

CHAPTER

4

Genetics of Lupus in Mice

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Just over 50 years ago a report of spontaneous autoimmune hemolytic anemia in the NZB/B1 lupus strain [1] provided the first example of a lupus-related manifestation in mice and supported the possibility of this autoimmune disease being an inherited trait. Since then, the importance of genetic predisposition in SLE has been firmly established and recent linkage and association studies have identified many chromosomal regions linked to lupus traits as well as likely candidate genes [2]. Mice, which appear highly susceptible to lupus compared to other autoimmune diseases, have continued to serve an important role in genetic studies of SLE by facilitating the definition of specific genes that promote or inhibit lupus, the characterization of gene-related immunopathogenic mechanisms, and the delineation of gene interactions. This has substantially expanded the scope of genetic variations implicated in the development, severity, and types of lupus phenotypes as well as significantly deepened understanding of the basic underlying etiopathologic processes. Concomitant with this has been a growing constellation of mouse models from which have resulted a greater appreciation for the complexity of genetic susceptibility in SLE and a reconsideration of how knowledge of the genetics of SLE might impact the clinical arena.

MOUSE MODELS OF LUPUS

The availability of a broad range of lupus-prone strains, both spontaneous and induced, has made it possible to study the genetics of lupus in more detail than any other autoimmune disease (Table 4.1). The most commonly studied spontaneous models are the MRL-*Fas*^{lpr}, (NZBxNZW)F1 (BWF1) hybrid, and BXSB mice, strains that share characteristics such as hypergammaglobulinemia, antinuclear antibodies and glomerulonephritis (GN), and also possess unique features, such as arthritis and expanded CD4⁺CD8⁻

(double-negative, DN) T cells in MRL-*Fas*^{lpr} mice, hemolytic anemia in NZB mice, and monocytosis in BXSB mice. Details of the clinical manifestations and immunopathology for these and other mouse models of lupus models have been previously reviewed [3, 4].

Several recombinant inbred (RI) lines, derived from crosses of lupus-prone and non-autoimmune strains have also been generated (Table 4.1). These manifest a spectrum of phenotypes consistent with polygenic inheritance of traits. RI lines, derived from the NZB and NZW⁺ strains (NZM/Aeg2410 and NZM/Aeg2328), have been useful for studying recessive susceptibility genes. The BXD2 RI line derived from the non-autoimmune B6 and DBA/2 strains was recently discovered to develop lupus-like manifestations as well as erosive inflammatory arthritis [5]. This and other models have shown that significant autoimmune predisposing alleles are present in non-autoimmune strains. Interval-specific congenic strains with introgressed genomic regions encompassing susceptibility loci have also provided another important resource for genetic studies. Two such notable examples are the B6.*Sle* set congenics and the B6-*Fcgr2a*^{-/-} Yaa strain, which are discussed below.

In addition, gene knockout/knockin, transgenic, or mutagenic manipulation of non-autoimmune background strains has generated a large number of novel autoimmune mouse models with manifestations similar to spontaneous SLE (see below and Table 4.4). These strains provide insights into the potential contribution of individual genes in SLE and, in combination, a framework from which to build models of both immunopathologic processes and overall disease pathogenesis.

DISSECTING THE GENETICS OF LUPUS IN MICE

Genetic alterations that modulate lupus susceptibility in mice represent a continuum ranging from those that

TABLE 4.1 Spontaneous and induced mouse models of lupus

SPONTANEOUS DISEASE MODELS

NZ and related strains

NZB

NZW

(NZBxNZW)F₁(NZBxSWR)F₁

(NZBxNZW) recombinant inbred (RI) lines "NZM/Aeg" lines [316]

(NZBxSM)RI lines "(NXSM)RI"

(NZBxC58)RI lines "(NX8)RI"

MRL (*Fas*^{lpr} and wild-type) and related strainsMRL-*Fas*^{lpr}II (long-lived substrain) [317]MRL-*Fas*^{lpr},Yaa [318]SCG/Kj-*Fas*^{lpr} (BXSByMRL-*lpr*)RI [319]

BXSBy and related strains

BXSBy-II (long-lived; separate B6xSB/Le RI line) [320, 321]

(NZWxBXSBy)F₁(NZBxBXSBy)F₁

BXD2 [5]

(SJLxSWR)F₁ [322]

Palmerston North [323]

Motheaten strains [195, 196, 324]

INDUCED DISEASE MODELS

Heavy metal-induced autoimmunity [325]

Drug-induced lupus [326]

Pristane (TMPD)-induced [327]

Anti-idiotypic [328]

Graft-versus-host disease

BCG-injected NOD [329, 330]

Bovine thrombin-exposed galactose-alpha1-3-galactose-deficient mice [331]

reverse approach, which tests the effects of specific gene mutations on the development of lupus in normal or lupus-prone strains, has been used to identify genes with potential to predispose and/or suppress disease.

PREDISPOSING LOCI AND GENES IN SPONTANEOUS LUPUS MOUSE MODELS

Identification of genes predisposing to quantitative traits, such as those associated with lupus, typically involves four major steps: (1) trait mapping performed by genome-wide scans; (2) generation and analysis of interval-specific congenic strains to confirm mapping results and to identify the major intermediate phenotypes; (3) generation of smaller interval congenics to finely map the location of the susceptibility gene or genes; and (4) identification of candidate gene variations within the fragment selected on the basis of expression, structure, function or other characteristics.

Genome-wide scans to map lupus-associated manifestations have been performed in crosses of the four major lupus-prone strains and several induced or genetically manipulated models. Over 85 named and additional unnamed loci linked to one or more lupus traits distributed over all 19 of the mouse autosomal chromosomes have been identified (Table 4.2). Some loci, identified by different groups, appear likely to represent the same variant, whereas most others are unique loci. Susceptibility in these strains seems to be caused by different sets of a few major loci rather than a large number of common ones.

Several loci have been confirmed with interval congenic mice. These included *Sle1*, *Cgnz1*, *Nba2*, *BXSB1-4*, *Sle16*, and *Mag* (on chromosome 1); *Sle18* (chromosome 3); *Sle2*, *Adnz1*, *Lbw2*, and *Lmb1* (chromosome 4); *Lmb2* (chromosome 5); *Sle3*, *Sle5*, *Nba5*, *Lmb3* (chromosome 7); *Lmb4* (chromosome 10); *Ssb2* (chromosome 12); *Sgp3* and a NZB locus (chromosome 13); and *Sles1* (chromosome 17) [6–28]. These congenics, by isolating single chromosomal regions on new stable backgrounds, permit detailed examination of the effects of a single locus on immune and autoimmune responses. This is currently the most definitive and sensitive method for confirming quantitative trait loci (QTL) and provides the initial basis for precise mapping and gene identification. Characterization of these interval congenic mice has identified specific cellular, developmental, functional, and/or autoimmune phenotypes associated with the specific introgressed QTL intervals.

Studies of interval congenics have provided important insights about the genetic transmission of lupus beyond those obtained from QTL mapping studies that are likely also applicable to human SLE. (1) Phenotypes induced by QTLs in congenic mice do not always correlate with initial mapping studies and may range from no

can alone promote the development of severe lupus in otherwise normal strains to others that completely suppress disease development, with most residing between these extremes. Studies to identify such genetic changes have utilized both forward (phenotype→gene) and reverse (gene→phenotype) approaches. The forward approach, which finds genes based solely on their chromosomal location, has been used to identify predisposing loci and genes in both spontaneous and induced models, including conventional, mercury-induced, and ENU mutagenesis-derived. While the

TABLE 4.2 Susceptibility loci predisposing to lupus-related traits

Name	Chr	Mb	Best assoc Marker	Cross	Phenotype	Parental allele	Ref.
Bxs4	1	20	D1Mit3	B10×(B10×BXS)F1	LN	BXSB	[332]
Bxs1	1	64	D1Mit5	BXS _B ×(B10×BXS)F1	GN/ANA/spleen	BXSB	[333]
—	1	90	D1Mit48	(WxBa)F1×W	IgM ssDNA/IgM histone	BALB/c	[334]
Bxs2	1	63 cM	D1Mit12	BXS _B ×(B10×BXS)F1	GN/ANA/spleen	BXSB	[333]
—	1	129	D1Mit494	MRL-lpr _x (MRL-lprxC3H-1pr)F1	sialadenitis	MRL	[335]
Bana3	1	155	D1Mit396	(NOD×Ba)×NODBC	ANA (M.bovis)	NOD	[330]
Swrl1	1	170	D1Mit15	Bx(SWRxB)F1	dsDNA/histone	SWR	[336]
Slc1	1	170	D1Mit15	(NZMxB6)×NZM	GN	NZM (NZW)	[337]
Hmr1	1	170	D1Mit15	(NZMxB6)F2	dsDNA/GN/spleen	NZM(NZW)	[338]
—				(SILxDBA/2)F2	glom. dep. (HgIA resistance)	DBA/2	[339]
Slc16	1	170	D1Mit15	(129xB6)F2	ANA	129	[29]
—				(BxDBA/2)F2	glom. dep. (HgIA resistance)	DBA/2	[339]
Cgnz1	1	171	D1Mit36	(NZM2328xC57L)F1×NZM2328	chronic GN	NZM2328 (NZW)	[340]
Ldw7	1	171	D1Mit36	BWF2	chr/spleen	NZB	[341]
Nba2	1	171	D1Mit11	(BxSM)×W	GN	NZB	[342]
—				(BxSM)×W/(B6.H2 ^z xB)×B	ANA/bp70IC/GN	NZB	[343]
—				((B6.H2 ^z & Ba.H2 ^z)xB)F1xB	GN	NZB	[344]
Bxs3	1	178	D1Mit403	BXS _B ×(B10×BXS)F1	dsDNA	BXSB	[333]
Agnz1	1	184	D1Mit37	(NZM2328xC57L)F1×NZM2328	acute GN	NZM2328 (NZW)	[340]
—	1	191	D1Mit17	(WxBa)F1×W	ssDNA	NZW	[334]
Swrl5	1	191	D1Mit17	(SWRxB)F2	hyperIgG	SWR	[345]
Mag	1	82–100 cM	B6.MRLcl(82-100) congenic	B6.MRLcl(82-100) congenic	sp1/dsDNA/GN	MRL	[26]
—	2	103	D2Mit12	(MRL-lprxBa)F2	ssDNA/dsDNA	MRL +/+ ,pr/+	[346]
Rends (Wbw1)	2	153	D2Mit285	(WxPL)F1xB	mortality/GN	NZW	[347]
—				BxD RI	DNA	DBA/2	[5]
Slc2	3	79	D3Mit37	(B6.NZMc1xW)F1xW	dsDNA/GN (resistance)	NZW	[37]

(Continued)

TABLE 4.2 Susceptibility loci predisposing to lupus-related traits—cont'd

Name	Chr	Mb	Best assoc Marker	Cross	Phenotype	Parental allele	Ref.
BxS5	3	87	D3Mit40	B10x(B10xBxSB)F1	ANA/IgG3	BxSB	[332]
Sle18	3	125	D3Mit13	(129xB6)F2	ANA	129	[29]
Lprm2	3	137	D3Mit16	MRL-lprx(MRL-lprxC3H-lpr)F1 (BxBa,H2 ⁺)F2	vasculitis (resistance)	MRL	[348]
Nbw2	4	35	D4Mit11	(MRL-lprxC3H-lpr)BC & F ₂	GN/dsDNA	NZB	[349]
Arvm1	4	46	D4Mit89	(MRL-lprxC3H-lpr)BC & F ₂	vasculitis	MRL	[40]
Agnm1	4	56	D4Mit241	(MRL-lprxC3H-lpr)F ₂	GN	MRL	[350]
Lprm1	4	64	D4Mit82	MRL-lprx(MRL-lprxC3H-lpr)F1	vasculitis	MRL	[348]
Acl2	4	83	D4Mit79	W _x (WxBxSB)F1	CL	BxSB	[351]
Sle2	4	95	D4Mit9	(NZMxB6)xNZM	GN	NZM (NZW)	[337]
Spm1	4	99	D4Mit58	(B6xNZB)F ₁ xNZB	spleen	NZB	[352]
Adaz1	4	50 cM	D1Mit36	(NZM2328xC57L)F1xNZM2328	dsDNA	NZM2328	[340]
Agnm2	4	100	D4Mit187	(MRL-lprxC3H-lpr)F ₂	GN	MRL	[350]
Asm2	4	112	D4Mit199	MRL-lprx(MRL-lprxC3H-lpr)F1	stomatitis	MRL female	[335]
Lmb1	4	124	D4Mit12	(B6-lprxMRL-lpr)F ₂	B6	[353]	
Lbw2	4	124	D4Nds2	BWF2	mortality/GN/spleen	NZB	[341]
Sles2	4	124	D4Mit12	(B6,NZM1xW)F1xW	dsDNA/GN (resistance)	NZW	[37]
—	4	134	D4Mit70	(BxSM)xW	GN	NZB	[342]
Arvm2	4	125	D4Mit147	(MRL-lprxC3H-lpr)BC & F ₂	vasculitis	MRL	[40]
nba1	4	131	Epb4.1(ep-1)	BWF1xW	GN	NZB	[354]
Imh1/Mott	4	141	D4Mit48	BWF1xW	hyper IgM/GN/dsDNA	NZB	[355, 356]
Sle6	5	36	D5Mit4	(B6,NZM1xNZW)F1xNZW	GN	NZW	[37]
Nbba5	5	41	D5Mit353	(SWRxB)F2	GN	NZB	[345]
Lmb2	5	74	D5Mit356	(B6-lprxMRL-lpr)F ₂	lprx/dsDNA	MRL	[353]
Lprm4	5	54 cM	D5Mit23	MRL-lprx(MRL-lprxC3H-lpr)F1	spleen	MRL	[348]
Agnm3	5	105	D4Mit187	(MRL-lprxC3H-lpr)F ₂	GN	MRL	[350]
Lbw3	5	142	D5Mit101	BWF2	mortality	NZW	[341]
—	6	84	D6Mit8	MRL-lprx(MRL-lprxC3H-lpr)F1	GN (resistance)	MRL	[357]

