

Natural Killer Cells

Recognition, activation, cytotoxicity, and clinicopathologic relevance

Innate surveillance at the interface of cellular stress and host defense

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Learning outcomes

Recognize

Explain why an NK cell may spare a healthy cell but kill an abnormal one.

Mechanism

Trace inhibitory and activating receptor signals and CD16-mediated ADCC.

Clinical reasoning

Connect cytokine control and NK dysfunction to infection, cancer, and immune disease.

Use receptor balance—not a single marker—as the organizing principle.

NK cells belong to innate immunity

Innate cellular arm

- Acts early after infection or tissue damage
- Includes NK cells, phagocytes, and dendritic cells

Adaptive lymphocytes

- T and B cells express diverse antigen receptors
- Undergo antigen-driven expansion and differentiation

NK cells are lymphocytes classified by their role in innate defense.

The central task of an NK cell

Recognize and destroy severely stressed or abnormal host cells.

- Textbook examples: Virus-infected cells and tumor cells.
- An NK cell evaluates properties of the target cell surface.
- Effector action can be direct killing or cytokine secretion.

Three major NK-cell activities

Direct killing

Elimination of infected, stressed, or neoplastically transformed cells.

ADCC

Lysis of IgG-coated targets through CD16 engagement.

Cytokine release

Interferon- γ activates macrophage antimicrobial activity.

Target-cell destruction and macrophage activation are complementary functions.

NK cells in circulating lymphocytes

Approximately 5%–10% of peripheral blood lymphocytes are NK cells.

- This figure describes peripheral blood lymphocyte composition.
- Abundance is distinct from the strength of a particular NK response.
- The textbook does not specify a diagnostic cutoff for NK-cell deficiency.

NK cells versus phagocytes

NK cells

- Recognize abnormal host cells
- Destroy targets; Release IFN- γ

Phagocytes

- Ingest microbes and damaged cells
- Destroy ingested material and contribute to inflammation

Different mechanisms can cooperate against an intracellular infection.

NK cells versus dendritic cells

NK-cell emphasis

- Effector killing of damaged or infected host cells
- Early secretion of macrophage-activating cytokines

Dendritic-cell emphasis

- Capture and display protein antigens
- Connect innate sensing to T-cell activation

Recognition of danger and presentation of antigen are not interchangeable functions.

NK cells and cytotoxic T lymphocytes

NK cells

- Can kill without prior sensitization
- Integrate activating and inhibitory receptor signals

Cytotoxic T lymphocytes

- TCR recognizes peptide–MHC complexes
- Effector response depends on adaptive T-cell recognition

MHC class I can inhibit NK killing while enabling recognition by many CD8 T cells.

Three decisions preceding target killing

1. Detect

Does the target display an NK activating ligand?

2. Restrain

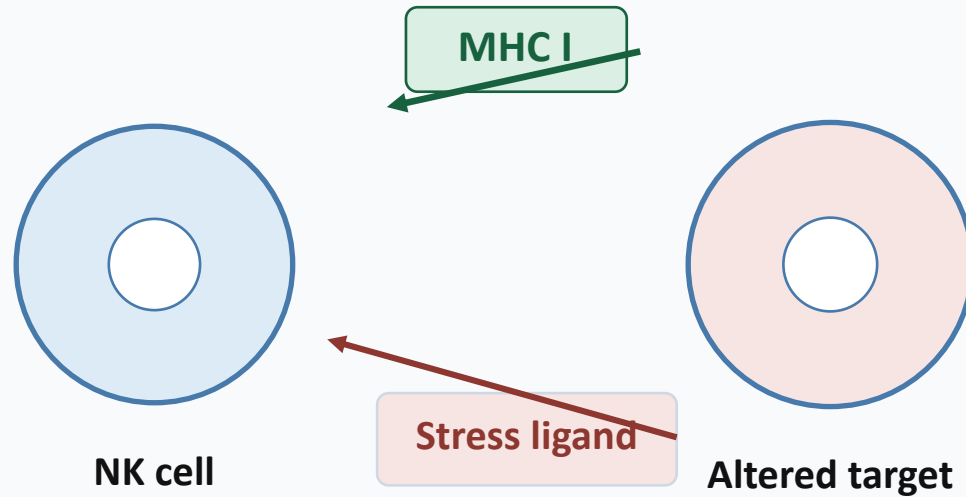
Does intact self MHC class I engage an inhibitory receptor?

3. Integrate

Does the net signal favor inhibition or activation?

NK cytotoxicity is governed by an integrated receptor balance.

Inhibitory and activating signals converge



- Activating receptors recognize ligands induced by cellular stress.
- Inhibitory receptors recognize self MHC class I molecules.
- Opposing receptor inputs regulate whether killing occurs.

Activating receptors sense cellular stress

Stress-induced surface ligands can stimulate NK-cell activating receptors.

- Infection may increase activating-ligand expression.
- DNA damage is another example of cellular stress.
- The ligand repertoire is diverse; The source does not assign a single universal ligand.

Triggers associated with NK recognition

Viral infection

Can change the target-cell surface in ways detected by NK cells.

