

Cytokines: Messenger Molecules of the Immune System

How soluble signals organize immunity, inflammation, and hematopoiesis

Innate initiation

Adaptive specialization

Immune regulation

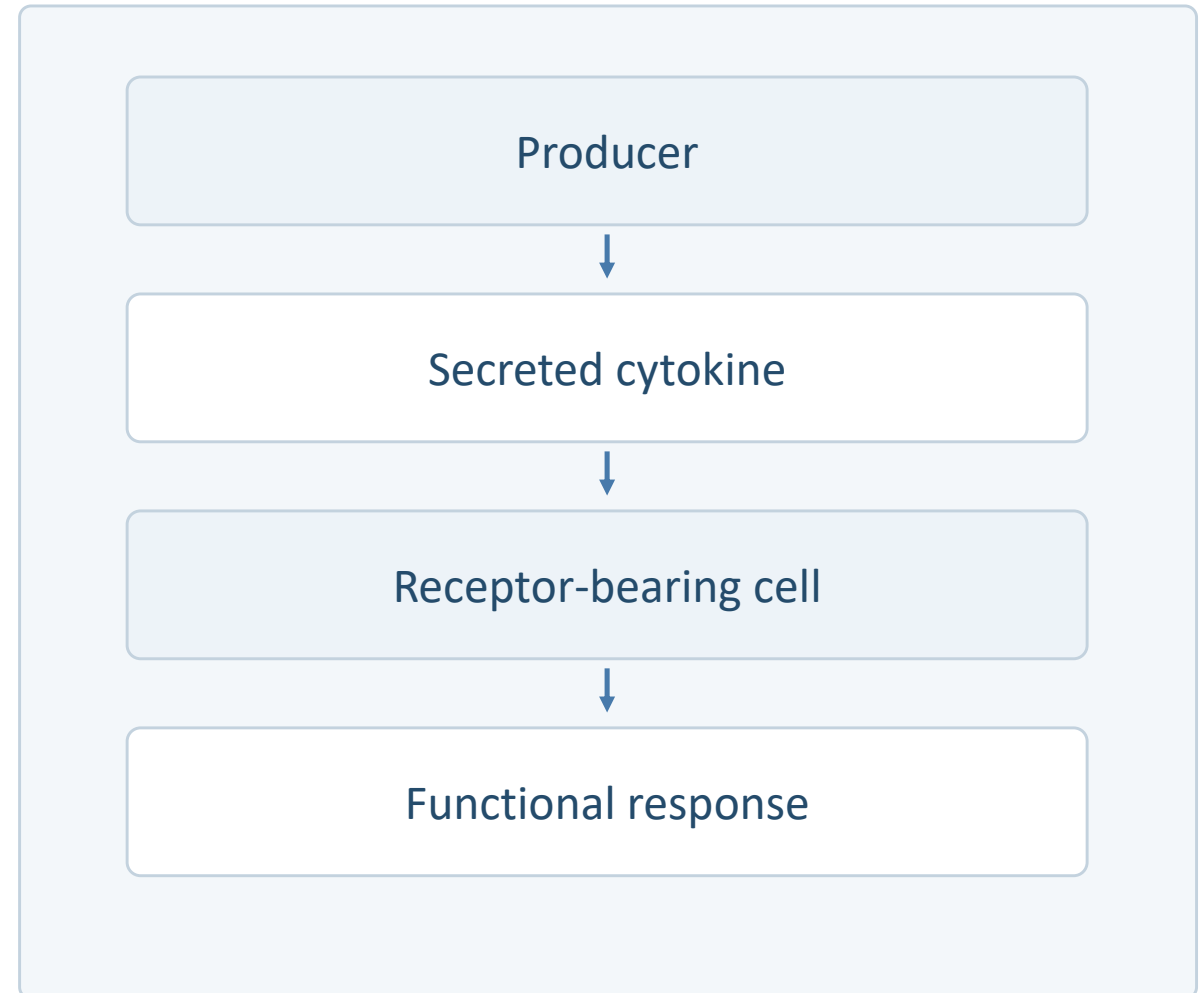
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What makes a cytokine a messenger?

- Secreted proteins transmit information between immune and other host cells.
- Cytokines regulate the magnitude, quality, and duration of inflammatory and immune responses.
- The effect depends on the producing cell, responsive cell, and biological context.



The immune response is a cellular conversation

- Lymphocytes, dendritic cells, macrophages, neutrophils, and endothelial cells interact.
- Direct cell–cell recognition and soluble cytokine signaling are complementary mechanisms.
- Cytokines allow one activated cell to change the behavior of many neighboring cells.

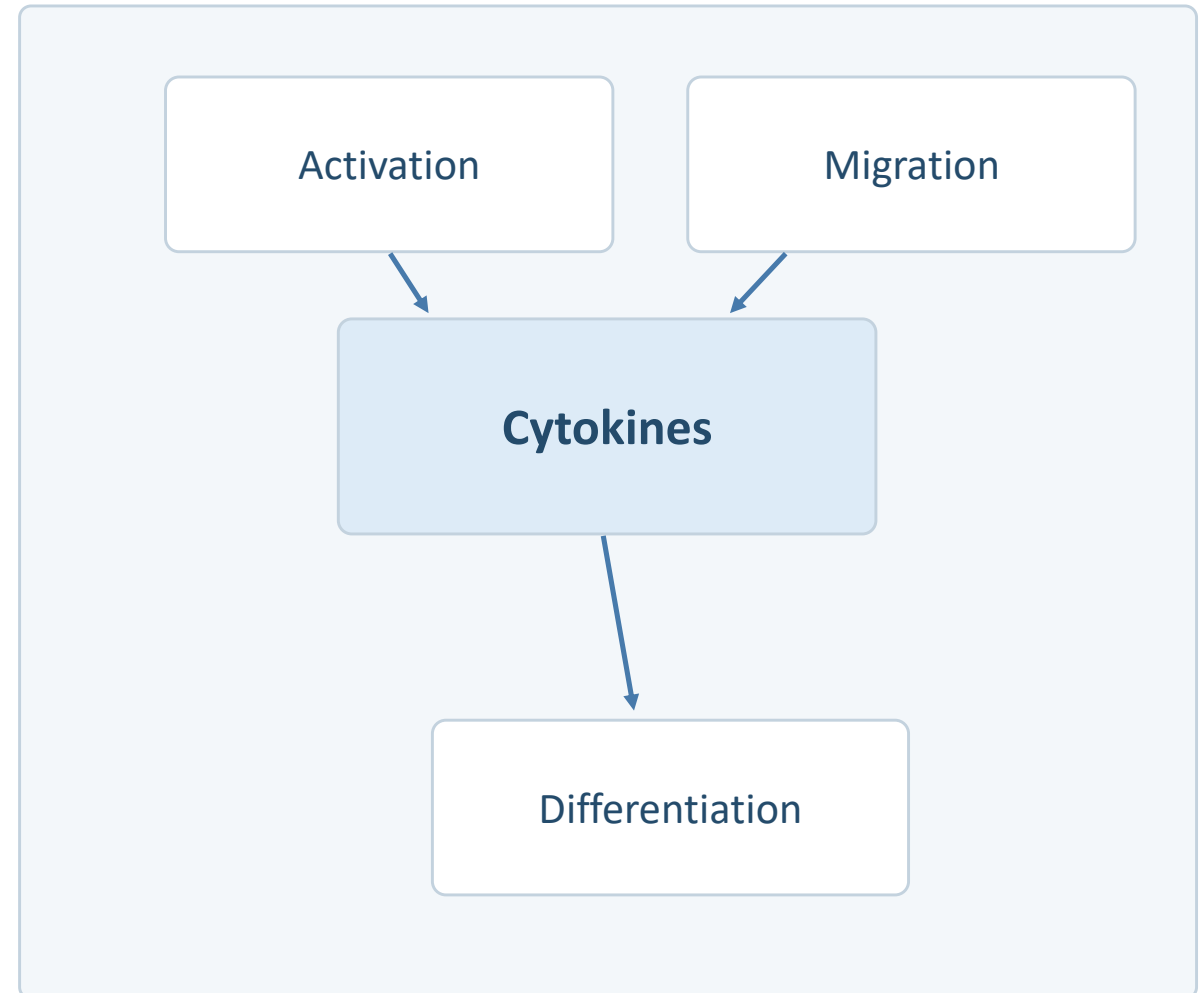
Cell–cell contact

Soluble cytokines

Compare the biological roles

Cytokines are proteins, not a single pathway

- Multiple molecularly distinct proteins share the functional label “cytokines.”
- Effects include leukocyte activation, migration, proliferation, differentiation, and regulation.
- No single cytokine explains the complete inflammatory response.



Interleukin is a historical functional name

- Interleukins were named for communication among leukocytes.
- Many interleukins act on endothelial, epithelial, stromal, and other nonleukocyte cells.
- “Interleukin” does not imply either a single cellular source or a leukocyte-only target.

Named by early
function

Actual cellular scope

Compare the biological roles

Cytokine production is widely distributed

- Macrophages and dendritic cells are major early sources during innate responses.
- Activated lymphocytes produce cytokines that direct adaptive effector functions.
- Endothelial, epithelial, stromal, and additional inflammatory cells can also contribute.

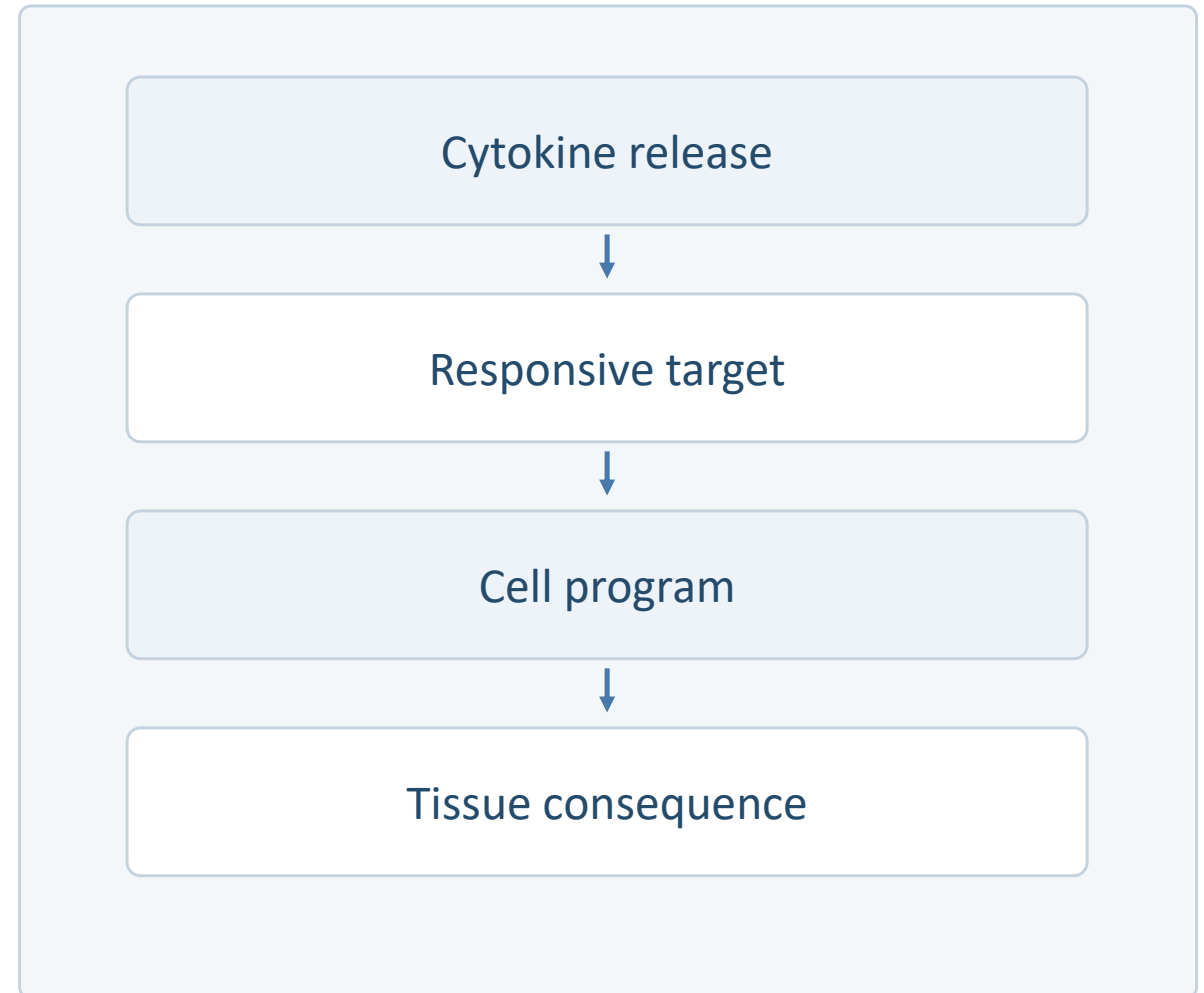
Immune cells

Barrier cells

Stromal / vascular cells

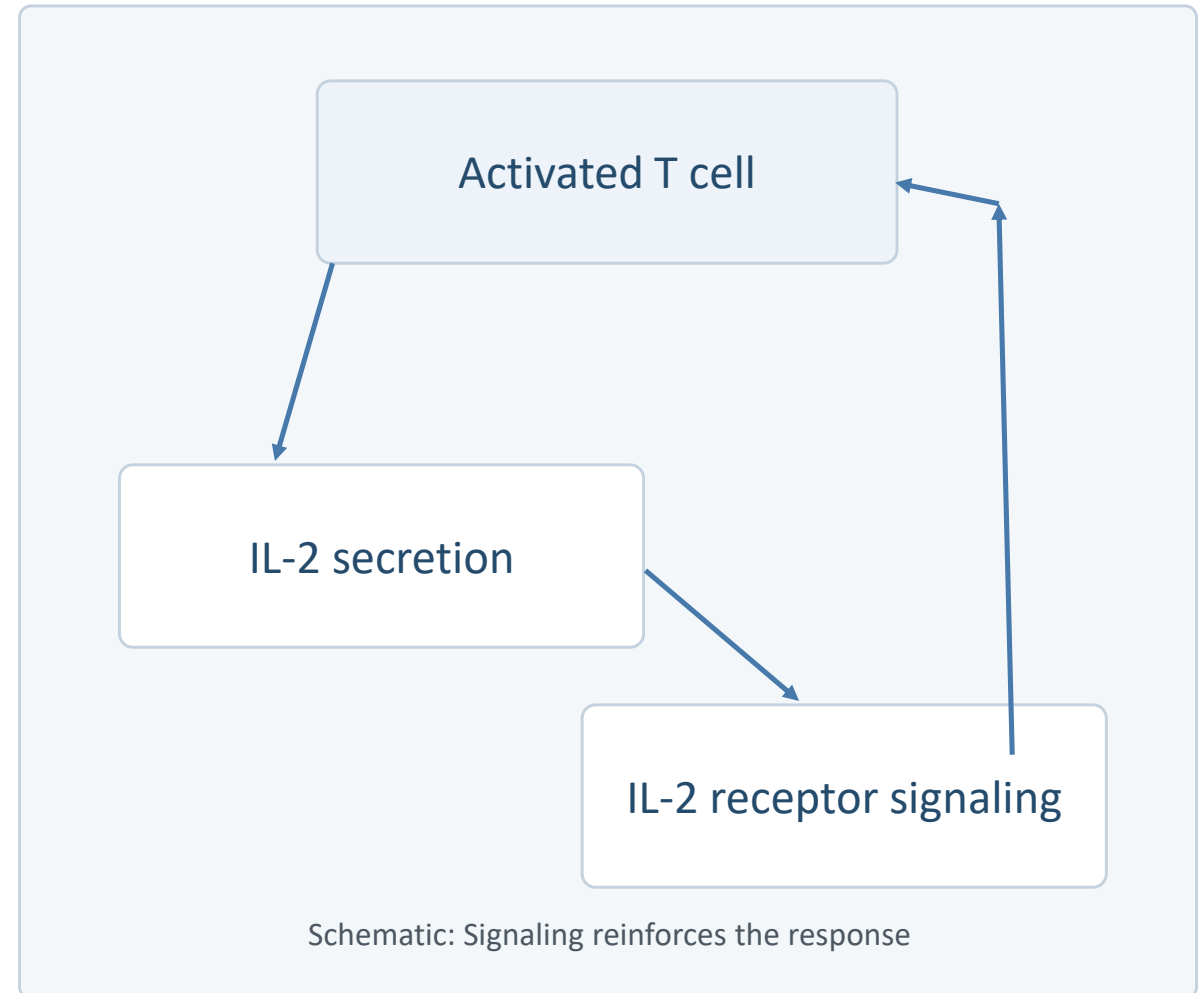
The target cell determines the effect

- A secreted cytokine acts only on cells capable of responding to its signal.
- Different target-cell programs can produce different outcomes to the same cytokine.
- Cytokine identity alone does not fully specify the tissue response.



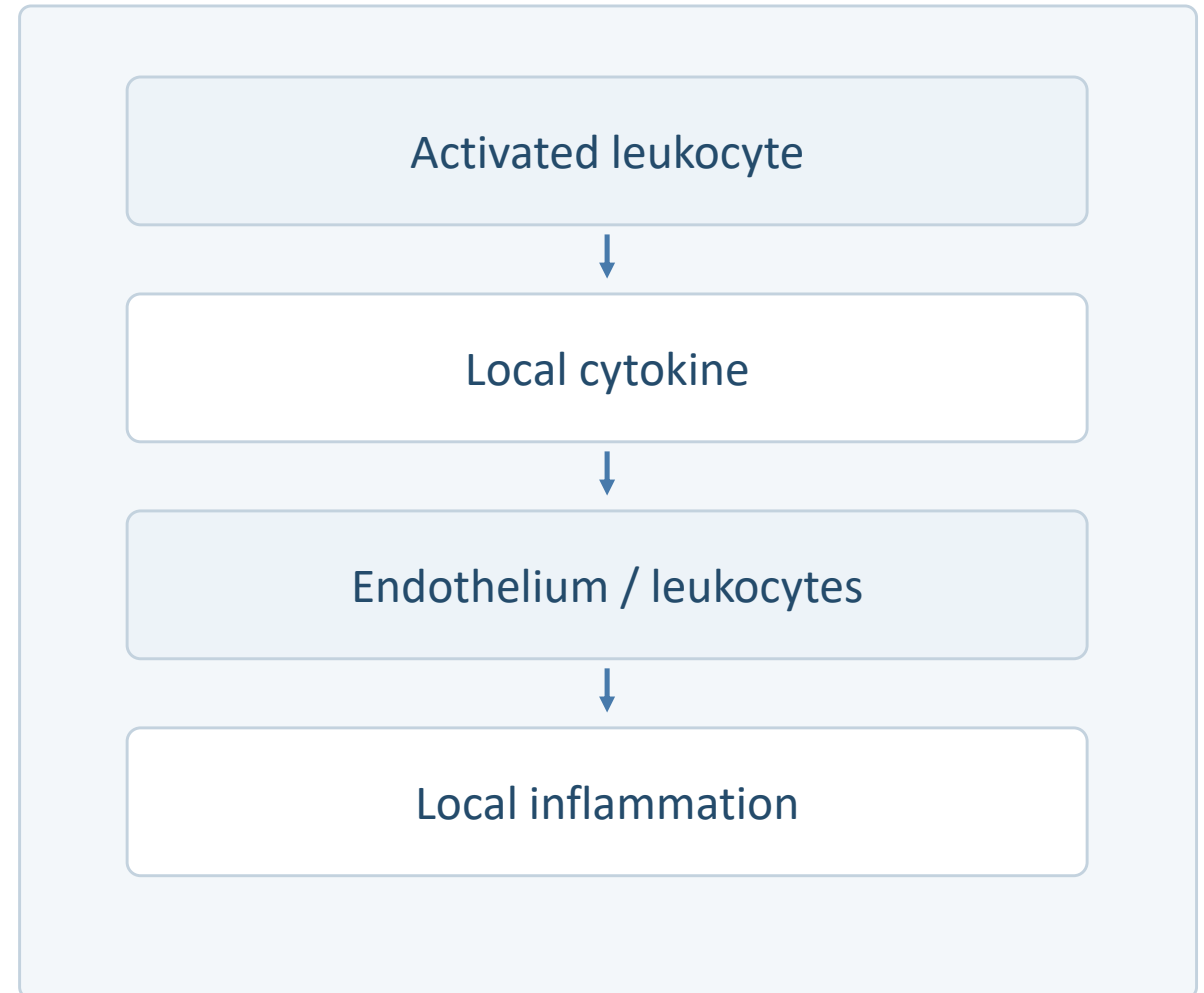
Autocrine signaling reinforces activation

- An activated cell can respond to a cytokine that it releases.
- IL-2 secreted by activated T cells is a key example.
- Autocrine signaling provides a mechanism for amplifying antigen-driven clonal expansion.



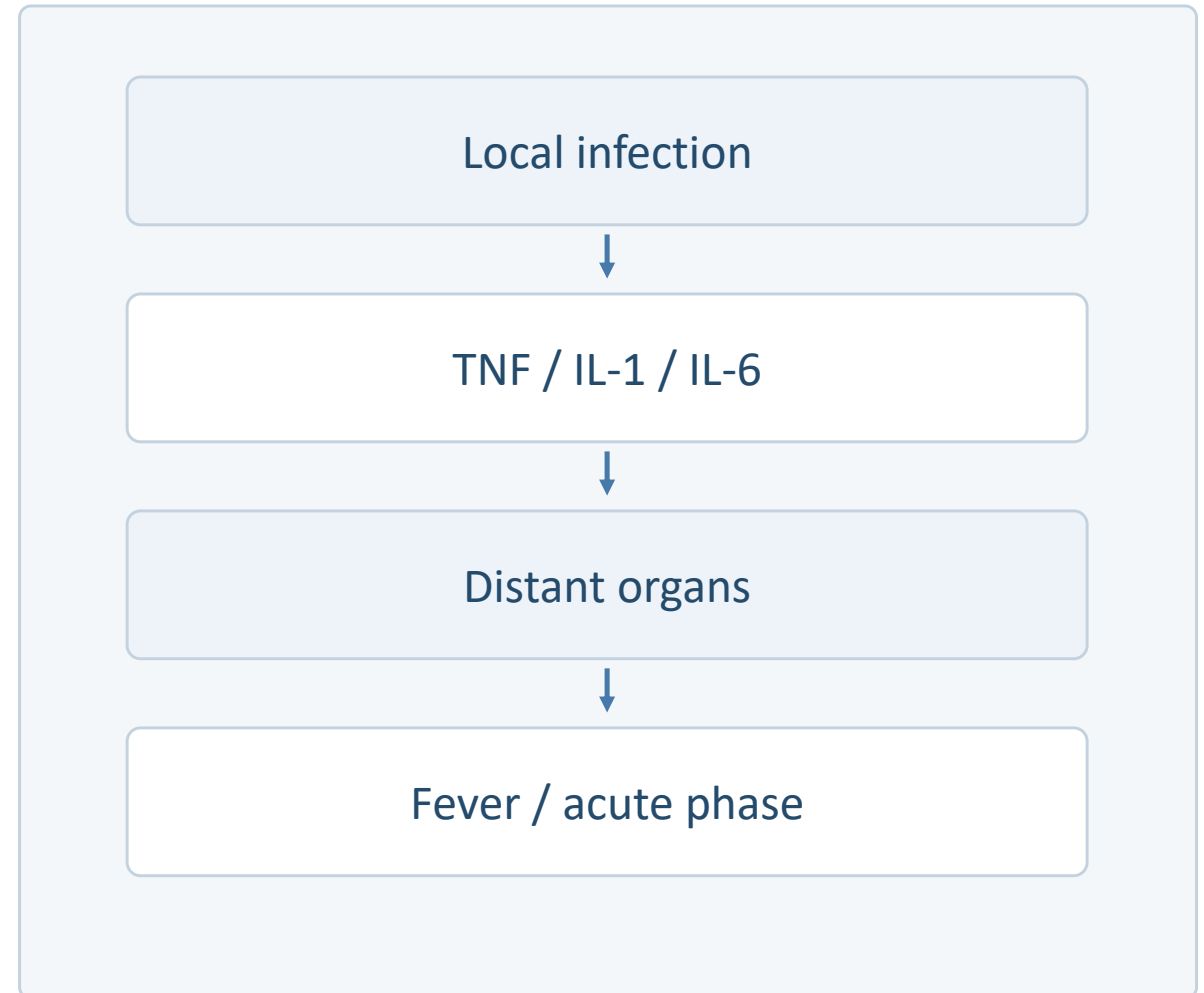
Paracrine signaling organizes local responses

- Cytokines act on adjacent leukocytes, endothelium, and stromal cells.
- Local signaling coordinates recruitment and activation at the inflamed site.
- The dominant inflammatory cytokine effects are often tissue-localized.



