the liver [82]. Immature NK cells carry a greater repertoire of inhibitory receptors [78] and ligation of these receptors educates NK cells to develop the capacity for the recognition of "missing self", an important mechanism for NK cell immune

surveillance and for triggering cytotoxic function [83–85]. NK cells expressing inhibitory receptors in the absence of cognate MHC class I or NK cells lacking inhibitory receptors during development become hypo-responsive or anergic [86]. Further, the strength of NK cell responses has a positive correlation with the number of inhibitory receptors that recognize self-MHC [87, 88]. Notably, NK cell developmental programming is not fixed [89]; indeed, impaired cells can be re-educated in periphery to regain function [90, 91].

The adaptive immune features of NK cells during virus infection has been best characterized following MCMV infection owing to the activation of Ly49H via direct engagement of the MCMV m157 glycoprotein in C57BL/6 mice [92, 93]. There is typically a three- to tenfold increase in $Ly49H^+$ cell numbers by day 7 post infection [94], accompanied by a parallel increase in $Ly49H^-$ populations. The impact of the NK cell response on the adaptive T cell response has been studied during MCMV infection. Important crosstalk between DC and NK cells includes the production of cytokines by DCs that activate NK cells as well as the impact of NK cell cytokines on DC function [95]. In addition to killing virus-infected cells to influence antigen cross-presentation, NK cells may directly kill DCs. Furthermore, NK cells are known to influence the polarization of T cells through the production of IFNγ as well as through the display of viral epitopes on MHC class I, processes that are documented but that require further study to relate to host defense [95].

Cell death pathways suppressed during CMV infection

Like all multicellular organisms, mammals rely almost exclusively on intrinsic (mitochondrial) apoptosis for developmental and homeostatic elimination of unnecessary, deleterious and diseased cells. Intracellular stress leads to mitochondria outer membrane permeabilization (MOMP) release of intermembrane space proteins to drive autoactivation of CASP9 and subsequent effector caspases (e.g., CASP3 and CASP7) activation [96]. This signaling process is tightly regulated through a balance of pro-apoptotic and anti-apoptotic Bcl-2 family proteins that control MOMP [97]. The pro-apoptotic members include those that initiate apoptosis (e.g., Bim, Bid, Noxa and Puma), those that provide MOMP function (e.g., Bax and Bak) and those that counteract (anti-apoptotic members Bcl-2, Bcl-XL and Mcl-1) encoded by mammals [98, 99]. Mimics encoded by viruses such as the viral mitochondrial inhibitor of apoptosis (vMIA) encoded by HCMV or the combination of vMIA and the viral inhibitor of Bak oligomerization (vIBO) encoded by MCMV block MOMP during infection [100]. These anti-apoptotic functions sequester Bax and Bak away from the initiators [101, 102]. Growth factor deprivation leads to FOXO3-driven Bim expression in lymphocytes [103] and DNA damage induces p56-dependent Noxa and Puma upregulation [104]. Bax and Bak recruitment to the mitochondria outer membrane results in MOMP-dependent release of mitochondrial contents [105], including cytochrome *c*, Apaf 1 and CASP9, to form an apoptosome complex [106] that activates CASP3 and/or CASP7 [106] and results in cleavage of many targets such as PARP, phosphatidylserine externalization, DNA degradation and cytoplasmic condensation, and the release of apoptotic bodies [96]. During HCMV infection, vMIA naturally blocks a caspase-independent death pathway mediated by the mitochondrial serine protease HtrA2/Omi [100].

