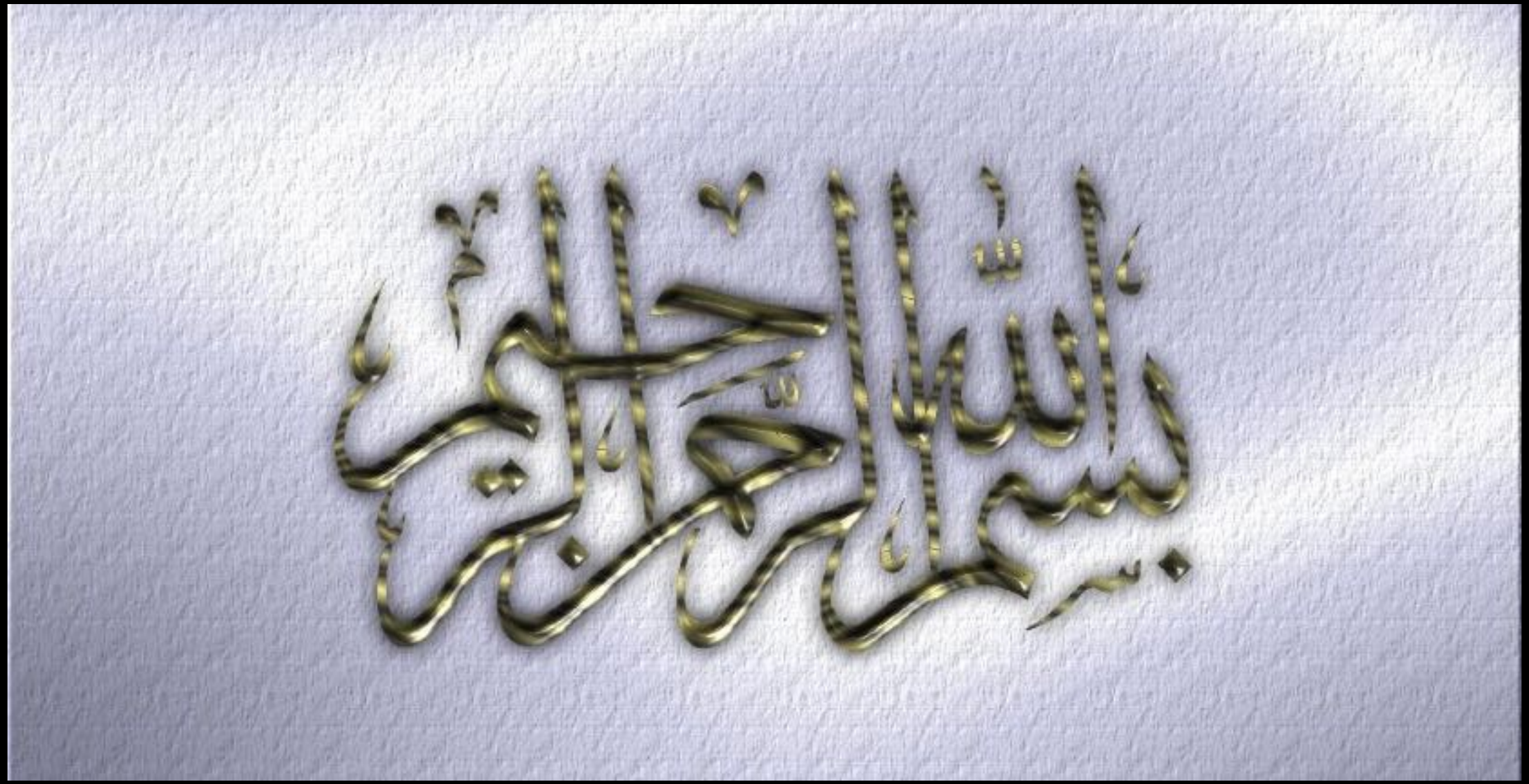
بسم الله الرحمن الرحيم

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UNIVERSITY

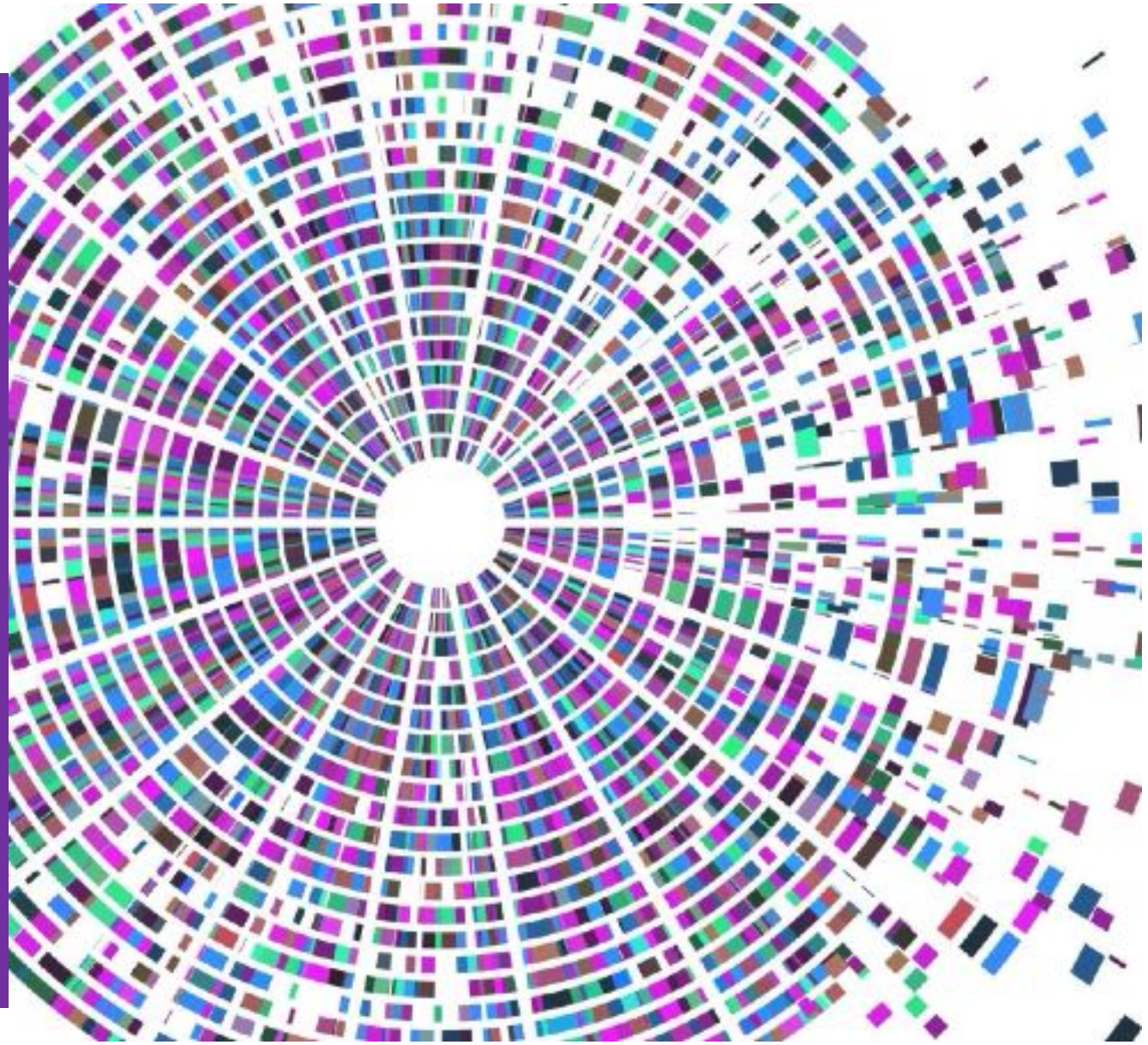
Lupus Nephritis

Complement system

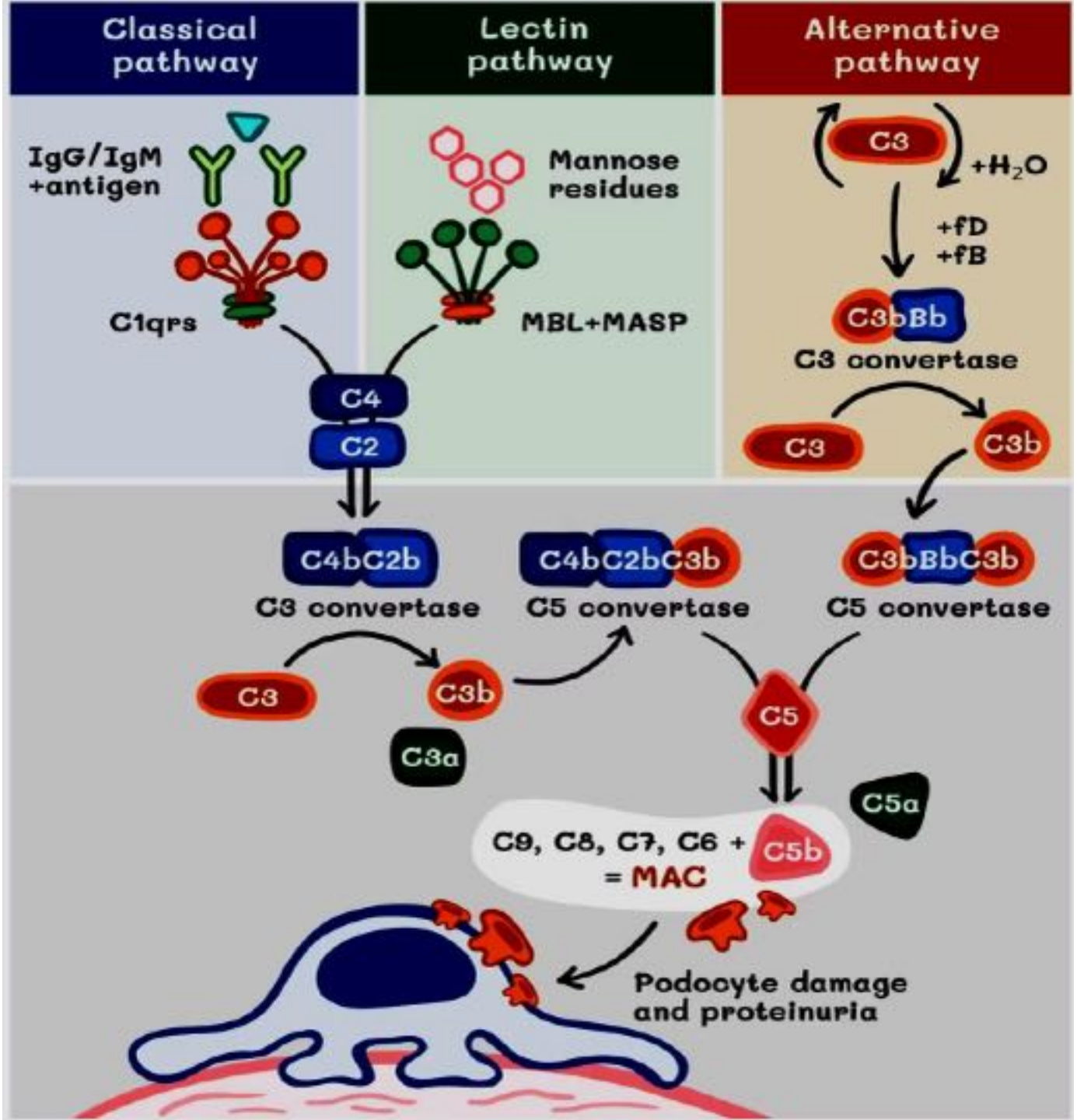
Central pathogenic role

and a useful disease marker.

Complement is the guardian of the intravascular space.
It works within seconds.
The speed with which it can activate and amplify is amazing.
It is a quick recognition system coupled to a powerful destructive force.



