Genetic Basis of Murine Lupus Nephritis

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Summary: Systemic lupus erythematosus is a generalized autoimmune disease affecting multiple end-organs including the kidneys. Glomerulonephritis is a leading cause of death in lupus, both in patients and murine models that develop disease spontaneously. Genetic mapping studies have uncovered several genetic intervals that confer susceptibility to nephritis both in human beings and in mice. This review surveys the genomic positions of these nephritis susceptibility loci in murine lupus. Currently we know very little about the molecular identities of the culprit genes within these mapped loci and whether these genetic elements contribute to nephritis directly in a renal-intrinsic fashion or indirectly by augmenting the formation of pathogenic autoantibodies. The next decade is likely to witness a significant broadening of our understanding of how different genes and molecules might facilitate end-organ damage in lupus.
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The kidney is a key target organ in systemic lupus erythematosus in human beings and in mice. Nephritis is the leading cause of death in this disease in both species. This review surveys the genetic basis of nephritis in murine lupus. The genetic basis of nephritis in human lupus has been reviewed comprehensively in an accompanying article by Morel and colleagues in this issue. The loci that we presently know to impact susceptibility to murine lupus nephritis arise from genetic mapping studies in mice with spontaneous lupus,[1-23] and from studies of congenic mice bearing various genetic susceptibility intervals for lupus nephritis.[24-28]

SYSTEMIC VERSUS LOCAL FACTORS CONTRIBUTING TO NEPHRITIS SUSCEPTIBILITY IN LUPUS

Glomerulonephritis in lupus is triggered in part by the deposition of antinuclear and antiglomerular antibodies and DNA/anti-DNA immune complexes in the glomeruli.[29-35] The relative contributions of direct antibody-mediated binding to glomerular substrate versus indirect binding of the antibodies mediated by other antigens (such as histones and collagens) have been reviewed previously.[32] Besides representing one of the diagnostic hallmarks of lupus,[29-31] these antibodies also play an important role in disease pathogenesis.[32-35] Thus, for example, it has been shown that antibodies directed to DNA and a couple of other charged antigens can induce various features of nephritis when administered to mice.[34,35]

However, there are several pointers from the literature indicating that antinuclear antibody production and renal disease in lupus may be under distinct genetic control. Importantly, discordance between serum levels of antinuclear autoantibodies and glomerulonephritis has been documented in murine and in human lupus, as reviewed.[29,31,32] Likewise, strongly nephrophilic seropositivity can be uncoupled from renal disease in experimental models. For instance, it has been shown that the absence of key molecular mediators (eg, Fc receptor [FcR], monocyte chemoattractant protein 1 [MCP-1], complement, tumor necrosis factor-α, intercellular adhesion molecule-1, and so forth) in the kidneys can ameliorate antibody (Ab)-mediated disease, despite the presence of potentially

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pathogenic autoantibodies.[36-41] Studies of this nature have illustrated very elegantly some of the molecular requirements for antibody-mediated renal disease, including the FcR and complement, various adhesion molecules, cytokines, and chemokines. More importantly, several of these studies have also included bone-marrow transfer approaches using mice deficient in various mediators to show that these molecules did indeed play a role locally in the end organs, rather than systemically. As a corollary, in certain models, high titers of nephrophilic Abs do not seem to be required for renal pathology to ensue. The New Zealand white (NZW) mouse strain is a classic example of this.[42-44] An extreme example of this is a lupus-prone strain that lacks serum Abs totally but still shows certain aspects of renal disease.[45] These studies show that certain aspects of nephritis still can develop in genetically predisposed individuals, even in the absence of autoantibodies.

