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An update on lupus animal models

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Abstract

Purpose of the review—The complexity and heterogeneity of the clinical presentation in systemic lupus of erythematosus (SLE), combined to the inherent limitations of clinical research, have made it difficult to investigate the etiology of this disease directly in patients. Various mouse models have been developed to dissect the cellular and genetic mechanisms of SLE, as well as to identify therapeutic targets and to screen treatments. The purpose of this review is to summarize the major spontaneous and induced mouse models of SLE and to provide an update on the major advances they have contributed to the field.

Recent findings—Mouse models of SLE have continued to contribute to understand the cellular, signaling and metabolic mechanisms contributing to the disease, and how targeting these pathways can provide therapeutic targets. Whenever possible, we discuss the advantage of using one model over the others to test a specific hypothesis

Summary—Spontaneous and induced models of lupus models are useful tools for the study of the etiology of the disease, identify therapeutic targets and screen treatments in pre-clinical studies. Each model shares specific subsets of attributes with the disease observed in humans, which provides investigators a tool to tailor to their specific needs.

Keywords

Systemic lupus of erythematosus; mouse models; therapeutic targets; T cells; B cells

Introduction

Systemic lupus of erythematosus (SLE) is a chronic disorder that is characterized by the over-production of antinuclear autoantibodies (ANA) resulting in the formation of immune complexes (IC) that induce tissue inflammation and destruction in multiple organs, including the kidneys (1). The exact etiology of SLE is still unknown, but there is a strong evidence that a combination of environmental exposures, genetic predisposition, cellular dysfunctions and hormonal factors lead to the development of SLE (2). Given the high degree of clinical heterogeneity in SLE patients, preclinical mouse models summarized below (Table 1) have

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been very valuable to investigate the etiology of SLE as well as to identify and validate therapeutic targets.

These mouse models of SLE are either spontaneous or induced, but none of them fully represents the entire clinical spectrum found in SLE patients. However, each model presents an overlapping subset of human lupus phenotypes, and offers specific features of interest to address specific preclinical purposes. In addition to polygenic models, a number of mouse models are based on a single gene knock-out or transgenic expression of genes which result in lupus-like phenotypes (11). These strains have been instrumental in delineating functional pathways in SLE as well as the involvement of specific genes in maintaining systemic immune tolerance, and preventing immune complex (IC)-induced inflammation. There have been numerous reviews of mouse models of SLE starting from the foundational work published over 30 years ago (12) that has been followed by many updates. Many reviews have focused on specific aspects of these models, such as the genetic links between human and mouse SLE (11), or the mechanisms leading to systemic autoimmunity and clinical lupus in these models (13). The present review will briefly summarize the most common mouse of SLE, stressing their unique features. We will then provide an update on the major advances they have contributed to the field, and whenever possible, we will discuss the advantage of using one model over the others to test a specific hypothesis.

Spontaneous Mouse Models of SLE

1. NZB/W F1

In the 1960s, the NZB/W F1 model of lupus refers to the F1 hybrid between the NZB and NZW strains (3). NZB mice show limited hemolytic autoimmune anemia while NZW mice are non-autoimmune. However, their F1 hybrids develop severe lupus-like phenotypes including a strong female bias, splenomegaly, elevated serum ANA mostly directed against DNA. IC-mediated nephritis develops by 5–6 months of age, leading to renal failure and death at 10–12 months of age (12). Overall, NZB/W F1 is a classic model used to study the genetic underpinning of SLE (11) as well as drug responses in many preclinical studies, including the inhibition of BAFF (14), the role of type 1 IFN (15), and the identification of biomarkers of lupus nephritis (16).

