

Autoimmunity

- ◆ Reactivity to self antigens:

- * T cells
- * B cells

Autoimmune Disease

- ◆ Autoreactivity:

- * Leading to tissue damage or dysfunction
- * Occurring in the absence of ongoing infection

SLE Pathogenesis

- Immune activation
- Target organ injury

Epidemiology

Prevalence: 17-48/100,000 worldwide but as high as 207/100,000 in an Afro-Caribbean population in England

Female:Male ratio is approximately 9:1 post-puberty and pre-menopausal

Ethnic Variance: More common in Black (3x), Hispanic (2-3x) and Asian 2x populations

ACR Criteria for Diagnosis

1. **Malar Rash:** fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
2. **Discoid Rash:** Erythematous raised patches with adherent keratotic scaling and follicular plugging: scarring may occur
3. **Photosensitivity:** Reaction to sunlight, resulting in the development of or increase in skin rash
4. **Oral Ulcers:** Oral or nasopharyngeal ulceration, usually painless
5. **Arthritis:** Nonerosive arthritis involving two or more peripheral joints
6. **Serositis:** Pleuritis or pericarditis
7. **Renal Disorder:** proteinuria greater than .5 gm/day and/or cellular casts
8. **Neurologic Disorder:** Seizures and/or psychosis in the absence of drugs or metabolic disturbances which are known to cause such effects
9. **Hematologic Disorder:** Hemolytic anemia , leukopenia (< 4000), lymphopenia (<1500) or thrombocytopenia (<100,000)
10. **ANA:** Positive test for antinuclear antibodies in the absence of drugs known to induce it.
11. **Immunologic Disorder:** Elevated serum antibody titers to dsDNA or Sm, a positive LE cell prep or a false positive serologic test for syphilis

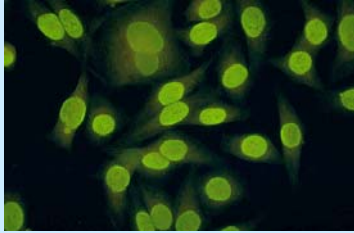
Signs and Symptoms

Symptoms Occurrence (ever)

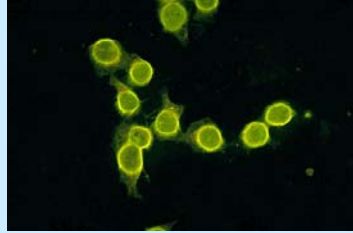
❖ Arthralgias	95%
❖ Fever more than 100 degrees F (38 degrees C)	90%
❖ Arthritis	80%
❖ Prolonged or extreme fatigue	81%
❖ Skin Rashes	74%
❖ Anemia	71%
❖ Kidney Involvement	50%
❖ Pleurisy	45%
❖ Sun or light sensitivity (photosensitivity)	30%
❖ Hair loss	27%
❖ Abnormal blood clotting problems	20%
❖ Raynaud's phenomenon	17%
❖ Seizures	15%
❖ Mouth or nose ulcers	12%

Anti-nuclear antibody patterns

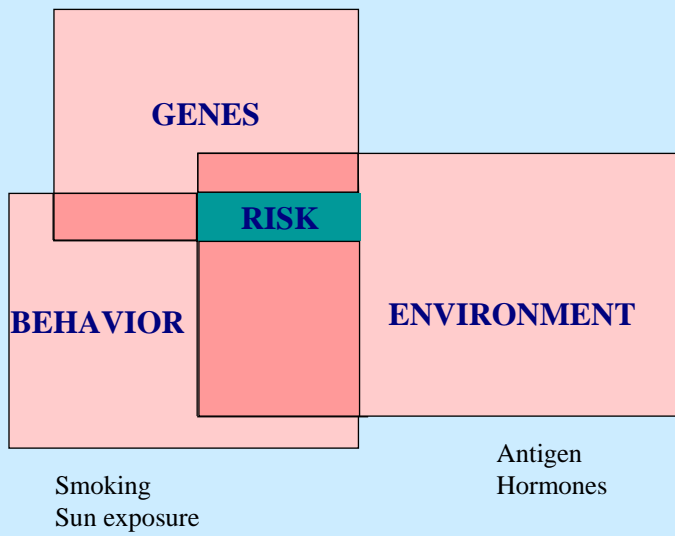
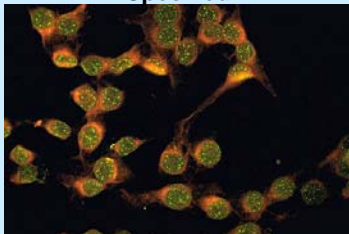
Homogeneous



