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Resistance of Lymphocytic Choriomeningitis Virus to Alpha/Beta Interferon and to Gamma Interferon

DEMETRIUS MOSKOPHIDIS,[1]* MANUEL BATTEGAY,[1] MARIE-ANNE BRUENDLER,[1] ELISABETH LAINE,[1] ION GRESSER,[2] AND ROLF M. ZINKERNAGEL[1]

Institute of Experimental Immunology, University of Zurich, CH-8091 Zurich, Switzerland,[1] and Laboratory of Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, 94802 Villejuif, France[2]

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The susceptibility to alpha/beta interferon (IFN-α/β) or to gamma interferon (IFN-γ) of various lymphocytic choriomeningitis virus (LCMV) strains was evaluated in C57BL/6 mice and in various cell lines. Anti-IFN-γ treatment in vivo revealed that the LCMV strains Armstrong, Aggressive, and WE were most susceptible to IFN-γ whereas Traub, Cl 13-Armstrong, and Docile were resistant. The same pattern of susceptibility to recombinant IFN-γ was observed in vitro. In vivo treatment with anti-IFN-α/β showed a sizeable increase in replication of Aggressive, Armstrong, and WE; effects were less pronounced for Docile, Cl 13-Armstrong, or Traub. Correspondingly, WE, Armstrong, and Aggressive were all relatively sensitive to purified IFN-α/β in vitro, and Cl 13-Armstrong, Docile, and Traub were more resistant. Overall, there was a good correlation between the capacity of LCMV strains to establish a persistent infection in adult immunocompetent mice and their relative resistance to IFN-γ and IFN-α/β.

Successful resolution of a viral infection depends upon a critical balance between the extent of viral spread and replication and the magnitude of the host's immune response. Class I-restricted antiviral cytotoxic T cells (CTL), antiviral cytokines, and antibodies are involved in the recovery of a host from many acute viral infections (for reviews, see references 9 and 21). Disturbance of this balance may lead to persistence of infectious virus in the host. This may be the result of different mechanisms such as modulation of viral or major transplantation antigens, escape from T- or B-cell response, hiding in privileged sites, or immune suppression; also, the rapid growth, distribution, and wide cell tropism of viruses in vivo seem to contribute crucially to persistence of non- or poorly cytopathic viruses in an immunocompetent host (for reviews, see references 3, 21, and 23).

Lymphocytic choriomeningitis virus (LCMV) is a noncytopathic RNA virus for which mice are the natural host and reservoir (11, 16, 24). Several LCMV strains have been isolated from human patients or from LCMV carrier mice (1, 8, 16, 26). These isolates vary widely (and according to the host genetics) with respect to their capacity to induce immunity, T-cell-mediated immunopathology, and/or persistence in immunocompetent mice (1, 11, 26). For example, infection of C57BL/6 mice with high doses of 10^6 or 10^7 PFU of LCMV WE, Aggressive, or Armstrong induces a $CD8^+$ antiviral CTL response which results in clearance of virus from the animals within 2 weeks. After infection with the same dose of LCMV Traub, virus is cleared only after 2 to 4 months; infection with LCMV Docile or LCMV Cl 13-Armstrong usually induces a long-lasting or even lifelong virus persistence. A remarkable property of the last two isolates is their ability to replicate more quickly in the mouse or in vitro when compared with parenteral LCMV isolate WE, Aggressive, or Armstrong.

Interferons (alpha/beta interferon [IFN-α/β] and gamma interferon [IFN-γ]) play an important role in the early phase of infection, inhibiting the replication of a wide variety of viruses before antiviral effector CTL or antiviral antibodies come into play. Attempts at evaluating resistance or susceptibility of LCMV to interferons have been made previously (9, 13, 18, 25, 27), but no comparative experiments have been made so far.

This study attempted to evaluate the susceptibility to IFN-α/β or IFN-γ of different LCMV isolates. The results reveal a correlation between the tendency of LCMV isolates to establish virus persistence in immunocompetent mice and their resistance to interferons.

