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CUTTING EDGE

Cutting Edge: The Direct Action of Type I IFN on CD4 T Cells Is Critical for Sustaining Clonal Expansion in Response to a Viral but Not a Bacterial Infection[1]

Colin Havenar-Daughton, Ganesh A. Kolumam, and Kaja Murali-Krishna[2]

The action of type I IFN (IFN-I) on APCs is well studied, but their direct effect on CD4 T cells is unclear. To address this, we transferred IFN-I receptor-deficient (IFN-IR^0) and -sufficient (wild-type, WT) TCR-transgenic CD4 T cells into WT mice and analyzed their response to immunization. In response to lymphocytic choriomeningitis virus immunization, WT CD4 T cells expanded ~100-fold, whereas IFN-IR^0 CD4 T cells expanded <10-fold. However, both WT and IFN-IR^0 CD4 T cells expanded ~10-fold after* Listeria monocytogenes *immunization. Poor expansion of IFN-IR^0 CD4 T cells after lymphocytic choriomeningitis virus immunization was not due to a defect in proliferation or initial activation but to poor survival of the daughter cells. Thus, direct IFN-I signals can play either a critical or minimal role in CD4 T cell clonal expansion depending on the specific pathogen. The Journal of Immunology,* 2006, 176: 3315–3319.

Efficient functioning of Ag-experienced CD4 T cells is dependent on two major processes: clonal expansion and effector differentiation. It is generally accepted that type I IFN (IFN-I)[3], a set of innate antiviral cytokines produced in large quantities following infection (1), facilitate clonal expansion via their actions on APC (2, 3). The direct effects of IFN-I on T cells are less clear (4–8). We found recently that action of IFN-I on CD8 T cells is critical for clonal expansion in response to lymphocytic choriomeningitis virus (LCMV) infection in mice (9). However, the direct effect of IFN-I on CD4 T cell responses in vivo remains unclear. In this study, we address the consequences of direct IFN-I-mediated signals on CD4 T cells by comparing the response of adoptively transferred wild-type (WT) and IFN-IR-deficient (IFN-IR^0) CD4 T cells in WT hosts using two well-characterized murine infection models: 1) acute infection with the intracellular bacterial pathogen *Listeria monocytogenes* (LM) and 2) acute infection with LCMV.

Materials and Methods

Animals

B6.J.129S2-Ifnar<tm1Agt>, IFN-IR^0 mice on a 129/SvEv background described in (10) that were backcrossed to C57BL/6 mice as described (9) will be referred to hereafter as IFN-IR^0. Dr. P. J. Fink (University of Washington, Seattle) provided B6J.Cg-Tg(TcraTcrb)425Cbn, the $OVA_{323–339}$-specific OT-II CD4 TCR transgenic (Tg) mice on a C57BL/6 background. These mice will be referred to hereafter as OT-II. B6-Tg(TcrLMCV)1Aox, LCMV-$GP_{61–80}$-specific SMARTA TCR Tg mice described in (11) were obtained on a C57BL/6 background from Dr. C. Surh (The Scripps Research Institute, La Jolla, CA) via Dr. M. J. Bevan (University of Washington, Seattle). These mice will be referred to hereafter as SMARTA. These mice were bred with C57BL/6 IFN-IR^0 mice to generate IFN-IR^0 OT-II and IFN-IR^0 SMARTA mice. Congenically marked mice were generated by cross to B6.PL-*Thy1^a*/CyJ (B6 Thy1.1) or B6.SJL-*Ptprc^a Pep3^b*/BoyJ (B6 Ly5.1) purchased from The Jackson Laboratory. Male OT-II or either male or female SMARTA mice at 4–12 wk of age were used for experiments. Sex-matched mice were used for adoptive transfers. All mice were maintained under specific pathogen-free conditions at the University of Washington animal care facility under the guidelines of the Institutional Animal Care and Use Committee.

