Clinic Rev Allerg Immunol (2017) 53:181–197
DOI 10.1007/s12016-017-8605-8

Dysregulated Lymphoid Cell Populations in Mouse Models of Systemic Lupus Erythematosus

Aurélie De Groof[1] · Patrice Hémon[2] · Olivier Mignen[2] · Jacques-Olivier Pers[2] · Edward K. Wakeland[3] · Yves Renaudineau[2,4] · Bernard R. Lauwerys[1,5]

Published online: 13 May 2017

Abstract Biases in the distribution and phenotype of T, B, and antigen-presenting cell populations are strongly connected to mechanisms of disease development in mouse models of systemic lupus erythematosus (SLE). Here, we describe longitudinal changes in lymphoid and antigen-presenting cell subsets in bone marrow, blood and spleen from two lupus-prone strains (MRL/*lpr* and B6.*Sle1.Sle2.Sle3* tri-congenic mice), and how they integrate in our present understanding of the pathogenesis of the disease. In particular, we focus on (autoreactive) T cell activation patterns in lupus-prone mice. Break of T cell tolerance to chromatin constituents (histone peptides) is key to the development of the disease and is related to T cell intrinsic defects, contributed by genetic susceptibility factors and by extrinsic amplificatory mechanisms, in particular over-stimulation by antigen-presenting cells. We also describe shifts in B cell sub-populations, going from skewed immature B cell populations as an indication of disturbed central and peripheral tolerance checkpoints, to enriched long-lived plasma cells, which are key to persistent autoantibody production in the disease. B cell activation mechanisms in SLE are both T cell-dependent (break of tolerance and production of specific autoantibodies) and -independent (polyclonal B cell activation, production of autoantibodies by long-lived plasma cells). By providing a comprehensive evaluation of B and T cell surface markers in two major mouse models of SLE and a description of their changes before and after disease onset, this review illustrates how the study of lymphoid cell phenotype delivers key information regarding pathogenic pathways and supplies tools to assess the beneficial effects of novel therapeutic interventions.

Keywords Systemic lupus erythematosus · Autoimmunity · Mouse models · T cell · B cell · Flow cytometry

✉ Bernard R. Lauwerys
Bernard.Lauwerys@uclouvain.be

[1] Pôle de Pathologies Rhumatismales Systémiques et Inflammatoires, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium

[2] INSERM U1227, UFR Médecine, Brest, France

[3] Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[4] Laboratoire d'Immunologie et Immunothérapie, CHRU Brest, Brest, France

[5] Department of Rheumatology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Introduction

Mouse models of systemic lupus erythematosus (SLE) are widely used in order to test pathogenic hypotheses or acquire pre-clinical data on specific drugs. While these models share common phenotypes in terms of autoantibody profiles leading to end-organ involvement (e.g., nephritis), mechanisms of disease differ from strain to strain, and, most notably, from the human situation. Acquiring thorough knowledge of the main pathogenic features of each mouse model is therefore an important step in order to instruct adequate experimental interventions and help with their interpretation.

In the present review, we intend to describe key characteristics of common lupus-prone strains of mice (e.g., BWF1 and derived strains, MRL/*lpr*, and BXSB), in terms of pathogenic mechanisms leading to the development of autoimmunity, and also in terms of aberrant distribution and functions of lymphoid and myeloid cell populations.

Genetic Susceptibility to SLE in Mouse Models of the Disease

By definition, genetic factors play a determinant role in the development of SLE in inbred models of the disease. In these models, and also in humans, it is generally accepted that genetic susceptibility impacts the development of autoimmunity at different stages of a multi-step process, i.e., impaired clearance of immune complexes and apoptotic cells leading to a loss of tolerance to autoantigens (e.g., anti-chromatin autoantibodies), amplification of the T and B cell autoimmune response, and finally susceptibility to end-organ involvement (Fig. 1).

Genetic requirements to reach the first level (loss of tolerance to autoantigens) are frequently met in mice and humans, as illustrated by the detection of anti-nuclear antibodies in up to 5% of healthy individuals under normal conditions, or at a higher rate after disruption of immune homeostatic mechanisms (by a viral infection in humans, or a genetic knock-out or transgenic modification in mice). Even when a strong accelerator is present (e.g., *lpr* mutation leading to MRL/lpr mice or *Yaa*-containing Y chromosome in BXSB animals), genetic susceptibility to SLE is polygenic. Susceptibility is related to the additive or synergistic effects of frequent gene variants that, taken individually, only display a modest effect on the mechanisms leading to the development of autoimmunity, but have the ability to push the immune system beyond a (theoretical) autoimmunity threshold, when combined in the same genome [1, 2]. Interestingly, susceptibility variants that push the immune system toward more (auto)immunity might have been subjected to positive evolutionary pressure, due to their favorable effect on immune responses to infectious triggers [3]. This potentially explains why so many mouse strains

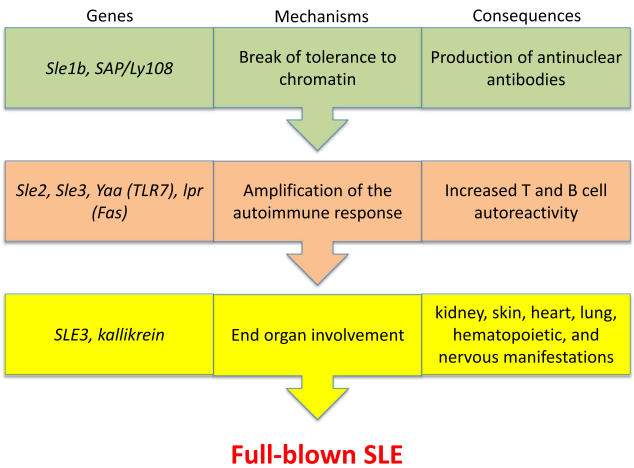

Fig. 1 The development of SLE is a multi-step process. Genetic susceptibility to SLE is related to the additive or synergistic effects of allelic variants of numerous genes involved in the regulation of the immune system. This non-exhaustive list (restricted to mouse susceptibility genes) illustrates how these variants impact the development of the disease in a multistep process

(e.g., 129, MRL, NZB, and NZW) readily develop autoimmune features (production of autoantibodies) in various experimental conditions.

Conversely, the same autoimmune phenotype may be due to different combinations of genetic variants in different mouse species and in humans, and it is therefore not a surprise that genetic association studies in murine models of SLE led to the identification of very different susceptibility loci according to the strain explored. That genetic susceptibility to SLE is complex is well illustrated in human genetic association studies, in which high prevalence of susceptibility alleles in controls, and the possibility of developing the disease based on alternative sets of genetic variants (a definite probability when the patients belong to different ethnic backgrounds), result in overall low genetic effects (odd ratios between 1.1 and 1.5, except for HLA alleles that can have odd ratios >2) for individual candidate genes, even for those having important mechanistic roles. In humans, variations in epigenetic and environmental factors are additional layers of complexity in our understanding of the development of the disease [4–7].

Thus, genetic association studies performed in SLE-prone mice resulted in the identification of numerous susceptibility loci, containing one or sometimes several susceptibility genes. The telomeric end of chromosome 1, one of the non-MHC loci displaying the strongest association with the development of the disease across different strains of mice (and also in humans), is such a cluster of numerous candidate genes. Using NZM2410 lupus-prone mice, a homozygous strain derived from the prototypical $(NZB \times NZW)_{F1}$ (or BWF1) model, Morel et al. identified, in addition to the *H-2* locus, *Sle1* on the telomeric end of chromosome 1, and also *Sle2* on chromosome 4 and *Sle3* on chromosome 7, three chromosomal regions that are strongly associated with the development of the disease [8]. It is important to note that C57Bl/6 mice congenic for each of these loci do not develop SLE [9], but display patterns of immune cell activation that will be further described in the next paragraphs. By contrast, transfer of the three loci in the C57Bl/6 genome is sufficient to induce full-blown SLE, with a very high penetrance of immune complex-mediated nephritis [10].

Amplification of the autoimmune response is the step in which loss of tolerance to chromatin translates into pathogenic events, e.g., due to the maturation of the autoantibody response, and the production of high-affinity autoantibodies. In humans, type I interferons (IFN) play such amplificatory roles on autoreactive T and B cell activation, and several strategies are being developed in order to block these cytokines in SLE patients [11–14]. By contrast, a strong IFN bias is not spontaneously observed in most common mouse models of SLE. Clinical disease is exacerbated in SLE-prone mice overexpressing IFNα after injection of a recombinant adenoviral vector [15–17], and this experimental strategy was used in order to obtain pre-clinical data on IFN blockade in SLE animals.

The lymphoproliferation (*lpr*) trait of MRL/*lpr* mice is due to a *Fas* mutation, resulting in the accumulation of immune cells in secondary lymphoid organs, including autoantibody producing B cells. In humans, the *Fas* mutation also results in a lymphoproliferative disease (Canale-Smith syndrome), but very few of these patients display autoimmune features. Similarly, C57Bl/6 mice carrying the *Fas* mutation only develop minor autoimmune manifestations [18]. This observation emphasizes that *lpr* is an amplifier, rather than the cause of autoimmunity in MRL/*lpr* mice, and led to the identification of multiple susceptibility loci, associated with the development of the disease in MRL/*lpr* strain [18–24].

In BXSB mice, SLE symptoms are more prevalent in males, a very unique situation for a disease with such a strong female bias, due to the presence of the chromosome Y-associated accelerator (*yaa*). A few years ago, it appeared that *yaa* was related to the translocation on the Y chromosome of a fragment of chromosome X, resulting in a duplication of 16 genes, including the *Toll-like receptor 7* (*Tlr7*) gene in the genome of male animals [25, 26]. In BXSB mice, *Tlr7* duplication in male is strongly associated with the development of the disease, and the contribution of *TLR7* is further substantiated by in vivo experiments indicating that overexpression or downregulation of *TLR7* gene expression in lupus-prone animals worsens or improves disease manifestations, respectively (see below).

In SLE, end-organ involvement is dependent on the autoantibody profile, e.g., anti-double stranded (ds)DNA antibodies are associated with renal involvement [27–29]. However, some data indicate that genetic factors are also involved. Thus, injection of rabbit anti-glomerular basement membrane nephrotoxic serum leads to more severe renal disease and pathological changes in NZW compared to other control strains (C57Bl/6, BALB/c), despite similar glomerular deposits of the pathogenic antibodies [30], an observation that points to the presence of inborn mechanisms of end-organ reactivity to autoimmune aggressions. Similarly, the *Sle3* variant of the gene encoding kallikrein on chromosome 7 is characterized by a decreased renal expression of kallikrein in response to anti-GBM antibody challenge in B6.*Sle3* mice (C57Bl/6 mice congenic for *Sle3*), and exogenous administration of kallikrein using an adenoviral vector has a protective effect on disease progression in these animals [31].

T Cell Phenotype in SLE Mouse Models

That the production of anti-dsDNA antibodies is CD4 T cell driven was one of the most important discoveries of the early nineties in the field of SLE. Thus, Mohan et al. isolated CD4 T cell clones from $(SWR \times NZB)_{F1}$ (or SNF1) lupus-prone mice, based on their ability to provide help in the production of anti-dsDNA antibodies by syngeneic B cells, and found that these CD4 T cells were specifically stimulated by nucleosomes. The authors further demonstrated that purified splenic CD4 T cells from not only SNF1, but also BWF1 mice proliferated in response to purified nucleosomes or histones presented by syngeneic splenic antigen-presenting cells (APC) from 1-month-old (disease-free) animals. Finally, immunization of young SWF1 mice with nucleosomes significantly accelerated the development of nephritis [32]. Thus, in these mice, anti-dsDNA antibody-producing B cells capture nucleosomes, process them, and present histone peptides to histone-specific T cells, which in turn provide bystander help in the production of anti-dsDNA antibodies. Similar reactivity against histones or non-histone chromosomal proteins was reported in human CD4 T cells isolated based on their ability to stimulate the production of anti-dsDNA antibodies [33].

Not surprisingly, chronic administration of inhibitory anti-CD4 monoclonal antibodies to BWF1 mice efficiently prevents or treats nephritis, through decreased production of IgG anti-dsDNA autoantibodies [34–37]. Similar effects of in vivo CD4 T cell inhibition were observed in the production of (both IgM and IgG) anti-dsDNA antibodies in MRL/*lpr* mice, although treated mice finally do develop nephritis in this model [38–40]. IFNα-induced acceleration of disease in 3-month-old BWF1 mice is also significantly prevented by the injection of a depleting anti-CD4 monoclonal antibody that, in particular, impacts production of IgG anti-dsDNA autoantibodies and renal disease [15].