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Lbw4	6	65 cM	D6Mit25	BWF2	mortality	NZB	[341]
—	6	134	D6Mit374	(NZMxB6)F2	dsDNA	B6	[338]
Sle5	7	3	D7Mit178	(NZMxB6)F2	dsDNA	NZM(NZW)	[338]
Lrdm1	7	26	Pou2F(Otf-2)	(MRL-lprxCast)F1xMRL-lpr	GN	MRL	[358]
Sle3	7	38	D7Mit25	(NZMxB6)F2	GN	NZM(NZW)	[338]
Lbw5	7	51	D7Nds5(Ngfg)	BWF2	mortality	NZW	[341]
Lmb3	7	28 cM	D7Mit211	(B6-lprxMRL-lpr)F2	Lprn/dsDNA	MRL	[353]
Sle3	7	63	P	(NZMxB6)xNZM	GN	NZM (NZW)	[337]
Aem2	7	89	D7Mit30	(B6xB)F1xB	RBC	NZB	[352]
—	7	116	D7Mit17	(BxSM)xW	GN	NZB	[342]
—	7	126	D7Mit7	(BxW)F1xW	dsDNA	NZB	[359]
Myo1	7	150	D7Mit14	Wx(WxBxSB)F1	MI	BxSB	[351]
Pbat2	8	31	D8Mit96	Wx(WxBxSB)F1	platelet	BxSB	[351]
Asbb1	9	37	D9Mit67	(B6xBa)F2-FcγRIIb ^{-/-}	spleen (FcγRIIb ko)	BALB/c	[360]
Baa1	9	49	D9Mit22	(WxBa)F1xW	IgM ssDNA/IgM histone	BALB/c	[334]
Gpl1	9	105	D9Mit53	BxSBx(B10xBxSB)F1	gp70IC	BxSB	[361]
Baa2	9	114	D9Mit81	(BxBa,H2 ^Z)F2	Tubulointerstitial damage	BALB/c	[349]
Bana2	10	20	D10Mit213	(NODxBa)xNODBC ⁺	ANA (M.bovis)	BALB/c	[330]
Asm1	10	70/72	D10Mit115/259	MRL-lprx(MRL-lprxC3H-lpr)F1	sialadenitis	MRL	[335]
Aem3	10	82	D10Mit42	(B6xB)F1xB	RBC	NZB	[352]
Lmb4	10	92	D10Mit11	(B6-lprxMRL-lpr)F2	Lprn/GN	MRL	[353]
—	10	122	D10Mit35	(NZMxB6)F2	GN	NZM & B6 [#]	[338]
—	10	125	D10Mit297	(B10,A ^Z xB)F1xB	chr	B10	[362]
—	11	12/34	D11Mit2/84	(Ba,H2zxB)F1xB	GN	NZB	[344]
—	11	45	D11Mit20	(NZMxB6)F2	GN/dsDNA	NZM	[338]

(Continued)

TABLE 4.2 Susceptibility loci predisposing to lupus-related traits—cont'd

Name	Chr	Mb	Best assoc Marker	Cross	Phenotype	Parental allele	Ref.
Lbw8	11	53	IL4	BWF2	chr	NZB	[341]
—	11	55	D11Mit207	(W \times Ba)F1 \times W	ssDNA	NZW	[334]
—	11	94	D11Mit70	(MRL-lpr \times Ba)F2	dsDNA/ssDNA/CL	MRL	[346]
Nbw1	12		D12Mit291	(Bx \times Ba)H2 z)F2	ANA/GN/gp70IC/RBC	NZB	[349]
Asbb2	12	25	D12Mit12	(B6 \times Ba)F2-FcγRIIB $^{-/-}$	ANA (FcγRIIB ko)	B6	[360]
Lrdm2	12	27 cM	D12NyU3	(MRL-lpr \times CAST)F1 \times MRL-lpr	GN	MRL	[358]
Sta-1	12	30	D12Mit85	(NZB \times NZW)F1 \times NZW	CD4 T cell activation	NZB	[363]
Bxs6	13	64	D13Mit253	BXS \times (B10 \times BXS \times B)F1 and B10 \times (B10 \times BXS \times B)F1	gp70/gp70IC	BXS \times B	[361]
Spg3 (Yaa1)	13	56+12	D13Mit250	B6 \times (W \times B6-Yaa)F1	gp70IC	NZW	[364]
Nba6	13	92	D5Mit353	(SWR \times B)F2	dsDNA	NZB	[345]
—	13	104	D13Mit226	(B10.A \times B)F1 \times B	gp70IC/GN	B10	[362]
—	13	115	D13Mit31	(NZM \times B6)F1 \times NZM	dsDNA	NZM	[337]
—	13	115	D13Mit150	(Bx \times SM) \times W	GN	NZB	[342]
—	14	19.5 cM	D14Nds4	(W \times Ba)F1 \times W	histone	NZW	[334]
Swrl2	14	63	D14Mit37	B \times (SWR \times B)F1	GN/dsDNA	SWR	[336]
—	14	72	D14Mit34	((B6.H2 \times & Ba.H2 \times B)F1 \times B	GN	NZB	[344]
Myo2	14	73	D14Mit68	W \times (W \times BXS \times B)F1	MI	BXS \times B	[351]
Iprm3	14	88	D14Mit195	MRL-lpr \times (MRL-lpr \times C3H-lpr)F1	GN (resistance)	MRL	[348]
Paam1	15	32	D15Mit111	MRL-lpr \times (MRL-lpr \times C3H-lpr)F1	arthritis in males	MRL	[365]
Iprm5	16	29	D16Mit3	MRL-lpr \times (MRL-lpr \times C3H-lpr)F1	dsDNA	MRL	[348]
Bah2	16	32	D16Mit58	(NOD \times Ba) \times NODBC	RBC (M.bovis)	BALB/c	[330]

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nwal	16	38 cM	D16Mit5	(W \times Ba)F1 \times W (B \times W)F1 \times W	Histone GN/dsDNA	NZW	[334] [359]
Asbb3	17	28	D17Mit198	(B6 \times Ba)F2-Fc γ RIIb $^{-/-}$	ANA/spleen (Fc γ RIIb ko)	BALB/c	[360]
Aclal	17	34	D17Mit16	W \times (W \times BXSB)F1	CL	NZW/BXSB	[351]
Sles1	17	35	H2/ \times DI7Mit34	(B6.NZMcl \times W)F1 \times W	GN/dsDNA (resistance)	NZW	[37]
Bana1/Bah1	17	38	D17Mit24	(NOD \times Ba) \times NODBC	ANA/RBC (M.bovis)	NOD	[330]
Pbat1	17	19 cM	D17Nds2	W \times (W \times BXSB)F1	platelet	NZW/BXSB	[351]
Wbw2	17	49	D17Mit177	(W \times PL)F1 \times B	mortality/GN	NZW	[347]
Agmnz2	17	88	D17Mit130	(NZM2328 \times C57L)F1 \times NZM2328	acute GN	C57L	[340]
Swrl3	18	40	D18Mit17	B \times (SWR \times B)F1	dsDNA/histone	SWR	[336]
—	18	41	D18Mit227	MRL-lprx(MRL-lprxC3H-lpr)F1	sialadenitis	MRL	[335]
Lbw6	18	75	D18Mit8	BWF2	mortality/GN	NZW	[341]
nwa2	19	42	D19Mit11	(W \times Ba)F1 \times W	ssDNA	NZW	[334]
—	19	50	D19Mit3	(NZM \times B6) \times NZM	dsDNA	NZM	[337]

[#]complex inheritance: either parental strain promotes GN, but heterozygosity protects.

This table includes only named loci with linkages $p < 0.01$ or lod > 1.9 . Loci are listed by their approximate chromosomal locations based on the marker with the highest association. Chr = chromosome. Mb and cM distances are based on the Mouse Genome Informatics (Jackson Laboratory). Abbreviations for mouse strains (Cross column): B = NZB, B6 = C57BL/6, B10 = C57BL/10, Ba = BALB/c, CAST = CAST/Ei, lpr = *Fas^{lpr}*, NOD = NOD/Lt, NZM = NZM/Aeg2410, PL = PL/J, W = NZW, (MRL-lprxC3H-lpr)BC & F2=both MRL-lprx(MRL-lprxC3H-lpr)F1 & (MRL-lprxC3H-lpr)F2 crosses, (NOD \times Ba)NODBC = NOD backcrossed to (NOD \times BALB/c)F1 in all four combinations. Original phenotypes that mapped to loci are shown: chr = anti-chromatin autoantibody, CL = anticalcdiolipin autoantibody, CL = anti-disDNA autoantibody, glom. dep. = glomerular IgG deposits, GN = glomerulonephritis, gp70IC = gp70 IC immune complexes, histone = anti-histone autoantibody, LN = lymphadenopathy, Lpma = lymphoproliferation, MI = myocardial infarct, platelet = antiplatelet autoAb and thrombocytopenia, RBC = antiRBC autoAb, spleen = splenomegaly. Autoantibodies are IgG unless otherwise specified. Table does not include gp70 loci that were not linked to autoimmunity [366]. Induced or genetically modified models are indicated under phenotype in parentheses; M. bovis = *M. bovis* i.v., HgIA = mercury-induced autoimmunity.

*formerly named *elp-1*.

discernable phenotype to the presence of multiple additional effects. Thus, the contribution of variants is often highly dependent on other genes and on some backgrounds may be difficult to detect. (2) The association of QTL to lupus traits is complicated by additive and epistatic interactions. This has been shown using double and triple congenic mice as well as by backcrossing QTL onto more than one background. (3) A single locus when defined in more detail often consists of a cluster of loci. This has been documented for most of the QTL examined with subcongenics, including *Sle1*, *Nba2*, *Sle2*, *Lbw2*, *Sle3*, *Lmb3*, and *Lbw5*. (4) QTLs can have highly specific and unexpected effects on disease pathogenesis. For example, NZM2328 congenic mice (NZM2328.C57Lc4) that have the non-susceptible C57L interval replacing the NZM2328 *Adnz1* locus on chromosome 4, develop selective loss of anti-DNA antibodies, but no reduction in the severity of glomerulonephritis [17]. (5) In terms of identifying the responsible genes, several highly attractive candidates have been subsequently excluded or reduced in significance once subcongenic mice were examined. This demonstrates the limitation of identifying potential genes by candidate or expression screening alone and the necessity of using smaller-interval congenics.

Although a detailed description of the various QTL and related congenics is beyond the scope of this chapter, *Sle16*, a 129-derived chromosome 1 locus, is notable because of its implication for genetically engineered mice that develop lupus-like disease [29] (Table 4.2). The reason for generating this congenic line came from the finding that lupus-like manifestations associated with homozygous SAP knockout alleles (on chromosome 1) appeared to depend on the mixed 129xB6 background and not SAP deficiency [29, 30]. Strikingly, mapping studies showed that lupus-like disease including autoantibodies and immune complex GN developed in (129xB6) hybrids, and autoantibody-prone loci were associated with chromosomes 1 (*Sle16*, 129-derived), 3 (*Sle18*, B6-derived), and 4 (B6-derived) and this was confirmed in B6.*Sle16* and 129.*Sle18* congenic mice [24, 28, 31, 32]. *Sle16* overlaps with *Sle1*, *Nba2*, *Bxs3*, and *Cgnz1*, and may be caused by some of the same genetic variant(s). Thus, because gene knockout mice are commonly analyzed in 129xB6 mixed lines, lupus manifestations might be completely or partially due to this background (Table 4.4).

Several susceptibility or disease-suppressing genes have been identified through mapping and cloning of variants within lupus-related chromosomal intervals (Table 4.3). These include genes involved in apoptosis (*Fas*, *Fasl*, *Ifi202*), T- and/or B-cell activation (*Ly108*, *Fcgr2b*, *Cr2*), actin dynamics (*Coro1a*), TLR-mediated cell activation (*TLR7*, *Yaa*), and antigen presentation (*H-2*). Within the H-2 complex there are several other

potential candidate genes, including TNF [33, 34], complement components C2 and C4 [35], IEX-1 [36] and a recessive NZW locus (*Sles1*) that appears to suppress autoimmunity in NZW mice [37]. Several other possible candidates have also been identified. Among these are CD22 [38], C1q [39], other SLAM family genes [15], CD72 [40], P2X₇ receptor [41], *Baff* [42] and *Marco* [43].

SYSTEMIC AUTOIMMUNITY IN NORMAL BACKGROUND GENE KNOCKOUT/ MUTATED AND TRANSGENIC MICE

The role of specific genes in the immune system and possible mechanisms of systemic autoimmunity are being defined through genetic manipulation of non-autoimmune background strains. Deletion or over-expression of single genes results in remarkable examples of tolerance loss and systemic autoimmunity that have yielded valuable new models to investigate SLE immunopathogenesis. Thus far, there are nearly 100 lupus-modifying genes reported in the literature, but some of these may be due, as noted previously, to the use of mixed background (B6x129). Nevertheless, the differing autoimmune phenotypes produced by the specific genetic changes and the finding of a high frequency of autoimmunity in ENU mutagenized mice wherein a remarkably high 1 in 7 pedigrees develop ANA positivity [44] suggests the plausibility of the large number of potential susceptibility genes. Although the relevance of many of these models to spontaneous disease is uncertain, they have been particularly informative in dissecting molecular studies of potential mechanisms of autoimmunity. Thus far, gene defects have been shown to enhance B- or T-cell activation, expand DCs, inhibit certain apoptotic pathways, alter antigen presentation, reduce clearance of apoptotic bodies or soluble self-antigens, modify cytokine milieu, alter cell signal transduction, reduce glycosylation, and enhance cell cycling, as well as other mechanisms (Tables 4.4 and 4.5). Common mechanisms derived independently from different molecular defects have also emerged. Individual genes organized by the most likely mechanism will be discussed briefly below with additional details provided in Table 4.4.

B-cell Activation Genes

The fate of B cells following antigen receptor (BCR) engagement is a complex process that involves direct or indirect interaction of the BCR with numerous molecules that can promote or inhibit cell activation. Among these are several tyrosine kinases (lyn, fyn, Btk, Blk, Syk), phosphatases (CD45, SHP-1, SHP-2, and SHIP)

TABLE 4.3 Spontaneous lupus susceptibility or resistant genes

Gene	Chr	Mb	Locus or Allele	Strain*	Type of change	Gene function	Trait In congenic mice	Ref.
Ifi202	1	95.3	Nba2	NZB/B1	Incr. expression	Unknown; anti-apoptotic, cytoplasmic DNA sensor; proliferation	anti-nuclear Ab	[367, 368]
Fasl	1	163.7	gld	C3H/He	Loss-of-function	Pro-apoptotic	lymphoproliferation, DN T cells, autoAbs, GN	[369]
Ly108 (Slamf6)	1	173.8	Sle1b	NZW/Lac	Enhanced function	Co-stimulation	anti-nuclear Ab, impaired B cell tolerance	[370]
Fegr2b	1	172.9		NZB/B1, NZW/Lac	Loss-of-function	Inhibitory signal: B cells, DC, macrophage	autoAb	[371, 372]
Cr2	1	197.0	Sle1c	NZW/Lac	Loss-of-function	C3 fragment binding; activation B cells	anti-nuclear Ab	[373]
Corola	7	133.8	Lmb3	B6-Fas ^{lpr} /Scr substrain	Loss-of-function*	Actin dynamics	Impaired migration, TCR-mediated activation, and survival of T cells	[374]
H-2	17	34-36	H2	NZW, BXSB	Variant	Antigen presentation	modifies severity of autoimmunity	[375]
Fas	19	34.4	Lpr, Lpr ^{eg}	MRL/Mp- Fas ^{lpr}	Loss-of-function	Pro-apoptotic	lymphoproliferation, DN T cells, autoAbs, GN	[376, 377]
Tlr7	Y	X-chr dupl.	Yaa	BXSB; SB/Le	Gain-of-function	Activation (ssRNA) B cells, DC	accelerated autoimmunity, enhanced Ab responses to foreign and self-antigens	[376, 377]

* Original strain.