Early complement
(C1q, C2, C4) =
tolerance
&
susceptibility



Late complement
(C3, C5–9) =
inflammation
&
injury

ISN KI REPORTS

Figure by @CTeodosiu

Functions of the complement system

TOLERANCE	CLEARANCE
T – Tolerance to self	**C** – Clears immune complexes
O – Own cells spared	**L** – Labels debris (C3b)
L – Limits complement activation	**E** – Eliminates apoptotic cells
E – Endogenous cell protection	**A** – Aids phagocytosis
R – Regulatory (DAF, CD59)	**R** – Removes waste
A – Avoids self-damage	**A** – Assists macrophages
N – No MAC on host cells	**N** – Non-inflammatory cleanup
C – Controlled activation	**C** – Circulation cleanup
E – Ensures self-safety	**E** – Efficient resolution

Classical Pathway

Antibodies bind antigens to initiate

Lectin-Binding Pathway

Mannose-binding lectins bind bacterial carbohydrate motifs to initiate

Alternative Pathway

Initiation is spontaneous and continuous

C1q → prevents autoimmunity

C3 Convertase

C3b → mostly protective (clearance of IC)

C5 Convertase

C5a → mostly pathogenic (inflammation & damage)

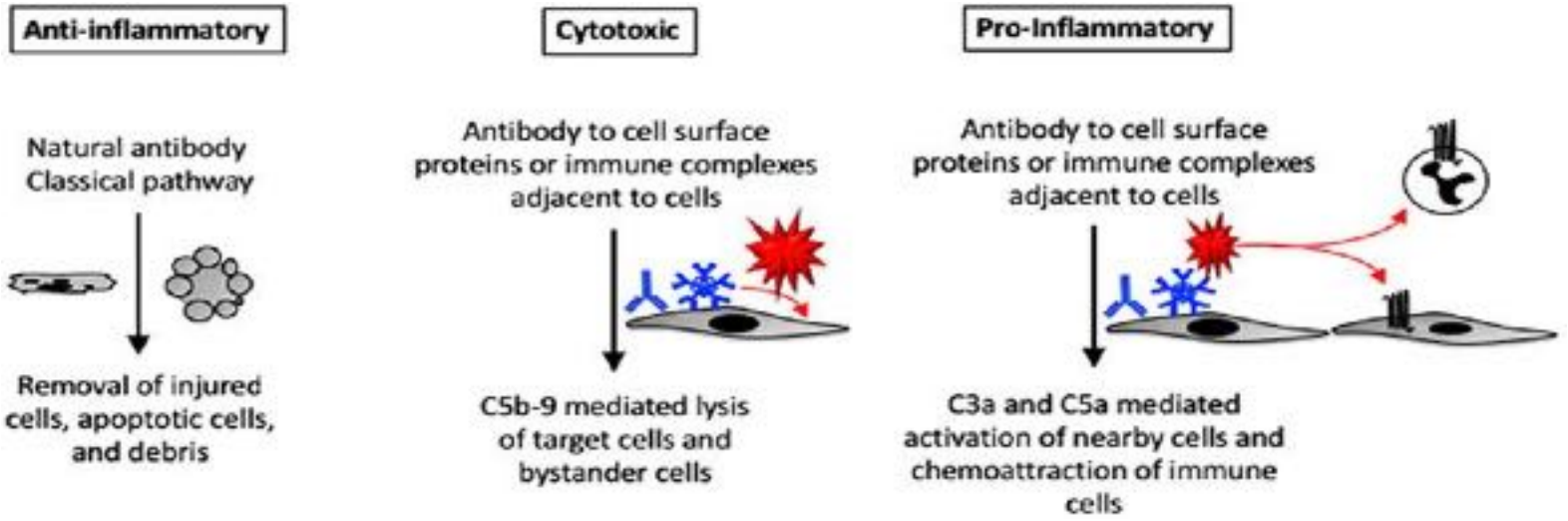
C5b (initiates MAC formation)

Membrane attack complex

@ghobby

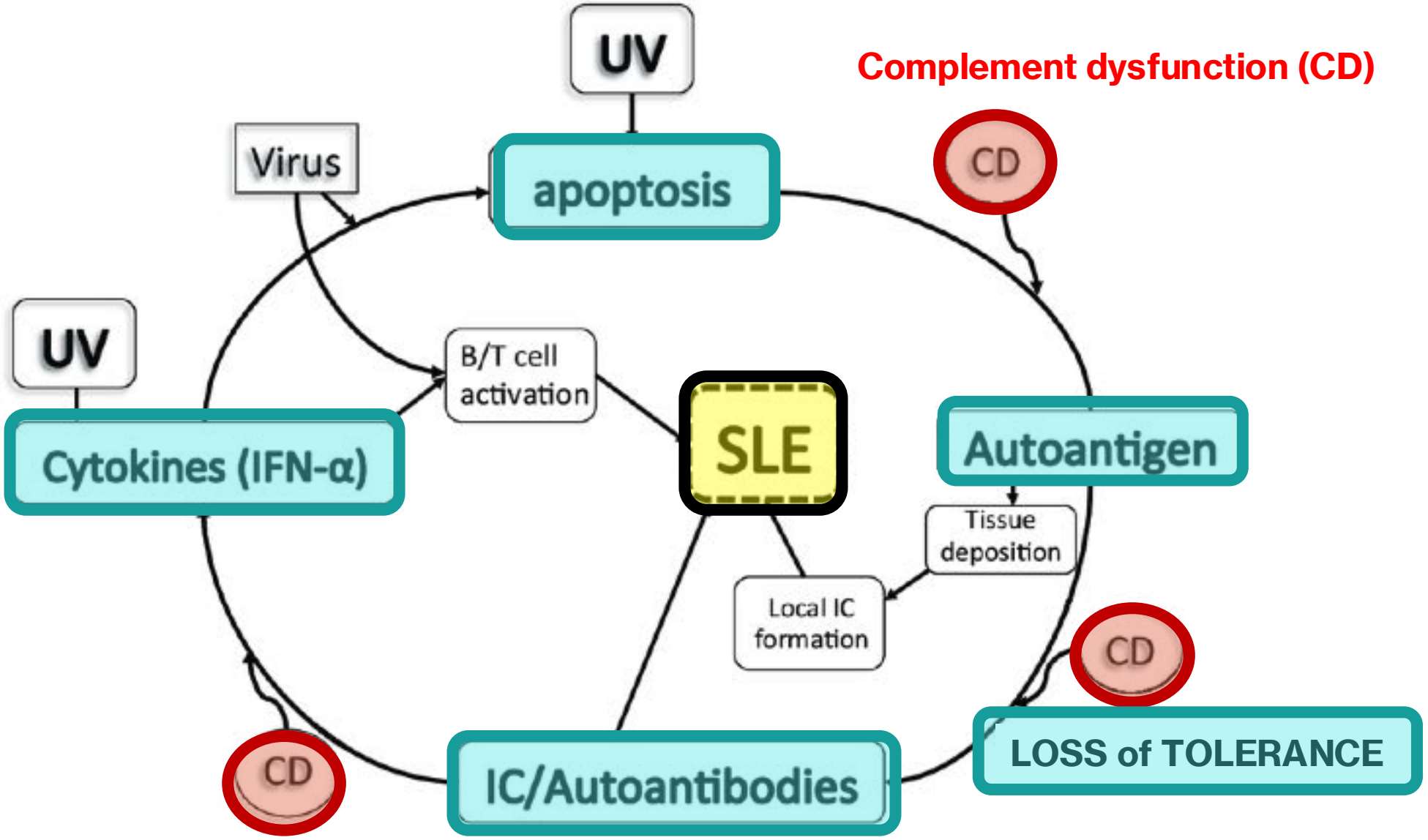
LUPUS PARDOXE

It is a quick recognition system coupled to a powerful destructive force.



LUPUS PARDOXE

SLE and Serum Complement: Causative, Concomitant or Coincidental?



The Open Rheumatology Journal 2017, 11(1):113-122. DOI:10.2174/1874312901711010113

The complement system has a PARADOX in SLE

Protection

Disease exacerbation
Disease manifestations

The complement system has a PARADOX

Causing lupus
or
Preventing it

“Immunology Paradoxes”

Tolerance

Normal cell turnover

↓

Apoptotic cells release nuclear debris (DNA, histones)

↓

Early complement activation (C1q → C4 → C2)

↓

Complement opsonizes apoptotic debris

↓

Macrophages clear debris silently (no inflammation)

↓

Nuclear antigens are NOT presented to immune system

↓

Self-tolerance maintained

↓

NO LUPUS

Autoimmune

Complement deficiency (↓ C1q / C4 / C2)

↓

Impaired clearance of apoptotic debris

↓

Accumulation of nuclear antigens

↓

Dendritic cells present nuclear antigens

↓

Loss of self-tolerance

↓

Autoantibody production (anti-dsDNA, anti-Sm)

↓

Immune complex formation

↓

SLE


THIS WAY
THAT WAY
CONFUSED

How complement prevents lupus

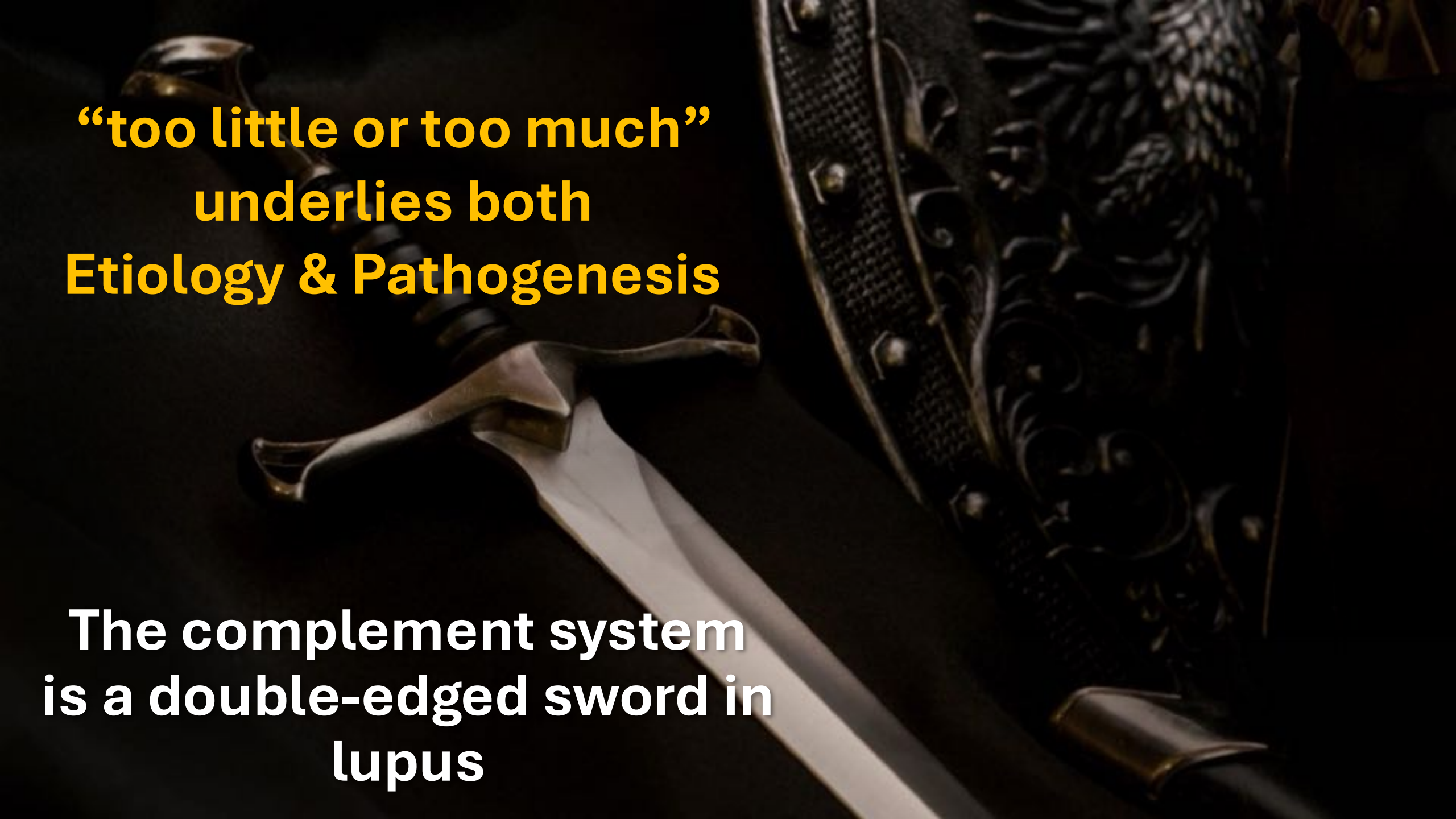
C1q, C2, and C4 — are crucial for immune selfcare.

1. **Silent Clearance of apoptotic cells**
   When cells die normally, they release nuclear debris (DNA, histones). Complement tags this debris so macrophages can remove it *quietly*.
2. **Maintaining self-tolerance**
   Efficient clearance prevents nuclear antigens from being seen by the immune system as “foreign.”
3. **Suppressing autoreactive B cells**
   Complement-coated immune complexes send inhibitory signals that help prevent autoantibody production.

How complement causes or worsens lupus

Once lupus has started, complement reverse roles

- Immune complexes (anti-DNA antibodies + nuclear antigens) form
- These complexes activate complement continuously
- This leads to:
  - C3a and C5a → potent inflammatory mediators
  - C5b-9 (MAC) → direct tissue injury


“too little or too much”
underlies both
Etiology & Pathogenesis
The complement system
is a double-edged sword in
lupus

Double-edged sword in lupus

1

On one hand, in its absence, systemic autoimmune disease develops.

2

Deficiency of C1q, C1r, C1s, C4, or C2, represents a deficiency state that causes lupus.

3

80% of patients with a total C1q or C4 deficiency develop SLE or a lupus-like disease.

Double-edged sword in lupus

1

On the other hand, complement activation .

