

CD4+ T Cell–Mediated Inflammation

Type IV hypersensitivity · mechanisms · morphology · clinical examples

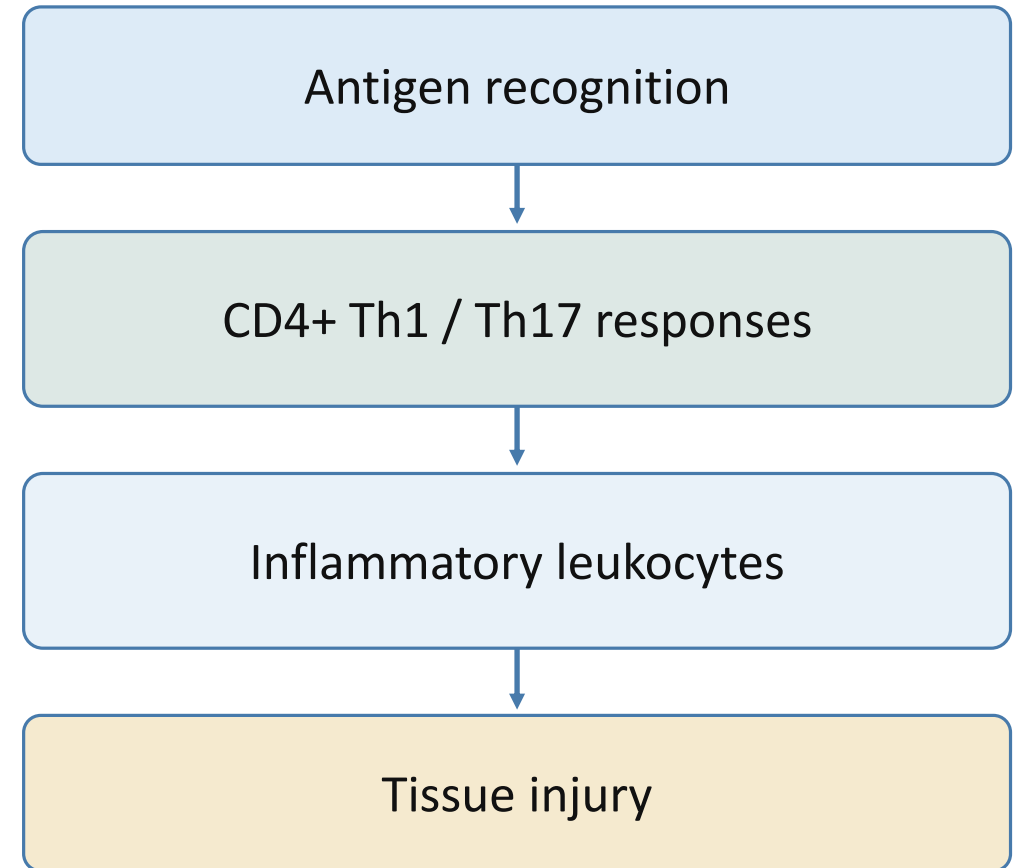
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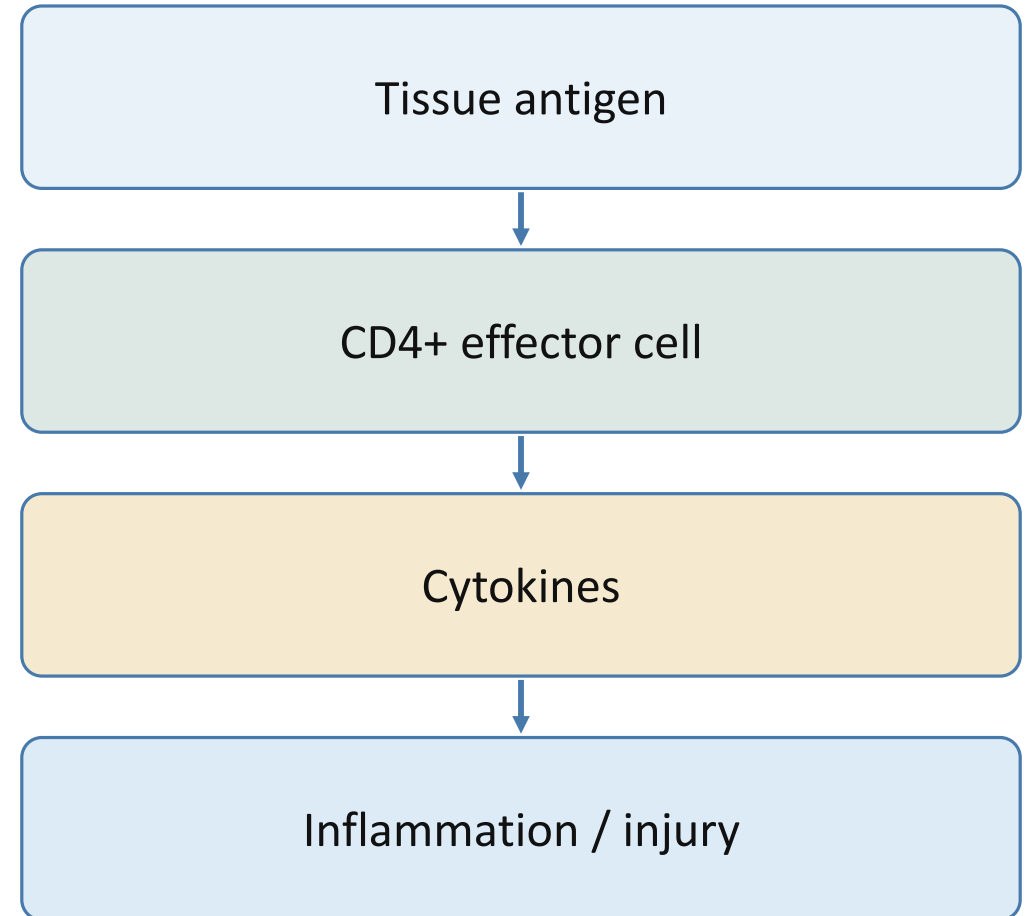
Learning objectives

- Explain how antigen-specific CD4+ T cells generate delayed inflammatory injury.
- Compare Th1–macrophage and Th17–neutrophil pathways.
- Recognize the time course and morphology of delayed-type hypersensitivity.
- Relate contact dermatitis, granulomas, and selected diseases to mechanism.
- Distinguish cytokine-driven inflammation from CD8+ cytotoxicity.



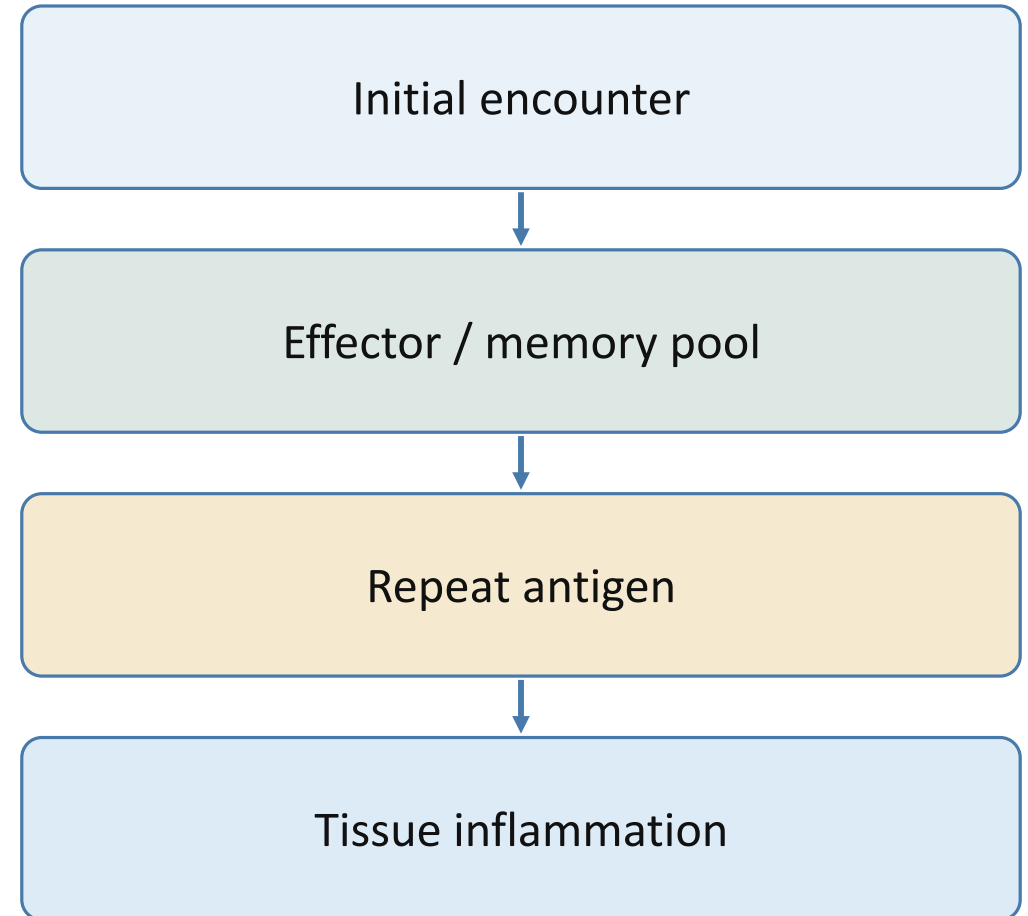
Type IV hypersensitivity: The cellular arm

- Cell-mediated hypersensitivity is driven mainly by cytokines from CD4+ T lymphocytes.
- The resulting inflammation may be chronic and destructive.
- CD8+ cytotoxicity is a distinct, sometimes coexisting, mechanism.

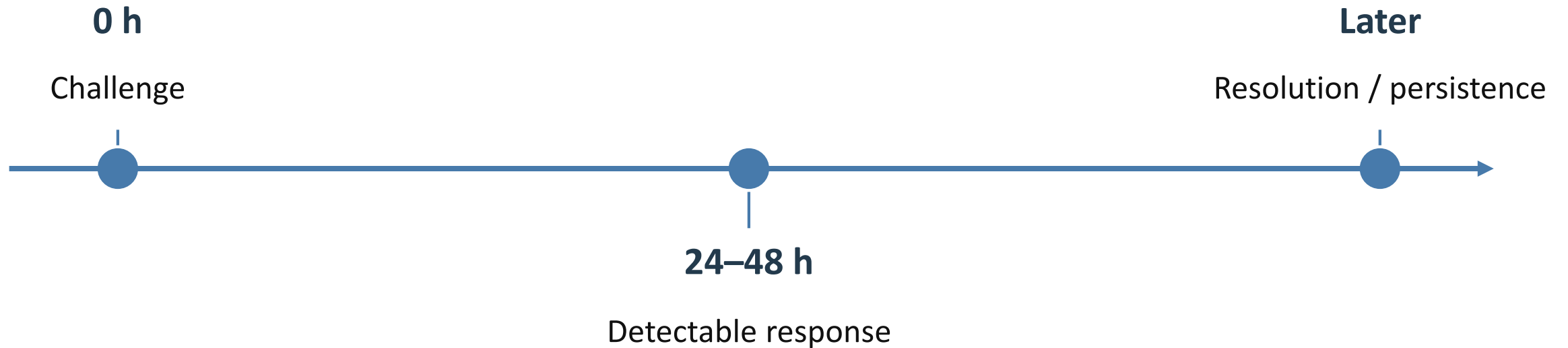


Prior sensitization is essential to classic DTH

- An initial antigen encounter generates differentiated and memory T cells.
- A subsequent tissue antigen challenge engages antigen-specific effector responses.
- The visible reaction follows cellular recruitment and activation.



Why the reaction is delayed



DTH is distinct from immediate hypersensitivity in its kinetics. • A cutaneous reaction becomes detectable after approximately 24–48 hours. • Timing reflects the cellular inflammatory response to antigen challenge.

Two ways T cells injure tissues

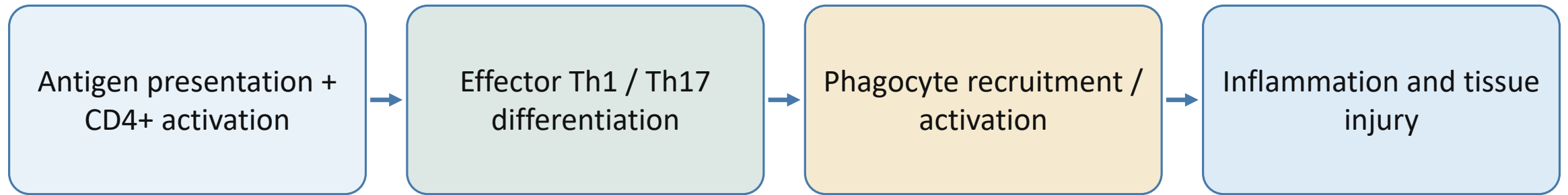
CD4+ inflammation

Cytokines recruit and activate
leukocytes

CD8+ cell killing

Recognized target cells are directly
injured

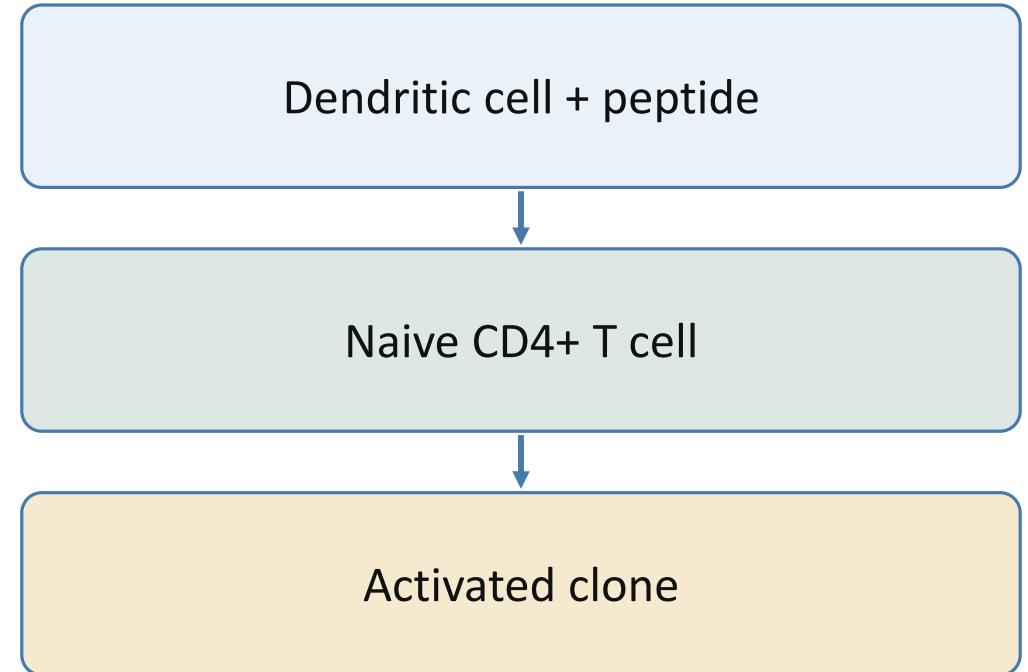
Three stages of CD4+ inflammatory injury



The pathogenesis follows a causal sequence from recognition to tissue effect.

