

Cells and Mediators of Chronic Inflammation

Cellular circuits linking persistent injury, host defense, and tissue repair

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Learning objectives

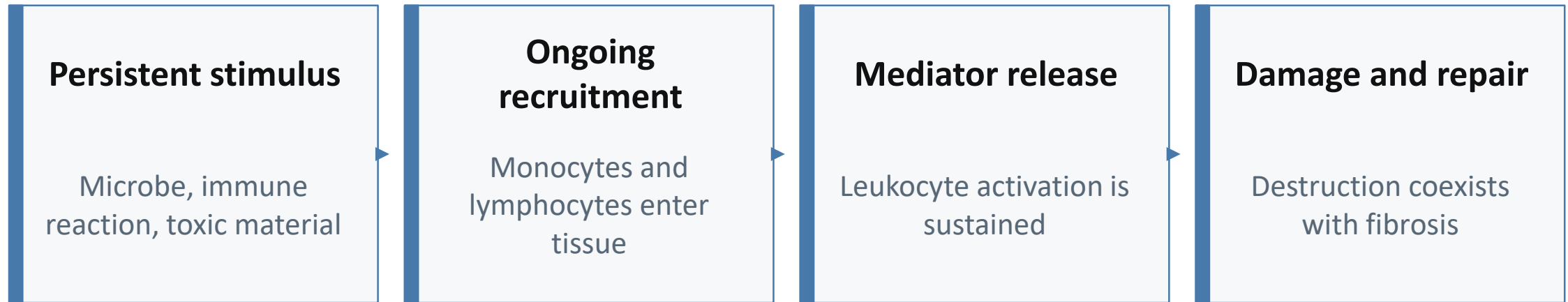
- Identify the principal cellular populations in chronic inflammation.
- Explain macrophage recruitment, activation, and functional consequences.
- Connect T-cell cytokines to macrophage and granulocyte responses.
- Interpret how persistent inflammation produces injury and fibrosis.

The chronic inflammatory response has three linked components



- Cellular activation produces mediators that connect all three components.
- Their proportions vary with the stimulus and stage of disease.

Persistence drives continuing cellular activation



- A stimulus that cannot be cleared maintains the local inflammatory circuit.

Acute and chronic inflammation differ in their dominant pattern

Acute inflammation

- Vascular dilation and exudation prominent
- Edema and neutrophils often predominate
- Often resolves when stimulus clears

Chronic inflammation

- Mononuclear leukocyte infiltrates
- Tissue destruction by agents and cells
- Angiogenesis and fibrosis may coexist

Three etiologic settings commonly initiate chronic inflammation

Persistent infection

Mycobacteria; Selected viruses, fungi, and parasites

Immune dysregulation

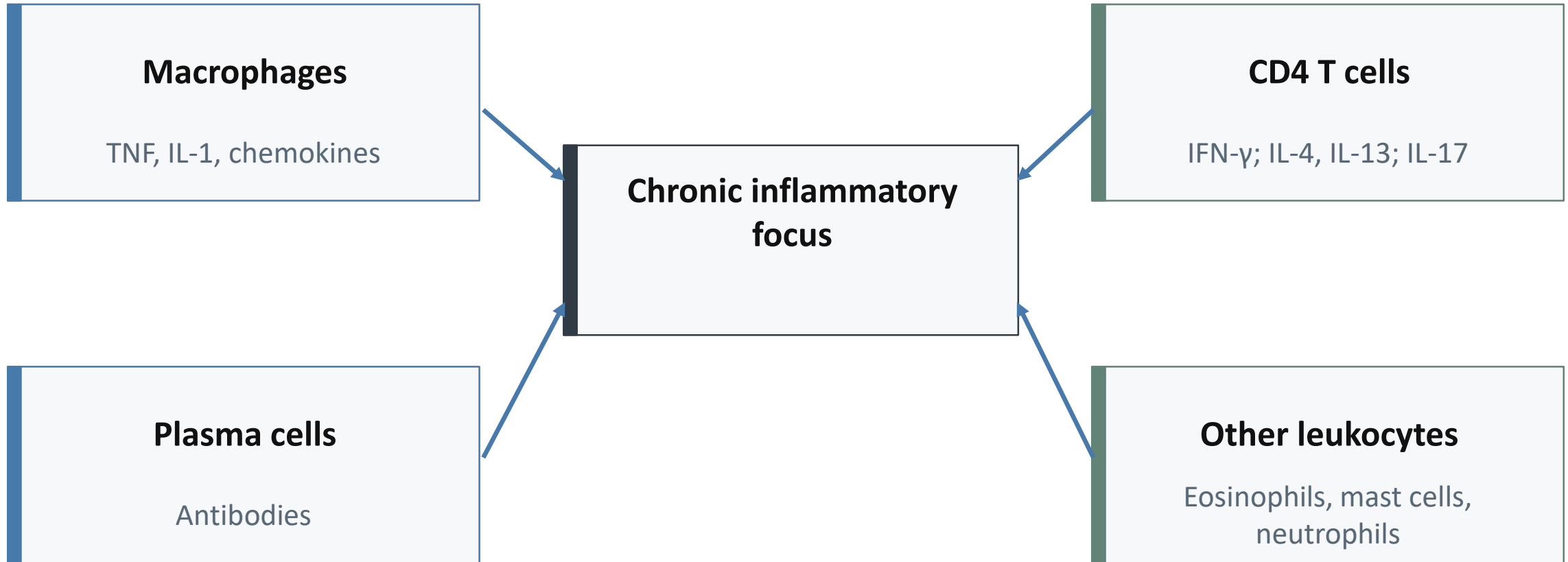
Autoimmunity, allergic responses, inappropriate responses to microbes

Prolonged toxic exposure

Silica particles or endogenous lipid accumulation

These are representative categories, not an exhaustive classification.

Many cell types act through overlapping mediator networks



The integrated response—not any single cytokine—determines injury and repair.

Macrophages usually dominate the cellular response

- Professional phagocytes remove microbes and damaged tissue.
- Activated macrophages secrete inflammatory cytokines and growth factors.
- They present antigen and communicate with T lymphocytes.
- They can both damage tissue and initiate repair.