2. NZM

An accidental backcross between NZB/W F1 and NZW followed by brother-sister mating generated 27 different recombinant inbred strains of New Zealand Mixed (NZM) mice among which NZM2328 and NZM2410 are now used as lupus models (4–6). The clinical manifestations in NZM strains are similar to that of NZB/W F1 mice, although there are some differences in renal pathology (16, 17), and the response to BAFF inhibition (18). The main advantage of the NZM strains over NZB/W F1 is that they have homozygous genomes, which has facilitated genetic analyses (11). From the NZM2410 strain, a novel congenic model has been produced that combines the three susceptibility loci, *Sle1*, *Sle2*, and *Sle3*, that are necessary and sufficient to induce a lupus phenotype on a non-autoimmune C57BL/6 (B6) genetic background (19). The B6.NZM2410.*Sle1.Sle2.Sle3* has the unique advantage to share 95% of its genome with B6, providing a robust control for

immunological and genetic studies. The corresponding single (mostly *Sle1*) and bi-congenic (*Sle1.Sle3*) are well suited to breed to B6-based gene knock-outs. For instance, deletion of the plasmacytoid dendritic cells (pDC)-specific transcription factor *Tcf4* in B6.*Sle1.Sle3* mice provided genetic evidence that pDCs are critically involved in the development of SLE (20) *.

3. MRL/*lpr*

The MRL strain was developed by crossing several stains including LG/J, C3H/Di, C57BL/6, and AKR/J (12). One of the MRL substrains carrying a spontaneous mutation named *lpr* for lymphoproliferation developed an SLE-like phenotype characterized by accumulation of double negative (DN: $CD4^{-}CD8^{-}$) $B220^{+}$ T cells. DN T cells are autoreactive (21) and expanded in SLE patients (22), making this model specifically relevant to SLE pathogenesis. *Lpr* corresponds to non-functional transcripts of the *Fas* gene, a major regulator of apoptosis in immune cells (23). Both male and female MRL/*lpr* mice are affected and produce of autoantibodies against dsDNA and Sm, leading to large amounts of IC that induce renal and skin pathology (7). MRL/*lpr* mice develop a massive lymphadenopathy that is not observed in SLE patients. However, in addition to expanded DN T cells, this model has the advantage of a rapid and severe disease development as compared to the other spontaneous models. Notably, the MRL/*lpr* strain has been used to dissect the role of TRL7 and TLR9 in lupus (24), to compare TLR activation in B cells and dendritic cells (25), and to dissect the development of extrafollicular autoreactive B cells (26) *. In addition, B6.*lpr* mice, which develop systemic autoimmunity without clinical pathology and a reduced lymphadenopathy, have been used to investigate various pathways, including the involvement of Th17 T cells in lupus (27).

4. BXSB/*Yaa*

A recombinant inbred strain derived from the backcross of (B6 X SB/Le) F1 to SB/Le, termed BXSB/Mp (BXSB/*Yaa*), develops a lupus-like disease with lymphoid hyperplasia, IC-mediated nephritis, ANA and high-serum retroviral glycoprotein gp70 titers (7, 28). Nephritis leads to the death of BXSB/*Yaa* males in about 5 months and BXSB females in 14 months. The rapid-onset disease in males is attributable to the Y-autoimmune accelerator (*Yaa*) locus, which is due to a translocation from the X to the Y chromosome, duplicates 16 genes, including TLR7 (29, 30). TLR7, regulates the activation of the type 1 IFN pathway by ribonucleic acid complexes, a critical pathway in SLE pathogenesis (31). Therefore, in spite of its presentation in males, the BXSB/*Yaa* strain is uniquely suited to model the consequences of an overeactive TLR7/Type 1 IFN pathway.

Induced mouse models of SLE

1. Pristane-Induced lupus

Pristane is an isoprenoid alkane found at high concentration in mineral oil. Intraperitoneal injection of pristane is a standard method to obtain ascitic fluid enriched in monoclonal antibodies. Anti-ribonucleoprotein, anti-DNA and anti-histone autoantibodies are found in BALB/c mice after pristane injections. Pristane-treated mice also have IC deposition in the kidney causing severe nephritis (32). Strain differences in the response to pristane have been

observed (33), illustrating the role of gene/environment interactions in lupus susceptibility. Pristane-induced lupus is more severe in females than in males, at least in the SJL strain (34). Pristane-induced lupus is driven by a strong type 1 IFN response (35), and this model is therefore well-suited to investigate the type 1 IFN signature present in many SLE patients, but much weaker in spontaneous mouse models of this disease. This model is also useful to test the impact of a specific gene on lupus development directly in a non-autoimmune strain, such the protective effect of TLR9 evaluated in BALB/c.Tlr9$^{-/-}$ mice treated with pristane (36)*****.

