Systemic Lupus Erythematosus (SLE)

• Clinical features

• A chronic autoimmune disease with variable tissue injury in multiple organs, including kidney, brain, skin, joints, heart, lungs, muscles and blood

• Strong genetic predisposition MHC and non MHC immune response genes, females>> males (>10/1)

• The onset may be insidious or fulminant, typically appearing in a previously healthy person in adolescence or young adulthood

• The course is characterized by multiple flares and remissions

• Therapy involves intensive use of high dose corticosteroids and alkylating agents or other non specific immunosuppressive drugs

Major Clinical Manifestation of SLE

Manifestation	Percent
Arthralgias/arthritis	95
Hematological	90
Rash	81
Fever	77
Neurologic	59
Renal	53
Pulmonary	48
Cardiac	38

Lupus Erythematosus: Epidemiologic findings

• Primarily a disease of young adults

Peak incidence age 15-45

• Marked female preponderance

Sex ratio during peak incidence is 10 : 1, female : male

• Distinctive ethnic distribution

Greatly increased incidence among African-Americans (0.3%), compared to Caucasoids or Blacks in Africa. Similarly increased incidence among Hispanics, Mestizo Indians in Mexico, Sioux Indians, and generally among Chinese and Filipinos, but not among most other Asian peoples.

Systemic Lupus Erythematosus (SLE)

• SLE is the prototypic systemic autoimmune disease where the dominant autoimmune response is the production of an array of autoantibodies to self antigens including nuclear components (DNA, RNA, histones) as well as autoantibodies to cell membrane determinants on hematopoietic cells including (RBC, platelets and leukocytes).

• The autoantibodies induce injury by forming immune complexes with autoantigens which deposit in vessels walls to cause vasculitis and glomerulonephritis. The auto antibodies may also directly bind to cell membranes and destroy cells by activating complement killing and by triggering FcR mediated inflammatory and cytotoxic mechanisms.

• The B cell autoantibody response is in turn driven by MHC-restricted CD4+ T cells that recognize self peptides likely bound by HLA-DR2 & DR3 MHC molecules.

Clinical features of SLE which reflect an ongoing immune response

- lymphadenopathy with active germinal center formation, splenomegaly
- polyclonal hypergammaglobulinemia
- anti-nuclear antibodies, anti-dsDNA, multiple antibodies to other nuclear structures
- lymphopenia, thrombocytopenia, hemolytic anemia
- cytokine mediated systemic phenomena: fever , malaise, weight loss (TNFα, IL-1β)

Autoantibodies in SLE

I. Antibodies to DNA
   - double-stranded DNA (unique to SLE)
   - double- and single-stranded DNA
   - single-stranded DNA

II. Antibodies to Deoxyribonucleoprotein
   - Antigen: complex of DNA and histone

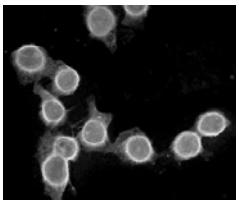
III. Antibodies to Other Nuclear and Cytoplasmic Constituents
   - histones
   - nonhistone nuclear proteins
     a. Small nuclear ribonucleoproteins (snRNPs)
        Sm antigen (SLE specific), Ro / La,
     b. ENA (not specific for SLE), RNA

IV. Antibodies to Cell Membrane Antigens
   - red blood cells, platelets
   - T cells, B cells, macrophages, granulocytes
   - β2 microglobulin, cardiolipin

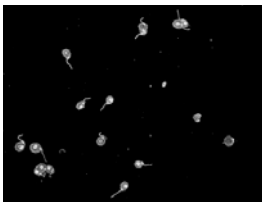
V. Antibodies to soluble proteins
   - Anti-Antibodies: rheumatoid factors
   - Anti-β glycoprotein 1, clotting factors

Antinuclear autoantibodies in SLE

Anti dsDNA antibodies are highly specific for SLE

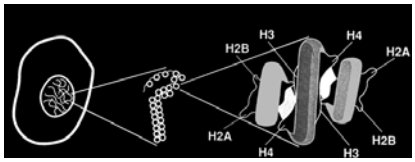


Rim ANA pattern on Hep 2 cells that accompanies anti dsDNA antibodies, may include anti lamin and anti Ku



