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
Risk
Behavior
Environment

Antigen
Hormones

Smoking
Sun exposure
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
  - Silica

Silica may be a surrogate for endotoxin

Clearance of Apoptotic Cells

- Natural autoantibodies: DNA, PS, phospholipid

macrophage
dendritic cell
TLR 3
TLR 7
TLR 9
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
- TNF-α
- IL-10

APC

CD40L

CD40

CD4

B7

CD28

MHC II

TCR

Activated T

Peptide

Anti-DNA/RNP

B cell

IL-2

IFN-γ

Disease Progression

Regulatory cells

Regulatory T cell

Functionally Unresponsive T cell

Production of IL-10 or TGF-β

Contact-dependent mechanisms

Inhibitory Pathways

Activation

Inhibition

FcR II
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

Therapeutic Strategy

Treat during remission: Increase stringency of negative selection
Vasculitis

A systemic process in which blood vessel architecture is destroyed by inflammatory cells. Vasculitis-induced injury may lead to increased vascular permeability, vessel weakening and aneurism formation, intimal proliferation and thrombosis resulting in obstruction and tissue ischemia.

Vasculitis

- Heterogenous group of disorders
- All share a propensity for angiocentric inflammation and necrosis
- Represent a remarkably diverse range of clinical symptoms, severities and outcomes
Primary Vasculitis/Classification

**Large Vessel Vasculitis**
- Takayasus Arteritis
- Giant Cell Arteritis

**Medium-Sized Vessel Vasculitis**
- Polyarteritis Nodosa
- Kawasaki’s
- Primary CNS Angiitis

**Small Vessel Vasculitis**

- ANCA+
  - Wegener’s Granulomatosis
  - Churg Strauss
  - Microscopic Polyarteritis

- ANCA-
  - Henoch Schonlein Purpura
  - Cryoglobulinemia
  - Behcet’s
  - Hypersensitivity vasculitis

ANCA+ Vasculitides

- Wegener’s granulomatosis (WG), Churg Strauss (CS) and Microscopic Polyarteritis (MPA)
  - All involve medium to small vessels
  - Peak age onset 55
  - Male:female ratio is approximately 2:1
ANCA/Pathophysiology

cANCA
• targets proteinase3; very specific for Wegener’s (99%)
• isolated reports in amoebiasis, lymphoma and SLE

pANCA
• Targets myeloperoxidase; associated with Churg-Strauss
• reported commonly in RA, autoimmune hepatitis, ulcerative colitis with different antigen targets (lactoferrin, elastase, cathepsin G)

ANCA/Pathogenicity?
• Mouse myeloperoxidase-ANCA induce vasculitis in Rag2 mice
• ANCA binding to neutrophils or monocytes in vitro induces a respiratory burst, degranulation and release of pro-inflammatory molecules resulting in tissue damage
• ANCA binding to proteinase3 on activated endothelial cells induces cell injury and death
• Increased surface expression of PR3 on PMNs correlates with disease activity