Endocrine signaling produces systemic effects

- Some cytokines reach distant tissues or act systemically.
- IL-1, TNF, and IL-6 contribute to fever and acute-phase responses.
- Systemic activity can be protective or pathologic depending on intensity and duration.



Autocrine, paracrine, endocrine: Compare

- Autocrine: The producer itself is the responder.
- Paracrine: A nearby cell is the responder.
- Endocrine: A distant tissue responds through systemic exposure.

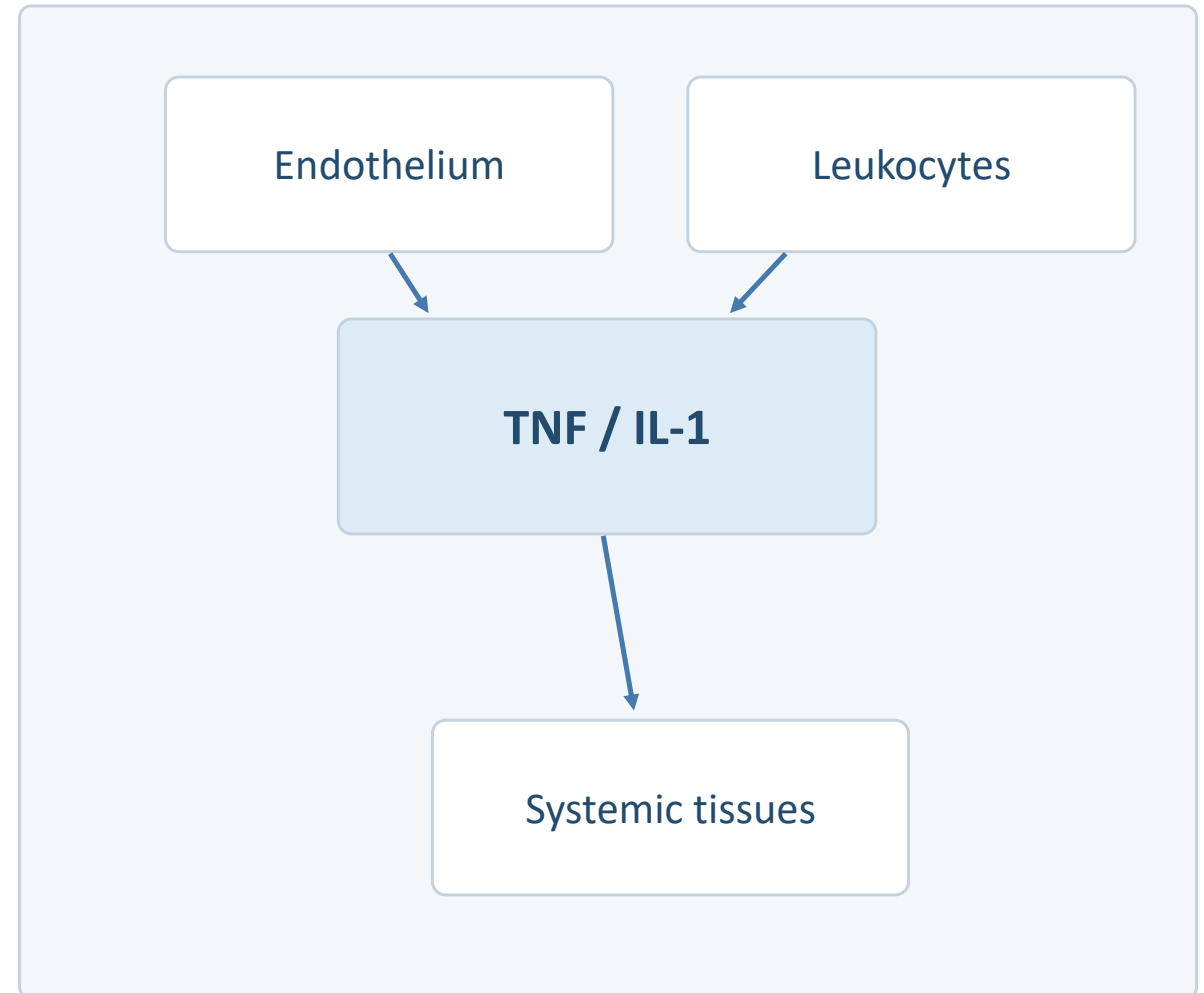
Same cell

Neighboring cell

Distant tissue

One cytokine may have several effects

- Cytokines commonly act on multiple responsive cell populations.
- TNF and IL-1 activate vascular endothelium and also contribute to systemic inflammation.
- This broad activity explains why blocking one cytokine may influence several tissue functions.



Cytokine effects overlap

- TNF and IL-1 share important endothelial-activating actions.
- Different cytokines can contribute to related processes such as neutrophil recruitment.
- Overlapping actions make cytokine networks robust but can complicate therapy.

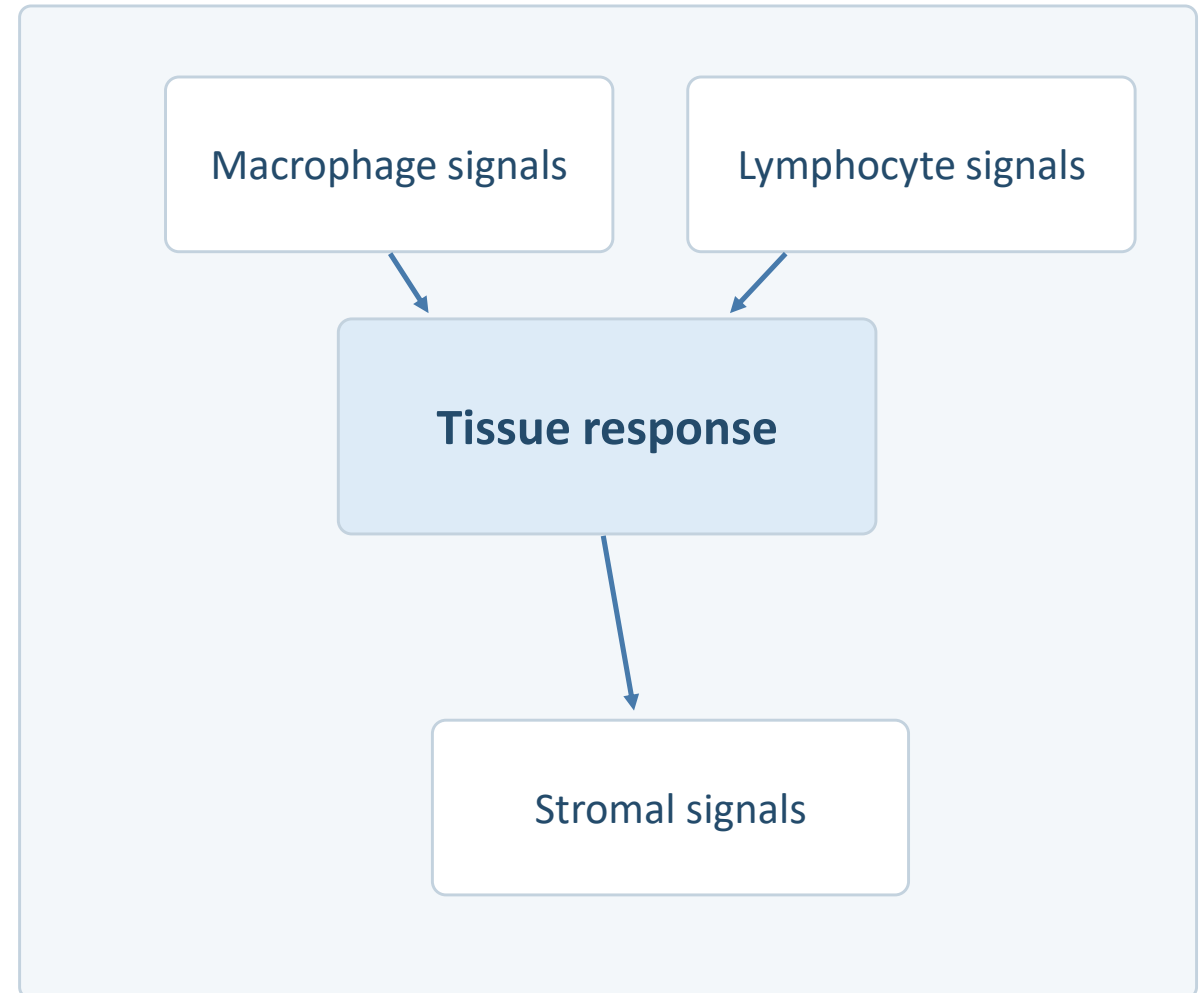
TNF → endothelium

IL-1 → endothelium

Compare the biological roles

Sources and targets form a network

- An individual cytokine may be released by several cell types.
- One producer can release multiple mediators in response to a stimulus.
- Tissue phenotype reflects coordinated signaling rather than an isolated protein.



Three functional domains of cytokines

- Innate-response cytokines rapidly initiate defense and inflammation.
- Adaptive-response cytokines drive lymphocyte expansion and specialized effector function.
- Hematopoietic cytokines replenish leukocytes consumed during immune responses.

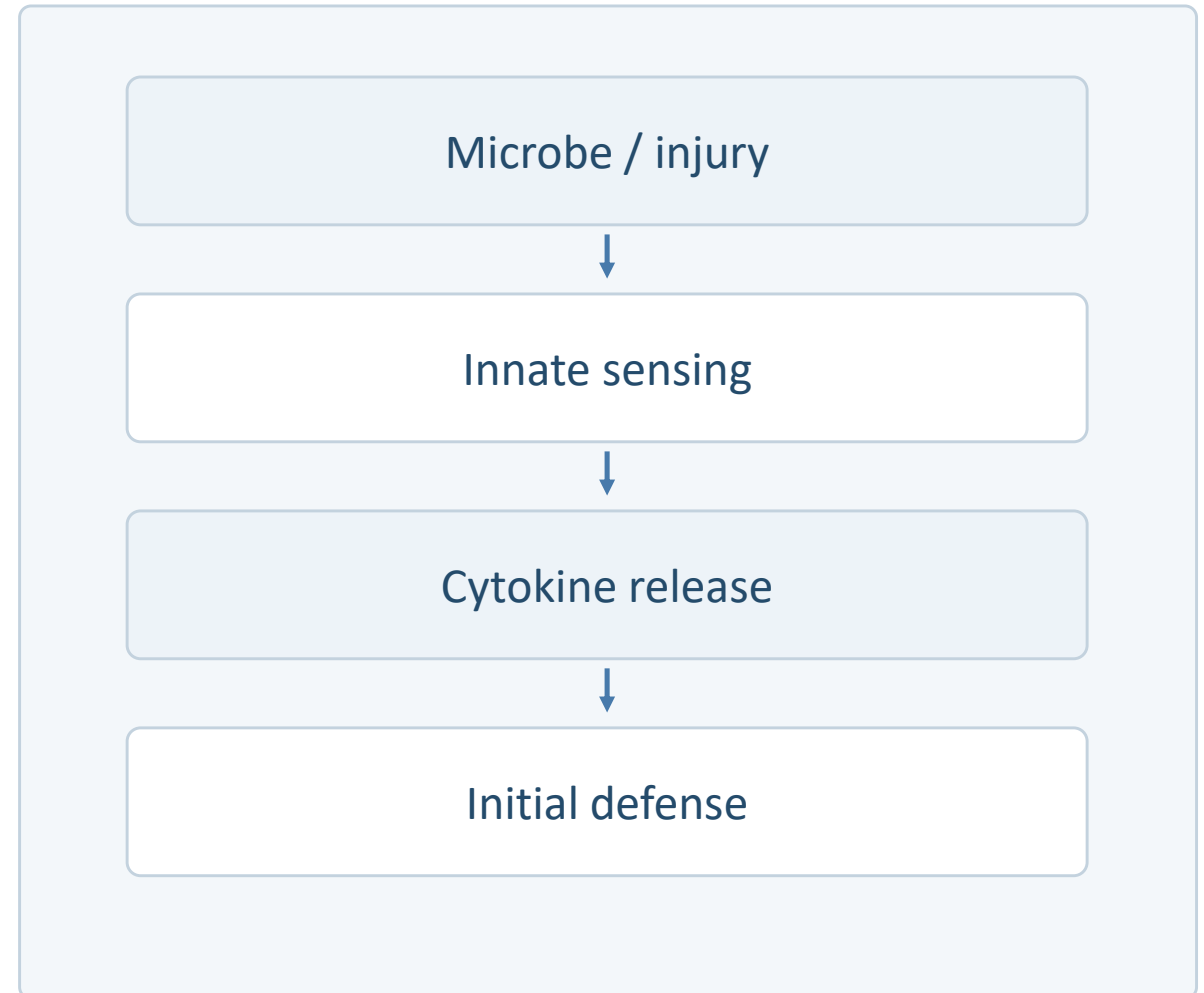
Innate defense

Adaptive effectors

Hematopoiesis

Innate cytokines appear early

- Microbial products and tissue injury activate innate immune cells.
- Secreted mediators initiate leukocyte recruitment and antiviral defense.
- They prepare the tissue environment in which adaptive immunity develops.



Innate cytokine sources are diverse

- Activated macrophages and dendritic cells are principal producers.
- Innate lymphoid and natural killer cells also contribute.
- Barrier, endothelial, and stromal cells add signals in the relevant tissue.

Macrophages / DCs

ILCs / NK cells

Barrier / stromal cells

Key innate cytokine families

- TNF and IL-1 support inflammatory cell recruitment.
- Type I interferons establish antiviral responses.
- IL-12 and IFN- γ connect innate activation with cell-mediated defenses; Chemokines guide cell migration.

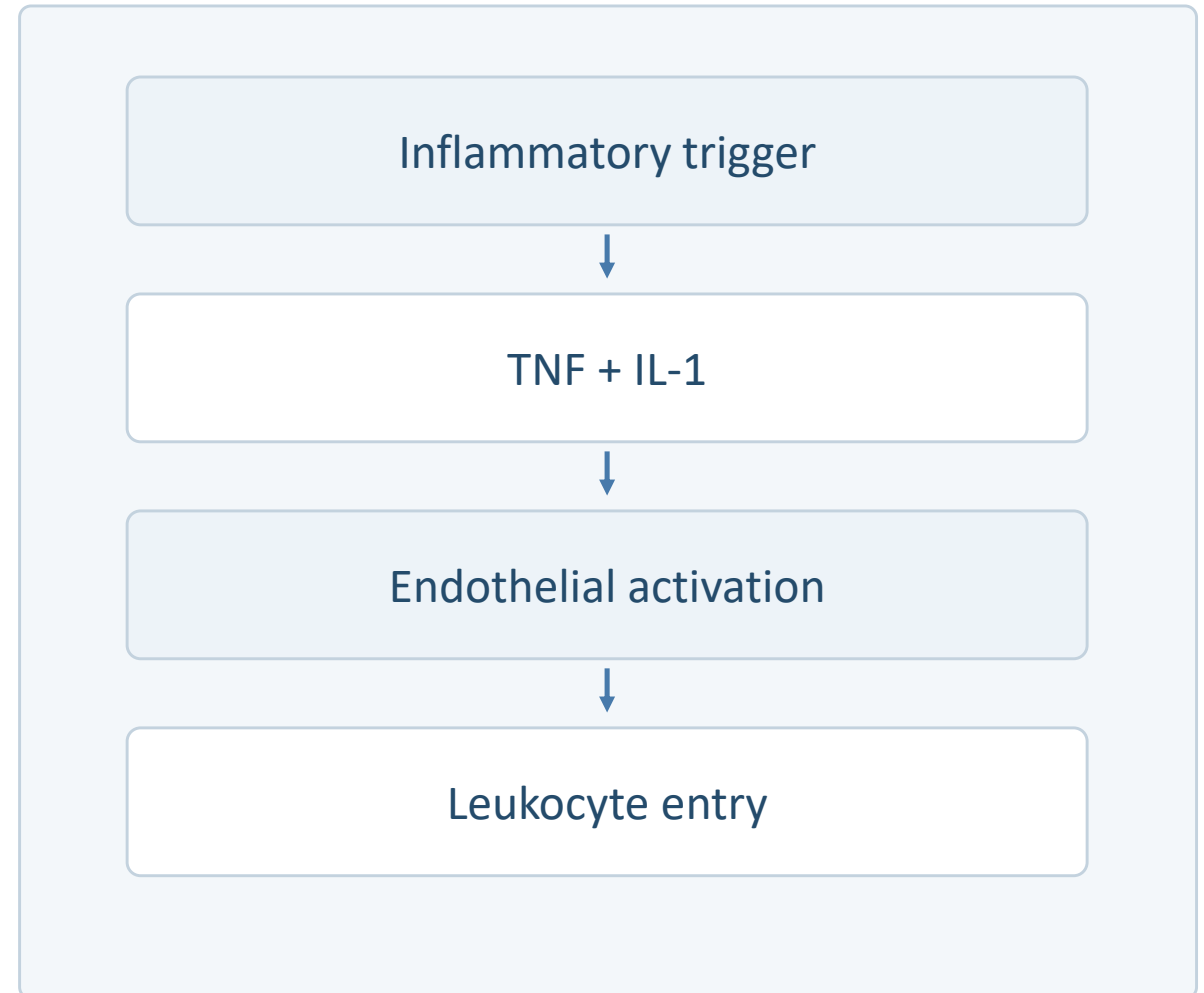
TNF / IL-1

Type I IFNs

IL-12 / IFN- γ / chemokines

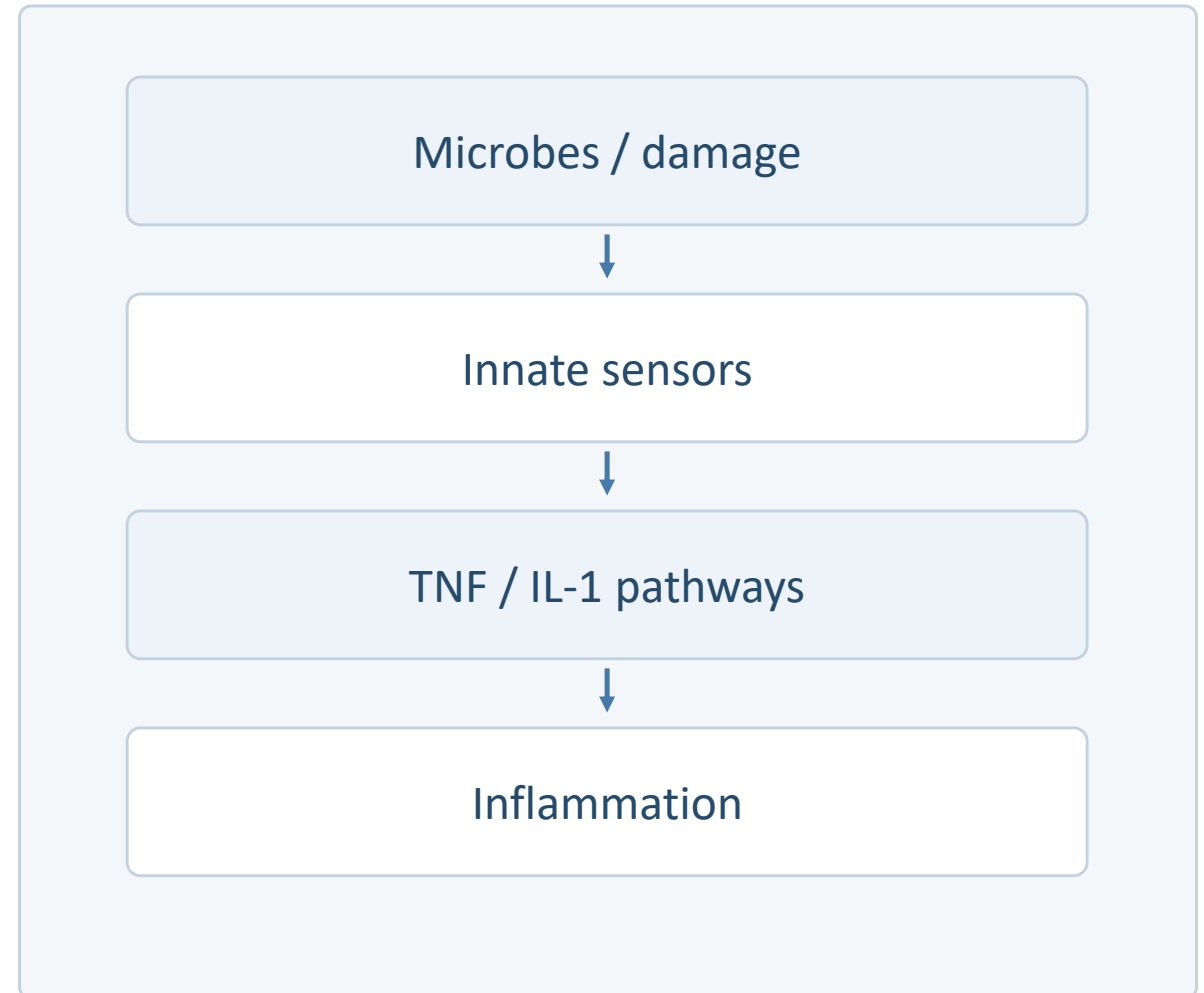
TNF and IL-1: Shared inflammatory roles

- Both are produced during responses to microbes, damage, and other inflammatory stimuli.
- Both activate endothelium to support leukocyte adhesion and entry into tissues.
- Both contribute to systemic manifestations of inflammation.



