

Role of Macrophages

Origins • activation • chronic inflammation • tissue repair

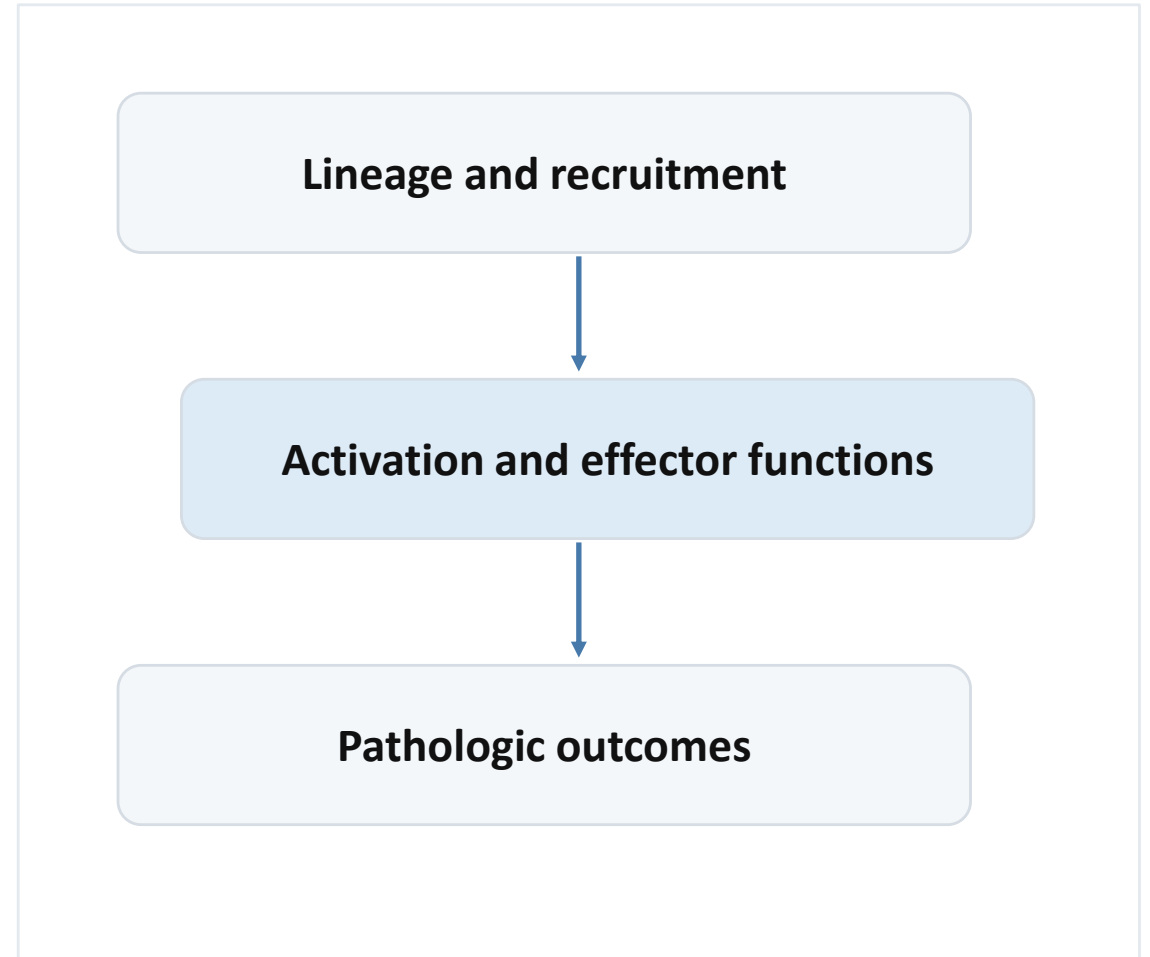
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Learning outcomes: Explain what macrophages do

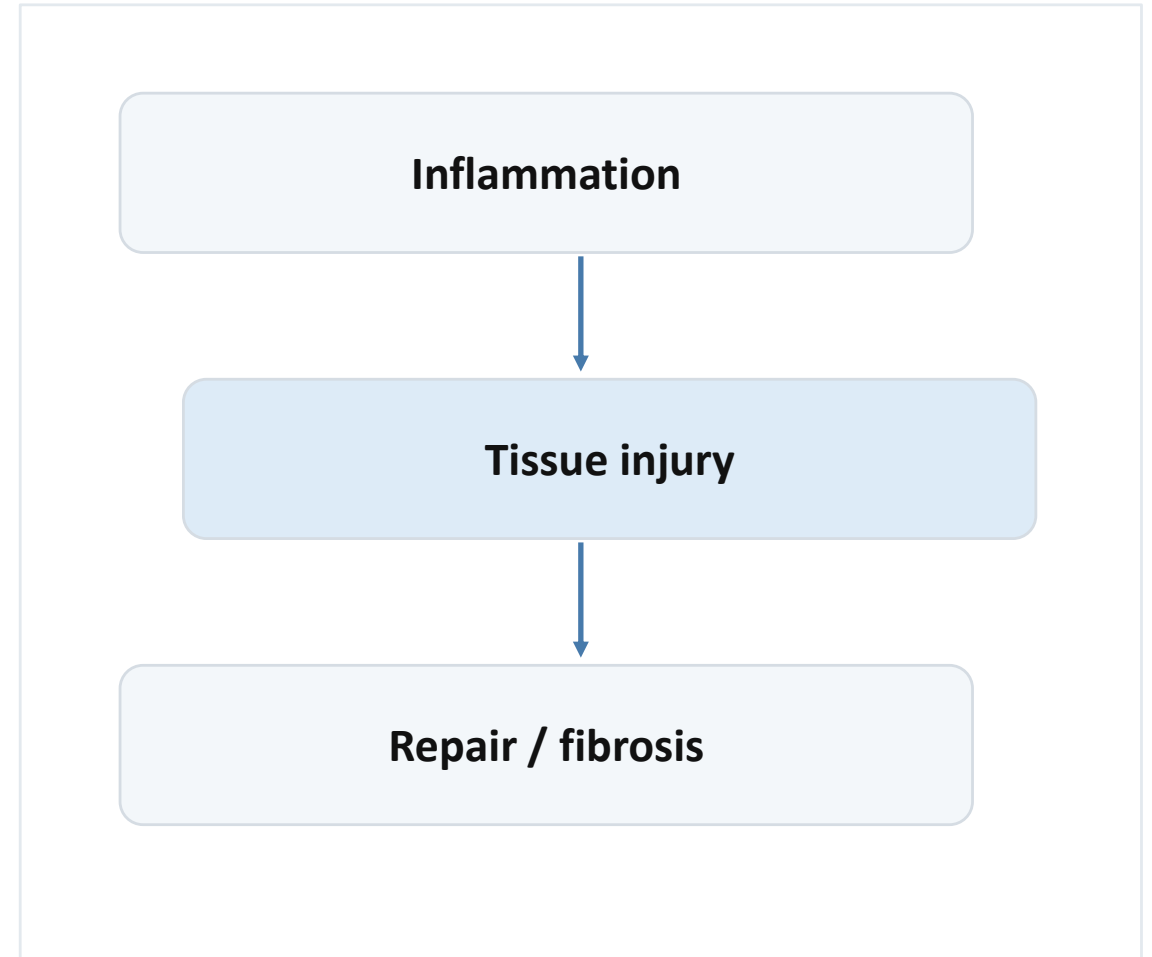
- Identify developmental sources and tissue-specific macrophage populations.
- Explain recruitment, activation and effector functions in chronic inflammation.
- Connect macrophage–T cell signaling to tissue injury, repair and granulomas.



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Chronic inflammation combines three simultaneous processes

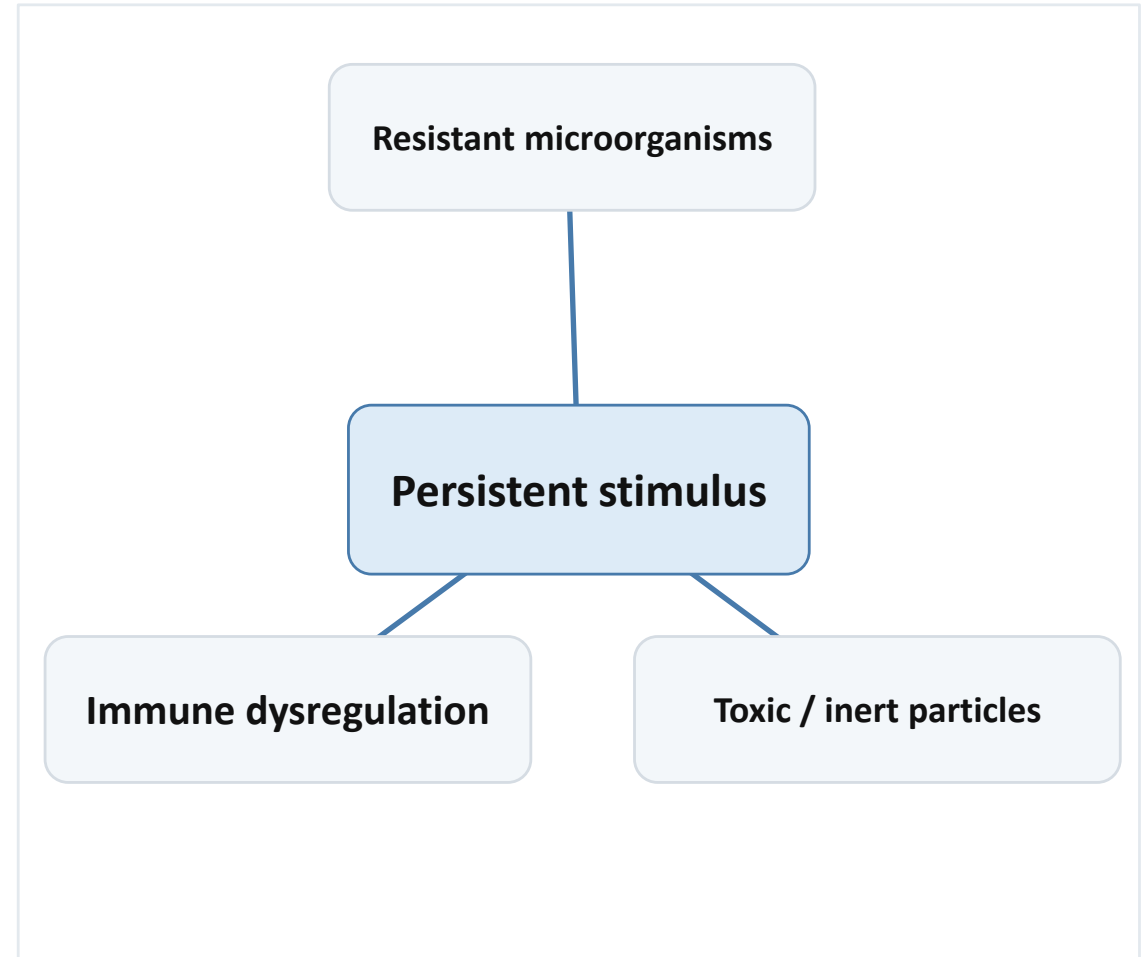
- Prolonged inflammation often continues for weeks or months.
- Tissue injury coexists with the cellular inflammatory response.
- Healing reactions occur at the same site, frequently with fibrosis.



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Why chronic inflammation persists

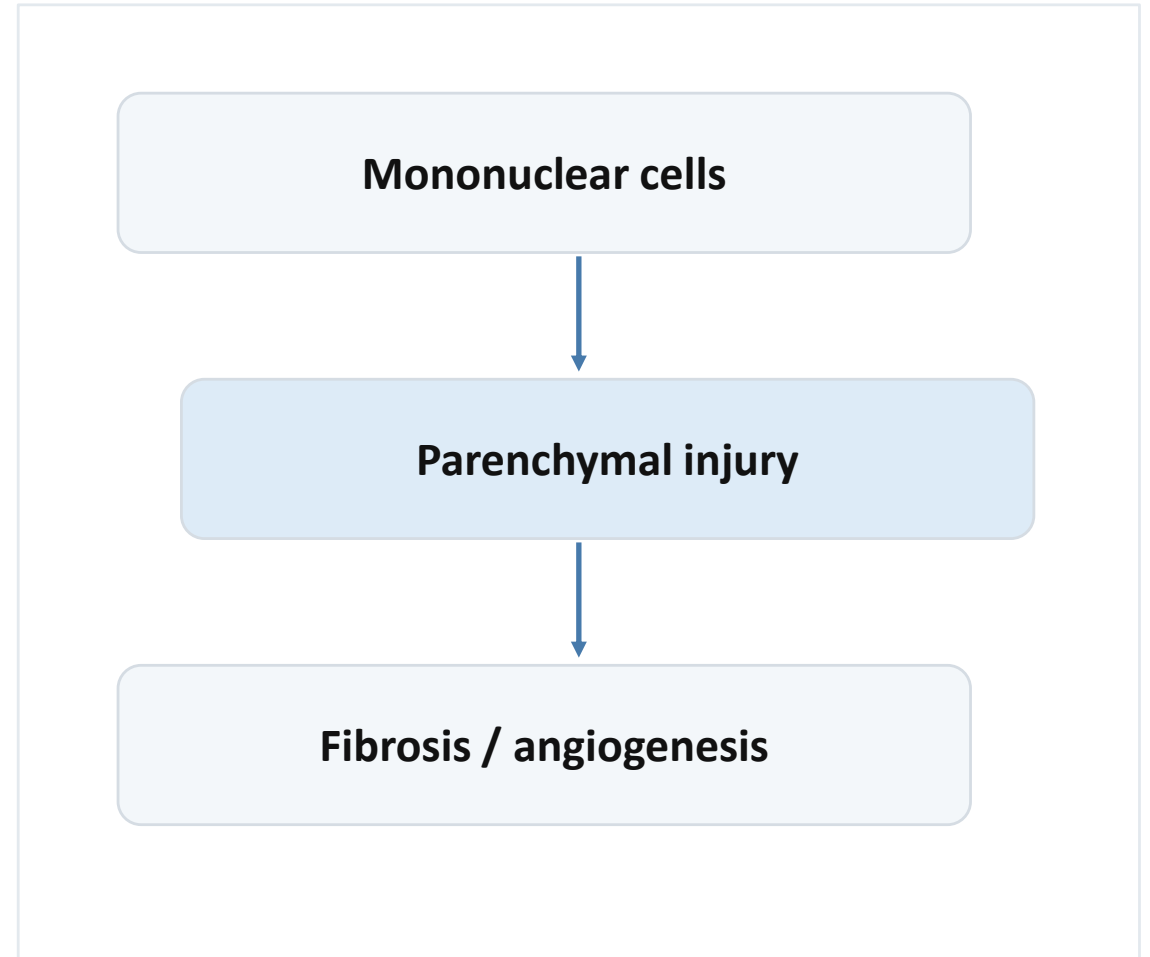
- Persistent microbes resist elimination and maintain inflammatory stimulation.
- Inappropriate immune reactions can amplify injury against self or environmental antigens.
- Nondegradable or toxic material may provide a continuing stimulus.



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The histologic triad of chronic inflammation

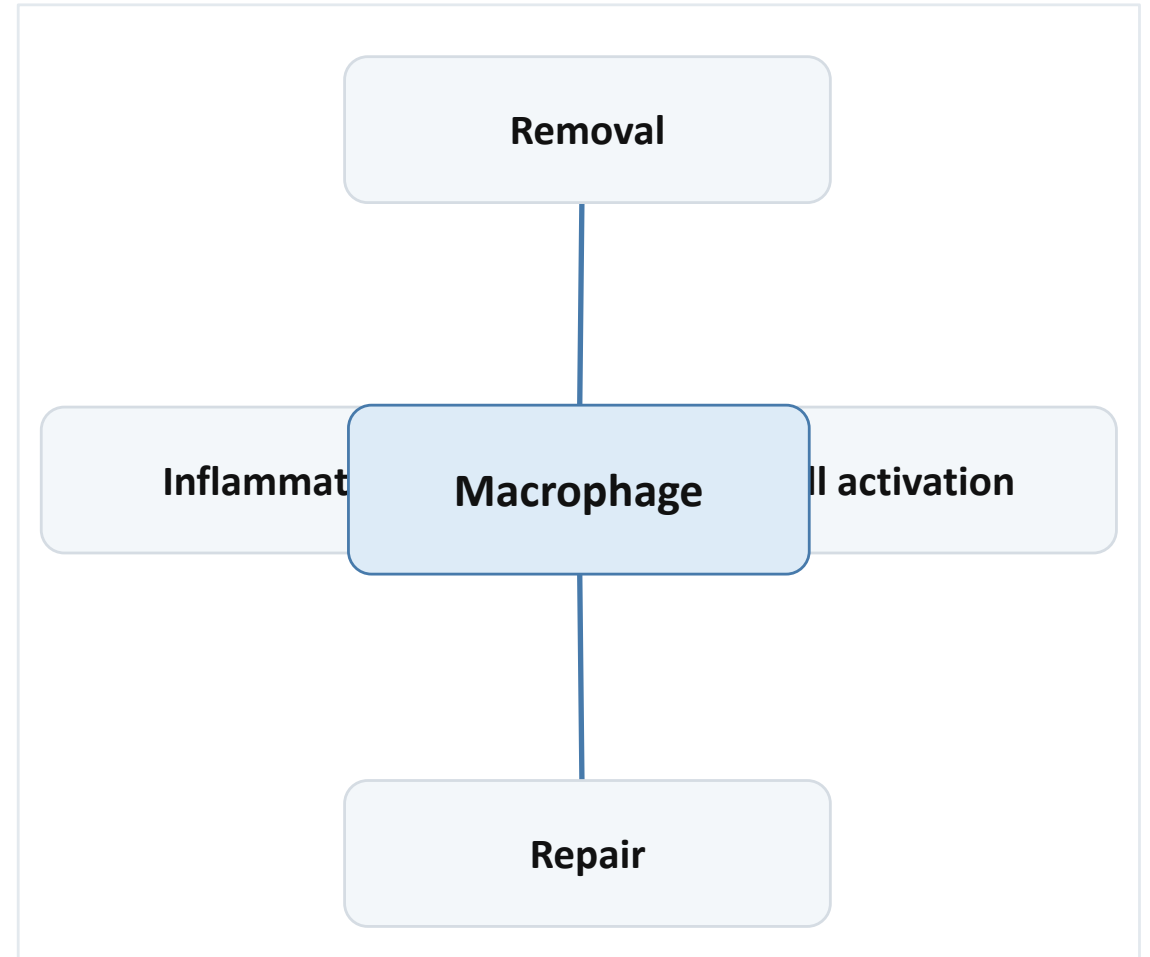
- Mononuclear infiltrates include macrophages, lymphocytes and plasma cells.
- Tissue destruction results from the agent, inflammatory cells, or both.
- Angiogenesis and connective-tissue deposition mark attempted healing.



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Macrophages are central—not merely scavengers

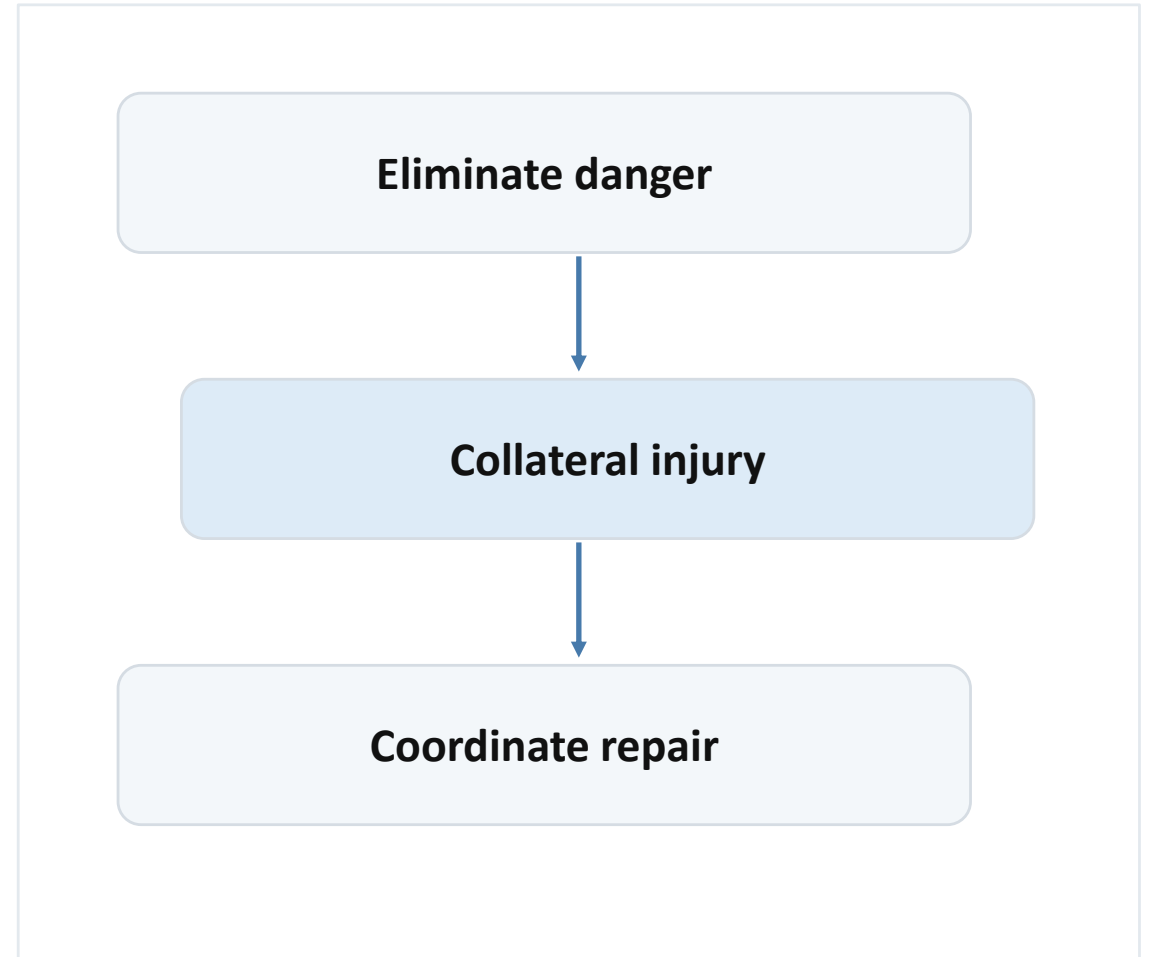
- They eliminate microbes and damaged tissues by phagocytosis.
- They secrete cytokines and growth factors that change neighboring cell behavior.
- They communicate with T lymphocytes and organize the tissue response.



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One cell population can protect and damage tissue

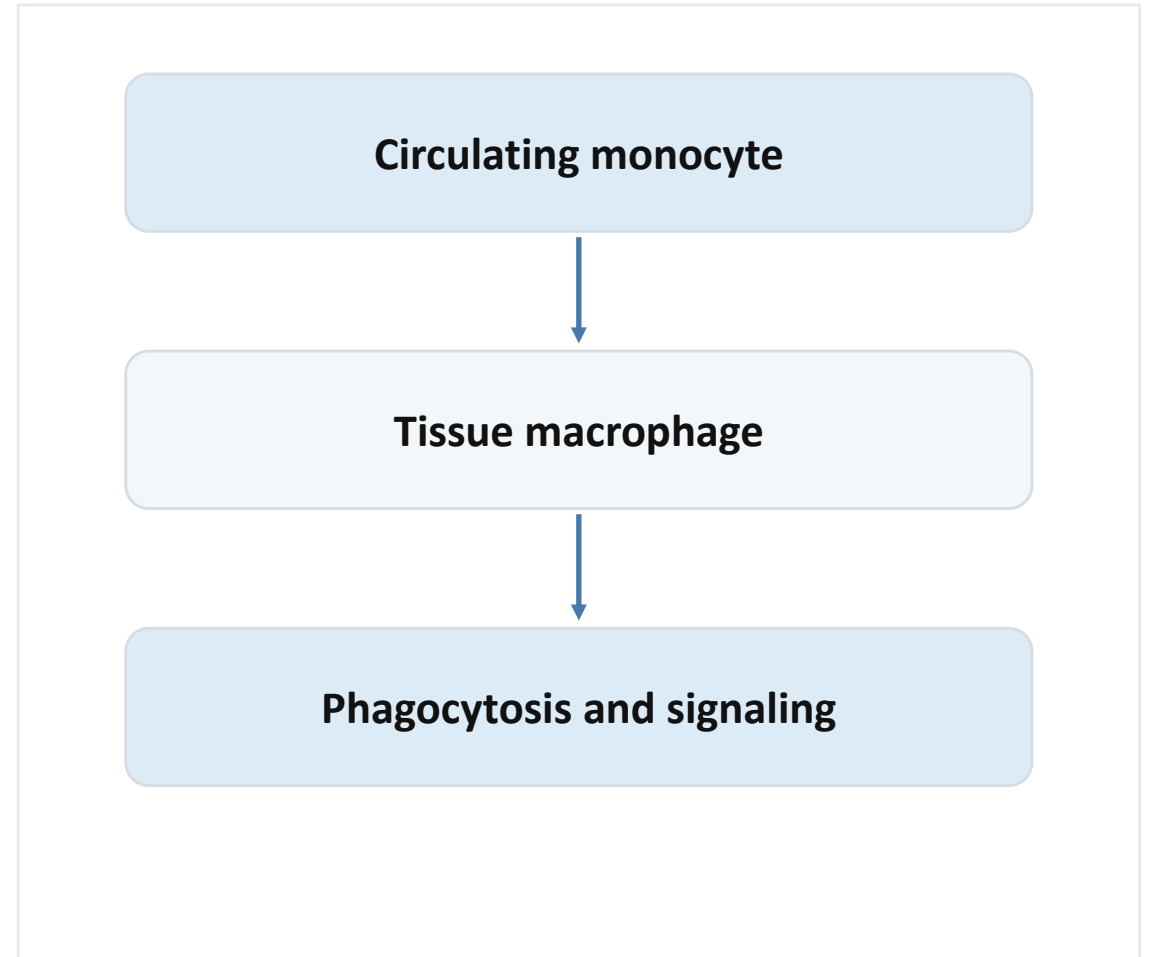
- Microbicidal products support host defense.
- Excessive or inappropriate activation can injure normal tissue.
- Growth factors also initiate the repair response after injury.



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The mononuclear phagocyte system

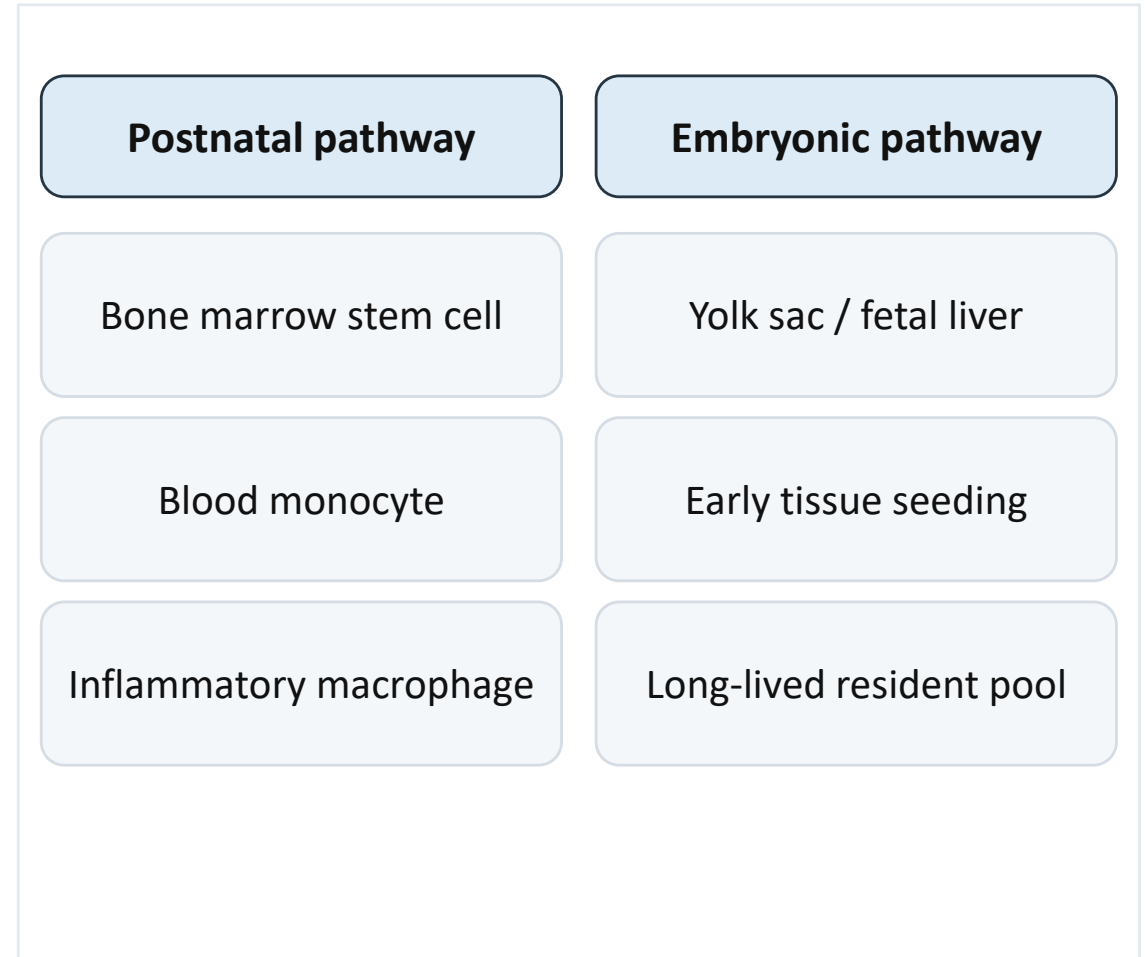
- Monocytes are circulating cells of the macrophage lineage.
- Macrophages are resident or recruited tissue phagocytes.
- The historical term “reticuloendothelial system” is imprecise.