Reagents, Abs, in vitro cultures, adoptive transfers, and staining

Universal IFN-I were from PBL Biomedical Laboratories. OVA was from Sigma-Aldrich. All Abs were purchased from either BD Biosciences or eBioscience. Splenocytes from WT and IFN-IR^0 CD4 TCR Tg mice were cultured at a concentration of 0.1×10^6 cells per well in 96-well plates for 66 h, either with or without peptide (10 μg/ml), or peptide plus 1000 U/ml IFN-I. Intravenous adoptive cell transfers contained $1–2 \times 10^5$ Tg CD4 T cells unless otherwise indicated. Intracellular cytokine staining was done as described (9).

Virus, bacteria, and immunizations

A total of 2×10^5 PFU of LCMV (Armstrong) was injected i.p. 24–48 h after cell transfer. A total of $1–2 \times 10^4$ CFU of WT LM or rLM-Ova was injected i.p. OVA (1 mg) was injected by s.c., i.v., and i.p. routes on 1–3 subsequent days after infection.

Results

IFN-IR^0 CD4 T cells are similar to WT CD4 T cells in phenotype and proliferation but are not inhibited by IFN-I during in vitro culture

Previous reports suggest that IFN-I exert an antiproliferative effect on anti-CD3-stimulated CD4 T cells during in vitro culture (6, 7). We asked whether IFN-I have similar effects when CD4 T cells were stimulated with cognate Ag in vitro. CD4 T cells derived from both WT and IFN-IR^0 SMARTA mice were

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[3] Abbreviations used in this paper: IFN-I, type I IFN interfere; IFN-IR^0, IFN-IR-deficient; LCMV, lymphocytic choriomeningitis virus; LM, *Listeria monocytogenes*; Tg, transgenic; WT, wild type.

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low for expression of CD44, CD25, and CD69, and were high for expression of CD62L (Fig. 1*A*). Both up-regulated CD25 (Fig. 1*B*) and underwent multiple cycles of proliferation (Fig 1*C*, *middle*) when cultured in vitro with cognate antigenic peptide for 3 days. The addition of exogenous IFN-I during in vitro cultures strongly inhibited the proliferation of peptide-stimulated WT but not IFN-IR^0 CD4 T cells (Fig. 1*C*, *bottom*). Similar findings were made with OVA-specific OT-II CD4 T cells (data not shown). Together, the above observations raise the question of what would be the direct effect of IFN-I on CD4 T cells during an immune response in vivo.

Direct IFN-I action on CD4 T cells is important for clonal expansion in vivo following LCMV immunization

IFN-I have multiple effects on the cells of both the innate and adaptive immune systems. IFN-I also influence pathogen clearance and hence alter the antigenic load (10, 12–13). Consequently, the comparison of CD4 T cell responses in infected WT and IFN-IR^0 mice cannot specifically address the direct role of IFN-I on CD4 T cells during infection. Hence, we adoptively transferred a mixture of LCMV-specific WT and IFN-IR^0-naive SMARTA CD4 T cells into WT hosts and compared their response to LCMV immunization (Fig. 2*A*). As expected, in recipient mice that were left uninfected, WT and IFN-IR^0 SMARTA donor cells were recovered at a low frequency in a ratio similar to the inoculum (Fig. 2*B*, *top*). Donor SMARTA CD4 T cells expanded in response to LCMV (Fig. 2*B*, *bottom left*), but ~99% of the expanded donor cells were WT (Fig. 2*B*, *bottom right*, and Fig. 2*C*). IFN-IR^0 CD4 donor T cells in the same host expand, but only marginally (Fig. 2*B*, *bottom*, and Fig. 2*C*). The difference in expansion between WT and IFN-IR^0 SMARTA CD4 T cells was not restricted to the spleen, as it was seen in several tissues (Fig. 2*D*). Thus, IFN-I produced in response to LCMV immunization act directly on virus-specific CD4 T cells and greatly contribute to their clonal expansion.