2

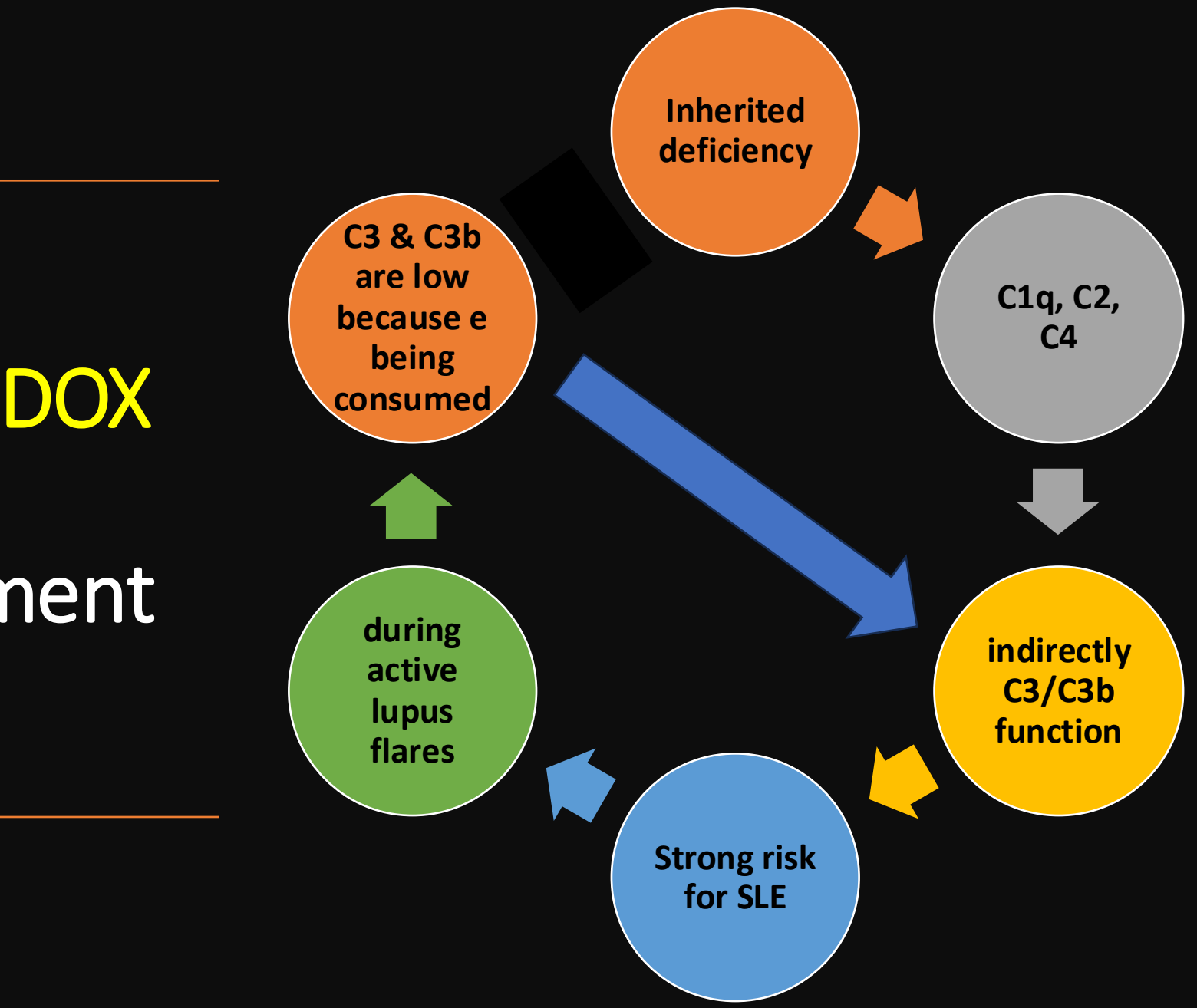
As a result of the abundant immune-complexes characteristic of SLE .

3

Glomerular inflammation, damage and lupus nephritis.

LUPUS PARADOX

low complement

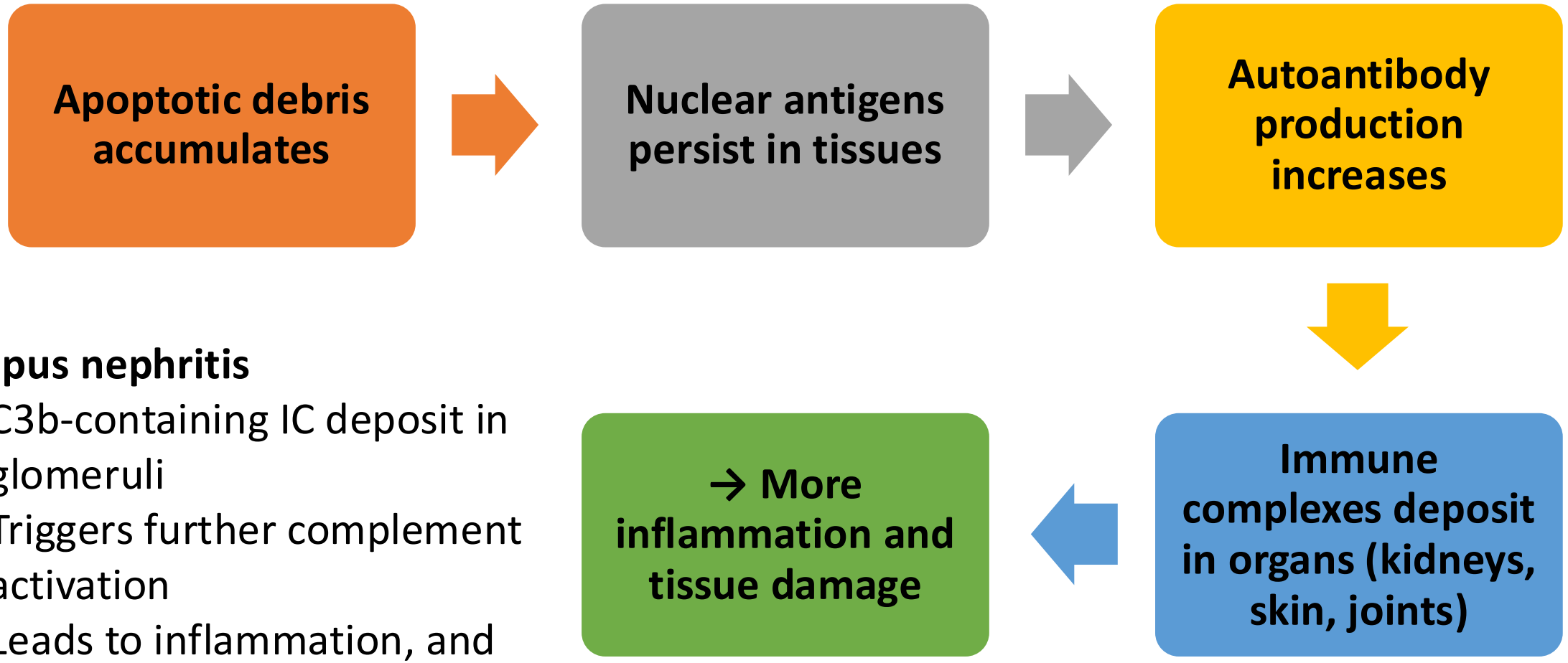


C3b plays a protective; but paradoxical role.

When works properly, it helps *prevent flares*; when it's deficient or dysregulated, lupus gets worse.

C3b normally protects against lupus by clearing IC & apoptotic cells, but when it's deficient or overconsumed, IC accumulate and drive inflammation—worsening SLE.

If C3b is insufficient or dysfunctional

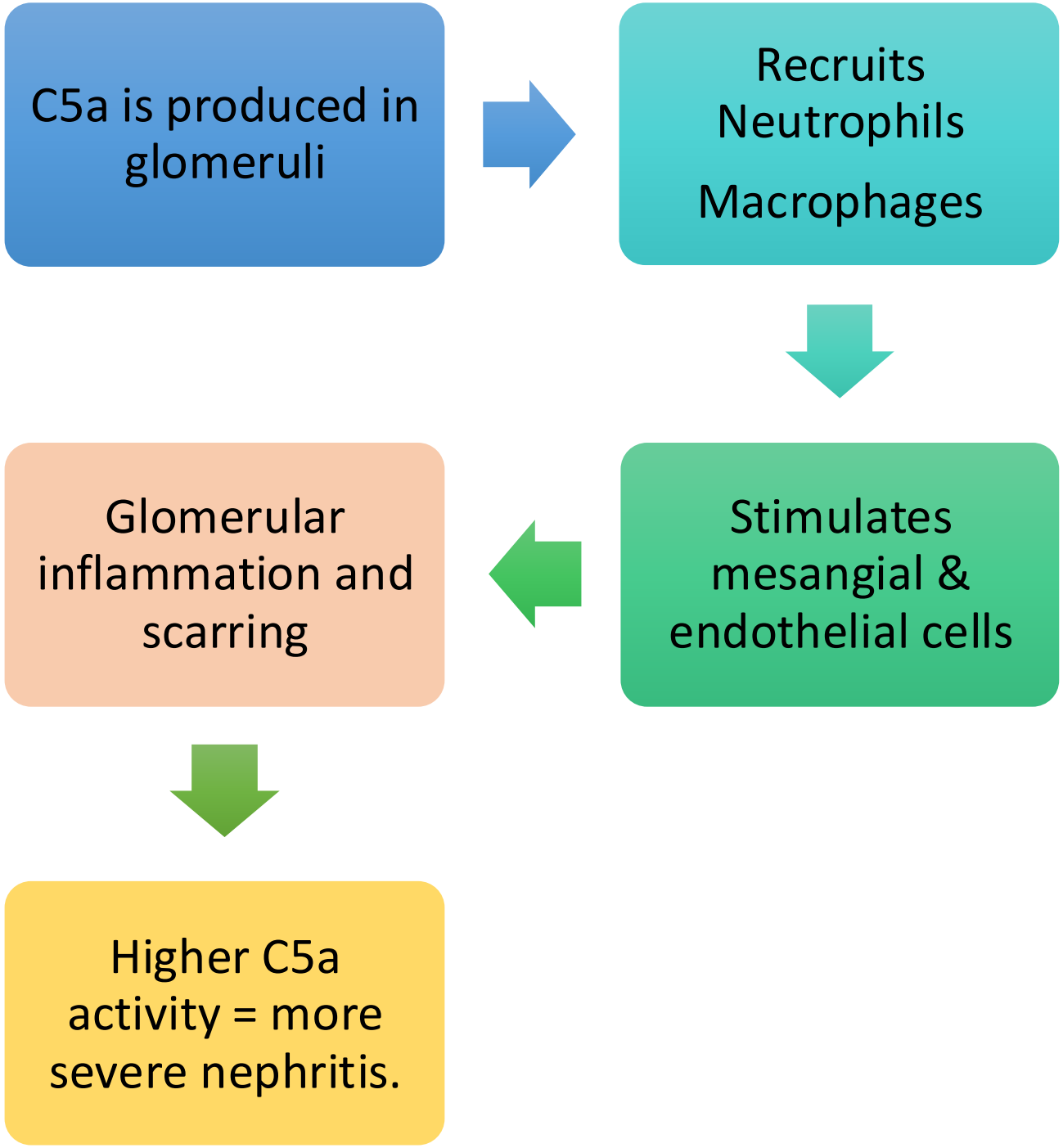


In lupus nephritis

1. C3b-containing IC deposit in glomeruli
2. Triggers further complement activation
3. Leads to inflammation, and kidney damage

