

Cellular Receptors for Microbes, Products of Damaged Cells, and Foreign Substances

Pattern recognition, danger sensing, and early innate immune responses

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Learning objectives

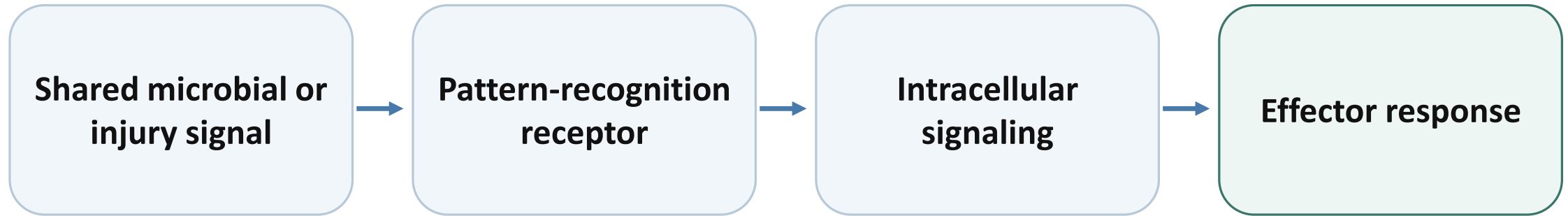
- Distinguish microbial PAMPs from host-derived DAMPs.
- Locate major pattern-recognition receptor families in cellular compartments.
- Explain TLR, inflammasome, RLR, STING, and surface-receptor responses.
- Connect sensing pathways with selected inflammatory and immune disorders.

Innate immunity detects danger before clonal antigen recognition



- The initiating signal need not be an antigen recognized by a T- or B-cell receptor.
- Early recognition is distributed across phagocytes, dendritic cells, and epithelial cells.

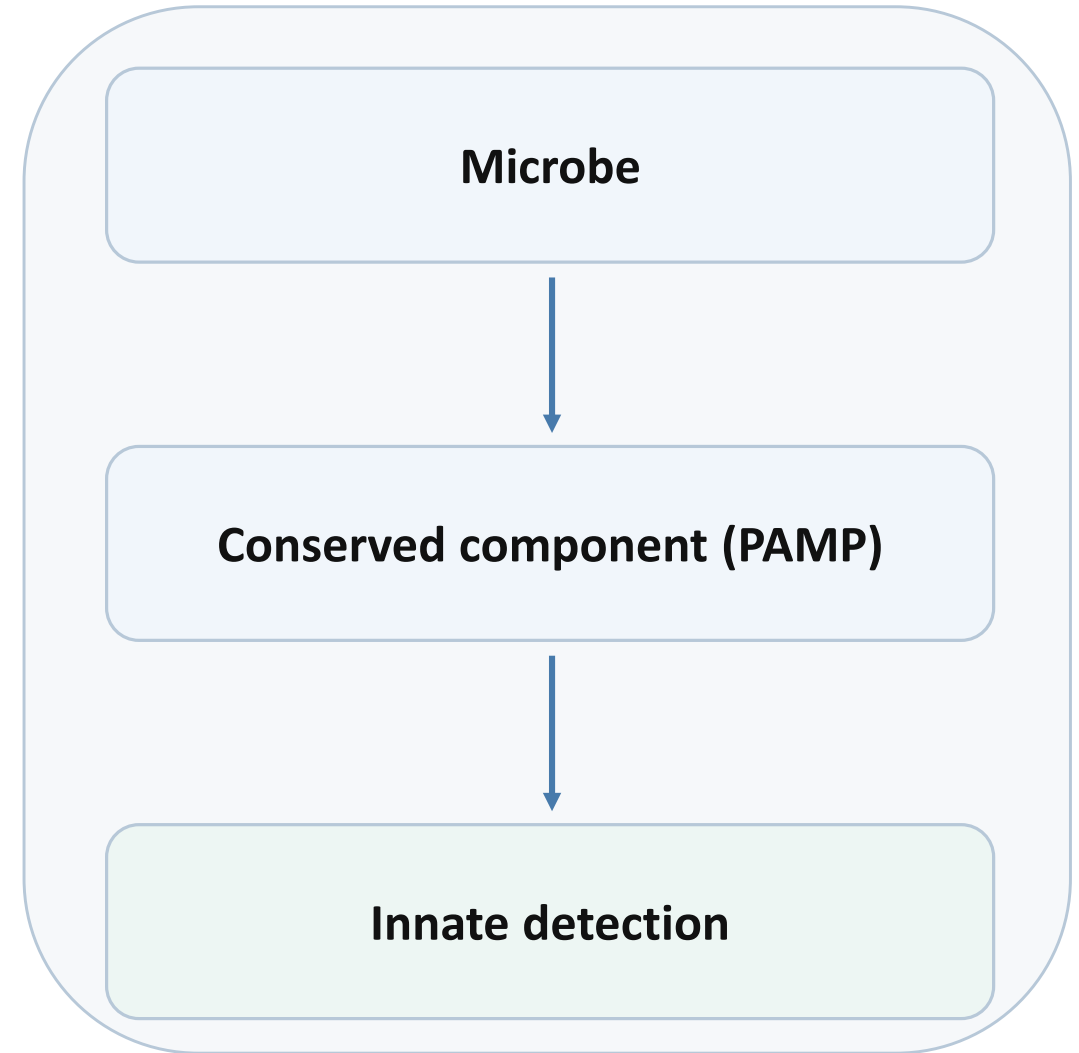
A receptor converts a molecular signature into a response



- Receptor specificity determines which danger signals are sensed.
- The signaling pathway determines cytokine production, chemotaxis, or uptake.

PAMPs are shared microbial molecular patterns

- Pathogen-associated molecular patterns (PAMPs) occur in related microbes.
- They are frequently important for microbial infectivity or survival.
- Recognition is directed at conserved features rather than unique antigen clones.



Conservation makes PAMP recognition robust

Conserved pattern

- Shared across multiple microbes
- May be constrained by microbial function
- Supports broad early recognition

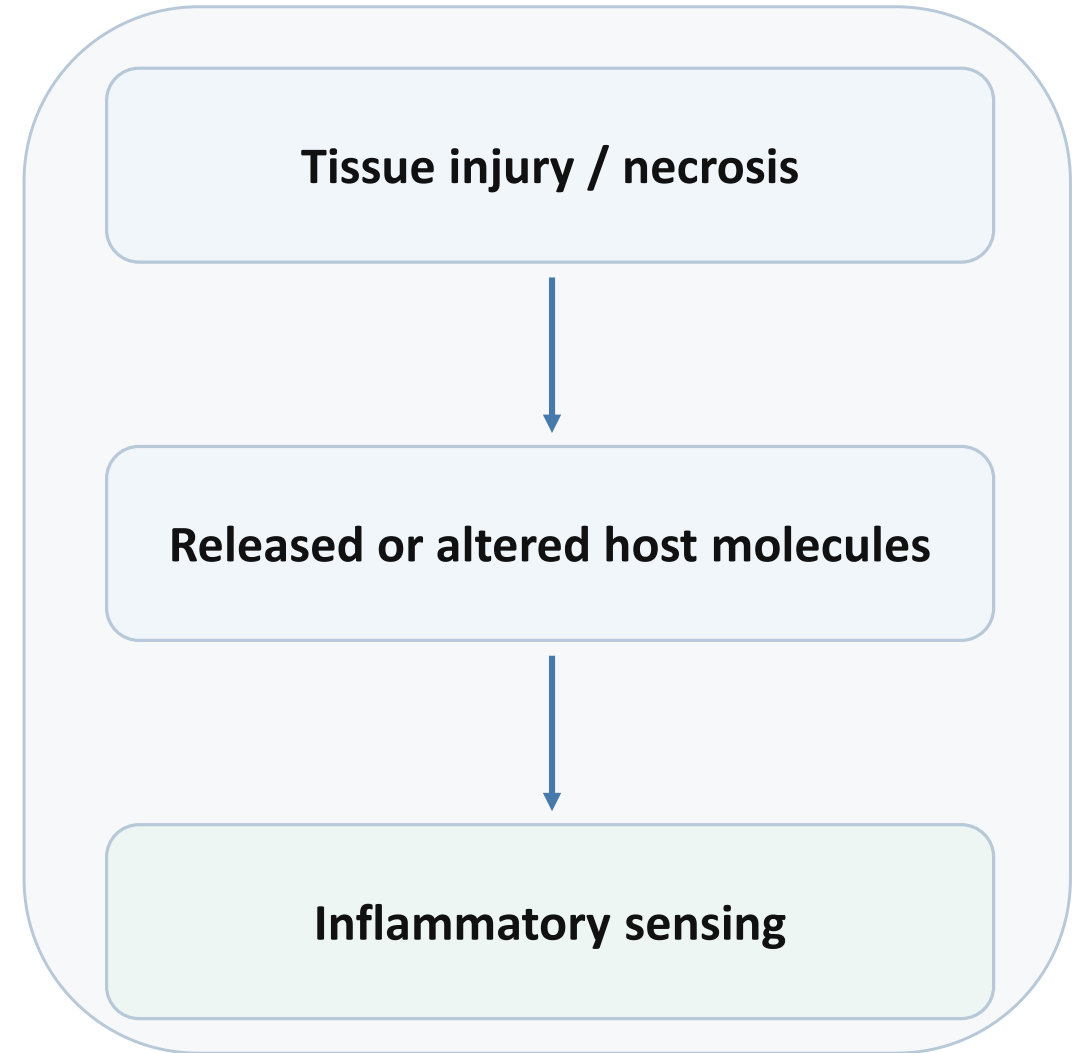
Highly variable feature

- More easily altered by microbial evolution
- Not the defining target of PRRs
- Not needed to explain this mechanism

A PRR recognizes a class of danger-associated structures—not every possible microbial epitope.

DAMPs signal injury without requiring infection

- Damage-associated molecular patterns (DAMPs) are released or exposed by injured and necrotic cells.
- They provide evidence of disrupted host tissue integrity.
- ATP and uric acid are source-described examples of danger-associated signals.



PAMPs and DAMPs differ in origin—not in the need for sensing

PAMP

- Source: Microbes
- Biological meaning: Infectious threat
- Example category: Microbial nucleic acids

DAMP

- Source: Injured host tissue
- Biological meaning: Tissue damage
- Examples: Extracellular ATP, uric acid

Both can initiate innate immune signaling through appropriate receptor pathways.

Localization organizes pattern recognition

Plasma membrane

Samples extracellular microbes and their surface products.

