



Review

Molecular Aspects in the Pathogenesis of Human Systemic Lupus Erythematosus

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Abstract. Systemic lupus erythematosus is a common and often devastating systemic autoimmune disease of unknown etiology. In this communication we review the latest developments of the molecular pathogenesis of human lupus. Novel genetic studies of multiplex lupus families have revealed potential disease-associated genome intervals, put special emphasis on genetic loci mapping in the long arm of chromosome 1 and have underscored the complexity of the underlying genetic background. New data have emerged on the role of estrogens in the function of lymphocytes and a number of studies have recently emphasized the relative Th-1/Th-2 cytokine imbalance in favor of a Th-2 type cytokine immune response. Finally, novel experiments have revealed an abnormal antigen receptor-mediated signaling process in lupus T and B cells, which may influence the aberrant expression and function of costimulatory molecules as well as of other aspects of immune cell function. It is important to decipher the underlying molecular mechanisms that govern the expression of human lupus, because we may design novel, rational approaches in the treatment of a human lupus, a disease that has high morbidity and mortality.

Key words: autoimmunity; lymphocytes; antigen receptor; signal transduction; costimulatory molecules.

Systemic lupus erythematosus (SLE) is an autoimmune disease underscored by chronic inflammatory tissue damage that is partly mediated by immune complexes, autoantibodies and autoreactive lymphocytes. SLE pathogenesis is incompletely understood. However, light has been shed recently into the multiple genetic, environmental, hormonal and immunoregulatory factors believed to contribute to the development of the disease.

Genetic Factors

One out of 10 patients with SLE has a first-degree relative with the disease. The concordance rates for

SLE in monozygotic twins is 25–57% while in dizygotic twins it is 2–9%. It is currently thought that multiple genes confer susceptibility to SLE expression in a cumulative/additive manner. These thoughts are not in contrast with the widely held opinion that SLE is a genetically heterogeneous disease^{35, 44}.

SLE is more common in African-Americans, Afro-Caribbeans and East Asians; such populations may also have a worse overall course and prognosis. Specific clinical manifestations (e.g. discoid lupus, nephritis) and serological profiles (e.g. anti-Sm autoantibodies) are more frequent among African-American patients.

The association of SLE with MHC alleles or haplotypes is not clear. Associations with DR3, DQ2- and

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DR2, DQ6-containing MHC Class II haplotypes confer a relatively low risk for SLE. Nevertheless, associations between MHC alleles or haplotypes and serum autoantibody profiles are stronger. The MHC class II genes have also been associated with SLE. Hereditary deficiencies of early complement components are associated with SLE. Genes for C2 and C4 map within the MHC, while the gene for C1q maps on chromosome 1. Complement receptor types 1 (CR1) and 2 (CR2) map also on the long arm of chromosome 1, and their expression in SLE red blood cells and B lymphocytes, respectively, has been reportedly decreased⁵³. Polymorphisms of the TNF- α gene promoter (also encoded within the MHC-III region) in HLA-DR2 positive patients with lupus nephritis are associated with decreased TNF- α production¹⁸.

Modern genetic approaches employ microsatellite markers to screen the genome in multiplex lupus-family members. Such studies had previously focused on genetic loci mapping on the long arm of chromosome 1. The 1q23 locus is particularly interesting since it harbors at least two genes with potential association with lupus nephritis. Fc γ RIIA³⁹ and Fc γ RIIIA⁵⁴ encode the receptors for the Fc fragment of IgG types IIA (CD32) and IIA (CD16). A polymorphism of the functional domain of Fc γ RIIA, which consists of a single aminoacid change of an arginine to histidine at position 131, predominates in African-American patients with lupus nephritis. This change correlates with defective Fc γ RIIA function, decreased IgG2 binding, impaired immune-complex handling, and clinically with immune-complex deposition in the kidneys and lupus nephritis.