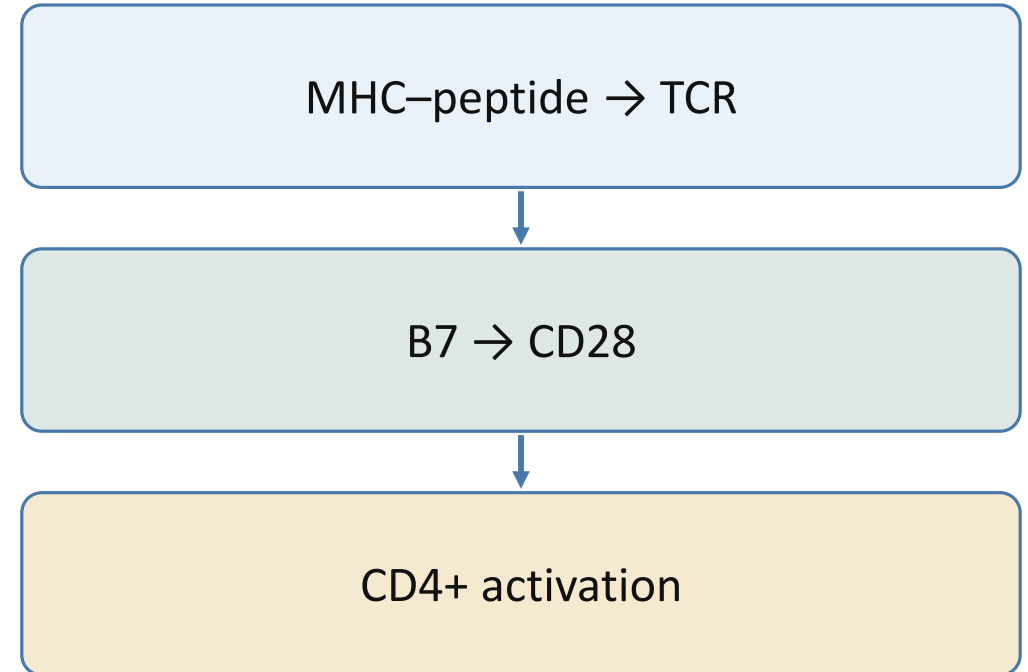
Dendritic cells initiate antigen-specific activation

- Naive CD4+ T cells recognize antigen-derived peptides displayed by dendritic cells.
- The antigen-presenting cell supplies the context for clonal activation.
- The primed population can later respond in tissue.

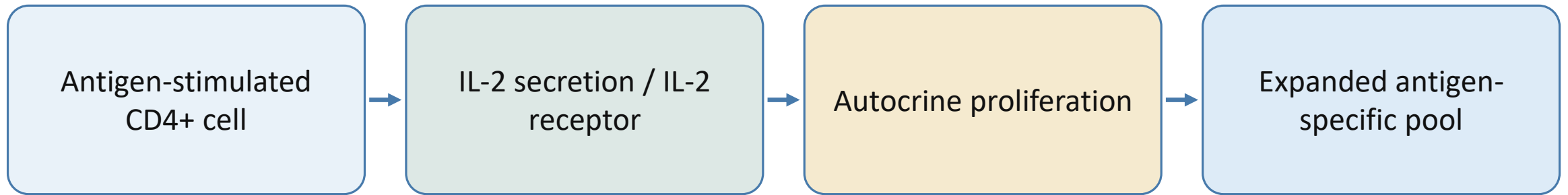


Costimulation accompanies antigen recognition

- Antigen recognition is the first activation signal.
- B7 proteins (CD80/CD86) on antigen-presenting cells engage CD28 on naive T cells.
- Antigen and costimulation cooperate in the initiating response.

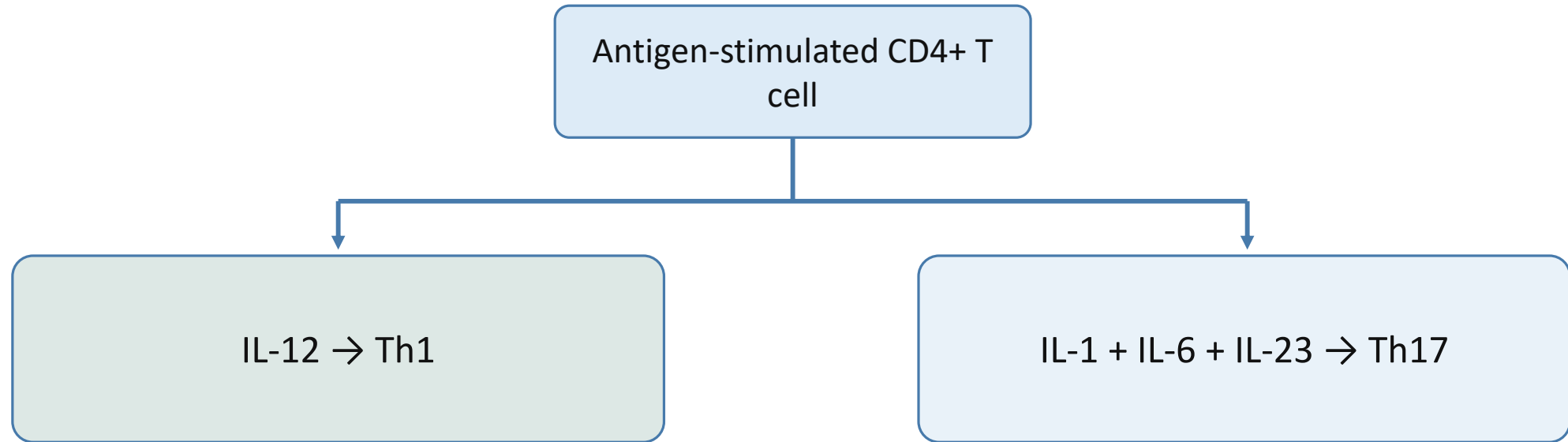


IL-2 expands the responsive T-cell clone



- Activated CD4+ cells secrete IL-2 and express its high-affinity receptor.
- IL-2 functions as an autocrine proliferation signal.
- Clonal expansion increases the number of antigen-responsive cells.

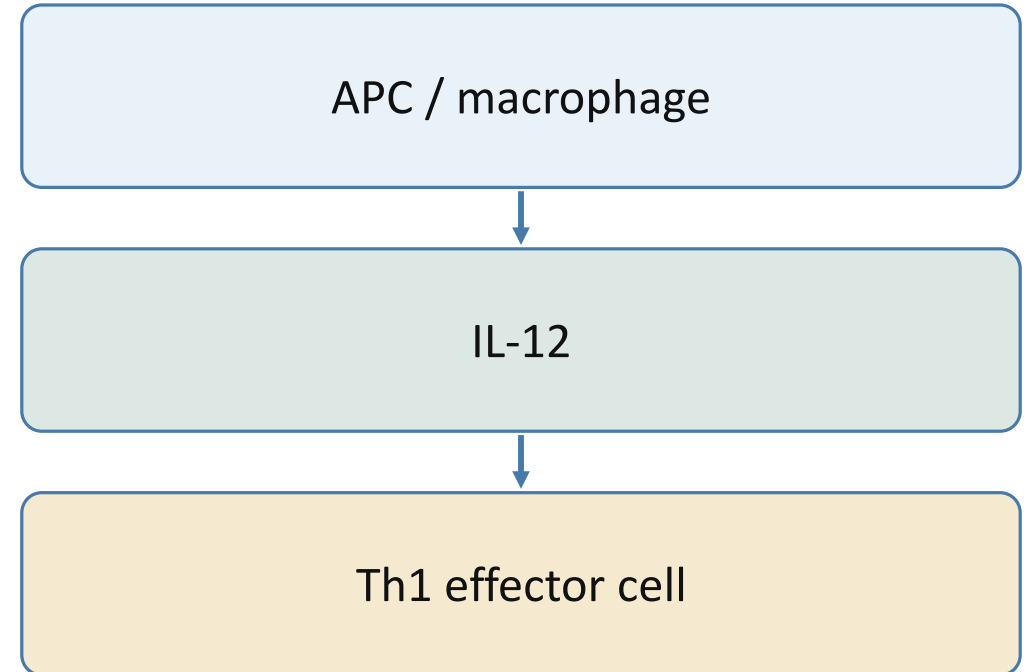
The APC cytokine milieu guides differentiation



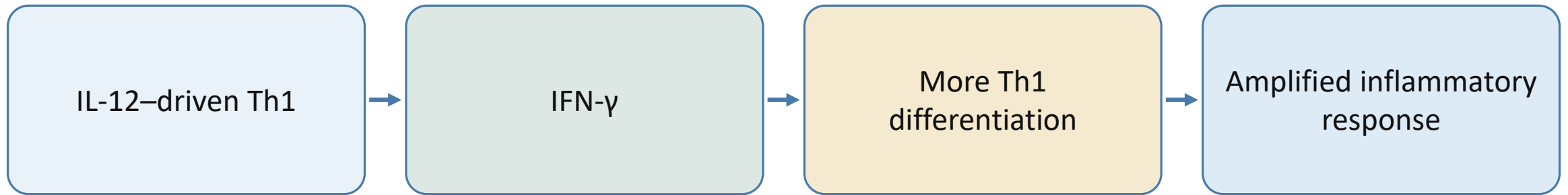
The pattern of cytokines at initial activation helps determine helper-T-cell fate. Th1 and Th17 populations subsequently produce distinct inflammatory responses.

IL-12 programs the Th1 pathway

- Dendritic cells and macrophages can supply IL-12.
- IL-12 induces differentiation toward the Th1 subset.
- Th1 cells are linked to macrophage-dominant inflammatory injury.



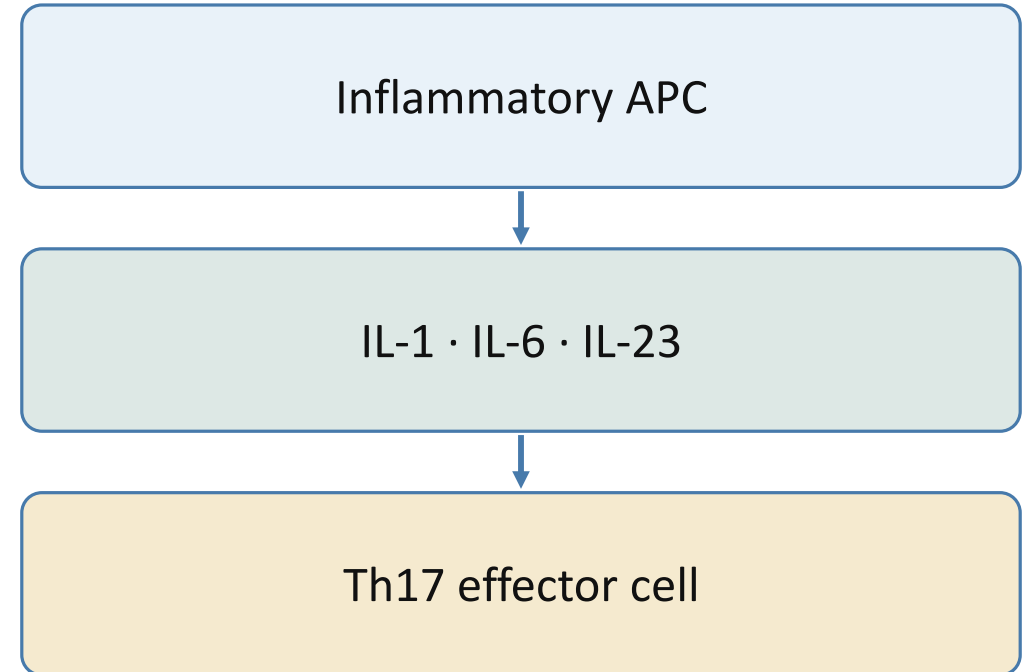
IFN- γ reinforces Th1 development



- Effector Th1 cells produce interferon- γ (IFN- γ).
- IFN- γ promotes further Th1 development and amplifies the reaction.
- It is also the principal macrophage-activating effector cytokine.

IL-1, IL-6, and IL-23 support Th17 differentiation

- Activated antigen-presenting cells produce inflammatory cytokines.
- IL-1, IL-6, and IL-23 promote the Th17 pathway.
- Th17 responses preferentially recruit neutrophils and monocytes.

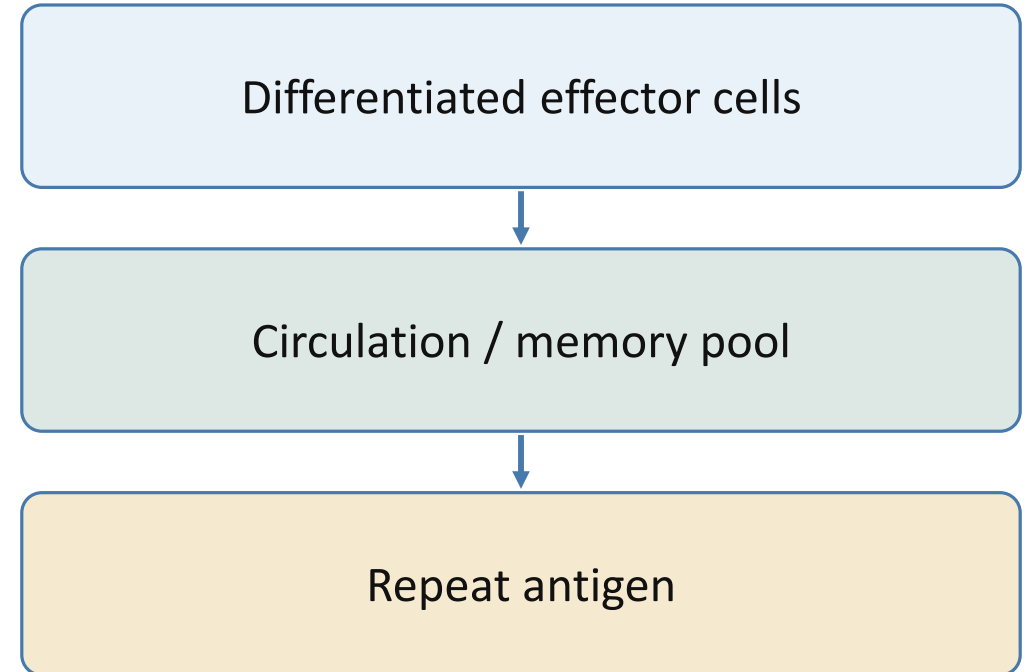


Th1 and Th17 have different effector signatures

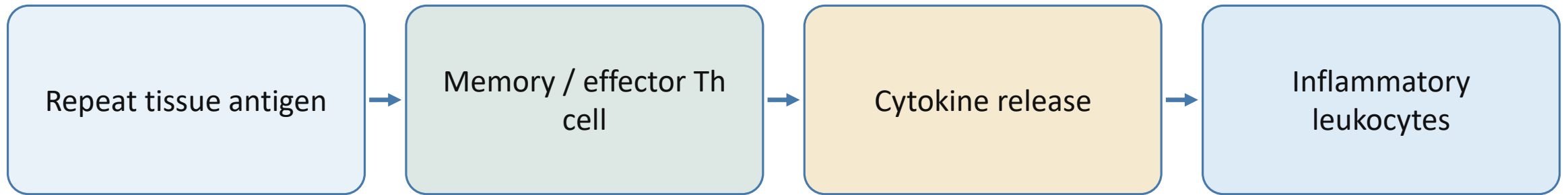
Feature	Th1 response	Th17 response
Inducing cytokines	IL-12	IL-1, IL-6, IL-23
Principal effector signals	IFN- γ	IL-17, IL-22, chemokines
Dominant recruited / activated cells	Activated macrophages	Neutrophils and monocytes
Common tissue pattern	Macrophage-rich inflammation	Neutrophil-rich component

Memory cells enable rapid recall responses

- Some differentiated T cells enter the circulation.
- They become part of long-lived memory T-cell populations.
- Persistent immune memory explains reactions to a later antigen encounter.



