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Analysis of Granulomatous Arteritis in MRL/Mp Autoimmune Disease Mice Bearing Lymphoproliferative Genes

The Use of Mouse Genetics to Dissociate the Development of Arteritis and Glomerulonephritis

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MRL/Mp mice bearing the lymphoproliferation gene (lpr) spontaneously develop systemic granulomatous arteritis coincident with glomerulonephritis (GNP). Although the association of lpr-dependent lymphoproliferation in these mice seems to be a prerequisite for the development of granulomatous arteritis, the genetic basis is poorly understood. The first approach to this problem was to study the ability of another, nonallelic, lymphoproliferative gene, gld (generalized lymphoproliferative disease), inducing arteritis in MRL/Mp mice. The gld gene was placed on an MRL/Mp background by producing reciprocal (MRL/Mp-+/+ × C3H/HeJ-gld/gld)F2 hybrid mice. Seventeen percent of these mice with lymphoproliferation had arteritis and GNP, suggesting that more than one lymphoproliferative gene could induce GNP and arteritis in an MRL/Mp background. Next, the effect of rearrangements in the genetic background of MRL/Mp-lpr/lpr mice by hybridization with non-autoimmune lpr-bearing mice was examined. This was done by making MRL/Mp-lpr/lpr × reciprocal (MRL/Mp-lpr/lpr × C57BL/6-lpr/lpr)F1 mice. Thirty-three percent of these mice developed arteritis, but one third of these did not get GNP, thus showing that susceptibility to arteritis was separate from GNP. The histopathologic features of the arteritis in both the F2 hybrids and the backcross mice were granulomatous and were identical to those seen in MRL/Mp-lpr/lpr mice. These findings suggested that it might be possible to dissociate two components (arteritis and GNP) of a severe autoimmune disease of MRL/Mp mice and to study their pathogenesis separately. (Am J Pathol 1989, 135:271–280)

Systemic vasculitis is a major complication of many human autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and other connective tissue disorders.[1–5] Although vasculitis is a regular feature, several distinct variations in the histopathology, the tissue localization, and the caliber of the vessels involved exist. This regular variation suggests that different types of lesions may have different pathogenetic mechanisms. The analysis of these different forms of vasculitis may have important implications for therapy and prognosis, but study of these problems in humans is quite difficult. Fortunately, there are several strains of inbred mice that spontaneously develop autoimmune disease and arteritis.[6–10] These mice have proven very useful as models to dissect the etiopathogenesis and host genetic basis of these disorders.

MRL/Mp-*lpr/lpr* (MRL/lpr) mice spontaneously develop a granulomatous arteritis of medium-sized muscular arteries at an early age, following an immune-complex-mediated glomerulonephritis (GNP).[11–15] This disease complex is associated with massive lymphoproliferation of unusual T lymphocytes expressing cell surface antigens specified by Thy-1$^+$ (dull), Ly-1$^+$ (dull), I-A$^-$, and Ly-5$^+$ (B220).[16–19] However, MRL/Mp-+/+ mice not carrying the *lpr* gene develop the arteritis at a much later stage of

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life and with a reduced incidence.[15] Furthermore, mice of C3H/HeJ, AKR, and B6 strains carrying the *lpr* gene never develop arteritis or other lupus-like lesions, although they do have increases in rheumatoid factors, anti-gp70, and/or anti-DNA antibodies, and a decrease in IL-2 production.[20-22] These findings suggest that the *lpr* gene may act as an accelerator gene that enhances the formation of granulomatous arteritis in mice with an MRL/Mp genetic background.[23,24]

Another gene associated with lymphoproliferation is the *gld* gene (generalized lymphoproliferative disease gene) in C3H mice.[25] This gene specifies a T lymphocyte cell surface phenotype almost identical to that of the *lpr* gene, and mice bearing this mutant gene also sustain an unusual T cell proliferation.[26] Although the *gld/gld* genotype is associated with lymphadenopathy, hypergammaglobulinemia, and several types of autoantibodies,[25] the C3H/HeJ-*gld/gld* mice develop neither significant GNP nor arteritis.