Endosomal membrane

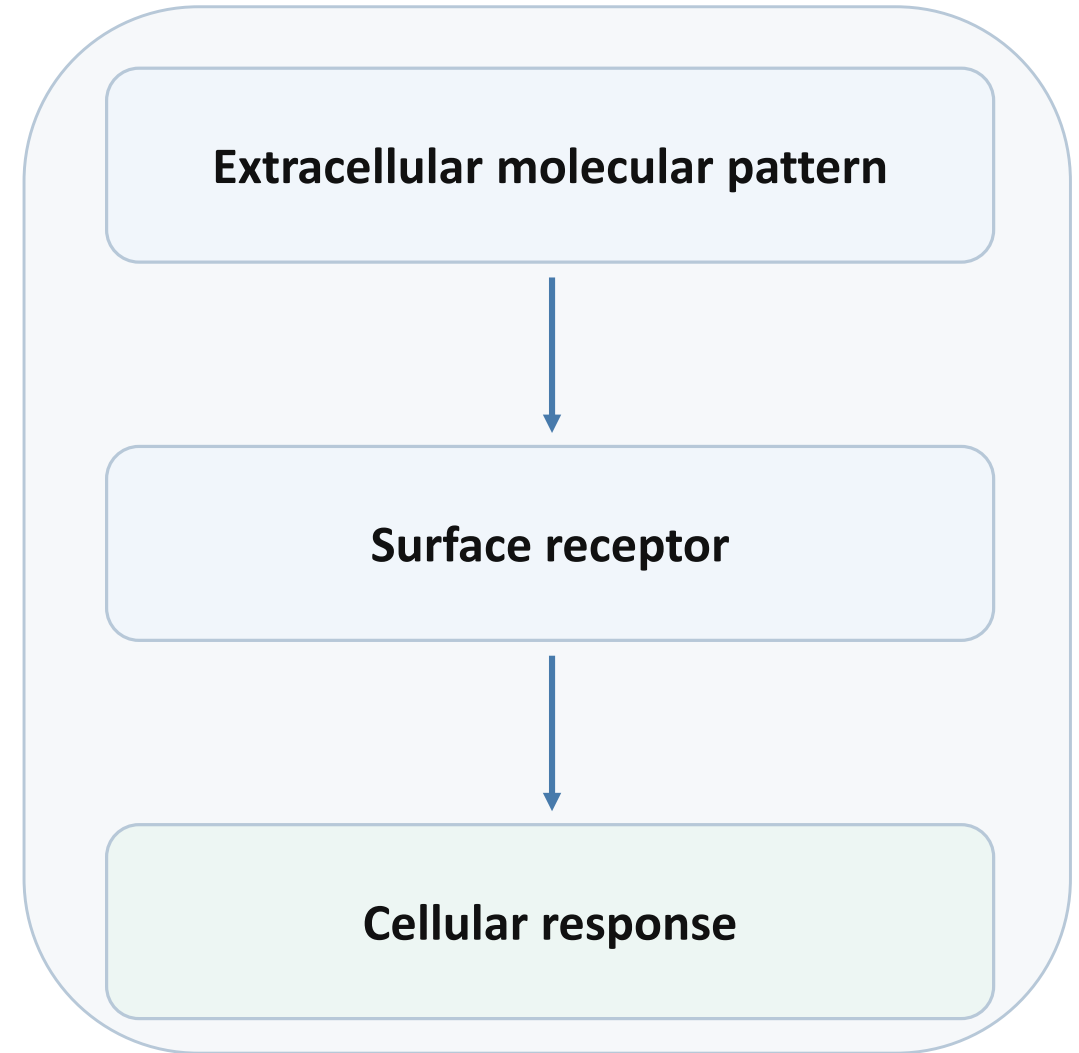
Samples nucleic acids of internalized microbes.

Cytosol

Detects cytoplasmic nucleic acids and damage-related perturbations.

Surface receptors detect material outside the cell

- Plasma-membrane TLRs recognize selected microbial products.
- C-type lectins bind fungal glycans.
- Leukocyte G protein–coupled receptors detect N-formylated bacterial peptides.
- Mannose receptors promote microbial uptake.



Endosomal receptors sample internalized material



- The membrane-bound compartment creates an additional surveillance site.
- Compartmentalization enables recognition after microbial uptake.

Cytosolic sensing covers intracellular invasion

NOD-like receptors

Microbial products, injury signals, and ionic disturbance.

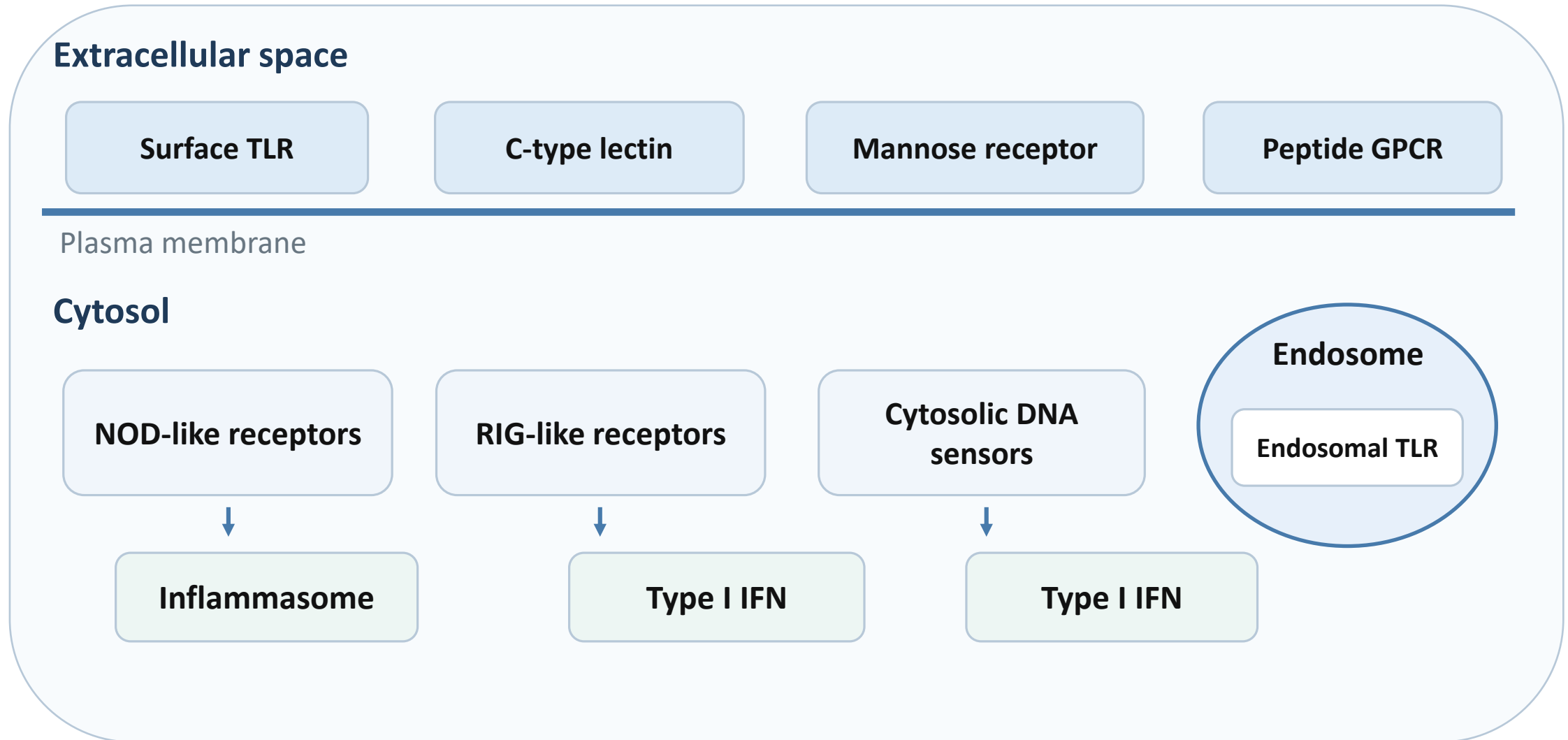
RIG-like receptors

RNA from viruses replicating in the cytosol.

DNA sensing → STING

Cytosolic microbial DNA or mislocalized self DNA.

Receptor families occupy distinct cellular compartments



Innate sentinel cells express overlapping receptor sets

Phagocytes

Sense and ingest microbes;
Macrophages can also
sustain inflammation.

Dendritic cells

Detect danger and
produce cytokines in
addition to antigen
presentation.

Epithelial cells

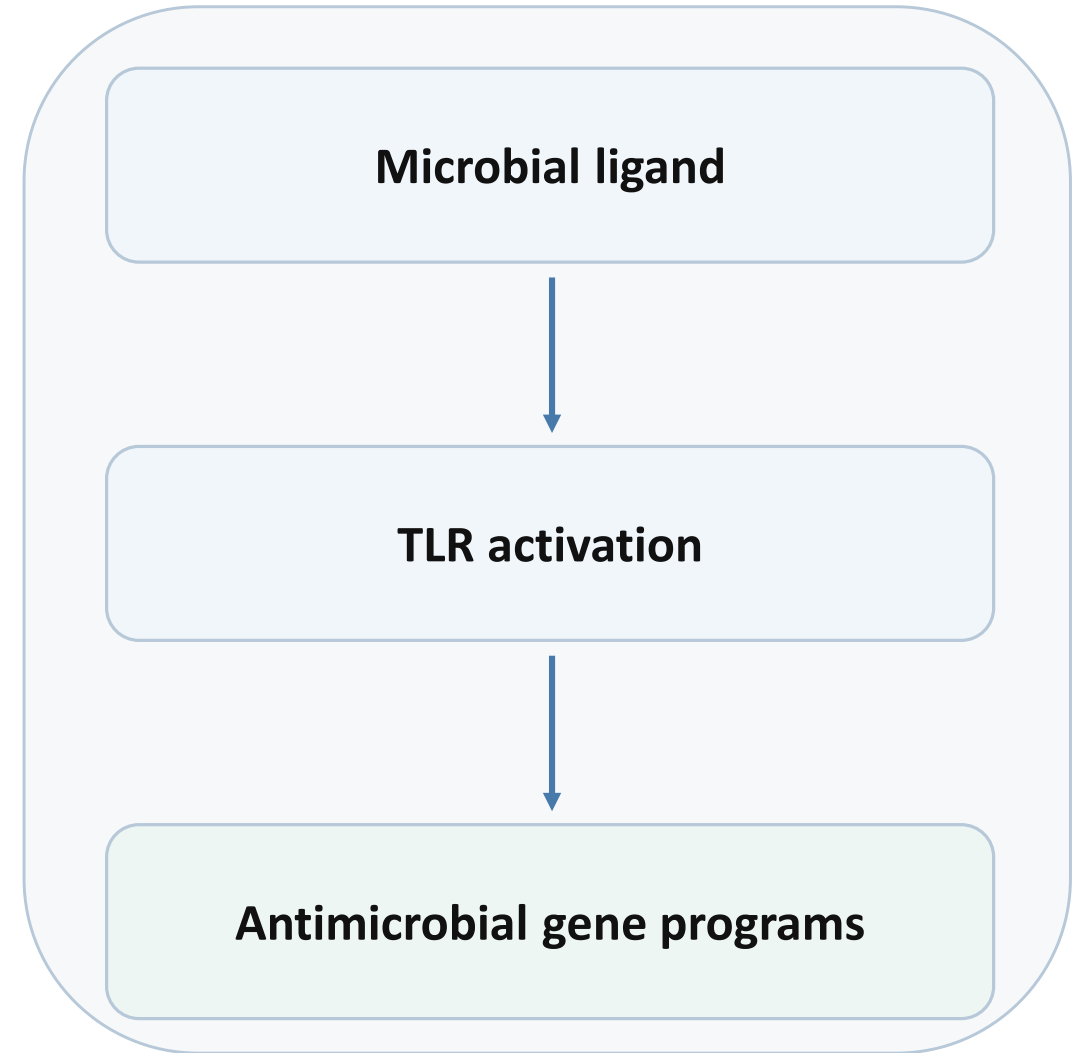
Participate in sensing at
barrier surfaces.