2. Chronic graft-versus-host disease (cGVHD) models

Induced cGVHD models require injections of donor lymphocytes into a semi-allogenic recipient to induce a lupus-like syndrome. In the parent → F1 model, DBA/2 strain spleen cells are injected into (C57BL/6 X DBA/2) F1 (BDF1) recipients while in the other, B6 spleen cells are injected into class II MHC-missmatched B6.bm12 recipients or reversely. In both models, donor CD4^{+} T cells react to host B cells triggering the polyclonal activation of autoreactive B cells, and eventually, lupus-like syndrome (10). Compared with the other models, cGVHD is easy to control, adjustable to investigator's needs, and generally presents with a reduced inter-individual variability. In addition, autoimmune and clinical manifestations of SLE develop relatively rapidly over a period of weeks, instead of months for the other models. Finally, because the activation and expansion of donor T cells play an essential role in cGVHD response, it is easy to track them relative to host cells by flow cytometry. These models also allow the study of the effect of treatments or genetic modifications in donor cells to alter the course of the cGVHD response. The bm12 model is particularly useful to test the effect of single genes or alleles on the development of systemic autoimmunity on a B6 genetic background. This approach has been used to evaluate *Slamf6* isoforms as lupus susceptibility alleles for the *Sle1b* locus (37, 38), and to identify the association of a naturally occurring polymorphism in the G-CSF gene with resistance to autoimmune activation (39, 40).

Recent investigations of therapeutic targets with mouse models of lupus

Table 2 lists recent treatments or genetic approaches that have been used in mouse models of lupus.

1. T cell targets

Cellular metabolism has been identified as a major checkpoint of CD4^{+} T cell effector functions (67). Consequently, manipulating T cell metabolism may be a promising avenue to treat immune-related diseases (68). In lupus mice as well as SLE patients, CD4^{+} T cells have an elevated metabolism. Treatment with a combination of metformin and glucose inhibitor 2-deoxyglucose normalized T cell metabolism and reversed disease in several mouse models of SLE (41**, 42*). Natural compounds isogarcinol and quercitrin ameliorated disease in a cGVHD mouse model by decreasing CD4^{+} T cell activation as well autoantibody production (43, 44). Quercitrin is a derivative of quercetin, a glycolytic inhibitor, suggesting that metabolic inhibition was a mechanism responsible for the therapeutic effect.

The interactions between B7-1 and 2 on the B cell/antigen presenting cell side and CD28/CTLA-4 on the T cell side are cardinal regulatory pathway of the immune response, and there have been numerous attempts to target them therapeutically (69). Based on studies in mouse models, CTLA-4-Ig (abatacept) is now in clinical trial for the treatment of lupus nephritis (70). In the pristane-induced lupus model, the specific blockade of the interaction between B7-1 and CD28 decreased serum ANA and anti-dsDNA IgG (45).

