Published in final edited form as:

Semin Nephrol. 2007 January ; 27(1): 47–58.

T cells and B cells in Lupus Nephritis

Mary H. Foster, M.D.

Associate Professor, Department of Medicine, Division of Nephrology, Duke University Medical Center

Introduction

The immune system plays a central role in the pathogenesis of systemic lupus erythematosus. This review will focus on B and T lymphocytes, two pivotal cellular components of adaptive immunity and key culprits in mediation of glomerulonephritis, a common and serious complication of lupus. Glomerular Ig deposition and renal lymphocyte and macrophage infiltration lead to clinical renal involvement at some point in the clinical course of up to 75% of lupus patients. Lymphocytes and their soluble mediators participate at all levels in disease pathogenesis: initiation, perpetuation, amplification, regulation, tissue and organ destruction, and disease relapse. They thus pose prime targets for novel interventions. Intense laboratory and clinical investigation over the past decade has brought important insights into cellular subsets, signaling, mediators and regulatory pathways, and introduced promising new immunotherapies.

Initiation of Nephritogenic Autoimmune Responses

Tolerance and autoimmune susceptibility

Lupus is a disease of failed immune tolerance to self. The repertoire of Ig and T cell receptors is vast and self recognition is common, generated by gene recombinatorial and somatic events in the thymus and bone marrow and, in the case of mature B cells, by somatic mutation in the peripheral lymphoid organs. It is estimated that up to 75% of newly formed, and up to 40% of mature germinal center, B cells recognize self antigens (1,2). This autoreactivity is normally held in check by regulatory mechanisms that operate on developing lymphocytes in the central lymphoid organs and on mature cells in the spleen and lymph nodes (Table 1) (3).

Specific tolerance is induced by interaction of the lymphocyte antigen receptor with self-antigen, either in native conformation for recognition by B cells or as peptide antigen presented by cell-bound MHC molecules for recognition by TCR α beta-expressing T cells (Figure 1). The strength of this signal may influence the type of tolerance induced (deletion or anergy). Induction of tolerance by antigen contact requires an appropriate microenvironment and non-inflammatory milieu that limits lymphocyte signaling to that initiated by antigen alone, also referred to as “signal 1”. Delivery of “signal 2” to an autoreactive lymphocyte converts a tolerogenic signal into an activating one, triggering an autoimmune response. Signal 2 is typically delivered by costimulatory molecules expressed on activated antigen presenting cells (APC) and lymphocytes. Major costimulators involved in T-B cell collaboration are CD40/CD40L and members of the B7/CD28 family (B7/CD28, ICOSL/ICOS) (4). Additionally,

Mailing address: Dr. Mary H. Foster, Department of Medicine, Division of Nephrology, Box 3014, Duke University Medical Center, Durham, N.C. 27710, Phone 919-286-6947, FAX 919-286-6879, Email mhfooster@duke.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

potent mitogens or microbial products can trigger “danger” signals that permit bypass of tolerance by binding toll-like receptors (TLR) on B cells and APC (5).

Failure or bypass of one or more regulatory mechanisms permits autoreactive lymphocytes to survive and expand (Table 2, Figure 2). Dysregulation of sufficient magnitude or at a sufficient number of checkpoints in combination with lymphocyte activation, antigen exposure and a permissive end-organ microenvironment ultimately leads to tissue destruction and disease. Dysregulation results from environmental exposures and inherited autoimmune susceptibility, often acting in concert (6,7). Considerable data suggest that different influences alter different pathways, and that different regulatory mechanisms are breached in different individuals. It is evident from animal models that a wide variety of immune abnormalities can lead to a similar lupus-like disease.

Exogenous agents can provoke acquired defects in immune tolerance leading to a lupus phenotype. Procainamide and hydralazine induce systemic autoimmunity in man and rodents. In vitro they inhibit DNA methylation and upregulate T cell lymphocyte function-associated antigen-1 (LFA-1) costimulator expression to promote T cell autoreactivity. Adoptive transfer of T cells overexpressing LFA-1 induces lupus-like disease including glomerulonephritis in naïve recipient mice (8). Procainamide has also been shown to alter T cell thymic selection and signaling thresholds (9). Mercuric chloride and gold induce Th2-type autoreactive CD4⁺ T cells, interleukin (IL) 4 production and an IFN-gamma-dependent lupus nephritis in rodents (10,11). A similar phenotype is reported in allogeneic reactions. Heavy metals, hydrocarbon oil (pristane), and microbial products are potent B cell mitogens with the potential to activate non-tolerant (ignorant) autoreactive cells or reverse anergy.

Autoimmune susceptibility arises from allelic variants or mutations in genes encoding a variety of immune relevant proteins of diverse function (7). Transgenic over-expression or targeted disruption of molecules involved in B and T cell signaling, lymphocyte selection, adhesion, activation and survival can lead to spontaneous lupus-like disease and nephritis. Genetic mapping studies in common murine lupus strains [MRL/lpr, (NZBxNZW)F1, BXSB], their congenic variants and derivatives have identified loci that modify tolerance. Autoreactive B and T cell receptor transgenes established on lupus-prone backgrounds reveal defects in B cell tolerance, induction of T cell anergy, and defects in central T cell deletion (12,13). Studies in human lupus reveal associations with MHC class II alleles, molecules critical to antigen presentation, complement components that regulate B cell activation, tolerance and effector functions, and Fcγ receptors that regulate APC activation (7).