Five principal recognition systems in this section

System	Recognized signal	Main response
Toll-like receptors	Various microbial molecules	NF- κ B / IRF signaling
NOD-like receptors	Cell damage / microbial cues	Inflammasome–IL-1 pathway
RIG-like receptors	Cytosolic viral RNA	Type I interferons
Cytosolic DNA sensing	Cytosolic DNA	STING–type I interferons
Surface lectin / other receptors	Glycans, peptides, sugars	Inflammation, movement, uptake

Toll-like receptors are a major PRR family

- The Toll family was first linked to development in *Drosophila*.
- Related mammalian Toll-like receptors are essential to host defense.
- A family of 10 mammalian TLRs.



TLRs are distributed across membranes

Plasma-membrane TLRs

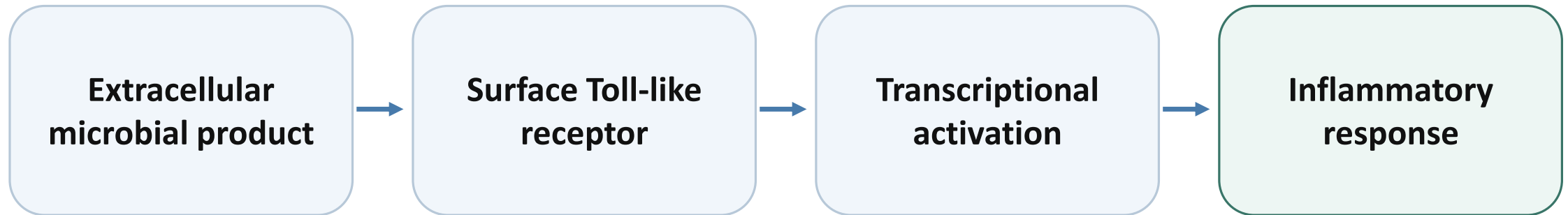
- Face extracellular microbial products
- Recognize selected ligand classes
- Can trigger inflammatory transcription

Endosomal TLRs

- Face contents of internalized vesicles
- Detect microbial nucleic acids
- Can induce antiviral gene programs

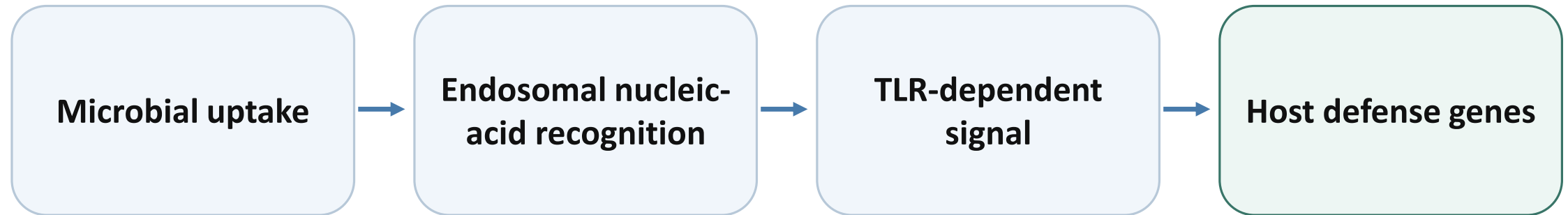
Location influences the material available for detection.

Extracellular microbes can activate surface TLRs



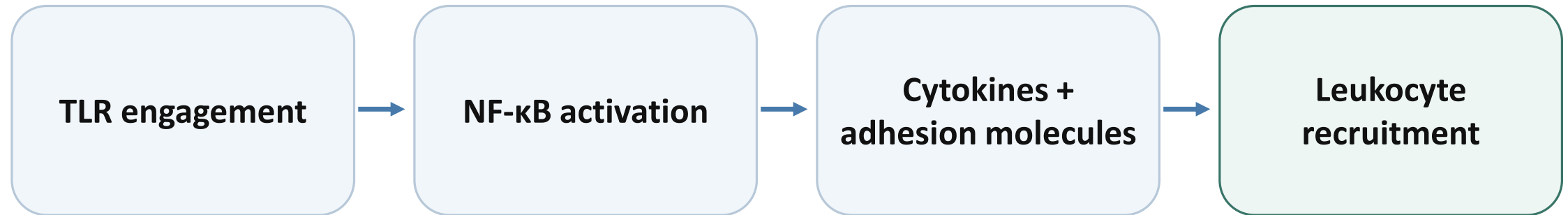
- This is a compartment-based schematic, not a complete catalog of TLR–ligand pairs.

Microbial nucleic acids can activate endosomal TLRs



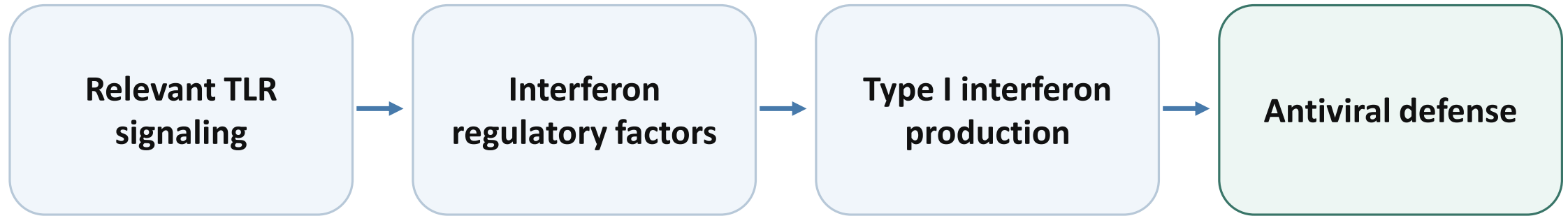
- Vesicle localization permits detection of nucleic acids from ingested microbes.

NF- κ B drives the inflammatory arm of TLR signaling



- Cytokine production and adhesion-molecule expression are both central to inflammation.

IRFs initiate the type I interferon arm



- IRFs are transcription factors; Type I IFNs are secreted antiviral cytokines.

TLR signaling yields two major effector programs

NF- κ B program

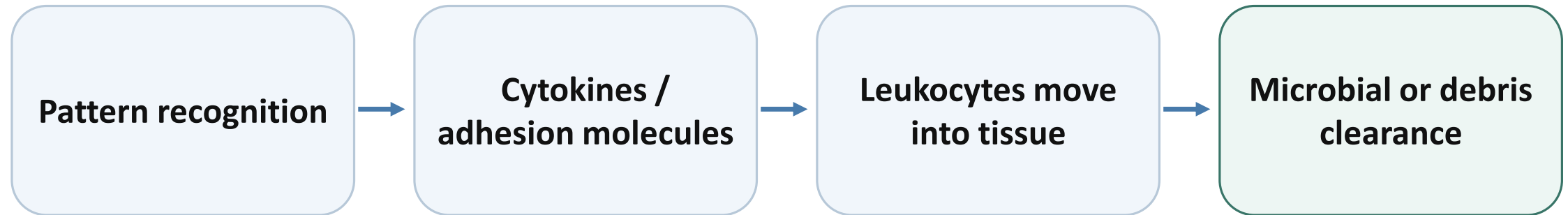
- Inflammatory cytokine secretion
- Adhesion molecule expression
- Recruitment and activation of leukocytes

IRF program

- Type I interferon production
- Antiviral cytokine signaling
- Restriction of viral threat

Pathway usage depends on the receptor and stimulus; This is a functional summary, not a claim that every TLR equally engages both arms.

Receptor signaling translates into tissue inflammation



- The tissue outcome follows coordinated signaling and cellular recruitment.

Defective TLR signaling can impair host defense

- Inherited loss-of-function variants in TLRs or their pathways can cause rare severe immunodeficiency.
- A normal receptor–signal axis is necessary for appropriate early defense.
- The textbook does not specify a universal clinical phenotype for all such defects.

