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

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

Genes Implicated in Murine SLE
- MHC
- Apoptotic pathways
- Cytokines: costimulatory
- Signalling molecules
- Clearance of cellular debris
- Regulatory pathways

Clearance of Apoptotic Cells
- Natural autoantibodies: DNA, PS, phospholipid
Interferon Signature

Infection
- Bacterial
- EBV

Somatic Mutation, Affinity Maturation and the Generation of Autoreactivity

Germinal Center

Hormonal Regulation
- Estrogen-increases Bcl-2, decreases BCR signal

UV Light

Malar Rash

Lupus Band Test

Disease Progression

Nucleic acid-antibody complexes

Hormonal Regulation
- Estrogen-increases Bcl-2, decreases BCR signal

Disease Progression

Regulatory cells

Inhibitory Pathways

Production of IL-10 or TGF-β
Contact-dependent mechanisms
Pathogenicity of anti-dsDNA Antibodies
B. Hahn, NEJM 1998

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

Target Organ Vulnerability
Kidney
Cellular infiltration Sclerosis

Late Sequelae
• Heart-accelerated atherosclerosis
• Brain-cognitive impairment

Tissue Damage
Mechanisms
- cytotoxic cells
- cytokines
- antibodies

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

4
Stringency of lymphocyte selection and predisposition to autoimmunity

Leakiness in Negative Selection

Protective repertoire

Negative selection

Therapeutic Strategy

Treat during remission: Increase stringency of negative selection