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Two developmental routes contribute macrophages

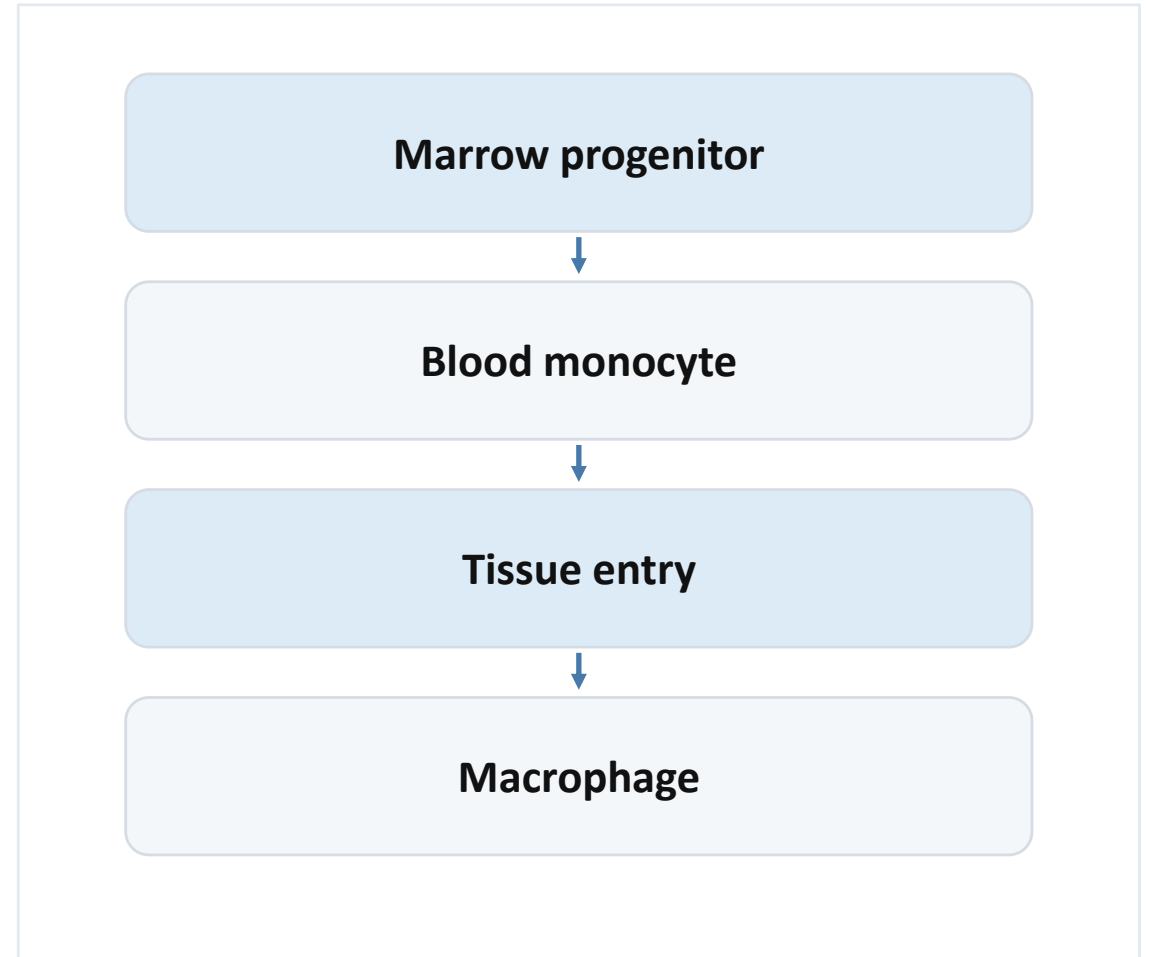
- Hematopoietic stem cells in bone marrow generate circulating monocytes.
- Embryonic yolk sac and fetal liver provide precursors to selected resident populations.
- Origin depends on tissue and inflammatory context.



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Bone marrow-derived macrophage development

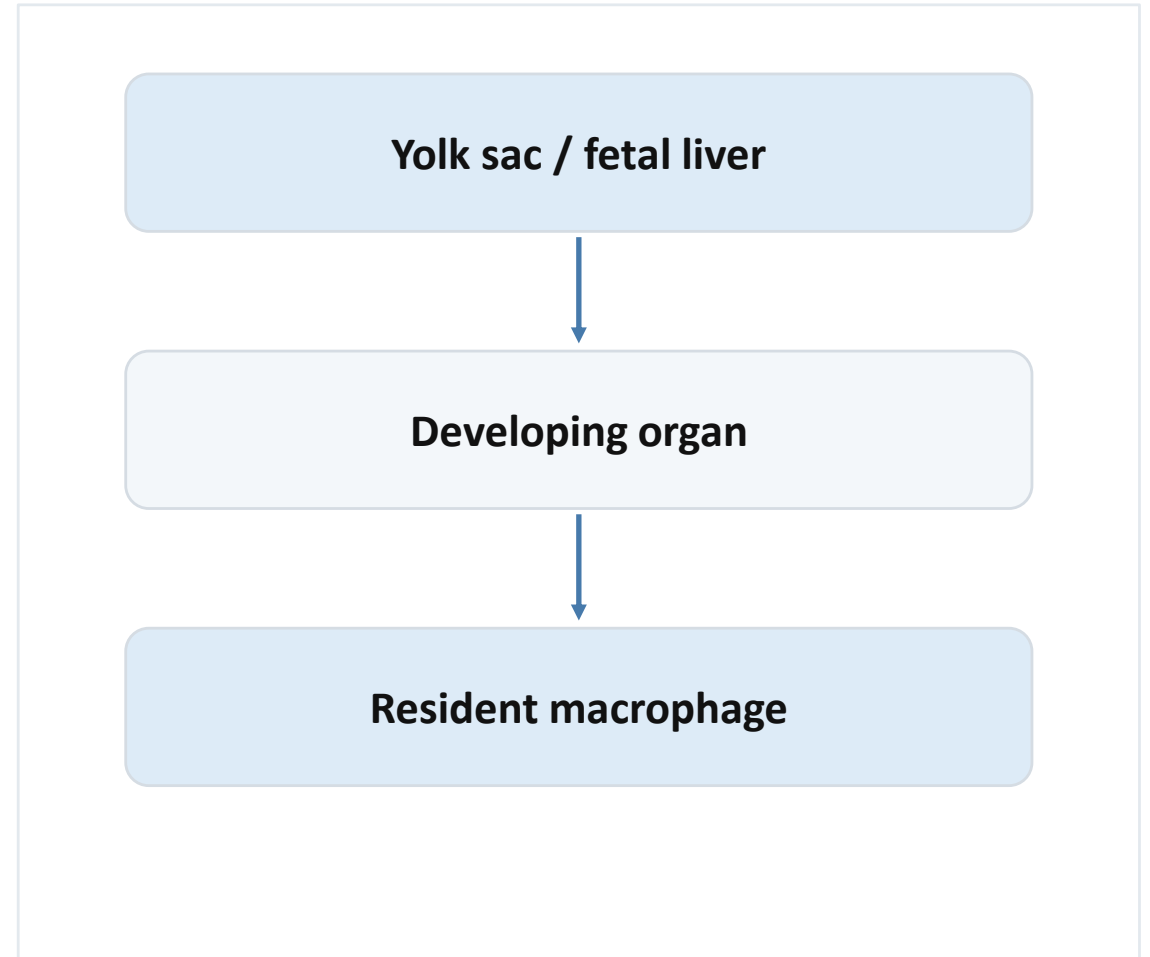
- Committed marrow precursors produce monocytes.
- Monocytes enter blood before crossing vascular endothelium.
- Differentiation within tissues yields macrophages.



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Embryonic precursors establish resident populations

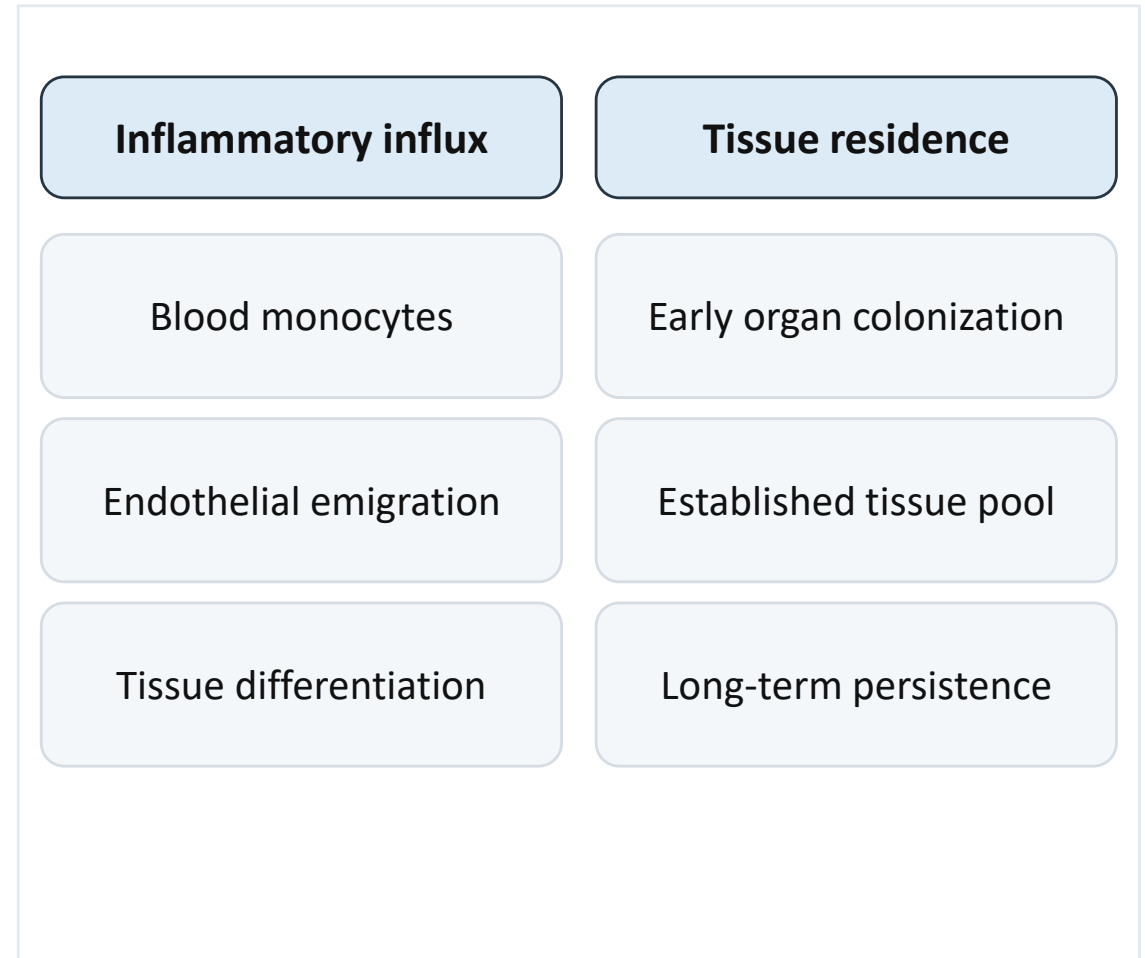
- Progenitors arise early in the yolk sac or fetal liver.
- They enter developing organs and establish tissue macrophage populations.
- Some resident populations are maintained long term.



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Inflammatory and resident macrophages: Origins differ

- Inflamed tissues often contain recruited monocyte-derived macrophages.
- The brain, liver and lung contain populations seeded during development.
- A tissue label does not by itself identify the origin of every macrophage in disease.



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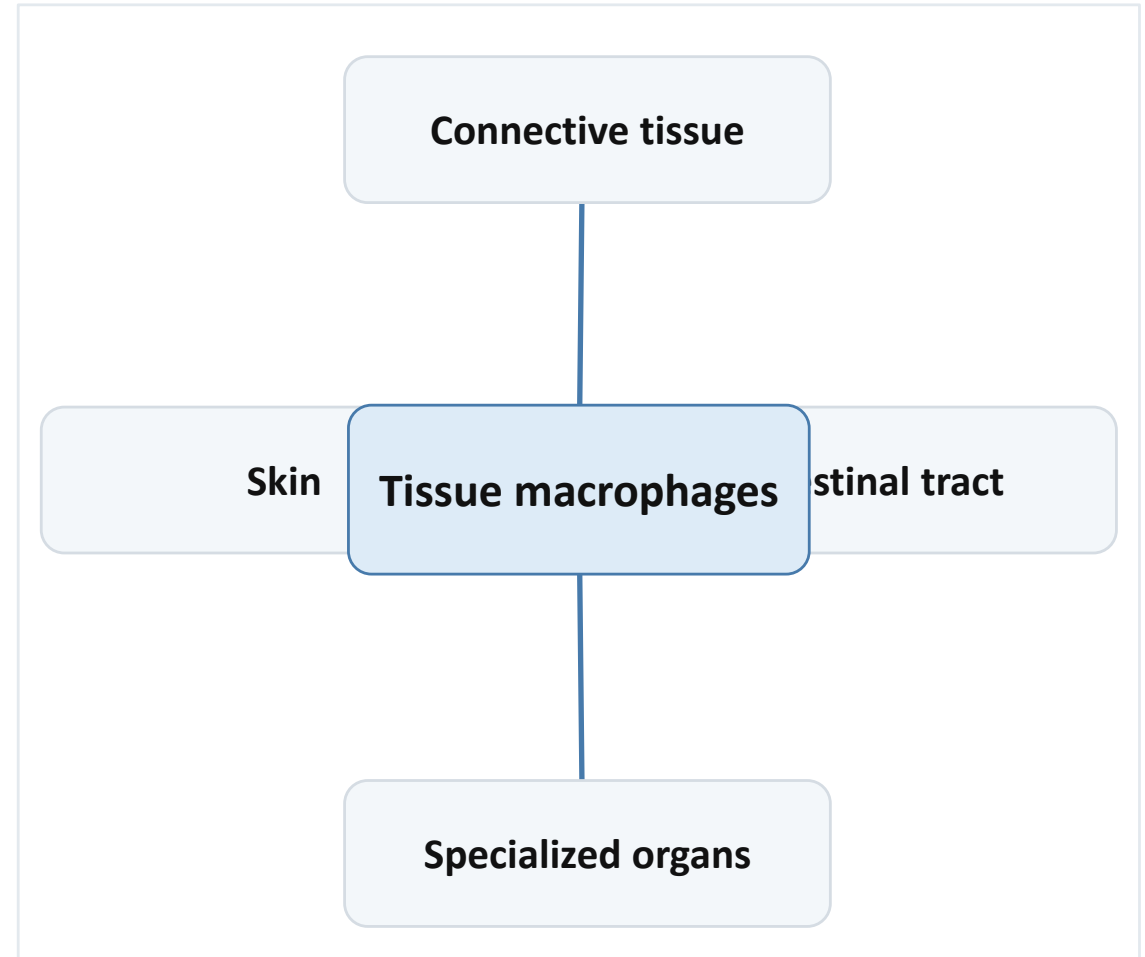
Different organs assign different macrophage names

Location	Macrophage name
Liver	Kupffer cell
Brain / CNS	Microglia
Lung alveolus	Alveolar macrophage
Spleen / lymph-node sinuses	Sinus histiocyte

- Kupffer cells are liver macrophages.
- Microglia are macrophages in the central nervous system.
- Alveolar macrophages reside in the lung; Sinus histiocytes occur in lymphoid organs.

Macrophages are also dispersed in connective tissues

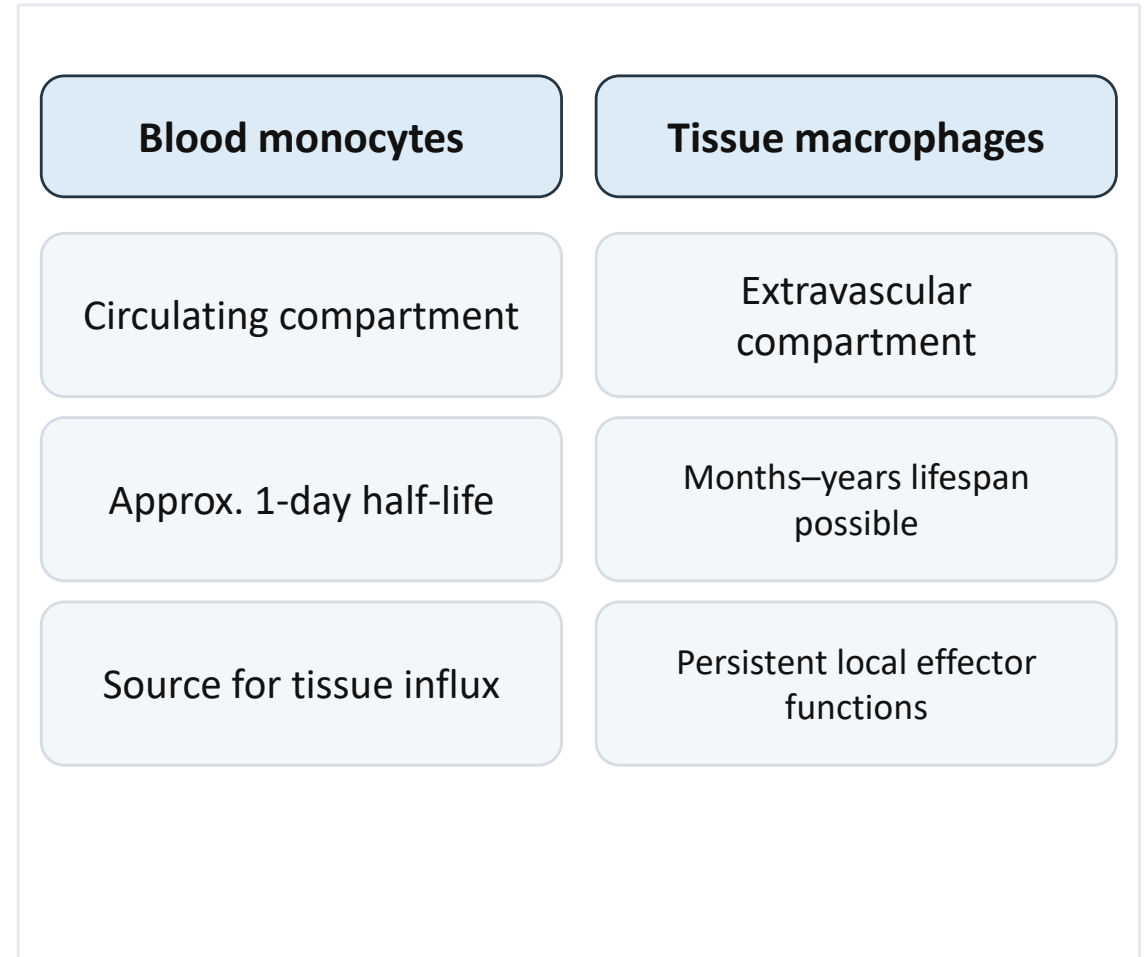
- They are present beyond specialized organ compartments.
- Skin and intestinal tissues can receive monocyte-derived macrophages.
- Location and recent recruitment together shape local macrophage composition.



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Monocytes and macrophages have different kinetics

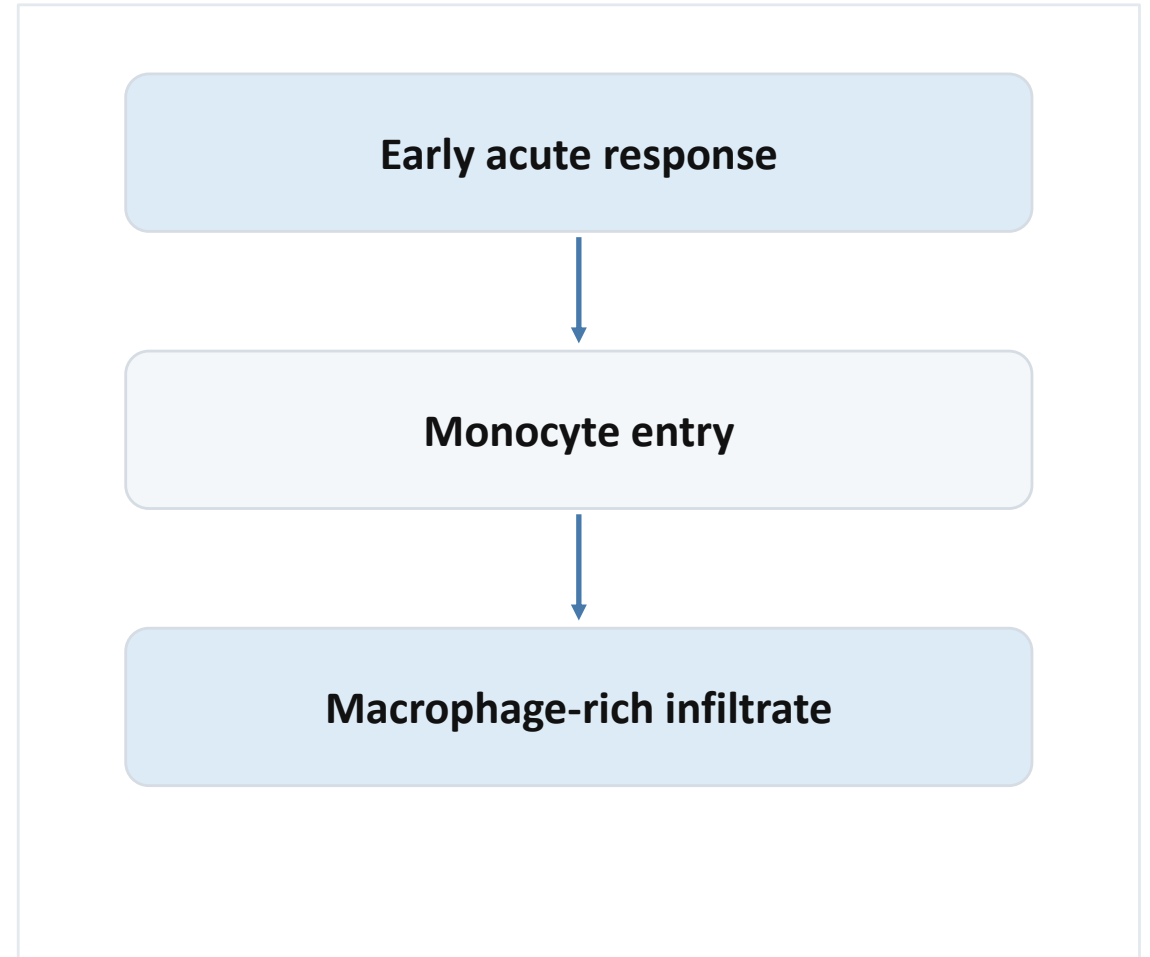
- Blood monocytes have an approximate half-life of one day in the cited text.
- Tissue macrophages may survive for months to years.
- This difference permits prolonged local macrophage activity.



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Macrophages can dominate after the early response

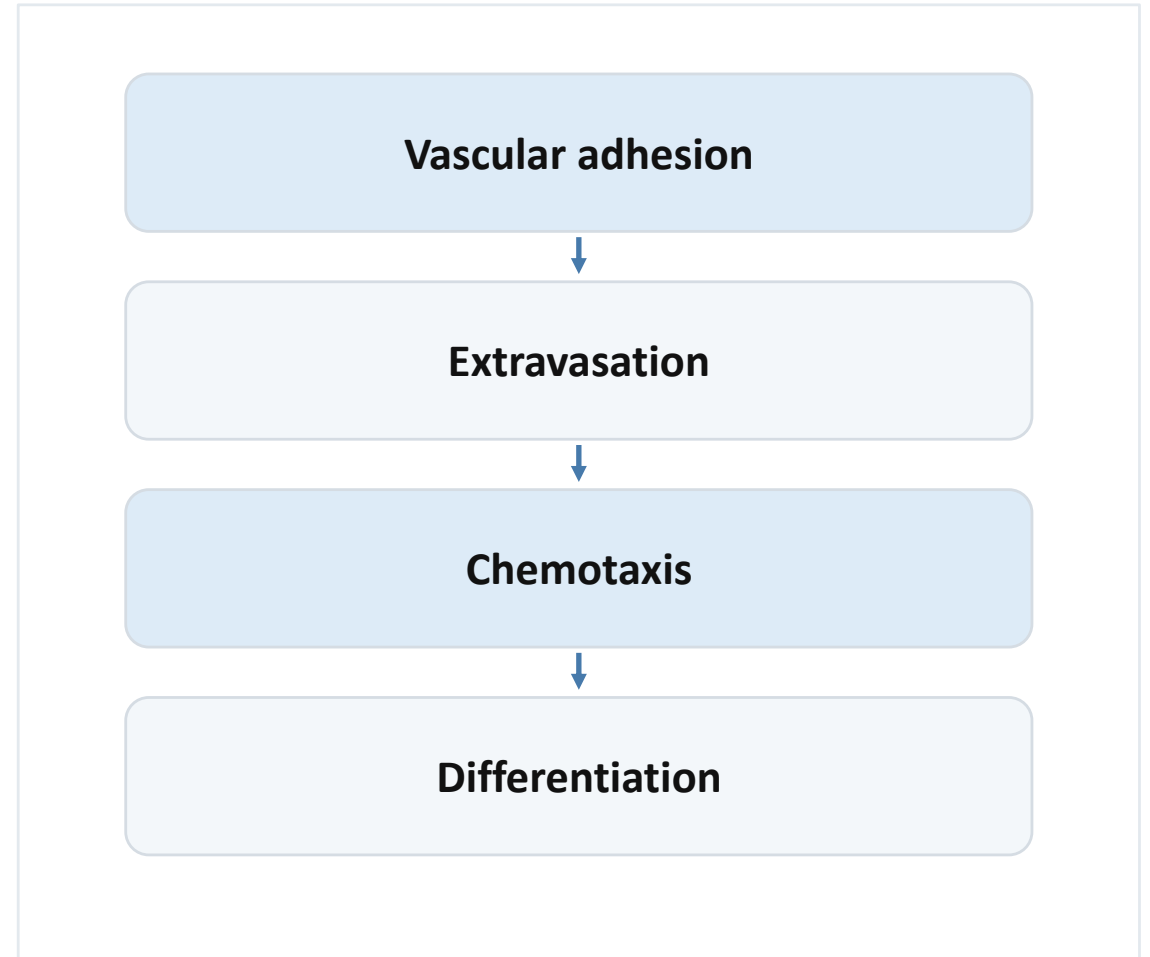
- Monocytes begin entering inflamed tissues relatively early.
- Within about 48 hours, macrophages may become the predominant cell type.
- Timing is a pattern, not a universal diagnostic cutoff.