Loss of pathway function



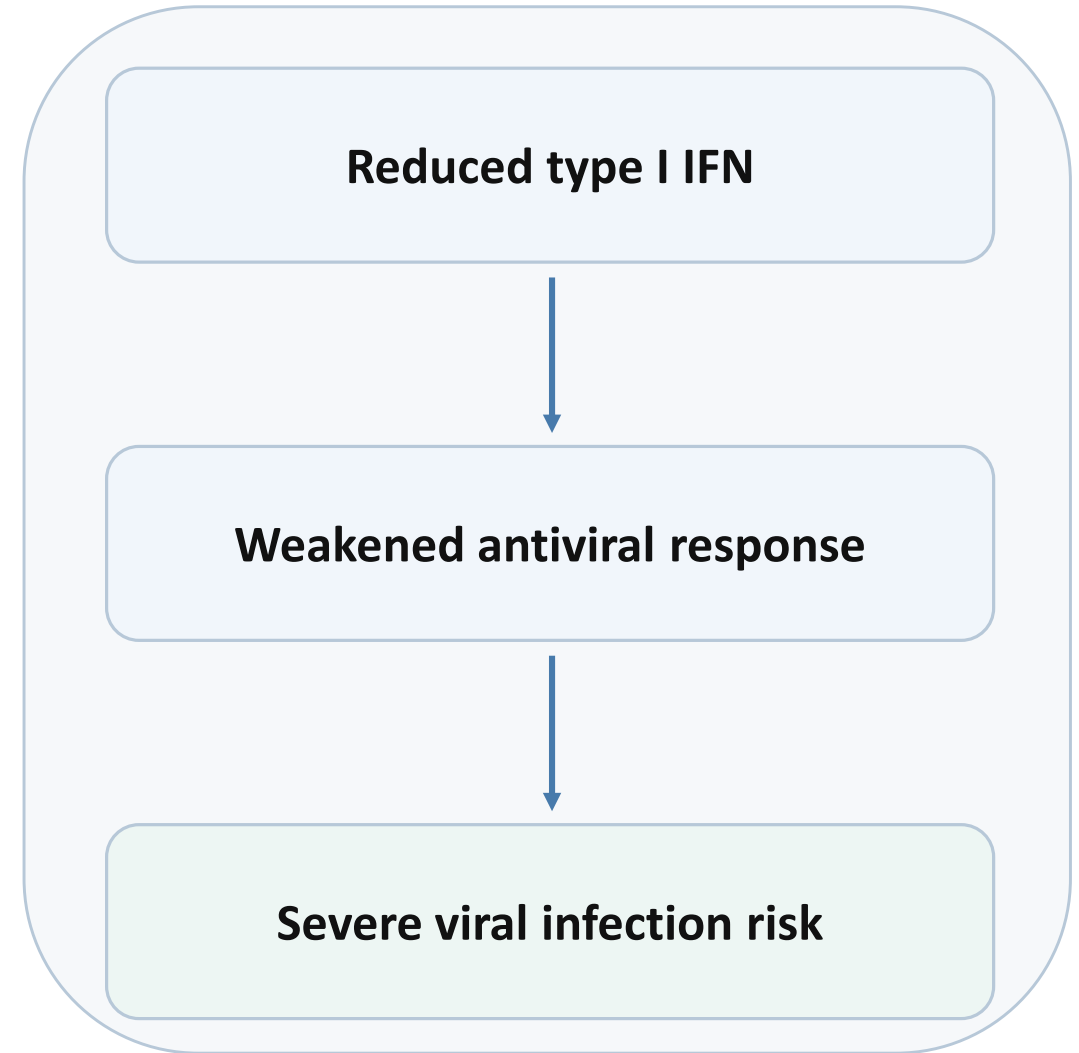
Reduced innate signal



Susceptibility to infection

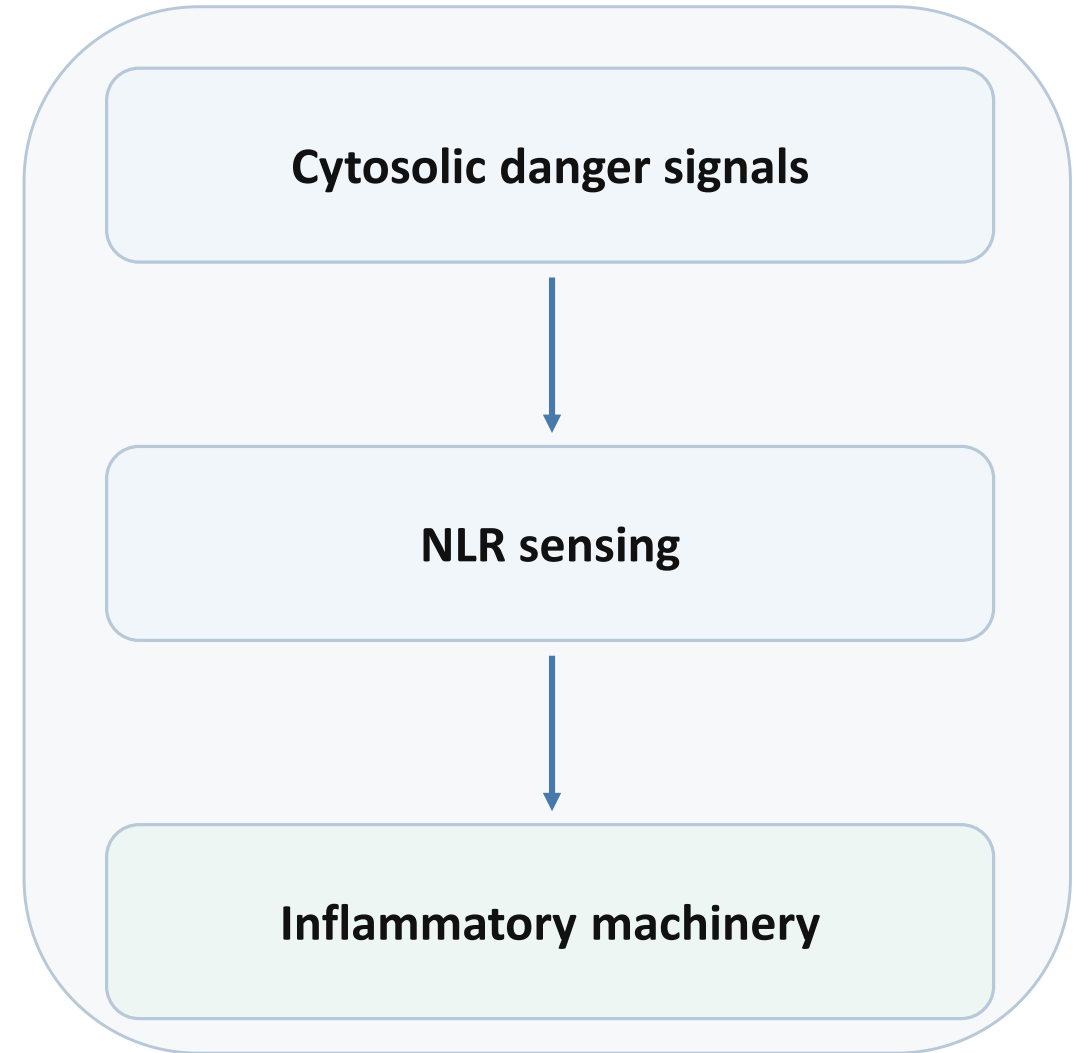
Type I IFN defects heighten viral vulnerability

- Inherited or acquired impairment of type I IFN production/function may cause severe viral disease.
- The source explicitly cites severe SARS-CoV-2 infection as an example.
- IFN insufficiency and IFN overactivation have distinct pathological consequences.



NOD-like receptors survey intracellular danger

- NOD-like receptors (NLRs) are cytosolic pattern-recognition proteins.
- The family name derives from NOD2: Nucleotide-binding oligomerization domain-containing protein 2.
- Family members respond to multiple microbial and host injury-related cues.



NLRs respond to diverse signs of cellular damage

Microbial products

Intracellular microbial structures can be recognized.

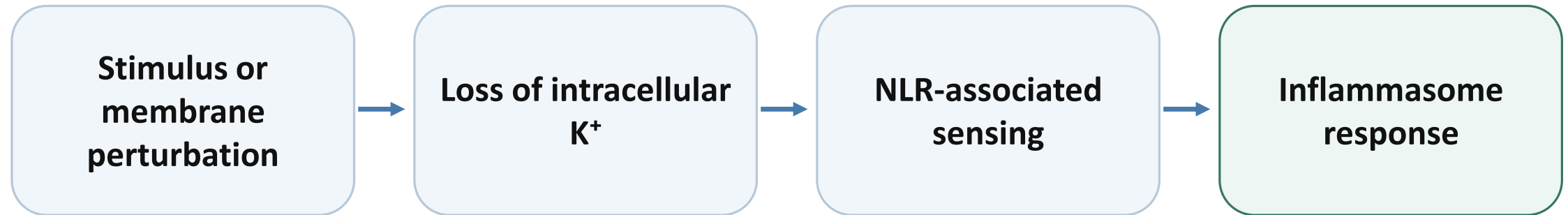
Injury-related molecules

Extracellular ATP and uric-acid-associated signals are examples.

Ionic disturbance

Reduced cytosolic K^+ is another detectable danger state.

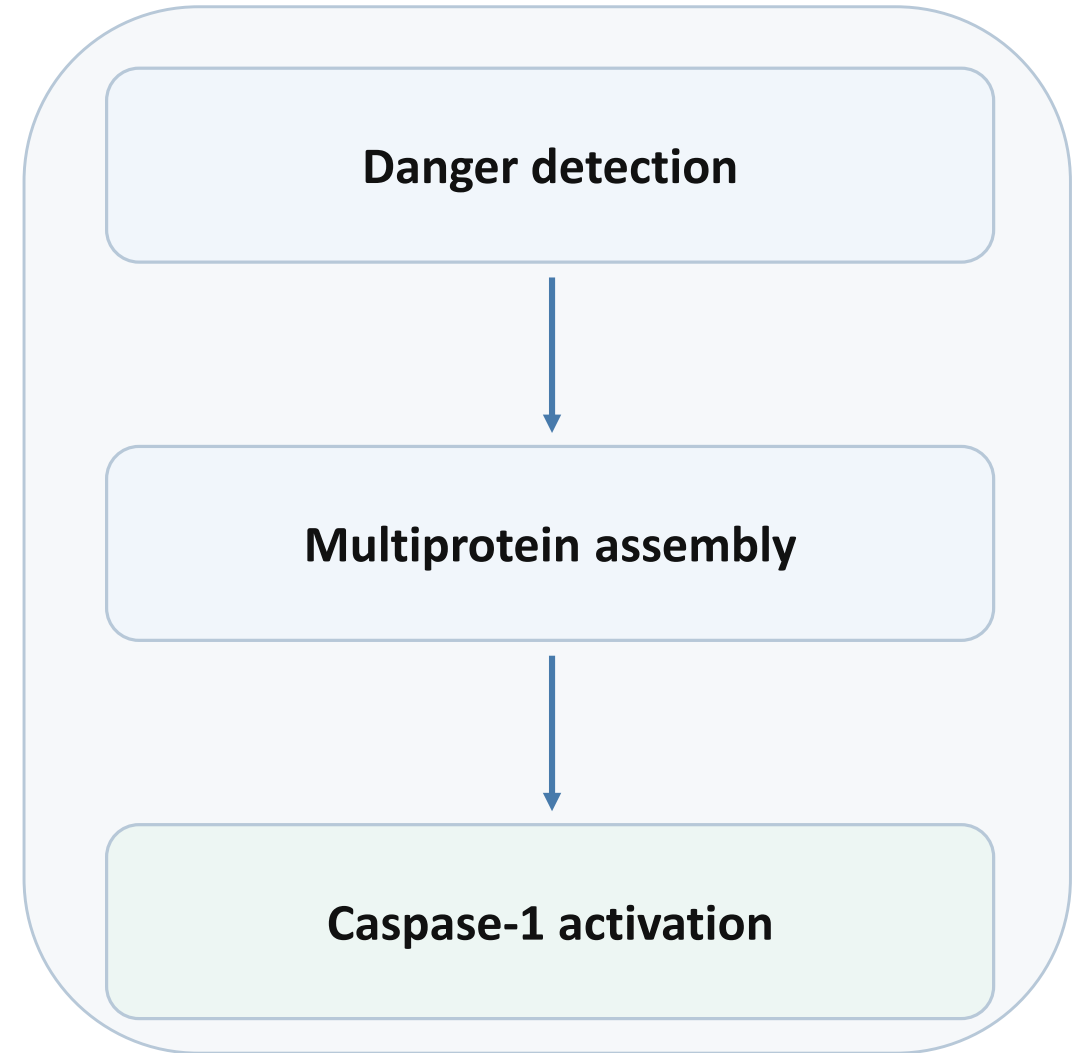
K⁺ efflux is a danger-associated cellular change



- The textbook recognizes loss of K⁺ as a signal; Its molecular recognition details remain incompletely understood.

