

Spectrum of autoantibodies in systemic lupus erythematosus

Diagnostic patterns · pathogenic mechanisms · clinicopathologic correlations

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Learning outcomes

- Classify SLE autoantibodies by target and pathogenic mechanism.
- Interpret HEp-2 immunofluorescence patterns and antigen-specific confirmation.
- Relate anti-dsDNA, anti-Sm, anti-Ro/La, and antiphospholipid antibodies to clinical findings.
- Explain immune-complex injury, cytopenias, and the amplification of autoimmunity.

SLE is defined by heterogeneous autoimmunity

- Antinuclear antibodies are the most characteristic laboratory hallmark.
- Targets extend beyond the nucleus to circulating proteins, blood cells, and cellular compartments.
- Immune complexes and antibody binding to cells cause much of the tissue injury.
- The serologic profile contributes to diagnosis and clinicopathologic interpretation.

Autoantibody targets occupy distinct compartments

Nuclear

DsDNA · chromatin · Sm · U1-RNP

Ro / La

SS-A and SS-B nucleoproteins

Plasma / membrane

Phospholipid–protein
complexes

Blood cells

Erythrocytes · leukocytes ·
platelets

Autoantibodies injure by more than one mechanism

Autoantibodies + self antigens



Soluble or deposited immune complexes

Cell-reactive antibodies



Opsonization and cell destruction

Antiphospholipid antibodies



Prothrombotic clinical phenotype

Diagnostic specificity differs sharply among antibodies

Sensitive screening

Generic ANA

Frequent in SLE but also detectable in other autoimmune conditions.

Disease-associated specificity

Anti-dsDNA and anti-Smith

High diagnostic specificity; Anti-dsDNA also linked to nephritis.

Major SLE autoantibodies: Approximate positivity

Antibody	Positive in SLE	Main association
Generic ANAs	95–100%	Not specific for SLE
Anti-dsDNA	40–60%	Nephritis; SLE specific
Anti-Sm	20–30%	SLE specific
Anti-U1-RNP	30–40%	Ribonucleoprotein reactivity
Anti-Ro/La	30–50%	Neonatal lupus / congenital heart block
Antiphospholipid	30–40%	Antiphospholipid syndrome association

Approximate ranges reproduced Table 6.10; Positivity varies by population and assay.

Anti-dsDNA links serology and renal injury

Antibody target

DsDNA

- Targets double-stranded DNA, a nuclear self antigen.
- Relatively specific for SLE compared with generic ANAs.
- Associated with nephritis; DNA–anti-DNA immune complexes may deposit in glomeruli.
- Interpret serology alongside urinary findings, complement, and the clinical picture.

Anti-Sm identifies an SLE-associated nuclear antigen

Antibody target

Sm

- Recognizes Smith proteins of small ribonucleoprotein particles.
- Reported in a minority of SLE patients (approximately 20–30%).
- Highly specific association with SLE; Absence does not exclude SLE.
- May be suggested by coarse speckled HEp-2 nuclear fluorescence.

U1-RNP illustrates antigen overlap across diseases

Antibody target

U1-RNP

- Recognizes U1 ribonucleoprotein within the nuclear RNA-processing machinery.
- Present in a substantial subset of patients with SLE.
- Coarse speckled ANA staining may accompany anti-U1-RNP.
- An antigen-specific result must be interpreted with the clinical phenotype.

Anti-Ro/La connects maternal antibodies with fetal effects

Antibody target

Ro / La

- Ro/SS-A and La/SS-B are nucleoprotein autoantigens.
- These antibodies with neonatal lupus and congenital heart block.
- A positive result is clinically relevant beyond the patient's current organ symptoms.
- The maternal and fetal clinical contexts determine the significance.

Antiphospholipid antibodies target protein complexes

Antibody target

APL

- The antigenic targets are plasma proteins interacting with phospholipids, not simply naked phospholipid.
- Examples discussed include β 2-glycoprotein I and prothrombin.
- These antibodies are present in approximately 30–40% of patients with SLE.
- Only a subset of antibody-positive patients develop clinical antiphospholipid syndrome.

Generic ANAs are not equivalent to SLE

What positivity indicates

Autoimmune reactivity

Nuclear/cellular self-reactivity may support a broader diagnostic assessment.

What it does not establish

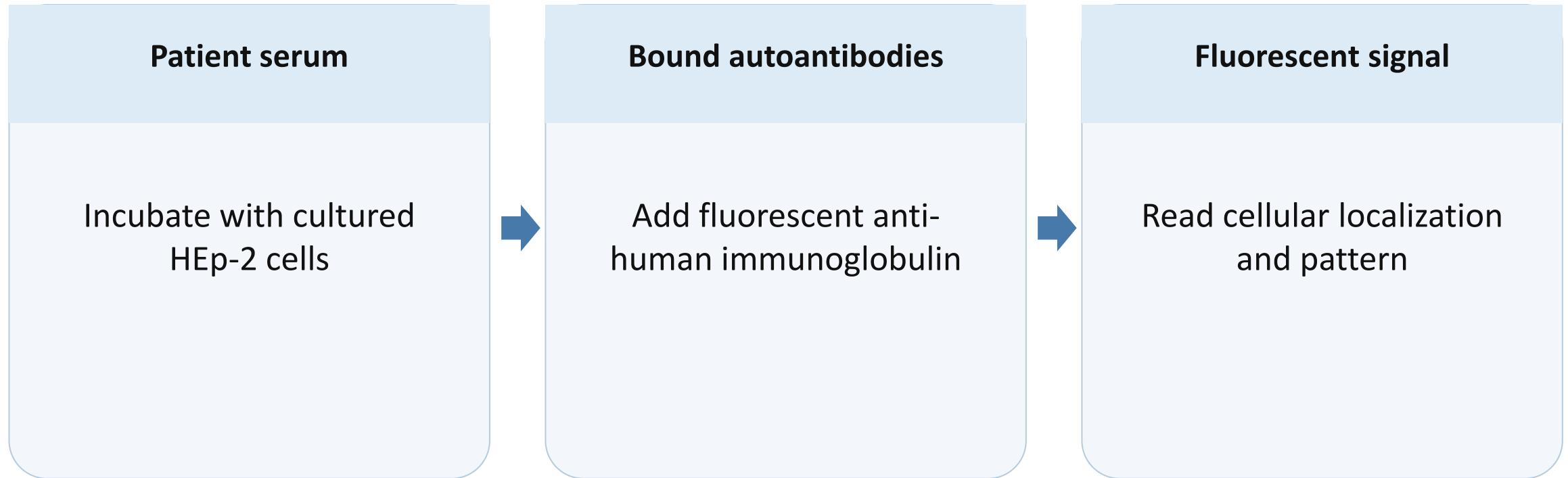
Disease identity

Generic ANA alone is not specific enough to establish SLE.

