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Induction of high serum levels of retroviral *env* gene products (gp70) in mice by bacterial lipopolysaccharide

(NZB xenotropic virus/G_{IX} differentiation marker/p30 viral protein/peptide mapping)

IKUO HARA, SHOZO IZUI*, PATRICIA J. MCCONAHEY, JOHN H. ELDER, FRED C. JENSEN, AND FRANK J. DIXON

Department of Immunopathology, Research Institute of Scripps Clinic, La Jolla, California 92037

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ABSTRACT In the present study, mice each given a single intraperitoneal injection of *Escherichia coli* lipopolysaccharide (LPS) responded with increased serum levels of the major envelope glycoprotein, gp70, of endogenous retrovirus. Concentrations of gp70 in their sera began to increase 4 hr after LPS injection, reached maximal 5- to 15-fold increases after 12-24 hr, and returned to the preinjection levels within 3 days. This response occurred only in the strains characterized by high base line levels of serum gp70 (>10 μg/ml) such as NZB, NZB × NZW F_1, BXSB, MRL, NZW, DBA/2, LG, 129(G_{IX^+}), and C57BL/6(G_{IX^+}). However, strains such as DBA/1, C3H/St, BALB/c, C57BL/6(G_{IX^-}), and 129(G_{IX^-}) with lower base line levels of serum gp70 (<5 μg/ml) made little or no response. This serum gp70 induced by LPS was structurally similar to the gp70 of NZB xenotropic virus that is dominantly expressed in sera from virtually all strains of mice. However, (*i*) the induced gp70 was virion-free; (*ii*) xenotropic virus was not isolatable from BXSB, MRL/1, or 129(G_{IX^+}) mice injected with LPS; and (*iii*) amounts of the major structural viral protein, p30, did not increase correspondingly in sera. All of these findings indicate that the increased expression of serum xenotropic viral gp70 in response to LPS did not result from activation of replication-competent xenotropic virus. In addition, the serum gp70 response to LPS was abolished by simultaneous inoculation of an inhibitor of protein synthesis, D-galactosamine. These results strongly suggest that LPS selectively stimulates synthesis of the *env* gene product, gp70, of NZB xenotropic virus but not other viral gene products.

It is now clear that mice inherit determinants for their endogenous retroviruses as chromosomal genes. Sequences homologous to the complete viral genome have been identified in the cellular DNA of all laboratory murine strains as well as wild house mice (1). However, certain viral gene segments seem to be expressed selectively, depending on their site of integration into chromosomal loci, in which induction is linked to the differentiated state of the cells (2). The major envelope glycoprotein, gp70, of such retroviruses is a constituent of the surface of various epithelia and also thymocytes, and it shares immunologic and biochemical properties with the thymocyte differentiation marker, G_{IX} (3-6).

A distinct gp70 circulates in the blood of virtually all strains of mice but is not associated with viral particles (2, 7-11). According to tryptic peptide analysis, this serum gp70 molecule resembles the envelope protein of NZB-type xenotropic virus, which is found only in NZB mice and NZB × NZW F_1 hybrids (NZB×W) (11, 12). However, the mechanism controlling expression of serum xenotropic viral gp70 is not at all clear. Recent data demonstrate that bacterial lipopolysaccharide (LPS) activates xenotropic virus in cultured spleen cells from various strains of mice (13-15). Because serum gp70 resembles xenotropic viral gp70 (11, 12), we investigated the *in vivo* effect of LPS on the expression of serum gp70 in relation to the activation of xenotropic virus. Our results from testing various murine strains indicate that LPS induced high serum levels of the retroviral *env* gene product, gp70, but only in murine strains high in serum gp70, and usually without detectable activation of other xenotropic viral genomes.

MATERIALS AND METHODS

Mice. Mice used in this study were 6-8 weeks old. NZB, NZW, NZB×W, BXSB, MRL/1, MRL/n, DBA/2, 129(G_{IX^+}), 129(G_{IX^-}), C3H/St, C57BL/6(G_{IX^-}), and BALB/c mice were obtained from the mouse breeding colony at Scripps Clinic. LG, AKR, and DBA/1 mice came from The Jackson Laboratory. C57BL/6(G_{IX^+}) mice were kindly provided by E. A. Boyse (Memorial Sloan-Kettering Cancer Center, New York). Mice were bled from the retroorbital plexus, and the resulting sera were stored at −20°C until use.