Macrophages have three complementary effector roles

Elimination

Phagocytosis and destruction of microbes or dead cells

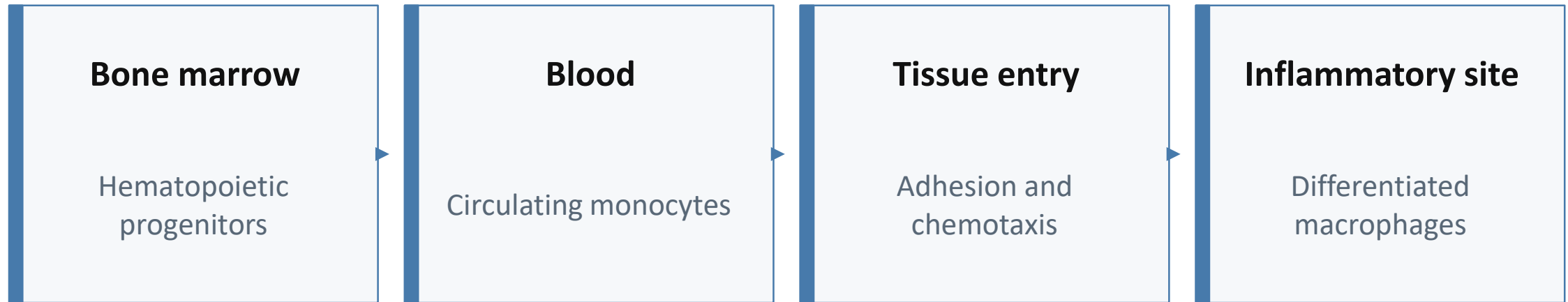
Inflammatory coordination

Cytokines and lipid mediators propagate leukocyte responses

Repair and remodeling

Signals promote healing, scarring, and fibrosis

Inflammatory macrophages commonly derive from blood monocytes



- The same general trafficking machinery recruits neutrophils and monocytes.

Some resident macrophages have embryonic origins

Macrophage ontogeny

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graph TD; A[Macrophage ontogeny] --> B[Postnatal marrow]; A --> C[Yolk sac / fetal liver]; B --> D[Blood monocytes]; B --> E[Inflammatory macrophages]; C --> F[Embryonic tissue seeding]; C --> G[Stable resident populations];
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Postnatal marrow

Blood monocytes

Inflammatory macrophages

Yolk sac / fetal liver

Embryonic tissue seeding

Stable resident populations

Monocytes and tissue macrophages have different residence times



Circulating monocytes

Blood half-life ~1 day



Recruitment into inflammation

Monocytes can predominate within 48 hours



Tissue macrophages

Survival may extend for months or years

These are typical values from the text, not universal lifespans.

Resident and recruited populations coexist

Resident macrophages

- Often seeded early in development
- Maintain stable local populations
- Examples: Microglia, Kupffer cells, alveolar macrophages

Monocyte-derived macrophages

- Arise from postnatal marrow progenitors
- Accumulate after blood recruitment
- Prominent at inflammatory sites; Also in some normal tissues

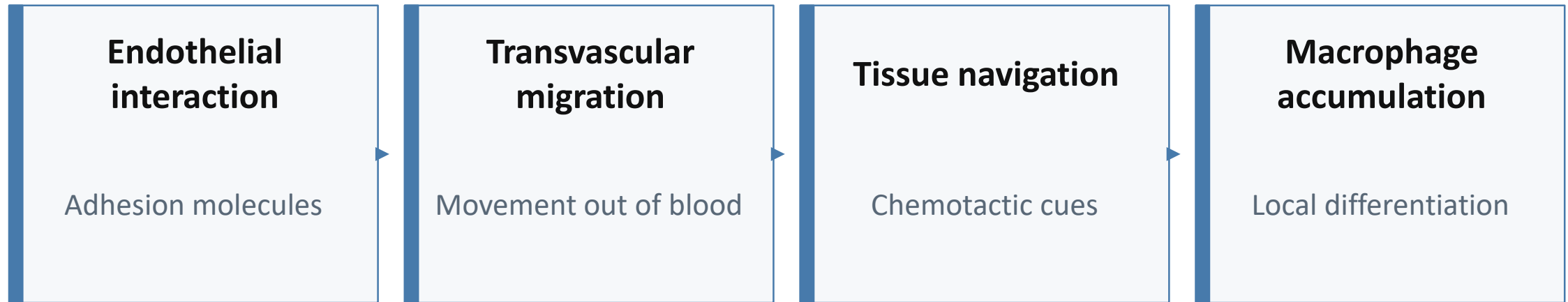
Organ-specific macrophages share a phagocyte lineage

Site	Resident phagocyte	Practical association
Brain	Microglia	Local immune surveillance
Liver	Kupffer cells	Liver macrophages
Lung	Alveolar macrophages	Alveolar clearance
Spleen / lymph node	Sinus histiocytes	Sinus-associated phagocytes

Mononuclear phagocyte system is the preferred collective term

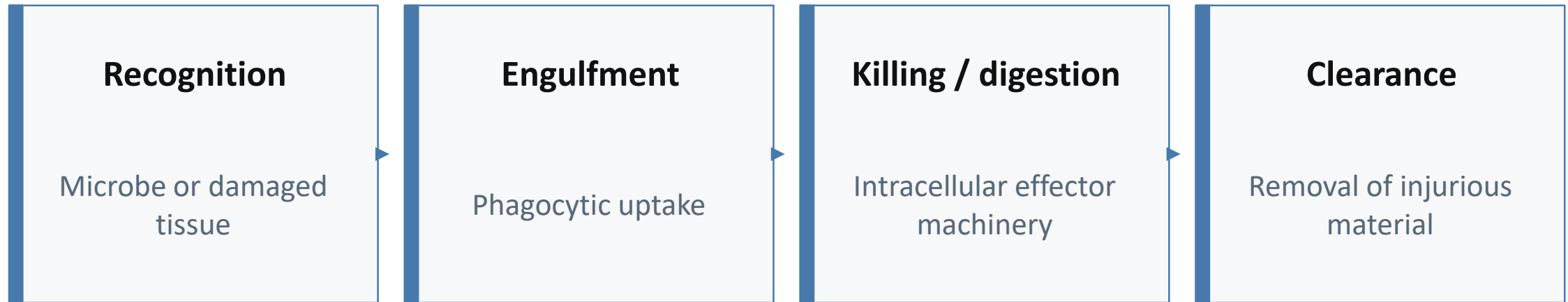
- Includes monocytes and diverse tissue macrophage populations.
- Macrophages are found diffusely in connective tissue and in specialized organ locations.
- “Reticuloendothelial system” is a historical and inaccurate synonym.

Monocyte recruitment relies on adhesion and chemotaxis



- Recruitment continues while the inflammatory stimulus persists.