MATERIALS AND METHODS

Mice. C57BL/6 mice were purchased from the Institut für Versuchstierkunde, University of Zürich, and used at the age of 6 to 12 weeks. Animal experiments were performed and mice were kept according to federal and cantonal laws and rules.

Virus. Cl 13-Armstrong is a variant isolated from spleen cells of an adult BALB/WEHI mouse neonatally infected with LCMV Armstrong. Both the original LCMV Armstrong and Cl 13-Armstrong were obtained originally from M. B. A. Oldstone, Scripps Clinic and Research Foundation, La Jolla, Calif. (8), and R. Ahmed, University of California at Los Angeles, Los Angeles (1). LCMV WE and LCMV Traub were obtained from F. Lehmann-Grube, Hamburg, Germany (16, 32). LCMV Aggressive and LCMV Docile variants isolated from an LCMV WE(UBC) carrier mouse were obtained from C. Pfau, Troy, N.Y. (26). Second-passage virus derived from plaque-purified isolates was propagated on BHK cells (Armstrong, Cl 13-Armstrong) or L929 fibroblast cells (WE and Traub) or on MDCK cells (Docile, Aggressive). The viruses were titrated on L929 cell monolayer cultures (17) or mostly with an immunological focus assay (4); titers are expressed as PFU per gram of organ or milliliter of supernatant. The sensitivity of the immunological focus assay is within a factor of 2 to 3 comparable to virus titers detected by in vivo infection.

The quantification of infectious virus in mouse tissues has been described in detail previously (17). Briefly, at intervals after intravenous (i.v.) infection, mice were killed by cervical

* Corresponding author. Mailing address: Institute of Experimental Immunology, University of Zürich, Sternwartstr. 2, CH-8091 Zürich, Switzerland. Fax: (1) 255-4420.

dislocation. Organs were weighed and homogenized with known volumes of Hanks' balanced salt solution and titrated in vitro.

Immune reagents. The IFN-γ-specific polyclonal antiserum has been described in detail previously (19). Briefly, a sheep was initially immunized intramuscularly with 100 μg of recombinant murine IFN-γ (Ernst Boehringer Institut für Arzneimittelforschung, Vienna, Austria) at a titer of 1×10^7 to 2×10^7 U/mg in Freund's complete adjuvant; it was then boosted five times with the same amount of recombinant IFN-γ in Freund's incomplete adjuvant. The immune sera exhibited a neutralizing titer of 5×10^5 NU/ml against IFN-γ with no measurable activity against IFN-α/β (19). The sheep anti-IFN-α/β has been described in detail previously (10). It was produced by immunization of a sheep with partially purified IFN-α/β; the sera were decomplemented and extensively absorbed on murine cells. The immunoglobulin fractions were separated by ammonium sulfate precipitation. The anti-mouse IFN-α/β globulins did not neutralize IFN-γ. Its neutralizing titer was 6.4×10^6 against 8 IU of C-243 cell mouse IFN-α/β.

Serotherapy with polyclonal IFN-α/β or IFN-γ antiserum. Mice infected with various LCMV isolates i.v. were treated with 2×10^4 NU of anti-IFN-γ intraperitoneally. Treatment was started 4 h before and continued every second day after inoculation of virus and for the periods of time indicated for the individual experiments. For in vivo neutralization of IFN-α/β, C57BL/6 mice received 1.2×10^5 NU of anti-IFN-α/β intraperitoneally 4 h before and 36 and 72 h after inoculation of LCMV as described previously (25). Control mice were treated with a preparation of normal sheep serum by the same protocol as that described above.