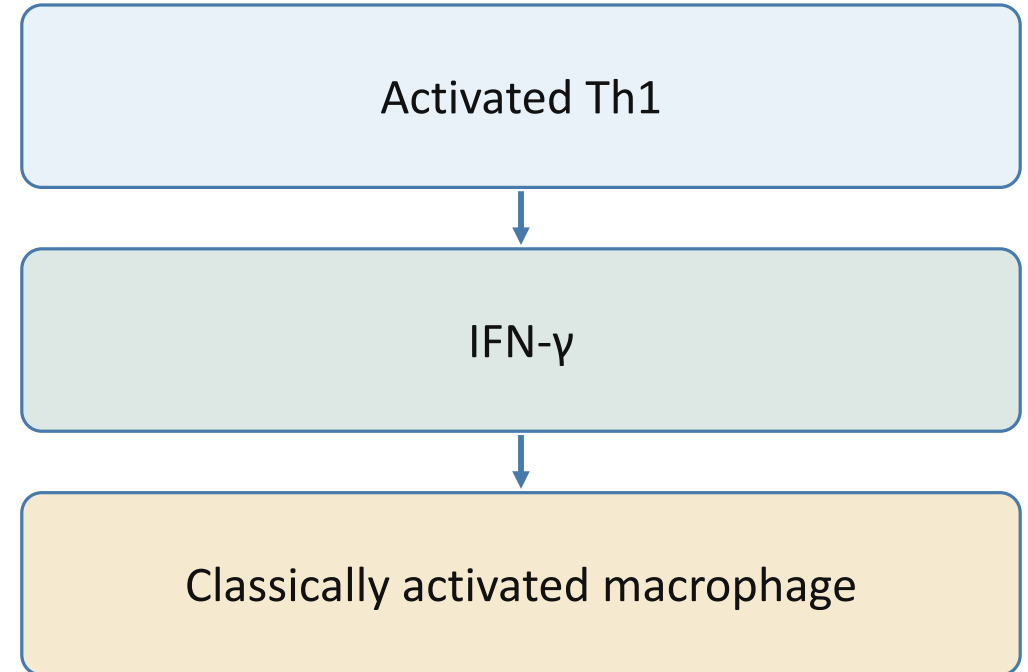
Effector-phase responses require antigen re-exposure



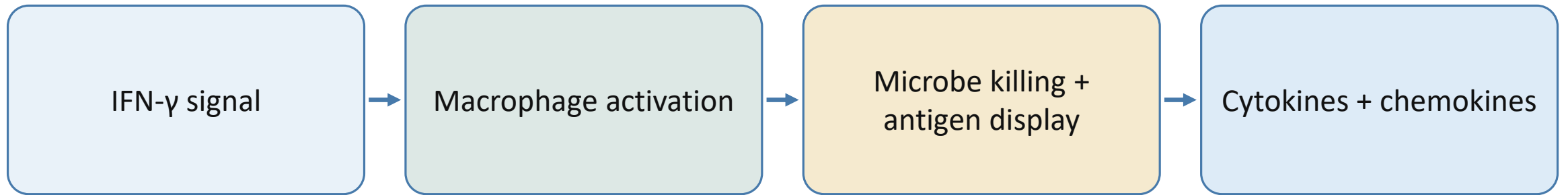
- A primed Th1 or Th17 cell encounters its target antigen again.
- Local cytokine production triggers inflammatory-cell recruitment.
- The downstream phagocytes are major effectors of tissue injury.

IFN- γ is the central Th1 effector signal

- On repeat antigen encounter, Th1 cells produce IFN- γ .
- IFN- γ produces the characteristic activated-macrophage response.
- Sustained activation can turn a protective response into tissue injury.



Classical macrophage activation changes cell function

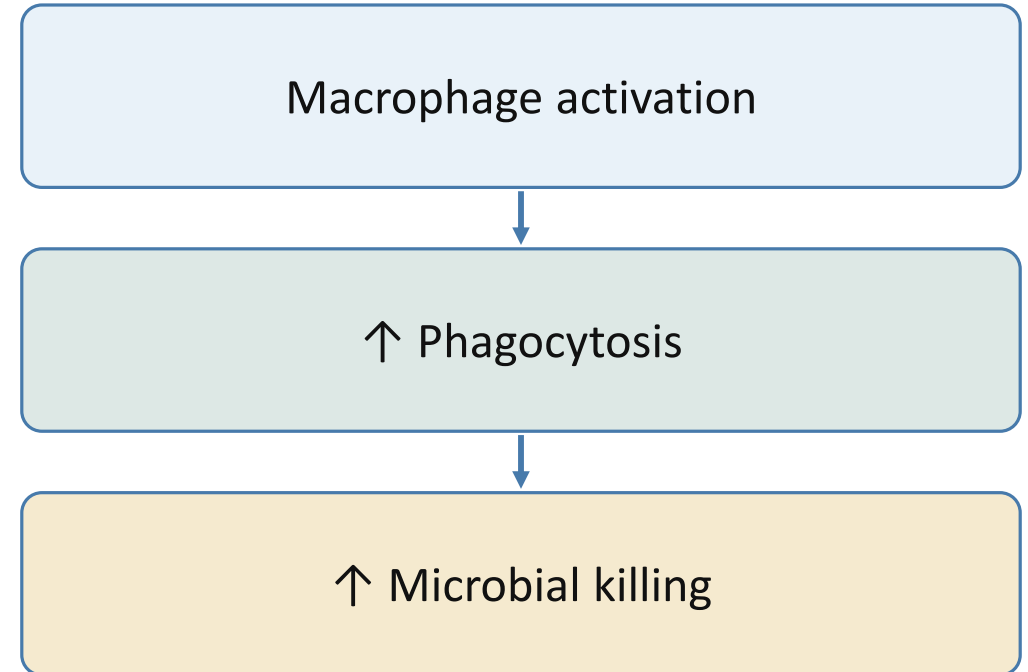


IFN- γ induces a broad macrophage activation program.

Antimicrobial activity, antigen presentation, and inflammatory output all increase.

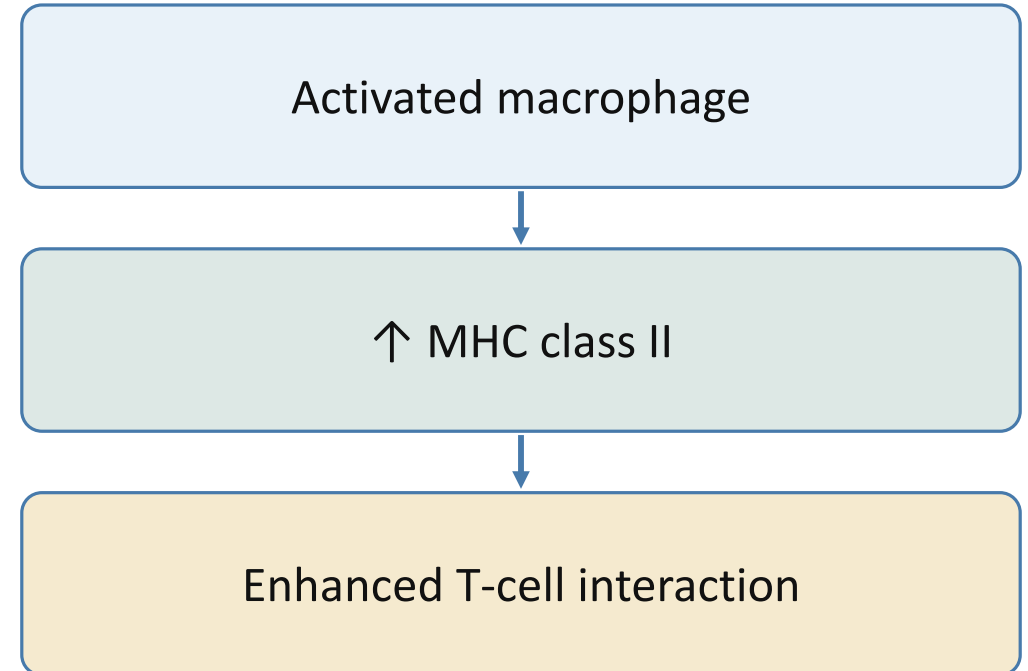
Activated macrophages increase microbicidal activity

- Macrophages acquire greater capacity to phagocytose microbes.
- Their ability to kill ingested microorganisms is augmented.
- This response is beneficial when the antigen is a persistent intracellular microbe.



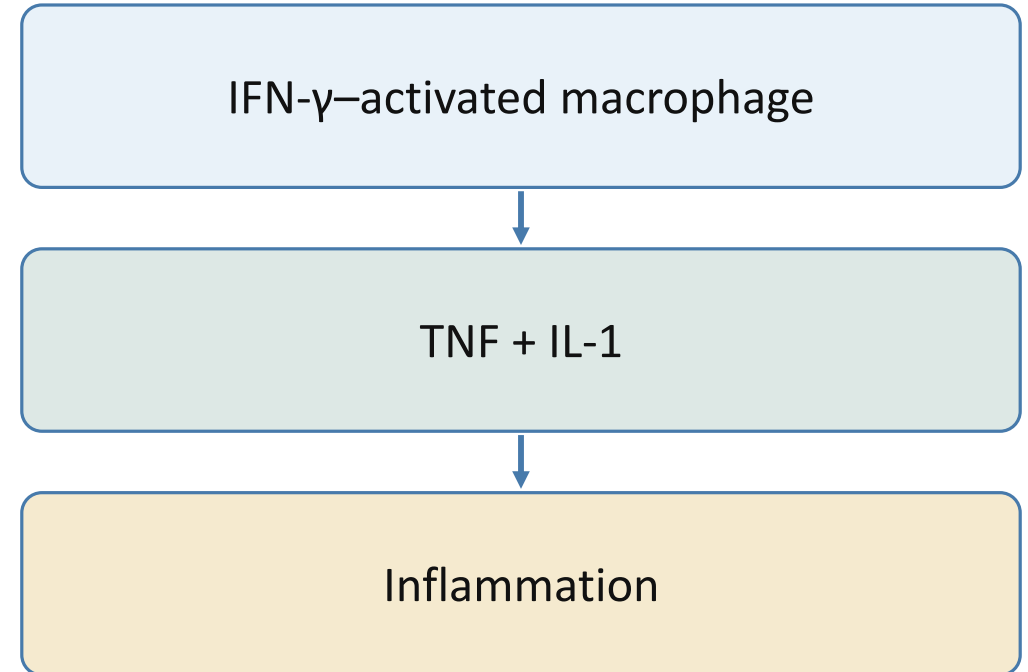
Macrophage MHC II expression amplifies recognition

- IFN- γ –activated macrophages express more MHC class II molecules.
- Increased peptide display enhances interaction with helper T cells.
- The macrophage becomes a stronger antigen-presenting participant.



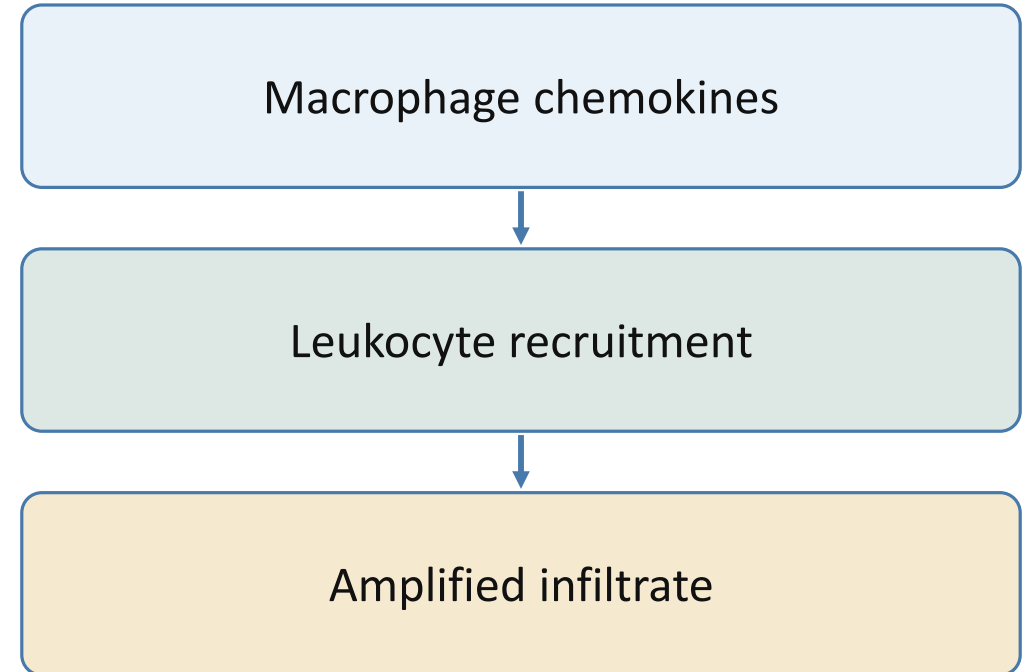
TNF and IL-1 convert activation into inflammation

- Activated macrophages secrete TNF and IL-1.
- These mediators promote local inflammatory changes.
- Their continued production contributes to the damaging reaction.

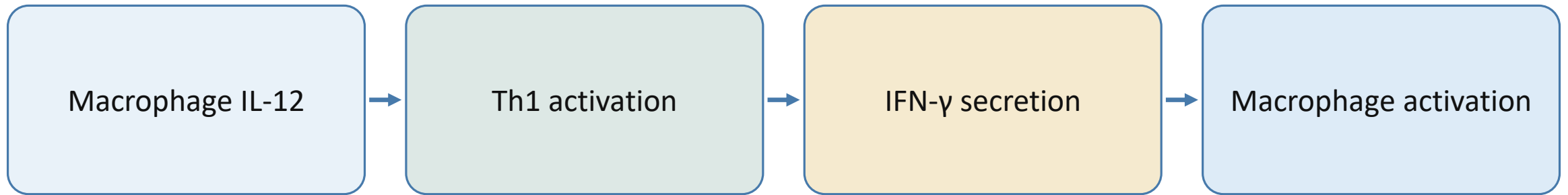


Chemokines increase inflammatory-cell recruitment

- Classically activated macrophages produce chemokines.
- Chemokine-dependent recruitment expands the local infiltrate.
- The recruited cells sustain the cytokine-driven lesion.



Macrophage IL-12 creates a reinforcing loop



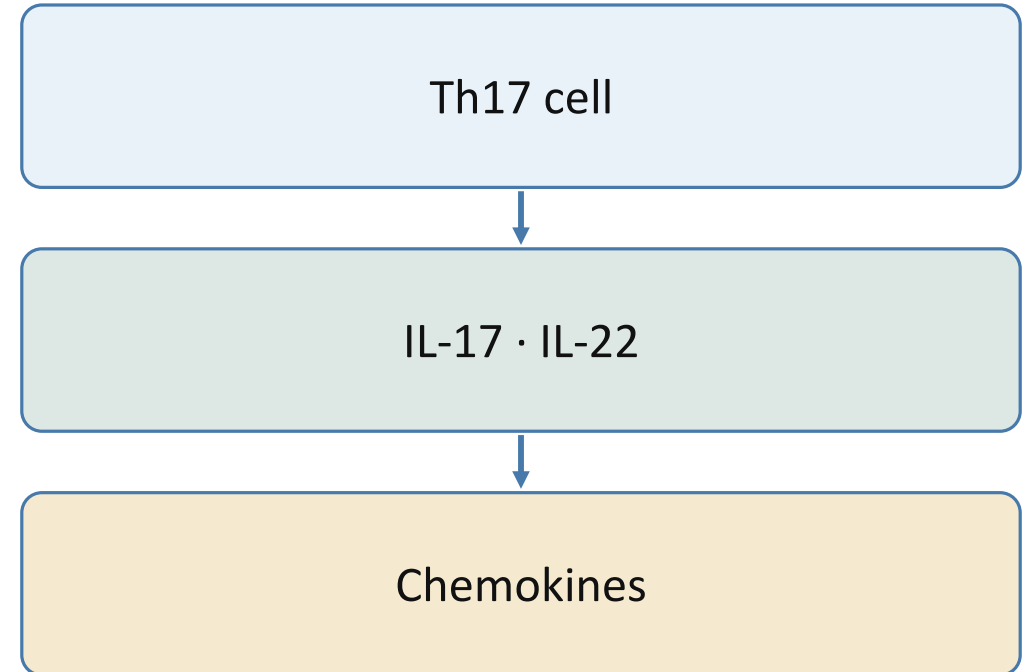
- Activated macrophages can produce additional IL-12.
- IL-12 supports the Th1 population that makes IFN-γ.
- This positive-feedback architecture explains persistent activity.