Extrinsic apoptosis is mediated via autoactivation of CASP8 in mice (Fig. 1). Humans encode CASP8 as well as the closely related CASP10. The CASP8 pathway has been extensively studied with TNF death receptor (DR) family members, such as TNFR1, Fas, TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (TRAIL-R1 and TRAIL-R2 in humans and TRAIL-R2 in mice). These receptors contain a death domain (DD) exposed to the cytosol that orchestrates recruitment of preformed cell death machinery [107]. As the key adaptor, Fas-associated protein with death domain (FADD) consists of a carboxyl-terminal DD and an amino-terminal death effector domain (DED). Importantly, ligation of a receptor such as TNFR1 either promotes cell survival or triggers death. RIPK1 and FADD-like interleukin-1-β-converting enzyme-inhibitory protein (cFLIP), together with CASP8 determine cell fate [20]. RIPK1 comprises an N-terminal kinase domain (KD) followed by the central region that includes a RIP homotypic interaction motif (RHIM), and a carboxyl-terminal DD (Fig. 1). Upon engagement of TNF, TNFR1 recruits RIPK1 via the intermediary TRADD, forming a membrane-associated complex, where RIPK1 is heavily ubiquitinated by E3 ubiquitin ligases working together with other adaptors [108–110]. RIPK1 polyubiquitination presents a platform for NF-κB and MAPK activation, where NF-κB induces the expression of $cFLIP_L$, cIAPs and XIAP which promote cell survival. Cell stress, inhibition of E3 ubiquitin ligases, or activation of deubiquitinases (such as A20 or CYLD) results in RIPK1 deubiquitination [111] and the formation of a death complex that executes apoptotic cell death [112]. TRADD is replaced by FADD in a cytosolic RIPK1–FADD–CASP8–cFLIP complex (Fig. 1) termed as ripoptosome [113]. A similar complex forms independent of DR in other signaling cascades, most notably Toll-like receptor (TLR)3 and TLR4 or ZBP1, together with RIPK1 and RIPK3. Conformational changes in FADD, now bound to RIPK1 within the ripoptosome, may expose the DED to recruit the autoactivating caspase CASP8. Like all caspases, Procaspase-8 is expressed as a zymogen, consists of an amino-terminal pro-domain