To determine whether the diminished expansion of IFN-IR^0 CD4 T cells was due to a defect in initial activation, we compared the response of WT and IFN-IR^0 SMARTA CD4 T cells early after LCMV immunization (Fig. 3*A*). By 36 h after LCMV immunization, neither WT nor IFN-IR^0 CD4 T cells

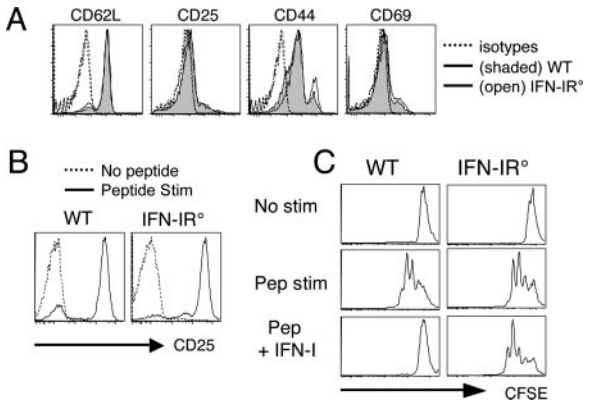

FIGURE 1. Phenotype and in vitro responses of WT and IFN-IR^0 CD4 T cells. *A*, Expression of indicated markers on WT and IFN-IR^0 SMARTA CD4 T cells. *B*, Spleen cells from WT and IFN-IR^0 SMARTA mice were cultured in vitro for 3 days and analyzed for CD25 expression. Data are gated on CD4 T cells. *C*, CFSE-labeled splenocytes were cultured for 3 days under the indicated conditions. Data are representative of at least two independent experiments.

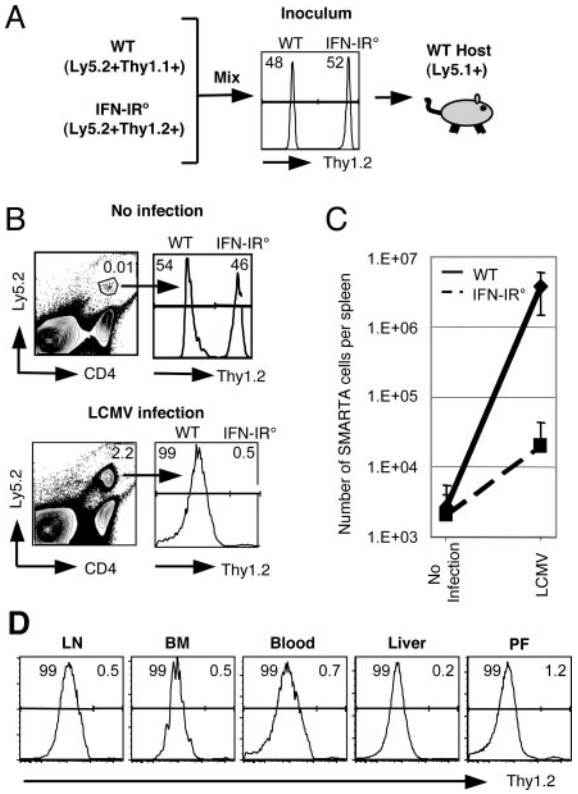

FIGURE 2. IFN-I action on LCMV-specific CD4 T cells is critical for clonal expansion. *A*, WT and IFN-IR^0 SMARTA CD4 T cells were mixed at near a 1:1 ratio and transferred into WT hosts. *B*, Recovery of the donor cells from the spleens of uninfected recipients (*top*), or after 7 days post-LCMV infection (*bottom*). Histograms indicate the ratio of WT to IFN-IR^0 CD4 T cells in the gated donor population. *C*, Expansion of donor SMARTA CD4 T cells ($n = 2$). *D*, Ratio of WT to IFN-IR^0 CD4 T cells among the donor population, in the indicated tissues of LCMV-immunized mice. LN, inguinal lymph node; BM, bone marrow; and PF, peritoneal fluid. Data are representative of three experiments.

expanded (Fig. 3*B*, *middle*). The ratio of WT to IFN-IR^0 CD4 T cells did not change substantially despite activation as indicated by CD25 up-regulation and CD62L down-regulation. However, by 7 days after LCMV-immunization WT SMARTA CD4 T cells expanded far better than IFN-IR^0 SMARTA CD4 T cells (Fig. 3*B*, *bottom*). Thus, direct signals mediated by IFN-I on LCMV-specific CD4 T cells have little influence on initial activation but greatly effect clonal expansion.