Replication of LCMV isolates in L929 fibroblast or RAW265 macrophage cell cultures in the presence of IFN-γ or IFN-α/β. L929 fibroblast cells or RAW265 macrophage cells (originally obtained from W. C. Raschke, La Jolla Cancer Research Foundation, La Jolla, Calif.) were seeded at a concentration of 5×10^4 or 5×10^5, respectively, per well into 24-well plates and incubated for 20 h at 37°C in minimal essential medium or IMDM containing 5% fetal calf serum and various concentrations of murine recombinant IFN-γ (Ernst Boehringer Institut für Arzneimittelforschung) (10,000, 100, or 10 U/ml) or purified mouse IFN-α/β (Lee Biomolecular Research Inc., San Diego, Calif.) (1,000, 100, or 10 U/ml). The cell monolayers were infected with various strains of LCMV at a multiplicity of infection (MOI) of 0.1 to 0.0001. After 1 h of adsorption of virus at 37°C, the inoculum was removed and the cells were washed twice to remove nonadherent virus. Finally, 1.5 ml of fresh minimal essential medium (L929 cells) or IMDM (RAW265 cells) containing 5% fetal calf serum and the same concentration of IFN-α/β or recombinant IFN-γ was added. Supernatants were harvested from individual wells at various time intervals and titrated as described above.

RESULTS

Role of endogenous IFN-γ in the replication of LCMV strains in the spleens of C57BL/6 mice. To assess the influence of endogenous IFN-γ on the replication in situ of various LCMV strains, C57BL/6 mice were infected i.v. with 100 PFU of WE, Aggressive, Docile, Armstrong, Cl 13-Armstrong, or Traub; endogenous IFN-γ was neutralized by treatment of mice with sheep anti-IFN-γ serum (Fig. 1a to f and Table 1). Treatment with anti-IFN-γ enhanced virus replication in comparison with control antibodies in mice infected with LCMV WE ($P < 0.001$ on days 1, 2, 3, and 4 and $P < 0.002$ on day 1.5), Aggressive ($P < 0.001$ on days 1.5 and 3 and $P < 0.002$ on day 4.5), and Armstrong ($P < 0.001$ on days 1.5, 3, and 5) (Fig. 1a, b, and d). In contrast, the treatment had no significant influence on virus titers in the spleens of mice infected with 10^2 PFU of LCMV Docile, Cl 13-Armstrong, or Traub (Fig. 1c, e, and f). Comparable results were obtained in mice infected with 30 PFU of LCMV Cl 13-Armstrong or Traub (panels e and f, respectively).

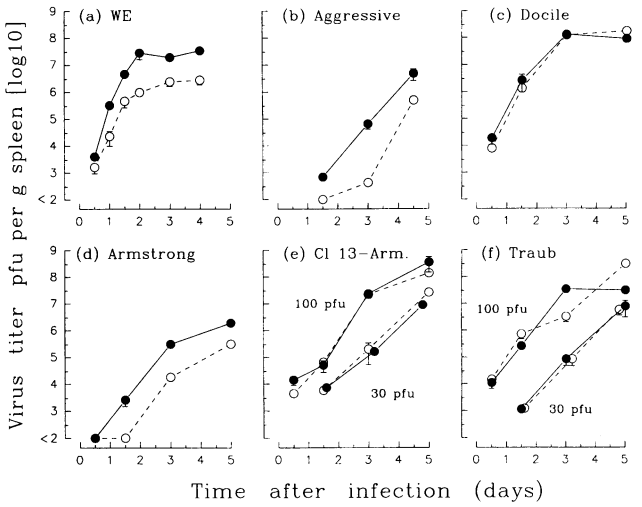

FIG. 1. Kinetics of virus titers of LCMV isolates in mice treated with polyclonal IFN-γ-specific antibodies. C57BL/6 mice were infected with different isolates of LCMV and treated with anti-IFN-γ (●——●) or control sheep serum (○----○) as has been described in Materials and Methods. Mice were infected with 100 PFU (a to f) or with 30 PFU (e and f) i.v. Virus was quantified and expressed as PFU per gram of spleen, mean of 5 to 10 mice ± standard error of the mean (SEM).