For this article, we studied the genetics of arteritis in MRL/Mp mice by manipulating the autosomal recessive genes *lpr* and *gld* in these mice. Hybrid mice of reciprocal (MRL/Mp-+/+ × C3H/HeJ-*gld/gld*)F2 and backcross mice of MRL/Mp-*lpr/lpr* × reciprocal (MRL/Mp-*lpr/lpr* × C57BL/6-*lpr/lpr*)F1 were prepared for these analyses. We found that mice bearing the *gld/gld* genotype on an MRL/Mp background suffered from granulomatous arteritis, similar to that of the *lpr/lpr* mice. Furthermore, the results of studies using backcross mice suggested that the background genes for the development of arteritis are independent of those influencing GNP.

Materials and Methods

Animals

MRL/Mp-*lpr/lpr* (MRL/lpr), MRL/Mp-+/+ (MRL/+/+), C57BL/6-*lpr/lpr*(B6/lpr) and C57BL/6-+/+ (B6/+/+), C3H/HeJ-*gld/gld*(C3H/gld), C3H/HeJ-+/+ (C3H/+/+) mice were purchased from The Jackson Laboratory, Bar Harbor, Maine. From these mice we obtained hybrid mice, reciprocal (MRL/+/+ × C3H/*gld*)F2, and backcross mice, MRL/*lpr* × reciprocal (MRL/*lpr* × B6/*lpr*)F1 and B6/lpr × (MRL/*lpr* × B6/*lpr*)F1. All were maintained under conditions free from specific pathogens in the animal research institute of Tohoku University School of Medicine, Sendai, Japan. Sixteen-to-twenty-week-old mice of either sex were used in this study.

Histopathologic Studies

Each mouse was bled under ether anesthesia. At autopsy, sections of heart, lungs, kidneys, spleen, liver, pancreas, salivary glands, thymus, and lymph nodes were fixed in 10% formalin in 0.01 M phosphate buffer (pH 7.2), and embedded in paraffin. They were stained with hematoxylin and eosin (H & E) and Elastica-Masson (EM) for histologic examination by light microscopy.

Incidence of arteritis or glomerulonephritis was calculated as follows. An individual with one or more granulomatous arteritis lesions in at least one section of any organ, and in which histopathologic manifestations involved at least the destruction of the arterial wall including the external elastic lamina, was considered positive for arteritis. An individual positive for glomerulonephritis was defined as one having mesangial and/or membranous proliferative glomerular lesions in more than 50% of a total of 20 renal glomeruli.

Lymphoproliferation was defined as positive when spleen weight increased by more than 0.2 g, accompanied by significant swelling of axillary lymph nodes (larger than a rice grain). These criteria were chosen because spleen weight (+2SD) of MRL/+/+ (N = 34), C3H/+/+ (N = 25), or B6/+/+ (N = 18) mice was never more than 0.2 g and axillary lymph nodes of these mice were never larger than a rice grain in our preliminary study.

Results

Development of Arteritis in Reciprocal (MRL/+/+ × C3H/gld)F2 Mice

Our first set of experiments was designed to determine if the presence of the *gld* genotype in an MRL background could influence the development of arteritis. A total of 221 mice randomly selected from reciprocal (MRL/+/+ × C3H/gld)F2 mice were necropsied at 16 to 20 weeks of age. Fifty-eight (26.2%) of these had evidence of gross lymphoproliferation (Table 1). Tissues from these 58, as well as from an additional 67 not showing lymphoproliferation (125 total), were processed for histopathologic study. Ten animals (8.0%) had lesions of granulomatous arteritis, and 44 (35.2%) had GNP, which was almost exclusively of the mesangial proliferative type. The ten exhibiting granulomatous arteritis also were positive for GNP and lymphoproliferation; thus, the incidence of arteritis in the 58 mice with lymphoproliferation reached 17.2%. There was no observed difference in the incidence of arteritis between the male and female F2 mice. Neither of the parental groups, MRL/+/+ nor C3H/gld, developed arteritis. This set of experiments suggested that the development of arteritis on an MRL/Mp background could be accelerated by the presence of the *gld* genotype, as well as by the *lpr* genotype.

