MAJOR HISTOCOMPATIBILITY COMPLEX-LINKED SUSCEPTIBILITY OR RESISTANCE TO DISEASE CAUSED BY A NONCYTOPATHIC VIRUS VARIES WITH THE DISEASE PARAMETER EVALUATED

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The association between susceptibility to disease and products of the MHC has been one of the first observations signaling the involvement of MHC products in immune recognition (1–5). This linkage has become better understood since the discovery that T cells recognize antigens only in association with major transplantation antigens and that they recognize foreign antigen fragments that are noncovalently bound to major histocompatibility antigens (6–10). The pathophysiology of the linkage between major histocompatibility antigens and disease is more complex, however, and usually not readily reduced to MHC-dependent immune responsiveness, because the initiating antigens or agent are not known (11, 12).

It is interesting that many diseases that exhibit MHC association of susceptibility are immunologically mediated (1–4, 11), some examples being ankylosing spondylitis, Reiter's disease (2–4, 13, 14), and juvenile diabetes. Juvenile diabetes, an autoimmune disease, has recently been shown to be linked to a particular type of amino-acid substitution on HLA or H-2 antigens (12). In addition, induction of immunopathological processes, including autoimmune diseases, have often been linked to infections but direct evidence is still scarce (15, 16). Infectious agents may directly cause disease by cytopathic effects or indirectly by causing immune-mediated cell destruction or inflammatory processes (17–21). MHC disease associations may rather rarely become manifest for cytopathic viruses or bacteria, because MHC-regulated non- or low responders would have been eliminated during evolution. In contrast, noncytopathic infectious agents that do not cause disease directly, but rather indirectly via induced immune responses, may exhibit MHC-disease association more often because of their low to absent evolutionary pressure (11); hepatitis B virus (5, 22, 23) or *Mycobacterium leprae* (24) infections may serve as examples of such a phenomenon in humans.

Murine model diseases have been used to better understand the pathophysiology of MHC-disease associations (25, 26); they offer the advantage that the complexities present in human examples may be reduced by defining parameters of both the host and of the inducing antigen or infectious agent. We have searched for evidence of

MHC-disease associations in systemic infection of mice with lymphocytic chorio-meningitis virus (LCMV),[1] a virus that is non- or poorly cytopathic in its natural host (17–21, 27). LCMV has been particularly well studied for its capacity to induce a lethal T cell–mediated choriomeningitis. However, some LCMV (so called viscerotropic) isolates injected intravenously also cause a severe hepatitis in T cell–competent mice but not in T cell–deficient or CD8+ T cell–depleted mice (28, 29). This model infection in mice is used here to show that H-2 class I–regulated antiviral cytotoxic T cell responses directly influence the severity of disease (27, 30). Importantly, the studies show how MHC linkage of disease susceptibility caused by one infectious agent may vary, dependent upon which aspect of a disease is evaluated.

Materials and Methods

Mice. Mice of either sex were used at an age of 8–16 wk. Outbred ICR mice were obtained from the Institut für Zuchthygiene, Tierspital, Zürich. Inbred B10.G (H-2^q), B10.AKM (H-2^q), and B10.BR (H-2^k) were purchased from Harlan-Olac, U.K. Ltd., Bicester, U.K.

Virus and Infection. LCMV-aggressive (LCMV-AGG) and LCMV-docile (LCMV-DOC) of known concentration (measured in plaque-forming units [PFU]) were obtained directly from Dr. C. Pfau (30–32), Rensselaer Polytechnical Institute, Troy, NY. Stocks were diluted in medium containing 5% heat-inactivated FCS. The LCMV-AGG isolate is a neurotropic strain of LCMV-UBC and LCMV-DOC is a hepato-viscerotropic variant; both LCMV viruses had been isolated from the same 40-wk-old carrier mouse (32). The two isolates were triple plaque purified, then grown on MDCK cells as second passage virus; from this stock virus aliquots were grown by using low input multiplicity (0.01) of infection (31, 32). The LCMV-AGG and LCMV-DOC pair of viruses are in many ways comparable with the LCMV-Armstrong and the clone 13 pair of LCMV viruses described by Ahmed et al. (33). Mice were infected intravenously with 6 × 10^2–10^5 PFU of LCMV.