T and B cell abnormalities and interactions in induction of lupus

Abnormalities in B and T cells characterize murine and human lupus, reflecting both lymphocyte-intrinsic defects and extrinsic influences (14–17). Lupus T cells manifest decreased DNA methylation, defective T cell receptor (TCR) signaling, heightened calcium responses, lowered activation threshold, upregulated expression of costimulatory molecules CD40L, ICOS, beta2 integrins CD11a/CD18 (LFA-1), and CD11c/CD18 (Mac-1), upregulated focal adhesion kinase pp125FAK, decreased expression of TCR zeta chain, increased intracellular phosphorylation, upregulated FcγR chain expression, mutations in type I protein kinase A regulatory subunit alpha, deficient activation-induced death, deficient IL-2 production, upregulated COX-2, mitochondrial dysfunction, overexpression of perforin and regulatory defects in cbl and extracellular signal-related kinase (ERK) pathways. Paradoxical concurrent spontaneous T cell hyperresponsiveness and defective in vivo and ex vivo T cell proliferative responses are reported. Lupus B cells are hyperactive and exhibit enhanced phosphorylation of MAPK pathways, altered Lyn expression, upregulated bcl2, upregulated CD40L, and defective BCR-induced apoptosis (18–20). Circulating B-cell-activating factor (BAFF, or BLyS), a B cell survival factor, is elevated in a significant proportion of lupus

patients, and mice over-expressing BAFF develop a lupus-like disease (21). BAFF rescues autoreactive B cells from peripheral deletion and initiates CD40L-independent IgG isotype class switch (22). Circulating plasmablasts and cells bearing germinal center markers are reported in lupus patients, and plasmablasts and ectopic germinal centers and follicles populate murine lupus kidneys (18,23).

Local Regulation of immune responses

Renal parenchymal cells, and proximal tubular epithelial cells (TEC) in particular, may play a key role in modulating nephritogenic immune responses in lupus (24,25). IFN-gamma-stimulated TEC downregulate proliferation in autoreactive T cell clones derived from MRL/lpr kidneys. Murine lupus TEC express MHC molecules and present antigen *ex vivo* for recognition by CD4⁺ T cells. This interaction can lead to either anergy or activation of responding T cells, depending on whether antigen-presenting TEC concomitantly upregulate costimulatory or inhibitory molecules. The reported tissue distribution of the costimulatory family molecules suggest that the pathways most likely engaged in parenchymal cell regulation of T lymphocytes are ICOS/ICOS-L and inhibitory PD-1/PD-L interactions. Collectively, these findings suggest that TEC-T cell interactions in the kidney are primarily regulatory and maintain tolerance to self antigen. A similar role may apply to other parenchymal cells, such as mesangial cells, glomerular podocytes and endothelium, that have inducible antigen presenting functions.

T cells and Cellular Immunity in Lupus Nephritis

Regulation by T cell subsets

T cells play central and multiple roles in pathogenesis of lupus nephritis (Figure 2). They provide help for B cell production of nephritogenic autoantibodies, regulate B cell responses, and modulate T helper and effector functions and expansion. T cells infiltrate the kidney to injure renal parenchymal cells directly via cytotoxicity or indirectly through activation and recruitment of macrophages and NK cells.

The importance of T cells in lupus is well documented (15,26). Oligoclonally expanded IFN-gamma-producing T cells autoreactive to classic lupus-associated autoantigens can be isolated from peripheral blood of lupus patients and from lupus mice. Most lines or clones isolated to date are CD4⁺ TCR alpha/beta phenotype, although recovery of CD8⁺ and TCR gamma/delta T cells is reported. An imbalance in number and function of T cell subsets is reported, including an increase in CD4⁺ relative to CD8⁺ T cells, increased frequency of circulating double-negative CD4[−] CD8[−] T cells, and altered Th1 and Th2 cytokine production. Patient and murine lupus alpha/beta, gamma/delta and CD4[−] CD8[−] T cells facilitate autoantibody production by B cells. Chromatin-reactive CD4⁺ T cells isolated from lupus patients and mice augment production of anti-DNA and anti-chromatin antibodies (27). Evidence of T cell help is found in the lupus autoantibodies themselves; IgG isotype switch and accumulation of replacement mutations suggest that they are products of an antigen-driven T cell-dependent immune response.

Definitive evidence of the requirement for T cells comes from rodent lupus models, in which T cell helper and effector subsets have been depleted and costimulatory pathways interrupted using monoclonal antibodies, fusion proteins and gene-targeted deletion (reviewed in (28)). In general, murine lupus nephritis is delayed and ameliorated by depletion of CD4⁺ and alpha/beta T cell subsets and antagonism of CD28/B7, CD40/CD40L, and ICAM-1/LFA-1 costimulatory interactions. Each strategy can delay nephritis and variably decrease proteinuria, improve urea and creatinine clearances, lessen renal histopathological injury and lymphocytic infiltration, and lower autoantibody production (29–31). Recent results from interruption of

the ICOS/ICOSL pathway vary by strain and experimental strategy; anti-ICOS mAb improved nephritis in BWF1 mouse whereas targeted deletion of ICOS had no effect on MRL/lpr nephritis (32,33). Efficacy of T depletion and costimulatory blockade in prolonging survival and ameliorating disease in non-renal organ systems is variable, and persistence of some lupus manifestations in mice lacking alpha/beta T cells suggests alpha/beta-independent mechanisms (34).

Notably, each major T cell subset has regulatory as well as pathogenic effector roles, such that the net effect of a given intervention appears to be context dependent and may be unpredictable. In this regard, deletion of Class I MHC and CD8+ T cells has yielded conflicting observations. Targeted deletion of beta2-microglobulin, which eliminates both classical and nonclassical (CD1) MHC Class I expression and thus eliminates CD8+ and NK1 T cells, ameliorates kidney injury but accelerates skin disease in MRL/lpr mice (35,36). The effect is attributed to CD8+ T cell depletion, because isolated CD1-deletion does not alter MRL/lpr nephritis. Conversely, beta2-microglobulin deletion in BWF1 mice accelerates disease (37), and prolonged anti-CD8 mAb treatment fails to alter disease in MRL/lpr and (NZWxBXSB)F1 mice, in contrast to a favorable response induced with anti-CD4 mAb (38,39).