To assess whether diminished expansion of the IFN-IR^0 CD4 T cells was due to a defect in proliferation, we compared the proliferation of CFSE-labeled WT and IFN-IR^0 SMARTA CD4 T cells in WT mice after LCMV immunization. By 2.5 days postimmunization, both WT and IFN-IR^0 CD4 T cells were recruited to proliferate (Fig. 3*C*, *middle*). Despite their proliferation, the expansion of the IFN-IR^0 CD4 T cells was greatly reduced at this time point (Fig. 3*D*), indicating that most of the daughter cells generated from the donor IFN-IR^0 CD4 T cells failed to survive.

IFN-I promote IFN-γ production, at least in vitro, but this process is less efficient in murine CD4 T cells, compared with human CD4 T cells (4, 5). Therefore, we assessed whether IFN-IR^0 SMARTA CD4 T cells that were responding to LCMV Ag in vivo could produce IFN-γ. Donor CD4 T cells were able to produce IFN-γ irrespective of whether they could receive IFN-I-mediated signals or not (Fig. 3*E*, *middle* and *bottom*). The lack

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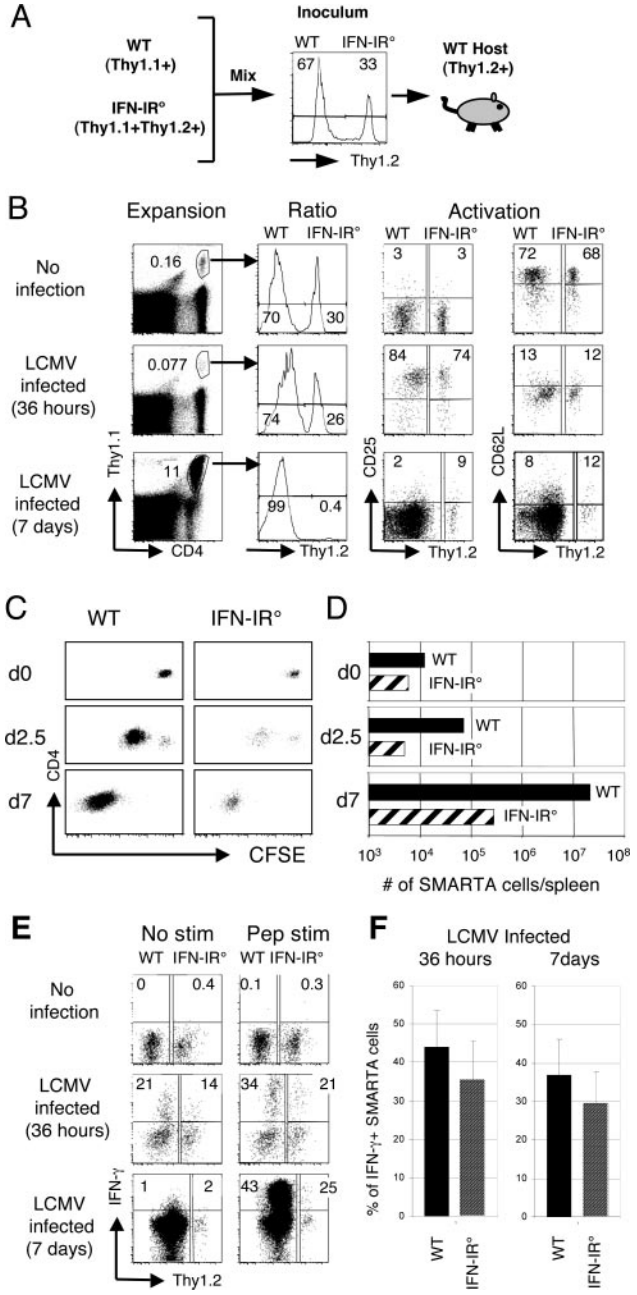