Serum Sampling. Mice were anesthetized with ether; blood was obtained from the retro-orbital venous plexus. In experiments where serum was collected at only r e time point, mice were ether anesthetized and bled by cutting the thoracic inferior vena cava and thereafter collecting blood from the thoracic cavity. The blood was transferred to Microtainer tubes (Becton Dickinson & Co., Mountain View, CA) and processed (28). Serum samples were analyzed individually or in pools of two to five donors.

Determination of Serum Enzyme Concentrations. Asparate aminotransferase (AST; EC 2.6.1.1), alanin aminotransferase (ALT; EC 2.6.1.2), and glutamate dehydrogenase (GLDH; EC.1.4.1.3) were determined by standard methods (28). All reagents were purchased from Boehringer Mannheim Biochemicals, Mannheim, FRG. A selective analyzer was used for the analyses (model 705, Hitachi Ltd., Nacka Works, Japan).

Cytotoxic T Cell Assay. Activity of cytotoxic T cells was tested in ^{51}Cr release assays (27, 28, 30). Target cells were established fibroblast or firbrosarcoma cell lines: L929 (H-2^k), FS-9 (H-2^k) (30), AKM (K^{k}D^q), and DBA/1 (K^q,D^q, a kind gift of Dr. F. Lehmann-Grube, Hamburg, FRG). The test was performed in round-bottomed 96-well plates. Effector cells and target cells (10^4) were each added in 100 μl to give E/T cell ratios of 50:1, 13:1, and 4:1. They were mixed well and spun at 1,000 g for 4 min. The test duration was usually 5 h. Spontaneous ^{51}Cr release is indicated in the tables and figures.

Isolation of Lymphocytes from Livers. All livers were processed individually and were kept on ice. Single cell suspensions were made by gently teasing the liver through a stainless steel grid with a rubber–coated plastic syringe plunger. The resulting cell suspension was washed thrice in medium. The samples (7 ml) were underlaid with 5 ml of Ficoll-Hypaque solution (Seromed; Biochrom KG, Berlin, FRG) in a 15-ml glass tube. The tubes were spun at 2,500 g

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[1] *Abbreviations used in this paper:* ALT, alanin aminotransferase; AST, asparate aminotransferase; GLDH, glutamate dehydrogenase; LCMV, lymphocytic choriomeningitis virus; LCMV-AGG, LCMV-AGGRESSIVE; LCMV-DOC, LCMV-DOCILE.

for 20 min in a Centra-7 centrifuge. Cells retrieved from the interphase were washed thrice in medium, counted, and resuspended in the appropriate volume of medium for use in the cytotoxic T cell assay (28).

Determination of LCMV Titers in Livers. Livers were homogenized in glass tubes with Teflon pestles in 4 ml of medium. Because of toxicity for the cell monolayers, low titers of virus could not be determined by plaque assays in liver homogenates diluted 1:10 and 1:100. Therefore, all virus titrations were performed as follows. The frozen and thawed samples were serially diluted 10-fold in medium before 30-μl aliquots were injected into four footpads. Footpad swelling (34) on day 7–9 was recorded and the greatest dilution still giving a positive reaction in at least two of four footpads was multiplied by the initial dilution factor and was taken as the titer of ID_{50} of LCMV. The ratio of ID_{50} to PFU was ~10:1 for LCMV-DOC and ~2:1 for LCMV-AGG.