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How monocytes reach injured tissue

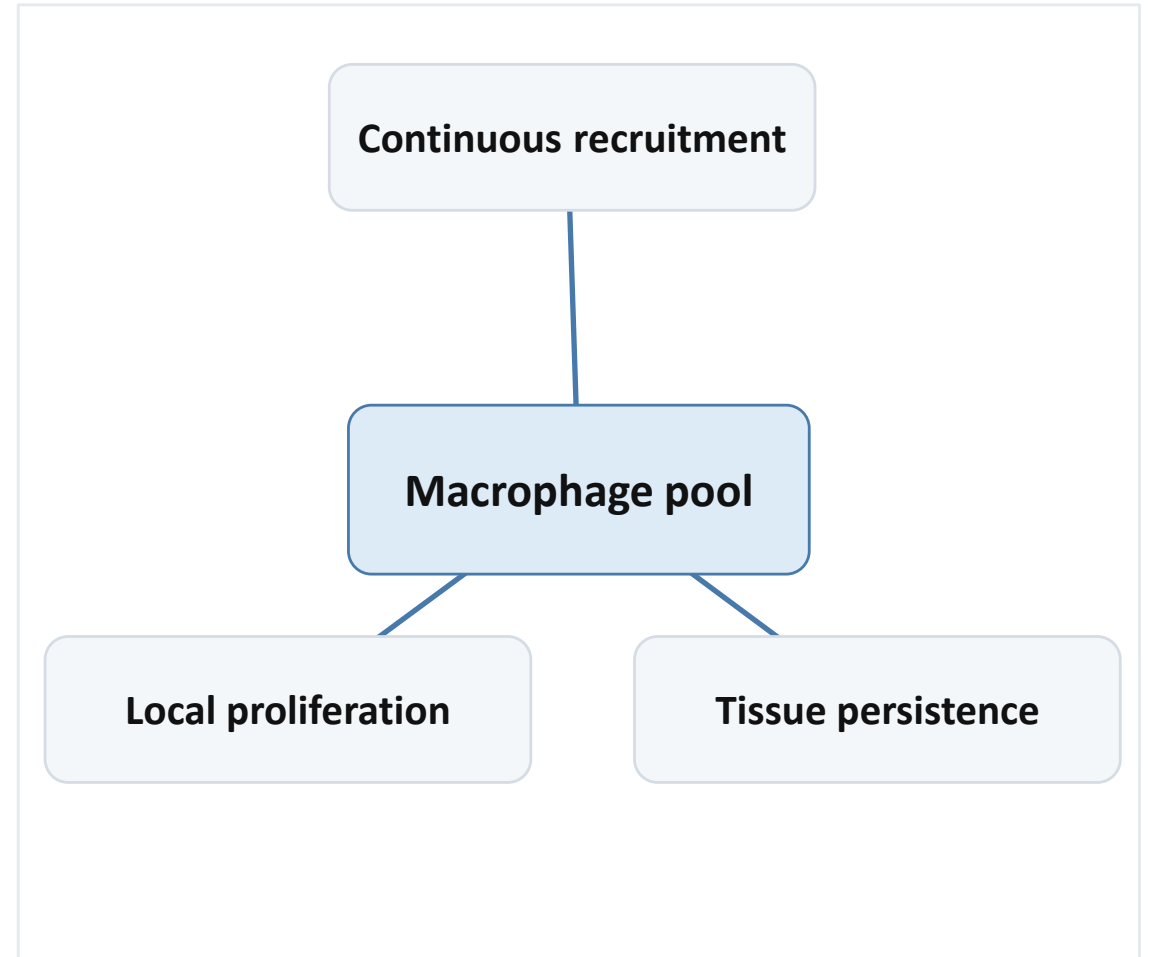
- The processes depend on endothelial adhesion molecules.
- Chemotactic factors guide monocytes toward the inflammatory stimulus.
- After exiting blood, monocytes differentiate into tissue macrophages.



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Two processes can maintain macrophage accumulation

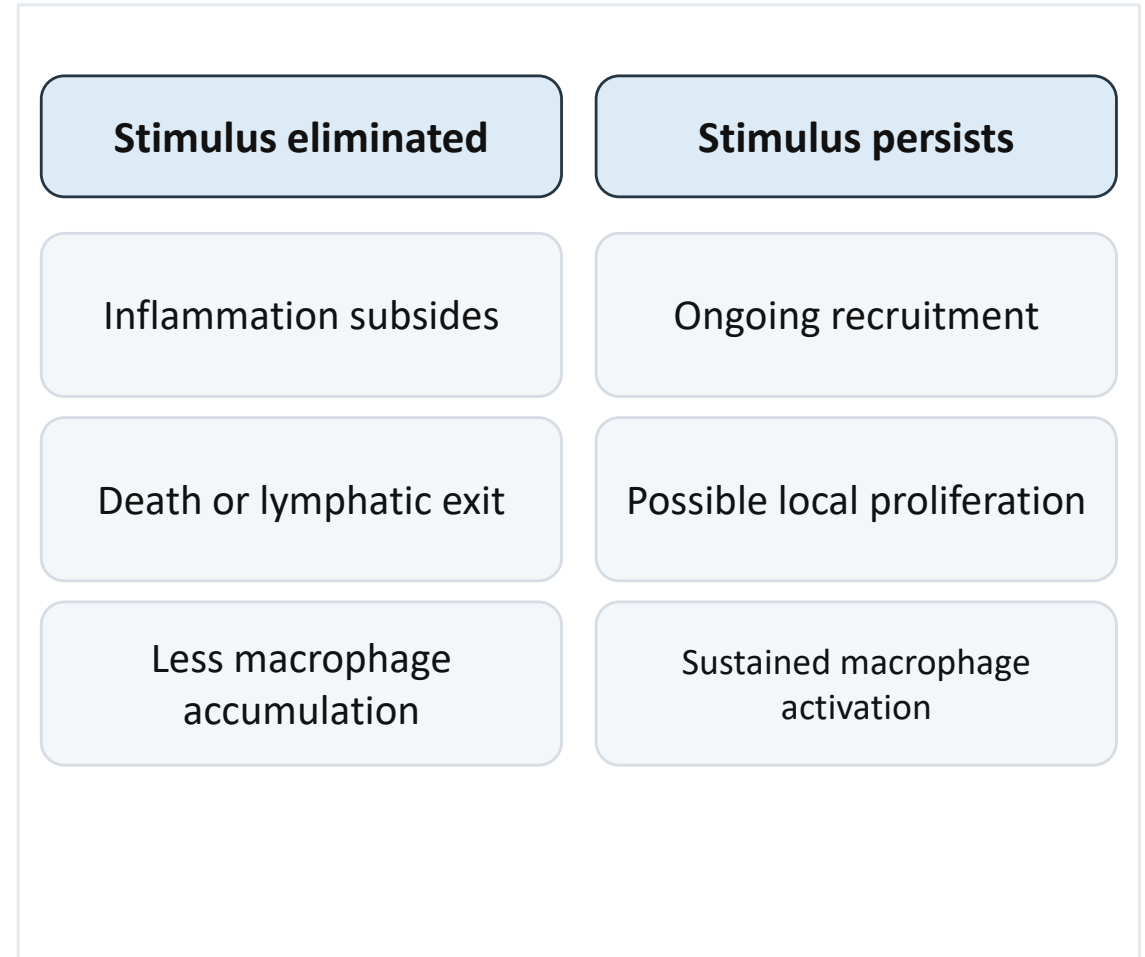
- Continued recruitment replenishes macrophages from the circulation.
- Local macrophage proliferation can enlarge the tissue population.
- Persistent accumulation helps maintain chronic inflammation.



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Macrophages may disappear after the stimulus resolves

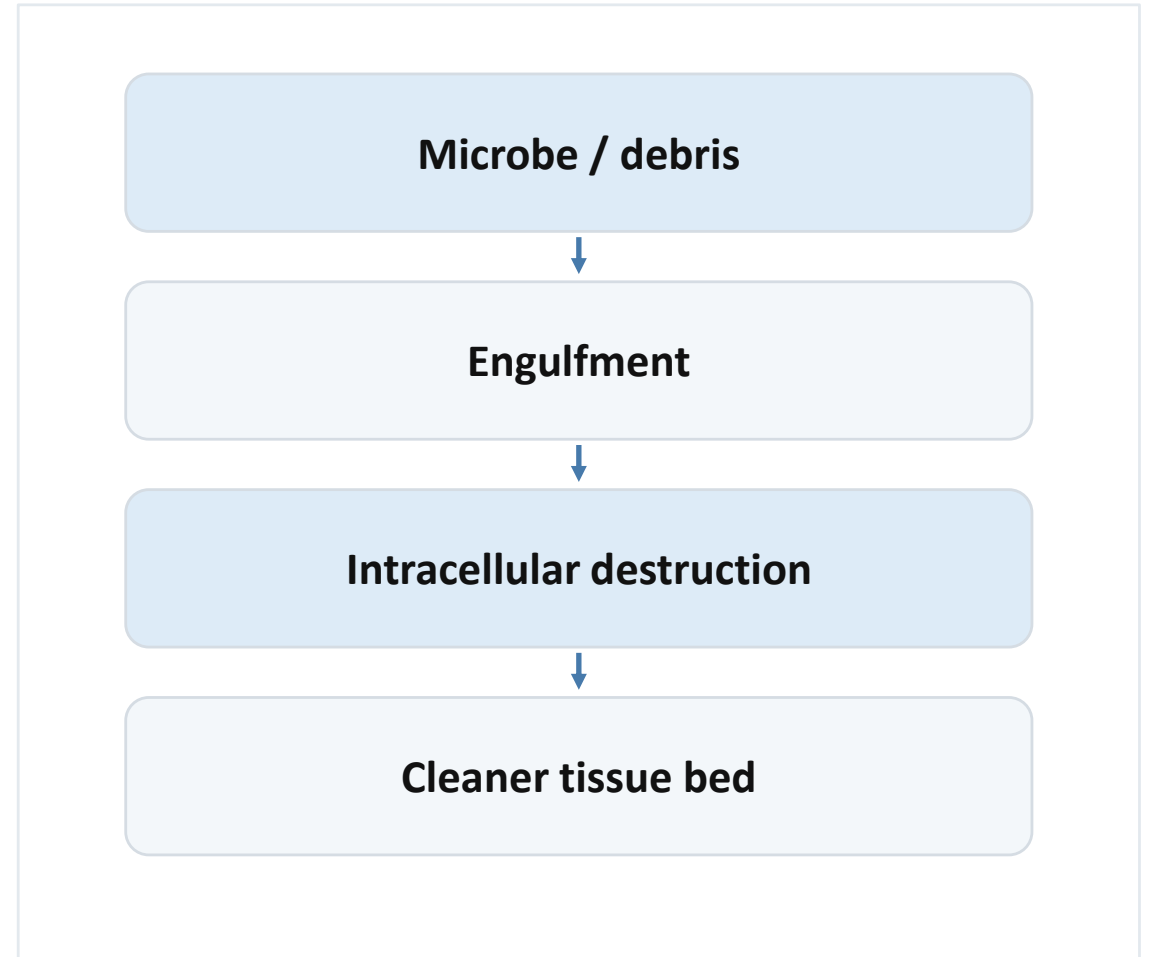
- Removal of the irritant permits the inflammatory response to subside.
- Some macrophages die; Others depart through lymphatics and lymph nodes.
- Failure to remove the stimulus favors persistence.



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Phagocytosis removes microbes and dead tissue

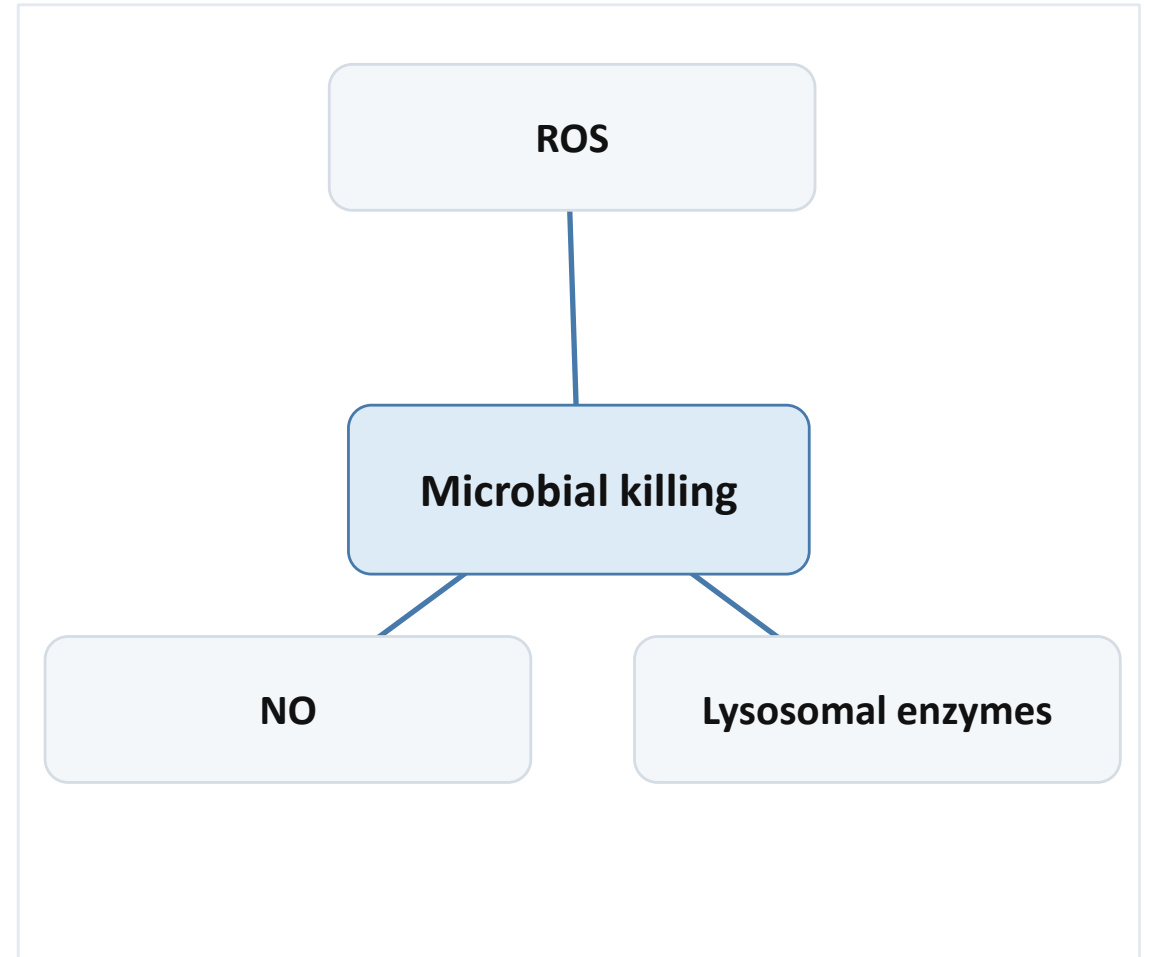
- Macrophages are professional phagocytes.
- Targets include infectious agents and necrotic cellular material.
- Clearance is both defensive and preparatory for repair.



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Activated macrophages deploy microbicidal effectors

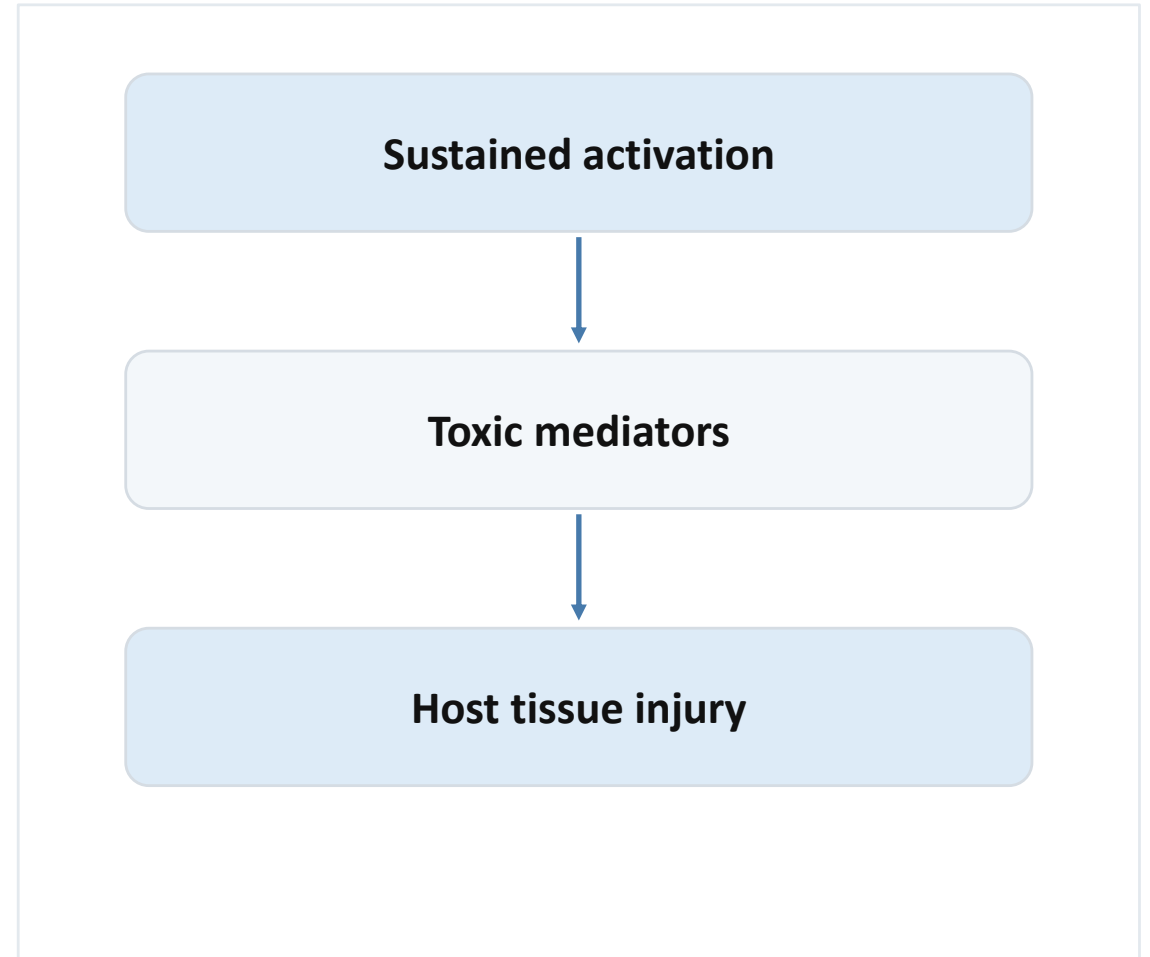
- Classically activated macrophages produce reactive oxygen species (ROS).
- Nitric oxide (NO) contributes to microbial killing.
- Lysosomal enzymes digest material taken into phagocytic compartments.



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The same effector products can injure host tissue

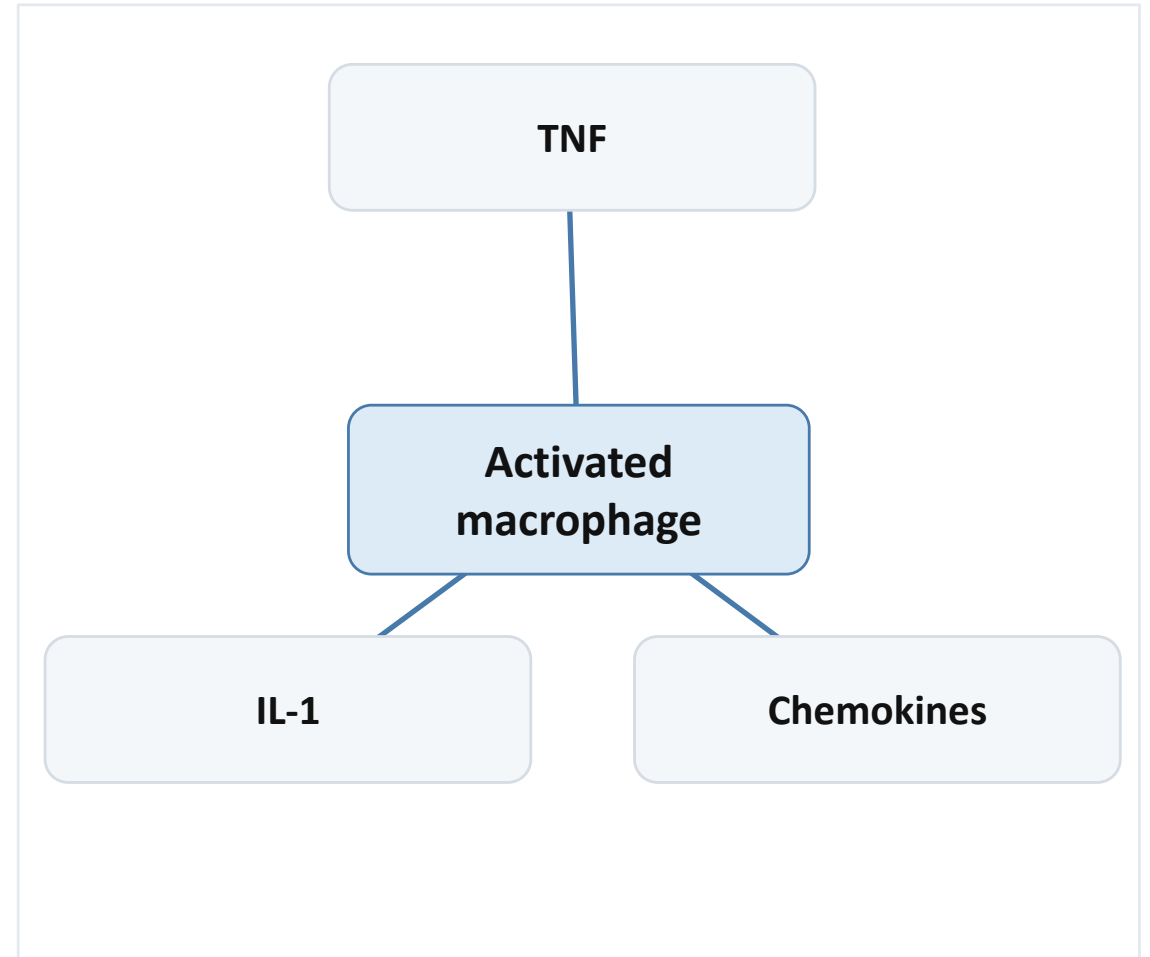
- ROS, NO and enzymes are useful in antimicrobial defense.
- Excess activation can damage normal tissue components.
- Collateral destruction explains part of the morphology of chronic inflammation.



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Macrophages transmit inflammation by cytokines

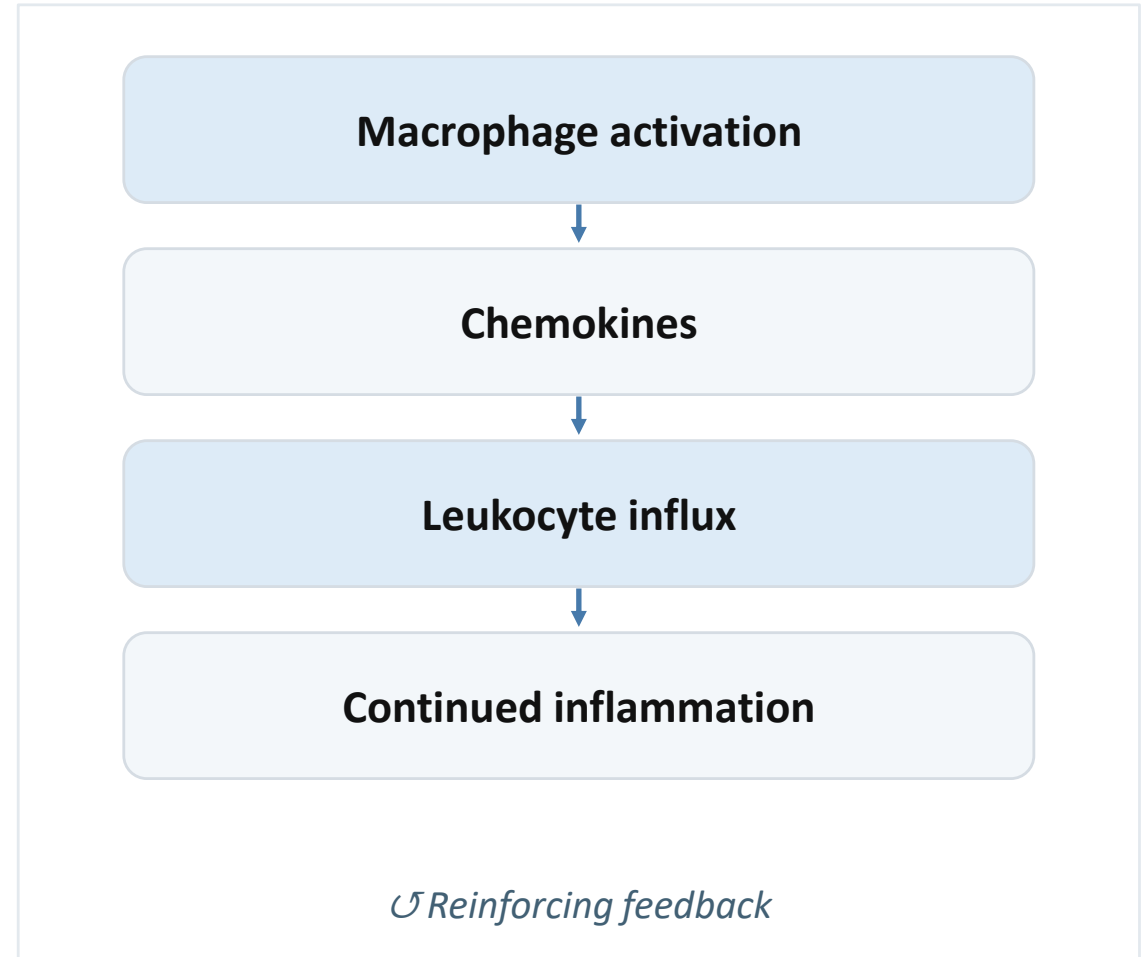
- Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are examples.
- Chemokines direct additional leukocyte recruitment.
- These mediators help initiate and propagate inflammatory reactions.



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Chemokines reinforce leukocyte recruitment

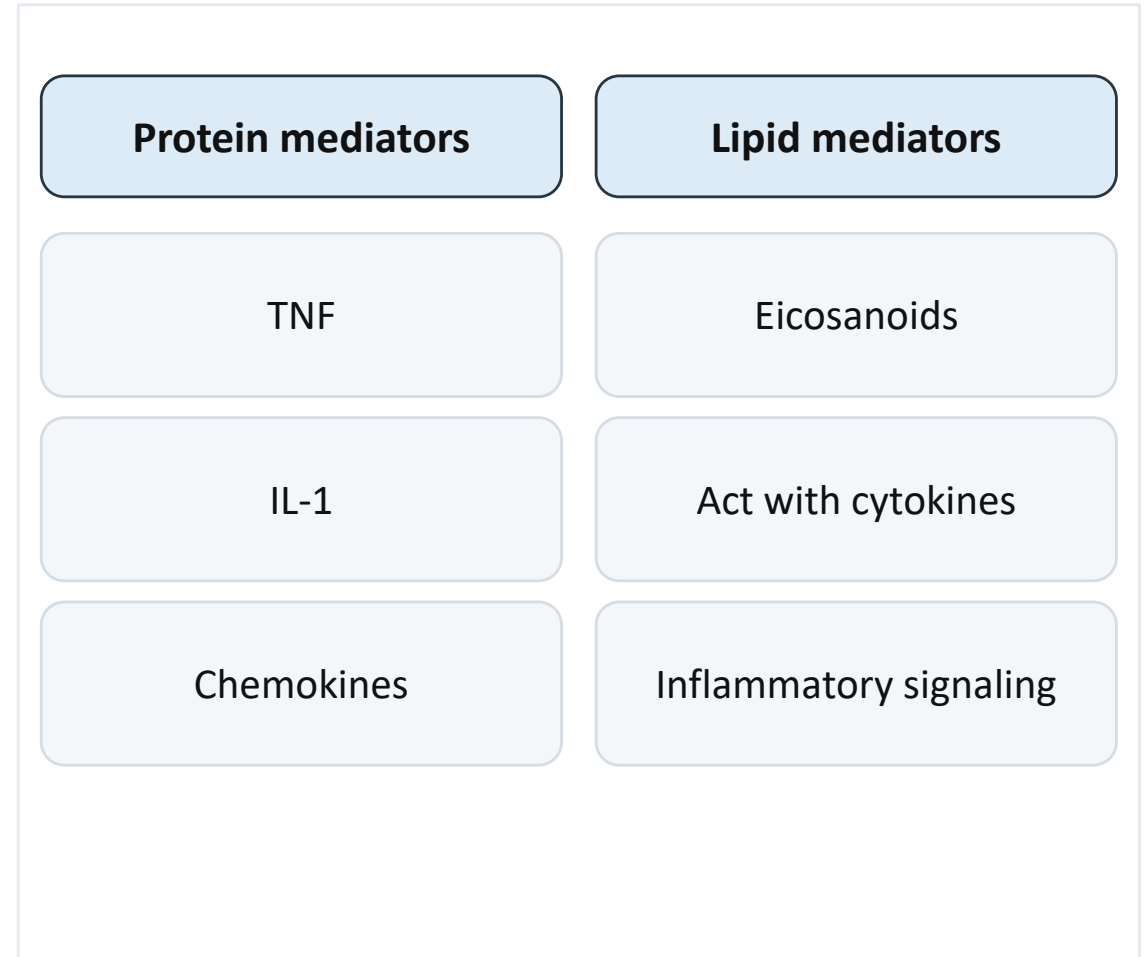
- Activated macrophages contribute chemotactic mediator signals.
- Newly arriving leukocytes can expand the inflammatory infiltrate.
- Recruitment creates a potential positive feedback mechanism.