LPS. LPS purified from *Escherichia coli* 0111:B4 was generously provided by D. C. Morrison (Department of Microbiology, Emory University School of Medicine, Atlanta, GA). *E. coli* 0111:B4 LPS, which had been extracted with aqueous phenol, was further fractionated by Sepharose 4B column chromatography, and fraction II of this preparation was used in this study. The LPS preparation was diluted to the desired concentrations with sterile saline and used at a final volume of 0.4 ml to inject the mice intraperitoneally (i.p.).

Inhibitor of Protein Synthesis. D-Galactosamine hydrochloride was obtained from Sigma; it was dissolved in pyrogen-free saline immediately before use and administered to the mice i.p.

Radioimmunoassay for gp70 and p30. Concentrations of gp70 in sera from these mice were determined by inhibiting the binding of goat antibody to feline leukemia virus to ^{125}I-labeled gp70 from Rauscher murine leukemia virus (MuLV). The major viral structural protein, p30, in serum was quantitated in a competitive radioimmunoassay by using ^{125}I-labeled Rauscher MuLV p30 and guinea pig antibody to MuLV p30. These assays were performed as described (10).

Sucrose Density Gradient Ultracentrifugation. The sedimentation characteristics of serum gp70 and Scripps leukemia virus (SLV) were determined by sucrose density gradient ultracentrifugation. Samples (0.025 ml) were layered over 15-50% (wt/vol) linear sucrose gradients in 0.01 M phosphate-buf-

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Abbreviations: NZB×W, NZB × NZW F_1 hybrid; LPS, lipopolysaccharide; i.p., intraperitoneally; MuLV, murine leukemia virus; SLV, Scripps leukemia virus.

* To whom reprint requests should be addressed.

fered saline, pH 7.2, and centrifuged at 35,000 rpm for 16 hr at 4°C with a SW 60 rotor in a Beckman L-75 ultracentrifuge. The position of gp70 was established by a radioactive marker. The gradients were divided into 17 fractions. Each fraction was radioimmunoassayed for the presence of gp70.

Quantitation of Xenotropic Virus. Heparinized blood or spleen cell suspensions were prepared aseptically and cocultured with mink embryo fibroblasts or rabbit endothelial cells. After 2 or 3 weeks of subculturing, replication of xenotropic virus was tested by determining RNA-dependent DNA polymerase activity in supernatants according to the method reported (16). Negative cultures were incubated further and, if still negative, terminated after 55 days.

Isolation of Serum or Viral gp70 and Two-Dimensional Peptide Analysis. The gp70 from xenotropic virus or from sera of NZB mice was purified by immunoaffinity column chromatography and sodium dodecyl sulfate/polyacrylamide gel electrophoresis as described (11, 17). Tryptic peptides of immunoprecipitated bands from sodium dodecyl sulfate/polyacrylamide gels were analyzed two-dimensionally (11, 17).

RESULTS

Effect of LPS on Serum gp70 Concentration. The expression of retroviral gp70 in response to LPS was studied in murine strains whose sera characteristically contain notably high (>10 μg/ml) or low (<5 μg/ml) amounts of this form of gp70. First, 2-month-old NZB×W female mice with relatively high concentrations of gp70 in their sera (32.9 ± 5.8 μg/ml, mean ± SD) were injected i.p. with 25 μg of LPS from *E. coli* 0111:B4. Compared with preinjection levels, amounts of serum gp70 increased significantly 4 hr after the injection (Fig. 1). The amounts peaked between 12 and 24 hr and returned to the pretreatment levels within 72 hr. At the peak response, serum levels of gp70 were about 10 times higher than those before injection of LPS. These responses were almost abolished by the simultaneous injection of 7.5 mg of D-galactosamine hydrochloride, an inhibitor of protein synthesis (18) (Fig. 1), indicating that LPS promoted the synthesis of serum gp70. The injection of D-galactosamine hydrochloride alone temporarily decreased serum levels of gp70 from 30.1 ± 3.5 μg/ml to 9.5 ± 2.0 μg/ml. Control mice injected with sterile saline had no significant changes in the amounts of serum gp70 throughout the experiments.

