

Mechanisms of Viral Injury

Pathogenesis • cellular tropism • tissue damage

Viral tropism

Direct cytopathic effects

Host immune injury

Cellular transformation

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Learning objectives

- Explain how viral receptors and cell-specific factors determine tissue tropism.
- Trace the cellular pathways by which viral replication produces injury.
- Distinguish direct cytopathic damage from immune-mediated tissue injury.
- Explain viral transformation and its relationship to chronic inflammation.

Three routes from infection to disease

Direct viral injury

Host synthesis shutoff; Toxic proteins; ER stress; Lysis or fusion

Immune-mediated injury

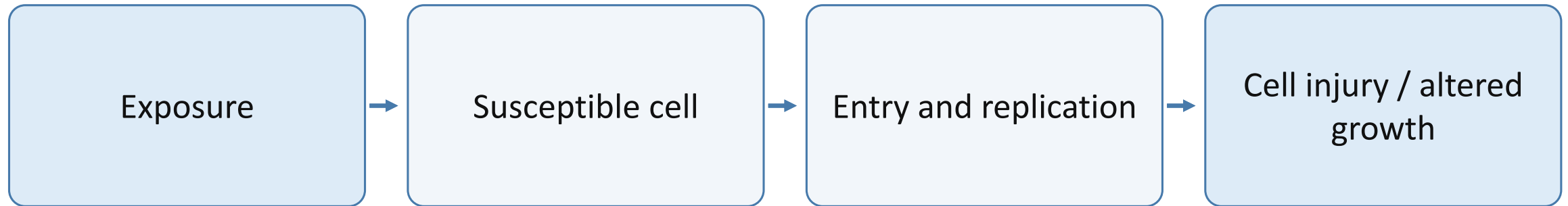
Host lymphocytes destroy infected cells; Inflammation can damage tissue

Altered growth and survival

Viral oncogenes or inactivation of tumor suppressor pathways

These pathways may coexist within an infected tissue.