Anti dsDNA staining of *Crithidia* kinetoplast. Very specific

Antinuclear autoantibodies in SLE
Anti histone and anti DNA antibodies (nucleosome)



Anti ds DNA
(>50-75%), Specific for SLE
Anti ssDNA, non specific

Anti histone
(30-40%)SLE, not specific for SLE,
>90% in drug induced lupus

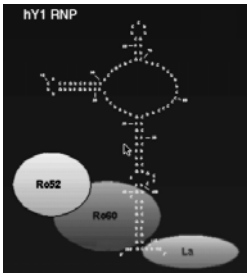
Many SLE autoantigens are large complexes of RNA and multiple proteins

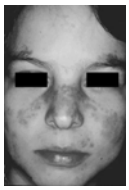
Anti Ro 52kD, Ro 60kD, La

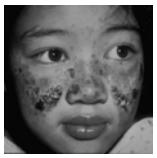
- Four small uridine-rich RNA molecules, hY1, 3, 4, 5 RNA variably associate with Ro and La proteins

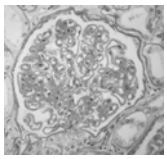
Anti Ro 52kD and anti 60kD
60% SLE,
90% Sjogren's syndrome

Anti La
15% SLE,
60% Sjogren's syndrome

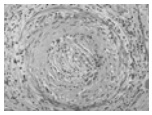


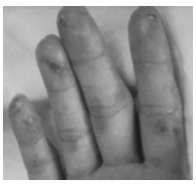


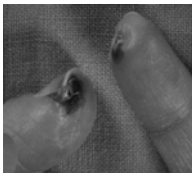




Infarction of distal vessels by reactive vascular proliferation and occlusion induced by deposition of immune complexes







- May occur in nearly any organ

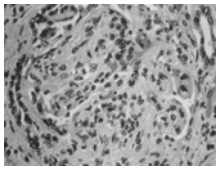
Lupus Nephritis

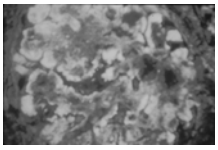
Diffuse, segmental proliferative / necrotizing glomerulitis, Class IV

>50% of glomeruli involved with endocapillary or mesangial hypercellularity, epithelial crescents, or fibrinoid necrosis

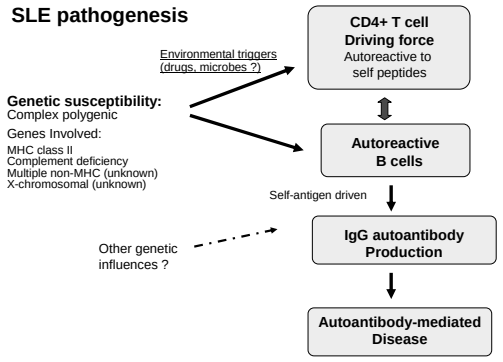
Large subendothelial deposition of immune complexes in glomerular basement membrane

Clinically: Most severe. Renal insufficiency in >50%. Red cell casts, hematuria and HBP.





SLE pathogenesis



Lupus Erythematosus

Strong familial aggregation: 25% cases have affected blood relative. 50% concordance of identical twins

Genetic associations

MHC genes: HLA-DR2, and HLA-DR3 (DRB1*0301)

MHC genes: C2, C4(?) deficiency

Polymorphism of FcRIIa and FcRIII

Fas gene deficiency

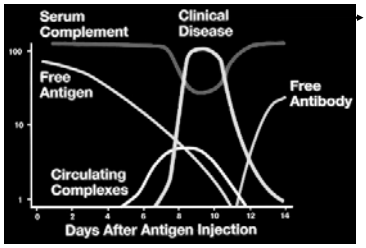
Two major mechanisms of antibody-mediated tissue injury operating in SLE

Type of antibody induced injury	Mechanism of injury	Clinical consequences
Immune complex formation and deposition	Ag/Ab complexes deposit in vessel walls, causing inflammation by activation of complement cascade and activation of FcR on phagocytes, mesangial cells, NK cells	glomerulonephritis Dermatitis Serositis (arthritis, pleuritis, pericarditis) Diffuse vasculitis
Direct binding to and lysis of cells	Antibody binds to and kills cells by activating the complement attack complex or interacting with FcR expressing phagocytes or NK cells	Hemolytic anemia Thrombocytopenia Leukopenia Aplastic anemia