Similarly, LPS greatly increased amounts of gp70 in most other strains with preexisting high levels (>10 μg/ml), including NZB, BXSB, MRL, NZW, LG, and DBA/2; the single exception was AKR mice (Table 1). Although at the LPS dose used, the magnitude of gp70 responses varied among these strains, increases ranged between 5 and 15 times preinjection levels and 70–500 μg/ml in concentration. Only the AKR mice exhibited no response, even to a dose of 50 μg of LPS.

In contrast, the second group tested, whose content of gp70 is normally low (<5 μg/ml), experienced little or no increase in serum gp70. DBA/1, C57BL/6, and BALB/c mice had no increase at all. The slight rise observed in C3H/St mice remained below 10 μg/ml. The higher dose of LPS (50 μg) produced a response identical to that obtained with 25 μg of LPS. The possibility that these low or nonresponder mice might synthesize gp70 in a kinetic pattern different from that of high responder mice was excluded, because the peak response, if any, was between 12 and 24 hr after LPS injection in all the strains of mice.

We next examined the serum gp70 response induced by LPS in two pairs of congenic strains, 129(G_{IX^+}) or 129(G_{IX^-}) and C57BL/6(G_{IX^+}) or C57BL/6(G_{IX^-}), because gp70 shares immunologic and biochemical properties with the thymocyte differentiation marker G_{IX} (2–6), and G_{IX^+} mice have higher concentrations of serum gp70 than G_{IX^-} mice (3, 6, 10, 19). The injection of 25 μg of LPS increased serum gp70 levels from 8.6 ± 2.4 μg/ml to 62.1 ± 9.2 μg/ml in 129(G_{IX^+}) mice and from 17.0 ± 6.6 μg/ml to 87.6 ± 24.1 μg/ml in C57BL/6(G_{IX^+}) mice

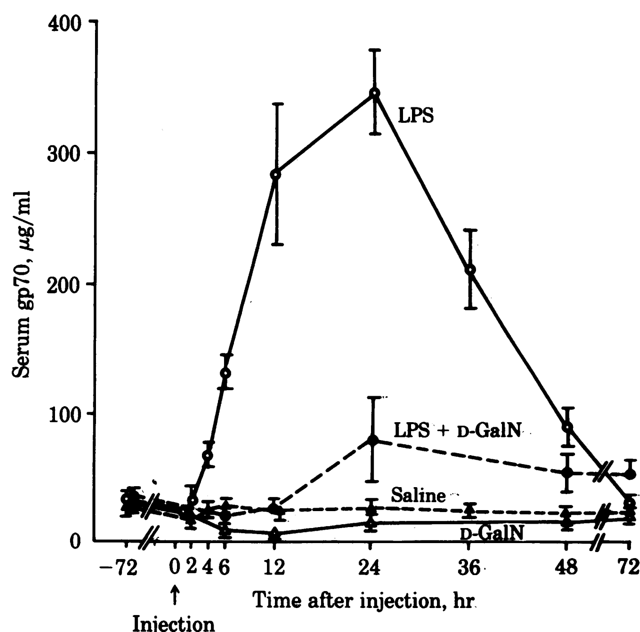

FIG. 1. Response of serum retroviral gp70 after a single i.p. injection of 25 μg of LPS from *E. coli* 0111:B4 with or without 7.5 mg of D-galactosamine hydrochloride (D-GalN) in 2-month-old NZB×W female mice. Each point represents the mean value ± 1 SD for five mice.