Viral injury begins with successful infection

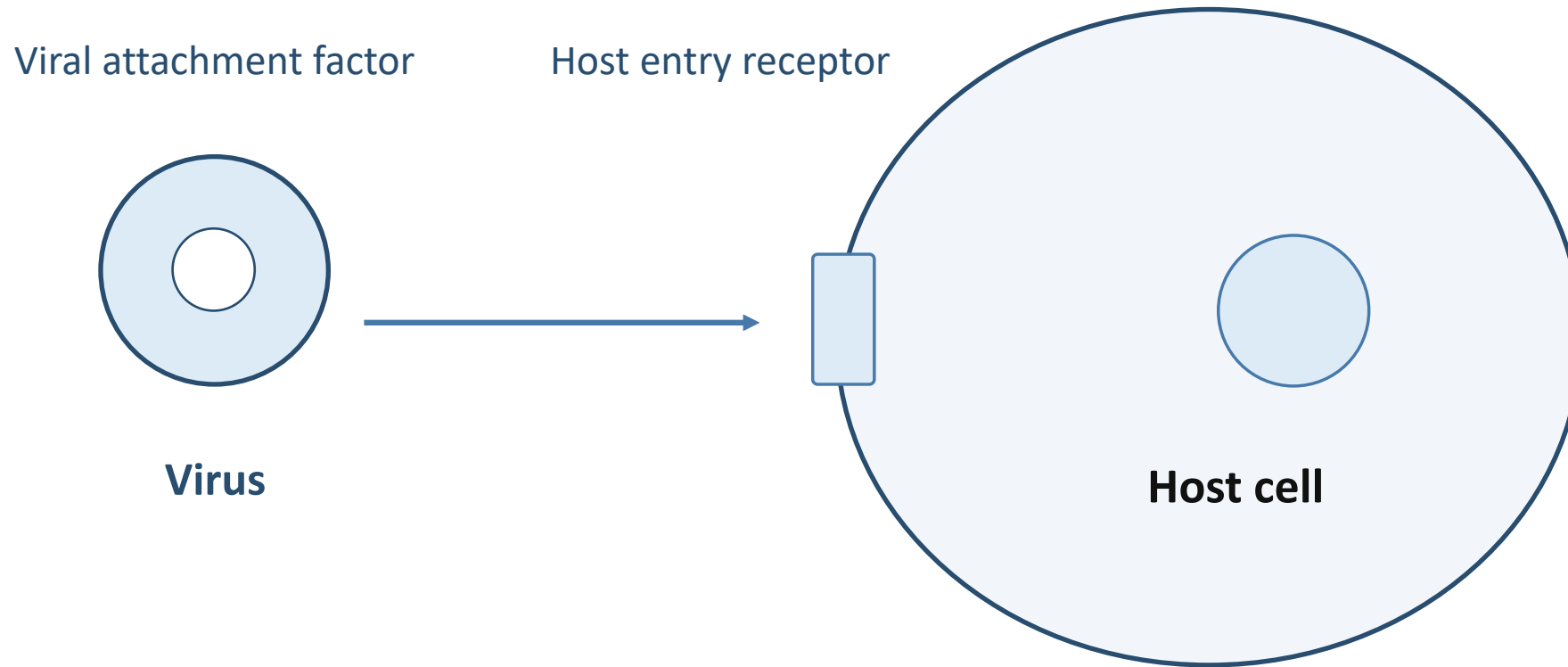


An encountered virus produces damage only if host and cellular conditions permit infection.

Tropism: Preferential infection of particular cells

- Tropism is the tendency of a virus to infect some cell types but not others.
- Host-cell entry receptors are a major determinant of this selectivity.
- Post-entry factors and local physical conditions also constrain tropism.

Receptor availability is an entry gate



A cell lacking a required entry molecule is generally resistant at the entry step.

Viral receptors have normal host functions

Normal host role

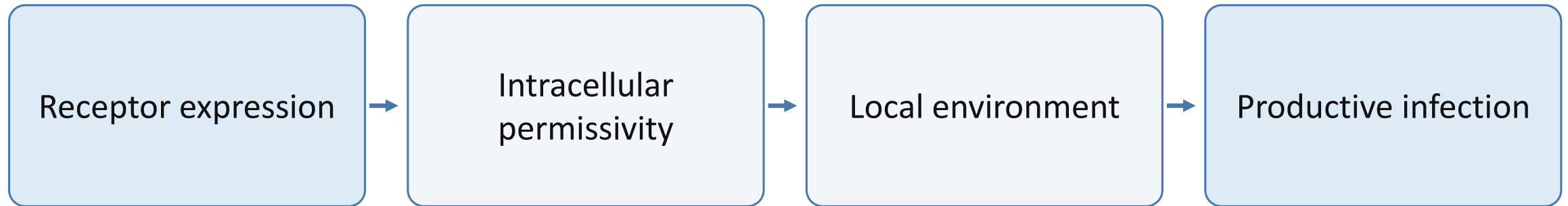
- Cell signaling receptors
- Adhesion-associated surface molecules
- Other physiological membrane proteins

Viral exploitation

- Binding to host-cell surface
- Use of receptor for attachment/entry
- New route for intracellular replication

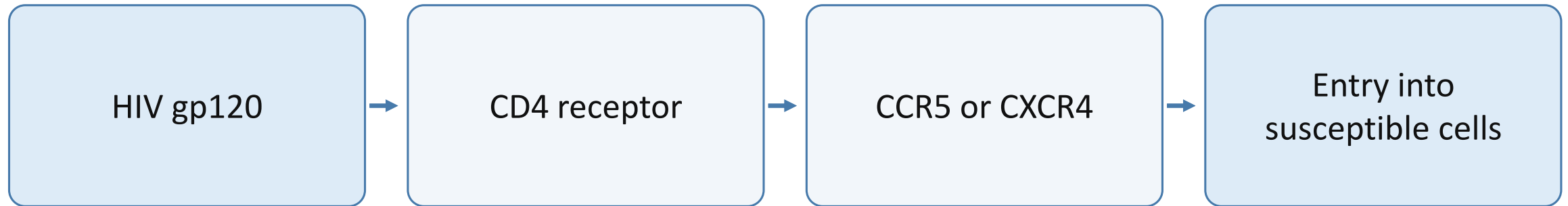
Viral binding does not imply that a receptor exists solely for infection.