DNA damage

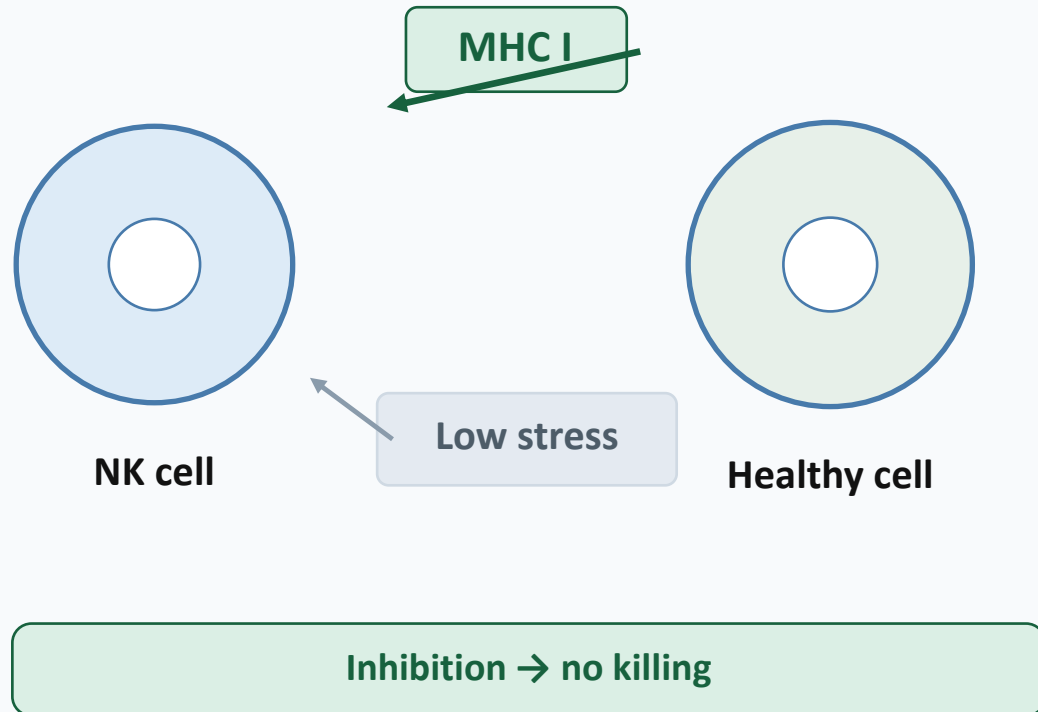
May induce ligands for NK activating receptors.

Transformation

Neoplastic cells may acquire activating ligands and reduce MHC I.

The target is evaluated as an altered self cell.

Self MHC class I generates a stop signal



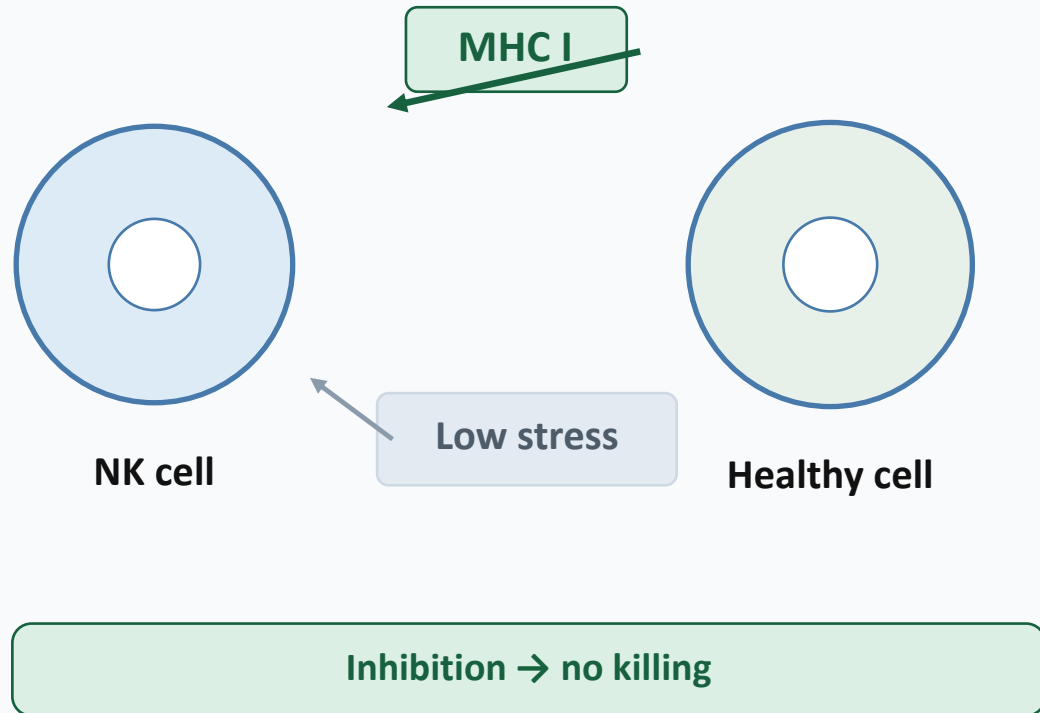
- Inhibitory NK receptors bind self MHC class I on healthy cells.
- Engaged inhibition prevents inappropriate killing.
- Intact self recognition is a critical safeguard.

Why normal tissues are protected

Engagement of inhibitory receptors restrains NK-cell cytotoxicity.

