

Causes of Inflammation

Etiologic triggers, tissue recognition, and clinicopathologic consequences

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Learning objectives

- Distinguish the principal infectious and noninfectious causes of inflammation.
- Explain why necrotic cells and deposited substances provoke sterile inflammation.
- Connect recognition of microbes and damage signals to inflammatory effector responses.
- Interpret selected clinical presentations by identifying the underlying inflammatory trigger.

Inflammation is a host response, not a disease

- A protective reaction to microbial invasion or tissue injury.
- Vascular and cellular responses bring leukocytes and plasma proteins to the affected tissue.
- Protection can itself produce local tissue damage and clinical disease.

Clinical / mechanistic interpretation

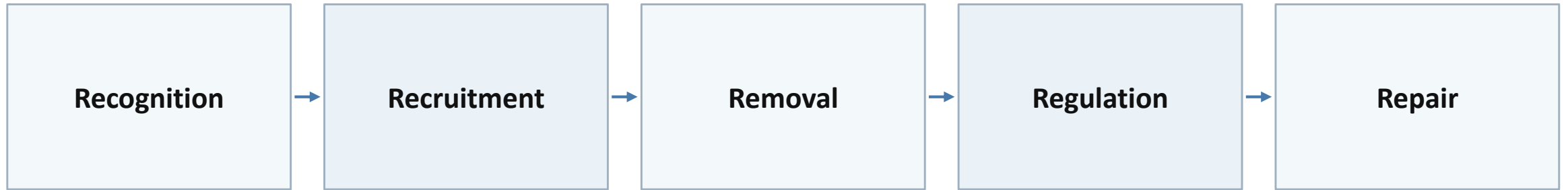
Inflammatory injury can arise even when the initial stimulus is noninfectious.

The inflammatory response follows a reproducible sequence



- The trigger determines what is sensed; The response mobilizes mechanisms of host defense.
- Persistent triggers sustain activation and may convert a protective response into injury.

The five R's organize the response



- Recognition starts the reaction; Recruited cells and proteins eliminate offending agents.
- Regulation limits collateral damage; Repair restores integrity or leaves a scar.

Four major classes of inflammatory stimuli

Infections

Microbes and their toxins

Tissue necrosis

Damage caused by ischemia, trauma, or physical/chemical agents

Foreign bodies

Exogenous material and deposited endogenous substances

Immune reactions

Responses against self, environmental, or microbial antigens

Infectious versus sterile triggers

Infection-associated inflammation	Sterile inflammation
Microorganisms or microbial toxins are present.	Tissue injury or endogenous material initiates a response without infection.
Microbial molecular components can be recognized.	Products of dead or injured cells can be recognized.
Examples: Bacterial infection; Fungal infection.	Examples: Myocardial infarction; Urate crystal deposition.

Separate the cause from the inflammatory reaction

- The etiologic stimulus is not synonymous with the resulting vascular or leukocyte response.
- Different stimuli converge on shared mediators and cellular processes.
- The nature and persistence of the stimulus influence acute versus chronic patterns.

Clinical / mechanistic interpretation

Diagnose the cause first;
Interpret the inflammatory pattern second.

Microbes activate inflammation through recognition



- Epithelial and immune cells recognize foreign material in multiple cellular compartments.
- Host protection and host-mediated tissue damage may occur in the same reaction.

Infections are major medical causes of inflammation

- Bacteria, viruses, fungi, and parasites can each initiate inflammatory responses.
- Microbial toxins may also act as inflammatory stimuli.
- The resulting pathology ranges from mild, transient disease to severe systemic reactions.
- Some infections produce persistent inflammation and extensive tissue injury.

Bacterial infection: Pathogen and host both matter

- Bacterial agents commonly trigger responses that recruit leukocytes and plasma proteins.
- In some infections the offending organisms are successfully eliminated with limited damage.
- In other infections the inflammatory response may become widespread or severe.

Clinical / mechanistic interpretation

The presence of bacteria alone does not define the severity of inflammatory injury.

Viral infection can sustain inflammatory responses

- Viruses are one of the major infectious classes in the Robbins etiologic framework.
- Inflammatory patterns depend on viral properties and the host response.
- An agent that is difficult to eradicate may be associated with prolonged inflammation.