Phenotype and function of CD4 T cells were extensively studied in C57Bl/6 animals carrying congenic NZM2410-derived SLE susceptibility fragments. Thus, B6.*Sle1* mice have elevated IgG anti-chromatin autoantibodies but do not develop renal disease. Spleens and lymph nodes from B6.*Sle1* mice have higher percentages of activated (CD69-positive) CD4 T cells. In addition, purified B6.*Sle1* spleen and lymph node T cells proliferate and produce IFNγ in response to purified histones (H2A, H2B, H3, and H4) [41]. T cell activation in these mice is still present in B6.*Sle1*.μMT mice with no circulating B cells, suggesting an intrinsic effect of *Sle1* on T cells [42]. However, in B6 radiation chimera receiving mixed bone marrows from C57Bl/6 and B6.*Sle1* mice, increased expression of CD69 is also found in CD4 T cells of C57Bl/6 origin, thereby indicating that T cell activation is at least partly secondary to loss of tolerance in the B cell compartment of B6.*Sle1* mice [43]. *Sle1* is a cluster of 4 sub-loci (*Sle1a* to *d*) among which *Sle1b* recapitulates many of the features typical of *Sle1*, due to the presence of an activating polymorphic variant of *SLAM family member 6* (*SAP*/*Ly108*), a cell surface receptor expressed on NK, T, and B cells [44]. In addition to increased percentages of splenic activated $CD4^+CD69^+$ cells compared to C57Bl/6 controls, B6.*Sle1b* female mice have larger proportions of splenic $CD4^+CD44^{high}CD62L^{high}$ effector memory and $CD4^+CD44^{high}CD62L^{low}$ short-lived effector T helper cells.

Percentages of $CD4^+CXCR5^{high}PD\text{-}1^{high}$ T follicular helper cells are also higher in B6.*Sle1b* compared to C57Bl/6 control mice, in parallel with increased numbers of germinal centers observed in their spleens [45]. T follicular helper cells are key in the selection and affinity maturation of autoantibody-producing B cells in germinal centers. Numbers of circulating $CD4^+CXCR5^+$ $ICOS^+$ or $PD\text{-}1^+$ T follicular helper cells are significantly increased in SLE patients compared to controls [46, 47].

B6.*Sle3* congenic mice also have larger numbers of $CD4^+CD69^+$ activated T cells in the spleen, in particular when they are aging, and an increased CD4/CD8 ratio in spleen and lymph nodes. In vitro expansion of CD4 T cells upon anti-CD3 stimulation is significantly higher in B6.*Sle3* compared to control C57Bl/6 mice, due to increased proliferation and reduced activation-induced cell death [48]. This phenotype is not due to an intrinsic T cell defect, but results from the *Sle3*-dependent activation of antigen-presenting cells (see below).

Activated T cells are not only found in secondary lymphoid organs in SLE-prone mice, but also in the kidney. This is also reflected in high-throughput transcriptomic studies performed on the kidneys of nephritic BWF1 animals, in which T cell and plasma cell gene expression signatures are predominant [49, 50]. Fairhurst et al. studied the profile of infiltrating inflammatory cells in the kidneys of B6.*Sle1.yaa* (C57Bl/6 mice congenic for both *Sle1* and *yaa*) nephritic mice and found a predominant population of CD4 T cells and $Gr1^{high}$ monocytes. CD4 T cells were activated, as demonstrated by increased expression of ICOS and PD-1. $GR1^{high}$ monocytes also had an activated phenotype, overexpressing CD69 and CXCR4, and this was also the case for infiltrating B cells. TLR7 played a role in this renal phenotype, and *TLR7* deletion on the X chromosome, resulting in a 2-fold decrease in the TLR7 copy number in B6.*Sle1.yaa.TLR7*-mice, prevented the development of nephritis and kidney infiltration by inflammatory cells, despite the persistence of high titers of IgG antinuclear antibodies [26]. Conversely, transgenic overexpression (4- to 8-fold) of TLR7 in a non-autoimmune background leads to the development of an SLE-like disorder, characterized by the production of anti-RNA autoantibodies, expansion of $CD11c^+$ $MHCII^-$myeloid cells, and immune complex-mediated nephritis [51]. Interestingly, moderate (two-fold, i.e., similar to the level of over-expression observed in *yaa* mice) overexpression of TLR7 in a C57Bl/6 background does not lead to any symptoms, but when combined with *Sle1* in B6.*Sle1.Tg7* animals, increased TLR7 expression led to severe nephritis similar to the B6.*Sle1.yaa* strain [52].

By contrast to the overwhelming evidence demonstrating the role of CD4 T effector cells in SLE-prone mice and patients, characterization of T regulatory (Treg) cell number and function did not deliver concordant results across the studies, probably in view of the methodological difficulties related to the identification and functional analyses of these cells. Percentages of $CD4^+CD25^+CD69L^{high}$ or $CD4^+Foxp3^+$ Treg cells are decreased in spleens and lymph nodes of BWF1 mice, at least in pre-diseased animals, but this is not the case in older mice [53, 54] or in the MRL/lpr lupus-prone strain, in which Treg cells are rather increased [55, 56]. Using B6.*Sle1a* congenic mice, the group of Laurence Morel found that decreased Treg cell numbers and function in this strain were not intrinsic to Treg cells themselves, but were instead related to increased IL6 production by bone marrow dendritic cells [57, 58]. In any case, Treg cell modulation in lupus-prone mice, either by injection of purified Treg cells, or by administration of low-dose IL2, resulted in significant improvements in disease activity [53, 59, 60]. Interestingly, preliminary studies in patients with SLE also indicated that low-dose IL2 administration resulted in increased circulating Treg cells, which augurs well for potential clinical benefits of this therapeutic strategy [61].

Natural killer T (NKT) cells are cells from the lymphoid lineage with innate, but also adaptive functions due to the expression of T cell receptors. While type II NKT cells display a diverse TCR repertoire, type I or invariant NKT (iNKT) cells express an invariant TCRα chain that recognizes CD1d molecules. Again, inconsistent results were reported on the role and functions of these cells in mouse models of SLE. Thus, numbers of iNKT cells in blood and spleen of 7-, 14-, and 24-week-old BWF1 mice are similar compared to age-matched Balb/c animals. Yet, cytokine production, either directly by iNKT themselves or by transactivated T and B cells, is lower in BWF1 compared to Balb/c animals in response to α-GalCer, a typical iNKT cell ligand, and this effect is more pronounced in younger animals [62]. Functional defects in iNKT cell functions might be relevant in the pathogenesis of SLE, in view of their contact- and CD1d-dependent inhibitory effects on autoantibody-producing B cells (by contrast to their rather Th2 cytokine-dependent stimulatory effects on non-autoantibody producing B cells that express less CD1d) [63, 64]. Nevertheless, injections of α-GalCer to lupus-prone mice generated contradictory results according to the injection schedule and age of the recipients: disease worsening in older mice receiving repeated injections, versus protective effect in younger animals after short-term treatment [65, 66].

Finally, this chapter on T cells would not be complete without addressing the dual role of CD8 T cells in the pathogenesis of SLE. In BWF1 mice, CD8 T cells expand less compared to CD4 T cells, resulting in decreased CD8 T cell percentages and increased CD4/CD8 ratios in secondary lymphoid organs [67]. While in vivo CD4 T cell inhibition prevented disease progression in BWF1 mice, injection of anti-CD8 antibodies resulted in increased disease severity, due to the blockade of a CD8 T cell sub-population with suppressive properties [68]. CD8 T suppressor cells are $CD44^+CD122^+Ly49^+$ CD8 T cells that inhibit the expansion of CD4 T follicular helper cells and the production of autoantibodies through recognition of Qa-

1 at the surface of T follicular helper cells. Qa-1 deficient mice develop a lupus-like disorder characterized by the presence of dysregulated T helper follicular cells, autoantibody production, and nephritis [69]. Conversely, suppressor function of $CD44^+CD122^+Ly49^+$ CD8 T cells is significantly impaired in B6.*yaa* lupus-prone mice, underscoring the role of suppressor CD8 T cells in regulating autoimmune mechanisms at the systemic level [70]. By contrast to these immunosuppressive effects at the systemic level, CD8 T cells locally amplify renal inflammatory mechanisms in mouse models of immune glomerular injury [71] and are also involved in periglomerular and tubular cell damage, e.g., after rupture of the Bowman's capsule and cross-presentation of cryptic glomerular antigens by resident interstitial antigen-presenting cells [72]. In humans with lupus nephritis, increased CD8 T cell numbers in kidney biopsies are associated with poorer response to therapy, an observation in line with a pathogenic role for CD8 T cells in the target organ [73].

In order to illustrate alterations in T cell phenotype in SLE-prone mice, both of our groups used flow cytometry panels in order to compare MRL/*lpr* versus C57Bl/6 (in Brest) and B6.*Sle1.Sle2.Sle3* versus C57Bl/6 (in Brussels) mice before and after disease onset (disease manifestations are apparent at age 5 months in B6.*Sle1.Sle2.Sle3* mice and at age 12 weeks in MRL/*lpr* animals). Although the flow cytometry data are presented in the same figures, they were not generated using the same antibody panels, as indicated in the figure legends and summarized in Tables 1, 2, and 3. In B6.*Sle1.Sle2.Sle3* mice, results were expressed as percentages of positive cells compared to a reference population, while absolute numbers were used in MRL/*lpr* experiments. Despite these differences in our methodological approaches, the data displayed in the figures are representative of the changes observed in these mice, as discussed in the above paragraphs. Thus, our results confirmed the presence of activated (i.e., CD69-positive) CD4 and CD8 T cells in the blood of B6.*Sle1.Sle2.Sle3* compared to C57Bl/6 mice, from disease onset (5 months) to later stages of the disease. In B6.*Sle1.Sle2.Sle3* mice, percentages of blood CD4 and CD8 T cells were not different compared to C57Bl/6 controls. Percentages of CD8 T cells were lower in the spleens of B6.*Sle1.Sle2.Sle3* compared to C57Bl/6 mice. In MRL/*lpr* mice, sheer numbers of conventional CD4 and CD8 T cells were more elevated in peripheral blood, spleen, as well as in thymus and lymph nodes compared to C57Bl/6 animals (Figs. 2 and 3, and data not shown).

B Cell Phenotype in SLE Mouse Models

SLE is not only characterized by the production of specific CD4 T cell-driven anti-chromatin autoantibodies, but also by a polyclonal B cell activation and hypergammaglobulinemia [74–77]. In SLE patients, circulating B cells have an activated phenotype (overexpression of CD95, HLA class II, and co-stimulatory molecules) and display a skewed differentiation pattern characterized by a decrease in naïve and unswitched memory B cells, and an increase in switched memory, double-negative B cells, and in plasmablasts [78, 79]. B cell development occurs in the bone marrow, where two thirds of autoreactive B cells are eliminated. B cells leave the bone marrow as transitional B cells, and this stage of development is also an important autoreactivity checkpoint, with reported alterations in SLE patients. In particular, proportions of $CD24^{high}CD38^{high}$ transitional B cells are higher in SLE compared to control individuals [80]. Last but not least, qualitative and quantitative modifications of the $CD5^+$ B1 cell subsets are also reported in SLE patients [81, 82].

Table 1 Peripheral blood T cells, B cells, and dendritic cells (DC) in lupus-prone mice

Subset	Phenotype	B6.*Sle1, Sle2, Sle3* vs C57Bl/6	Mrl/lpr vs C57Bl/6
CD4 T cell	$CD4^+$	normal	expanded
Activated	$CD4^+CD69^+$	expanded	NT
Treg	$CD4^+CD25^+CD127^{low}$	NT	normal
CD8 T cell	$CD8^+$	normal	expanded
Activated	$CD8^+CD69^+$	expanded	NT
B cells	$CD19^+$ or $B220^+$/CD138-	normal	normal
Immature/T1	$B220^{int}$ CD21-CD23-IgM^+	NT	expanded
Mature	$B220^{high}IgM^+$	NT	normal
Activated	$CD19^+CD69^+$	normal	NT
Plasmablasts	$CD19^+CD138^+$	reduced	NT
Plasma cells	CD19-$CD138^+$	expanded	NT
	$B220^+CD138^+$	NT	highly expanded
DC	$CD11c^+CD11b^+$	NT	reduced
pDC	$CD11c^+SiglecH^+$	expanded	NT

NT not tested

Table 2 Spleen T cells, NK cells, B cells, and dendritic cells (DC) in lupus-prone mice

Subset	Phenotype	B6.*Sle1, Sle2, Sle3* vs C57Bl/6	Mrl/lpr vs C57Bl/6
CD4 T cell	$CD4^+$	normal	expanded
Treg	$CD4^+CD5^+CD25+$	normal	NT
Treg	$CD4^+CD5^+CD25^+CD127^{low}$	NT	expanded
CD8 T cell	$CD8^+$	reduced	expanded
NK cells	CD49b CD5-	normal	NT
	$NK1.1^+$	NT	reduced
B cells	$CD19^+$ or B220+	normal	normal
T1	$CD19^+B220^+CD93^+CD23$-IgM+	normal	NT
	$B220^+CD21$-CD23-IgM+	NT	normal
T2	$CD19^+B220^+CD93^+CD23^+$IgM+	normal	NT
	$B220^+CD21^+CD23^+$IgM+	NT	reduced
T3	$CD19^+B220^+CD93^+CD23^+$IgM-	reduced	NT
Mantle zone	$B220^+CD93$-$CD21^+CD23$-	normal	NT
	$B220^+CD21^+CD23$-IgM+	NT	expanded
Follicular	$B220^+CD93$-$CD21^{int}CD23$+	reduced	NT
	$B220^+CD21^{int}CD23^+IgM^{low}$	NT	reduced
B1a	$B220^+CD93$-IgM^+IgD-CD21-CD23-$CD5^+$	expanded	NT
Plasma cells	$B220^+$CD138+	expanded	highly expanded
DC	$CD11c^+$CD11b+	NT	expanded
pDC	$CD11c^+$SiglecH+	normal	NT
cDC	$CD11c^+$SiglecH-	normal	NT

