## 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

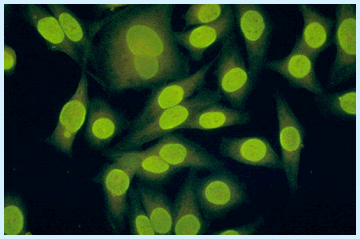
# Signs and Symptoms

**Symptoms Occurrence** (ever)

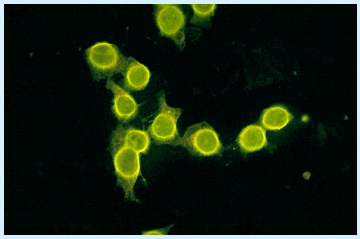
| | |
|---|---|
| ❖ Arthralgias | 95% |
| ❖ Fever more than 100 degrees F (38 degrees C) | 90% |
| ❖ Arthritis | 80% |
| ❖ Prolonged or extreme fatigue | 81% |
| ❖ Skin Rashes | 74% |
| ❖ Anemia | 71% |
| ❖ Kidney Involvement | 50% |
| ❖ Pleurisy | 45% |
| ❖ Sun or light sensitivity (photosensitivity)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

## Anti-nuclear antibody patterns

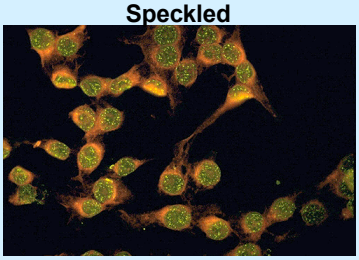
Homogeneous

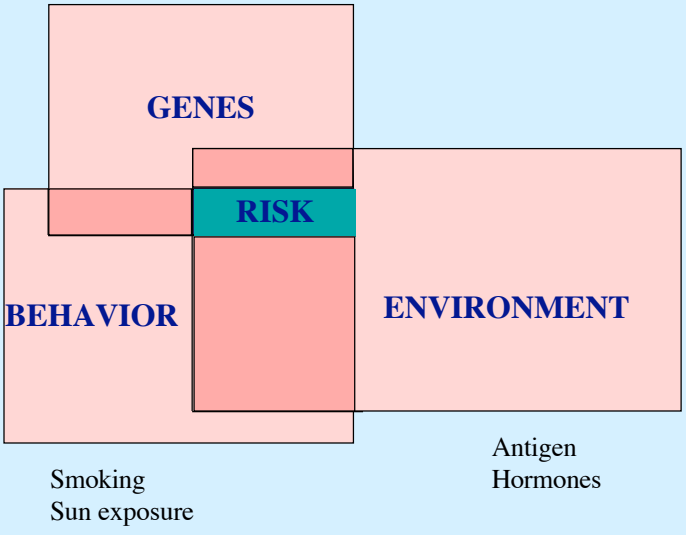


Rim



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

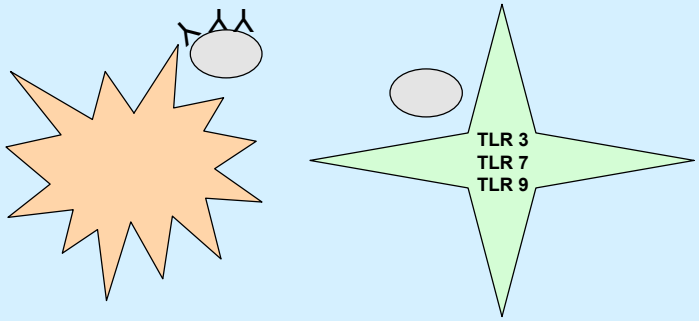
# Etiology

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

Silica may be a surrogate for endotoxin

# Clearance of Apoptotic Cells

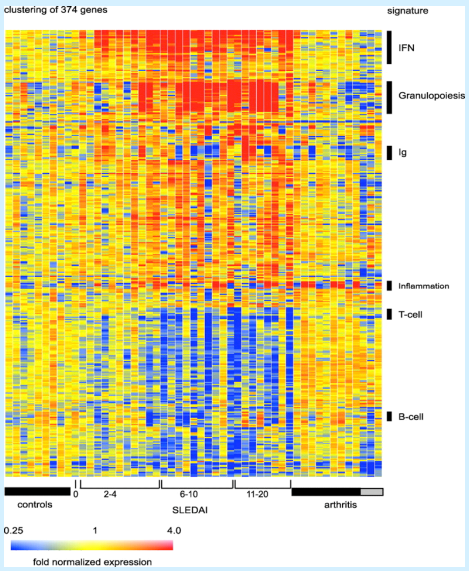
•Natural autoantibodies: DNA, PS, phospholipid