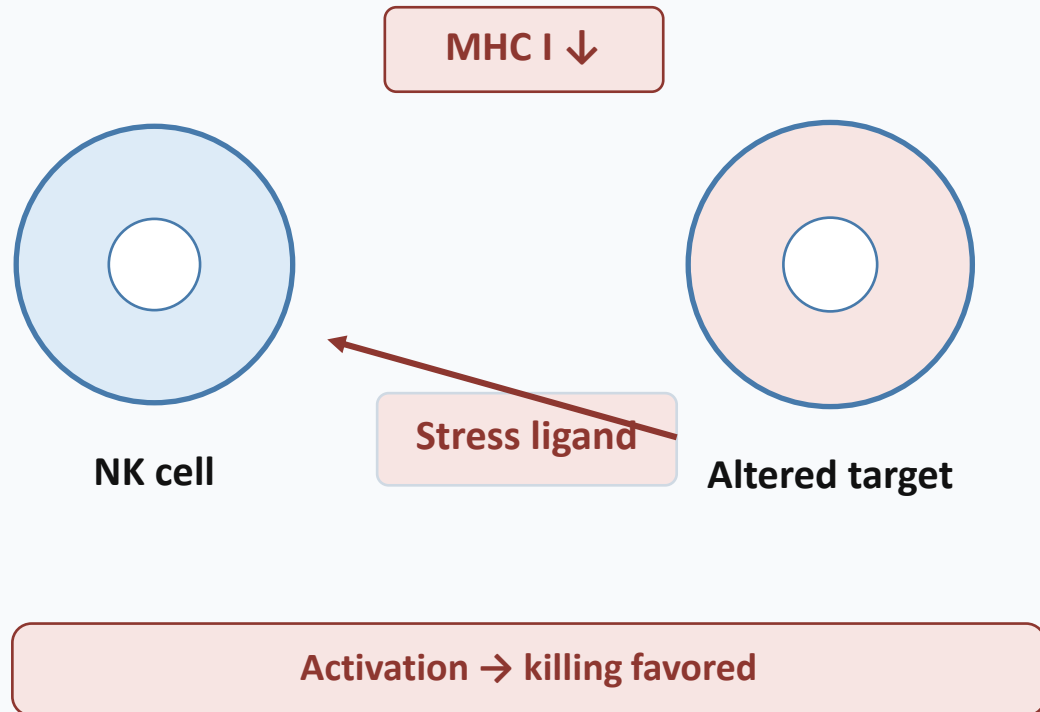
- Most healthy nucleated cells express MHC class I.
- An inhibitory signal can dominate even if activating signals are present.
- Protection requires interpreting both sides of the receptor balance.

Healthy target: Inhibition prevails



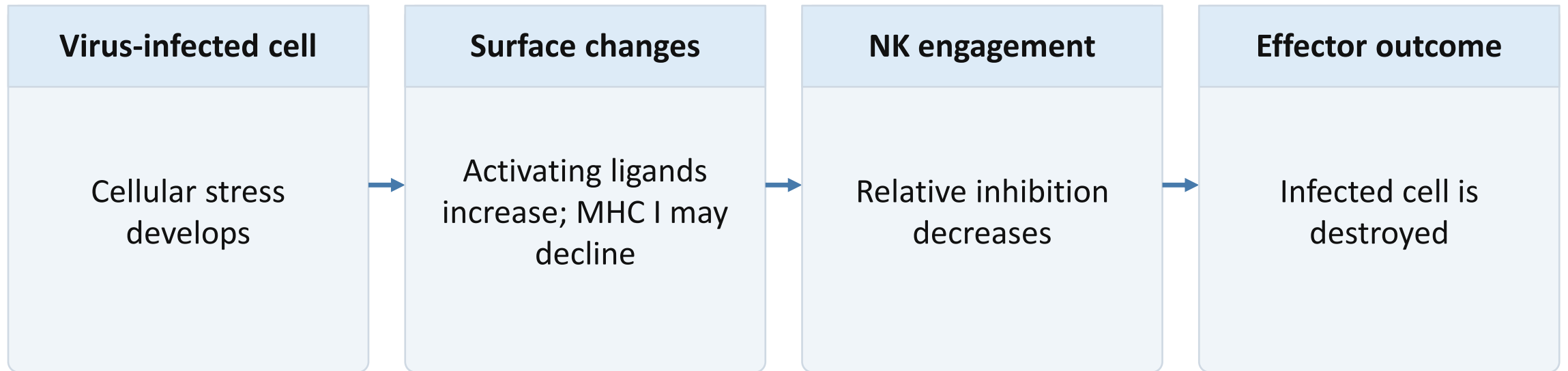
- Self MHC class I is present on the target.
- The inhibitory receptor is engaged.
- NK activation and target-cell killing are prevented.