TABLE 4.4 Genes associated with lupus-like manifestations in knockout/mutated and transgenic normal background mice

Name	Gene	Chr*	Mb	Major autoimmune manifestations	Ref.
KNOCKOUT/MUTATED					
CTLA-4	<i>Cd152</i>	1	60.9	multiorgan lymphoproliferative disease, myocarditis, pancreatitis (mixed 129xB6; 129xBALB/c)	[78-80]
PD-1 (programmed cell death 1)	<i>Pdcd1</i>	1	95.9	proliferative arthritis, GN, glomerular IgG3 deposits. (129xB6N11)	[85]
CD45 (protein tyrosine phosphatase, receptor type C)	<i>Ptprc</i>	1	140.0	lymphoproliferation, dsDNA, splenomegaly, GN (mixed 129xB6) no autoimmunity (B6)	[378]
Ro, SS-A (TROVE domain family, member 2)	<i>Trove2</i>	1	145.6	anti-ribosome and anti-chromatin autoAb, GN (129xB6)	[174]
Fasl (spontaneous)	<i>Fasl</i>	1	163.7	lymphoproliferation, DN T cells, autoAbs, GN (gld mutation)	[379]
serum amyloid P component	<i>ApcS</i>	1	174.8	anti-chromatin Ab, GN, female predominance (129xB6) no autoimmunity (B6)	[177]
mannoside acetyl glucosaminyltransferase 5	<i>Mgat5</i>	1	129.1	proliferative GN, enhanced EAE (129)	[114]
roquin (RING CCHC (C3H) domains 1)	<i>Rc3h1</i>	1	162.8	autoAbs, lupus-like disease, incr. follicular T helper cells and GCs. M199R mutation. (B6)	[112]
FcγRIIb (Fc receptor, IgG, low affinity IIb)	<i>Fcgr2b</i>	1	172.9	exacerbates autoimmunity in B6- <i>Fas^{lpr}</i> mice, autoAb, GN, arthritis	[380]. Does this fit here
IL-2R α	<i>Il2ra</i>	2	11.6	lymphoproliferation, hyperIgG, autoAb, anti-RBC Ab (129xB6)	[138]
Nrf2 (nuclear factor, erythroid derived 2, like 2)	<i>Nfe2l2</i>	2	75.5	hyperIgG, anti-dsDNA Ab, GN, splenomegaly (129/B6/ICR); (no disease in MRL- <i>lpr Nfe2l2</i> ^{-/-} , see below)	[207]
Ras GRP1 (RAS guanyl releasing protein 1)	<i>Rasgrp1</i>	2	117.1	spont. recessive mutation prevents translation of Ras GRP1 protein, CD4 $^{+}$ T cells resistant to AIID, lymphoprolif., autoAb (129xB6)	[150]
TYRO3 protein tyrosine kinase 3 (Tyro 3 family)	<i>Tyro3</i>	2	119.6	triple knockout (<i>Tyro3, Axl, Mer</i>): lymphoproliferation, increased activated T and B cells, autoAb, GN (129xB6)	[168]
c-mer proto-oncogene (Tyro 3 family)	<i>Merk</i>	2	128.5	autoAb (<i>Mer</i> knockout alone), (also see TYRO3 above) (129xB6N10)	[170]
Bim (Bcl2-like 11)	<i>Bcl2l11</i>	2	128.0	lymphoid/myeloid cell accumulation, autoAb, GN, vasculitis (129xB6)	[129]
IL-2	<i>Il2</i>	3	37.0	lymphoproliferation, hyperIgG, autoAb, anti-RBC Ab (129xB6)	[137]
TSAd (SH2 domain protein 2A)	<i>Sh2d2a</i>	3	87.7	hyperIgG, autoAbs, GN (129xB6N9)	[381]
Shc1 p66 isoform (p66, ShcA)	<i>Shc1</i>	3	89.2	lymphoid hyperplasia, low penetrance autoAb and GN (129)	[110]

TABLE 4.4 Genes associated with lupus-like manifestations in knockout/mutated and transgenic normal background mice—cont'd

Name	Gene	Chr*	Mb	Major autoimmune manifestations	Ref.
lyn	<i>Lyn</i>	4	3.6	enhanced B cell activation, splenomegaly, hyperIgM, autoAb, GN (129xB6)	[45, 46]
	<i>Lyn</i> ^{up/up}			gain of function (Y508F) mutation: autoAb, GN, reduced survival (B6x129 mixed background)	[47]
CD72	<i>Cd72</i>	4	43.5	autoAb, mild GN (129xB6>N7; by genome scan no residual 129 beyond D4Mit53)	[51]
Zinc finger CCCH type containing 12A	<i>Zc3h12a</i>	4	124.8	Lymphoid hyperplasia, early mortality, autoAb, anemia (prob. autoimmune), (mixed 129xB6)	[211]
E2F transcription factor 2	<i>E2f2</i>	4	135.7	enhanced T cell activation, autoAb, GN, widespread inflammatory infiltrates (129xB6)	[107]
C1q α , β , γ polypeptides (different genes)	<i>C1qa</i>	4	—	autoAb, GN (129xB6)	[153, 382, 383]
	<i>C1qb</i>	4	136.5		
	<i>C1qc</i>	4	136.5		
	<i>C1q</i>			Allele — down regulates C1q levels in NZB mice	[39]
GADD45 (growth arrest and DNA-damage-inducible 45 alpha)	<i>Gadd45a</i>	6	67.0	autoAb, GN, mortality (129xB6)	[121]
Docking protein 1	<i>Dok1</i>	6	83.0	<i>Dok1/Dok2</i> dko: autoAb, GN (see chr. 14) (129xB6>N8)	[111]
C-type lectin domain family 4, member a2 (Dcir)	<i>Clec4a2</i>	6	123.1	auto Ab, inflammatory arthritis (129xB6N8)	[180]
SHP-1 (spontaneous)	<i>Ptpn6</i>	6	—	autoAb (<i>me</i> and <i>me^v</i> mutations)	[195, 196]
TGF β 1	<i>Tgfb1</i>	7	26.5	multiorgan lymphocytic and monocytic infiltrates (129xB6)	[77]
AXL receptor tyrosine kinase (Tyro3 family)	<i>Axl</i>	7	26.5	(see TYRO3 above) (129xB6)	
Zfp-36 (tristetraprolin)	<i>Zfp36</i>	7	29.2	complex systemic disease: cachexia, dermatitis, arthritis (129xB6)	[187, 188, 384]
CD22	<i>Cd22</i>	7	31.6	enhanced B cell activation, autoAb (129xB6)	[385, 386]
MFG-E8 (milk fat globule-EGF factor 8)	<i>Mfge8</i>	7	86.3	splenomegaly, incr. GCs, autoAbs, GN, reduced engulfment of apoptotic cells (129xB6)	[160]
LAT (linker for activation of T cells)	<i>Lat</i>	7	133.5	mutation inhibits T cell development, but induces Th2 cell lymphoproliferation and polyclonal B cell activation (129xB6)	[98]
PLC γ 2	<i>Plcg2</i>	8	120.0	D993G (ENU) gain-of-function; arthritis (C3H); autoAb and GN (C3HxB6N2-3; wt littermates were normal)	[66]
Cbl ko (B cell only)	<i>Cbl</i>	9	44.0	(<i>Cbl/Cblb</i> dko; B cell conditional ko) autoAb, GN (mixed 129xB6)	[103]

(Continued)

TABLE 4.4 Genes associated with lupus-like manifestations in knockout/mutated and transgenic normal background mice—cont'd

Name	Gene	Chr*	Mb	Major autoimmune manifestations	Ref.
Three prime repair exonuclease 1	<i>Trex1</i>	9	109.0	Aicardi-Goutieres syndrome (AGS) and chilblain lupus; mice:	[171, 172]
PCMT (protein-L-isoaspartate (D-aspartate) O-methyltransferase 1	<i>Pcm1</i>	10	7.3	wild-type mice reconstituted with PCMT(-/-) BM develop high titer anti-DNA Ab and GN (129xB6)	[118]
fyn (+lyn)	<i>Fyn</i>	10	39.1	synergizes with the <i>Lyn</i> ko to accelerate disease (129xB6)	[387]
Traf3 interacting protein 2 (Act1, CIKS)	<i>Traf3ip2</i>	10	39.3	AutoAb, GN, early mortality, Sjogren's syndrome (129xBALB/c); in another study no B cell hyperactivity or lupus-like disease (129xB6>N10; 129xBALB/cN2)	[60, 388, 389] [61]
TACI (tumor necrosis factor receptor superfamily, member 13b)	<i>Tnfrsf13b</i>	11	60.9	fatal lymphoproliferation, autoAb, GN (129xB6)	[390]
Gadd45β	<i>Gadd45b</i>	10	80.4	splenomegaly, glomerular immune complexes, no autoAbs; synergizes with Gadd45β ^{-/-} to produce marked splenomegaly, dsDNA/histone Abs, immune complex GN. (129xB6)	[122]
Aiolos (IKAROS family zinc finger 3)	<i>Ikzf3</i>	11	98.3	activated B cells, increased IgG, autoAb (129xB6)	[58]
PECAM-1/CD31	<i>Pecam1</i>	11	106.5	enhanced B cell activation, autoAb, GN (129xB6)	[73]
Stra13 (stimulated by retinoic acid 13)	<i>Stra13</i>	11	120.6	lymphoid organ hyperplasia, autoAb, IC GN (B6x129)	[151]
G protein-coupled receptor 132	<i>Gpr132</i>	12	114.1	lymphoid hyperplasia, hyperIgG, autoAb, GN (129xBALB/cN3-6)	[104]
Src homology 2 domain-containing transforming protein C3 (Rai)	<i>Shc3</i>	13	51.5	autoAb, glom. IC dep, mild GN (129xB6N12; 129)	[71]
CD100 (sema domain, immunoglobulin domain, transmembrane domain and short cytoplasmic domain 4D)	<i>Sema4d</i>	13	51.8	suppressed BCR signals, incr MZ B cells, autoAb, GN (129xB6 backcrossed >8 generations with B6)	[52]
Gadd45γ	<i>Gadd45g</i>	13	51.9	synergizes with Gadd45β knockout (chr 10). (129xB6)	[122]
Protein kinase Cδ	<i>Prkcd</i>	14	31.4	splenomegaly, lymphadenopathy, hyperIgM/IgG1/IgG2a, dsDNA, GN (129xB6)	[64]
Docking protein 2	<i>Dok2</i>	14	71.2	<i>Dok1/Dok2</i> dko: autoAb, GN (see chr 6) (129xB6>N8)	[111]
IL-2Rβ (CD122)	<i>Il2rb</i>	15	78.3	lymphoproliferation, hyperIgG, autoAb, anti-RBC Ab (129xB6)	[139]
Dnase1	<i>Dnase1</i>	16	4.0	ANA, immune complex GN (129xB6)	[156]
SOCS-1 (suppressor of cytokine signaling 1)	<i>Socs1</i>	16	10.8	(+/ko), or ko with expr. in lymphocytes: hyperact. lymphocytes, autoAb, GN (129xB6 backcrossed >7 generations to B6)	[193]

TABLE 4.4 Genes associated with lupus-like manifestations in knockout/mutated and transgenic normal background mice—cont'd

Name	Gene	Chr*	Mb	Major autoimmune manifestations	Ref.
Surrogate light chain: (Vpreb1-λ5 and Vpreb2)	<i>Vpreb1</i>	16	16.9	Triple ko: anti-nuclear and cardiolipid autoAb (129xB6, backcrossed to B6 >10 generations, genotyped B6 at Chr 1)	[63]
	<i>Igll1</i>	16	16.9		
	<i>Vpreb2</i>	16	18.0		
Interferon (alpha and beta) receptor 1	<i>Ifnar1</i>	16	91.5	exacerbated disease in MRL-lpr mice: lymphoproliferation, autoAb, GN	[260]
Cbl-b ko Cbl-b (B cell only)	<i>Cblb</i>	16	52.0	multiorgan lymphoid infiltrates, anti-dsDNA Ab (<i>Cbl/Cblb dko</i> ; B cell conditional ko) autoAb, GN (mixed 129xB6)	[102] [103]
IRF-4 binding protein (differentially expressed in FDCP6, IPB, SLAT)	<i>Def6</i>	17	28.3	hyperIgG, autoAb (mixed B6x129); not confirmed	[124, 125]
p21 cyclin-dependent kinase inhibitor 1A	<i>Cdkn1a</i>	17	29.2	anti-chromatin Ab, GN, female predominance minimal to no disease (129xB6)	[126] [127, 128]
Complement component 4	<i>C4</i>	17	34.9	impaired immune complex clearance, ANA, GN, female predominance (129xB6)	[155]
α-mannosidase II	<i>Man2a1</i>	17	65.0	hyperIgG, autoAb, GN (129xB6)	[202]
Signal-induced proliferation associated gene 1 (SPA-1)	<i>Sipa1</i>	19	5.7	autoAb, GN (129xB6>N10)	[72]
Emk (ELKL motif kinase, Par-1, MAP/microtubule affinity-regulating kinase)	<i>Mark2</i>	19	7.3	growth retardation, hypofertility, splenomegaly, lymphoid infiltrates, immune complex GN (129xB6)	[203]
Metastasis-associated gene family, member 2	<i>Mta2</i>	19	9.0	autoAb, GN (mixed B6/129)	[210]
Pten (+/- mice)	<i>Pten</i>	19	32.8	lymphadenopathy, autoAb, GN, decreased survival, female predominance	[146]
Fas (spontaneous)	<i>Fas</i>	19	34.4	lymphoproliferation, DN T cells, autoAbs, GN, arthritis (<i>lpr</i> and <i>lpr^{sg}</i> mutations)	[375]
TRANSGENIC					
Bcl-2 (B cell promoter)	<i>Bcl2</i>	1	59.8	lymphoid hyperplasia, hyperIgG, autoAb, GN	[131]
CD19	<i>Cd19</i>	7	133.6	increased B cell activation, B1 cell population, IgG, autoAb	[49]
BAFF (α1anti-trypsin or β-actin promoter, BLyS, TALL-1, THANK)	<i>Tnfsf13b</i>	8	10.0	autoAb (RF, CIC, dsDNA Ab), GN	[54, 55]
Fli-1 (class I promoter)	<i>Fli1</i>	9	32.2	lymphoid hyperplasia, autoAb, GN	[68]
IFN-γ (keratin promoter)	<i>Ifng</i>	10	117.9	autoAb, GN, female predominance	[179]
IL-4 (class I promoter)	<i>Il4</i>	11	53.4	hyperIgG1/IgE, autoAb, GN	[181]
miR-17-92 (CAG romoter/Rosa26 knockin, huCD2-iCre-dependent expression: T and B cells)	<i>Mir17-92</i>	14	115.4	Lymphoproliferation, less AICD, autoAb, GN	[74]
IEX-1 (Ig μ enhancer; immediate early response 3)	<i>Ier3</i>	17	36.0	lymphoproliferation, autoAb, GN, skin lesions, arthritis	[36]

(Continued)

TABLE 4.4 Genes associated with lupus-like manifestations in knockout/mutated and transgenic normal background mice—cont'd

Name	Gene	Chr*	Mb	Major autoimmune manifestations	Ref.
LIGHT (prox. lck promoter, hu CD2 locus control)	<i>Tnfsf14</i>	17	57.3	T cell hyperact., lymphoproliferation, autoAb, GN, lymphoid infiltration in peripheral organs	[94]
CD154/CD40L (B cell- or epidermis-specific promoter)	<i>Cd40lg</i>	X	54.5	B cell promoter: late onset autoAb, GN epidermis promoter: dermatitis, lymphadenopathy, hyperIgG, dsDNA, GN	[59] [178]
<i>MISC Tg</i>					
6-19 IgG3 anti-IgG2a RF cryoglobulin	<i>Igh</i>	12	NA	chronic lethal GN, necrotizing arteritis	[391]

* ND = not determined.