Phagocytosis supports clearance of persistent stimuli

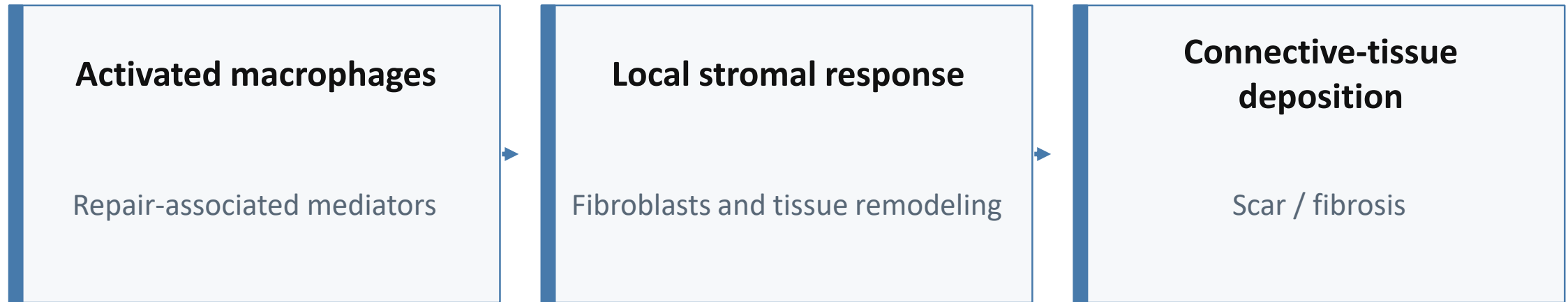


- Persistent or resistant agents may prevent complete resolution.

Macrophages produce key inflammatory mediators

Mediator	Source role	Main effect here
TNF	Activated macrophages	Promotes inflammation and cell recruitment
IL-1	Activated macrophages	Amplifies inflammatory signaling
Chemokines	Activated leukocytes	Direct migration of other leukocytes
Eicosanoids	Activated macrophages	Contribute to inflammatory responses

Growth and repair signals link inflammation with fibrosis



- Macrophages participate in tissue repair as well as tissue destruction.

Macrophage activation can protect and injure the host

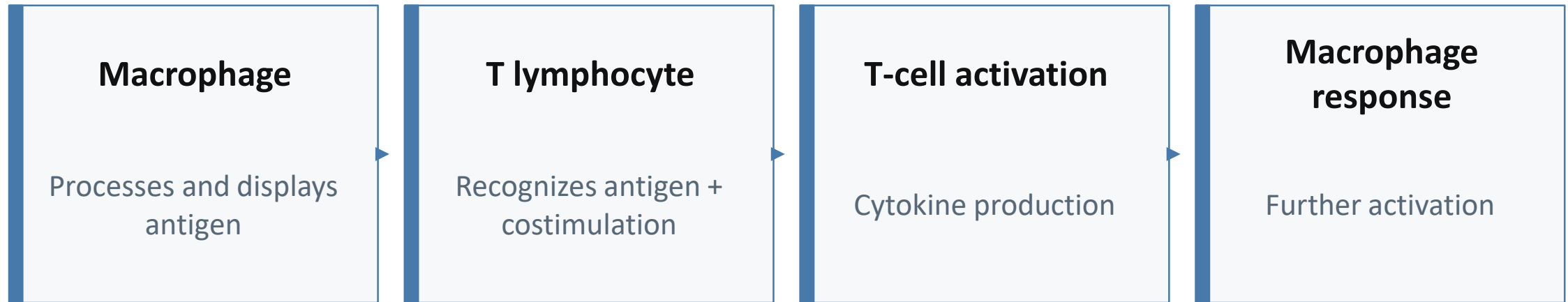
Protective functions

- Kill ingested microbes
- Remove necrotic material
- Organize defense with T cells

Potential costs

- Oxidants and enzymes may injure host tissue
- Cytokines sustain destructive inflammation
- Excessive repair can produce fibrosis

Antigen presentation places macrophages in adaptive immunity



- Reciprocal signaling creates a self-reinforcing response.

Macrophage activation has two illustrative poles

Classical activation (M1-like)

- Microbial signals; IFN- γ
- Microbicidal effectors and inflammation
- ROS, NO, lysosomal enzymes

Alternative activation (M2-like)

- IL-4 and IL-13
- Resolution-associated and reparative responses
- Tissue repair and remodeling

Classical activation begins with microbial and immune signals

Microbial molecules

Engage Toll-like receptors and other sensors

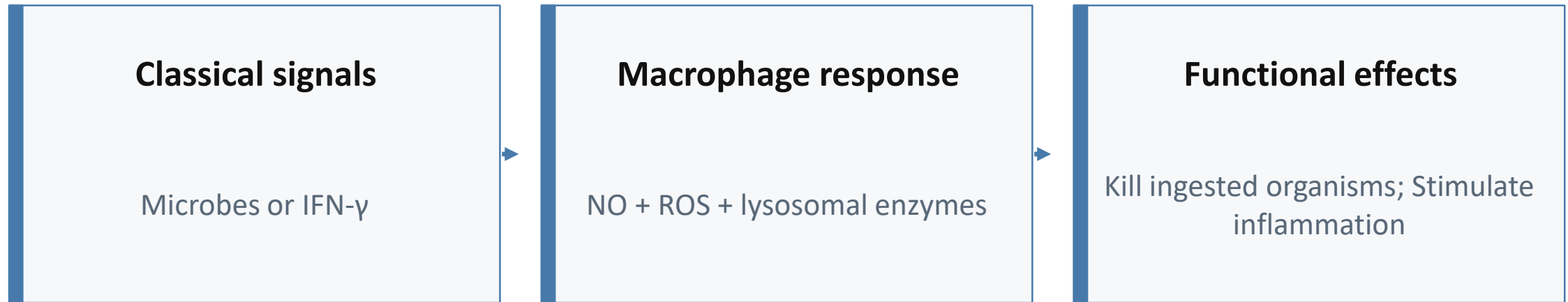
IFN- γ

Produced by T lymphocytes during immune responses

Particulates / crystals

Foreign substances can stimulate macrophage activation

Classical activation increases antimicrobial capacity



- The same effector products can damage neighboring host tissue.

Reactive effector products contribute to chronic tissue injury

Reactive oxygen species

Help kill microbes but can injure host cells

Nitric oxide

Participates in microbicidal effector function

Lysosomal enzymes

Digest targets but can damage surrounding tissue

Alternative activation is favored by IL-4 and IL-13



- Alternative activation is not primarily a microbicidal program.