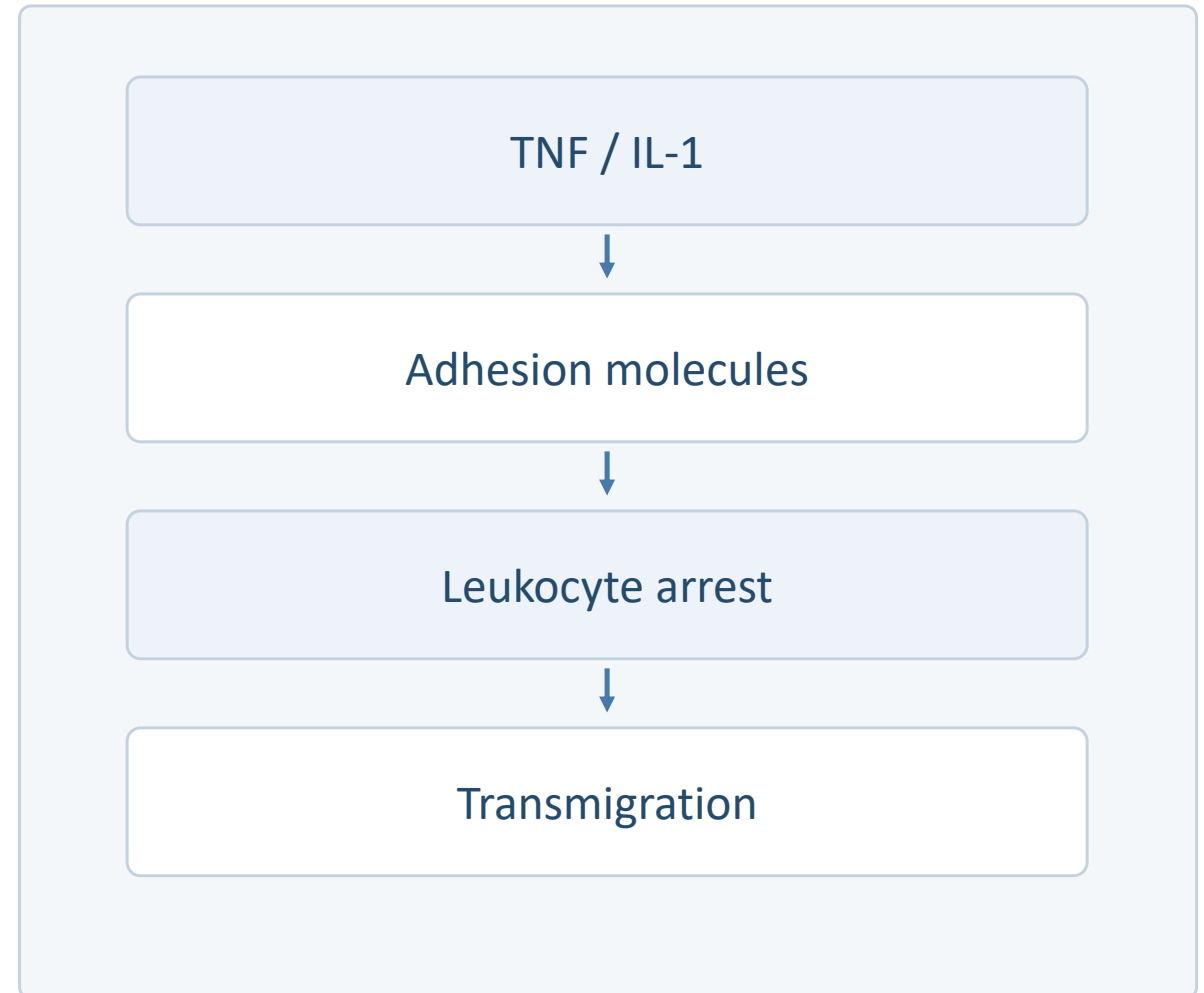
What induces TNF and IL-1?

- Microbial products, dead cells, immune complexes, foreign bodies, and physical injury can initiate release.
- Microbial recognition receptors induce TNF production.
- IL-1 synthesis also requires activation; Maturation of active IL-1 involves the inflammasome.



Endothelial activation enables recruitment

- TNF and IL-1 increase expression of endothelial adhesion molecules.
- The stimulated endothelium also produces chemokines and other inflammatory mediators.
- These changes help circulating leukocytes attach and enter tissues.



Endothelial response extends beyond adhesion

- TNF and IL-1 induce endothelial secretion of mediators and growth factors.
- They also increase endothelial procoagulant activity.
- The same signal therefore links inflammation to vascular and hemostatic changes.

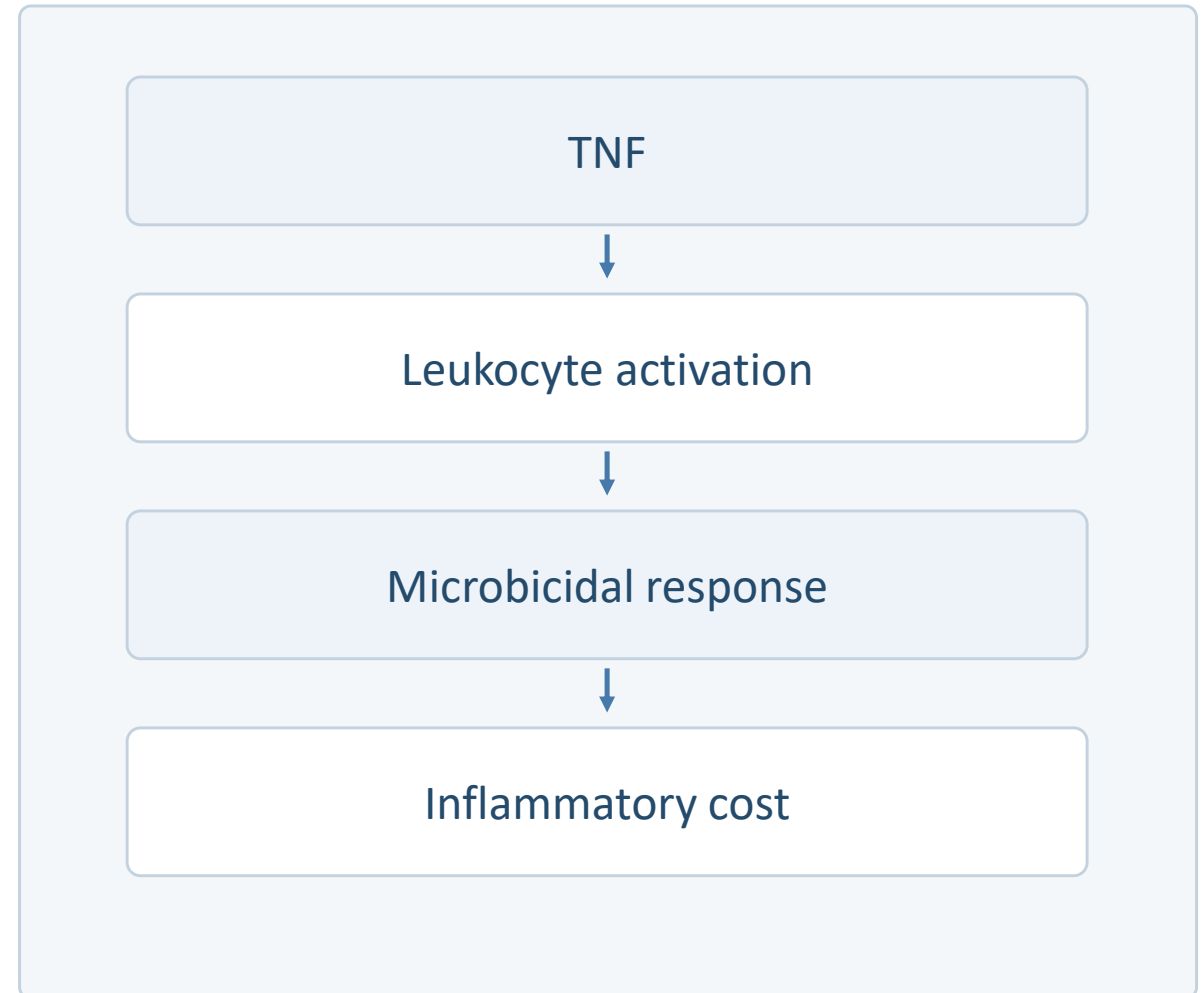
Cell adhesion

Mediator release

Procoagulant state

TNF amplifies leukocyte antimicrobial activity

- TNF enhances neutrophil responses to additional stimuli.
- It promotes macrophage microbicidal activity.
- Persistent or excessive TNF activity may also contribute to tissue injury and systemic illness.



IL-1 has tissue-specific additional roles

- IL-1 contributes prominently to cytokine-associated fever.
- It stimulates fibroblast collagen synthesis and proliferation of some mesenchymal cells.
- IL-1 can also enhance Th17-type inflammation.

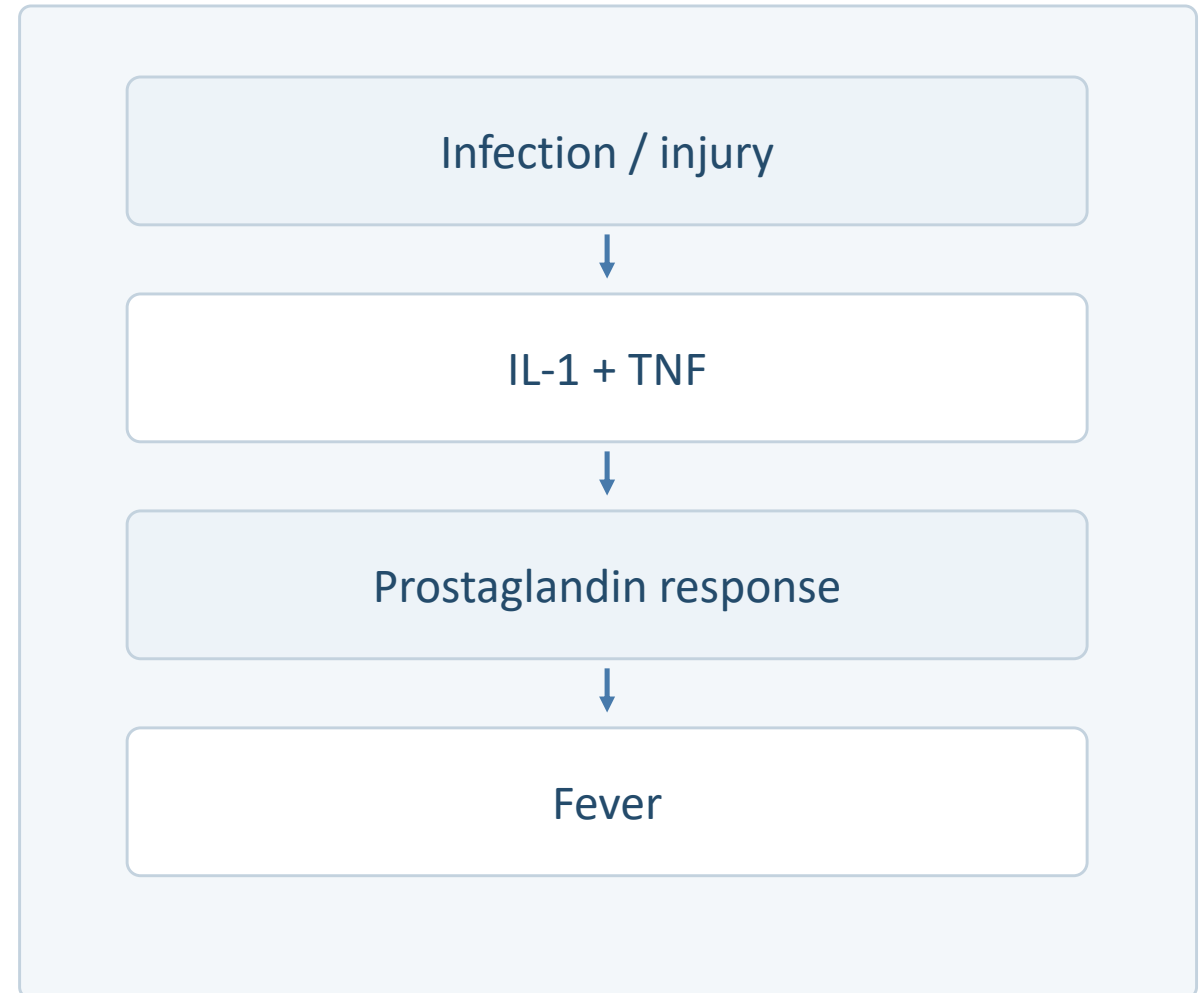
Fever

Fibroblast activation

Th17 responses

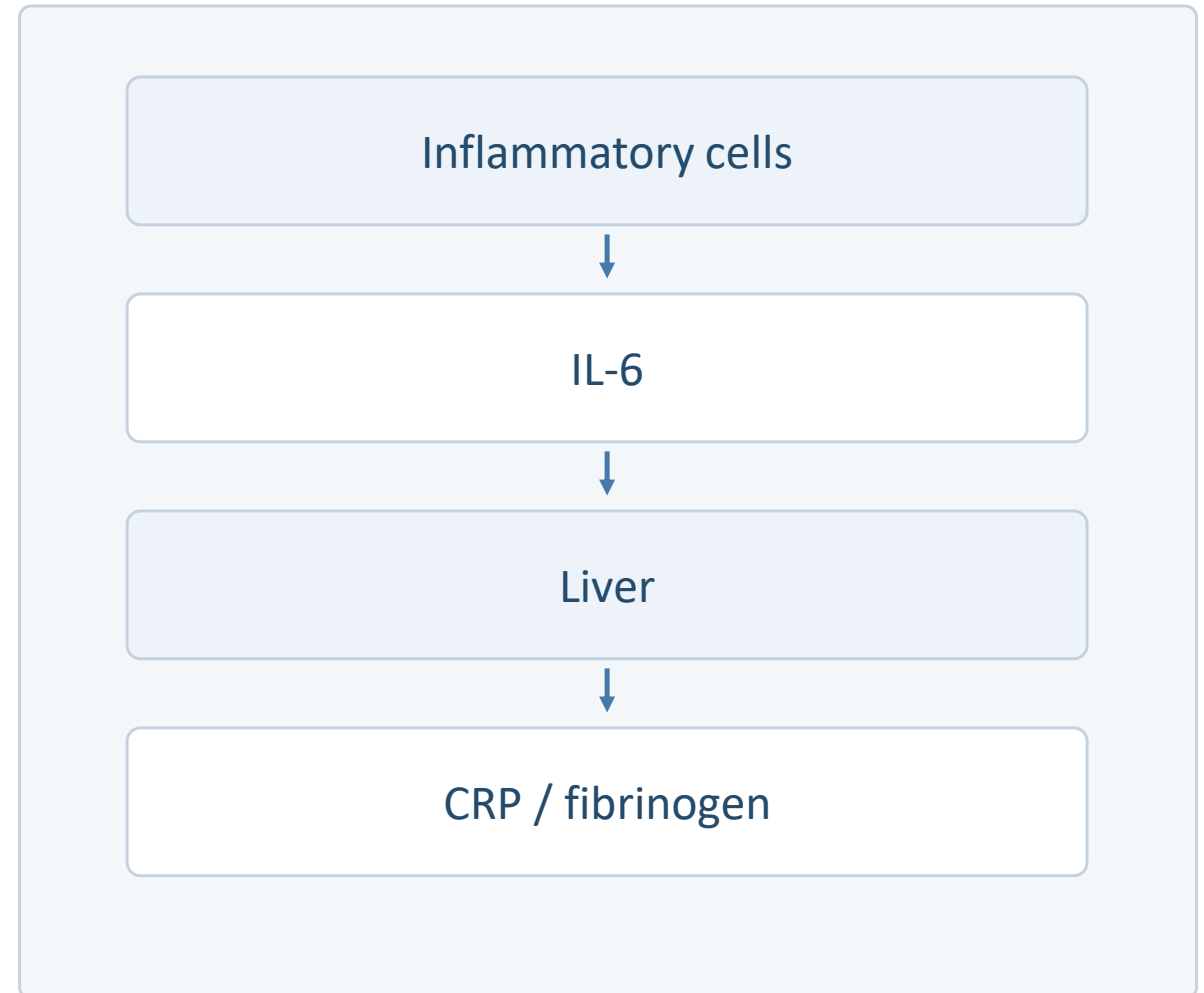
Inflammatory cytokines cause fever

- IL-1 and TNF act as endogenous pyrogens.
- They promote prostaglandin-dependent changes in thermoregulation.
- Fever is a systemic response to an underlying immune or inflammatory trigger.



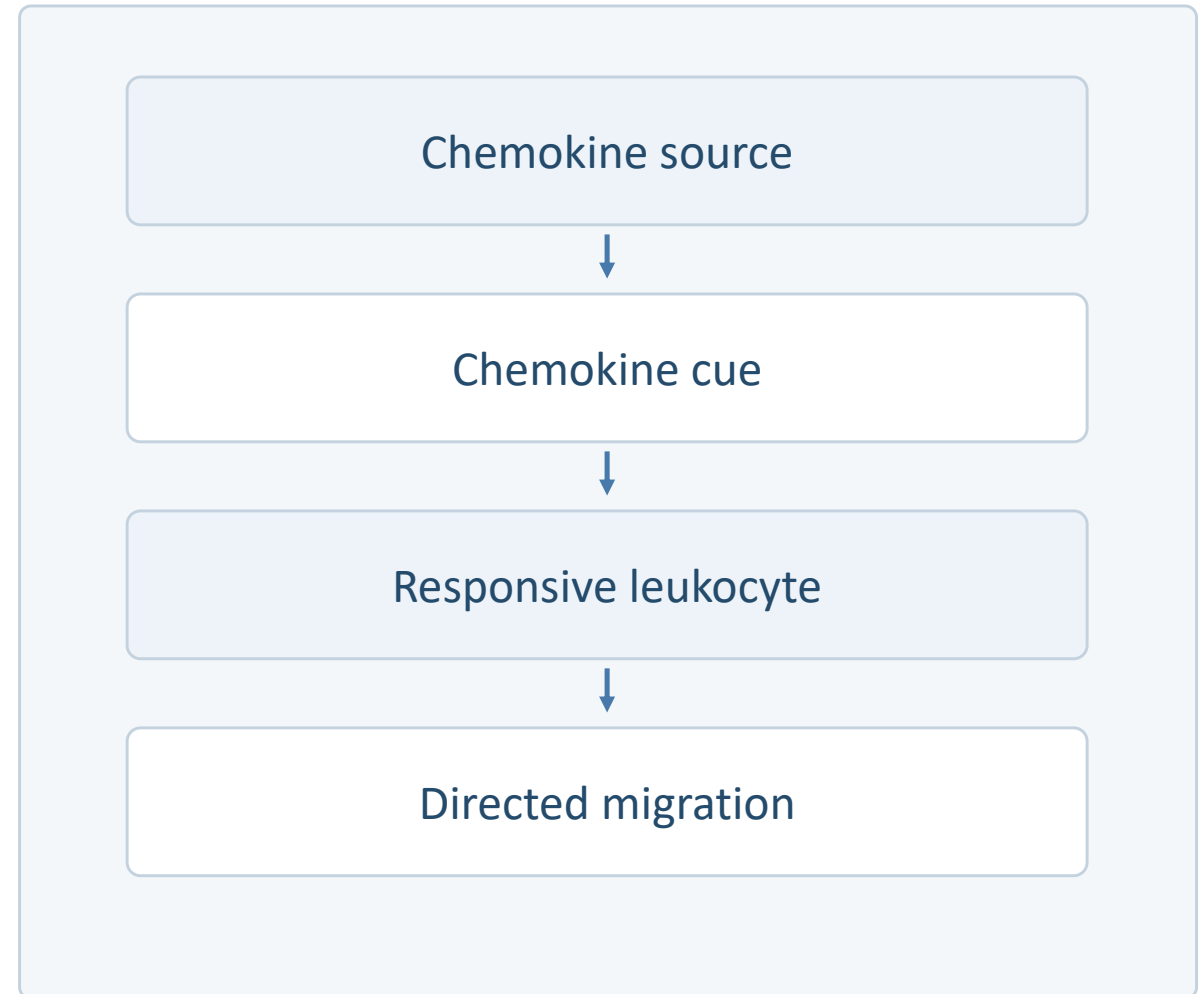
IL-6 drives the acute-phase response

- IL-6 is produced by macrophages and other cells during inflammation.
- It stimulates hepatic synthesis of important acute-phase proteins.
- CRP and fibrinogen therefore reflect inflammation but do not identify its cause.



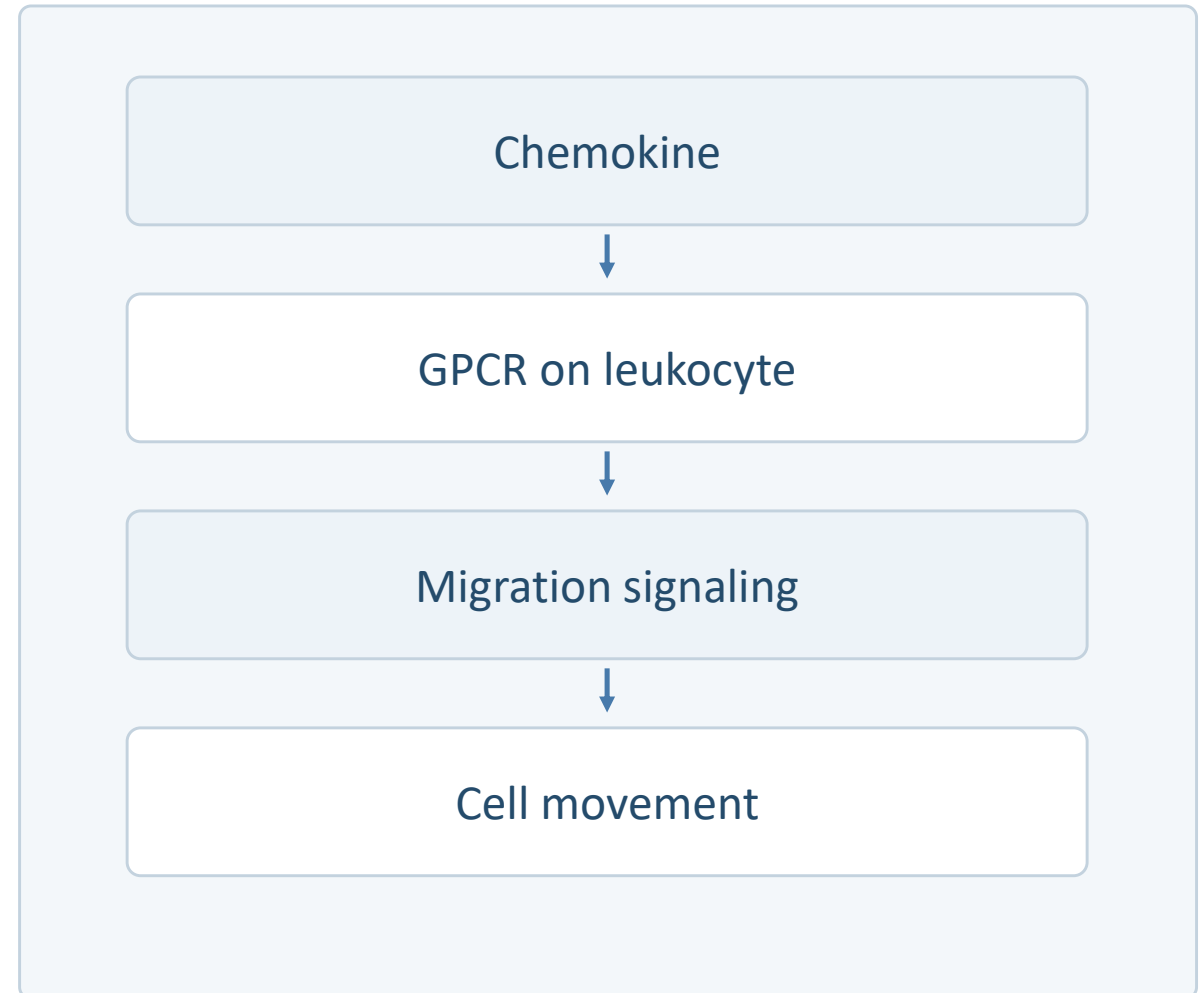
Chemokines direct leukocyte trafficking

- Chemokines are small cytokine-family proteins with chemotactic activity.
- They coordinate movement of selected leukocyte populations.
- Their functions include both inflammation and positioning of cells in normal lymphoid tissue.



Chemokine receptors translate positional cues

- Chemokine receptors are seven-transmembrane G protein–coupled receptors.
- Leukocytes often express more than one chemokine receptor.
- Receptor expression contributes to which cell populations follow a chemokine cue.