Endogenous IFN-α and -β influence the replication of LCMV strains in distinct patterns. To evaluate the role of IFN-α and -β on replication of various LCMV strains, C57BL/6 mice were treated with anti-IFN-α/β or control serum 4 h before and 36 and 72 h after infection with 100 PFU of LCMV i.v.; virus titers were determined in the spleen (Fig. 2). Neutralization of IFN-α/β enhanced the replication of all LCMV isolates. However, neutralization of IFN-α/β caused two distinct effects on virus replication. In anti-IFN-α/β-treated mice, LCMV isolate WE, Armstrong, or Aggressive exhibited an accelerated kinetics very early on day 1.5. In mice infected with LCMV Docile, Cl 13-Armstrong, or Traub, virus titers in the spleens did not differ on day 1.5; instead, anti-IFN-α/β caused significantly higher titers only on day 3 and day 5 (Fig. 2 and Table 1).

Replication of LCMV strains in the presence of recombinant IFN-γ or purified IFN-α/β. To further characterize the various LCMV strains, their ability to grow in fibroblast (L929 cells, MOI of 0.01) or macrophage (RAW265 cells, MOI of 0.1) cell lines was tested in the presence of different concentrations of recombinant murine IFN-γ or purified IFN-α/β (Fig. 3 and 4). The kinetics of virus titers of different LCMV isolates in the supernatants of cells treated with IFN-γ or with IFN-α/β revealed that 32 h after infection of L929 (and 42 h for RAW265 cells [not shown]) was the earliest time point when virus titers could be measured reliably in controls and treated cultures. Representative results obtained for LCMV Armstrong and Cl 13-Armstrong at these time points in three experiments are illustrated in Fig. 3; the other (Fig. 3) time points were also evaluated for all combinations and gave

TABLE 1. Effects of IFN-γ or IFN-α/β on the replication of LCMV isolates in mice or in cell cultures[a]

Virus strain	Tendency of virus to persist in adult C57BL/6 mice[b]	Virus titer differences (log_{10}) between treated and control cultures				
		Mice[c]		Cell cultures[d]		
		Anti-IFN-γ	Anti-IFN-α/β	IFN-γ (L929)	IFN-γ (RAW265)	IFN-α/β (L929)
WE	−	1.5	2.4	1.5	1.5	2.1
Aggressive	−	2.2	3.2	2.4	2.7	2.3
Docile	+	<0.1	1.3	0.8	0.7	1.2
Armstrong	−	1.2	>2.2	1.6	2.4	1.7
Cl 13-Armstrong	±	<0.1	1.4	0.4	1.5	1.1
Traub	±	<0.1	1.4	0.6	0.9	0.9

[a] Compilation of data from Fig. 1, 2, and 3, from references 1 and 22, and from unpublished observations.
[b] C57BL/6 mice were infected with 10^2 to 10^7 PFU i.v. of the indicated LCMV isolate. Virus titers were determined later after infection (>250 days) in spleen, thymus, and kidney as PFU per gram of tissue on the basis of 5 to 10 mice ± SEM. +, all mice of the group had virus titers of 10^4 to 10^7 PFU per g of tissue until >250 days; ±, group of mice which had virus titers of 10^4 to 10^7 PFU per g of tissue and some of which had no detectable virus on day 250; −, mice had eliminated the virus within 3 weeks after infection.
[c] Maximal differences of virus titers between mice treated with anti-IFN-γ or anti-IFN-α/β and mice infected with LCMV and treated with control sheep serum; values are given as log_{10} differences of virus titers expressed as PFU per gram of spleen.
[d] Values represent the maximal differences of virus titers (log_{10} PFU per milliliter of supernatant) in the supernatants of cells infected with virus and treated with IFN-γ or IFN-α/β versus untreated cultures.