There are also clues from mapping studies, notably loci that are linked strongly to nephritis but not autoantibodies, both in mice and in human beings.[11,46] For instance, Quintero-Del-Rio et al[46] had reported genetic loci on human chromosomes 2, 10, and 11 that were linked to nephritis rather than antinuclear autoantibodies. Finally, there have been reports of familial clustering of primary/idiopathic nephritis and nephritis after lupus, diabetes, and hypertension.[47-53] In particular, Freedman et al[50-52] made the interesting observation that end-stage renal disease in lupus shows strong familial clustering among African Americans. All of the above point to the potential importance of genetics in determining intrinsic susceptibility to renal disease in lupus, as well as in other diseases. However, our current understanding of which genetic loci and genes are responsible for nephritis in lupus is rudimentary.

LESSONS FROM MAPPING STUDIES IN MURINE LUPUS

Mapping studies have been performed in many different mouse models that develop lupus spontaneously. These studies have revealed the existence of several susceptibility loci for nephritis in murine lupus.[1-23] Among the mapped loci some confer susceptibility to autoantibody production and nephritis, whereas others confer susceptibility to nephritis only. However, these mapping studies do not offer definitive evidence regarding whether these loci impact disease in a kidney-intrinsic fashion or otherwise. For example, a genetic locus that is linked to antinuclear or antiglomerular autoantibody production may well be expected to influence renal disease simply because the autoantibodies that arise as a consequence of the genetic locus may also have the potential to inflict renal disease.

As portrayed in Table 1, nephritis susceptibility loci have been identified in all mouse strains that develop lupus spontaneously, including BXSB, NZM2410, NZB/NZW, MRL/*lpr*, and so forth. It should be pointed out that genetic loci that confer susceptibility to only autoantibody formation but not renal disease have been excluded from Table 1. As is evident from Table 1, chromosomes 1, 4, 7, and 17 have been implicated most frequently in harboring nephritis susceptibility loci. On chromosome 1, a region between 88-101 cM frequently has been linked to nephritis in murine lupus, on multiple genetic backgrounds. Mapped using the NZM2410 lupus strain, this interval was named *Sle1*.[3] Likewise, mapped using the NZM2328 strain, 2 linkage peaks were reported within the same interval—one for acute nephritis, termed *Agnz1*, and one for chronic nephritis, termed *Cgnz1* (Table 1).[4] Importantly, it should be pointed out that *Sle1*, *Agnz1*, and *Cgnz1* are all of NZW parental origin, an inbred strain that had contributed significantly toward the construction of the NZM2410 and NZM2328 lupus-prone mouse strains. An interval on distal chromosome 1, termed *Nba2*, also has been implicated in lupus nephritis in studies using the NZB inbred strain.[5-7] It is also of interest that strong linkage of this region of chromosome 1 to antinuclear autoantibodies also has been observed in additional inbred strains, including the BXSB and SWR.[2,14]

Mid–chromosome 4 appears to be a second genetic interval that harbors loci that may impact murine lupus nephritis. A locus of NZM2410/NZW origin, named *Sle2*, was reported to be linked strongly to lupus nephritis.[3] Likewise, a very similarly positioned nephritis-