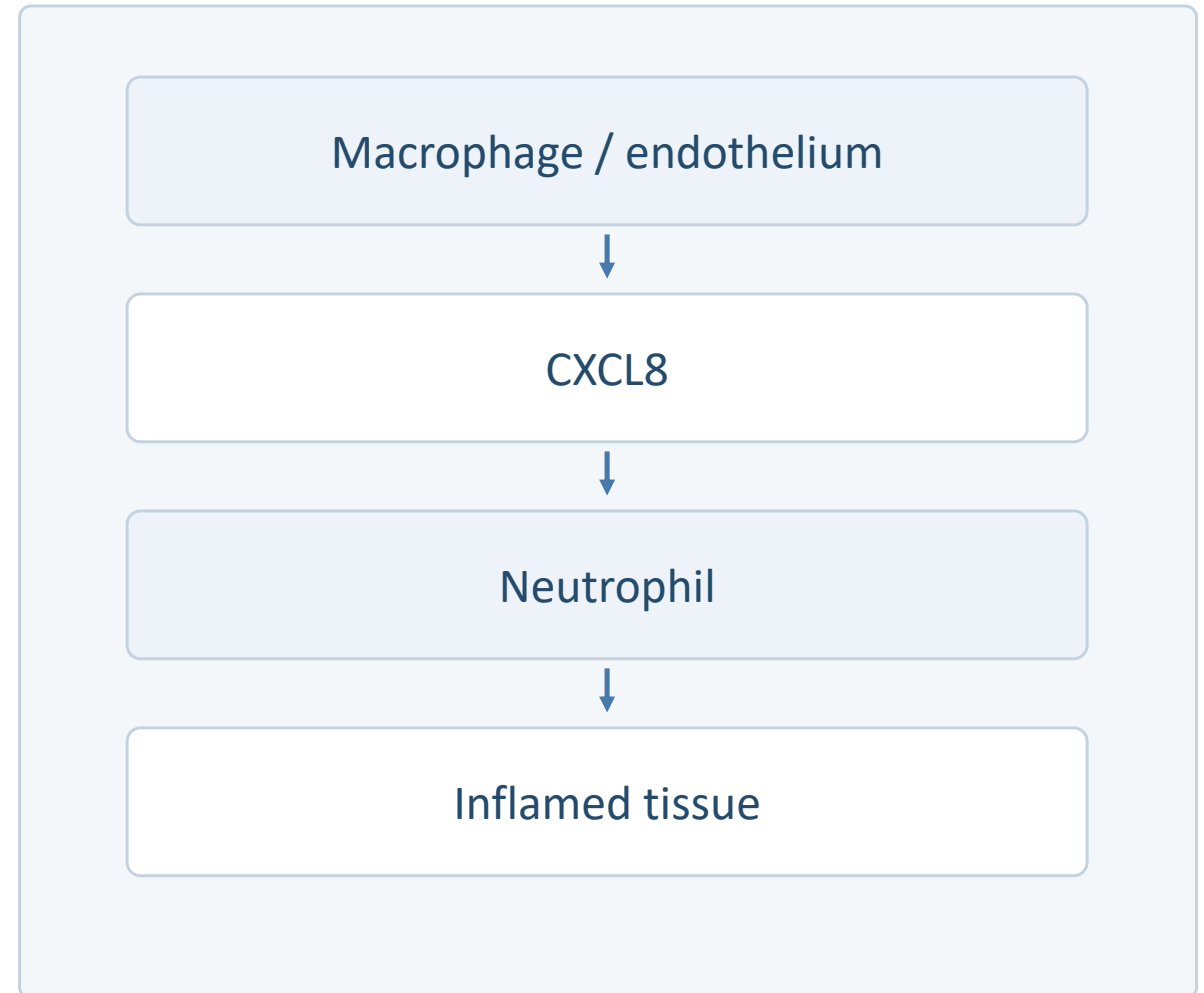
Four structural chemokine families

- CXC, CC, C, and CX3C classes are defined by the pattern of conserved cysteines.
- This classification describes molecular structure, not a strict one-to-one target cell assignment.
- Members of a family may have overlapping actions.



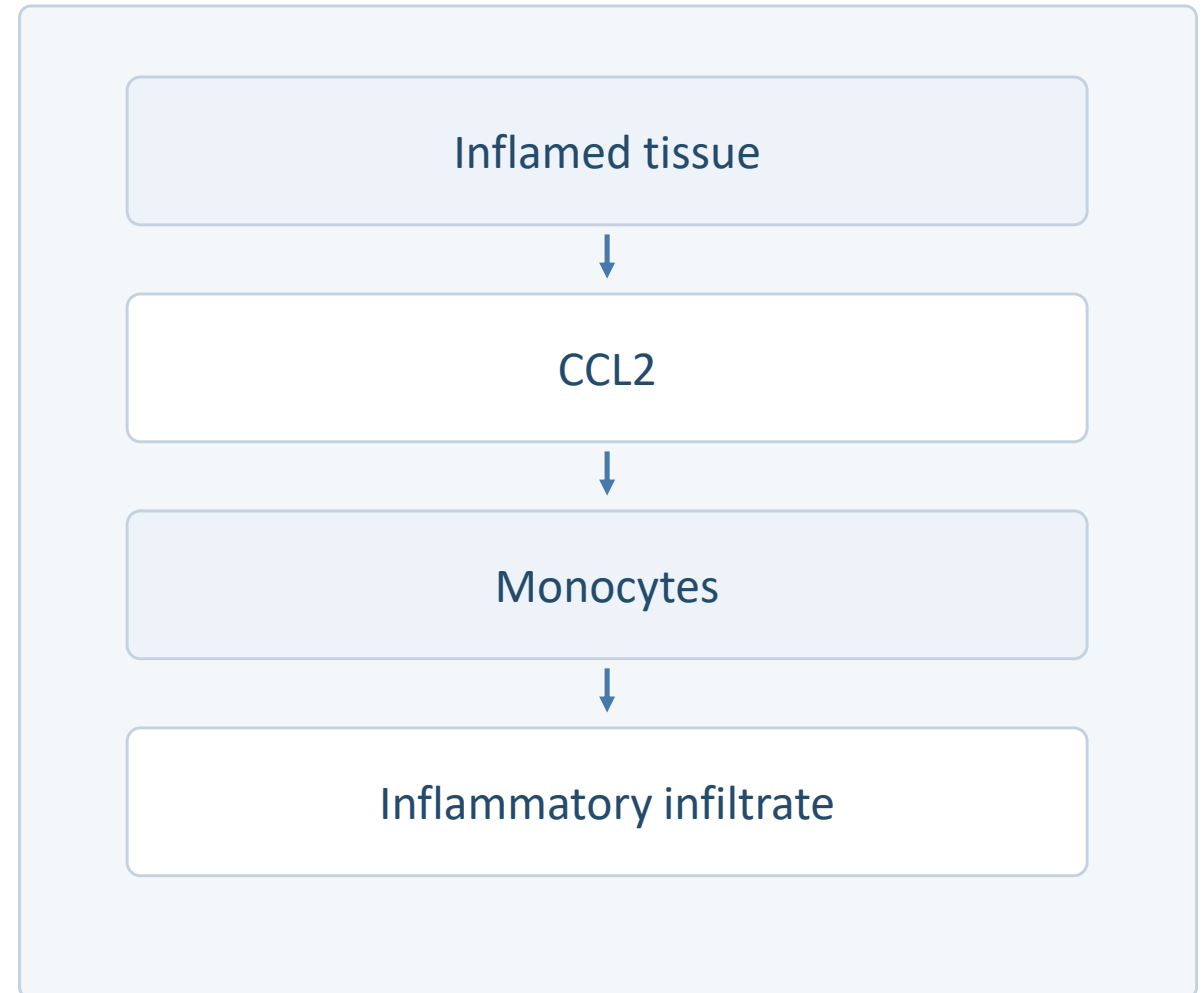
CXCL8 helps recruit neutrophils

- CXCL8, historically IL-8, belongs to the CXC chemokine family.
- Activated macrophages and endothelial cells are among its sources.
- CXCL8 activates and attracts neutrophils at inflammatory sites.



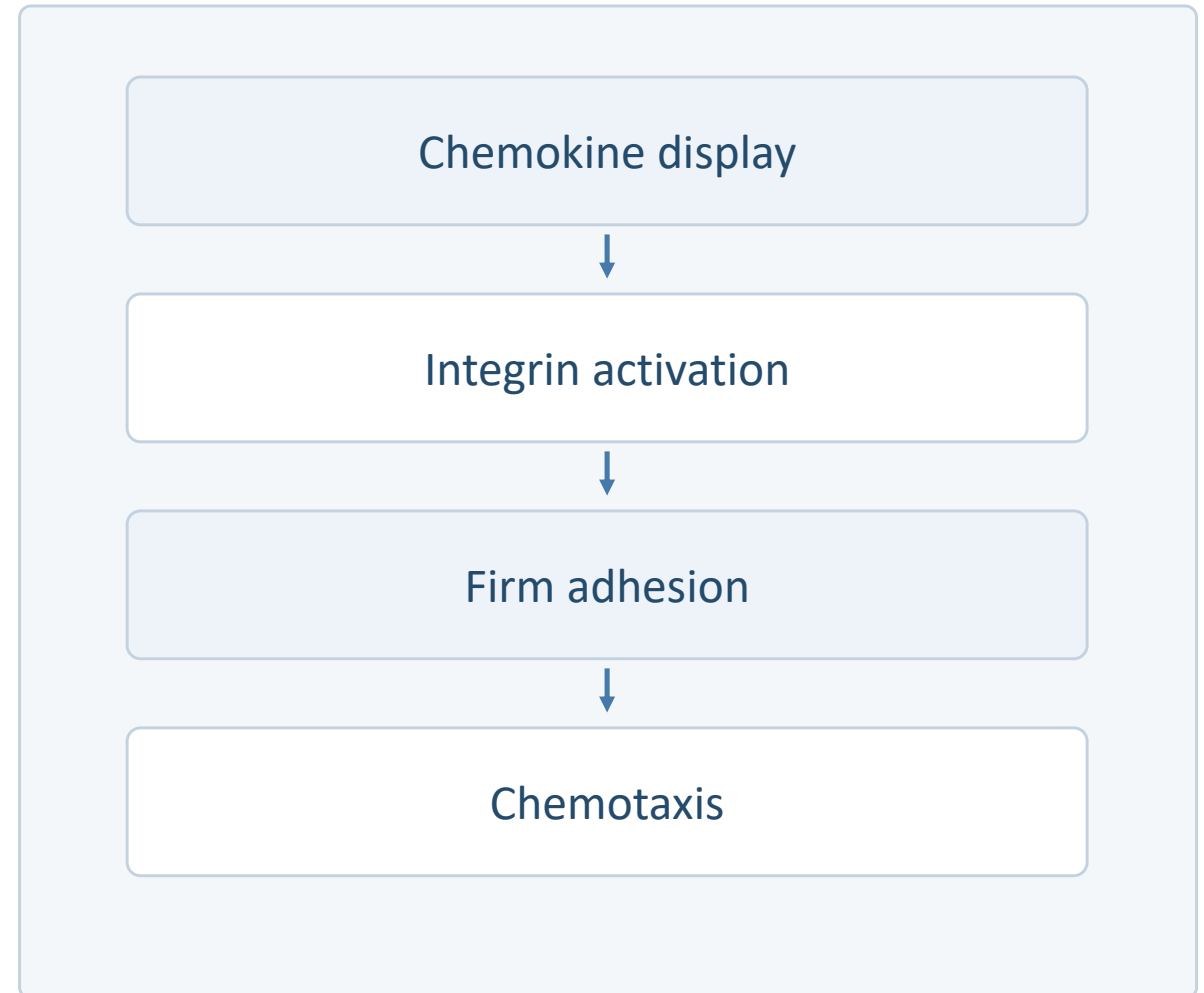
CCL2 attracts monocytes

- CCL2, also known as MCP-1, is a CC chemokine.
- CC chemokines commonly recruit monocytes and other mononuclear leukocytes.
- This chemokine axis contributes to inflammatory cell accumulation in tissues.



Chemokines support arrest and migration

- Endothelium presents chemokines to passing leukocytes.
- Chemokines increase leukocyte integrin affinity, promoting attachment to endothelium.
- They then guide chemotaxis through tissue toward the inflammatory stimulus.



Homeostatic chemokines organize lymphoid tissue

- Not all chemokines are induced by acute inflammation.
- Constitutively produced chemokines organize spatially distinct T-cell and B-cell regions.
- Normal immune architecture therefore depends on positional cytokine signals.

Inflammatory
trafficking

Homeostatic
positioning

Compare the biological roles

Type I interferons inhibit virus replication

- Type I interferons are rapidly produced in innate antiviral responses.
- Their principal function is to generate an antiviral state in responsive cells.
- This activity is distinct from IFN- γ -driven macrophage activation.

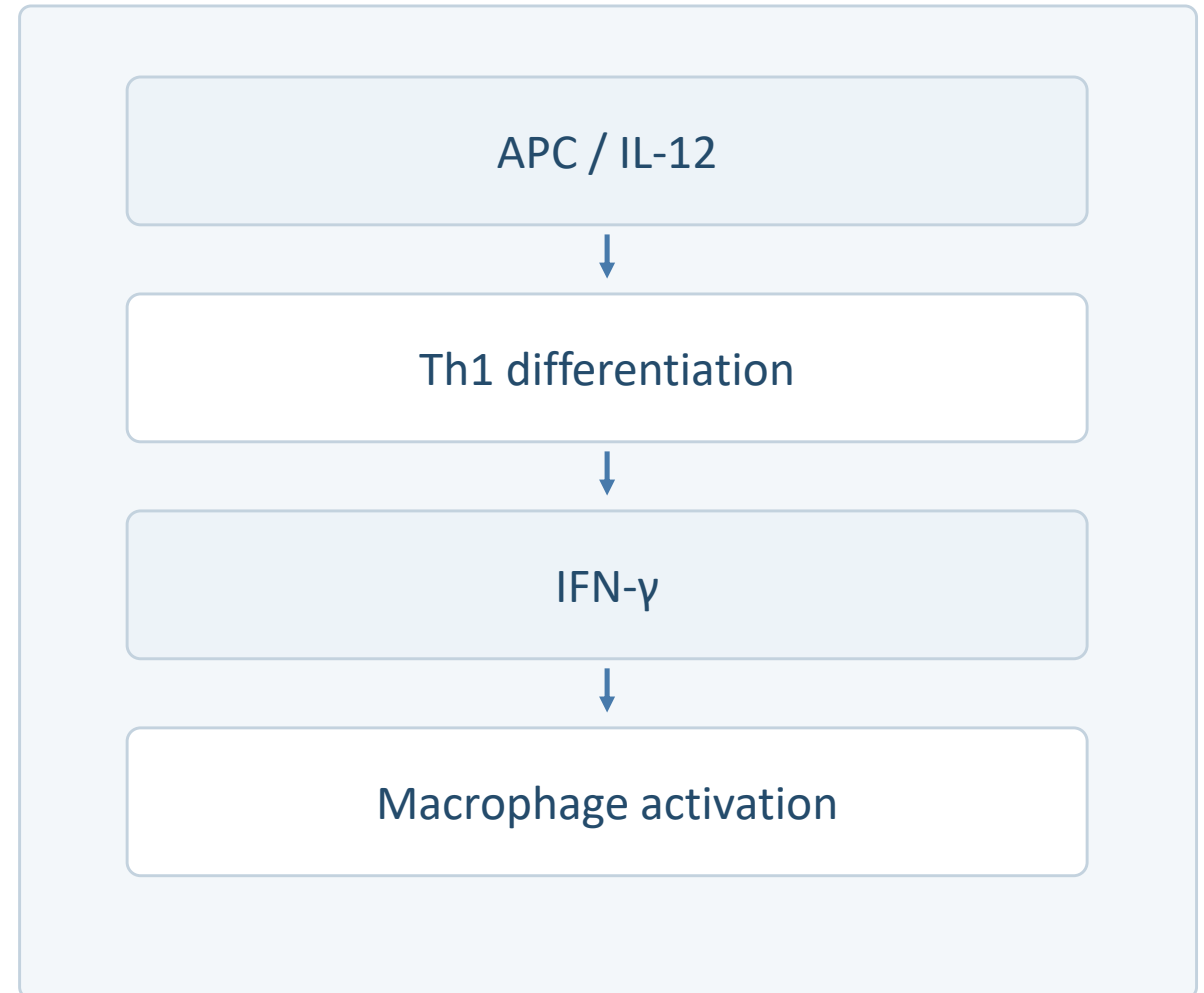
Type I IFNs: Antiviral

IFN- γ : Macrophage
activation

Compare the biological roles

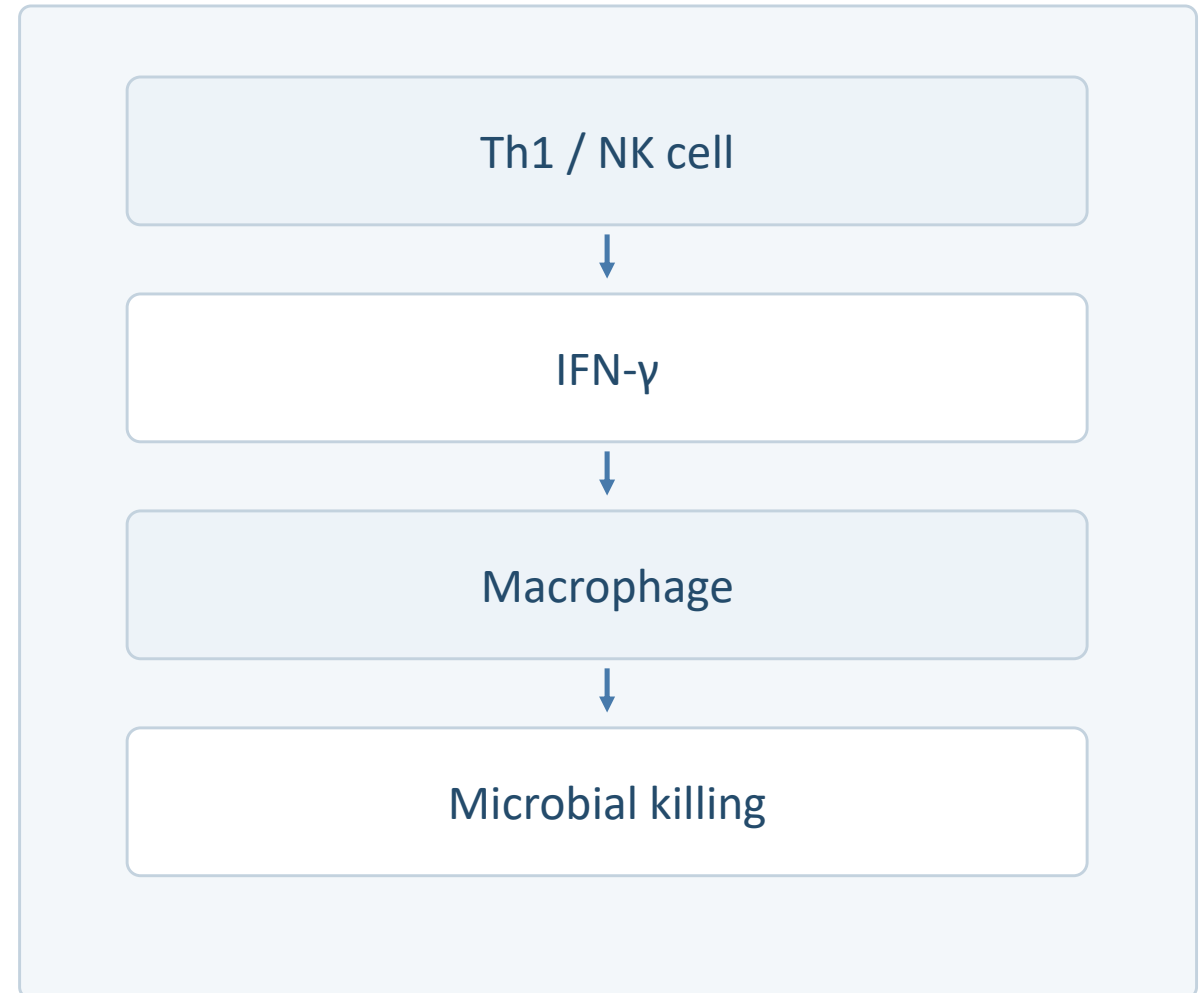
IL-12 connects sensing to cell-mediated defense

- Macrophages and dendritic cells secrete IL-12 in relevant infections.
- IL-12 promotes development of Th1 responses.
- Th1 cells subsequently release IFN- γ to activate macrophages.



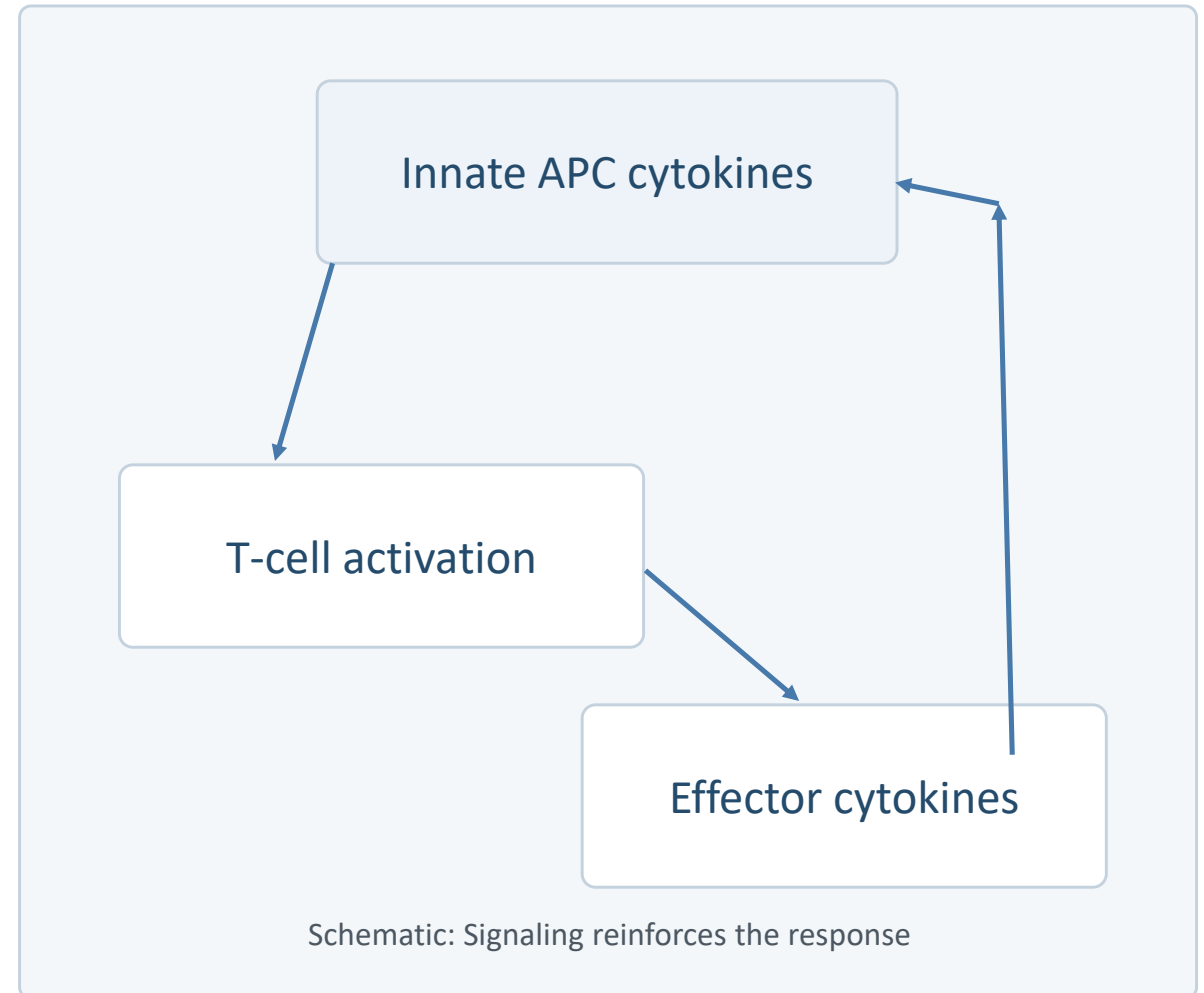
IFN- γ activates macrophages

- NK cells and T lymphocytes are important sources of IFN- γ .
- IFN- γ increases macrophage capacity to kill ingested microbes.
- Th1-derived IFN- γ cooperates with CD40-dependent signals for classical macrophage activation.