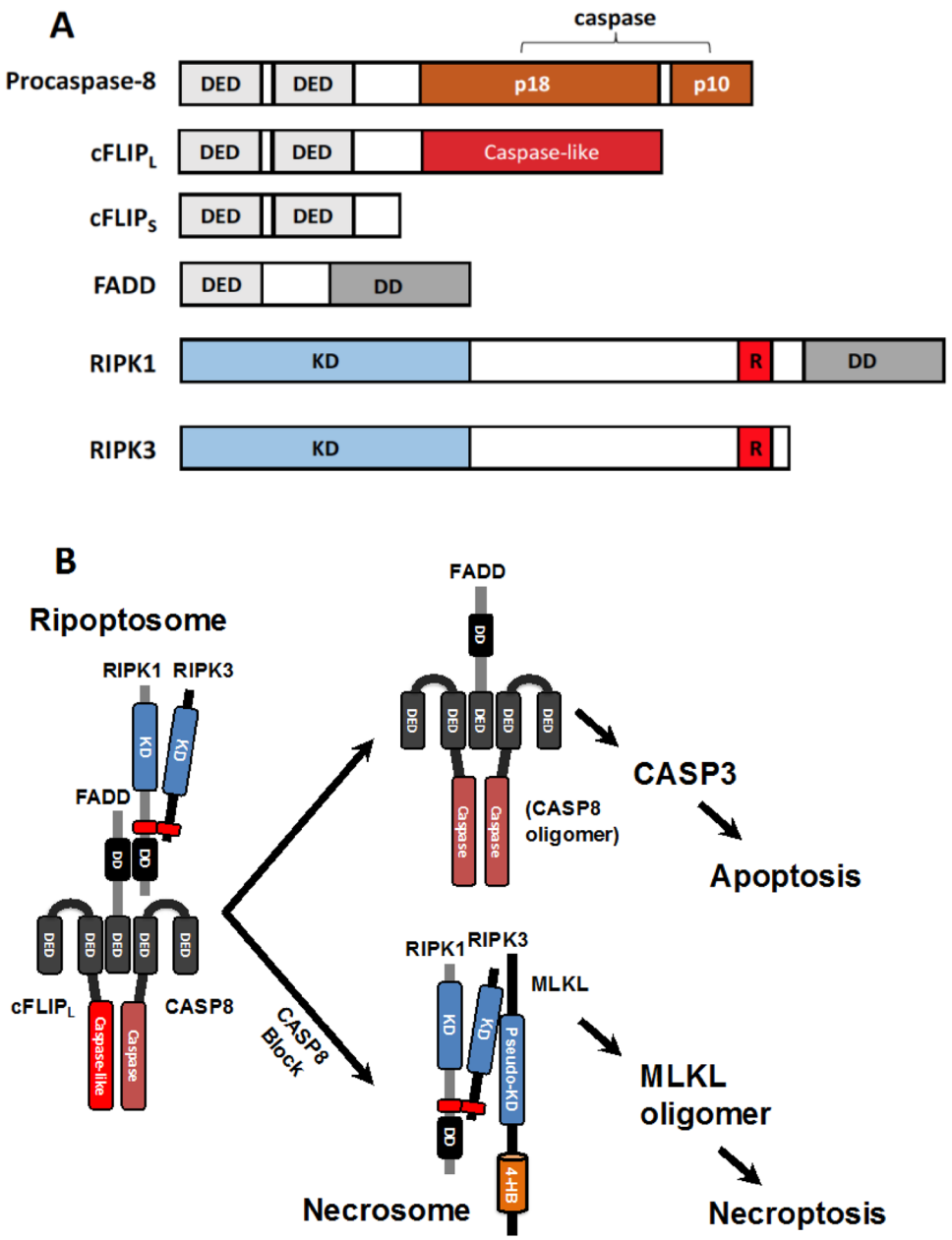

Fig. 1 CASP8 determines the outcomes of extrinsic pathway. **a** Schematic diagram of proteins in DISC. **b** Following extrinsic pathway activation, FADD recruits CASP8, cFLIP$_L$, RIPK1, and RIPK3 to form a DISC (or ripoptosome). Procaspase-8 dimerization leads to auto-cleavage that releases both large and small subunits for full CASP8 activation, and subsequent apoptosis initiation. Association with cFLIP$_L$ blocks procaspase-8 auto-cleavage, which delays but not impairs apoptosis activation upon DR stimulation. cFLIP$_L$-CASP8 association maintains CASP8 basal catalytic activities sufficient for suppressing RIP kinases-dependent necroptosis. CASP8 catalytic activity inhibition initiates necroptosis. Activation of RIPK1 and RIPK3 by phosphorylation leads to the recruitment and activation of MLKL, which triggers necroptosis

comprising two DED domains, followed by one large proteolytic subunit (p20/p18), a short linker region and a smaller proteolytic subunit (p12/p10) (Fig. 1). Once procaspase-8 is recruited to FADD through DED interactions [114], autocleavage [115] releases the active pro-apoptotic protease [113]. Both major isoforms of cellular cFLIP block cell death. The long form (cFLIP$_L$) and a short form (cFLIP$_S$) are produced from spliced mRNA variants (Fig. 1) whose levels are under the influence of cell type as well as inflammatory environment. cFLIP$_S$ inhibits CASP8 autocleavage by preventing the oligomerization of procaspase-8 necessary for auto-activation [116]. cFLIP$_L$ is a catalytically inactive caspase-like protein [117], and is physiologically important for holding basal CASP8 activity in check [118]. The conserved CMV-encoded viral inhibitor of CASP8-induced apoptosis (vICA) prevents activation of procaspase-8 [20]. If activated, CASP8 may cleave CASP3/CASP7 directly or cleave Bid to activate Bax and Bak [107], representing different convergence points between extrinsic and intrinsic pathways. The fact that $Bak^{-/-}Bax^{-/-}$ [119] or $Bid^{-/-}$ [120] mice resist Fas-mediated hepatitis shows that Bid-mediated mitochondrial amplification is physiologically important. During MCMV infection, however, the viral cell death suppressors vMIA/vIBO and vICA assure that apoptosis pathways remain silenced [20].

Programmed necrosis

Necrosis is conventionally viewed as unprogrammed destructive cell death caused by chemical toxicity or physical stress, characterized by swelling organelles and cell leakage. Regulated or programmed necrosis [121] initially emerged from studies of caspase inhibition during DR activation [20], where RIPK1–RIPK3 RHIM-dependent interactions resulted in the formation of a necrosome and recruitment of the pseudokinase mixed lineage kinase domain-like (MLKL) [122] (Fig. 1). Once phosphorylated by RIPK3, MLKL translocates to the plasma membrane, where, in association with highly phosphorylated forms of inositol phosphate [123], nanopores form and allow osmotic force-induced membrane leakage [124, 125]. Necroptosis is kept in check by CASP8 activity, so this leakage type of death has been considered as an alternate to extrinsic apoptosis [20]. Following DR activation and the formation of a FADD–RIPK1–CASP8–cFLIP-$_L$ complex, procaspase-8–cFLIP$_L$ heterodimers are enzymatically active sufficient to suppress necroptosis [118]. The actual mechanism of regulation by CASP8 is unknown, but evidence supports cleavage/inactivation of RIPK1 [126] or RIPK3 [127]. Notably, CASP8 inhibition, compromise or active site mutation (*Casp8*^{C362A} in mouse or *Casp8*^{R248W} in human) [118, 128] sensitizes to necroptosis (Fig. 1B). Necroptosis is inhibited by mutations [129, 130] or pharmacological inhibitors [128, 130] that compromise RIPK1, RIPK3 or MLKL activation [131]. Given that CASP8 inhibition is a common strategy of DNA viruses, we have viewed this protease as a pathogen super sensor that is able to switch death pathways to eliminate infected cells [20]. Although the precise spatial and temporal mechanisms remain to be elaborated, it is clear that a balance between extrinsic apoptosis and necroptosis is important to avoid calamity during mammalian development as well as to direct appropriate responses to danger signals for innate immune clearance of intracellular pathogens.