Table 1. *Incidence of Arteritis, Glomerulonephritis and Lymphoproliferation in Reciprocal (MRL/+/+ × C3H/gld)F2 Mice*

Populations	Number of animals			
	Autopsied cases	Lymphoproliferation	Arteritis	Glomerulonephritis
F2 populations				
(MRL/+/+ × C3H/gld)F2				
Female	62	16		
	(41)	(16)	(2)*†	(16)*
Male	88	23		
	(52)	(23)	(3)*†	(15)*
(C3H/gld × MRL/+/+)F2				
Female	41	13		
	(22)	(13)	(3)*†	(8)*
Male	30	6		
	(10)	(6)	(2)*†	(5)*
Total	221	58		
	(125)	(58)	(10)*†	(44)*
Parents				
MRL/+/+				
Female	49	0		
	(21)	(0)	(0)	(1)
Male	41	0		
	(35)	(0)	(0)	(0)
C3H/gld				
Female	32	31		
	(22)	(22)	(0)	(1)
Male	43	43		
	(20)	(20)	(0)	(0)

( ) Number of animals examined in histopathologic studies.
* Associated with lymphoproliferation (see Materials and Methods).
† Accompanied by glomerulonephritis (see Materials and Methods).

Dissociation of Arteritis from GNP in MRL/lpr × Reciprocal (MRL/lpr × B6/lpr)F1 Mice

In the next set of experiments we studied the incidence of arteritis in MRL/lpr × reciprocal (MRL/lpr × B6/lpr)F1 backcross mice. These mice are homozygous for the *lpr* genotype even if other genes rendering MRL/Mp mice susceptible to arteritis are manipulated in hybrids with a B6 genetic background. A total of 99 backcross mice were analyzed, 88 of which had lymphoproliferation at necropsy. Of these 88 animals, 29 (33.0%) had arteritis and 59 (67.0%) had GNP. Nine of the 29 backcross mice with arteritis (27%) did not show signs of significant GNP. This contrasted with the 49 MRL/lpr control mice with arteritis, 100% of which also had severe GNP (Table 2). Furthermore, no arteritis cases were detected in B6/lpr × (MRL/lpr × B6/lpr)F1 mice (N = 20), although two mice showed GNP and all displayed massive lymphoproliferation (data not shown).

The results of this set of experiments clearly showed that development of GNP could be dissociated from development of arteritis by manipulating background genes.

Histopathologic Similarity of Arteritis Lesions in MRL/lpr Mice to Those in Hybrid F2 and Backcross Mice

In the studies just described, we reported on the incidence of arteritis and GNP in MRL/lpr mice or hybrid F2 and backcross mice on an MRL/Mp background. It is also important to compare the nature of the pathologic lesions to see if they are similar. MRL/lpr mice develop an arteritis that is characteristic of granulomatous inflammation (Figure 1), and the development coincides with severe GNP (Figure 2).

Similar arterial lesions were observed in the renal arteries of some of the hybrid mice, ie, the reciprocal (MRL/+/+ × C3H/gld)F2. Although the arteritis in the hybrids was not as severe as in the MRL/lpr mice, the histopathologic features were virtually identical, ie, granulomatous lesions associated with infiltration of mononuclear cells (Figure 3). The pathologic picture of the GNP was also very similar in the two types of mice, that is, mesangial proliferation with mononuclear cell infiltration and eosinophilic dense deposits in the mesangium and glomerular capillary walls were seen (Figure 4).

Arteritis in the backcross mice, MRL/lpr × reciprocal (MRL/lpr × B6/lpr)F1 was found in the kidneys and/or other organs including the pancreas and salivary glands. In these mice, granulomatous lesions in the arterial wall and the periarterial regions were accompanied by severe mononuclear cell infiltration in the surrounding tissues (Figure 5). Intimal thickening was also evident, as was destruction of external and internal elastic lamina (Figure 6). All of these findings are also typical of affected MRL/lpr mice. Some of the backcross mice also had severe GNP (Figure 7).

Table 2. *Incidence of Arteritis and Glomerulonephritis in MRL/lpr × Reciprocal (MRL/lpr × B6/lpr)F1 Backcross Mice*

Populations	Number of animals		
	Autopsied cases*	Arteritis	Glomerulonephritis
Backcrosses			
MRL/lpr × (MRL/lpr × B6/lpr)F1			
Female	25	4 + 2†	16
Male	33	9 + 4†	16
MRL/lpr × (B6/lpr × MRL/lpr)F1			
Female	20	3 + 2†	18
Male	10	4 + 1†	9
Total	88	20 + 9†	59
Parents			
MRL/lpr			
F	31	27	31
M	26	22	25
B6/lpr			
F	13	0	0
M	15	0	0

* All were examined by histopathologic studies.
† Not accompanied with glomerulonephritis.
Note: F1 (Female) × MRL/lpr (Male) mice in N1 crosses were not examined.