TCRgamma/delta T cells and Natural Killer T (NKT) cells play an equally complex role in lupus (40). MRL/lpr mice lacking TCRgamma/delta T cells develop accelerated nephritis and mortality accompanied by polyclonal expansion of CD4+ T cells, suggesting a dominant negative regulatory function for this T cell subset (41). Conversely, TCRgamma/delta effectors appear to be responsible for the residual mild autoimmunity and nephritis observed in TCRalpha/beta deficient MRL/lpr mice, because autoantibody production and disease are absent in TCRalpha/beta TCRgamma/delta double-deficient MRL/lpr mice (41). NKT cells express an invariant TCR and NK cell receptor NK1.1 and recognize glycolipid presented by CD1d. Activated NKT cells produce immunomodulatory cytokines and mediate cytotoxicity. As noted above, CD1-deficiency does not alter MRL/lpr nephritis, whereas in vivo activation of NKT cells has variably been associated with exacerbation and amelioration of murine lupus (42).

Collectively these observations support an important role for regulatory T cell subsets in lupus. This is consistent with numerous early reports of abnormalities of T cell suppression in lupus, including decreased numbers of CD4+ CD25+ T cells in peripheral blood of SLE patients with active disease (15). Suppression of autoantibody production and nephritis in lupus mice using tolerogenic peptides to expand CD4+ CD25+ regulatory T cells and TGF-beta-producing inhibitory CD8+ T cell subsets is reported (43).

T cell effector mechanisms in lupus

Differentiated T cell effectors exert their functions by interactions with other cells or through overproduction of immunodulatory cytokines, such as IFN-gamma, TNF-alpha, TGF-beta, IL-4, and IL-17. Activated CD4+ and CD8+ T cells, and, in MRL/lpr mice, the unique population of B220+ class I-restricted double-negative (DN) CD4- CD8- TCR-alphabeta T cells are present in glomerular lesions in murine and human lupus, recruited by chemokines to exert actions locally (44,45). In addition to promoting autoantibody responses, T cell-generated proinflammatory cytokines amplify disease by upregulating adhesion and MHC Class II molecules, recruit macrophages, promote fibrosis, and induce intrarenal nephritogenic cytokines CSF-1, GM-CSF and TNF-alpha (46,47). Autoreactive DN T cell clones propagated from nephritic lupus mouse kidneys induce MHC class II and ICAM-1 expression and proliferate in response to renal parenchymal cells (48). Autoreactive cytotoxic CD4+ TCR alpha/beta T cells can be isolated from nephritic kidneys of mice with chronic graft-versus-host-disease (GVHD), a lupus-like syndrome with glomerulopathy (49). GVHD-derived T cell effectors induce glomerular crescents and a focal mononuclear infiltration when transferred to

naïve syngeneic recipients by renal subcapsular transfer. In non-lupus model systems, nephritogenic CD4⁺ and CD8⁺ T cell clones have been shown to mediate MHC-restricted, perforin and granzyme-mediated cytotoxicity toward cultured renal proximal tubular cells (50). It is notable therefore that T cell cytotoxicity in lupus may be predominantly regulatory, directed toward controlling pathogenic lymphocytes. Cytotoxic responses are mediated primarily through Fas, perforin and TNF. Deficiency in each of these pathways introduced in lupus-prone mice by gene-targeted deletion of Fas, FasL, perforin or TNF-receptor leads to acceleration, not improvement, of autoimmunity and nephritis (51). This may explain in part the association of drug-induced lupus with anti-TNF-alpha therapy.

Cytokines involved in CD4⁺ Th1/Th2 T helper cell differentiation received early attention due to their pro- (IFN-gamma, IL-12, TNF-alpha/beta) or anti- (IL-4, IL-10) inflammatory actions and potential therapeutic efficacy. However, in vivo biologic or genetic modulation of cytokine production or function has shown inconsistent results in modulating lupus nephritis (reviewed in (52). In vivo administration of either IL-10 or IFN-gamma accelerates nephritis in lupus-prone BWF1 mice, whereas antibody blockade of either cytokine delays disease. Nephritis in MRL/lpr mice is ameliorated by targeted disruption of either IFN-gamma or IL-4. Administration of IL-12 accelerates nephritis and promotes intrarenal accumulation of IFN- γ -secreting CD4⁺, CD8⁺, and double-negative T cells in lupus mice. These results fail to implicate disease dependence on a single CD4⁺ T helper subset. Notably, levels of both Th1 and Th2 cytokines are elevated in murine lupus, and proteinuria and glomerulonephritis in MRL/lpr lupus is ameliorated by histone deacetylase inhibitors that downregulate transcription of both subsets (IL12, IFN γ , IL6 and IL10) (53).

Recognition that IL-23 and IL-27, additional members of the IL-6/IL-12 family influence Th1 responses as well as development of a third lineage of CD4⁺ T helper cell, termed Th17 cells, explains some of the previous conflicting findings. Th17 cells develop under the influence of IL-6, TGF-beta and IL-23 and produce the pro-inflammatory cytokine IL-17 (54). Notably, deficiency for WSX-1, a component of the IL-27 receptor, alters the cytokine profile and phenotype of lupus glomerulonephritis in MRL/lpr lupus mice. (55). A significant decrease in IFN-gamma production by CD4⁺ T cells accompanies a shift from diffuse proliferative GN to a clinical and pathological picture resembling human membranous nephropathy. The importance and nature of local cytokines that mediate renal immune injury was elucidated using an innovative strategy of implanting genetically modified cytokine-secreting renal tubular cells under the kidney capsule. IL-12, macrophage growth factors and the chemokine RANTES, but not IL-6, elicit autoimmune injury in lupus mouse kidneys (56).