NT not tested

In mouse models of SLE, increase in the percentage of ($CD19^+IgM^+CD43^+CD5^+$) B1a cells is one of the most common features of the disease [83–85]. Enrichment in B1a cells is under genetic control and is a major characteristic of B6.*Sle2* congenic mice. *Sle2* is a cluster of 3 susceptibility loci, one of which is characterized by a decreased expression of the protein encoded by the *Cdkn2c* gene: cyclin-dependent kinase inhibitor p18, found to be a regulator of the B1a cell

Table 3 Bone marrow B cells in lupus-prone mice

Subset	Phenotype	B6.*Sle1, Sle2, Sle3* vs C57Bl/6	Mrl/lpr vs C57Bl/6
B cell lineage	$B220^+$	normal	reduced
Pre/Pro B	$B220^+CD24^{int}$CD43+	normal	NT
	$B220^+CD43^{high}$	NT	normal
Developing B	$B220^+CD24^{high}$CD43-	reduced	NT
Pro B/Pre B	$B220^+CD24^{high}$CD43-IgD-IgM-	expanded	normal
Pro B	$B220^+CD43^{int}$	NT	reduced
Pre B	$B220^+$CD43-	NT	reduced
Immature	$B220^+CD24^{high}$CD43-IgM^{int}IgD-	expanded	NT
	$B220^+IgM^+$IgD-	NT	normal
Transitional	$B220^+CD24^{high}$CD43-IgM^+IgD-	expanded	NT
	$B220^+IgM^+IgD^{int}$	NT	normal
Mature	$B220^+IgM^+IgD^{high}$	NT	reduced
Early mature	$B220^+CD24^{high}$CD43-IgM^+IgD+	reduced	NT
Late mature	$B220^+CD24^{high}$CD43-IgM-IgD+	expanded	NT
Plasma cells	CD138+	normal	expanded

NT not tested

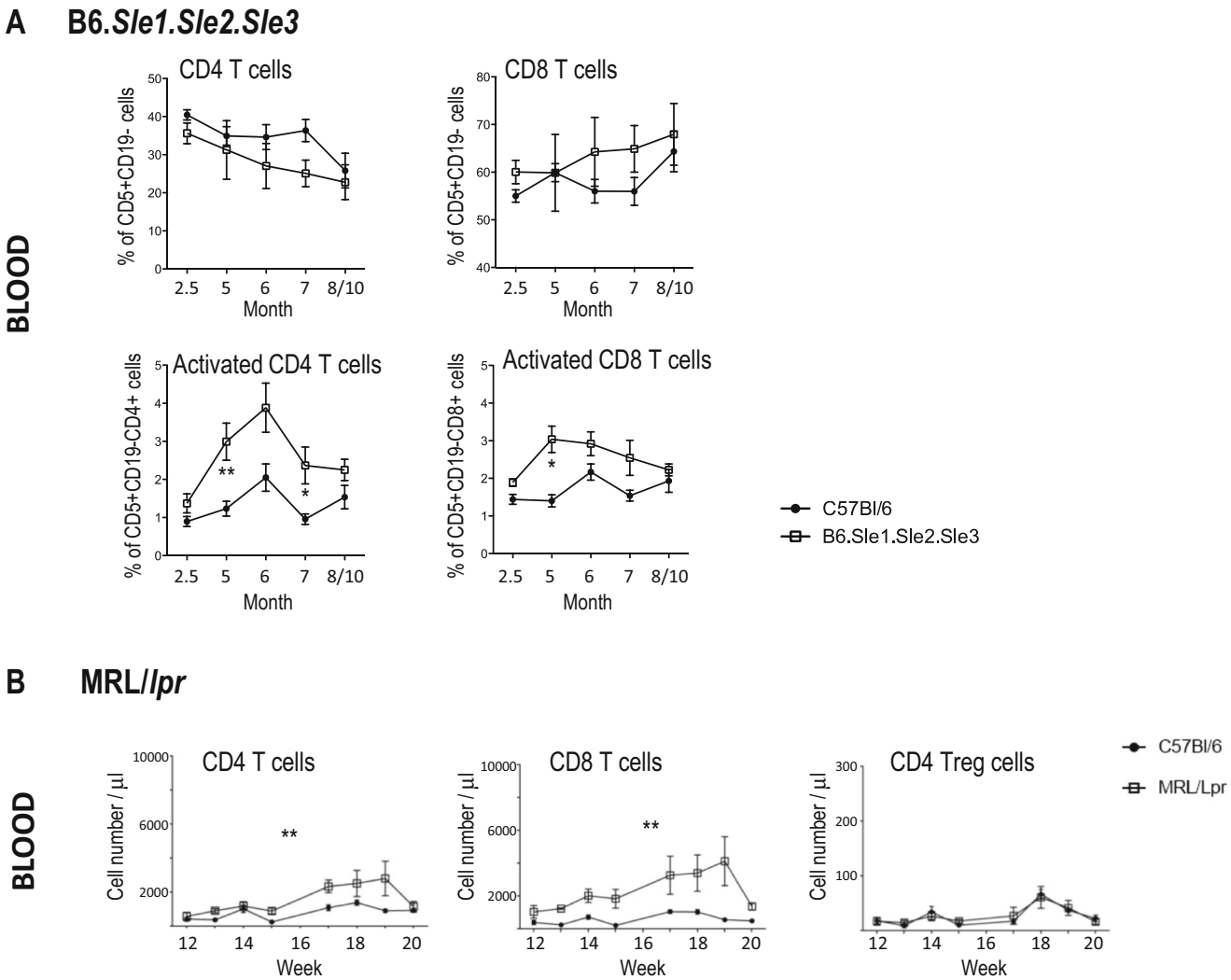

Fig. 2 Blood CD4 and CD8 T cells in lupus-prone mice. **a** Blood samples from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice were harvested at the indicated time points and stained with a viability dye and the following antibodies: CD5, CD4, CD8a, and CD69. Cell activation was defined based on CD69 expression. Percentages are calculated in reference to the population indicated on the *Y* axis. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Blood samples from MRL/*lpr* and C57Bl/6 mice were harvested at the indicated time points and stained with the following antibodies: B220, CD5, CD8, CD4, CD127, and CD25. Treg cells were defined as $CD25^+$ $CD4^+CD127^{low}$ cells $**p < 0.01$ using Mann-Whitney tests

pool [86, 87]. B1a cells are self-renewing, natural IgM antibody-producing cells, and their contribution to disease pathogenesis is not fully understood [88]. Natural antibodies may display a low affinity to autoantigens, thereby potentially giving rise to high affinity autoantibodies in specific conditions (e.g., in the presence of an autoimmune accelerator). However, autoantibody production is not restricted to $CD5^+$ B cells in BWF1 mice, as evidenced by in vitro or in vivo reconstitution experiments with either $CD5^-$ or $CD5^+$ B cells [89]. Other than antibody-producing cells, B1a cells also play a role as antigen-presenting cells, due to their expression of co-stimulatory molecules (B7.1, B7.2, CD24, LFA-1, ICAM-1) [83], and are also known to produce IL-10, a cytokine strongly overexpressed in SLE patients, and in mouse models of the disease [81, 90–92].

In mice, immature B cells that escaped bone marrow checkpoints migrate to the spleen as transitional (T1) B cells. The T1 cell stage is an important tolerance checkpoint, and many autoreactive B cells are eliminated at this stage. In particular, T1 B cells with a strong affinity for self-antigens undergo apoptosis, and this mechanism is impaired in NZB [93] and in TLR7 transgenic mice [94]. Similarly, T1 B cells from B6.*Sle1b* animals transgenic for a lysozyme B cell receptor are efficiently eliminated after strong B cell receptor (BCR) stimulation with the antigen, but they resist apoptosis when weak antigen stimulation is applied, by opposition to T1 B cells from BCR transgenic controls not carrying the *Sle1b* susceptibility interval, thereby emphasizing the role of *Sle1b* on B cell tolerance [95]. T1 transitional B cells further differentiate into T2 cells, next into mature follicular B cells, or, in some

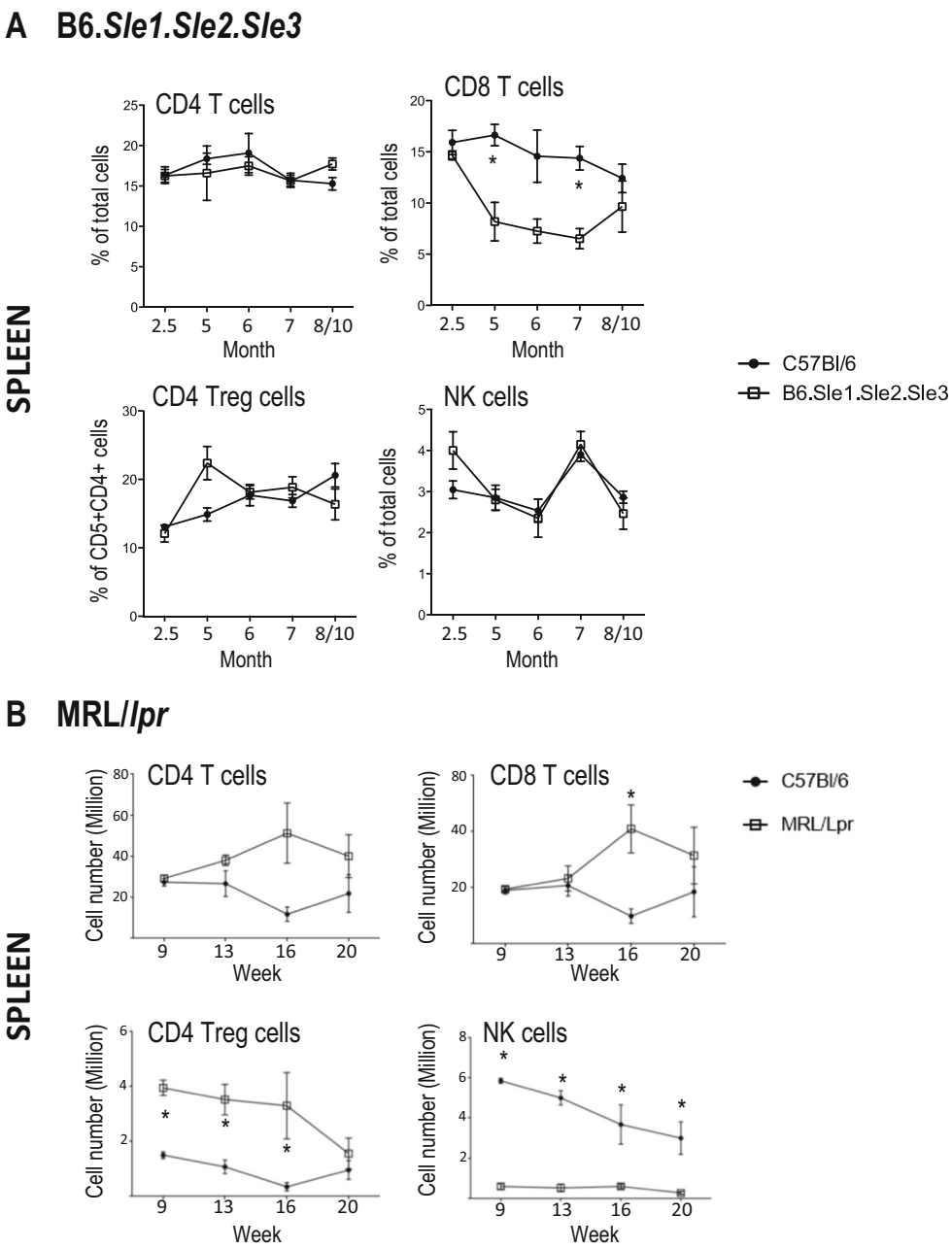

Fig. 3 Spleen T and NK cells in lupus-prone mice. **a** Spleens from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice were harvested at the indicated time points and stained with a viability dye and the following antibodies: CD5, CD4, CD8a, CD25, and CD49b. Treg cells were defined as $CD25^{+}CD5^{+}CD4^{+}$ cells. NK cells were defined as $CD49b^{+}CD5^{-}$ cells. Percentages are calculated in reference to the population indicated on the *Y* axis. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Spleens from MRL/*lpr* and C57Bl/6 mice were harvested at the indicated time points and stained with the following antibodies: B220, CD5, CD8, CD4, CD127, CD25, and NK1.1. Treg cells were defined as $CD25^{+}CD5^{+}CD4^{+}CD127^{low}$ cells. NK cells were defined as NK1.1 cells, $*p < 0.05$ using Mann-Whitney tests

circumstances, into marginal zone B cells. Marginal zone B cells are involved in T cell-independent mechanisms of antibody production and display higher sensitivity to TLR9 stimulation, while mature follicular B cells will differentiate into mature naïve B cells that further recirculate to secondary lymphoid organs and are involved in T cell-dependent responses. Peripheral tolerance checkpoints can be disrupted in numerous situations, as is the case in BAFF-transgenic mice that are characterized by increased transitional and MZ B cells and develop a lupus-like autoantibody-mediated syndrome [96]. However, increase in overall numbers of transitional and marginal zone B cells is not a typical feature found in BWF1 mice themselves. These mice rather display a decrease in mature follicular cells, as a sign of disrupted B cell development and tolerance checkpoints. They also display a decrease in transitional T3 cells, a sub-population of anergic B cells with a still unclear ontology [97].