The evolution of these lesions is also of interest. The initial damage to the arterial wall in MRL/lpr mice was induced by mononuclear cell infiltration from the adventitial side (Figure 8), as shown by Moyer et al.[27] Subsequent destruction of the medial muscles and the internal elastic lamina appeared to cause intimal thickening (Figure 9). The early lesions in the hybrid F2 (Figure 10) and backcross (Figure 11) mice clearly resembled those of the MRL/lpr mice (Figure 8). Finally, the histopathologic features of arteritis damage in the backcross mice were identical regardless of whether or not the mice also had GNP (Figures 5, 6, and 12).

Discussion

The genetic basis of autoimmune disease mice has been extensively investigated in the NZ strain.[28-35] By studying (NZB × NZW) × NZB backcross mice, Knight et al[28,29] have suggested that at least three dominant genes are closely linked in the development of GNP. Subsequently, Shirai et al[31,32] found a close link between the predisposition to GNP and the genes for several autoimmune traits including anti-DNA and anti-gp70 antibodies in the same backcross system. Furthermore, they found that the genes for anti-DNA and anti-gp70 autoantibodies are closely linked to the H-2^z complex of the NZW strain. These findings reinforce the emerging notion that autoimmunity is a very complex condition. Thus, what appears to be a predisposing genetic background to autoimmunity in mice may, in fact, be the result of a number of independently segregating genes that each give rise to various autoimmune traits.

Recently, another class of genes influencing autoimmunity has begun to receive attention. These new mutant genes described in the BXSB male mouse (*Yaa*)[11] and the MRL/Mp mouse (*lpr*) can accelerate the autoimmune disease to a severe and juvenile form.[11] However, the effect of these genes varies among mouse strains. They can only induce disease in the face of particular genetic backgrounds (eg, BXSB, NZB, NZW, or MRL/Mp mice).[23,24,36] When the *lpr* gene is transferred to mice with no predisposition towards autoimmunity (C3H/HeJ, B/6, or AKR),[11] mice fail to exhibit pathologic evidence of GNP, arteritis, or arthritis.[22] However, the mice of these crosses that are homozygous for the *lpr* gene develop significant lymphoproliferation, anti-DNA antibodies, rheumatoid factors, and circulating immune complexes.[20,21,37] Thus, there is a clear dissociation between autoimmune disease and the occurrence of autoimmune traits. On the basis of these findings, it can be concluded that particular background genes contribute to the development of autoimmune disease when expressed in association with certain accelerator genes, such as those promoting lymphoproliferation.

In this study, we examined genetic factors influencing granulomatous arteritis in MRL/lpr mice. Initially, we studied the effect of substituting the autosomal recessive *gld* gene onto an MRL background by means of making reciprocal F2 hybrids. This gene induces generalized lymphoproliferation of unusual T cells.[25,26] A significant number of the hybrids developed granulomatous arteritis and GNP (Table 1, Figures 3 and 4), and arteritis was limited to mice expressing the *gld* phenotype (Table 1). Thus, in this instance two distinct, nonallelic genes, *gld* and *lpr*, accelerated lymphoproliferation and arteritis when superimposed on an MRL/Mp background.