The inflammasome is a multiprotein signaling platform

- Several NLR family members signal through cytosolic inflammasome complexes.
- An inflammasome couples danger sensing to protease activation.
- Its key downstream enzyme is caspase-1.



The NLRP3 inflammasome contains distinct components

Sensor

NLRP3 recognizes or responds to activating danger states.

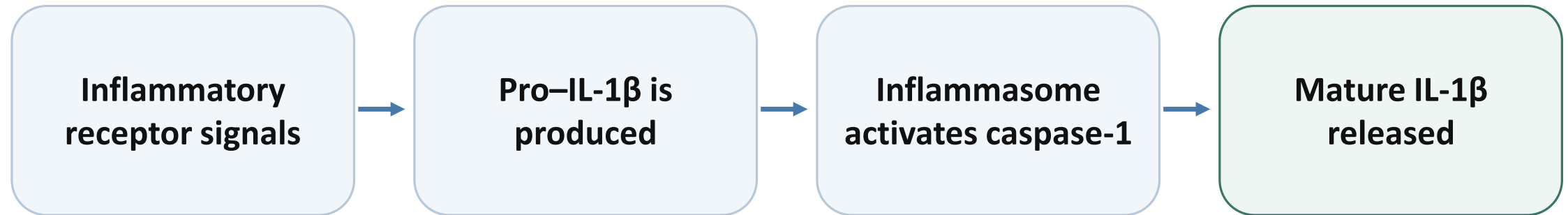
Adaptor

Links signaling components within the complex.

Effector protease

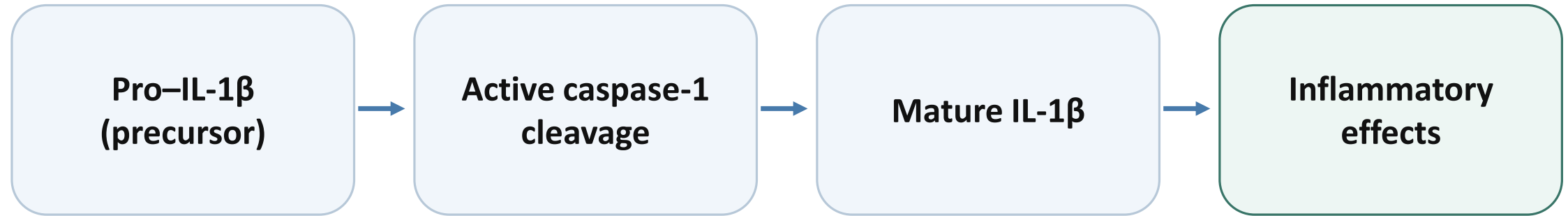
Caspase-1 is activated within the assembled complex.

Inflammasome activation couples synthesis with processing



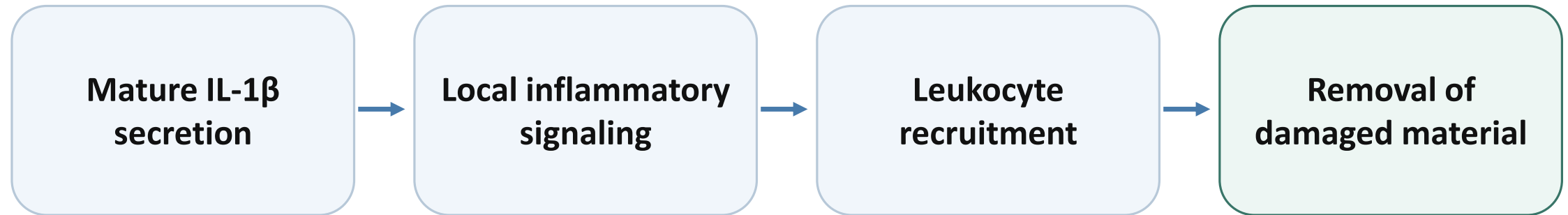
- The source figure depicts receptor-induced pro-IL-1 production and subsequent proteolytic processing.

Caspase-1 converts inactive precursor into active IL-1



- Proteolytic activation is distinct from transcriptional induction of the precursor.

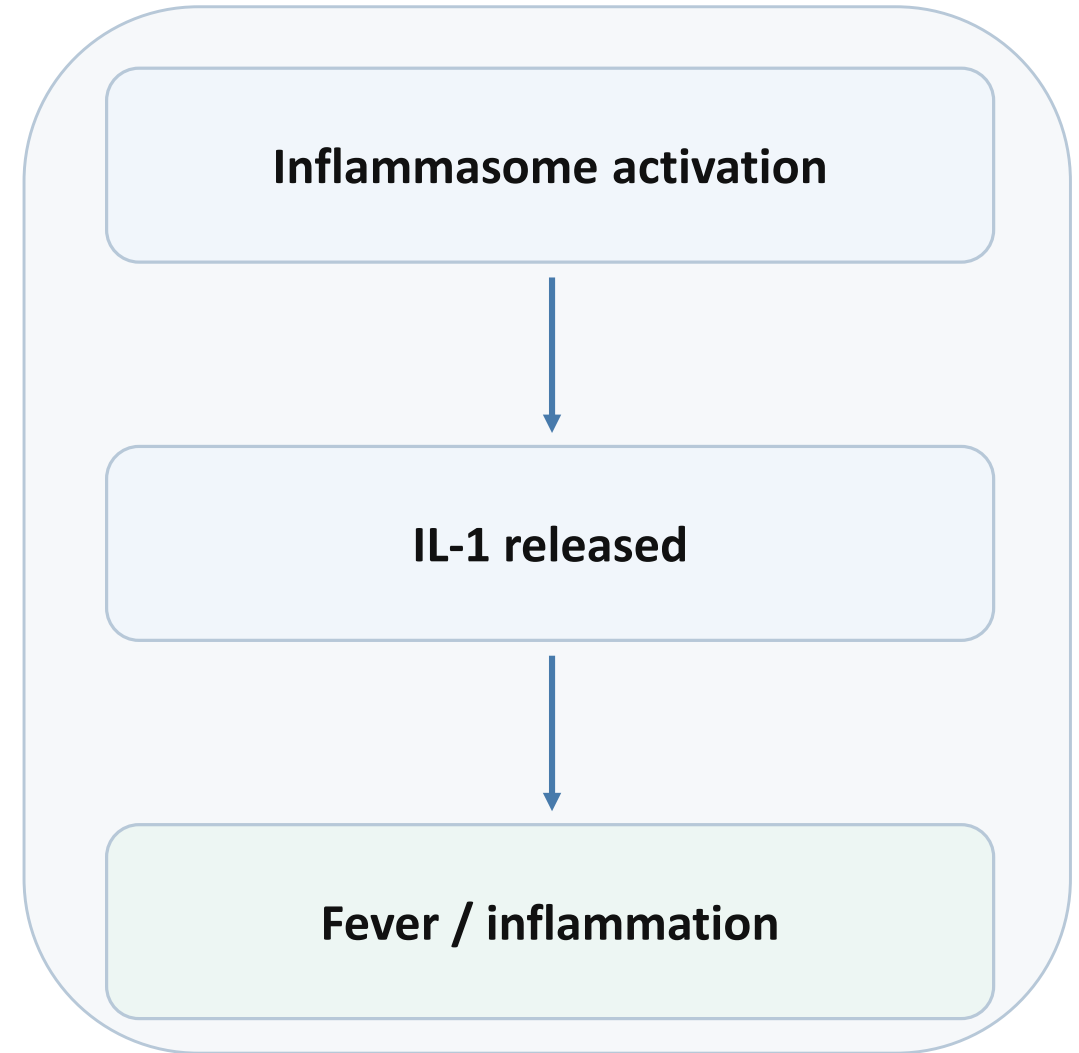
IL-1 promotes recruitment of inflammatory cells



- Inflammatory signaling is protective when appropriately regulated, but injurious if excessive.

IL-1 signaling can produce fever

- IL-1 is an important endogenous inflammatory mediator.
- Cytokine release links cellular danger recognition with a systemic febrile response.
- Repeated inappropriate activation provides a mechanistic explanation for periodic fever syndromes.



Inflammasome dysregulation causes autoinflammation

- Gain-of-function changes in NLRs or related proteins can amplify responses.
- Loss of inhibitory regulators can also permit excessive pathway activity.
- The resulting disorders may present with periodic fever and other inflammatory symptoms.

Excess inflammasome activity



High IL-1 signaling



Recurrent inflammation

Autoinflammation is not synonymous with autoimmunity

Autoinflammatory syndromes

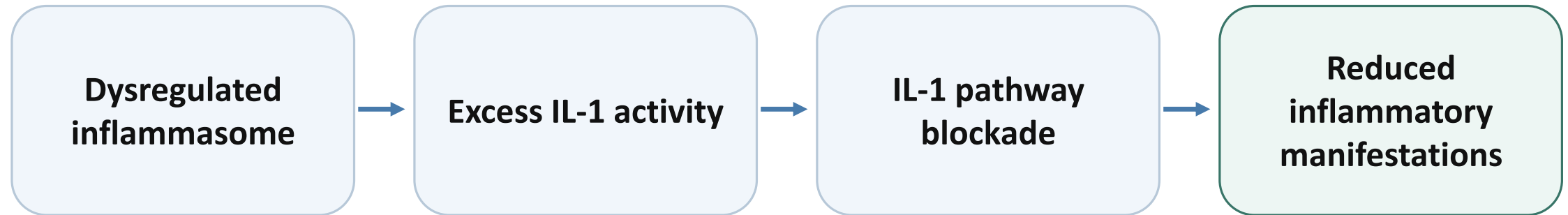
- Primary abnormality in innate inflammatory pathways
- May feature periodic fever
- Inflammasome / IL-1 pathway may be central

Autoimmune diseases

- Driven by reactions of T and B cells to self antigens
- Adaptive immune specificity is pivotal
- Different initiating pathobiology

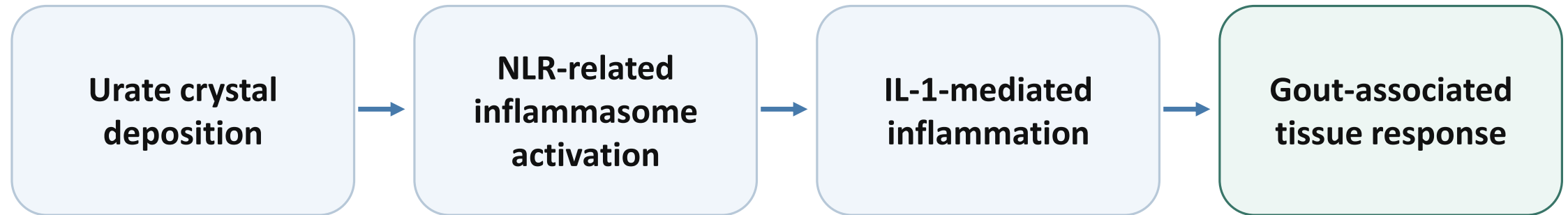
Clinical manifestations can overlap; The mechanistic distinction concerns the dominant initiating immune system.