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Eicosanoids add another mediator class

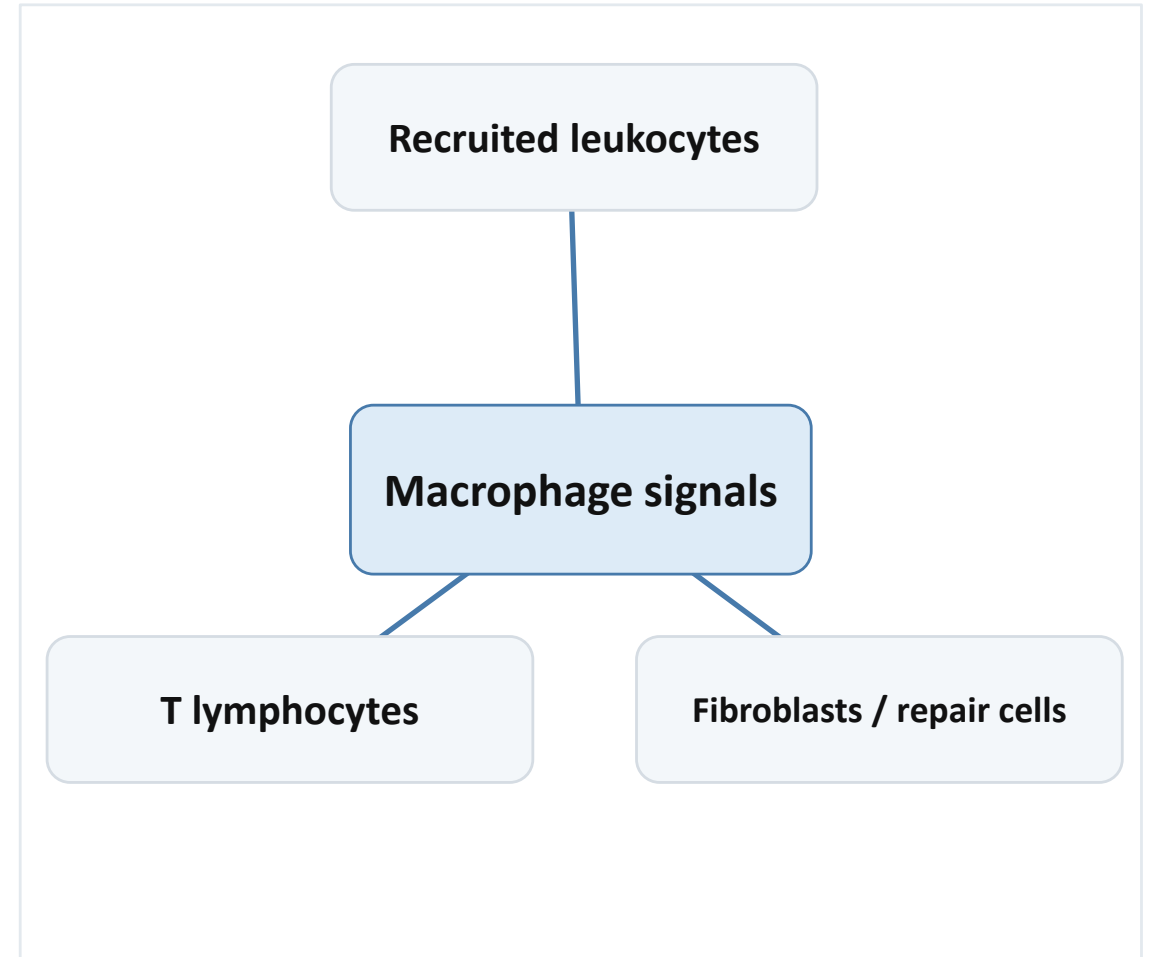
- Macrophages can generate eicosanoid inflammatory mediators.
- They act alongside protein mediators such as cytokines.
- Macrophage influence therefore extends beyond direct phagocytosis.



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Macrophage-derived signals have distinct recipients

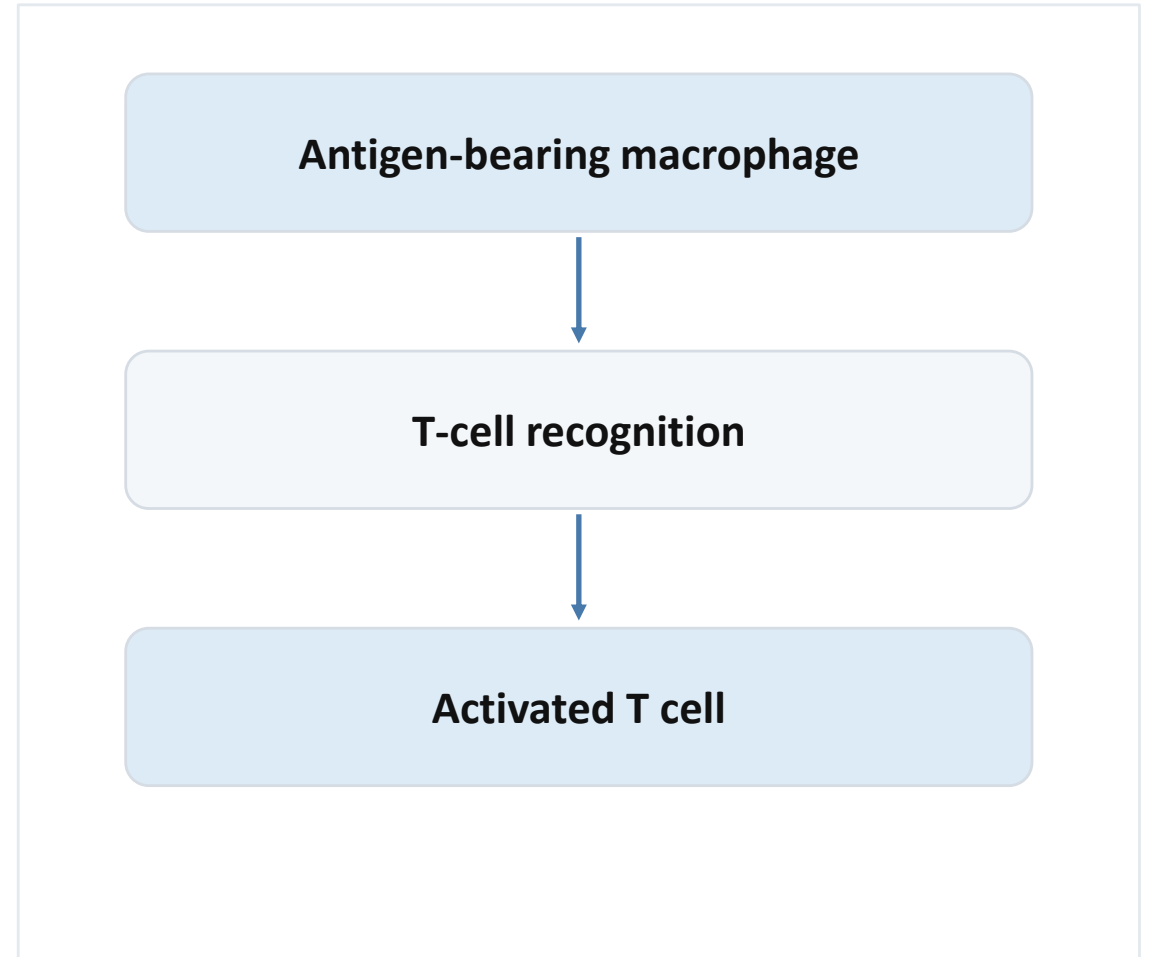
- Leukocytes respond to recruitment and activation mediators.
- T lymphocytes respond to antigen presentation and cytokines.
- Fibroblasts and reparative cells respond to growth factors.



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Antigen presentation links innate and adaptive responses

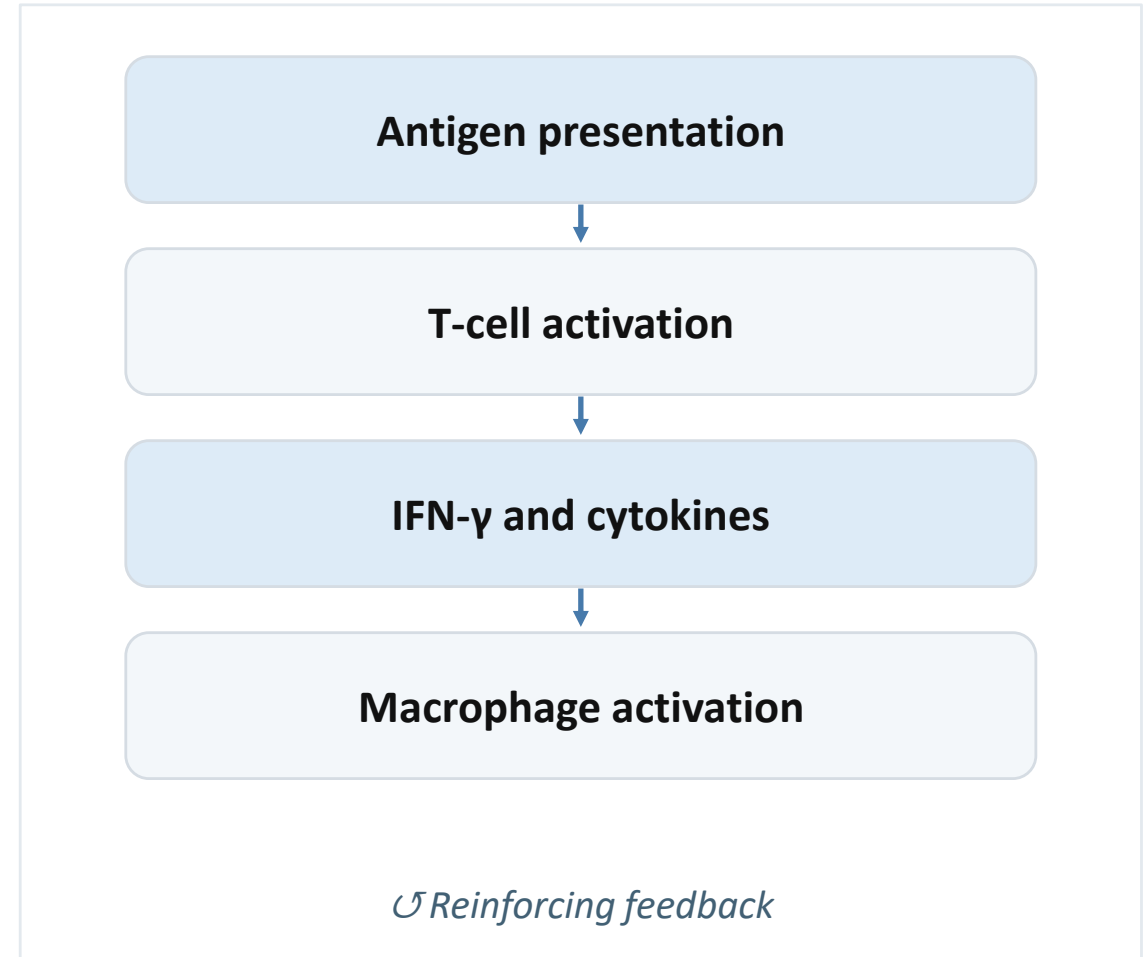
- Macrophages display antigens to T lymphocytes.
- Costimulatory molecules participate in T-cell activation.
- Inflammatory cytokines, including IL-12, strengthen this communication.



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Macrophages and T cells activate one another

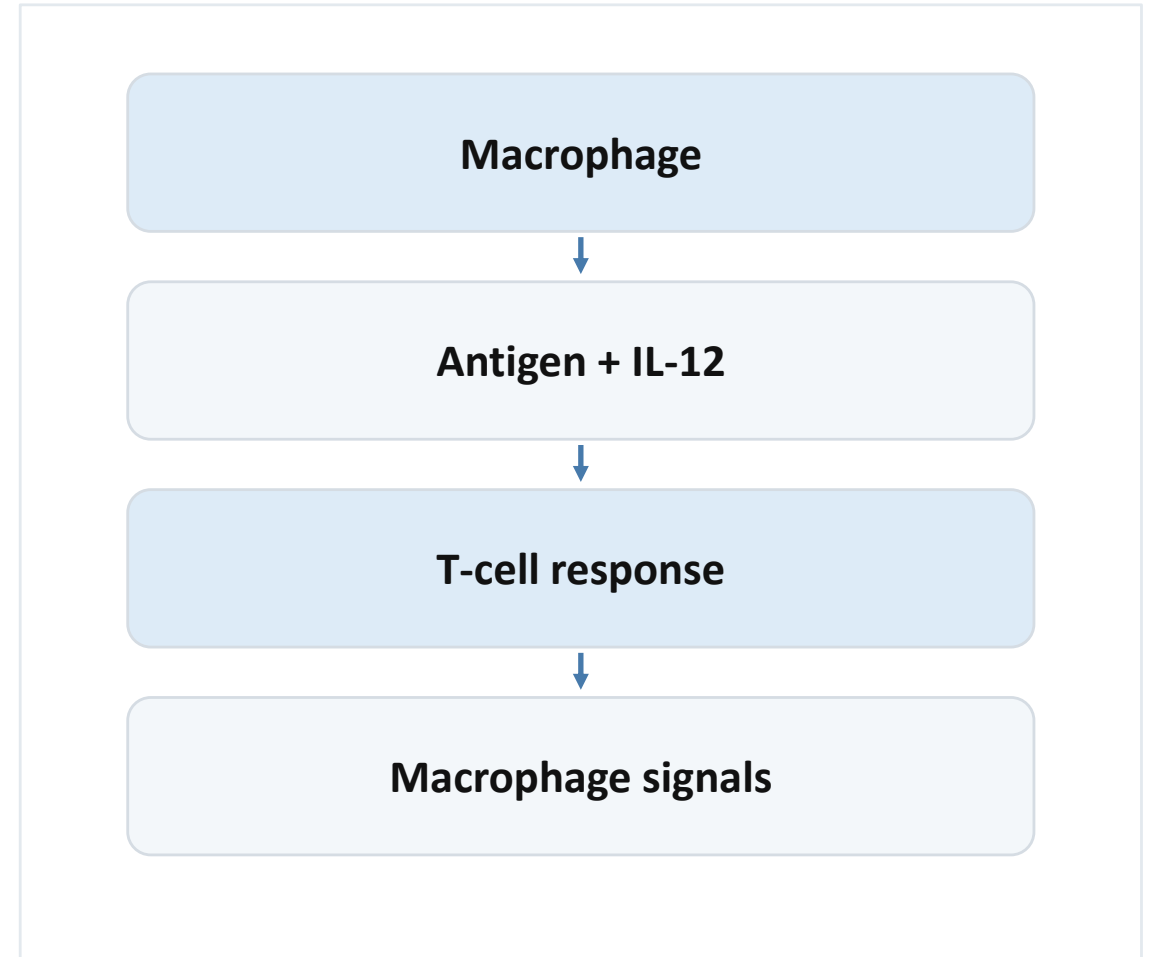
- Macrophages present antigen and secrete T-cell-stimulating cytokines.
- Activated T cells secrete macrophage-activating signals.
- This bidirectional circuit sustains chronic inflammation.



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IL-12 is part of the macrophage-to-T-cell arm

- Activated macrophages can produce IL-12.
- Along with antigen display and costimulation, IL-12 supports T-cell responses.
- The responding T cells can further influence macrophage behavior.



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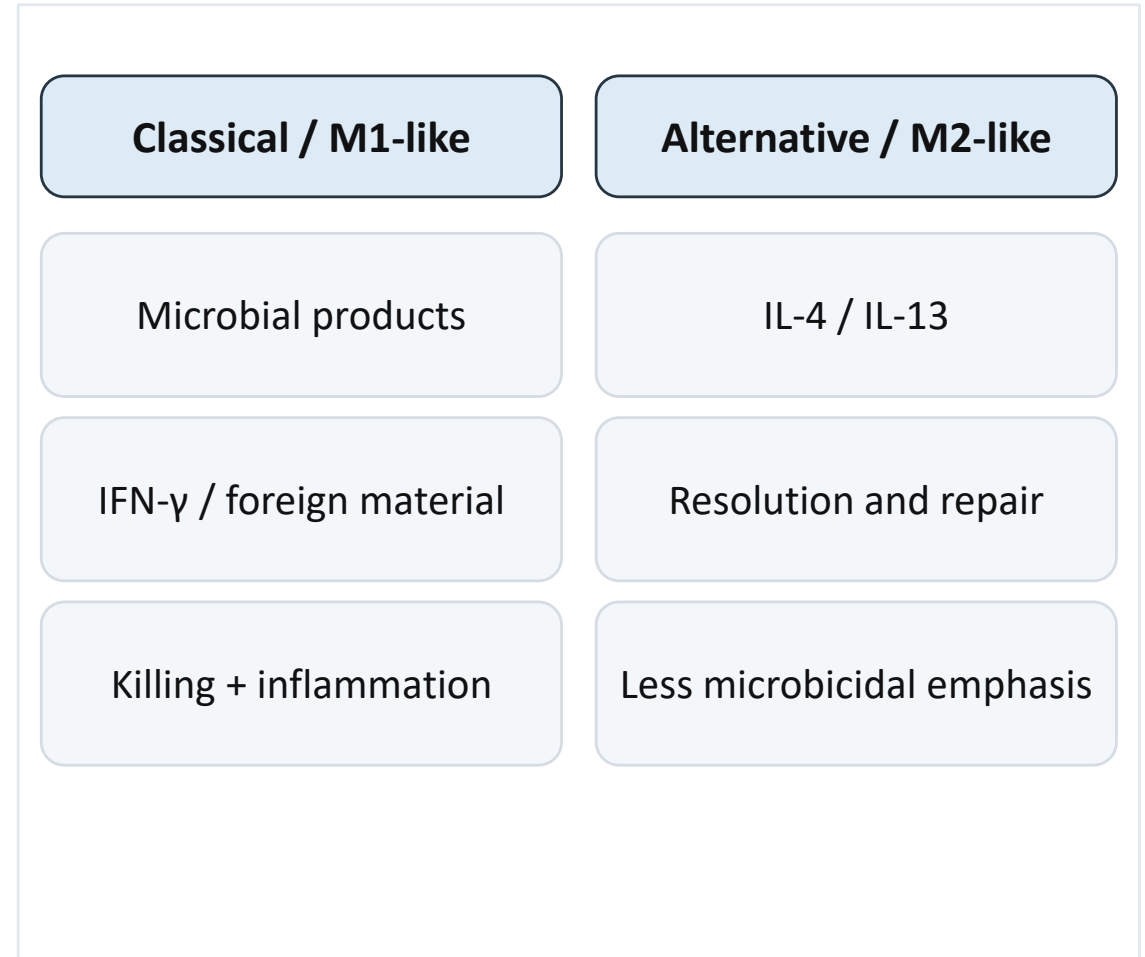
T-cell subsets deliver different macrophage signals

T-cell setting	Principal signal	Relevant result
Th1	IFN- γ	Classical macrophage activation
Th2	IL-4 / IL-13	Alternative activation
Th17	IL-17-linked chemokines	Leukocyte recruitment

- Th1 cells generate IFN- γ , promoting classical activation.
- Th2-associated IL-4 and IL-13 promote alternative activation.
- Th17-driven chemokine pathways favor further neutrophil and monocyte recruitment.

Activation states reflect external signals

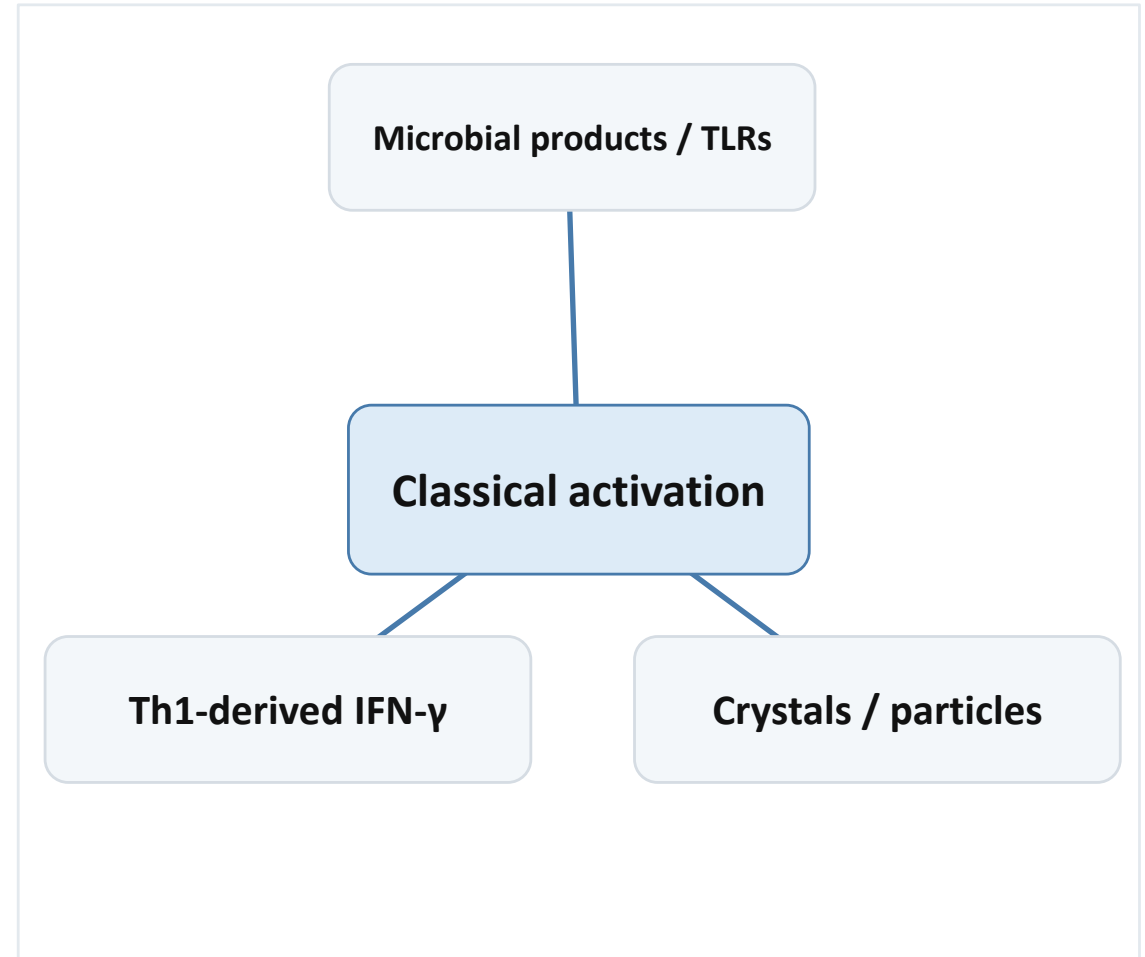
- Different stimuli change macrophage effector programs.
- Classical and alternative activation as broad pathways.
- These are conceptual poles rather than exhaustive cell subsets.



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Classical activation has several initiating stimuli

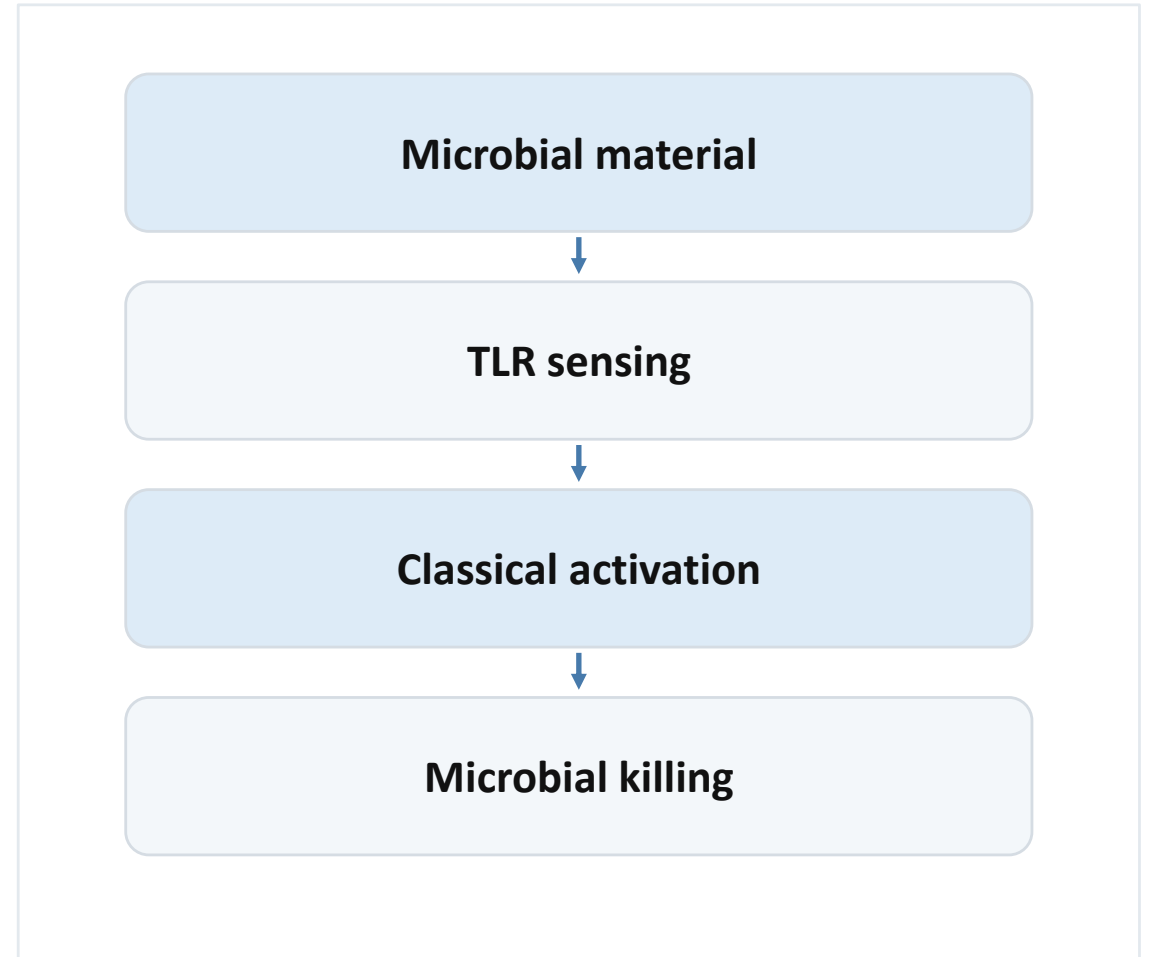
- Microbial endotoxin engages toll-like receptors (TLRs) and related sensors.
- IFN- γ supplied by T cells is a major immune signal.
- Crystals and particulate material may also induce classical activation.