Clinical features attributable to SLE autoantibodies reacting with cell surface structures or soluble proteins

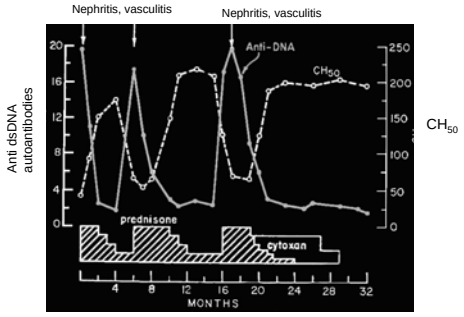
Autoantibodies directed to cells or soluble antigens	Clinical consequences
bone marrow stem cells	aplastic anemia
red cells	combs positive hemolytic anemia
leukocytes	granulocytopenia, lymphopenia
platelets	autoimmune thrombocytopenic purpura (ITP like syndrome)
clotting factors	β2-glycoprotein I (anti-phopholipid syndrome)-thrombosis

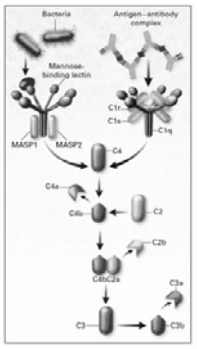
Serum Sickness develops after injection of soluble foreign antigens



Disease:
Vasculitis
Glomerulitis
Arthritis
Pleuritis
Pericarditis
Dermatitis

SLE course reflecting presence of immune complex disease





An important normal function of complement is to regulate the disposition of immune complexes

- C1q binds to IgG in complex and activates C3
- C3b attaches and mediates binding of the complex to CR1 (CD35) on red blood cells
- The immune complexes are solubilized or transported to the spleen on RBC where the immune complexes are phagocytosed and degraded by macrophages and removed from the circulation

If excess immune complexes are not physiologically cleared they deposit in tissues and initiate inflammatory programs

- Interact with FcR or CR on circulating or tissue cells (Monocytes, macrophages, neutrophils, NK cells, etc.) and initiate a receptor mediated proinflammatory program, e.g. leukocyte mediated killing, cytokine release & vasculopathy
- Deposit in blood vessel wall or in glomerulus where initiate inflammation by either interacting with complement and CR of a tissue cell, or interacting directly with FcR on the tissue cells, initiating a receptor mediated proinflammatory program resulting in immune complex disease

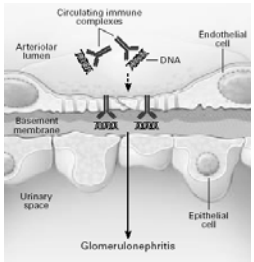
Several genetic diseases emphasize the importance of a normal complement system in preventing autoimmunity

- Inherited C1q deficiency strongly predisposes to SLE, perhaps through a central role of C1q in handling disposal of apoptotic cells
- Inherited C2 deficiency results in a disease with many features of SLE, but without nephritis
- The MHC haplotype HLA-A1-B8- DR3 strongly predisposes to SLE. This haplotype contains a defective C4 gene in the class III region of the MHC as well as the known HLA-DR3 susceptibility gene

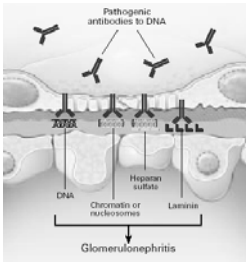
The role of FcR- immune complex interactions in mediating inflammation and immune injury in SLE

- Immune complexes interact with Fc receptors to initiate a receptor mediated proinflammatory program
- Polymorphism of FcRIIa and FcRIII in humans affect affinity of these FcR for IgG and influence the occurrence and severity of nephritis in SLE
- FcRIII α or γ-chain plays a critical role in initiating immune complex inflammation in mice with spontaneous autoimmune diseases as shown by the absence of this pathway of injury in FcRIII "knockout" mouse strains despite the presence of immune complexes

Two similar mechanisms of immune complex glomerulitis



Deposition of preformed soluble complexes



In situ formation of complex on "planted" autoantigen

Why do SLE patients make autoantibodies?