M2-like responses support repair rather than microbicidal killing

Inflammatory emphasis

- Eliminate microbes and debris
- Inflammatory cytokines propagate the reaction
- Collateral tissue destruction possible

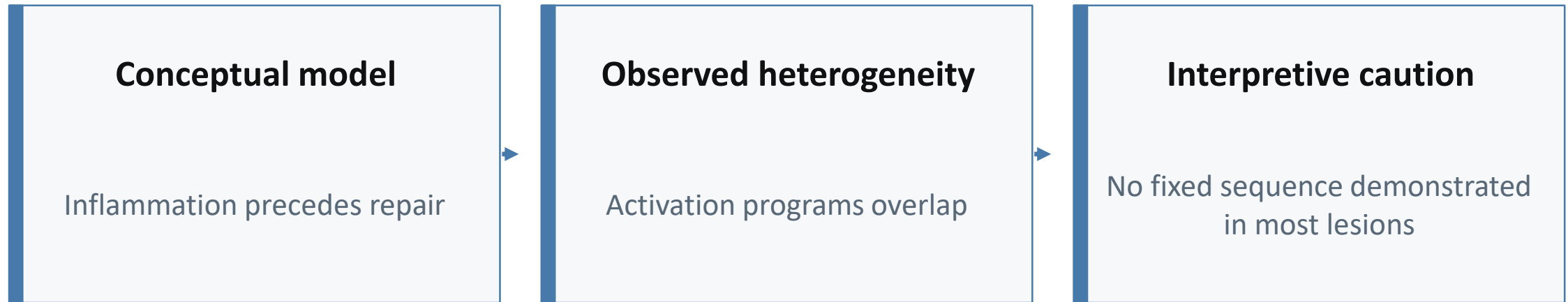
Reparative emphasis

- Down-regulate inflammatory response
- Support tissue repair
- Excessive repair may culminate in scar formation

M1 and M2 are conceptual endpoints, not rigid cell classes

- Intermediate macrophage states may not fit either label.
- Defining markers for these subsets are imprecise.
- Different macrophage phenotypes often coexist within one lesion.
- The terms “M1-like” and “M2-like” reflect this limitation.

A universal M1-to-M2 sequence is not established



- Do not infer macrophage phenotype solely from lesion age.

Macrophage accumulation can persist by two processes

Persistence of macrophages

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graph TD; A[Persistence of macrophages] --> B[Continued recruitment]; A --> C[Local proliferation]; B --> D[Monocytes enter from blood]; B --> E[Ongoing stimulus sustains entry]; C --> F[Resident or recruited cells divide]; C --> G[Tissue population remains expanded];
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Continued recruitment

Monocytes enter from blood

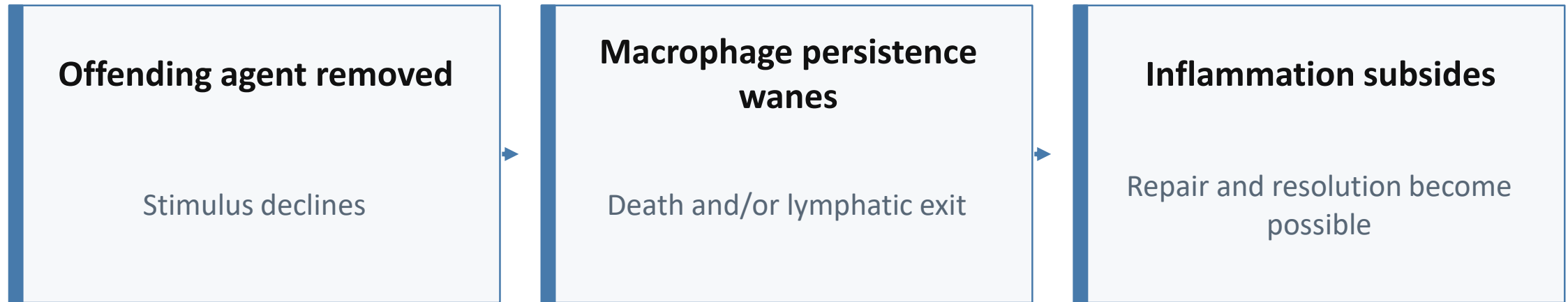
Ongoing stimulus sustains entry

Local proliferation

Resident or recruited cells divide

Tissue population remains expanded

Removal of the stimulus permits macrophage clearance

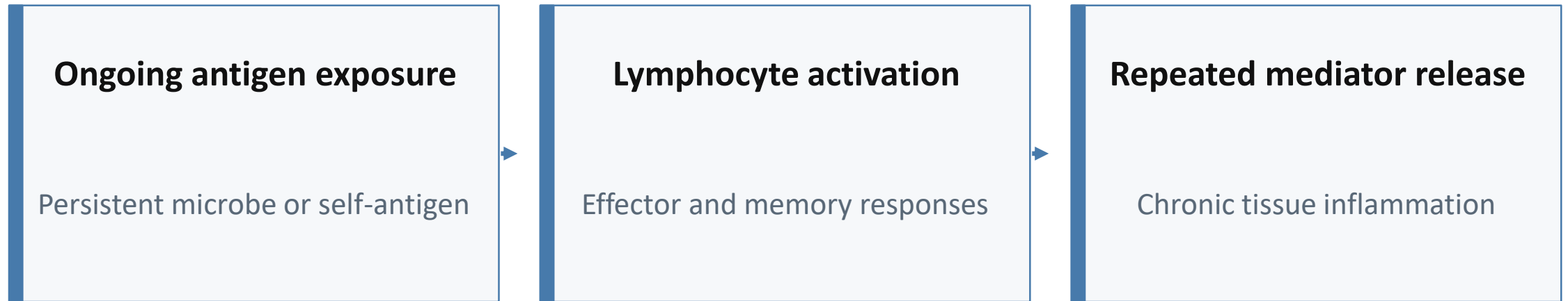


- Failure to remove an agent allows accumulation and injury to continue.

Lymphocytes can amplify and prolong inflammation

- Persistent microbes and environmental antigens activate T and B lymphocytes.
- Memory lymphocytes contribute to long-lived responses.
- Lymphocytes may dominate infiltrates in autoimmune diseases.
- Activated T cells determine the pattern of leukocyte recruitment.

Immunologic memory can sustain a chronic tissue reaction

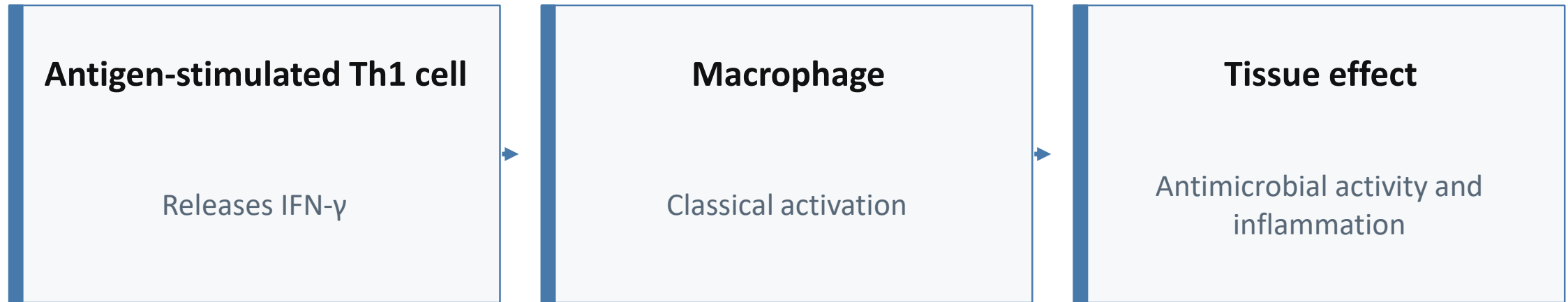


- The source associates persistent severe reactions with long-lived immune memory.

