Pathways in Systemic Lupus Erythematosus: Systemic Inflammation

Ashira D Blazer, MD
Assistant Professor of Medicine
Division of Rheumatology
Hospital for Special Surgery

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- Company — Nature of Relationship
  - GSK — Medical Educators Network, Disparities
  - Novartis — Consultant: Diversity, Equity, and Inclusion

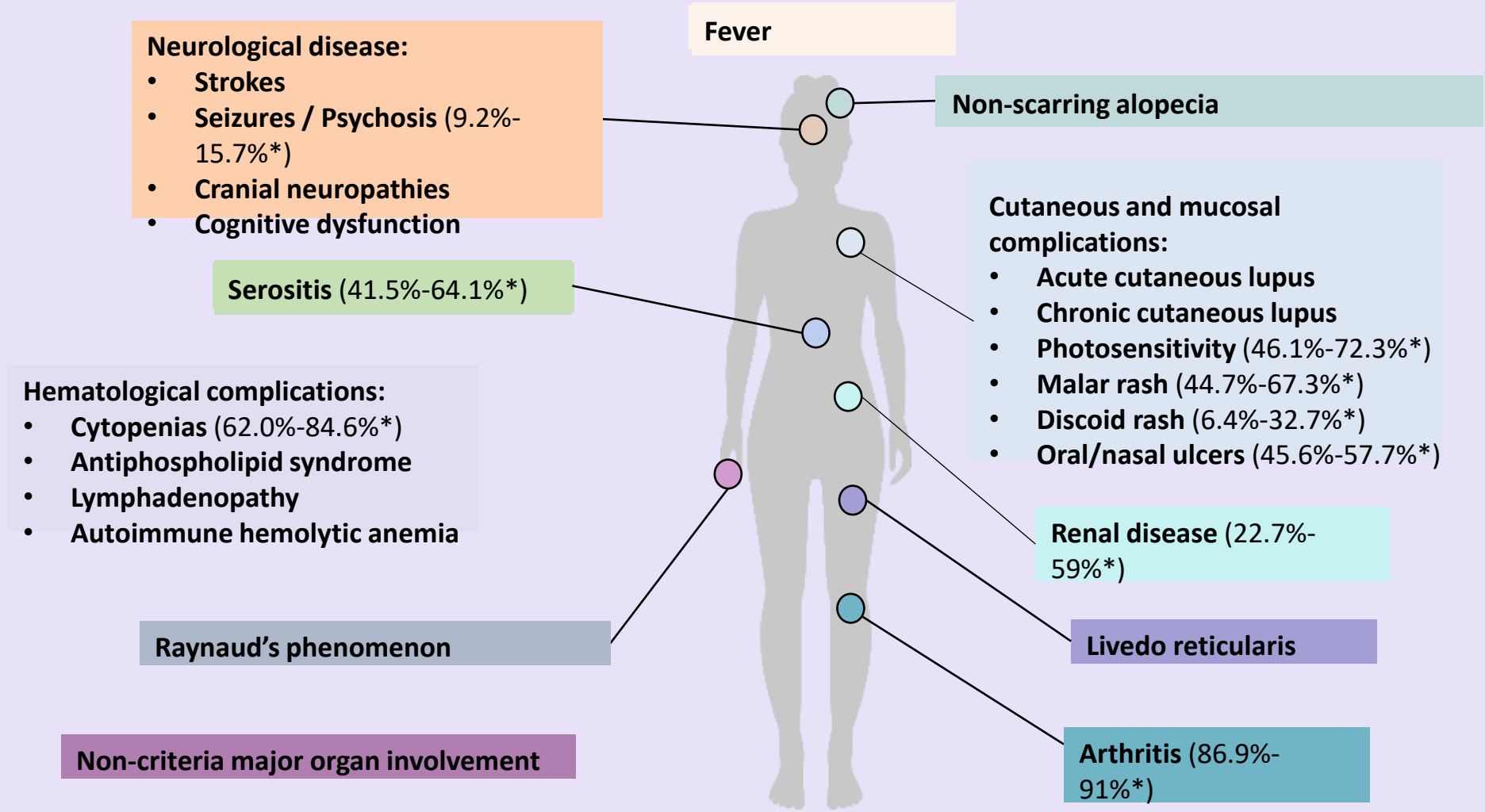
- Grant Support:
  - K23AI163359 (NIH/NIAID)

Learning Objective

- Assess the latest evidence in the pathophysiology, assessment, treatment, and management of systemic lupus

Lupus Overview: What is Lupus?

- Heterogeneous, multi-organ system autoimmune disorder
- Characterized by
  - Production of autoantibodies
  - Immune Complex Deposition



SLE Classification Criteria: Recent Revision

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Chief Complaint

Pleasant 26yo woman with history of seizure disorder presents to the rheumatology service with migratory arthritis, pleuritic chest pain, abdominal pain, and low grade fever

Patient Baseline

GI

- Recurrent intermittent diarrhea

Neuro

- Has had a seizure disorder since age 18

MISC

- Intermittent fatigue
- Mild myalgias and low back pain

History of Present Illness

Three Months PTA

- Migratory joint pains (wrists, MCP, PIP)
- Lower abdominal pain with large volume diarrhea

Two Months PTA

- Mild, Sharp chest pain
- Low grade fever
- Myalgias

Two Weeks PTA

- Sun exposure
- Redness over face requiring makeup
- Severe fatigue

OVERVIEW OF PATHOGENESIS OF SLE

PREDISPOSITION

Susceptibility Genes

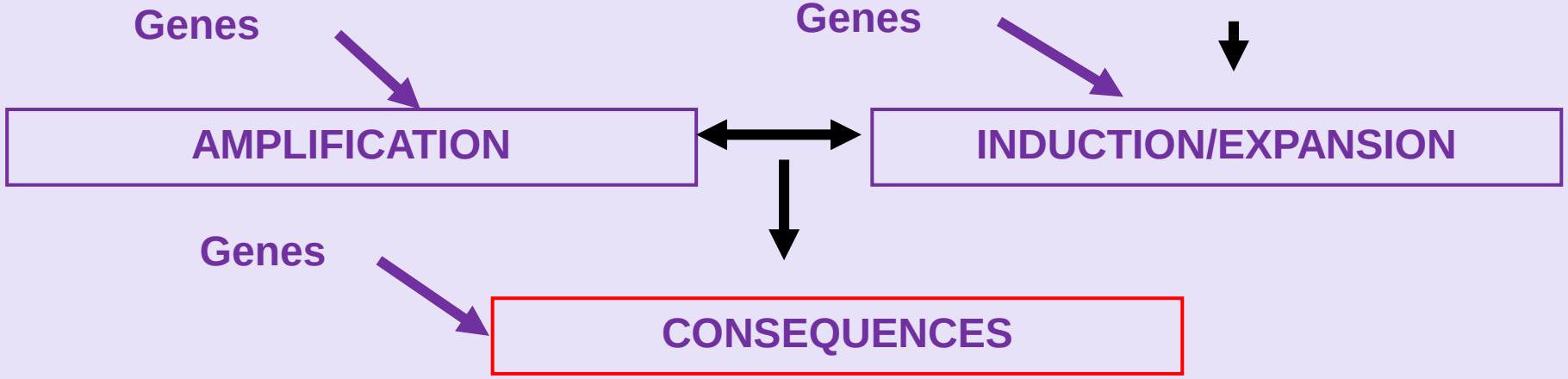
Prediction: if you cross critical threshold number you develop SLE early

Environment

UV light

Female gender ?

Infections - EBV



Systemic Lupus Erythematosus: Is it Genetic?

(Somers E, Arth Rheum,2013, Lim S, Arth Rheum, 2013, Izmirly P, Arth Rheum, 2017)

Most Recent Incidence Data

5.5 per 100,000

Most Recent Prevalence Data

72.8 per 100,000

1 per 537 black females

Female: Male Ratio

5.6: 1 (age 10 – 19 yr)

10-15: 1 (age 20 – 50 yr)

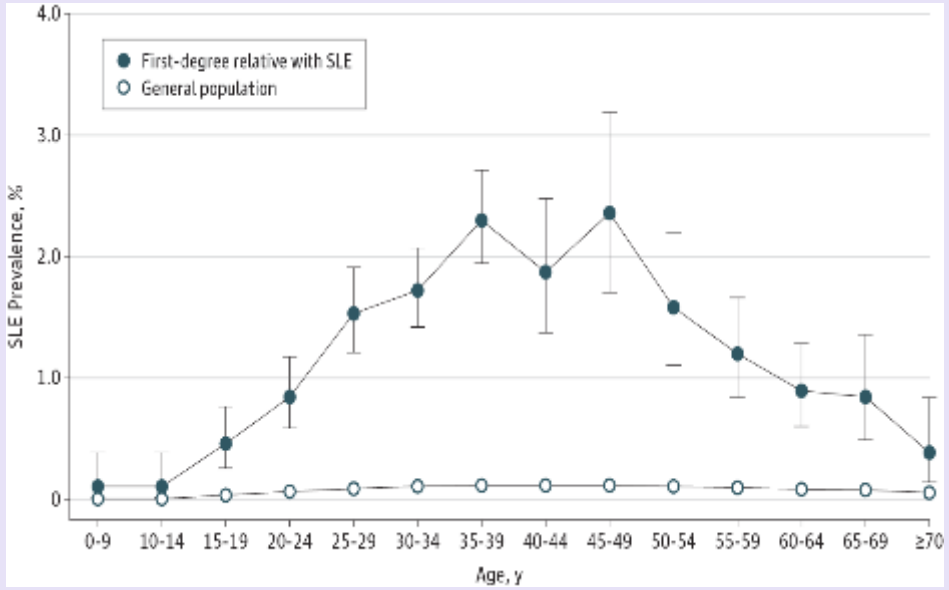
8: 1 (age >50 yr)