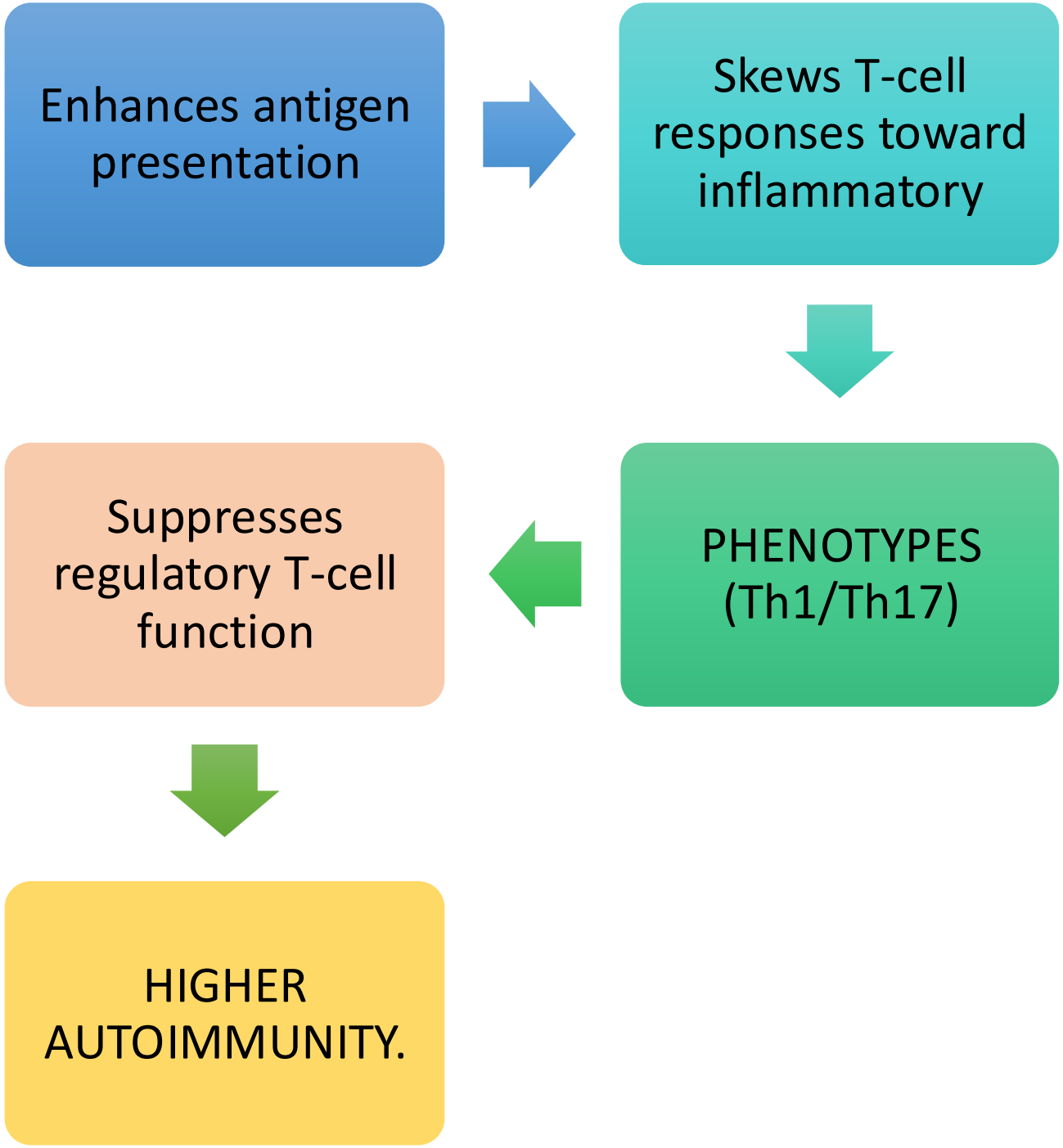
C5a ⟶ Key player in lupus nephritis

It is the major inflammatory driver



C5a ⟶ Key player in lupus nephritis

AMPLIFIES AUTOIMMUNITY



C5a acts not only on immune cells but also on kidney resident cells

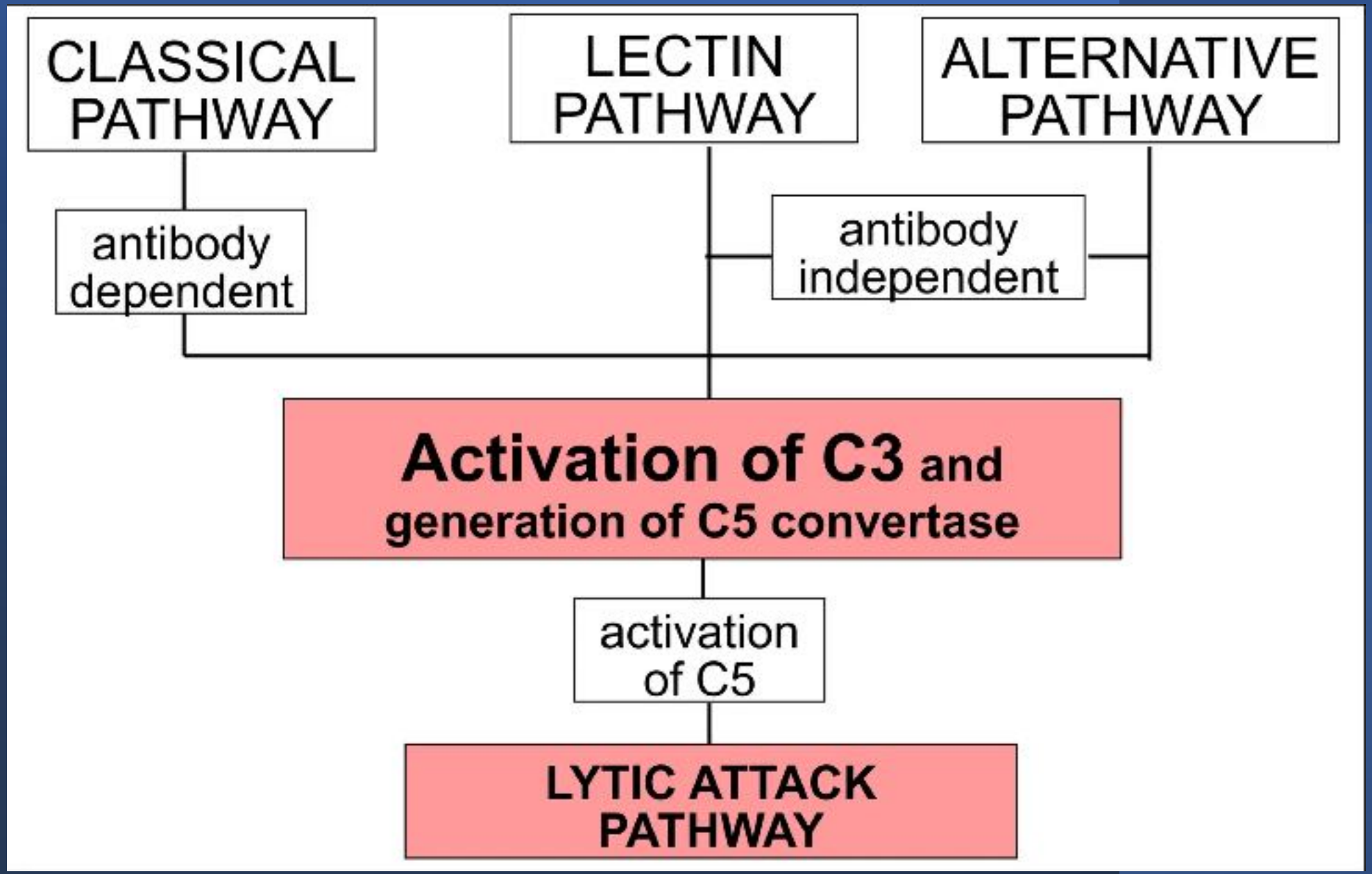
Mesangial	Podocytes	Tubular
Increased cytokine and chemokine production	INJURY	INFLAMMATION
PROLIFERATION	LOSS	FIBROSIS

Complement in Lupus

1. Classical pathway — THE MAIN ONE

2. Alternative pathway — Amplifies injury

3. Lectin pathway — Minor role ????


CLASSICAL PATHWAY
LECTIN PATHWAY
ALTERNATIVE PATHWAY
antibody dependent
antibody independent
Activation of C3 and generation of C5 convertase
activation of C5
LYTIC ATTACK PATHWAY

Role of Complement in SLE Pathogenesis

- Genetic Risk Factors
- Autoantibody Production
- Disease Manifestations
- Biomarkers for Diagnosis & Monitoring

Complement in SLE

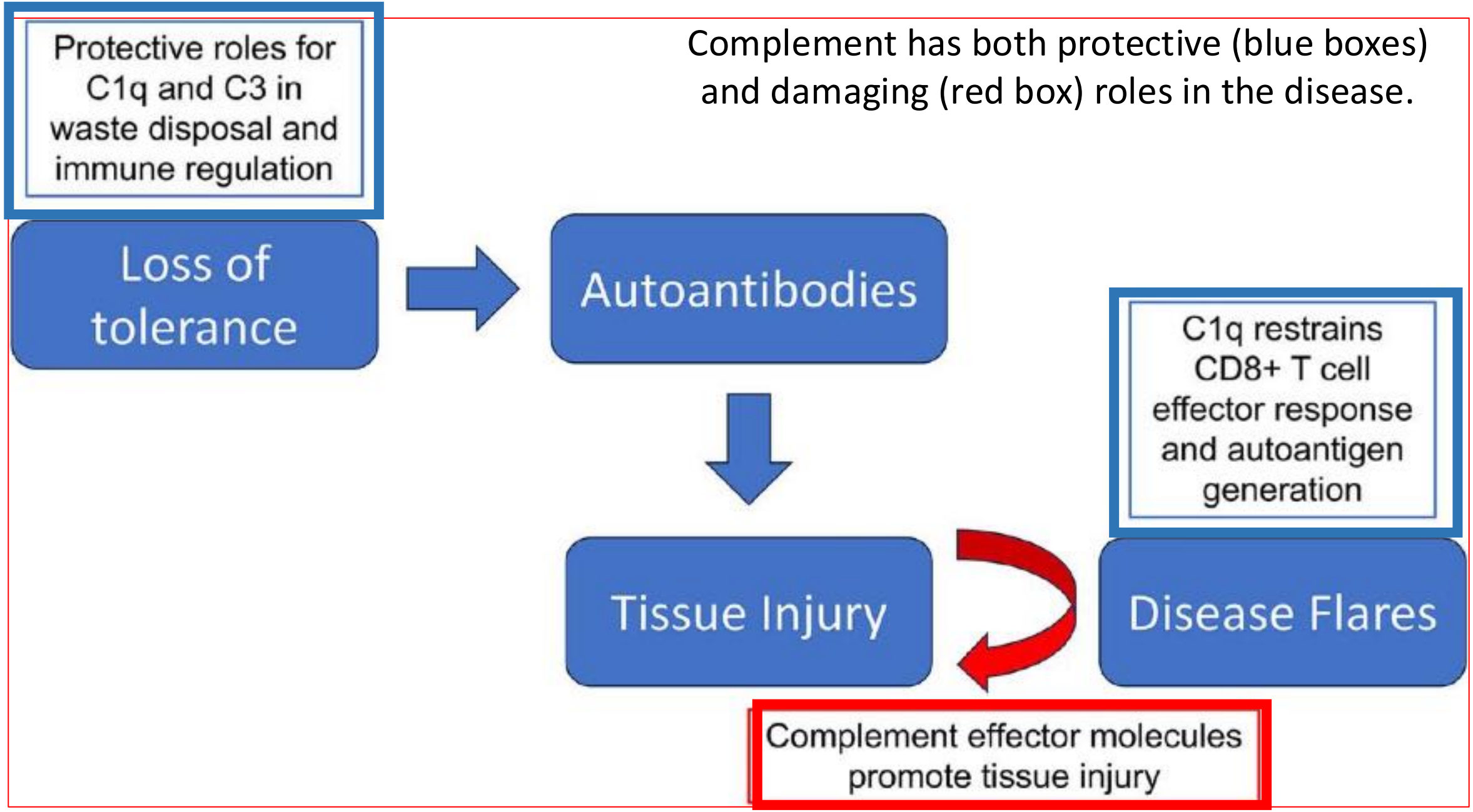
- **LOSS OF TOLERANCE**
- **AUTOANTIBODY PRODUCTION**
- **INTERFERON-DRIVEN AMPLIFICATION**
- **IMMUNE-COMPLEX DEPOSITION**
- **TISSUE INJURY.**

Lupus results from defective clearance of apoptotic nuclear debris

Classical pathway and lupus nephritis

Autoantibodies	(anti-dsDNA, anti-C1q) form IC
C1q binds IC	→ C1r & C1s → activates C4 & C2 → C3 convertase
C3 convertase C3 → C3a + C3b	• C3b opsonizes immune complexes • C3a is an inflammatory mediator
Downstream C5 → C5a + C5b	C5b helps form MAC → glomerular cell injury

Complement has both protective (blue boxes) and damaging (red box) roles in the disease.



Matthew C Pickering and Marina Botto Eur. J. Immunol. 2024;54:2350918, DOI: 10.1002/eji.202350918

Complement in Lupus

Core mechanism is failure of apoptotic cell clearance

AUTOANTIBODIES

form

IMMUNE COMPLEXES.

Activate the C-P

Recruitment of Neutrophils Monocytes Macrophages	Opsonization of immune complexes for clearance	Tissue injury via (MAC)

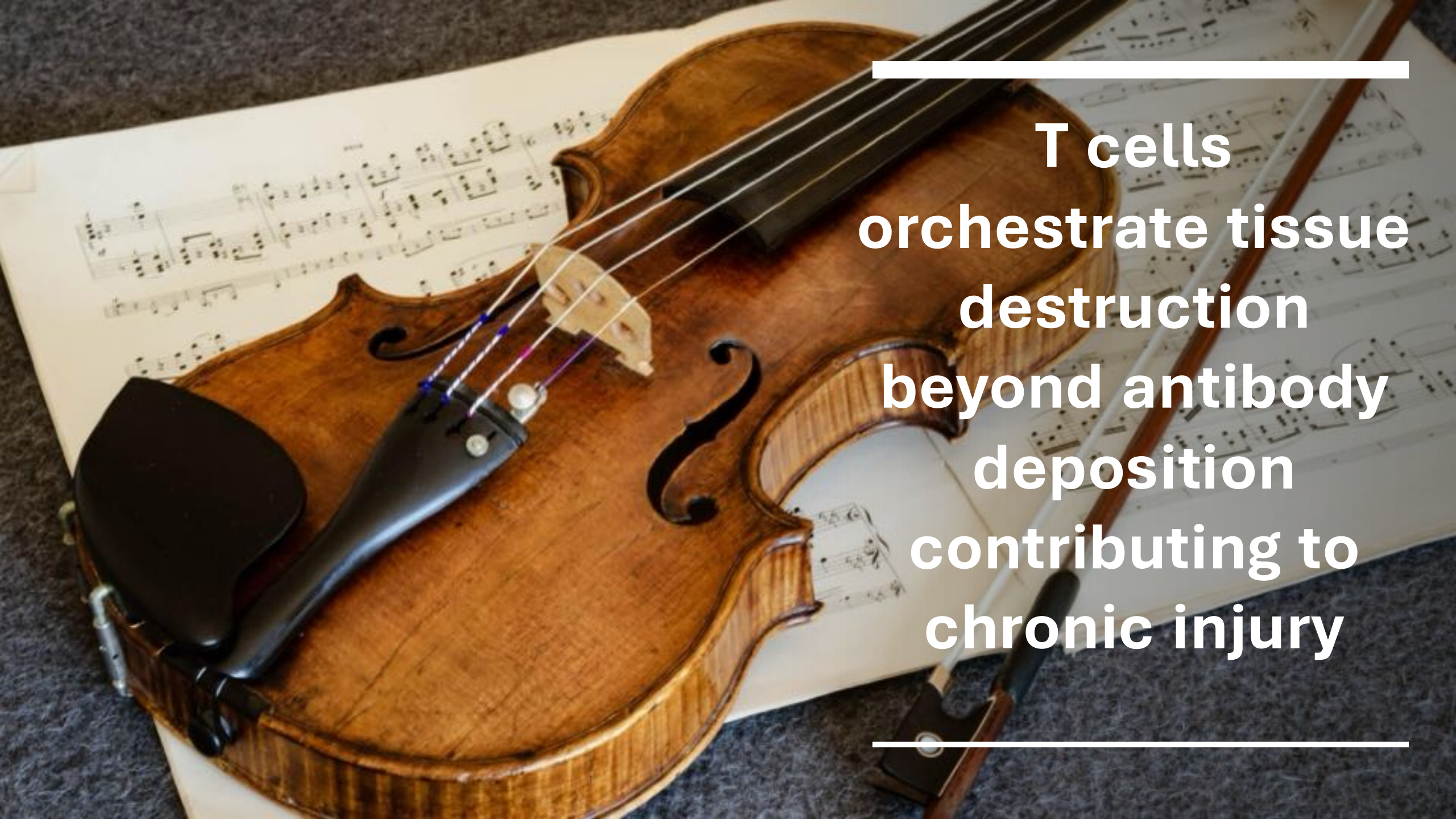
A subtle but important part of lupus immunology

A subtle but important part of lupus immunology

"T CELLS DESTROY"

