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Antibody Prevents the Establishment of Persistent Arenavirus Infection in Synergy with Endogenous T Cells†

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A cardinal feature of the biology of lymphocytic choriomeningitis virus (LCMV) is its ability to establish persistent infections in mice. Persistence is usually established by infection of the mouse during the in utero or neonatal period. Susceptibility can be extended to the adult by treatment with immunosuppressive agents or by infection with immunosuppressive strains of LCMV. In this study we investigated the capacity of passively acquired anti-LCMV antibodies to prevent the establishment of persistence in both neonatal and adult mice. Suckling BALB/c mouse pups nursed by mothers immunized against LCMV before pregnancy had higher survival rates following infection than controls and withstood challenge doses of up to 400 PFU without becoming persistently infected. To establish that maternal antibody alone and not maternally derived T cells provided this protection, nonimmune mothers were infused with monoclonal anti-LCMV neutralizing antibodies within 24 h after delivering their pups. Pups nursing on these passively immunized mothers were resistant to persistent LCMV infection. The establishment of persistence in adult BALB/c mice by the immunosuppressive, macrophage-tropic LCMV variant, clone 13 was also prevented by prophylactic treatment with anti-LCMV monoclonal antibodies. However, the protection afforded by passively acquired antibody was found to be incomplete if the recipients lacked functional $CD8^+$ T cells. While 65% of neonatal athymic (*nu*/*nu*) mice nursed by immune *nu*/+ dams resisted low-dose viral challenge (25 PFU), the majority of nude pups challenged with high doses of virus (100 PFU) became persistently infected. Also, protection was incomplete in β_2-microglobulin knockout mice, which lack functional $CD8^+$ T cells, suggesting that a cooperative effect was exerted by the combination of neutralizing antibody and endogenous T cells. These results indicate that antibodies provide an effective barrier to the establishment of persistent infections in immunocompetent mice and reaffirm that vaccines which induce strong humoral responses may provide efficient protection against arenavirus infections.

The AIDS epidemic has refocused our attention on the potential devastation resulting from persistent viral infections. Several viruses, including human immunodeficiency virus (HIV), hepatitis B virus, and papillomaviruses, are now recognized to establish in humans persistent infections which are associated with chronic diseases (9). Furthermore, as techniques for identifying persistent viruses become more refined and with growing awareness that the pathology may result months to years after initial infection, it is likely that other diseases now of unknown etiology will be linked with persistent viral infections. Thus, it is of considerable importance that prophylactic and therapeutic regimens be defined, including methods for preventing the establishment of persistent infections and for the amelioration of established infections.

Viruses achieve persistence through a variety of mechanisms. Fundamental to all of these is the ability to avoid immune clearance. This is readily accomplished in immunocompromised individuals, such as neonates, who lack a fully competent immune system, and in immunosuppressed adult organ transplant recipients (20). While some viruses avoid recognition by selectively infecting cells within immune privileged sites such as the central nervous system, others infect lymphocytes and/or antigen-presenting cells and suppress the immune function of these cells. Lymphocytic choriomeningitis virus (LCMV) is a member of the *Arenaviridae* which commonly infects cells of the immune system and readily establishes persistent infections in mice (7, 11). The ability of LCMV to initiate persistence by congenital or neonatal infection is well documented, and immunosuppressive variants of the virus which are capable of establishing persistent infections in immunocompetent adults have been isolated and characterized (2, 5). Here we demonstrate the effectiveness of neutralizing antibody in preventing the establishment of persistence by the neurotropic Armstrong strain of LCMV in neonates and by the immunosuppressive clone 13 (Cl-13) variant in immunocompetent adult mice.

The viruses used for these studies were the Armstrong strain 4 (ARM-4) and Armstrong strain 5 variants of LCMV (22, 23) and the immunosuppressive LCMV variant Cl-13 (2). All of the strains were originally plaque purified from LCMV Armstrong CA-1371. Working stocks were obtained from infected BHK-21 cells (multiplicity of infection of 0.1) 48 h postinfection and stored in 1-ml aliquots at −70°C.