Peak Age: 15 – 44 yr

Disease Concordance

2-5% in dizygotic twins

24-58% in monozygotic twins

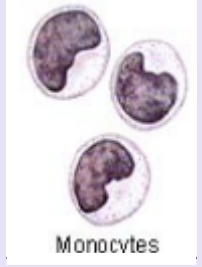


Risk ratio for spouse: 4.4**

Chang-Fu Kuo et al, JAMA 2015

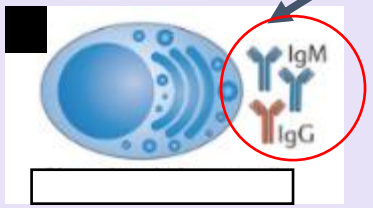
Immune Dysregulation in SLE Involves both Innate and Adaptive Leukocytes

First Responders: Innate Immunity



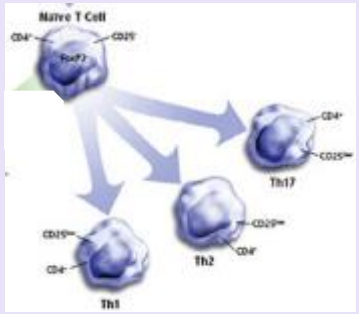
Second Responders: Adaptive Immunity

B Cells



Antibodies

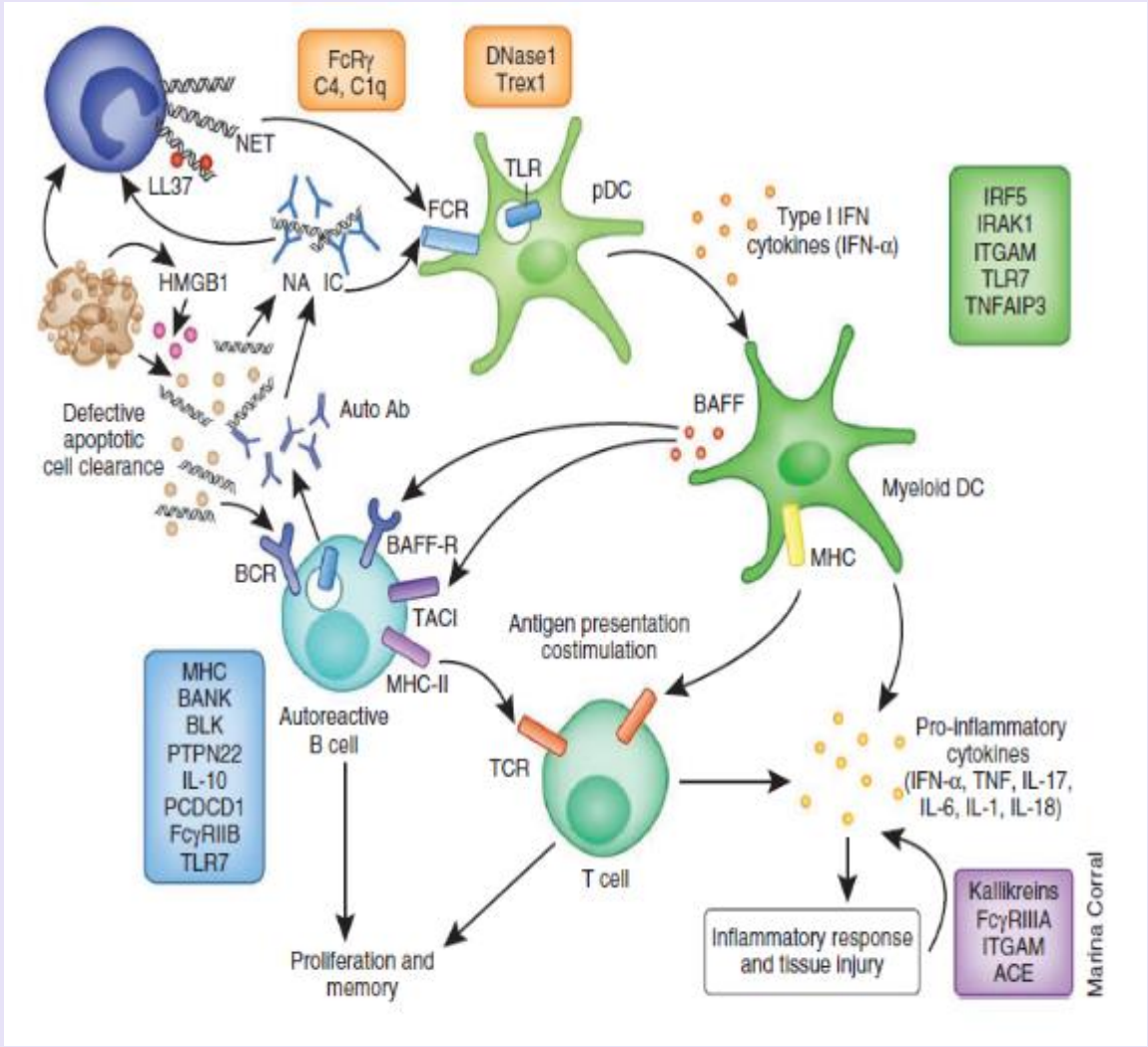
T Cells



Many of the Genetic Risk Factors for SLE Reveal Clues About Disease Pathogenesis

A. Immune complex clearance

B. Intra and extracellular IFN signaling



C. Lymphocyte Response

Relevant Medications

- Lacosamide 200mg bid (anti-epileptic)
- Oxcarbamazepine 600 tid (anti-epileptic)
- Ibuprofen 200mg q6 hours

Other History Points

Social history

- Works in medical records
- One new sexual partner X4 months
- No ETOH, Illicits, or tobacco.

Family History

- Cousin with SLE
- Mother with HTN

Allergies

- Shellfish (angioedema)
- Lamictal (rash)