A single antibody result must not replace clinicopathology

- Clinical phenotypes vary widely because multiple organ systems may be involved.
- Antibody specificity provides evidence, not a complete clinical diagnosis.
- The accompanying morphology, blood counts, urinary findings, and complement state add context.
- Distinguish a classification rule from the clinical act of diagnosing a patient.

HEp-2 indirect immunofluorescence: Basic assay



HEp-2 IFA detects more than nuclear structures

Nucleus

Chromatin and nuclear proteins

Nucleolus

RNA-processing components

Cytoplasm

Ribosomal proteins or mitochondria

Mitotic apparatus

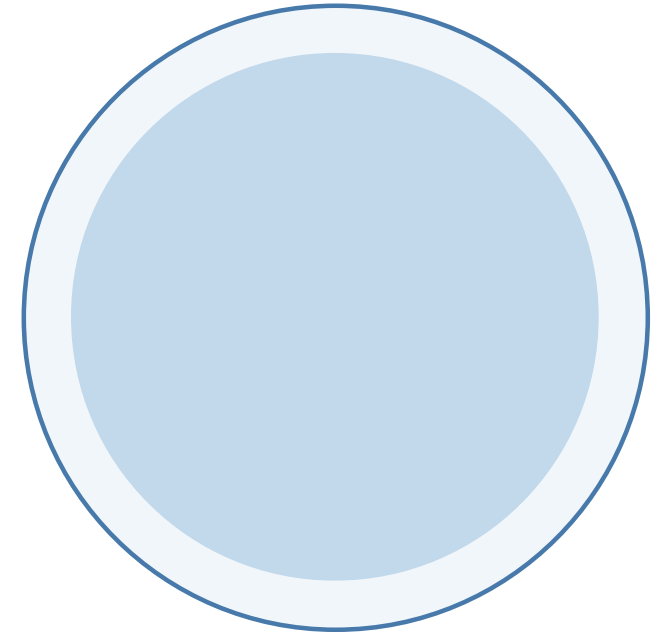
Cell-cycle-associated structures

The fluorescence pattern is a clue, not proof

- Autoantigens occupy characteristic subcellular sites and create recurring patterns.
- More than 30 ICAP patterns in a classification hierarchy.
- A pattern provides a presumptive antigen family rather than a confirmed specificity.
- Use an antigen-specific assay to identify the antibody implicated by a pattern.

Homogeneous nuclear pattern

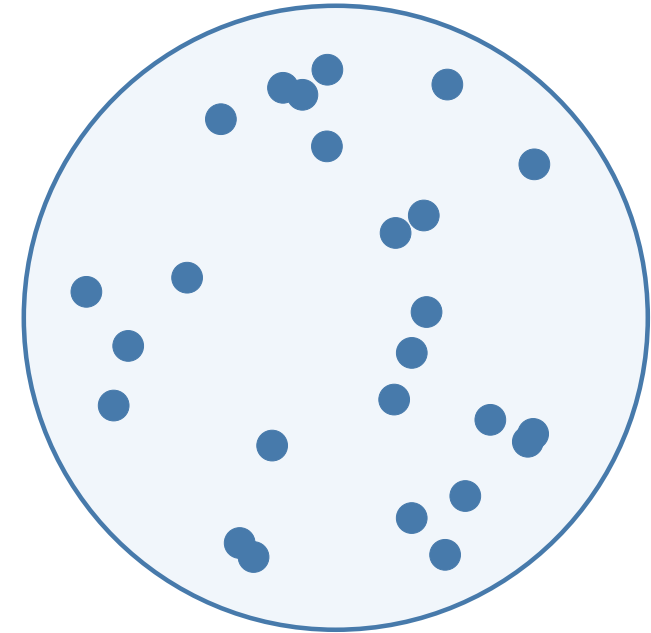
- Diffuse nuclear fluorescence suggests antibodies to chromatin, dsDNA, or sometimes histones.
- This pattern is common in SLE.
- The same visual pattern does not identify a single unique autoantibody.



Schematic fluorescence distribution — not a HEp-2 micrograph

Coarse speckled nuclear pattern

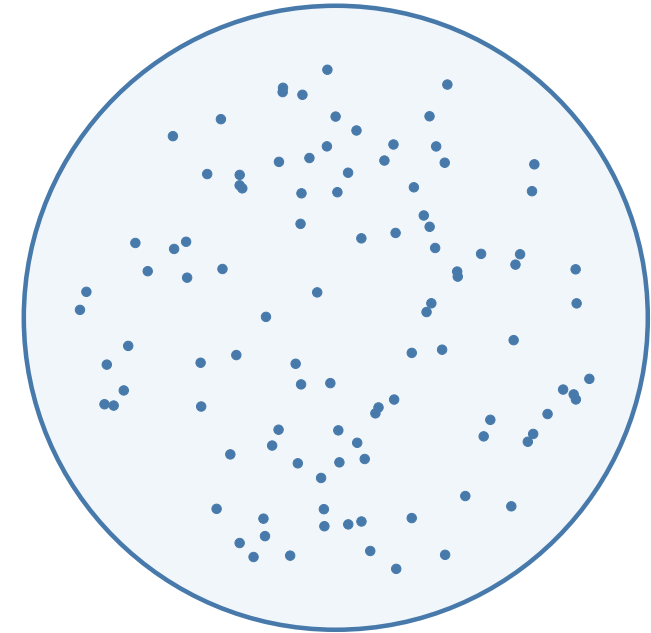
- Variable-sized intranuclear speckles suggest ribonucleoprotein reactivity.
- Commonly associated with Sm and U1-RNP antibodies.
- Can occur in SLE as well as other connective tissue diseases.



Schematic fluorescence distribution — not a HEp-2 micrograph

Fine speckled nuclear pattern

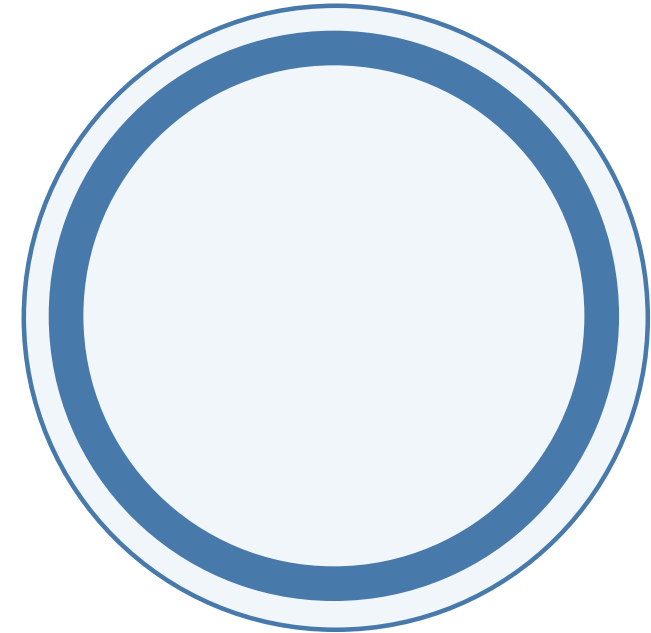
- Numerous small, evenly distributed intranuclear speckles.
- Frequent pattern but of low diagnostic specificity.
- Requires clinical correlation and directed antigen-specific testing.