Sustained autoantibody production in patients or mice receiving strong immunosuppressive agents (such as corticosteroids and cyclophosphamide) led to the identification of the

role of depletion-resistant long-lived plasma cells in the pathogenesis of the disease. Using BrdU in the drinking water of BWF1 mice in order to track dividing cells in their spleen, Hoyer et al. demonstrated that the spleen of BWF1 mice contained anti-DNA antibody producing CD138-positive plasma cells, which did not divide for at least 12 weeks (the time of BrdU feeding). An estimated 40% of autoantibody-producing $CD138^+$ cells were such long-lived plasma cells in the spleen. These cells express low MHC II, by opposition to short-lived plasma cells, and are resistant to in vivo cyclophosphamide therapy [98]. Not only the spleen, but also bone marrow and kidneys of BWF1 mice host long-lived plasma cells [99]. Transfer of BWF1 CD138-positive cells into *Rag1* −/− mice results in the establishment of autoantibody-producing long-lived plasma cells in spleen and bone marrow of recipient mice and the development of nephritis, thereby demonstrating the ability of these cells to cause disease manifestations, independent of any additional stimulus [100].

By contrast to conventional immunosuppressive or cytotoxic drugs, bortezomib, a proteasome inhibitor, targets both short-lived and long-lived plasma cells, by activation of the terminal unfolded protein response. Thus, bortezomib administration induces a drastic decrease in total and anti-dsDNA antibody-producing $CD138^{high}CD25^-$ intracellular κ light $chain^+$ plasma cells in spleen and bone marrow of BWF1 mice, resulting in decreased serum dsDNA antibody titers and prevention of glomerulonephritis [101]. Optimal therapy was achieved by not only depleting long-lived plasma cells with bortezomib, but also the pool of precursors from which they are generated, using cyclophosphamide or anti-CD20 [102, 103].

Rituximab, a depleting anti-CD20 antibody, does not target plasma cells that are CD20 negative. The drug is commonly used in the treatment of refractory lupus nephritis, but also other autoimmune disorders [104–109]. Mahévas et al. reported the presence of autoantibody secreting cells in the spleen of patients with idiopathic thrombocytopenic purpura, resistant to rituximab therapy. Intriguingly, transcriptomic profiling of plasma cells in the spleen from rituximab-treated patients was different compared to non-treated patients or healthy donors and characterized by the expression of molecular signatures associated with a long-lived phenotype (overexpression of anti-apoptotic genes and negative regulator of the cell cycle and downregulation of genes involved in positive regulation of cell cycle). Increased production of BAFF in the supernatants of spleen cell cultures from rituximab-treated patients is suspected to explain the generation of long-lived plasma cells in rituximab-treated patients [110, 111].

Alterations in B cell phenotype in B6.Sle123 and MRL/lpr mice are illustrated in Figs. 4, 5, and 6. In our experiments, terminally differentiated plasma cells were more numerous in blood and spleens of both B6.*Sle1.Sle2.Sle3* and MRL/*lpr* mice compared to controls. MRL/*lpr* mice also had increased numbers of plasma cells in peripheral blood, and even in the spleen as well as in thymus and lymph nodes (Figs. 4 and 5, and data not shown). In MRL/*lpr* mice, numbers of T1 B cells were significantly increased in the peripheral blood, in line with similar observations in other strains of lupus-prone mice and in humans. In the spleens of both lupus-prone strains, we observed decreased follicular B cells compared to C57Bl/6 mice, as discussed earlier. Percentages of T3 transitional B cells were also significantly decreased while B1a cells were significantly increased in B6.*Sle1.Sle2.Sle3* spleens (Figs. 4 and 5). In the bone marrow (Fig. 6), we found differences in developing B cell populations between the two lupus-prone strains, potentially indicative of dysregulated tolerance checkpoints. In particular, we observed decreased overall developing B cells in both lupus-prone strains compared to control mice, although differences in developing B cell subpopulations were not entirely overlapping between B6.*Sle1.Sle2.Sle3* and MRL/*lpr* animals.

Role of Antigen-Presenting Cells in Mouse Models of SLE

The role of myeloid cells in autoimmune disorders is extensively reviewed in another contribution of this series of reviews [112]. In the next paragraphs, we focus on reports highlighting the links between antigen-presenting cell dysfunctions and T or B cell activation in SLE. In humans, impaired clearance of apoptotic material by SLE macrophages in lymph nodes is an important step in the pathogenesis of the disease, resulting in the availability of nuclear autoantigens for presentation by professional antigen-presenting cells such as dendritic cells [113]. Among them, $CD11b^-CD11c^-CD123^+$ plasmacytoid dendritic cells (pDC) produce high levels of IFNα in response to stimulation and are therefore under particular scrutiny in SLE research. Thus, heterozygous deletion of *Tcf4*, a gene encoding E2-2, a transcription factor involved in the development of pDC, led to a significant improvement of disease manifestations in TLR7 transgenic mice, i.e., a decrease in $CD11c^+$ $MHCII^-$ myeloid cells, and decreased renal deposition of immunoglobulins and nephritis. Similarly, decreased T cell activation and production of autoantibodies and significant improvement of immune complex-mediated nephritis were observed in *Tcf4*+/− B6.*Sle1.Sle3* compared to wild-type B6.*Sle1.Sle3* lupus-prone animals [114].

However, in vitro depletion experiments using human cells indicated that pDC are not the sole IFNα producers in SLE patients [115], underscoring the potential role of $CD11b^+CD11c^+$ myeloid DC in the pathogenic process. By breeding B6.*Sle1.Tg7* mice that conditionally overexpress TLR7 with a CD11c-Cre reporter strain, Celhar et al. normalized TLR7 expression in CD11b-positive conventional DC (cDC) and pDC, resulting in decreased production of anti-

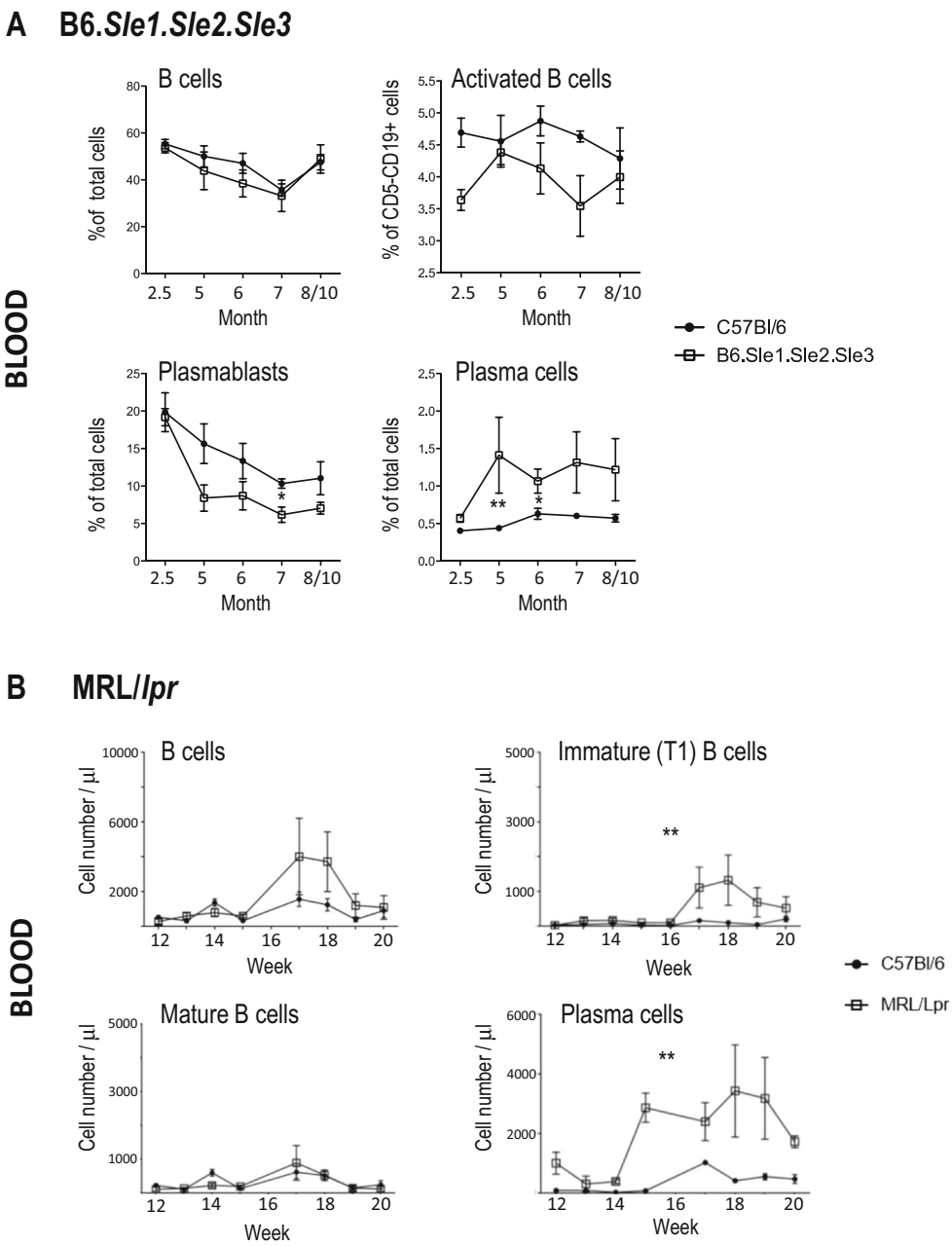

Fig. 4 Blood B cells in lupus-prone mice. **a** Blood samples from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice were harvested at the indicated time points, and stained with a viability dye and the following antibodies: CD5, CD69, CD19, and CD138. Cell activation was defined based on CD69 expression. Plasmablasts were identified as $CD19^{+}CD138^{+}$ cells, and plasma cells as $CD19^{-}CD138^{+}$ cells. Percentages are calculated in reference to the population indicated on the *Y* axis. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Blood samples from MRL/*lpr* and C57Bl/6 mice were harvested at the indicated time points and stained with the following antibodies: B220, CD23, CD21/35, IgM, and CD138. Plasma cells were identified as $CD138^{+}$ cells, $**p < 0.01$ using Mann-Whitney tests

dsDNA and anti-snRNP autoantibodies, inhibition of immunoglobulin deposition in the kidney and prevention of nephritis. In addition, TLR7 inhibition in dendritic cells from B6.*Sle1.Tg7* mice resulted in normalization of TLR7-induced changes in cell populations in the spleen, i.e., reduction in numbers of expanded CD11b-positive myeloid cells, decreased expression of activation markers on CD4 and CD8 T cells, decrease in the percentage of $CD62L^{low}CD44^{high}$ effector memory cells. Numbers of pDC were not increased in B6.*Sle1.Tg7* mice compared to B6.*Sle1* controls and were not affected by the decrease in TLR7 expression in B6.*Sle1.Tg7.CD1c-Cre* animals [116].