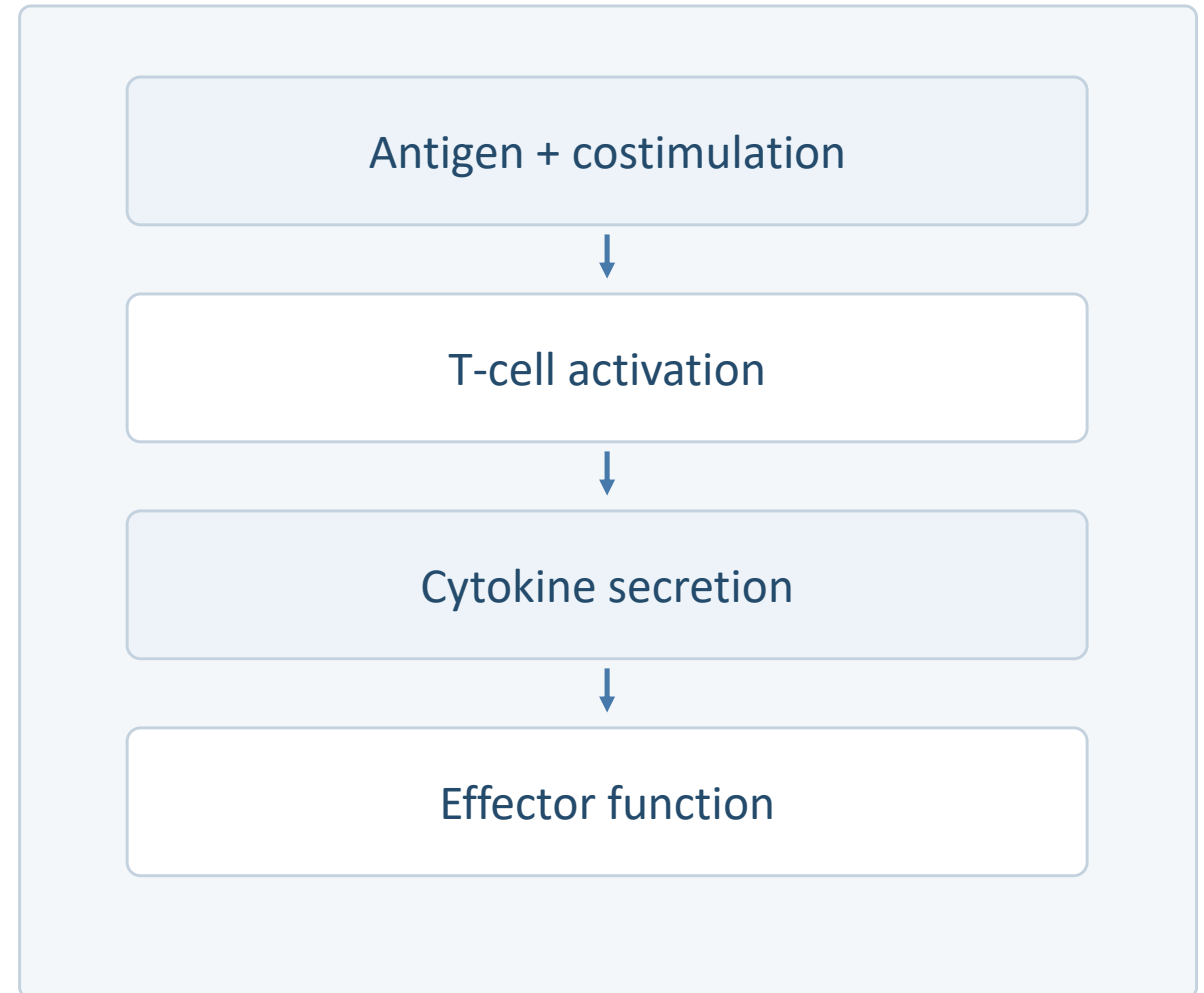
Innate and adaptive signals reinforce one another

- Innate macrophage and dendritic-cell signals shape the T-cell response.
- Activated T cells send cytokine signals back to phagocytes.
- This cooperation strengthens defense but may perpetuate chronic inflammation.



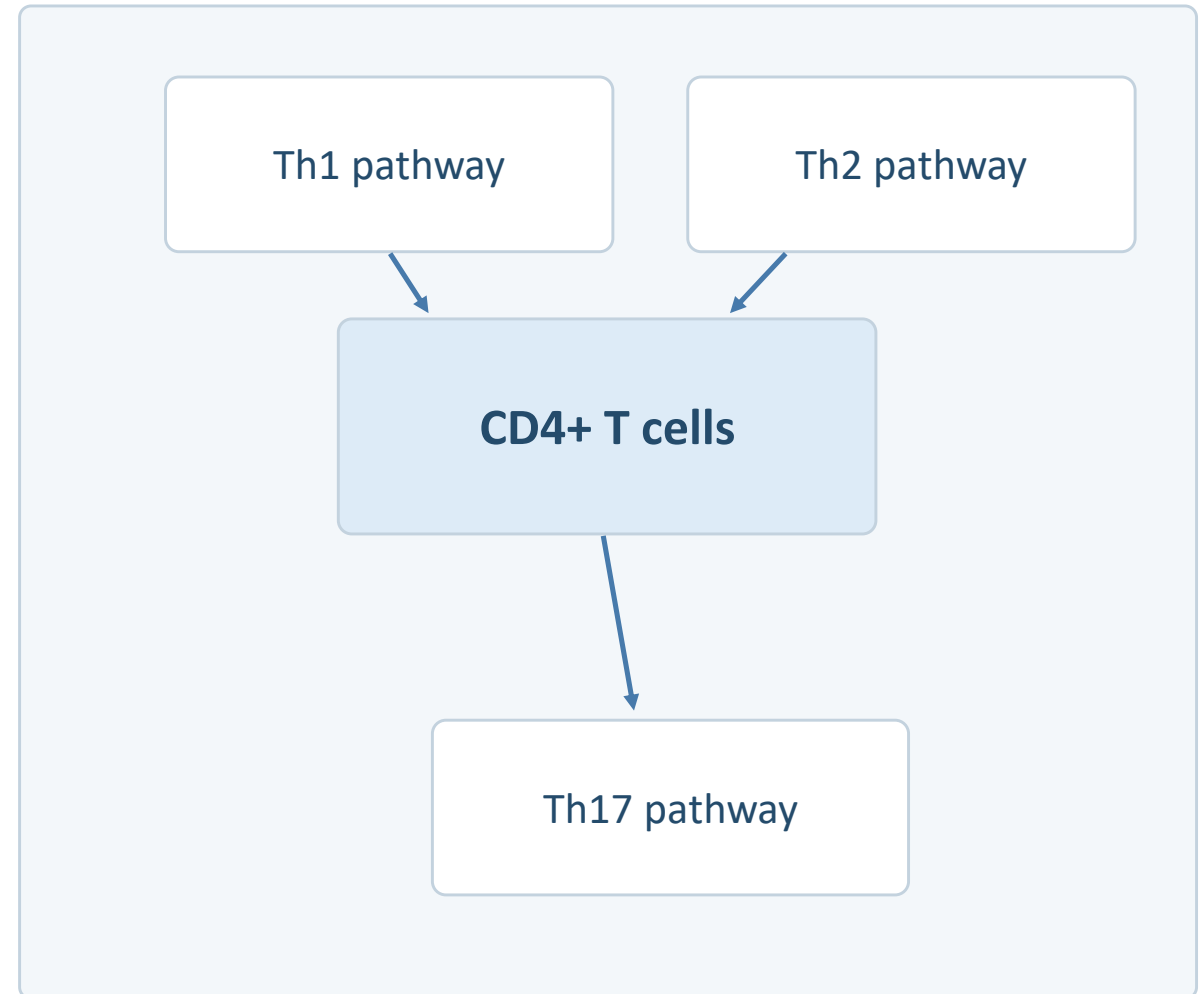
Antigen recognition is only the first step

- T-cell activation requires recognition of antigen and costimulatory context.
- Early helper T-cell cytokine production supports proliferation.
- Differentiated effector T cells then deliver specialized cytokine programs.



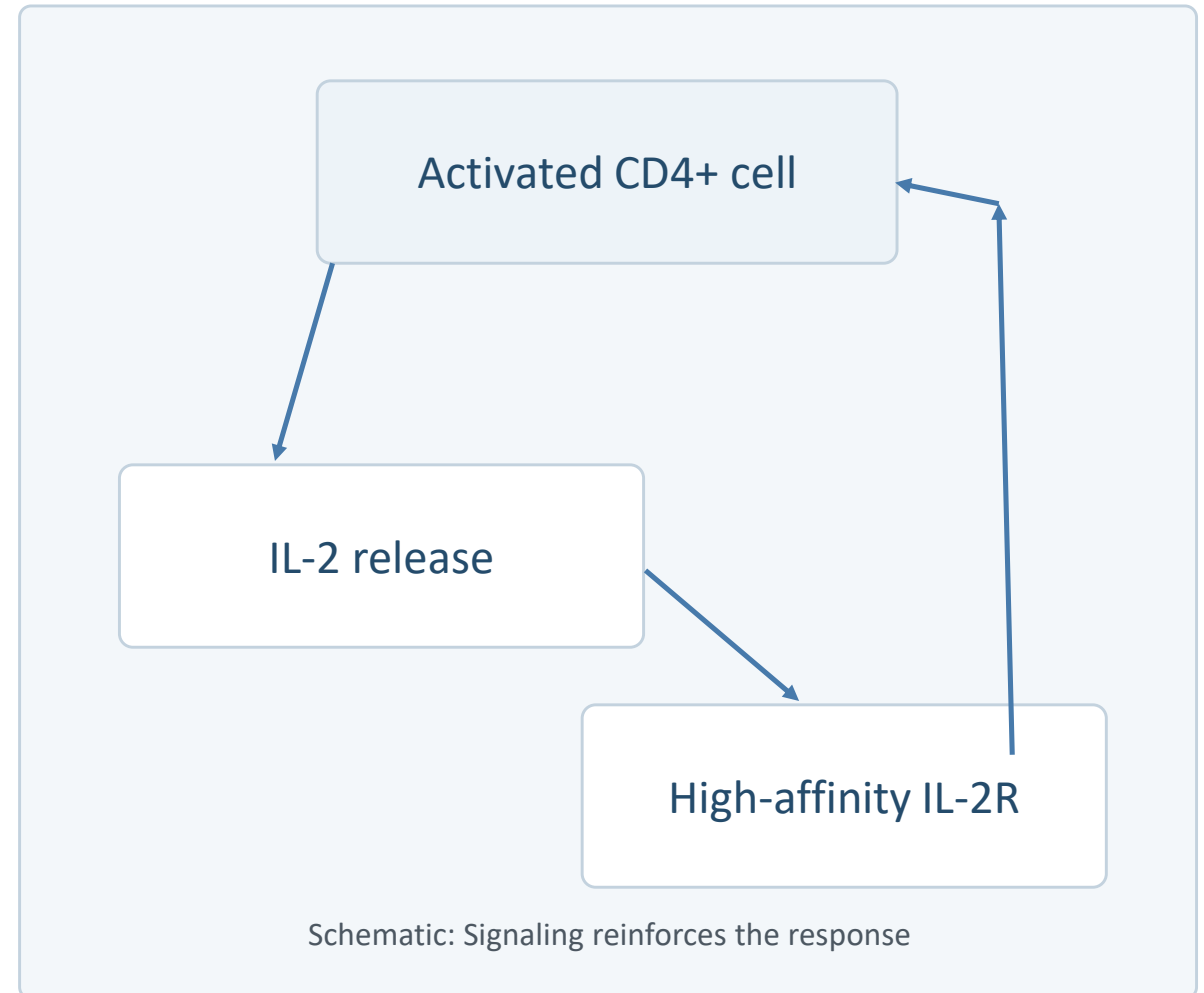
CD4 T cells coordinate adaptive immunity

- Activated CD4+ helper cells are major producers of adaptive cytokines.
- Distinct helper subsets release different characteristic cytokines.
- Their cytokine programs determine whether macrophages, eosinophils, neutrophils, or B cells are emphasized.



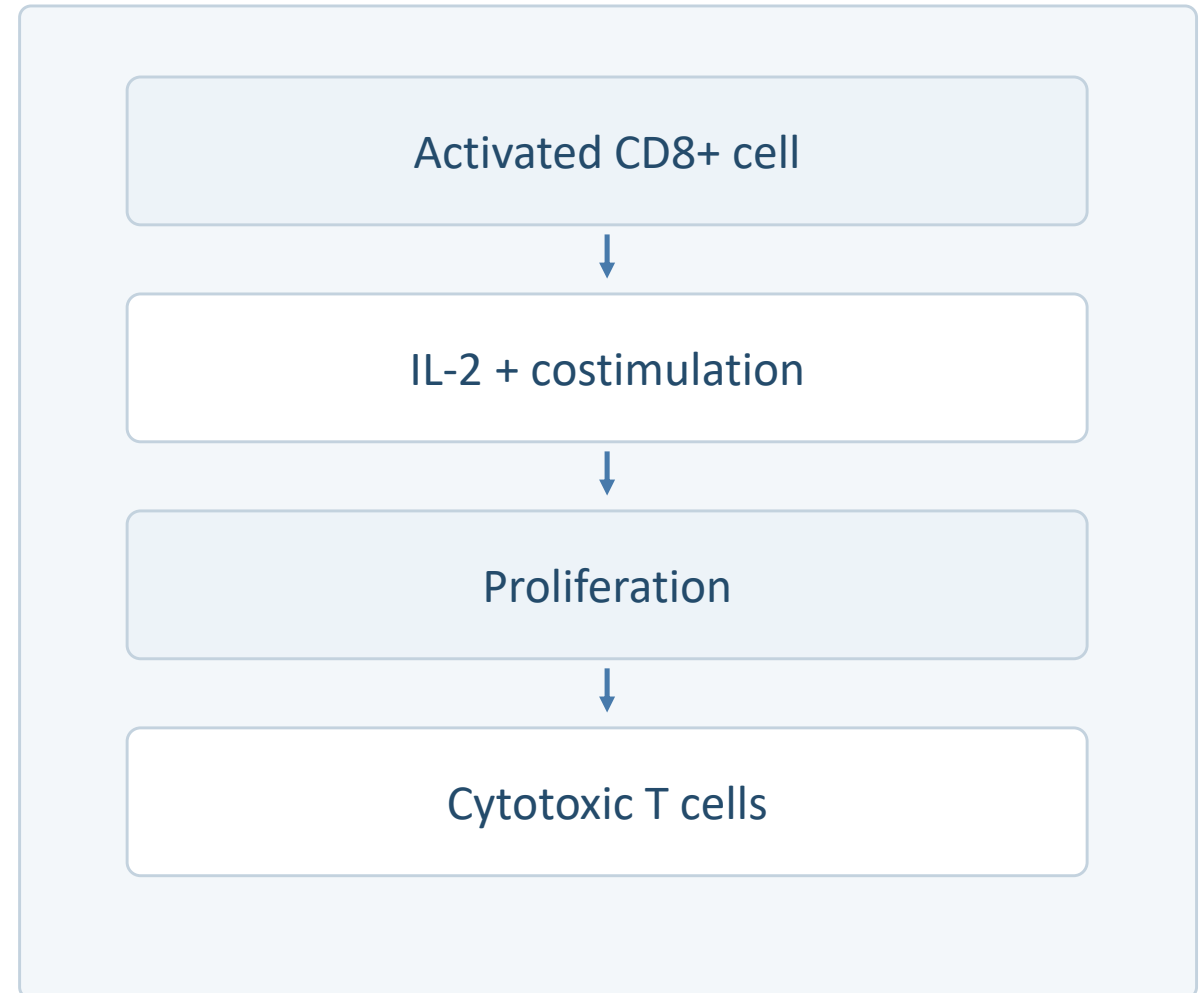
IL-2 supports clonal expansion

- Activated CD4+ T cells produce IL-2 and upregulate high-affinity IL-2 receptors.
- IL-2 then acts as an autocrine T-cell growth factor.
- The result is expansion of antigen-specific lymphocytes.



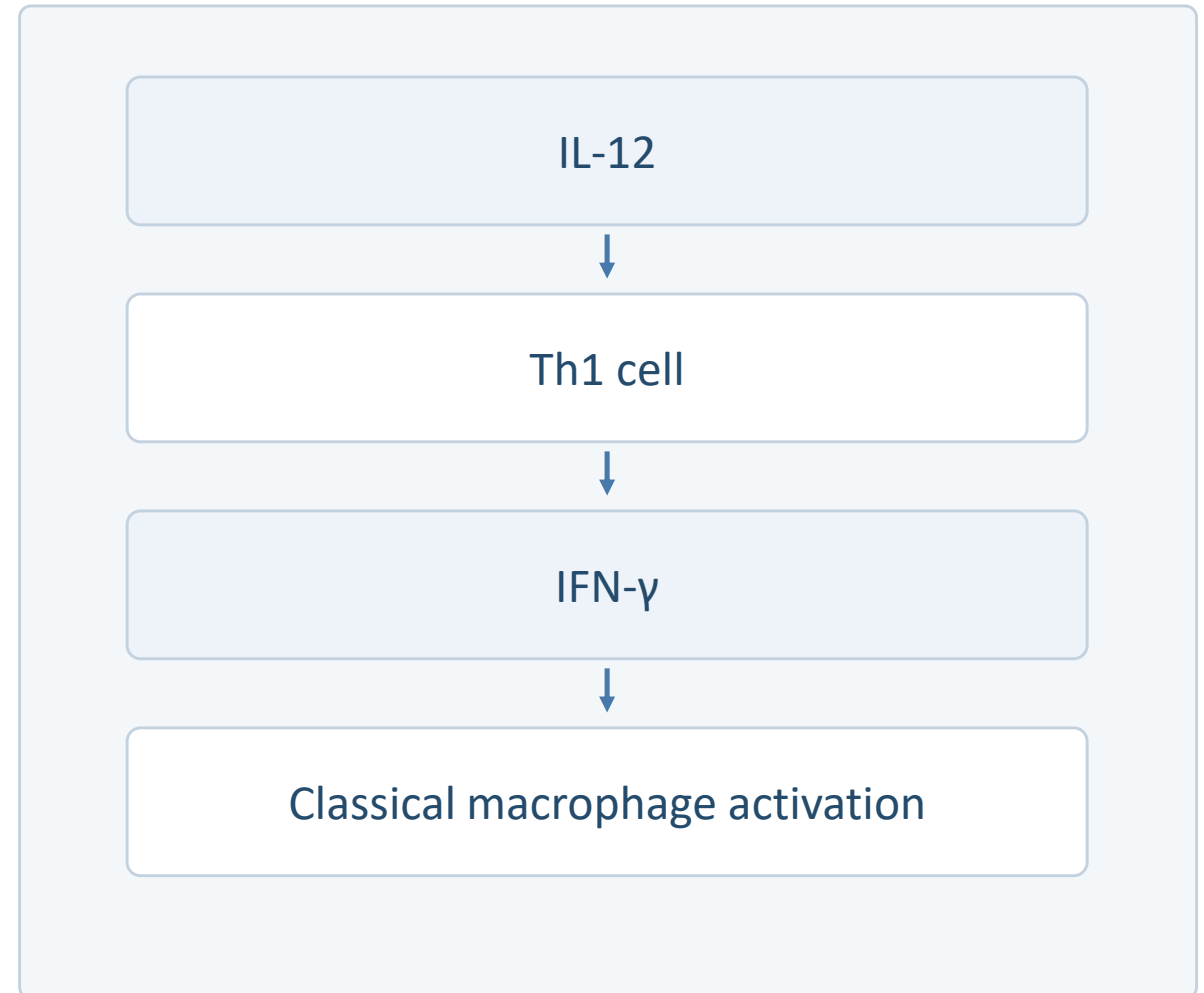
IL-2 also supports CD8 responses

- CD8+ T cells receive activating antigen and costimulatory signals.
- Costimulation and IL-2 promote their proliferation.
- The expanded cells differentiate into cytotoxic effector T lymphocytes.



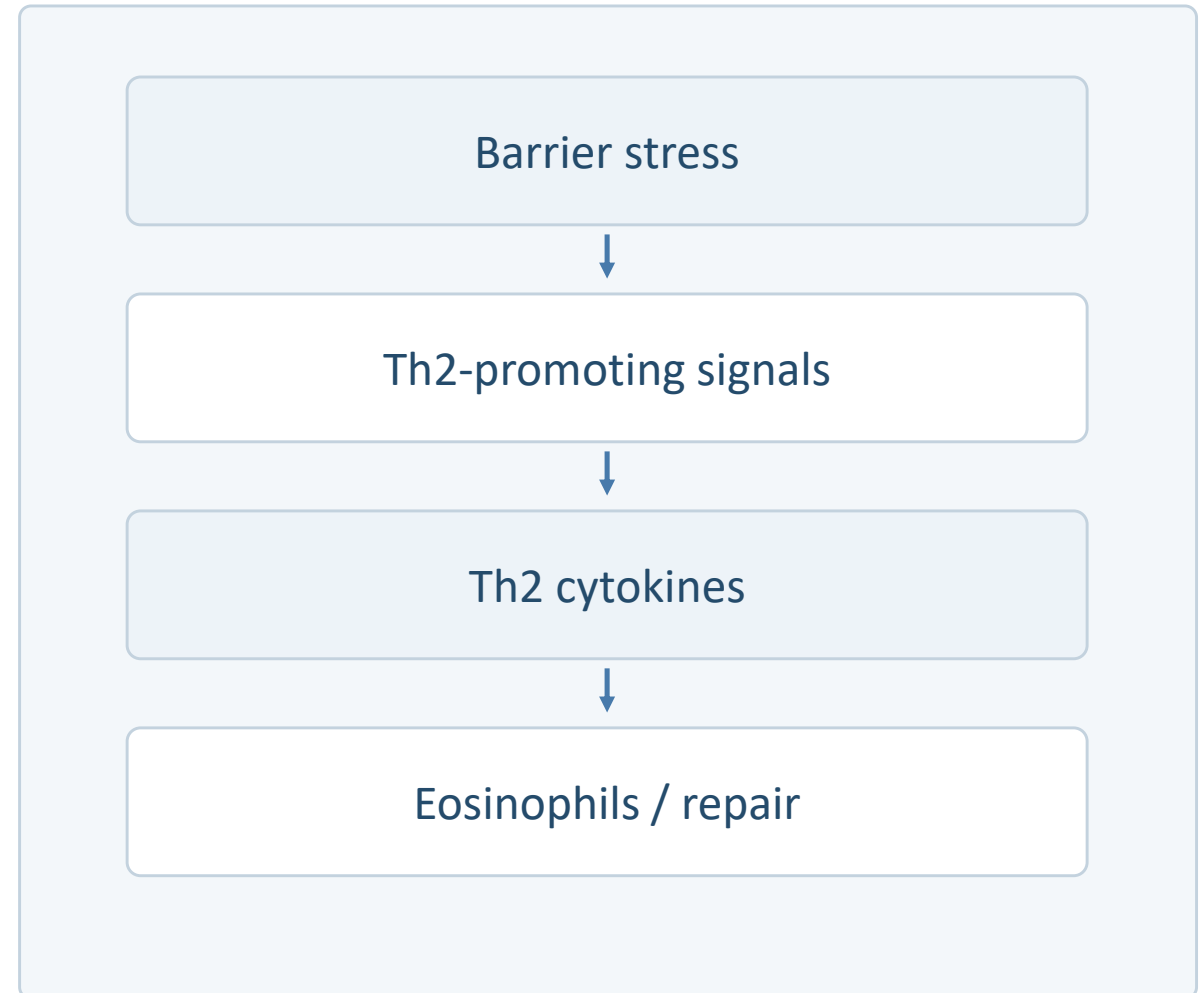
Th1 immunity targets intracellular microbes

- IL-12 promotes differentiation toward the Th1 subset.
- Th1 cells produce IFN- γ , which strongly activates macrophages.
- This program is important when pathogens survive within phagocytes.