CD4 T-cell subsets create distinct cytokine programs

T-cell subset	Principal cytokines	Characteristic downstream response
Th1	IFN- γ	Classical macrophage activation
Th2	IL-4, IL-13; IL-5	Alternative macrophage activation; Eosinophils
Th17	IL-17 and others	Chemokines; Neutrophil and monocyte recruitment

Th1-derived IFN- γ drives classical macrophage activation



- Th1–macrophage interactions are central to many persistent cellular immune responses.

Th2 cells coordinate eosinophils and alternative activation

Activated Th2 lymphocyte

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graph TD; A[Activated Th2 lymphocyte] --> B[IL-5]; A --> C[IL-4 and IL-13]; B --> D[Eosinophil recruitment and activation]; D --> E[Helminths / allergy]; C --> F[IgE response and M2-like activation]; F --> G[Repair-associated response];
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IL-5

Eosinophil recruitment and activation

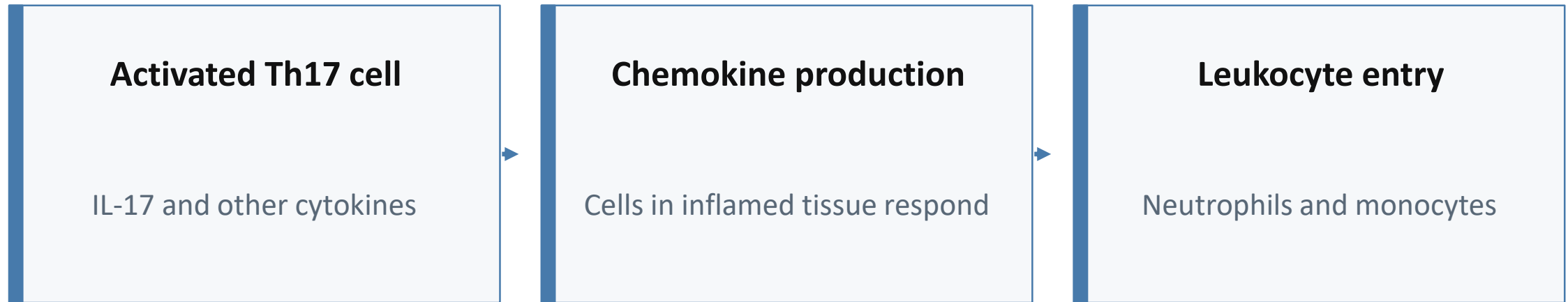
Helminths / allergy

IL-4 and IL-13

IgE response and M2-like activation

Repair-associated response

Th17 cytokines support ongoing granulocyte recruitment



- Th17 activity helps explain neutrophils in some chronic lesions.

T-cell programs vary with the offending stimulus

Th1 / Th17 emphasis

- Defense against many microbes
- Can contribute to autoimmune tissue injury
- Macrophage activation or neutrophil recruitment

Th2 emphasis

- Responses to helminth parasites
- Allergic inflammatory conditions
- IgE, eosinophils, alternative macrophage activation

Cytokine effects depend on cellular source and target

Signal	Typical cellular source	Relevant target or consequence
IFN- γ	Th1 cells	Classical macrophage activation
IL-4 / IL-13	Th2 cells	Alternative activation; IgE response
IL-5	Th2 cells	Eosinophil recruitment / activation
IL-17	Th17 cells	Chemokine-mediated cell recruitment
IL-12	Macrophages	T-cell stimulation