Genes are listed in order of their chromosomal locations. Gene names and chromosomal locations are from the Mouse Genome Informatics. Background strain is included in the Major Autoimmune Manifestations column (N = number of backcrosses to the indicated strain).

Abbreviations for autoimmune manifestations: Ab = antibodies, dsDNA = anti-dsDNA autoAb.

and accessory molecules (CD19, CD22, Fc γ IIb, CD72). As might be expected, genetic manipulation of many of these B-cell regulatory molecules has resulted in systemic autoimmunity. These include Lyn [45–47], CD22 [48], SHP-1 [48], CD19 [49], Fc γ RIIb [50], CD72 [51] and its ligand CD100 [52], and CD45 [53].

Several genes affecting B-cell survival and maturation have also been implicated. Overexpression of *Tnfsf13b* (BAFF, BlyS) [54, 55] or deficiency of its inhibitory receptor, *Tnfrsf13b* (TACI), leads to the development of lupus-like disease. Moreover, elevations in *Tnfsf13b* are present in both BWF₁ and MRL-*Fas*^{lpr} mice, and blocking *Tnfsf13b* function with a soluble TACI-IgGFc fusion protein can inhibit proteinuria and prolong survival [56]. Importantly, *Tnfrsf13b* inhibition has shown promise in human SLE [413]. BAFF Tg-induced lupus-like disease does not require T cells, but needs MyD88, suggesting surprisingly that Baff-induced activation of B cells in this model is TLR, but not T-cell-dependent [57]. Another gene, *Aiolos*, a zinc finger transcription factor, is highly expressed in mature B cells and, to a lesser extent, in developing bone marrow B cells and thymocytes. *Aiolos*^{-/-} mice develop defects primarily in the B-cell compartment, with hyperresponsiveness to BCR and CD40 stimulation and increased numbers of conventional B cells, a marked reduction in B1 cells, increased proportion of B cells with activated phenotype, hypergammaglobulinemia (particularly of IgE and IgG1), a three-fold reduction in IgM, and positive ANAs [58]. Likewise, ectopic transgenic expression of CD40L on B cells (normally expressed on T cells) results in enhanced polyclonal IgG, anti-dsDNA and, in about half of mice, the development of immune complex GN [59]. Mice deficient in Act1 (or CISK), a NF- κ B-related adaptor protein that negatively regulates BAFF and CD40L, were also reported to develop B-cell

hyperactivity, autoantibody production, immune complex GN, Sjogren syndrome-like disease, and early mortality [60]. Another independent Act1 knockout, however, did not demonstrate B-cell hyperactivity or autoimmunity [61] indicating a significant role for background genetic factors.

Deletion of the surrogate light-chain (SLC, encoded by the VpreB1/2 and λ 5 genes), which is thought to play an important role in the maturation and selection of pre-B cells, results in reduced B cell numbers and serum Ig levels [62]. SLC^{-/-} mice, however, have elevated levels of ANA and higher proportion of potentially autoreactive Abs [63]. Thus, it was proposed that the pre-BCR mediates negative selection of self-reactive B cells during early stages of B-cell development.

Protein kinase C δ (PKC- δ) is highly expressed in developing pro- and pre-B cells, and mediates BCR signaling. PKC- δ ^{-/-} mice develop splenomegaly, lymphadenopathy, increased numbers of B2 cells, germinal center formation and IL-6 production, mild increases of IgM, IgG1 and Ig2a, anti-nuclear and IgG1 anti-DNA autoantibodies, as well as GN [64, 65]. BCR-mediated B-cell activation *in vitro* and *in vivo* was not affected, and PKC- δ was postulated to play a role in tolerogenic, but not immunogenic, B-cell responses.

Phospholipase (PL) C γ 2 is a member of the PLC family primarily expressed in B cells that catalyzes phosphoinositides to diacylglycerol and inositol phosphates. A gain-of-function PLC γ 2 mutant (D993G, Ali5 mutation) generated by ENU mutagenesis developed lymphocyte-independent inflammatory arthritis in the C3H strain (ENU-treated strain), but anti-DNA and GN in B6xC3H mice [66]. Lupus-like disease occurred in both homozygous and heterozygous mutants, but not in littermates, which strongly suggests that the PLC γ 2 mutation and not background genes are responsible.

TABLE 4.5 Mechanisms for induction of systemic autoimmunity

ENHANCED B-CELL ACTIVATION*	
Lyn, CD22 or SHP-1 knockout	p21 ^{cip1/waf1} knockout (pancyclin kinase inhibitor, primarily T cells)
Fc γ RIIb knockout	Mgat5 knockout (enhanced T-cell activation)
Aiolos knockout	Roquin M199R mutation
PKC δ knockout (tolerance pathway)	PCMT knockout
CD19 transgenic	DEFECTIVE APOPTOSIS
Tnfsf13b (BAFF, BlyS, TALL-1, or THANK) transgenic	Fas or FasL mutations (lpr and gld mice, ALPS in humans; also caspase 10)
Fli-1 transgenic	Bim knockout (not related to Fas)
CD40L transgenic (B cell-specific expression)	Bcl-2 transgenic
PECAM-1/CD31	IEX-1 transgenic
TACI knockout	TSAd knockout (primarily T cells)
CD45 E613R knockin mutation	IL-2 or IL-2R knockout (primarily T cells)
PLC γ 2 D993G (ENU) gain-of-function B cells and innate inflammatory cells	Pten ^{+/-} knockout
Shc2 (Rai) knockout (also enhanced T-cell activation and increased survival) PI3K/AKT pathway	RasGRP1 mutation (loss-of-function RNA splicing defect)
CD72 knockout (also enhances survival)	Stra13 knockout
Shc1 knockout, also enhances survival and affects T cells; (AgR signaling adapter; also localizes to mitochondria-unknown function)	IRF-4 binding protein (IBP)
miR-17-92 transgenic (B and T cells)	DEFECTIVE CLEARANCE OF PROINFLAMMATORY/IMMUNOSTIMULATORY APOPTOTIC MATERIAL
REDUCED B-CELL ACTIVATION	C1q knockout
CD100 (incr. MZ B cells)	C4 knockout
DEFECTIVE NEGATIVE SELECTION OF B CELLS (CENTRAL TOLERANCE DEFECT)	DNase I knockout
Surrogate light chain (Vpreb1- λ 5, Vpreb2) double (3 gene) knockout	Tyro3 family (Tyro3, Axl, Mer) triple-gene knockout
ENHANCED B CELL SURVIVAL	Ro (Trove2) knockout
BAFF transgenic (ADD)	MFG-E8 knockout
Act1 knockout (negative regulator of BAFF, CD40L)	Trex1 knockout
ENHANCED T-CELL ACTIVATION	ENHANCED ANTIGEN PRESENTATION
CTLA-4 knockout	CD40L transgenic (keratin-14 promoter)
IL-2 or IL-2R knockout	SAP knockout (MAYBE)
CD45 E613R knockin mutation (B cells as well)	PLC γ 2 D993G (ENU) gain-of-function B cells and innate inflammatory cells (also listed for B cells)
PD-1 knockout (probably B cells as well)	EXPANDED DC POPULATION
TGF- β deficiency (knockout/dominant negative)	Dcir (<i>Clec4a2</i>) knockout
Cbl-b knockout	CYTOKINE-MEDIATED ACTIVATION
Gadd45a knockout	IL-4 transgenic
Gadd45 β knockout (with and without Gadd45 γ knockout)	IFN- γ transgenic
LAT Y136F knockin mutation (Th2 cell lymphoproliferation; triggers polyclonal B cell activation)	TTP (Zfp-36) deficiency (excessive TNF α)
G Protein-Coupled Receptor G2A knockout	TNF α transgenic
LIGHT (<i>Tnfrsf14</i>) transgenic (T cell-specific promoter)	STAT-4 knockout
E2F2 knockout	Zc3h12a knockout (RNase) incr. IL-6, IL-12p40, but likely also other proinflammatory agents
	DEFECTIVE SIGNAL TRANSDUCTION
	<i>Cblb</i> knockout (enhanced activation of T cells, possibly B cells)
	<i>Cbl/Cblb</i> double knockout

Pten^{+/−} knockout (defective Fas from increased PIP-3 elevating Akt levels)

SOCS-1 knockout (CD4 T cell dependent; excess cytokines, impaired Treg)

OTHER MECHANISMS

α -mannosidase II knockout

Emk knockout

Nrf2 knockout (anti-oxidant)

Mta2 knockout (expression in non-T cells important) part of NuRD (nucleosome remodeling histone deacetylase) complex

* Genes are categorized according to the most likely or predominant mechanism.

The D993G mutation was associated with increased and sustained IgM-induced Ca²⁺ flux in B cells, enhanced B-cell proliferation, and an increased proportion of marginal zone B cells.

Fli-1 is an Ets transcription factor family member that binds the consensus GGA(A/T) motif [67]. Overexpression of a Fli-1 resulted in lymphoid hyperplasia, hypergammaglobulinemia, elevated antinuclear antibodies, and severe immune complex GN associated with hyper-responsive and apoptosis-resistant B cells [68]. Fli-1 expression is also increased in murine SLE and heterozygous Fli-1^{+/−} deletion in MRL-*Fas*^{lpr} mice (homozygous Fli-1 is lethal) showing reduced serum IgG, autoantibodies, and GN as well as improved survival [69, 70], which further supports the possible importance of Fli-1 in lupus.

Rai (Shc3), an adaptor protein, enhances survival by activating the PI3K/Akt pathway and, in B and T cells, negatively regulates antigen-receptor signaling and cell activation. Rai^{−/−} mice develop lymphoid organ hyperplasia, anti-dsDNA, and mild immune complex GN [71].

SPA-1 is a Rap1 GTPase-activating protein, which inhibits the activity of Rap1 in controlling cell adhesion and MAP kinases. Deletion of SPA-1 leads to inefficient receptor editing in B cells, expansion of the B1a population, and the development of anti-dsDNA, anti-RBC, IgM and C3 glomerular deposits, and GN [72].

Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), an Ig superfamily member with two ITIM domains, is expressed on endothelial and hematopoietic cells. PECAM-1^{−/−} mice developed ANA by 9 months of age and immune complex GN by 17 months associated with enhanced B-cell activation, reduced B2, but increased B1a cells, and a block in immature to mature B-cell transition [73].

MicroRNAs (miRNA) are short single-stranded regulatory RNA molecules (~22 nucleotides) that typically pair with a large number of gene-coding mRNAs leading to their degradation or translational repression.

The miR-17-92 cluster, the precursor to seven miRNA molecules, is amplified and overexpressed in certain cancers including lymphomas. Of considerable interest, targeted overexpression of this cluster in lymphocytes resulted in lymphoproliferation, lymphoid organ hyperplasia, elevated Ig, anti-dsDNA, and immune complex GN [74]. Enhanced proliferation and reduced activation-induced apoptosis were observed in transgenic B and T cells, which was attributed at least in part to transgene-mediated reduction in PTEN and Bim expression. Thus, these and other findings suggest that alterations in miRNA expression might affect predisposition to lupus [414].

T-cell Activation Genes

Similar to B-cells, alteration in genes that primarily affect T-cell function have also resulted in systemic autoimmunity (Tables 4.4 and 4.5). These include genes that affect activation, proliferation, and survival. TGF- β 1 knockout mice rapidly develop massive necrotizing lymphocytic and monocytic infiltrates in multiple organs and die by 3 weeks of age [75, 76]. Serum IgG autoantibodies to nuclear antigens as well as Ig glomerular deposits are detectable, but they appear to play a minor role in overall disease severity [77].

CTLA-4, a surface glycoprotein expressed exclusively on T cells, acts as an inhibitor of the CD28-B7.1/B7.2 co-stimulatory pathway in part by binding with higher affinity to B7.1 and B7.2. Deficient mice develop a multi-organ lymphoproliferative disease associated with increased frequency of activated B and T cells, hypergammaglobulinemia and early mortality at 3–4 weeks of age, accompanied by severe myocarditis and pancreatitis [78–80].

PD-1, a 55-kDa ITIM-containing membrane glycoprotein expressed on activated T and B lymphocytes and monocytic cells, is necessary for maintaining homeostasis of lymphocytes and myeloid cells following activation [81, 82]. Engagement of PD-1 by its ligands, PD-L1 and PD-L2, inhibits TCR-mediated lymphocyte proliferation and cytokine secretion [83]. Mice deficient for PD-1 develop moderate hyperplasia of lymphoid and myeloid cells, increases in several Ig isotypes (particularly IgG3), enhanced B-cell responses, and alterations in peritoneal B1 cells [84]. Older B6-PD-1^{−/−} mice spontaneously develop mild GN and proliferative arthritis, but not elevated anti-dsDNA antibodies or rheumatoid factor [85]. Acceleration of GN and arthritis occurs when the PD-1 deletion is combined with the *Fas*^{lpr} mutation. By contrast, BALB/c mice-PD-1^{−/−} mice develop anti-cardiac troponin I antibodies and cardiomyopathy [86]. SLE has been linked in one population group to a regulatory polymorphism in the PD-1 gene (*PDCD1*) [87] and in other studies to other autoimmune

diseases [88–91]. Deficiency of its ligand, PD-L1, also promotes autoimmunity or inflammation depending on the strain background [92, 93].

LIGHT (*Tnfsf14*), a TNF superfamily member expressed transiently on activated T cells and on immature dendritic cells, is a co-stimulatory molecule for T-cell activation [94]. Overexpression of LIGHT on T cells resulted in peripheral lymphoid organ hyperplasia, activation and expansion of mature T cells, increased T-cell cytokine production, including IFN- α and IL-4, as well as anti-DNA antibodies, RF, immune complex GN, and inflammation of the intestines and skin [94]. In contrast, another LIGHT transgenic driven by the CD2 promoter had some of the above manifestations, but no lupus-like manifestations [95], possibly because of the different promoters [96] or background differences.

LAT, a transmembrane scaffolding protein, is tyrosine-phosphorylated following TCR engagement and then recruits multiple signaling molecules critical for T-cell activation [97]. Mutation of the Tyr¹³⁶ position to phenylalanine (Y136F) leads to a severe, but incomplete, block in T-cell development, but paradoxically by 4 weeks of age, lymphoproliferation with activated CD4 $^{+}$ T cells, B cells, macrophages and eosinophils, lymphocytic infiltrates in various organs, high production of IL-4, hypergammaglobulinemia, and autoantibodies to nuclear antigens [98, 99]. This was attributed to defective PLC γ 1-mediated calcium signaling in early T-cell development, leading to inefficient negative selection of self-reactive T cells and their exportation to the periphery wherein activation of these cells may not depend on LAT or PLC- γ 1 [98].