Rim



Speckled



Genes Implicated in Murine SLE

- MHC
- Apoptotic pathways
- Cytokines:costimulatory
- Signalling molecules
- Clearance of cellular debris
- Regulatory pathways

Genes Implicated in Human SLE

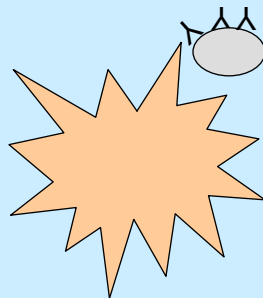
- HLA
- Signaling: PTPN22 and CD22
- Apoptosis: BCL-2
- Cytokines: IL-10
- Regulatory mechanisms:CTLA4, PD-1 and FcRIIb
- Clearance of apoptotic debris: complement, DNase, activating FcRs

Etiology

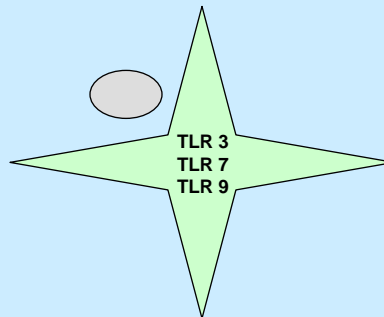
- Genes
- Triggers
 - Apoptotic debris
 - Infection
 - UV light