When host defense becomes tissue damage

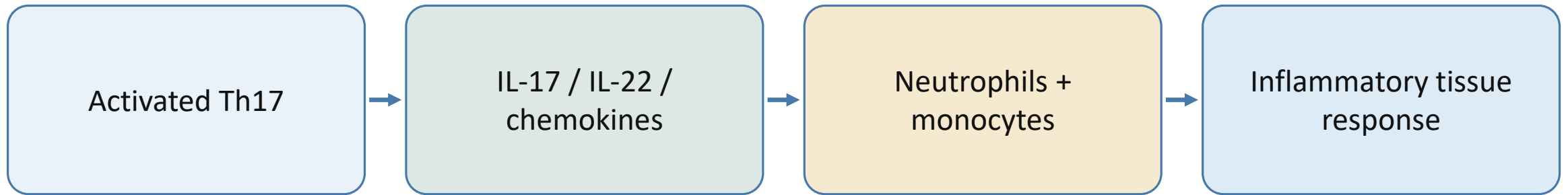
Containment / defense	Persistence / pathology
Phagocytes eliminate the offending antigen	Antigen or stimulation persists
Macrophage activation supports microbial killing	Continued activation sustains inflammation
Response subsides when the trigger resolves	Repeated cytokine release injures tissue

Th17 cells deploy IL-17 and IL-22

- Activated Th17 cells secrete IL-17 and IL-22.
- They also produce chemokines and additional cytokines.
- Their combined output organizes a leukocyte-rich inflammatory reaction.



Th17 responses recruit neutrophils and monocytes

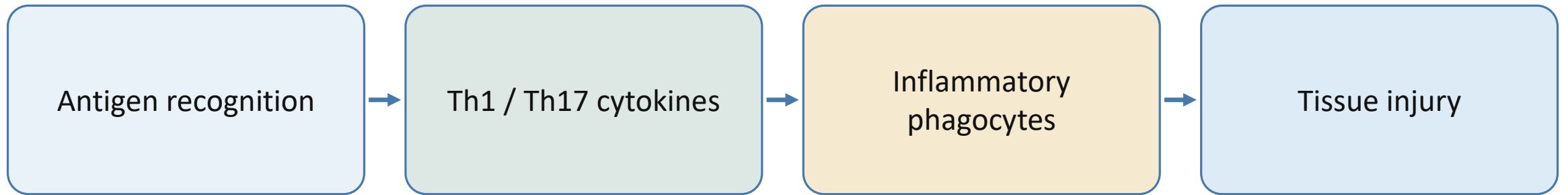


- Th17-associated cytokines mobilize inflammatory leukocytes.
- Neutrophils are a more prominent component than in classic Th1 responses.
- Monocytes also enter the inflammatory tissue.

Predict infiltrate composition from T-cell pathway

Feature	Th1-dominant	Th17-dominant
Key Th-cell cytokine	IFN- γ	IL-17 / IL-22
Characteristic phagocyte	Activated macrophage	Neutrophil, plus monocyte
Typical pathologic emphasis	Macrophage-rich inflammation	More prominent neutrophil component
Key diagnostic consideration:	Responses may coexist	Responses may coexist

A unified map of CD4⁺ inflammatory injury

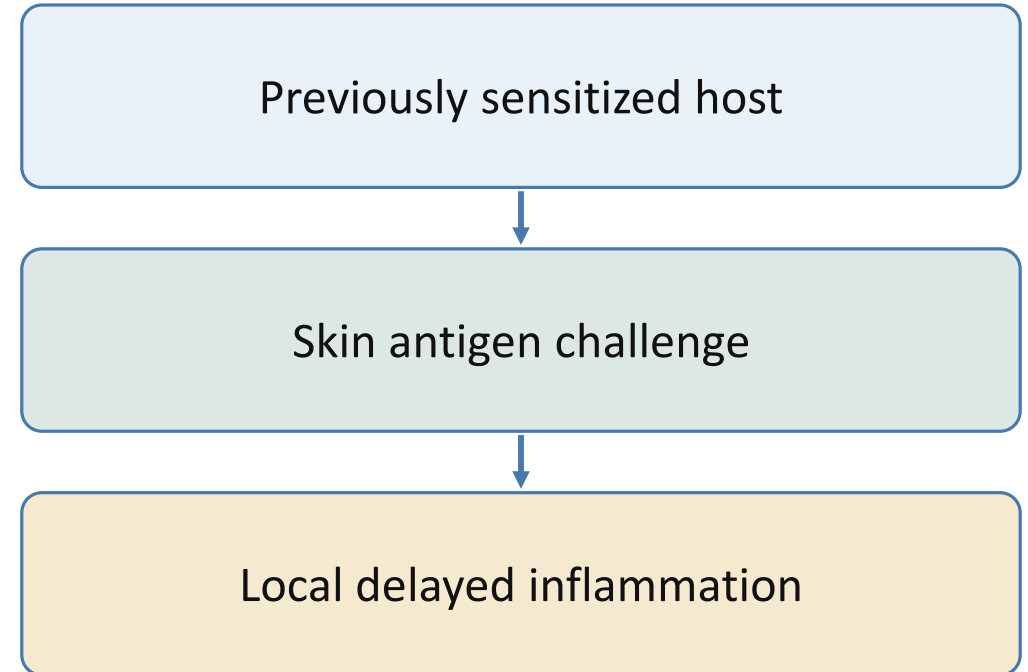


Cytokines connect antigen-specific CD4⁺ cells to tissue injury.

The principal route differs by the Th1 or Th17 effector program.

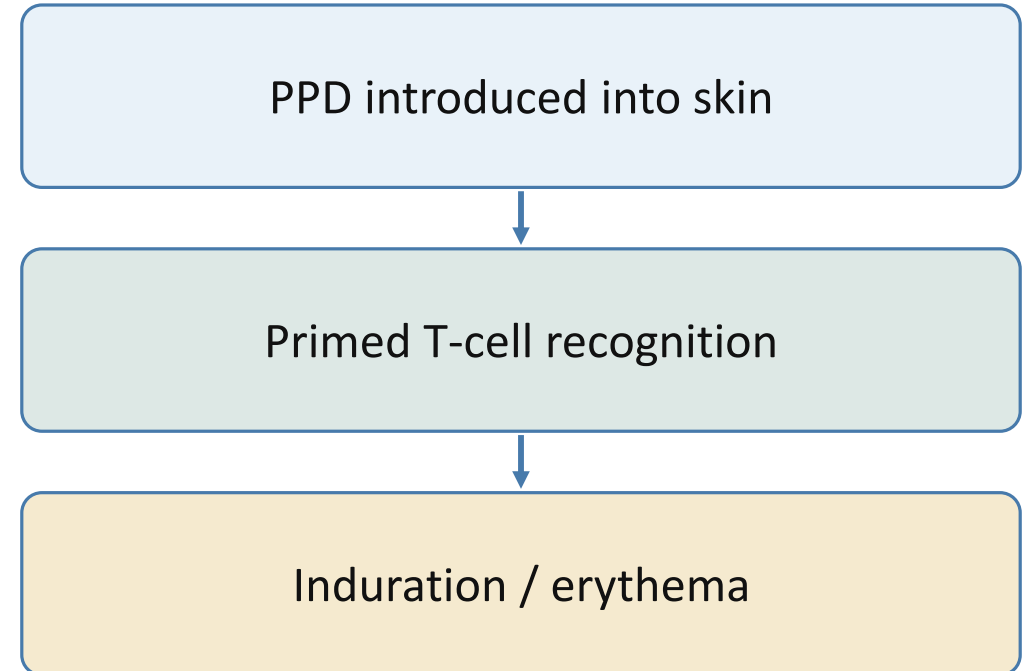
DTH: A recall reaction in previously immunized skin

- Delayed-type hypersensitivity (DTH) is the classic model of CD4+ inflammation.
- Antigen is introduced into skin of a sensitized individual.
- The response develops over hours rather than immediately.

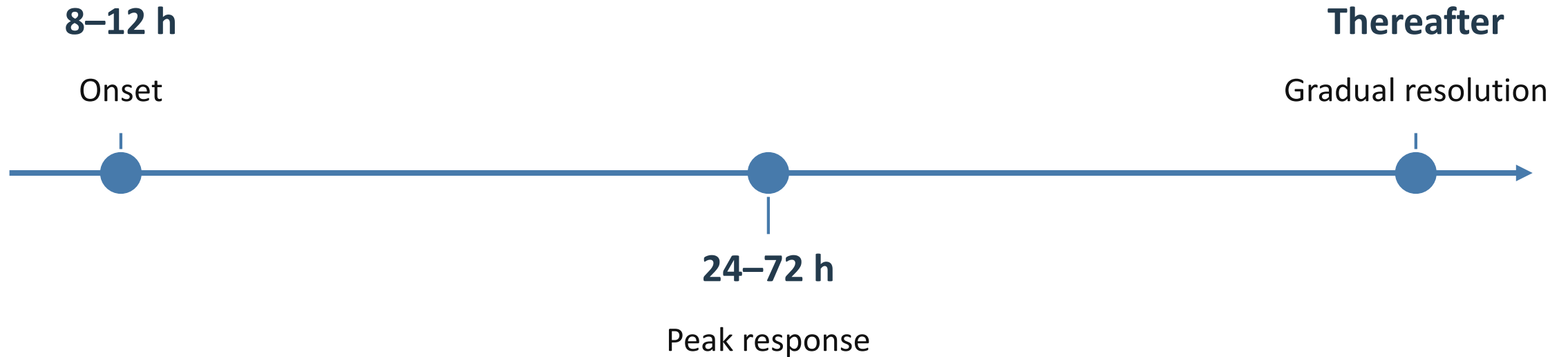


Tuberculin is an antigenic recall challenge

- Purified protein derivative (PPD; Tuberculin) contains antigen from the tubercle bacillus.
- An intradermal challenge elicits DTH in a previously sensitized individual.
- The reaction illustrates a local, antigen-specific inflammatory memory response.



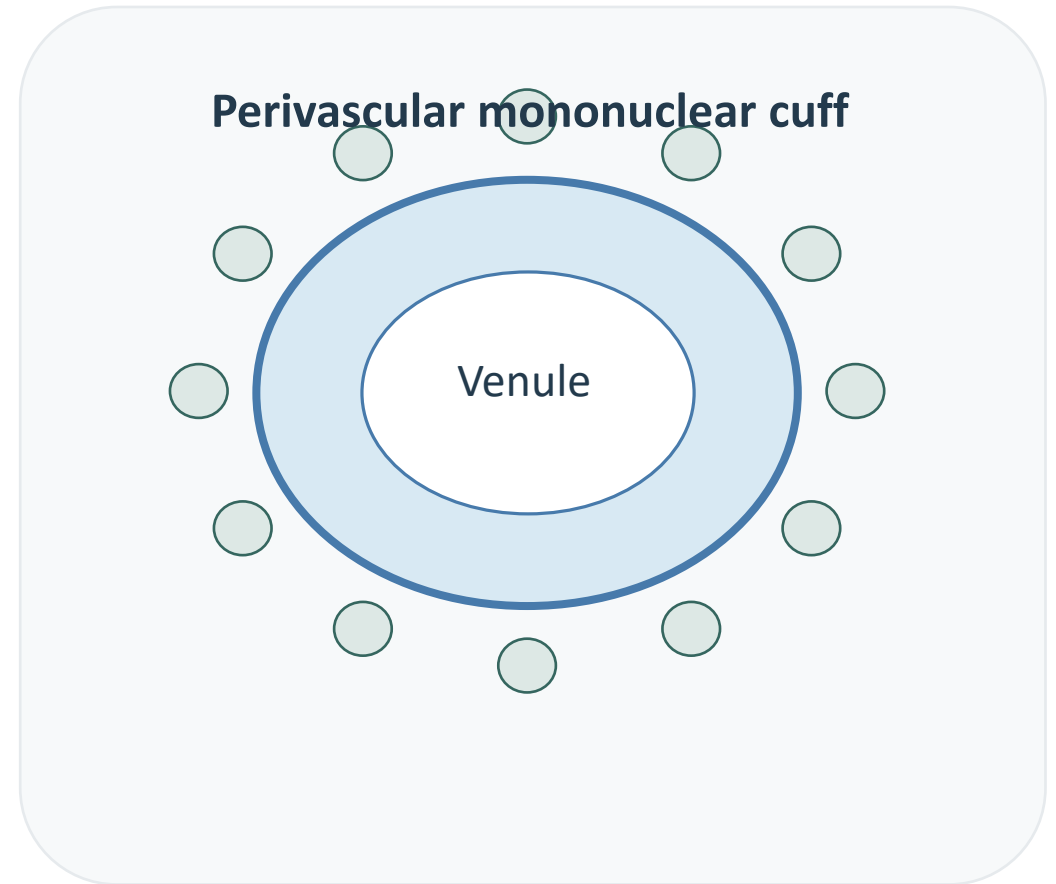
The tuberculin reaction has a characteristic course



Redness and induration begin after about 8–12 hours. • The response peaks around 24–72 hours. • The local lesion then gradually subsides.

DTH morphology: Perivascular mononuclear cuffing

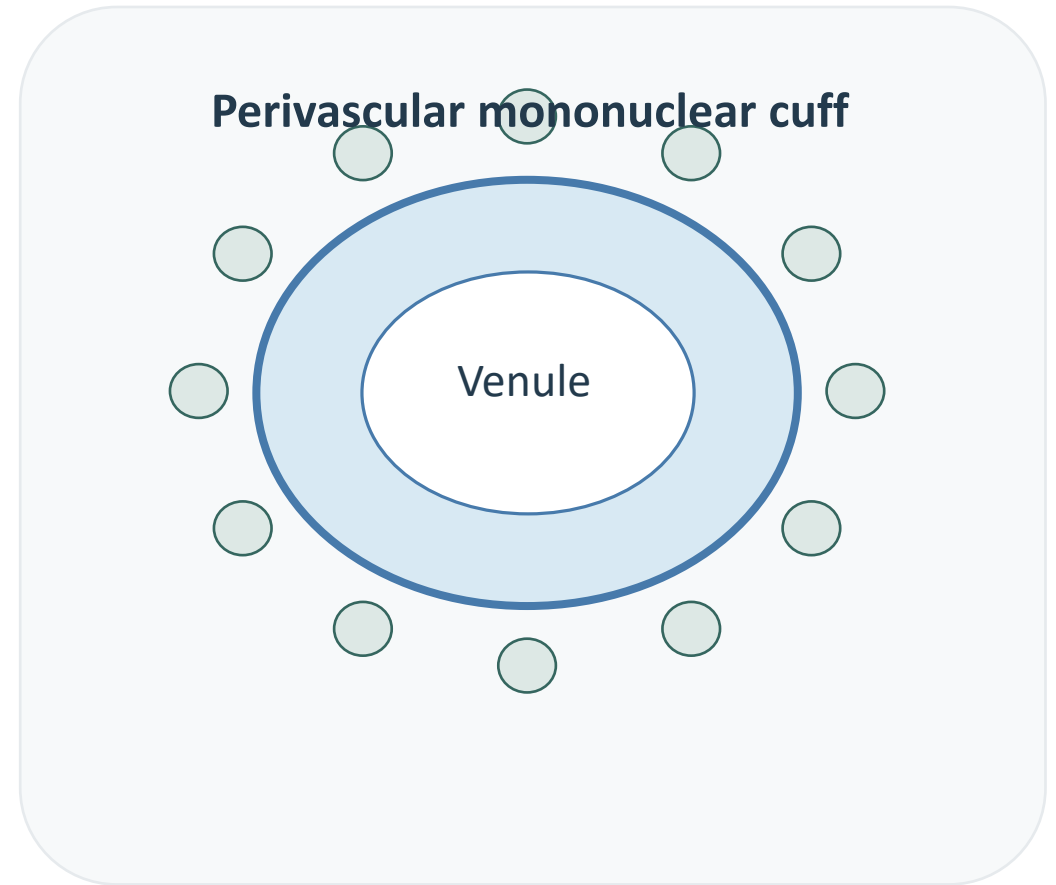
- CD4+ lymphocytes and macrophages collect around dermal venules.
- Their perivascular aggregation produces a cuff-like infiltrate.
- This is the classic microscopic pattern of the cellular reaction.