The first study of lupus families⁴⁶ reported a linkage between SLE and the locus 1q41–42. The search for this association was guided by findings in murine strains of lupus. Genes found in the human 1q41–42 locus are not well characterized yet, but the authors recently narrowed the locus of interest to the *PARP* gene that produces an apoptosis related protein⁴⁵. Two larger multiplex lupus family studies were recently reported. MOSER et al.³² studied 94 pedigrees and reported that potential SLE loci are found at chromosomes 1q23, 1q41 and 11q14–23 in African-Americans. In European-Americans potential lupus loci were at 14q11, 4p15, 11q25, 2q32, 19q13, 6q26–27, and 12p12–11. In the combined pedigrees, potential lupus loci were at 1q23, 13q32, 20q13, and 1q31. The stronger linkage was for locus 1q23 in African-Americans. Candidate genes for this interval are those for Fc γ RIIA, Fc γ RIIIA, Fc γ RIIIB and for the ζ chain of the T cell receptor.

The study by GAFFNEY et al.¹⁵ analyzed 105 sib-pair

lupus families, almost entirely European-Americans. The study reported that the stronger linkage was found near the MHC locus at 6p11-q21 and the three additional intervals, at 16q13, 14q21–23 and at 20p12. The two latter studies did not use the same markers for screening; it is interesting that there was partial only agreement on linkage scores for some, but not all, markers that mapped closely. Moreover, loci with the strongest linkage reported in one study are not found in the other. Linkage with locus 1q41–42 was strong in two of the three studies, but in the first it crossed ethnic barriers while in the other it predominantly affected African-American lupus families.

The long arm of human chromosome 1 harbors several potential lupus loci found in these genome-wide screens and also others that have been implicated in lupus. Such genes are those encoding for Fc γ RIIA, Fc γ RIIIA, TCR ζ , FasL, IL-10, CR1, CR2 and C1q proteins⁴⁹.

It is obvious that multiple genetic loci or genes contribute to susceptibility for the development of SLE. The pathogenetic contribution and interaction of lupus-susceptibility genes needs to be further clarified. The precise role and contribution of each of the lupus-related genes should be addressed since the most important may represent potential targets for future gene therapy.

Hormonal Factors

Lupus afflicts predominantly women. While before puberty SLE affects equally boys and girls, during puberty and throughout the reproductive years lupus expresses its striking preference for females. It is thus concluded that female hormonal factors play at least a permissive role, while male hormonal factors play a protective one in the expression of SLE⁷.

There is evidence that endogenous estrogens are abnormally metabolized. Patients with SLE and their relatives produce increased amounts of estrone and estradiol due to increased 16 α hydroxylation of estradiol²⁴ and also have decreased androgen levels¹³. Not only estrogens, but other female hormones (e.g. progesterone, prolactin) may play a role; hyperprolactinemia has been correlated with the appearance of anti-dsDNA, anti-Sm and anti-Ro autoantibodies³. The role of exogenously provided estrogens was explored in the Nurses' Health Study which reported that long-term estrogen replacement therapy was associated with an increased risk for the development of SLE (relative risk 3.5)⁴⁰.

Generally, estrogens act into target after binding

their cytoplasmic estrogen receptors (ER). The complex estrogen-ER becomes a transcription factor that, following its entrance in the nucleus and its binding on specific estrogen-response elements, modulates the transcription of estrogen-dependent genes. Estrogens modulate the immune system by altering the function and activity of T and B cells²¹. Whether estrogens augment or inhibit immune cell function is a matter of debate, but in the immune cells of lupus-prone mice estrogens enhance autoimmunity. Immune cells possess functional ER but there are no differences between the ER found in lupus immune cells and those found in normal T and B lymphocytes and monocytes.

ER are found on the cell-surface membrane as well, and mediate quite distinct functions compared to those of the classic endoplasmic ER. In murine T cells, membrane ER upon binding to estradiol mediate a rise in the concentration of intracellular calcium ($[Ca^{2+}]_i$), a pivotal second messenger. Also, estrogen-response elements are located in the protooncogene *c-fos* and *c-jun* promoters. Estrogens thus alter the transcription of the *fos* and *jun* proteins, that together represent the transcription factor AP-1.