Table 1. Susceptibility Loci for Lupus Nephritis Mapped in Murine Studies

Name of Locus	Chromosome*	cM†	Disease Strain	Resistant Strain	χ^2, P Value or LOD Score	Mapped Phenotypes	Reference
Bxs4/Sle10	1	11	BXSB	C57BL/10	$\chi^2 = 9.6$	Nephritis	1
Bxs1/Yaa2	1	32.8	BXSB	C57BL/10	$\chi^2 = 15.7$, $P = 7 \times 10^{-5}$	Nephritis, ANA, and so forth	2
Bxs2/Yaa3	1	63.1	BXSB	C57BL/10	$\chi^2 = 20.2$, $P = 7 \times 10^{-6}$	Nephritis, anti-dsDNA, and so forth	1,2
Sle1	1	88	NZM2410	C57BL/6	$\chi^2 = 36.7$, LOD = 10.1	Nephritis	3
Cgnz1	1	92.3	NZM2328	C57L/J	$P = 1 \times 10^{-6}$	Chronic nephritis, proteinuria	4
Nba2	1	94.2	NZB	NZW, B6, BALB/c	$P = 1 \times 10^{-4}$	Nephritis, ant-DNA, gp70IC	5-7
Agnz1	1	101	NZM2328	C57L/J	$P = .0002$	Acute nephritis	4
Wbw1	2	86	NZW	NZB	$\chi^2 = 16.8$, LOD = 4.0	Proteinuria	8
No name	3	32.8	BXSB	C57BL/10	$\chi^2 = 11.3$	Nephritis, ANA	1,2
Nbwa2/Sle15	4	31.2	NZB	BALB/c	$P = 1.4 \times 10^{-4}$	Nephritis	9
Lbw2	4	42.6	NZB	NZW	$\chi^2 = 13.8$	Nephritis, mortality	10
Sle2	4	44.5	NZM2410	C57BL/6	$\chi^2 = 24.2$, LOD = 6.52	Nephritis	3
No name	4	48.5	NZB	B6 and BALB/c	$P < .0034$	Nephritis	5
Sles2	4	57.6	C57BL/6	NZW	LOD = 2.15	Nephritis, anti-dsDNA	11
Nba1	4	70	NZB	NZW,SWR	$\chi^2 = 13.07$, $P < .0005$	Nephritis	12-14
Nba4	5	15	NZB	SWR	LOD = 2.98	Nephritis	15
Sle6	5	20	NZW	C57BL/6	LOD = 3.63	Nephritis	11
Lxw2	6	25.5	NZW	BXSB	$P = .0038$	Nephritis	16
No name	6	35	C3H	MRL	$\chi^2 = 11.6$ $P = .0007$	Nephritis	17
Lrdm1	7	6	MRL-lpr	CAST/El	LOD = 3.0	Nephritis, anti-DNA, and so forth	18
No name	7	16	NZM2410	C57BL/6	LOD = 5.5, $P = 3 \times 10^{-6}$	Nephritis, anti-dsDNA	19
No name	7	25	NZW	C57BL/6	LOD = 4.9	Nephritis, anti-DNA, gp70 IC	20
Sle3	7	28	NZM2410	C57BL/6	$\chi^2 = 16.7$, LOD = 4	Nephritis, autoantibodies	3
Nba3	7	31	NZB	SWR	LOD = 1.94	Nephritis	21
Sle12	10	69	NZM2410	C57BL/6	LOD = 3.5, $P = 3 \times 10^{-4}$	Nephritis	19
Sle13	11	20	NZM2410	C57BL/6	LOD = 3.3, $P = 5 \times 10^{-4}$	Acute nephritis, anti-dsDNA	19
Nbwa1/Sle14	12	3.5	NZB	BALB/c	LOD > 3.6	Nephritis, ANA	9
Lrdm2	12	61.8	MRL-lpr	CAST/Ei	LOD = 2.9	Nephritis, anti-DNA, and so forth	18
Swrl2	14	27.5	SWR	NZB	LOD = 2.71	Nephritis, IgG ANA	14
No name	14	40	NZB	BALB/c	LOD = 4.7, $P = 3 \times 10^{-3}$	Nephritis	5
Lprm3	14	44.3	C3H	MRL	$\chi^2 = 12.4$, $P = .0004$	Nephritis	22
No name	16	38	NZW	NZB	$P = .003$	Nephritis, anti-dsDNA, and so forth	13
H2	17	19	Several‡	Several‡	$P < .0034$, at least	Nephritis, mortality, ANA, and so forth	Several‡
Lbw6	18	47	NZW	NZB	$\chi^2 = 15.1$, $P < .001$	Nephritis, mortality	10

*Indicated are the chromosomal positions of the loci.
†Listed are the positions of the locus on the chromosome in centimorgans.
‡Several nephritis susceptibility loci have been mapped to *H2*.[3-5,8,10-11,13,14,16,23]

associated locus of NZB origin, termed *Nbwa2/Sle15/Lbw2*, also was reported.[5,9,10] In addition, a second, more distally located locus on NZB chromosome 4 also was documented to be linked to nephritis[12-14]; this locus was termed *Nba1*. On chromosome 7, a nephritis-associated locus was reported at about 16-31 cM, both in the NZM2410/NZW strains (termed *Sle3*) and in the NZB strain, termed *Nba3* (Table 1).