B Cells and Humoral Immunity in Lupus Nephritis

Multifunctional B cells

B cells serve diverse regulatory functions in immune biology and lupus (Figure 2 and Table 3) (reviewed in (57,58). Although best appreciated for antibodies release, B cell production of regulatory cytokines and direct interactions with T cells and dendritic cells have a profound impact in shaping cellular immune responses. B cells are highly efficient antigen presenting cells, capable of capturing antigen via cell surface Ig receptors for subsequent internalization, processing and presentation via Class I or II MHC molecules. B cell presentation of autoantigen peptides directly activates autoreactive T cells. B cells modulate T cell memory and regulate dendritic cell development and activation. Distinct subsets of differentiated effector and regulatory B cells produce significant amounts of immune modulatory cytokines, such as IL-10 and TGF-beta (59). IL-10 suppresses macrophage activation and cytokine production and skews T helper differentiation toward a Th2 phenotype. Notably, generation of IL-10-producing regulatory B cells occurs under inflammatory conditions, appears to involve a marginal zone B cell precursor, occurs in man, and can be induced by Toll-like receptor (TLR)

signaling. This latter observation is consistent with recent reports of apparent paradoxical immunosuppressive effects of TLR agonists. TGF β suppresses inflammation, induces apoptosis in effector T cells and skews T helper differentiation toward a Th17 phenotype. Experimental manipulations suggest multiple additional mechanisms, many of which are listed in Table 3, by which B cells modulate T cell expansion and function, induce T cell tolerance, and dampen inflammation. Secreted antibodies also function in regulation, via protective self-antigen specificities, IgG constant region engagement of inhibitory Fc γ RIIB receptors on APC, or within regulatory idiotypic networks (60). There has been a recent resurgence of interest in the regulatory role of B cells and autoantibodies with the discovery of B cell dependence in autoimmune disease models previously thought to be primarily T cell mediated and conversely, exacerbation of several murine autoimmune and inflammatory diseases in B cell-deficient mice as compared to their B cell-sufficient counterparts. These diverse roles raise some concern regarding the predictability of outcomes with B cell targeted therapies. Nonetheless, B cell ablation through gene deletion or anti-CD20 monoclonal antibody administration eliminates early mortality, immune infiltrates and organ injury in murine lupus, and early reports suggest similar therapeutic efficacy of anti-CD20 therapy in human lupus, suggesting a dominant pathogenic role for B cells in this disease (19,58)

B cells serve multiple functions in lupus. Best characterized is their production of anti-nuclear and polyreactive autoantibodies, the cornerstone of diagnosis and characteristic feature of lupus glomerulonephritis. Autoantibodies deposit in the kidney and induce injury by a variety of mechanisms. It is clear, however, that the B cell contribution to pathogenicity extends beyond antibody production [Shlomchik, 2001 #3335]. Nephritis and vasculitis do not develop in B cell-deficient MRL/lpr mice, whereas glomerulonephritis and early death are unaffected in MRL/lpr mice bearing genetically manipulated B cells incapable of secreting antibody (61). B cell-deficient MRL/lpr mice fail to develop the activated CD8 and CD4 T cells found in B cell-sufficient mice, a finding attributed to loss of B cell-CD4 T cell interactions since activated CD8 T cells persist in MRL/lpr mice lacking MHC Class I antigen on B cells. Tissue infiltrating antibody-secreting B cells and plasma cells are abundant in nephritic BWF1 kidneys, and B cells secreting nephropathic anti-DNA autoantibodies can be isolated from nephritic MRL/lpr kidneys (23). BWF1 mice ectopically express a B cell chemoattractant that promotes renal and other organ trafficking of B-1 B cells (62). IL-10-producing regulatory B cells are also present in murine lupus, where they may play a role in limiting disease. This may in part explain the conflicting results obtained from ablation of the marginal zone B cell population, a proposed precursor of regulatory B cells, in BWF1 and BXSB lupus-prone mice (57).

Nephritogenic autoantibodies and antibody-mediated Injury

Glomerular antibody deposition is a hallmark of lupus glomerulonephritis. Renal bound antibodies engage cell-bound Fc receptors, activate complement, mediate thrombosis, and directly alter cell functions. Mechanisms of immune deposition and injury have been reviewed extensively elsewhere (63,64), and will be briefly summarized here, with emphasis on recent new insights. Extensive investigation has revealed multiple IgG subclasses and diverse antigen specificities, avidity, and charge among Ig eluted from nephritic lupus kidneys or isolated from lupus serum or monoclonal antibodies. IgG is the predominant isotype deposited, but IgM and IgA are also typically present in human lupus nephritis, accompanied by C3, C4 and C1q. Specificity for DNA is important for pathogenesis for a subset of lupus Ig, but multiple experimental models indicate that anti-DNA activity is neither necessary nor sufficient to induce lupus nephritis, and many Ig eluted from lupus kidneys do not bind to DNA.

These nephritogenic antibodies localize to the kidney by multiple mechanisms. In situ formation of immune complexes may be a dominant mechanism of renal Ig deposition. Direct binding of crossreactive anti-DNA Ig to purified glomerular antigens, including alpha-actinin

and alpha-enolase, and to cultured parenchymal cells can be demonstrated in vitro and in experimental models. Nuclear antigens with intrinsic affinity for glomerular cell or basement membrane surfaces can serve as planted antigen for subsequent binding by anti-DNA and anti-nucleosome antibodies. Collagen, laminin, fibronectin and some cells have binding sites for DNA, whereas charge interactions attract anionic DNA to cationic immune complexes, histones and nucleosomes previously captured by anionic sites in glomerular basement membrane or on cell membranes. Rheumatoid factors and anti-C1q Ig can engage previously deposited IgG or C1q. Murine IgG3 has a unique capacity to form cryoglobulins and occlude glomerular capillaries. Additional mechanisms of renal injury are proposed: disruption of cell functions by autoantibodies that gain intracellular access; disruption of glomerular permeability by masking anionic sites; thrombus formation due to interference with phospholipid-dependent coagulation; and complement-mediated cytotoxicity of renal parenchymal cells.