Environmental Factors

It is thought that environmental factors may influence a genetically susceptible host triggering the expression of SLE. Factors such as UV light, heavy metals, organic solvents and infections have been implicated.

UV light causes photosensitivity and is a known disease-exacerbating factor. UV light causes the apoptotic cell death of keratinocytes leading to the expression on the cell-surface of the dying keratinocyte of specific autoantigens that were previously "hidden" in the cytoplasm and/or nucleus. Autoantigens presented this way in surface membrane blebs now become "visible" or accessible for immune recognition and attack. The latter may result in local inflammation and the appearance of autoantibodies in the circulation. The UV-mediated apoptotic cell death of epidermal cells may consist a molecular basis for the accessibility of hidden intracellular antigens, and may explain the flooding of the immune system with autoantigens that activate T and B cells^{4, 5}.

Respirable silica has been previously associated with the appearance of antinuclear antibody (ANA) and other autoantibodies in the serum and with the development of autoimmune diseases. An analysis of 1130 men from Sweden with silicosis reported significantly

more hospitalizations due to SLE and other connective tissue autoimmune diseases². Inhaled silica particles phagocytosed by alveolar macrophages act as a potent inflammatory stimulus. Moreover, *in vitro* silica acts as a polyclonal T cell activator⁵⁰.

Previous studies reported that organic solvents found in hair dyes are associated with the development of connective tissue diseases. The Nurses' Health Study did not find any association between hair dye use (even for > 15 years) and the development of SLE. Smoking was also reported to correlate with SLE development. Two studies found an increased risk, but in the second (and smaller) one, the increased risk was not significant^{1, 33}. Among others, cigarette smoking affects the activity of enzymes involved in estrogen metabolism, thus it further complicates the already complex interaction between environmental, hormonal and genetic factors for the development of SLE.

Despite the common clinical observation regarding the development of SLE, following an infection, a lupus-causing microorganism was never isolated. It has been hypothesized that an infectious agent(s) can disproportionately trigger an endogenously aberrant immune system for the development or the exacerbation of SLE. Epstein-Barr virus (EBV) among the common pathogens has received most attention. Antibodies against EBV cross-react with the lupus-specific autoantigen Sm. It was recently reported that newly diagnosed young patients with lupus have a significantly higher percentage of EBV seropositivity compared to a control group. Almost all (116 of 117) young SLE patients tested had seroconverted to EBV compared to 70% of their matched controls. Other herpesviruses tested did not follow this striking pattern. EBV DNA was found in the lymphocytes of all 32 young SLE patients tested, while it was present in 23 only of 32 controls¹⁹. Whether EBV-infected individuals become more susceptible to the development of lupus, or SLE patients are/become more susceptible to EBV infection, or finally, if a third factor increases susceptibility to both, is currently unknown.

Drugs and Lupus

Drug-induced lupus has both similarities and differences to idiopathic SLE. Since it represents a syndrome where the inciting factor is known, exogenous and fully controllable, it represents a good model to study aspects of SLE pathogenesis. Drugs that cause a SLE-like syndrome have been reported to induce DNA hypomethylation. Induced autoreactivity of pre-

viously non-autoreactive T cells was first shown with the known DNA-hypomethylator 5-azacytidine. Pharmaceutical agents most commonly associated with the drug-induced lupus like procainamide and hydralazine also bind to DNA and inhibit its methylation. The methylation status of a gene determines the transcription rate of the gene¹¹. It can be assumed thus that alterations in the methylation status of some autoreactivity-related genes contribute to the development of autoimmunity, but this hypothesis has not been substantiated yet.