BALB/c ByJ, C57BL/6, and athymic BALB/WEHI nude mice were obtained from the rodent breeding colony at the Scripps Research Institute. Dams were immunized with 10^5 PFU of LCMV by intraperitoneal (i.p.) inoculation 30 days or more prior to mating. BALB/WEHI *nu*/+ females were bred with athymic BALB/WEHI *nu*/*nu* males. β_2-microglobulin knockout ($\beta_2-/-$) mice were obtained from Beverley Koller (13). As these mice were bred on a B6 background, we utilized C57BL/6 control mice for experiments with $\beta_2-/-$ mice.

Neonatal mice born to and nursed by immune dams resist the establishment of persistent infection by LCMV. We sought

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TABLE 1. Nursing pups of immune mothers resist induction of persistent infection

Maternal status[a]	Maternal treatment	Challenge dose (PFU)[b]	Days postweaning[c]	Tissue (no. of samples)	Virus titer $\log_{10}$ PFU[d]
Normal		40	21	Brain (3)	5.91 (0.13)
				Spleen (3)	6.84 (0.29)
				Kidney (3)	6.74 (0.03)
Immune		40	21	Brain (7)	<2[e]
				Spleen (7)	<2
				Kidney (7)	<2
Normal		100	21	Brain (6)	5.67 (0.13)
				Spleen (6)	7.11 (0.30)
				Kidney (6)	5.04 (0.62)
Immune		100	21	Brain (9)	<2
				Spleen (9)	<2
				Kidney (9)	<2
Immune		100	65	Brain (30)	<2
				Spleen (30)	<2
				Kidney (30)	<2
Immune		400	65	Brain (6)	<2
				Spleen (6)	<2
				Kidney (6)	<2
Normal	MAb[f]	100	21	Brain (23)	<2
				Spleen (23)	<2
				Kidney (23)	<2

[a] Pups were born to and nursed by normal or immune BALB/cByJ mothers.
[b] Pups were challenged i.p. within 24 h of their birth.
[c] Tissue was collected from pups on the indicated day after they were weaned.
[d] To determine the induction of a persistent infection, tissue was assayed for virus content by plaque assay on Vero cells. Values in parentheses are standard deviations.
[e] Below the levels detectable by plaque assay.
[f] Ascites containing MAb 2.11.10, which is specific for LCMV.

to determine whether maternal antibody could prevent the establishment of persistent LCMV infections in neonatal mice. BALB/c pups were challenged with 25 PFU of LCMV by i.p. injection within 24 h following birth and allowed to mature. Pups nursing on immune dams were weaned at 3 to 4 weeks of age, but pups from nonimmune dams appeared to be runted and could not be weaned until 5 weeks. Throughout the course of these studies we found that challenged pups born to immune dams had greater overall survival rates (88%) than pups born to nonimmune dams (30%). The sera of immune dams had neutralizing-antibody titers ranging from 1/250 to 1/3,500 50% plaque reduction dose (PRD_{50}), and the anti-LCMV titers of their nursing pups reached levels equivalent to those of the dams in less than 5 days, reflecting efficient secretion of maternal immunoglobulin in the mothers' milk and uptake by the pups (data not shown). To determine whether pups were persistently infected, tissues were harvested 3 weeks or later after weaning and virus concentrations were determined by plaque assay (Table 1). Virus was undetectable in mice born to and nursed by immune mothers when the route of viral challenge was i.p., regardless of whether mice were challenged with low (40 PFU), moderate (100 PFU), or high (400 PFU) doses of virus. However, all pups that survived viral challenge and nursed on nonimmune mothers became persistently infected and expressed high levels of virus (>5 $\log_{10}$ PFU/g) in their brains, spleens, and kidneys (Table 1).

We have previously shown that the neutralizing monoclonal antibody (MAb) 2.11.10 is efficiently transferred through mother's milk to nursing pups and protects them from lethal acute lymphocytic choriomeningitis following intracerebral (i.c.) challenge at 10 to 14 days of age (3). We extended this observation to establish whether maternal antibodies provided sufficient protection to block establishment of persistent infection following neonatal infection. Passive immunization of pregnant BALB/cByJ females was accomplished by i.p. infusion with 0.2 ml of ascites fluid containing MAb 2.11.10, specific for glycoprotein GP-1, during the terminal stages of pregnancy (~18 to 20 days) and postpartum every other day until the pups reached 14 days of age (3). Following challenge none of the pups nursing on these passively immunized dams contained virus detectable by plaque assay in their tissues (Table 1).