T follicular help cells (Tfh) are a $CD4^+$ helper T cell subset specialized for provision of help of B cells which plays an essential role in germinal center (GC) formation, affinity maturation and the development of most high-affinity antibodies (71). Tfh cells are expanded in mouse models of lupus, and the level of circulating Tfh cells correlates with disease severity in SLE patients (72). Consequently, therapeutic targeting of Tfh cells has been proposed for SLE patients and lupus mouse models through the IL-21, ICOS, OX40 pathways,. Genetic approaches or a soluble IL21R-Fc protein have demonstrated that blocking the IL-21 pathway prevented or greatly ameliorated disease in several mouse strains (52*, 73). A recent pre-clinical study showed that treatment of B6.Sle1.*Yaa* mice with an anti-IL-21 antibody reduced GC B cells, $CD138^{hi}$ plasmablasts, IFN-γ-dependent IgG2c production, and autoantibodies, indicating that Tfh cell-derived IL-21 is critical for pathological B cell cues in lupus (49). However, targeting the IL-21 pathway may have unintended consequences in $CD8^+$ T cells. In BXSB.Yaa, IL-21 signaling is essential for the maintenance of $CD8^+$ suppressor T cells (74). Moreover, in the parent → F1 cGVHD model, treatment with IL-21 strongly promoted donor $CD8^+$ T cell expansion and rescued defective donor anti-host CTLs, resulting in host B cell elimination, decreased autoantibody levels, and attenuated renal disease, despite evidence of concurrently enhanced $CD4^+$ T cell help for B cells (50*). Another approach to eliminate Tfh cells has been to target ICOS/B7RP-1 interactions. Treatment of NZB/WF1 mice with an anti-B7RP-1 antibody decreased the number of Tfh cells and GC B cells and ameliorated disease manifestations (47). It is also been reported that the selective ablation of ICOS ligand in $CD11c^+$cells, but not in B cells, dramatically ameliorated kidney and lung inflammation in MRL/*lpr* mice (48)**.

2. B cell targets

BAFF is a cytokine that is required for B-cell development and survival. Largely based on studies in mouse models (75), BAFF blockade has been the first and only biologic treatment approved to treat lupus. BAFF also plays a previously unappreciated role in lupus nephritis by inducing renal tertiary lymphoid structures and regulating the position of T cells in the glomeruli of MRL/*lpr* mice (54). Moreover, genetic approaches in the NZM2328 mice demonstrated that the three BAFF/APRIL receptors (BAFF-R, TACI and BCMA) have compensatory roles, suggesting a therapeutic benefit to target multiple receptors (55).

Bruton's tyrosine kinase (Btk) regulates signaling downstream of the B cell receptor and Fcγ receptor and it is also involved in TLR signaling. Treatment with Btk inhibitors alleviate lupus symptoms in MRL/*lpr* (56), NZB/WF1 (57, 58), *B6.Sle1.Sle3* (76), and BXSB.Yaa mice (59) as well as in pristane-induced lupus (59). Overall, based on these pre-clinical studies, FDA-approved Btk inhibitor ibrutinib has great potential as a therapeutic agent in SLE.

Finally, two miRNAs have been identified as potent regulators of B cell tolerance. Elevated miR-148a expression impaired B cell tolerance by promoting the survival of immature B cells after engagement of the B cell receptor by suppressing the expression of the autoimmune suppressor Gadd45α, the tumor suppressor PTEN and the pro-apoptotic protein Bim. Increased expression of miR-148a, facilitated the development of lethal autoimmune disease in MRL/*lpr* mice (60)**. Reduction of miR-148a expression upregulated PTEN in the glomeruli and improved renal function in MRL/*lpr* mice. (77). Conversely, miR155 is overexpressed in B cells from B6.*lpr* mice, and miR155 deletion decreased B cell activation, autoantibody production and autoimmune pathology (61).

3. Other targets

Abundant ICs can trigger the activation of the NLRP3 inflammasome in macrophages in SLE patients and in mouse models, leading to cell dysfunction and tissue damage (78). In the NZB/WF1 model, a NLRP3 inhibitor termed “Citral” alleviates lupus symptoms by inhibiting levels of ROS, NAPDH and COX-2 (63). In the pristane-induced model, a more severe lupus-like syndrome developed in mice carrying the $Nlrp3^{-R258W}$ gain-of-function mutation, providing evidence that NLRP3 plays a role in the development of SLE (64). In a related pathway, serine/threonine kinase IL-1R–associated kinase (IRAK)4 is a regulator of innate immunity involved in TLR signaling. Treatment with an IRAK4 inhibitor ameliorate lupus symptom in NZB/WF1 and MRL/*lpr* mice (65). Finally, It has been proposed that topoisomerase I plays a role in anti- dsDNA antibody binding, and treatment with a topoisomerase inhibitor prevented proteinuria and prolonged survival in MRL/*lpr* mice (66).