Results

LCMV-induced Immunopathology of the Liver: Dependence upon Virus Isolate and H-2. Groups of four to five mice of three H-2 congenic B10 mouse strains were infected intravenously with varying doses of the LCMV isolates LCMV-DOC or LCMV-AGG and bled on days 7, 13, and 21 after infection (Table I). ALT and GLDH concentrations in serum were measured by standard methods (28) to assess liver cell destruction; both enzyme values changed in parallel, therefore, only GLDH values are reported. These values varied depending upon which isolate of LCMV was used; LCMV-DOC, a viscerotropic isolate (27–29, 32, 33) induced increased GLDH con-

TABLE I

Influence of Time after Infection with LCMV, of Virus Isolate, of Virus Dose, and of H-2 on Increases in Serum GLDH Concentrations

Mouse strain H-2 (KID)	Virus dose	Serum concentration of GLDH ± SEM* at time after intravenous infection with:			
		LCMV-DOC‡			LCMV-AGG‡
		Day 7	Day 13	Day 21	Days 7, 13, and 21§
	pfu		*U/liter*		
B10.BR (kkk)	6 × 10⁵	11 ± 3	508 ± 57	83 ± 49	ND
	6 × 10⁴	15 ± 14	807 ± 64	21 ± 7	≤20 ± 12
	6 × 10³	11 ± 6	1,786 ± 328	37 ± 25	≤26 ± 9
	6 × 10²	12 ± 8	809 ± 127	18 ± 3	≤16 ± 7
	None	13 ± 8			
B10.AKM (kkq)	6 × 10⁵	480 ± 73	1,763 ± 424	14 ± 11	ND
	6 × 10⁴	290 ± 54	125 ± 49	15 ± 10	<32 ± 14
	6 × 10³	122 ± 35	17 ± 8	16 ± 8	<14 ± 6
	6 × 10²	37 ± 22	9 ± 7	12 ± 6	<12 ± 4
	None	16 ± 9			
B10.G (qqq)	6 × 10⁵	239 ± 43	801 ± 421	28 ± 7	ND
	6 × 10⁴	257 ± 29	42 ± 35	16 ± 5	<45 ± 16
	6 × 10³	154 ± 33	7 ± 5	9 ± 5	<17 ± 10
	6 × 10²	45 ± 18	8 ± 4	14 ± 7	<10 ± 5
	None	6 ± 5			

* Mice were infected intravenously with the indicated doses of LCMV. Determination of GLDH has been detailed previously (28); values represent means ± SEM of groups of four to five mice.
‡ The LCMV isolates are described in detail previously (22, 23).
§ Values indicated represent maximally reached values measured on days 7, 13, and 21.

centration in serum in all mouse strains tested. LCMV-AGG (6×10^4 PFU), a neurotropic isolate, failed to induce such changes; greater doses were not tested because LCMV-AGG replicates only to ~1/10 of the titer of LCMV-DOC in vitro (27–29, 32).

Virus Dose and Time Dependence of H-2D-regulated LCMV Hepatitis.   The increases in serum GLDH concentrations varied according to the virus dose, the time after infection, and the H-2 type of the mouse infected according to the following rules (Table I). On day 7, GLDH concentrations were increased in B10.AKM (D^q) and B10.G (D^q) but not in B10.BR (D^k) mice. In B10.AKM (D^q) and B10.G (D^q) mice, GLDH concentrations correlated with the infectious dose of LCMV-DOC; doses $<6 \times 10^3$ failed to cause a significant rise of GLDH concentations. Although no GLDH increases were seen in B10.BR (D^k) mice on day 7, they showed high GLDH concentrations on day 13. The increase was inversely related to virus dose from 6×10^5 PFU causing ~508 U/liter, 6×10^4 PFU causing 807 U/liter, and 6×10^3 PFU causing 1,786 U/liter. For both B10.AKM (D^q) and B10.G (D^q) mice, the greatest virus doses of 6×10^5 PFU/mouse still caused the greatest GLDH concentrations on day 13 after infection. In contrast to B10.BR (D^k) mice, lower doses of LCMV-DOC did not cause increased GLDH concentrations in D^q mice on day 13. On day 21, the GLDH concentrations were at control levels, except for B10.BR (D^k) mice injected with the highest dose of 6×10^5 PFU LCMV-DOC/mouse.