(1) Anti-self immunity: abrogation of self tolerance
SLE might be the result of insufficient elimination of autoreactive T cell clones in the thymus or periphery. This might result in such autoreactive T cells being released into the peripheral circulation and causing the autoimmune features of the disease

(2) Hidden antigens
The nuclear and cytoplasmic antigens that are associated with autoimmunity are not commonly exposed to the immune system. If such antigens (dsDNA, for example) are liberated during cellular turnover, they may incite an immune response. Thereafter, further release of such antigens might form the nidus for IC

Why do SLE patients make autoantibodies?

(3) Cross reactivity
SLE might be a disease caused by an unknown pathogen such as a virus or a bacterium. The interaction of pathogen derived peptides with a susceptible HLA haplotype may elicit "autoimmune" diseases by activating pathogenic T cells. Such a pathogen has not been identified in SLE, but no feature of the disease suggests that this could not be the etiology.

(4) Abnormal regulation: failure of suppression
SLE might arise as a consequence of abnormalities in regulatory CD4+ or CD8+ T cells.

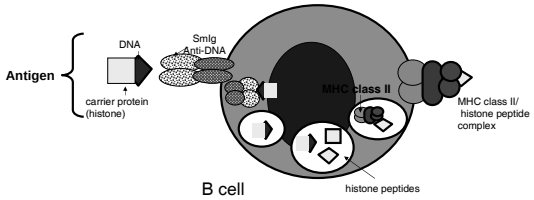
Evidence that T cells are important in the development of SLE

• The pathogenic anti-DNA antibodies in SLE are high affinity IgG molecules. Because it is known that class switching to IgG as well as somatic mutation and affinity maturation requires T cells we infer that anti-DNA antibody-producing B cells are expanded in SLE by a process that mimics the normal CD4+ T cell-dependent responses, involving common mechanisms of somatic mutation, affinity maturation, and IgM to IgG class switching.

• The MHC class II restriction and the known association of DR2 and DR3 with susceptibility to SLE also strongly point to a predominant role CD4+ T cells in the induction of autoimmunity in SLE.

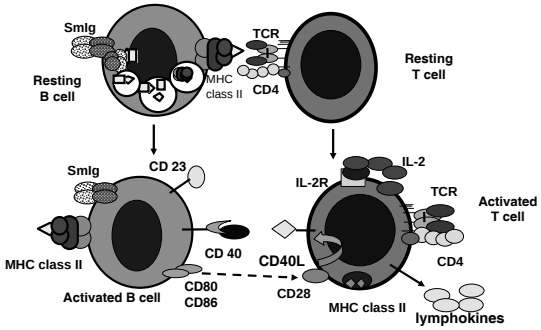
• Finally, animal models of SLE are effectively treated with molecules which block key functions of CD4+ T cells.

Antigen Presentation by B cells in SLE

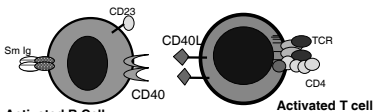


Antigen binds specifically to SmIg, is internalized into vesicles and cleaved into peptides which displace and bind to MHC class II molecules. The peptide/MHC complex is then transported to the surface membrane.

Expression of Membrane Proteins Following Antigen Specific Activation of T and B Cells

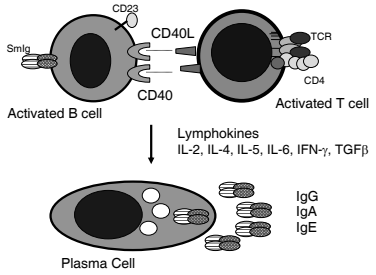


CONSEQUENCES OF CD40L/CD40 INTERACTIONS DURING T-B CELL INTERACTIONS



Triggering of B cell proliferation
Rescue from apoptosis
Induction of Ig isotype class switching
Up-regulation of B71 and B72
Germinal center formation
Up-regulation of CD23
Downregulation of CD40L expression

Final Phases of B cell Differentiation are Mediated by Contact T cell signals (CD40L/CD40) and Lymphokines



Molecular Interactions of Helper T Cells and APC/B Cells: Potential targets of therapy for SLE