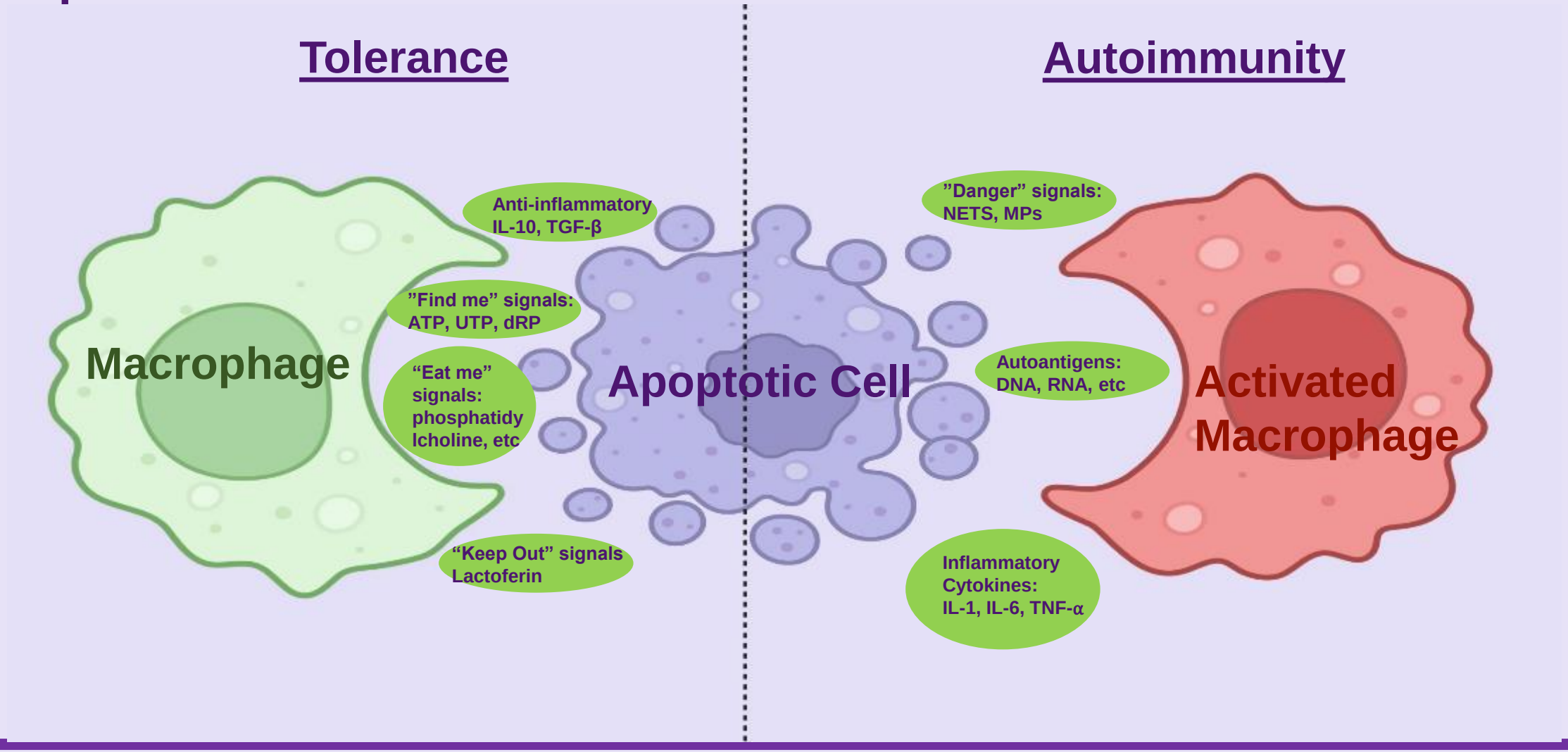
Polling Question

- What is the ratio of SLE cases between female and male patients in the ages of 20 – 50 years?
  A. 1 : 1
  B. 4-6 : 1
  C. 10-15 : 1
  D. 20:1

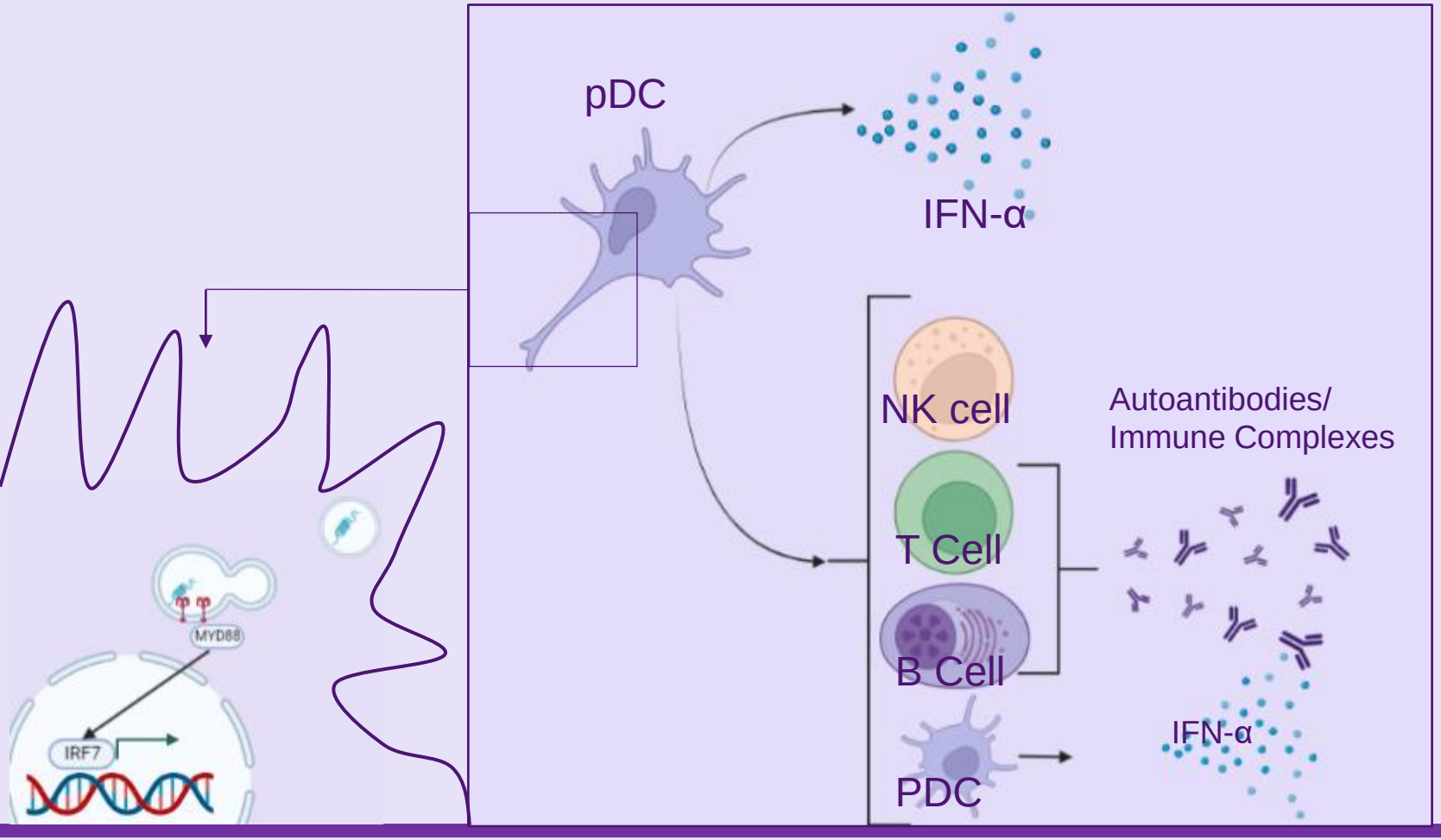
SLE Exacerbating Factors Create Apoptotic Debris

- Infection
- Ultraviolet light exposure
- Severe injury
- Exhaustion/stress

Breaking Tolerance: An Imbalance Between Apoptotic Debris Production and Clearance

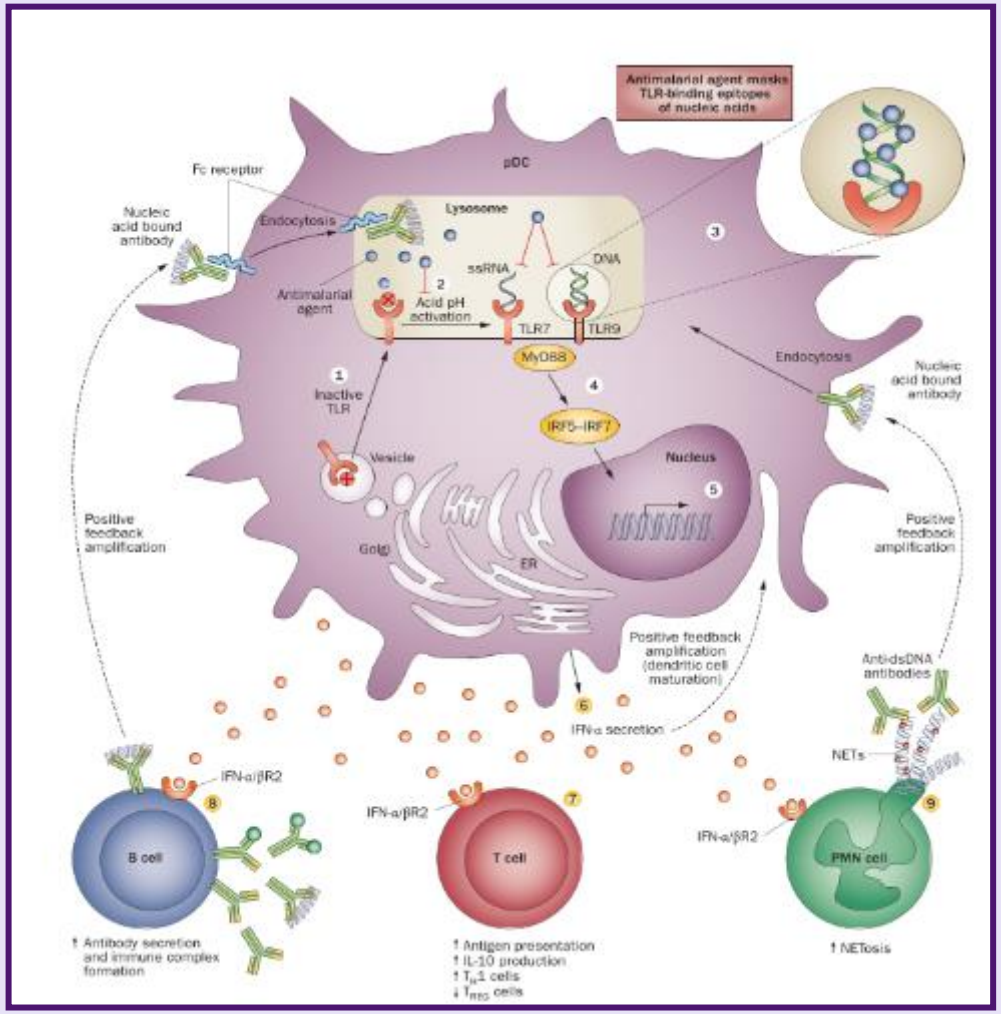


Innate Immune Dendritic Cells Contribute to Breaking Tolerance



- Dendritic cells become activated by autoantigens
- Produce IFN-α
- Activate NK cells, T Cells, B cells, and other pDCs
- Initiate the cascade of autoantibody/immune complex production