Macrophages activate T cells through multiple inputs

Antigen presentation

Processed antigen displayed to T cells

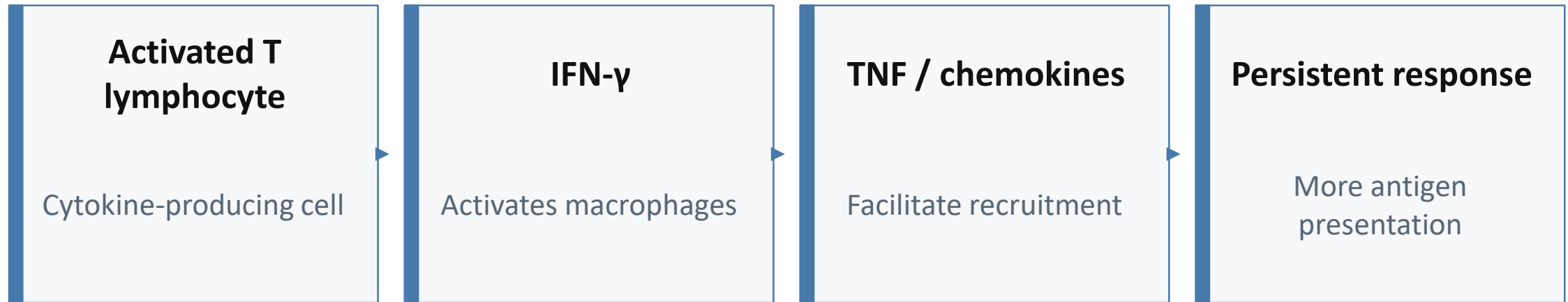
Costimulation

Macrophage membrane molecules provide signals

Cytokine output

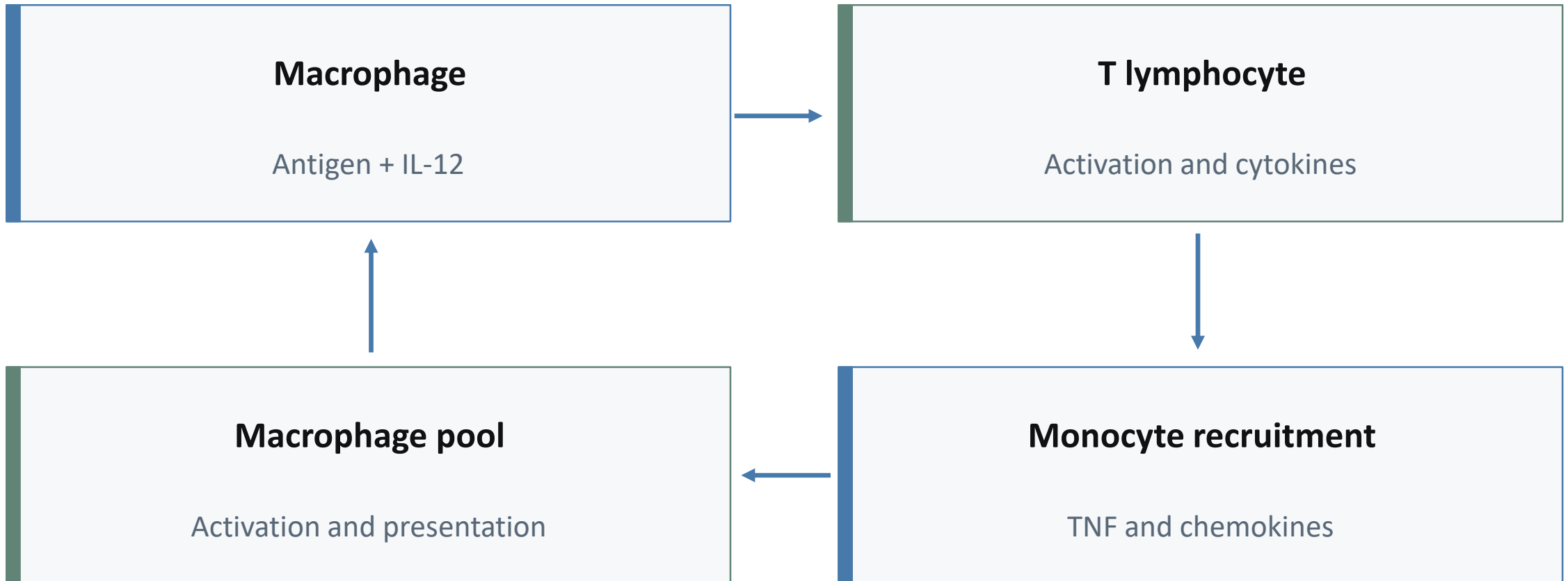
IL-12 and other mediators stimulate T cells

Activated T cells recruit and stimulate macrophages



- Recruitment and activation are related but distinct cytokine effects.

Macrophage–T-cell feedback sustains chronic inflammation



Reinforcing signals can continue while antigen persists.

Recruitment and activation should be distinguished

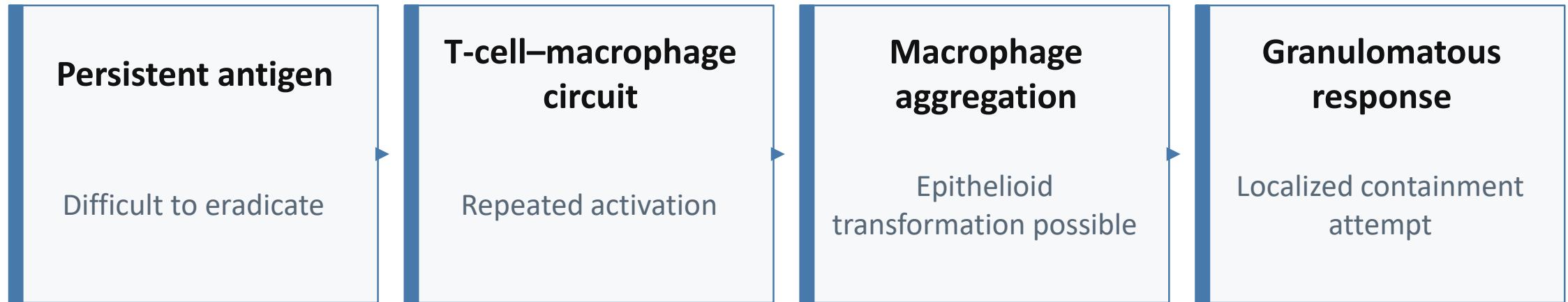
Recruiting cells

- TNF, chemokines and IL-17-associated signals
- Increase leukocyte accumulation at tissue site
- Changes the number and composition of cells

Activating effector cells

- IFN- γ activates macrophages
- IL-4 / IL-13 favor alternative activation
- Changes functional state of existing cells

Sustained T-cell–macrophage reactions may form granulomas



- Granulomatous inflammation is a separate specialized chronic inflammatory pattern.

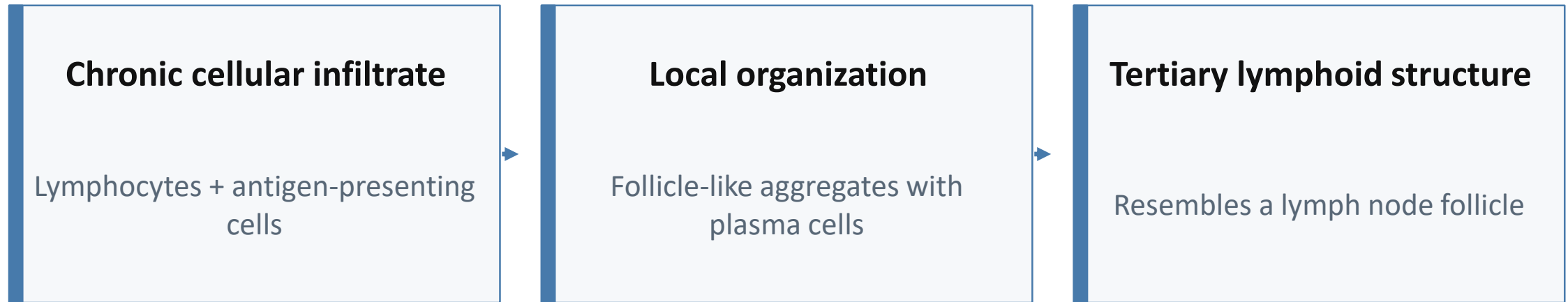
Activated B cells and plasma cells are common participants

- Plasma cells are terminally differentiated antibody-secreting B cells.
- Antibodies may bind persistent microbial, self, or altered tissue antigens.
- B-cell and plasma-cell infiltrates often accompany T cells and macrophages.

Antibody detection does not establish pathogenic contribution

- Antibodies may be directed against persistent foreign antigens.
- Others may recognize self-antigens or altered tissue components.
- The contribution of antibodies to many chronic inflammatory disorders remains unclear.
- Interpret plasma-cell infiltration within the etiologic and tissue context.

Some lesions develop organized tertiary lymphoid structures



- Reported in rheumatoid synovium, Hashimoto thyroiditis, and some tumors.