Antibody prevents the establishment of persistent infection by the immunosuppressive LCMV variant Cl-13. Infection of immunocompetent adult mice with the macrophage-tropic, immunosuppressive LCMV variant Cl-13 results in persistent infection (2). Experiments were designed to determine whether passive MAb could prevent the establishment of persistent infection by Cl-13. BALB/cByJ females, 5 weeks old, were challenged intravenously with 2×10^6 PFU of LCMV Cl-13 as described by Ahmed et al. (2). Treatment with neutralizing MAb specific for the spike glycoprotein GP-1 consisted of injections the day before, the day of, and the day after challenge with Cl-13. Two of these antibodies, 258.2.11 and 197.2.1, have previously been shown to protect against acute lymphocytic choriomeningitis (23), while a third antibody, 36.1, does not (3). Mice receiving infusions with MAb 258.2.11 or 197.2.1 were resistant to the establishment of persistence by Cl-13, while the nonprotective MAb, 36.1, failed to prevent infection (Table 2). Finally, MAb 2.11.10, which recognizes an LCMV epitope not expressed on Cl-13, also failed to prevent persistence, demonstrating that antibody-mediated protection against persistent infection exhibits antigen specificity paralleling that of the MAb. Immunohistochemical examination of the spleens from Cl-13-infected mice indicated that by 3 to 4 days after challenge, macrophages in the marginal zones were heavily infected. Corresponding titers in the range of 10^5 PFU/g were observed in the spleens from unprotected, Cl-13-infected mice. Treatment with the protective MAb 197.2.1 reduced virus titers in the spleens to levels below the threshold of detection (Table 2).

Prevention of persistence by antibody is incomplete in the absence of endogenous T cells. We previously hypothesized that protective anti-LCMV antibodies functioned by restricting the spread of the viral infection until sterilizing cytotoxic T lymphocytes (CTLs) could be elicited (3). To address whether passively acquired antibody was sufficient to block the establishment of persistence, studies with mouse strains lacking competent T-cell responses were designed. LCMV readily establishes a persistent infection in athymic nude mice even when they are infected as adults. Therefore, we allowed neonatal nude mice to receive maternal antibodies by nursing for 7 days before challenging them with LCMV by i.p. injection. While 65% of the BALB/WEHI nude pups born to immune *nu*/+ mothers resisted the induction of persistent LCMV infection at low challenge doses (25 PFU), this resistance was readily overcome by increasing the virus challenge dose to 100 PFU (Table 3), suggesting that protection is incomplete in the absence of a well-developed T-cell response.

To further address the requirement for functional T cells to sustain successful protection, we utilized $\beta_2-/-$ mice. $\beta_2-/-$ mice are unable to assemble major histocompatibility complex

TABLE 2. Prophylactic MAbs block induction of persistence by LCMV variant Cl-13

MAb[a]	Tissue	No. positive/total[b]	Virus titer, $\log_{10}$[c]
None	Brain	12/12	5.48 (0.54)
	Spleen	12/12	5.07 (0.52)
	Kidney	12/12	6.66 (0.44)
258.2.11	Brain	0/11	<2.2
	Spleen	0/11	<2.2
	Kidney	0/11	<2.2
197.2.1	Brain	0/11	<2.2
	Spleen	0/11	<2.2
	Kidney	1/11	3.90
36.1	Brain	4/8	3.29 (1.06)
	Spleen	6/8	4.49 (0.18)
	Kidney	7/8	6.49 (0.67)
2.11.10	Brain	8/8	4.51 (1.15)
	Spleen	7/8	4.07 (0.74)
	Kidney	8/8	7.18 (0.25)

[a] All mice were challenged with 2×10^6 PFU of LCMV Cl-13 by intravenous injection. MAb-treated mice were infused by i.p. injection with 0.2 ml of MAb-containing ascites the day before, the day of, and the day following virus challenge.

[b] Virus was detected by plaque assay, which has a detection threshold of about 2.2 $\log_{10}$ PFU/g. The number of samples exhibiting virus by plaque assay per total number of tissues sampled is given. Samples were collected 24 days postchallenge.