Clinical / mechanistic interpretation

Do not infer a particular leukocyte pattern solely from the word “viral.”

Fungal infection may be acute or persistent

- Fungi are recognized causes of infectious inflammation.
- Organisms that are readily eliminated can evoke self-limited responses.
- Infections that persist may cause long-standing inflammation and tissue damage.

Clinical / mechanistic interpretation

Acute versus chronic behavior reflects persistence and host–pathogen interactions.

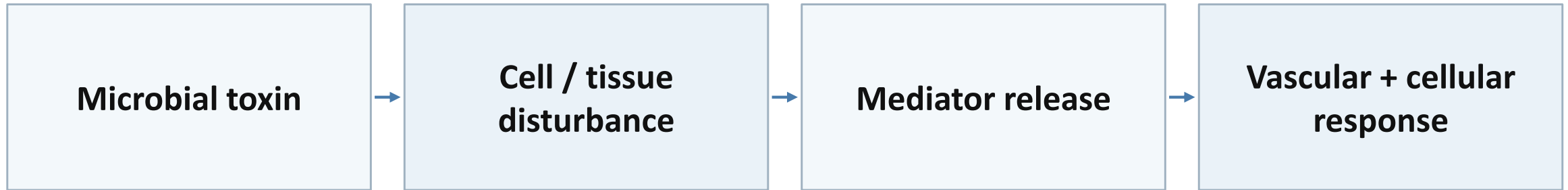
Parasitic infections belong in the same etiologic class

- Parasitic organisms can initiate inflammation, alongside bacterial, viral, and fungal pathogens.
- The type of pathogen contributes to the intensity and persistence of the response.
- The source emphasizes host response and pathogen identity over a universal histologic pattern.

Clinical / mechanistic interpretation

Etiologic categories classify stimuli, not fixed microscopic appearances.

Microbial toxins can trigger inflammation



- The toxin itself may be a stimulus even when the teaching question centers on microbial products.
- Inflammation can add to direct toxic tissue injury.

Infection outcomes form a severity spectrum

Mild acute response

Agent eradicated; Little or no permanent injury

Severe systemic response

Widespread potentially fatal inflammation

Persistent response

Long-term stimulus and tissue injury

Modifying factors

Pathogen type, host response, other host characteristics

Pathogen properties and host responses jointly shape outcome

Agent-related determinants	Host-related determinants
Type of infectious pathogen.	Magnitude and character of inflammatory response.
Potential for prolonged persistence.	Efficiency of elimination and termination.
Microbial products that act as stimuli.	Additional incompletely characterized host factors.

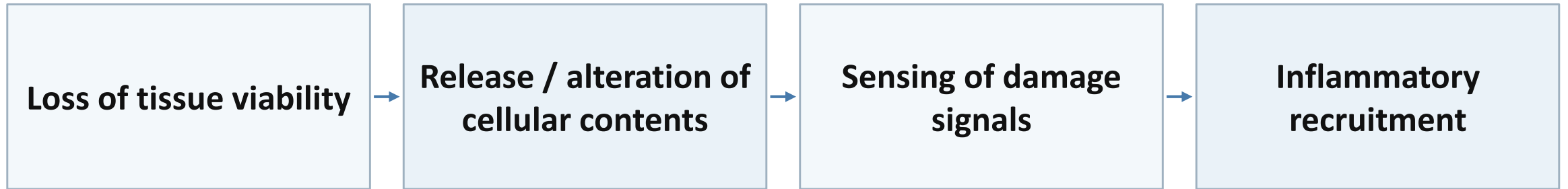
Sepsis illustrates the systemic end of the spectrum

- Local infection and localized inflammation do not automatically imply sepsis.
- In some disseminated infections inflammation becomes systemic and causes widespread abnormalities.
- Cytokines are central contributors to the injurious response in septic shock.

Clinical / mechanistic interpretation

Systemic spread of inflammation may create life-threatening host injury.

Necrosis initiates inflammation without microorganisms



- Necrotic tissue evokes inflammation regardless of the reason that cells died.
- This is the conceptual basis of many sterile inflammatory reactions.

Major routes to inflammatory tissue necrosis

- Ischemia: Reduction in tissue blood flow.
- Trauma: Direct physical tissue disruption.
- Thermal injury: Heat or cold, including burns and frostbite.
- Irradiation and exposure to selected environmental chemicals.