FIGURE 3. IFN-I action on LCMV-specific CD4 T cells is critical for their sustained expansion, but not early activation, proliferation, or effector functions. *A*, The ratio of WT to IFN-IR^0 SMARTA CD4 T cells in the inoculum. *B*, Frequency of donor cells from the spleen (*far left panels*). The ratio of the WT to IFN-IR^0 cells in the donor population (*second from left*). CD25 and CD62L expression among WT and IFN-IR^0 SMARTA donor CD4 T cells (*third and fourth from left*). *C*, CFSE labeled WT and IFN-IR^0 SMARTA CD4 T cells were transferred into WT hosts as indicated in *A*. data are gated on WT or IFN-IR^0 donor CD4 T cells in the spleens at indicated points post LCMV infection. *D*, Recovery of WT and IFN-IR^0 SMARTA CD4 T cells per spleen. *E*, Same as in *B*, except that splenocytes were stimulated for 6 h in vitro and then stained for intracellular IFN-γ. Data are gated on donor CD4 T cells. *F*, Percent of WT and IFN-IR^0 SMARTA CD4 T cells producing IFN-γ at the specified time points. All data are representative of two experiments.

of IFN-I-mediated signals has no substantial effect on IFN-γ production (Fig. 3*F*). In addition, both WT and IFN-IR^0 SMARTA CD4 T cells populations contained TNF-α- and IL-2-producing cells (data not shown). Together, the above results show that the absence of IFN-I action on LCMV-specific CD4 T cells in mice did not have a major affect on their ability to become activated, their ability to proliferate, or their ability to differentiate into IFN-γ producing effectors, but greatly affected their ability to survive during Ag-driven proliferation and, as a consequence, drastically dampened clonal expansion.

IFN-I-mediated direct signals have a minimal contribution to the clonal expansion of CD4 T cells following LM immunization

We next asked whether Ag-specific CD4 T cells become similarly dependent on IFN-I under the conditions of immunization with an intracellular bacterial pathogen, LM. For this, we transferred CFSE-labeled OVA-specific WT and IFN-IR^0 OT-II CD4 TCR Tg T cells into WT hosts and analyzed their response to immunization with recombinant LM expressing OVA (rLM-Ova). Both WT and IFN-IR^0 OT-II CD4 T cells proliferated (Fig. 4*A*, *right*) and expanded (Fig. 4*B*) in response to rLM-Ova.

In a different set of experiments, we transferred WT and IFN-IR^0 OT-II CD4 T cells together into WT hosts and gave exogenous OVA following either LM or LCMV immunization. Both WT and IFN-IR^0 OT-II CD4 T cells expanded similarly to each other in response to exogenous OVA protein under the conditions of LM immunization (Fig. 4*C*) and produced IFN-γ upon in vitro restimulation (as described in the Fig. 4 legend). In contrast, in response to exogenous OVA under the conditions of LCMV immunization, WT OT-II CD4 T cells expanded markedly, whereas IFN-IR^0 OT-II CD4 T cells did not (Fig. 4*D*). The diminished expansion of IFN-IR^0 OT-II CD4 T cells in response to exogenous OVA in LCMV-immunized mice was not due to a lack of proliferation, as determined by CFSE dilution (Fig. 4*F*), but due to increased death during proliferation, as suggested by annexin staining (Fig. 4*G*).

Thus, IFN-I produced in response to LCMV immunization provide direct survival signals to Ag-specific CD4 T cells, greatly contributing to their clonal expansion. In contrast, CD4 T cells primed under the conditions of LM are minimally dependent on direct IFN-I-mediated signals.

Discussion

CD4 T cell expansion requires not only Ag-receptor-mediated signals but also costimulatory signals via APCs. It is well established that inflammatory cytokines induced by infection, such as IFN-I, contribute to T cell expansion via their ability to upregulate costimulatory molecules on APC. Our study shows that the responding CD4 T cells also need direct survival signals mediated by IFN-I. In addition, we demonstrate that the pathogen determines the extent to which CD4 T cells are dependent on direct signals mediated by IFN-I. Thus, this study not only unravels a novel mechanism by which IFN-I contribute to sustaining CD4 T cell expansion in vivo, but also highlights how such fundamental immune mechanisms become redundant depending on the immunogen. These results have implications in dissecting the critical factors involved in host-pathogen interactions, microbial pathogenesis, and therapeutic and vaccination strategies.