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Microbial sensing promotes classical activation

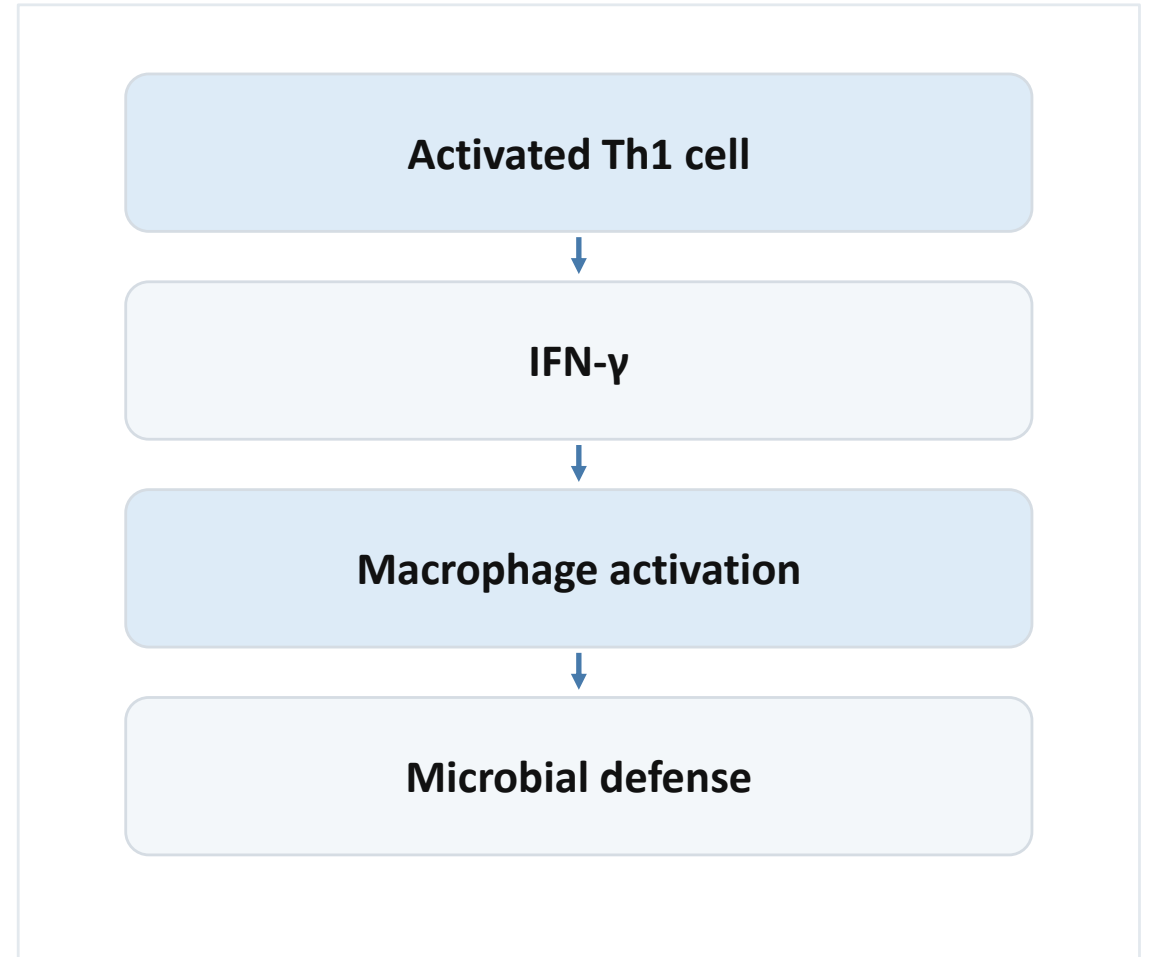
- Bacterial products are detected by innate immune receptors such as TLRs.
- Activation boosts microbicidal machinery and inflammatory mediator release.
- The response is useful when a microbial threat must be destroyed.



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IFN- γ bridges Th1 immunity and macrophage killing

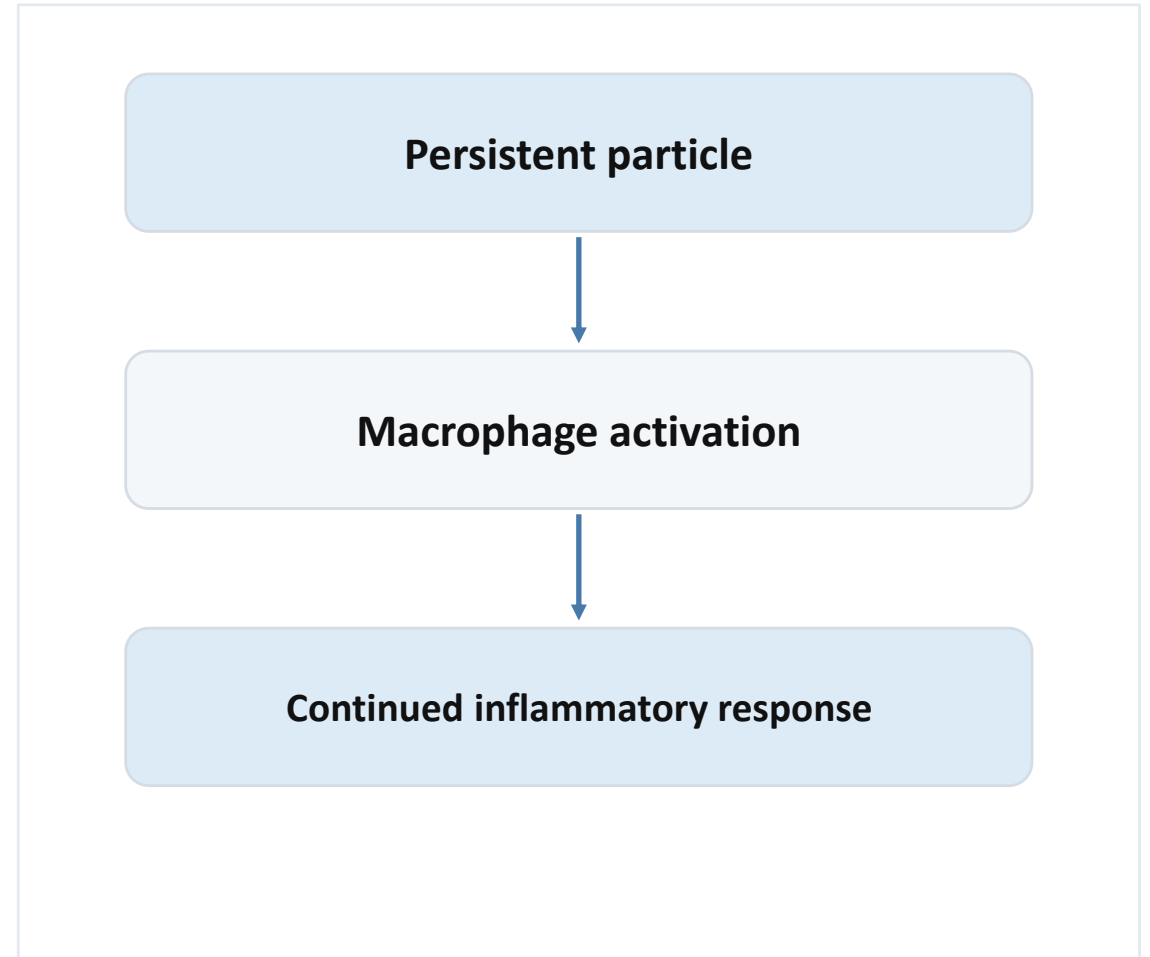
- Th1 cells produce interferon- γ (IFN- γ).
- IFN- γ strongly activates macrophages by the classical pathway.
- This signaling underlies important cell-mediated immune defenses.



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Particulate matter can drive macrophage activation

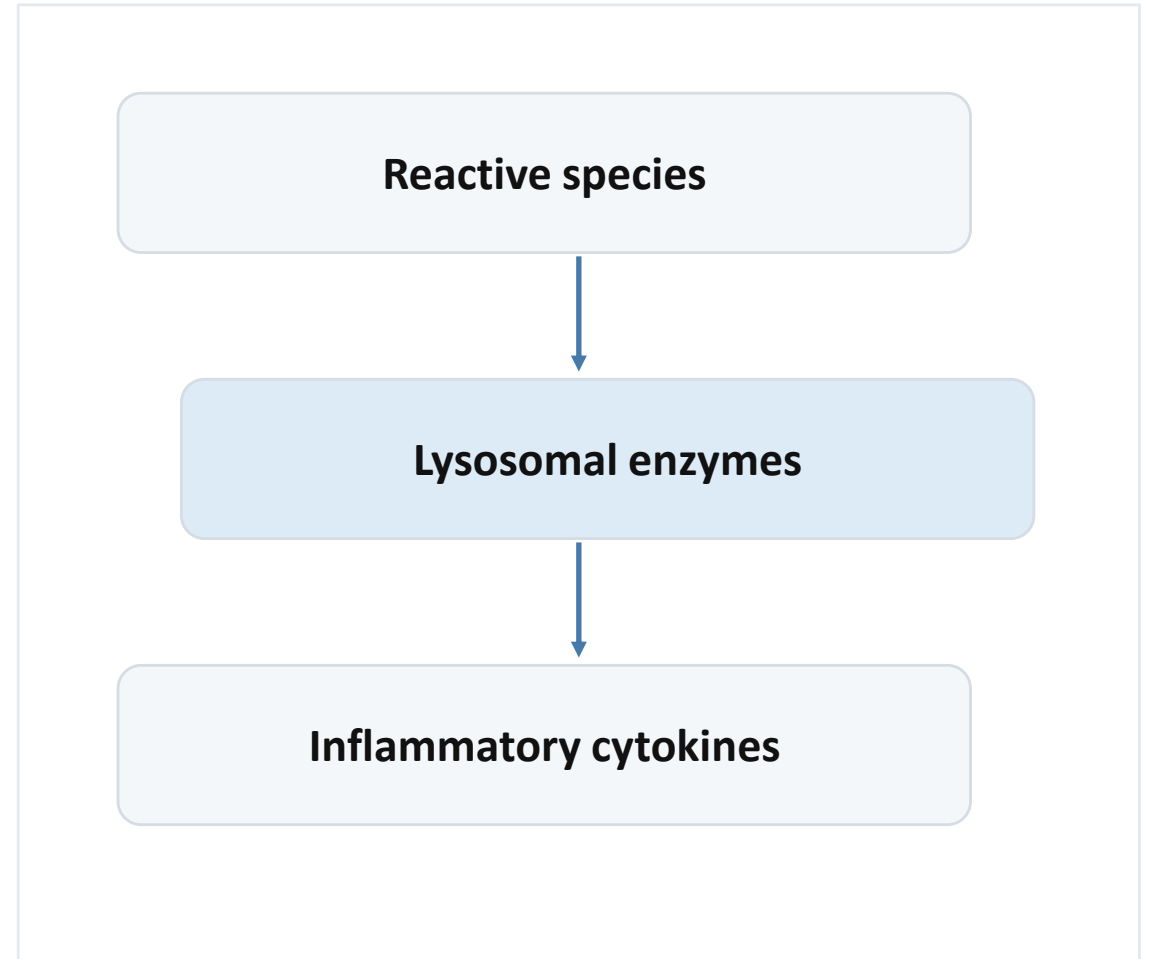
- Crystals and inert particles may stimulate macrophages.
- Exposure can continue when material is difficult to degrade or clear.
- Persistent stimulation can link macrophage activation to chronic injury.



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Classically activated cells emphasize destruction

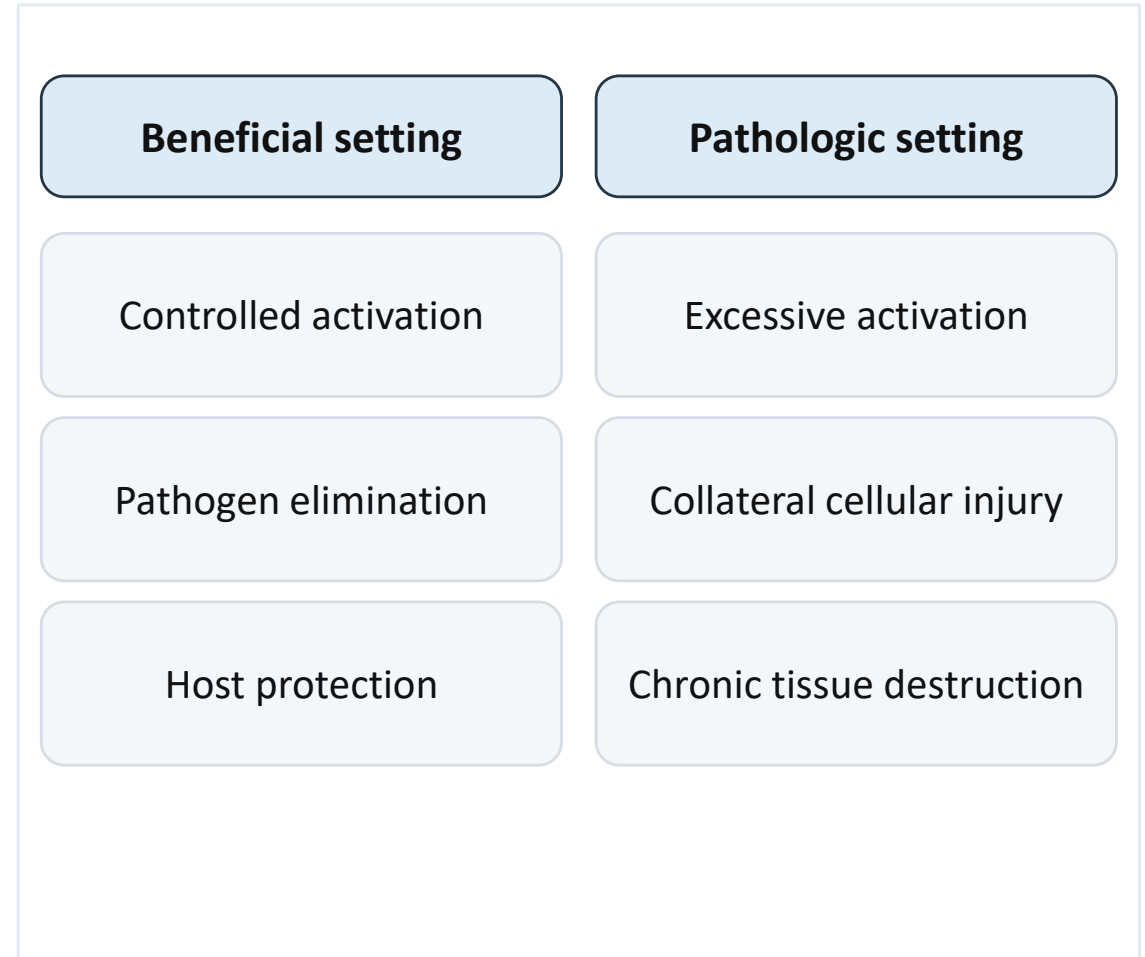
- NO and ROS enhance microbial killing.
- Lysosomal enzymes destroy ingested material.
- Inflammatory cytokines amplify host recruitment and activation.



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ROS and NO illustrate the defense–injury tradeoff

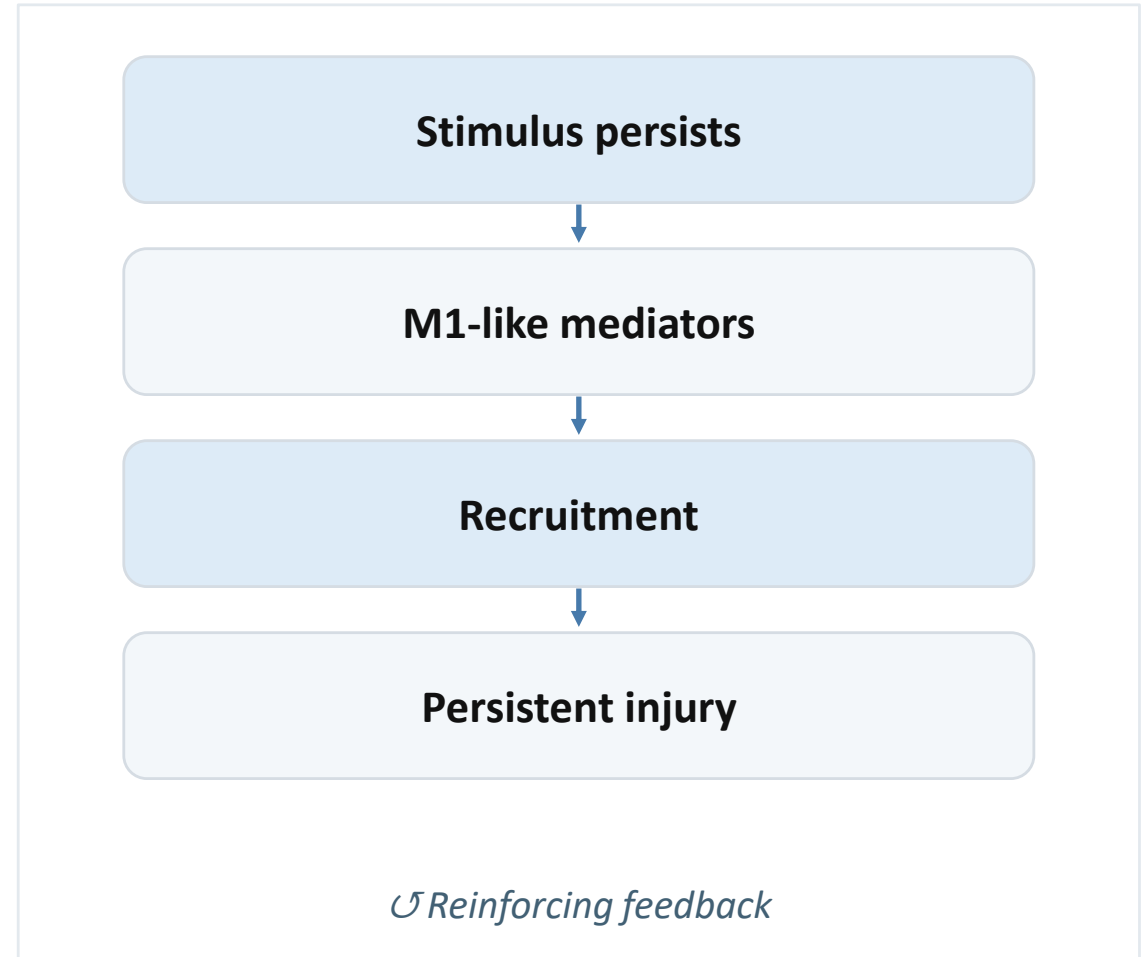
- Both reactive species are part of the macrophage microbicidal arsenal.
- Production helps eliminate pathogens.
- Inappropriately sustained release can contribute to tissue damage.



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Classical activation can prolong inflammation

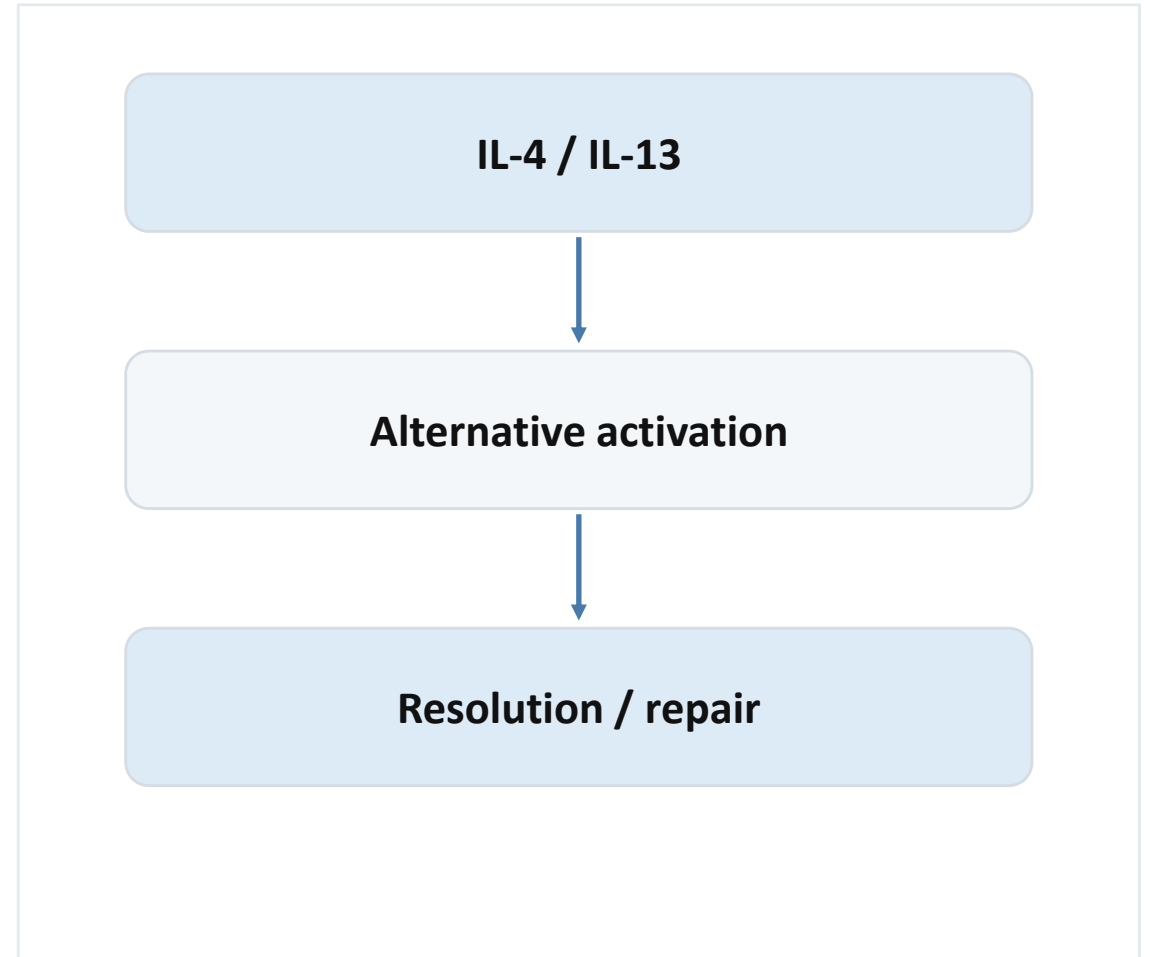
- Classically activated macrophages secrete inflammatory cytokines.
- Additional cell recruitment increases the number of active leukocytes.
- Persistent stimulation can maintain a destructive tissue microenvironment.



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

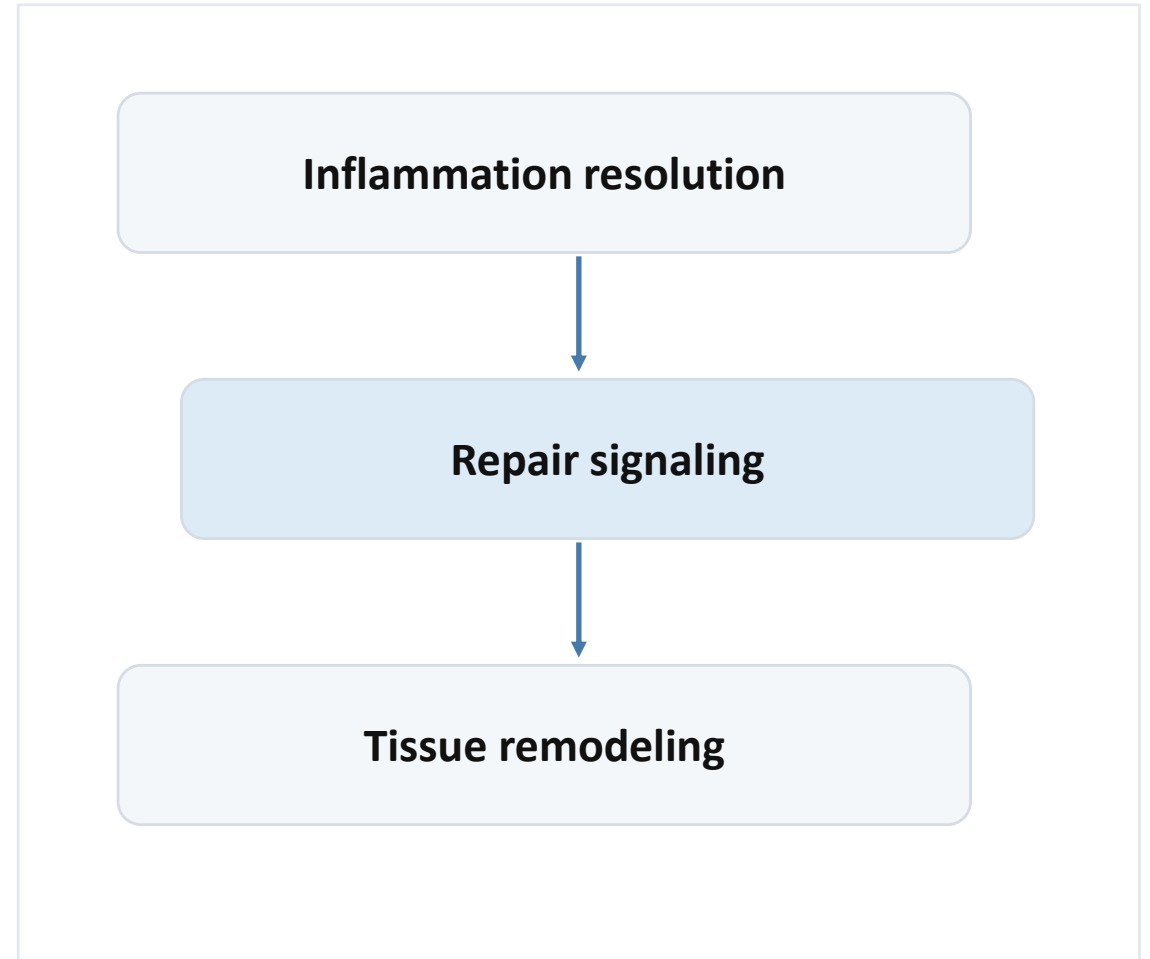
- IL-4 and IL-13 can be released by T lymphocytes and other cells.
- These signals promote an alternative macrophage program.
- The pathway contrasts with IFN- γ -driven classical activation.



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Alternatively activated macrophages promote repair

- They are relatively less focused on direct microbial killing.
- They help dampen or terminate inflammatory responses.
- They stimulate tissue repair programs after injury.



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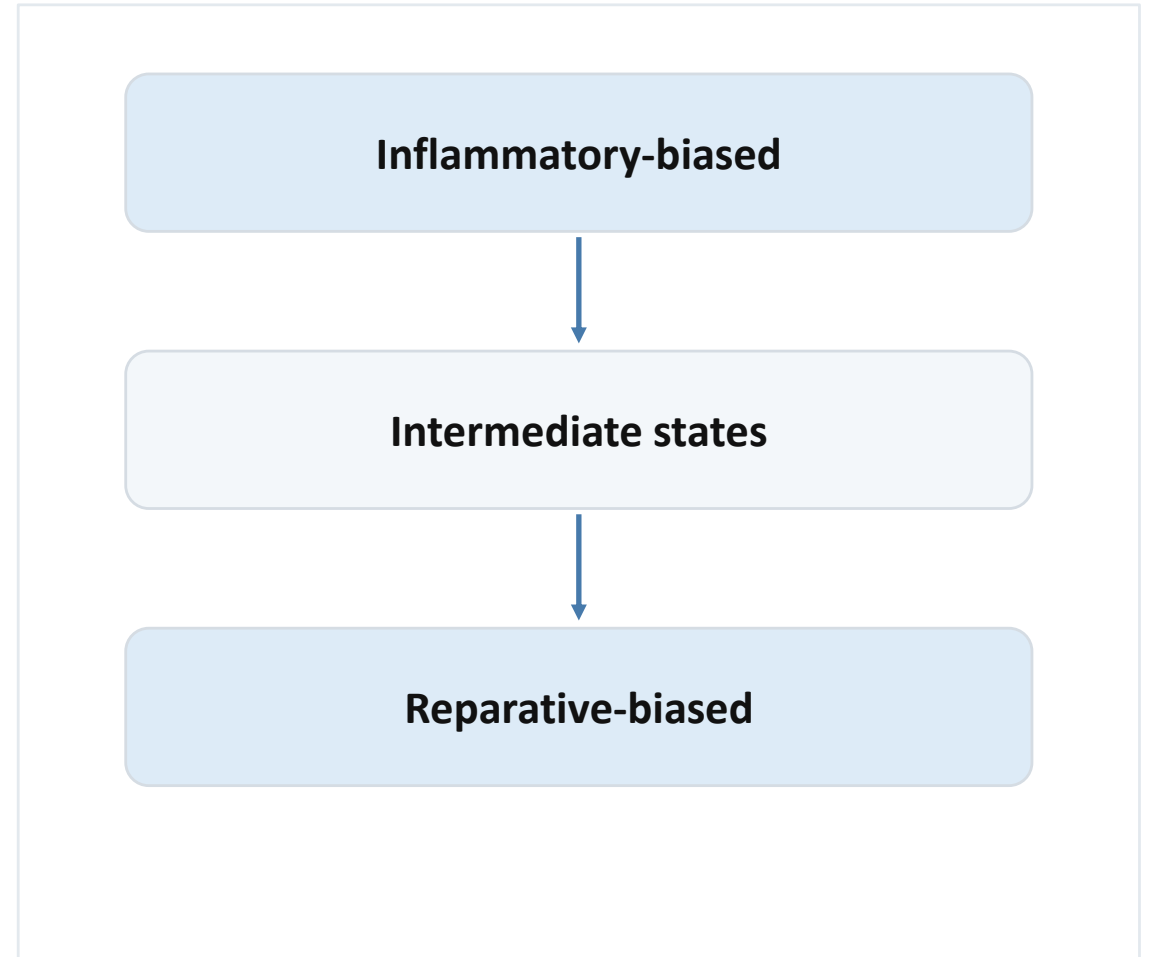
M1-like versus M2-like: A functional comparison

Dimension	M1-like / classical	M2-like / alternative
Typical inducer	TLR signals; IFN- γ	IL-4; IL-13
Strongest emphasis	Killing and inflammation	Resolution and repair
Characteristic outputs	NO, ROS, cytokines	Reparative mediators
Clinical tension	Microbe killing vs injury	Healing vs fibrosis

- The categories summarize different stimulus–response patterns.
- Neither class describes every macrophage in a real lesion.
- Interpret phenotype by function and local signals, not a single absolute label.