Table 1. Serum gp70 responses to LPS* in various strains of mice

Strain	Sex	Serum levels of gp70, μg/ml† Day 0	Serum levels of gp70, μg/ml† Day 1	Mean value of increased amounts of gp70, μg/ml	Ratio of increase
NZB	F	47.9 ± 6.2	375.8 ± 72.8	327.9	7.8
	M	55.1 ± 9.1	358.5 ± 33.6	303.4	6.5
NZB×W	F	32.9 ± 5.8	391.5 ± 24.7	358.6	11.9
	M	62.4 ± 10.5	589.6 ± 68.9	527.2	9.4
BXSB	F	10.5 ± 1.3	151.8 ± 37.0	141.3	14.5
	M	38.5 ± 8.1	245.2 ± 58.4	206.7	6.4
MRL/1	F	16.2 ± 1.7	96.7 ± 30.6	80.5	6.0
MRL/n	F	12.1 ± 6.2	89.0 ± 15.1	76.9	7.4
LG	F	13.3 ± 2.8	112.7 ± 35.6	99.4	8.5
DBA/2	M	21.1 ± 2.5	165.2 ± 46.9	144.1	7.8
NZW	F	54.2 ± 10.7	316.4 ± 38.9	262.2	5.8
AKR	M	17.5 ± 2.1	13.5 ± 2.9	−4.0	0.8
C3H/St	F	1.4 ± 0.5	4.6 ± 1.1	3.2	3.3
	M	3.4 ± 0.7	12.0 ± 3.2	8.6	3.5
DBA/1	F	4.8 ± 0.9	6.5 ± 2.3	1.7	1.4
C57BL/6	F	1.5 ± 0.3	2.1 ± 0.5	0.6	1.4
BALB/c	F	0.9 ± 0.2	1.2 ± 0.5	0.3	1.3
	M	1.5 ± 0.5	1.4 ± 0.3	−0.1	0.9

* Twenty-five micrograms of LPS from *E. coli* 0111:B4 was injected i.p. on day 0 into 6- to 8-week-old mice.

† Mean ± 1 SD for five mice.

Table 2. Correlation between expression of G_{IX} antigen and serum gp70 response induced by injection of LPS*

Strain	Serum levels of gp70, μg/ml† Day 0	Day 1	Mean value of increased amounts of gp70, μg/ml
129(G_{IX^+})	8.6 ± 2.4	62.1 ± 9.2	53.5
129(G_{IX^-})	0.4 ± 0.3	2.3 ± 2.3	1.9
C57BL/6(G_{IX^+})	17.0 ± 6.6	87.6 ± 24.1	70.6
C57BL/6(G_{IX^-})	3.1 ± 0.6	3.5 ± 1.1	0.4

* Twenty-five micrograms of LPS from *E. coli* 0111:B4 was injected i.p. on day 0 into 2-month-old 129 female and C57BL/6 male mice.
† Mean ± 1 SD for five mice.

(Table 2). However, this LPS-enhanced serum gp70 expression was markedly limited (<2 μg/ml) in the congenic G_{IX^-} mice.

Characterization of Serum gp70 Induced by LPS. The structural characteristics of gp70 isolated from NZB murine sera were examined 24 hr after LPS injection. Shown in Fig. 2 are the tryptic peptide maps of gp70s for the predominant xenotropic virus endogenous to NZB mice (Fig. 2*A*) and free gp70s from the sera of control (Fig. 2*B*) and of LPS-injected NZB mice (Fig. 2*C*). As reported previously (11, 12, 20), the predominant free gp70 of serum in NZB mice was identical to NZB xenotropic viral gp70, i.e., containing a rapidly migrating peptide (arrows, Fig. 2) that was lacking in other gp70s, including those of AKR ecotropic virus, amphotropic virus, and xenotropic virus isolated from murine strains other than NZB and NZB×W mice. However, in addition to the NZB xenotropic viral gp70, markers of a second, closely related, gp70 were evident (brackets, Fig. 2). These marker peptides were reminiscent of, but not identical to, those from the same region reported previously for other xenotropic viruses (20). Of note, both the NZB xenotropic marker (arrow) and markers of the second gp70 (bracket) were present in serum gp70 from LPS-injected NZB mice, indicating that gp70 induced by LPS was structurally identical to that from control animals.

To analyze the sedimentation characteristics of serum gp70 induced by LPS injection, we collected 0.025 ml of serum from a 2-month-old NZB mouse 24 hr after LPS injection (352 μg of gp70 per ml) and from a control NZB mouse containing 48 μg of gp70 per ml, then immediately layered the samples on a sucrose density gradient. For comparison, virion-associated gp70 from SLV and radiolabeled gp70 purified from Rauscher MuLV were analyzed in a parallel run. After ultracentrifugation, sera from both control and LPS-treated mice showed that only a single peak of gp70 sedimented in the fractions containing the labeled marker of free gp70 (density of 1.09 g/cm³) (Fig. 3). No gp70 was found in the fraction containing retrovirus-associated gp70 (density of 1.16 g/cm³), indicating that almost all of the gp70 present in sera of mice stimulated with LPS was separate from the viral particles. Fig. 3 also shows that the peak concentration of gp70 in sera from LPS-injected mice was approximately 7 times higher than in control mice.