The cbl-b and cbl adaptor proteins are E3 ubiquitin ligases that inhibit receptor and non-receptor tyrosine kinases by promoting ubiquitination [100]. Cbl-b-deficient T cells exhibit enhanced proliferation to antigen receptor signaling [101, 102]. Cbl-b $^{-/-}$ mice have increased susceptibility to experimental autoimmune encephalomyelitis [101] and develop a generalized autoimmune disease characterized by multiorgan lymphoaccumulation with parenchymal damage, increased plasma cells, and anti-dsDNA by 6 months of age [102]. Spontaneous autoimmunity, however, occurred in only one [102] of two Cbl-b knockout studies, suggesting that background strain, environment or other factors are also important factors. Mice with conditional *Cbl/Cblb* double knockout (dko) in B cells have impaired BCR downmodulation and anergy to self-antigen, and develop spontaneous lupus-like disease with anti-dsDNA, ANA, massive leukocytic infiltrates in multiple organs, and immune complex GN [103].

G2A is a G protein-coupled receptor expressed in various tissues that appears to negatively regulate proliferation and to integrate extracellular signals with

cytoskeletal reorganization [104]. G2A $^{-/-}$ mice showed a normal pattern of T and B lineage differentiation, but with age, develop enlarged secondary lymphoid organs, T- and B-cell expansion, enhanced T-cell proliferation responses and, when over 1 year of age, a progressive wasting syndrome, lymphocytic infiltration into various tissues, hypergammaglobulinemia, immune complex GN, and anti-nuclear autoantibodies [104]. A lower threshold for activation coupled with defective Fas-mediated apoptosis has also been considered to be a major contributor to the MRL-*lpr* lymphadenopathy and spontaneous lupus-like disease [105].

E2F2 is a member of the E2F family of DNA-binding heterodimers sequestered by Rb and released after Rb phosphorylation by activated cyclin/CDK kinases [106]. Mice lacking E2F2 developed late-onset autoimmunity consisting of perivascular inflammatory infiltrates in multiple organs, splenomegaly, skin lesions, anti-dsDNA autoAbs, and GN associated with increases in effector/memory T cells [107]. The mechanism appeared to be lowering of the TCR activation threshold and more rapid entry of activated T cells into S phase.

The docking protein Shc1 (ShcA) encodes three isoforms p46, p52, and p66 that have multiple functions in diverse tissues, including tissue morphogenesis and oxidative stress response [108, 109]. Mice deficient for the p66 isoform, although living longer, developed with age spontaneous activation of T and B cells, enlarged spleens, elevated IgG, anti-dsDNA, and mild immune complex GN [110]. Evidence suggests that p66 may function in suppressing antigen-receptor signaling in both T and B lymphocytes. The adaptor proteins, Dok-1 and Dok-2, expressed in hematopoietic cells, negatively regulate the Ras-Erk pathway, and suppress TCR signaling by inhibiting ZAP-70. Dok-1/Dok-1 dko mice develop anti-dsDNA and diffuse proliferative GN with age [111].

Roquin (*Rc3h1*) is a 1130-residue ubiquitously expressed member of the E3 ubiquitin ligase family based on the presence of a highly conserved amino terminal RING-1 zinc finger domain [112]. A loss-of-function M199R mutation within the conserved ROQ domain of Roquin was generated by ENU mutagenesis (*sanroque* mouse strain) that resulted in ANA, anti-dsDNA autoantibody, GN, necrotizing hepatitis, anemia, and immune thrombocytopenia [112]. Lymphoid organ hyperplasia, polyclonal hypergammaglobulinemia, increased germinal centers, and expansion of memory/effector CD4 $^{+}$ T cells, particularly follicular helper T (T_{FH}) cells, were observed, along with overexpression of ICOS and IL-21 [415]. Further studies indicated that systemic autoimmunity was in large part mediated by the *sanroque*-associated accumulation of T_{FH} cells and the resulting enhancement of GC formation [113].

Expansion of circulatory T_{FH}-like cells was also detected in human SLE and associated with severe disease. The presence of a CCCH zinc finger common to several RNA-binding proteins and localization of Roquin to cytosolic RNA granules suggested that Roquin regulates mRNA translation and stability, and likely acts as a repressor of ICOS [112].

Mice deficient for Mgat5 (β 1,6 N-acetylglucosaminyltransferase V), an enzyme in the N-glycosylation pathway, develop proliferative GN suggestive of an autoimmune-mediated disease, however, autoantibodies were not examined [114]. Absence of this enzyme lowered the T-cell activation threshold by enhancing TCR clustering. This was thought to be related to the known function of Mgat5 in initiating GlcNAc β 1,6 branching on N-glycans and increasing N-acetyllactosamine, the ligand for galectins, which are known to modulate T-cell proliferation and apoptosis [114–116]. The findings indicate that a galectin-glycoprotein lattice strengthened by Mgat5-modified glycans restricts TCR recruitment to the site of antigen presentation, and therefore, dysregulation of Mgat5 increases T-cell activation and susceptibility to autoimmunity.

Protein carboxyl methyltransferase (PCMT) is a highly conserved enzyme that repairs isomerized and racemized derivatives of L-asparaginyl and L-aspartyl residues produced in cells by spontaneous degradation [117]. PCMT^{-/-} mice accumulate significant amounts of aspartyl derivatives in brain, heart, liver and RBCs, have growth retardation, and develop fatal seizures around 42 days of age [117]. T cells from PCMT knockout mice are hyper-responsive to stimulation, while B-cell responses are unaffected [118]. Mice reconstituted with PCMT-deficient bone marrow develop dsDNA autoantibodies 7–9 months after transfer, but no apparent immune complex GN.

The Gadd45 (growth arrest and DNA damage-inducible gene) family is composed of three members, α , β and γ , that play pivotal roles in replication, growth arrest, and apoptosis [119, 120]. Gadd45 α is a negative regulator of T-cell proliferation induced by antigen receptor-mediated activation, and deletion leads to the development of a lupus-like syndrome, particularly when coupled with deletion of the p21 cyclin-kinase inhibitor [121]. More recently, it was found that Gadd45 β deficiency is also associated with enhanced T-cell proliferation and resistance to activation-induced cell death (ACID), splenomegaly, and mild immune complex glomerular deposits [122]. Gadd45 β ^{-/-} mice are also more susceptible to EAE. The related Gadd45 γ also regulates proliferation and death of CD4 $^{+}$ T cells, however, Gadd45 γ -deficiency is not associated with autoimmunity [122]. The addition of the Gadd45 γ knockout mutation to Gadd45 β ^{-/-} mice, however, results in significant worsening of all lupus-like disease

parameters suggesting that Gadd45 γ deficiency may promote autoimmunity in certain susceptible backgrounds.

IRF-4-binding protein (*Def6*) is a Cdc42/Rac-1 guanine nucleotide exchange factor predominantly expressed in T cells where, following TCR engagement, it is recruited to the immune synapse and acts to promote optimal Ca $^{2+}$ signaling and activation [123]. *Def6*-deficient mice on a mixed 129xB6 background were reported to develop lupus-like disease with increases in effector/memory T cells and memory B cells, hypergammaglobulinemia, and autoantibodies [124]. This, however, was not confirmed in B6-*Def6*^{-/-} mice, suggesting that the development of lupus may be related to the 129xB6 background and not *Def6* deficiency [125]. Similarly, gene knockout of the cyclin inhibitor p21^{cip1/waf1} in mixed background C57BL/6 x 129/Sv mice was also reported to result in systemic autoimmunity characterized by lymphoid hyperplasia, elevated IgG1, IgG antinuclear antibodies, GN and early mortality [126], however, other studies of mixed B6/129 or BXSB female p21-deficient mice were not able to confirm the development of lupus suggesting that background effects may have been responsible for the initial findings [127, 128].

Apoptosis Genes

Altered expression of Bcl2 family members is associated with the development of lupus. Deficiency of Bim, a proapoptotic BH3 member, results in an incomplete-penetrant embryonic-lethal phenotype, but in the surviving offspring, however, alterations in the homeostasis of multiple hematopoietic cell lineages develop with lymphoid hyperplasia, thymus defects, granulocytosis and monocytosis, and, with age, systemic autoimmunity manifested a marked expansion of plasma cells, hyper IgM, IgG and IgA, antinuclear antibodies, immune complex GN, vasculitis and reduced survival [129]. Combined deficiency of Bim(Bcl2l11) and Fas results in accelerated lupus associated with enhanced activation of antigen-presenting cells [130]. Similarly, transgenic expression of the bcl-2 gene in B cells resulted in similar lymphoid hyperplasia, hypergammaglobulinemia, high titers of antinuclear antibodies, and immune complex GN [131]. Constitutive bcl-2 expression may promote autoimmunity by blocking apoptosis of autoantibody-producing B cells that normally arise spontaneously in germinal centers during the primary response to foreign antigens [132–134].

Deficiencies of IL-2 [135–137], IL-2R α [138], or IL-2R β [139] result in late immunosuppression with defective antibody and CTL responses as well as lymphoproliferation, expansion of memory/effector phenotype T cells, polyclonal hypergammaglobulinemia, autoantibodies and immune-mediated hemolytic anemia. Mice lacking

IL-2 [140] or IL-2R α [138], but not IL-2R β (88) also develop an inflammatory bowel disease resembling ulcerative colitis. Autoimmunity has been attributed to resistance of IL-2-deficient T cells to activation-induced cell death and a reduction in T_{reg} cells because of their dependence on IL-2 [141].

The T-cell-specific adaptor protein (TSAd) is encoded by the *Sh2d2a* gene and expressed in thymocytes and activated T cells [142, 143]. TSAd $^{-/-}$ mice develop elevated levels of IgG and IgM, anti-dsDNA, anti-cardiolipin, and IgG (RF), GN, and lymphocytic infiltrates, particularly in the lung [94]. TSAd $^{-/-}$ mice are also more susceptible to TMPD-induced autoimmunity. TSAd-deficient T cells are more resistant to superantigen-induced cell death *in vivo* (similar to Bim knockout mice), which may be caused by reduced IL-2 synthesis [142].

The proto-oncogene PTEN that dephosphorylates phosphatidylinositol (3,4,5)-triphosphate (PIP-3) is associated with a wide range of malignancies as well as the autosomal dominant disorders Cowden disease, Lhermitte-Duclos syndrome and Bannayan-Zonana syndrome [144, 145]. PTEN $^{-/-}$ is embryonic-lethal, but heterozygous mice develop an autoimmune disorder characterized by severe polyclonal lymphadenopathy, diffuse inflammatory cell infiltrates of most organs, hypergammaglobulinemia, anti-DNA, GN and decreased survival [146]. Defective Fas-mediated activation-induced cell death of T and B lymphocytes from increases in PIP3 and the survival factor, Akt [146] and a requirement for reduced PIP3 for induction and maintenance of B-cell anergy [147] have been suggested as possible mechanisms.

IEX-1 (also IER3) is an early response gene that regulates cell growth and apoptosis in response to a variety of external stimuli in part by targeting the mitochondrial F1Fo-ATPase inhibitor for degradation [148]. Mice transgenic for IEX-1 (H-2k b promoter and Ig heavy chain (μ) enhancer for specific expression in lymphocytes) exhibited decreased apoptosis of activated T cells, increased duration of an immune response effector phase, splenomegaly, lymphadenopathy, accumulation of activated T cells, increased polyclonal IgG2a and anti-dsDNA autoantibodies, alopecia of the skin, arthritis, and immune complex GN [36]. IEX-1 gene maps within the MHC locus of humans and mice, a region with strong linkage to SLE.

RasGRP1 is a Ras guanine nucleotide exchange factor critical for the transition of the double positive to the single positive thymocyte stage [149]. Despite this, mice with a spontaneous function-impairing RasGRP1 mutation (designated *lag* for lymphoproliferation-autoimmunity-glomerulonephritis), which impaired normal joining of exon 3 to exon 4 resulting in undetectable RasGRP1 protein levels, developed severe systemic autoimmunity by 5–8 months of age [150]. Major manifestations included enlarged spleens and LNs, hyperplastic germinal centers,

hypergammaglobulinemia, ANAs, anti-dsDNA autoantibodies, diffuse proliferative GN with IgG and C3 deposits, and early mortality. *Lag* CD4 $^{+}$ T cells were resistant to activation induced cell death (AICD), while B cells were expanded, but exhibited normal proliferation and apoptosis.

Stra13, a member of the basic helix-loop-helix family of transcriptional repressors, is expressed in lymphoid cells [151, 152]. Although Stra13-deficient CD4 $^{+}$ T cells had reduced proliferation, due in part to impaired IL-2 secretion, Stra13 knockout mice developed systemic autoimmunity by 4–5 months with lymphoid organ hyperplasia, increased numbers and activation of T and B cells, germinal center expansion, antinuclear antibodies, and GN [151]. Gradual accumulation of T and B cells appeared due to greater resistance to AICD because of impaired differentiation of CD4 $^{+}$ T cells into effector cells and reduced expression of FasL following T-cell activation. Consistent with a negative regulatory role, transgenic mice expressing Stra13 (IgH promotor and enhancer) in B- and T-cells had reduced numbers of T- and B-cells, hyporesponsive B cells, and impaired T-dependent humoral response [152].

Defective Clearance of Proinflammatory/Immunostimulatory Self-antigens

Deficiencies of early complement components (C1q-s, C2, or C4) in humans are known to result in predisposition to SLE, indicating an important regulatory role in suppressing autoimmunity. Homozygous C1q-deficient mice in some backgrounds recapitulated the human disorder with the development of mild, but typical, features of lupus [153]. Notably, an atypical accumulation of apoptotic bodies in the glomeruli of C1q-deficient mice was observed indicating that C1q plays an essential role in the clearance of apoptosis byproducts. As noted above a C1q polymorphism in NZB mice within the *Nba1/Lbw2/Imh1/Mott* interval on chromosome 4 that downregulates C1q levels has been identified [39]. In C4 deficiency, lupus was evident only on a *Fas*^{lpr} background [154], indicating that lack of C4 alone is not sufficient to induce autoimmunity. Nevertheless, early complement components may be vital for maintaining self-tolerance by virtue of their role in presenting tolerizing antigens to B cells [155].

DNase1 is a 32–38-kDa protein that is the major nuclease present in the blood, urine and secretions. Knockout of the DNase1 gene in non-autoimmune background mice was reported to increase the incidence of SLE manifestations, including positive ANA, anti-DNA, and immune complex GN [156]. Reduced DNase1 activity, as observed in sera of lupus patients [157], may contribute to overall SLE susceptibility. Interestingly, an

identical heterozygous nonsense mutation in *DNASE1* was detected in two SLE patients [157].

Milk fat globule-EGF factor 8 (MFG-E8) protein functions as a bridging protein between phosphatidylserine on apoptotic cells to $\alpha v\beta 3$ or $\alpha v\beta 5$ integrins on phagocytic cells, thereby promoting apoptotic cell engulfment [158, 159]. In the spleen and LN, MFG-E8 is primarily expressed on tingible body macrophages ($CD68^+$) within germinal centers [160]. MFG-E8-null mice develop splenomegaly with abundant germinal centers and tingible macrophages with increased numbers of unengulfed apoptotic cells. By 40 weeks, MFG-E8^{-/-} mice have ANA and anti-dsDNA, large glomerular deposits of IgG, and hypercellular glomeruli. Taken together, these findings suggest inefficient phagocytosis of apoptotic B cells within germinal centers promotes autoimmunity. This is consistent with recent studies demonstrating that DNA and RNA in apoptotic material can activate B cells and dendritic cells through TLR9, TLR7, and TLR8 [161–166].