In idiopathic SLE T cells it was reported that DNA is hypomethylated and the activity of the methylation-inducing enzyme, DNA methyltransferase is decreased. Non-T cells from patients with SLE did not show this abnormality, which affected only half of the lupus patients tested, and finally, the abnormality was not disease-specific. Treatment of T cells with inhibitors of DNA methylation induces the upregulation of the adhesion/costimulatory molecule lymphocyte function-associated antigen-1 (LFA-1). In animal models with T cells overexpressing LFA-1, anti-dsDNA autoantibodies are detected and glomerulonephritis appears. Intracellular adhesion molecule-1 (ICAM-1) is the ligand for LFA-1 and estrogens induce ICAM-1 upregulation on endothelial cells. It was reported that procainamide caused more severe disease in female experimental animals compared to procainamide-treated male counterparts, with 2–7 times more cells homing to the spleen and higher anti-double-stranded DNA (anti-dsDNA) antibody titers^{37, 38, 56}.

The latter example integrates at least two independent lupus-precipitating factors, drugs and estrogens. The exogenous factor (procainamide) caused DNA hypomethylation, resulting in the upregulation of LFA-1 on the surface of T cells. This caused disease (or more severe disease) preferably to female animals since their circulating estrogens make their endothelial cells more susceptible to LFA-1-mediated T cell binding, resulting in heavier splenic infiltration and higher of the pathogenic anti-dsDNA autoantibodies. The extent to which this intriguing example may apply to the human disease is unknown, but LFA-1 is reportedly overexpressed on the surface of lupus lymphocytes^{6, 55, 57}.

Anti-DNA Autoantibodies in SLE

SLE is characterized by the production of a large and still growing list of antibodies against an array of non-organ specific self-constituents present in the nucleus, the cytoplasm, the cell-surface membrane or

even the circulation. In the past it was thought that immune responses against self were uniformly harmful; now we understand that immune responses against self are a common part of normal immune responses. Immune cells with autoreactive potential are present in good numbers in the normal subject and germline genes encoding for antigen-receptors of autoreactive T and B cells are part of the normal gene repertoire. "Normal autoimmunity" is a limited and strictly regulated process.

Therefore, antibodies to DNA are produced by the normal host. These are IgM antibodies that bind single-stranded (denatured) DNA; they have low affinity for DNA and broad cross-reactivity with a variety of other self-antigens. They unusually undergo isotype switching and are encoded by germline genes; affinity maturation by the process of somatic mutation does not occur. On the contrary, the anti-DNA antibodies encountered in the sera of patients with SLE have undergone isotype switching to IgG; new amino acids are introduced into their variable regions to enhance their affinity (somatic mutations and hypermutations). Since DNA is anionic, positively charged amino acids are introduced into the autoantibody variable regions, particularly arginine, to enhance DNA binding. Lupus anti-DNA antibodies thus are usually charged, IgG high-affinity and relatively low cross-reactivity antibodies that recognize double-stranded (native) DNA (dsDNA) as well; in fact, anti-DNA antibodies that recognize exclusively dsDNA are unusual. These are anti-dsDNA autoantibodies encountered essentially only in patients with SLE. In fact, among the various ANA specificities detected in the sera of at least 95% of lupus patients, only the anti-dsDNA and the anti-Sm autoantibodies are virtually lupus-specific¹⁶.

Anti-dsDNA antibodies are pathogenic and they cause glomerulonephritis. Pathogenicity of anti-dsDNA antibodies is associated with high complement-fixing capability, high affinity for DNA and other cross-reactive antigens and a highly cationic charge. Circulating DNA-anti-dsDNA immune complexes are trapped in the glomerular basement membrane and the inflammation that follows can cause nephritis. Alternatively, immune complexes are formed *in situ*, since the cationic anti-dsDNA antibodies may bind either negatively charged constituents of the glomerular basement membrane itself (laminin, heparan sulfate) or DNA fragments pre-deposited passively there.

Is DNA the autoantigen? The characters of lupus anti-DNA antibodies predict that the answer should be yes. Nevertheless, efforts to induce anti-dsDNA antibodies and glomerulonephritis by immunizations with

mammalian, microbial or viral DNA were not highly successful possibly because naked DNA is a poor immunogen. However, when DNA is administered in the form of chromatin or nucleosomes, then the anti-DNA antibodies produced have enhanced pathogenicity³⁰. T cells from patients with SLE activated by nucleosomes provide help to lupus B cells to produce anti-dsDNA of the IgG class.