macrophage

dendritic cell

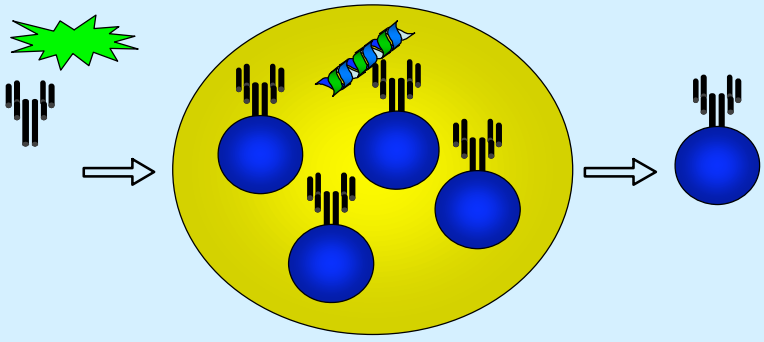
## Interferon Signature




## Infection

- Bacterial
- EBV

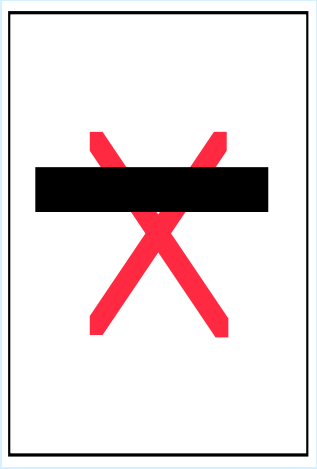
**Somatic Mutation, Affinity Maturation and the Generation of Autoreactivity**