Abnormal target: Activation may prevail



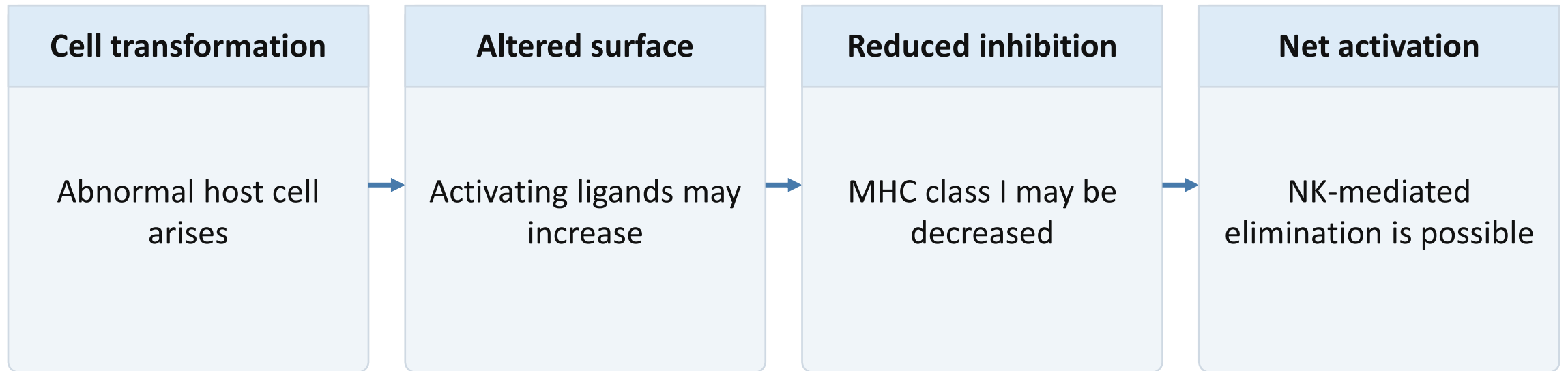
- Stress-induced ligands engage activating receptors.
- MHC class I is reduced, weakening inhibitory signaling.
- Net activation can result in target-cell killing.

From viral infection to NK killing



This is the mechanism illustrated Fig. 6.4.

From transformation to NK recognition



This as an important mode of tumor-cell surveillance.

Healthy and stressed targets: Two contrasts

Healthy target

- MHC class I retained
- Inhibitory receptor engaged
- NK cell restrained

Infected or stressed target

- MHC class I may be reduced
- Activating ligands induced
- NK cell can become activated

The decision depends on the combined inputs, not merely whether a virus is present.

Four receptor-state scenarios

Target surface	Inhibitory engagement	Interpretation
MHC I present; Little stress signal	Engaged	Typical healthy-cell restraint
MHC I present; Some activating ligands	Engaged	Inhibition can still protect
MHC I reduced; Activating ligands present	Weak or absent	NK activation favored
MHC I reduced; Ligand status unknown	Uncertain net balance	Insufficient information for prediction

The last row is deliberately indeterminate: Receptor integration matters.

Why one signal cannot predict killing

Neither MHC class I status nor an activating ligand should be interpreted in isolation.

- An activating ligand may coexist with inhibitory self recognition.
- Weak inhibitory input can permit an activating signal to dominate.
- The illustrated outcome is a balance of multiple receptor inputs.

MHC class I has a dual immunologic role

For many CD8 T cells

- Displays intracellularly derived peptide antigens
- Supports antigen recognition by the TCR

For NK cells

- Is recognized by inhibitory receptors
- Normally restrains cytotoxicity against self

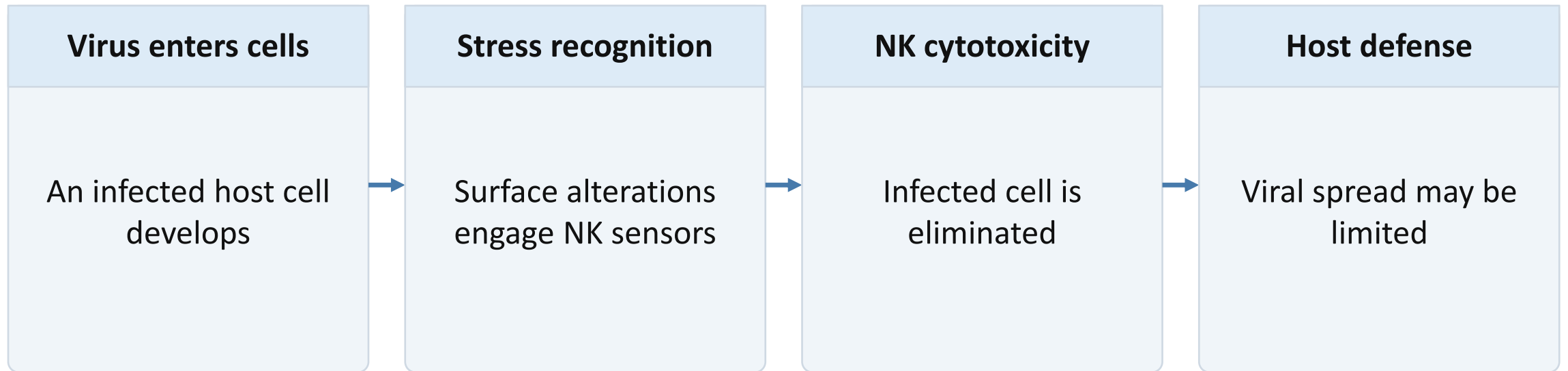
Loss of MHC I can impair one recognition pathway while removing restraint from another.

NK recognition does not require priming

NK cells can kill susceptible tumor cells without prior sensitization.

- This contrasts with antigen-specific activation of adaptive T cells.
- Early activity fits the NK role in innate host defense.
- No prior sensitization does not mean indiscriminate target killing.

NK cells in early antiviral defense



This pathway complements, rather than replaces, interferon-mediated antiviral defense.

NK-cell killing versus type I interferons

NK effector response

- Directly eliminates infected cells
- Involves target recognition and cytotoxicity

Type I IFN response

- Acts on infected and uninfected cells
- Induces an antiviral state inhibiting viral replication

Innate antiviral defenses include both cell killing and noncytolytic restriction.

Intracellular bacteria also engage NK defense

NK cells contribute to early responses to many intracellular bacterial infections.