Immunoregulatory Factors

Aberrations of the immune cells are believed to play a major role in lupus pathogenesis⁴⁷.

Helper/suppressor T cell function imbalance

Maintenance of high levels of pathogenic autoantibodies in SLE may reflect either increased help provided by specialized helper T cell subsets, or decreased suppression, or both. Several subsets of T cells have been described to provide excessive help to lupus B cells for the production of autoantibodies. Apart from the classic CD4⁺ T cells other subsets such as CD8⁺, and the greatly expanded unusual CD3⁺CD4[−]CD8[−]TCRαβ and CD3⁺CD4[−]CD8[−]TCRγδ T cells from patients with SLE have been reported to provide help to autologous B cells to produce anti-DNA autoantibodies^{25, 36, 41}. The double-negative T cell is an intermediate cell-type during thymic maturation and increased numbers of them in lupus patients may reflect possible perturbations in the processes of intrathymic positive and/or negative selection in SLE resulting in tolerance defects.

Th1/Th2-type cytokine imbalance

Decreased production of Th1-type cytokines. SLE T cells produce decreased amounts of IL-2 *in vitro* and this correlates with disease activity. The production of tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) from lupus peripheral blood mononuclear cells (PBMC) is deficient. IL-2, TNF-α, IFN-γ and IL-12 are the Th1-type cytokines that enhance cytotoxic cell responses and suppress antibody production. The production of IL-12 was recently reported to be decreased¹⁷. IL-12 drives the cytokine production profile towards the Th1-type.

Increased production of Th2-type cytokines. Cytokines of the Th2-type include IL-4, IL-5, IL-6 and IL-10. Their role is to promote humoral and suppress cell-mediated immunity. The production of IL-6, a cyto-

kine that promotes immunoglobulin production in lupus is increased. Also, IL-6 levels in the cerebrospinal fluid of patients with central nervous system lupus is increased, and following successful treatment, IL-6 levels fall. Lupus B cells secrete large amounts of IL-6 and express increased amounts of IL-6 receptors. Finally, in the classic (NZB×NZW) F1 murine lupus model IL-6 infusion accelerates the disease.

Most attention has drawn to IL-10 production in lupus. It has been demonstrated that IL-10 production is significantly elevated in patients with SLE and that IL-10 overproduction is implicated in the production of anti-DNA antibodies²⁹. Overproduction of IL-10 characterizes not only lupus patients but also healthy members of their families and even their first- and second-degree relatives²⁸. Healthy members of lupus families produce 5.9 times more IL-10 compared to healthy controls. Moreover, two groups of lupus patients (members and non-members of multiplex families) produced 8.5 and 9.1 times respectively more IL-10 than normal individuals.

Monocytes and an unknown B cell subset are responsible for IL-10 overproduction in both patients and healthy relatives; IL-10 is absent from B cells of normal controls. IL-10 is potent B cell stimulator and a potent inhibitor of antigen presenting-cell (APC) function. This may explain the defective APC function and B7-1 upregulation previously reported in lupus non-B cells⁴⁸. The familial pattern of IL-10 dysregulation points towards a potentially intrinsic defect. The human *IL-10* gene maps on chromosome 1. Functionally, IL-10 overproduction is important. Use of an anti-IL-10 mAb *in vitro* diminished the production of anti-dsDNA autoantibodies. It is possible that the continuously high levels of IL-10 encountered in SLE are responsible for the decreased production of Th1-type cytokines (IL-10 decreases the production of IL-2, TNF-α and IFN-γ) and for the perpetuation of the humoral (auto) immune response.