[c] Mean $\log_{10}$ PFU/gram of tissue only for those samples positive for plaques. Values in parentheses are standard deviations.

class I antigen complexes and lack functional $CD8^+$ T cells (13). Others have reported that $\beta_2-/-$ are unable to clear acute LCMV infection and become persistently infected (8, 14). Our findings agree with this observation. In preliminary experiments we measured plasma viremia over a 7-week period following i.p. inoculation with LCMV ARM-4 and found stable titers of 3 to 4 $\log_{10}$ from 2.5 through 7 weeks. When the passive immunotherapy protocol was applied to $\beta_2-/-$ mice, we found that they were still unable to clear virus infection. β_2-Microglobulin knockout mice were challenged by i.c. inoculation with 5×10^2 PFU of LCMV ARM-4 followed immediately by i.p. infusion of ascites containing MAb. Mice receiving passive immunoglobulin exhibited a chronic disease consisting of ruffled fur, inactivity, and marked failure to thrive. A few of these animals died between 10 and 25 days after infection, in contrast with 7 days in the LCMV-challenged C57BL/6 controls. Surviving mice were sacrificed at 49 days to determine virus titers. $\beta_2-/-$ mice receiving no antibody, nonprotective MAb 36.1, or MAb 2.11.10 exhibited virus titers from 4.76 to 5.5 $\log_{10}$ PFU in their spleens and similar titers in their brains and kidneys (Table 4). In contrast, C57BL/6 control mice receiving MAb 2.11.10 survived challenge and contained no detectable virus in their tissues at 49 days. All of the C57BL/6 control mice in groups receiving no antibody or nonprotective MAb 36.1 died of typical lymphocytic choriomeningitis disease 7 days after i.c. challenge.

TABLE 3. Incomplete resistance to induction of persistent infection by nude pups of immune heterozygous mothers

Pups genotype[a]	Maternal status[b]	Challenge dose (PFU)[c]	% Persistently infected[d]
nu/*nu*	Normal	100	100 (11)
nu/*nu*	Immune	100	35 (34)
nu/+	Immune	100	0 (3)
nu/*nu*	Immune	200	40 (5)
nu/*nu*	Immune	400	80 (5)

[a] Pups were born to BALB/WEHI *nu*/+ mothers; thus, approximately half the litter had the athymic (nude) phenotype and half were normal.

[b] Pups were born to and nursed by either immune or normal dams. The mothers were immunized one or two times with immunizing doses of 5×10^5 PFU of ARM-4 at least 30 days prior to mating.

[c] Pups were challenged by i.p. inoculation of virus when they were 7 days old.

[d] Brains, spleens, and kidneys from all animals were examined for viral concentration by plaque assay. If virus was recovered from any tissue, that animal was considered persistently infected. The number of animals per group is in parentheses.

TABLE 4. Passive antibody does not prevent persistence in $\beta_2-/-$ mice

Group[a]	MAb[b]	% Mortality	% persistently infected[c]	Virus titer (mean $\log_{10} \pm$ SD)
$\beta_2-/-$	None	14.3	85	5.5 ± 0.81
	36.1	0	100	4.8 ± 0.72
	2.11.10	28.6	71.4	4.9 ± 0.69
C57BL/6	None	100	0	
	36.1	100	0	
	2.11.10	0	0	<1.0

[a] Mice were challenged with 5×10^2 PFU of ARM-4 by i.c. injection.

[b] Mice received infusions of the indicated MAb immediately following virus challenge by i.p. injection.

[c] Tissues were removed from all surviving mice 49 days postchallenge and assessed for virus by plaque assay.

Viruses use a variety of mechanisms to avoid immune recognition which allow them to become persistently established in the host, e.g., selective immunosuppression by infection of elements of the reticuloendothelial system, including antigen-presenting cells. In addition, viruses can establish persistent infections in immunocompromised individuals, such as neonates and nutritionally deprived individuals. Under appropriate conditions, LCMV can initiate persistence in mice. The Cl-13 variant of LCMV ARM has been shown to persistently infect neonatal or adult mice and to specifically suppress $CD8^+$ T-cell responses to the virus (1, 6, 12). In this report, we demonstrate that maternal antibody to specific epitopes on the viral glycoprotein efficiently blocks the establishment of persistent LCMV infections in neonates and that passive MAb administered before infection prevented the establishment of persistence by the immunosuppressive Cl-13 variant. The results further indicate that endogenous T cells are required to cooperate with the passive antibody to ensure the avoidance of a persistent LCMV infection.