- They are part of the broader innate cell-mediated arm.
- IFN- γ from NK cells augments macrophage microbicidal function.
- This supports defense against organisms sheltered inside host cells.

Cytotoxicity is only part of NK function

Target recognition

Stress and self-MHC cues determine activation.

Cell elimination

Activated NK cells destroy selected abnormal cells.

Cytokine coordination

IFN- γ strengthens macrophage killing of ingested microbes.

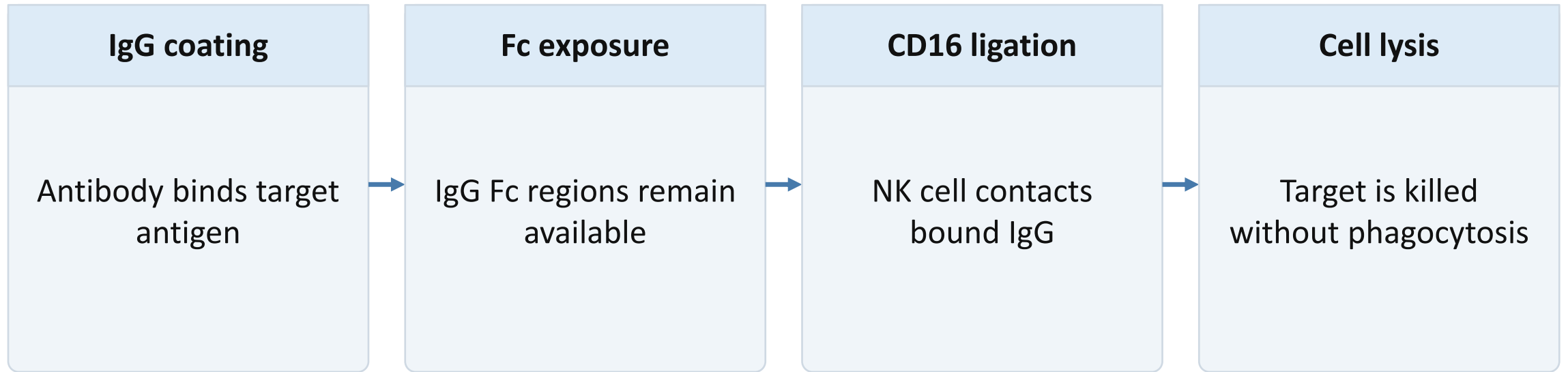
The effector program acts on both infected targets and other immune cells.

CD16 links antibodies to NK activity

CD16 is an NK-cell Fc receptor that binds the Fc region of IgG.

- IgG recognizes and coats its target through antigen binding.
- NK cells contact the antibody-coated target through CD16.
- CD16 engagement can initiate antibody-dependent cellular cytotoxicity.

Antibody-dependent cellular cytotoxicity



ADCC uses antibodies as targeting adaptors for innate effector cells.

Fab specificity and Fc recognition

Antibody Fab region

- Binds antigenic structures on the target
- Determines antibody target specificity

Antibody Fc region

- Is recognized by NK-cell CD16
- Connects the coated target to cytotoxic effector action

The NK receptor recognizes the antibody Fc—not the antigen-specific binding site.

What makes cytotoxicity antibody-dependent?

The target must be coated with IgG that can engage Fc receptors on the effector cell.

- Antibody supplies specificity for the target.
- CD16 supplies the link to NK-cell killing.
- The mechanism is distinct from the stress-ligand recognition schematic.

ADCC versus opsonophagocytosis

ADCC

- NK cells and macrophages can be effectors
- Antibody-coated cell is lysed without engulfment

Opsonophagocytosis

- Phagocytes bind IgG Fc or complement fragments
- Coated material is internalized and destroyed

Both use antibody coating but differ in the immediate cell-destruction mechanism.

ADCC versus complement-mediated lysis

NK-cell ADCC

- Fc receptor-dependent effector cell contact
- Target lysis without phagocytosis

Complement membrane attack

- Complement cascade assembles membrane attack complex
- Membrane integrity is disrupted

Do not label every antibody-associated killing event as ADCC.

Compare antibody-directed effector pathways

Pathway	Recognition	Immediate mechanism
NK-cell ADCC	CD16 binds IgG Fc	Effector-mediated cell lysis
Phagocytic removal	IgG Fc or deposited C3b	Engulfment and intracellular destruction
Complement attack	Antibody-dependent complement activation	Membrane attack complex injury

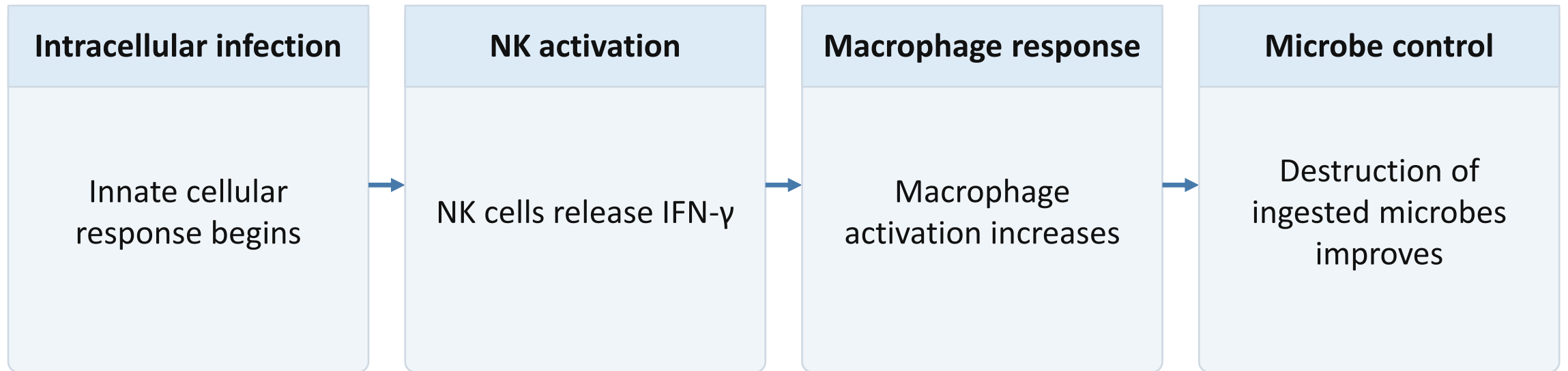
Shared antibody recognition need not imply identical mechanisms.