As discussed previously, B6.*Sle3* congenic mice are characterized by the presence of spontaneously activated and hyperproliferative T cells [48]. In B6.*Sle3* animals transgenic for an OVA-specific T cell receptor (TCR), Zhu et al. confirmed increased T cell responses to antigenic stimulation and decreased activation-induced cell death compared to B6

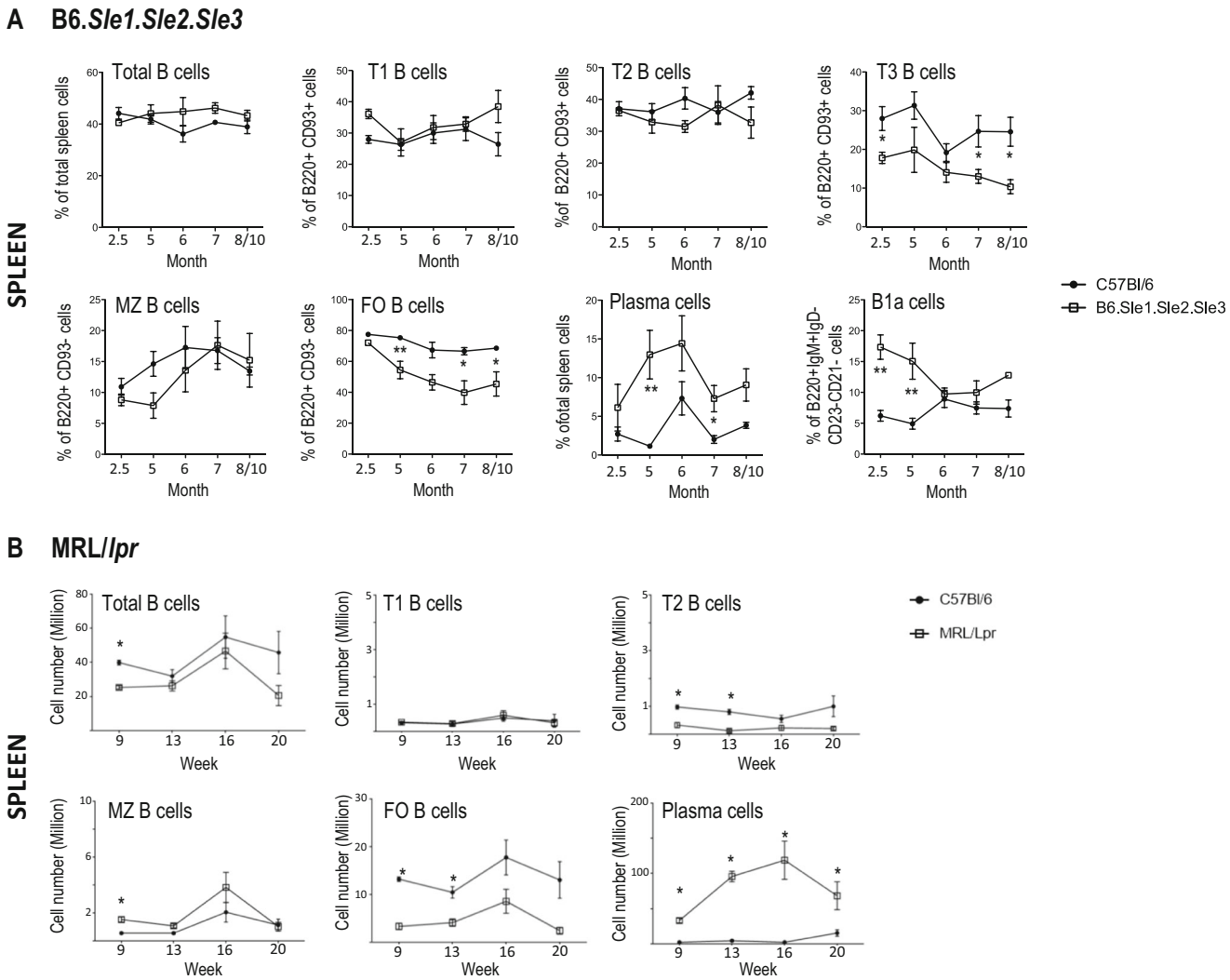

Fig. 5 Spleen B cell subsets in lupus-prone mice. **a** Spleens from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice were harvested at the indicated time points and stained with a viability dye and the following antibodies: CD5, B220, IgD, IgM, CD23, CD21, CD93, and CD138. T1, T2, and T3 B cells were defined based on CD23 and IgM expression in $B220^{+}CD93^{+}$ cells. Follicular (FO) and mantle-zone (MZ) B cells were defined based on CD23 and CD21 expression in $B220^{+}CD93^{-}$ cells. B1a cells were identified based on CD5 expression in $B220^{+}$CD93-IgM + IgD-CD23-CD21- cells. Plasma cells were identified as CD138+ cells. Percentages are calculated in reference to the population indicated on the *Y* axis. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Spleens from MRL/*lpr* and C57Bl/6 mice were harvested at the indicated time points and stained with the following antibodies: B220, CD23, CD21/35, IgM, and CD138. Plasma cells were identified as CD138+ cells, $*p < 0.05$ using Mann-Whitney tests

OVA TCR transgenic controls not carrying the *Sle3* congenic interval. However, this T cell phenotype was not intrinsic to T cells, as demonstrated by adoptive transfer of B6.*Sle3* TCR transgenic T cells in C57Bl/6 mice, resulting in the loss of their activated phenotype. Looking at phenotype and function of antigen-presenting cells, the authors found increased numbers of macrophages and lymphoid dendritic cells in the spleen of B6.*Sle3* mice, and, more importantly, increased activation status of all myeloid cell types studied, i.e., increased expression of the co-stimulatory molecules CD40 and CD80, and cell adhesion molecules (VCAM-1/CD106) on macrophages, neutrophils, lymphoid, and myeloid dendritic cells, increased expression of Fcγ Receptor on neutrophils, lymphoid, and myeloid dendritic cells, increased expression of CD86 in myeloid dendritic cells, resulting in increased activation of antigen-specific T cells [117].

Macrophages and dendritic cells also infiltrate nephritic kidneys of SLE-prone mice. Comparing the transcriptomic profiles of nephritic BWF1, NZW × BXSB, and NZM2410 mice to their pre-nephritic counterparts, Bethunaickan et al. found increased expression of macrophage activation-associated transcripts (CD68, activating Fcγ receptors,

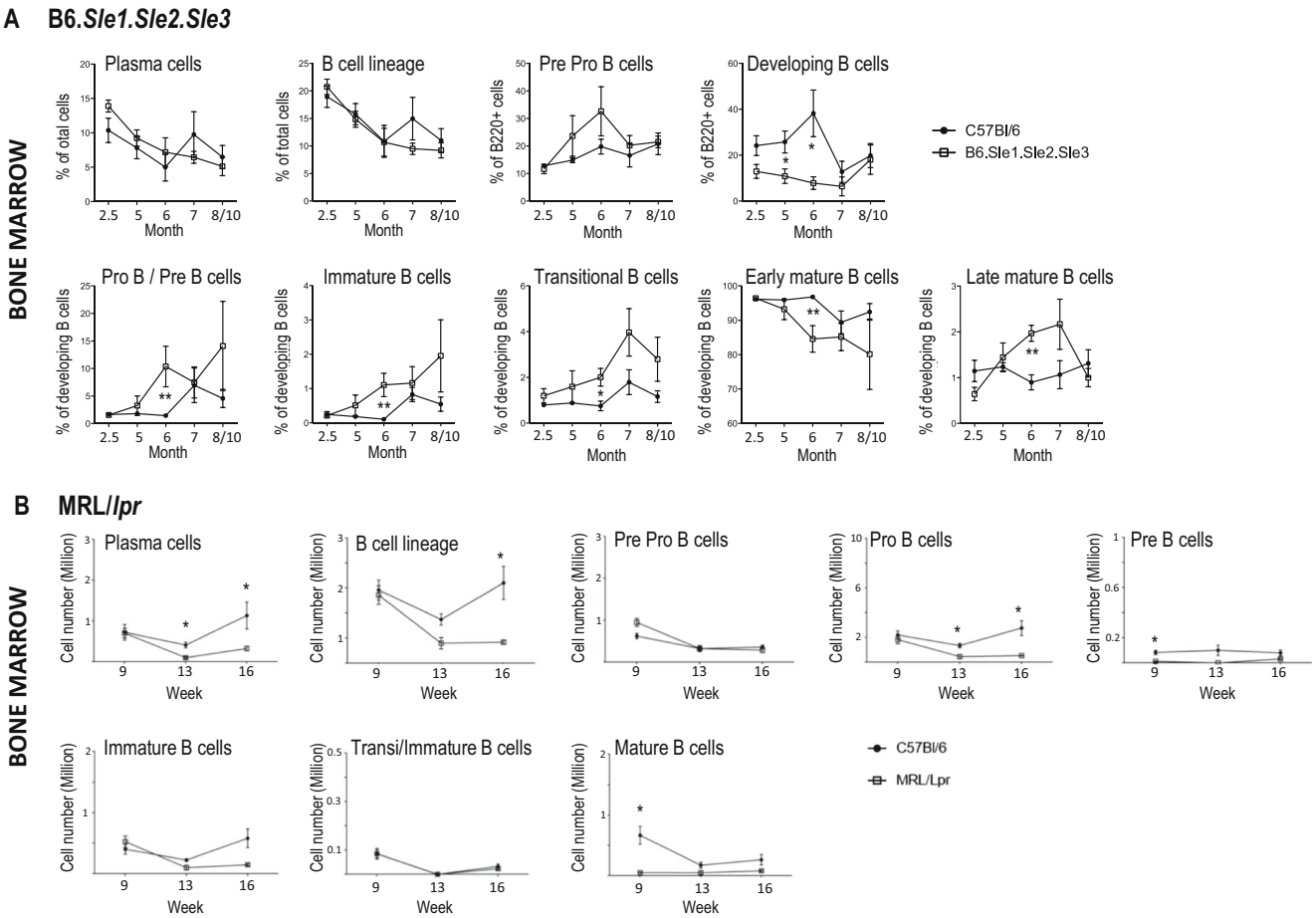

Fig. 6 Bone marrow B cell precursors in lupus-prone mice. **a** Bone marrow was obtained from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice at the indicated time points and stained with a viability dye and the following antibodies: B220, CD24, CD43, IgM, IgD, and CD138. Plasma cells were defined as CD138+ cells. B cell lineage was defined as B220+ cells. PrePro B cells were identified as $B220^{+}CD24^{intermediate}CD43+$ cells. Developing B cells were defined as $B220^{+}CD24^{high}CD43-$ cells. Pro B/Pre B, immature, transitional, early, and late mature B cells were defined based on IgM and IgD expression in $B220^{+}CD24^{high}CD43^{-}$ cells. Percentages are calculated in reference to the population indicated on the *Y* axis. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Bone marrow from MRL/*lpr* and C57Bl/6 mice was obtained at the indicated time points and stained with the following antibodies: B220, CD43, IgM, IgD, and CD138. Plasma cells were defined as $CD138^{+}$ cells. PrePro B cells were identified as $B220^{+}CD43^{high}$ cells. Pro B cells were identified as $B220^{+}CD43^{+}$ cells. Pre B cells were identified as $B220^{+}CD43^{-}$ cells. Immature, transitional, and mature B cells were defined based on IgM and IgD expression in B220+, $*p < 0.05$ using Mann-Whitney tests

FPR2, C type lectins, cathepsins, HLA-DM) in the nephritic kidneys of all three strains of mice. In the two models with proliferative nephritis (BWF1, NZW × BXSB), they also found overexpression of other macrophage or dendritic cell-associated transcripts (CD11c, IKBKE, FCGR3A, CXCL13) [50]. Purification of macrophages and dendritic cells infiltrating BWF1 kidneys showed the presence of different populations with heterogeneous functional characteristics. The most enriched population was made of $CD11b^{high}CD11c^{high}F4/80^{low}$ dendritic cells able to induce the proliferation of allogeneic CD4 T cells. $CD11b^{high}F4/80^{high}CD11c^{low/intermediate}$ macrophages were also strongly enriched in BWF1 kidneys. These cells also induced proliferation of allogeneic CD4 T cells, had a high phagocytic activity, and had increased expression of TLR3, TLR5, TLR9, ITGAM, CCL7, and CX3CR1 compared to the other cell subtypes. There was also a slight increase in $CD11c^{high}CD11b^{low/intermediate}F4/80^{low}CD103^{+}$ dendritic cells with high CD4 T cell proliferation abilities, by contrast to $CD11b^{high}CD11c^{low}F4/80^{low}$ macrophages that had little effects on the activation of CD4 T cells [118].

In our flow cytometry data (Fig. 7), numbers of dendritic cells (DC) in the spleen, lymph nodes, and thymus of MRL/*lpr* mice were higher as compared to C57Bl/6 animals. We did not find differences in percentages of cDC or pDC in the spleens of B6.*Sle1.Sle2.Sle3*, but percentages of pDC in the blood were higher in B6.*Sle1.Sle2.Sle3* compared to C57Bl/6 mice.