Tertiary lymphoid structures are context-dependent findings

Established observation

- Organized follicles can form at non-lymphoid inflammatory sites
- T cells, B cells, and antigen-presenting cells colocalize
- Identifiable in some chronic lesions

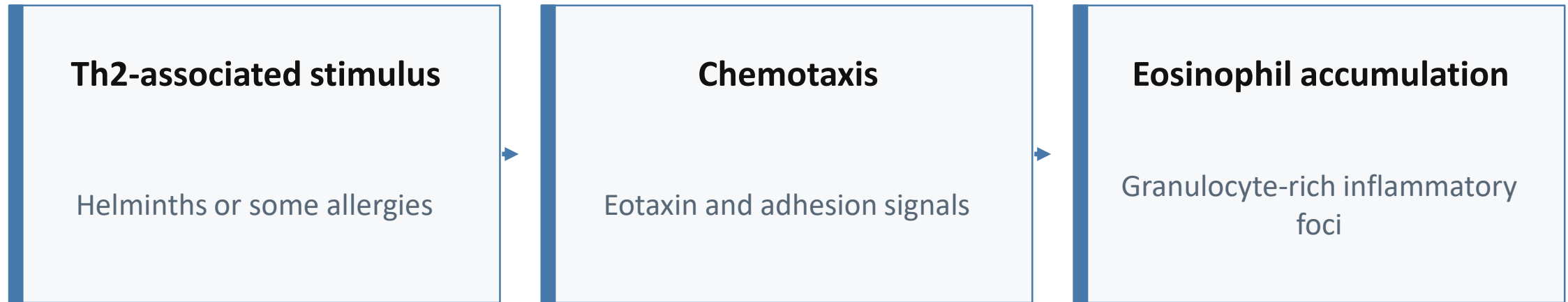
Unresolved interpretation

- Local follicles may perpetuate immune reactions
- The source does not establish their causal importance
- Presence alone does not prove a specific mechanism

Other inflammatory cells reflect the dominant stimulus

Cell population	Common setting	Key mediator or action
Eosinophils	Th2 reactions, helminths, allergy	Major basic protein
Mast cells	Immediate hypersensitivity; Chronic lesions	IgE/FcεRI and cytokines
Neutrophils	Persistent infection or irritants	Continued recruitment and injury

Eosinophil recruitment is prominent in Th2-type reactions



- Eotaxin can arise from leukocytes and epithelial cells.

Eosinophil major basic protein is protective and injurious

Host defense

- Granule protein is toxic to helminths
- Useful in responses to some parasites

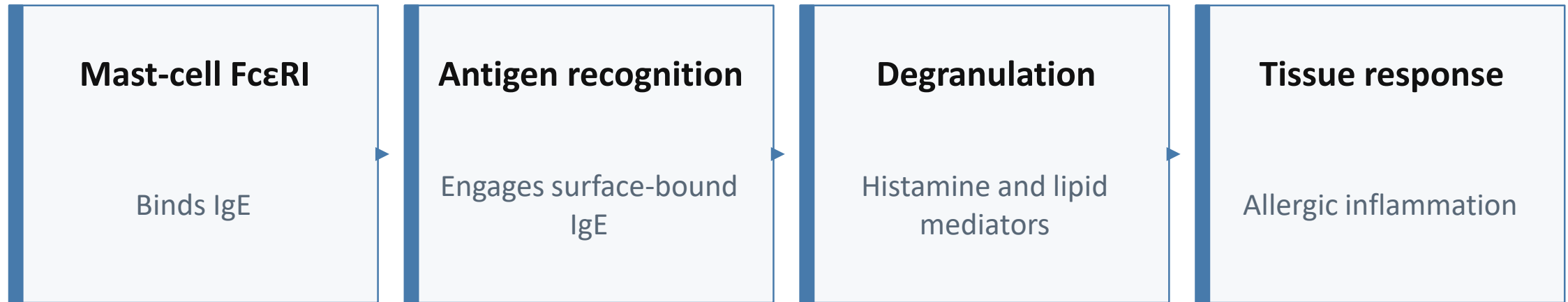
Collateral injury

- Major basic protein can injure host epithelium
- Contributes to damage in allergic disorders

Mast cells participate in both acute and chronic inflammation

- Mast cells are widely distributed in connective tissue.
- They express high-affinity FcεRI receptors that bind IgE.
- Antigen recognition through bound IgE can trigger degranulation.
- Mast-cell cytokines can contribute to chronic inflammation.

Mast-cell activation links antigen recognition to mediators



- Immediate allergic activation is distinct from the broader chronic cytokine contribution.

Mast-cell cytokines can maintain inflammation

Immediate response

Histamine and prostaglandins
after IgE-dependent activation

Chronic role

Multiple cytokines can promote
inflammatory responses

Interpretation

Mast cells are not restricted to
acute hypersensitivity

Neutrophils are not exclusive to acute inflammation

- Chronic inflammatory lesions may continue to contain neutrophils.
- Persistent microbes can maintain their recruitment.
- Activated macrophages and T cells supply recruiting signals.
- Mixed acute and chronic inflammation is therefore compatible with a chronic process.

Chronic osteomyelitis can maintain neutrophilic exudates

Clinical / morphologic scenario

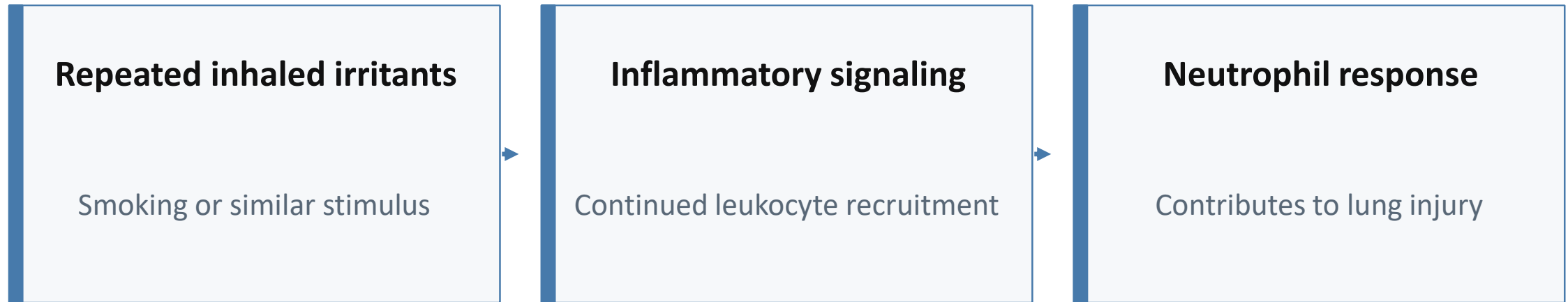
A bone lesion has persisted for months. Histology shows ongoing neutrophilic exudate together with chronic tissue injury.

Does a neutrophilic infiltrate alone exclude chronic inflammation?

Interpretation

No. Persistent bacterial infection can sustain neutrophils during chronic osteomyelitis.

