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Systemic lupus erythematosus – recent clues from congenic strains

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Summary

Systemic lupus erythematosus is a polycongenic autoimmune disease characterized by the production of antinuclear antibodies that lead to subsequent end organ damage. The study of lupus is complicated by its polycongenic origin, contributions from hormones and the environment, epistasis among susceptibility loci, suppressive modifiers, and the fact that a single susceptibility locus may encompass multiple susceptibility genes. Murine models that develop lupus spontaneously have greatly contributed to our understanding of this disease. In particular, the advent of "congenic strains" has greatly simplified the study of this complex autoimmune disease. Thus, congenic strains bearing NZB/NZW/NZM2410, BXSB, and MRL lupus susceptibility loci are steadily replacing the traditionally studied murine lupus models as the models of choice for research. This review summarizes how researchers have used congenic strains over the past few years to dissect out and reconstruct the individual elements contributing to lupus pathogenesis.

Key words: **lupus • murine lupus • congenic strains • autoantibodies**

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GENETIC STUDIES OF MURINE LUPUS

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with fairly well defined phenotypes, including antinuclear autoantibodies, glomerulonephritis, and activated T and B cells. The presence of these distinct phenotypes is fortuitous because it renders the disease more amenable to a careful genetic analysis. Indeed, recent classical genetic approaches, aimed at identifying and characterizing the genes that mediate disease susceptibility, have offered priceless glimpses into the mechanisms at play in this disease.

Various genetic intervals predisposing to lupus have been identified using microsatellite marker-based genome scans of spontaneous models of murine disease: BXSB, (New Zealand Black (NZB)/New Zealand White (NZW)) F1, MRL, and NZM2410, a recombinant inbred strain derived from NZW and NZB. The NZM2410 strain is a particularly intriguing model since it expresses highly penetrant phenotypes and develops early-onset disease. These phenotypes are highly distinct from the phenotypes of its "parental" strains, which are almost disease-free. The novelty of these phenotypes suggests that susceptibility genes contributed by both parental strains (i.e. NZB and NZW) must be acting in a synergetic fashion to impact autoimmunity. Not surprisingly, linkage analysis has identified several genetic intervals that contribute to lupus in this strain. The first few loci to be identified in this model have been designated *Sle1*, *Sle2*, *Sle3*, *Sle4* (*H2*), and *Sle5*[7, 8, 10, 11]. Already, studies of these loci have begun to yield valuable clues regarding the culprit genes that may potentially be responsible for the observed lupus phenotypes, and the underlying pathogenic mechanisms through which they may be operative.

THE ADVENT OF CONGENIC STRAINS

With the discovery of the major histocompatibility complex in classical genetic experiments carried out by George Snell arose a novel and powerful tool for the study of complex polygenic diseases like SLE. By selective breeding, a single genetic interval of interest can be "extracted" from the genome of one strain (typically from a disease-prone strain) and bred or "introgressed" onto a new strain background (typically a disease-free or disease-resistant strain) to generate a "congenic" strain. This powerful approach has been widely utilized by biologists for a couple of reasons. It complements genetic mapping studies by allowing the mapped loci to be "isolated" for further assessment. This approach also allows one to "position" the locus onto a totally "new" background in order to determine how a locus functions in the context of a "normal" genome, or a disease-prone one. Hence it is not a surprise that congenic studies have been used extensively in the study of autoimmunity.

More recently, Wakeland et al.[20], as well as other groups, have devised strategies to derive congenic strains more rapidly, by using a marker-assisted breeding strategy for the production of "speed congenics". This modification was truly useful since it almost halved the number of generations required to produce these strains. Essentially, in this modified approach one institutes marker-assisted screening at the earliest breeding generations, so that offspring with excessive irrelevant donor gene content can be selected against while offspring bearing the target genetic interval can be positively selected[14, 15, 20]. The congenic strains that resulted from these initial studies (B6.*Sle1*, B6.*Sle2*, B6.*Sle3*, B6.*Sle4*, and B6.*Sle5*) shared more than 99% of their genome with the C57BL/6 control strain[14, 15]. Similar studies have also been performed, beginning with other murine lupus models to produce strains such as the B6.*Nba2* and B6.NZW-*Sgp3*, as summarized in Table 1[1, 5, 6].