Antigen Receptor-Mediated Signal Transduction of Lymphocytes in SLE

The immune system has evolved to recognize and respond to antigens that bind to specialized receptors present on the surface of T and B lymphocytes (TCR and BCR, respectively). Engagement of TCR or BCR elicits a series of well-regulated interacting intracellular biochemical events that transmit extracellular signals to the cell nucleus. Because other membrane receptor-initiated specific signals are integrated along with the antigen-receptor signal, the outcome of the TCR or

BCR pathway can vary considerably. Antigen-receptor linkage can result in cell activation, proliferation, secretion of soluble mediators (cytokines or antibodies), phenotypic changes, acquisition of effector functions, anergy and apoptotic programmed cell death⁵². Since TCR- or BCR-signaling biochemical events principally direct these diverse but equally important outcomes, it was assumed that the diverse cellular aberrations described in lupus patients may reflect the product of signaling biochemical defect(s) that potentially play a central role in SLE pathogenesis.

The aberrant TCR and BCR signaling in lupus lymphocytes

Following the engagement of the antigen-receptor multiple intracellular signaling pathways are triggered. A critical event in these pathways is the mobilization of Ca^{2+} from intracellular stores, followed by an influx of Ca^{2+} from the extracellular space. Antigen receptor early signaling events Ca^{2+} , IP3 and protein tyrosine phosphorylation are increased in lupus T and B cells^{27, 51}. These abnormalities were present in T cells despite the fact the TCR ζ chain (member of the zeta-family of proteins, part of the hetero-oligomeric TCR/CD3 complex) was frequently missing²⁶. Also the cAMP-dependent protein kinase A type I (PKA-I) is defective in lupus T cells and this may account for the increased Ca^{2+} responses since activation of this enzyme in normal T cells downregulates Ca^{2+} responses²⁰.

Molecular and functional consequences of abnormal signaling in lupus lymphocytes

Clinical disease activity changes reflect immunoregulatory cell changes. It is thus pivotal to distinguish between immunological parameters characterizing the disease (unrelated to disease activity and/or treatment) and parameters that appear as disease-outcomes (related to activity and/or treatment). The signaling aberrations analyzed above (TCR- and BCR-signaling and TCR ζ deficiency), are independent of disease activity, treatment status, and the presence or absence of specific SLE clinical manifestations; they may thus represent intrinsic abnormalities of the lupus lymphocyte. Importantly, these abnormalities are also disease-specific, because they were not found in normal lymphocytes or in lymphocytes from patients with other systemic autoimmune rheumatic diseases. T and B cell signaling aberrations mentioned above are similar and they could substantiate a hypothesis that a common background underlies some heterogeneous lymphocytic functional defects.

The Ca^{2+} pathway critically influences the NFAT-mediated transcription of genes such as those of CD40-ligand and Fas-ligand (CD40L and FasL). It is thus anticipated that lupus lymphocytes should express more CD40L and FasL on their surface membrane due to their higher Ca^{2+} responses. This is indeed the case, because it has been shown that following activation, lupus T cells overexpress both functional FasL and CD40L^{22, 23}. CD40L is considered to be a T cell marker but lupus B cells display increased CD40L on their surface, which is enhanced following activation¹⁰. Because both T and B cells also express CD40, it is possible that an excessive CD40-CD40L interaction takes place in lupus cell-cell contact⁹.

T cells lacking TCR ζ (but expressing an intact CD3 ϵ chain) are not only able to transduce early signaling events, but surprisingly display enhanced production of tyrosyl phosphorylated proteins compared to cells that preferentially signaled via TCR ζ . Nevertheless, TCR ζ cells displayed decreased IL-2 production. CD3 ζ chain deficiency may also account for decreased CD2-signaling and TGF- β production as well as decreased antigen induced cell death that have been reported in lupus cells.

In $\zeta^{-/-}$ experimental models, both positive and negative selection of thymocytes is deficient. Decreased negative selection may explain the presence of potent autoreactive T cells in lupus patients ($\zeta^{-/-}$ animals are also autoimmune); decreased positive selection may explain the decreased responses of lupus T cell to exogenous antigen^{34, 42, 43}.