An entry receptor does not explain every tropism



Tropism integrates access to the cell with the cell's ability to support viral gene expression.

HIV gp120 engages CD4 and a coreceptor



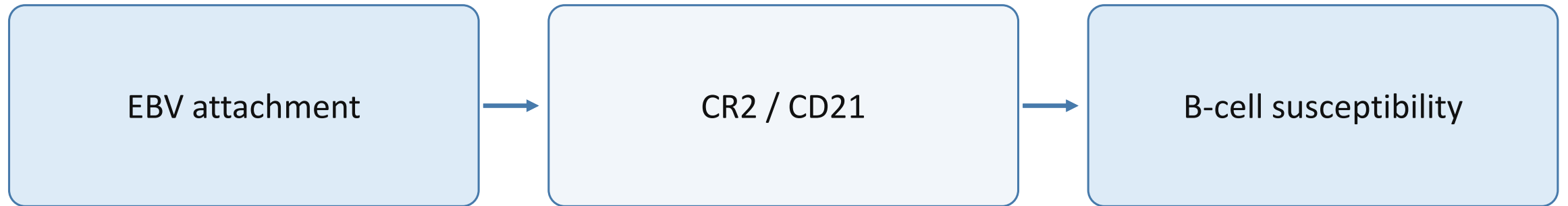
CD4 binding and chemokine coreceptors cooperate to determine cellular entry.

HIV coreceptors and cellular targeting

Component	Cellular association	Mechanistic role
CD4	Host cell surface receptor	Binding partner for gp120
CXCR4	Mainly T cells	Chemokine coreceptor
CCR5	Mainly macrophages	Chemokine coreceptor

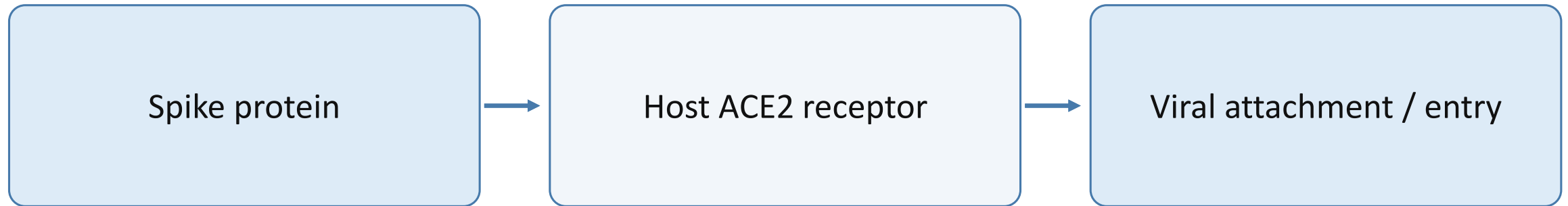
These are characteristic associations, not absolute cell-type restrictions.

EBV uses CD21 on B cells



Complement receptor 2 (CR2), also designated CD21, is the cited receptor.

SARS-CoV-2 spike binds ACE2



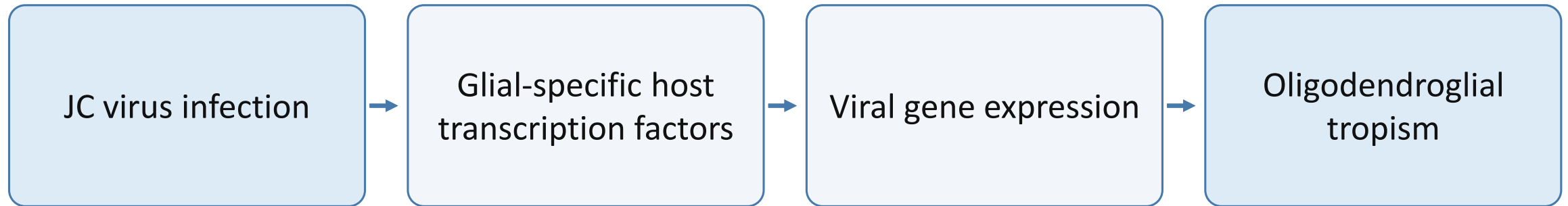
The receptor interaction is an example of molecular tropism; Injury mechanisms follow after infection.