Conclusions

The use of murine models has led to discovery of potential therapeutic targets in diverse signaling pathways dysregulated in SLE. Immune cells including T cells, B cells, antigen presenting cells and macrophages, are all potential targets in different models of SLE (Figure 1). Clinical lupus is an extremely complex and diverse disease, and establishment of a mouse model with all features of the disease is very difficult. Various mouse models of SLE, spontaneous, induced or genetically engineered, have been used during the past 30 years, to answer the question of how the alteration of the immune system and target organs leads to break of tolerance to self.

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Key Points

- Spontaneous and induced models of lupus models are useful tools for the study of the etiology and mechanisms of the disease.
- Mouse models of lupus have advanced the field through the identification therapeutic targets and the evaluation of corresponding treatments in pre-clinical studies.
- Each model shares specific subsets of attributes with the disease observed in humans, which provides investigators a tool to tailor to their specific needs.

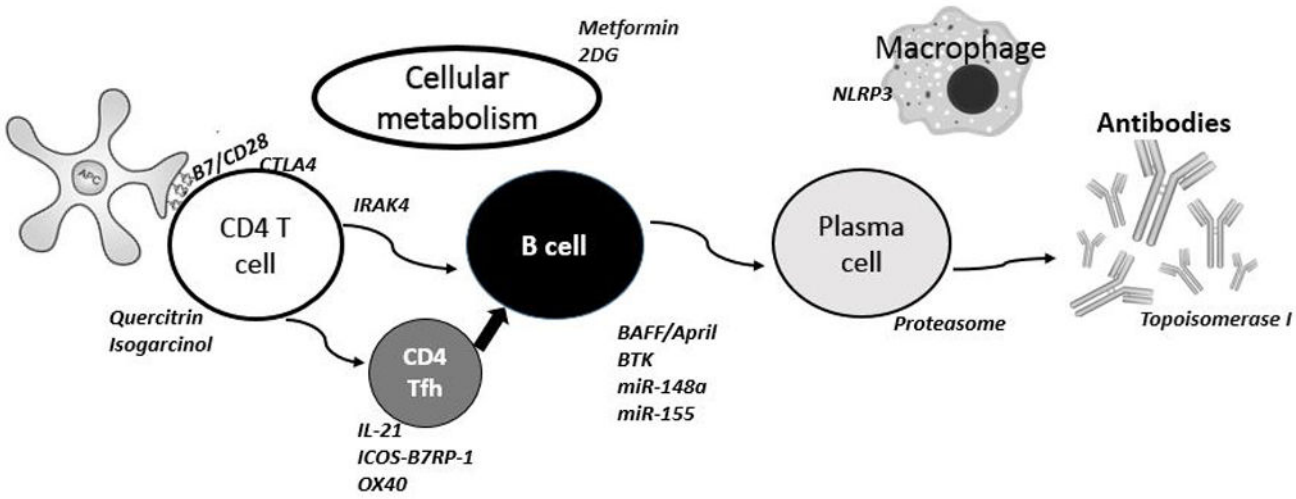

Figure 1.
Potential therapeutic targets investigated in mouse models of SLE.

Table 1

Classical mouse models of lupus.