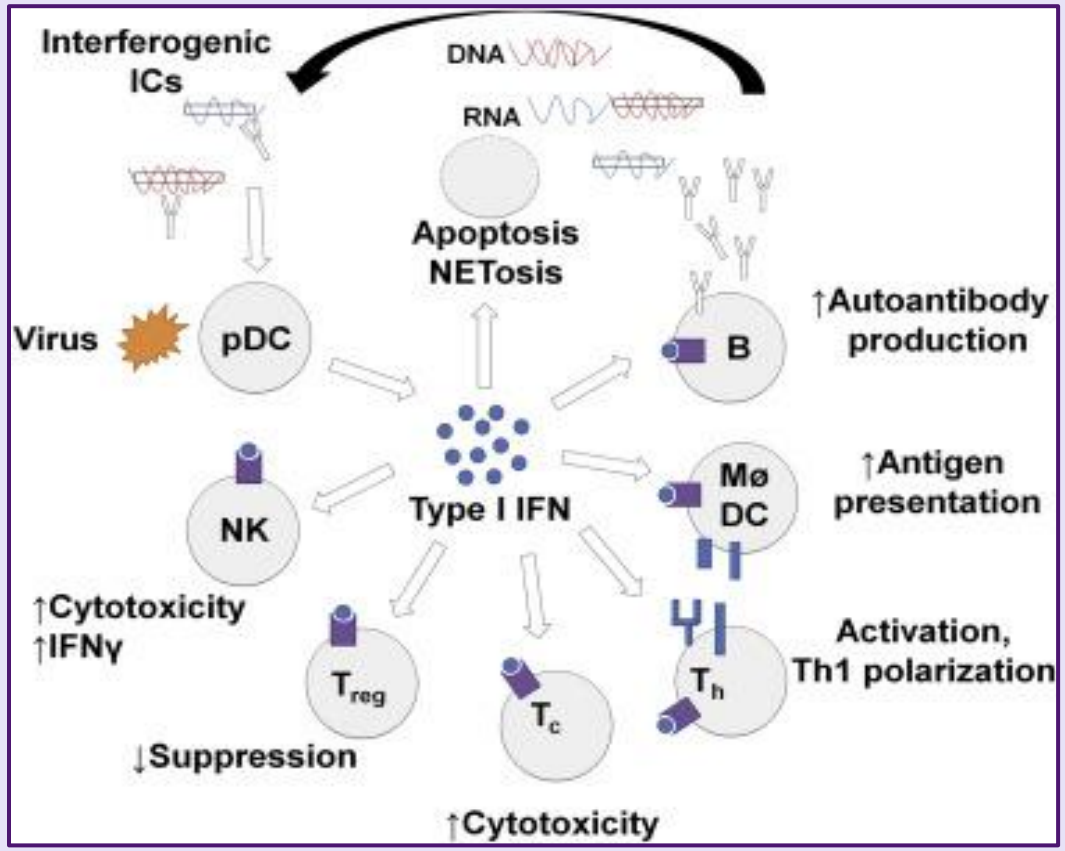
Hydroxycholroquine Has Major Effects on Dendritic Cell TLR Ligation



- TLR activation happens in the lysosome and is dependent on an acidic PH
- Antimalarial drugs are weak bases with affinities for the lysosome→ prevent acidification
- Bonus! Antimalarials may out-compete nucleic acids blocking TLR activation
- Extra bonus! Antimalarials have an affinity for melanin
  - Concentrate in the epidermis
  - Block UV rays preventing UV damage

Type I Interferons are at The Center Of SLE Disease Pathogenesis

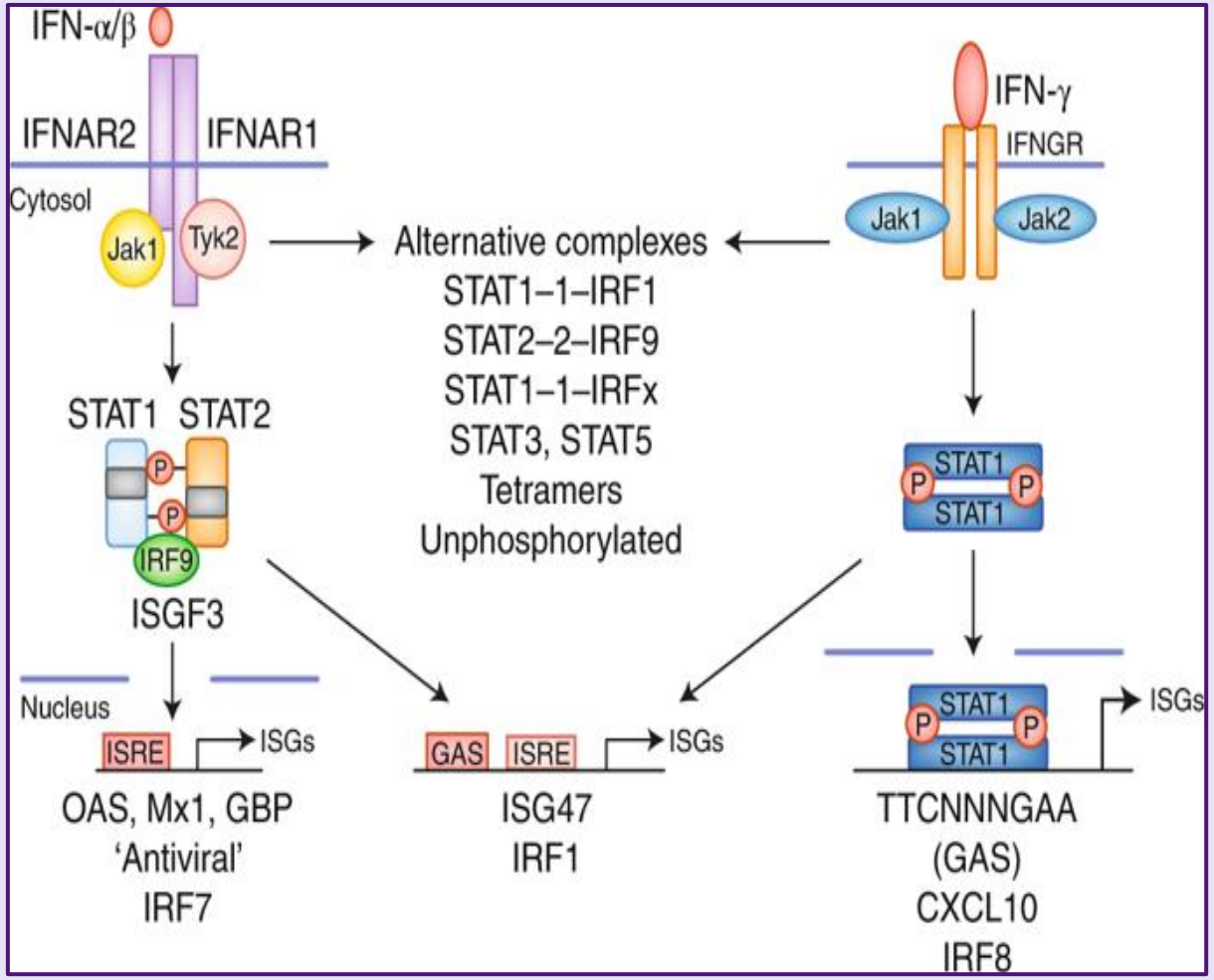
- Immune complexes result in IFN production
- IFN and breaking self-tolerance
  - Promotes autoantibody production
  - Suppresses T regulatory cells
  - Promotes T cell cytotoxicity
- IFNs is a therapeutic target in SLE
  - Anifrolumab
  - Phase 2 LILAC trial (BIIB059)



Schematic: The Role of IFN in SLE Pathogenesis

(Hagberg et al, Systemic Lupus Erythematosus Ch 19 (2016))

JAK/STAT Pathway may be Targeted to Affect Interferon Signaling



- JAK1 is a signal transducer downstream of IFNAR1/2
- Activated JAKs phosphorylate STATs causing dimerization
- STAT complexes then activate IRFs
- Result: ISG transcription

Schematic of IFN Stimulated Genes (Barrat et al, Nat Immunol (2019))

Pertinent Review of Systems

Reports

Diffuse weakness, periorbital edema in the morning

8 lb weight loss X 2 months

Denies

- Oral/nasal ulcers, alopecia, photosensitivity, dyspnea, Raynaud's

Denies

- Sick Contacts
- Asymmetrical leg swelling

Physical Exam

Vitals: BP: 120/62 P: 84 T: 38.5 R: 18

Gen: Alert and Oriented

CV: RRR, no m/g/r, 1+ pedal edema

Resp: Poor inspiratory effort (pain on deep inspiration)

HEENT: No oral ulcers

Neck: Cervical adenopathy

Abd: Diffuse tenderness

Skin: Rash over malar area

Musculoskeletal Exam

Hands

- Boggy edematous 2nd and 3rd MCPs
- Tenderness at PIPs

Wrists

- fullness in the wrists bilaterally with decreased range of motion and tenderness to palpation

Admission labs

Heme

- WBC: 1.9 Hgb: 7.3 PLT: 267 ALC: 0.8
- 2+ Microcytes, 1+ teardrops, schistocytes