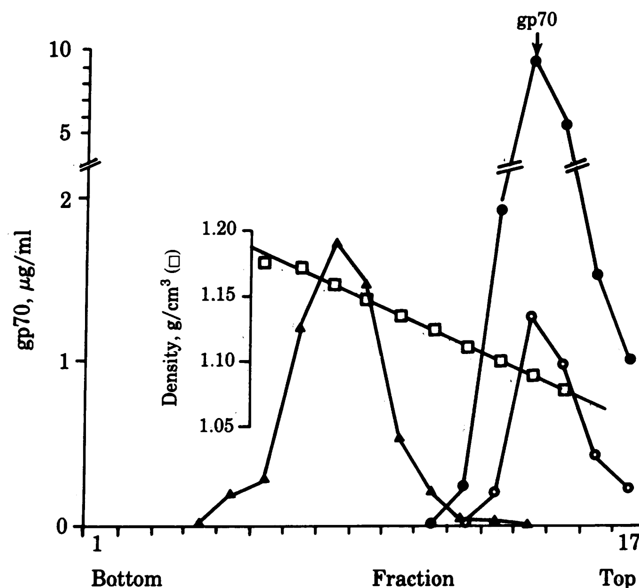

FIG. 3. Ultracentrifugation analysis of serum gp70 from control 2-month-old NZB mice (○) and NZB mice injected with 25 μg of LPS from *E. coli* 0111:B4 (●). ▲, SLV-associated gp70 marker. The position of free gp70 is indicated by an arrow.

To study whether the production of serum gp70 induced by LPS was related to the activation of endogenous xenotropic virus, we measured amounts of xenotropic virus and the major structural protein, p30, in sera of mice injected with LPS. Although all four of the LPS-injected strains [NZB, BXSB, MRL/1, and 129(G_{IX^+}) mice] produced substantial amounts of gp70

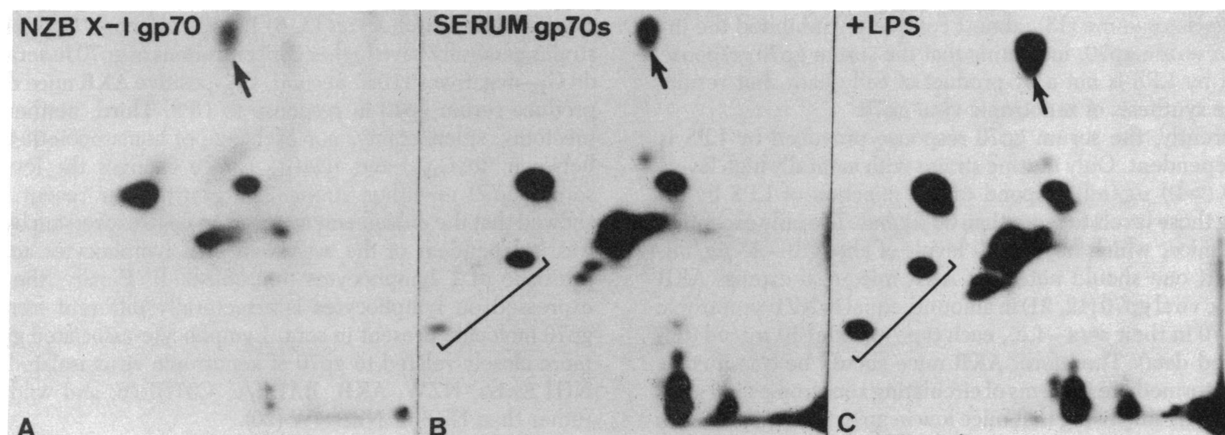

FIG. 2. Comparison of tryptic peptides of gp70s from predominant xenotropic virus of NZB mice (NZB X-1) (20) (*A*) and free gp70s of the sera from control (*B*) and LPS-injected (*C*) NZB mice. Arrows indicate a marker peptide characteristic of NZB xenotropic viral gp70. Brackets in *B* and *C* indicate a constellation of peptides that denotes a second closely related gp70 present in serum. Note that both marker peptides are present in free gp70 of sera from control and LPS-injected mice.