***T** – **T**-cell help to B cells → autoantibodies*
***C** – **C**ytokines (IFN-γ, IL-17)*
***E** – **E**nhance macrophage activation*
***L** – **L**ure inflammatory cells (neutrophils, monocytes)*
***L** – **L**oss of T-reg suppression*

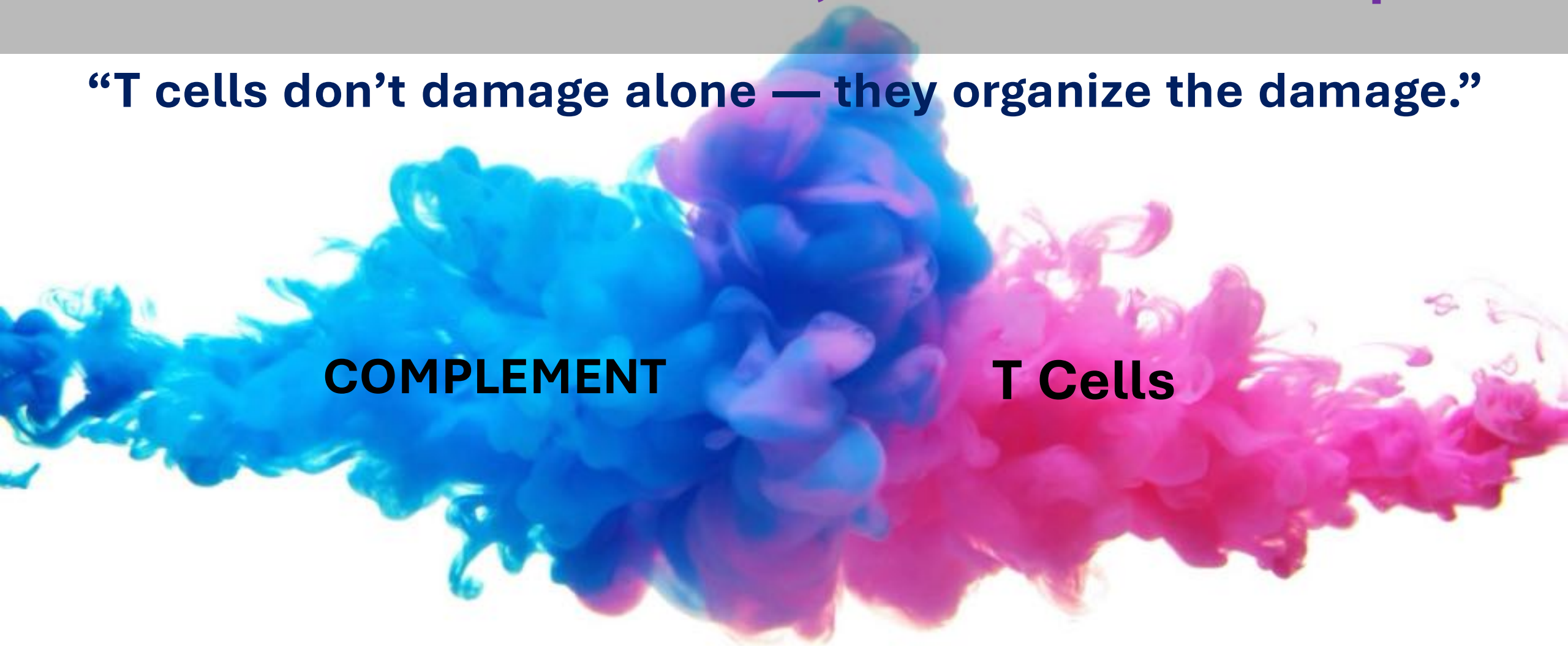
***D** – **D**irect CD8⁺ cytotoxic damage*
***E** – **E**nd-organ immune complex deposition*
***S** – **S**ustain inflammation (IFN-α loop)*
***T** – **T**issue destruction*
***R** – **R**emodeling & fibrosis*
***O** – **O**ngoing autoimmunity*
***Y** – **Y**ielding organ damage*



T cells orchestrate tissue destruction beyond antibody deposition contributing to chronic injury

T cells are the conductors, not the main weapons.

“T cells don’t damage alone — they organize the damage.”



T cells orchestrate tissue damage in lupus by helping B cells make autoantibodies, activating macrophages, recruiting inflammatory cells, and directly injuring tissues.

How COMPLEMENT and T Cells are Connected

Immune complexes + complement activation → T-cell recruitment

C3a & C5a are chemotactic—they attract T cells and other immune cells to the kidney.

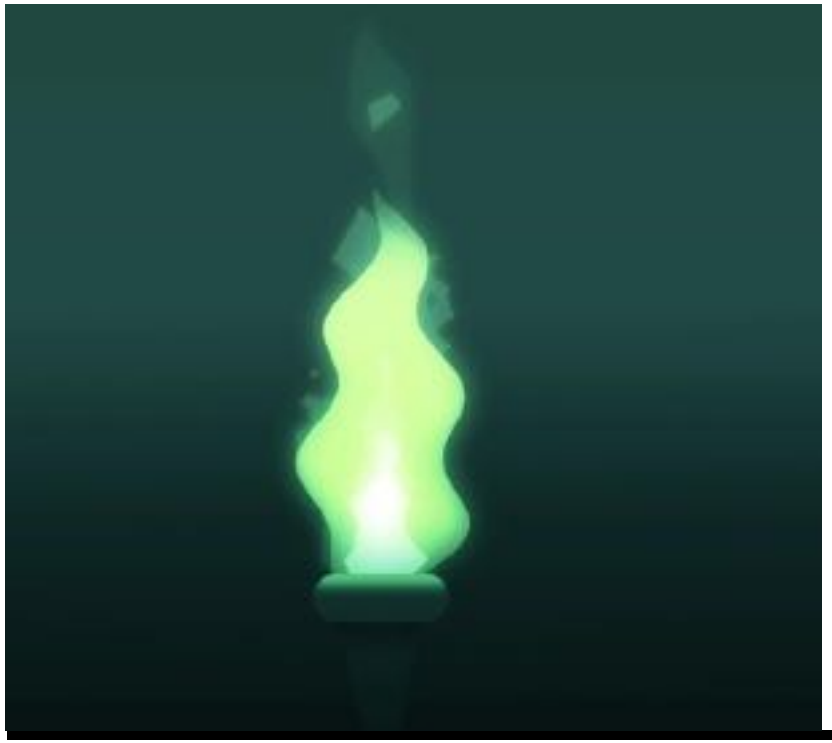
This links antibody-mediated (humoral) injury to cell-mediated injury.

Amplification loop

T cells activate B cells → more autoantibodies → more immune complexes → more complement activation → more inflammation → more T-cell activation.

Autoreactive $CD4^+$ T cells abnormally activate B cells through excessive CD40–CD40L signaling and cytokines (especially IL-21), leading to loss of tolerance and pathogenic autoantibody production.

T-Cell Mediated Tissue Damage



1. Self-antigens trigger the process

- Nuclear self-antigens (DNA, RNA, histones) from apoptotic cells are poorly cleared.
- B cells bind these self-antigens via their BCR and present them on MHC II.

2. Autoreactive $CD4^+$ T cells provide help

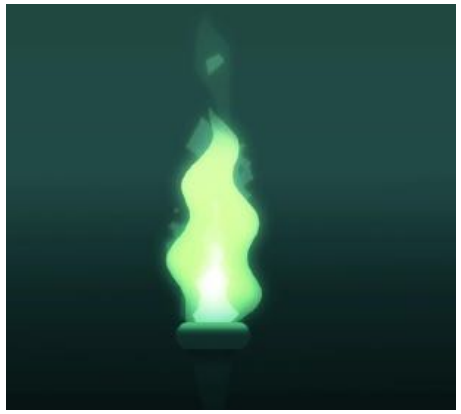
- Tolerance fails, so autoreactive T cells are not deleted or suppressed.
- These T cells recognize self-peptides presented by B cells.

3. Excessive CD40–CD40L signaling

- Lupus T cells overexpress CD40L (CD154).
- Strong CD40 signaling → excessive B-cell activation and survival.

4. Cytokine imbalance favors B cells

T-Cell Mediated Tissue Damage



CD4+ T cells become overactive or dysregulated

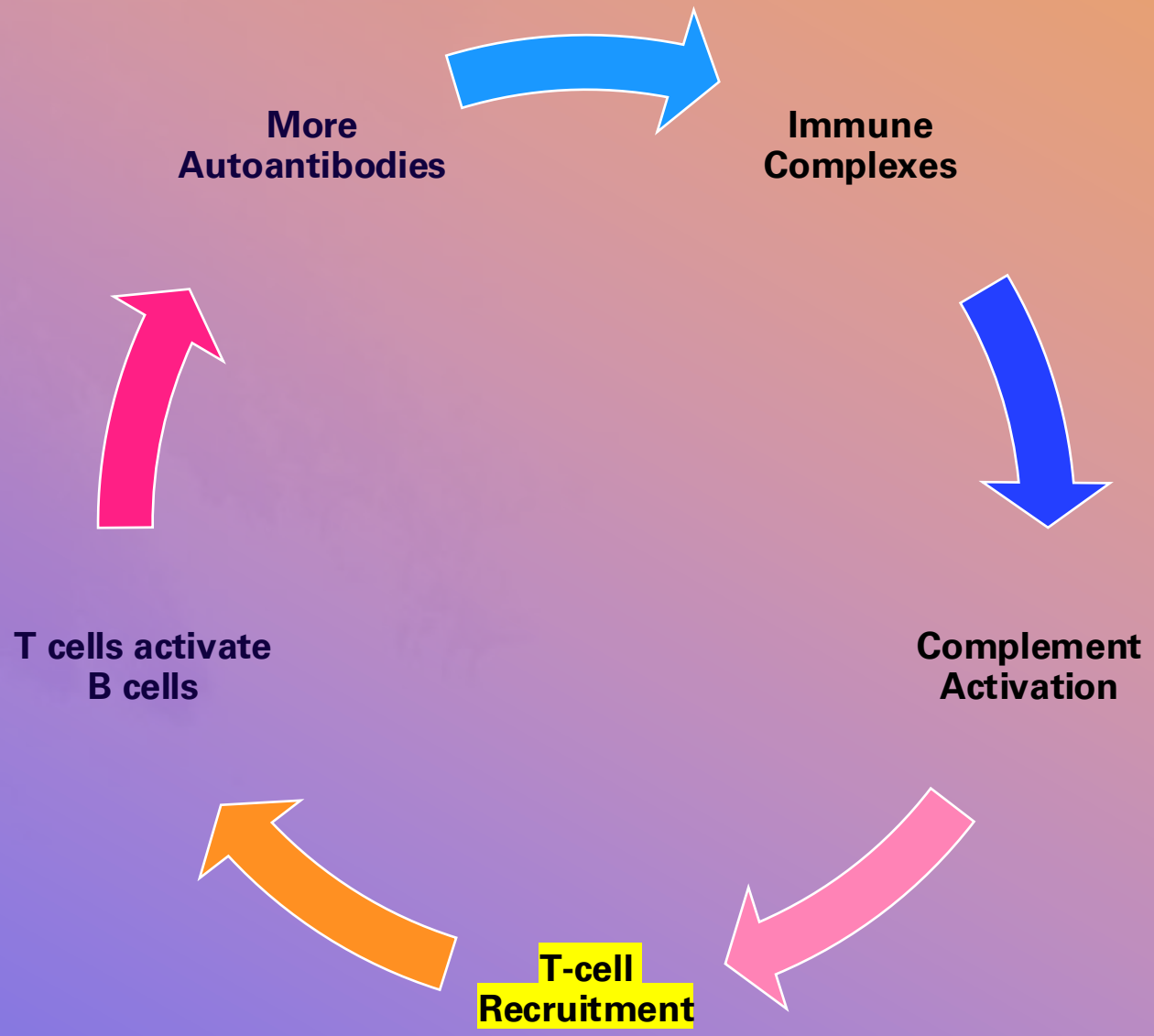
They produce cytokines like IFN-γ, IL-17, and TNF-α.