Ischemia → infarction → sterile inflammation



- Myocardial infarction is a textbook example of necrosis due to ischemia.
- Inflammation following infarction does not by itself establish an infection.

Why infarcted tissue becomes inflamed

- Ischemic injury can kill cells even when no microbe is involved.
- Necrotic cell products are recognized as evidence of tissue damage.
- Recruited phagocytes remove dead tissue and enable subsequent repair.

Clinical / mechanistic interpretation

The target of this response is damaged host tissue, not necessarily a pathogen.

Trauma triggers overlapping inflammatory signals

- Physical disruption may directly damage cells and vascular structures.
- Necrosis and the products of injured cells provide sterile inflammatory stimuli.
- If a wound introduces microbes or foreign material, additional triggers may coexist.

Clinical / mechanistic interpretation

A single injury can combine sterile damage, foreign bodies, and infection.

Thermal burns provoke tissue damage and inflammation

- Excessive heat is a physical cause of cellular injury and necrosis.
- Damaged tissue provides the stimulus for an inflammatory response.
- Extensive physical injury can contribute to systemic inflammation even without infection.

Clinical / mechanistic interpretation

Distinguish the initial thermal injury from the ensuing inflammatory amplification.

Frostbite shows that cold injury is also inflammatory

- Extreme cold can cause tissue damage and necrosis.
- Cell death generates signals that recruit inflammatory cells.
- The resulting response may be sterile at initiation.

Clinical / mechanistic interpretation

Inflammation is a response to injured tissue, not only to heat or microbes.

Irradiation may initiate sterile tissue inflammation

- Irradiation is listed among physical causes of cell injury and necrosis.
- Inflammation can follow the damage even when infection is absent.
- The temporal sequence is important: Injury precedes host recognition.

Clinical / mechanistic interpretation

A nonmicrobial exposure can initiate inflammatory mediator production.

Environmental chemicals can damage tissue

- Selected environmental chemicals produce physical or chemical cellular injury.
- When cell death ensues, released molecules can initiate inflammation.
- Direct chemical toxicity and secondary inflammatory injury are different processes.

Clinical / mechanistic interpretation

The cause may be chemical;
The subsequent pathologic reaction is inflammatory.

Damage-associated signals have several sources

Uric acid

A product of DNA breakdown

ATP

Released by damaged mitochondria

Reduced intracellular K⁺

A consequence of membrane integrity loss

Mislocalized DNA

DNA in the cytoplasm rather than sequestered in nuclei

Sterile inflammation has an identifiable sensor pathway



- NOD-like receptors are among the intracellular sensors of tissue injury.
- Not every inflammatory stimulus must follow precisely the same pathway.

Infection and infarction: Same response, different origin

Infection	Myocardial infarction
A microbial stimulus is present.	Ischemia causes myocardial cell necrosis.
Recognition can involve microbial receptors.	Recognition involves products of damaged cells.
Inflammation acts against infection.	Inflammation removes dead tissue and contributes to repair.

Foreign bodies can stimulate inflammation directly

- Splinters, dirt, and sutures are examples of exogenous foreign material.
- A foreign body may be inflammatory in its own right.
- Associated injury or introduced microorganisms provide additional mechanisms.

Clinical / mechanistic interpretation

A foreign-body response is not proof that the material is infected.

Three mechanisms of foreign-body inflammation

Material itself

Presence of nonself material in tissue

Traumatic injury

Physical disruption caused by introduction or retention

Microbial carriage

Microorganisms introduced on or with the material

Combined effects

More than one mechanism can operate together

Splinters and dirt illustrate exogenous triggers

- A splinter introduces material that is not normally present in living tissue.
- Dirt may be retained at a traumatic site and may also carry microbes.
- Both direct tissue injury and contamination must be considered.

Clinical / mechanistic interpretation

The etiologic assessment should distinguish retained material from infection.

Sutures illustrate an iatrogenic foreign body

- Suture material may remain within tissue after a surgical procedure.
- Inflammatory responses to material can occur without a microbial infection.
- Postsurgical inflammation therefore requires etiologic interpretation.

Clinical / mechanistic interpretation

Do not equate a reaction around sutures with proven infection.