The M1–M2 dichotomy is an imperfect model

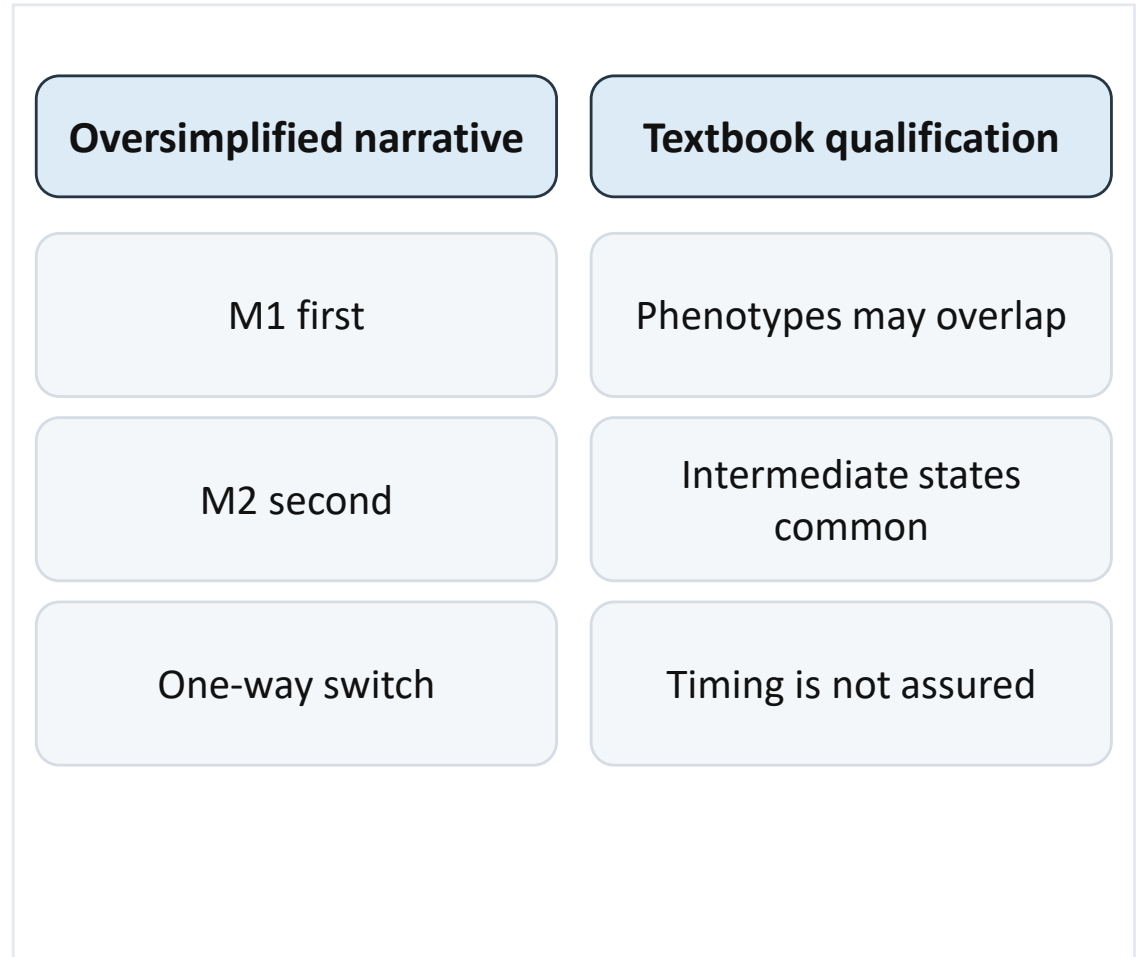
- Intermediate phenotypes exist between the two textbook extremes.
- There are no precise defining markers for all macrophage states.
- “M1-like” and “M2-like” better convey a continuum of activation.



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Macrophage phenotypes can coexist in one lesion

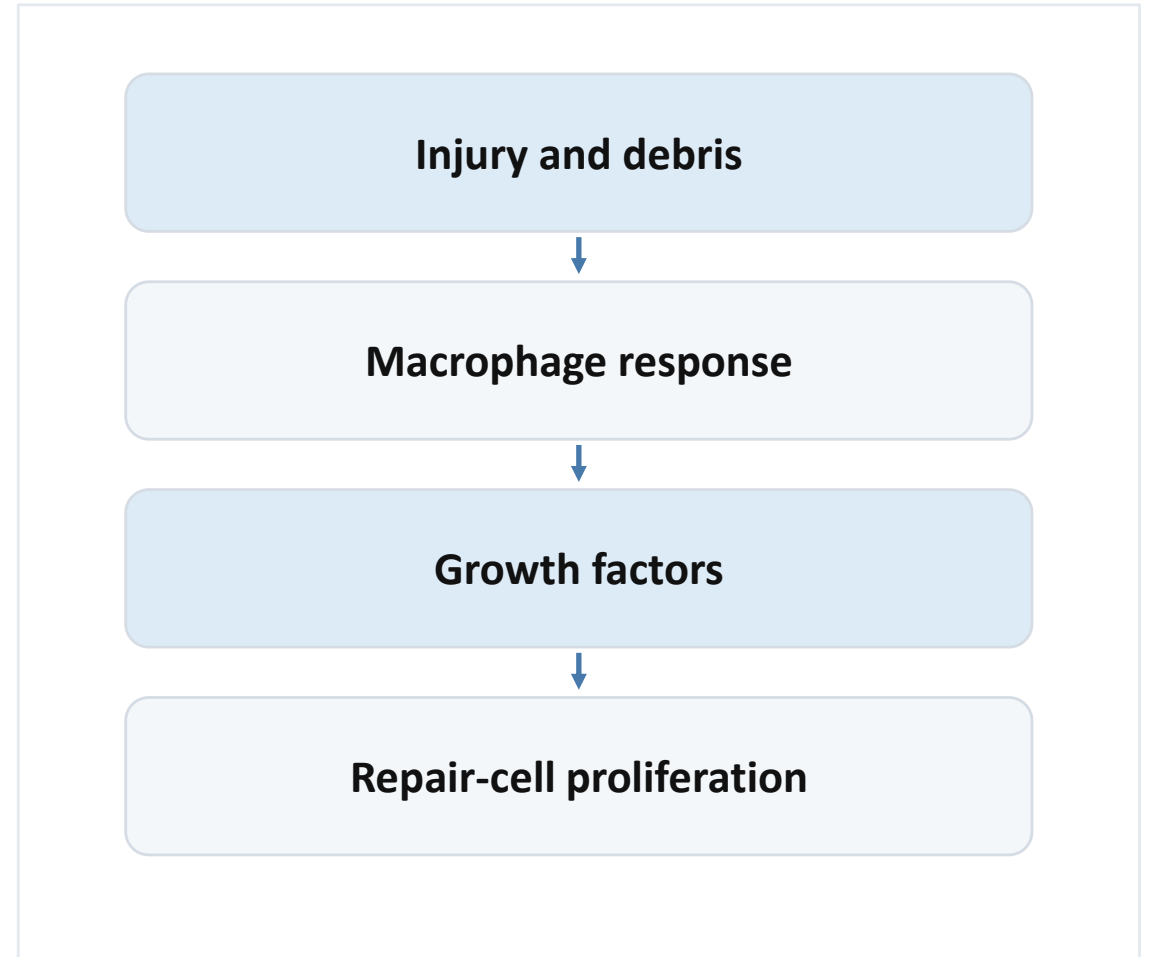
- Inflammatory reactions may contain several activation states at once.
- A clean sequence of M1 then M2 is plausible but not usually demonstrated.
- Never infer an obligatory temporal switch from a single histologic field.



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Macrophages initiate tissue repair

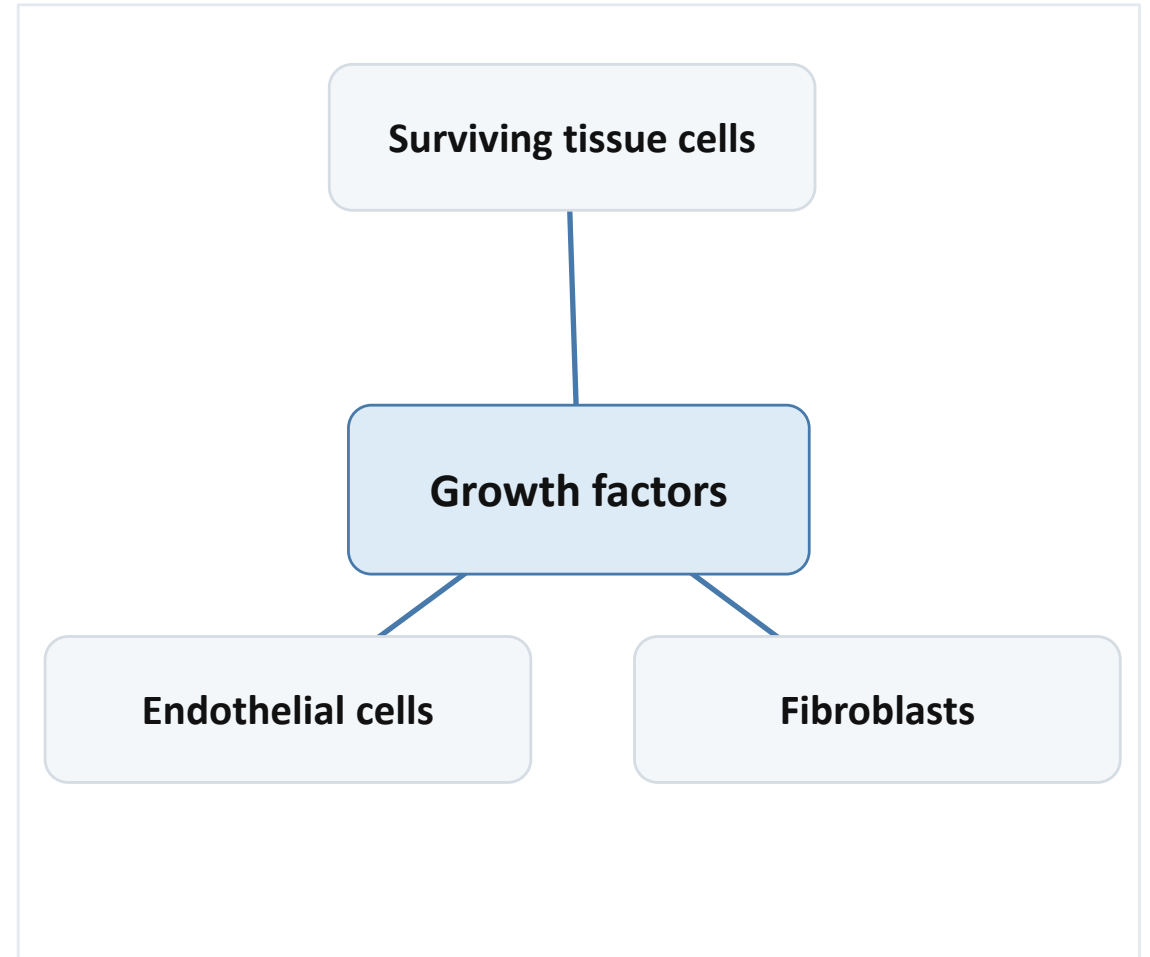
- Phagocytosis removes dead tissue and injurious material.
- Growth factors produced by activated macrophages stimulate local cell proliferation.
- The same cellular response that fights injury can help rebuild tissue.



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Growth factors connect macrophages to regeneration

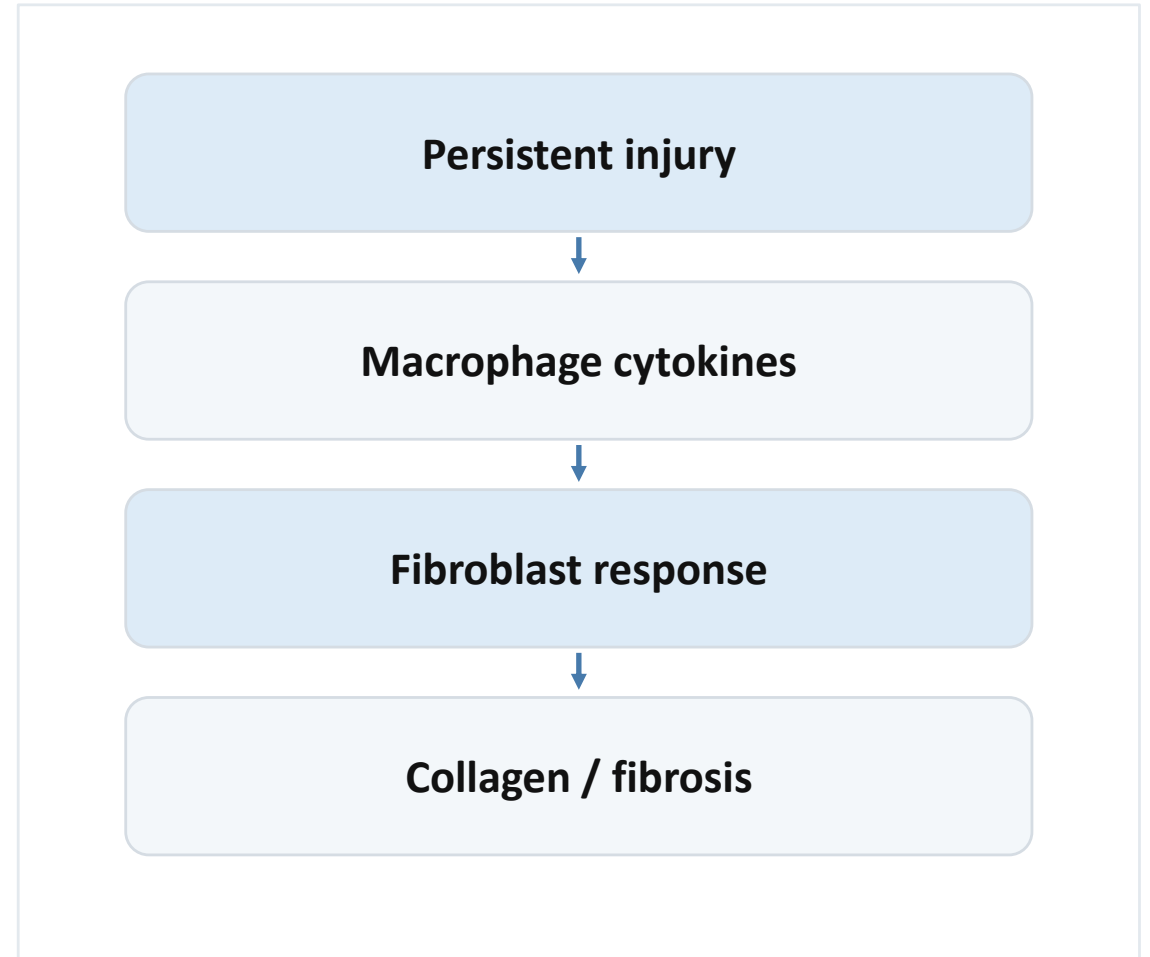
- Activated macrophages are major growth-factor sources at injured sites.
- Growth factors act on surviving parenchymal and stromal cells.
- Regeneration also depends on tissue proliferative capacity and intact ECM.



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Fibrosis is one possible outcome of sustained repair

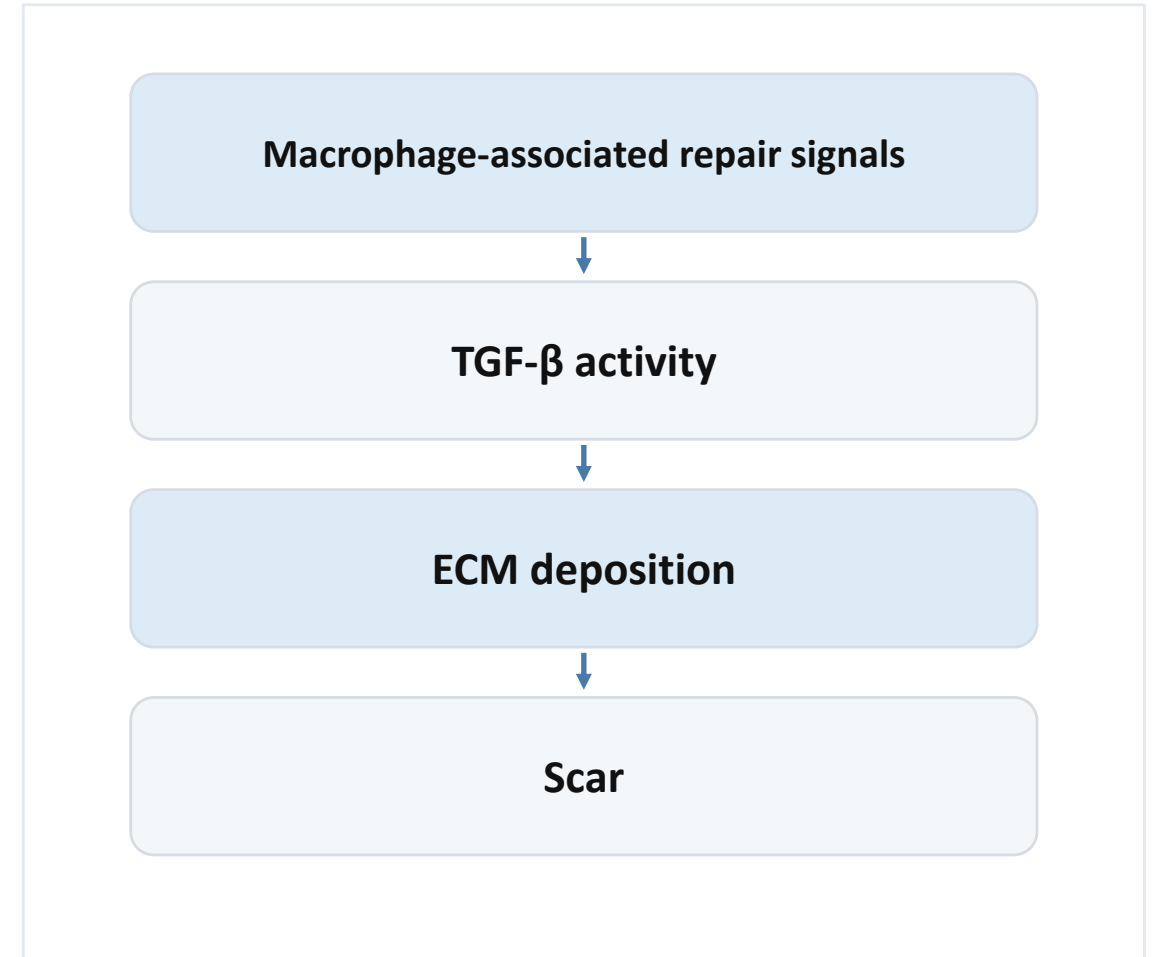
- Macrophage- and lymphocyte-derived cytokines activate fibroblasts.
- Fibroblasts and myofibroblasts deposit extracellular matrix (ECM).
- When tissue architecture is lost, connective tissue replaces damaged parenchyma.



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TGF- β has a central fibrogenic role

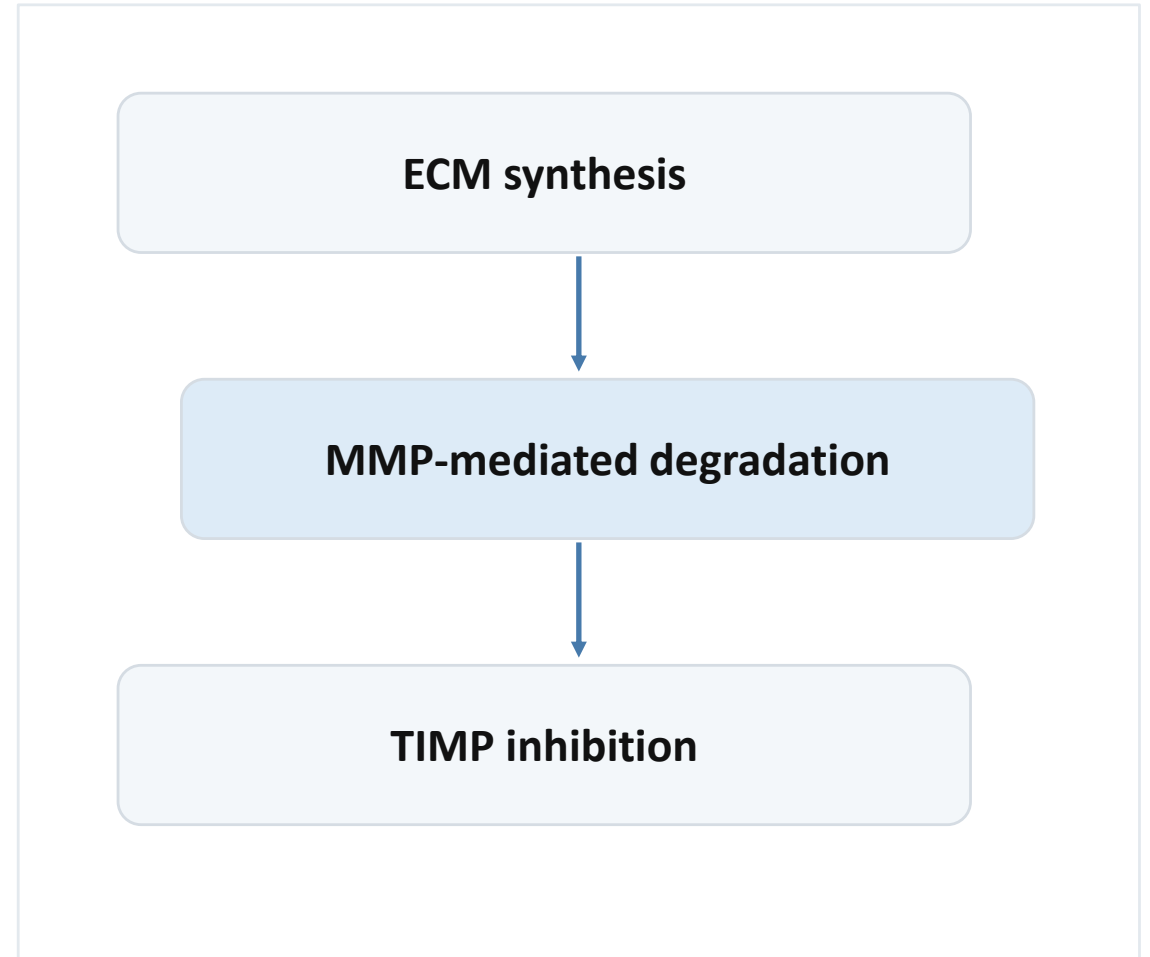
- Transforming growth factor- β (TGF- β) is a potent driver of fibrosis.
- It helps promote ECM accumulation during repair.
- In persistent injury, reparative signaling may produce excessive scarring.



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Scar remodeling requires matrix turnover

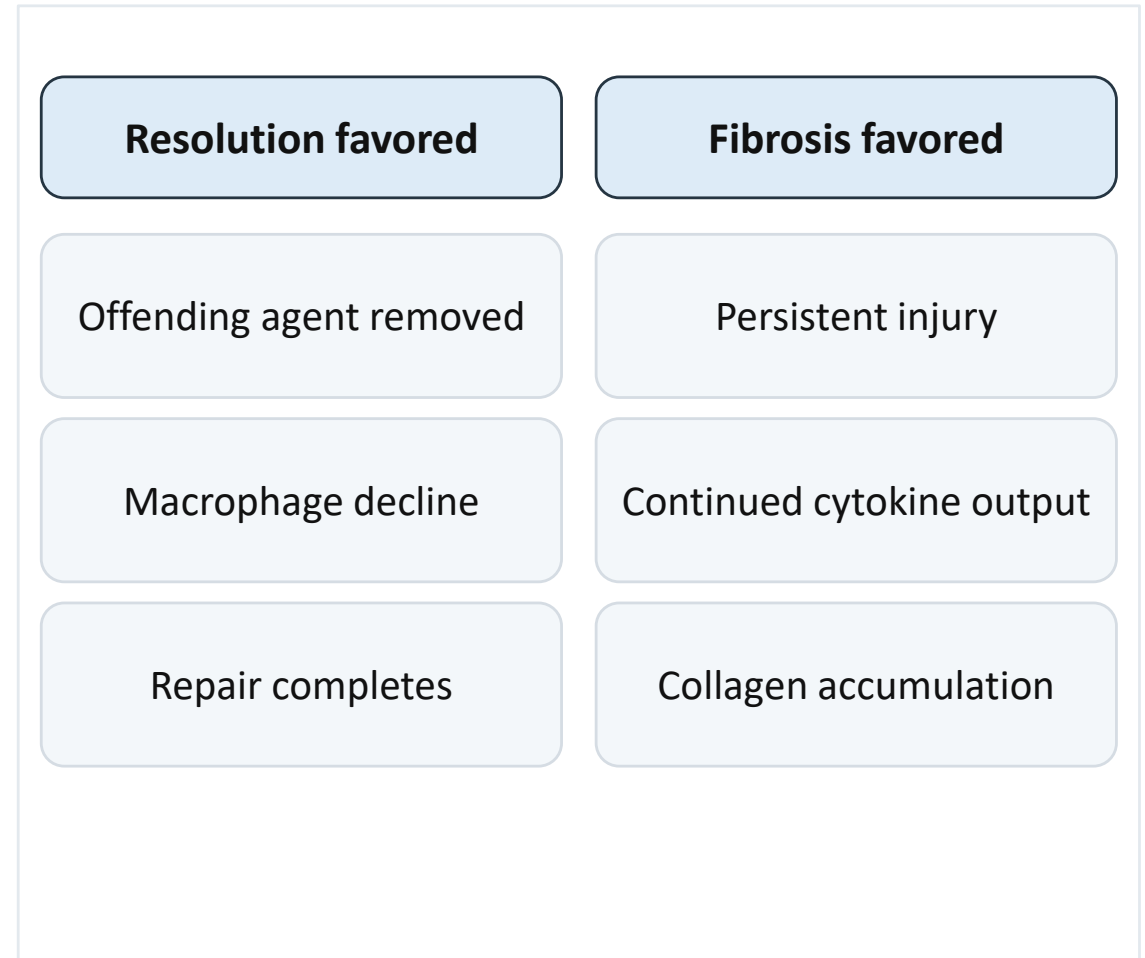
- Matrix metalloproteinases (MMPs) digest ECM constituents.
- Macrophages are one of several cellular sources of MMPs.
- Tissue inhibitors of metalloproteinases (TIMPs) restrain enzyme activity.