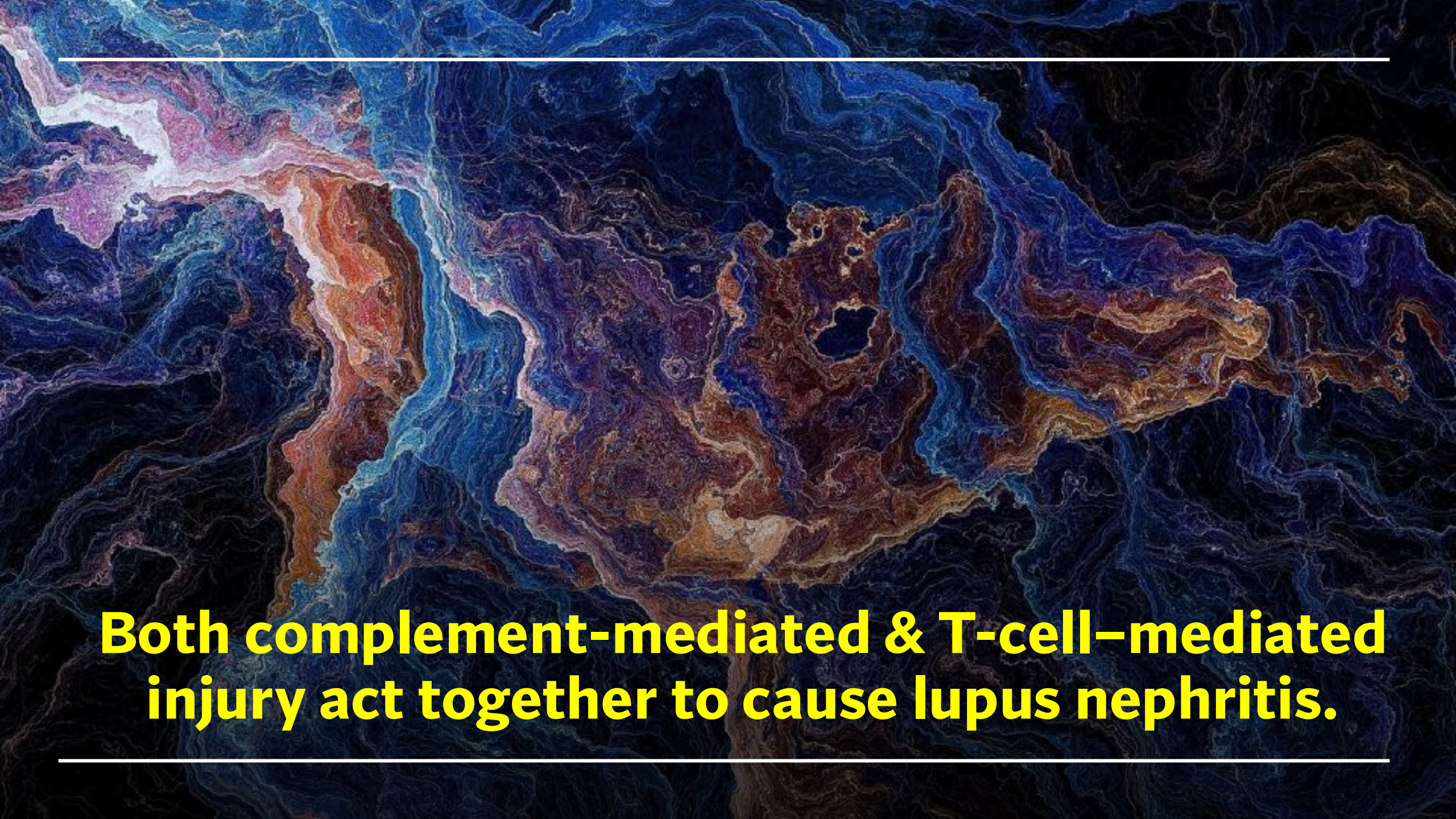
These cytokines:

Activate B cells → more autoantibody production	Recruit macrophages → direct tissue damage	kidney cells to produce inflammatory molecules → fibrosis & glomerular damage

Complement amplifies immune activation by helping self-antigens stimulate B cells and T cells, which fuels autoimmunity.

T cells Orchestrate Tissue Destruction




Both complement-mediated & T-cell–mediated injury act together to cause lupus nephritis.

Pathogenic role as a driver of kidney injury

Immune complex DEPOSITION	**Complement ACTIVATION**	**Inflammatory INJURY**
Autoantibodies form immune complexes These deposit in the **glomeruli** **Mesangial** **Subendothelial** **Subepithelial**	Immune complexes activate classical pathway Leads to consumption of: • C3 • C4	**C3a, C5a** → potent anaphylatoxins Recruit neutrophils & monocytes Increase vascular permeability

Cellular direct injury by MAC

Endothelial cells	Podocytes	Mesangial cells

Light Microscopy

INFLAMMATION,
PROLIFERATION,
FIBROSIS,
SCARRING.

“Full-house” immunofluorescence (classic pathology point)

DEPOSITION

IgG, IgA, IgM

C3

C1q

This full-house pattern reflects extensive complement involvement.

📌 Presence of **C1q** helps distinguish lupus nephritis from many other immune-complex GN

C1q → prevents autoimmunity

C3b → mostly protective (clearance of IC)

C5a → mostly pathogenic (inflammation & damage)

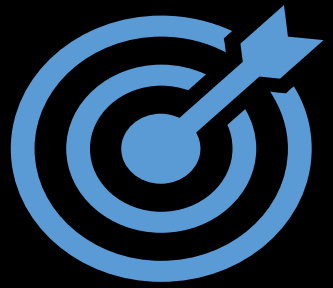
C1q is a key piece of the puzzle

C1q is a major player

IC- CLEARANCE

SITS AT THE CROSSROADS

TOLERANCE



TARGET OF AUTOANTIBODIES

COMPLEMENT ACTIVATION

C1q is a major player

Prevents autoimmunity

Initiates classical activation

Deposits in glomeruli

Target of C1q autoantibodies,

C1q is a major player

1. Defective C1q-mediated clearance of apoptotic nuclear material promotes autoantibody formation

2. IC–bound C1q activates the classical pathway, contributes to glomerular injury & full-house deposition in LN.

C1q = peacekeeper of the classical pathway.

- ❑ C1q binds:
  1. Apoptotic cells
  2. Immune complexes

- ❑ Silent non-inflammatory clearance and maintains tolerance.

- ❑ C1q deficiency or anti-C1q antibodies → impaired apoptotic clearance → SLE

- ❑ Anti-C1q levels correlate with:
  1. Active proliferative LN
  2. Disease flares
  3. Low C3/C4 levels

No C1q

“No C1q = No Cleanup = Lupus”

↓ apoptotic cell clearance

↑ nuclear antigen exposure

↑ immune complexes

↑ autoimmunity

Anti-C1q antibodies

Anti-C1q antibodies

Many SLE patients develop anti-C1q antibodies

Bind to C1q already deposited in glomeruli

Amplify local complement activation

Associated with: Proliferative LN & flares

Rising anti-C1q levels can precede renal flares

Anti-C1q antibodies They cause trouble in two major ways.

1. They block C1q's protective function (lupus initiation side)

Anti-C1q antibodies bind C1q
↓
C1q cannot bind apoptotic debris effectively
↓
Impaired clearance of dying cells
↓
Persistence of nuclear antigens
↓
Loss of self-tolerance
↓
Autoantibody production increases

📌 **This functionally mimics C1q deficiency**,
Strong association of with early disease and flares

2. They amplify complement-mediated inflammation (lupus damage side)

Immune complexes deposit in tissues (esp. kidney)
↓
C1q binds immune complexes
↓
Anti-C1q antibodies bind C1q already fixed in tissue
↓
Formation of C1q–anti-C1q immune complexes IN SITU
↓
Massive classical complement activation
↓
C3a, C5a release + MAC formation
↓
Severe local inflammation and tissue injury

📌 **This is why anti-C1q is strongly linked to lupus nephritis**.

1. Genetic susceptibility

Predisposes to loss of self-tolerance

- HLA-DR2, DR3

Doesn’t cause disease alone

Immune regulation genes (IRF5, STAT4, PTPN22)

Complement deficiencies

- C1q, C2, C4 (very high risk)

Push susceptible individuals over the edge.

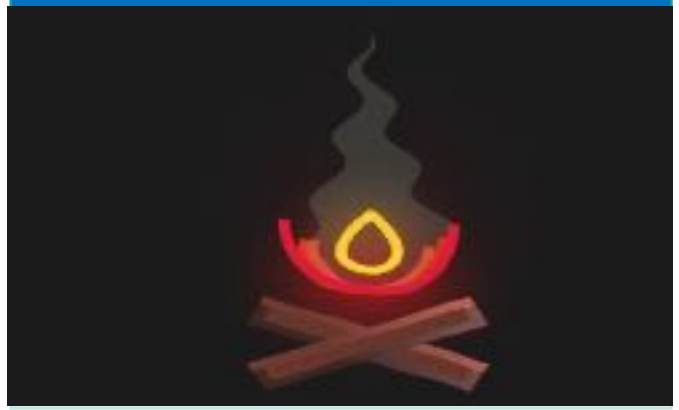
Increase cell death & nuclear antigen exposure.

2. Environmental triggers

Common triggers:

- **UV light → keratinocyte apoptosis**
- **Viral infections (e.g. EBV)**
- **Drugs, hormones (estrogen)**

3. Defective clearance of apoptotic debris

This is a central event.	Normally: (C1q, C4) & Phagocytes	In lupus: Clearance is impaired
	Clear apoptotic cells.	Nuclear material (DNA, histones) persists extracellularly

4. Loss of immune tolerance

5. Type I interferon activation

- ❑ A key amplification loop.
- ❑ Plasmacytoid dendritic cells detect DNA/RNA via TLR7/9
- ❑ Produce large amounts of IFN-α

- **IFN-α:**
    1. Activates B cells
    2. Enhances antigen presentation
    3. Sustains autoimmunity
- **This is the “interferon signature” of lupus.**

6. Autoantibody production

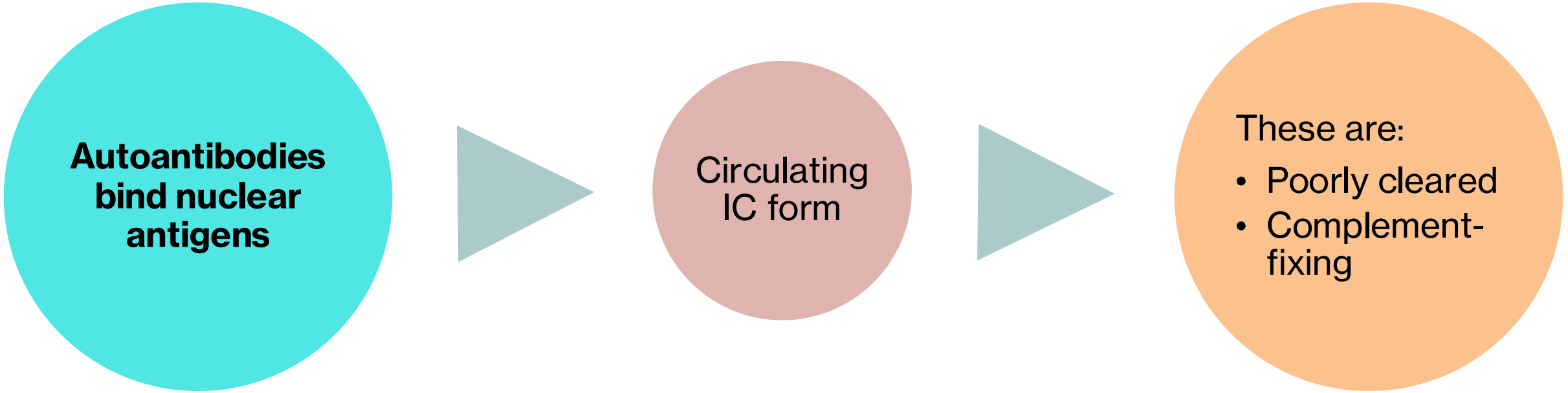
Activated B cells differentiate into plasma cells.

Major Autoantibodies:

Anti-dsDNA is the most pathogenic.	Anti-phospholipid	Anti-Smith

Both innate and adaptive immunity participate in the pathogenesis of SLE.

7. Immune complex formation



8. Tissue deposition of immune complexes

Immune complexes deposit in:

1. Kidneys (glomeruli → lupus nephritis)
2. Skin
3. Joints
4. Serosa
5. Blood vessels

In lupus nephritis, renal dendritic cells & infiltrating macrophages present self nuclear antigens on MHC II to $CD4^+$ T helper cells, activating them locally in the kidney. These T cells then drive B-cell autoantibody production, macrophage activation, and cytokine release, leading to immune-complex deposition, complement activation, and glomerular damage.

9. Complement activation (classical pathway)

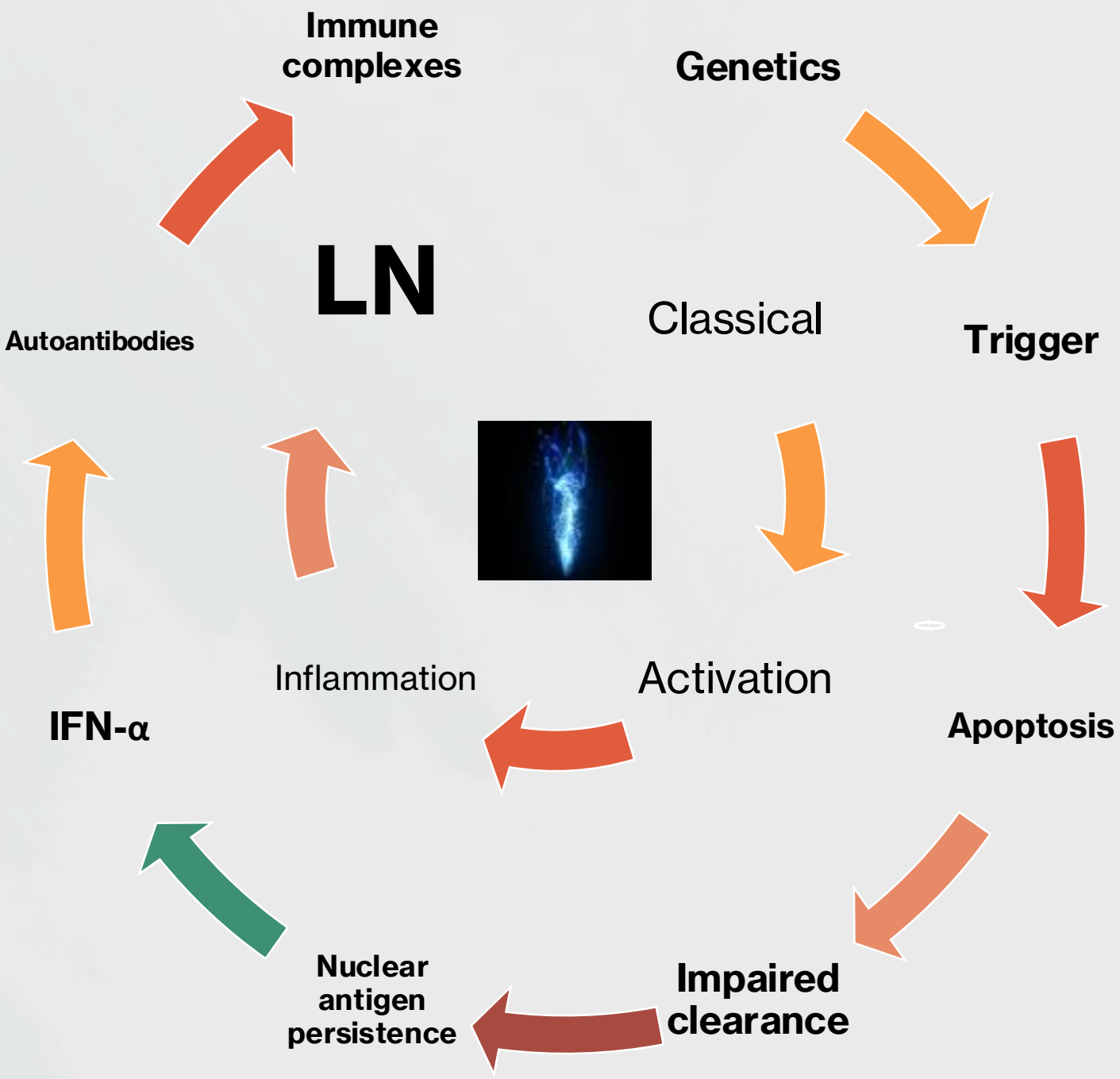
This is where damage happens.