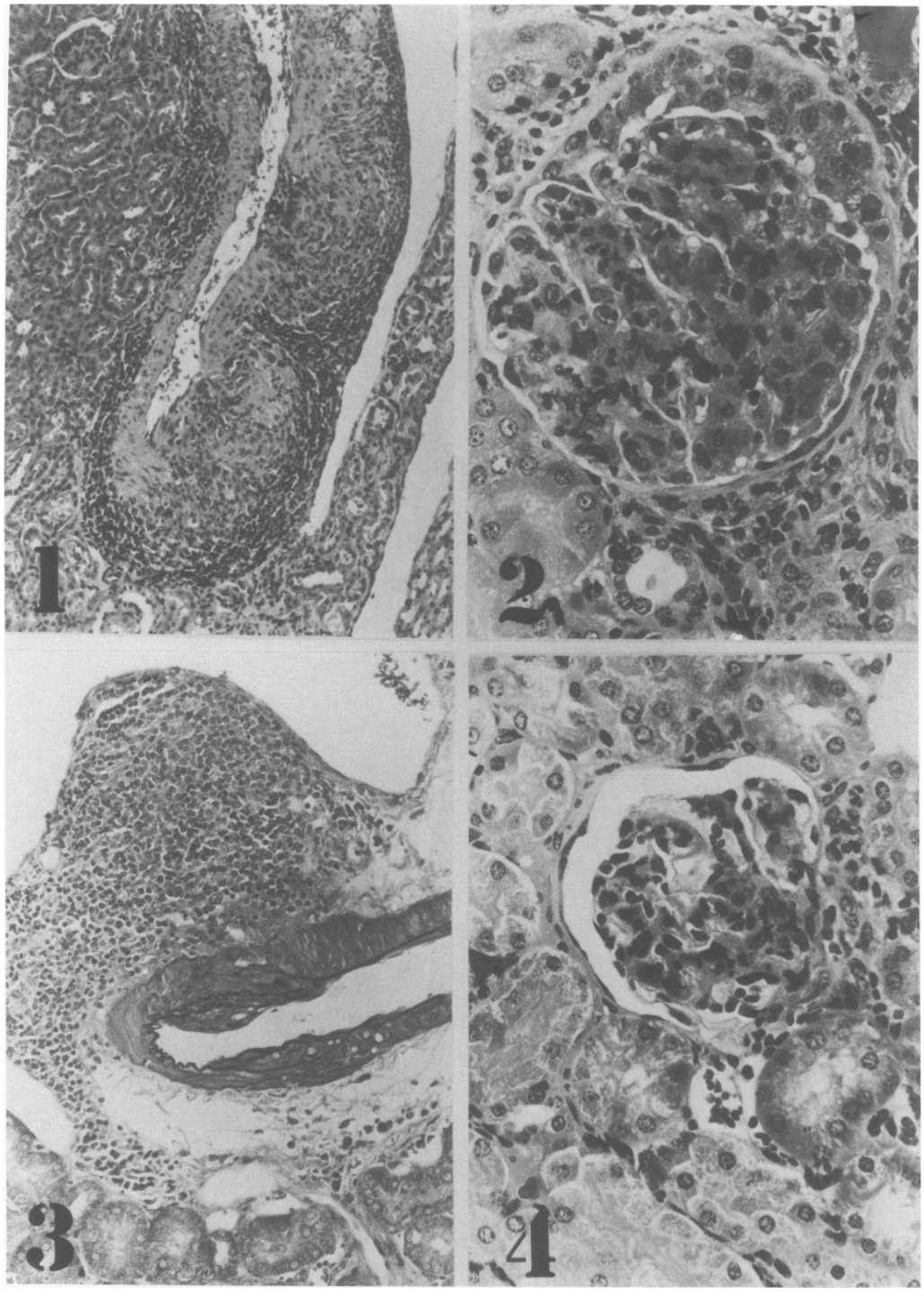

Figure 1. *Arteritis of renal artery in a female 24-week-old MRL/lpr mouse. This picture presents typical histopathologic features of arteritis in this strain of mice, characterized of granulomatous bead-like lesions involving the arterial media and adventitia (H&E, ×120).* **Figure 2.** *Glomerulonephritis in the same MRL/lpr mouse as in Figure 1 shows mesangial proliferation with significant lobulation of glomerular tufts and eosinophilic dense deposits. Accompanying epithelial proliferation is a remarkable, manifesting a crescentic lesion (H&E, ×480).* **Figure 3.** *Arteritis of renal artery in a female 20-week-old (MRL/+/+ × C3H/gld)F2 mouse shows accumulation of lymphocytes and histiocytic cells in adventitia, destruction of external elastic lamina, and intimal proliferation (EM, ×240).* **Figure 4.** *Glomerulonephritis in the same (MRL/+/+ × C3H/gld)F2 mouse as in Figure 3. Mesangial expansion with eosinophilic dense deposits and inflammatory cell infiltrates are remarkable (H&E, ×480).*