Mouse Model	Generation/Protocol	Sex Bias	Main Clinical Manifestations
Spontaneous Models			
NZB/W F1[3]	F1 hybrid between NZB and NZW strains	Female	Lymphadenopathy, splenomegaly, Anti-dsDNA IgG, IC-mediated GN
NZM2410/2328[4–6]	Backcross between NZB/W F1 and NZW followed by brother-sister mating	Female	Overlaps with NZB/W F1
MRL/*lpr*[7]	*lpr* mutation in Fas gene on MRL background	Both	Lymphadenopathy due to accumulation of DN B220$^+$ T cells, DNA and RNA-directed autoantibodies, IC-mediated GN and dermatitis
BXSB/*Yaa*[8]	Backcross of (B6 X SB/Le) F1 to SB/Le	Male	Lymphadenopathy, anti-DNA, RNA and gp70 autoAbs, monocytosis, IC mediated GN.
Induced Models			
Pristane-Induced lupus[9]	*i.p* injection of pristane	Female	Type I interferon mediated, AutoAb, GN, arthritis, anemia, serositis (strain dependent)
cGVHD[10]	1) DBA -> BDF1 (injection of spleen cells)	Female	AutoAb, GN, polyclonal B-cell and T-cell activation, proteinuria (CD8+ T cell dependent)
	2) B6 <-> B6.Bm12 (injection of spleen cells)	Female	AutoAb, GN, polyclonal B-cell and T-cell activation, proteinuria (donor CD4+ T cell dependent)

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Table 2

Treatments tested in mouse models of SLE

Gene Target	Cell Target	Model	Treatment	Main manifestations	Ref
T cell targets					
Cellular metabolism	CD4 T cells	B6.Sle1.Sle2.Sle3BWF1B6.*lpr*	Metformin,2-deoxyglucose	autoAb↓, GN↓immune activation↓	(41, 42)
Cellular metabolism	CD4 T cells	cGVHD	Isogarcinol	Proteinuria↓, autoAb↓, GN↓	(43)
Cellular metabolism	CD4 T cells	cGVHD	Quercitrin	Proteinuria↓, autoAb↓, GN↓	(44)
B7-1	T-cell-APC interaction	Pristane-induced	B7-1 shRNA and anti-B7-1 mAb	ANA↓, anti-dsDNA IgG↓	(45, 46)
ICOS-B7RP-1	Tfh	BWF1	Anti-ICOS-B7RP-1	Proteinuria↓, anti-dsDNA IgG↓	(47)
ICOS-B7RP-1	Tfh	MRL/*lpr*	ablation of ICOS ligand in $CD11c^{+}$ cells	Kidney/lung inflammation↓	(48)
IL-21	Tfh	B6.Sle1.Yaa	Anti-IL-21 MAb	GC B cells↓, CD138hi↓IgG2c↓, autoantibodies↓	(49)
IL-21	Tfh	cGVHD	IL-21	host B cell↓, autoantibody↓, renal disease↓	(50)
IL-21	Tfh	MRL/*lpr*, BWF1, BXSB	IL-21R Fc	IgG↓, proteinuria↓, anti-dsDNA↓	(51–53)
B cell targets					
BAFF	B cells	MRL/*lpr*	BAFF-R Fc	Tertiary lymphoid structures and nephritis↓	(54)
BAFF	B cells	NZM2328	KO BCR3 with TACI or BCMA	BAFF-BCMA and/or BAFF-TACI combinations contribute to SLE,	(55)
BTK	B cells	BWF1, MRL/*lpr*, pristane-induced, BXSB	Various Btk inhibition	GN↓, ANA↓, IC↓	(56–59)
miR-148	B cells	MRL/*lpr*	Increased miR148	GN↓	(60)
miR-155	B cells	B6.*lpr*	miR155 KO	ANA↓ B cell signaling↓	(61)
Proteasome	Plasma cells	BWF1, MRL/*lpr*	Proteasome inhibitor	ANA↓, GN↓, Survival↑	(62)
Other Targets					
NLRP3	Macrophages	BWF1	NLRP3 inhibitor	ROS/NAPDH/COX-2↓, GN↓	(63)
NLRP3	Macrophages	Pristane-induced	NLRP3 gain-function	proteinuria↑ and GN↑	(64)
IRAK4	TLR pathway	BWF1, MRL/*lpr*	IRAK 4 inhibitor	proteinuria↓, dsDNA↓, GN↓	(65)
Topoisomerase I	dsDNA binding	MRL/*lpr*	Topoisomerase I inhibitor	nephritis and skin lesions↓	(66)

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