Centromeric chromosome 17 at about 20 cM, encompassing the *H2* locus, appears to be another locus that frequently has been linked to nephritis in lupus, and several other component phenotypes, including antinuclear autoantibodies.[3-5,8,10,11,13,14,16,23] This locus is rather interesting from several different perspectives. First, this was the very first locus that had been implicated in murine and human lupus. Second, in most mapping studies, this constitutes one of the strongest locus for lupus and lupus nephritis. Third, this locus has been uncovered in almost all strains studied, including the NZM2410, NZB, NZW, SWR, and C57BL/6 strains.[3-5,8,10,11,13,14,16,23] Fourth, it is of interest that even a normal strain, such as C57BL/6, may harbor the disease-associated allele at this locus.[3,11] Fifth, this locus has been associated with a wide spectrum of phenotypes including increased autoantibody levels, hypergammaglobulinemia, nephritis, mortality, and so forth. Finally, it should also be pointed out that although this locus maps to the *H2* interval, it remains to be shown conclusively that the *H2* genes within this interval are indeed responsible for the disease association.

Hence, it is clear that several nephritis loci have been mapped repeatedly to distal chromosome 1 (88-101 cM), mid–chromosome 4 (31-48 cM), proximal chromosome 7 (16-31 cM), and centromeric chromosome 17 (around *H2*), suggesting that these 4 intervals are likely to harbor genes that influence lupus or lupus nephritis in almost all genetic backgrounds associated with spontaneous lupus. However, a note of caution is warranted. It is apparent that most of these genetic loci also are linked to autoantibody formation, suggesting that these loci may be impacting renal disease because of their capacity to elicit pathogenic autoantibody formation. Currently, the culprit genes within most of these loci remain to be decoded.

LESSONS FROM CONGENIC MOUSE STRAINS

As alluded to earlier, we do not currently know if any of the mapped nephritis susceptibility loci operate in a kidney-intrinsic fashion. One approach that permits further analysis of this issue is the study of congenic mouse strains harboring identified nephritis susceptibility intervals. A couple of laboratories have bred congenic strains with susceptibility loci for lupus nephritis introgressed onto a disease-resistant strain background. A good illustration of the congenic dissection strategy arises from the work of Wakeland, Mohan, and Morel, as illustrated in Figure 1.[3,19,25,26,54-66] After their original observation that there were 4 major susceptibility loci for lupus in the NZM2410 strain, each locus was individually back-crossed onto the relatively healthy C57BL/6 strain to generate a series of congenic strains.

Essentially, to generate congenic mice bearing NZM2410-derived disease loci on the C57BL/6 genetic background, one begins with a straightforward NZM2410 X C57BL/6 cross. F1 offspring from such a cross then are mated back to the parental C57BL/6 strain (termed a *back-cross*). It is of importance to note that offspring from this back-cross will bear genomes comprising 25% NZM2410 origin and 75% C57BL/6. Among these offspring, mice that still harbor the NZM2410 disease alleles of selected lupus susceptibility loci then can be remated to the C57BL/6 strain; derived off-spring from this cross will bear only 12.5% of the NZM2410-derived genome. Hence, after each back-cross, the content of the NZM2410-derived genome in the offspring is halved. Through this recursive back-crossing regimen, one can breed strains of mice that bear the NZM2410 alleles of lupus susceptibility loci on a genetic background that is progressively more C57BL/6-like.