Schematic fluorescence distribution — not a HEp-2 micrograph

Peripheral nuclear envelope pattern

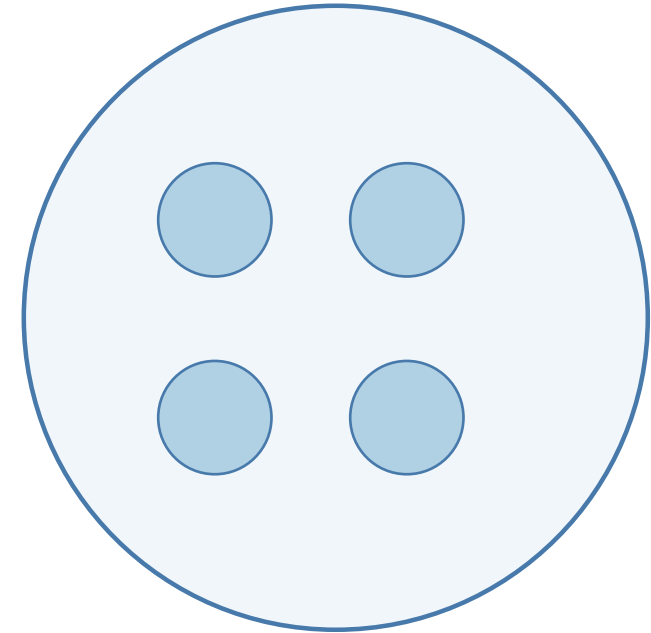
- Emphasis at the nuclear envelope rather than diffuse nucleoplasm.
- May reflect anti-gp210, anti-p68, or anti-lamin reactivity.
- Points toward additional autoimmune disease contexts, not specifically SLE.



Schematic fluorescence distribution — not a HEp-2 micrograph

Nucleolar patterns favor a different disease spectrum

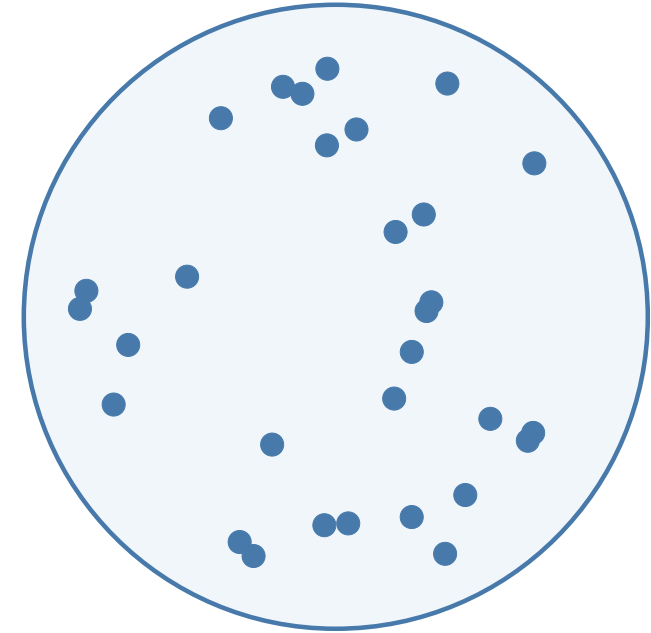
- Homogeneous, clumpy, and punctate nucleolar patterns reflect different antigen families.
- Examples include Th/To, fibrillarin/U3-RNP, and RNA polymerase I.
- At high titer, nucleolar patterns suggest systemic sclerosis more than typical SLE.



Schematic fluorescence distribution — not a HEp-2 micrograph

Centromere pattern localizes to discrete nuclear foci

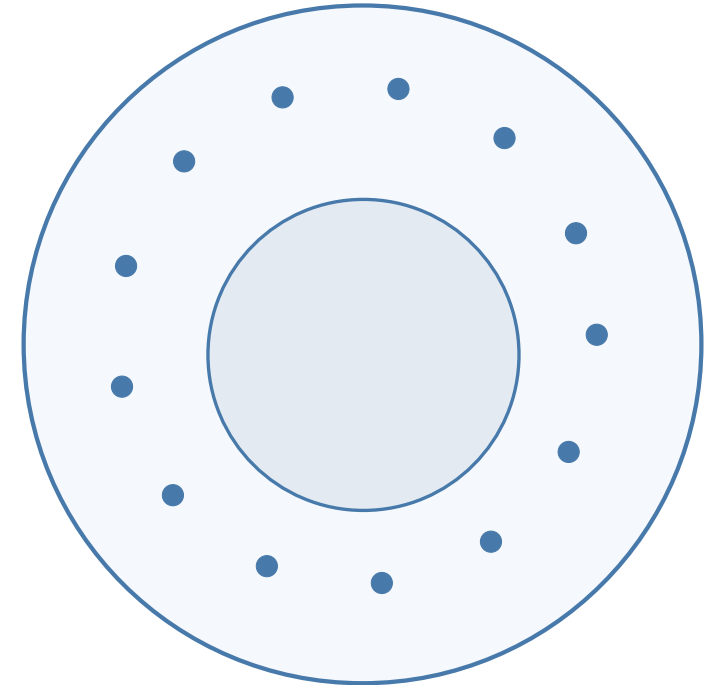
- Associated with centromeric proteins CENP-A, CENP-B, and CENP-C.
- More characteristic of systemic sclerosis and certain other autoimmune disorders.
- Can occur occasionally in SLE; Morphology alone is not diagnostic.



Schematic fluorescence distribution — not a HEp-2 micrograph

Cytoplasmic reticular pattern suggests mitochondria

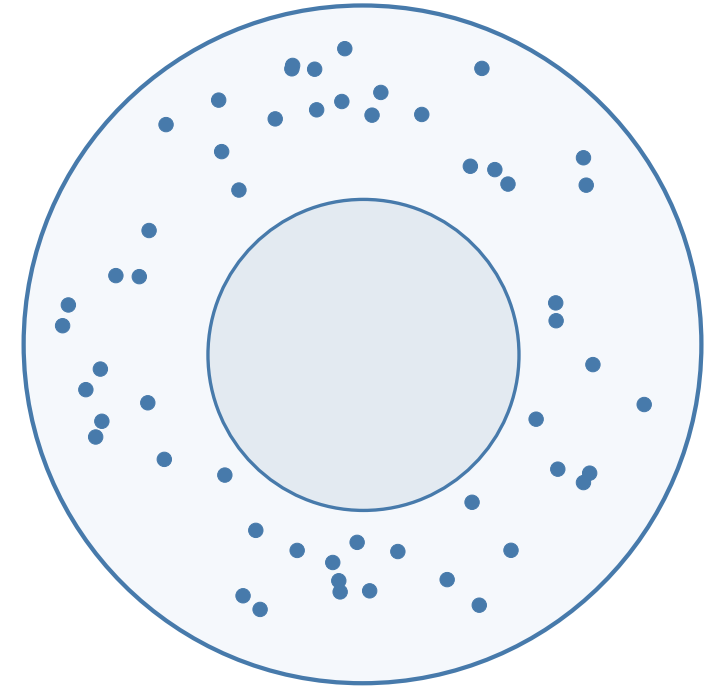
- Cytoplasmic reticular staining corresponds to mitochondrial structures.
- Associated with reactivity to pyruvate dehydrogenase E2.
- Serves as a differential clue toward primary biliary cholangitis.