ADCC in immunopathology: A limitation

ADCC is a biologically established mechanism, but its contribution to common hypersensitivity diseases is uncertain.

- The textbook also describes antibody-mediated phagocytosis and complement injury.
- Do not automatically attribute a clinical cytopenia to NK-cell ADCC.
- Separate a plausible mechanism from a demonstrated disease-specific contribution.

IFN- γ couples NK cells to macrophages



This collaboration is a central noncytolytic NK contribution.

IFN- γ is a macrophage-activating cytokine

NK-cell IFN- γ promotes macrophage killing of ingested microbes.

- Its target in this context is an immune effector cell.
- The major outcome is enhanced destruction of internalized pathogens.
- Cytokine secretion can contribute even when the NK cell is not killing the infected cell.

Type I interferons and IFN- γ are not synonyms

Type I IFNs

- Induce antiviral state in infected and nearby cells
- Inhibit viral nucleic acids and replication

IFN- γ

- Can be secreted by NK cells and T cells
- Activates macrophage antimicrobial activity

Both are interferons, but these textbook-described dominant functions differ.

Cytokines regulating NK responses

IL-2

Stimulates NK-cell
proliferation.

IL-15

Stimulates NK-cell
proliferation.

IL-12

Enhances NK killing and
IFN- γ secretion.

Growth and effector activation are related but distinct regulatory outputs.

IL-2 supports NK-cell expansion

IL-2 is one of the cytokines stimulating NK-cell proliferation.

- Expansion increases the pool of potential innate effector cells.
- Robbins groups IL-2 with IL-15 for this effect.
- Proliferation should not be confused with immediate target recognition.

IL-15 supports NK-cell expansion

IL-15 is among the cytokines that stimulate NK-cell proliferation.

- IL-15 as a proliferative stimulus.
- Its receptor shares a common γ -chain component with other cytokine receptors.
- Loss of the common γ -chain can be accompanied by NK-cell deficiency.

IL-12 enhances NK effector function

IL-12 promotes both killing of target cells and secretion of IFN- γ .

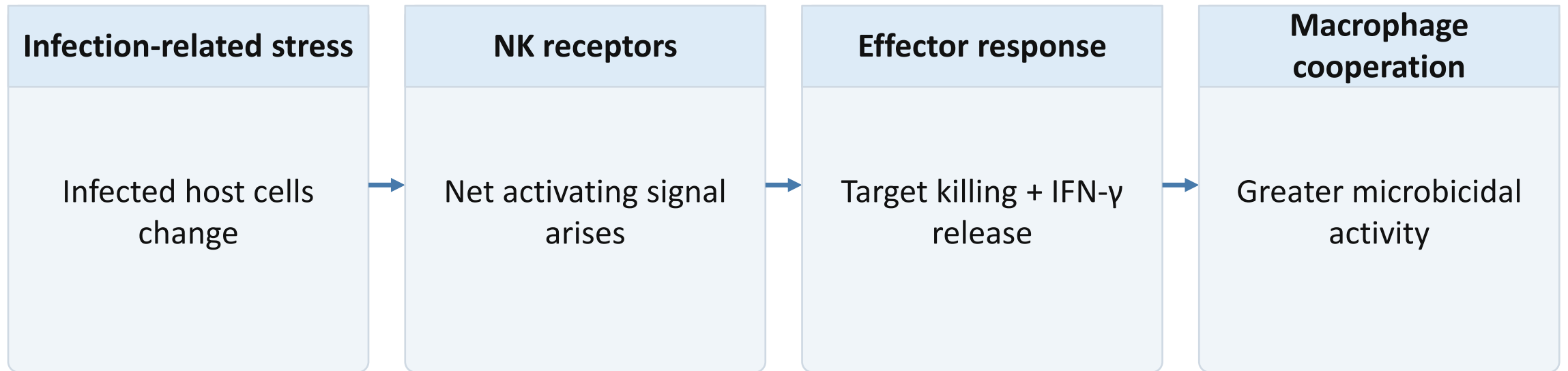
- This supports a cytotoxic effector response.
- Simultaneous IFN- γ secretion recruits macrophage antimicrobial mechanisms.
- These are functional outputs, not surface antigens used for identifying NK cells.

NK cytokines: Discriminate their effects

Cytokine	Effect emphasized	Interpretation
IL-2	NK-cell proliferation	Expands the cell population
IL-15	NK-cell proliferation	Supports NK availability
IL-12	Killing and IFN- γ secretion	Enhances effector activity

These simplified roles are the ones explicitly described in the source section.