Through such a breeding process, Wakeland et al[25,26,54,55] generated several congenic strains such as B6.*Sle1* (ie, C57BL/6 mice bearing the NZM2410 allele of *Sle1* as a congenic interval), B6.*Sle2*, B6.*Sle3*, and so forth. It was observed

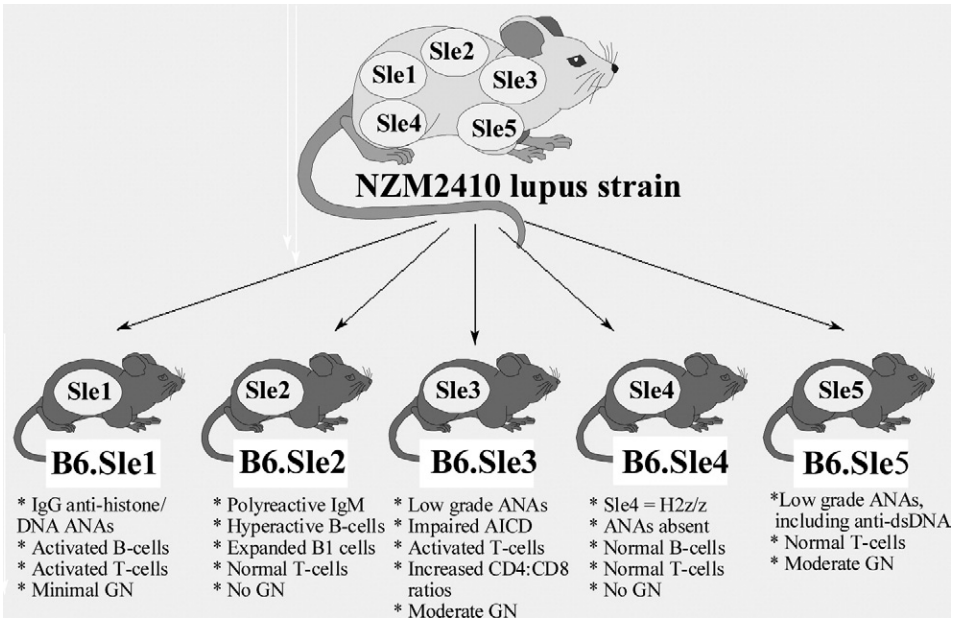

Figure 1. Genetic dissection of lupus nephritis using congenic mouse strains. A good illustration of the congenic dissection strategy arises from the initial work of Wakeland et al as shown by other investigators.[3,19,25,26,54-66] After their original observation that there were 4 major susceptibility loci for lupus in the NZM2410 strain, each locus was individually back-crossed onto the relatively healthy C57BL/6 strain to generate a series of congenic strains. Interestingly, each of the congenic strains showed very different immunophenotypes, as summarized in the text.

that B6.*Sle1* mice, congenic for the *Sle1* locus on chromosome 1, spontaneously developed high levels of antichromatin autoantibodies but minimal nephritis.[25,55] This strain showed high levels of antibodies to histone/DNA complexes, particularly targeting the H2A/H2B/DNA epitopes, with relatively weak reactivity to histone-free double-stranded DNA (dsDNA). Although sera from these mice stained Hep-2 nuclei very brightly, these antibodies did not appear to be pathogenic, at least based on the observation that these mice had minimal evidence of renal disease.[25,55] The peripheral lymphocytes from these mice showed evidence of being more activated, based on the higher levels of various activation molecules on their surface. However, no generalized defects in lymphocyte apoptosis or proliferation were noted in these mice.