Schematic — not a histologic specimen

Endothelial hypertrophy accompanies activation

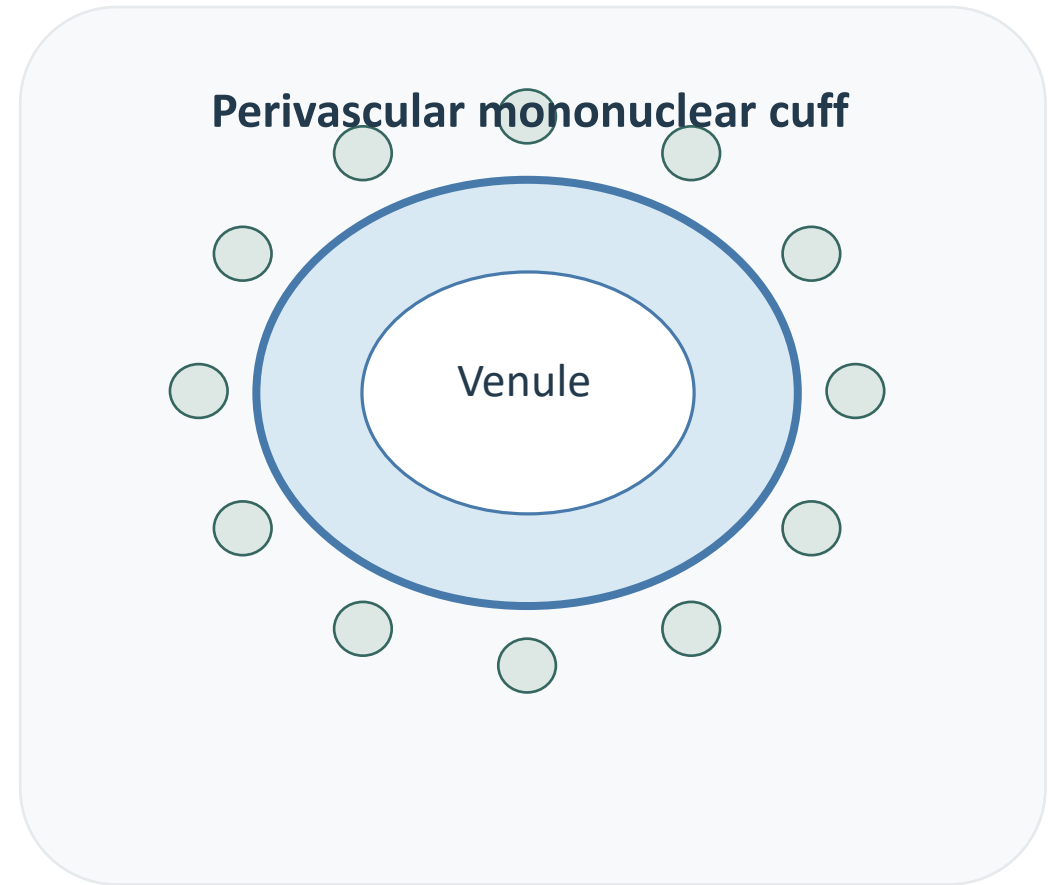
- Fully developed DTH lesions show hypertrophic venular endothelial cells.
- The change reflects cytokine-mediated endothelial activation.
- It accompanies the surrounding inflammatory-cell accumulation.



Schematic — not a histologic specimen

Dermal edema and fibrin support the tissue reaction

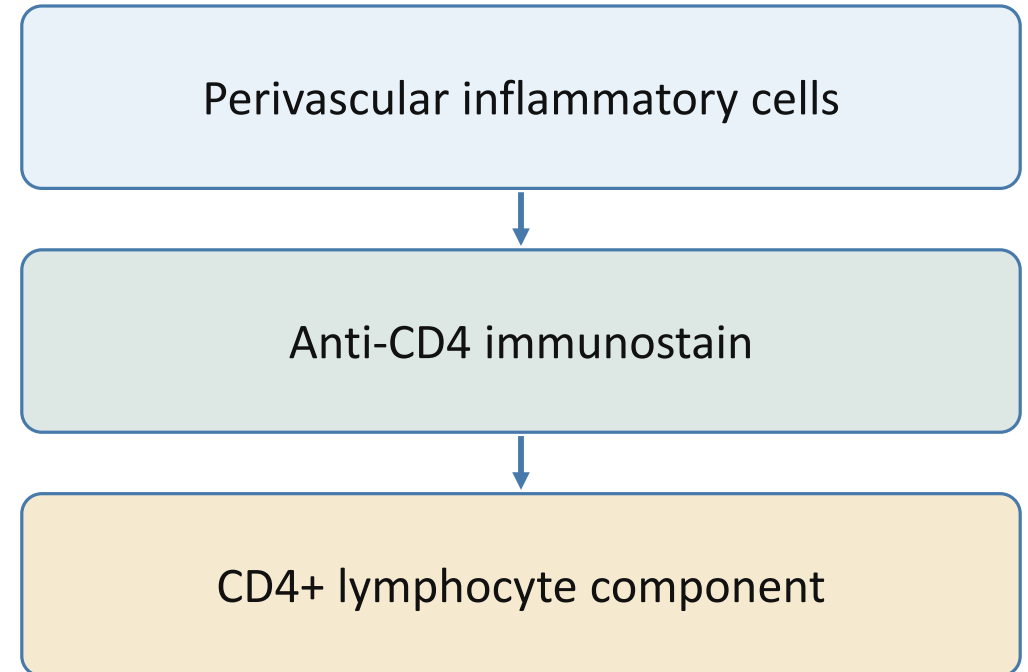
- The textbook DTH example includes dermal edema.
- Fibrin deposition can accompany the perivascular mononuclear infiltrate.
- These associated findings add context to the vascular-centered pattern.



Schematic — not a histologic specimen

Anti-CD4 staining identifies the T-cell component

- The illustrated source lesion contains a predominantly perivascular CD4-positive infiltrate.
- Immunoperoxidase staining localizes the helper-T-cell component.
- CD4 labeling supports cellular identity; It does not by itself establish the antigen.



Transient DTH versus sustained antigenic stimulation

Short-lived recall response	Persistent tissue stimulus
Cellular response peaks then subsides	Inflammation remains active
Perivascular T cells and macrophages	Macrophages increasingly predominate
Prototype: Tuberculin skin reaction	Possible progression to granulomatous inflammation

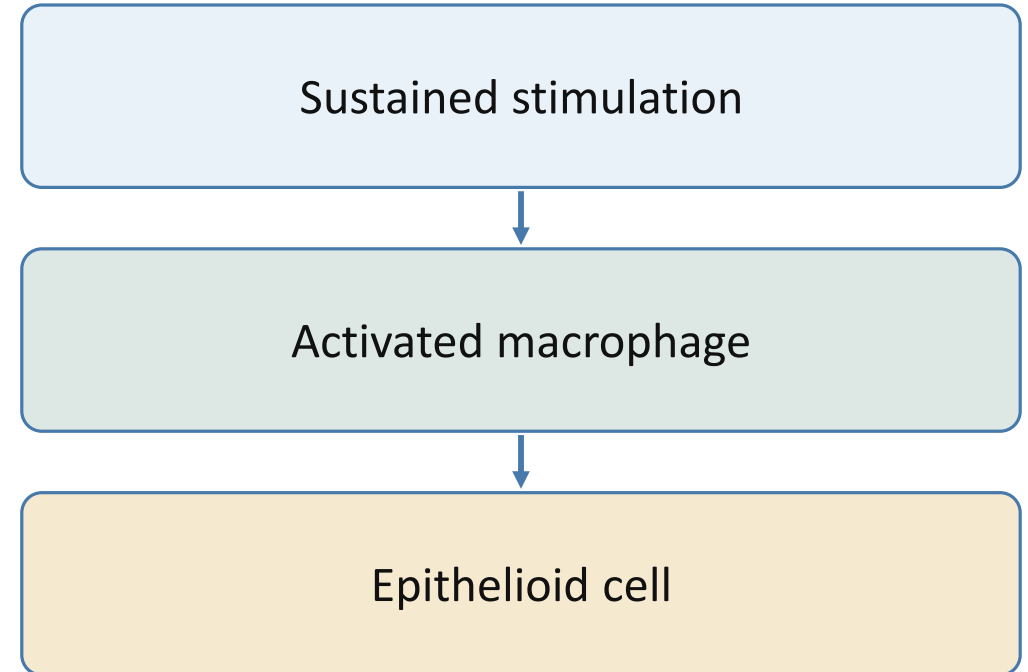
Persistent antigens alter the cellular infiltrate



Indigestible or persisting antigens can maintain the response. • Macrophages become dominant over approximately 2–3 weeks. • The chronic response can organize into granulomas.

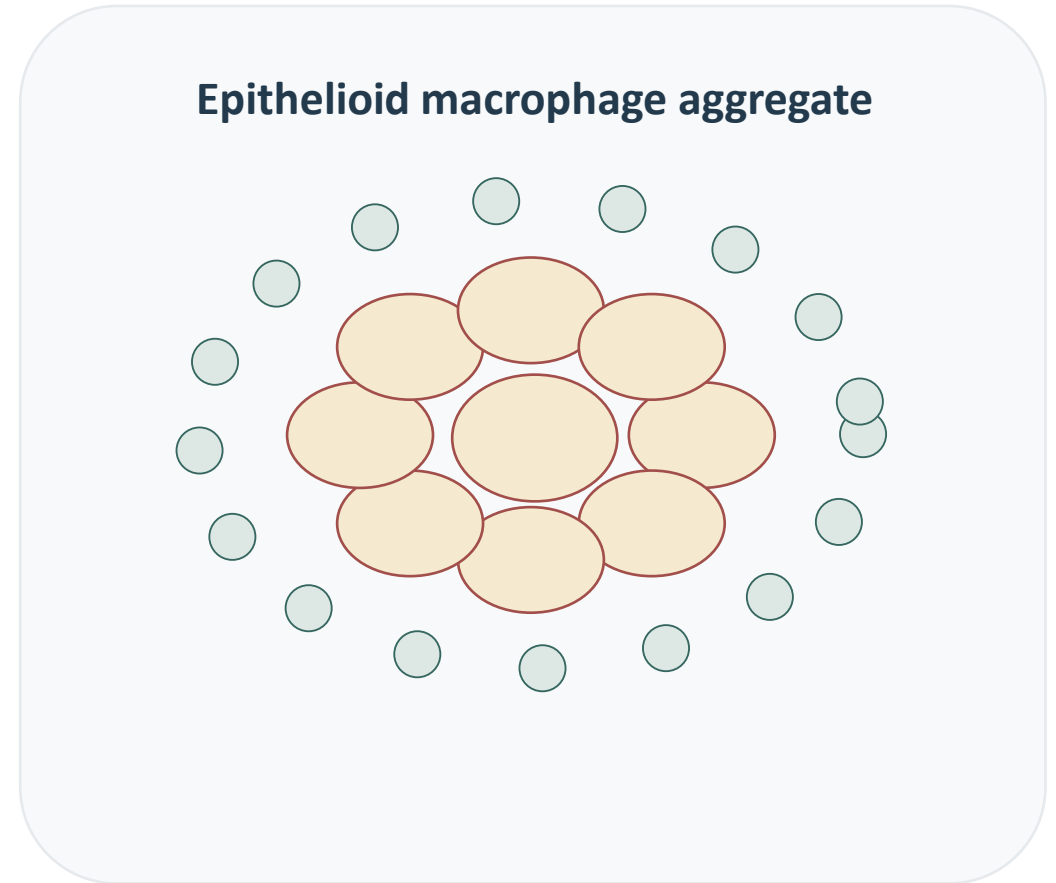
Epithelioid cells are transformed macrophages

- Sustained activation changes macrophage morphology.
- They become larger, with abundant cytoplasm: Epithelioid cells.
- Epithelioid transformation is a component of the granulomatous response.



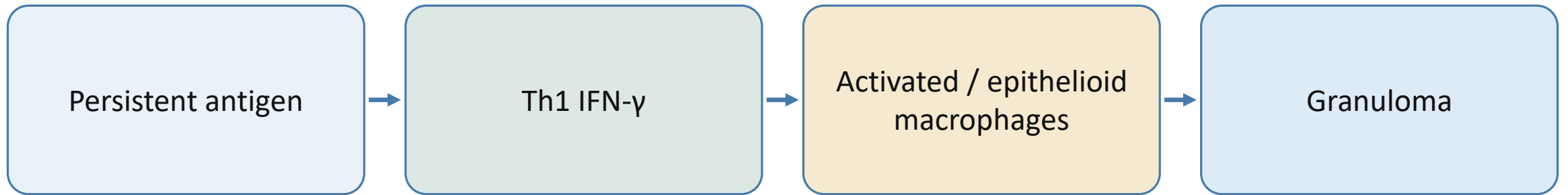
Granulomas organize macrophages and lymphocytes

- Epithelioid macrophages form circumscribed cellular aggregates.
- Lymphocytes commonly surround the activated macrophage core.
- Such aggregates can form small visible granule-like nodules.



Schematic — not a histologic specimen

Strong Th1 activity favors immune granulomas



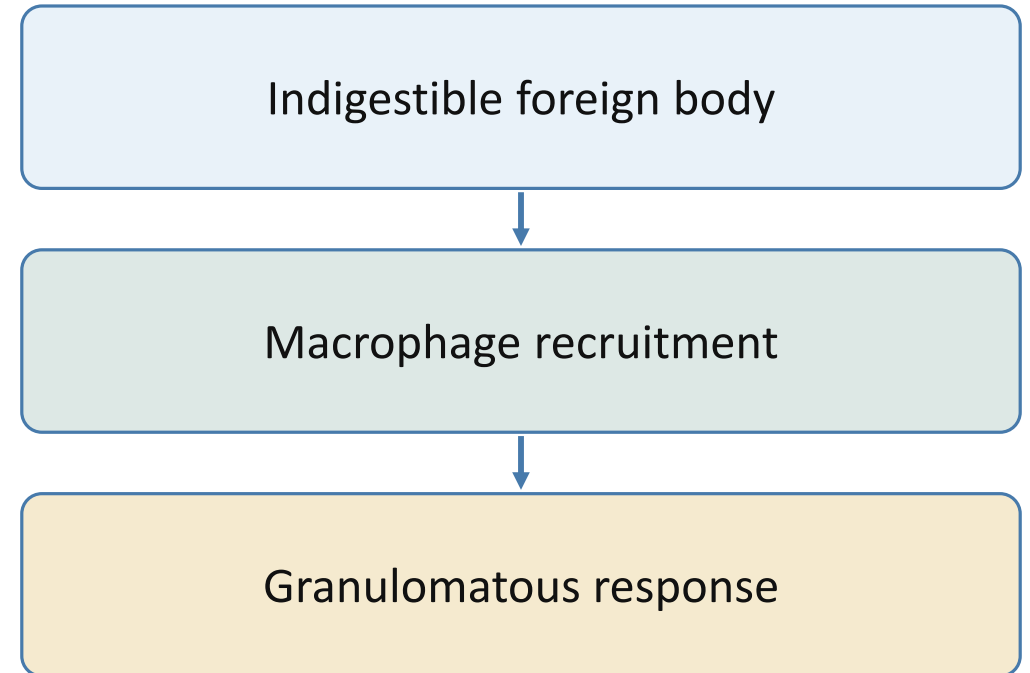
- Persistent antigen maintains helper-T-cell activation.
- IFN- γ promotes sustained macrophage activation.
- Aggregated activated macrophages characterize granulomatous inflammation.