IL-1 antagonism targets the effector pathway



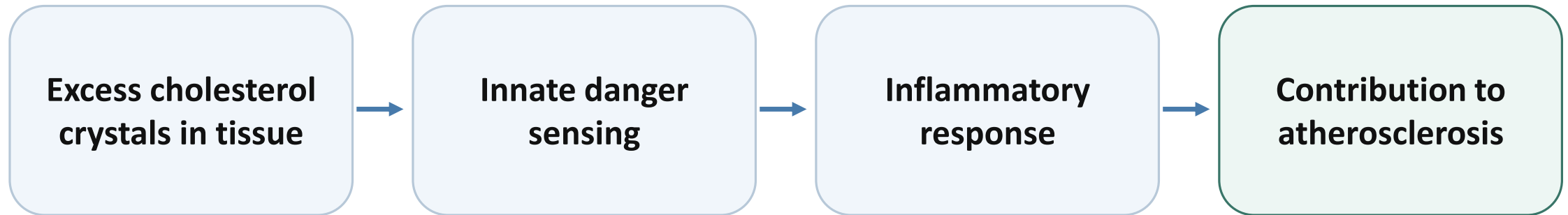
- Inflammasome-related autoinflammatory syndromes respond well to IL-1 antagonists.
- No specific drug, regimen, or response rate is asserted.

Urate crystals link inflammasome sensing to gout



- The core principle is sterile crystal-induced inflammation rather than microbial invasion.

Cholesterol crystals may amplify atherosclerotic inflammation



- The textbook uses qualified language: This pathway may contribute to atherosclerosis.
- Do not interpret this mechanism as the sole cause of the disease.

Crystals can provoke sterile inflammation through a shared route

Urate crystals

- Clinical association: Gout
- Activates inflammasome-related inflammation
- Established example in source

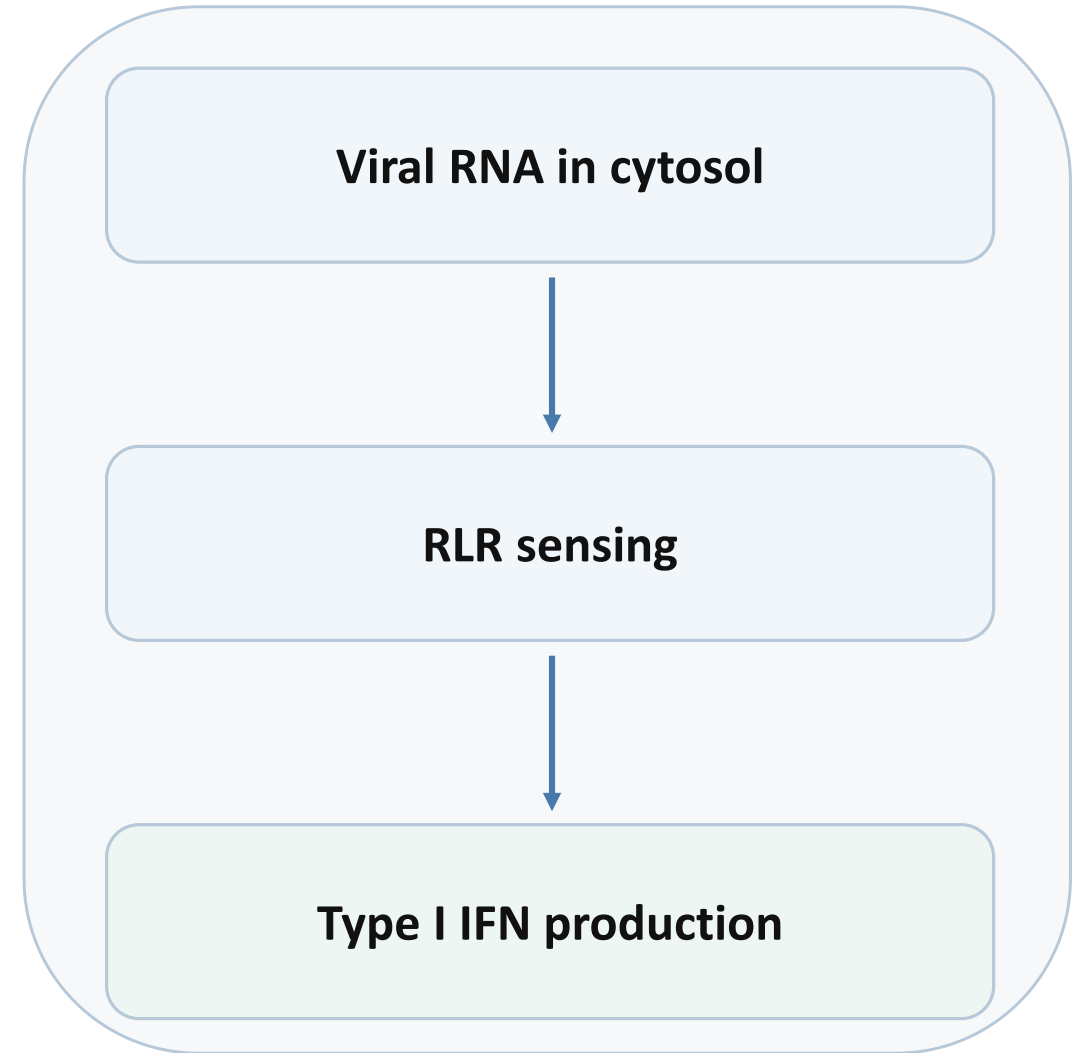
Cholesterol crystals

- Present when tissue cholesterol accumulates
- Can elicit receptor-associated inflammation
- Possible contribution to atherosclerosis

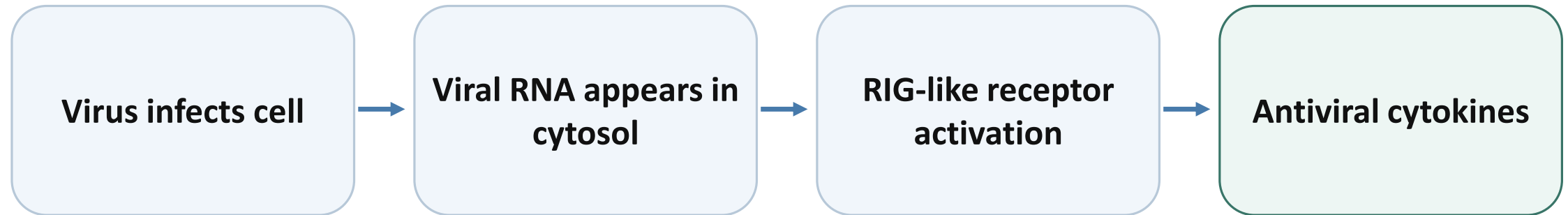
Both illustrate how nonmicrobial material may engage innate immune injury pathways.

RIG-like receptors detect cytosolic viral RNA

- RIG-like receptors (RLRs) occur in the cytosol of many cell types.
- They were named for RIG-I: Retinoic acid-inducible gene I.
- They recognize RNA associated with viruses replicating inside the cytosol.



Viral replication places RNA within the sensing compartment



- RLRs recognize the intracellular molecular context of infection.

Cytosolic DNA can signal microbial or host danger

Microbial DNA

May derive from viruses present within the cell.

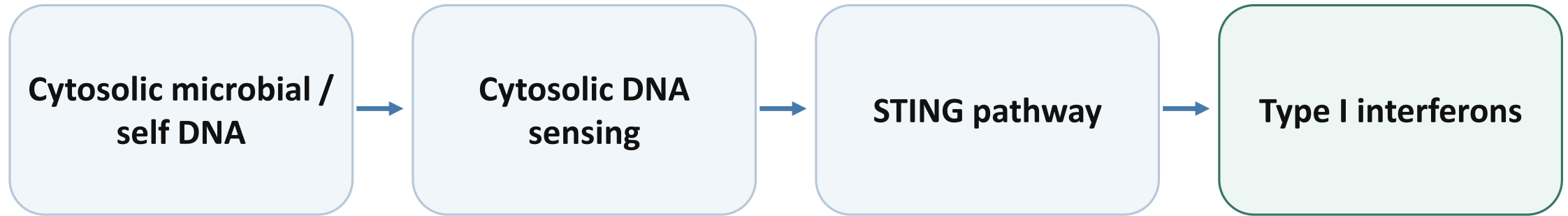
Mislocalized self DNA

Accumulation of host DNA in cytosol can also trigger sensing.

Common outcome

DNA sensors engage the STING pathway for type I IFN generation.