compatible results (not shown). The growth of LCMV Docile, Cl 13-Armstrong, and Traub on L929 (Fig. 4A) or RAW265 (Fig. 4B) cells was minimally reduced in the presence of various concentrations of recombinant IFN-γ. In contrast, a significant decrease of virus titers was measured in cell cultures infected with WE, Armstrong, or Aggressive (Fig. 4A and B and Table 1). The influence on virus replication of IFN-α/β tested on LCMV-infected L929 cells (Fig. 4C) or RAW265 cells (data not shown) was less pronounced but correlated with the observations in mice treated with antibodies against IFN-α/β. LCMV WE, Aggressive, and Armstrong were inhibited considerably by a factor of about 100 during the early phase of infection, whereas Docile, Cl 13-Armstrong, and Traub were much less affected by a factor of 5 to 10 (even when treated with 10^3 U of IFN-α/β per ml). These findings were confirmed in further experiments with MOI of 0.1 and 0.001 (L929 cells) or 0.01 (RAW265 cells) and additional determinations of virus titers 20, 32, and 42 h after infections of cells (data not shown).

Thus, the observed patterns of replication of the various LCMV isolates in mice treated with antibodies against IFN-γ or IFN-α/β correlated with those found for the same LCMV isolates in infected fibroblast or macrophage cell cultures exposed to interferons.

Comparable levels of IFN-γ or IFN-α/β in C57BL/6 mice infected with different LCMV isolates. The lack of effect on the virus titers in the spleens of C57BL/6 mice infected with certain LCMV isolates (Docile or Cl 13-Armstrong or Traub) and

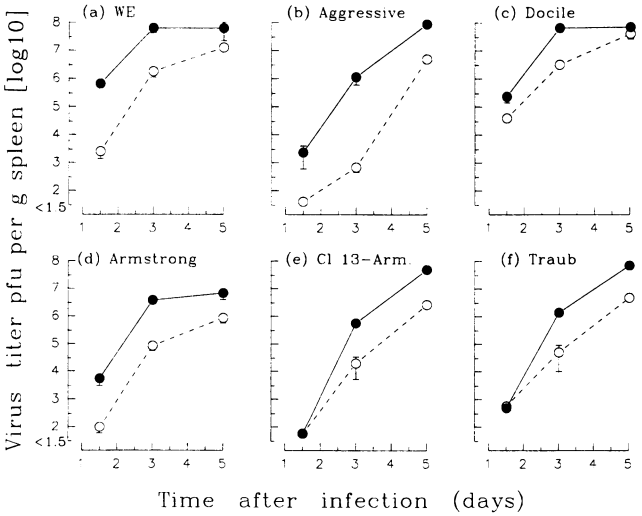

FIG. 2. Kinetics of LCMV virus titers in mice treated with polyclonal anti-IFN-α/β. C57BL/6 mice were infected with 100 PFU i.v. of LCMV isolates and treated with anti-IFN-α/β (●——●) or normal sheep serum (○----○) as has been described in Materials and Methods. Each symbol represents virus titers expressed as PFU per gram of spleen, mean of 5 to 10 mice ± SEM.