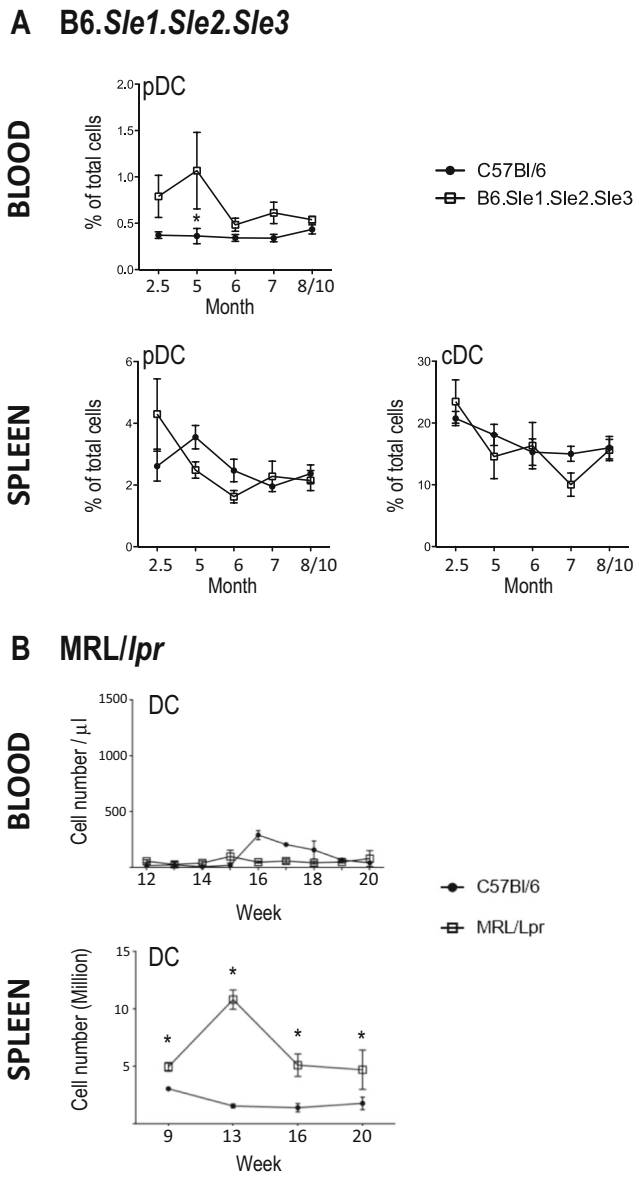

Fig. 7 Blood and spleen dendritic cells in lupus-prone mice. **a** Blood samples and spleens from B6.*Sle1.Sle2.Sle3* and C57Bl6 mice were harvested at the indicated time points and stained with a viability dye and the following antibodies: CD11b, CD11c, SiglecH, Gr1, CD115, B220, and CD8a. pDC were defined as $CD11c^{+}SiglecH^{+}$ cells. In the spleen, cDC were defined as $CD11c^{+}SiglecH-$ cells. 8/10: 8-month-old B6.*Sle1.Sle2.Sle3* were compared to 10-month-old C57Bl/6 mice, $*p < 0.05$, $**p < 0.01$ using Mann-Whitney tests. **b** Blood samples and spleens from MRL/*lpr* and C57Bl/6 mice were harvested at the indicated time points and stained with the following antibodies: CD11b and CD11c. DC were defined as $CD11c^{+}CD11b^{+}$ cells, in blood and in spleen, $*p < 0.05$, using Mann-Whitney tests

Concluding Remarks

Phenotypic changes in lymphoid and myeloid cell populations in mouse models of SLE are strongly associated with intrinsic pathogenic events characteristic of the disease and are frequently used in order to assess the effects of therapeutic interventions or genetic modifications.

Recently, the development of multi-panel staining strategies contributed to a better identification of lymphoid cell subsets in the bone marrow and in the periphery. In particular, skewed distribution of immature B cell populations in mice and in humans with SLE is indicative of defective central and peripheral tolerance checkpoints, an essential step in the development of autoimmunity. Similarly, activation of myeloid cell subsets appears to be a necessary step for the activation of autoreactive T cells in the disease.

The recent identification of long-lived plasma cells in kidneys and bone marrow of lupus-prone mice nicely illustrates how the local–inflammatory–environment shapes the representation and function of innate and adaptive immune effectors, and our present 'systemic' approach to our understanding of the mechanisms of disease needs to be adjusted, in order to consider the important role of these 'organ-specific' modifications.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Funding This work was supported by a grant from the Fonds National de la Recherche Scientifique. A. De Groof is supported by the "Chaire UCB/UCL sur les rhumatismes inflammatoires et systémiques". B. Lauwerys is supported in part by the Fonds National de la Recherche Scientifique (Communauté française de Belgique), and P. Hemon by a SATT Ouest Valorisation grant.

Ethical Approval All animal experiments reported in this manuscript were approved by the ethical committee of the Université catholique de Louvain (Secteur des Sciences de la Santé), and by the ethical committee of the Université de Bretagne Occidentale (Brest).

References

1. Wandstrat A, Wakeland E (2001) The genetics of complex autoimmune diseases: non-MHC susceptibility genes. Nat Immunol 2(9):802–809. doi:10.1038/ni0901-802
2. Lauwerys BR, Wakeland EK (2005) Genetics of lupus nephritis. Lupus 14(1):2–12
3. Limaye N, Belobrajdic KA, Wandstrat AE, Bonhomme F, Edwards SV, Wakeland EK (2008) Prevalence and evolutionary origins of autoimmune susceptibility alleles in natural mouse populations. Genes Immun 9(1):61–68. doi:10.1038/sj.gene.6364446
4. Konsta OD, Le Dantec C, Charras A, Brooks WH, Arleevskaya MI, Bordron A, Renaudineau Y (2015) An in silico approach reveals associations between genetic and epigenetic factors within regulatory elements in B cells from primary Sjogren's syndrome patients. Front Immunol 6:437. doi:10.3389/fimmu.2015.00437
5. Konsta OD, Le Dantec C, Brooks WH, Renaudineau Y (2015) Genetics and Epigenetics of Autoimmune Diseases. eLS:1–9. doi:10.1002/9780470015902.a0023593

6. Renaudineau Y, Ballestar E (2016) Epigenetics: DNA methylation signatures in Sjogren syndrome. Nat Rev Rheumatol 12(10):565–566. doi:10.1038/nrrheum.2016.144
7. Charras A, Konsta OD, Le Dantec C, Bagacean C, Kapsogeorgou EK, Tzioufas AG, Pers JO, Bordron A, Renaudineau Y (2017) Cell-specific epigenome-wide DNA methylation profile in long-term cultured minor salivary gland epithelial cells from patients with Sjogren's syndrome. Ann Rheum Dis 76(3):625–628. doi:10.1136/annrheumdis-2016-210167
8. Morel L, Rudofsky UH, Longmate JA, Schiffenbauer J, Wakeland EK (1994) Polygenic control of susceptibility to murine systemic lupus erythematosus. Immunity 1(3):219–229
9. Morel L, Yu Y, Blenman KR, Caldwell RA, Wakeland EK (1996) Production of congenic mouse strains carrying genomic intervals containing SLE-susceptibility genes derived from the SLE-prone NZM2410 strain. Mammalian genome : official journal of the International Mammalian Genome Society 7(5):335–339
10. Morel L, Croker BP, Blenman KR, Mohan C, Huang G, Gilkeson G, Wakeland EK (2000) Genetic reconstitution of systemic lupus erythematosus immunopathology with polycongenic murine strains. Proc Natl Acad Sci U S A 97(12):6670–6675
11. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, Drappa J, Wang L, Greth W, investigators CDs (2016) Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis 75(11):1909–1916. doi:10.1136/annrheumdis-2015-208562
12. Peng L, Oganesyan V, Wu H, Dall'Acqua WF, Damschroder MM (2015) Molecular basis for antagonistic activity of anifrolumab, an anti-interferon-alpha receptor 1 antibody. MAbs 7(2):428–439. doi:10.1080/19420862.2015.1007810
13. Lauwerys BR, Hachulla E, Spertini F, Lazaro E, Jorgensen C, Mariette X, Haelterman E, Grouard-Vogel G, Fanget B, Dhellin O, Vandepapeliere P, Houssiau FA (2013) Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon alpha-kinoid. Arthritis & Rheumatism 65(2):447–456. doi:10.1002/art.37785
14. Ducreux J, Houssiau FA, Vandepapeliere P, Jorgensen C, Lazaro E, Spertini F, Colaone F, Roucairol C, Laborie M, Croughs T, Grouard-Vogel G, Lauwerys BR (2016) Interferon alpha kinoid induces neutralizing anti-interferon alpha antibodies that decrease the expression of interferon-induced and B cell activation associated transcripts: analysis of extended follow-up data from the interferon alpha kinoid phase I/II study. Rheumatology (Oxford) 55(10):1901–1905. doi:10.1093/rheumatology/kew262
15. Liu Z, Bethunaickan R, Huang W, Lodhi U, Solano I, Madaio MP, Davidson A (2011) Interferon-alpha accelerates murine systemic lupus erythematosus in a T cell-dependent manner. Arthritis & Rheumatism 63(1):219–229. doi:10.1002/art.30087
16. Mathian A, Weinberg A, Gallegos M, Banchereau J, Koutouzov S (2005) IFN-alpha induces early lethal lupus in preautoimmune (New Zealand black x New Zealand White) F1 but not in BALB/c mice. J Immunol 174(5):2499–2506
17. Fairhurst AM, Mathian A, Connolly JE, Wang A, Gray HF, George TA, Boudreaux CD, Zhou XJ, Li QZ, Koutouzov S, Banchereau J, Wakeland EK (2008) Systemic IFN-alpha drives kidney nephritis in B6.Sle123 mice. Eur J Immunol 38(7):1948–1960. doi:10.1002/eji.200837925
18. Vidal S, Kono DH, Theofilopoulos AN (1998) Loci predisposing to autoimmunity in MRL-Fas lpr and C57BL/6-Faslpr mice. J Clin Invest 101(3):696–702. doi:10.1172/JCI1817
19. Ichii O, Konno A, Sasaki N, Endoh D, Hashimoto Y, Kon Y (2008) Autoimmune glomerulonephritis induced in congenic mouse strain carrying telomeric region of chromosome 1 derived from MRL/MpJ. Histol Histopathol 23(4):411–422
20. Santiago-Raber ML, Haraldsson MK, Theofilopoulos AN, Kono DH (2007) Characterization of reciprocal Lmb1-4 interval MRL-Faslpr and C57BL/6-Faslpr congenic mice reveals significant effects from Lmb3. J Immunol 178(12):8195–8202
21. Kong PL, Morel L, Croker BP, Craft J (2004) The centromeric region of chromosome 7 from MRL mice (Lmb3) is an epistatic modifier of Fas for autoimmune disease expression. J Immunol 172(5):2785–2794
22. Yamada A, Miyazaki T, Lu LM, Ono M, Ito MR, Terada M, Mori S, Hata K, Nozaki Y, Nakatsuru S, Nakamura Y, Onji M, Nose M (2003) Genetic basis of tissue specificity of vasculitis in MRL/lpr mice. Arthritis & Rheumatism 48(5):1445–1451. doi:10.1002/art.10952
23. Kamogawa J, Terada M, Mizuki S, Nishihara M, Yamamoto H, Mori S, Abe Y, Morimoto K, Nakatsuru S, Nakamura Y, Nose M (2002) Arthritis in MRL/lpr mice is under the control of multiple gene loci with an allelic combination derived from the original inbred strains. Arthritis & Rheumatism 46(4):1067–1074
24. Nishihara M, Terada M, Kamogawa J, Ohashi Y, Mori S, Nakatsuru S, Nakamura Y, Nose M (1999) Genetic basis of autoimmune sialadenitis in MRL/lpr lupus-prone mice: additive and hierarchical properties of polygenic inheritance. Arthritis & Rheumatism 42(12):2616–2623. doi:10.1002/1529-0131(199912)42:12<2616::AID-ANR16>3.0.CO;2-O
25. Subramanian S, Tus K, Li QZ, Wang A, Tian XH, Zhou J, Liang C, Bartov G, McDaniel LD, Zhou XJ, Schultz RA, Wakeland EK (2006) A Tlr7 translocation accelerates systemic autoimmunity in murine lupus. Proc Natl Acad Sci U S A 103(26):9970–9975. doi:10.1073/pnas.0603912103
26. Fairhurst AM, Hwang SH, Wang A, Tian XH, Boudreaux C, Zhou XJ, Casco J, Li QZ, Connolly JE, Wakeland EK (2008) Yaa autoimmune phenotypes are conferred by overexpression of TLR7. Eur J Immunol 38(7):1971–1978. doi:10.1002/eji.200838138
27. Hanrotel-Saliou C, Segalen I, Le Meur Y, Youinou P, Renaudineau Y (2011) Glomerular antibodies in lupus nephritis. Clinical reviews in allergy & immunology 40(3):151–158. doi:10.1007/s12016-010-8204-4
28. Seret G, Canas F, Pougnet-Di Costanzo L, Hanrotel-Saliou C, Jousse-Joulin S, Le Meur Y, Saraux A, Valeri A, Putterman C, Youinou P, Rojas-Villarraga A, Anaya JM, Renaudineau Y (2015) Anti-alpha-actinin antibodies are part of the anti-cell membrane antibody spectrum that characterize patients with lupus nephritis. J Autoimmun 61:54–61. doi:10.1016/j.jaut.2015.05.009
29. Renaudineau Y, Croquefer S, Jousse S, Renaudineau E, Devauchelle V, Gueguen P, Hanrotel C, Gilburd B, Saraux A, Shoenfeld Y, Putterman C, Youinou P (2006) Association of alpha-actinin-binding anti-double-stranded DNA antibodies with lupus nephritis. Arthritis & Rheumatism 54(8):2523–2532. doi:10.1002/art.22015
30. Xie C, Zhou XJ, Liu X, Mohan C (2003) Enhanced susceptibility to end-organ disease in the lupus-facilitating NZW mouse strain. Arthritis & Rheumatism 48(4):1080–1092. doi:10.1002/art.10887
31. Li QZ, Zhou J, Yang R, Yan M, Ye Q, Liu K, Liu S, Shao X, Li L, Zhou XJ, Wakeland EK, Mohan C (2009) The lupus-susceptibility gene kallikrein downmodulates antibody-mediated glomerulonephritis. Genes Immun 10(5):503–508. doi:10.1038/gene.2009.7
32. Mohan C, Adams S, Stanik V, Datta SK (1993) Nucleosome: a major immunogen for pathogenic autoantibody-inducing T cells of lupus. J Exp Med 177(5):1367–1381
33. Lu L, Kaliyaperumal A, Boumpas DT, Datta SK (1999) Major peptide autoepitopes for nucleosome-specific T cells of human lupus. J Clin Invest 104(3):345–355. doi:10.1172/JCI6801
34. Wofsy D, Seaman WE (1985) Successful treatment of autoimmunity in NZB/NZW F1 mice with monoclonal antibody to L3T4. J Exp Med 161(2):378–391