Necroptosis, like extrinsic apoptosis, is initiated by pathogen recognition receptors and cytokines in addition to classical DR signaling. TLR3 and TLR4, via TRIF [132], and ZBP1, after activation, recruit RIPK3 [133] to execute necroptosis [134–136]. Considerable experimental evidence supports the physiological interplay between alternate CASP8-mediated apoptosis and either RIPK1–RIPK3- or ZBP1–RIPK3-mediated cell death in host defense against HCMV [100, 137] and MCMV [134, 135, 138–141], vaccinia virus [142–144] and HSV [145, 146], as well as MHV-68 and Sendai virus [147] and human influenza A virus [148–151]. Studies with the natural mouse pathogen MCMV have provided the most complete and unambiguous evidence demonstrating the importance of CASP8 [152] and ZBP1–RIPK3 [134, 135, 140] pathways as well as interactions between these pathways in anti-viral host defense [141]. These anti-viral host defense pathways are countered by MCMV M36-encoded vICA and M45-encoded viral inhibitor of RIP activation (vIRA) [135], to evade cell death and sustain infection, dissemination, and persistence. MCMV or HCMV vICA blocks basal activity as well as auto-cleavage activation of CASP8 [138, 139]. M45-encoded vIRA is a RHIM-signaling competitor that naturally suppresses recruitment/activation of RIPK3 by ZBP1 [134], but also prevents TRIF [132] and RIPK1 [135] initiation in mouse or human cells, preventing subsequent phosphorylation of MLKL [153]. M45mutRHIM and combined ΔM36/M45mutRHIM mutant viruses both fail to sustain infection in the host because infected cells die before producing progeny [100, 135, 141]. Importantly, vICA- or vIRA-deficient viruses replicate as well as WT virus in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice [141], reinforcing the importance of both pathways in restricting virus infection in vivo. HCMV and MCMV encode evolutionarily conserved CASP8 inhibitors [138, 139], but these related betaherpesviruses block at different points in the necroptotic pathway [137, 154] although RHIM signaling suppression by MCMV is remarkably similar to HSV, an alphaherpesvirus. In human cells, HSV ICP6 functions analogously to MCMV vIRA [145, 146]. HSV ICP6 also functions as a suppressor of CASP8 activation in human cells, through a mechanism that parallels CMV vICA [139, 154, 155]. HCMV employs a novel approach to block necroptosis that acts downstream of MLKL [137], possibly at the point where phospho-MLKL interacts with inositol phosphate [123, 156]. Overall, CASP8 and RIPK3 orchestrate the cell-autonomous innate host defenses that eliminate virus infected cells unless countered by virus-encoded cell death suppressors [20, 100].

CASP8 has been implicated in lymphocyte development, activation and response, initially linked to promotion of homeostatic and immune T cell proliferation [157, 158] through NF-κB signaling in a pattern conserved in mice and humans [159]. Importantly, none of the early studies accounted for unleashed CASP8-independent death [20] revealed in our seminal report of viable *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice [21] as well as incisive studies employing T cell-specific CASP8-deficient mice [160]. Mice with germ-line deficiency in either CASP8 or FADD exhibit mid-gestational death (E10.5) that is reversed by elimination of RIPK1, RIPK3 or MLKL, or knock-in of kinase inactive RIPK3 [21, 118, 129–131, 161]. Mice with CASP8 or FADD deficiency specifically in T cells do not mount antiviral T cell responses needed in the control of virus infections because cells die following TCR stimulation; however, cross with *Ripk3*$^{-/-}$ mice rescues fully functional T cells [160].