B6.*Sle2* mice, congenic for the *Sle2* susceptibility interval on chromosome 4, showed features of generalized B-cell hyperactivity but with no evidence of nephritis.[25,54] Interestingly, these mice showed an expansion of B1a cells (B cells bearing CD5 on their surface), initially in their peritoneal cavities and later in their spleens. These B cells may have been responsible for the high levels of polyreactive antibodies in these mice. It is of interest, however, that these congenics showed minimal evidence of antinuclear antibodies and nephritis. B6.*Sle3* mice bearing the *Sle3* locus on chromosome 7 showed modest degrees of serologic autoreactivity and glomerulonephritis.[25,26] Interestingly, these congenics showed increased CD4:CD8 ratios, and more activated CD4 T cells that had defects in activation-induced cell death. Although sera from these mice showed only modest levels of antinuclear antibodies, it is of interest to note that they were reactive to dsDNA as well.

The advantages of working with congenic mice such as those described earlier are manifold. First, it allows one to perform mixed bone-marrow transfer experiments of various types to ascertain the cell types within which different loci must be operating. To execute adoptive transfers of these types, a variant of the C56BL/6 strain was used that possessed allelic markers on their B cells, T cells, and antibodies. For example, whereas B6.*Sle1* and B6.*Sle3* mice are of antibodies that bear the b allotype (eg, IgM^b) just like C57BL/6 mice, the variant strain

used for the BM transfer studies was almost identical to C57BL/6 genetically except that it possessed a couple of variant alleles, including one that encoded antibodies of the a allotype (eg, IgM^a). Essentially, this allows one to distinguish the antibodies secreted by *Sle1*- or *Sle3*-bearing B cells from Abs elaborated by B cells lacking these lupus-susceptibility alleles. Bone marrow from these different strains then can be transferred adoptively into healthy C57BL/6 hosts to generate mixed allotype-marked bone marrow chimeras, in which lymphocytes of diverse genetic origins codevelop within the same host. Importantly, the availability of the allelic markers on the lymphocytes and antibodies allows the investigator to determine whether the lupus susceptibility locus had to be intrinsic to B cells (or T cells) for various autoimmune manifestations to arise.

Through such experiments, we now know that the *Sle1* locus operates in a B-cell intrinsic fashion. Thus when *Sle1*-bearing and non–*Sle1*-bearing lymphocytes were engineered to codevelop within the same C57BL/6 host, a striking observation was made that only B cells bearing *Sle1* had the capacity to generate antichromatin antibodies, suggesting that the culprit genes within the *Sle1* disease locus had to operate in a B-cell intrinsic fashion, at the very least.[56] Likewise, when *Sle3*-bearing and non–*Sle3*-bearing bone marrow were cotransferred into a C57BL/6 host, it was intriguing to observe that T cells of both origins showed increased activation and CD4:CD8 ratios, suggesting that *Sle3* had the capacity to function in a non–lymphocyte-intrinsic fashion.[57] More recently, these predictions have been confirmed through a detailed analysis of the myeloid cell compartment from these mice.[58] Importantly, the latter studies indicated that *Sle3*-bearing dendritic cells were more activated, elaborated more cytokines, costimulated T cells better, and also had the capacity to trigger autoimmunity on adoptive transfer in healthy C57BL/6 mice.[58]

A second use of having congenic strains is that they can be used to reconstitute lupus and lupus nephritis, an approach that is converse to the genetic dissection studies described previously. Having all of these different disease susceptibility intervals on the C57BL/6 background essentially allows one to readily breed bicongenic and polycongenic strains bearing multiple disease-promoting loci. Thus, for instance, when B6.*Sle1* congenics were bred to B6.*Sle3* congenics to derive B6.*Sle1*.*Sle3* bicongenics, it was apparent that several lupus phenotypes including nephrophilic anti-DNA antibodies and severe nephritis (grade 4 on the World Health Organization scale) were contingent on the epistatic interplay of both these loci.[59] Likewise, even more profound disease was reconstituted when all 3 loci, *Sle1*, *Sle2*, and *Sle3*, were bred back together on the C57BL/6 background.[60] Besides breeding together these monocongenic strains, several of these also have been bred to other C57BL/6-based strains bearing various genetic aberrations. For instance, breeding B6.*Sle1* with B6.FAS^{lpr} mice resulted in the B6.*Sle1*.*lpr* strain, which also showed severe lupus nephritis.[61] Because all of these strains show parallel increases in their titers of anti-dsDNA antibodies and nephritis, it is tempting to postulate that these 2 phenomena may be linked causally; however, other possibilities need to be entertained, in light of the observation that discordances between these phenotypes also have been reported,[28-30,45] as well as the observation that some of these loci also might impact renal disease directly, as discussed later.