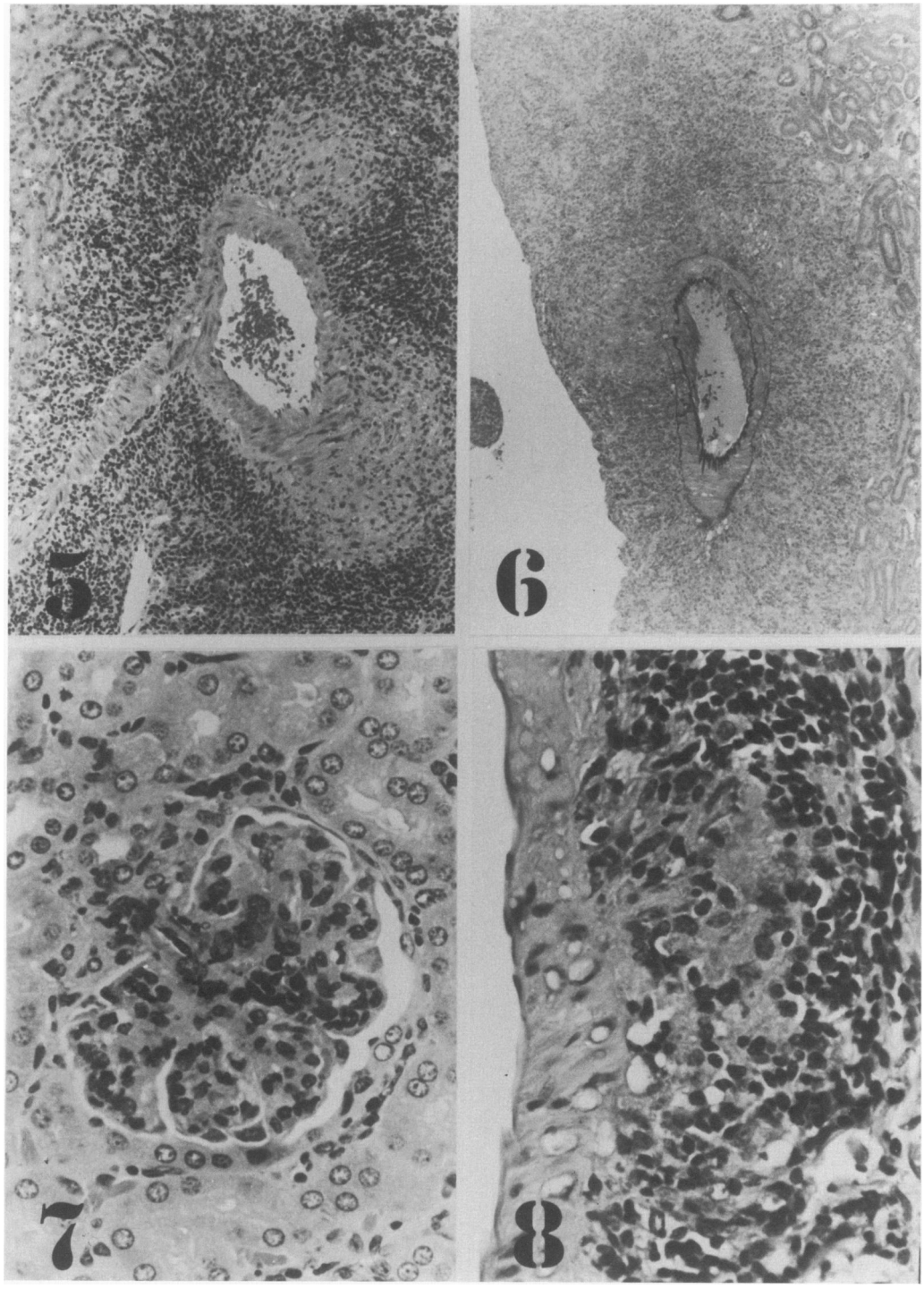

Figure 5. *Arteritis of renal artery in a female 21-week-old MRL/lpr × (MRL/lpr × B6/lpr)F1 mouse shows granulomatous lesions extending into perivascular tissue with severe mononuclear cell infiltration. This case did not have accompaning with glomerulonephritis (H&E, ×120).* **Figure 6.** *Advanced case of arteritis of renal arteries in a female 21-week-old MRL/lpr × (MRL/lpr × B6/lpr)F1 mouse. Destruction of both external and internal elastica lamina are remarkable. This case had accompanying glomerulonephritis (EM, ×60).* **Figure 7.** *Glomerulonephritis in a male 22-week-old MRL/lpr × (MRL/lpr × B6/lpr)F1 mouse. Histopathologic features resemble those in MRL/lpr mice, but this case did not exhibit arteritis in any organ (H&E, ×480).* **Figure 8.** *An early lesion of arteritis of renal artery in a female 20-week-old MRL/lpr mouse. Destruction of external elastic lamina and medial muscles seems to follow granulomatous change of adventitia (H&E, ×480).*