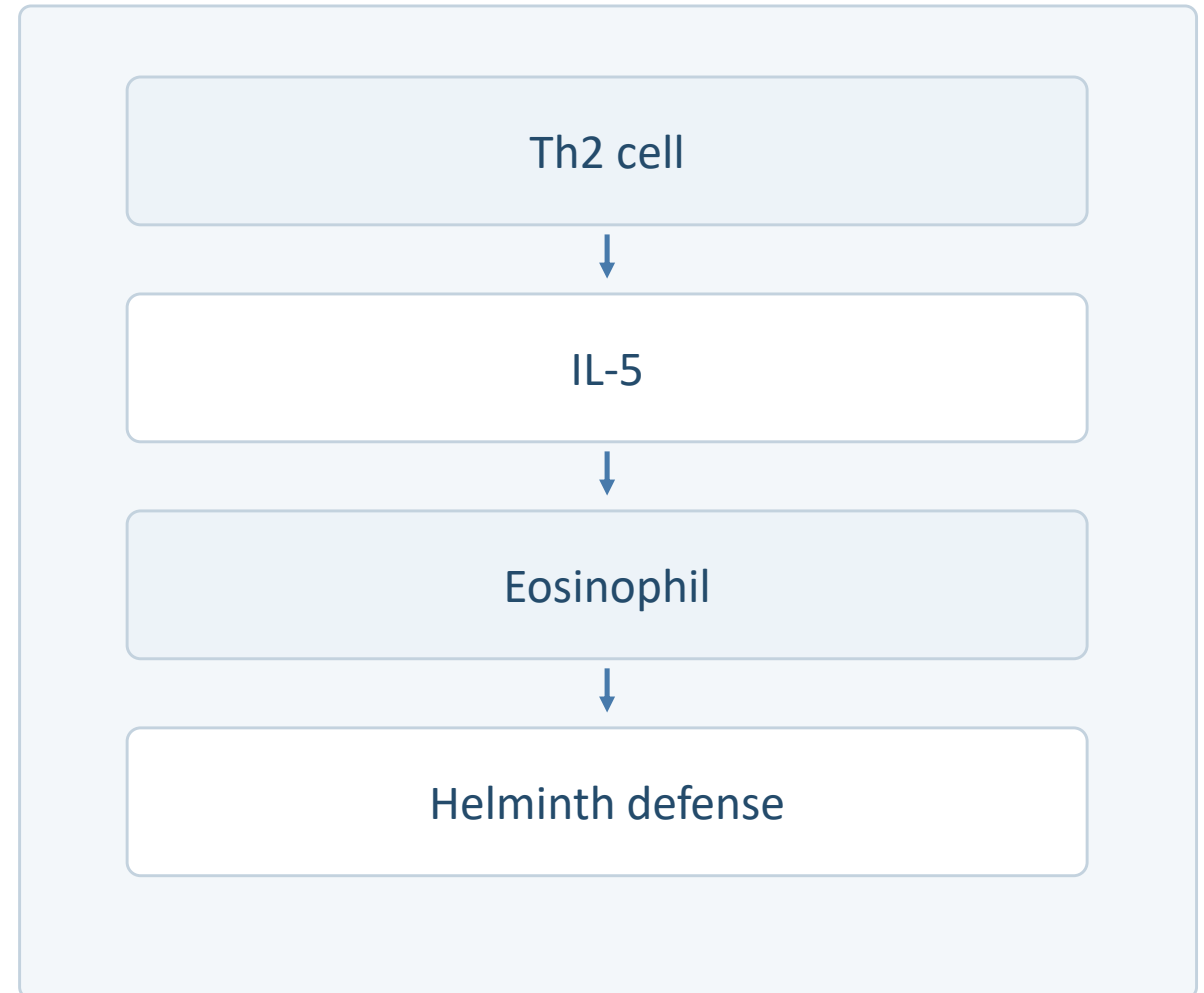
Th2 immunity emphasizes barrier defense

- Damaged epithelia release signals including IL-25, IL-33, and TSLP.
- Th2 effector cells release IL-4, IL-5, and IL-13.
- These cytokines support eosinophil responses and alternative macrophage activation.



IL-5 links helper T cells to eosinophils

- Th2 cells produce IL-5.
- IL-5 activates eosinophils involved in defense against helminths.
- A similar cytokine program may contribute to allergic inflammation.



IL-4 and IL-13 reshape tissue responses

- Th2-derived IL-4 and IL-13 induce alternative macrophage activation.
- This macrophage program is associated with tissue repair and fibrosis.
- The same cytokine environment is associated with IgE-mediated immunity.

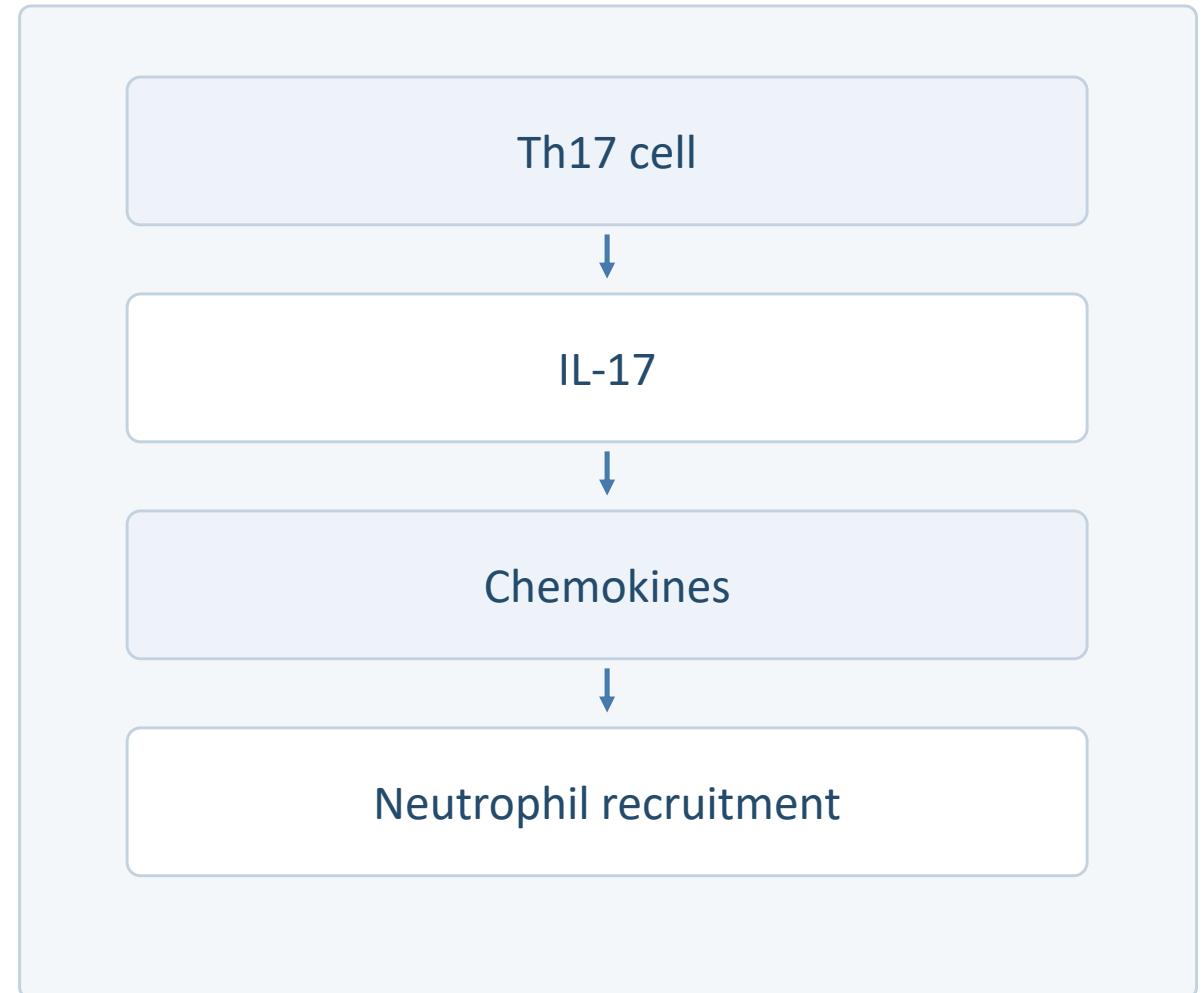
Alternative activation

Repair / fibrosis

IgE-related responses

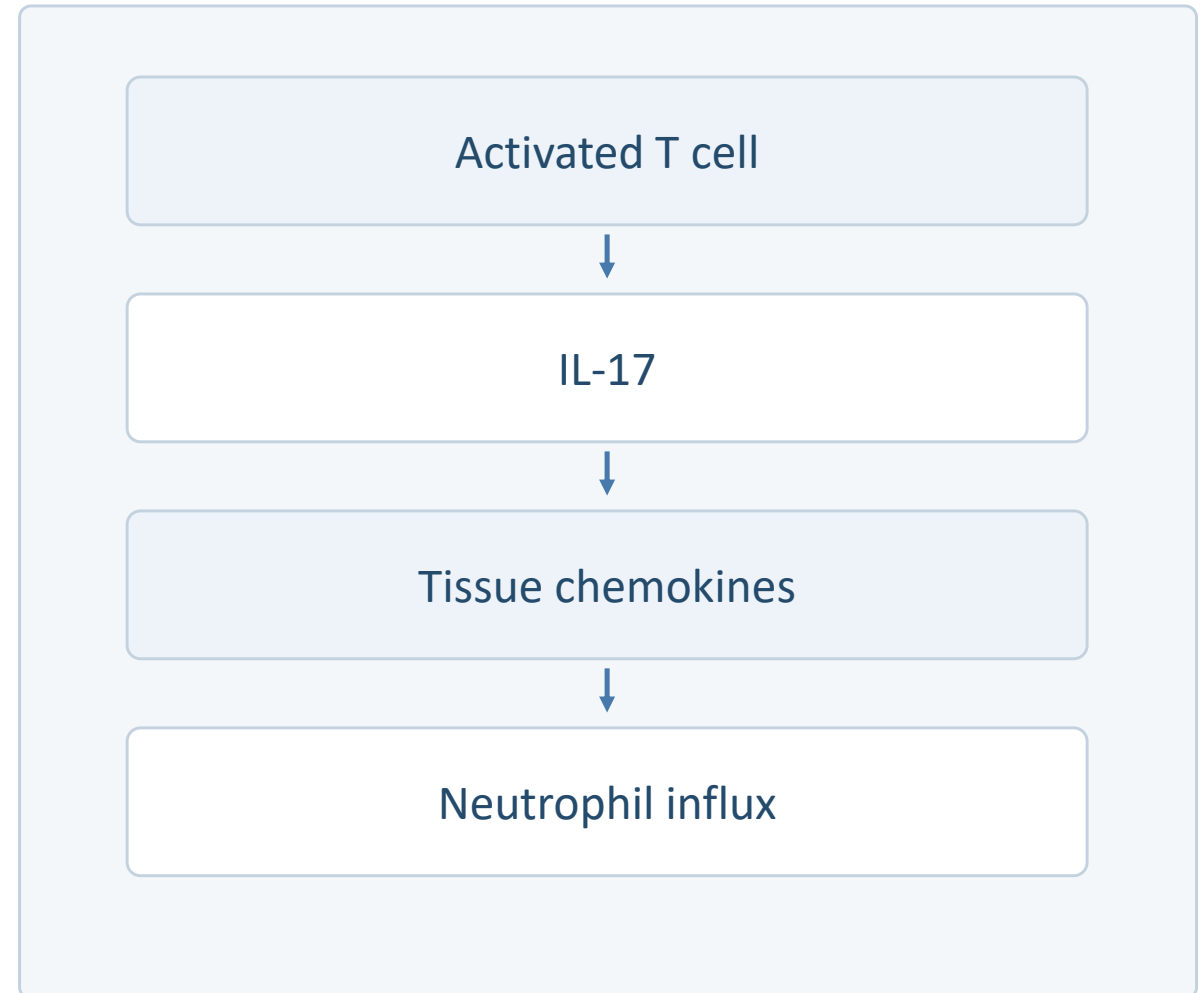
Th17 immunity recruits phagocytes

- Th17 cells produce IL-17 as a signature effector cytokine.
- IL-17 induces chemokines that recruit neutrophils and monocytes.
- This response is prominent in defense against extracellular bacteria and fungi.



IL-17 links lymphocytes to acute inflammation

- A lymphocyte-derived cytokine can provoke a neutrophil-rich tissue response.
- IL-17 acts in part by stimulating chemokine production by other cells.
- Thus, adaptive immunity can amplify the cellular pattern typical of acute inflammation.



Helper programs are functionally distinct

- Th1: IFN- γ –dominated macrophage activation.
- Th2: IL-4, IL-5, and IL-13–associated eosinophilic and repair responses.
- Th17: IL-17–dependent recruitment of neutrophils and monocytes.

Th1 → macrophages

Th2 → eosinophils

Th17 → neutrophils

Early tissue cues shape helper-cell fate

- Intracellular infection favors IL-12 and a Th1-type response.
- Barrier epithelial stress provides signals promoting Th2 immunity.
- Fungal and some bacterial stimuli induce cytokine environments favoring Th17 responses.

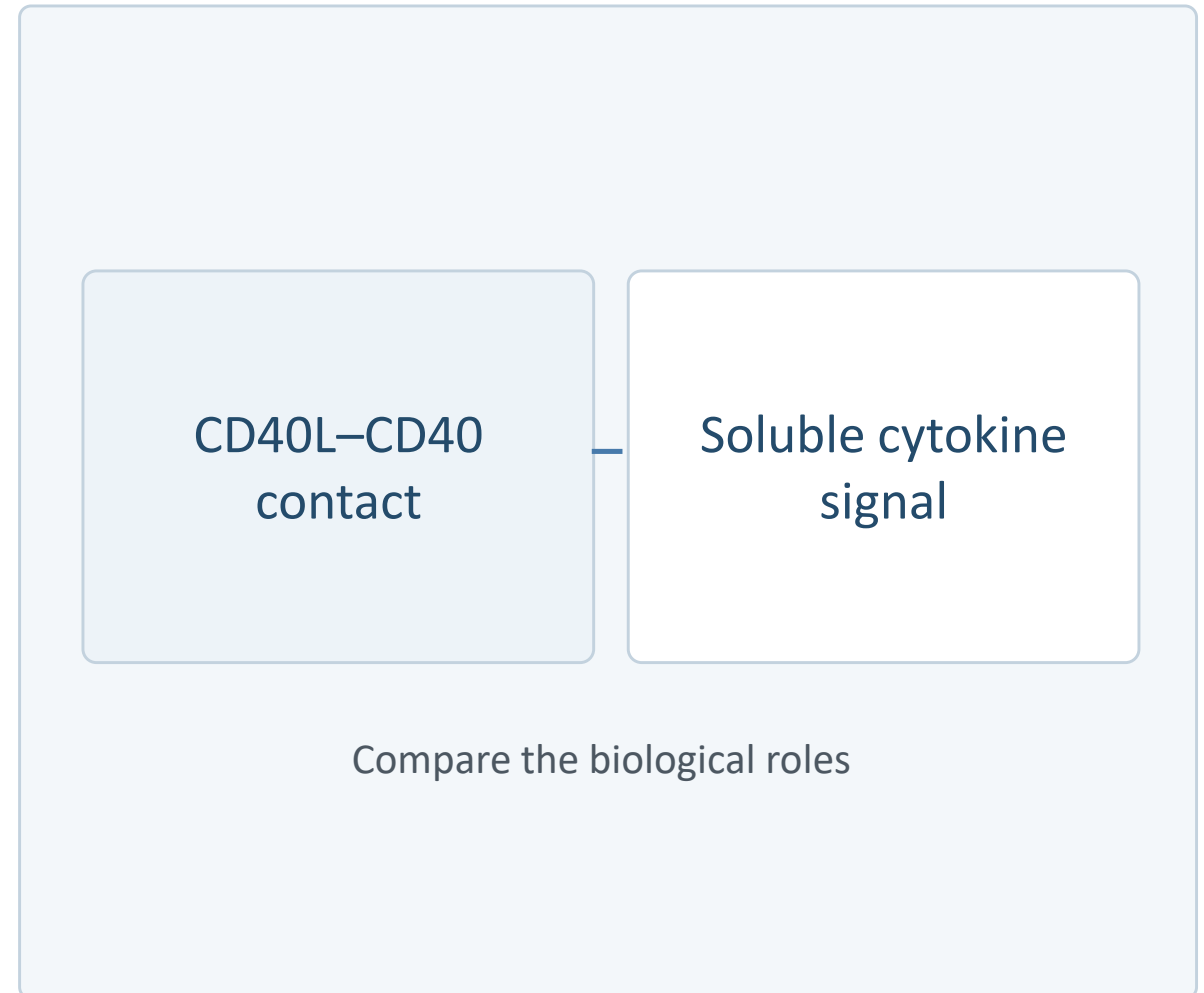
IL-12 / Th1

Epithelial cues / Th2

Innate cues / Th17

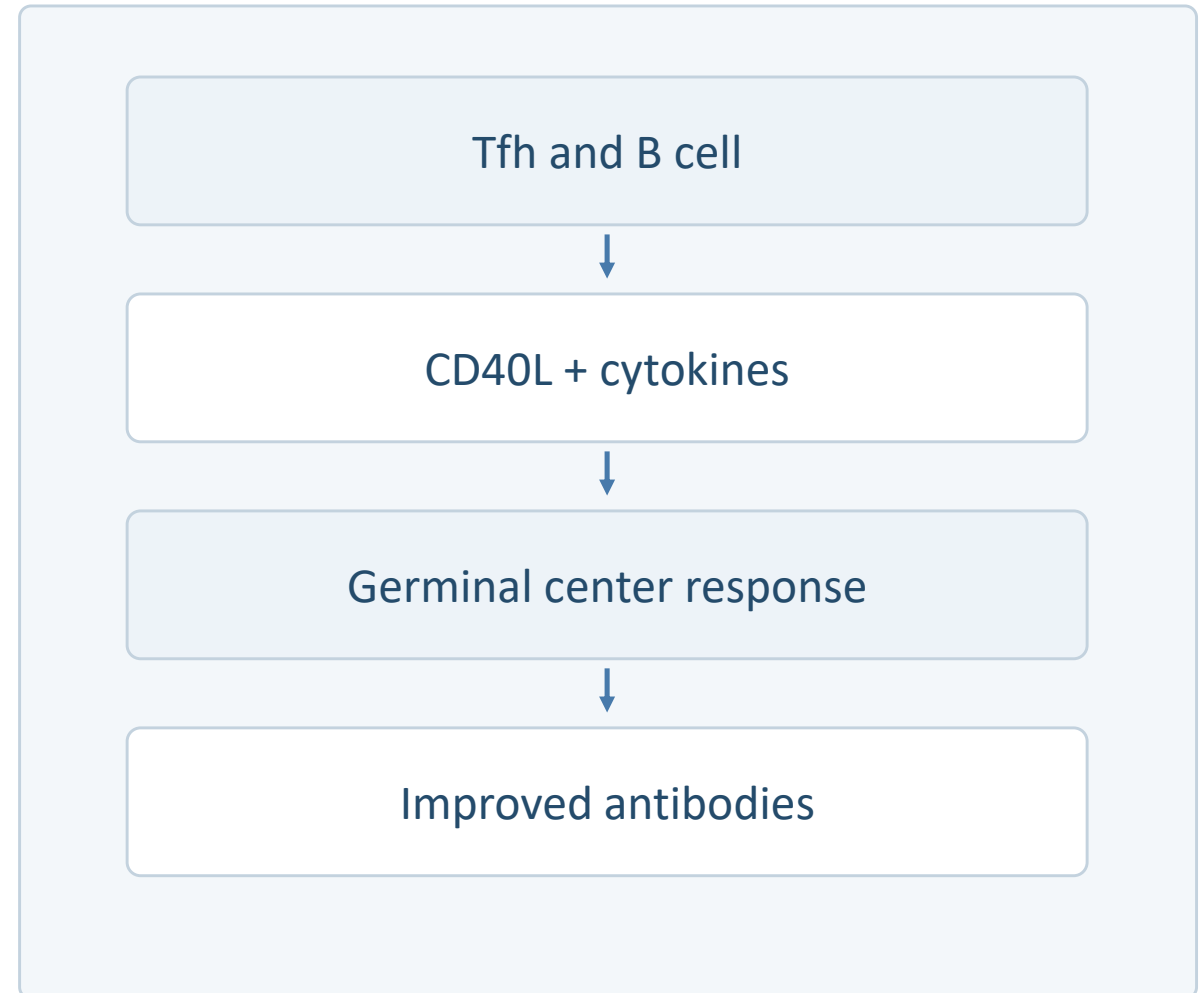
Cytokines cooperate with contact-dependent help

- T helper cells also express CD40 ligand when engaging macrophages or B cells.
- CD40 signaling and cytokines work together to activate the responding cell.
- Cytokines should not be represented as replacing antigen recognition or cell contact.



Tfh-cell help improves antibody responses

- T follicular helper cells reside in lymphoid follicles with B cells.
- Their helper signals include cytokines as well as CD40 ligand.
- T-dependent responses undergo class switching and affinity maturation.



Regulatory cytokines restrain responses

- IL-10 and TGF- β are prominent cytokines that limit immune reactions.
- Immune responses require active downregulation after their protective purpose is served.
- Unchecked effector signals can sustain tissue-damaging inflammation.

Effector cytokines

IL-10 / TGF- β
restraint

Compare the biological roles

Effective immunity needs both accelerator and brake

- Inflammatory cytokines help eliminate pathogens.
- Regulatory cytokines prevent excessive or persistent responses.
- The clinical outcome depends on the balance between host defense and collateral injury.