A third use of congenic strains is that it allows one to rapidly zoom-in onto the precise positions of the responsible culprit genes and also to identify them eventually. Beginning with a congenic strain, it is relatively straightforward to recursively breed offspring with progressively shorter genomic intervals spanning the disease loci. One then can study the disease phenotypes in these recombinants to determine where the disease gene must lie. However, this genetic exercise often springs unexpected surprises. Thus, for instance, when recombinants were generated spanning the *Sle1* disease interval on distal chromosome 1, Morel et al[62] stumbled on the observation that there were at least 3 loci (ie, at least 3 genes) within the *Sle1* interval that potentially could impact antichromatin levels, albeit to different degrees. These 3 loci were named *Sle1a*, *Sle1b*, and *Sle1c*, with distinct impacts on the immune system.[62]

The advantage of having narrower disease intervals is that it greatly facilitates candidate gene testing and positional cloning, as recently illustrated.[63-65] By using the former approach, Boackle et al[65] showed allelic polymorphisms of *Cr1/Cr2* to represent the culprit genes within the *Sle1c* locus. By using the latter approach, Wandstrat et al[63] showed that the *SLAM* family of genes represented the culprit genes within the *Sle1b* interval. Among the 7 members of this family of costimulatory molecules, several showed functional and/or structural polymorphisms when one compared the NZM2410/NZW strains with C57BL/6. One challenge that remained was to detail and understand the precise molecular mechanisms through which these polymorphisms actually may contribute to lupus and lupus nephritis.

More recently, Kumar et al[64] showed that polymorphisms in the *Ly108* gene, a member of the SLAM family of molecules, may constitute an important culprit gene for lupus, owing to its impact on B-cell tolerance. Whereas the C57BL/6 strain possesses a *Ly108* allele that predominantly encodes the Ly108.2 isoform, the NZM2410/NZW allele encodes the Ly108.1 isoform, with these 2 isoforms differing in the numbers of intracellular tyrosine-based switch motifs (ITSM) signaling motifs they possess.[63] Kumar et al[64] showed that immature B cells from B6.*Sle1* mice preferentially express the Ly108.1 isoform and are defective in several tolerance mechanisms (including deletion and receptor editing). Importantly, transfection studies indicate that the lupus-associated Ly108.1 isoform impeded deletion and receptor-editing in immature B cells.[64] Collectively, these works suggest that lupus genes may operate by infringing B-cell censoring mechanisms, leading to the emergence of autoantibodies. Although it is clear that *Sle2* and *Sle3/Sle5* intervals also harbor multiple disease-susceptibility genes,[58,66] their identities are currently unknown.

In addition to the earlier-described congenic strains bearing different NZM2410-derived lupus susceptibility loci, congenic strains bearing lupus-susceptibility loci derived from other lupus-prone strains also have been characterized. Importantly, a couple of these congenic strains also show an impact on end-organ disease.[24-28] Thus, B6.NZBc1(85-106) congenic mice bearing the *Nba2* interval of NZB origin on distal chromosome 1 (that is positioned similarly to *Sle1* of NZM2410/NZW origin) and B6.MRLc7 bearing the *Lmb3* locus of MRL origin (that is positioned similarly to *Sle3* of NZM2410/NZW origin) both show nephritis (Table 2).[24,27] Conversely, replacing the NZM2328/NZW nephritis-associated interval on distal chromosome 1 with the healthy C57L/J-derived interval ameliorates renal disease in the NZM.2328.*Cgnz1* congenic model (Table 2).[28] Analysis of these congenic strains reveals in most cases that the nephritis-promoting loci in these reported studies also had the capacity to influence autoantibody production. This raises the possibility that the nephritis observed in these congenic strains may have been the consequence of pathogenic autoantibody production, although this notion needs to be shown formally.