CD28/CTLA4: CD80/CD86-mediated costimulation in lupus immune cells

In addition to the TCR/CD3-mediated signal, at least one costimulatory signal provided by an APC is required for the initiation, maintenance and/or down-regulation of an effective T cell response. The role of CD40 : CD40L interaction is currently appreciated as a potential therapeutic target. Experiments show that administration of even a single dose of anti-CD40L mAb in lupus models significantly delays the appearance of nephritis and substantially improved the survival of such animals without compromising the non-autoimmune response³¹.

T cell costimulation involves interactions between the CD28 and CTLA4 molecules on the surface of T cells and their counter-receptors, CD80 (B7-1) and CD 86 (B7-2) molecules on APC. CD 28- and CTLA4-mediated signals have distinct effects on T cells, by integrating additional biochemical events in the TCR-sig-

naling pathway. CD28- plus TCR-mediated signals result in secretion of cytokines, upregulation of CTLA4 mRNA, T cell proliferation and differentiation. In the absence of CD28-mediated signaling, impaired cytotoxic responses and/or a long-lasting anergic state ensue. In contrast, CTLA4 delivers a downregulatory signal to previously activated T cells, provided that it functionally couples with TCR ζ chain. It may also mediate the induction of peripheral tolerance.

Abnormalities in the expression of CD80 and CD86 on the cell surface of peripheral blood B cells from patients with SLE have also been reported. CD86 expression on resting and activated lupus B cells was 7- and 2.5-times greater than the levels of normal B cells respectively. CD80 was also significantly overexpressed in activated, but not in resting B cells from patients with lupus, though at lower than CD86 levels¹⁴. Therefore, overexpression of costimulatory molecules on circulating B cells in patients with SLE may play a role in the continuous autoreactive T to B cell help.

On the other hand, non-B APC from patients with SLE but not from normal persons, fail to upregulate the *in vitro* surface expression of CD80 following stimulation with IFN- γ in a disease-independent fashion. Replenishment of functional CD80 molecule in the culture environment significantly increased the responses of SLE T cells to tetanus toxoid and to an anti-CD3 antibody⁴⁸.

Taken together, the above findings suggest that aberrantly regulated and/or expressed costimulatory molecules on T cells and APC at different disease in patients with SLE may contribute to pathology. Interrupting the cross talk of CD28 with CD80 and CD86 may be of clinical value. To test this hypothesis, lupus-prone (NZB $\times$ NZW) F1 mice were treated with CTLA4-Ig, a soluble recombinant fusion protein blocking the engagement of CD28. CTLA4-Ig blocked autoantibody production and prolonged the survival of mice, even when it was administered late, during advanced stages of clinical illness¹². In these lupus-prone animals, combined CTLA4-Ig and anti-CD40L mAb treatment gave the most promising results⁸.

Conclusion

Multiple genetic, environmental and hormonal factors instigate a number of cellular and cytokine abnormalities in SLE. These abnormalities lead to increased production of autoantibodies, which either directly, or after forming complexes with autoantigens and activating complement, deposit in tissues and ignite an inflam-

matory response. Immune complexes are formed in excessive amounts in lupus patients and are cleared at decreased rates because the numbers and/or the function of Fc and complement receptors are decreased. Moreover, activated T cells may home inappropriately in tissues and cause pathology (vasculitis).

It is imperative to identify the specific molecular defect(s) encountered in human lupus. This is the only way to design and use any novel and rational treatments, since currently treatment of lupus is largely empiric and more or less unsatisfactory. Rational approaches to the treatment of lupus may include: specific tyrosine kinase inhibitors (according to the example of experimental allergic encephalomyelitis); anti-cytokine treatment (as in rheumatoid arthritis); blocking cell-cell cross talk (as with the use of anti-CD40L or CTLA4-Ig); blocking of calcium-dependent cytoplasmic events (with cyclosporin A, FK506, rapamycin and other newer compounds); gene therapy; finally, any combination of the above will be answered by studies that will help us understand better the molecular mechanisms implicated in the pathogenesis of this prototypic autoimmune disease.

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Important Dates in the year 2000

February Second Announcement and Call for Abstracts

March 31 Deadline for abstract submissions

Deadline for low pre-registration fee