TAM (Tyro3, Axl and Mer) receptors, expressed on APCs, promote clearance of apoptotic cells and inhibit TLR-induced cytokine cascades [167]. Mutant triple TAM knockout mice develop severe systemic autoimmunity characterized by splenomegaly, lymphadenopathy, increases in activated T and B cells, autoantibodies to phospholipids associated with thromboses and hemorrhage, autoantibodies to collagen and dsDNA, and deposition of immune complexes in tissues [168]. Furthermore, mice with a cytoplasmic truncation of *mer* alone are deficient in the clearance of apoptotic thymocytes and develop a mild form of lupus-like disease with antibodies to chromatin [169, 170].

Trex1, the most abundant cytoplasmic 3' to 5' ssDNA exonuclease, degrades intracellular nucleic acid and negatively regulates the intracellular IFN-stimulatory DNA response [171, 172]. Deficiency of Trex1 in humans causes Aicardi-Goutieres syndrome and chilblain lupus, but in mice an inflammatory myocarditis and antibodies to heart tissue, not lupus-like disease. Interestingly, Trex1 deficiency was associated with the accumulation of endogenous retroelement-derived DNA. The development of lupus traits in Trex1-deficient humans, but not in Trex1-null mice may be related to differences in background genes.

Ro, a conserved RNA-binding protein encoded by the *Trove2* gene, is a common target for autoantibodies in SLE, Sjogren syndrome, subacute cutaneous LE, neonatal lupus and primary biliary cirrhosis [173]. Mice deficient in Ro were reported to develop ANAs and immune complex GN [174]. Disease severity, however, lessened as the knockout mutation was backcrossed to the B6 background, suggesting the possibility of 129xB6 background effects. More recently, knockout of the autoantigen Ro52 (*Trim21*) also

resulted in lupus-like systemic autoimmunity [175]. Despite this null mutation being generated directly in the B6, however, autoimmunity was not observed in Ro52^{-/-} mice generated by another group suggesting the possibility of bystander effects related to the method of gene disruption [176].

Deletion of serum amyloid P component (SAP), a highly conserved plasma protein, was also reported to be associated with lupus [177], however, as described above, subsequent studies, have shown that the association of SAP deficiency with lupus-like disease is mostly or even entirely due to the mixed 129xB6 background used in the initial study [29, 30].

Enhanced Antigen Presentation

Targeted expression of CD40L to the basal keratinocytes of the epidermis of mice (keratin-14 promoter) leads to activation of resident tissue APCs (Langerhans cells) and dermatitis, lymphadenopathy, hypergammaglobulinemia, anti-dsDNA, and immune complex GN [178]. These findings are similar to mice transgenic for IFN- γ under the involucrin promoter [179]. Overall, they indicate that *in situ* activation of APCs in the skin can lead not only to local, but also systemic, autoimmune and inflammatory responses, presumably due to the migration of activated APC to the secondary lymphoid organs, and the activation of self-reactive T cells.

Mice deficient in Dcir (*Clec4a2*), an ITIM-containing C-type lectin receptor highly expressed in DC, develop spontaneous enthesitis, salivary gland infiltrates, and ANA [180]. Evidence suggests this is caused by the expansion of DCs leading to enhanced antigen presentation.

Cytokine Ligand and Receptor Genes

Systemic autoimmunity can develop in mice transgenic for the major Th1 and Th2 cytokines, IFN- γ and IL-4, respectively, in certain circumstances. As noted above, expression of IFN- γ in the suprabasal layer of the epidermis resulted not only in a severe inflammatory skin disorder, but also anti-dsDNA and -histone, and an immune complex proliferative GN [179]. Similarly, C3H mice transgenic for the IL-4 gene (MHC class I promoter) also developed systemic autoimmunity characterized by hyper IgG1 and IgE, anemia, ANAs, and GN from direct IL-4-induced polyclonal activation of B cells [181]. The role of IL-4 in promoting lupus, however, is more complicated, since autoimmunity was not observed in other transgenics expressing IL-4 in B or T cells [182–185] and, in a spontaneous model of lupus, expression of an IL-4 transgene did not exacerbate disease, but was instead protective [186].

Tristetraprolin (TTP or Zfp-36) is a widely expressed zinc-binding protein that binds to an AU-rich element in the TNF- α mRNA destabilizing the mRNA [187].

TTP-null mice develop a complex syndrome of cachexia, patchy alopecia, dermatitis, conjunctivitis, erosive arthritis, myeloid hyperplasia, glomerular mesangial thickening and ANAs [188] due to excessive TNF α production [188, 189]. In contrast, physiological levels of TNF- α may suppress systemic autoimmunity. TNFR1 (p55)-null C57BL/6-*Fas*^{lpr} mice exhibit accelerated lymphoproliferation and autoimmune disease [190] and deletion of both TNF receptors enhances lupus-like disease in NZM2328 mice [191].

Defective Signal Transduction

Suppressor of cytokine signaling (SOCS)-1 is a negative regulator of Janus kinases that acts as a feedback inhibitor of cytokine signaling [192]. Although complete deficiency of SOCS-1 results in fatty liver degeneration, lymphopenia, macrophage infiltration, and mortality before 3 weeks, partial deficiency was reported to promote lupus-like systemic autoimmunity with increased Ig levels, autoantibodies, glomerular immune complex deposits, and mesangial proliferation, as well as perivascular infiltrates in multiple organs and cutaneous alterations, including eczema and small ulcers [193].

Other Mechanisms

SHP-1 is a protein tyrosine phosphatase expressed in hematopoietic lineage cells and inhibits cell activation following its recruitment by negative regulatory molecules containing ITIMs [194]. Two spontaneous recessive mutations of the SHP-1-encoding *Ptpn6* gene, the motheaten (*me*) and motheaten viable (*me^v*) both lead to similar early lethal phenotypes, which differ slightly in severity because of more complete gene deletion in the *me* variant. Although increased Ig levels and autoantibodies are detected, the major disease manifestations are not similar to spontaneous lupus, and do not require the adaptive immune response. However mice lacking SHP-1 only in B cells develop both autoimmunity and inflammatory disease [417].

The α -mannosidase II enzyme resides in the Golgi apparatus and is critical for the glycosylation of cell surface proteins [200, 201]. Mice deficient in α -mannosidase II develop a lupus-like syndrome characterized by anti-dsDNA, anti-Sm and anti-histone, hyperIg, and GN [202]. No clear explanation for appearance of systemic autoimmunity was evident, but a possibility is that alterations in N-glycan branching among some glycoproteins and tissues may lead to the formation of neoepitopes.

Emk (ELKL motif kinase, MARK2) is a serine/threonine kinase expressed in thymus and mature T and B cells that regulates cell polarity, cell cycle progression, and microtubule dynamics [203]. Emk^{-/-} mice exhibit growth retardation and hypofertility [203, 204], but

with age, develop splenomegaly, lymphadenopathy, activated phenotype T cells, lymphoid infiltrates in various tissues, and membranoproliferative GN [203].

The basic leucine zipper transcription factor Nrf2 (NF-E2-related factor 2) regulates a number of genes encoding detoxifying and anti-oxidant enzymes [205, 206]. Nrf-2-deficient female mice over 5 months of age develop severe immune complex GN along with elevated serum IgG, anti-dsDNA antibody, and slight splenomegaly [207]. Mice deficient in heme-oxygenase-1 (HO-1), a gene potentially regulated by Nrf2, also develop GN resembling that of the Nrf2-deficient mice [208]. In contrast, Nrf2 deficiency in MRL-*Fas*^{lpr} mice results in increased sensitivity to TNF-mediated apoptosis and disease suppression [209]. These findings suggest that the effect of Nrf2 on lupus depends on the underlying disease pathogenesis or that increased lupus susceptibility in the Nrf2 knockout may be due to background.

Mice deficient for Mta2, a component of the NuRD complex that acts in nucleosome remodeling and histone deacetylation, have greater than 50% embryonic/perinatal lethality, multiple developmental abnormalities, small body size and female infertility, but also develop with age autoantibodies, GN, skin lesions, and liver inflammation [210]. T cells exhibited enhanced proliferation and production of IL-4 and IFN- γ . Findings suggest that defects in chromatin remodeling and histone modification can predispose to lupus, however, the use of mixed 129xB6 mice suggests some caution in interpretation of these results.

Zc3h12a is an RNase activated by TLR signaling that promotes the degradation of mRNA. Zc3h12a^{-/-} mice have early mortality (50% ~ 6 weeks) associated with severe hemolytic anemia, lymphoproliferation, and ANAs associated with expansions of activated and memory B cells, activated T cells, and plasma cells, as well as enhanced cytokine production [211].

GENE KNOCKOUT AND TRANSGENIC LUPUS BACKGROUND MICE

Direct examination of the role of deleted or over-expressed immune-related genes in lupus-predisposed mice have provided important information on the crucial molecules and pathways, as well as a deeper understanding of the molecular basis for the diverse manifestations. (Table 4.6, listed by chromosome and chromosomal location).

B-cell-related Genes

Studies in MRL-*Fas*^{lpr} and MRL-+/+ mice with deletion of the Jh locus (no B cells) [212, 213] have clearly

TABLE 4.6 Effects of genetic manipulation of lupus-prone mice

Name and alteration	Gene	Chr [#]	Mb	Strain*	Result	Ref.
CD28 ko	<i>Cd28</i>	1	60.8	MRL- <i>lpr</i>	reduced GN	[248]
STAT-4	<i>Stat4</i>	1	52.1	NZM2410 B6-TC	exacerbates GN, reduces IgG anti-dsDNA reduces autoAb, GN	[275] [274]
STAT-1	<i>Stat1</i>	1	52.2	BALB/c-TMPD-induced	reduced autoAb	[276]
ICOS	<i>Icos</i>	1	61.0	MRL- <i>lpr</i>	reduced autoAb, no effects on GN or skin	[233, 234]
CD55 (Daf1)	<i>Cd55</i>	1	132.3	MRL- <i>lpr</i>	exacerbates autoimmunity	[291]
IL-10 ko	<i>Il10</i>	1	132.9	MRL- <i>lpr</i>	enhanced lymphoproliferation, IgG2a autoAb, GN, skin lesions, mortality	[277]
CD45 +/− ko	<i>Ptprc</i>	1	140.0	C3H/HeJ- <i>gld</i>	reduced IgG, autoAb, DN T cells	[284]
P-selectin ko	<i>Selp</i>	1	166.0 Mb	MRL- <i>lpr</i>	enhanced GN, mortality, incr. CCL2 (kidney)	[305]
FcR γ-chain ko	<i>Fcer1g</i>	1	173.2	BWF1	same autoAb, glom. dep., but reduced GN, mortality	[299]
CD21/CD35 ko	<i>Cr2</i>	1	197.0	MRL- <i>lpr</i>	no effect on GN	[392]
soluble Crry Tg (complement receptor related protein)	<i>Crry</i>	1	197.0	<i>lpr</i>	accelerated disease	[35, 154, 393]
Nrf2, Nuclear factor, erythroid derived 2, like 2	<i>Nfe2l2</i>	2	75.5	MRL- <i>lpr</i>	reduced GN, no effect on glom. dep., autoAb, lymphoproliferation	[290]
beta-2 microglobulin ko (MHC class I ko)	<i>B2m</i>	2	122.0	MRL- <i>lpr</i> C3H- <i>lpr</i> & - <i>gld</i> NZB MRL- <i>lpr</i>	reduced lymphoproliferation reduced lymphoproliferation reduced anti-RBC Ab inhibits inhibits nephritis, accelerates skin disease	[220, 221] [219] [394] [223]
CD1 ko	<i>Cd1d1</i>	3	86.8	MRL- <i>lpr</i> MRL- <i>lpr</i>	no effect on disease reduced skin disease exacerbates nephritis	[223]
TNFR2 (p75)	<i>Tnfrsf1b</i>	4	144.8	TMPD-induced BWF1	exacerbates nephritis	[224]
DNA fragmentation factor, beta subunit (caspase-activated DNase, 40kDa)	<i>Dffb</i>	4	153.3	NZM2328	accelerated autoAb, GN (only with dko: <i>Tnfrsf1a/Tnfrsf1b</i>)	[225, 226] [191]
				TMPD-induced	impaired nuclear autoAb, less effect on cytoplasmic and cell surface self Ag, no effect on mild GN	[245]

I. BASIS OF DISEASE PATHOGENESIS

cappuccino (single nucleotide deletion)	<i>Cno</i>	5	37.1	EOD (MRL- <i>lpr</i> xBxSB)RI	reduced glom. crescent, plat. dysfunction, no effect on autoAb, IgC deposits	[304]
osteopontin ko (Eta-1, secreted phosphoprotein 1 ko)	<i>Spp1</i>	5	104.9	B6- <i>lpr</i>	reduced polyclonal and autoAb, delayed lymphoproliferation and kidney disease	[279]
P-selectin ligand ko	<i>Selp/lg</i>	5	114.3	MRL- <i>lpr</i>	enhanced GN, mortality, incr. CCL2 (kidney)	[305]
CD8 ko	<i>Cd8a</i> <i>Cd8b</i>	6	71.3	MRL- <i>lpr</i>	reduced lymphoproliferation	[218]
Arachidonate 5-lipoxygenase ko	<i>Alox5</i>	6	116.4	MRL- <i>lpr</i>	slight accelerated mortality (males only)	[395]
Activation-induced cytidine deaminase (AID) ko	<i>Aicda</i>	6	122.5	MRL- <i>lpr</i>	reduced autoAb, GN, early mortality (incr. IgM autoAb)	[216]
CD4 ko	<i>Cd4</i>	6	124.8	MRL- <i>lpr</i>	increased lymphoproliferation; decreased autoAb, GN, mortality	[218, 396]
TNFR1 (p55)	<i>Tnfrsf7a</i>	6	125.3	B6- <i>lpr</i>	enhanced lymphoproliferation, autoAb, GN	[190]
apolipoprotein E ko	<i>Apoe</i>	7	20.3	NZM2328	accelerated autoAb, GN (only with dko: <i>Tnfrsf1a/Tnfrsf1b</i>)	[191]
kallikrein related-peptidase family	<i>Klk</i>	7	51.0-51.4	B6- <i>lpr</i>	exacerbated autoAb, GN	[312]
IL-21R ko	<i>Il21r</i>	7	132.7	BxSB	severity of nephritis (nephrotoxic serum model)	[303]
Integrin- α L (CD11a, LFA-1) ko	<i>Igal</i>	7	134.4	MRL- <i>lpr</i>	reduced monocyteosis, IgG, autoAb, GN, early mortality	[282]
Single immunoglobulin and toll-interleukin 1 receptor (TIR) domain ko	<i>SigIRR</i>	7	148.3	B6- <i>lpr</i>	reduced autoAb, GN, mortality	[254]
ICAM-1 ko	<i>Icam1</i>	9	20.8	MRL- <i>lpr</i>	enhanced lung disease, GN (I29xB6, backcrossed 6 generations to B6)	[244]
Pou domain, class 2, associating factor (OBF-1)	<i>Pou2af1</i>	9	51.0	MRL- <i>lpr</i>	reduced mortality, autoAb, GN, vasculitis	[295]
					but same autoAb, lymphoproliferation and GN	
					reduced pulmonary inflammation and mortality,	
					Prevents development of lupus-like phenotypes	[397]

(Continued)