Foreign substances are not always exogenous

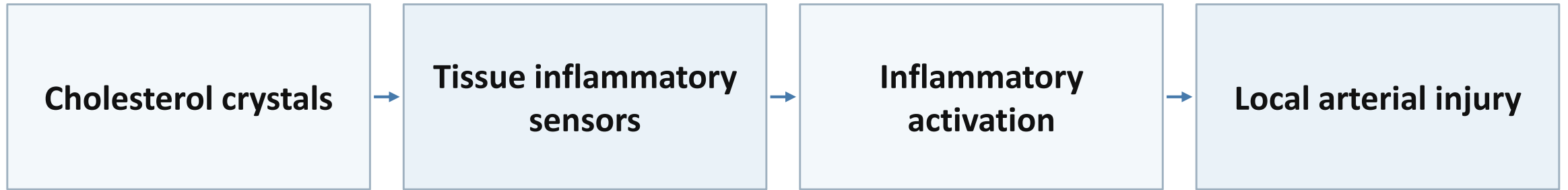
Exogenous objects	Endogenous deposits
Splinters, dirt, or sutures enter or remain in tissue.	Substances produced within the body accumulate in tissue.
Mechanical tissue injury and microbial carriage may contribute.	Deposits can act as inflammatory stimuli.
Identify retained material and possible contamination.	Identify the material and the disorder causing its deposition.

Urate crystal deposition drives gout-associated inflammation



- Urate crystals as an endogenous cause of inflammation.
- The inflammasome is implicated in reactions to urate deposits.

Cholesterol crystals contribute to arterial inflammation



- Cholesterol crystals occur as endogenous deposits in atherosclerosis.
- The source implicates the inflammasome in cholesterol-associated inflammation.

Crystal-associated inflammation can be sterile

- The deposited material originates from the individual rather than an invading microorganism.
- Intracellular sensing mechanisms can respond to crystal-associated disturbance.
- Leukocyte recruitment can nevertheless be intense and clinically consequential.

Clinical / mechanistic interpretation

Sterile and severe are not mutually exclusive.

Immune responses can become the cause of injury

- Immune reactions are also termed hypersensitivity reactions.
- The immune system's normal protective function can be misdirected or excessive.
- Tissue inflammation then becomes a principal mechanism of disease.

Clinical / mechanistic interpretation

The host's response—not necessarily the antigen alone—causes pathology.

Three antigen contexts for immune injury

Self antigens

Autoimmune disease

Environmental antigens

Allergic disorders

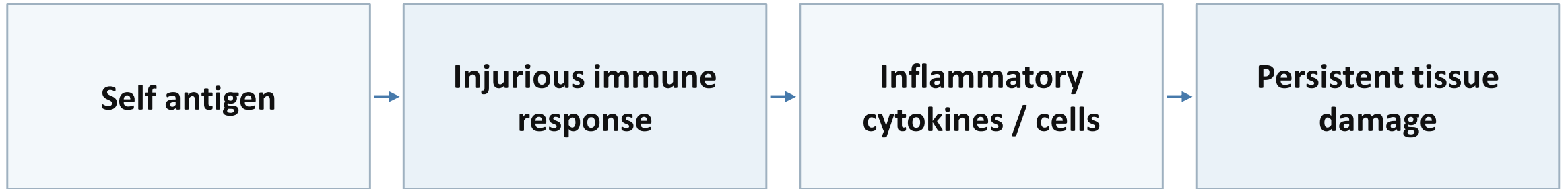
Microbial antigens

Injurious responses directed against
microbes

Common consequence

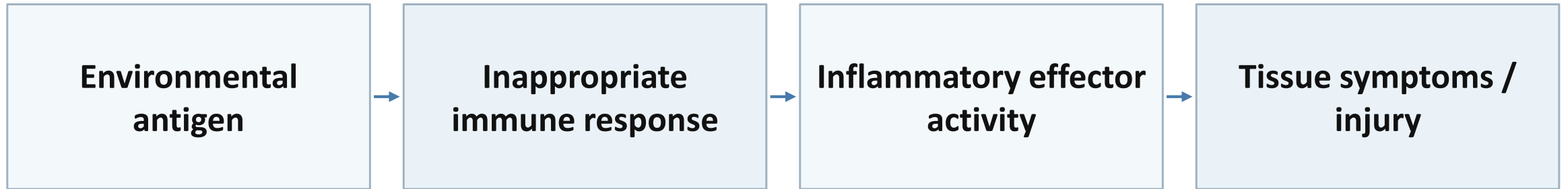
Inflammation damages host tissues

Autoimmunity converts self-recognition into tissue injury



- The trigger may be a self antigen that cannot be eliminated.
- Persistent recognition favors chronic inflammation.