Schematic fluorescence distribution — not a HEp-2 micrograph

Cytoplasmic dense fine speckles have distinct targets

- Can reflect antibodies to ribosomal P proteins (P0, P1, P2), which are specific for SLE.
- Alternatively, antibodies against tRNA synthetases can produce related cytoplasmic staining.
- Pattern recognition must be followed by antigen-specific discrimination.



Schematic fluorescence distribution — not a HEp-2 micrograph

Interpret fluorescence in three sequential levels

Localization

Nuclear · nucleolar ·
cytoplasmic



Pattern

Homogeneous · speckled ·
rim · discrete foci



Specific antigen

Confirm with an
appropriate immunoassay

HEp-2 IFA and antigen assays serve different roles

HEp-2 IFA

Broad screening

Shows the spatial pattern of reactivity across many cellular targets.

Antigen-specific assay

Specificity confirmation

Tests a selected antigen; Can resolve a suggested antibody identity.

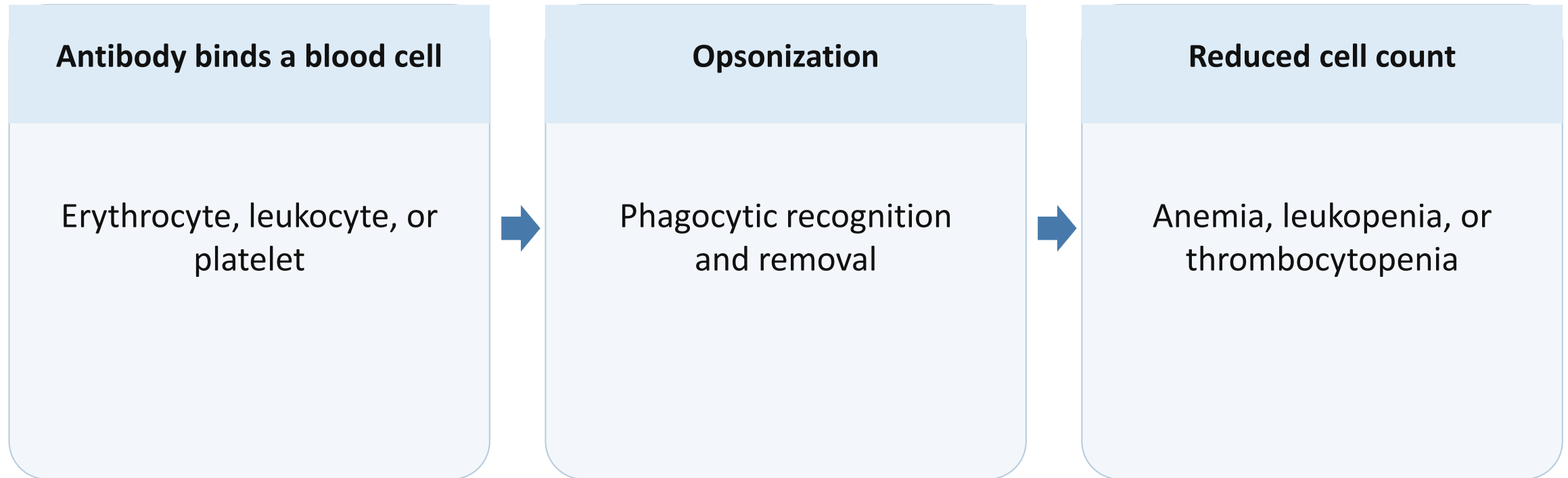
Multiplex tests require clinical targeting

- Solid-phase platforms use purified, recombinant, or extracted cellular antigens.
- Multiplex panels can examine several relevant specificities in one clinical scenario.
- Their role is complementary to fluorescence pattern assessment.
- Avoid inferring a complete antibody spectrum from any single limited antigen panel.

Autoantibody panels are interpreted as patterns of evidence

Result or pattern	Suggests	Does not itself prove
Generic ANA positive	Broad self-reactivity	SLE as a specific disease
Anti-dsDNA positive	SLE-associated specificity	Active nephritis without clinical data
Anti-Sm positive	Specific SLE association	That all organ manifestations are present
Antiphospholipid positive	Prothrombotic antibody class	Clinical thrombosis or obstetric syndrome
Coarse speckled IFA	Sm/U1-RNP family possible	The precise antigen identity

Blood-cell-directed autoantibodies explain cytopenias



Antiphospholipid complexes reveal cryptic epitopes

Phospholipid surface

A platform for associated plasma proteins

Bound protein

Newly exposed or configured epitopes

Specific autoantibody

Protein–phospholipid complex recognized

Lupus anticoagulant: An in-vitro versus in-vivo paradox

In laboratory coagulation tests

Apparent anticoagulation

Some antibodies prolong phospholipid-dependent clotting assays, including PTT.

In patients

Hypercoagulability

These patients can experience venous and arterial thrombosis.

Why syphilis screening may be falsely positive

Antiphospholipid antibody

Reacts with cardiolipin-associated assay antigen



Serologic cross-reaction

Non-treponemal syphilis test can be positive



Clinical interpretation

Do not equate this signal with confirmed infection

Antiphospholipid syndrome: Clinical consequences

- Venous or arterial thrombosis is a major clinical manifestation.
- Recurrent spontaneous pregnancy losses may occur.
- Focal cerebral or ocular ischemia can accompany thrombosis.
- Antibody positivity alone and the full clinical syndrome are distinct findings.

Primary and SLE-associated antiphospholipid syndromes

Primary syndrome

No underlying SLE

Clinical antiphospholipid syndrome occurs without an associated systemic disorder.

Secondary syndrome

Occurs with SLE

Similar thrombosis/obstetric manifestations accompany established lupus.