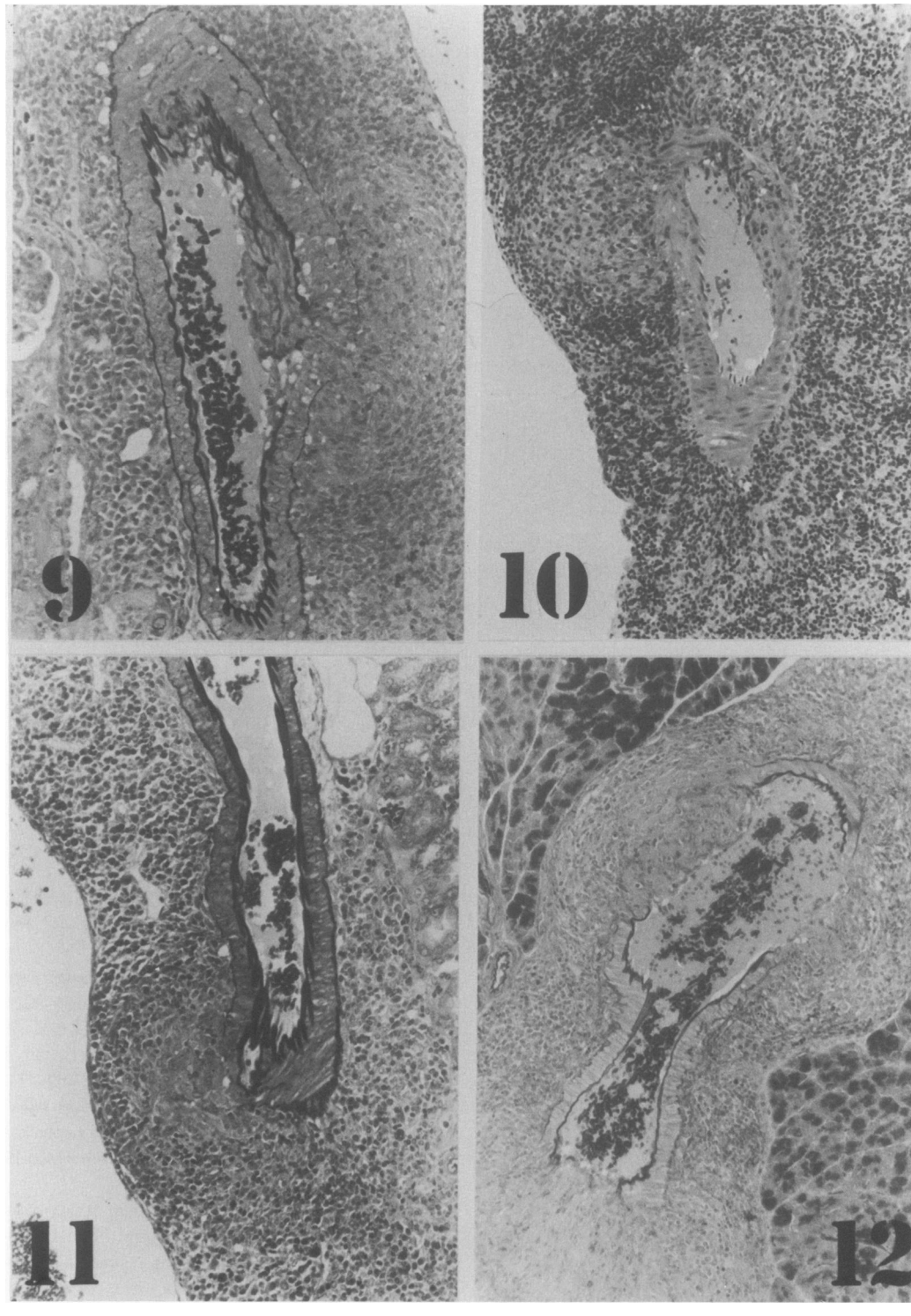

Figure 9. *Advanced arteritis of renal artery in a male 21-week-old MRL/lpr mouse. (EM, ×240).* **Figure 10.** *An early lesion of arteritis of renal artery in a male 21-week-old (MRL/+/+ × C3H/gld)F2 mouse. Internal elastic lamina is still conserved (EM, ×240).* **Figure 11.** *An early lesion of arteritis of renal artery in a male 21-week-old MRL/lpr × (MRL/lpr × B6/lpr)F1 mouse. (H&E, ×120).* **Figure 12.** *Arteritis of pancreatic artery in a female 21-week-old MRL/lpr × (MRL/lpr × B6/lpr)F1 mouse, which did not have accompanying glomerulonephritis. The complete destruction of the medial muscles is significant. They were replaced with granulomatous and partly fibrous lesions (EM, ×120).*