Allergic inflammation targets environmental substances



- The inciting substance need not be intrinsically harmful.
- Repeated or persistent exposure may sustain or reactivate inflammation.

Microbe-directed immunity can injure host tissues

- Responses against microbial antigens may damage the individual's own tissues.
- Such damage is distinct from tissue injury directly produced by the organism.
- Microbial infection and immune-mediated injury can contribute simultaneously.

Clinical / mechanistic interpretation

Immune reactivity may be protective and pathogenic in the same disease.

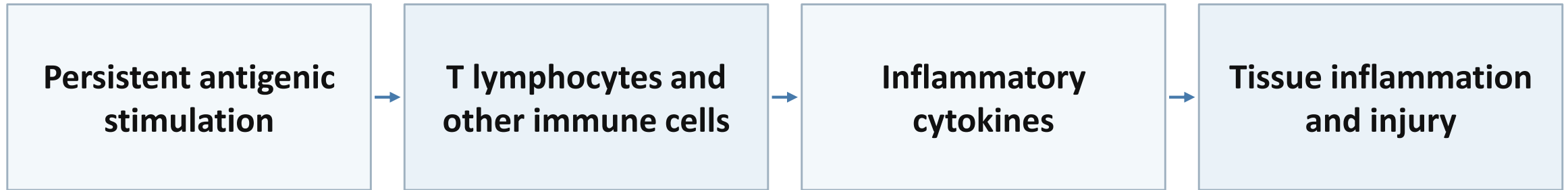
Persistence explains many chronic immune disorders

- Self antigens generally cannot be removed from the body.
- Environmental antigens can be difficult to avoid completely.
- Continuing stimulation contributes to chronic inflammation and difficult-to-cure disease.

Clinical / mechanistic interpretation

Persistent stimulus →
repeated immune activation
→ ongoing tissue injury.

T lymphocyte cytokines drive much immune inflammation



- Cytokines produced by T cells and other immune cells.
- Immune-mediated disease may therefore persist beyond an initial acute episode.

Examples of inflammation-mediated disease

Rheumatoid arthritis

Lymphocytes and macrophages; Antibodies may contribute

Asthma

Eosinophils and IgE-associated immune responses

Glomerulonephritis / vasculitis

Antibodies, complement, and inflammatory leukocytes

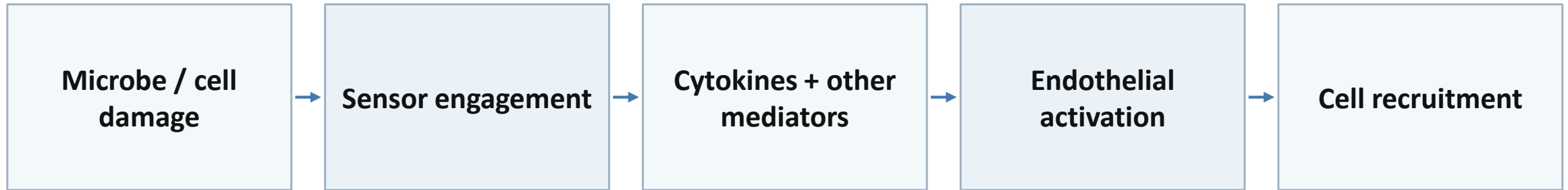
Septic shock

Systemic cytokine-mediated injury

Inflammatory injury is not restricted to infections

Typical initiating stimulus	Illustrative condition
Microorganisms or microbial products.	Infections; Septic shock in severe systemic reactions.
Necrosis due to ischemia.	Inflammation after myocardial infarction.
Endogenous crystals.	Gout or atherosclerosis.
Self/environmental antigens.	Autoimmune disease or allergy.

Recognition precedes mediator production



- Recognition is an initiating event, not merely an effect of inflammation.
- Sensors occur on cells and in circulating proteins.