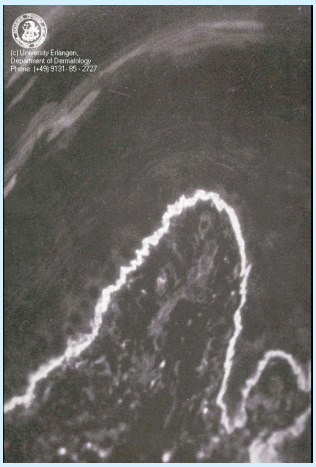
**Germinal Center**

# UV Light

## Malar Rash

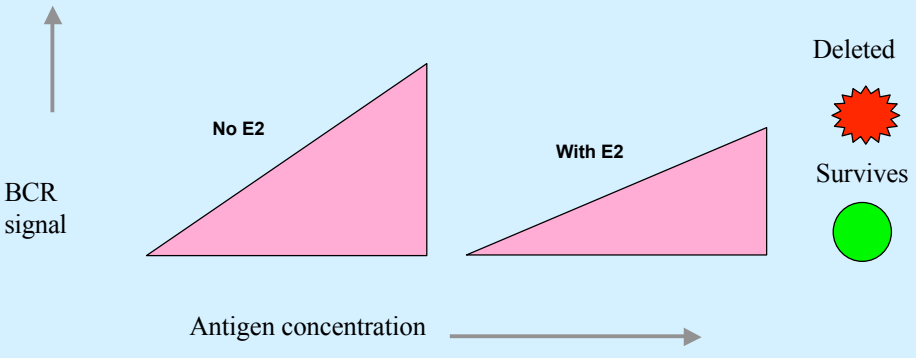


## Lupus Band Test



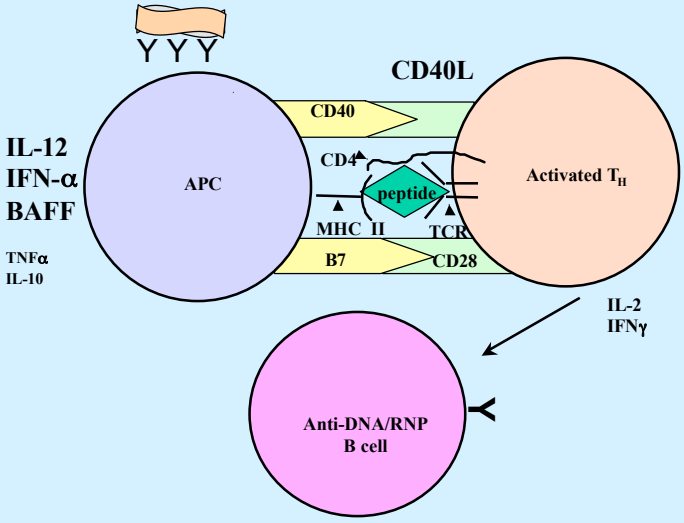
# Hormonal Regulation

•Estrogen-increases Bcl-2, decreases BCR signal

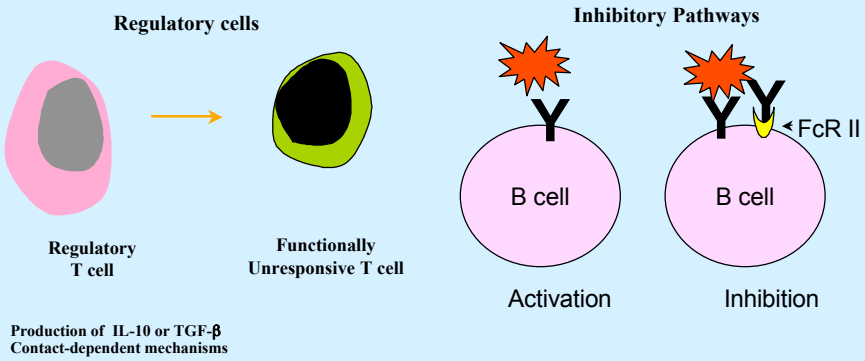


## Disease Progression

**Nucleic acid-antibody complexes**

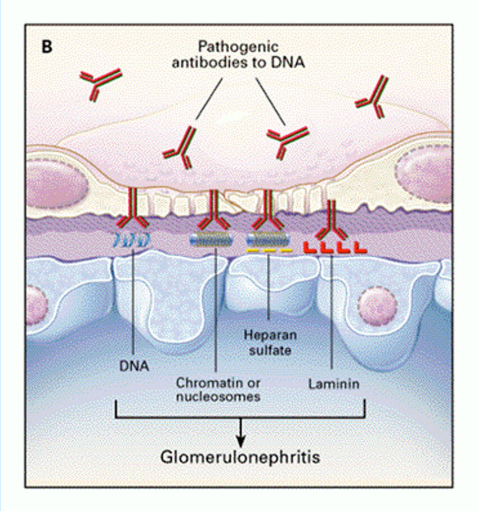



## Disease Progression



# Pathogenicity of anti-dsDNA Antibodies

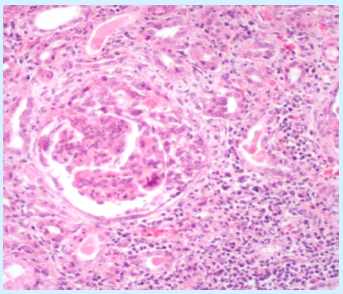
B. Hahn, NEJM 1998



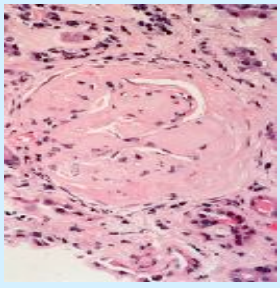

Target Organ Vulnerability

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

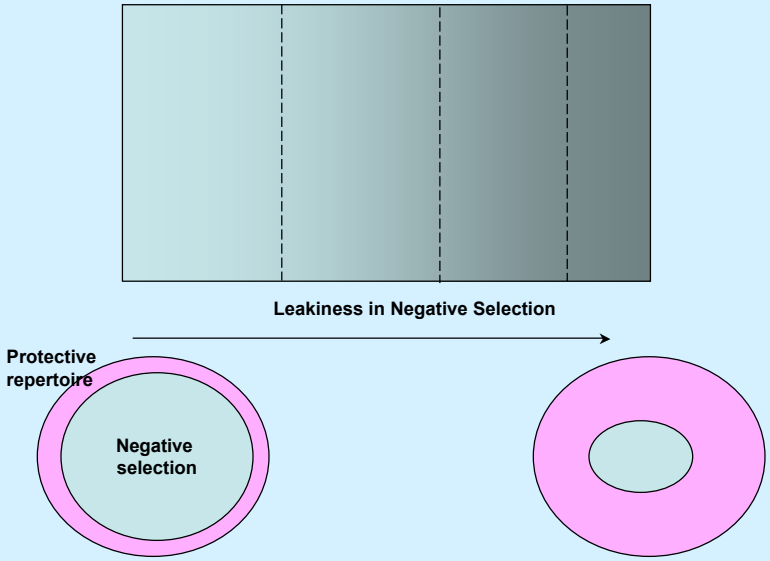
# Therapy

**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



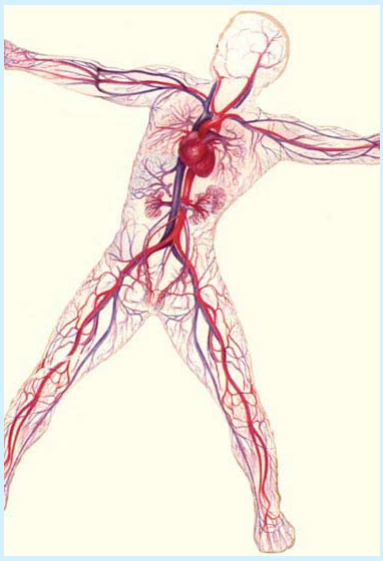

## Therapeutic Strategy

**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+

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-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