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The injury–repair balance determines tissue outcome

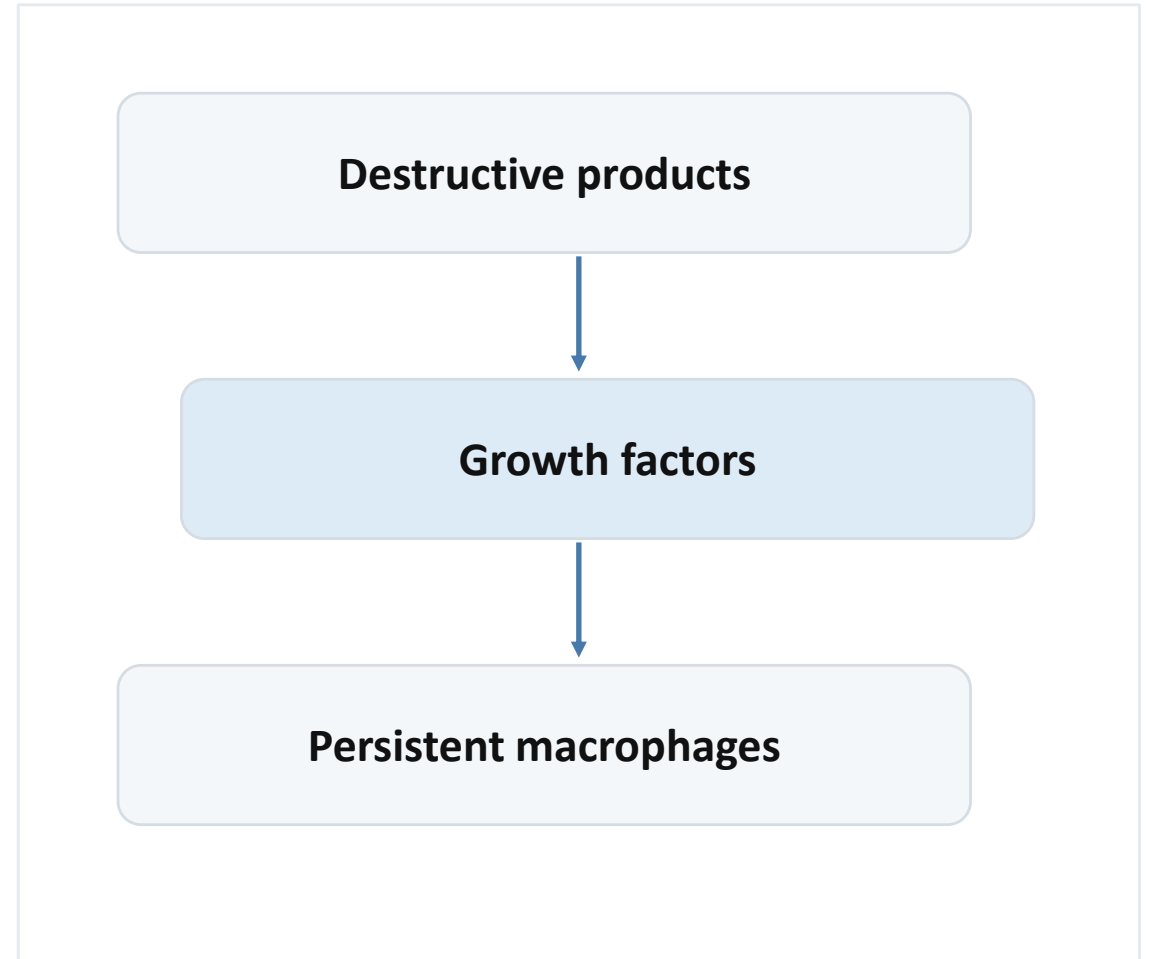
- Effective removal of the stimulus favors resolution.
- Continuing inflammation drives ongoing damage and repair signaling.
- Fibrosis becomes important when normal architecture cannot be restored.



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Chronic lesions combine damage and healing

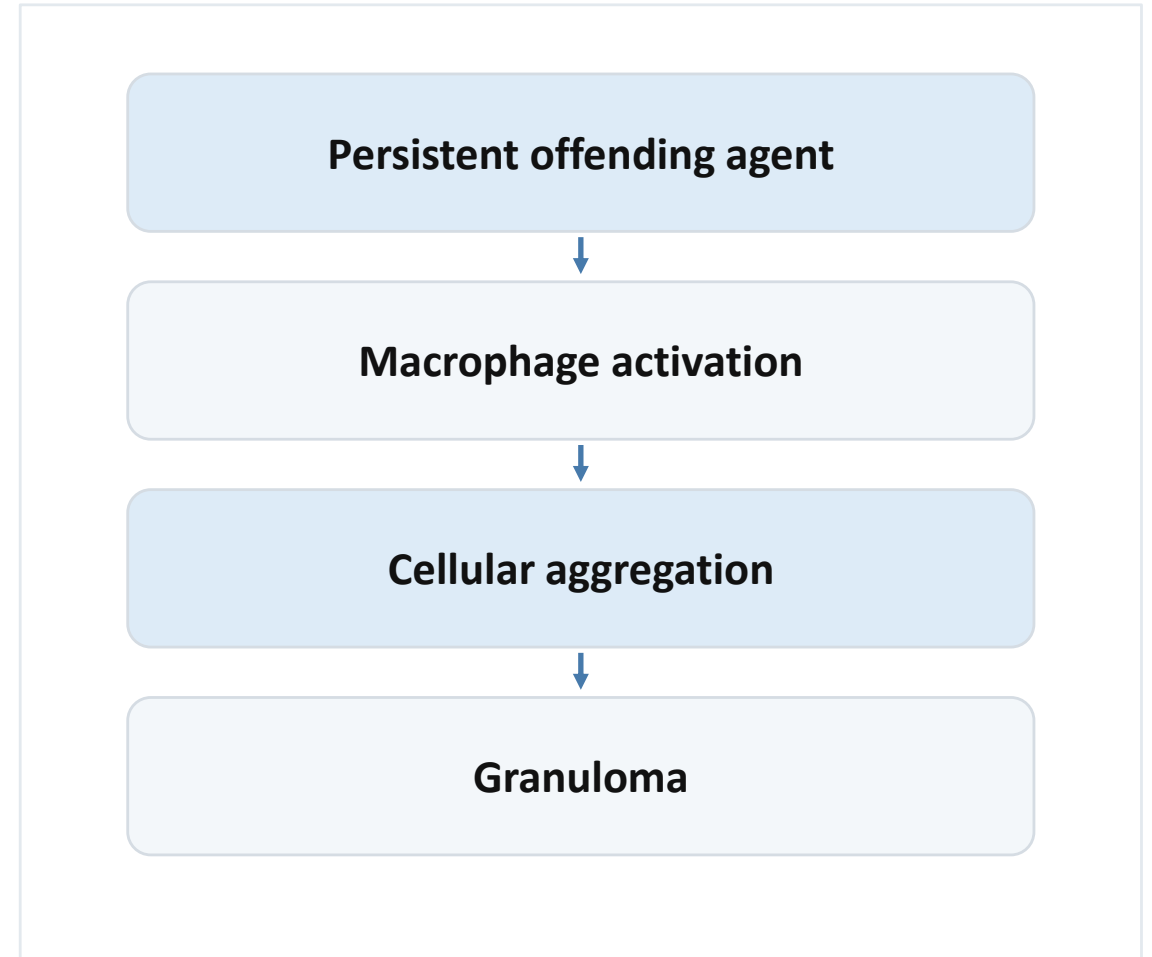
- Activated macrophages are a source of tissue-destructive products.
- Other macrophage outputs stimulate fibroblasts and angiogenic repair.
- Both effects can be present within the same chronic lesion.



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Granulomas represent organized macrophage-rich responses

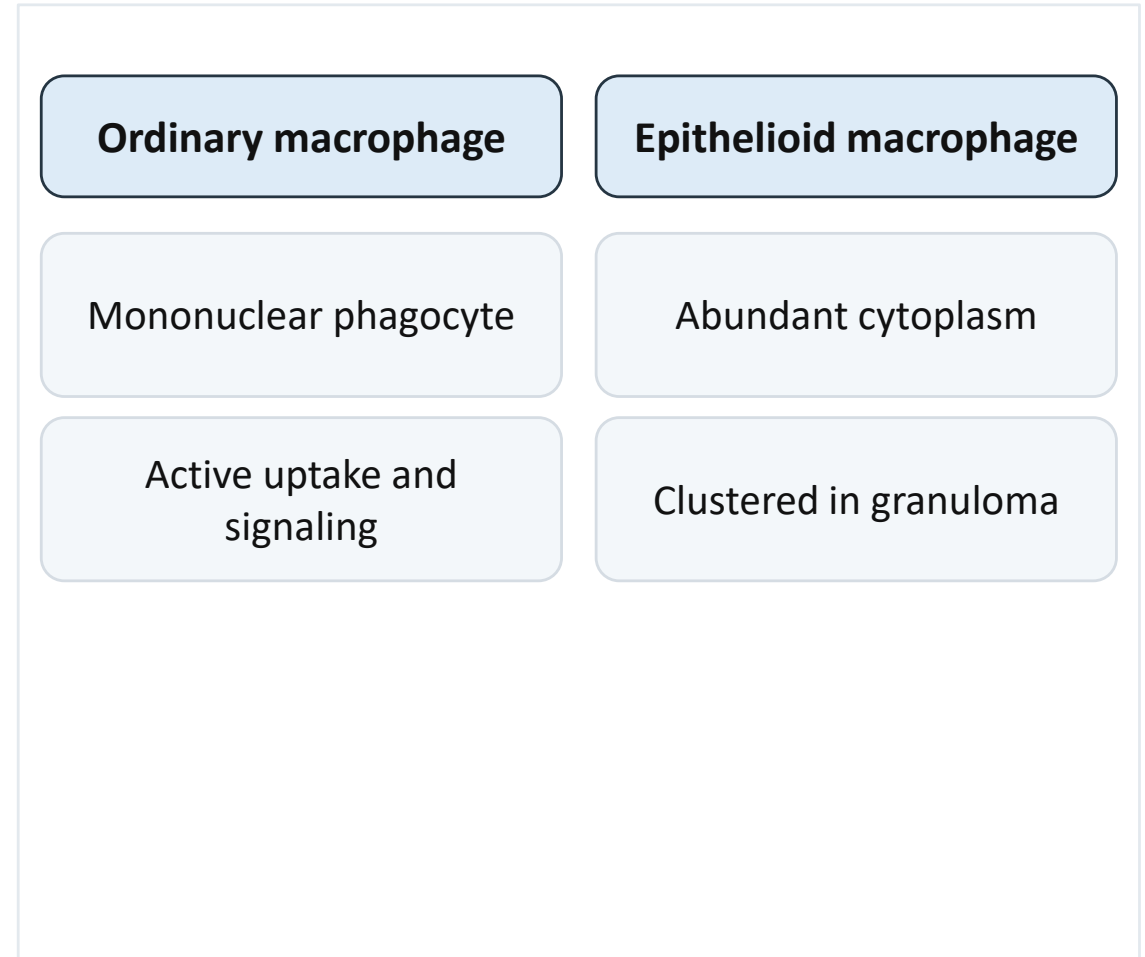
- Granulomatous inflammation contains collections of activated macrophages.
- T lymphocytes are often present; Necrosis may occur.
- Organization attempts to contain agents difficult to eradicate.



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Epithelioid cells are activated macrophages

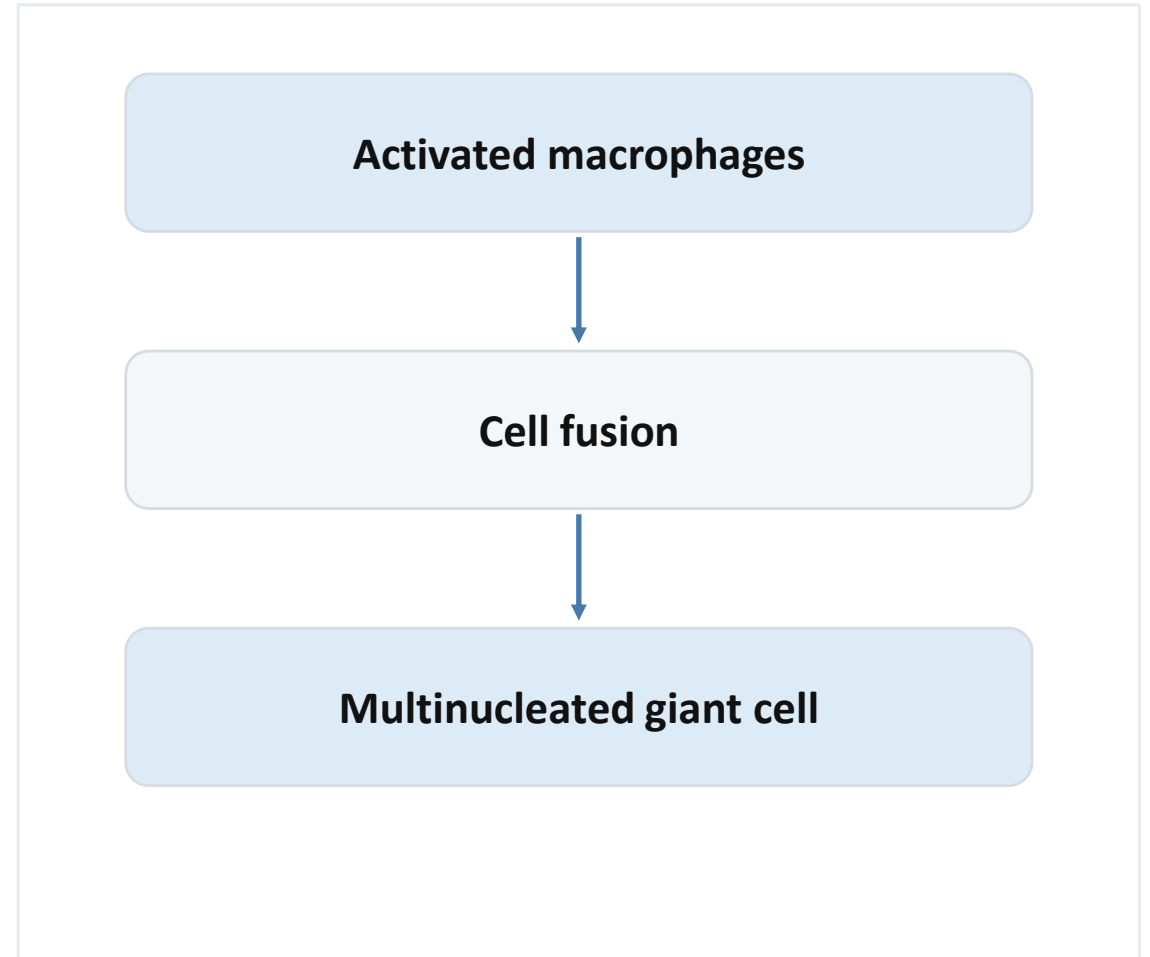
- Activated macrophages may gain abundant cytoplasm.
- Their appearance can resemble epithelial cells, hence “epithelioid.”
- This is a morphologic response, not epithelial lineage conversion.



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Multinucleated giant cells arise by macrophage fusion

- Some activated macrophages fuse into multinucleate giant cells.
- Giant cells may occur around foreign material or within immune granulomas.
- Their presence must be interpreted within the full lesion context.



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Foreign-body and immune granulomas differ mechanistically

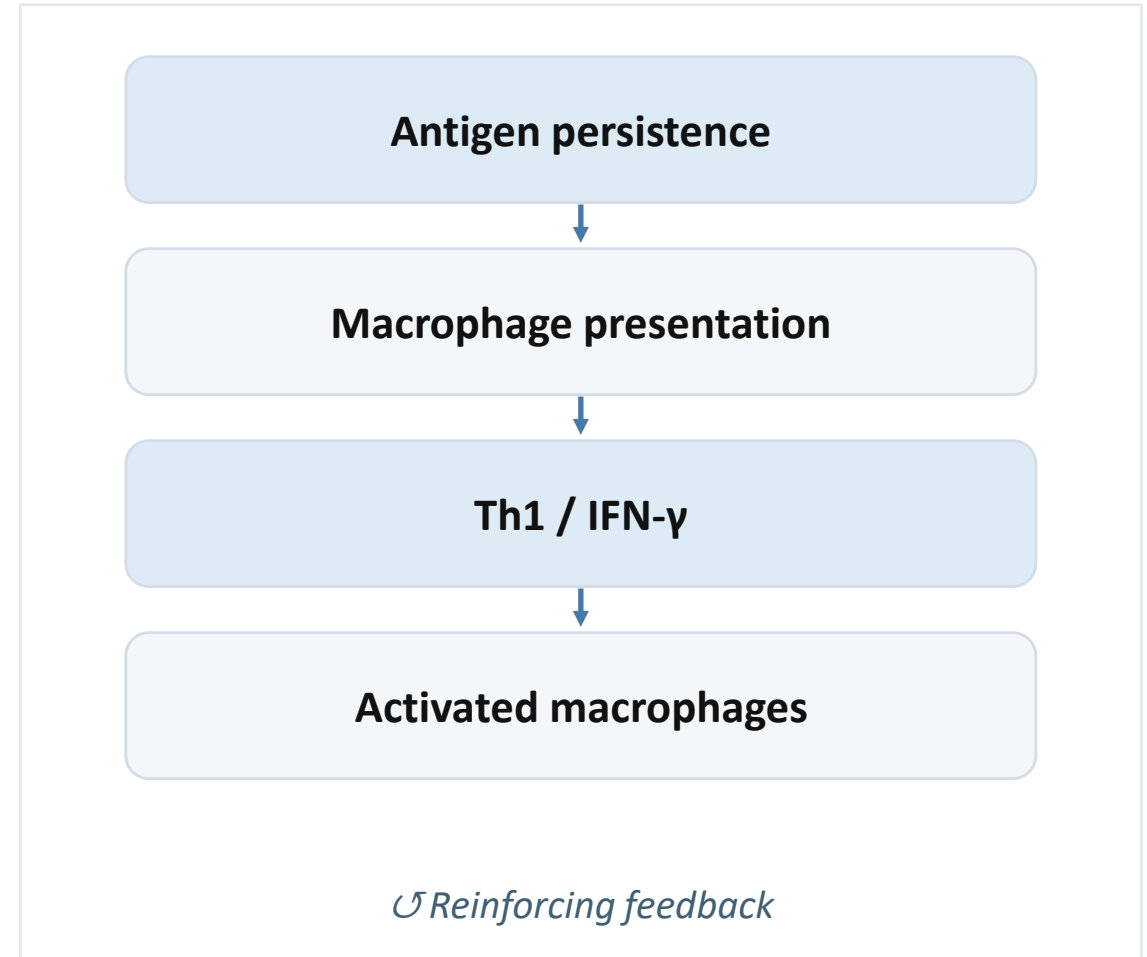
- Foreign-body granulomas form against material too large for phagocytosis.
- Immune granulomas result from persistent T-cell-mediated responses.
- Both contain macrophage-derived epithelioid cells and potentially giant cells.

Foreign-body granuloma	Immune granuloma
Inert / large material	Persistent antigen
No specific T-cell response required	T-cell activation
Macrophages surround object	Macrophage activation via cytokines

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Th1–macrophage circuits can sustain granulomas

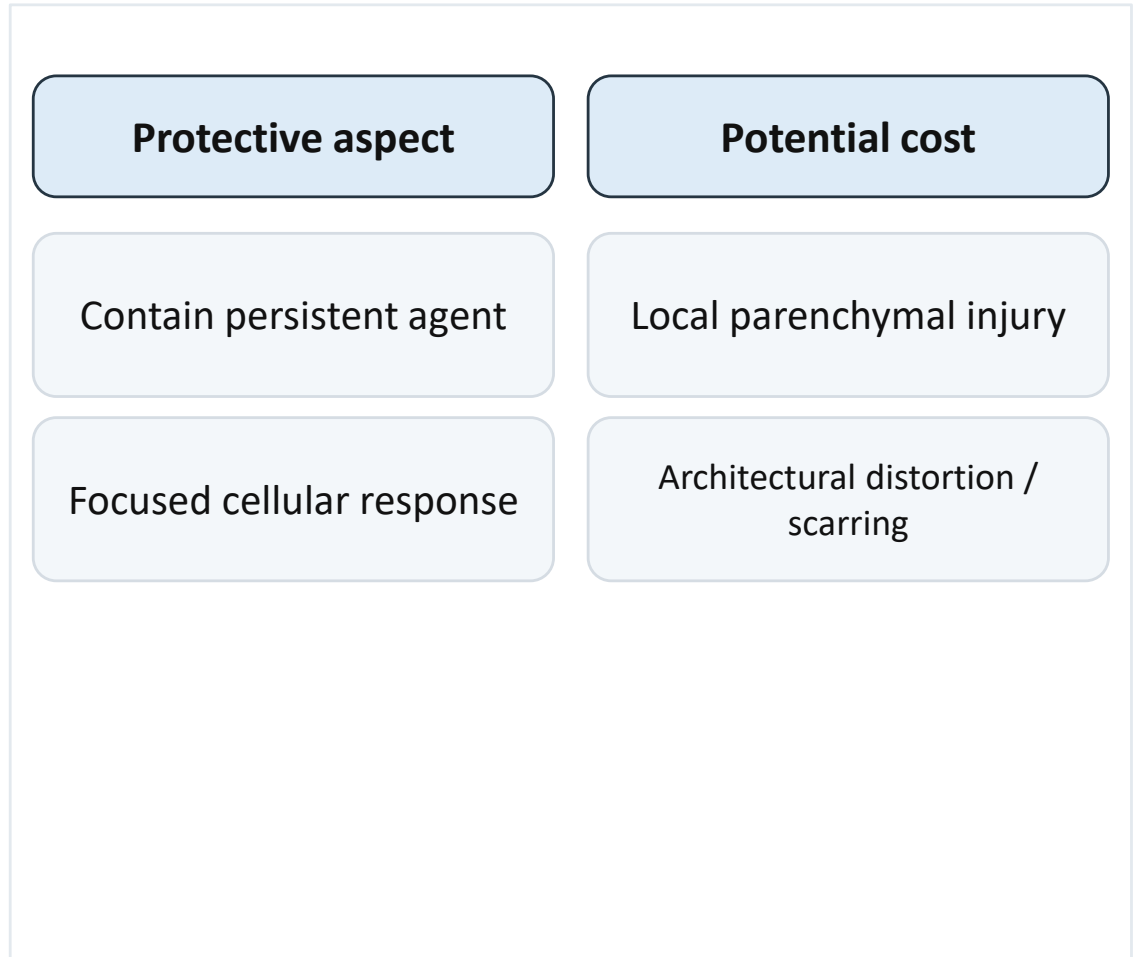
- Antigen presentation and macrophage-derived cytokines stimulate T cells.
- Th1-derived IFN- γ activates macrophages.
- Continued interaction maintains the granulomatous response.



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Granuloma formation is not necessarily harmless

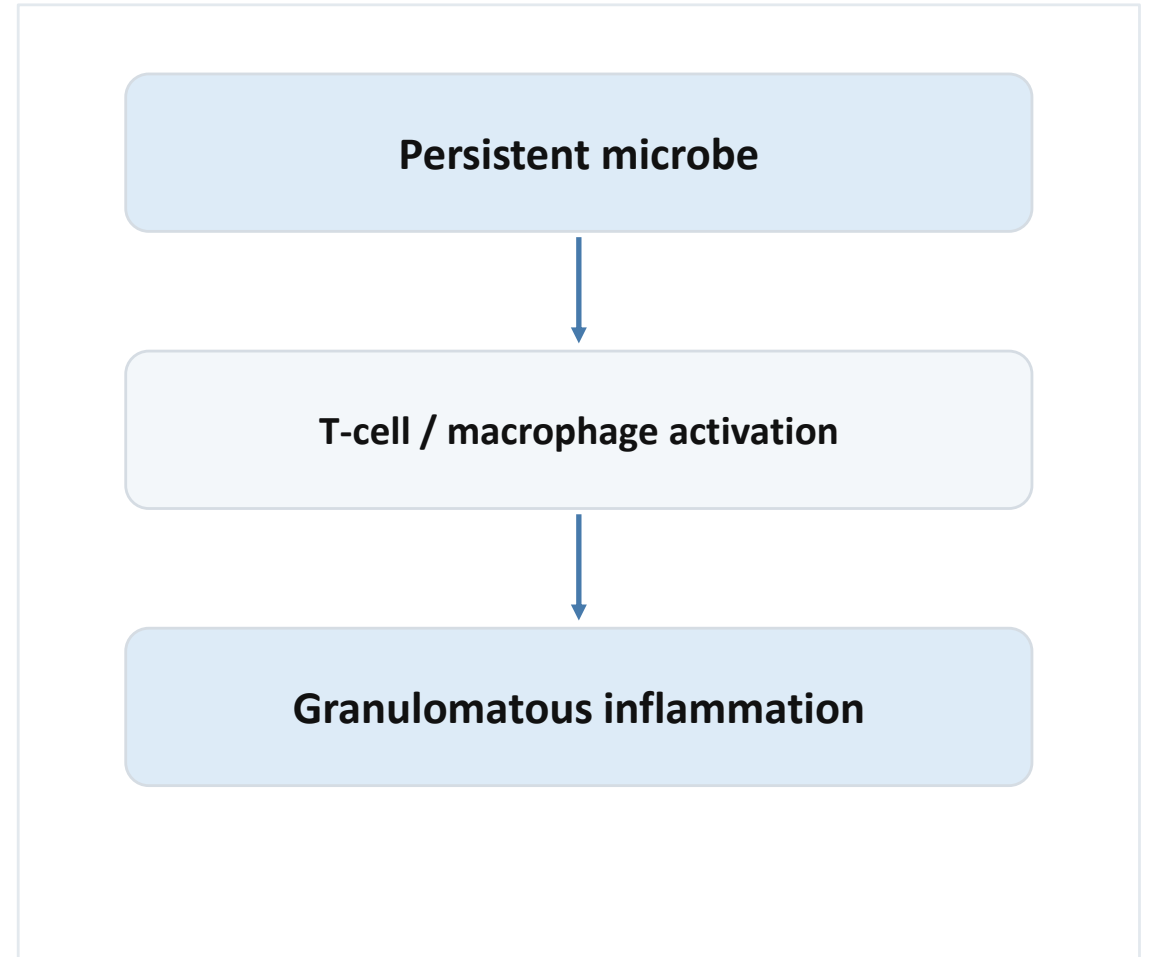
- Aggregation may help contain persistent injurious agents.
- Activated macrophages also release tissue-injuring mediators.
- The containment response can therefore distort or destroy tissue.



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Persistent infection: A macrophage-centered example

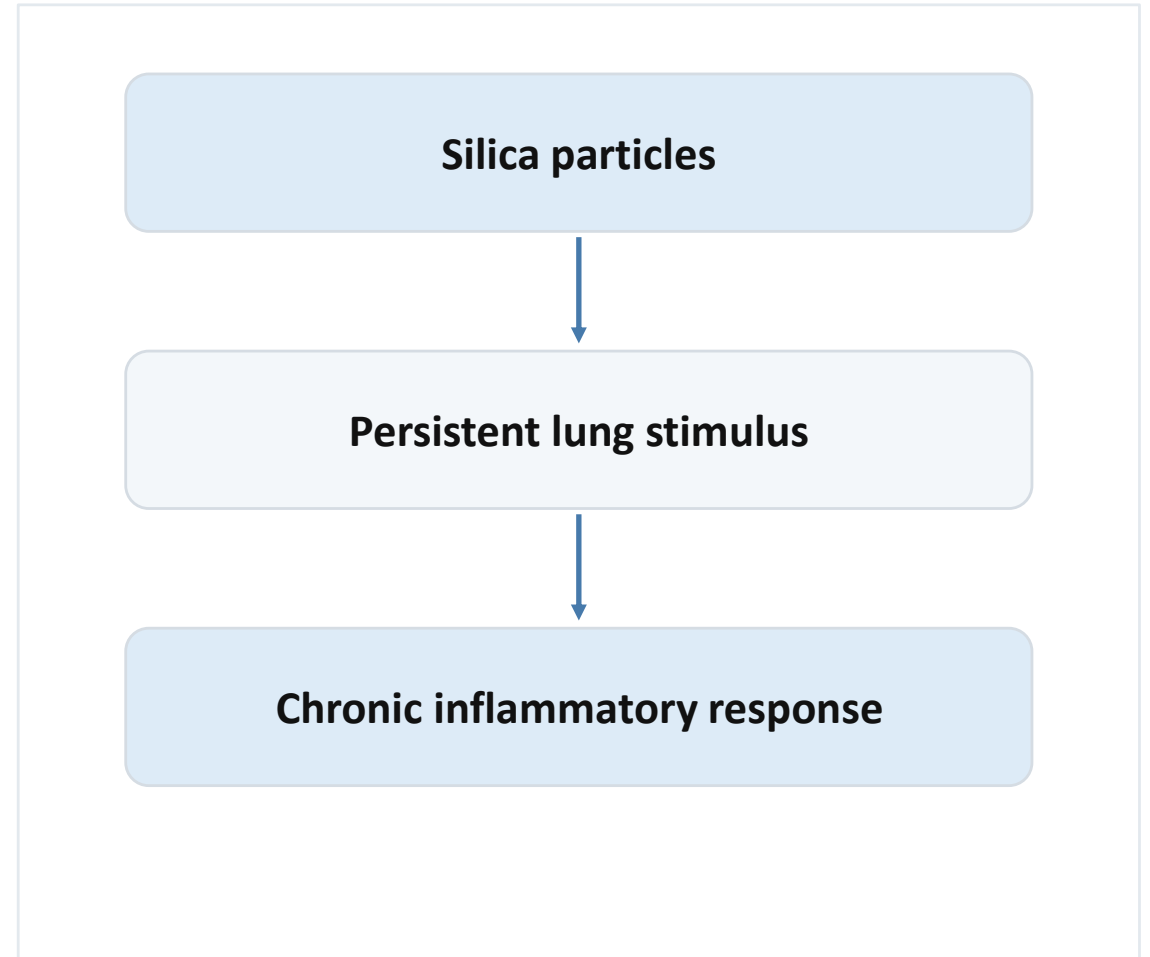
- Mycobacteria can evoke long-standing cell-mediated inflammation.
- Th1 and macrophage responses may produce immune granulomas.
- Morphologic recognition must prompt evaluation for an infectious cause.