35. Wofsy D, Seaman WE (1987) Reversal of advanced murine lupus in NZB/NZW F1 mice by treatment with monoclonal antibody to L3T4. J Immunol 138(10):3247–3253
36. Carteron NL, Wofsy D, Schimenti C, Ermak TH (1990) F(ab')2 anti-CD4 and intact anti-CD4 monoclonal antibodies inhibit the accumulation of CD4+ T cells, CD8+ T cells, and B cells in the kidneys of lupus-prone NZB/NZW mice. Clin Immunol Immunopathol 56(3):373–383
37. Connolly K, Roubinian JR, Wofsy D (1992) Development of murine lupus in CD4-depleted NZB/NZW mice. Sustained inhibition of residual CD4+ T cells is required to suppress autoimmunity. J Immunol 149(9):3083–3088
38. Santoro TJ, Portanova JP, Kotzin BL (1988) The contribution of L3T4+ T cells to lymphoproliferation and autoantibody production in MRL-lpr/lpr mice. J Exp Med 167(5):1713–1718
39. Merino R, Iwamoto M, Fossati L, Izui S (1993) Polyclonal B cell activation arises from different mechanisms in lupus-prone (NZB x NZW)F1 and MRL/MpJ-lpr/lpr mice. J Immunol 151(11): 6509–6516
40. Chesnutt MS, Finck BK, Killeen N, Connolly MK, Goodman H, Wofsy D (1998) Enhanced lymphoproliferation and diminished autoimmunity in CD4-deficient MRL/lpr mice. Clin Immunol Immunopathol 87(1):23–32
41. Mohan C, Alas E, Morel L, Yang P, Wakeland EK (1998) Genetic dissection of SLE pathogenesis. Sle1 on murine chromosome 1 leads to a selective loss of tolerance to H2A/H2B/DNA subnucleosomes. J Clin Invest 101(6):1362–1372
42. Sobel ES, Satoh M, Chen Y, Wakeland EK, Morel L (2002) The major murine systemic lupus erythematosus susceptibility locus Sle1 results in abnormal functions of both B and T cells. J Immunol 169(5):2694–2700
43. Sobel ES, Mohan C, Morel L, Schiffenbauer J, Wakeland EK (1999) Genetic dissection of SLE pathogenesis: adoptive transfer of Sle1 mediates the loss of tolerance by bone marrow-derived B cells. J Immunol 162(4):2415–2421
44. Wandstrat AE, Nguyen C, Limaye N, Chan AY, Subramanian S, Tian XH, Yim YS, Pertsemlidis A, Garner HR Jr, Morel L, Wakeland EK (2004) Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. Immunity 21(6):769–780. doi:10.1016/j.immuni.2004.10.009
45. Wong EB, Khan TN, Mohan C, Rahman ZS (2012) The lupus-prone NZM2410/NZW strain-derived Sle1b sublocus alters the germinal center checkpoint in female mice in a B cell-intrinsic manner. J Immunol 189(12):5667–5681. doi:10.4049/jimmunol.1201661
46. Simpson N, Gatenby PA, Wilson A, Malik S, Fulcher DA, Tangye SG, Manku H, Vyse TJ, Roncador G, Huttley GA, Goodnow CC, Vinuesa CG, Cook MC (2010) Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. Arthritis & Rheumatism 62(1):234–244. doi:10.1002/art.25032
47. Jacquemin C, Schmitt N, Contin-Bordes C, Liu Y, Narayanan P, Seneschal J, Maurouard T, Dougall D, Davizon ES, Dumortier H, Douchet I, Raffray L, Richez C, Lazaro E, Duffau P, Truchetet ME, Khoryati L, Mercie P, Couzi L, Merville P, Schaeverbeke T, Viallard JF, Pellegrin JL, Moreau JF, Muller S, Zurawski S, Coffman RL, Pascual V, Ueno H, Blanco P (2015) OX40 ligand contributes to human lupus pathogenesis by promoting T follicular helper response. Immunity 42(6):1159–1170. doi:10.1016/j.immuni.2015.05.012
48. Mohan C, Yu Y, Morel L, Yang P, Wakeland EK (1999) Genetic dissection of Sle pathogenesis: Sle3 on murine chromosome 7 impacts T cell activation, differentiation, and cell death. J Immunol 162(11):6492–6502
49. Bethunaickan R, Berthier CC, Zhang W, Eksi R, Li HD, Guan Y, Kretzler M, Davidson A (2014) Identification of stage-specific genes associated with lupus nephritis and response to remission induction in (NZB x NZW)F1 and NZM2410 mice. Arthritis & Rheumatology 66(8):2246–2258. doi:10.1002/art.38679
50. Bethunaickan R, Berthier CC, Zhang W, Kretzler M, Davidson A (2013) Comparative transcriptional profiling of 3 murine models of SLE nephritis reveals both unique and shared regulatory networks. PLoS One 8(10):e77489. doi:10.1371/journal.pone.0077489
51. Deane JA, Pisitkun P, Barrett RS, Feigenbaum L, Town T, Ward JM, Flavell RA, Bolland S (2007) Control of toll-like receptor 7 expression is essential to restrict autoimmunity and dendritic cell proliferation. Immunity 27(5):801–810. doi:10.1016/j.immuni.2007.09.009
52. Hwang SH, Lee H, Yamamoto M, Jones LA, Dayalan J, Hopkins R, Zhou XJ, Yarovinsky F, Connolly JE, Curotto de Lafaille MA, Wakeland EK, Fairhurst AM (2012) B cell TLR7 expression drives anti-RNA autoantibody production and exacerbates disease in systemic lupus erythematosus-prone mice. J Immunol 189(12): 5786–5796. doi:10.4049/jimmunol.1202195
53. Scalapino KJ, Tang Q, Bluestone JA, Bonyhadi ML, Daikh DI (2006) Suppression of disease in New Zealand black/New Zealand White lupus-prone mice by adoptive transfer of ex vivo expanded regulatory T cells. J Immunol 177(3):1451–1459
54. Humrich JY, Morbach H, Undeutsch R, Enghard P, Rosenberger S, Weigert O, Kloke L, Heimann J, Gaber T, Brandenburg S, Scheffold A, Huehn J, Radbruch A, Burmester GR, Riemekasten G (2010) Homeostatic imbalance of regulatory and effector T cells due to IL-2 deprivation amplifies murine lupus. Proc Natl Acad Sci U S A 107(1):204–209. doi:10.1073/pnas.0903158107
55. Yang CH, Tian L, Ling GS, Trendell-Smith NJ, Ma L, Lo CK, Stott DI, Liew FY, Huang FP (2008) Immunological mechanisms and clinical implications of regulatory T cell deficiency in a systemic autoimmune disorder: roles of IL-2 versus IL-15. Eur J Immunol 38(6):1664–1676. doi:10.1002/eji.200838190
56. Divekar AA, Dubey S, Gangalum PR, Singh RR (2011) Dicer insufficiency and microRNA-155 overexpression in lupus regulatory T cells: an apparent paradox in the setting of an inflammatory milieu. J Immunol 186(2):924–930. doi:10.4049/jimmunol.1002218
57. Cuda CM, Wan S, Sobel ES, Croker BP, Morel L (2007) Murine lupus susceptibility locus Sle1a controls regulatory T cell number and function through multiple mechanisms. J Immunol 179(11): 7439–7447
58. Wan S, Xia C, Morel L (2007) IL-6 produced by dendritic cells from lupus-prone mice inhibits CD4+CD25+ T cell regulatory functions. J Immunol 178(1):271–279
59. Weigert O, von Spee C, Undeutsch R, Kloke L, Humrich JY, Riemekasten G (2013) CD4+Foxp3+ regulatory T cells prolong drug-induced disease remission in (NZBxNZW) F1 lupus mice. Arthritis research & therapy 15(1):R35. doi:10.1186/ar4188
60. Yan JJ, Lee JG, Jang JY, Koo TY, Ahn C, Yang J (2017) IL-2/anti-IL-2 complexes ameliorate lupus nephritis by expansion of CD4+ CD25+Foxp3+ regulatory T cells. Kidney Int 91(3):603–615. doi:10.1016/j.kint.2016.09.022
61. von Spee-Mayer C, Siegert E, Abdirama D, Rose A, Klaus A, Alexander T, Enghard P, Sawitzki B, Hiepe F, Radbruch A, Burmester GR, Riemekasten G, Humrich JY (2016) Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus. Ann Rheum Dis 75(7): 1407–1415. doi:10.1136/annrheumdis-2015-207776
62. Yang JQ, Kim PJ, Halder RC, Singh RR (2013) Intrinsic hyporesponsiveness of invariant natural killer T cells precedes the onset of lupus. Clin Exp Immunol 173(1):18–27. doi:10.1111/cei.12079
63. Yang JQ, Wen X, Kim PJ, Singh RR (2011) Invariant NKT cells inhibit autoreactive B cells in a contact- and CD1d-dependent