Sentinel cells detect threats within tissues

- Epithelial cells may encounter microbes at entry sites.
- Macrophages and dendritic cells survey tissue microenvironments.
- Other leukocytes also express receptors that identify invading microbes.

Clinical / mechanistic interpretation

Resident tissue cells can initiate inflammation before large-scale leukocyte influx.

Microbial sensors operate in several compartments

Plasma membrane

Recognition of extracellular microbes

Endosomes

Recognition of microbes taken into cells

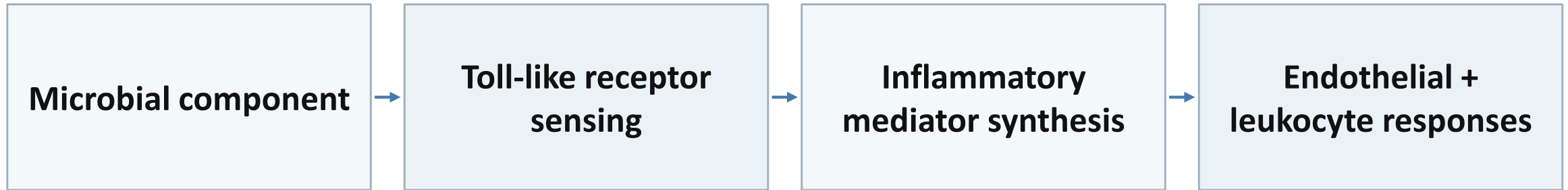
Cytosol

Recognition of intracellular microbes

System-level advantage

Threats can be sensed in distinct cellular locations

Toll-like receptors initiate inflammatory signaling



- TLRs are a well-defined family of cellular microbial sensors.
- TLR signaling promotes cytokines and molecules involved in leukocyte recruitment.

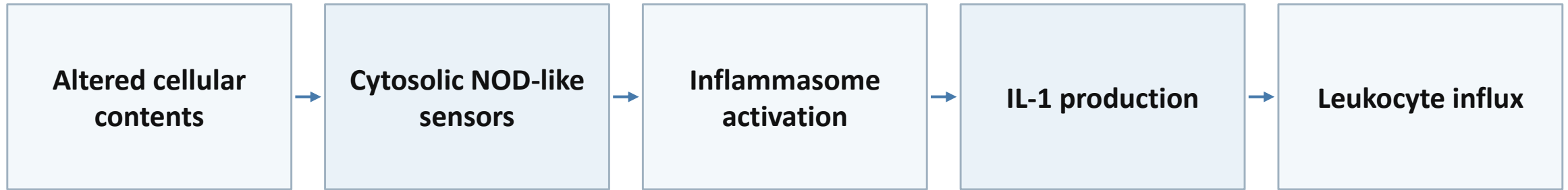
Endothelial adhesion molecules follow recognition

- Cells that recognize microbes produce proinflammatory signals.
- These signals increase expression of endothelial adhesion molecules.
- Leukocytes can then adhere to vascular lining and move into affected tissue.

Clinical / mechanistic interpretation

Molecular sensing is coupled to vascular recruitment of effector cells.

NOD-like receptors detect injury-associated changes



- The source describes NOD-like receptors as important damage sensors.
- Different damage signals converge on inflammatory activation.

ATP and intracellular ion changes indicate damage

- ATP can be released in the setting of damaged mitochondria.
- Reduced intracellular potassium reflects loss of normal membrane homeostasis.
- These alterations are recognized in damage-associated inflammatory signaling.

Clinical / mechanistic interpretation

Inflammation can respond to disturbed homeostasis, not simply foreign molecules.

Mislocalized DNA is another cellular alarm

- DNA is normally sequestered in the nucleus.
- DNA abnormally present in the cytoplasm can be recognized as a danger signal.
- Alongside uric acid and ATP, it exemplifies injury-associated changes.

Clinical / mechanistic interpretation

Location matters: A normal constituent in an abnormal compartment can signal damage.

The inflammasome connects sensing to IL-1



- The inflammasome is a multiprotein cytosolic complex.
- Its activation is one mechanism linking tissue injury to inflammation.

IL-1 promotes clearance of damaged tissue

- Inflammasome signaling promotes production of interleukin-1 (IL-1).
- IL-1 recruits leukocytes to sites containing damaged and dead cells.
- Phagocytic clearance removes potentially harmful residual necrotic material.

