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

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**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

RISK

BEHAVIOR

ENVIRONMENT

Smoking
Sun exposure

Antigen
Hormones
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

Germinal Center
UV Light

Malar Rash

Lupus Band Test

Hormonal Regulation

• Estrogen-increases Bcl-2, decreases BCR signal
Disease Progression

Nucleic acid-antibody complexes

- IL-12
- IFN-α
- BAFF
- TNFα
- IL-10
- APC
- CD40
- CD40L
- MHC II
- B7
- TCR

Activated T helper cell

Anti-DNA/RNP B cell

- IL-2
- IFNγ

Disease Progression

Regulatory cells

- Regulatory T cell
- Functionally Unresponsive T cell

Inhibitory Pathways

- B cell
- Activation
- B cell
- Inhibition

Production of IL-10 or TGF-β
Contact-dependent mechanisms
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 i.e. 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

Leakiness in Negative Selection

Protective repertoire

Negative selection

Therapeutic Strategy

Treat during remission: Increase stringency of negative selection