The strong correlation between viral persistence and infection of neonates is attributed to the inability of neonates to mount a competent $CD8^+$ T-cell response in the immature immune system. In humans, maternal antibodies cross the placenta and provide the fetus with protection against infection which persists and is supplemented after birth with colostral antibody. However, if the mother is seronegative or acquires a primary infection during pregnancy, the neonate may not be afforded adequate protective antibody, leaving them susceptible to viral infection.

Immunoprophylactic protection of infants may be a prime approach to stem the establishment of persistent viral infections. This has already been accomplished successfully with hepatitis B virus infections by using a combination of passive immunoglobulin and active immunization of infants born to carriers (10). Also, Scarlatti et al. (21) report that mothers with

neutralizing antibodies to HIV type 1 have a reduced risk of infecting their children. While passive immunotherapy is known to be an effective means of combatting hepatitis B virus infections, clearance of other viruses, such as LCMV, is believed to be predominantly dependent upon T-cell-mediated events (17). Although $CD8^+$ CTLs appear to be the effector cells for virus clearance in the LCMV model, $CD4^+$, presumably helper T cells are necessary to sustain CD8 responses and effect viral clearance (16). Nonetheless, our results indicate that passive antibody very effectively prevents the establishment of persistent LCMV infection in neonatal BALB/c mice and that passive transfer of MAbs to mothers results in efficient delivery of antibodies to the offspring. This form of therapy may benefit both the mother and baby by decreasing free-virus load and the associated symptoms of infection in the mother, allowing her to better nurture the fetus. As we have demonstrated (3), this strategy also results in efficient transfer of protective immunoglobulin to the offspring. This scenario may work best for viruses that infect during or shortly after birth, such as herpes simplex virus and cytomegalovirus, which infect the child during movement down the birth canal. Thus, therapeutic MAb treatment of the mother would decrease the risk of transmission by decreasing free-virus load in maternal blood and secretions and by providing the baby with protective antibody prior to exposure.

Many viruses capable of establishing persistent infections have a tropism for cells of the reticuloendothelial system. This is graphically illustrated by immunosuppressive HIV, which predominantly infects $CD4^+$ T cells and macrophages. The LCMV variant Cl-13 is an immunosuppressive virus which is macrophage tropic and can establish persistent infections in immunocompetent adult mice (2, 5, 15). Adult mice inoculated with Cl-13 fail to trigger a competent CTL response to the virus. This deficit apparently resides in the inductive phase of the antiviral CTL response, since Cl-13-infected target cells are fully susceptible to CTL-mediated killing (2, 6). Oldstone and colleagues (19) have generated vaccines composed of CTL epitopes which successfully block the establishment of persistence in Cl-13-challenged mice. Our results indicate that prophylactic neutralizing antibody also contributes to protection against the establishment of persistent infections in adult mice by the macrophage-tropic variant Cl-13. These results are consistent with the notion that actively induced virus-neutralizing antibodies, such as those elicited by vaccination, may provide an efficient barrier to the establishment of persistence.

In evaluating therapeutic and prophylactic regimens it is critical to understand the route and timing of infection. This is highlighted in the LCMV model where passive antibody prevents the establishment of persistence following neonatal infection (Table 1) but exacerbates disease in congenitally infected pups (18). Also if the primary site of infection is in a privileged site, such as the central nervous system, which is not readily accessible to the circulating immunoglobulin, the virus is more likely to establish persistence. Thus, each viral model will need to be assessed for the most advantageous mode of therapy. But our results reported here and results reported previously (3, 4, 22) support the concept that a neutralizing, GP-1-specific antibody may provide early protection against arenavirus infections, provided functional $CD8^+$ T cells are available. We propose that the antibody works by lowering viral burden and restricting secondary spread of infection, thus limiting the target tissue available for CD8 T-cell stimulation and response. We have previously described this scenario as attenuation of CD8 cell-mediated immunopathology (3). Taken together, our results provide evidence that preexisting antiviral antibodies can effectively restrict the establishment of persistent viral infections and that actively induced antibody, such as that derived by immunization, should provide protection in immunocompetent individuals against human arenavirus infections.

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