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 nasopharyngial 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

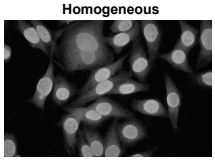
Signs and Symptoms

Symptoms Occurrence (ever)

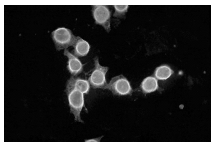
Arthralgias	95%
Fever more than 100 degrees F (38 degrees C)	90%
Arthritis	80%
Prolonged or extreme fatigue	81%
Skin Rashes	74%
Anemia	71%
Kidney Involvement	50%
Pleurisy	45%
Sun or light sensitivity (photosensitivity)	30%
Hair loss	27%
Abnormal blood clotting problems	20%
Raynaud's phenomenon	17%
Seizures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

Anti-nuclear antibody patterns

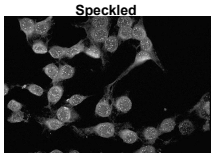
Homogeneous

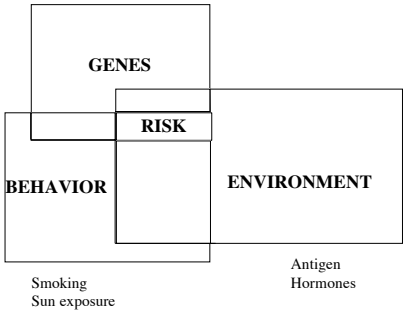


Rim



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

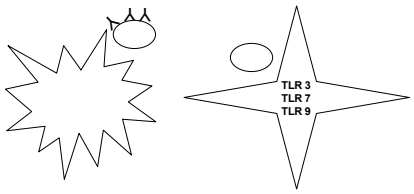
Etiology

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

Silica may be a surrogate for endotoxin

Clearance of Apoptotic Cells

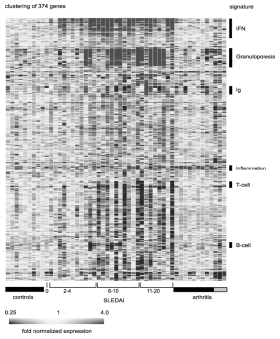
- Natural autoantibodies: DNA, PS, phospholipid



macrophage

dendritic cell

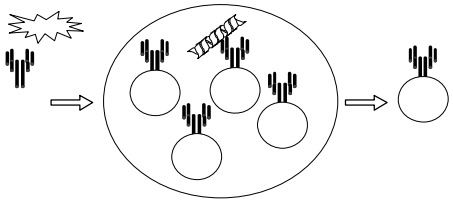
Interferon Signature



Infection

- Bacterial
- EBV

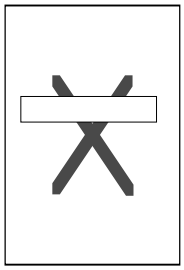
Somatic Mutation, Affinity Maturation and the Generation of Autoreactivity



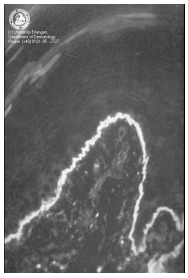
Germinal Center

UV Light

Malar Rash

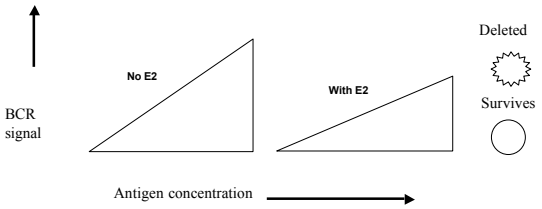


Lupus Band Test



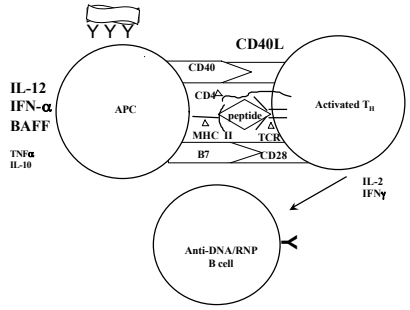
Hormonal Regulation

- Estrogen-increases Bcl-2, decreases BCR signal

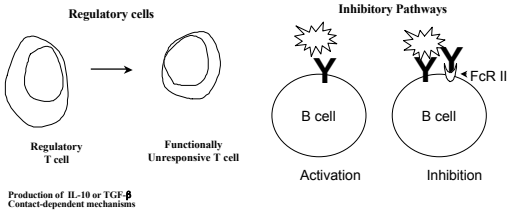


Disease Progression

Nucleic acid-antibody complexes

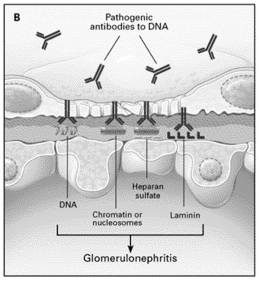


Disease Progression



Pathogenicity of anti-dsDNA Antibodies

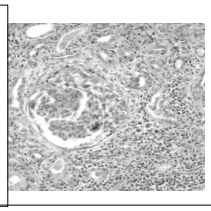
B. Hahn, NEJM 1998



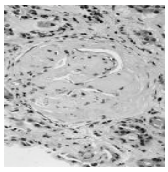
Target Organ Vulnerability

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

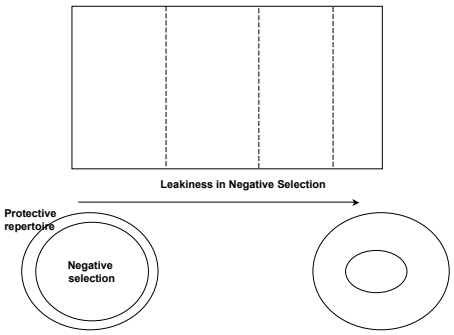
Therapy

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



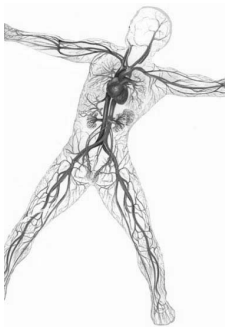
Therapeutic Strategy

Treat during remission: Increase stringency of negative selection

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+	ANCA-
Wegener's Granulomatosis Churg Strauss Microscopic Polyarteritis	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-inflammotory 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