Granulomatous inflammation has diverse triggers

Trigger	Adaptive helper-T-cell context	Inflammatory character
Persistent mycobacterial antigen	Strong Th1 / IFN- γ response	Macrophage / epithelioid-rich
Indigestible foreign body	Adaptive T-cell response not required	Direct macrophage response
Schistosome eggs	Strong Th2 response	Eosinophil-rich granulomas

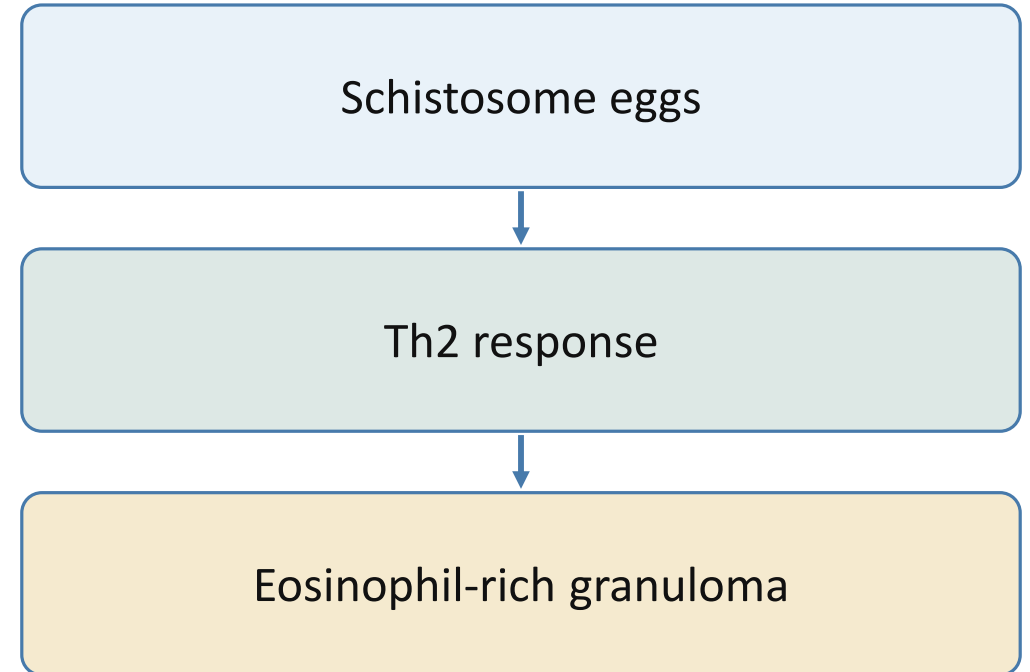
Foreign bodies can produce nonimmune granulomas

- An indigestible foreign material can activate macrophages.
- Granuloma formation in this setting need not require adaptive immunity.
- Thus, granuloma morphology alone does not establish a Th1 mechanism.



Schistosomal eggs produce a different granuloma

- Eggs deposited in tissues elicit granulomatous reactions.
- The accompanying helper-T-cell response is commonly Th2-polarized.
- Eosinophils are prominent in these granulomas.

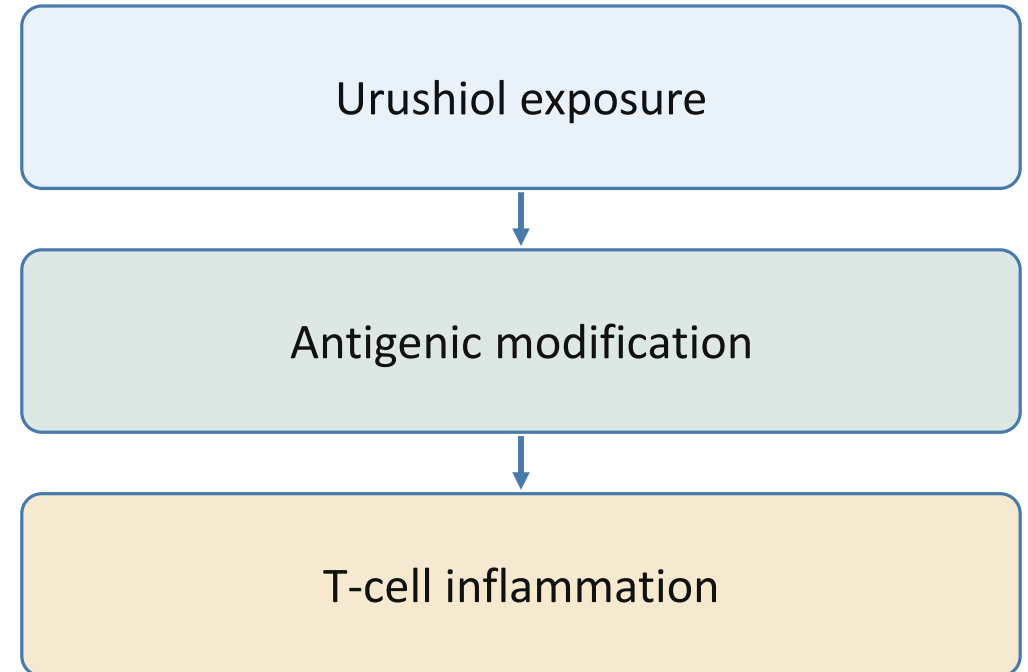


Histology should be interpreted with mechanism

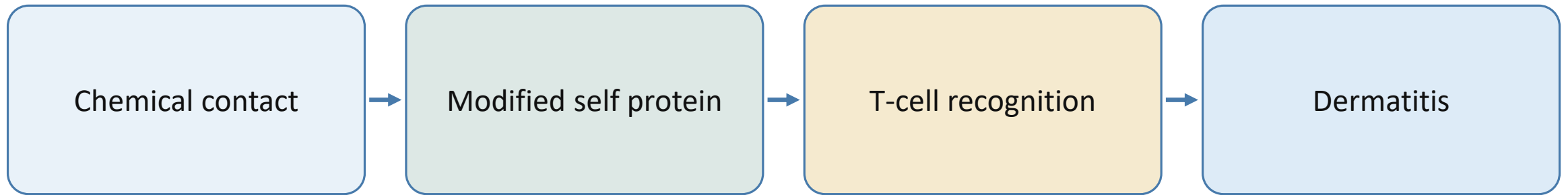
Observation	Potential explanation	Limit
Perivascular CD4+ mononuclear infiltrate	Delayed-type cellular inflammation	Antigen not identified by CD4 alone
Macrophage-rich epithelioid aggregate	Chronic / persistent activation	Foreign body or Th2 triggers possible
Prominent eosinophils in granuloma	Can accompany helminth-associated Th2 response	Not typical Th1-only pattern

Contact sensitivity is an environmental DTH example

- Poison ivy and poison oak contain urushiol, a trigger of contact sensitivity.
- The clinical lesion is an itchy, vesicular dermatitis.
- This is an example of delayed inflammatory skin injury.



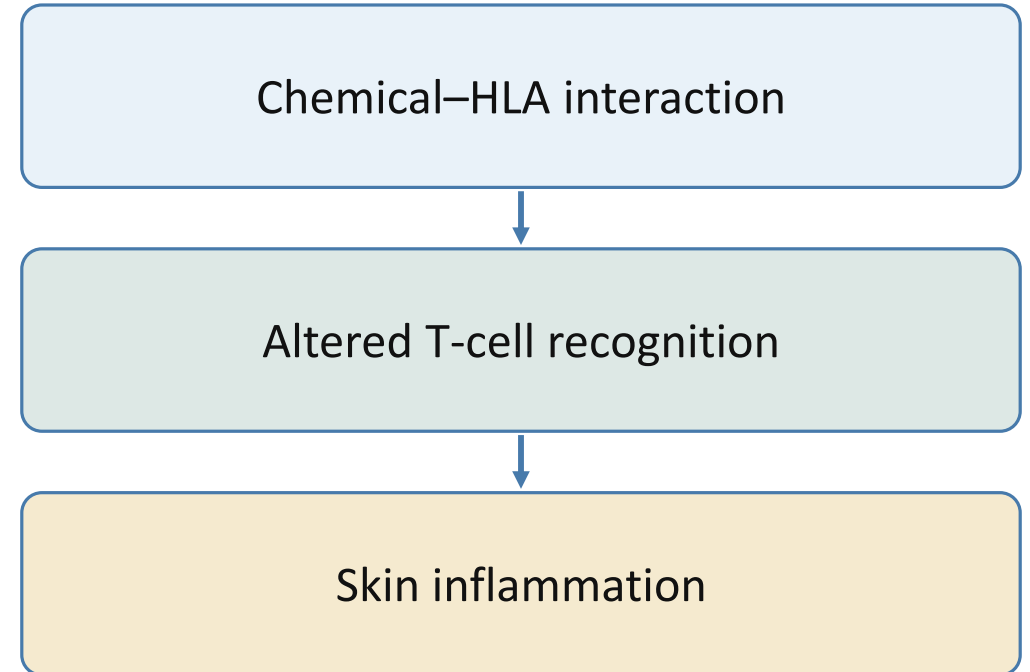
Small environmental chemicals can alter self proteins



- Environmental compounds may bind to self proteins and change their structure.
- Peptides from modified proteins are then recognized by T cells.
- The resulting response can damage the epidermis and dermis.

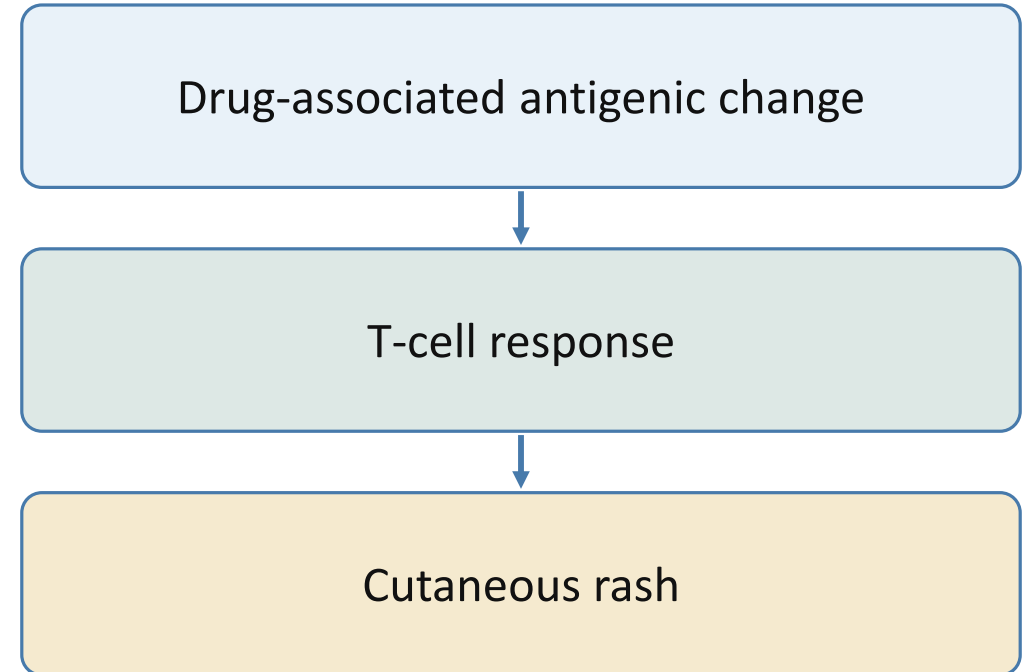
Some chemicals alter HLA recognition directly

- Certain chemicals can modify HLA molecules.
- Altered HLA may appear foreign to T lymphocytes.
- This is an alternative proposed route for chemical-elicited T-cell responses.



Drug reactions may use related T-cell mechanisms

- Similar immunologic reactions account for many drug hypersensitivity presentations.
- Skin rash is a common clinical manifestation.
- A chemical–protein or HLA interaction is a possible initiating mechanism.



Contact dermatitis: Cause and morphology

Mechanism	Tissue manifestation
Urushiol or other chemical exposure	Pruritic skin eruption
Altered self proteins / possible altered HLA	T-cell mediated inflammatory response
Tissue inflammation and injury	Epidermal necrosis, dermal inflammation and blisters

Three classic manifestations of CD4+ inflammation

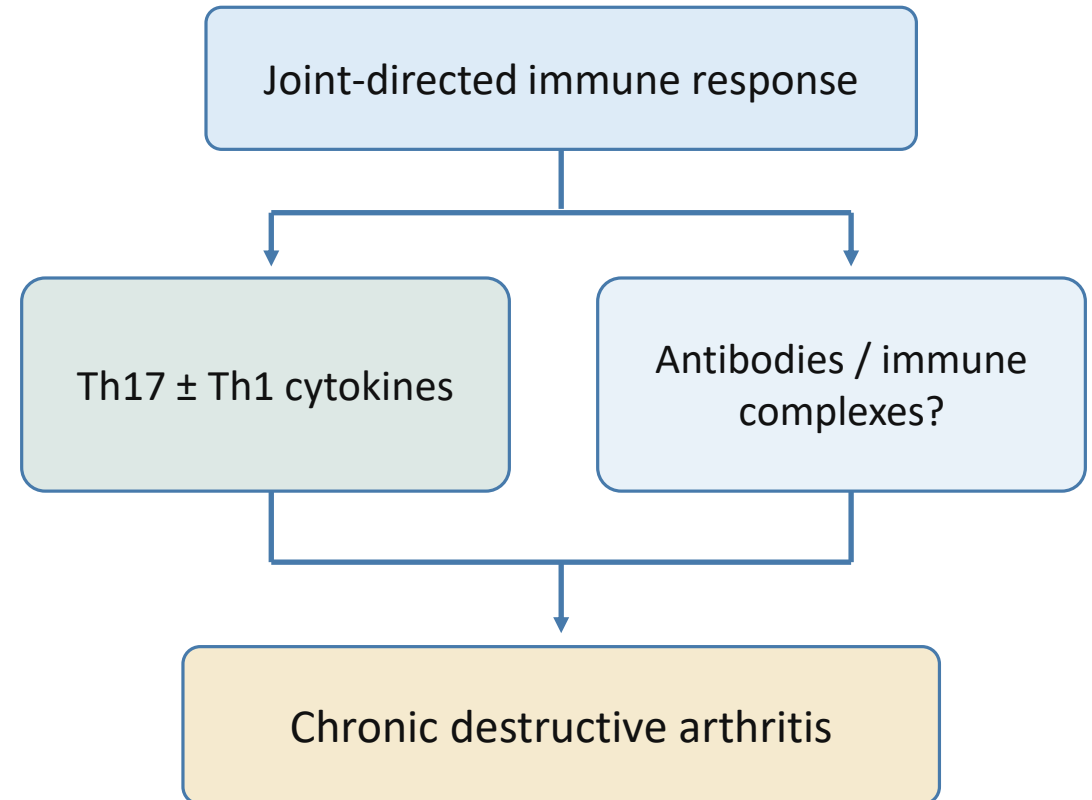
Setting	Dominant lesson	Typical lesion
Tuberculin skin response	Antigen-specific delayed recall	Erythema / induration; Mononuclear cuffing
Persistent antigen	Chronic macrophage activation	Epithelioid granuloma
Contact sensitivity	Chemically modified antigenic target	Pruritic vesicular dermatitis

Selected disorders associated with Th1 / Th17 pathways

Disease	Pathway noted	Tissue consequence
Rheumatoid arthritis	Th17; Possible Th1, antibody / complex roles	Chronic destructive arthritis
Multiple sclerosis	Th1 and Th17; Activated macrophages	Inflammatory CNS demyelination
Inflammatory bowel disease	Th1 and Th17	Chronic intestinal inflammation
Psoriasis	Mainly Th17 cytokines	Inflammatory skin plaques

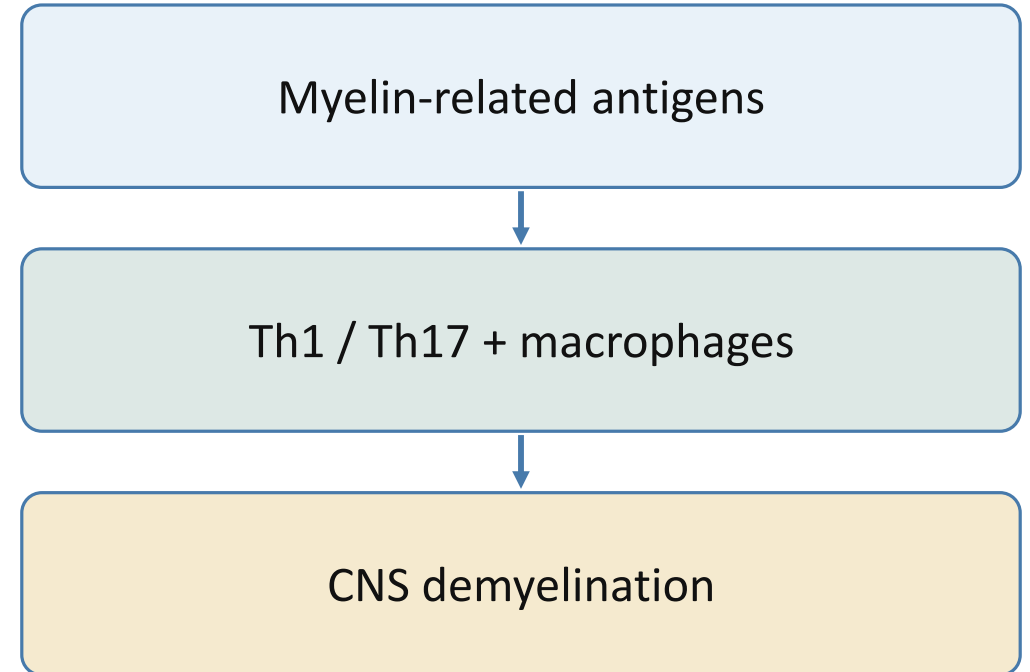
Rheumatoid arthritis: Multiple mechanisms may overlap

- Th17 cytokines are implicated; A Th1 contribution is discussed as possible.
- Antibodies and immune complexes may also contribute.
- The resulting chronic synovial inflammation damages articular cartilage.