Clearance of Apoptotic Cells

- Natural autoantibodies: DNA, PS, phospholipid

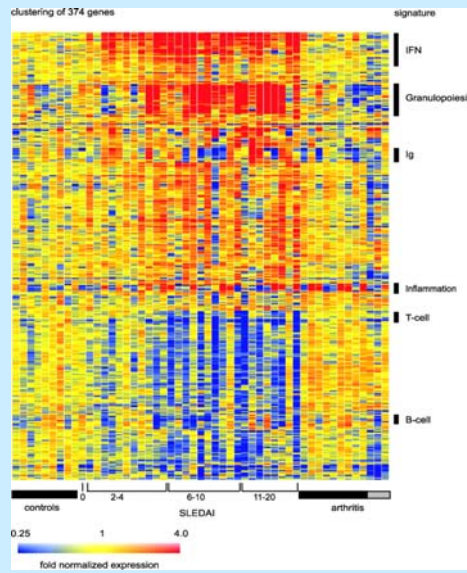


macrophage



dendritic cell

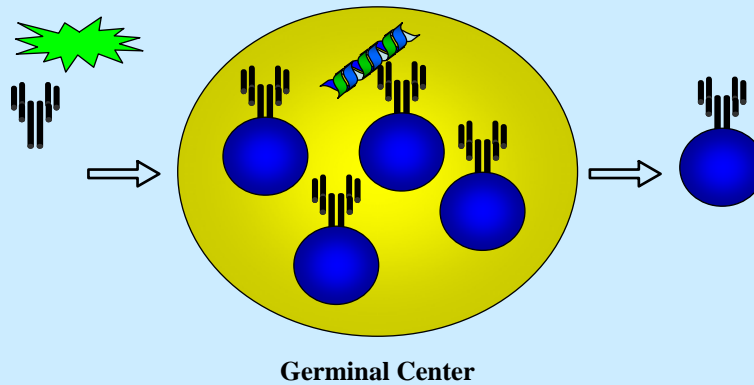
Interferon Signature



Infection

- Bacterial
- EBV

Somatic Mutation, Affinity Maturation and the Generation of Autoreactivity

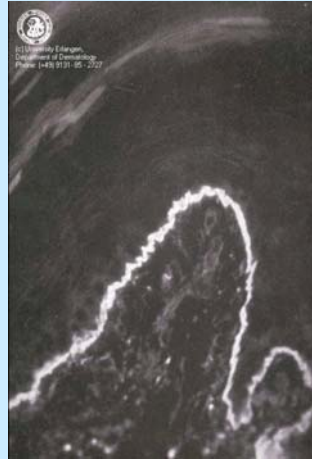


UV Light

Malar Rash

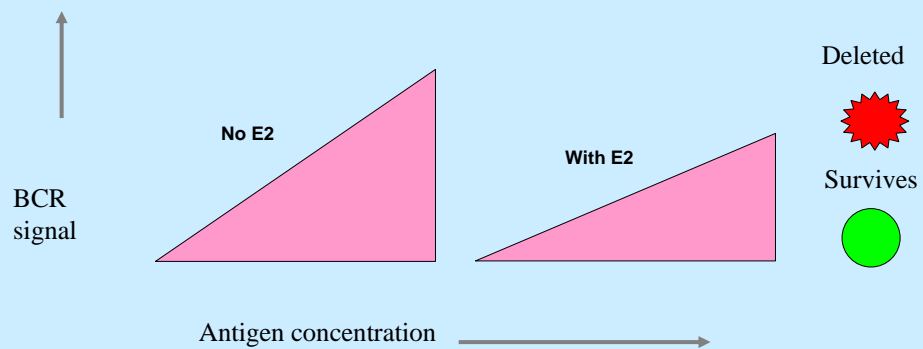


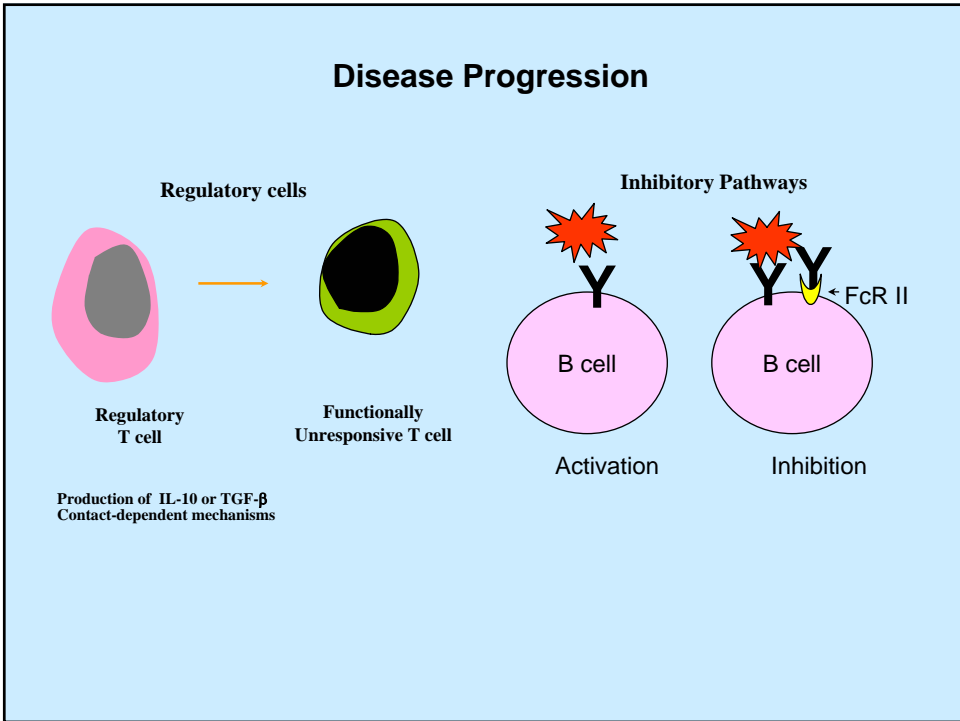
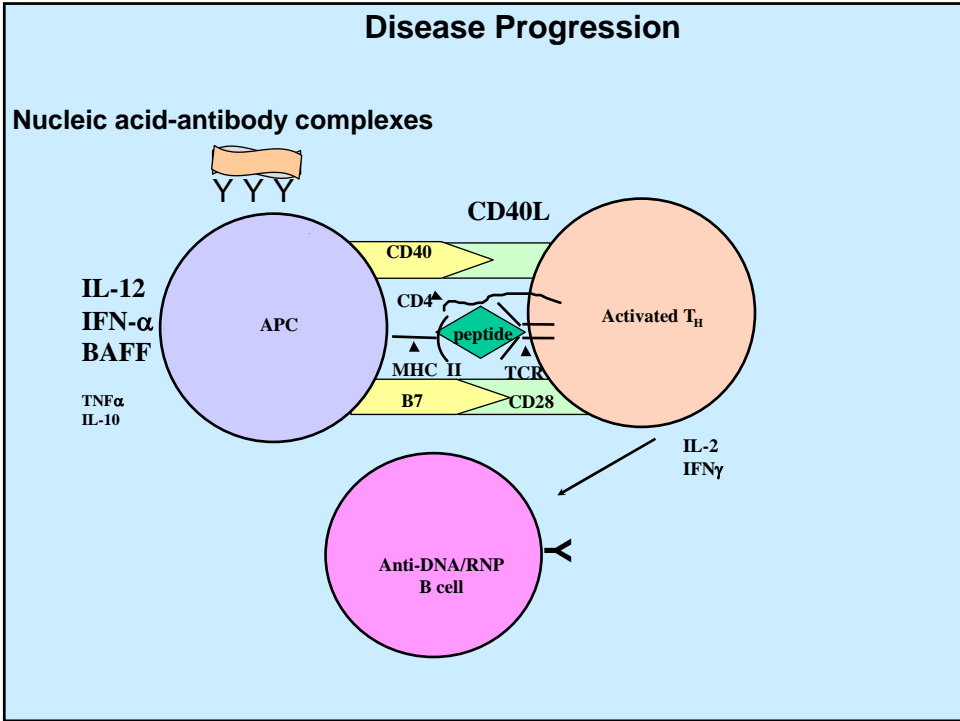
Lupus Band Test