Correlation of LCMV-specific CTL Activity and H-2D-dependent LCMV Hepatitis.   There existed a time-dependent correlation of CTL activity, LCMV titers in liver, and GLDH serum concentrations in B10 mice (Table I and Fig. 1). A small infectious dose (i.e., 6×10^2 PFU) of LCMV-DOC triggered a good CTL response in livers and spleens of B10.G (D^q) mice (30); in D^q mice this CTL response started very
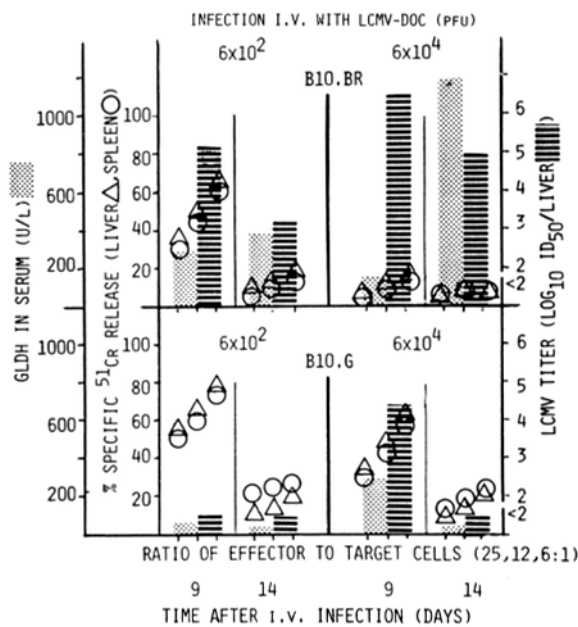

Figure 1.   Correlations between dose of LCMV-DOC or time after infection or H-2 of infected host (B10.BR, H-2^k, B10.G, H-2^q) and CTL induction in spleen (O), or livers (△), serum GLDH increases, and LCMV titers in liver. GLDH values and CTL activities were determined and lymphocytes were isolated from spleens and livers as detailed in reference 28. The cytotoxic activity of immune cells from B10.G mice were tested on AKM (K^k, D^q) target cells, for those from B10.BR mice on infected L929 (K^{k}D^k) and AK1 (K^{b}D^k) cells for 5 h at 37°C. Spontaneous ^{51}Cr release was <20% for all targets tested. All ^{51}Cr release seen on H-2-incompatible infected targets or on uninfected H-2-compatible targets was <20%. LCMV titers were determined as detailed in reference 17. All values are means of four to five individually tested mice: SEM were <10% for cytotoxicity assays, <0.8 log$_{10}$ for LCMV titers, and <12% for GLDH values.

early on day 6 (not shown) and peaked around day 9 (Fig. 1). This contrasted with the CTL response found in B10.BR (D^k) mice, which has been shown to start later by day 8 (30) and was still lower on day 9 than in B10.G (D^q) (Fig. 1) or B10.AKM (D^q) mice (not shown) (30). Virus titers in livers were below detection level in B10.G (D^q) mice on day 9 vs. ~5 $\log_{10}$ PFU in B10.BR (D^k) mice. GLDH serum concentrations were increased in B10.BR (D^k) but remained normal in B10.G (D^q) mice. With greater infectious doses of LCMV (6 × 10^4 PFU/mouse), CTL responses were barely detectable in B10.BR (D^k) mice on day 9, whereas in B10.G (D^q) mice, they were well developed. LCMV titers in livers were considerably greater in B10.BR (D^k) than in B10.G (D^q) mice, both on day 9 and on day 14. Whereas GLDH values were greater in B10.G(D^q) mice on day 9 than in B10.BR (D^k) mice, they had fallen to background levels on day 14 in B10.G (D^q) mice but were still very high in B10.BR (D^k) mice (>1,200 U/liter). This result suggested that liver cells were destroyed later in D^k mice than in D^q mice.