Chem

- Na: 134 K: 4.3 Creatinine: 1.2

LFT

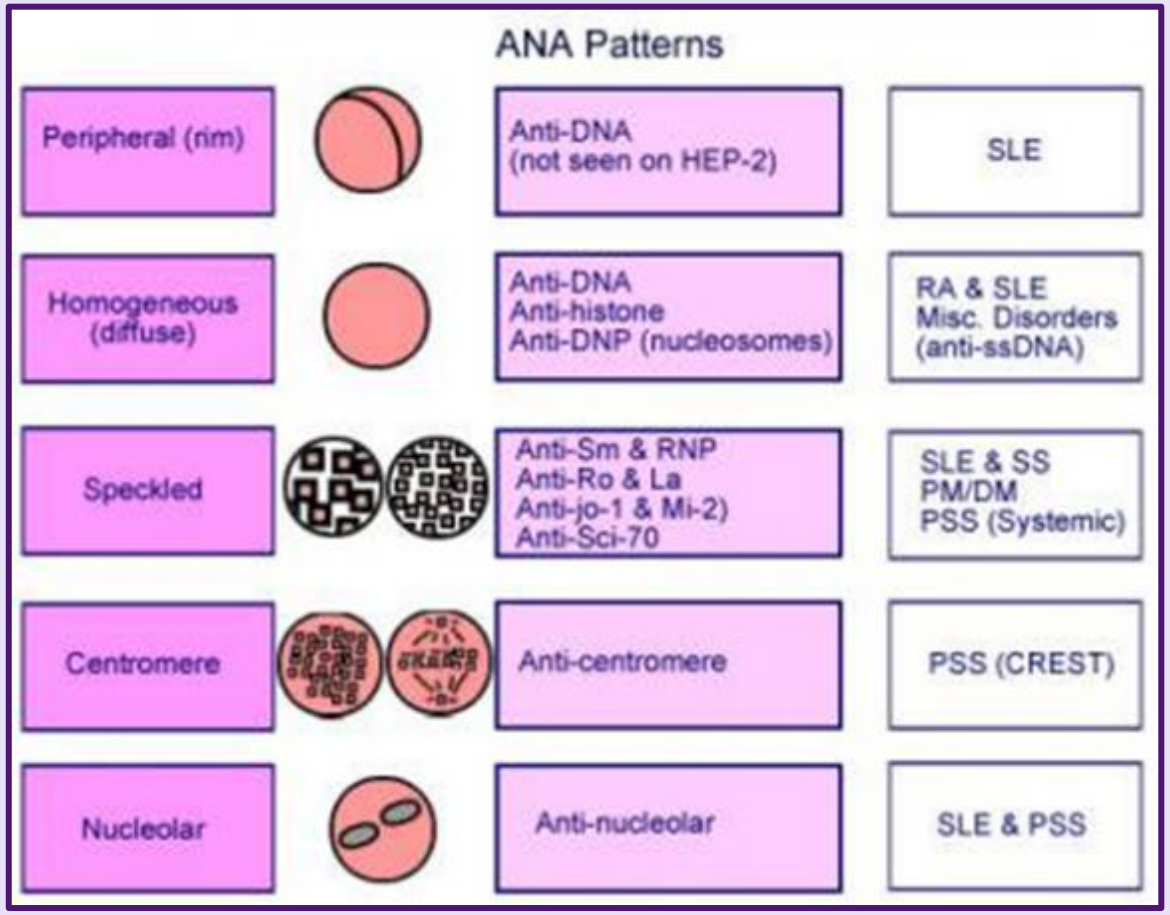
- Albumin: 2.8, total protein 6.5
- Honorable mention: LDL: 160

Lupus Serologies

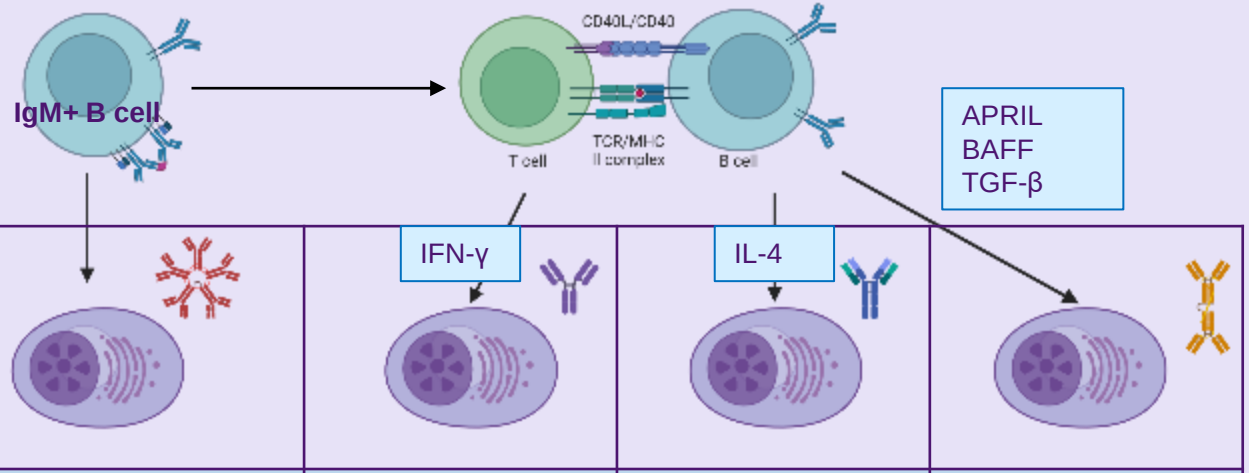
ANA/C3 C4	• Positive • C3: <40 • C4: 12
SLE Specific	• Smith: 1.5 (positive) • dsDNA: 255
Sjogrens	• SSA/Ro: >8.0 (positive) • SSB/La: 1.2 (positive)
MCTD	• RNP: 1.0 (positive)
APLS	• LAC: not detected • Cardiolipin: IgG/IgM negative • Beta-2 Glycoprotein: IgG/IgM negative

What is an Antinuclear Antibody?

- An antibody produced by an auto-reactive plasma cell
- Directed against an antigen—usually nucleic acid (RNA or DNA), or nuclear protein
- Can cause organ-specific inflammation in the body
- Testing the serum for anti-nuclear antibodies can help give diagnostic and prognostic information in lupus.