Hormonal Regulation

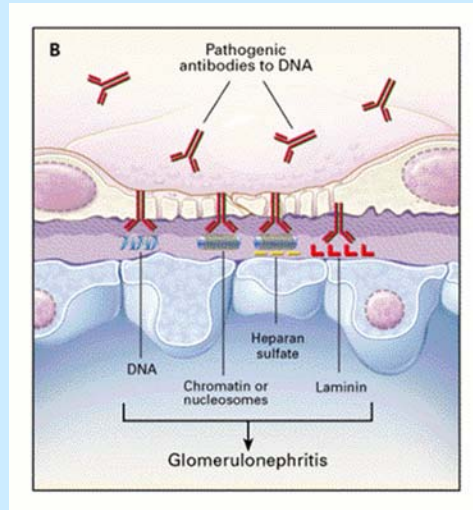
- Estrogen-increases Bcl-2, decreases BCR signal





Pathogenicity of anti-dsDNA Antibodies

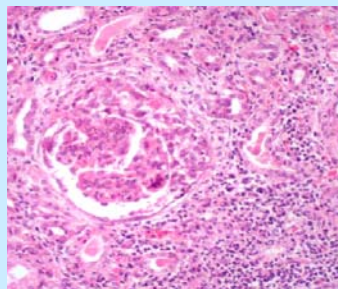
B. Hahn, NEJM 1998



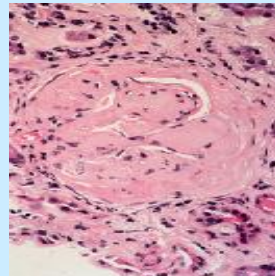
Target Organ Vulnerability

Kidney

Cellular infiltration



Sclerosis



Tissue Damage

Mechanisms

- cytotoxic cells
- cytokines
- antibodies

Critical Considerations

- 1) Mechanism of autoreactivity may differ from mechanism of organ damage.**
- 2) What exacerbates autoimmunity may ameliorate tissue damage
ie. Low TNF**

Late Sequelae

- Heart-accelerated atherosclerosis
- Brain-cognitive impairment

Therapy

Immunosuppression:current

Global

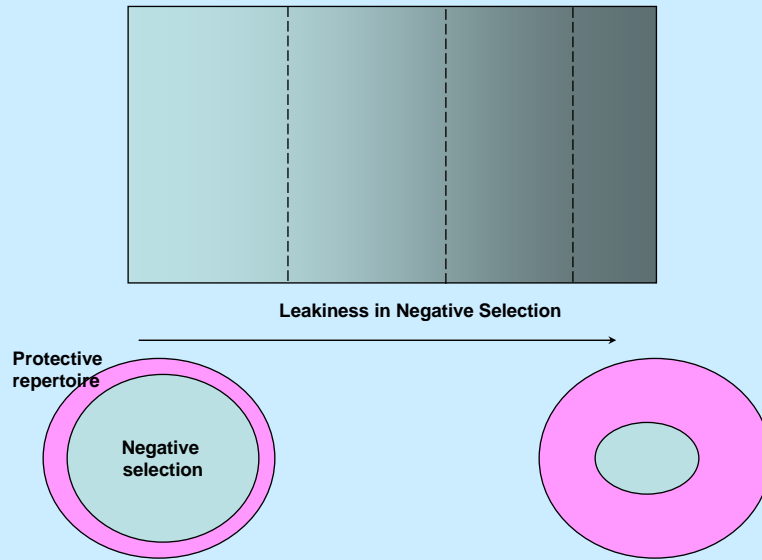
Immunosuppression: novel

- 1) Immunoablation: B cell ablation
- 2) Costimulatory blockade
- 3) Cytokine blockade
- 4) Induction of immune deviation
- 5) Induction of regulatory cells

Antigen-specific Therapy:fantasy

- 1) vaccines,
- 2) toxic conjugates
- 3) tolerance induction

Stringency of lymphocyte selection and predisposition to autoimmunity



Therapeutic Strategy

Treat during remission: Increase stringency of negative selection