Irritant exposure may sustain chronic neutrophilic injury



- Smoking-associated chronic lung injury.

A mixed inflammatory infiltrate needs etiologic interpretation

Cellular clues

- Neutrophils suggest ongoing active recruitment
- Macrophages and lymphocytes suggest chronic response
- Eosinophils suggest some Th2-type settings

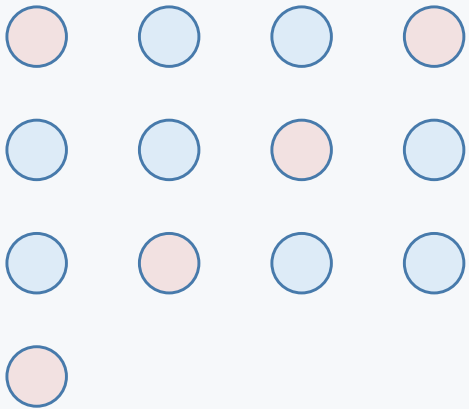
Interpretive requirement

- Identify persistent infection, immune reaction, or toxin
- Assess tissue destruction and fibrosis
- Avoid diagnosing etiology from one cell type alone

A chronic lesion is simultaneously destructive and reparative

Schematic tissue response (not a histologic specimen)

Mononuclear infiltration



Macrophages / lymphocytes

Parenchymal destruction



Tissue loss

Fibrous replacement



Connective tissue

Clinical example: Rheumatoid synovium

Clinical / morphologic scenario

A chronically inflamed synovium contains macrophages, lymphocytes, plasma cells, and follicle-like lymphoid aggregates.

Which two processes can sustain the lesion?

Interpretation

Persistent adaptive immune activation and reciprocal macrophage–lymphocyte signaling;
Organized follicles may coexist.

Clinical example: Allergic or helminth-associated inflammation

Clinical / morphologic scenario

An inflammatory focus contains numerous eosinophils and activated lymphocytes.

Which T-helper program and damaging effector are consistent with this pattern?

Interpretation

Th2 responses (including IL-5); Eosinophil major basic protein may injure host epithelium.

Clinical example: Sustained macrophage activation

Clinical / morphologic scenario

A persistent pathogen stimulates T cells and macrophages. IFN- γ activity is prominent and local tissue damage progresses.

Which macrophage pathway and consequence are expected?

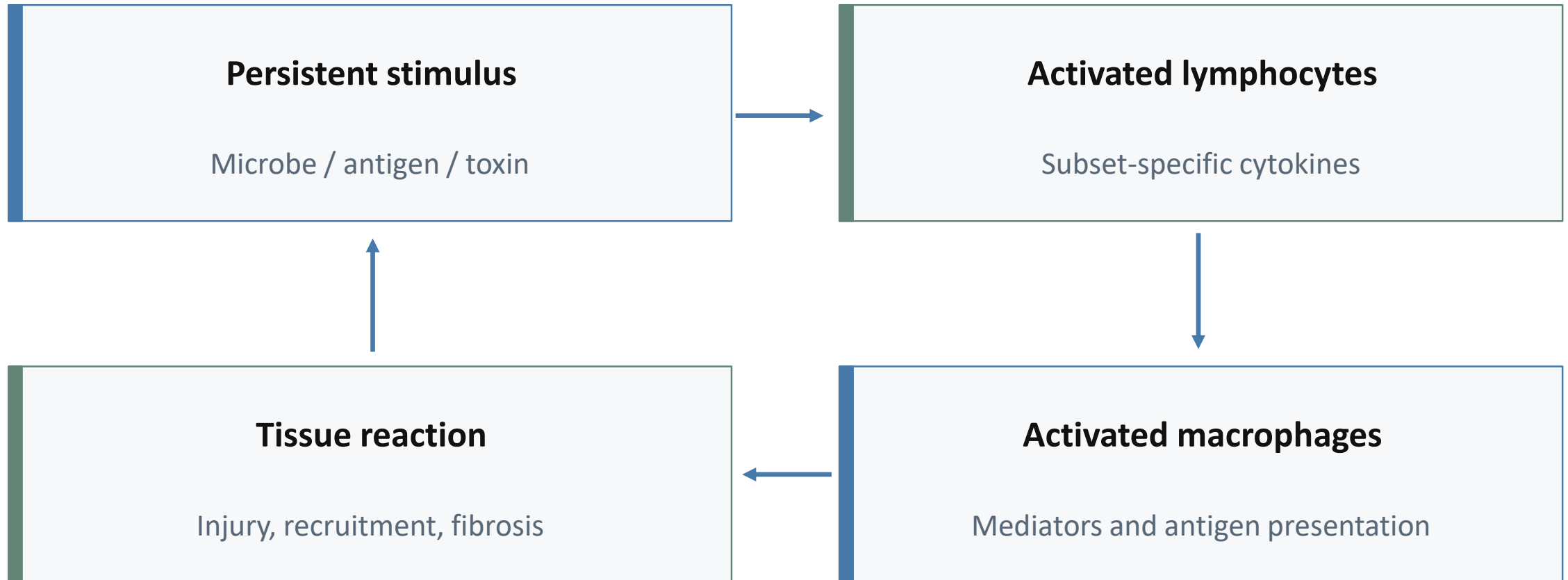
Interpretation

Classical (M1-like) activation with antimicrobial ROS/NO/enzyme activity and possible host-tissue injury.

Match mediators to the cellular processes they regulate

Process	Representative mediator(s)	Tissue consequence
Macrophage activation	IFN- γ	Microbicidal activity; Potential damage
Alternative activation	IL-4 and IL-13	Repair-oriented responses
Eosinophil response	IL-5; Eotaxin	Helminth defense; Epithelial injury
Leukocyte recruitment	Chemokines; IL-17-associated signals	Persistent cellular infiltration
Local amplification	TNF, IL-1	Sustained inflammatory responses

The central mechanism is a self-sustaining cellular circuit



Breaking stimulus persistence changes the circuit; Otherwise repair may coexist with continuing damage.

Synthesis: Interpret cells, mediators, and tissue consequences together

- Macrophages coordinate phagocytosis, inflammation, and repair.
- Th1, Th2, and Th17 programs produce different cellular patterns.
- B cells, eosinophils, mast cells, and neutrophils modify the reaction.
- Persistent activation explains simultaneous tissue destruction and fibrosis.

Reference and source scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 3: Inflammation and Repair.
- Sections: Chronic Inflammation; Cells and Mediators of Chronic Inflammation; Role of Macrophages; Role of Lymphocytes; Other Cells in Chronic Inflammation.
- Original explanatory schematics are constructed from the supplied textbook excerpt; they are not reproduced textbook figures.