Table 3. Serum levels of gp70 and p30 and xenotropic virus activity in circulating blood from NZB, BXSB, MRL/1, and 129(G_{IX^+}) mice injected with LPS*

Strain	Day	Protein, μg/ml†		Activity of RNA-dependent DNA polymerase‡	
		gp70	p30	Mink	Rabbit
NZB	0	67.3 ± 6.9	0.137 ± 0.036	270 ± 237	1,076 ± 495
	1	549.3 ± 95.1	0.303 ± 0.088	19,578 ± 9137	16,567 ± 4958
	2	349.3 ± 49.0	0.141 ± 0.049	41 ± 99	118 ± 66
	3	77.2 ± 27.0	0.101 ± 0.027	<10	<10
BXSB	0	44.0 ± 23.2	<0.05	NT	NT
	1	268.8 ± 98.8	<0.05	10	27 ± 16
MRL/1	0	13.0 ± 2.0	<0.05	NT	NT
	1	63.8 ± 13.1	<0.05	35 ± 16	<10
129(G_{IX^+})	0	7.6 ± 0.7	<0.05	NT	NT
	1	59.3 ± 3.3	<0.05	<10	14 ± 25

* Fifty micrograms of LPS from *E. coli* 0111:B4 was injected i.p. on day 0.

† Mean ± 1 SD for five mice.

‡ Xenotropic virus replication was tested by determining RNA-dependent DNA polymerase activity in culture supernatants 2 weeks after coculturing with mink embryo fibroblasts or rabbit endothelial cells. Enzyme activity is expressed as cpm of polymerized [^{3}H]dTMP (mean ± 1 SEM for five mice). NT, not tested.

within 1 day, only NZB mice had detectable amounts of xenotropic virus in their blood, and control NZB mice had essentially none (Table 3). The time when xenotropic virus appeared in NZB mice was similar to that of the serum gp70 response. In parallel, the injection of LPS caused a slight but significant increase in the p30 content of sera from NZB mice (0.166 μg/ml); it was, however, far less than that of gp70 (480 μg/ml). None of the strains other than NZB exhibited detectable viral activity in circulating blood or spleens after LPS inoculation. Furthermore, their sera did not contain measurable amounts (<0.05 μg/ml) of p30.

DISCUSSION

Our investigation demonstrated that a single injection of bacterial LPS enhanced expression of the xenotropic viral *env* gene product, gp70, in strains of mice that have high levels of this protein, which all mice carry to some extent. This expression was generally unrelated to activation of endogenous xenotropic virus. The simultaneous injection of a protein synthesis inhibitor, D-galactosamine (18), almost completely inhibited the increase in serum gp70, indicating that the serum gp70 response induced by LPS is not a by-product of cell death, but results from the synthesis of xenotropic viral gp70.

Apparently, the serum gp70 response provoked by LPS is strain dependent. Only murine strains with naturally high levels of gp70 (>10 μg/ml) respond to the injection of LPS by increasing those levels to more than 60 μg/ml. The only exception is AKR mice, which have gp70 levels of about 10–20 μg/ml. However, one should note that AKR mice also express AKR ecotropic viral gp70 (12, 21) in amounts equal to NZB xenotropic viral gp70 in their sera—i.e., each type at about 10 μg/ml (unpublished data). Therefore, AKR mice should be classified as low or intermediate in terms of circulating xenotropic viral gp70 content. It is surprising that mice low in gp70 (<5 μg/ml) make little or no response to the injection of LPS. For example, the serum gp70 concentration of DBA/1, C57BL/6, and BALB/c mice do not increase at any time after injection of LPS at any dose. Significantly, the LPS mitogenic response of B lymphocytes in strains low in gp70 is no different from that of strains high in gp70 (unpublished data). Apparently, the expression of this viral protein is simply controlled differently in the two types of mice.