TABLE 4.6 Effects of genetic manipulation of lupus-prone mice—cont'd

Name and alteration	Gene	Chr [#]	Mb	Strain*	Result	Ref.
TLR9	<i>Tlr9</i>	9	106.1	MRL- <i>lpr</i>	reduced disease exacerbation of disease	[398]
Myeloid differentiation primary response gene 88	<i>MylD88</i>	9	119.2	MRL- <i>lpr</i>	reduced autoAb, GN, mortality; autoAb & GN induced by poly(I:C)	[240, 399]
ERα (estrogen receptor 1)	<i>Esr1</i>	10	5.3	BWF1, NZM2410, MRL- <i>lpr</i>	females less autoAb, GN, mortality females less autoAb, GN	[294] [293]
IFN-γR ko	Ifngr Ifngr2	10 16	19.3 91.5	MRL- <i>lpr</i> BWF1	reduced GN reduced GN, mortality	[263, 400] [265]
fyn ko	<i>Fyn</i>	10	39.1	MRL- <i>lpr</i>	reduced DN T cells, autoAb, GN	[283, 401]
perforin ko	<i>Pfif1</i>	10	60.8	MRL- <i>lpr</i>	accelerated disease	[232]
MIF	<i>Mif</i>	10	75.3	MRL- <i>lpr</i>	reduced GN, early mortality; no other major change	[302]
Integrin-β2 (CD18) ko	<i>Igfb2</i>	10	77.0	MRL- <i>lpr</i>	reduced autoAb, GN, mortality	[254]
complement factor D ko	<i>Cfd</i>	10	79.4	MRL- <i>lpr</i>	reduced C3 dep., kidney pathology; no effect on autoAb, leg dep. proteinuria, mortality	[287]
IFN-γ ko	<i>Ifng</i>	10	117.9	(MRL- <i>lpr</i>)F ₂ MRL- <i>lpr</i> HgIA	reduced GN, mortality, autoAb reduced GN, not IgG anti-dsDNA reduced ANA, but not GN reduced autoAb, GN	[262] [264] [266]
STAT-6	<i>Stat6</i>	10	127.1	NZM2410 B6-TC	reduced GN, not IgG anti-dsDNA reduced ANA, but not GN	[275] [274]
IL-12b (p40) Tg (antagonist)	<i>Il12b</i>	11	44.2	MRL- <i>lpr</i> -cg	reduced autoAb, slightly reduced GN and survival	[272]
IL-4 ko	<i>Il4</i>	11	53.4	MRL- <i>lpr</i> F ₂ BXSB	reduced GN no effect	[262] [273]
IRF-1 (interferon regulatory factor 1)	<i>Irif1</i>	11	53.6	MRL- <i>lpr</i>	reduced autoAb, GN, lymphoproliferation, early mortality	[270]

I. BASIS OF DISEASE PATHOGENESIS

Nitric oxid synthetase 2 ko	<i>Nos2</i>	11	78.7	MRL- <i>lpr</i> (N4)	same autoAb, GN, arthritis reduced vasculitis
MCP-1 ko (chemokine (C-C) motif ligand)	<i>Ccl2</i>	11	81.8	MRL- <i>lpr</i>	[298] [402]
T-box 21 Tg (T-bet) (Expressed in T cells)	<i>Tbx21</i>	11	97.0	(B6 \times B \times SB)F1	reduced GN, mortality; same autoAb and glom. dep.
T-box 21 ko (T-bet)	<i>Tbx21</i>	11	97.0	MRL- <i>lpr</i>	enhanced autoAb, GN, mortality
Jh (no B cells)	<i>Igh-J</i>	12	114.5	MRL- <i>lpr</i>	[268]
Jh, mlg Tg (B cells with mlg, no Abs)		12	114.5	MRL- <i>lpr</i>	[212][213]
angiotensin II receptor, type 1a (AT1a)	<i>Agtr1a</i>	13	30.4	MRL- <i>lpr</i>	no disease
TCR $\alpha\delta$ ko (no $\alpha\beta^+$ or $\gamma\delta^+$ T cells)	<i>Tcr/Tcrd</i>	14	54.4	MRL- <i>lpr</i>	[214]
TCR δ ko (no $\gamma\delta^+$ cells)	<i>Tcrd</i>	14	54.4	MRL- <i>lpr</i>	[306]
TCR α ko (no $\alpha\beta^+$ cells)	<i>Tcr</i>	14	54.4	MRL- <i>lpr</i>	no IgG autoAb, GN disease acceleration
B7.2 ko	<i>Cd86</i>	16	36.6	B \times SB	major disease reduction
B7.1 ko	<i>Cd80</i>	16	38.5	MRL- <i>lpr</i>	marked disease reduction
B7.1/B7.2 double ko	<i>Cd80/86</i>	16	37-38	MRL- <i>lpr</i>	reduced GN
Interferon (alpha and beta) receptor 1	<i>Ifnar1</i>	16	91.5	NZB	more severe, distinct GN
MHC class II ko	<i>H2-Aa</i> <i>H2-Ea</i>	17	34.4	B6/129- <i>lpr</i>	marked disease reduction
human DR Tg	<i>H-2</i>	17	34.4	MRL- <i>lpr</i>	reduced autoAb, GN, anti-RBC
complement C4 ko	<i>C4</i>	17	34.9	NZM/Aeg2410	reduced autoAb, GN, same lymphoproliferation
complement factor B ko	<i>Cfb</i>	17	35.0	MRL- <i>lpr</i>	autoAb repertoire alterations
Tnf +/- ko	<i>Tnf</i>	17	35.3	NZB \times B6.129-Tnf $^{/\alpha}$)F1	[154, 289]
				MRL- <i>lpr</i>	[285]
					reduced autoAb, GN, vasculitis
					enhanced disease

(Continued)

TABLE 4.6 Effects of genetic manipulation of lupus-prone mice—cont'd

Name and alteration	Gene	Chr [#]	Mb	Strain*	Result	Ref.
C3 ko	C3	17	57.3	MRL- <i>lpr</i>	worse proteinuria and glom. dep., but same GN score, autoAb and CIC	[288]
				129xMRL- <i>lpr</i> /C4 ko	no difference vs. 129xMRL- <i>lpr</i> /C4 ko	[289]
TdT ko	Dnmtt	19	41.1	BWF1	same autoAb, reduced GN and mortality	[410] [310]
				MRL- <i>lpr</i>	reduced hyperIgG autoAb, GN, mortality, vasculitis	[310]
CD40L ko	CD40lg	X	54.5	MRL- <i>lpr</i>	reduced autoAb, GN	[247]
SH2 domain protein 1A (SAP)	Sh2d1a	X	39.9	129/pristane-induced MRL- <i>lpr</i>	reduced IgG, autoAb, GN spont. mutation; markedly reduced disease (check paper)	[252] [253]
TLR7 ko	Tlr7	X	163.7	MRL- <i>lpr BXSB TMPD</i>	reduced RNA-associated Ab, GN	[237] [411] [238]
protein kinase CK2 alpha ko (casein kinase II) (transgenic)	Csnk2a1 Csnk2a2 Csnk2b	2 8 17	152.0 98.0 35.3	MRL- <i>lpr</i>	accelerated lymphoproliferation, autoAb, GN	[412]

* MRL-*lprF2* = mixed background derived from (MRL-Fas^{lpr}χB6x129F1)F2. lpr = Fas^{lpr}, gld = Fas^{gld}.[#]ND = not determined.

Genes are listed by their approximate chromosomal locations. Genes are deficiencies by homologous recombinant knockout unless otherwise stated.

Abbreviations: antibody = Ab, glom. CIC = circulating immune complexes, glom. dep. = glomerular IgG deposits.

shown the crucial role of B cells in lupus disease manifestations, confirming the central role of autoantibodies in pathogenesis. Furthermore, genetic manipulation of MRL-*Fas*^{lpr} mice resulting in B-cell expression of surface, but not secreted, immunoglobulin, demonstrated that B cells alone could promote local cellular infiltration and inflammation, but not GN [214]. Indeed, Fas deficiency in germinal center B cells is sufficient for the severe *lpr*-associated lymphoproliferation [215].

Activation-induced cytidine deaminase (AID) is required for class-switch recombination and somatic hypermutation of immunoglobulins. As expected, IgG autoantibodies are absent in MRL-*Fas*^{lpr} AID^{-/-} mice, but IgM autoantibodies are increased [216]. These mice have reduced GN and survival is prolonged.

T-cell-related Genes

A wide diversity of intercross of congenic mice rendered defective for MHC, CD4, CD8 or T-cell receptor genes have been used to assess the role of helper and cytotoxic T cells, and $\alpha\beta$ - and $\gamma\delta$ -T-cell subsets in lupus. In MRL-*Fas*^{lpr} mice, deletion of MHC class II [217] or CD4 [218] reduced autoantibodies and GN, but had no effect on lymphadenopathy. In contrast, β 2m- (class I) [219-222] or CD8-deficient [218] MRL-*Fas*^{lpr} or C3H-*Fas*^{lpr} mice showed reduced lymphoproliferation and expansion of DN B220⁺ cells, but only partial diminution in autoantibody levels and GN.

MRL-*Fas*^{lpr} mice deficient in β 2m are discordant in skin and kidney disease, with the former accelerated and the latter ameliorated [223]. The skin disease was not, however, accelerated in CD1-deficient MRL-*Fas*^{lpr} mice, suggesting that the effect of β 2m deletion (affects all MHC class I including CD1) in this manifestation was not mediated by NK T cells that depend on CD1 or by CD1 expression on skin Langerhans or B cells. CD1 deficiency did not affect disease severity, including nephritis and vasculitis. In contrast, another group reported that CD1-deficiency exacerbated skin disease in MRL-*Fas*^{lpr} [224], TMPD-induced lupus nephritis [225], and GN in (NZBxNZW)F1 females [226] consistent with a regulatory role of CD1d and iNKT cells. Findings suggest that local conditions in target organs can affect disease manifestations. In NZB mice, CD4 or β 2m deficiency delayed onset and reduced incidence of anti-RBC antibodies [227].

Although the combined results clearly demonstrate the importance of TCR $\alpha\beta$ cells in spontaneous lupus, TCR α gene deletion in MRL-*Fas*^{lpr} mice only partially inhibited disease [228, 229]. Based on the fact that TCR $\alpha\beta$ /TCR $\gamma\delta$ double-knockout MRL-*Fas*^{lpr} mice fail to generate class-switched autoantibodies and immune complex GN [230, 231], this suggests that TCR $\gamma\delta$ cells

can also help drive the autoimmune B cells. Paradoxically, however, MRL-*Fas*^{lpr} TCR $\gamma\delta$ -deficient mice showed disease exacerbation. These results suggest that TCR $\alpha\beta$ cells are the major provider of B-cell help in intact MRL-*Fas*^{lpr} mice, whereas TCR $\gamma\delta$ cells suppress this process, but can concomitantly provide lesser degrees of non-MHC-restricted polyclonal B-cell help. In contrast, TCR $\alpha\beta$ -deficient BXSB mice are resistant to lupus [406]. In addition, knockout of the perforin gene in MRL-*Fas*^{lpr} mice resulted in disease exacerbation, suggesting that cytolytic cells may be involved in suppressing autoreactivity [232].

ICOS (CD278) is a member of the CD28 family of co-stimulatory molecules on T cells that plays an important role in the formation and function of follicular helper T cells (T_{FH}). MRL-*Fas*^{lpr} ICOS^{-/-} mice had reduced lymphadenopathy, anti-dsDNA, renal vasculitis, but the amount of immune complex deposits in the kidney, severity of GN and cutaneous lupus were unchanged [233, 234].

Genes Related to Nucleic Acid Recognition and Degradation

Studies have shown that certain arms of the innate immune system, particularly the endosomal TLR pathway, are critical for the development of lupus-like disease in mouse models [235]. Specifically, TLR7, Un93b1, and MyD88 have been clearly shown to be required for optimal autoantibody production and end-organ disease in several lupus-prone strains [236-241]. This supports the current paradigm that uptake of nucleic acid complexes into endosomes by antigen receptors on B cells or Fc receptors on DC leads to activation of endosomal TLRs (primarily TLR7), which promotes loss of tolerance to nucleic acids and nucleic-acid-containing material, essential for generating high titers of anti-nucleic acid Abs [235, 242]. In contrast, the role of TLR9 in lupus is less clearly defined. Deletion of TLR9 exacerbated disease in most models, but reductions in anti-DNA Abs and in overall disease severity have also been reported by others [235].

Sigirr (single immunoglobulin and toll-IL1 receptor domain, Tir8) is a member of the IL-1R-like family that is thought to inhibit signaling by IL-1 family members (including IL-1, -18, -33) and TLR-mediated activation [243]. Deletion of Sigirr in B6-*Fas*^{lpr} mice exacerbates lymphoproliferation and results in severe autoimmune lung and kidney disease [244]. This was attributed to a reduction in CD4+CD25+ T cells and its function as an inhibitor of RNA- and DNA-mediated DC- and B-cell activation.

Caspase-activated DNase (CAD, Dffa) is a major mediator of DNA fragmentation in apoptosis [218].

Mice lacking Dffa have impaired intranuclear chromatin fragmentation, nuclear degradation, and apoptotic membrane blebbing, but are able to phagocytize apoptotic material and have a functional immune system [245]. In the TMPD-model, B6-Dffa^{-/-} mice have markedly reduced autoantibodies to nuclear antigens, but are able to produce antibodies to intracytoplasmic antigens and develop similar mild GN as wt mice.

Co-Stimulatory Molecules

Studies in MRL-*Fas*^{lpr} mice deficient for CD40L [246, 247] or CD28 [248] demonstrate the prerequisite for co-stimulation in lupus development. MRL-*Fas*^{lpr} mice deficient for either B7.1 or B7.2 were used to further dissect the CD28-B7 axis [249]. Although neither of these deletions affected autoantibody levels compared to wild-type MRL-*Fas*^{lpr} mice, GN was substantially worse in B7.1-deleted mice, but less severe in B7.2 knockouts, consistent with findings in BWF1 mice showing antibodies to B7.2, but not B7.1, suppressed disease [250].

SH2D1A (SLAM-associated protein or SAP) is a signal transduction adaptor protein for several SLAM family members and is mostly expressed in T cells [251]. Deficiency of SH2D1A is responsible for the X-linked lymphoproliferative syndrome (XLP) in which patients manifest severe infectious mononucleosis, B-cell lymphomas, and/or dys-gammaglobulinemia because of impaired CTL, NK T cell, and Ab responses. SH2D1A deficiency is associated with reduced lupus-like disease in the TMPD-induced model [252] and in MRL-*Fas*^{lpr} mice with a spontaneous adenyl nucleotide insertion at codon 21 of the 1st exon that impairs SH2D1A protein function and expression [253]. This was attributed to defective germinal center formation and a reduction in the T-dependent humoral immune response [252].

Leukocyte Adhesion Genes

The leukocyte β-integrins LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18), and p150/95 (CD11c/CD18) are ligands for ICAM-1 that mediate diverse immune and inflammatory responses. Deficiency of either CD11a (*Itgal*) or CD18 (*Itgb2*) in MRL-*Fas*^{lpr} mice was associated with reduced lymphoproliferation, autoAb, GN and dermatitis [254]. Survival was prolonged in CD11a^{-/-} mice, but not examined in CD18-deficient mice because of occasional fatal infections. In contrast, CD11b-deficiency had no ameliorating effect.