The ultimate renal disease phenotype is dependent on several factors, including antibody specificity and isotype and effector functions determined by Ig constant region domains, each subclass of which has a unique profile of interactions with complement and multifunctional Fc gamma receptors. Outcomes are regulated in turn by a complex system of regulatory proteins and cytokines. Ig engage activating Fc gamma receptors on macrophages, neutrophils and renal parenchymal cells to promote leukocyte adhesion and trigger release of multiple inflammatory mediators (65). However, nephritis is variably attenuated in lupus mice with targeted deletion of the common Fc receptor gamma-chain gene (66,67). Discordant outcomes reflect in part the importance of Fc receptors in immune complex clearance; loss of activating Fc gamma receptors in *non*-autoimmune mice markedly increases immune deposition (65). Loss of the inhibitory IgG Fc receptor, FcγRIIB, induces lupus-like nephritis in a strain-specific manner in non-autoimmune mice and accelerates disease in lupus-prone strains (68).

Notably, secreted IgG, autoantibodies and antigen-IgG immune complexes also serve regulatory roles to modulate lupus phenotypes. Autoantibodies reactive with phospholipids are implicated in clearance of apoptotic bodies, one source of lupus self immunogen. Nucleic acid (DNA and RNA) and chromatin-containing IgG immune complexes are potent amplifiers of autoimmunity. Dendritic cells and B cells capture and internalize DNA/anti-DNA immune complexes by activating Fcγ receptors, FcγRIIa and FcγRIII, or by IgG-binding (rheumatoid factor) B cell receptors. This sets the stage for subsequent nucleic acid engagement of TLR9 or TLR7 in cytoplasmic compartments, promoting cell maturation and activation and, in autoreactive B cells, switch to pathogenic IgG isotypes (65,69). Conversely, inhibitory Fc gamma RIIB receptors on B cells down modulate B cell receptor signaling and plasma cell expansion (65). Immune complexes also inhibit B cell signaling by engaging complement-receptor CD21/CD35; deficiency of this inhibitory receptor interrupts induction of B cell energy and, in permissive backgrounds, promotes lupus nephritis (70).

Summary and Conclusion

T and B lymphocytes play diverse roles at multiple stages in the development and progression of lupus nephritis. Disease phenotype depends on the balance of pathogenic effector and immune regulatory cell subsets and their secreted products. New insights into their biology has brought the promise of new therapies in lupus nephritis (Table 4). Major recent advances include appreciation of a key modulatory function for innate immune elements, novel regulatory roles for B cells and antibodies, a newly discovered T cell subset (Th17), elucidation of additional immune regulatory checkpoints, an expanding list of genetic or acquired lymphocyte abnormalities that predispose to autoreactivity, and recognition of new functions of effector molecule cascades, including components that potently impact both the inductive and effector limbs of disease, sometimes with opposite effects on outcomes. Support for

ongoing research in this effort is crucial, to broaden the arsenal of non-toxic targeted interventions for lupus nephritis and systemic autoimmunity.

Acknowledgements

This work was supported by a Department of Veterans Affairs Merit Review Grant and National Institutes of Health Grant DK47424. The author apologizes to colleagues for the inability to cite many primary references due to space constraints.

References

1. Wardemann H, Yurasov S, Schaefer A, et al. Predominant autoantibody production by early human B cell precursors. *Science* 2003;301:1374–1377. [PubMed: 12920303]
2. Jacobi AM, Diamond B. Balancing diversity and tolerance: lessons from patients with systemic lupus erythematosus. *J Exp Med* 2005;202:341–344. [PubMed: 16061723]
3. Goodnow C, Sprent J, Fazekas de St Groth B, et al. Cellular and genetic mechanisms of self tolerance and autoimmunity. *Nature* 2005;435:590–597. [PubMed: 15931211]
4. Keir M, Sharpe A. The B7/CD28 costimulatory family in autoimmunity. *Immunol Rev* 2005;204:128–143. [PubMed: 15790355]
5. Peng S. Signaling in B cells via Toll-like receptors. *Curr Opin Immunol* 2005;17:230–236. [PubMed: 15886111]
6. Rao T, Richardson B. Environmentally induced autoimmune diseases: potential mechanisms. *Environ Health Perspect* 1999;107 (Suppl 5):737–742. [PubMed: 10502539]
7. Lauwerys B, Wakeland E. Genetics of lupus nephritis. *Lupus* 2005;14:2–12. [PubMed: 15732281]
8. Yung R, Powers D, Johnson K, et al. Mechanisms of drug-induced lupus. II T cells overexpressing lymphocyte function-associated antigen 1 become autoreactive and cause a lupus-like disease in syngeneic mice. *J Clin Invest* 1996;97:2866–2871. [PubMed: 8675699]
9. Kretz-Rommel A, Rubin R. Disruption of positive selection of thymocytes causes autoimmunity. *Nat Med* 2000;6:298–305. [PubMed: 10700232]
10. Prigent P, Saoudi A, Pannetier C, et al. Mercuric chloride, a chemical responsible for T helper cell (TH)2-mediated autoimmunity in brown Norway rats, directly triggers T cells to produce interleukin-4. *J Clin Invest* 1995;96:1484–1489. [PubMed: 7657819]
11. Kono DH, Balomenos D, Pearson DL, et al. The prototypic Th2 autoimmunity induced by mercury is dependent on IFN-gamma and not Th1/Th2 imbalance. *J Immunol* 1998;161:234–240. [PubMed: 9647229]
12. Erikson J, Mandik L, Bui A, et al. Self-reactive B cells in nonautoimmune and autoimmune mice. *Immunol Res* 1998;17:49–61. [PubMed: 9479567]
13. Michaels M, Kang H, Kaliyaperumal A, et al. A defect in deletion of nucleosome-specific autoimmune T cells in lupus-prone thymus: role of thymic dendritic cells. *J Immunol* 2005;175:5857–5865. [PubMed: 16237078]
14. Nagy G, Koncz A, Perl A. T- and B-cell abnormalities in systemic lupus erythematosus. *Crit Rev Immunol* 2005;25:123–140. [PubMed: 15952933]
15. Hoffman RW. T cells in the pathogenesis of systemic lupus erythematosus. *Clin Immunol* 2004;113:4–13. [PubMed: 15380523]
16. Zielinski C, Jacob S, Bouzazhah F, et al. Naive CD4+ T cells from lupus-prone Fas-intact MRL mice display TCR-mediated hyperproliferation due to intrinsic threshold defects in activation. *J Immunol* 2005;174:5100–5109. [PubMed: 15814741]
17. Xu L, Zhang L, Yi Y, et al. Human lupus T cells resist inactivation and escape death by upregulating COX-2. *Nat Med* 2004;10:411–415. [PubMed: 14991050]
18. Grammer AC, Lipsky PE. B cell abnormalities in systemic lupus erythematosus. *Arthritis Res Ther* 2003;5 (Suppl 4):S22–27. [PubMed: 15180894]
19. Renaudineau Y, Pers JO, Bendaoud B, et al. Dysfunctional B cells in systemic lupus erythematosus. *Autoimmun Rev* 2004;3:516–523. [PubMed: 15546800]