Influence of LCMV Isolate, Virus Dose, and H-2 of Infected B10 Mice on Mortality after Intravenous Infection. The LCMV isolate, the virus dose, and the H-2D of infected B10 mice also influenced mortality due to general wasting and fulminant heptatitis after intravenous infection. When great doses of LCMV-DOC were used to infect mice intravenously, a significant number of B10.G (D^q) or B10.AKM (D^q) mice died in the various experiments, usually between day 8 and 12, rarely thereafter. Mice did not die of the classical lymphocytic choriomeningitis central nervous disease but rather of general wasting, usually accompanied by very high liver enzyme concentrations in serum (Table I). In contrast, B10.BR (D^k) or C57BL/10 (H-2^b) mice only rarely succumbed to infection (Table II). LCMV-AGG caused no mortality, except in a few B10.G (D^q) mice. It is noteworthy that B10.G (D^q) and B10.AKM (D^q) mice were apparently more susceptible to 6 × 10^3 or 6 × 10^4 PFU than to the highest dose tested of 6 × 10^5 PFU. The lowest dose of 6 × 10^2 PFU/mouse tested caused no mortality.

TABLE II

Influence of LCMV Isolate, Virus Dose, and H-2 of Mice on Mortality after Intravenous Infection

| Virus isolate | Dose of virus | Mortality* | | | |
		C57BL/10 bbb‡	B10.BR kkk	B10.AKM kkq	B10.G qqq
LCMV-DOC	6 × 10^5	0/6 (0)§	0/18 (0)	2/6 (35)	2/6 (35)
	6 × 10^4	0/6 (0)	1/18 (5)	8/18 (45)	9/18 (50)
	6 × 10^3	0/6 (0)	0/6 (0)	4/6 (65)	3/6 (50)
	6 × 10^2	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)
LCMV-AGG	6 × 10^4	0/6 (0)	0/18 (0)	0/6 (0)	2/18 (10)
	6 × 10^3	0/6 (0)	0/18 (0)	0/18 (0)	2/18 (10)
	6 × 10^2	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)

* Number of mice dead by day 12/number of mice injected intravenously.
‡ H-2K, I, D.
§ Numbers in parentheses represent percent mortality.

TABLE III

Summary of the Results and their Interpretation

	LCMV-DOC							
	High virus dose injected (10^5–10^6 PFU)				Low virus dose injected (10^2–10^3 PFU)			
Host response anti-LCMV-CTL	T cell–mediated hepatitis		Virus clearance	Virus persistence	T cell–mediated hepatitis		Virus clearance	Virus persistence
	Early	Late			Early	Late		
High responder D^q	+ + + + (fulminant hepatitis)	+	+ + + +	–	–	–	+ + + +	–
Low responder D^k	–	± (± chronic hepatitis)	±	+ + +	–	+ + +	±	+ +

Discussion

The presented experiments and the MHC-disease linkages found may be summarized as follows (Table III). Infection with a noncytopathogenic virus such is LCMV may cause in mice (or in man, hepatitis B virus infections) various disease symptoms, i.e., a hepatitis as revealed by (a) increases of liver enzymes in serum (or by histology; not shown); (b) death; or (c) a transient or long-term virus persistence. The type of disease depends upon virus isolate, virus dose, and the H-2 D allele of the murine host. There are two major parameters that influence severity of disease: immune responsiveness and virus spread. The earlier, and thus the more efficient, an antiviral cytotoxic T response is generated in mice (H-2D^q high responders vs. H-2D^k low responders [28]), the quicker the virus is eliminated and the more limited is the T cell–mediated tissue damage. The greater the virus dose that initiates the infection (high doses of LCMV) or the quicker it may replicate and spread (LCMV-DOC replicates faster, to higher titers, and in many more cells than does LCMV-AGG [27–29, 32]) before an efficient T cell response is generated, the more infected host cells will subsequently be destroyed. Thus, the extent of T cell–mediated immunopathology depends upon the relative starting level and the growth kinetics of the virus and/or the kinetics of H-2 class I–dependent antiviral CTL responses (Table III).