The first pathogenic step is loss of self-tolerance

Self-reactive clones survive

B-cell and helper T-cell
checkpoints fail



Self nuclear antigen persists

Incomplete disposal of
nuclear material



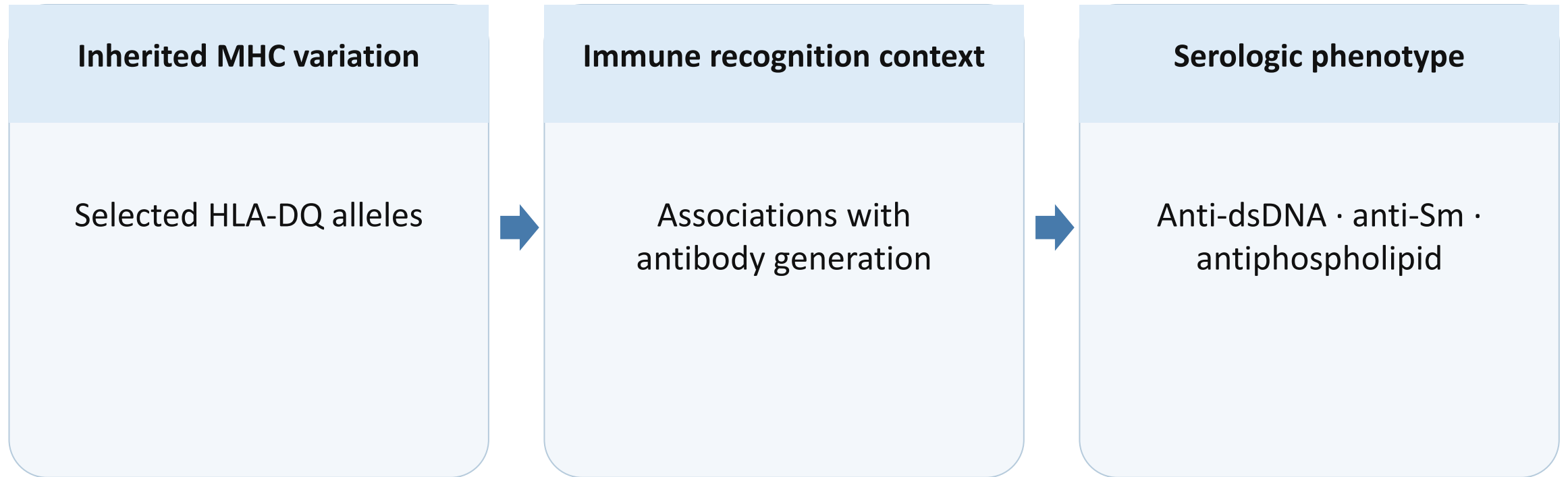
Adaptive immune activation

Autoantibody production
is sustained

Genetic risk is polygenic rather than deterministic

- Both MHC and non-MHC loci contribute to susceptibility.
- Family and twin observations support inherited predisposition.
- Multiple associated loci influence lymphocyte signaling and interferon responses.
- Environmental and immune factors remain important; No single locus explains most SLE.

HLA-DQ variation can shape the antibody repertoire



Early complement components support immune homeostasis

- Inherited C1q, C2, and C4 deficiencies occur in some lupus patients.
- Complement supports clearance of immune complexes and apoptotic debris.
- Inefficient disposal increases the availability of nuclear self antigens.
- Defective complement activity can therefore promote autoimmunity as well as reflect consumption during active disease.

Inefficient apoptotic-cell clearance increases antigen load

Cell death

Nuclear DNA and nucleoproteins become accessible

Incomplete clearance

Self antigens remain in the extracellular compartment

Immune recognition

Autoreactive lymphocytes encounter persistent targets

B- and T-cell dysregulation cooperate

B-cell tolerance defect

Autoreactive B cells persist

Central or peripheral deletion and control mechanisms fail.

Helper T-cell response

Antibody maturation supported

CD4+ cells responding to nucleosomal antigens assist autoreactive B cells.