20. Tsubata T. B cell abnormality and autoimmune disorders. *Autoimmunity* 2005;38:331–337. [PubMed: 16240466]
21. Mackay F, Sierro F, Grey S, et al. The BAFF/APRIL system: an important player in systemic rheumatic diseases. *Curr Dir Autoimmun* 2005;8:243–265. [PubMed: 15564724]
22. Thien M, Phan T, Gardam S, et al. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* 2004;20:785–798. [PubMed: 15189742]
23. Sekine H, Watanabe H, Gikleson GS. Enrichment of anti-glomerular antigen antibody-producing cells in the kidneys of MRL/MpJ-Fas(lpr) mice. *J Immunol* 2004;172:3913–3921. [PubMed: 15004199]
24. Kelley VR, Diaz-Gallo C, Jevnikar AM, et al. Renal tubular epithelial and T cell interactions in autoimmune renal disease. *Kidney Internat* 1993;39:S108–115. [Review] [99 refs]
25. Yokoyama H, Zheng X, Strom T, et al. B7(+)-transfectant tubular epithelial cells induce T cell anergy, ignorance or proliferation. *Kidney Int* 1994;45:1105–1112. [PubMed: 8007580]
26. Kyttaris VC, Tsokos GC. T lymphocytes in systemic lupus erythematosus: an update. *Curr Opin Rheumatol* 2004;16:548–552. [PubMed: 15314492]
27. Datta S. Major peptide autoepitopes for nucleosome-centered T and B cell interaction in human and murine lupus. *Ann N Y Acad Sci* 2003;987:79–90. [PubMed: 12727626]
28. Peng S. Experimental use of murine lupus models. *Methods Mol Med* 2004;102:227–272. [PubMed: 15286389]
29. Jevnikar AM, Grusby MJ, Glimcher LH. Prevention of nephritis in major histocompatibility complex class-II-deficient MRL-lpr mice. *J Exp Med* 1994;179:1137–1143. [PubMed: 7908320]
30. Daikh DI, Finck BK, Linsley PS, et al. Long-term inhibition of murine lupus by brief simultaneous blockade of the B7/CD28 and CD40/gp39 costimulation pathways. *J Immunol* 1997;159:3104–3108. [PubMed: 9317105]
31. Kinoshita K, Tesch G, Schwarting A, et al. Costimulation by B7-1 and B7-2 is required for autoimmune disease in MRL-Fas(lpr) mice. *J Immunol* 2000;164:6046–6056. [PubMed: 10820290]
32. Iwai H, Abe M, Hirose S, et al. Involvement of inducible costimulator-B7 homologous protein costimulatory pathway in murine lupus nephritis. *J Immunol* 2003;171:2848–2854. [PubMed: 12960306]
33. Zeller G, Hirahashi J, Schwarting A, et al. Inducible co-stimulator null MRL-Fas(lpr) mice: uncoupling of autoantibodies and T cell responses in lupus. *J Am Soc Nephrol* 2006;17:122–130. [PubMed: 16291836]
34. Peng SL, Madaio MP, Hughes DPM, et al. Murine lupus in the absence of $\alpha\beta$ T cells. *J Immunol* 1996;156:4041–4049. [PubMed: 8621947]
35. Christianson GJ, Blankenburg RL, Duffy TM, et al. Beta2-microglobulin dependence of the lupus-like autoimmune syndrome of MRL-lpr mice. *J Immunol* 1996;156:4932–4939. [PubMed: 8648144]
36. Chan O, Paliwal V, McNiff J, et al. Deficiency in beta(2)-microglobulin, but not CD1, accelerates spontaneous lupus skin disease while inhibiting nephritis in MRL-Fas(lpr) mice: an example of disease regulation at the organ level. *J Immunol* 2001;167:2985–2990. [PubMed: 11509649]
37. Mozes E, Lovchik J, Zinger H, et al. MHC class I expression regulates susceptibility to spontaneous autoimmune disease in (NZBxNZW)F1 mice. *Lupus* 2005;14:308–314. [PubMed: 15864917]
38. Merino R, Fossati L, Iwamoto M, et al. Effect of long-term anti-CD4 or anti-CD8 treatment on the development of lpr CD4⁺ CD8⁺ double negative T cells and of the autoimmune syndrome in MRL-lpr/lpr mice. *J Autoimmun* 1995;8:33–45. [PubMed: 7734035]
39. Adachi Y, Inaba M, Sugihara A, et al. Effects of administration of monoclonal antibodies (anti-CD4 or anti-CD8) on the development of autoimmune diseases in (NZW x BXSB)F1 mice. *Immunobiology* 1998;198:451–464. [PubMed: 9562869]
40. Kapp J, Kapp L, McKenna K. Gammadelta T cells play an essential role in several forms of tolerance. *Immunol Res* 2004;29:93–102. [PubMed: 15181273]
41. Peng SL, Madaio MP, Hayday AC, et al. Propagation and regulation of systemic autoimmunity by $\gamma\delta$ T cells. *J Immunol* 1996;157:5689–5698. [PubMed: 8955223]

