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-menarche and post-menopause

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 nasopharyngal ulceration, usually painless
5. Arthritis: Nonspecific 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 or systemic disease
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 (IgM or IgG) 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
• Signalling: 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

TLR 3
TLR 7
TLR 9
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

Disease Progression
Regulatory cells
Inhibitory Pathways
- Produces IL-10 or TGF-β
- Contact-dependent mechanisms
- Regulatory T cell
- Functionally tolerant 3 cell
- B cell
- B cell
- FcR II
- Activation
- Inhibition
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

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**

• Takayasu Arteritis
• Giant Cell Arteritis

**Medium-Sized Vessel Vasculitis**

• Polyarteritis Nodosa
• Kawasaki’s
• Primary CNS Angiitis

**Small Vessel 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−

Wegener’s Granulomatosis
Churg Strauss
Microscopic Polyarteritis

Hepatitis Pupura
Cryoglobulinaemia
Behcet’s
Hypersensitivity vasculitis
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