Nuclear nucleic acids stimulate innate sensors

Immune complex uptake

DNA/RNA-containing complexes enter immune cells



Intracellular TLR engagement

Self nucleic acids act as activating ligands



Reinforced activation

B-cell autoantibodies and dendritic-cell cytokines increase

Type I interferon amplifies immune activation

Nucleic-acid stimulation

Dendritic cells receive innate signals

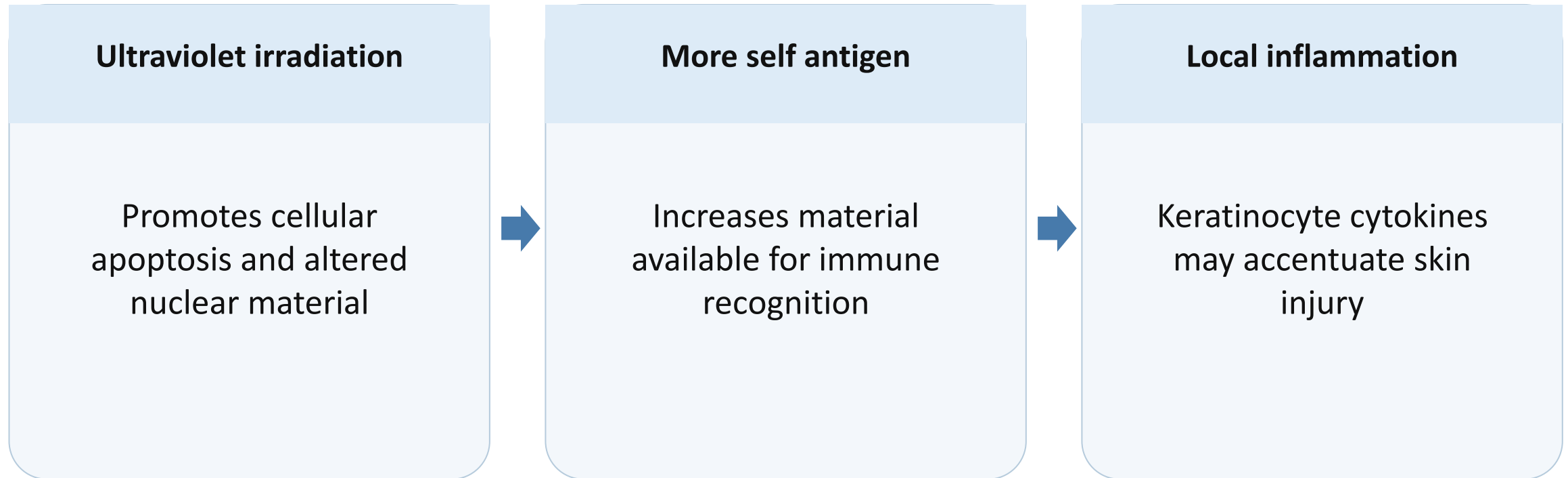
Type I interferon production

Antiviral cytokine activity becomes sustained

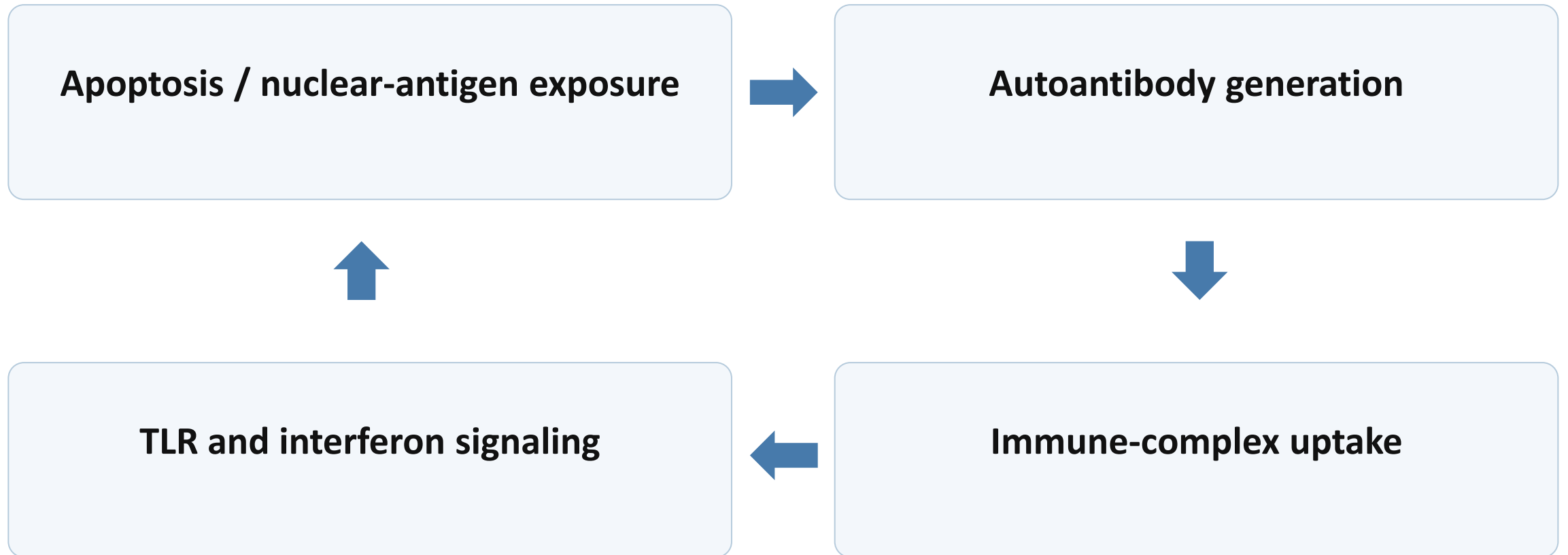
Immune amplification

B cells, T-cell help, and inflammatory responses may increase

Ultraviolet exposure supplies a plausible trigger



SLE autoimmunity forms a self-amplifying loop



Positive feedback: Each round can reinforce antigen exposure and autoreactivity

Most systemic lesions reflect type III hypersensitivity

Self antigen + antibody

Immune complexes form

Tissue deposition

Glomeruli and small blood vessels are vulnerable

Complement activation

Inflammation and tissue injury occur

Renal immune-complex deposits provide mechanistic evidence

- DNA–anti-DNA complexes can be detected in glomerular sites.
- Granular immunoglobulin and complement deposits support immune-complex deposition.
- Low serum complement can indicate immune-complex-associated consumption.
- Renal T-cell infiltrates may contribute additional tissue injury.

Type II hypersensitivity produces hematologic injury

Type III mechanism

Immune-complex deposition

Damage to glomeruli, vessels, and connective tissues.

Type II mechanism

Antibodies coat cells

Opsonized erythrocytes or platelets are removed by phagocytes.

Hematoxylin bodies are antibody-reactive nuclear remnants

Damaged cell exposes its nucleus

Nuclear material loses normal chromatin pattern



Autoantibody binds exposed antigen

A homogeneous LE / hematoxylin body forms



Phagocyte engulfs nuclear material

LE cell can be seen; Now chiefly historical

Neuropsychiatric injury has multiple proposed pathways

- Some autoantibodies may cross the blood–brain barrier and bind neuronal targets.
- Reactivity to neurotransmitter receptors has been proposed.
- Cytokines and vascular pathology may contribute to cognitive or CNS manifestations.
- That precise mechanisms remain incompletely defined.

Organ injury reflects antibody class and location

Kidney

Immune complexes →
glomerular injury

Blood

Cell-directed antibodies →
cytopenias

Vessels

Immune complexes / aPL →
vascular injury

Skin

Immune and inflammatory
injury → interface changes

Small-vessel vasculitis can contain fibrinoid necrosis

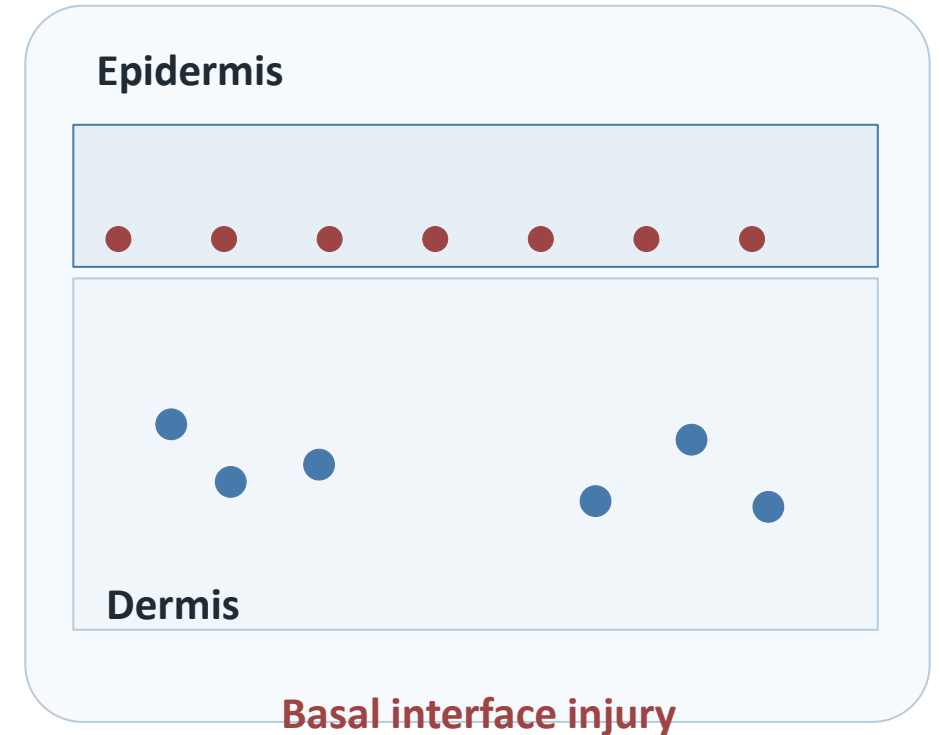
- Acute necrotizing vasculitis may affect capillaries, arterioles, and small arteries.
- Fibrinoid necrosis characterizes active vessel-wall injury.
- Chronic lesions may develop fibrous wall thickening and luminal narrowing.
- These changes fit an immune-mediated vascular injury mechanism.

Lupus nephritis is a major immune-complex complication

- The kidney may show glomerulonephritis and tubulointerstitial nephritis.
- Clinically significant involvement requires attention to proteinuria, hematuria, and casts.
- Renal morphology is varied; The detailed nephritis classification is addressed elsewhere.
- Antibody findings inform the evaluation but do not replace renal tissue and clinical assessment.