42. Forestier C, Molano A, Im J, et al. Expansion and hyperactivity of CD1d-restricted NKT cells during the progression of systemic lupus erythematosus in (New Zealand Black x New Zealand White)F1 mice. *J Immunol* 2005;175:763–770. [PubMed: 16002672]
43. La Cava A, Fang C, Singh R, et al. Manipulation of immune regulation in systemic lupus erythematosus. *Autoimmun Rev* 2005;4:515–519. [PubMed: 16214088]
44. Theofilopoulos AN, Dixon FJ. Murine models of systemic lupus erythematosus. *Advances in Immunology* 1985;37:269–390. [PubMed: 3890479]
45. Moore K, Wada T, Barbee S, et al. Gene transfer of RANTES elicits autoimmune renal injury in MRL-Fas(lpr) mice. *Kidney Int* 1998;53:1631–1641. [PubMed: 9607194]
46. Schwarting A, Tesch G, Kinoshita K, et al. IL-12 drives IFN-gamma-dependent autoimmune kidney disease in MRL-Fas(lpr) mice. *J Immunol* 1999;163:6884–6891. [PubMed: 10586090]
47. Wada T, Schwarting A, Chesnutt M, et al. Nephritogenic cytokines and disease in MRL-Fas(lpr) kidneys are dependent on multiple T-cell subsets. *Kidney Int* 2001;59:565–578. [PubMed: 11168938]
48. Kelley V, Diaz-Gallo C, Jevnikar A, et al. Renal tubular epithelial and T cell interactions in autoimmune renal disease. *Kidney Int Suppl* 1993;39:S108–115. [PubMed: 8096881]
49. Meyers CM, Tomaszewski JE, Glass JD, et al. The nephritogenic T cell response in murine chronic graft-versus-host disease. *J Immunol* 1998;161:5321–5330. [PubMed: 9820505]
50. Bailey NC, Kelly CJ. Nephritogenic T cells use granzyme C as a cytotoxic mediator. *Eur J Immunol* 1997;27:2302–2309. [PubMed: 9341773]
51. Peng S, Moslehi J, Robert M, et al. Perforin protects against autoimmunity in lupus-prone mice. *J Immunol* 1998;160:652–660. [PubMed: 9551899]
52. Foster MH. Relevance of Systemic Lupus Erythematosus (SLE) nephritis animal models to human disease. *Semin Nephrol* 1999;19:12–24. [PubMed: 9952277]
53. Mishra N, Reilly C, Brown D, et al. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. *J Clin Invest* 2003;111:539–552. [PubMed: 12588892]
54. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006;441:235–238. [PubMed: 16648838]
55. Shimizu S, Sugiyama N, Masutani K, et al. Membranous glomerulonephritis development with Th2-type immune deviations in MRL/lpr mice deficient for IL-27 receptor (WSX-1). *J Immunol* 2005;175:7185–7192. [PubMed: 16301622]
56. Kelley VR, Wuthrich RP. Cytokines in the pathogenesis of systemic lupus erythematosus. *Semin Nephrol* 1999;19:57–66. [PubMed: 9952281]
57. Mizoguchi A, Bhan AK. A case for regulatory B cells. *J Immunol* 2006;176:705–710. [PubMed: 16393950]
58. Shlomchik MJ, Craft JE, Mamula MJ. From T to B and back again: positive feedback in systemic autoimmune disease. *Nature Reviews* 2001;1:147–153.
59. Harris DP, Haynes L, Sayles PC, et al. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol* 2000;1:475–482. [PubMed: 11101868]
60. Sapir T, Shoenfeld Y. Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. *Clin Rev Allergy Immunol* 2005;29:185–199. [PubMed: 16391393]
61. Chan OT, Madaio MP, Shlomchik MJ. The central and multiple roles of B cells in lupus pathogenesis. *Immunol Rev* 1999;169:107–121. [PubMed: 10450512]
62. Ito T, Ishikawa S, Sato T, et al. Defective B1 cell homing to the peritoneal cavity and preferential recruitment of B1 cells in the target organs in a murine model for systemic lupus erythematosus. *J Immunol* 2004;172:3628–3634. [PubMed: 15004165]
63. Su W, Madaio M. Recent advances in the pathogenesis of lupus nephritis: autoantibodies and B cells. *Semin Nephrol* 2003;23:564–568. [PubMed: 14631564]
64. Foster MH. Nephritogenic properties of lupus autoantibodies. In: Lewis, EJ.; Schwartz, MM.; Korbet, SM., editors. *Lupus Nephritis*. Oxford University Press; 1999. p. 22–78.
65. Nimmerjahn F, Ravetch J. Fcγ receptors: old friends and new family members. *Immunity* 2006;24:19–28. [PubMed: 16413920]
66. Clynes R, Dumitru C, Ravetch JV. Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. *Science* 1998;279:1052–1054. [PubMed: 9461440]

67. Matsumoto K, Watanabe N, Akikusa B, et al. Fc receptor-independent development of autoimmune glomerulonephritis in lupus-prone MRL/lpr mice. *Arthritis Rheum* 2003;48:486–494. [PubMed: 12571859]
68. Bolland S, Ravetch J. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. *Immunity* 2000;13:277–285. [PubMed: 10981970]
69. Leadbetter EA, Rifkin IR, Hohlbaum AM, et al. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* 2002;416:603–607. [PubMed: 11948342]
70. Prodeus AP, Goerg S, Shen LM, et al. A critical role for complement in maintenance of self-tolerance. *Immunity* 1998;9:721–731. [PubMed: 9846493]

Figure 1.

Antigen regulation of autoimmunity. Self-antigen contact with T or B cell receptor can induce specific tolerance or activation in the responding lymphocyte. The outcome of the interaction depends on the microenvironment and whether an inflammatory milieu upregulates costimulatory signals. Ag, antigen; Breg, regulatory B cell; Treg, regulatory T cell; PC, plasma cell; CTL, cytotoxic T lymphocyte

Figure 2.
Diverse roles for B cells, T cells and dendritic cells (DC) in the control of autoimmunity and pathogenesis of lupus nephritis.