These studies provide physiological evidence that necroptosis suppression by CASP8 must be sustained in mammals [160, 162, 163]. Humans with defects in catalytic activity of CASP8 (but with WT CASP10) have severe lymphocyte activation defects [164, 165] comparable to CASP8-deficient T cells in mice, which fail to mount immune responses to viral infection [160]. Although able to control MCMV [21–23], *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice exhibit reduced inflammatory responses to LPS [166] or infectious insult by *Citrobacter rodentium*, *Yersinia*, and influenza A infection [148, 150, 167–170]. Thus, in addition to the death outcomes, CASP8 sustains innate immune signal transduction in these settings.

CASP8 scaffold function may also impact inflammasome formation and subsequent processing of pro-IL-1β and pro-IL-18 by CASP1 or CASP11 to mature proinflammatory cytokines [171]. When both CASP1 and CASP11 are eliminated in bone marrow-derived DC (BMDC), the NLRP3–ASC inflammasome depends on CASP8 to process IL-1β [172]. CASP8-dependent processing of IL-1β also occurs downstream of dectin-1, also known as CLEC7A [173]. Dectin-1 ligation triggers assembly of the CARD9–MALT1–BCL10 complex as an intermediary in pro-IL-1β expression, a complex that recruits CASP8 through ASC to process pro-IL-1β [173]. Following recruitment to the inflammasome, CASP1 and CASP11 activate gasdermin (GSDM)D to induce pore formation in the plasma membrane during pyroptosis [171]. A recent study shows that CASP8 can directly cleave GSDMD in response to Yersinia infection, leading to a pyroptosis-like outcome [174]; although cell culture studies do not reflect the cell–cell crosstalk that occurs during endotoxic shock in an intact animal [166]. Thus, growing evidence has revealed that the activities of CASP1/CASP11 and CASP8 are interchangeable, and that pyroptotic and apoptotic signaling is interdependent in vivo.

CASP8 regulation of antiviral T cells and NK cells

T cells and NK cells are the two central immune cell types that undergo dramatic expansion in response to virus infection and then abruptly contract following resolution of infection. Studies into the contribution of apoptosis to T cell fate have been complicated by the central role intrinsic apoptosis plays in all organ systems. *Casp3*$^{-/-}$ mice die before three weeks of age [175], *Casp3*$^{-/-}$*Casp7*$^{-/-}$ mice die within 10 days of birth [176] and most *Bak*$^{-/-}$*Bax*$^{-/-}$ mice die perinatally [177]. Mice lacking Bax/Bak activator Bim survive to adulthood and have provided the most complete evidence supporting intrinsic apoptosis in the control of T cell numbers generated in response to antigen. First shown using superantigen [178], later studies with virus infection demonstrated that Bim [179–181], Puma [181] and Bax/Bak [182] mediate contraction of both KLRG1^{hi} and KLRG1^{lo} antigen-specific T cells. Consistent with this evidence, overexpression of Bcl2 or Bcl_{XL} prolongs activated T cell survival [183]. Cytokines such as IL-7 support survival by activating Bcl-2 levels [184]. Neutralization of IL-7 or IL-15 accelerates contraction of both KLRG1^{hi}CD127^{lo} and KLRG1^{lo}CD127^{hi} CD8 T cell subsets [185], although IL-15 appears more important for antigen-specific CD8 T cell contraction [186]. IL-15 is also a critical prosurvival cytokine during NK cell development as well as activation of Ly49H^{+} NK cells by MCMV m157 [187].