UTILITY OF CONGENIC STRAINS

As a tool for discovery, congenic lines have been used extensively to dissect out the pathogenic mechanisms underlying lupus. Since most lupus congenics derived to date have been generated on the B6 background, one can easily breed them to existing mouse tools such as transgenics and knockouts (involving various molecules of immunological importance), many of which are also on the B6 background. This would then allow the scientist to study the roles of specific cells or molecules in the context of different lupus susceptibility loci. Moreover, the same methods used to create congenic strains can be repeatedly applied in order to further "narrow" the relevant congenic intervals. This is remarkably useful for positionally cloning the disease genes, as well as for reducing the pool of potential candidate genes encompassed by the interval. Since congenics share most of their genome with the host strain, this also facilitates studies designed to identify any differentially expressed molecules (through microarray studies or comparative proteomics) that may then shed light on potential molecular mechanisms through which these loci may be functioning. Reviewed below are some of these applications that have advanced our understanding of murine lupus in recent years.

The assortment of congenic lines produced to date has shed some light on the pathways that may poten-

Table 1. Lupus susceptibility loci studied using congenic strains

Congenic strain	Relevant disease strain	Relevant control strain	Locus	Chromosome	Position (cM)	Phenotype				Reference
						autoantibodies	B cell phenotypes	T cell phenotypes	nephritis	
Introgression of disease interval onto "normal" background										
B6.NZBc1(35–106)	NZB	C57BL/6J	*Nba2*, other	1	35–106	✓	✓	✓	✓	22
B6.NZBc1(85–106)	NZB	C57BL/6J	*Nba2*	1	85–106	✓	✓	✓		22
B6.*Nba2*$^{NZB/NZB}$	NZB	C57BL/6J	*Nba2*	1	79–109	✓	✓	✓		1
B6.*Sle1*$^{NZM2410/NZM2410}$	NZM2410	C57BL/6J	*Sle1*	1	85–122	✓	✓	✓		7, 14
B6.*Sle2*$^{NZM2410/NZM2410}$	NZM2410	C57BL/6J	*Sle2*	4	47–73		✓			8, 14
B6.*Sle3*$^{NZM2410/NZM2410}$	NZM2410	C57BL/6J	*Sle3*	7	15–45	✓		✓	✓	11, 14
B6.*MRLc7*	MRL	C57BL/6J	*Lmb3*	7	0.5–28.4	✓			✓	5
B6.NZW-*Sgp3*/1	NZW	C57BL/6J	*Sgp3*	13	21.9–25	✓				6
"Introgression of "normal" interval onto disease background										
NZM2328.*Cgnz1*$^{C57L/C57L}$	NZM2328	C57L/J	*Cgnz1*	1	87.9–112				✓	21
NZM2328.*Adnz1*$^{C57L/C57L}$	NZM2328	C57L/J	*Adnz1*	4	15.6–59.9	✓			✓	21

Monocongenic strains bearing the Fas-*lpr* and *Yaa* loci have been excluded from this table, as these strains have been extensively studied and documented previously.

tially impact lupus pathogenesis, as recently reviewed[23] and summarized in Table 1. In studies performed by Laporte et al.[6] it was observed that the B6.NZW-*Sgp3* strains developed antibodies against gp70, a viral glycoprotein found in immune complexes, and this correlated well with the development of glomerulonephritis. The series of congenic strains stemming from the NZM2410 model have been very useful in demonstrating that susceptibility to lupus is regulated in a threshold liability fashion[3, 13, 14]. When compared with each other, the phenotype of each B6.*Sle* congenic strain was distinctive. B6.*Sle1* mice were noted to suffer a breach in tolerance to chromatin, but minimal glomerulonephritis or further impairment in lymphocyte function was observed[7]. In contrast, the phenotypes of B6.*Sle2* and B6.*Sle3* mice appeared to have resulted from changes in the activation thresholds of B and T cells, respectively, accompanied by different types of serum antinuclear autoantibodies[7, 8, 9, 11, 14]. These findings are summarized in Table 1. Interestingly, the phenotype of each B6.*Sle* congenic strain represented a component of full-blown lupus, but none of these congenically expressed loci was sufficient to drive the entire disease process acting alone. These findings shore up the hypothesis that lupus pathogenesis is the end result of multiple susceptibility genes acting in a synergistic fashion to breach some critical threshold(s) in autoimmune regulation. Further evidence for this hypothesis has been generated by Rigby et al.[16, 17] in experiments using congenic intervals from NZW and NZB on the BALB/c background. In these strains, the genetic background, in combination with known susceptibility loci, produced novel lupus phenotypes that were absent in the original strains.

Wither and associates have reported interesting autoimmune phenotypes in a congenic strain bearing a single NZB interval from chromosome 1[22]. Although this interval includes the *Nba2* locus, the resultant B6.NZBc1(35-106) strain expresses a distinct phenotype that includes splenomegaly, B cell activation, and glomerulonephritis, in addition to the increased T cell activation and antinuclear antibody response that are typical of the B6.*Nba2* strain. This suggests that multiple susceptibility loci on chromosome 1 may be contributing to autoimmunity in the NZB strain.