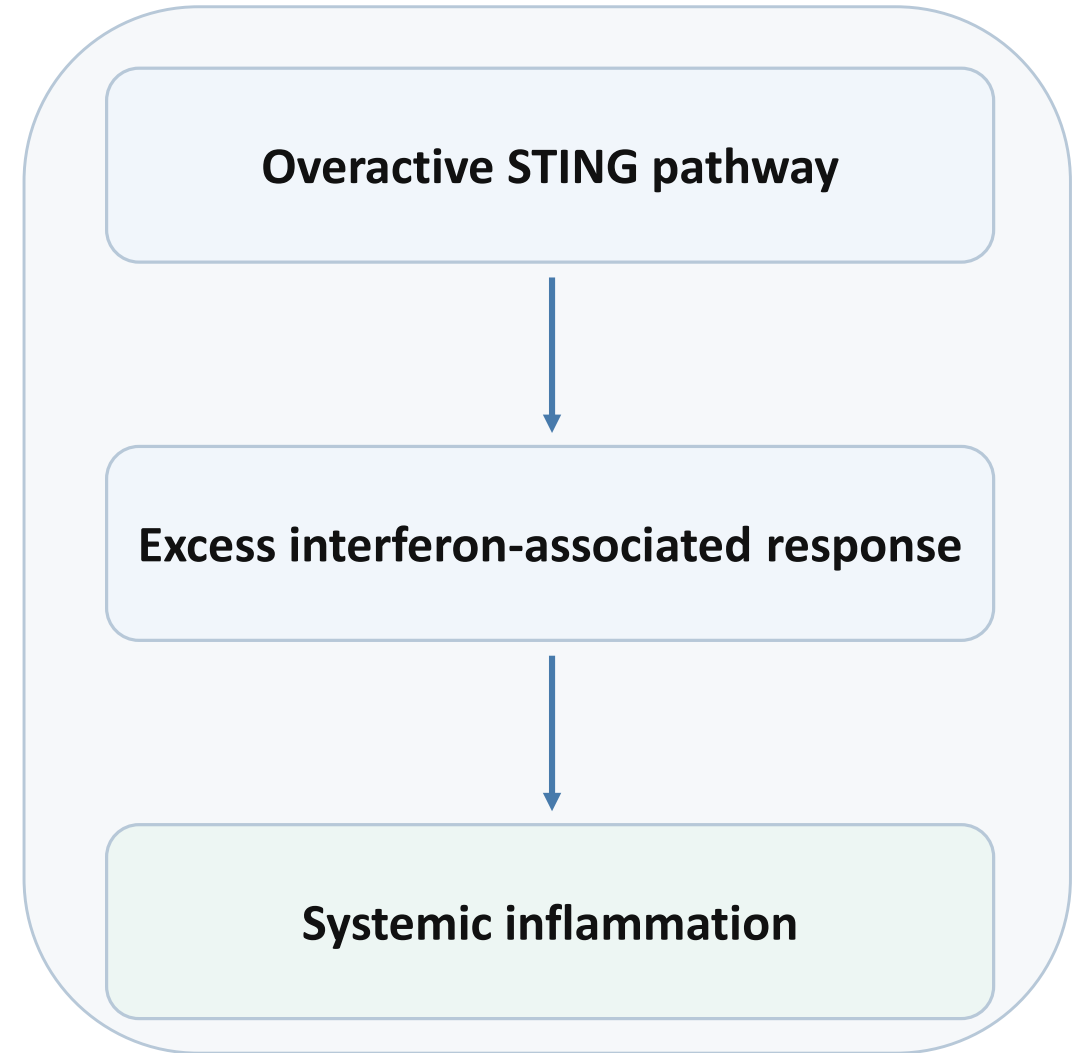
STING links cytosolic DNA recognition to interferons



- STING denotes stimulator of interferon genes; It is a signaling pathway component, not a synonym for every DNA sensor.

Excess STING pathway activity causes interferonopathies

- Antiviral signaling must be controlled in magnitude and duration.
- Excessive STING signaling can produce systemic inflammatory conditions.
- The textbook groups these conditions as interferonopathies.



RNA and DNA sensing converge on type I interferons

RIG-like receptor system

- Trigger: Cytosolic viral RNA
- Sensor: RIG-like receptor
- Product: Type I IFN

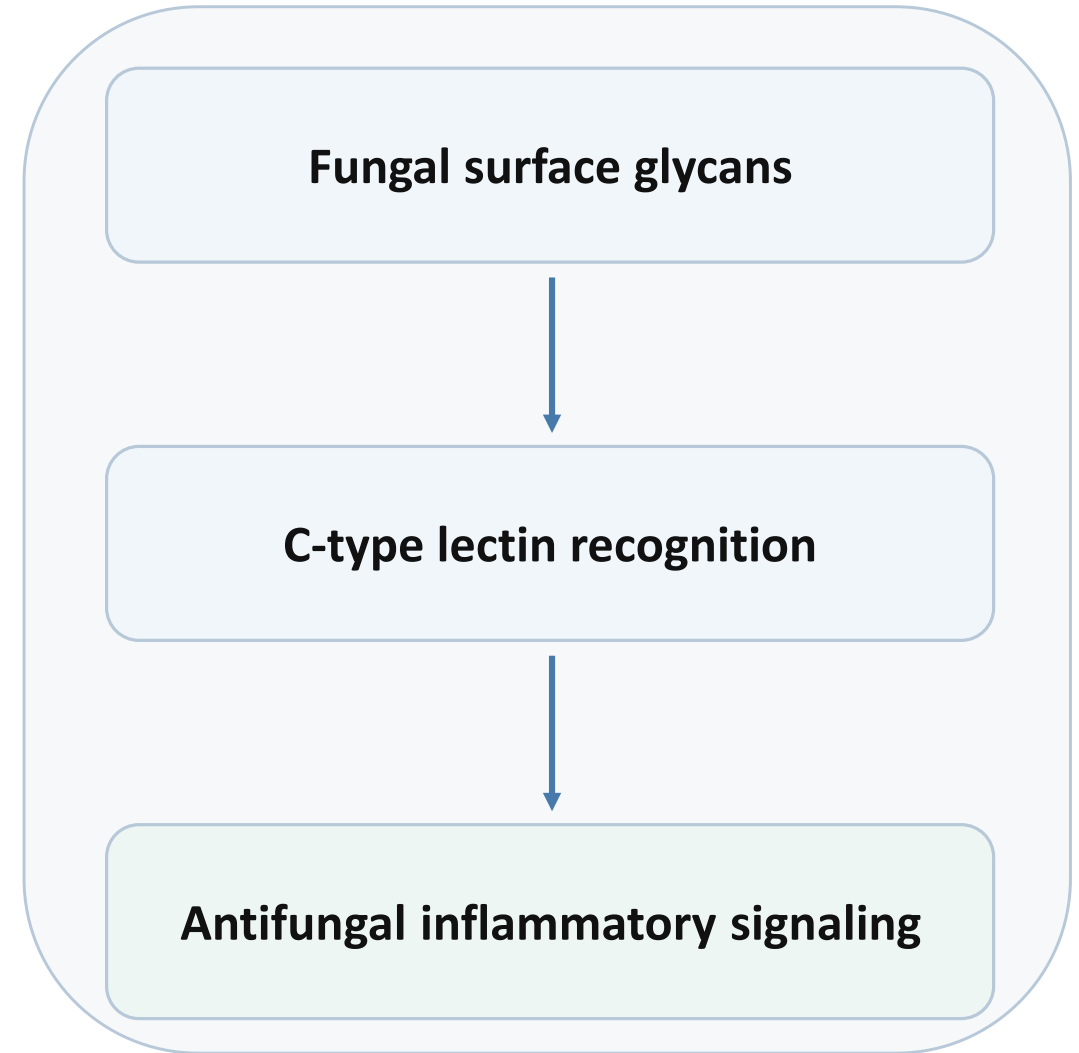
Cytosolic DNA system

- Trigger: Cytosolic DNA, microbial or host
- Signal: DNA-sensor → STING
- Product: Type I IFN

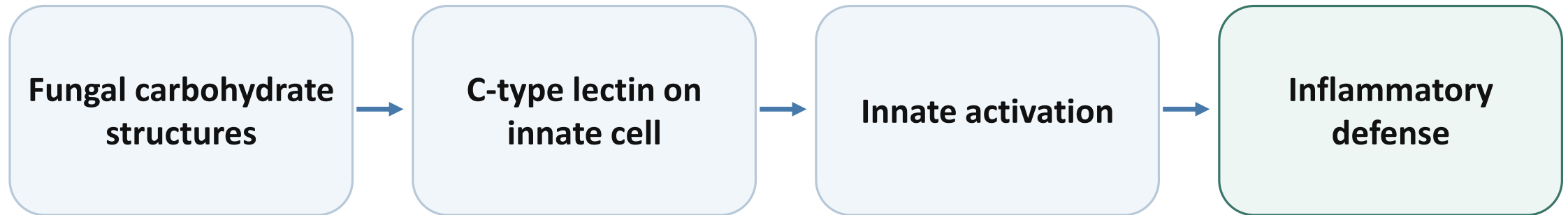
Distinct upstream sensors can engage an overlapping antiviral effector program.

C-type lectin receptors recognize fungal glycans

- C-type lectin receptors (CLRs), including Dectins, are expressed on macrophages and dendritic cells.
- They are located at the plasma membrane.
- Fungal glycans trigger inflammatory responses through these receptors.



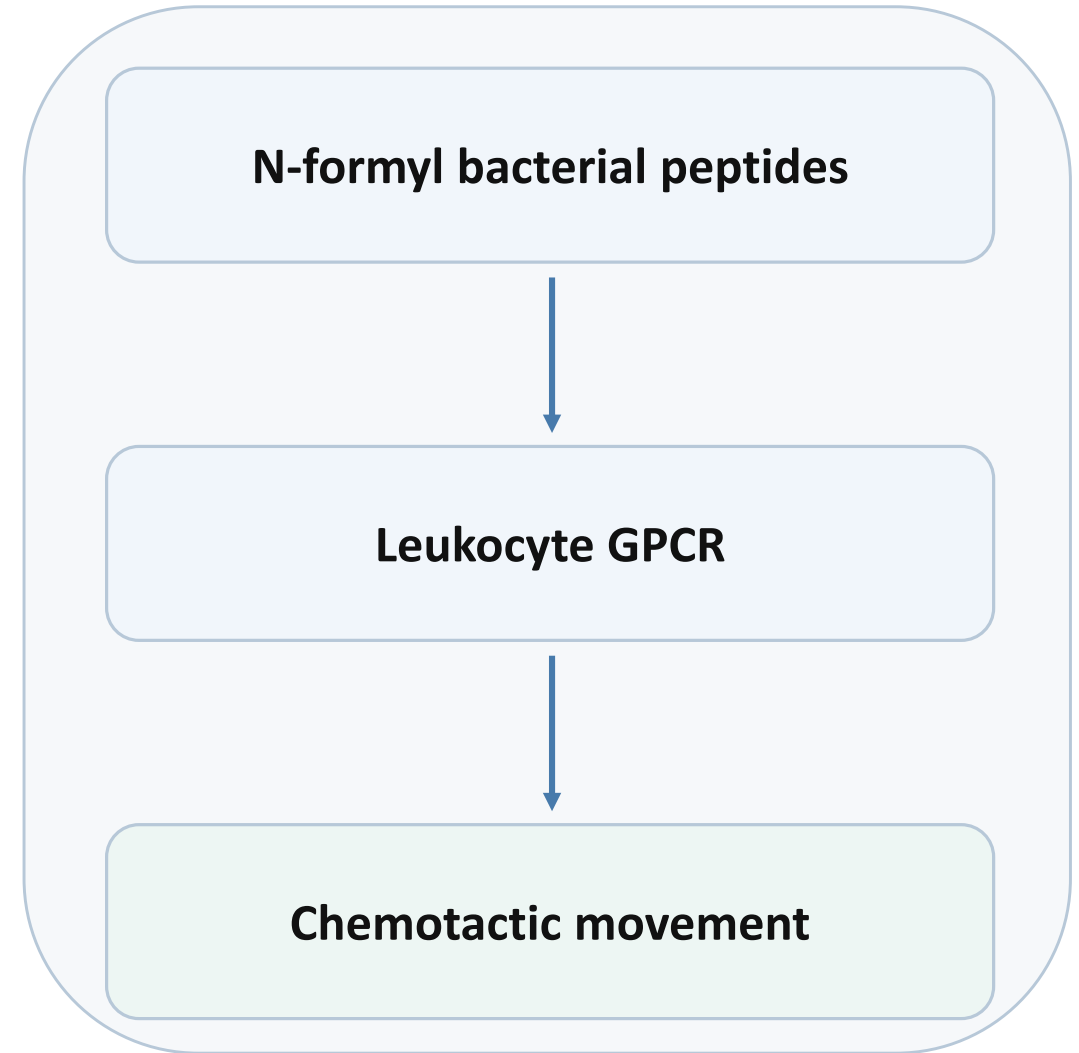
Fungal glycans provide a recognizable surface signature