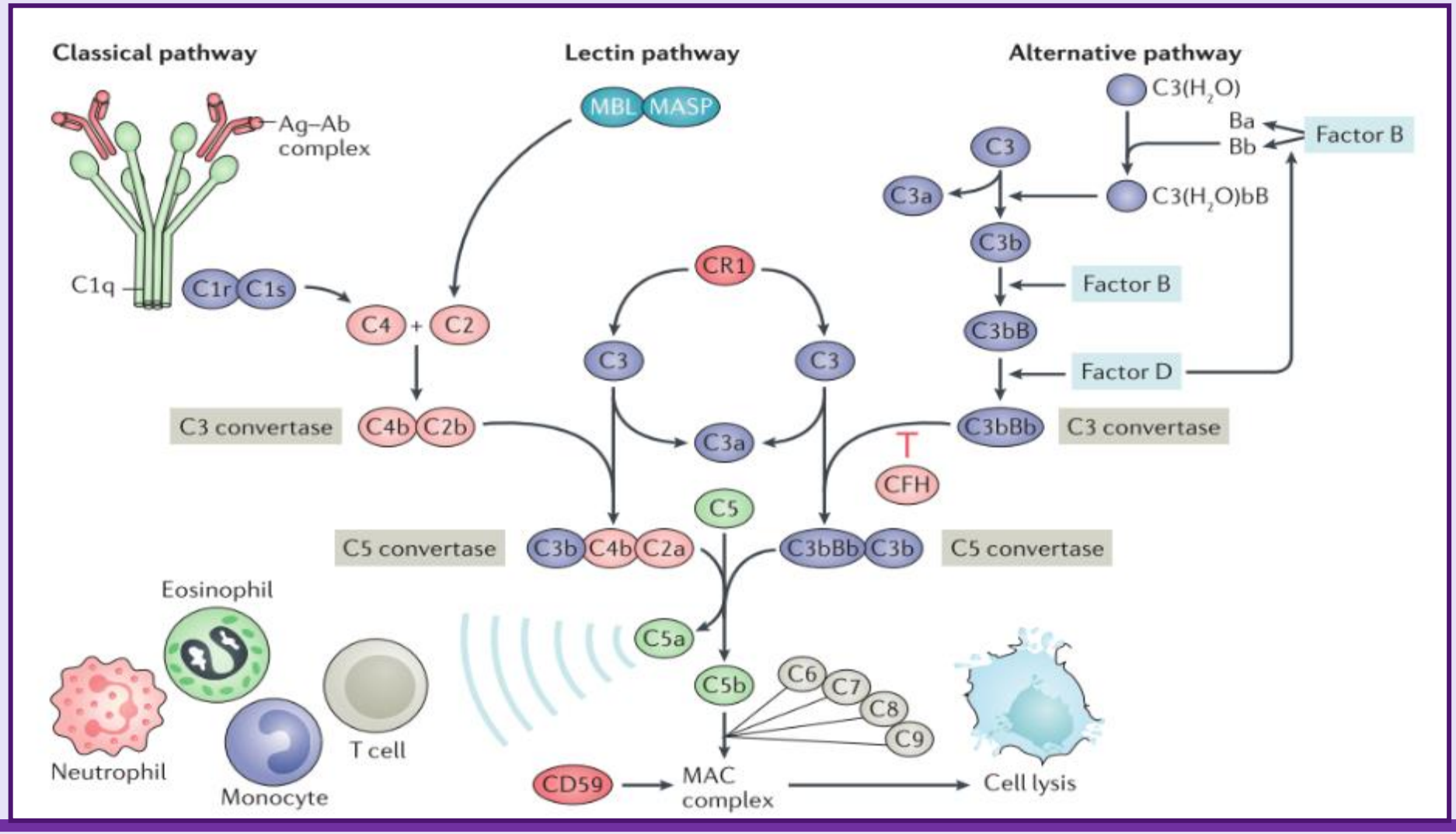


B and T Lymphocyte Interactions Enable Autoantibody Isotype Switching

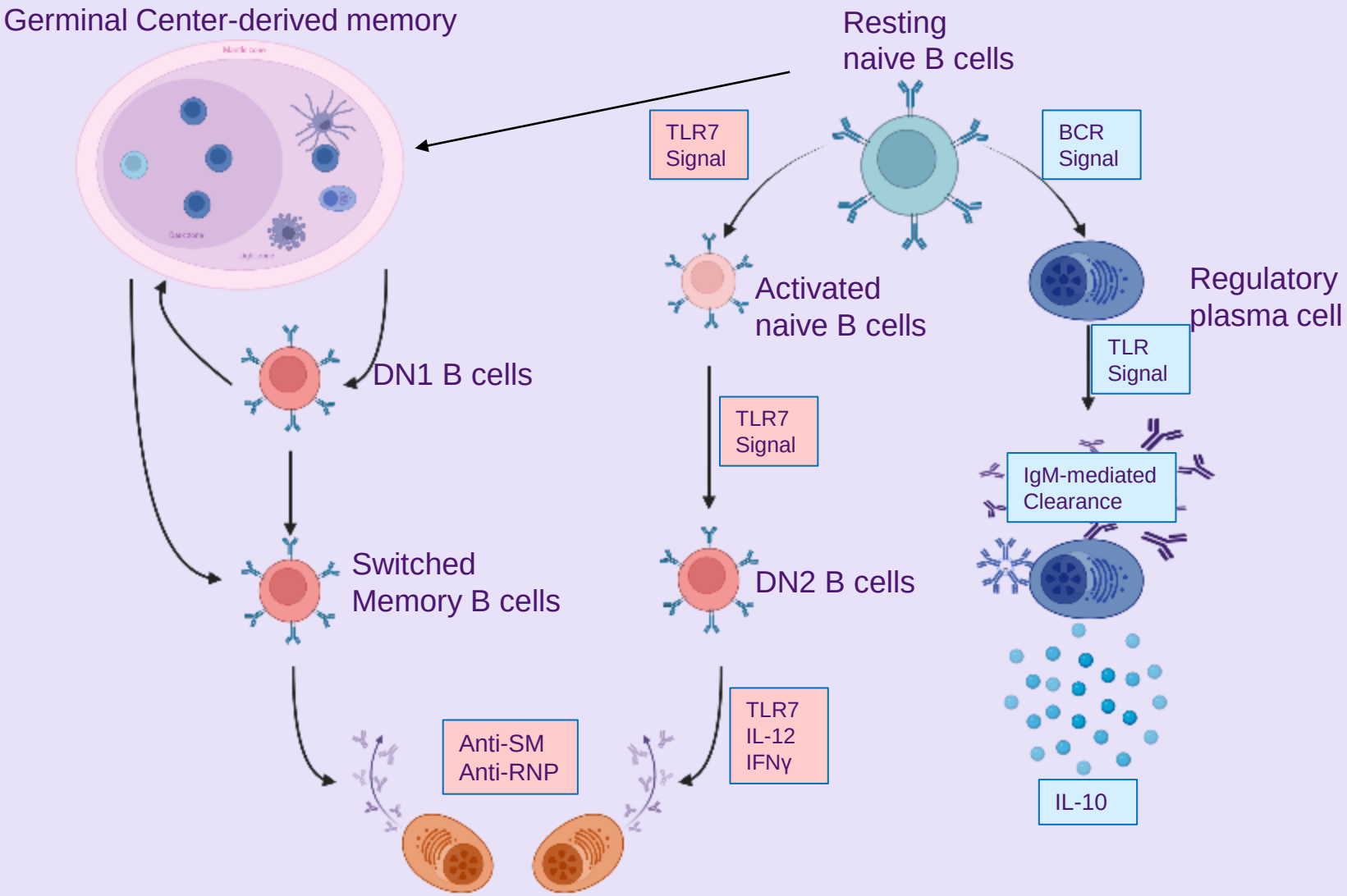


Isotype	IgM	IgG and subclasses	IgE	IgA
Effector Function	Complement Activation	FcR-dependent phagocytosis Complement activation Placenta transfer	Helminth immunity Mast cell degranulation	Mucosal Immunity