Coordinating early cellular host defense



Direct and indirect NK effects can function together.

IL-15 signaling and immunodeficiency

Some common γ -chain–associated SCID cases also show deficient NK cells.

- The common γ -chain is a component of the IL-15 receptor.
- Disrupted cytokine signaling can affect more than one lymphocyte population.
- A reduced NK population illustrates the clinical importance of cytokine support.

NK deficiency versus impaired killing

Too few NK cells

- A quantitative deficit may follow altered cytokine receptor signaling
- Example: Common γ -chain–related immunodeficiency

NK killing machinery fails

- Cytotoxic granule formation or deployment is disrupted
- Example: Familial forms of HLH

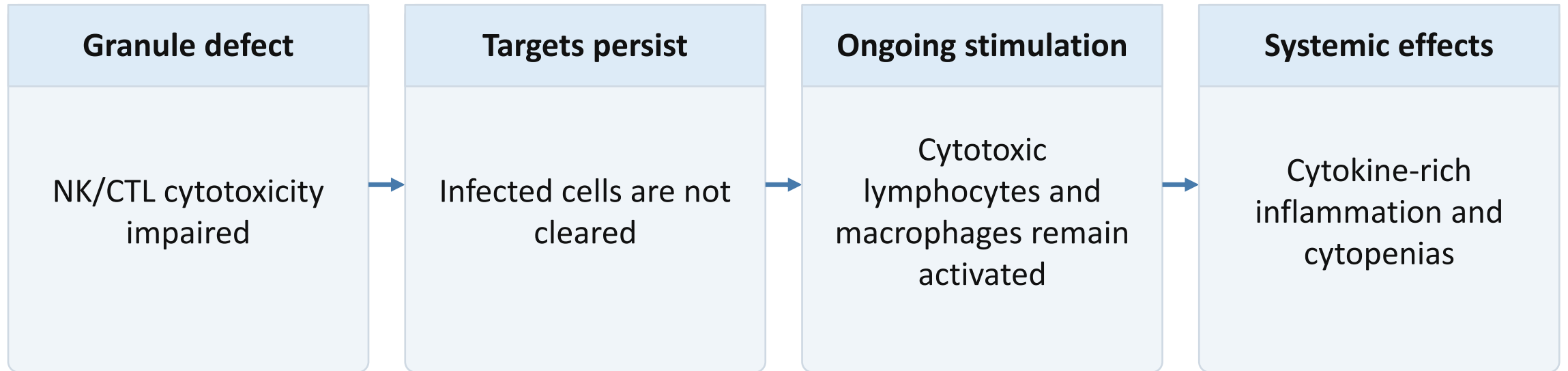
Numerical depletion and functional cytotoxic failure are different biologic problems.

Defective cytotoxic granules in familial HLH

Several familial HLH mutations impair the formation or deployment of cytotoxic granules by NK cells and CTLs.

- The proposed consequence is failure to eliminate some infected cells.
- Persistent targets may perpetuate immune-cell stimulation.
- This links defective killing to excessive systemic inflammation.

HLH: Failure to terminate a stimulus



This is a disease mechanism, not merely a numerical deficit in NK cells.

NK cells can recognize tumor immune escape

Tumor-cell loss of MHC class I may reduce inhibition of NK-cell killing.

- Some cancers become poorly recognized by MHC-restricted T-cell pathways.
- NK cells can recognize certain MHC I–low targets through receptor balance.
- The textbook supports experimental tumor lysis but emphasizes uncertainty in spontaneous human tumor control.

Experimental tumor killing versus clinical certainty

Established experimental observation

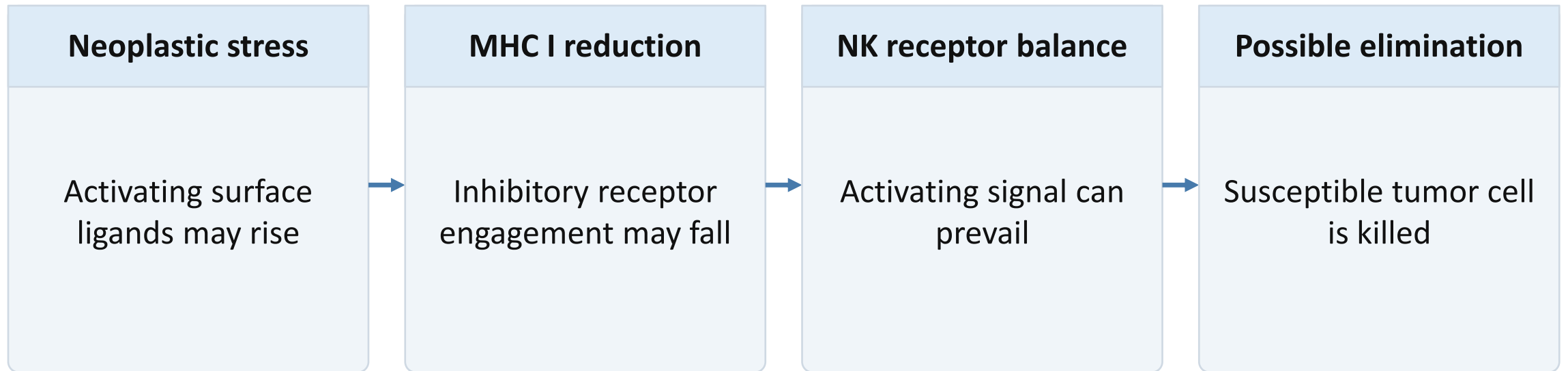
- IL-2/IL-15-activated NK cells can lyse human tumor cells
- Includes some MHC I–deficient tumor targets

Unresolved clinical inference

- Contribution to spontaneous tumor control is not fully established
- Immunotherapeutic strategies are under development

Avoid presenting promising laboratory activity as proven clinical efficacy.