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Silica exposure: The problem of a persistent particle

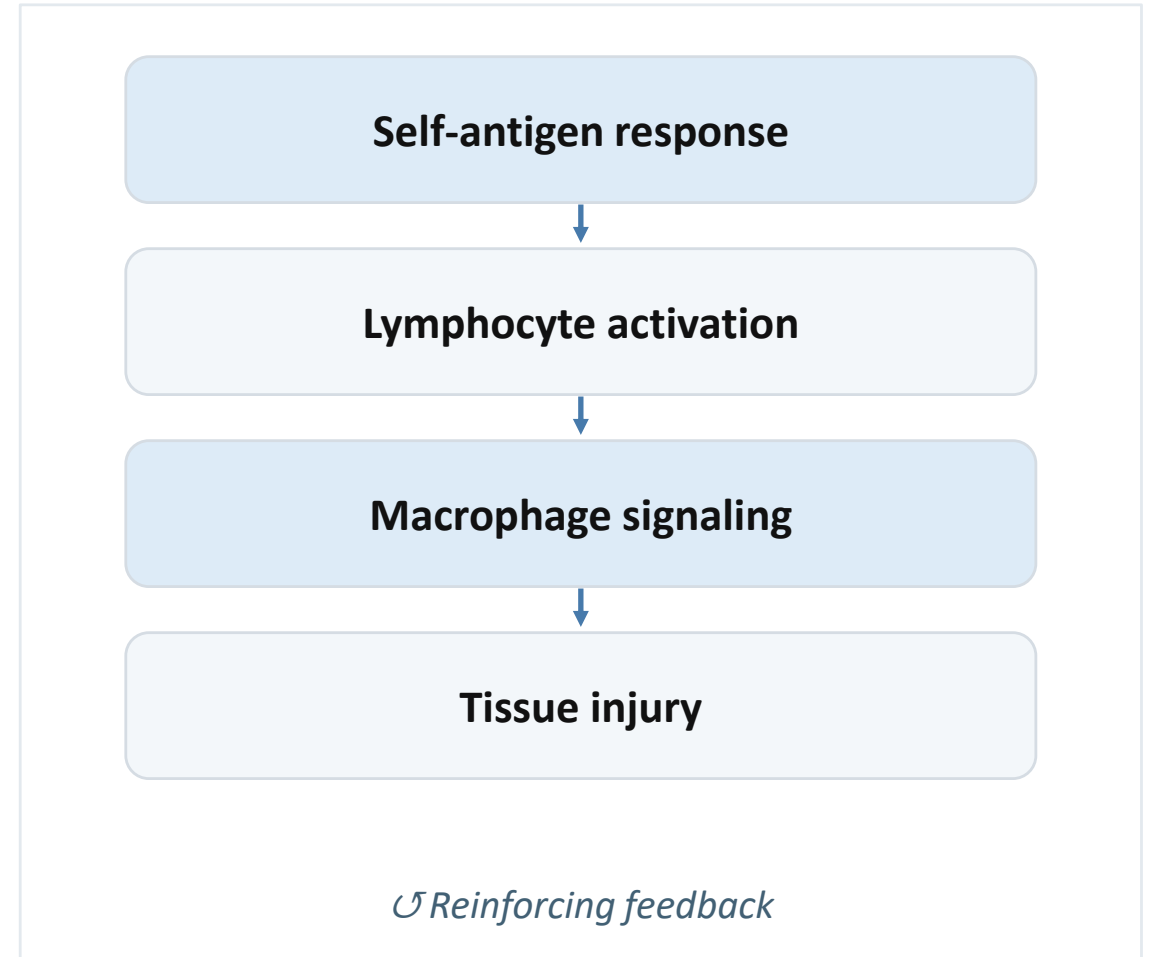
- Particulate silica is an exogenous agent linked to chronic lung inflammation.
- It is not readily degraded and may maintain tissue injury.
- This illustrates why persistent material can sustain macrophage-rich inflammation.



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Autoimmunity can perpetuate macrophage activation

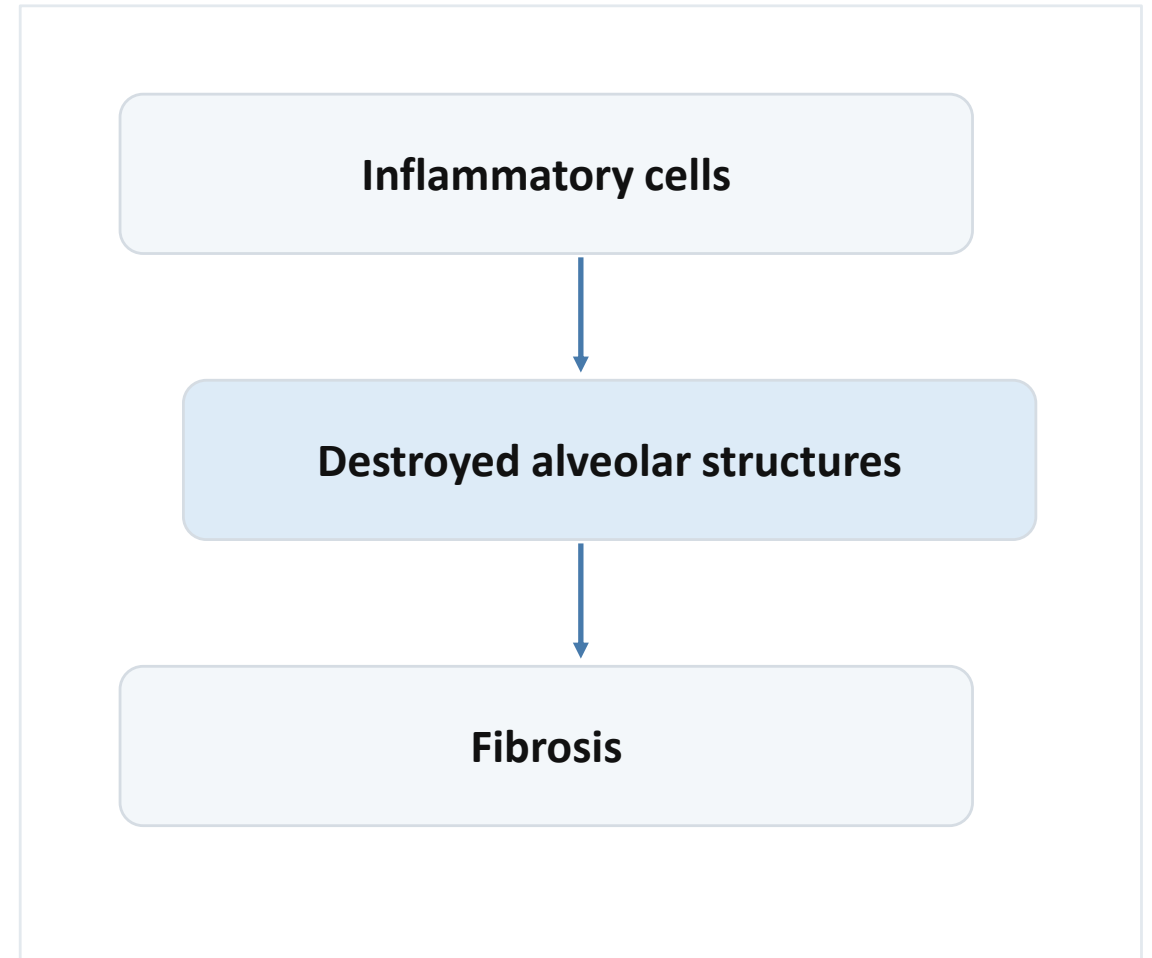
- Persistent immune recognition of self-antigens maintains inflammatory signaling.
- Macrophages and lymphocytes can reinforce one another.
- Tissue damage and later fibrosis are possible consequences.



SCHEMATIC

Macrophage-rich chronic lung injury: Interpreting a lesion

- A chronic infiltrate should be evaluated together with parenchymal destruction.
- Fibrosis indicates attempted repair and loss of architecture.
- These findings form a pathologic pattern; They do not alone establish etiology.



SCHEMATIC

Distinguish a chronic infiltrate from acute exudation

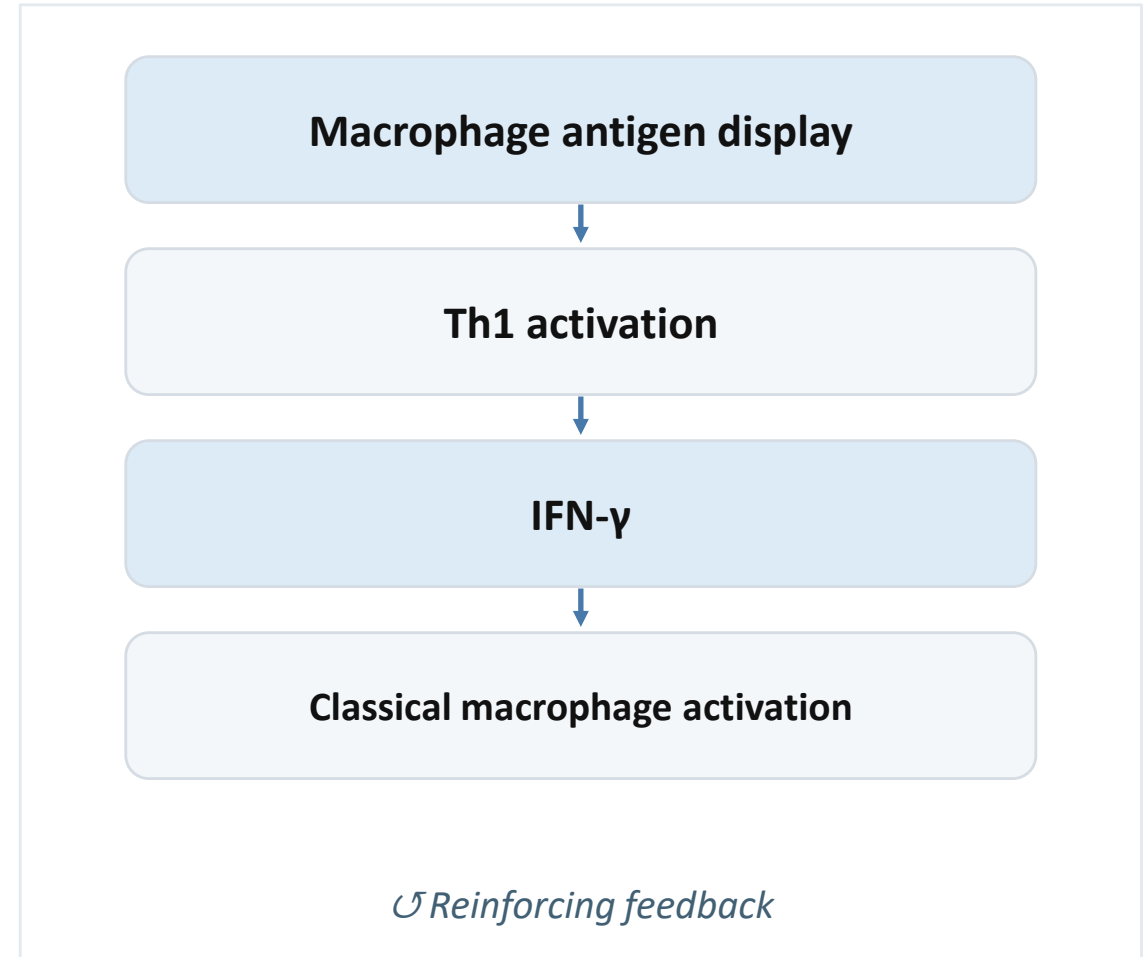
- Acute inflammation typically emphasizes neutrophils, vascular changes and edema.
- Chronic inflammation emphasizes mononuclear cells, damage and repair.
- Mixed acute and chronic patterns occur, especially with repeated injury.

Acute pattern	Chronic pattern
Neutrophil-rich exudate	Macrophages + lymphocytes
Edema / vascular change	Tissue loss + fibrosis

SCHEMATIC

Application: Persistent antigen and a T-cell loop

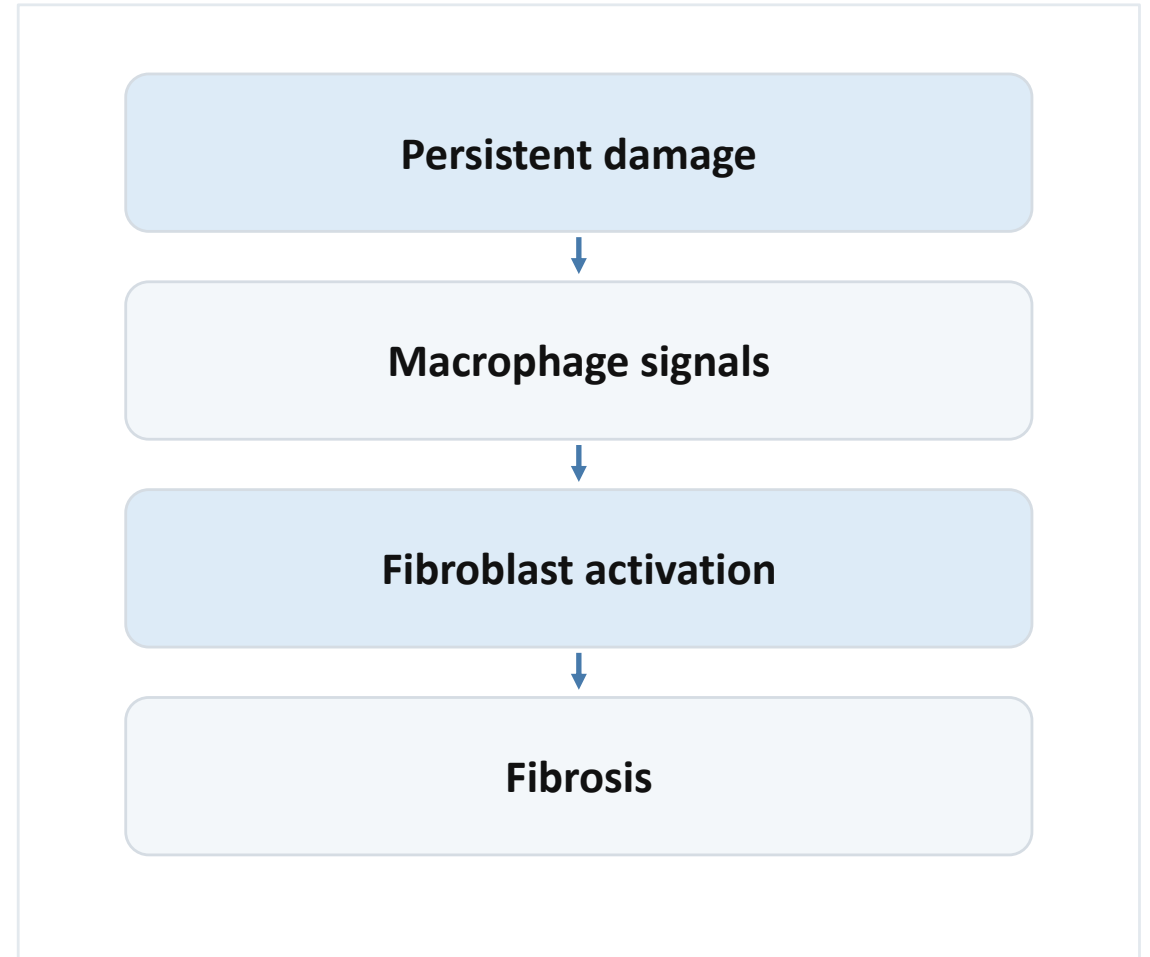
- A lesion remains inflamed despite an extended host response.
- Macrophages present antigen; T cells release IFN- γ .
- Interpretation: Reciprocal activation can explain persistent macrophage activity.



SCHEMATIC

Application: Healing response becomes scarring

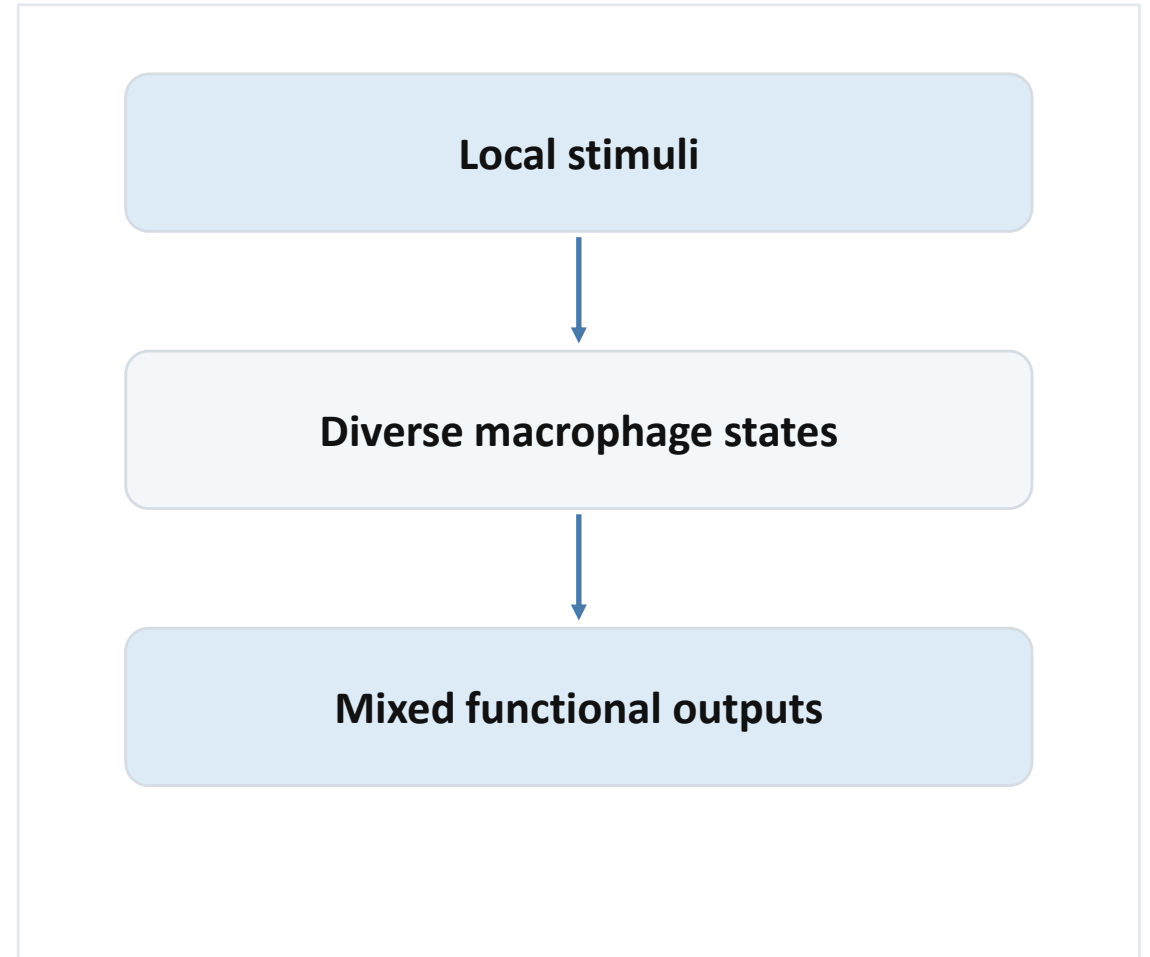
- An injurious agent persists while macrophages remain activated.
- Fibroblast stimulation and ECM deposition continue alongside injury.
- Interpretation: Repair signaling may become pathologic fibrosis.



SCHEMATIC

Application: Interpret macrophage activation labels

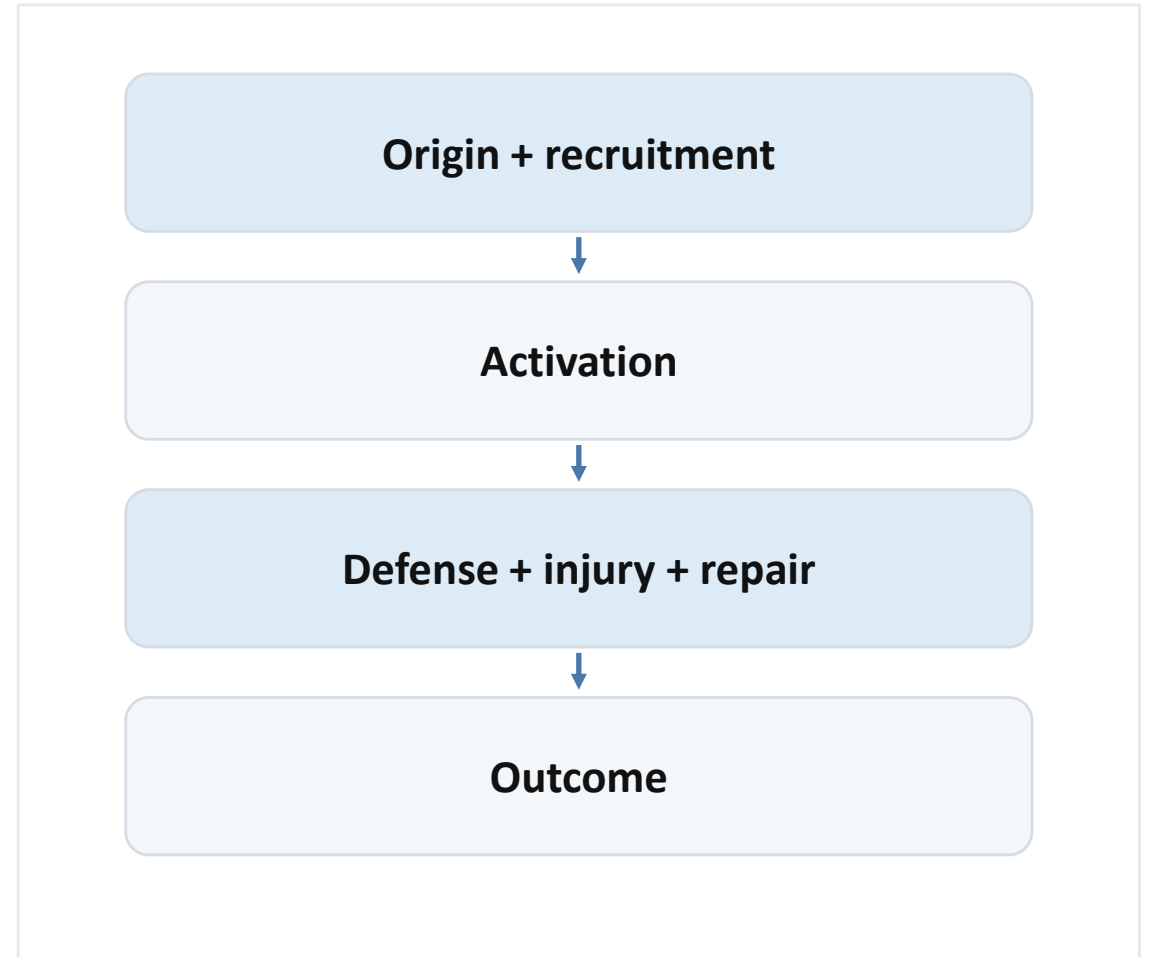
- A macrophage-rich lesion expresses inflammatory and reparative programs.
- M1/M2 are useful functional shorthand but do not define rigid populations.
- Interpretation: Macrophage states may be mixed and dynamic.



SCHEMATIC

Integrating macrophages into chronic inflammation

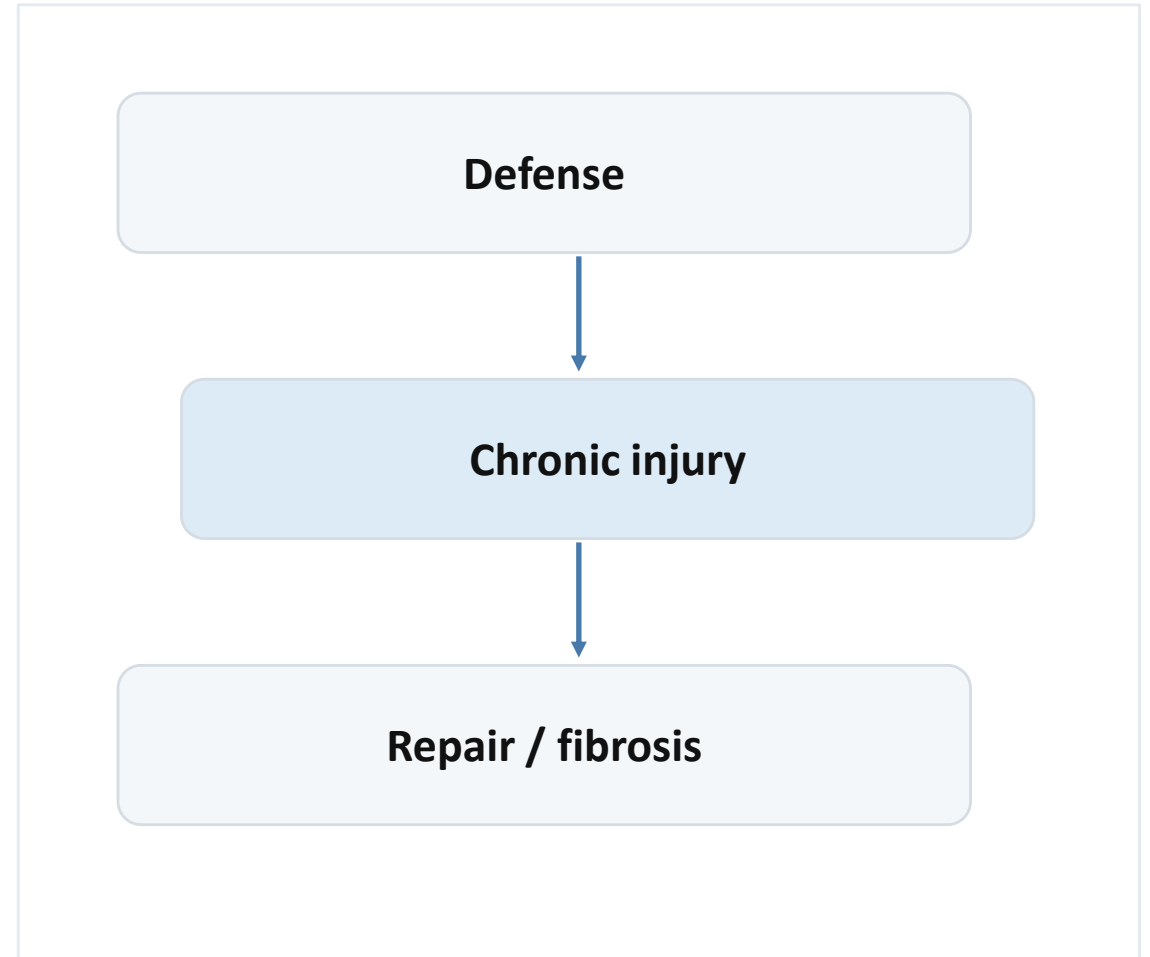
- Origins and recruitment set the cells available within a lesion.
- Activation signals determine inflammatory, microbicidal and reparative outputs.
- Outcome reflects stimulus persistence, T-cell interactions and tissue response.



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Final synthesis: Four mechanistic principles

- Macrophages can be long-lived tissue residents or recruited monocyte descendants.
- Activated cells destroy microbes and also risk collateral tissue damage.
- Interactions with T lymphocytes help sustain chronic inflammation.
- Macrophages coordinate repair; Persistent activation can lead to fibrosis.



SCHEMATIC

Reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026)

Inflammation and Repair