Why do CD4 T cells become highly dependent on direct IFN-I signals under the conditions of LCMV but not LM infection? We considered the possibility that the high-level antigenic load provided by LCMV due to its noncytopathic nature

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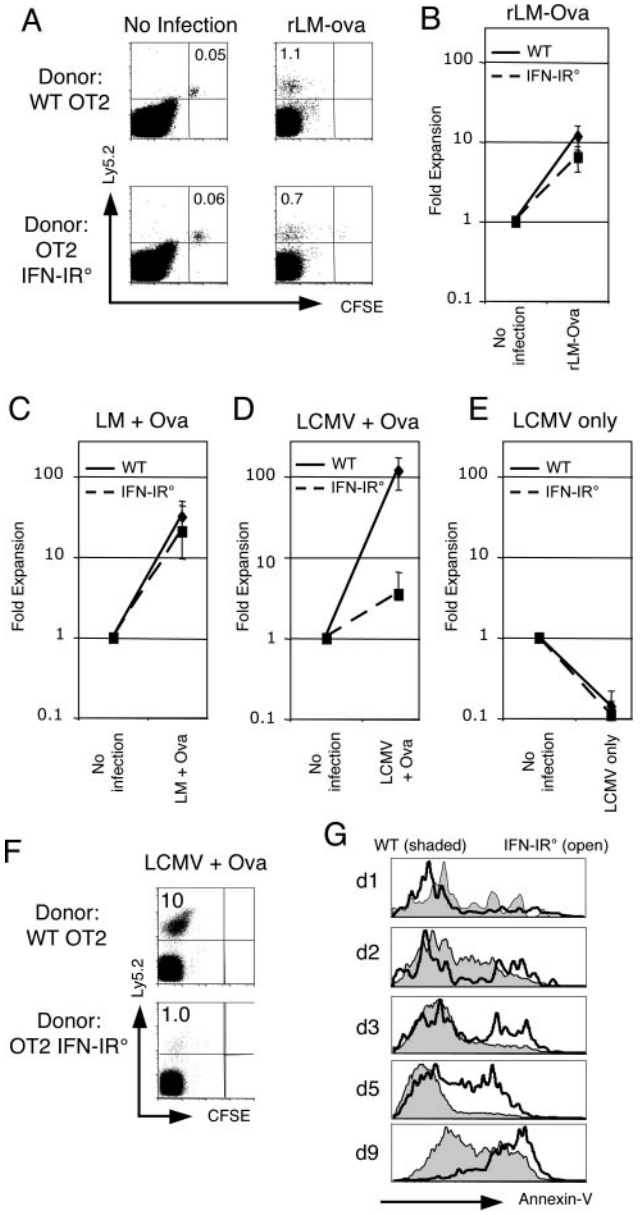

FIGURE 4. Direct signals mediated by IFN-I have minimal contribution for clonal expansion of CD4 T cells following LM immunization. *A*, Purified WT (Ly5.2$^+$) and IFN-R^0 (Ly5.2$^+$) OT-II CD4 TCR Tg CD4 T cells were labeled with CFSE and separately transferred into congenically marked WT (Ly5.1$^+$) hosts. The mice were immunized with rLM-Ova. Spleen cells were analyzed 6 days postimmunization. Data are gated on CD4 T cells. *B*, Fold expansion in the spleen. *C–E*, Same as in *B* except, WT (Thy1.2$^+$Ly5.1$^+$) and IFN-R^0 (Thy1.2$^+$Ly5.2$^+$) OT-II CD4 donor T cells were mixed and transferred together into Thy1.1, WT hosts. The mice were given soluble OVA after LM (*C*), or given soluble OVA after LCMV (*D*), or LCMV alone (*E*). In *C*, 15% of WT and 10% of IFN-IR^0 donor CD4 T cells produced IFN-γ upon in vitro peptide restimulation. In *D*, 43% of WT and 40% of IFN-IR^0 donor CD4 T cells produced IFN-γ upon in vitro peptide restimulation. *F*. Same as in *A*, except mice were given soluble OVA after LCMV immunization. *G*, Ex vivo annexin staining of WT and IFN-R^0 OT-II CD4 T cells derived from spleens of LCMV plus OVA immunized mice at the indicated time points postimmunization. Data are representative of at least two experiments.