The gp70 responsiveness to LPS evidently relates to the gene(s) governing expression of G_{IX} antigen on thymocytes, an antigen that crossreacts with the gp70 of NZB xenotropic virus (19). We find enhanced amounts of serum gp70 after LPS injection only in G_{IX}-positive strains of mice such as NZB, NZW, DBA/2, and 129(G_{IX^+}), but not in the G_{IX}-negative strains such as DBA/1, C57BL/6, and BALB/c (3, 6, 19). In addition, our experiment with congenic strains such as 129(G_{IX^+}) or 129(G_{IX^-}) and C57BL/6(G_{IX^+}) or C57BL/6(G_{IX^-}) shows that both G_{IX}-positive strains produce at least 25 times more serum gp70 than do their congenic G_{IX^-} counterparts. These observations clearly indicate that the gene(s) responsible for the serum gp70 response induced by LPS is closely related to that for expression of G_{IX} antigen. However, this does not imply that lymphocytes expressing G_{IX} antigen are the major source of serum gp70. In fact, several lines of evidence refute this possibility. First, levels of gp70 in serum do not correlate with amounts of G_{IX} antigen expressed on lymphocytes (3, 6, 10, 19), although G_{IX}-positive strains generally have higher concentrations of gp70 in sera than do G_{IX}-negative strains. Second, G_{IX}-positive AKR mice do not produce serum gp70 in response to LPS. Third, neither thymectomy, splenectomy, nor exchange of hematopoietic tissue between 129(G_{IX^+}) and 129(G_{IX^-}) mice changes the levels of serum gp70 in either strain (22). Fourth, our recent study showed that the enhancement of serum gp70 expression by LPS was independent of the activation of B lymphocytes and the presence of T lymphocytes (unpublished). Finally, the gp70 expressed on lymphocytes is structurally different from the gp70 molecule present in sera. Lymphocyte-associated gp70 is more closely related to gp70 of xenotropic virus isolated from NIH Swiss, NZW, AKR, BALB/c, C57BL/6, and wild mice rather than NZB or NZB×W (20).

Tryptic peptide maps of gp70 isolated from sera of the mice injected with LPS clearly showed that the gp70 induced thereby is no different from that normally expressed. The dominant serum gp70 present in LPS-injected mice is structurally related to gp70 of xenotropic virus isolated only from NZB and NZB×W

mice, but differs from gp70s of AKR ecotropic virus, amphotropic virus and xenotropic virus isolated from murine strains other than NZB and NZB×W mice (11, 12, 20). Although serum gp70 from LPS-injected mice carries unidentified peptides that are not components of any retroviral gp70s tested, it should be emphasized that these unidentified peptides are also present in freely circulating gp70 of every mouse strain.

Although LPS can activate and release xenotropic virus in cultured spleen cells of various strains of mice, including BALB/c, C57BL/6, and AKR mice (13–15), our results indicate that the enhancement of serum xenotropic viral gp70 is not dependent on the production of xenotropic virus. This conclusion is supported by the following evidence. First, according to sucrose density gradient analysis, no gp70 was present in the form of viral particles in sera from mice injected with LPS. Only a single peak sedimented at the 5S position contained gp70 in a free form, although mice that spontaneously develop autoimmune disease have rapidly sedimenting antibody-bound gp70 in their sera later in life, but not at 2 months of age (10). Second, no xenotropic virus could be isolated from circulating blood or spleens of LPS-responding strains such as BXSB, MRL/1, and 129(G_{IX^+}) mice, although significant viral activity was recovered from circulating blood of NZB mice after the injection of LPS. Finally, BXSB, MRL/1, and 129(G_{IX^+}) mice injected with LPS did not have detectable amounts (<0.05 μg/ml) of the major structural viral protein, p30, in their sera, even as their gp70 levels increased to more than 60 μg/ml. Only a slight and limited increase in serum p30 levels (0.166 μg/ml) was observed in NZB mice, paralleling the appearance of xenotropic virus in circulating blood. However, this small increase in p30 antigen does not account for the large increase (480 μg/ml) in serum gp70. If all the circulating gp70 synthesized after the injection of LPS were present as viral particles, p30 concentrations should be over 2 mg/ml in sera, because the weight ratio of gp70 to p30 in viral particles is about 1:6 (2). Clearly, far more gp70 is produced than would be combined with p30 in viral particles.

Our results are consistent with previous reports (2, 7–9, 11) that expression of the xenotropic viral *env* gene product, gp70, in sera is not coordinately linked to that of other viral gene products, indicating that the serum gp70 is probably a partial expression of a single provirus, which is expressed as complete virus only in NZB and NZB×W mice. Although the present study does not define the cellular source of normal or LPS-enhanced serum gp70, our unpublished work indicates that the LPS-induced gp70 synthesis occurs mainly in the liver and that in general serum retroviral gp70 behaves as other acute-phase reactants do (23).

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