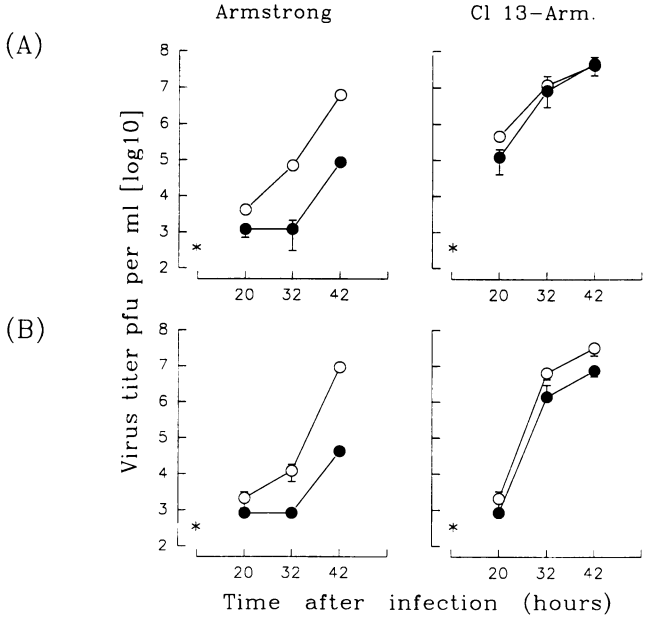

FIG. 3. Kinetics of LCMV titers in L929 cells treated with IFN-γ or IFN-α/β. Shown are the time kinetics of virus titers of LCMV isolates Cl 13-Armstrong and the parental Armstrong on L929 cells (MOI of 0.01) in the presence of IFN-γ (1,000 U/ml) (A) or IFN-α/β (100 U/ml) (B). Asterisks represent the initial virus titers after the adsorption time of LCMV isolates. Results represent mean titers of three independent wells ± SEM.

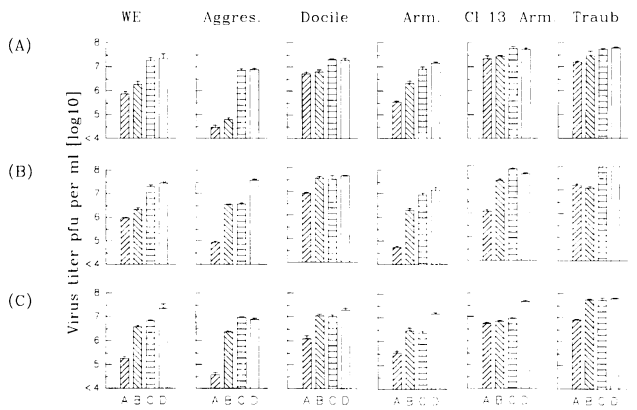

FIG. 4. Effects of IFN-γ or IFN-α/β on replication of LCMV isolates in L929 fibroblast or RAW265 macrophage cell lines. Murine fibroblast (L929) (A) or macrophage (RAW265) (B) cell lines were incubated with different concentrations of recombinant IFN-γ (A, 10^4 U/ml; B, 10^3 U/ml; C, 10^2 U/ml; D, medium control) starting 24 h before their infection with various LCMV isolates with an MOI of 0.01 for L929 or an MOI of 0.1 for RAW265 cells. L929 cells were treated with purified IFN-α/β (A, 10^3 U/ml; B, 10^2 U/ml; C, 10^1 U/ml; D, medium control) and were infected with an MOI of 0.01 of various LCMV isolates (C). Virus titers were determined at 32 h for L929 and at 42 h for RAW265 cells: these were the earliest times when both control and treated cultures exhibited measurable virus titers in the supernatants. Results represent mean titers of three to five independent wells ± SEM.

treated with antibodies against IFN-γ or IFN-α/β may reflect either resistance to these cytokines or lower levels of induced interferons by the various virus strains. To explore these possibilities, C57BL/6 mice were infected with a relatively low dose (100 PFU i.v.) of different LCMV isolates. IFN-γ levels were determined in sera of LCMV-infected mice, by enzyme-linked immunosorbent assay, but concentrations were all below the limit of detection (10 U/ml). In addition, the capacity of spleen cells taken at different times after infection to release IFN-γ into supernatants after culture in IMDM plus 10% fetal calf serum for 3 to 24 h at low or high cell density (2×10^6 or 2×10^7 cells per ml) was tested. No significant amounts of IFN-γ could be detected. Restimulation with immobilized CD3 antibody (clone KT3, American Type Culture Collection) yielded a level of IFN-γ production in the spleens of LCMV WE-infected mice tested at days 1 and 3 after infection comparable to that in LCMV Docile-infected mice. Similarly, levels of IFN-γ in LCMV Armstrong-infected mice were comparable to those in mice infected with LCMV Cl 13-Armstrong (data not shown).

The induction of IFN-α/β in C57BL/6 mice infected with LCMV Docile or Aggressive, determined in the serum, was described in an earlier study (18). The tested LCMV isolates induced comparable levels of IFN-α/β in C57BL/6 mice. These experiments could not reveal differences in levels of induced interferons that correlated with particular LCMV isolates.