Clinical / mechanistic interpretation

An inflammatory mediator can be essential for tissue cleanup while still causing symptoms.

Autoinflammatory syndromes implicate sensor dysregulation

- Gain-of-function variants affecting some inflammatory sensors can cause rare syndromes.
- These disorders may feature spontaneous IL-1 production and inflammation.
- IL-1 antagonism can be effective in these conditions.

Clinical / mechanistic interpretation

Inflammation can arise from dysregulated sensing rather than external infection.

Inflammasome-linked noninfectious conditions

Gout

Urate crystal deposits

Atherosclerosis

Cholesterol crystal deposits

Metabolic disorders

Lipid-related inflammatory signals

Neurodegeneration

Amyloid deposits implicated in brain inflammation

Opsonization facilitates microbial recognition

- Antibodies and complement components can coat microbes.
- Leukocyte Fc and complement receptors bind the coated targets.
- Recognition promotes microbial ingestion, destruction, and inflammation.

Clinical / mechanistic interpretation

Recognition can be direct or mediated by host proteins bound to a microbe.

Circulating proteins participate in recognition

Complement system

Reacts to microbes and generates inflammatory mediators

Mannose-binding lectin

Recognizes microbial sugars; Aids ingestion and complement activation

Collectins

Bind microbes and contribute to host defense

Shared function

Extend recognition beyond cell-associated receptors

Acute and chronic patterns reflect trigger behavior

Acute inflammation	Chronic inflammation
Typically rapid onset.	Often arises with difficult-to-eradicate stimuli.
Neutrophils commonly predominate.	Macrophages and lymphocytes are prominent.
Frequently limited and resolves after stimulus removal.	May involve progressive tissue destruction and scarring.

From cause to tissue consequence



- Common effector mechanisms can follow different triggers.
- Disease phenotype reflects both inciting cause and regulation of the response.

A practical etiologic triage for inflamed tissue

Question	Mechanism to consider
Are microbial agents or products present?	Infectious inflammation.
Is tissue necrotic after ischemia or direct injury?	Sterile tissue-damage inflammation.
Is foreign or deposited material present?	Foreign-body / crystal-associated inflammation.
Is the response directed against antigens?	Immune-mediated inflammation.

Case: Inflammation after myocardial infarction

Clinical presentation

A region of myocardium becomes necrotic following reduced coronary blood flow. Inflammatory cells subsequently accumulate.

Does the inflammatory infiltrate necessarily indicate infection?

Interpretation

No. Ischemic necrosis releases damage signals and initiates sterile inflammation. The sequence is ischemia → cell death → recognition → recruitment.

Case: Recurrent painful inflammation with urate deposits

Clinical presentation

A patient has an inflammatory joint episode associated with urate crystal deposition.

What etiologic class is most directly illustrated?

Interpretation

Endogenous deposited material. Urate crystals are nonmicrobial inflammatory triggers; Inflammasome activation is implicated.

Case: Symptoms after environmental antigen exposure

Clinical presentation

An otherwise harmless environmental substance precipitates a recurring immune reaction with tissue symptoms.

Why can this reaction persist or recur?

Interpretation

An inappropriate response to environmental antigen produces allergic inflammation. Repeat or continued exposure can sustain the response.

Case: Inflammation around retained suture material

Clinical presentation

Tissue around a retained suture is inflamed after an intervention; No organism has been identified.

Which mechanisms should remain in the differential?

Interpretation

Foreign-body inflammation from the material itself, local traumatic injury, and infection if microbes have been introduced. Inflammation alone does not prove infection.

Case: Why two infections cause different outcomes

Clinical presentation

Two individuals with infectious inflammation have different courses: One self-limited and the other persistent with tissue injury.

Which broad variables explain the difference?

Interpretation

Pathogen type and host inflammatory response; Additional poorly defined host factors may also influence outcome.

Essential etiologic conclusions

Infection

Recognize pathogen and microbial product triggers

Necrosis

Recognize sterile inflammation following cell death

Foreign material

Distinguish retained objects and endogenous deposits

Immune response

Recognize self- and environmental antigen-directed injury

Selected reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 3: Inflammation and Repair.
- Sections: General Features of Inflammation; Causes of Inflammation; Recognition of Microbes and Damaged Cells.