and its ability to infect a variety of cells could play a role. If this accounted for the difference that we observed, IFN-IR^0 OT-II CD4 T cells should have expanded similarly to WT cells in response to exogenous OVA administered under the conditions of LCMV infection. However, this was not the case. Data in Fig. 4*E* show that LCMV was not preferentially killing IFN-IR^0 OT-II CD4 donor T cells. Moreover, we observed that IFN-IR^0 SMARTA donor cells expand better in LCMV-infected IFN-IR^0 hosts than in WT hosts, despite having a much higher viral load (data not shown). The profile of cytokines induced and the dynamics of its regulation differ depending on the infectious agent, characteristics of its tropism, antigenic load, persistence, and host. LCMV induces high levels of IFN-I and almost no IL-12 (10, 12). This cytokine balance is somewhat skewed toward higher levels of IL-12 in LCMV-infected IFN-IR^0 mice (10). In contrast, LM induces IL-12 in addition to lower levels of IFN-I (14). IL-12 has been shown recently to prolong the survival of Ag-activated CD8 T cells (15, 16). Based on this, we predict that IL-12 might be involved in supporting clonal expansion of CD4 T cells under the conditions of LM infection and suggest that the IFN-I-dominated cytokine milieu induced by LCMV infection instructs the responding CD4 T cells to become highly dependent on direct signals mediated by IFN-I. An alternative possibility might be that high levels of IFN-I produced in response to LCMV may cause very high clonal expansion by directly signaling to CD4 T cells. In the absence of the IFN-I-mediated signal, the response is reduced to a level comparable to that seen for LM that does not cause high IFN-I production. However, we cannot rule out the involvement of other mechanisms and factors. For example, recent studies indicate that IFN-I can cause T cell death during LM infection via sensitization to listeriolysin O-mediated toxicity (17). This raises the possibility that IFN-IR^0 CD4 T cells responding under the conditions of LM infection, although suffering from the lack of IFN-I mediated survival signals could be simultaneously eluding listeriolysin O-mediated death. The combination of these positive and negative effects may balance each other, resulting in the expansion of IFN-IR^0 CD4 T cells similar to WT CD4 T cells under the conditions of LM infection. These issues, together with the consequences of the cytokine profile induced at the beginning of each infection and the way these dynamic profiles change over time, especially during chronic infection, remain unclear. Considering the difference in the amount of IFN-I and the composition of other cytokines induced in response to diverse viral and bacterial infectious agents, it is important to further understand how critical mediators of T cell survival, death, and expansion differ in different infections.

IFN-I are known to exert an antiproliferative effect on CD4 T cells at least in vitro (6, 7). Our results confirmed this observation, and yet we were unable to replicate this effect in vivo. One possible explanation for this is that the complex set of factors induced during host-pathogen interaction in vivo help to overcome the anti-proliferative functions of IFN-I. Interestingly, IFN-γ, which was originally thought to inhibit CD4 T cell proliferation in vitro, has recently been shown to support the expansion of adoptively transferred CD4 T cells in LCMV-infected WT mice (18, 19).

The mechanisms by which IFN-I affect T cell survival, especially in vivo, require further investigation. This is especially important given the widespread use of IFN-I as therapy for viral infection, cancer, and autoimmunity. Previous reports have established that the antiviral properties of IFN-I are conducted by STAT1 and STAT2 (1, 20). Recent studies have shown that

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experimental removal of STAT-1 allows IFN-I to provide pro-survival and proproliferative signals to T cells (6). Based on these studies, we suspect that IFN-I may be contributing to T cell expansion by modulating the balance of STAT signaling. It will be important to determine whether the dynamic changes in the level of IFN-I and TCR stimulation during clonal expansion alters this balance.

Acknowledgments

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Disclosures

The authors have no financial conflict of interest.

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