Cytokine Genes

The requirement for IFN-α in lupus has been shown for several lupus-prone strains [255–257] and treatment

with exogenous type I IFN has in most instances significantly exacerbated disease [258], consistent with the IFN signature observed in human SLE [259]. In contrast, MRL-*Fas*^{lpr} mice exhibit the opposite response to type I IFN, with disease worsened by deletion of the IFN-α receptor (*Ifnar1*) [260] and lessened by IFN-β treatment [261]. This suggests a significant difference in the pathogenesis of MRL-*Fas*^{lpr} mice and the other mouse models thus far examined for type I IFN-dependence.

Similar to type I IFN, IFN-γ is required for the development of systemic autoimmunity in all models of lupus examined [262–266]. IFN-γ is important in at least two steps of lupus pathogenesis: promotion of the response to self-antigens, perhaps because they are of low antigenicity [264, 266]; and acceleration of local inflammatory responses [264].

A variety of proto-oncogenes, kinases and transcription factors have been implicated in the Th1 versus Th2 polarization process, including interferon regulatory factor 1 (IRF-1) and T-box expressed in T-cell (T-bet, T-box 21) proteins for Th1 cells, and, for Th2 cells, the c-Maf proto-oncogene and the GATA3 zinc finger protein [267]. Deficiency of T-bet in lupus-prone mixed-background MRL-*Fas*^{lpr} mice resulted in reductions in mortality, GN, autoantibody production and hypergammaglobulinemia [268]. Overexpression of T-bet, on the other hand, reportedly accelerated GN and mortality [269]. MRL-*Fas*^{lpr} mice deficient for IRF-1 had reduced autoantibodies, less kidney and skin disease, and prolonged survival, although splenomegaly was unaffected [270]. IL-12 is an important regulator of Th1 cell differentiation and IFN-γ production [271]. Transgenic expression of a potent IL-12 antagonist, IL-12p40 in lupus-susceptible MRL-*Fas*^{lprgs} mice, suppressed the production of Th1 cells, IFN-γ and anti-dsDNA antibodies, but did not significantly improve clinical manifestations of disease, including lymphoproliferation, GN, and mortality [272].

In contrast to the dramatic effects seen with IFN-γ, deletion of IL-4 results in only partial or no reduction in disease, depending on the lupus-prone strain. IL-4^{-/-} MRL-*Fas*^{lpr} mice produced less serum IgG1 and IgE (Th2-dependent subclasses), but maintained comparable levels of IgG2a, IgG2b, and autoantibodies [262], although reduced lymphadenopathy and end-organ disease were also observed. In contrast, IL-4-deficient male BXSB mice had similar autoantibody levels, GN severity and mortality as their wild-type counterparts [273], suggesting that IL-4 plays little role in the immunopathogenesis of disease in this strain.

Other studies have examined the role of signaling pathways downstream of cytokine receptors on lupus susceptibility. Deficiency of Stat4, which transduces signals from IL-12, IL-23, and type 1 IFN cytokines, significantly reduced ANAs and GN in B6.TC (sle1-3

triple congenic B6) mice [274], while NZM2410 mice had exacerbation of GN, despite reduction in anti-dsDNA [275]. Lack of Stat6, which primarily mediates IL-4 and IL-13 signals, reduced anti-nuclear antibodies, but not GN in B6.TC mice [274], while NZM2410 mice had reduced GN, but no change in anti-dsDNA [275]. Stat1-deficient BALB/c mice have lower levels of autoantibodies following TMPD treatment [276].

The IL-10-null mutation in MRL-*Fas*^{lpr} mice exacerbated skin lesions, lymphadenopathy, IFN- γ levels, IgG2a anti-DNA, GN, and mortality, while administration of IL-10 was protective [277]. The protective effect of IL-10 in the MRL-*Fas*^{lpr} mice was attributed to inhibition of the T_H1 responses that predominate in this mouse.

Eta-1 (osteopontin)-deficient normal background mice were shown to have reduced type 1 immunity for viral and bacterial infection attributed to diminished IL-12 and IFN γ and increased IL-10 production [278]. C57BL/6-*Fas*^{lpr} mice rendered Eta-1-deficient were reported to display delayed onset of polyclonal B-cell activation and somewhat delayed lymphoaccumulation and kidney disease [279]. Earlier studies have shown increased expression of Eta-1 in MRL-*Fas*^{lpr} mice [280].

EBV-induced gene 2 (EBI3, IL-17B) is a subunit of IL-27 produced by antigen-presenting cells. Deletion of this gene in MRL-*Fas*^{lpr} mice altered renal pathology from diffuse proliferative to membranous GN with increased deposits of IgG1 attributed to reduced IFN- γ , but enhanced IL-4 expression [281].

IL-21, a cytokine produced by CD4 T cells, has diverse effects on lymphocytes and NK cells. Deletion of the IL-21R in BXSB significantly reduces Ig, autoantibodies, monnocytoisis, renal disease and early mortality [282]. IL-21 in BXSB mice is produced by ICOS-expressing CD4 splenic T cells. Interestingly, a polymorphism within IL-21R confers risk for SLE [419]. IL-23 is an IL-21 family member that promotes the stabilization and expansion of the Th17 subset of CD4 T cells. B6-*Fas*^{lpr} mice deficient for its receptor (IL-23R) had reduced lymphoid hyperplasia, anti-DNA Abs and GN [420].

Cell-signaling Molecules

Fyn is a tyrosine-protein kinase involved in proximal TCR signal transduction. MRL-*Fas*^{lpr} fyn-deficient mice have reduced frequency of DN B220⁺ T cells along with decreased autoantibody levels and immunopathology, indicating an essential role for fyn in signal transduction and expansion of DN B220⁺ T cells [283]. Of interest, *Fasl*^{ld} mice with only one functional CD45 allele (CD45^{+/−}) were reported to have a ten-fold reduction in DN T-cell population and decreased Ig and anti-DNA autoantibodies [284]. The finding

suggests that CD45 plays an essential role in the activation of the DN cells, which then accumulate due to the FasL defect.

Complement Components

MRL-*Fas*^{lpr} mice deficient for the complement factor B (Bf) were utilized to investigate the role of the alternative pathway of complement activation in lupus pathogenesis [285]. Bf is an acute phase reactant required to activate this pathway and local production of Bf can be detected in the kidneys of lupus-prone mice [286]. Deletion of Bf resulted in significant reduction in GN severity and incidence of vasculitis, along with lower levels of anti-dsDNA, IgG3 anti-IgG2a RF, and IgG3 [285]. These findings support a significant role for Bf and the alternative pathway in the immune complex autoimmune pathology of these mice. Factor D deficiency in MRL-*Fas*^{lpr} mice also mildly reduced glomerular disease with decreases in serum creatinine, glomeruli C3 deposits, and kidney pathology, however, IgG deposits, proteinuria, autoantibodies, and mortality were unaffected [287].

In contrast, MRL-*Fas*^{lpr} deficient for complement component C3 had the opposite effect with slightly accelerated proteinuria and greater glomerular IgG deposition [288]. Thus, C3, instead of promoting the development of GN, may have a mild beneficial role possibly in the clearance of immune complexes. Moreover, disease severity was the same in mixed 129xMRL-*Fas*^{lpr} C4 knockout mice with or without the C3 null mutation suggesting little to no role for C3 [289].

MRL-*Fas*^{lpr} mice overexpressing a soluble CR1-related gene Y (*Crry*) transgene, showed significant inhibition of complement activation and reduced mortality, kidney disease, and C3 deposition despite no effects on lymphadenopathy, autoantibodies, or IgG kidney deposits [290].

Decay-accelerating factor 1 (Daf1, CD55) is a GPI-anchored membrane protein that inhibits complement activation on autologous cells. MRL-*Fas*^{lpr} Daf1^{−/−} mice have exacerbated disease, consistent with an autoimmune inhibitory role for Daf1 [291]. Suppression of dermatitis, but not lymphoproliferation and anti-chromatin antibodies by Daf1 was dependent on C3 [292].

Sex Hormones

Estrogen receptor 1 (ER α) deficiency in female, but not male, NZM2410 and MRL-*Fas*^{lpr} mice had reduced GN and survival despite increased or the same autoantibody levels [293]. In (NZBxNZW)F1 mice, absence of ER α resulted in similar results except for a reduction in anti-dsDNA [294].

Local Immune and Inflammatory Response Regulation

Several genes required primarily for the development of local end-organ inflammation have been identified. MRL-*Fas*^{lpr} mice deficient for ICAM-1 showed improved survival, more as a result of reduced cutaneous vasculitis than changes in autoantibody levels and GN [295, 296] consistent with ICAM-1 being critical for leukocyte adhesion in the skin [297]. Similarly, deletion of the NOS2 gene in MRL-*Fas*^{lpr} mice resulted in partial disease abrogation, with significant reduction in vasculitis and IgG rheumatoid factor, but anti-DNA antibody levels and GN were equivalent [298]. In contrast, deletion of the FcR γ-chain in (NZB × NZW)F₁ mice resulted in decoupling of the immune and inflammatory processes, resulting in similar autoantibody levels and glomerular deposits of immunoglobulin or complement, but significantly less glomerular destruction and mortality [299]. A similar result was demonstrated in the anti-GBM antibody model [300]. Similar decoupling was observed in MRL-*Faslpr* mice with deletion of MCP-1 (macrophage chemoattractant protein-1, CCL2), a chemokine that recruits macrophages and T cells to tissues [301]. Likewise, MRL-*Fas*^{lpr} mice with deletion of macrophage migration inhibitory factor (MIF) have reduced GN and skin manifestations and prolonged survival despite no change in autoantibody levels [302]. More recently, kallikrein genes have also been implicated in susceptibility to nephritis in the lupus and GBM antibody-induced nephritis models [303].

The cappuccino (*Cno*) gene encodes the component of the biogenesis of lysosome-related organelle complex 1 (BLOC-1) that functions in organelle trafficking. A spontaneous function-impairing single nucleotide deletion in *Cno* in a recombinant BXSBxMRL-*Fas*^{lpr} strain (named EOD) that develops severe crescentic GN was found to significantly reduce crescentic GN, but not to affect autoAb or immune complex deposition [304]. This amelioratory effect of the *Cno* mutation was attributed to platelet dysfunction caused by the loss of cappuccino function.

P-selectin (*Selp*) and its ligand P-selectin glycoprotein ligand-1 (*Selp*_{lg}) promote leukocyte rolling on endothelial cells and subsequent emigration into tissues. Counterintuitively, deficiency of either *Selp* or *Selp*_{lg} in MRL-*Fas*^{lpr} mice resulted in enhanced GN and dermatitis possibly because of an observed enhanced expression of MCP-1 (CCL2) [305]. Thus, P-selectin and its ligand appear to play an unanticipated, but significant role in down-regulating inflammation in lupus.

The renin-angiotensin system is critical for blood pressure homeostasis and vascular reactivity, and may also play roles in immune responses and inflammation. Unexpectedly, MRL-*Fas*^{lpr} mice with deletion of one of

the major angiotensin II receptors AT1a developed accelerated GN and mortality despite similar lymphoproliferation, autoantibodies, and disease in extrarenal tissues [306]. This was due to compensatory increased expression and stimulation of the other angiotensin II receptor, AT1b, which is primarily expressed in podocytes, leading to podocyte injury, and inflammation.

Miscellaneous genes

Terminal deoxynucleotidyl transferase (TdT) is essential for adding nucleotides to the N-regions at the V-(D)-J junctions during B- and T-cell antigen receptor rearrangement, thereby enhancing repertoire diversity [307]. TdT-deficiency in BWF1, B6-*Fas*^{lpr}, and MRL-*Fas*^{lpr} mice were all associated with varying degrees of reduced autoimmune disease indicating that a highly diverse repertoire plays a significant role in the development of lupus [308–310].

B6 mice deficient in ApoE, a lipoprotein transport protein, have increased anti-oxLDL and anti-cardiolipin autoantibodies, while autoimmunity in GVHD model was exacerbated [311]. B6-*Fas*^{lpr} mice deficient in ApoE exhibit severe exacerbation with greater autoantibodies and severe proteinuria and enlarged glomerular tufts [312].

Protein kinase CK2 (casein kinase II) is a ubiquitous heterotetrameric serine-theonine kinase composed of lupus and catalytic and regulatory subunits [313]. It can phosphorylate a large range of protein substrates, including those involved in nucleic acid synthesis, nuclear transcription, signal transduction, protein synthesis and the cytoskeleton. CK2 is active in proliferating cells, and high levels are found in certain human cancers. Overexpression of CK2 in MRL-*Fas*^{lpr} did not change lymphoma incidence, but markedly accelerated lymphoproliferation and autoimmunity, with higher IgG2a and earlier ANA positivity and proliferative GN [314]. CK2-mediated enhancement of T-cell proliferative responses was postulated to be responsible.

Leukotrienes are potent proinflammatory lipid mediators produced through the 5-lipoxygenase pathway of arachidonic acid metabolism. Arachidonic acid metabolites, including the leukotrienes, have been suggested to promote autoimmune pathogenesis in MRL-*Fas*^{lpr} mice [315], but 5-lipoxygenase deficiency in these mice resulted in a modest acceleration of mortality and a slight increase in the prevalence of arthritis in males only.

IMPLICATIONS FOR HUMAN SLE

Based on mouse studies, a number of inferences can be made about the genetics of human SLE: (1) There is

potentially a large number of lupus-predisposing, -suppressing, and -modifying genes that could possibly include over 100 that could, as single mutations, induce ANAs. (2) Both ancestral and more recent genetic alterations are likely to affect the development of SLE, many of which are likely to be recessively inherited. This indicates that current efforts to define SLE-affecting genes by linkage analysis and SNP association studies will identify only a fraction of these genes. (3) Forward genetics approaches in mice have clearly documented the difficulty in identifying susceptibility genes when there is strong linkage disequilibrium in the region of interest and in confirming even highly appealing candidate genes. These potential impediments will be even more difficult in human SLE and mouse models may provide an important and even necessary part in verification. (4) Based on the high degree of genetic heterogeneity in mouse studies as well as the fact that most of the allelic variants associated with SLE are in unaffected individuals because of the relatively low frequency of SLE (~1:2000) and marker frequency of ~1%, it is unlikely that identification of susceptibility genes will have significant diagnostic or prognostic utility except in possibly highly selected subpopulations. (5) Despite these limitations, identification of SLE-affecting genes will provide important and novel insights into disease pathogenesis and should reveal new targets for intervention.

CONCLUSION

With advancing technologies, it will be feasible in the foreseeable future to consider identification and characterization of most, if not all, of the major genes with potential to predispose and/or suppress lupus-like disease in mice. This should yield vital information about the specific pathways and mechanisms involved in both the maintenance and loss of immunological tolerance. Of particular importance will be studies to identify and characterize genes required for the development of lupus-like disease as these have relevance not only for basic understanding of disease processes, but also for therapy. Definition of the genetics of SLE in mouse models has advanced tremendously over the past decade and studies using these models should continue to generate new insights not only for lupus and autoimmunity, but also for the normal function of the immune system, as well as to provide a valuable resource for investigating human candidate genes.

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