Initially, Fas-mediated extrinsic T cell death, assessed as activation-induced cell death (AICD), was predicted to be an important correlate to reveal mechanisms of contraction [188–190]. Anti-CD3/CD28 stimulation in culture results in a robust cycle of T cell proliferation and apoptosis that is rescued by preventing Fas–FasL interactions. In addition, mice carrying mutations that affect Fas DD signaling, *lpr* or *gld* mice, show lymphoid hyperplasia and accumulate abnormal CD3^{+}B220^{+}CD4^{-}CD8^{-} T cells as they age [191–194], cells that are thought to be derived from previously activated CD4 and CD8 T cells but that had failed to die owing to the deficiency in Fas-mediated extrinsic apoptosis [159]. Curiously, these mutant mice retain the ability to generate a T cell response to infection, with contraction more-or-less intact. Humans with Fas mutations develop autoimmune lymphoproliferative syndrome (ALPS) similar to *lpr* and *gld* mice, enlarged lymphoid organs due to accumulation of abnormal T cells [195]. Thus, Fas-mediated cell death has long been implicated in the homeostatic elimination of T cells [107]. Despite the role of CASP8 as the critical apoptosis initiator downstream of Fas and studies in Fas-signaling-deficient mice [196], this relationship was not appreciated until mice with combined deficiency in extrinsic apoptosis and necroptosis became available [21, 118, 129–131, 160, 162, 197, 198]. Once necroptosis has been eliminated, CASP8- or FADD-deficient mice show the same, age-dependent abnormal T cell accumulation as Fas-signaling-deficient mice. Elimination of CASP8 (or FADD) within T cells, in combination with germ-line RIPK3 deficiency, also phenocopies *lpr* mice [160, 198]; whereas, disruption of CASP8 (or FADD) alone in T cells simply leaves these cells susceptible to TCR-induced necroptosis [157, 199, 200]. Studies in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice reinforce the crucial contributions of intrinsic apoptosis, independent of extrinsic pathways, as the overarching mechanism controlling contraction of T cells [201]. Bim-deficient mice show a defect in CD8 T cell contraction in response to staphylococcal enterotoxin B [178], as well as herpesviruses HSV-1 and murine γ-herpesvirus-68 (MHV-68) [98, 202]. Following MCMV infection, *lprTnfr1*$^{-/-}$ mice exhibit modestly increased persistence in multiple organs [203], although the small impact

makes it likely that intrinsic apoptosis predominates as with other herpesviruses. In contrast, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice show robust and functional CD8 T cell immunity following MCMV infection with control of virus levels and contraction [21–23]. These mice allow pursuit of subtle CASP8 functions playing out in T cells. TCR activation by foreign antigen leads to formation of a CARMA–MALT1–BCL10 complex that may recruit CASP8 [204, 205], phosphorylate IκB kinases (IKK) and activate NF-κB. DD interactions between FADD and MALT1 may provide the necessary bridge to recruit CASP8 [81, 165, 206] and the paracaspase domain of MALT1 may directly suppress CASP8 activation during T cell activation [204]. Although a wealth of studies focused on the death-independent function of CASP8 in activated T cells, most previous experiments were performed in CASP8-deficient T cells and were confounded by unleashed necroptotic death following TCR activation. Therefore, a model with a combined deficiency of CASP8 and RIPK3 provides opportunities to more accurately understand non-death functions of CASP8. While there is little attention to CASP8 function within NK cells, NK cell activating receptors also induce a signaling cascade via CARMA–MALT1–BCL10 complexes that triggers NF-κB activation [81], making this an important area to investigate.

Studies with T cell-specific deficiency in CASP8 (or FADD) on a necroptosis-deficient background show enhanced accumulation of cells following TCR stimulation in culture [23, 198, 207, 208]; however, it has been unclear whether this represents a decrease in T cell death or enhancement of proliferation. Mice with combined deficiency in CASP8 and RIPK3 mount higher peak antiviral CD8 T cell responses to either MCMV or HSV1; whereas, littermate control RIPK3-deficient and WT C57BL/6 mice show similar response parameters [24]. This hyperaccumulation results from a greater proliferation of terminally differentiated KLRG^{hi} cell subsets, indicating that CASP8 normally restricts effector CD8 T cell proliferation following antigen stimulation but does not impact contraction. Antiviral *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ CD8 T cells exhibit a cell-autonomous survival advantage when transferred into WT mice. The MCMV m157-dependent NK cell response supports the survival of *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ CD8 T cells, by enhancing the survival of proliferating T cells. Markedly, long-term memory inflation characteristic of MCMV infection fails to take place in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice even though animals are immune to secondary challenge. One of the most surprising outcomes is that long-term infection of *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice results in reduced homeostatic accumulation of abnormal T cells [24]. Thus, T cell expansion in response to antigen stimulation is kept in check by CASP8 survival function.