manner. J Immunol 186(3):1512–1520. doi:10.4049/jimmunol.1002373
64. Wermeling F, Lind SM, Jordo ED, Cardell SL, Karlsson MC (2010) Invariant NKT cells limit activation of autoreactive CD1d-positive B cells. J Exp Med 207(5):943–952. doi:10.1084/jem.20091314
65. Zeng D, Liu Y, Sidobre S, Kronenberg M, Strober S (2003) Activation of natural killer T cells in NZB/W mice induces Th1-type immune responses exacerbating lupus. J Clin Invest 112(8):1211–1222. doi:10.1172/JCI17165
66. Yang JQ, Kim PJ, Singh RR (2012) Brief treatment with iNKT cell ligand alpha-galactosylceramide confers a long-term protection against lupus. J Clin Immunol 32(1):106–113. doi:10.1007/s10875-011-9590-y
67. Karpouzas GA, La Cava A, Ebling FM, Singh RR, Hahn BH (2004) Differences between CD8+ T cells in lupus-prone (NZB x NZW) F1 mice and healthy (BALB/c x NZW) F1 mice may influence autoimmunity in the lupus model. Eur J Immunol 34(9):2489–2499. doi:10.1002/eji.200424978
68. Ruiz PJ, Zinger H, Mozes E (1996) Effect of injection of anti-CD4 and anti-CD8 monoclonal antibodies on the development of experimental systemic lupus erythematosus in mice. Cell Immunol 167(1):30–37. doi:10.1006/cimm.1996.0004
69. Kim HJ, Verbinnen B, Tang X, Lu L, Cantor H (2010) Inhibition of follicular T-helper cells by CD8(+) regulatory T cells is essential for self tolerance. Nature 467(7313):328–332. doi:10.1038/nature09370
70. Kim HJ, Wang X, Radfar S, Sproule TJ, Roopenian DC, Cantor H (2011) CD8+ T regulatory cells express the Ly49 class I MHC receptor and are defective in autoimmune prone B6-Yaa mice. Proc Natl Acad Sci U S A 108(5):2010–2015. doi:10.1073/pnas.1018974108
71. Tsumiyama K, Hashiramoto A, Takimoto M, Tsuji-Kawahara S, Miyazawa M, Shiozawa S (2013) IFN-gamma-producing effector CD8 T lymphocytes cause immune glomerular injury by recognizing antigen presented as immune complex on target tissue. J Immunol 191(1):91–96. doi:10.4049/jimmunol.1203217
72. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, Hammerich L, Panzer U, Kaden S, Quaggin SE, Floege J, Grone HJ, Kurts C (2009) Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. J Clin Invest 119(5):1286–1297. doi:10.1172/JCI38399
73. Couzi L, Merville P, Deminiere C, Moreau JF, Combe C, Pellegrin JL, Viallard JF, Blanco P (2007) Predominance of CD8+ T lymphocytes among periglomerular infiltrating cells and link to the prognosis of class III and class IV lupus nephritis. Arthritis & Rheumatism 56(7):2362–2370. doi:10.1002/art.22654
74. Taher TE, Muhammad HA, Bariller E, Flores-Borja F, Renaudineau Y, Isenberg DA, Mageed RA (2013) B-lymphocyte signalling abnormalities and lupus immunopathology. Int Rev Immunol 32(4):428–444. doi:10.3109/08830185.2013.788648
75. Taher TE, Muhammad HA, Rahim A, Flores-Borja F, Renaudineau Y, Isenberg DA, Mageed RA (2013) Aberrant B-lymphocyte responses in lupus: inherent or induced and potential therapeutic targets. Eur J Clin Investig 43(8):866–880. doi:10.1111/eci.12111
76. Youinou P, Taher TE, Pers JO, Mageed RA, Renaudineau Y (2009) B lymphocyte cytokines and rheumatic autoimmune disease. Arthritis & Rheumatism 60(7):1873–1880. doi:10.1002/art.24665
77. Renaudineau Y, Pers JO, Bendaoud B, Jamin C, Youinou P (2004) Dysfunctional B cells in systemic lupus erythematosus. Autoimmun Rev 3(7–8):516–523. doi:10.1016/j.autrev.2004.07.035
78. Jacobi AM, Reiter K, Mackay M, Aranow C, Hiepe F, Radbruch A, Hansen A, Burmester GR, Diamond B, Lipsky PE, Dorner T (2008) Activated memory B cell subsets correlate with disease activity in systemic lupus erythematosus: delineation by expression of CD27, IgD, and CD95. Arthritis & Rheumatism 58(6):1762–1773. doi:10.1002/art.23498
79. Simonin L, Pasquier E, Leroyer C, Cornec D, Lemerle J, Bendaoud B, Hillion S, Pers J-O, Couturaud F, Renaudineau Y (2016) Lymphocyte disturbances in primary antiphospholipid syndrome and application to venous thromboembolism follow-up. Clinical reviews in allergy & immunology:1–14. doi:10.1007/s12016-016-8568-1
80. Sims GP, Ettinger R, Shirota Y, Yarboro CH, Illei GG, Lipsky PE (2005) Identification and characterization of circulating human transitional B cells. Blood 105(11):4390–4398. doi:10.1182/blood-2004-11-4284
81. Garaud S, Le Dantec C, de Mendoza AR, Mageed RA, Youinou P, Renaudineau Y (2009) IL-10 production by B cells expressing CD5 with the alternative exon 1B. Ann N Y Acad Sci 1173:280–285. doi:10.1111/j.1749-6632.2009.04616.x
82. Youinou P, Renaudineau Y (2011) CD5 expression in B cells from patients with systemic lupus erythematosus. Crit Rev Immunol 31(1):31–42
83. Mohan C, Morel L, Yang P, Wakeland EK (1998) Accumulation of splenic B1a cells with potent antigen-presenting capability in NZM2410 lupus-prone mice. Arthritis & Rheumatism 41(9):1652–1662. doi:10.1002/1529-0131(199809)41:9<1652::AID-ART17>3.0.CO;2-W
84. Xu Z, Morel L (2015) Contribution of B-1a cells to systemic lupus erythematosus in the NZM2410 mouse model. Ann N Y Acad Sci 1362:215–223. doi:10.1111/nyas.12607
85. Holodick NE, Zeumer L, Rothstein TL, Morel L (2016) Expansion of B-1a cells with germline heavy chain sequence in lupus mice. Front Immunol 7:108. doi:10.3389/fimmu.2016.00108
86. Xu Z, Butfiloski EJ, Sobel ES, Morel L (2004) Mechanisms of peritoneal B-1a cells accumulation induced by murine lupus susceptibility locus Sle2. J Immunol 173(10):6050–6058
87. Xu Z, Duan B, Croker BP, Wakeland EK, Morel L (2005) Genetic dissection of the murine lupus susceptibility locus Sle2: contributions to increased peritoneal B-1a cells and lupus nephritis map to different loci. J Immunol 175(2):936–943
88. Renaudineau Y, Bariller E, Pers JO (2014) B1- and CD5-positive B cells. In: eLS. John Wiley & Sons, ltd. doi:10.1002/9780470015902.a0024242
89. Ye YL, Chuang YH, Chiang BL (1996) In vitro and in vivo functional analysis of CD5+ and CD5- B cells of autoimmune NZB x NZW F1 mice. Clin Exp Immunol 106(2):253–258
90. Mageed RA, Garaud S, Taher TE, Parikh K, Pers JO, Jamin C, Renaudineau Y, Youinou P (2012) CD5 expression promotes multiple intracellular signaling pathways in B lymphocyte. Autoimmun Rev. doi:10.1016/j.autrev.2012.02.007
91. Garaud S, Taher TE, Debant M, Burgos M, Melayah S, Berthou C, Parikh K, Pers JO, Luque-Paz D, Chiocchia G, Peppelenbosch M, Isenberg DA, Youinou P, Mignen O, Renaudineau Y, Mageed RA (2016) CD5 expression promotes IL-10 production through activation of the MAPK/Erk pathway and upregulation of TRPC1 channels in B lymphocytes. Cellular & molecular immunology. doi:10.1038/cmi.2016.42
92. Garaud S, Morva A, Lemoine S, Hillion S, Bordron A, Pers JO, Berthou C, Mageed RA, Renaudineau Y, Youinou P (2011) CD5 promotes IL-10 production in chronic lymphocytic leukemia B cells through STAT3 and NFAT2 activation. J Immunol 186(8):4835–4844. doi:10.4049/jimmunol.1003050
93. Roy V, Chang NH, Cai Y, Bonventi G, Wither J (2005) Aberrant IgM signaling promotes survival of transitional T1 B cells and

prevents tolerance induction in lupus-prone New Zealand black mice. J Immunol 175(11):7363–7371
94. Giltiay NV, Chappell CP, Sun X, Kolhatkar N, Teal TH, Wiedeman AE, Kim J, Tanaka L, Buechler MB, Hamerman JA, Imanishi-Kari T, Clark EA, Elkon KB (2013) Overexpression of TLR7 promotes cell-intrinsic expansion and autoantibody production by transitional T1 B cells. J Exp Med 210(12):2773–2789. doi:10.1084/jem.20122798
95. Kumar KR, Li L, Yan M, Bhaskarabhatla M, Mobley AB, Nguyen C, Mooney JM, Schatzle JD, Wakeland EK, Mohan C (2006) Regulation of B cell tolerance by the lupus susceptibility gene Ly108. Science 312(5780):1665–1669. doi:10.1126/science.1125893
96. Batten M, Groom J, Cachero TG, Qian F, Schneider P, Tschopp J, Browning JL, Mackay F (2000) BAFF mediates survival of peripheral immature B lymphocytes. J Exp Med 192(10):1453–1466
97. Teague BN, Pan Y, Mudd PA, Nakken B, Zhang Q, Szodoray P, Kim-Howard X, Wilson PC, Farris AD (2007) Cutting edge: transitional T3 B cells do not give rise to mature B cells, have undergone selection, and are reduced in murine lupus. J Immunol 178(12):7511–7515
98. Hoyer BF, Moser K, Hauser AE, Peddinghaus A, Voigt C, Eilat D, Radbruch A, Hiepe F, Manz RA (2004) Short-lived plasmablasts and long-lived plasma cells contribute to chronic humoral autoimmunity in NZB/W mice. J Exp Med 199(11):1577–1584. doi:10.1084/jem.20040168
99. Mumtaz IM, Hoyer BF, Panne D, Moser K, Winter O, Cheng QY, Yoshida T, Burmester GR, Radbruch A, Manz RA, Hiepe F (2012) Bone marrow of NZB/W mice is the major site for plasma cells resistant to dexamethasone and cyclophosphamide: implications for the treatment of autoimmunity. J Autoimmun 39(3):180–188. doi:10.1016/j.jaut.2012.05.010
100. Cheng Q, Mumtaz IM, Khodadadi L, Radbruch A, Hoyer BF, Hiepe F (2013) Autoantibodies from long-lived 'memory' plasma cells of NZB/W mice drive immune complex nephritis. Ann Rheum Dis 72(12):2011–2017. doi:10.1136/annrheumdis-2013-203455
101. Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, Wiethe C, Winkler TH, Kalden JR, Manz RA, Voll RE (2008) The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med 14(7):748–755. doi:10.1038/nm1763
102. Khodadadi L, Cheng Q, Alexander T, Sercan-Alp O, Klotsche J, Radbruch A, Hiepe F, Hoyer BF, Taddeo A (2015) Bortezomib plus continuous B cell depletion results in Sustained plasma cell depletion and amelioration of lupus nephritis in NZB/W F1 mice. PLoS One 10(8):e0135081. doi:10.1371/journal.pone.0135081
103. Taddeo A, Khodadadi L, Voigt C, Mumtaz IM, Cheng Q, Moser K, Alexander T, Manz RA, Radbruch A, Hiepe F, Hoyer BF (2015) Long-lived plasma cells are early and constantly generated in New Zealand black/New Zealand White F1 mice and their therapeutic depletion requires a combined targeting of autoreactive plasma cells and their precursors. Arthritis research & therapy 17:39. doi:10.1186/s13075-015-0551-3
104. Seret G, Hanrotel C, Bendaoud B, Le Meur Y, Renaudineau Y (2013) Homozygous FCGR3A-158F mutation is associated with delayed B-cell depletion following rituximab but with preserved efficacy in a patient with refractory lupus nephritis. Clin Kidney J 6(1):74–76. doi:10.1093/ckj/sfs162
105. Devauchelle-Pensec V, Morvan J, Rat AC, Jousse-Joulin S, Pennec Y, Pers JO, Jamin C, Renaudineau Y, Quintin-Roue I, Cochener B, Youinou P, Saraux A (2011) Effects of rituximab therapy on quality of life in patients with primary Sjogren's syndrome. Clin Exp Rheumatol 29(1):6–12
106. Renaudineau Y, Devauchelle-Pensec V, Hanrotel C, Pers JO, Saraux A, Youinou P (2009) Monoclonal anti-CD20 antibodies: mechanisms of action and monitoring of biological effects. Joint Bone Spine 76(5):458–463. doi:10.1016/j.jbspin.2009.03.010
107. Jousse-Joulin S, Devauchelle-Pensec V, Morvan J, Guias B, Pennec Y, Pers JO, Daridon C, Jamin C, Renaudineau Y, Roue IQ, Cochener B, Bressollette L, Youinou P, Saraux A (2007) Ultrasound assessment of salivary glands in patients with primary Sjogren's syndrome treated with rituximab: quantitative and Doppler waveform analysis. Biologics : targets & therapy 1(3):311–319
108. Devauchelle-Pensec V, Pennec Y, Morvan J, Pers JO, Daridon C, Jousse-Joulin S, Roudaut A, Jamin C, Renaudineau Y, Roue IQ, Cochener B, Youinou P, Saraux A (2007) Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). Arthritis & Rheumatism 57(2):310–317. doi:10.1002/art.22536
109. Pers JO, Devauchelle V, Daridon C, Bendaoud B, Le Berre R, Bordron A, Hutin P, Renaudineau Y, Dueymes M, Loisel S, Berthou C, Saraux A, Youinou P (2007) BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjogren's syndrome. Arthritis & Rheumatism 56(5):1464–1477. doi:10.1002/art.22603
110. Mahevas M, Patin P, Huetz F, Descatoire M, Cagnard N, Bole-Feysot C, Le Gallou S, Khellaf M, Fain O, Boutboul D, Galicier L, Ebbo M, Lambotte O, Hamidou M, Bierling P, Godeau B, Michel M, Weill JC, Reynaud CA (2013) B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells. J Clin Invest 123(1):432–442. doi:10.1172/JCI65689
111. Mahevas M, Michel M, Vingert B, Moroch J, Boutboul D, Audia S, Cagnard N, Ripa J, Menard C, Tarte K, Megret J, Le Gallou S, Patin P, Thai L, Galicier L, Bonnotte B, Godeau B, Noizat-Pirenne F, Weill JC, Reynaud CA (2015) Emergence of long-lived autoreactive plasma cells in the spleen of primary warm autoimmune hemolytic anemia patients treated with rituximab. J Autoimmun 62:22–30. doi:10.1016/j.jaut.2015.05.006
112. Morell M, Varela N, Maranon C (2017) Myeloid populations are altered in systemic autoimmune diseases. Clinical reviews in allergy & immunology
113. Baumann I, Kolowos W, Voll RE, Manger B, Gaipl U, Neuhuber WL, Kirchner T, Kalden JR, Herrmann M (2002) Impaired uptake of apoptotic cells into tingible body macrophages in germinal centers of patients with systemic lupus erythematosus. Arthritis & Rheumatism 46(1):191–201. doi:10.1002/1529-0131(200201)46:1<191::AID-ART10027>3.0.CO;2-K
114. Sisirak V, Ganguly D, Lewis KL, Couillault C, Tanaka L, Bolland S, D'Agati V, Elkon KB, Reizis B (2014) Genetic evidence for the role of plasmacytoid dendritic cells in systemic lupus erythematosus. J Exp Med 211(10):1969–1976. doi:10.1084/jem.20132522
115. Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J (2001) Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. Science 294(5546):1540–1543. doi:10.1126/science.1064890
116. Celhar T, Hopkins R, Thornhill SI, De Magalhaes R, Hwang SH, Lee HY, Yasuga H, Jones LA, Casco J, Lee B, Thamboo TP, Zhou XJ, Poidinger M, Connolly JE, Wakeland EK, Fairhurst AM (2015) RNA sensing by conventional dendritic cells is central to the development of lupus nephritis. Proc Natl Acad Sci U S A 112(45):E6195–E6204. doi:10.1073/pnas.1507052112
117. Zhu J, Liu X, Xie C, Yan M, Yu Y, Sobel ES, Wakeland EK, Mohan C (2005) T cell hyperactivity in lupus as a consequence of hyperstimulatory antigen-presenting cells. J Clin Invest 115(7):1869–1878. doi:10.1172/JCI23049
118. Sahu R, Bethunaickan R, Singh S, Davidson A (2014) Structure and function of renal macrophages and dendritic cells from lupus-prone mice. Arthritis & Rheumatology 66(6):1596–1607. doi:10.1002/art.38410