However, there is emerging evidence that a subset of the earlier-described nephritis-associated loci may indeed have the capacity to influence renal disease directly. A case in point is the NZM2410-derived *Sle3* locus on mid–chromosome 7 that has been documented to show a variety of myeloid cell anomalies affecting multiple cell types, including dendritic cells, macrophages, and neutrophils.[26,58] More recently, we found that B6.*Sle3* congenic mice are more sensitive to anti-glomerular basement membrane (GBM) induced experimental nephritis and that B6.*Sle3*-derived mesangial cells are more proinflammatory (Xie and Mohan, unpublished data). Hence, the *Sle3* interval may turn out to be a lupus-susceptibility locus that potentially may harbor genes that influence lupus nephritis in a renal-intrinsic fashion. Bone-marrow transfer studies and kidney transplant experiments are in progress in several laboratories to determine if the nephritis-associated loci uncovered through murine congenic dissection studies actually can influence the development of nephritis in a renal-intrinsic fashion.

CONCLUSIONS

The aforementioned genetic studies have uncovered several murine loci that have the capacity to impact lupus and lupus nephritis. Presently, the

Table 2. Congenic Strains of Mice With Nephritis

Congenic Strain*	Disease Strain	Control Strain	Locus	Chromosomal Position†	Phenotypes Noted in Congenics‡				Reference
					Proteinuria	Nephritis	Deposits	Auto-Ab	
Introgression of disease interval onto normal strain background									
B6.NZBc1 (35–106)	NZB	C57BL/6	*Nba2*, others	1 (35–106)	Yes (low)	Yes	Yes	Yes	24
B6.NZBc1 (85–106)	NZB	C57BL/6	*Nba2*	1 (85–106)	No	Yes	Yes	Yes	24
B6.Sle1	NZM2410	C57BL/6	*Sle1*	1 (85–122)	No	Mild	No	Yes	25
B6.Sle3	NZM2410	C57BL/6	*Sle3*	7 (15–45)	No	Modest	Yes	Yes	25,26
B6.MRLc7	MRL	C57BL/6	*Lmb3*	7 (1–28)	NA	Yes	Yes	Yes	27
Introgression of normal interval onto disease-strain background									
NZM2328.Cgnz1	NZM2328	C57L/J	*Cgnz1*	1 (88–112)	Decreased	Decreased	Decreased	Decreased	28
NZM2328.Adnz1	NZM2328	C57L/J	*Adnz1*	4 (16–60)	No change	No change	No change	Decreased	28

*Indicated are monocongenic strains in which a disease susceptibility locus has been bred onto a resistant strain background (ie, the top 5 strains) or in which a disease-resistant locus has been bred onto a disease susceptible background (ie, the bottom 2 strains).
†Listed are the chromosomal locations of the backcrossed genetic intervals in centimorgans (cM).
‡Listed are the phenotypes in the congenic strains relative to the background strain.

culprit genes within these disease-associated intervals and their mode of action remain unknown for the most part with a few exceptions.[63-65,67-69] The challenge is to decipher the actual nephritis-causing genes within these susceptibility intervals and to ascertain if these genes contribute to lupus nephritis directly in a kidney-intrinsic fashion, or indirectly by facilitating the formation of pathogenic autoantibodies. It also is important to determine if the genes that facilitate lupus nephritis in mice also potentiate human lupus nephritis, as well as other forms of nephritis or end-organ diseases.

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