It is unclear why the enhanced inflationary CD8 T cell responses are not sustained in long-term infected *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice [24]. Signaling through two TNF superfamily receptors, OX40 and 4-1BB, supports optimal inflationary CD8 T cell responses [64, 65]. 4-1BB-elimination leads to enhanced inflationary subsets accumulation by day 7 post infection that contract overtime [64], a phenotype similar to *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice. Although 4-1BB is not known to crosstalk with FADD or CASP8 [20], stimulation of this receptor may increase cell surface expression of Fas, subsequently recruiting CASP8 to regulate inflationary CD8 T cell responses. The cytokine milieu makes a significant contribution to memory inflation. IL-2 is required for the optimal inflationary CD8 T cell responses [69], whereas IL-10 suppresses the magnitude [67]. We observed no defect of IL-2 production from CD4 T cell in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice through the course of infection [24], suggesting that the impaired memory inflation is independent of IL-2. *Casp8*$^{-/-}$*Ripk3*$^{-/-}$, as well as *lpr* mice, display increased serum IL-10 levels as they age [131, 209], which may depress memory inflation. Curiously, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice exhibit persistent virus replication in SGs [24], a phenotype that may either contribute to or be a consequence of the hypo-inflationary response. A previous study has shown that virus persistence in SG is not required for the generation and maintenance of the inflationary responses [210]; however, whether high levels of persistent MCMV replication in this organ dampen memory inflation remains to be established.

Abnormal B220^{+}CD3^{+} T cells accumulate in naïve aging *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice [21, 23], reminiscent of Fas DD signaling-deficient mice [211]. Surprisingly, MCMV infection depresses this accumulation in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice [24]. This beneficial impact of MCMV on ameliorating the accumulation of the abnormal T cells is unexpected because previous studies suggest that herpesvirus infection (including HSV-1, MCMV or MHV-68) exacerbates this lymphoid hyper-proliferative syndrome [98, 202, 212]. However, previous studies all ended before 10 weeks post infection (wpi), at which time cells expanded robustly in our experiments as well [24]. We observed the decrease in abnormal T cells later, between 16 and 25 wpi, indicating that the length of the infection may influence this abnormal homeostasis. Strikingly, the abnormal T cell numbers further decrease once IFNγ receptor is eliminated along with CASP8 and RIPK3 (*Ifngr*$^{-/-}$*Casp8*$^{-/-}$*Ripk3*$^{-/-}$; Fig. 2). This result is consistent with the known contribution of IFNγ signaling to lymphoid hyperplasia reported in *lpr* mice [213, 214], although, uninfected *Ifngr*$^{-/-}$*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice the same age as the infected mice shown in Fig. 2 have similar levels of B220^{+}CD3^{+} T cells (data not shown). *Ifngr*$^{-/-}$*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice exhibit even higher levels of persistent virus replication in SGs (Fig. 2b) than *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice and, in addition, exhibit persistent