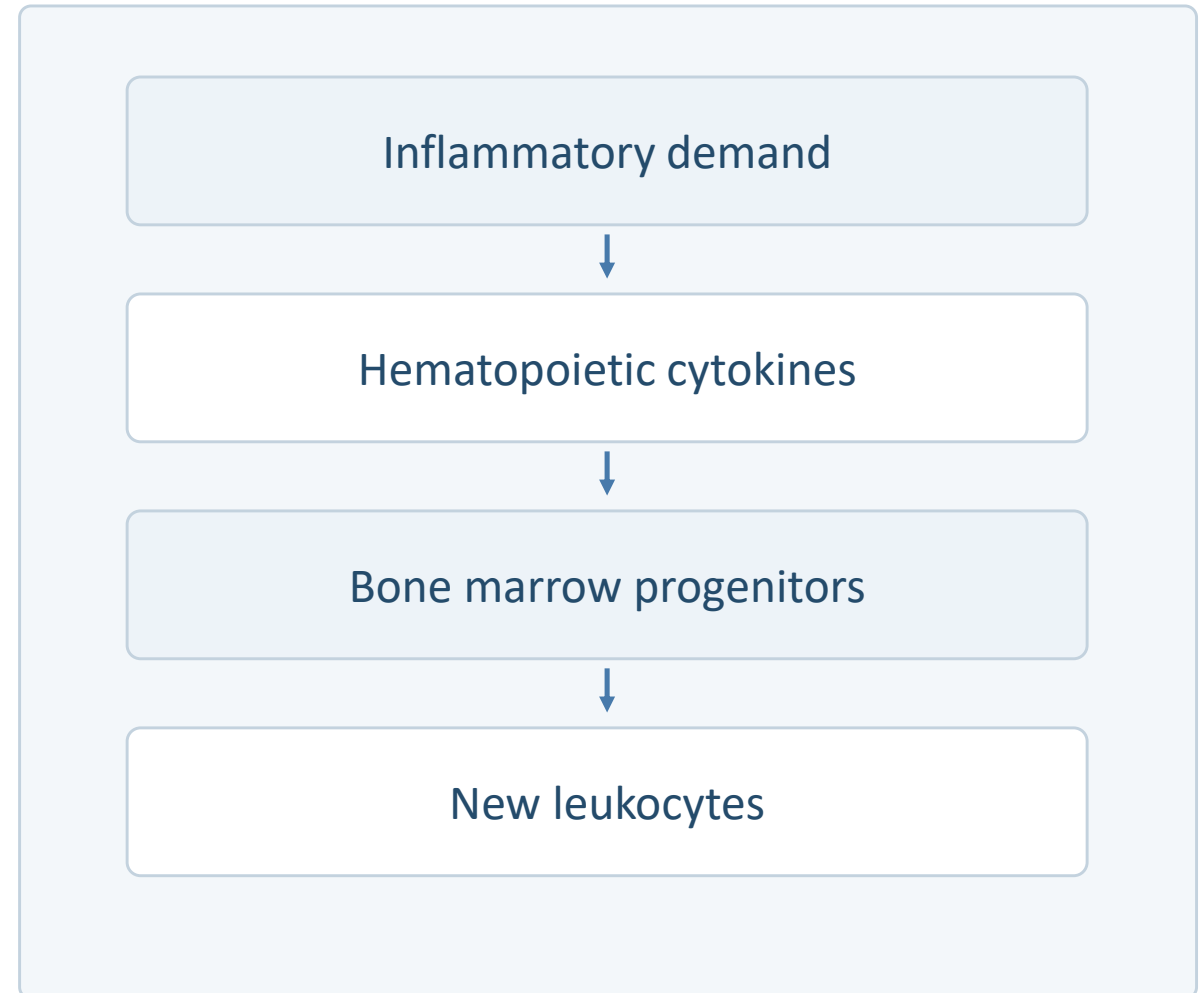
Host-defense signals

Regulatory signals

Compare the biological roles

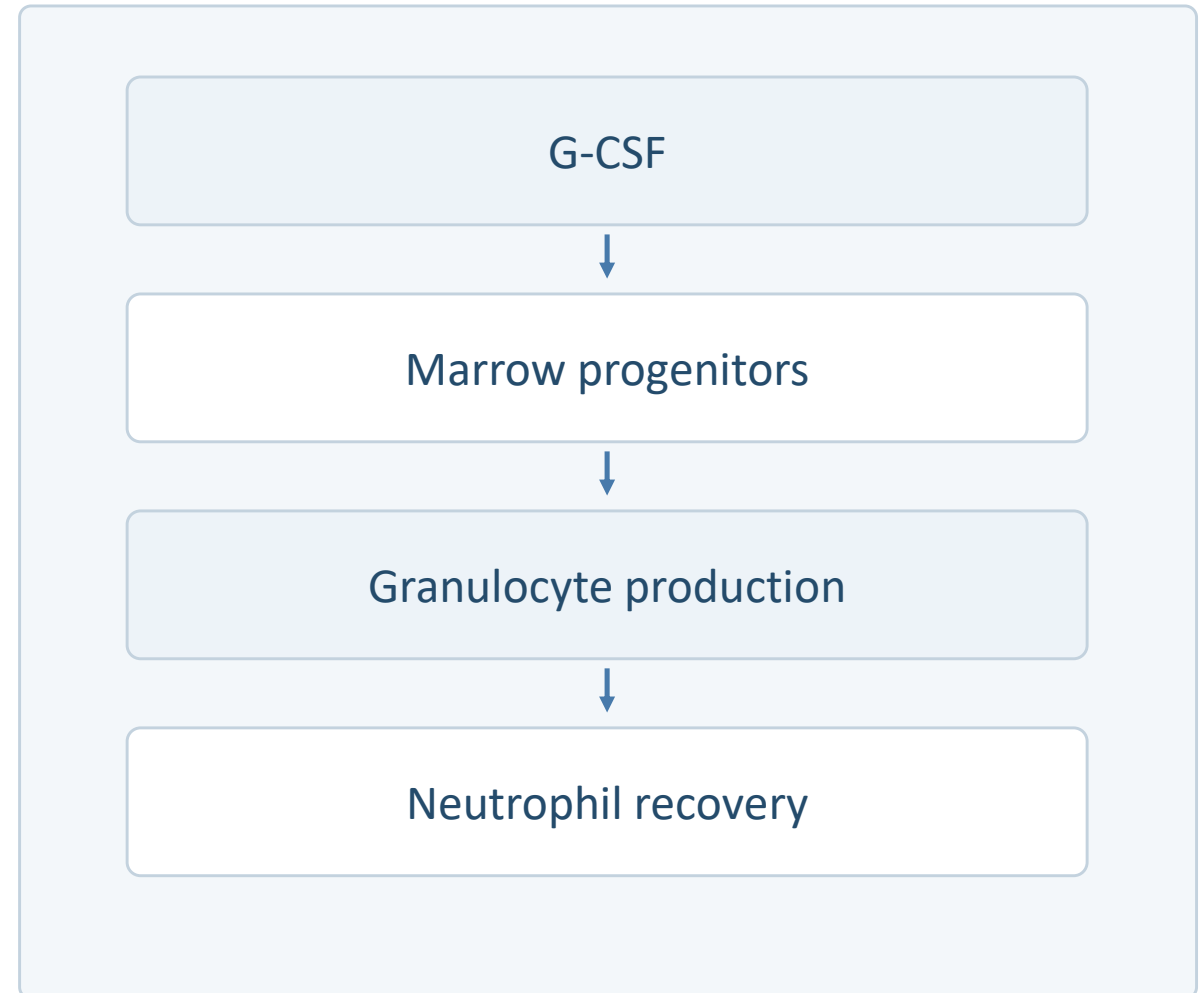
CSFs connect inflammation to bone marrow

- Some cytokines stimulate growth of hematopoietic precursors.
- They increase leukocyte production during immune and inflammatory responses.
- This replenishes cells consumed or lost during inflammatory defense.



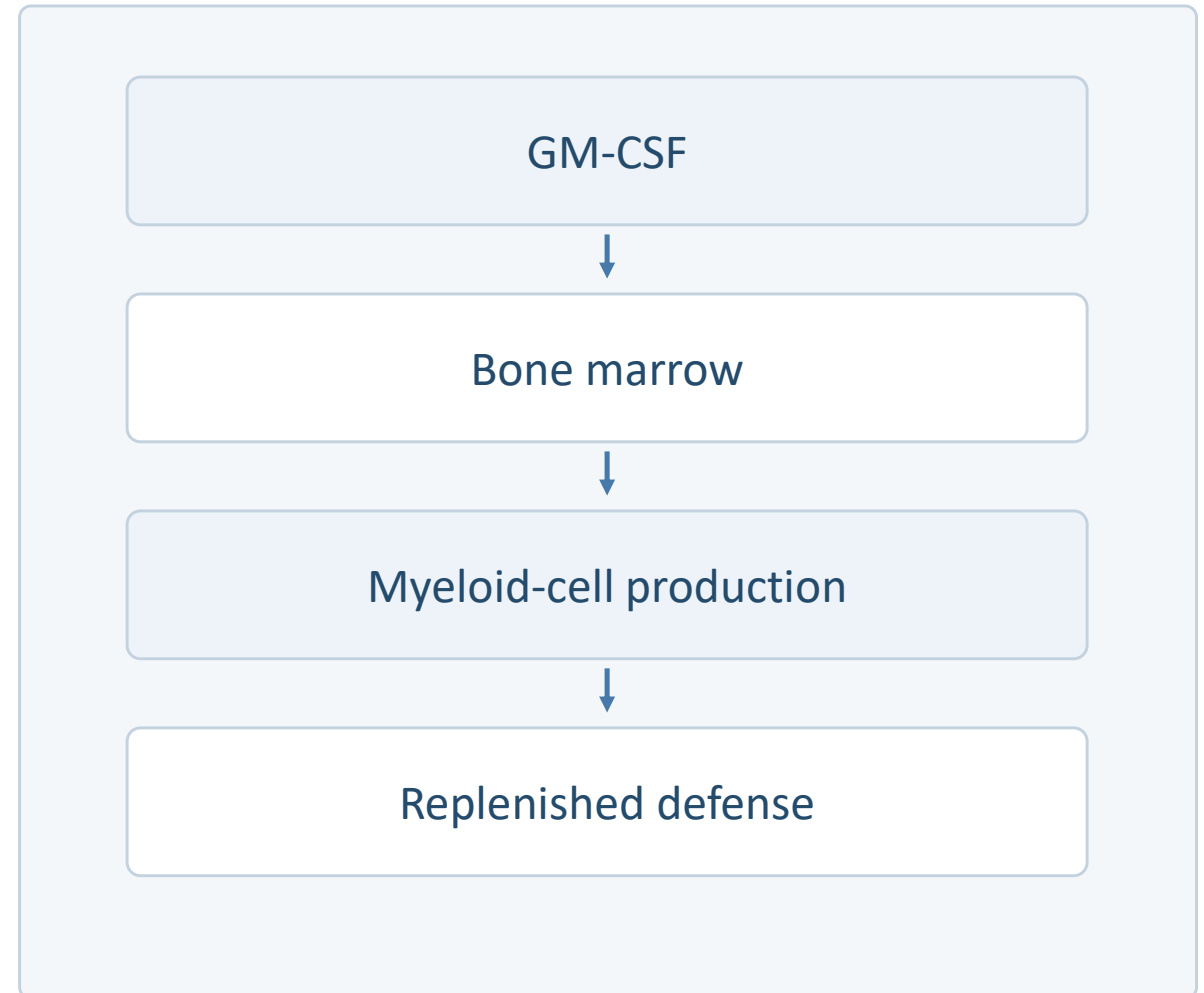
G-CSF supports granulocyte production

- G-CSF is a colony-stimulating factor involved in leukocyte production.
- It promotes expansion of the granulocytic compartment.
- Clinically administered G-CSF is used to support neutrophil recovery in selected settings.



GM-CSF supports hematopoiesis

- GM-CSF is a cytokine with colony-stimulating activity.
- Macrophages, T cells, and marrow stromal cells are among relevant sources of hematopoietic cytokines.
- Therapeutic administration can enhance cytokine-dependent blood-cell production.



IL-3 belongs to the hematopoietic group

- IL-3 is listed among colony-stimulating cytokines.
- These factors support increased blood-cell production when leukocyte demand rises.
- Their role differs from TNF/IL-1-mediated endothelial activation.

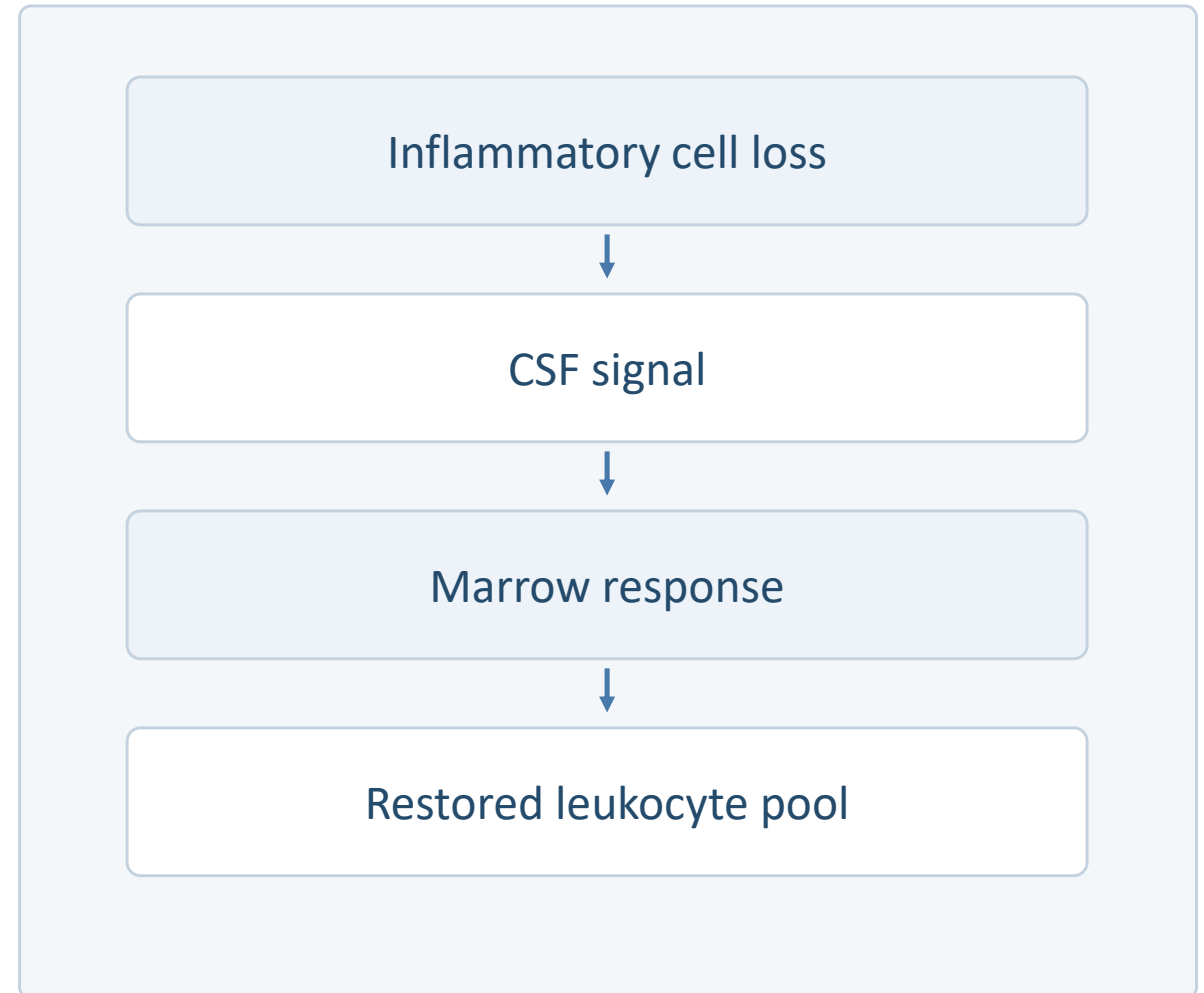
IL-3: Marrow
support

TNF/IL-1:
Inflammation

Compare the biological roles

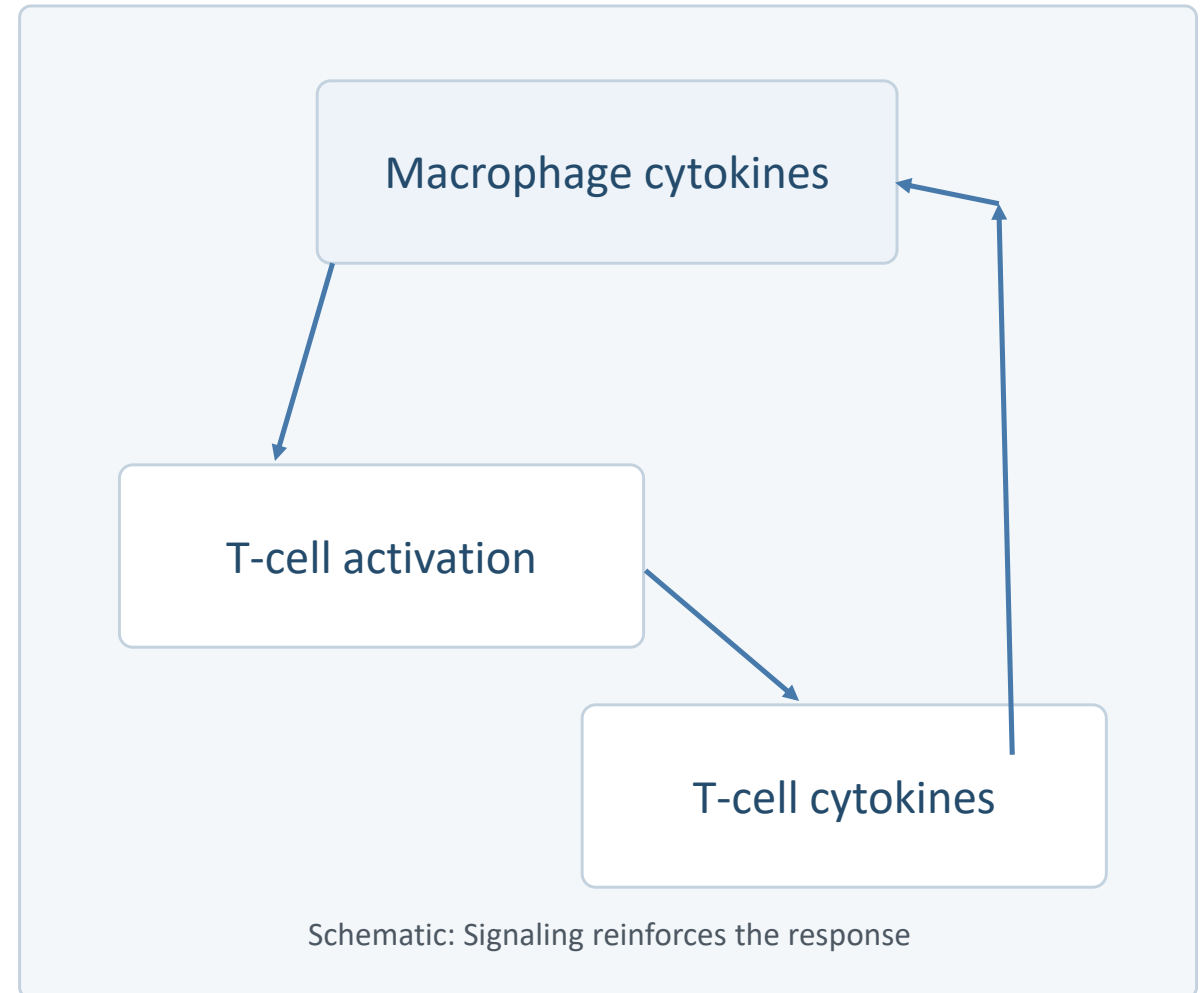
Cytokines scale leukocyte supply to demand

- Inflammation both recruits cells into tissues and consumes short-lived leukocytes.
- CSFs increase marrow output to replenish the peripheral pool.
- Defense therefore depends on recruitment signals and production signals working together.



Chronic inflammation can become self-sustaining

- Macrophages and activated lymphocytes reciprocally stimulate one another.
- Their cytokines drive recruitment, activation, and tissue injury.
- Persistent stimuli can maintain this network long after the initial response.



Systemic cytokines have costs

- TNF, IL-1, and IL-6 induce physiological acute-phase responses.
- Persistent excessive inflammatory signaling can produce illness and tissue damage.
- Mechanisms beneficial in short host defense may be harmful when prolonged.

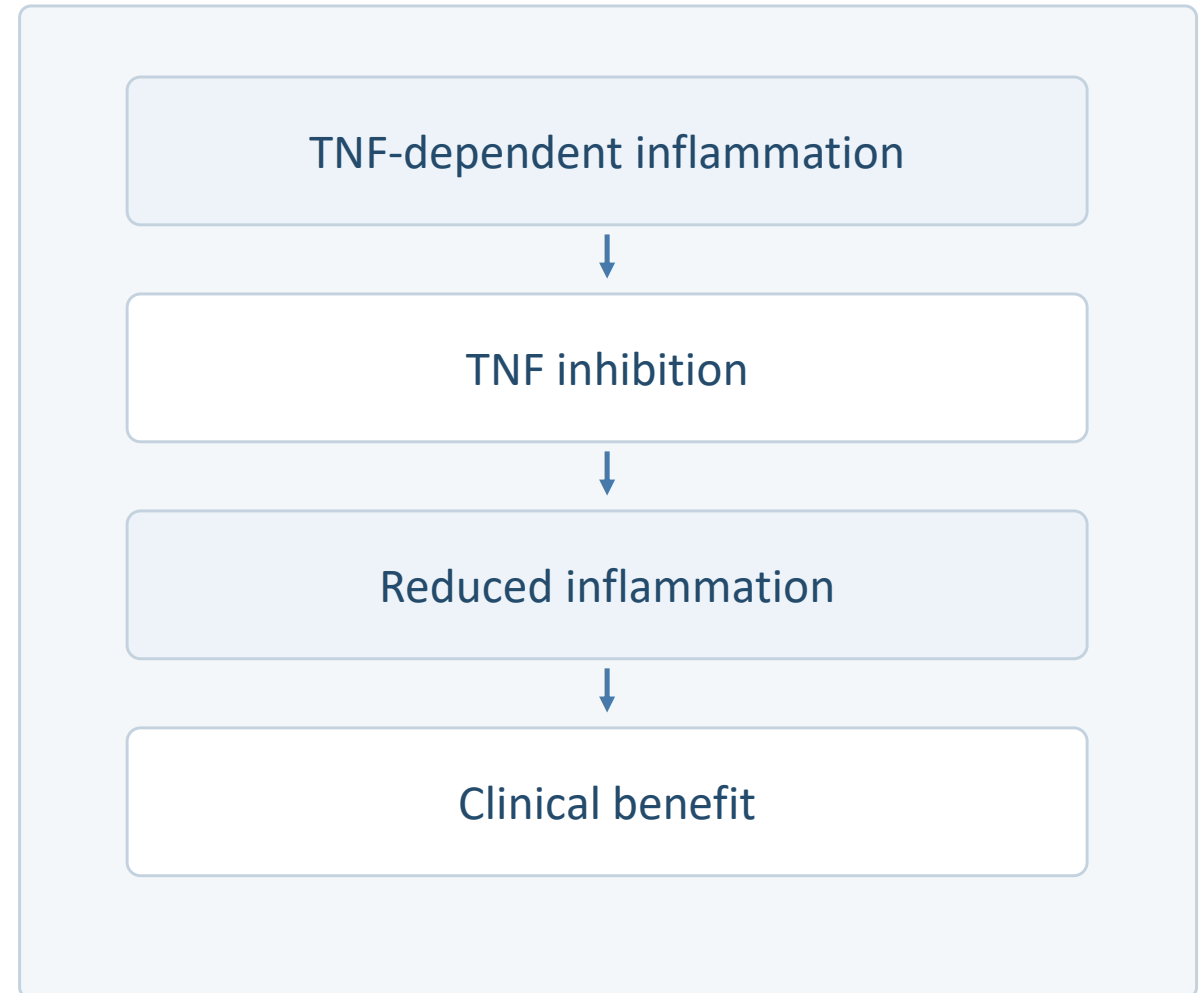
Local defense

Systemic response

Pathologic persistence

Anti-TNF treatment validates cytokine targeting

- TNF contributes to tissue-damaging chronic inflammatory diseases.
- TNF antagonists can yield substantial clinical responses in rheumatoid arthritis.
- Treatment demonstrates that cytokine blockade can interrupt a disease-driving mechanism.



Anti-cytokine therapies target distinct axes

- The Robbins inflammation chapter describes IL-6-receptor antagonism in juvenile arthritis.
- It also describes IL-17 antagonism in psoriasis.
- The target should match the disease-relevant inflammatory pathway.