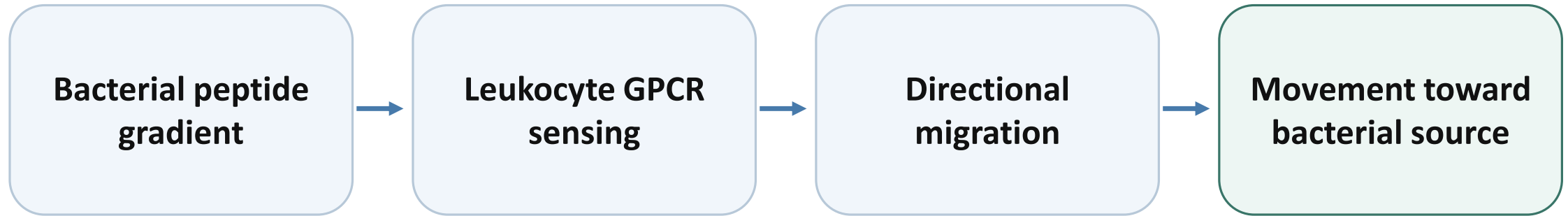
- CLRs are an additional surface-sensing system; They are not the same receptor family as TLRs.

Leukocyte GPCRs detect bacterial N-formyl peptides

- Neutrophils and macrophages express receptors for short N-formylmethionyl bacterial peptides.
- These are plasma-membrane G protein–coupled receptors.
- Detection provides directional information about the source of bacterial products.



Chemotaxis links bacterial detection to cell movement



- This pathway primarily explains movement toward a signal source, not direct microbial digestion.

N-formylmethionine distinguishes many bacterial proteins

Bacterial proteins

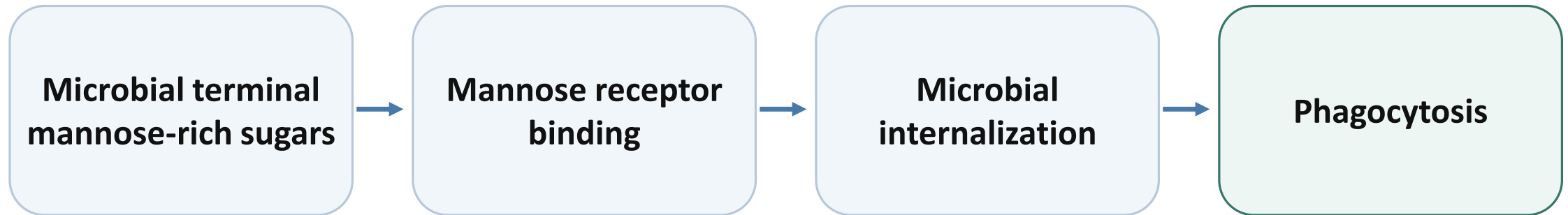
- Initiation commonly involves N-formylmethionine
- Provide N-formyl-containing peptides
- Recognized by leukocyte chemotactic receptors

Mammalian proteins

- Most cytosolic proteins lack this initiation feature
- Mitochondrially synthesized proteins are a notable exception
- Recognition is not perfectly exclusive to bacteria

The mitochondrial exception is important when interpreting specificity.

Mannose receptors support microbial phagocytosis



- Microbial glycosylation patterns differ from typical mammalian glycoproteins.

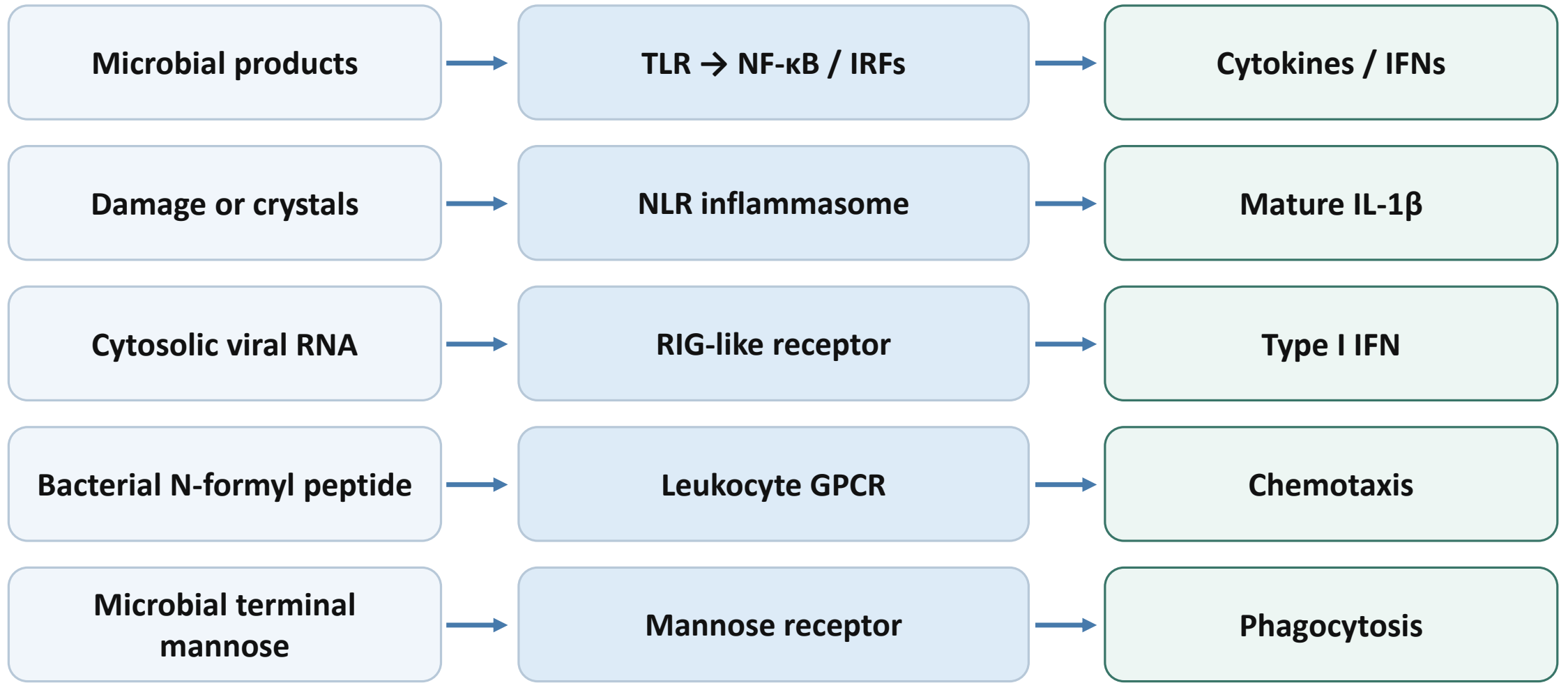
Different receptors produce different cellular actions

Receptor / pathway	Signal	Teaching endpoint
TLRs → NF-κB	Microbial products	Cytokines / adhesion molecules
TLRs or nucleic acid sensors → IFN	Microbial nucleic acids	Antiviral defense
NLR / inflammasome	Cell damage and selected stimuli	Caspase-1 → IL-1
N-formyl peptide GPCR	Bacterial peptide	Chemotaxis
Mannose receptor	Microbial sugars	Phagocytosis

Matching ligand, location, and receptor improves reasoning

Where is the signal?	What is being sensed?	Likely system
Outside cell	Fungal glycans	C-type lectin receptors
Endosome	Nucleic acids of ingested microbes	Endosomal TLRs
Cytosol	Viral RNA	RIG-like receptors
Cytosol	DNA	DNA sensors / STING
Cytosol	Damage / K ⁺ disturbance	NOD-like pathway

Innate receptor pathways diverge into distinct responses



Clinical reasoning: Acute crystal-associated inflammation

Crystals are deposited in tissue, followed by a marked inflammatory response without a pathogen being necessary.

Which innate pathway best connects the particulate danger signal to IL-1 activity?

NLR-related inflammasome activation → caspase-1 → mature IL-1.

This is the mechanistic association used explanation of gout.

Clinical reasoning: Severe viral disease with impaired interferons

An inherited or acquired defect reduces type I interferon production or function during viral infection.

Which immune consequence follows directly from the source-described mechanism?

Impaired early antiviral defense with increased risk of severe viral infection.

Type I IFN deficiency is associated with severe viral infections, including SARS-CoV-2 infection.

Clinical reasoning: Extracellular fungus and bacterial peptides

A macrophage encounters fungal glycans; A nearby neutrophil detects a concentration gradient of bacterial N-formyl peptides.

Which receptor function explains each response?

C-type lectin receptor → fungal inflammatory sensing; N-formyl peptide GPCR → chemotaxis.

Recognition of glycans and directed migration are distinct receptor outputs.

Frequent conceptual errors to avoid

Incorrect inference

- All PRRs reside at the cell surface.
- Every PRR recognizes microbial material only.
- STING and RIG-like receptors have identical upstream ligands.

Correct interpretation

- PRRs span surface, endosomal and cytosolic compartments.
- Host damage and crystals can trigger innate sensing.
- Cytosolic RNA and DNA engage different proximal systems.

A useful organizing question is: What ligand, in which compartment, activates what response?

Five outputs integrate receptor biology with pathology

Inflammation

NF- κ B, cytokines and adhesion molecules recruit leukocytes.

Antiviral defense

IRFs and cytosolic nucleic-acid pathways produce type I IFNs.

IL-1-driven pathology

Inflammasomes link danger to caspase-1 and fever.

Directed migration

N-formyl peptide receptors guide chemotaxis.

Particle uptake

Mannose recognition helps microbial phagocytosis.

Primary reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease.

11th edition (2026).

Section: Cellular Receptors for Microbes, Products of Damaged Cells, and Foreign Substances.

Conceptual schematics are original editable PowerPoint objects; they are not reproduced textbook figures.