The expression of *gld* is associated with several abnormal immunologic responses such as hypergammaglobulinemia, increased autoantibodies, decreased IL-2 secretion in response to Con A, and poor response in a mixed lymphocyte reaction.[25] Perhaps some of these phenomena are capable of effecting the rapid development of granulomatous arteritis on the MRL/Mp background. Lymphokines, implicated in polyclonal B cell activation and macrophage activation in MRL/lpr mice,[38–43] may also play a critical role in the genesis of the arteritis in the F2 hybrid mice.

The most striking finding of these studies was that we were able to separate completely development of arteritis from GNP. In the F2 hybrid mice, arteritis invariably accompanied GNP. Although this may have implied that common genetic factors give rise to both lesions, the backcross experiments suggested that development of arteritis may be segregated from development of GNP. Of 29 backcross mice with arteritis, nine had no GNP (Table 2). Thus, the predisposition to arteritis in these mice was not wholly synonymous with the predisposition to GNP. Because the arteritis lesions in all 29 of these mice appeared to be identical, these results suggest that the arteritis and the GNP may have different mechanisms of pathogenesis.

Traditionally, immune complexes (IC) have been considered a prime factor in the development of GNP and arteritis,[44,45] but our results suggest that some mice can get arteritis without also getting GNP. Thus, if IC are involved in the arteritis, they are not invariable nephritogenic. In preliminary experiments we assayed sera from MRL/lpr × reciprocal (MRL/lpr × B6/lpr)F1 mice for the presence of anti-ssDNA and anti-dsDNA antibodies and for IC that bind to C1q. No significant correlation was found in the serum titers of backcross mice with solitary arteritis or solitary GNP (Takahashi et al, manuscript in preparation), whereas Berden et al[46] reported that arteritis in MRL/lpr mice was associated with relatively late development of high levels of anti-DNA antibodies and circulating IC. Moyer et al,[27] using immunohistochemical methods, detected IC only in the advanced stages of MRL/lpr arteritis lesions. When their findings are considered with ours, it seems unlikely that IC play a critical role in the initiation of MRL/lpr arteritis.

Arteritis in the GNP-free backcross mice was also characterized by the presence of severe mononuclear infiltrates in the adventitia before the actual destruction of the arterial wall (Figure 5). In addition, in preliminary studies using immunoelectron microscopy, macrophages were occasionally found in endothelial and adventitial regions, and these macrophages contained phagosomes resembling the electron-dense bodies characteristic of IgG. Furthermore, we previously reported that resident peritoneal macrophages of MRL/lpr mice are remarkably activated when compared with those derived from MRL/+/+ mice.[14,42] Finally, macrophage functions are not augmented in B/6-*lpr/lpr* or C3H/HeJ-*gld/gld* mice, but are in some animals of reciprocal (MRL/Mp-+/+ × C3H/HeJ-*gld/gld*)F2 mice with lymphoproliferation.[42] Taken together, these findings support the hypothesis that large reactive mononuclear inflammatory cells lying adjacent to the vascular smooth muscle cells[27] may play an important role in the granulomatous arteritis of MRL/lpr mice.

Arteritis in SL/Ni autoimmune mice is initiated by antibodies to retrovirus-related antigens expressed on arterial myocytes.[47,48] It would also be interesting to study the role of endogenous retroviral expression in the mice described in the present work. In addition, further studies should be undertaken to determine whether retroviruses can induce the *in situ* activation of mononuclear inflammatory cells interacting with the arterial myocytes of MRL/lpr mice.

This article has considered an animal model in which two components of a severe autoimmune disease, granulomatous arteritis and GNP, were dissociated. This model may be a powerful tool with which to dissect the etiopathogenesis of arteritis, especially with regard to the pathologic role of IC in these disorders. We currently are performing further Mendelian analyses and mapping genes that predispose to arteritis to enhance these studies.

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