Immune Complexes Characteristic of SLE Fix and Consume Complement

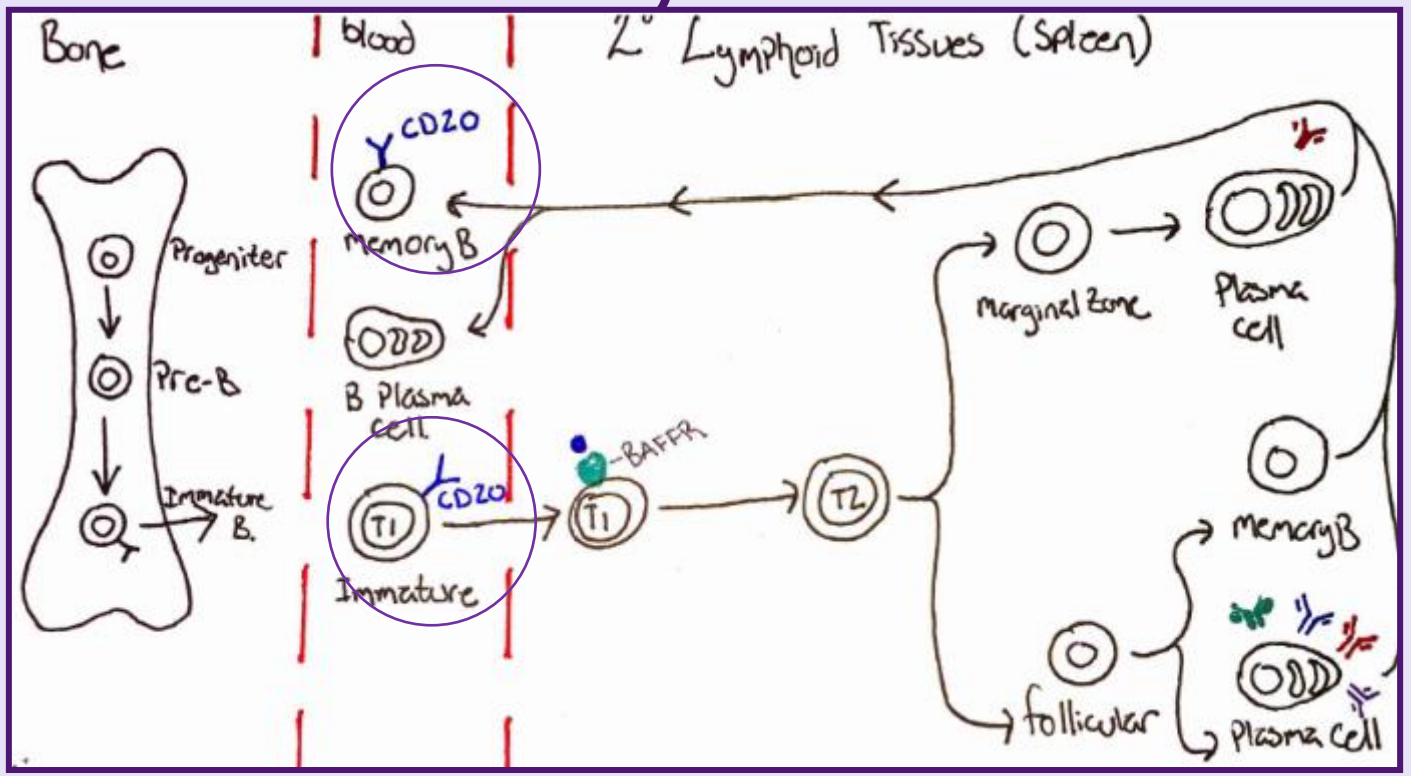


Unique Pathologic B Cell Subsets Characterize SLE



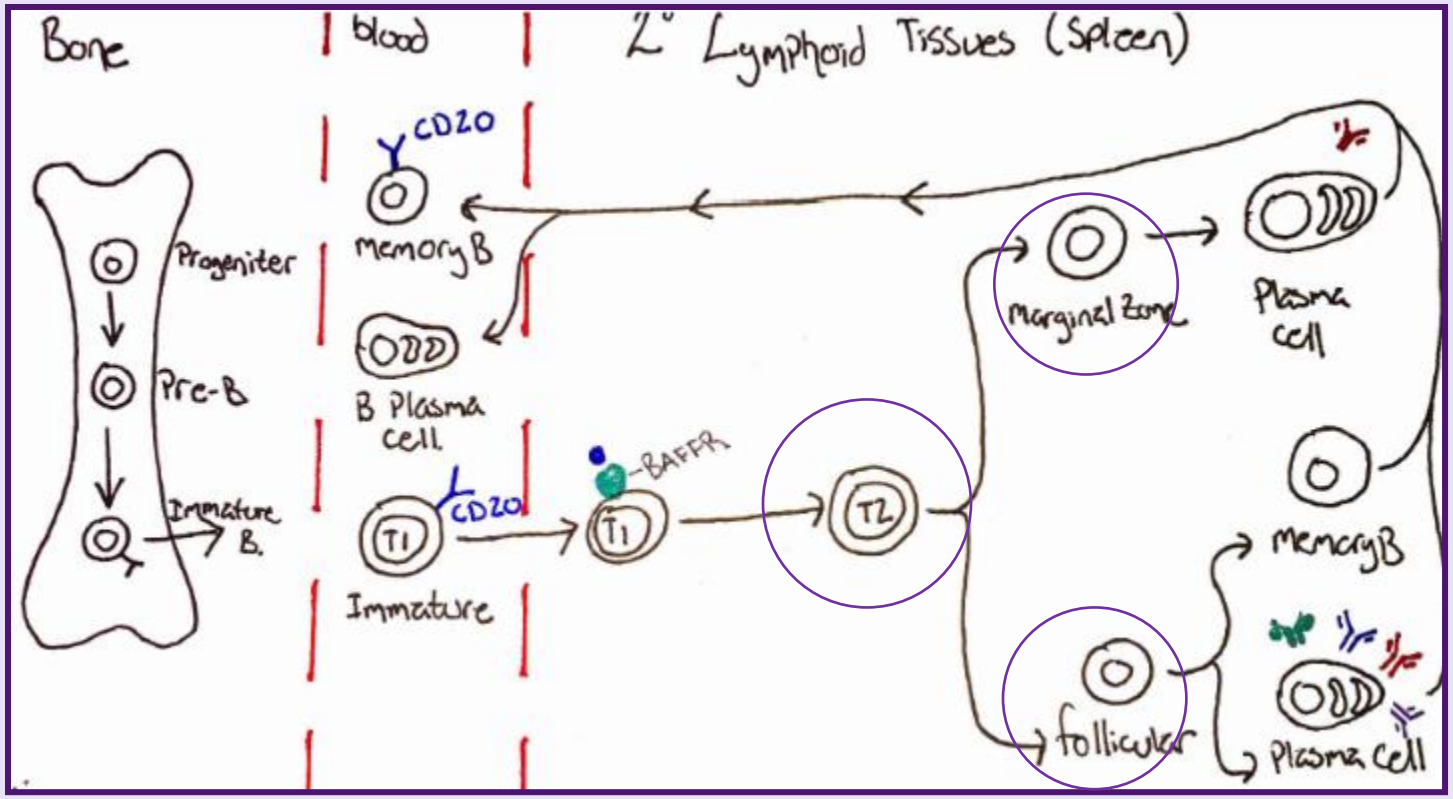
- Two pathways generate pathogenic plasma cells
  - Germinal center
  - Extrafollicular
- Pathologic B-cell production is TLR7 dependent
- Resting naïve B cells can also produce regulatory plasma cells

Targeting B Cells with Rituximab: Aim to Reduce Autoantibody Production



- Chimeric anti-CD20 monoclonal antibody
- Reduces circulating Naïve B cells and Memory B cells
- Spares Plasma cells
- Incomplete clearance of Transitional, Marginal Zone, Germinal Center

Targeting B Cells with Benlysta: Aim to Reduce Autoantibody Production



- B-Cell Activating Factor
- Stimulates B cell proliferation and differentiation
- Blockade better targets transitional, follicular, and marginal zone B cells

Anti B-cell Therapy: Where Did We Go Wrong?

- B cells are central to SLE pathogenesis (autoantibody production, T-cell activation, co-stimulatory effect, etc)
- Many open-label trials show efficacy with rituximab
  - Meta-analysis of 11 (201 patients) open-label LN trials using rituximab
  - Pooled CR: 36.1% (95% CI: 25.2–48.6%)
  - Pooled PR: 37.4% (95% CI: 28.5–78.8%)

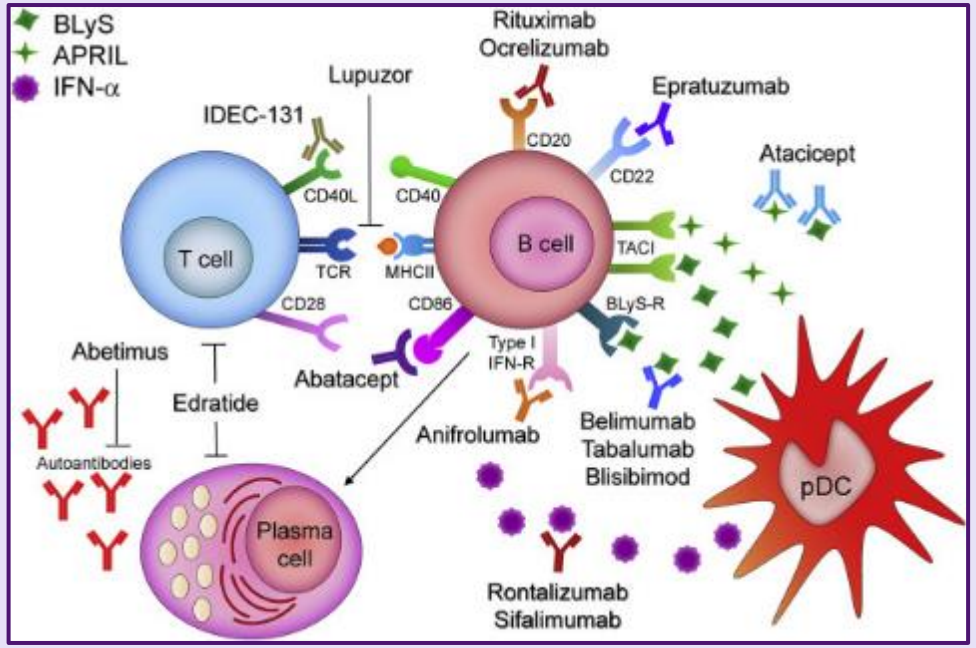
The Graveyard of Failed B-Cell Targeted Therapy RCTs

ALLEVIATE **EMBRACE** **ACCESS**

BELON G **LUNAR**

CALLIBRATE **RITUXILUP**

EXPLORER



Duxbury B et al. *Lupus.* 2013;22:1489-503; Gatto M et al. *J Autoimmun*. 2016;74:94-105.

Urine Studies

Gen

- Yellow, cloudy
- Spec Grav: 1.012

Sediment

- WBC: 12
- RBC: 18
- Protein: 3+

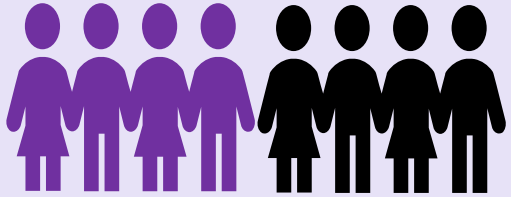
Casts

- 9 RBC casts
- 5 WBC casts

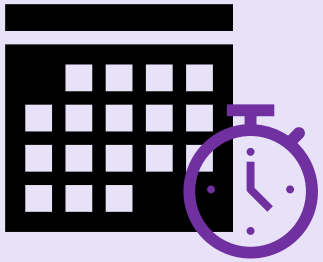
Urine Protein: How much is too Much?