Lupus skin lesions show interface injury

- Vacuolar injury occurs along the basal epidermal layer.
- Dermal edema and perivascular inflammation may accompany the rash.
- Immunoglobulin and complement may deposit along the dermoepidermal junction.



Original anatomical schematic — not histology

The lupus band is not independently disease-specific

What the finding shows

Immune deposition

Immunoglobulin and complement at the dermoepidermal junction.

Interpretive limit

Not exclusive to SLE

Comparable deposition can occur in other connective tissue diseases.

Articular lupus generally lacks erosive destruction

SLE

Typically nonerosive synovitis

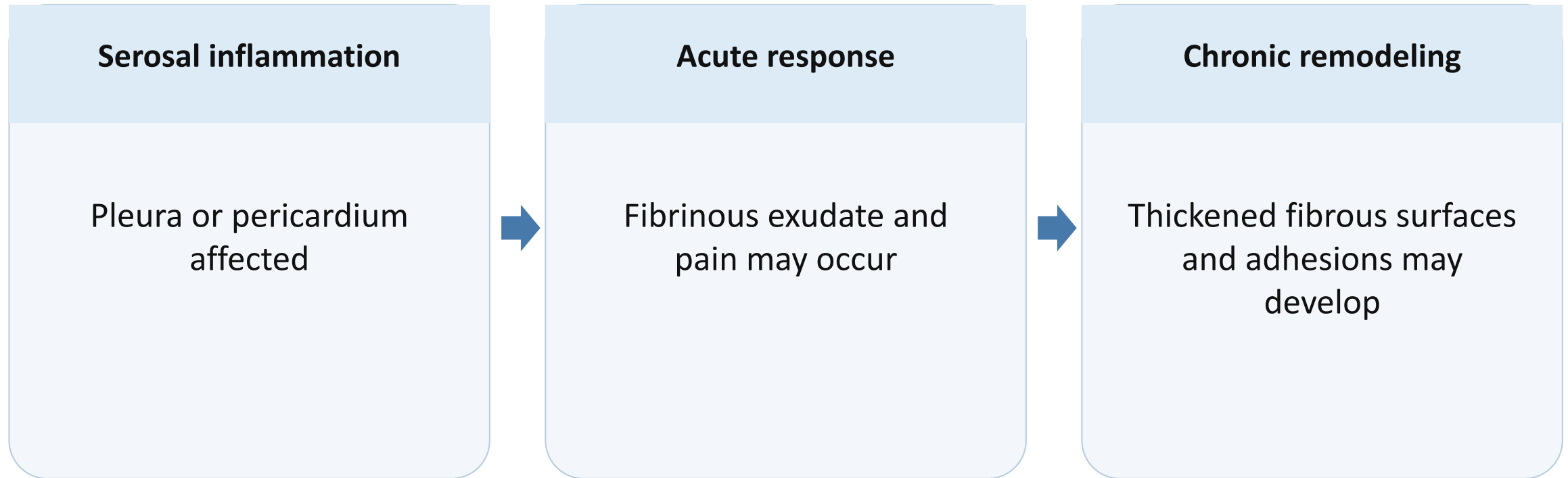
Pain and inflammation can occur with limited structural joint damage.

Rheumatoid arthritis

Erosive arthritis is a key contrast

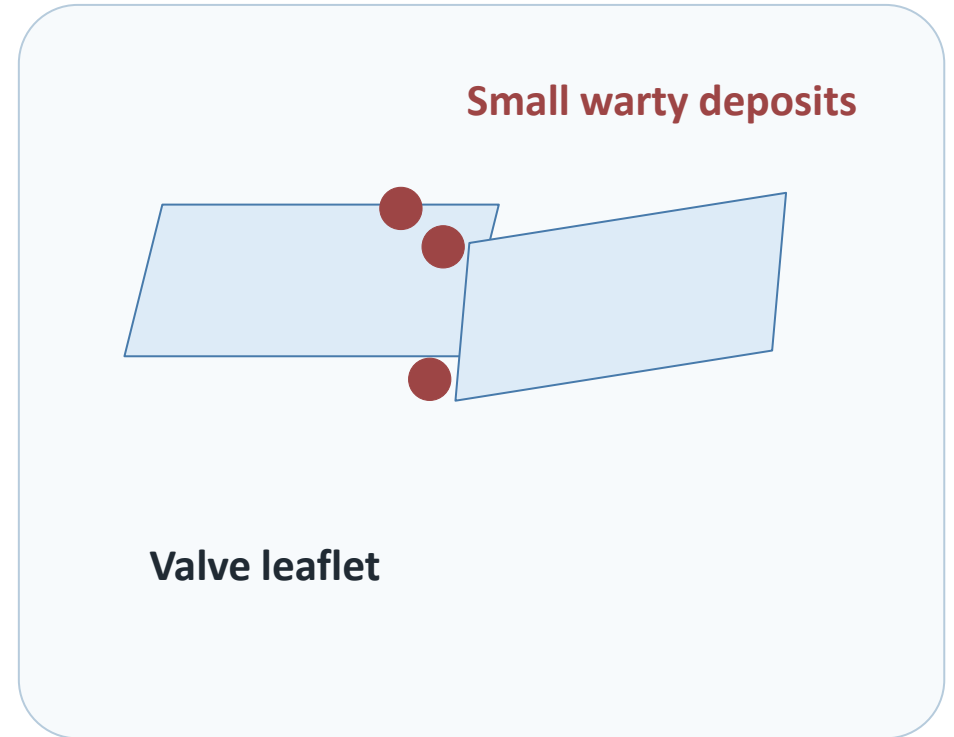
The morphologic distinction guides the differential diagnosis.