Table 1**Mechanisms Regulating Autoimmunity**

1	Deletion
2	Anergy
3	Receptor editing
4	Dual receptor expression
5	Clonal ignorance
6	Peritoneal homing
7	Follicular exclusion
8	Competition for survival factors or cognate cell help
9	Regulatory B and T cell subsets ^I
10	Th1, Th2, and Th17 skewing
11	Immune suppressive cytokines (TGFbeta, IL-10)
12	Receptor and coreceptor modulation
13	Idiotypic networks
14	Antigen sequestration

^I IL-10 or TGF-beta producing B cells; prototypic CD4+CD25+ Treg, T-helper-3 (Th3) T cells, T regulatory type 1 (Tr1) T cells, and inhibitory CD8+, TCRgamma/delta or NK T cells)

Table 2**Initiation and Amplification of Nephritogenic Autoimmune Responses in Lupus**

Altered DNA methylation or histone acetylation¹
 Dendritic cell activation²
 Antigenic mimicry due to foreign/self homology
 Exposure of cryptic or neo- (modified) self antigen
 Expression of dormant self antigen (heat shock protein)
 Imbalance or defect in T or B cell regulatory subsets
 Bystander activation
 Polyclonal activation (mitogens, superantigens, lectins)
 Biased T helper subset expansion (Th1/Th2/Th17 shift)
 Defective, abnormal or excessive apoptosis³
 Altered antigen receptor signaling (BCR, TCR)
 Decreased inhibitory receptor signaling (FcγRIIB, CD21, CD22, CD5)
 Enhanced accessory receptor signaling (TLR, costimulators, activating FcγR, adhesion molecules)
 Enhanced lymphocyte survival (elevated BlyS/BAFF, mutated Fas)
 Epitope spreading

¹ A given type of environmental challenge (infectious agents, chemicals, drugs, pharmacologic agents, ultraviolet light) may induce acquired defects by multiple mechanisms shown here.

² Activation of IFN-α/β-producing dendritic cells by viruses, nucleic acid-IgG immune complexes, or microbial products may be a major cause of loss of peripheral tolerance.

³ Apoptosis defects may contribute to autoimmunity at multiple levels. Apoptosis is crucial for autoreactive B and T cell deletion, and apoptotic cells expose a variety of lupus self-antigens that can either tolerize or immunize, depending on context.

Table 3**Diverse Roles for B Cells in Immunity and Lupus**

1	Produce pathogenic autoantibodies
2	Produce regulatory antibodies (anti-idiotypic, FcγRIIB-binding, mediator-neutralizing)
3	Produce immunomodulatory cytokines (IL-10, IL-6, TGF-β, IFN-γ, IL-12)
4	Differentiate into polarized B cell effectors
5	Process and present antigen to T cells for activation or tolerance induction
6	Coordinate T cell migration and differentiation
7	Directly cross regulate Th1 and Th2 cell differentiation
8	Inhibit or delete T cell effectors via direct contact or TGF-β
9	Recruit CD8 ⁺ and NKT regulatory T cells
10	Promote development of follicular dendritic cells
11	Regulate dendritic cell cytokine production
12	Maintain secondary lymphoid architecture

Table 4**Targeted Immunotherapy in Lupus Nephritis**

-
1. B and T cell signaling and activation thresholds
 - Upregulation or stimulation of B cell inhibitory Fc gamma RIIB
 - B cell tolerance induction (dsDNA oligomers) ¹
 - Inhibition of DNA methylation or histone deacetylation ²
 2. B and T cell survival, proliferation and differentiation, collaboration and costimulation
 - Anti-B cell therapy (anti-CD20 and anti-CD19 mAb)
 - Blockade of BAFF/BAFF receptor pathway (anti-BAFF mAb; TACI-Ig fusion protein) ³
 - Modulate activating or inhibitory surface receptors (anti-CD22 mAb)
 - Anti-T cell subset therapy
 - Blockade of B7/CD28 pathway (CTLA4-Ig, single-chain Fv CD28 inhibitor)
 - Blockade of CD40/CD40L (anti-CD40L mAb)
 - Blockade of ICOS/ICOSL pathway (anti-ICOSL mAb)
 - Blockade of CD137 (4-1BB)/4-1BBL pathway
 - Stimulation of T cell inhibitory pathways PD-1/PD1-L, CTLA4, BTLA
 - Modulation of TLR signaling (inhibitory GpG oligodeoxynucleotides)
 - Modified antigen presenting cells (dendritic cell therapy)
 3. Regulatory cell function
 - In vivo or ex vivo induction of regulatory T or B cells
 - Administration of tolerizing self-antigen-expressing dendritic or stem cells
 4. B and T effector cell function and inflammation
 - Blockade of Ig production
 - Inhibition of memory or plasma cell differentiation
 - Blockade or adsorption of autoantibody reactivity
 - Complement inhibition (anti-C5 mAb, soluble Crry or Crry-Fc fusion protein, C5a antagonist)
 - Blockade of activatory FcγRI, FcγRIII or FcγRIV
 - Stimulation of inhibitory FcγRIIB
 - Inhibition of secondary mediators (cytokines, chemokines, NO, ROS, lipid mediators, etc)
 - Anti-macrophage or neutrophil therapy
 - T helper subset skewing
-

¹ Selected examples of interventions currently in preclinical or clinical trials are indicated in parentheses.

² Some interventions modulate multiple checkpoints; for simplicity, only one category is shown.

³ Abbreviations: BlyS, B lymphocyte stimulator (also known as BAFF); TLR, toll-like receptor; Crry, complement receptor-1 related gene/protein Y; PD-1, programmed death-1; CTLA-4 (cytotoxic T lymphocyte antigen-4); BTLA, B and T lymphocyte attenuator