- Normal urine protein over 24 hours
  - 150-500mg (normal-ish)
  - Spot urine protein/creatinine ration: >500mg/g

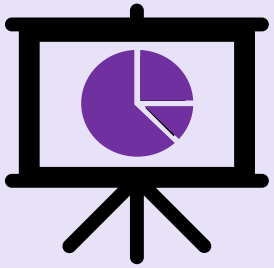
Lupus Nephritis Burdens and Outcomes



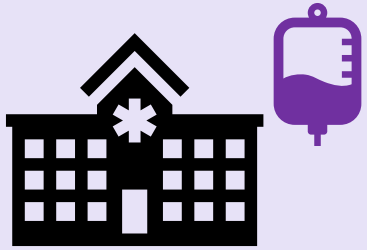
50-60% of patients with SE develop **lupus Nephritis (LN)**



Most patients develop LN within **5 years** of diagnosis



Fewer than 40% achieve **complete remission** after 1 year of treatment



Up to **30%** of people with LN progress to **ESRD**

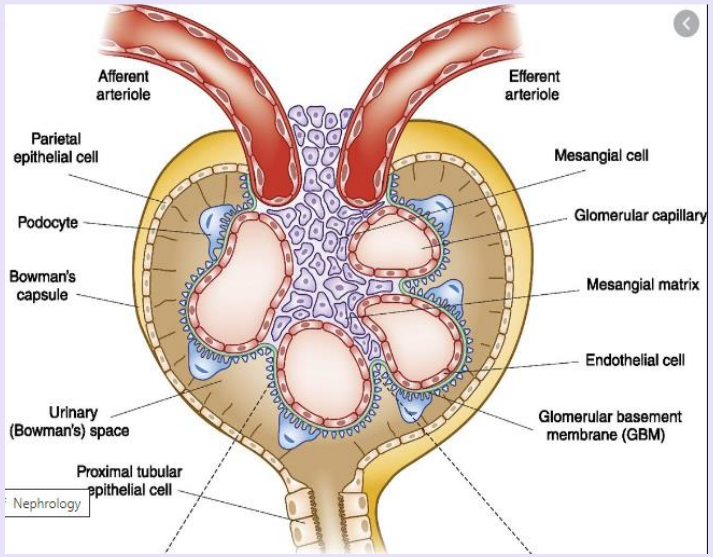
ISN/RPS Classification of Lupus Nephritis

- **Class I** Minimal Mesangial LN
- **Class II** Mesangial Proliferative LN
- **Class III** Focal LN
- III (A): Active lesions: Focal Proliferative LN
- III (A/C): Active and chronic lesions
- III (C): Chronic inactive lesions with scars
- **Class IV Diffuse LN**
- IV-S (A): Active lesions: Diffuse Seg. Prolif. LN
- IV-G (A): Active lesions: Diffuse Global Prolif.LN
- IV-S (A/C): Active and chronic lesions
- IV-G (A/C): Active and chronic lesions
- **Class IV-S** (C): Chronic inactive lesions with scars
- IV-G (C): Chronic inactive lesions with scars
- **Class V** Membranous LN
- **Class VI** Advanced Sclerotic LN

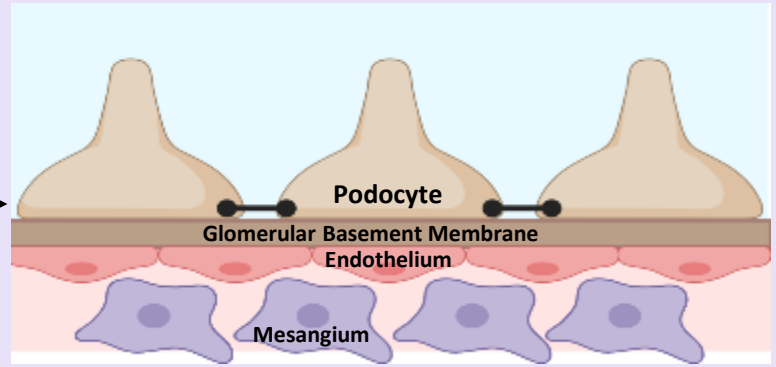
Lupus Nephritis Disease Mechanisms in the Kidney Parenchyma

- IgG, IgM, IgA deposition and complement activation
- Glomerular disease
  - Mesangial inflammation and expansion
  - Sub-endothelial (III and IV) immune complex deposition
  - Sub-epithelial (V) immune complex deposition
- Tubular-interstitial disease
- Perivascular injury

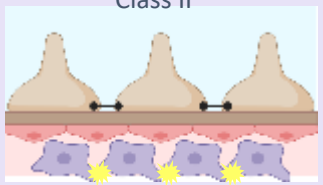
Schematic: Lupus Nephritis Classes Requiring Treatment



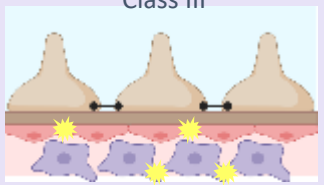
Glomerular filtration unit



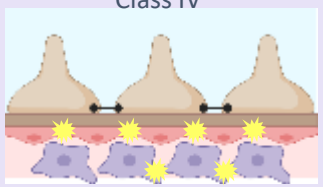
Class II



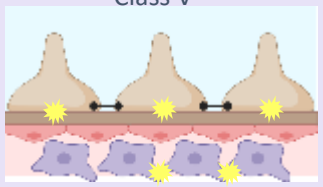
Class III



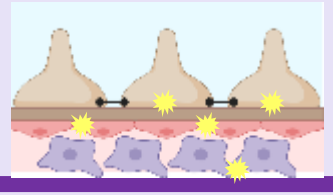
Class IV



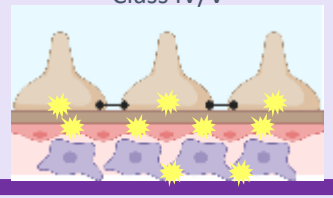
Class V



Class III/V



Class IV/V



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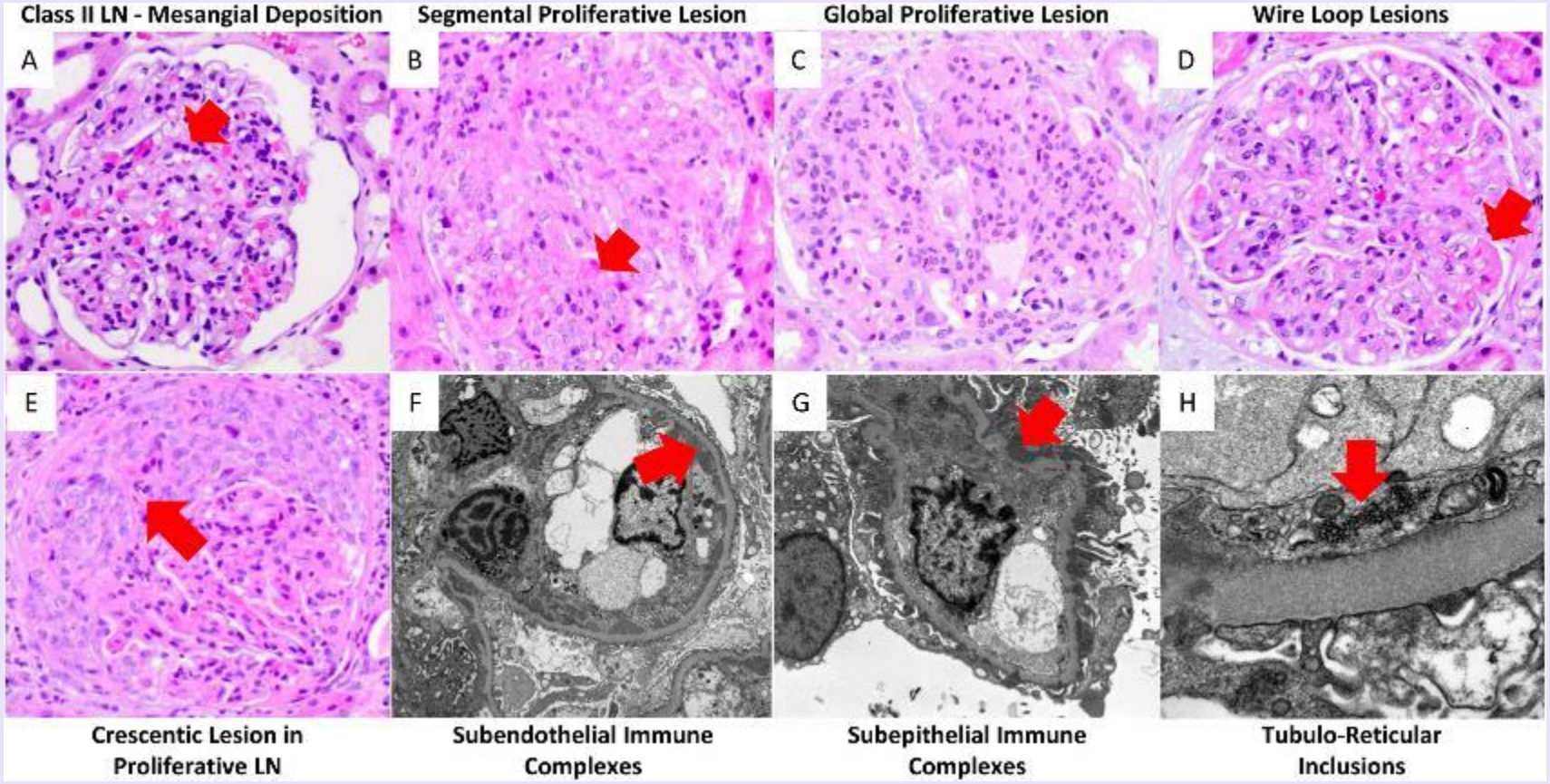
Common Renal Pathology Findings in LN



Back to Our Patient: Diagnosis of Lupus by Criteria

- Malar Rash
- Neurologic Disorder
- Nephritis←
- Arthritis
- Hematologic Disorder
- Immunologic Disorder
- Serositis
- ANA


Thank You!!