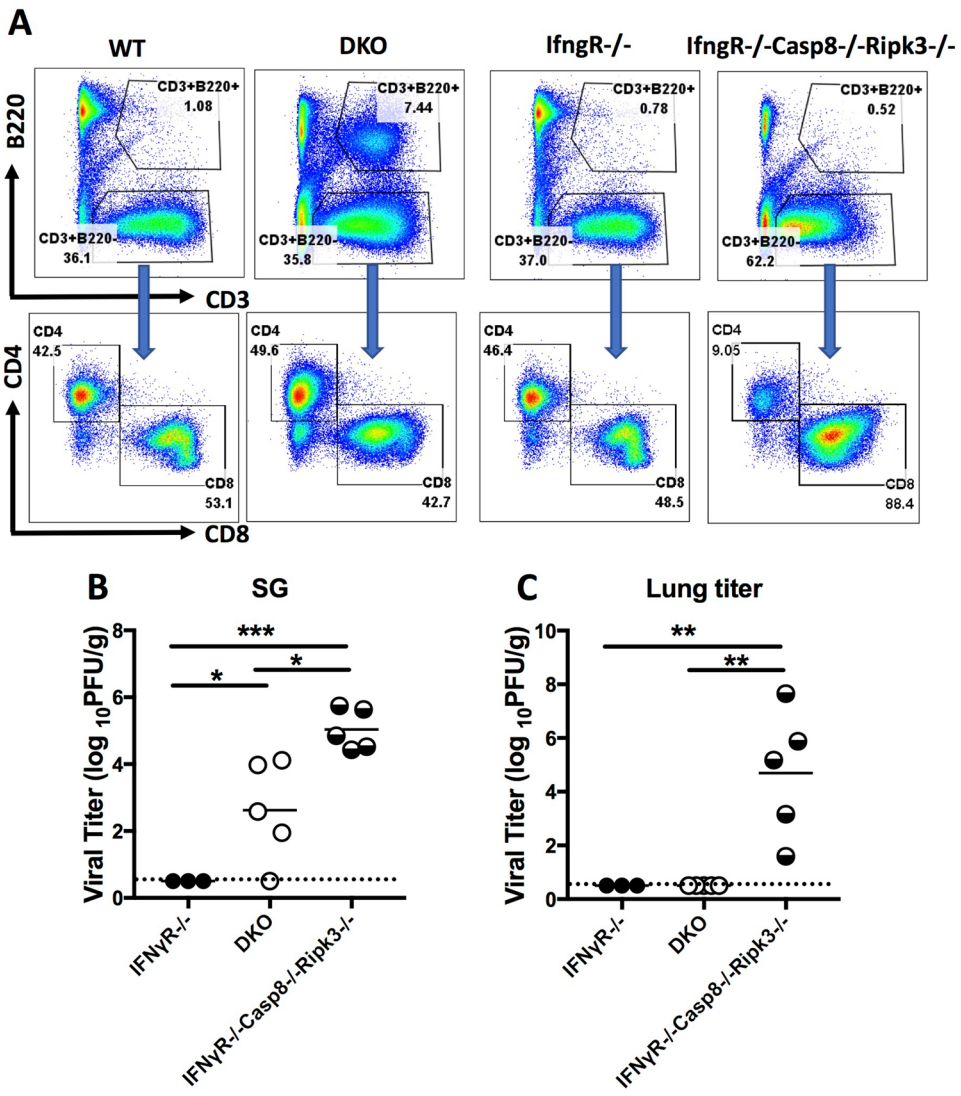

Fig. 2 Assessment of the abnormal T cell and virus titers in long-term-infected mice. WT, DKO, *Ifngr*$^{-/-}$ and *Ifngr*$^{-/-}$*Casp8* $^{-/-}$ *Ripk3* $^{-/-}$ mice were assessed 25 weeks post inoculation with K181-BAC virus (10^6 PFU, i.p.). Representative flow plots show the proportions of CD3$^+$B220$^+$ abnormal T cells and normal CD3$^+$B220$^-$ T cells in spleens after gating on CD45$^+$ leukocytes. Normal T cells were further broken down to CD4 and CD8 T cells (**a**). Graphs showing the virus titers in SGs (**b**) and lungs (**c**)

infection of lungs (Fig. 2c) at 25 wpi. The absence of IFNγ signaling and cell death pathways compromises host control over MCMV to a greater extent than in *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice. *Ifngr*$^{-/-}$ mice on a C57BL/6 background control MCMV infection in all organs, including SG, by this time. While our observations indicate the additional contribution of IFNγ signaling when cell death pathways are compromised, these data add complexity to the question of whether the decrease in abnormal T cell numbers is due to IFNγ elimination or higher levels of virus replication. CMV persistence has been shown to influence immune response characteristics against other pathogens, and MCMV-infected mice exhibit enhanced adaptive immune response to influenza vaccination or to *Listeria monocytogenes* and *Yersinia pestis* infection [215, 216]. No matter the mechanisms at play, these data suggest an underappreciated ability of natural herpesvirus infection to ameliorate symptoms of autoimmune disease.

The manner in which cell death machinery is able to crosstalk with proliferation pathways has focused on two cell cycle regulators p21 and p27 as natural substrates of CASP3 and CASP8 [217, 218]. Studies have revealed that CASP3 suppresses B cell proliferation through a p21-dependent mechanism [219], that abnormalities of T cell in *lpr* mice are reversed upon p21 overexpression [220], and that CASP3 supports proliferation of hair follicle sebocytes [221]. Anastasis is a process during which cells recover from apoptosis. Anastatic cells are widespread in the intestine, visceral muscle, eyes, antenna, central brain, nerve cords and reproductive system [222]. For those cells that are difficult to regenerate, such as neurons or cardiomyocytes, anastasis recovers cells that are not irreversibly damaged [223]. Future work will determine whether the enhanced proliferation capacity we have observed in T cells and NK cells represent the contribution of anastasis to lymphocyte biology and immune response regulation [224].

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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