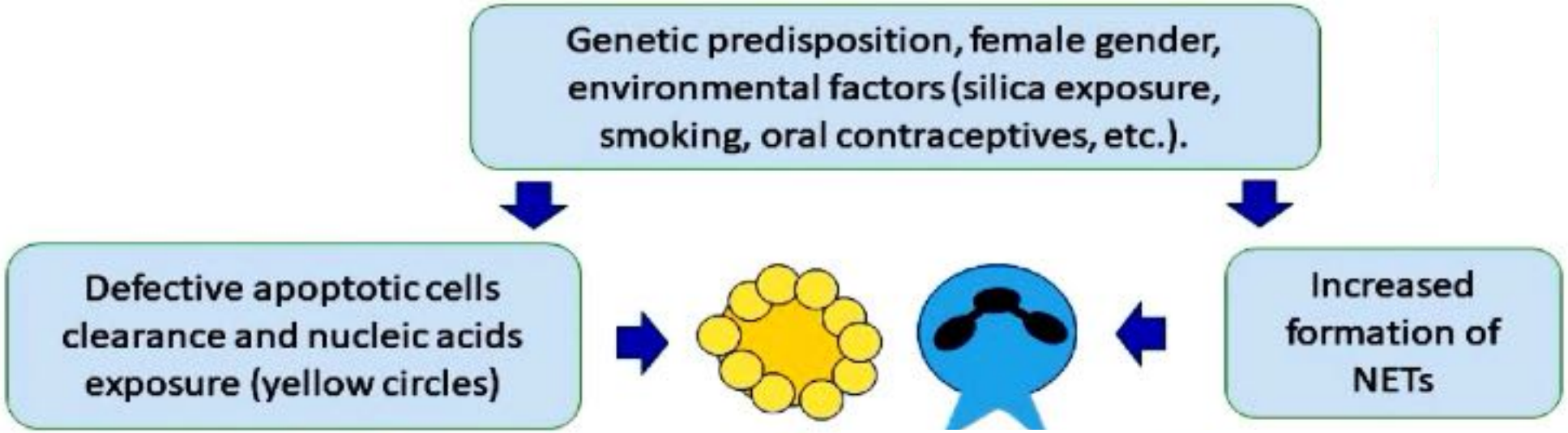
- **C1q** binds immune complexes
- Classical pathway activated
- **C3 and C4 consumed**
- **C3a, C5a** recruit inflammatory cells
- **Membrane attack complex** contributes to injury

10. Inflammation, tissue damage, clinical disease

Resulting manifestations:

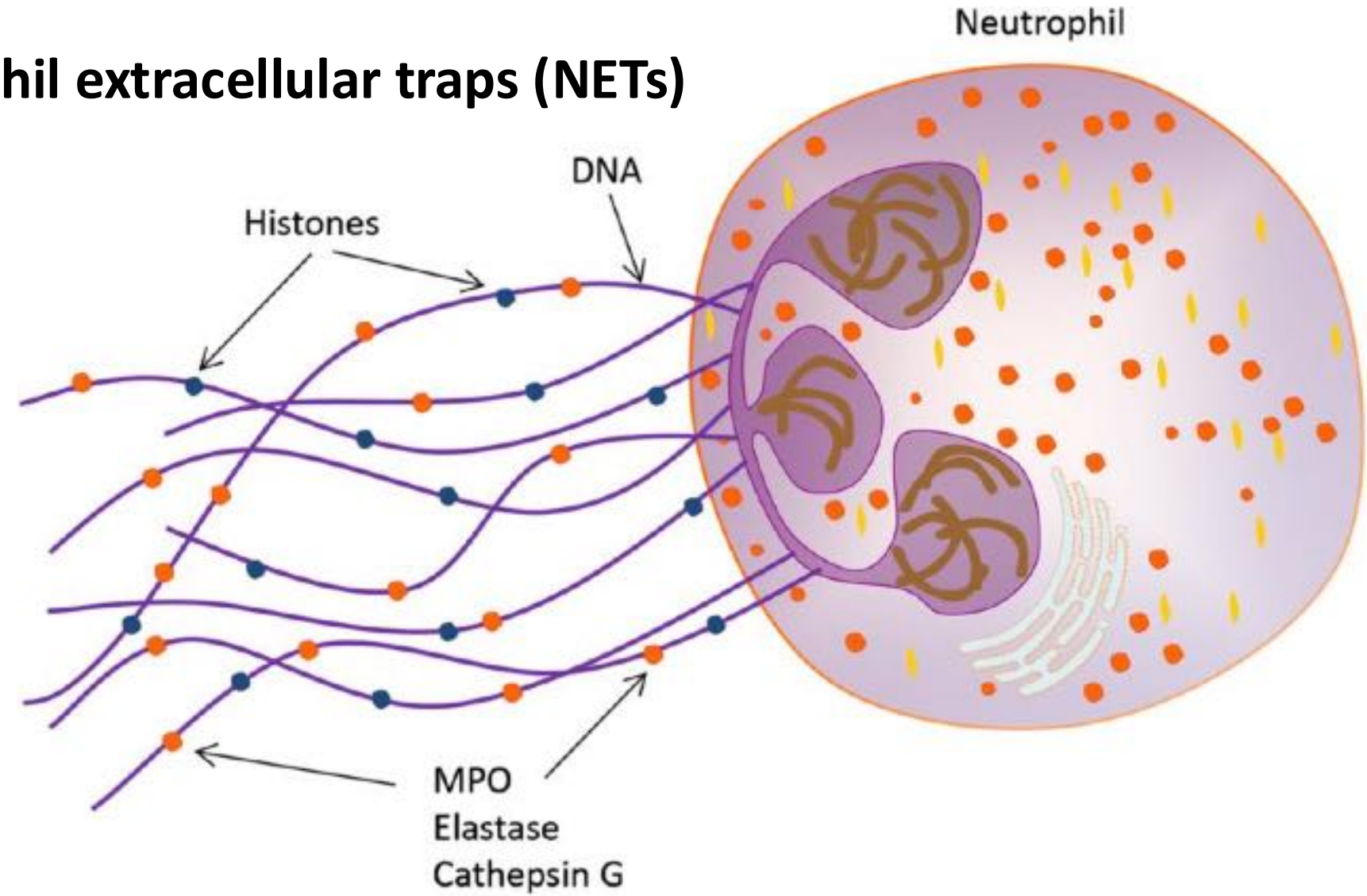
1. Nephritis
2. Rash
3. Arthritis
4. Cytopenias
5. Serositis & Vasculitis
6. Lab findings:
   - ↑ anti-dsDNA
   - ↓ C3, ↓ C4
7. “Full house” IF in kidneys


Immune complexes
Genetics
LN
Classical
Autoantibodies
Trigger
Inflammation
Activation
IFN-α
Apoptosis
Nuclear antigen persistence
Impaired clearance

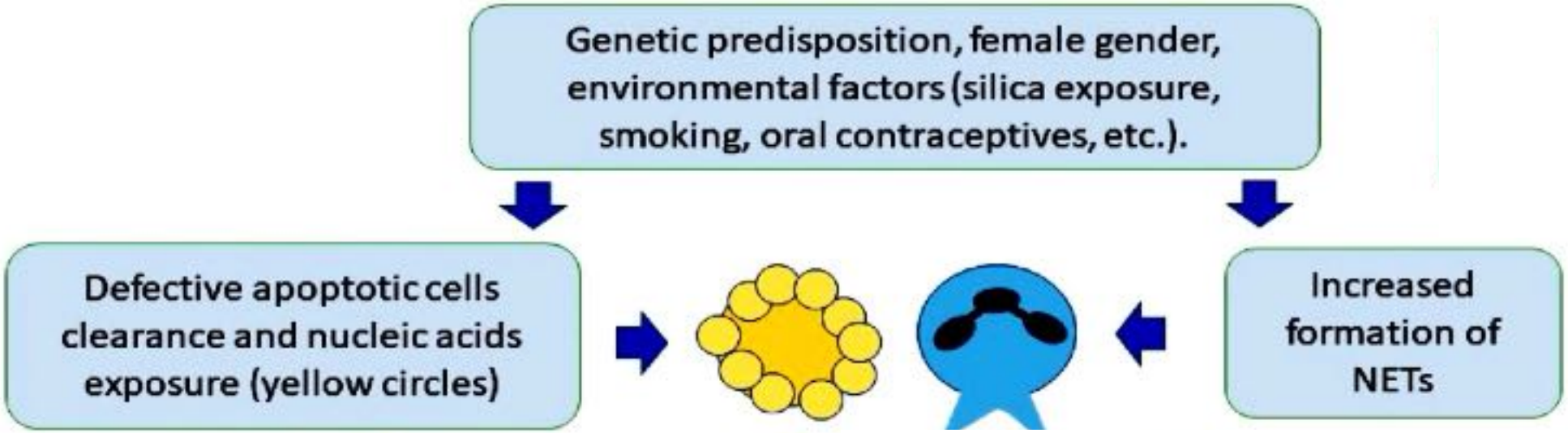


LUPUS PARDOXE

Neutrophil extracellular traps (NETs)



DOI:10.1007/s10753-021-01442-x



NETs feed the autoimmune response.

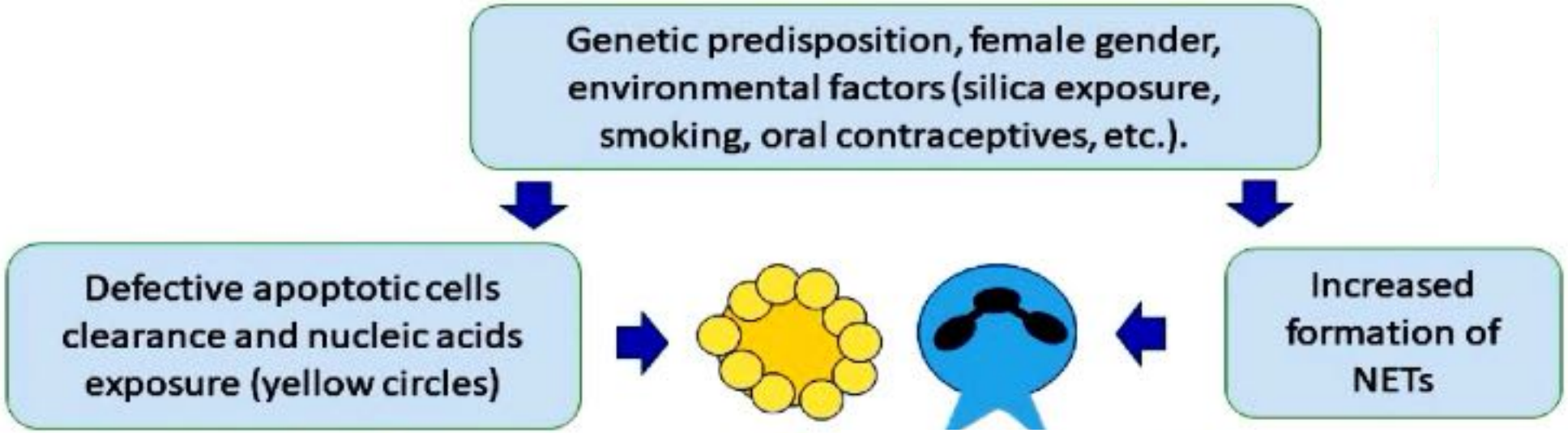
NETs are web-like structures released by neutrophils , expose large amounts of:

1. **Nuclear DNA**
2. **Histones**
3. **Ribonucleoproteins**

These are *exactly* the targets of lupus autoantibodies (anti-dsDNA, anti-histone, anti-Sm).