If disease is defined by fulminant hepatitis, i.e., early (day 7–9) increases of liver enzyme values in serum, then D^q mice are susceptible and D^k mice are resistant. High responder B10.G (D^q) and B10.AKM (D^q) mice developed a kind of fulminant T cell–mediated hepatitis accompanied by other systemic immunopathological processes leading to death in 30–70% between day 7 and 12. In contrast, low responder B10.BR (D^k) mice did not eliminate virus readily because they did not develop a good CTL response; therefore, they also did not die of fulminant systemic disease. The finding that B10.BR mice did not die later after infection (e.g., between day 14 and 30) when the CTL response would be expected to have risen may be explained by the phenomenon of "high dose immune paralysis" defined by Hotchin (17) in LCMV infections (19–21, 28, 29, 33, 34). High doses of some LCMV strains tend to initiate a CTL response that fades quickly; with some LCMV isolates (33), including LCMV-DOC (32), this transient CTL response fails to eliminate virus and, therefore, causes an adult virus carrier state. This phenomenon is still unex-

plained but may reflect immune suppression by LCMV not only of immune responses to unrelated antigens but also to LCMV itself (17, 18). If after infection with high doses of LCMV-DOC disease is defined by virus persistence, the D^k mice are susceptible and D^q mice are resistant.

The two discussed inversely related disease states, i.e., early aggressive hepatitis vs. virus persistence, may be linked pathophysiologically as follows. Slow and low CTL responses in D^k mice favor virus persistence and fail to cause early hepatitis; early and excellent CTL responses in D^q mice favor efficient and early LCMV clearance, but this may also cause early and acute T cell–mediated liver cell destruction.

In contrast to disease caused by high doses of LCMV-DOC, susceptibility to disease defined by increases in liver enzyme concentrations in serum caused by low doses of LCMV-DOC is linked to D^k; D^q mice do not show disease. In this case resistance correlates with early CTL induction whereas susceptibility correlates with later and weak or transient CTL induction in B10.BR. In parallel, resistance of D^q mice to disease caused by low doses of LCMV-DOC correlates with rapid clearance of virus from livers and everywhere else, whereas D^k-linked susceptibility correlates with slow clearance of virus.

These findings have obvious implications for the evaluation and the understanding of the pathophysiology of HLA-disease association in humans (1–4). The experimental results described here may offer an explanation to the finding in humans that HLA linkage of susceptibility to disease caused by hepatitis B virus (5, 22, 23) varies with the disease symptoms studied: hepatitis B surface antigen carrier status is weakly linked to HLA-B15 (relative risks of 2–5), whereas chronic active hepatitis is linked to HLA-A1 or B8, or DW3-DR3 or BW35 (relative risks vary from 2 to 5); no HLA association has been found with acute hepatitis in one study (summarized in reference 5).

The described model infection in mice reduced the complexity of the parameters influencing MHC disease associations in humans by defining host parameters (defined and homozygous MHC alleles on a constant non-MHC [B10] genetic background) and viral parameters (defined tropisms and virus doses); it therefore was able to show that MHC class I–linked and time-dependent disease susceptibility may be explained directly by class I–restricted (regulated) T cell responsiveness. Thus, disease caused by noncytopathic agents may reflect discrete balanced states between spread of an infectious agent or antigen and the immune response causing immunopathology. One and the same kind of infectious agent (e.g., human hepatitis B virus or LCMV in mice) or antigen may cause varying diseases dominated by differing symptoms dependent upon parasite and host parameters. The virus variant may determine cell and organ tropism, rapidity of replication, and spread; the host transplantation antigen allele determines T cell immune responsiveness, which controls virus replication and spread but also severity of T cell–mediated host cell destruction, i.e., immunopathology.

Summary

The influence of major transplantation antigens on susceptibility to T cell–mediated disease caused by infection with the noncytopathic virus lymphocytic choriomeningitis virus (LCMV) was evaluated in B10 H-2-congenic mice. Susceptibility to early T cell–mediated liver cell destruction (day 7–9) and early mortality (before

day 12) was H-2D^q linked and correlated directly with early (day 6-8) and high cytotoxic T cell activity. In contrast, susceptibility to become an LCMV carrier, inability to rapidly clear virus, or tendency to develop late hepatitis (day 14-17) was linked to D^k and correlated with absence of early cytotoxic T cell activity. Thus, H-2D-regulated T cell–immune responses controlling both virus spread and immunopathology may directly determine the type and severity of disease. The results illustrate that susceptibility to disease caused by one virus may be linked to distinct MHC alleles dependent upon the disease parameter studied.

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