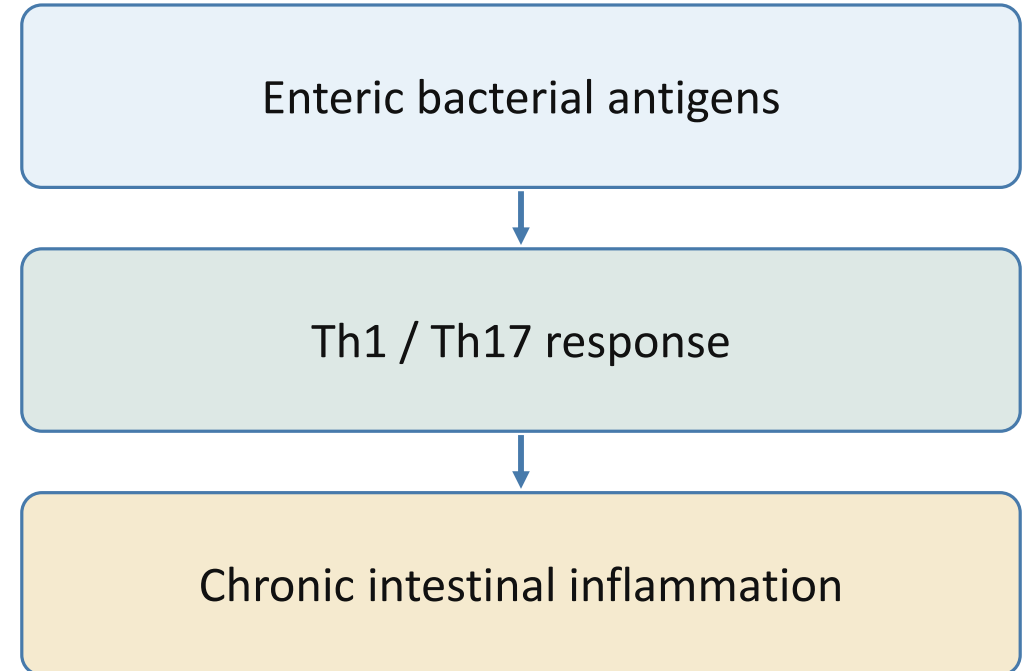
Multiple sclerosis: Inflammation and myelin injury

- The proposed pathogenic T-cell targets include myelin proteins.
- Th1/Th17 cytokines and activated macrophages contribute to myelin destruction.
- Consequences include inflammatory CNS demyelination and neurologic deficits.



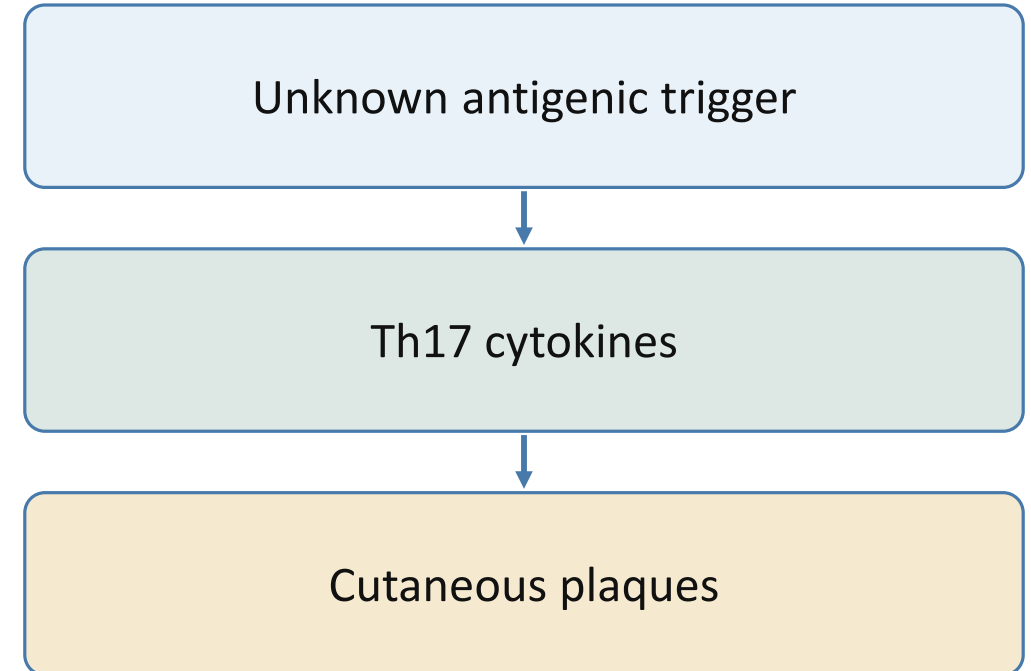
Inflammatory bowel disease and commensal responses

- Uncontrolled responses to enteric bacteria are implicated.
- Th1 and Th17 cytokines participate in intestinal inflammation.
- Sustained mucosal injury causes chronic intestinal pathology.



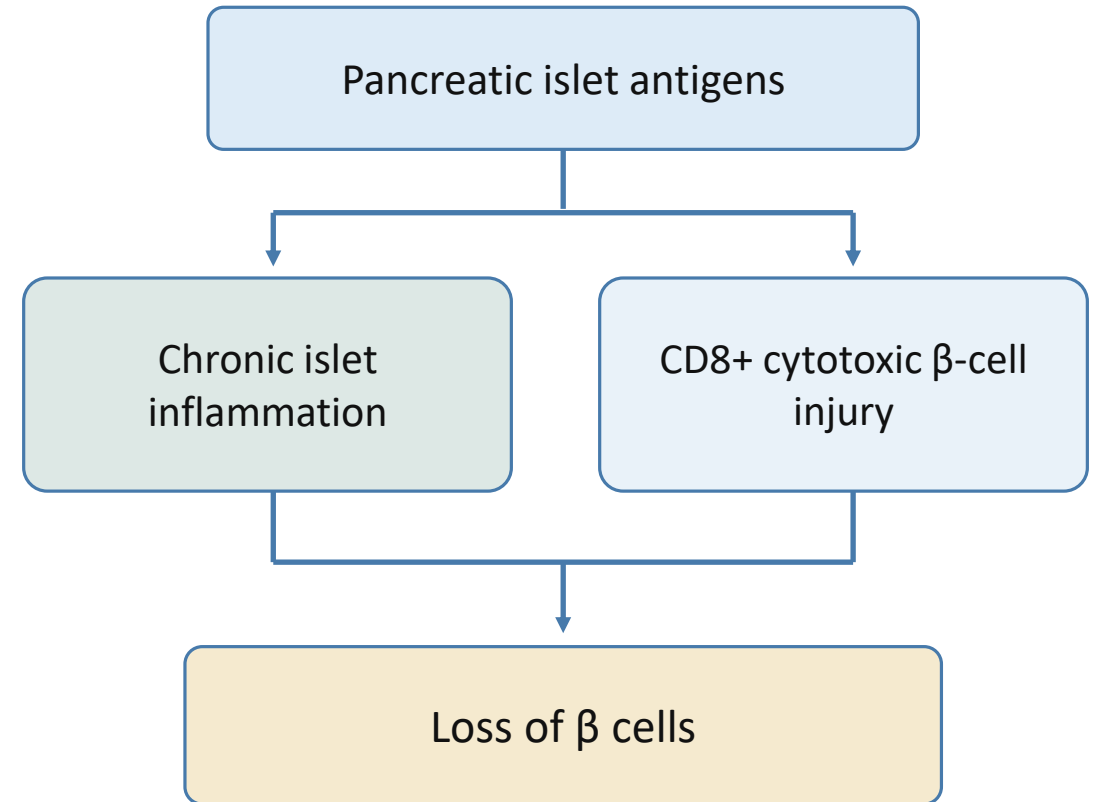
Psoriasis: Prominent Th17 cytokine involvement

- The source describes the pathogenic T-cell antigen as unknown.
- Th17-derived cytokines are the principal emphasized inflammatory mechanism.
- The clinical lesion consists of inflammatory plaques of skin.



Type 1 diabetes: Inflammation plus CTL cell killing

- Pancreatic islet antigens are implicated in the T-cell response.
- Insulitis denotes chronic inflammatory infiltration of the islets.
- CD8+ CTL destruction of β cells is a major injury mechanism.



T-cell disease mechanisms are not all the same

Disease	Inflammatory component	Direct cytotoxic component
Rheumatoid arthritis	Th17 ± Th1 cytokines	Not primary mechanism in table
Multiple sclerosis	Th1 / Th17, macrophage injury	Not primary mechanism in table
Type 1 diabetes	Islet inflammation	CD8+ CTLs destroy β cells
Contact sensitivity	Th1 ± Th17 inflammatory injury	Not specified as primary in Table 6.5

CD4+ inflammation versus CD8+ cytotoxicity

Criterion	CD4+ T-cell inflammation	CD8+ CTL injury
Main T-cell action	Secretion of inflammatory cytokines	Target-cell killing
Typical proximal effector	Macrophages / recruited leukocytes	Perforin- and granzyme-mediated apoptosis
Antigen context	Tissue antigens presented by APCs	Target antigen displayed by infected or altered cells
Dominant tissue effect	Inflammation and secondary injury	Loss of antigen-bearing target cells

Type IV differs from antibody-mediated injury

Mechanism	Principal mediator	Common injury process
T-cell mediated (type IV)	CD4+ cytokines and/or CD8+ cells	Cellular inflammation and/or direct killing
Antibody-associated (type II)	Antibodies to cellular / tissue targets	Opsonization, inflammation or receptor dysfunction
Immune complex (type III)	Deposited antigen–antibody complexes	Complement-driven inflammatory damage

Interpreting a suspected cellular hypersensitivity lesion

- Identify the dominant infiltrating cells and their tissue distribution.
- Ask whether the trigger is a repeat antigen exposure or a persistent stimulus.
- Distinguish a cytokine-associated phagocyte response from direct CTL cytotoxicity.
- Correlate lesion morphology with clinical context; A single stain is not definitive.

Which cells dominate the infiltrate?

Was there sensitization or persistence?

Cytokine activation or direct cytotoxicity?

Integrate morphology with exposure

Caution: Disease mechanisms are partly inferred

- Many pathogenic T-cell specificities remain uncertain.
- Some human disease mechanisms are inferred from experimental animal models.
- A Th1 or Th17 association is not proof of an exclusive pathway.
- Avoid turning candidate antigens into established diagnostic biomarkers.

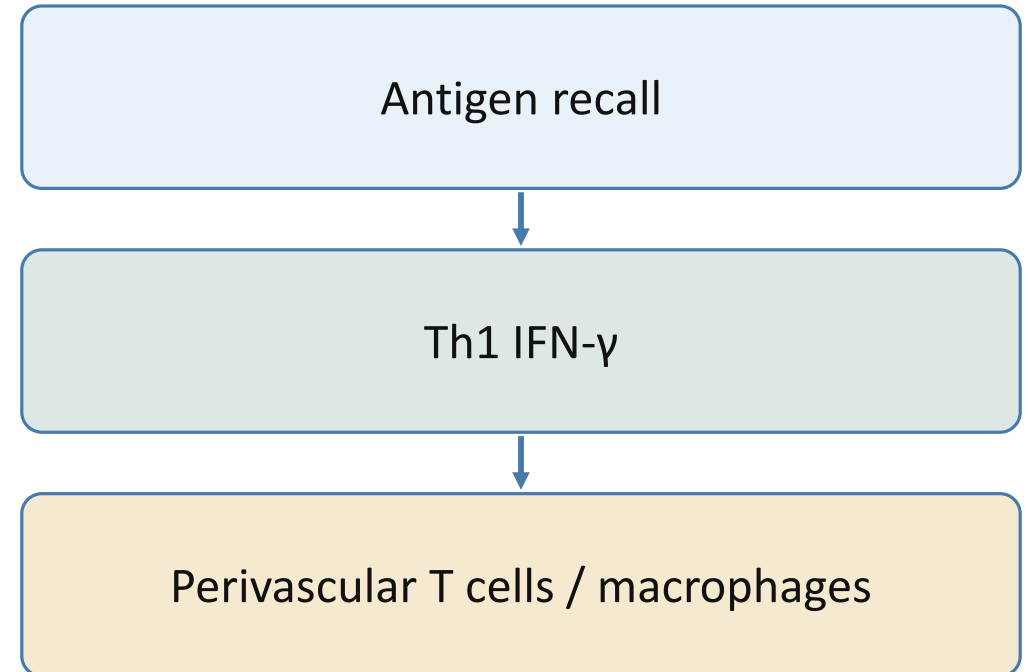
Antigen specificity $\neq$ always known

Mechanistic overlap is common

Inference is not direct proof

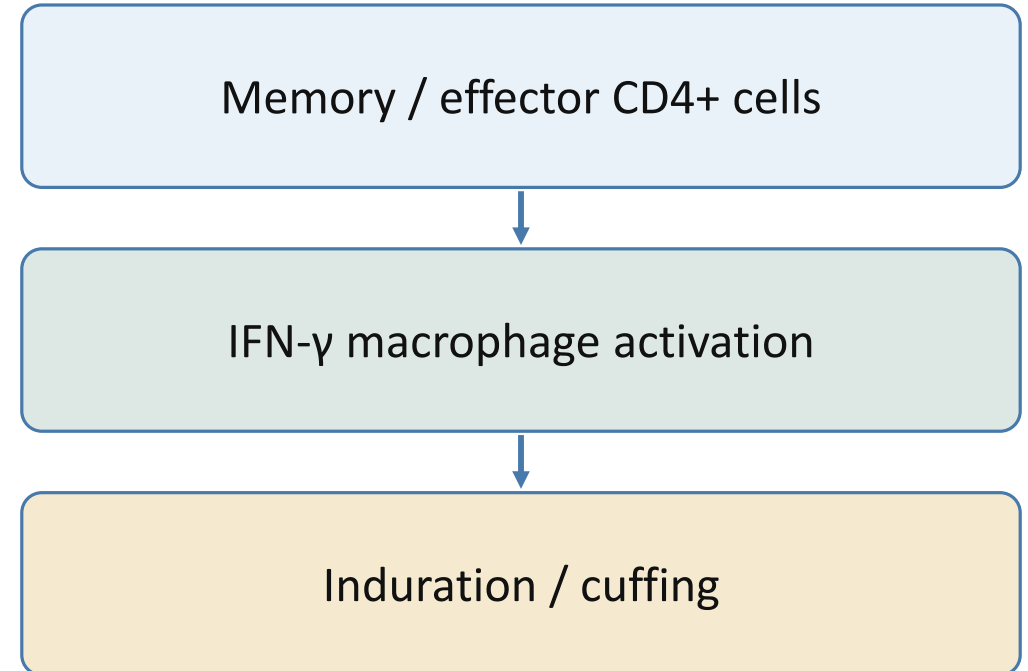
Case exercise: An indurated skin reaction

- A sensitized person develops an indurated reaction after an intradermal antigen challenge.
- Which immune-cell program and tissue morphology best explain the delayed response?
- Identify the expected timing of peak inflammatory activity.