DISCUSSION

The presented results suggest for various LCMV strains a correlation between resistance to IFN-α/β or IFN-γ in vivo and in vitro and their tendency to establish persistent infections in adult immunocompetent mice. The various LCMV strains may be tentatively arranged from most to least resistant to interferons and most to least capable of inducing a persistent virus infection in adult mice in the following order: Docile, Cl 13-Armstrong, Traub, WE, Aggressive, and Armstrong.

Several earlier studies have analyzed effects of interferon on LCMV infection in mice. The important role of IFN-α/β in controlling LCMV Pasteur (27) and Aggressive (25, 26) virus infection was documented by treatment of virus-infected mice with IFN-α/β-specific sheep antibodies. In both studies, treatment with anti-IFN-α/β drastically enhanced virus replication. In addition, anti-IFN-α/β-treated mice which were infected intracerebrally with LCMV Aggressive survived because of induction of high-dose immune paralysis due to rapid spread of virus in a broad range of tissues of the host (22). One study searched for differences and correlations between IFN-α/β levels in serum and T-cell-mediated immunopathology. LCMV Docile induced low levels of interferon and little immunopathology whereas Aggressive induced a higher level of IFN-α/β and a lethal immunopathology in Swiss mice (13). In contrast, a second study using a great number of mouse strains and the same LCMV isolates failed to reveal similar correlations (18). Several groups recently evaluated the effects of anti-IFN-γ, serum, or antibodies on the course of the virus infection and development of antiviral CTL responses in mice infected with LCMV WE (34), Aggressive (19), or Armstrong (15). All three studies revealed that anti-IFN-γ treatment enhanced replication and spread of the tested LCMV strains in different tissues of the mouse. Since anti-IFN-γ treatment had no effect on the induction of CTL against other viruses that poorly replicate extraneuronally in mice (12, 19), these data are rather compatible with the assumption that IFN-γ directly interfered with virus replication. The present experiments extend these various studies and further show that there exist relative differences in the susceptibility to the two types of interferon amongst the LCMV strains.

In the last few years, several findings emphasized the important role of antiviral cytokines such as IFN-γ and IFN-α/β in the control of virus infection in humans or animals (for reviews, see references 5 and 31). Nevertheless, there are only rare examples that we were able to find in the literature documenting virus isolates or mutants differing in their susceptibility to interferons. IFN-α/β-resistant viruses were found in several strains of measles virus that were selected by growth in brain tissue (6). These findings may suggest a possible role of such virus variants in virus persistence associated with subacute sclerosing panencephalitis. Adenoviruses are usually relatively resistant to interferon. This resistance was recently mapped to E1 proteins (14) that block interferon induction of oligoadenylate synthetase mRNAs at the transcriptional level (7). Resistance to IFN-α/β was also described for herpes simplex virus type 1 in comparison with a less virulent strain of herpes simplex virus type 1 (29, 30). In addition, the factor encoded by the 1,828-bp *Bam*HI DNA fragment of hepatitis B virus with suppressive activity for human IFN-β genes has been implied in virus persistance of hepatitis B virus in humans (33).

What are the mechanisms by which interferon resistance influences the ability of certain LCMV isolates to establish persistent infections in adult mice? The molecular basis for interferon resistance in certain LCMV strains and mutants is not known yet. The amino acid differences between Armstrong and Cl 13-Armstrong in the glycoprotein (amino acid 260) and changes in the L-RNA coding for the polymerase are possible candidates (2, 20, 28). The relevant sequence information is not available yet for LCMV Aggressive and Docile, but the amino acid position 260 is the same for the LCMV isolates Cl 13-Armstrong, Aggressive, and Docile (21a) and therefore cannot alone explain the differences.

Although probably the virus-host relationship is more com-

plicated than depicted here, the presented results may offer a simple and direct explanation: relative interferon resistance enhances replication and spread of LCMV in the host, facilitating exhaustion of antiviral CTL and virus persistence (22).

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