Serositis translates immune injury into effusions



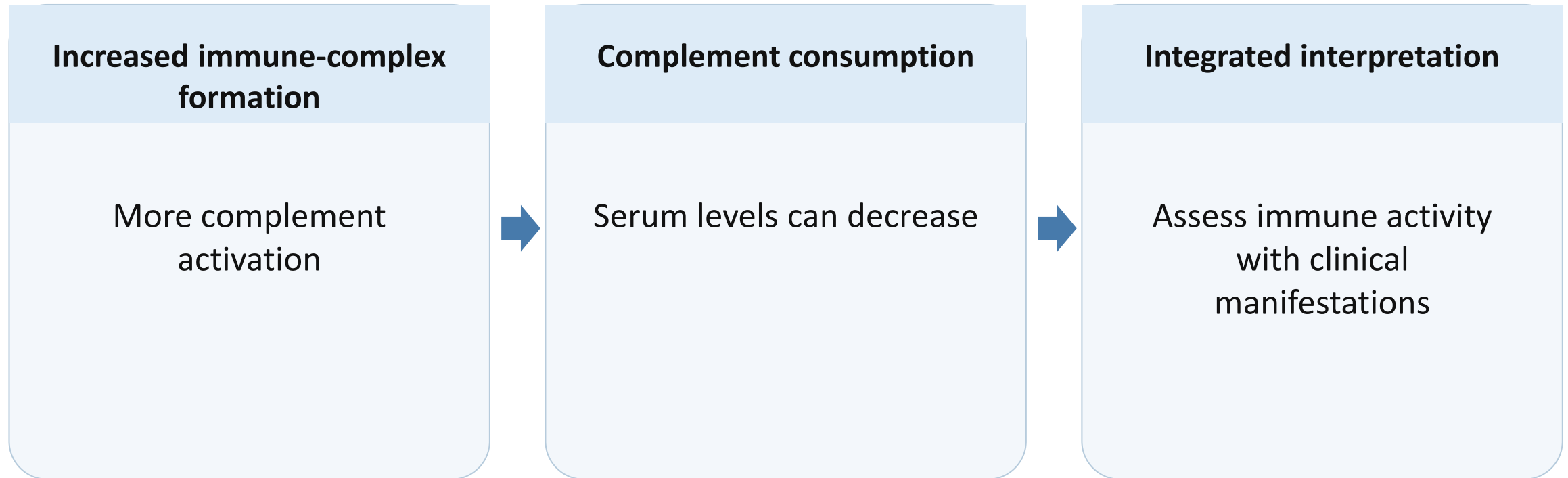
Libman–Sacks endocarditis is noninfective

- Small verrucous vegetations may involve either surface of valve leaflets.
- Mitral and aortic valves are particularly involved.
- This is morphologically distinct from typical infective or rheumatic valve vegetations.



Original valve schematic — not pathology imaging

SLE activity can deplete circulating complement



Clinical serology must be integrated with organ assessment

Serologic finding	Related clinical question	Corroborating evidence
Anti-dsDNA	Is renal involvement present?	Urinalysis and kidney evaluation
Blood-cell antibodies	Are cytopenias present?	Complete blood count
Antiphospholipid antibodies	Thrombotic phenotype?	Thrombosis / obstetric history
Low complement	Immune complex activity?	Current symptoms and organ findings
Anti-Ro/La	Neonatal/fetal risk context?	Maternal–fetal clinical assessment

Case: A positive ANA without disease-specific findings

Clinical stem

A patient has a positive generic ANA but no clear multisystem clinical syndrome.

Interpretive question

Question: Does the antibody result alone establish SLE?

Teaching answer

Interpretation: No. Generic ANAs are sensitive but not specific; Phenotype and directed testing are necessary.

Case: Anti-dsDNA with abnormal urinary findings

Clinical stem

A patient with suspected SLE has anti-dsDNA reactivity and new proteinuria.

Interpretive question

Question: What complication needs targeted evaluation?

Teaching answer

Interpretation: Possible lupus nephritis; Assess renal function, urine sediment, complement, and morphology as appropriate.

Case: Prolonged PTT and a thrombotic event

Clinical stem

A patient with lupus has a prolonged phospholipid-dependent clotting test and a thrombosis.

Interpretive question

Question: Does “anticoagulant” imply protection against clots?

Teaching answer

Interpretation: No. Antiphospholipid antibodies may prolong in-vitro tests yet coexist with thrombosis.

Case: Maternal anti-Ro/La reactivity

Clinical stem

Maternal Ro/SS-A or La/SS-B antibodies are identified during pregnancy.

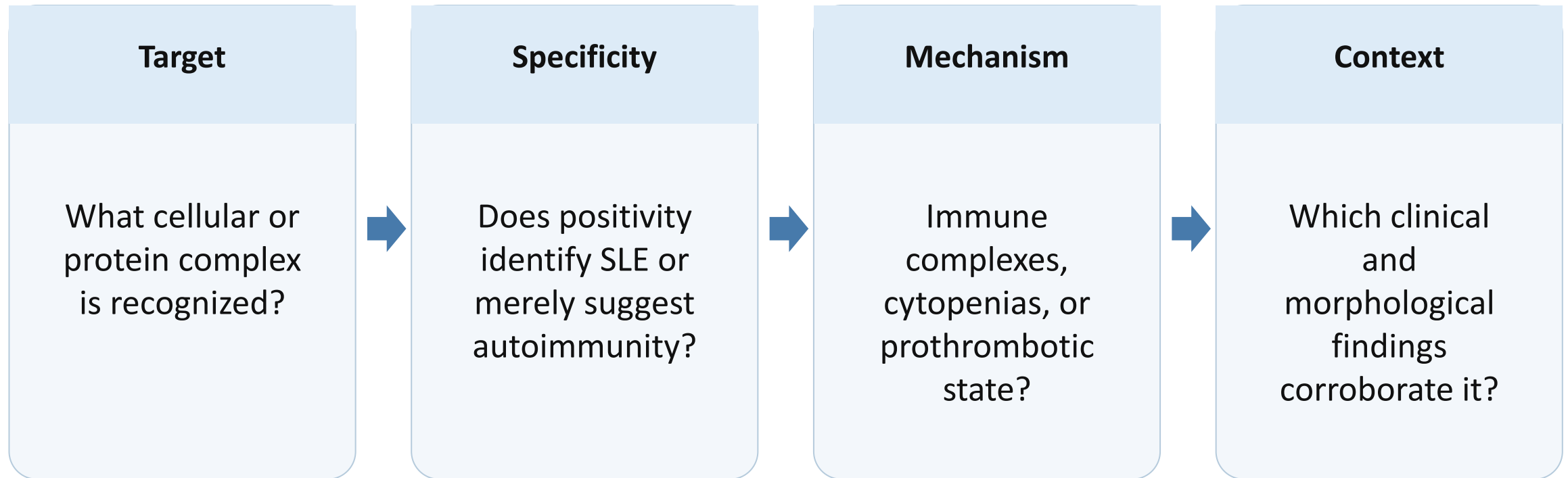
Interpretive question

Question: Which fetal-associated lupus manifestation is important?

Teaching answer

Interpretation: These antibodies with neonatal lupus and congenital heart block.

Final synthesis: Four decisions for every autoantibody



Central concepts to retain

- Generic ANA detection is broad; Anti-dsDNA and anti-Sm offer greater SLE specificity.
- The HEp-2 pattern proposes a target family, but antigen-specific assays confirm identity.
- Immune complexes dominate many organ lesions; Cell-reactive antibodies cause cytopenias.
- Antiphospholipid antibodies link abnormal assays with thrombosis, not protection from clotting.
- Loss of tolerance, persistent nuclear antigens, TLRs, and interferon sustain the response.

Source and interpretation boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 6, pp. 197–203.
- Topic scope: SLE autoantibodies, ANA staining patterns, immunologic pathogenesis, and clinicopathologic correlations.
- Approximate antibody positivity from Robbins Table 6.10; staining-pattern concepts from Figure 6.24 caption and text.
- Classification criteria shown in the source are historical; this lecture does not present them as contemporary diagnostic rules.