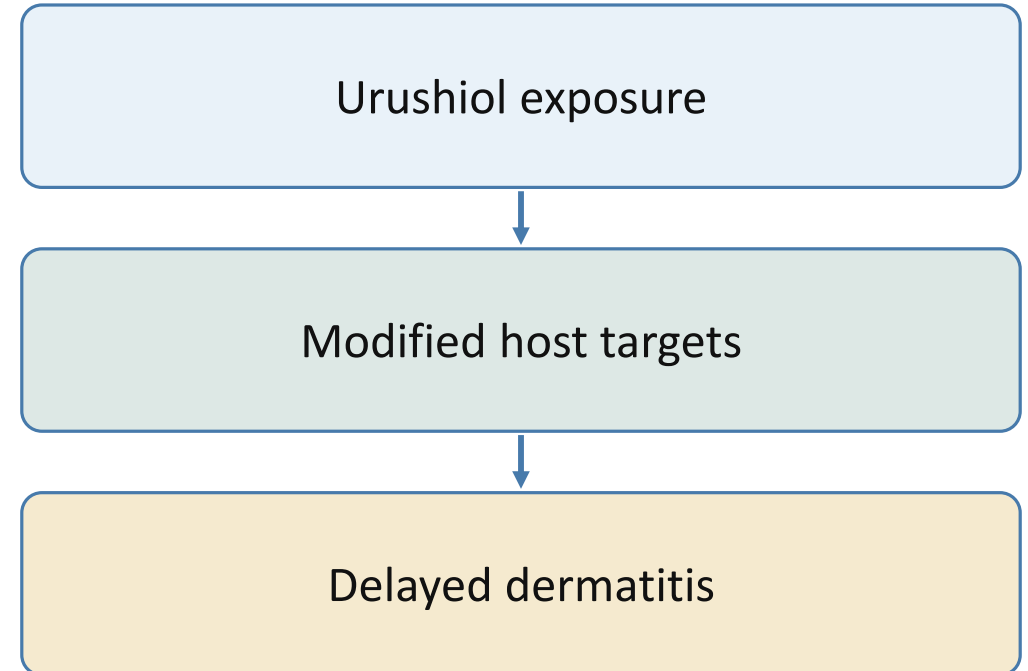
Case discussion: Delayed skin reaction

- The mechanism is a delayed, antigen-specific CD4+ T-cell inflammatory response.
- IFN- γ activates macrophages; Perivascular mononuclear cuffing is expected.
- For tuberculin, erythema and induration peak about 24–72 hours after challenge.



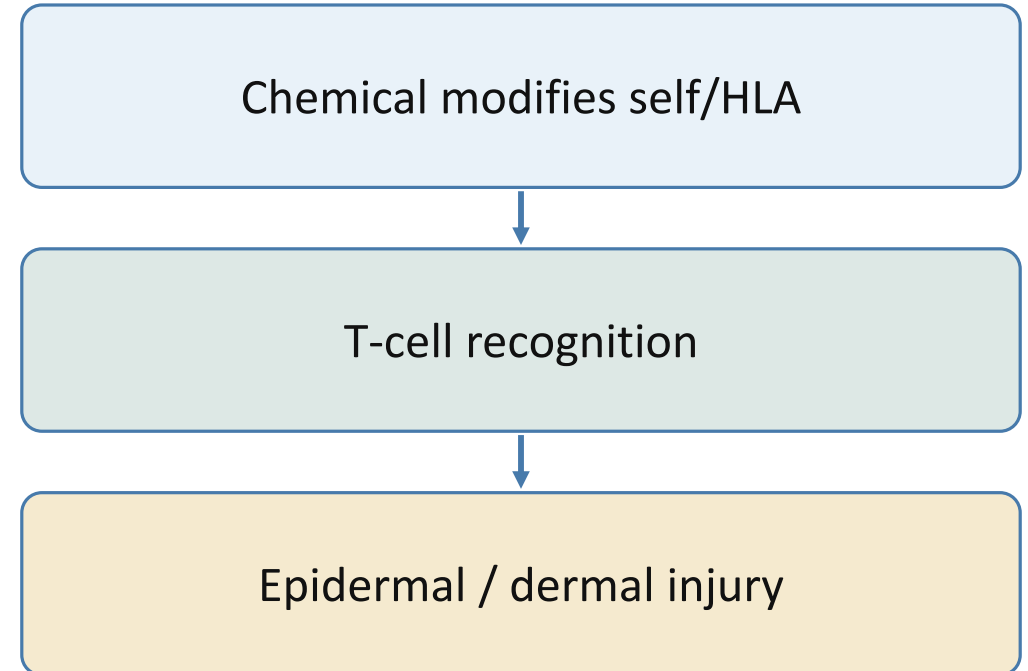
Case exercise: Vesicles after plant contact

- An individual develops a pruritic vesicular rash after poison ivy exposure.
- Explain how a small environmental chemical can trigger T-cell immunity.
- Predict the broad epidermal and dermal injury pattern.



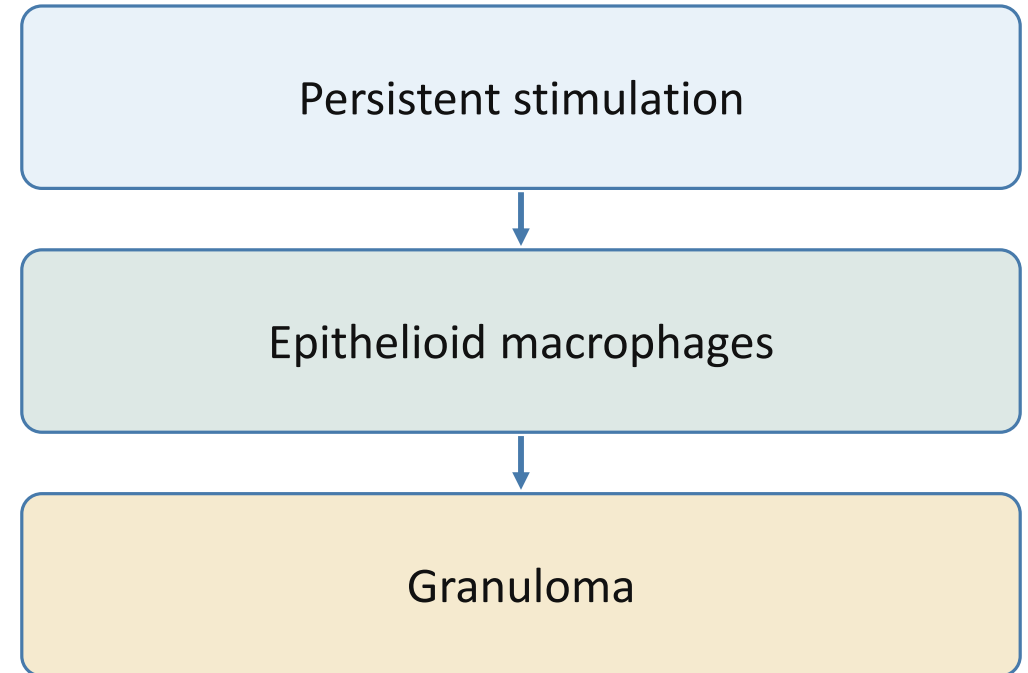
Case discussion: Contact sensitivity

- Urushiol can alter self proteins and render derived peptides recognizable to T cells.
- Chemical modification of HLA is another possible mechanism.
- T-cell inflammation produces dermal infiltrates, epidermal injury and vesicles.



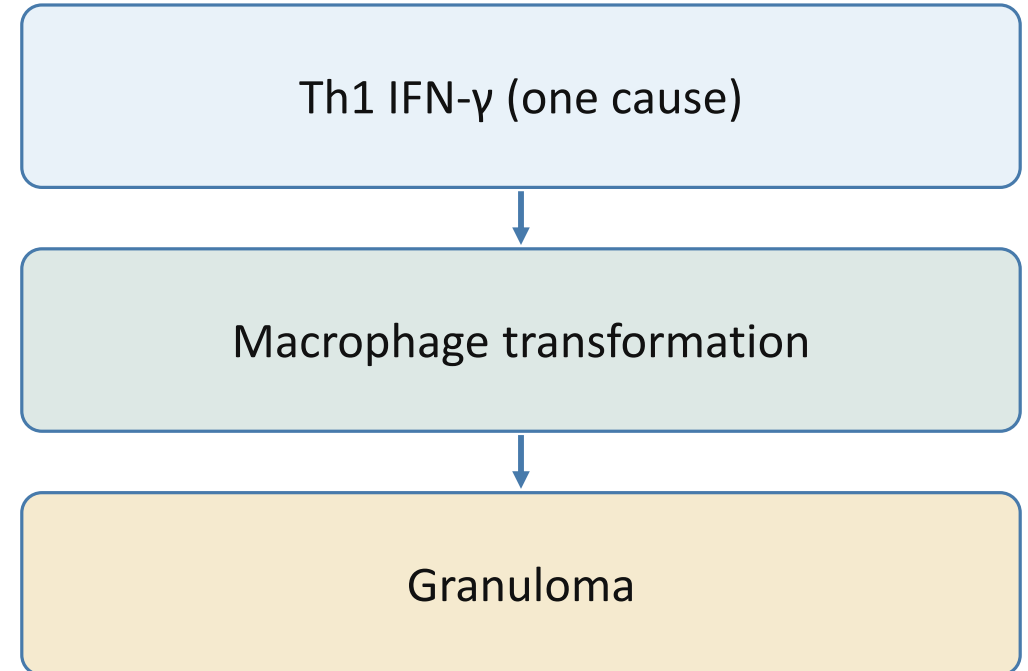
Case exercise: A macrophage-rich nodule

- Persistent tissue antigen is followed by a circumscribed epithelioid-cell aggregate.
- Which effector cytokine and helper-T-cell subset favor this pattern?
- Name a non–Th1-dependent alternative pathway to granuloma formation.

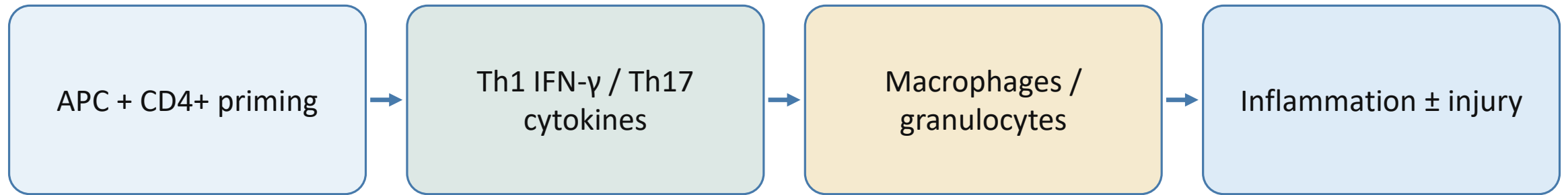


Case discussion: A granulomatous response

- Strong Th1-derived IFN- γ promotes sustained macrophage activation.
- Epithelioid macrophages aggregate and are often rimmed by lymphocytes.
- Indigestible foreign bodies or Th2 responses to schistosome eggs are alternatives.



Core mechanistic synthesis

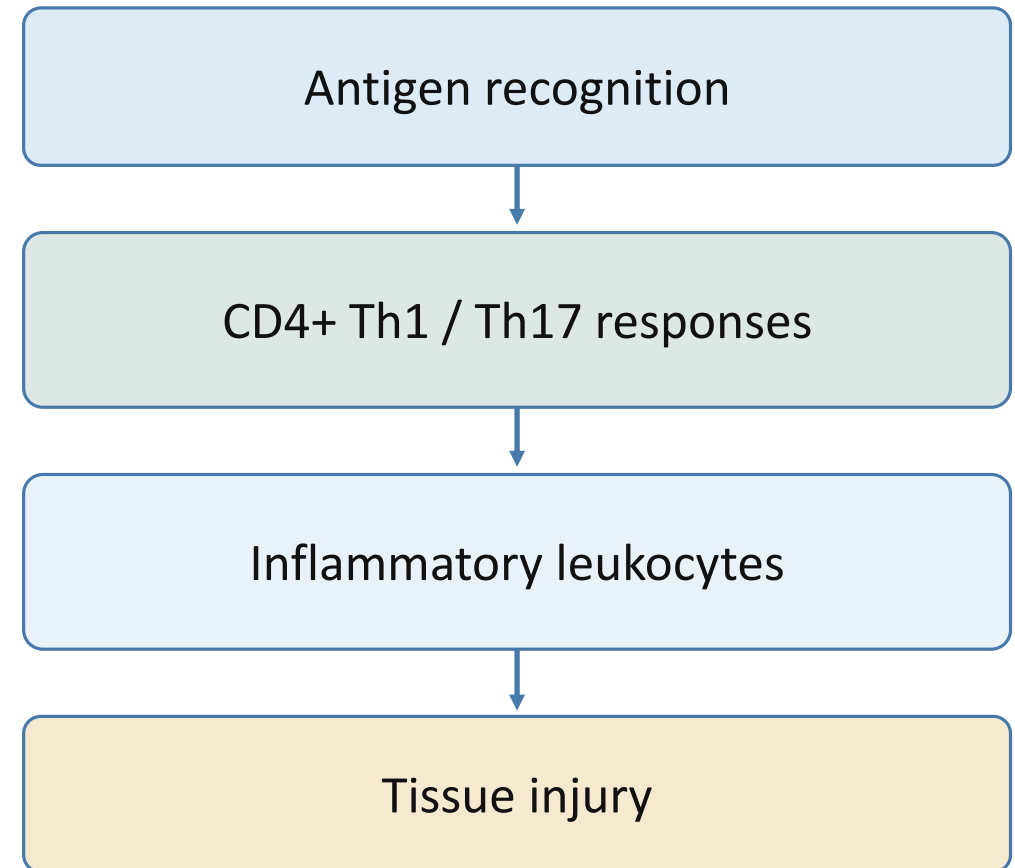


The type of cytokine response helps predict recruited cell populations.

Persistent stimulation, not cytokine identity alone, determines chronicity.

Five essential conclusions

- CD4+ T cells induce tissue injury chiefly through cytokine-driven inflammation.
- Th1–IFN- γ responses activate macrophages; Th17 promotes neutrophil-rich recruitment.
- Classic DTH is delayed and produces perivascular mononuclear inflammation.
- Persistent activation may generate epithelioid-cell granulomas.
- Clinical examples differ in triggering antigen, inflammatory cells and injury pathway.



Primary reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 6, Diseases of the Immune System; section “T Cell–Mediated (Type IV) Hypersensitivity,” pp. 189–191.
- Additional contextual sections: T-cell activation and cell-mediated immunity (pp. 177–178).
- Textbook Table 6.5 and Figures 6.18–6.19 informed original editable teaching diagrams; images were not reproduced.