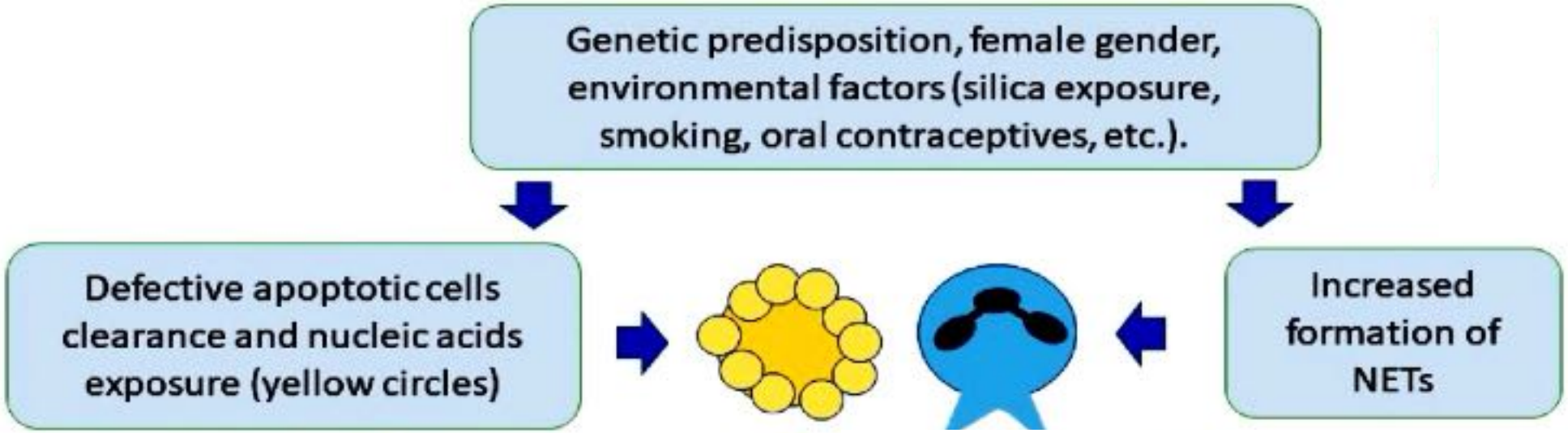
Act as a persistent source of nuclear autoantigens & Drive type I interferon production.

IFN-α is a central driver of lupus pathogenesis *“interferon signature”.*



NETs amplification loop = self-sustaining inflammatory cycle

NETs → IFN-α → more neutrophil activation → more NETs


Genetic predisposition, female gender, environmental factors (silica exposure, smoking, oral contraceptives, etc.).
Defective apoptotic cells clearance and nucleic acids exposure (yellow circles)
Increased formation of NETs

C1q vs C3/C4 roles

C1q = why lupus develops?

C3/C4 = how lupus damages organs ?

C1q vs C3/C4 roles

C1q = *Gatekeeper of Tolerance*

C3/C4 = *The effectors of inflammation*.

C1q vs C3/C4 roles

TOLERANCE MUST BREAK BEFORE INFLAMMATION STARTS

Normal Role in immune complex handling

C1q

1. *Binds:*
   - *Apoptotic cells*
   - *Immune complexes*
2. *Promotes non-inflammatory clearance by macrophages*
3. *Suppresses dendritic cell activation*
4. *Prevents exposure of nuclear antigens*

C3 / C4

1. *Opsonize immune complexes (C3b, C4b)*
2. *Promote:*
   - *Phagocytosis*
   - *Complement cascade propagation*
3. *Generate inflammatory mediators downstream*
4. *Clear complexes but at the cost of inflammation*

Role in lupus nephritis

C1q

- Classical pathway activation
- Deposited in glomeruli
- Anti-C1q antibodies worsen renal inflammation

INITIATOR

C3 / C4

- C3a, C5a → leukocyte recruitment
- C5b-9 → cell injury

AMPLIFIER

Feature	C1q	C3 / C4
Complement	**INITIATOR**	**AMPLIFIERS**
Main pathway	Classical	Classical, alternative, lectin
Key role	Clearance & tolerance	Inflammation & injury
Autoimmunity prevention	Major role	Minor role
In lupus	Deficiency → disease risk	Consumption → disease activity

Reduced serum C3 &C4 levels

Diagnosis of SLE

Biomarkers of activity.

A return towards normal denotes beneficial response of treatment

Complement 3 4 as a disease activity marker

- **Low complement levels**
  ↓ C3 and ↓ C4 indicate:
  Active immune complex disease
  Often correlate with active LN
- **Clinical use**
  Falling complement levels → **flare**
  Rising levels → **treatment response**
- **Important:** complement levels don’t always perfectly match kidney activity, but they’re still very useful.

THERAPEUTIC TARGET

THERAPEUTIC TARGET

Reduce inflammation
without blocking
early complement's protective functions

Therapeutic implications in LN

Recognition of complement's role has led to interest in:	
Complement inhibitors	(C5 inhibitors—investigational in LN)

Current therapies: Steroids, MMF, Cyclophosphamide.	
indirectly reduce complement activation	by suppressing immune complex formation

Therapeutic relevance of C5a vs C5b-9 Both matter in treatment

C5a → cell recruitment and inflammation

C5b-9 → direct podocytes injury

Because of their central role:

C5a or C5aR blockade

is an active therapeutic target

Therapeutic relevance of C5a vs C5b-9 Both matter in treatment

Unlike total C5 inhibition

C5aR inhibitors

Reduce inflammation

Without fully suppressing complement defense

Currently, no approved complement-targeted therapies are available for SLE, but clinical trials are ongoing.

Drugs in phase 2 trials for lupus nephritis include

1. **Ravulizumab**, an anti-C5 monoclonal antibody;
2. **Iptacopan,** a complement factor B inhibitor;
3. **Vemircopan**, a complement factor D inhibitor;
4. **Narsoplimab**, an anti-MBL-associated serine protease 2 monoclonal antibody;
5. **Pegcetacoplan**, a PEGylated C3 inhibitor.

Therapeutic implications in LN

First-line therapy:

MMF + steroids or cyclophosphamide ± hydroxychloroquine

Monoclonal antibodies

mainly used for refractory, relapsing, or difficult-to-treat LN

Belimumab

FDA-approved mAb specifically for active LN with standard therapy

B-cell targeted therapy

Rituximab

- **Target:** CD20 → depletes B cells
- **Use in LN:**
  - Off-label; considered for **refractory or relapsing LN** when standard therapy fails
- **Notes:**
  - Does **not** affect plasma cells (so autoantibody production may persist for a while)

Belimumab

- **Target:** → BLyS / BAFF
- **Use in LN:**
  - FDA-approved with standard therapy
  - Reduces autoantibody production, B-cell survival
- **Notes:**
- Can be used early in combination with MMF or cyclophosphamide
- Better safety profile than rituximab

Monoclonal antibody	Target	LN use	Notes
Rituximab	CD20 (B cells)	Refractory/relapsing	Off-label, depletes B cells, not plasma cells
Belimumab	BLyS / BAFF	Active LN adjunct	FDA-approved, used with standard therapy
Abatacept	CTLA-4 Ig	Investigational	Blocks T-cell costimulation
Anifrolumab	IFNAR1	SLE, LN trials	Type I interferon blockade
Eculizumab	C5	Rare, investigational	Complement-mediated injury; not routine in LN

”اللهم انفعنا بما علمتنا,
وعلمنا ماينفعنا,
وزدنا علما“


Thank you

1 Where the problem starts in lupus

- Lots of **self-antigens** (DNA, RNA, histones)
- Defective **clearance of apoptotic cells**
- Formation of **immune complexes** (self-antigen + autoantibody)

2 Complement activation on immune complexes

- Immune complexes activate the **classical complement pathway**:
- C1q binds to IgG/IgM in immune complexes
- Complement cascade → **C3 is cleaved**
- You get **C3b, iC3b, C3d** deposited on those complexes
- Now the self-antigen is “decorated” with complement fragments.

3 How complement activates B cells

- **Co-stimulation via CR2 (CD21)**
- **B cells express CR2 (CD21)**, which binds **C3d**
- When a B-cell receptor (BCR) binds a self-antigen **AND** CR2 binds C3d on the same antigen:
  - Activation threshold drops dramatically
  - Autoreactive B cells that should stay silent get activated
- 📌 In lupus:
- Complement **lowers the tolerance checkpoint** → autoantibody-producing B cells survive and expand.
- This leads to:
- Anti-dsDNA antibodies
- Anti-Sm antibodies
- More immune complexes → more complement activation (vicious cycle)

4 How complement indirectly activates T cells

- Complement doesn't strongly activate T cells *directly*—it works **through antigen-presenting cells (APCs)**.
- **a) Enhanced antigen uptake**
- Dendritic cells and macrophages have **complement receptors (CR1, CR3)**
- They efficiently take up **complement-coated immune complexes**
- This leads to:
- Increased presentation of self-antigens on **MHC II**
- Stronger activation of **$CD4^+$ T helper cells**
- **b) Local complement production**
- Activated immune cells (DCs, macrophages, even T cells) can **produce complement locally**.
- Complement fragments:
- **C3a and C5a** act as inflammatory signals
- Increase cytokine production (IL-6, IL-12, IFN-α)
- Promote **T-cell activation and survival**

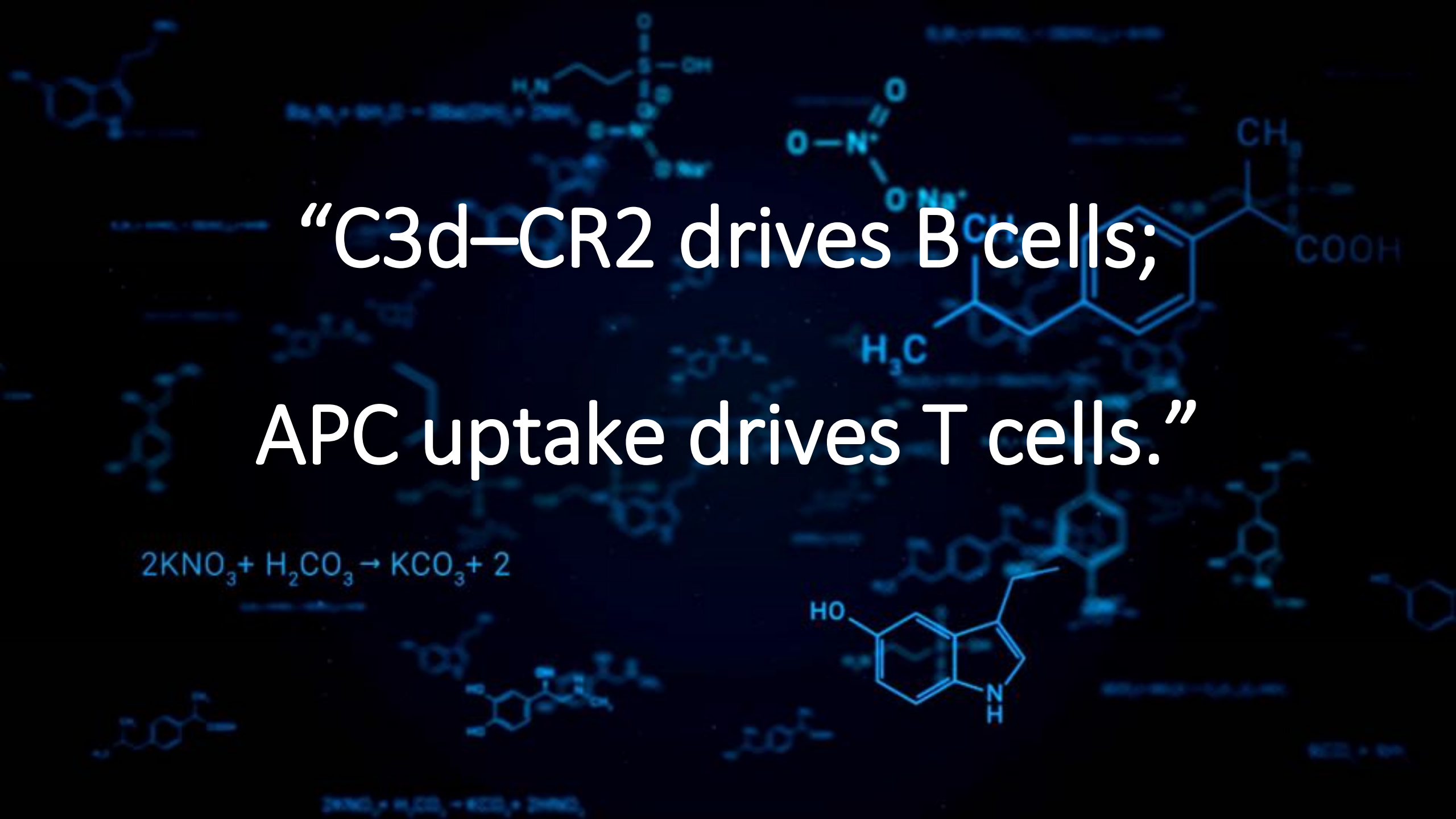
🧠 Core mnemonic: “C3d BRINGS LUPUS”

C3d → B-cell activation
R → Receptors on APCs
I → Immune complex uptake
N → Nuclear antigens presented
G → Greater T-cell activation

B-cell activation mnemonic

“C3d + CR2 = B-cell BOOST”

- ❑ **C3d** on immune complexes
- ❑ **CR2 (CD21)** on B cells
- ❑ Lowers activation threshold
- ❑ Activates autoreactive B cells


“C3d–CR2 drives B cells;
APC uptake drives T cells.”
2KNO3 + H2CO3 → KCO3 + 2
HO
NH
COOH
CH
H3C

Why T cells usually activate first

1 Antigen presentation

- APCs (dendritic cells) pick up antigen
- Present it on MHC II
- Activate naïve $CD4^+$ T helper cells
- This is the *initial gatekeeper step*.

2 Activated T helper cells then help B cells

- Provide CD40L–CD40 interaction, Secrete cytokines (IL-4, IL-21, etc.)
- Without this help:
    1. B cells don’t class switch
    2. No affinity maturation
    3. No long-lived plasma cells

3 T-cell activation → B-cell activation

Important lupus twist

- **In SLE, autoreactive B cells can be activated earlier or more easily** because:
    1. Self-antigens are coated with **C3d**
    2. **CR2 (CD21)** co-stimulation lowers the B-cell activation threshold
- **BUT Sustained, pathogenic autoantibody production still requires T-cell help**
- So even in lupus: **T cells still lead the process**