REVERSE CONGENIC STRAINS

"Reverse" congenic strains have also been used to study lupus pathogenesis. Importantly, recent congenic lines derived from the NZM2328 strain have been associated with interesting phenotypes. Unlike the NZM2410-derived B6.*Sle* congenics, these novel strains feature a "normal" genetic interval that has been introgressed onto a genetic background that is prone to autoimmunity. This inverse approach was employed by these authors to ascertain if "correcting" individual lupus susceptibility loci in an autoimmune-prone strain might be sufficient to thwart disease. In NZM.C57Lc1 (NZM2328.*Cgnz1*$^{C57L/C57L}$) mice, the loss of the *Cgnz1* disease locus on chromosome 1 led to a declined incidence of chronic glomerulonephritis and severe proteinuria, despite the presence of other susceptibility loci[21]. NZM.C57Lc4 (NZM2328.*Adnz1*$^{C57L/C57L}$) mice lack the *Adnz1* disease locus on chromosome 4, which had previously been associated with the production of autoantibodies, including anti-double-stranded (anti-

-ds)DNA antibodies. While these mice did develop chronic glomerulonephritis, they did not possess the nuclear and dsDNA targeted autoantibodies typically associated with lupus[21]. Thus, other nephritogenic antibodies have been suspected to be contributory in this novel congenic model. These findings are summarized in Table 1.

LESSONS FROM POLYCONGENIC STRAINS

In addition to the above monocongenic strains, the study of polycongenic strains has yielded additional insights. These studies have demonstrated that interactions between loci can not only lead to stronger or novel phenotypes, but may also facilitate the progression to full-blown lupus nephritis. One compelling illustration of this epistasis is the synergistic phenotype exhibited by the NZM2410-derived B6.*Sle* polycongenic strains (Table 2). Despite the modest autoimmune phenotypes noted in B6.*Sle1*, B6.*Sle2*, and B6.*Sle3* monocongenic mice, bicongenic and tricongenic offspring exhibit extremely high penetrance of lupus nephritis and early mortality, resembling the disease seen in the original NZM2410 strain[3, 10, 13, 23].

The epistatic interactions exhibited by the various combinations of NZM2410-derived B6.*Sle* congenic strains also support the threshold liability hypothesis of disease susceptibility. Whereas *Sle1* appears to provide a critical initial breach in tolerance to nuclear antigens, other loci such as *Sle2* and *Sle3* appear to be necessary to amplify disease and ultimately precipitate end-organ disease. When *Sle1* is co-expressed with the *Yaa* (Y accelerated autoimmunity and lymphoproliferation) locus, a strong phenotype that includes fatal glomerulonephritis ensues[13]. This epistatic pattern of expression could not be predicted from the phenotypes of mice expressing either locus alone. Similar epistatic relationships between *Fas^{lpr}* and *Sle1* have also been reported[19]. Likewise the epistatic interplay of *Fas^{lpr}* with *Lmb3* mediates production of antibodies to double-stranded DNA, a defect that is absent from mice bearing either single genetic defect[5].

Multiple discrete susceptibility loci have been identified in the BXSB model based on analysis of chromosome 1. Congenic studies performed by Haywood et al.[5] have revealed epistatic interactions between the various loci from BXSB chromosome 1, and the *Yaa* locus (see Table 2). While splenomegaly and ANA production are characteristic phenotypes in B10.*Yaa* mice, autoantibodies against ssDNA and dsDNA are not present. In combination with various *Bxs* susceptibility loci, the epistatic interaction between these loci leads to anti-dsDNA production, severe glomerulonephritis, and early mortality[4]. These lessons are summarized in Table 2.

Overall, the studies performed with these congenic strains can be viewed in the context of Koch's postulates to study causative agents in microbial pathogenesis. By dissecting out the loci that confer susceptibility to murine lupus, it has become feasible to dissect out the pathogenesis of SLE into a series of discrete steps. In keeping with Koch's postulates, an essential criterion in specifying causality is the reconstitution of disease by introducing the "factor" into a new, healthy host. In the case of SLE, fulfilling this postulate has entailed the breeding back of the individual

Table 2. Epistatic interactions between lupus susceptibility loci lead to novel phenotypes