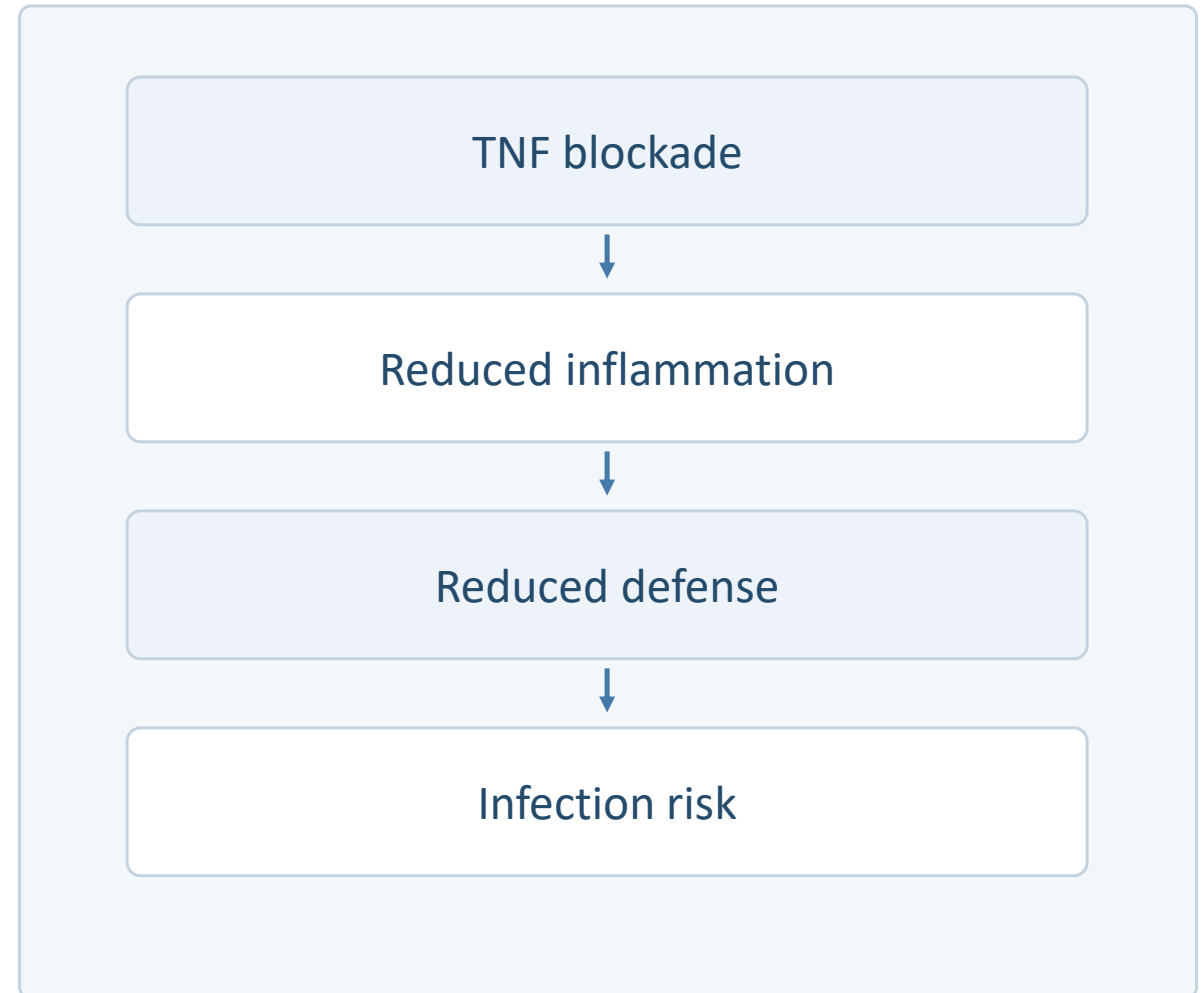
IL-6R inhibition

IL-17 inhibition

Compare the biological roles

Cytokine blockade has host-defense tradeoffs

- TNF contributes to macrophage-mediated protection from intracellular infection.
- TNF inhibition can increase susceptibility to mycobacterial infection.
- Immune-directed therapy requires mechanistic risk assessment, not efficacy alone.



Cytokines can also be administered therapeutically

- Blocking cytokine action reduces an excessive response.
- Administering selected cytokines supports functions dependent on those proteins.
- Hematopoietic support with erythropoietin and GM-CSF as examples.

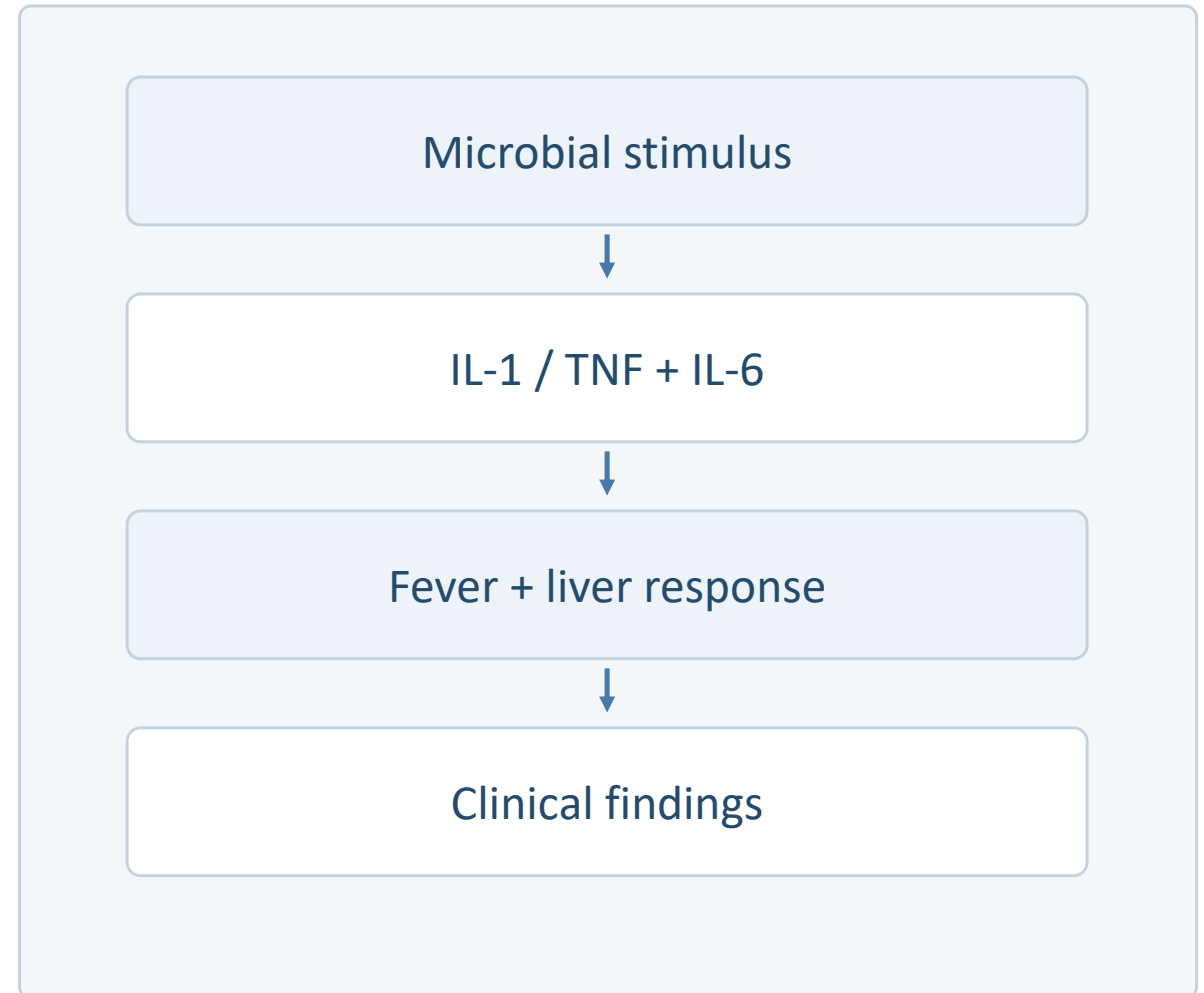
Block: Inflammation

Provide:
Hematopoiesis

Compare the biological roles

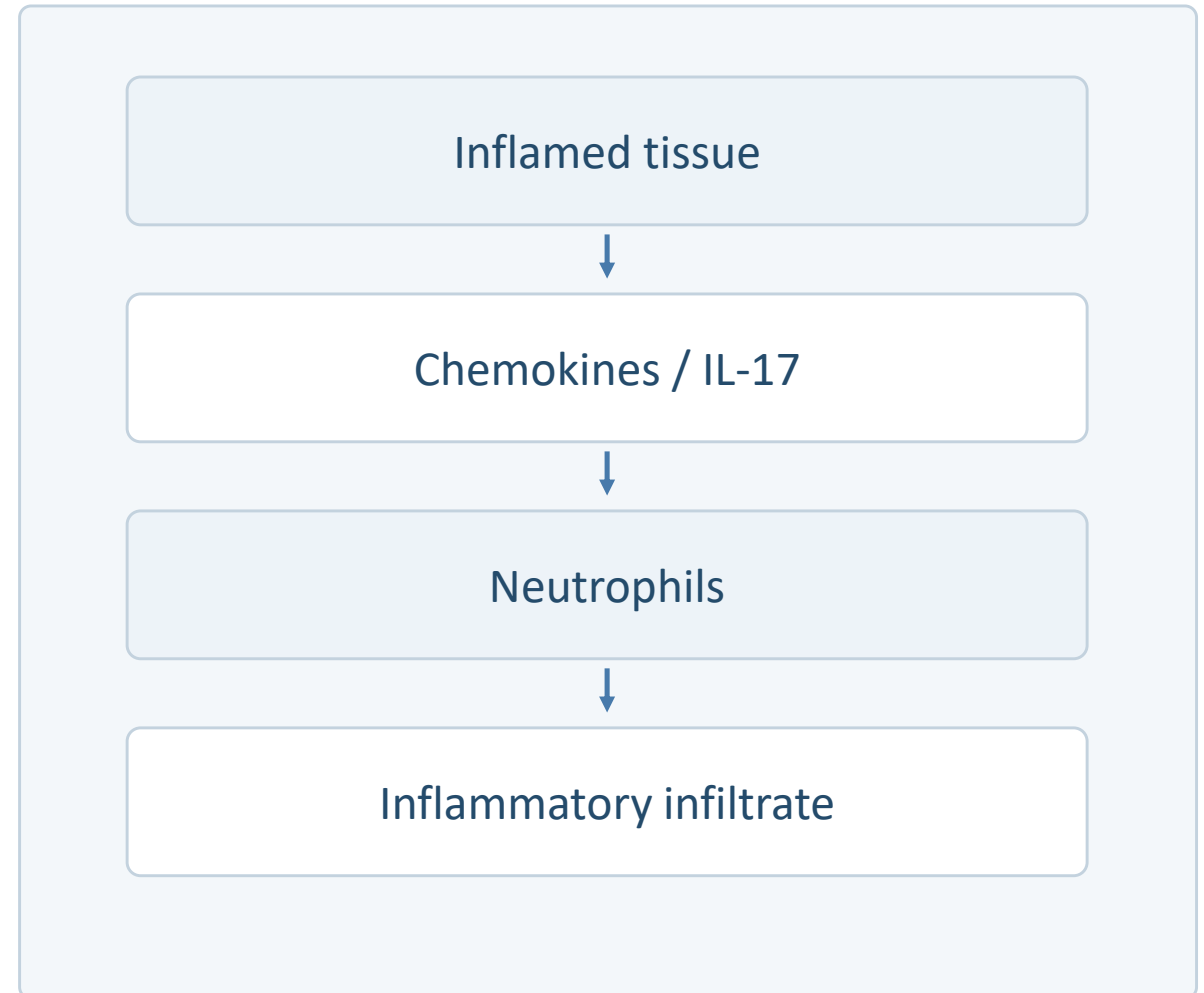
Case: Febrile infection with high CRP

- A microbial trigger activates macrophages and related innate cells.
- IL-1 and TNF contribute to fever; IL-6 promotes the hepatic acute-phase response.
- Interpret CRP as evidence of inflammation, not proof of a specific organism.



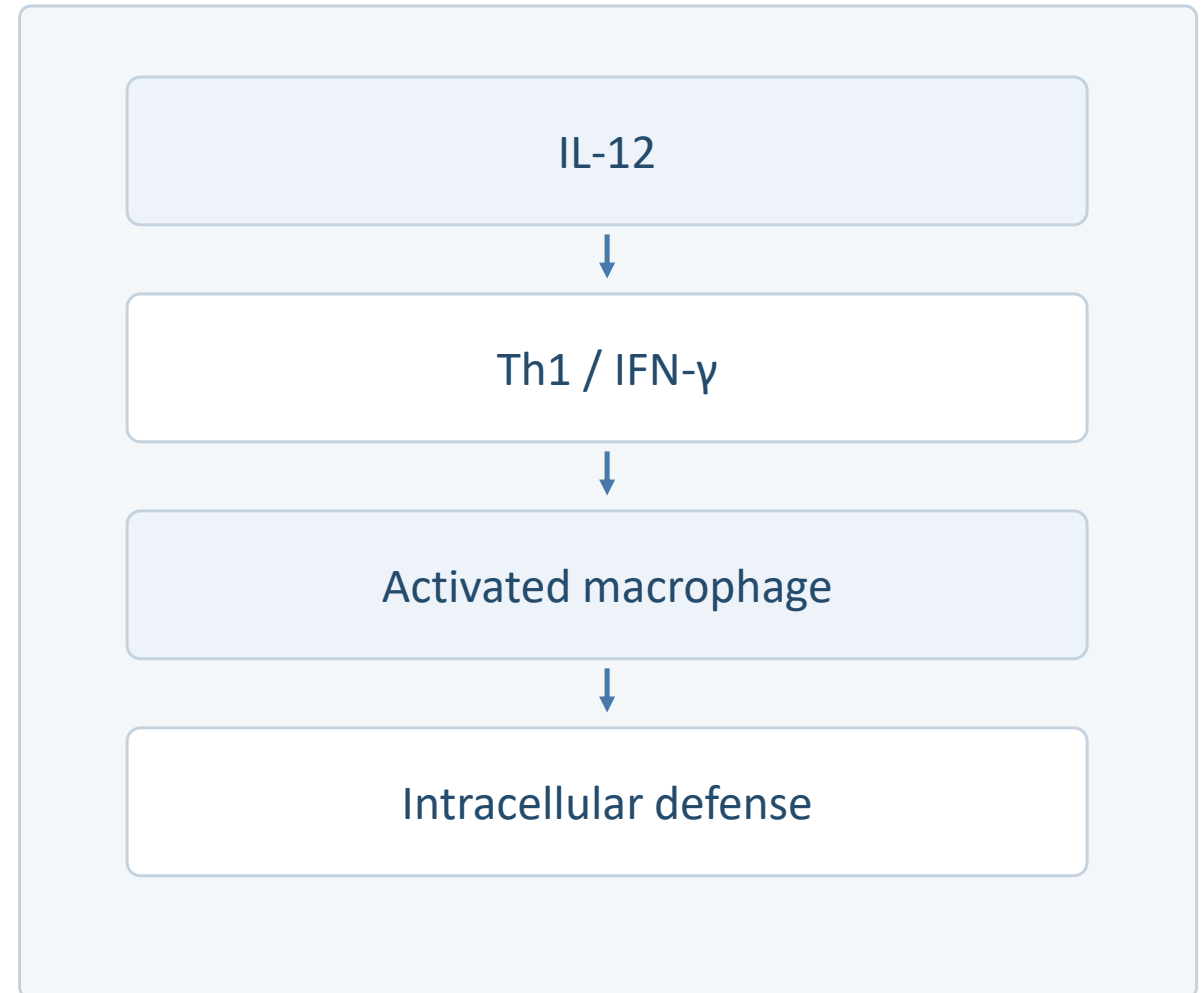
Case: Neutrophil-rich tissue inflammation

- An inflammatory signal induces chemokines at the affected site.
- CXCL8 recruits neutrophils; IL-17 can amplify neutrophil recruitment indirectly.
- Cellular recruitment follows communication between resident cells, endothelium, and leukocytes.



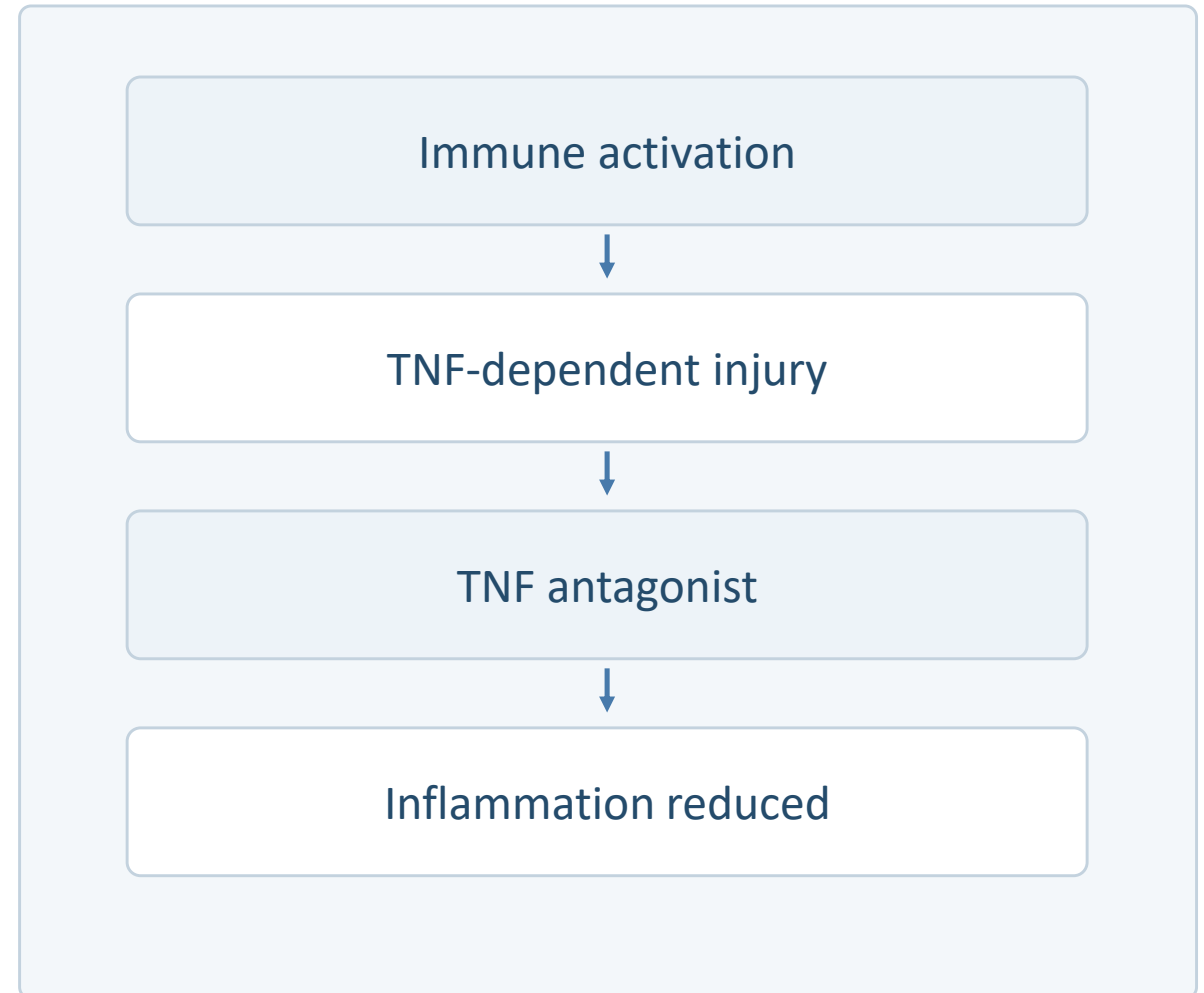
Case: Intracellular pathogen persistence

- Dendritic cells and macrophages can release IL-12.
- Th1-associated IFN- γ activates macrophages to improve intracellular killing.
- Interrupting this axis can impair host defense even if inflammation is reduced.



Case: Chronic inflammatory synovitis

- Persistent macrophage–T-cell signaling can sustain tissue inflammation.
- TNF is a targetable mediator in rheumatoid arthritis.
- Clinical benefit from blockade does not imply cytokines are dispensable for host defense.



Integrating cytokines into a tissue response

- Innate cells initiate inflammation and activate endothelium.
- Adaptive subsets tailor the effector response to the microbial challenge.
- Regulatory cytokines limit activity while colony-stimulating factors replenish leukocytes.

Initiation

Effector choice

Restraint

Replenishment

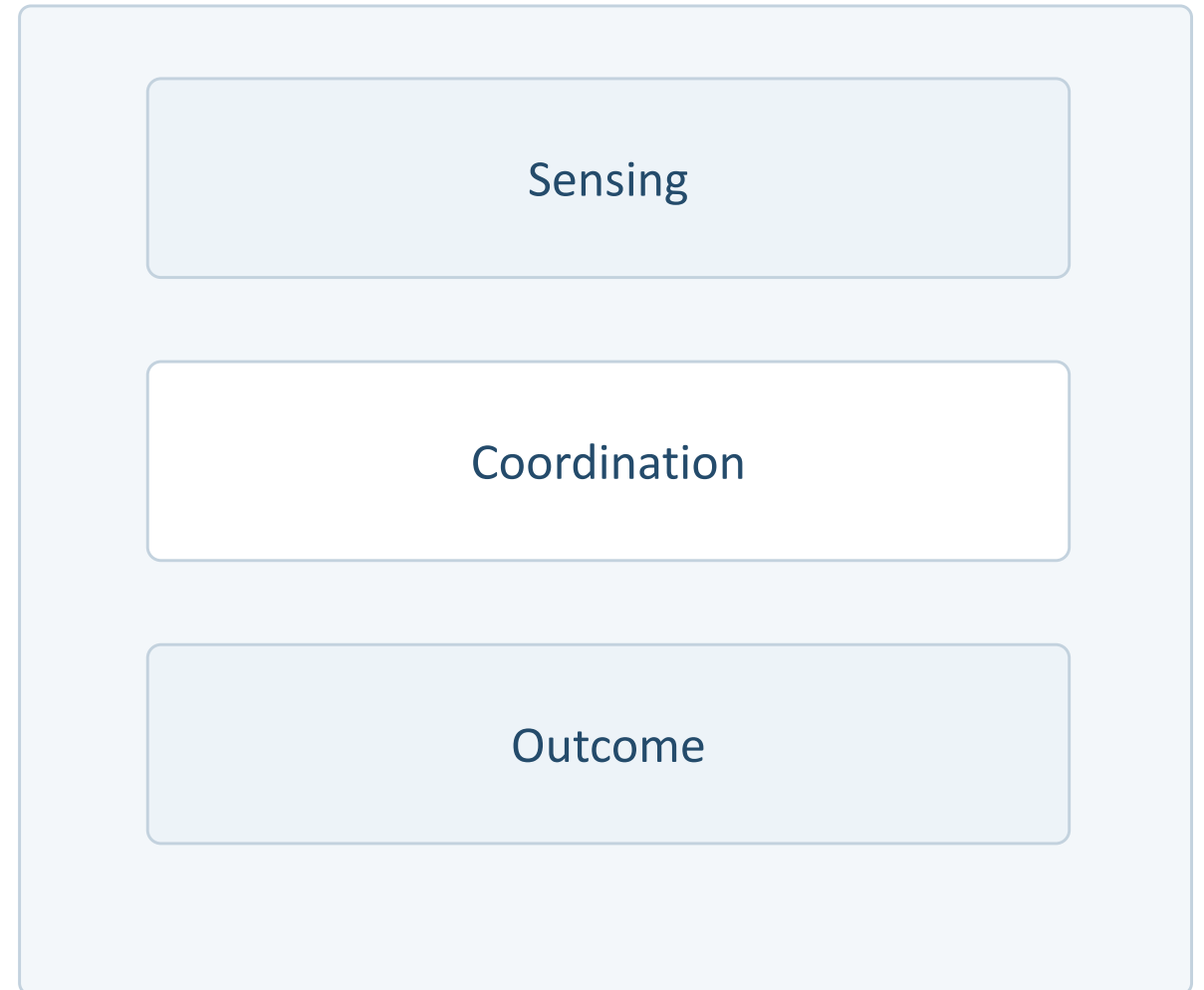
Six cytokine relationships worth retaining

- TNF/IL-1 → endothelial activation; IL-6 → acute-phase proteins.
- CXCL8 → neutrophil recruitment; IL-12 → Th1 differentiation.
- IL-2 → T-cell expansion; IFN- γ → macrophage activation.

CYTOKINE	MAJOR FUNCTION
TNF / IL-1	Endothelial activation
IL-6	Acute-phase response
CXCL8	Neutrophil recruitment
IL-2 / IFN- γ	T-cell expansion / macrophages

The cytokine system is an integrated network

- Cytokines connect immune sensing to cell recruitment and effector specialization.
- Their actions vary with source, target, and whether signaling is local or systemic.
- Targeted manipulation is valuable precisely because these pathways drive both protection and pathology.



Textbook basis and source boundaries

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026)

- Chapter 6: cytokines as immune messengers; lymphocyte activation and helper subsets.
- Chapter 3: TNF, IL-1, IL-6, chemokines, inflammation, and systemic effects.
- Related hematopoietic context: colony-stimulating factors.
- All teaching schematics are original, editable PowerPoint shapes; no textbook figures were reproduced.