Tumor immunosurveillance: Plausible sequence



A mechanistic account, not proof that all spontaneous tumors are controlled.

CMV illustrates sophisticated NK evasion

Cytomegalovirus can interfere with both arms of NK-cell receptor signaling.

- The virus may express ligands that block NK activating receptors.
- MHC class I–like viral proteins may engage NK inhibitory receptors.
- Viral MHC downregulation alone does not ensure escape from NK cells.

CMV evasion: Two receptor-level strategies

Diminish activation

- Viral ligands block activating receptors
- Positive NK signals are reduced

Strengthen inhibition

- Viral MHC I-like proteins engage inhibitory receptors
- A negative NK signal is supplied

Both changes can shift the integrated balance away from NK cytotoxicity.

CD16 and CD56 in lineage assessment

CD16 and CD56 are listed among NK-associated antigens.

- CD16 is also expressed by granulocytes.
- CD56 is also expressed by a subset of T cells.
- No single listed marker should be treated as absolutely NK-specific.

Markers shared across leukocyte populations

Antigen	Robbins distribution	Diagnostic caution
CD16	NK cells and granulocytes	Not exclusively NK-lineage
CD56	NK cells and a subset of T cells	Not exclusively NK-lineage
CD3	Thymocytes and mature T cells	T-cell lineage context
CD45	All leukocytes	Not lineage-specific

Immunophenotype is interpreted as a pattern, not by an isolated marker.

Natural killer cells are not NK-T cells

NK cells

- Innate effector lymphocytes
- Activation regulated by stress/self-MHC signals

NK-T cells

- T-cell subset sharing some NK markers
- Has a T-cell receptor; Recognizes glycolipids displayed by CD1

Shared surface markers do not make NK and NK-T cells identical.

Examples of NK-associated neoplasia

NK-cell rarity

NK-origin tumors are uncommon among lymphoid neoplasms.

Large granular lymphocytic leukemia

Can arise from cytotoxic T cells or NK cells.

Extranodal NK-/T-cell lymphoma

Usually NK-derived and strongly associated with EBV.

These are examples from the hematopathology chapter—not a complete classification.

Large granular lymphocytic leukemia

The Robbins spectrum includes indolent leukemia of cytotoxic T cells or NK cells.

- Associated with STAT3 mutations description.
- Can coexist with autoimmune phenomena and cytopenias.
- The lineage cannot be assumed from the term “large granular” alone.

Extranodal NK-/T-cell lymphoma

An aggressive neoplasm, usually NK-derived, with a strong EBV association.

- The name reflects a related NK/T-cell lymphoma category.
- Association with EBV is a clinically relevant etiologic feature.
- Definitive subtyping requires disease-specific workup beyond this NK-cell primer.

Application: A healthy host cell

An NK cell contacts a host cell expressing abundant self MHC class I. The cell also has some activating ligands.

What prevents inappropriate target-cell killing?

The self MHC I-recognizing inhibitory receptor can restrain the NK cell despite activating inputs.

Application: A virus-infected target

A virus-infected cell shows reduced MHC class I and increased stress-induced activating ligands.

What receptor balance and outcome are expected?

Inhibition is weakened, activation is favored, and susceptible infected cells can be killed.

Application: An antibody-coated cell

A target cell is coated with IgG. An NK cell engages the exposed Fc region through CD16.

Name the effector mechanism and its distinction from phagocytosis.

Antibody-dependent cellular cytotoxicity: Target lysis without engulfment.

Application: Cytokine-specific effects

An immune response increases IL-12 signaling to NK cells while other NK growth signals are unchanged.

Which two functional outputs are emphasized?

Increased target-cell killing and enhanced IFN- γ secretion.

Application: Persistent immune stimulation

An inherited defect impairs cytotoxic-granule deployment by NK cells and CTLs.

Why may severe systemic inflammation develop?

Failure to remove infected targets may perpetuate T-cell and macrophage activation, as described in familial HLH.

Synthesis: Read the target, then the response

Surface surveillance

Activating ligands indicate stress; Self MHC I provides restraint.

Two killing routes

Direct receptor-balanced cytotoxicity or CD16-mediated ADCC.

System coordination

IFN- γ activates macrophages; IL-2/IL-15/IL-12 regulate NK responses.

NK biology connects innate surveillance to antiviral, antitumor, and antibody-mediated immunity.

Three distinctions to retain

Do not equate

- Low MHC I with automatic NK killing
- CD16/56 positivity with definitive NK lineage
- Granule failure with NK-cell absence

Instead specify

- Net activating versus inhibitory signals
- Marker patterns and diagnostic context
- Functional versus quantitative immune defects

Precise mechanisms lead to better clinicopathologic interpretation.

Concluding mechanistic model

NK-cell output is the consequence of receptor balance, antibody recognition, and cytokine context.

- Self MHC I restrains; stress-induced ligands can activate.
- CD16 couples IgG coating to cytotoxic cell killing.
- IFN- γ recruits macrophage function; cytokines modulate growth and activity.