Locus 1		Locus 2		Locus 3		Observed phenotype					
name	chromosome	name	chromosome	name	chromosome	host background	autoantibodies	B cell phenotypes	T cell phenotypes	nephritis	References
Bxs1	1	*Yaa*	Y			C57BL/10				✓	4
Bxs1	1	*Bxs4*	1	*Yaa*	Y	C57BL/10	✓	✓	✓	✓	4
Bxs1	1	*Bxs2*	1	*Yaa*	Y	C57BL/10	✓				4
Bxs2	1	*Bxs3*	1	*Yaa*	Y	C57BL/6J	✓	✓	✓	✓	4
Sle1	1	*Sle2*	4			C57BL/6J	✓	✓		✓	13
Sle1	1	*Sle3*	7			C57BL/6J	✓	✓	✓	✓	10
Sle1	1	*Sle2*	4	*Sle3*	7	C57BL/6J	✓	✓	✓	✓	13
Sle1	1	*Yaa*	Y			C57BL/6J	✓			✓	13
Sle1	1	*Fas-lpr*	19			C57BL/6J	✓	✓	✓	✓	19
Sle2	4	*Sle3*	7			C57BL/6J		✓	✓	✓	13
Lmb3	7	*Fas-lpr*	19			C57BL/6J	✓		✓	✓	5
Sgp3/2	13	*Yaa*	Y			C57BL/6J	✓				6
Sgp3/3	13	*Yaa*	Y			C57BL/6J					6

Summarized in this table are studies based on bicongenic and tricongenic strains, where two or more lupus susceptibility intervals had been co-introgressed onto "normal" genetic backgrounds. The phenotypes of the relevant monocongenic strains have been summarized in Table 1.

susceptibility loci onto a single strain that is otherwise healthy. These "genetic reconstitution" studies demonstrate the role of genetic epistasis in causing complex polygenic diseases such as lupus.

CONGENICS AS FINE-MAPPING TOOLS

Congenic strains have also been used to fine-map disease intervals. By studying the *Sle1* locus, Morel et al.[12] have shown that at least three non-overlapping sub-loci (*Sle1a*, *Sle1b*, and *Sle1c*) are present within this interval. The sub-congenic strains originating from this discovery have helped elucidate the autonomous role of each sub-locus in lupus pathogenesis. Although each sub-locus influences tolerance to chromatin, their phenotypes diverge. This is evidenced, for example, by the properties noted in B6.*Sle1a* and B6.*Sle1b* congenics, with the former displaying predominantly T cell defects and the latter having more B cell defects. B6.*Sle1c* is somewhat unique in that defects have been observed in both compartments[3, 12]. The observed physical clustering of loci that individually impact the same as similar phenotype(s) has been suggested to result from functional and evolutionary pressures, and is apparently quite common among other autoimmunity susceptibility loci, as discussed elsewhere[12].

CONGENICS AND CANDIDATE GENES

Conceivably, one of the finest demonstrations of the power of congenic strains is their use in the identification of candidate genes. To date, a number of approaches have been implemented towards this goal, with positional cloning and microarray studies representing two successful methods. Importantly, positional cloning and sequencing of all genes within the *Sle1b* congenic interval is currently in progress with the ultimate goal of identifying the responsible candidate gene (Wandstradt et al., manuscript in press).

Within the distal region of chromosome 1 is the *Cr2* gene, encoding complement receptors CR1 and CR2. This gene has been proposed as a candidate for the susceptibility gene within the NZM2410-derived *Sle1c* interval[2]. Complement receptors have previously been implicated in B cell autoimmunity in murine models, and reduced expression of these molecules has been observed in lupus patients. Exploiting the genomic position of *Cr2* within the *Sle1c* interval on chromosome 1, the B6.*Sle1c* sub-congenic strain was used to assess if alterations in this gene might influence its expression or function. Boackle et al.[2] observed that the NZM2410 allele of this gene contained a polymorphism that introduced a new glycosylation site in the receptor. This variation is believed to reduce ligand binding and alter B cell signaling through the complement receptors. Hence these findings indicate that *Cr2* may indeed be a contributory gene in lupus pathogenesis[2].

Besides the positional candidate approach, microarray studies have also been useful in escorting scientists to the culprit genes within congenic intervals. Importantly, *Ifi202* and *Ifi203* have been proposed as candidate gene(s) within the NZB-derived *Nba2* locus, as a result of congenic-based microarray studies[18]. Microarray analysis implicated these as the only genes within the *Nba2* interval on chromosome 1 that were differentially expressed in the spleens of B6.*Nba2* mice when compared with C57BL/6J controls. Hence the *Ifi* genes appear likely to be bona fide lupus susceptibility genes in the NZB model. It has been proposed that the *Ifi* genes (or genes with similar functions) may also contribute to disease in lupus patients. Needless to say, this constitutes an area of intense research.

CONCLUDING REMARKS

To conclude, it is clear how congenic strains have been used in "genetic dissection" and "genetic reconstitution" of murine lupus as well as in unraveling the molecular pathogenesis and candidate genes underlying this complex autoimmune disease. These breakthroughs in our understanding of lupus pathogenesis are likely to represent only the beginning. The continued use of congenic strains in creative and innovative ways could elucidate the complex genetic and molecular blueprints that underlie the pathogenesis of SLE and pave the way towards more targeted therapies for this devastating disease.

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