Viral receptor examples: Compare the gate

Virus	Viral attachment factor	Host molecule
HIV	gp120	CD4 plus CCR5/CXCR4
Epstein–Barr virus	Viral attachment machinery	CR2 (CD21)
SARS-CoV-2	Spike protein	ACE2

The attachment molecule determines only one component of viral tropism.

JC virus: A post-entry tropism example



JC viral gene expression is restricted by host factors within oligodendroglial cells.

Cell lineage can control viral gene expression

Surface-level selectivity

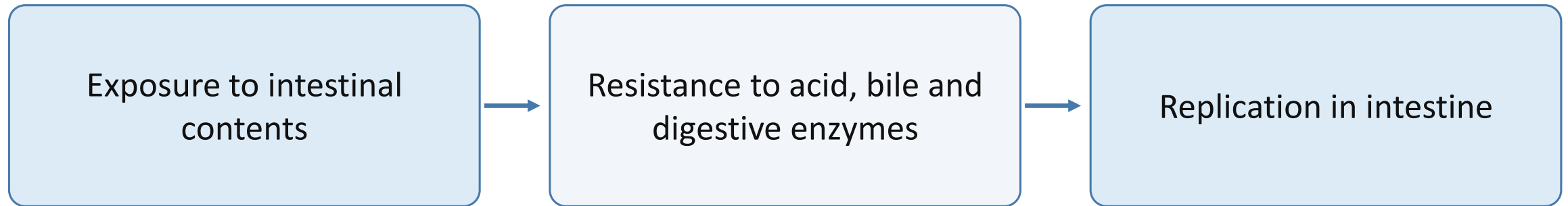
- Receptor–ligand compatibility
- Access and entry

Intracellular selectivity

- Lineage-specific transcription factors
- Support for viral gene expression

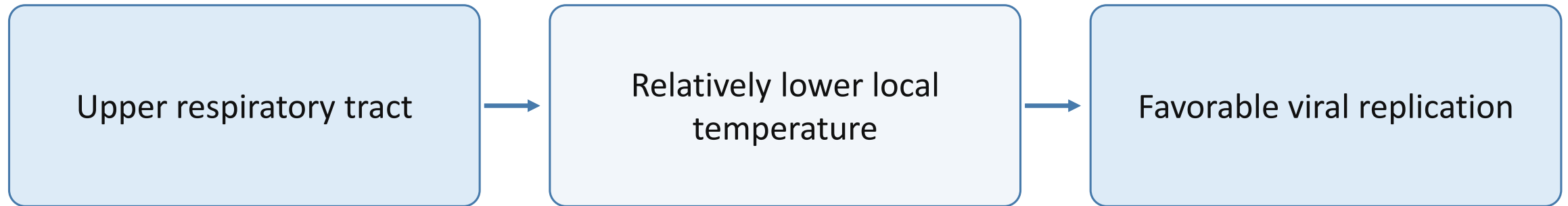
Receptor binding and gene expression are distinct restrictions on infection.

Enteroviruses withstand the intestinal milieu



Physical and chemical survival can determine which sites support infection.

Rhinoviruses favor cooler respiratory sites



Temperature sensitivity helps explain preferential upper respiratory replication.

Physical environment modifies tropism

Host-site factor	Source example	Why it matters
Luminal chemistry	Enteroviruses	Survival despite acid, bile, enzymes
Local temperature	Rhinoviruses	Replication favored at cooler sites
Lineage-specific factors	JC virus	Viral transcription permitted in glia

A receptor-centric account alone misses the conditions after exposure.

Tropism is a sequence of restrictions

1. Access

Virus reaches a tissue

2. Attachment

Appropriate entry
factor is present

3. Permissivity

Cell supports viral
gene expression

4. Replication

Local environment
permits growth

Failure at any stage may prevent productive infection.

Apply tropism: Why are all cells not infected?

Observation: Two cell populations encounter the same virus; Infection develops in only one.

1

First ask whether both populations express the entry receptor.

2

Then test whether their intracellular factors and local environments permit replication.

A simplified intracellular viral sequence

Attachment/entry

Contact with a compatible receptor

Uncoating

Genome released into cell

Replication

Viral genome and mRNA production

Translation

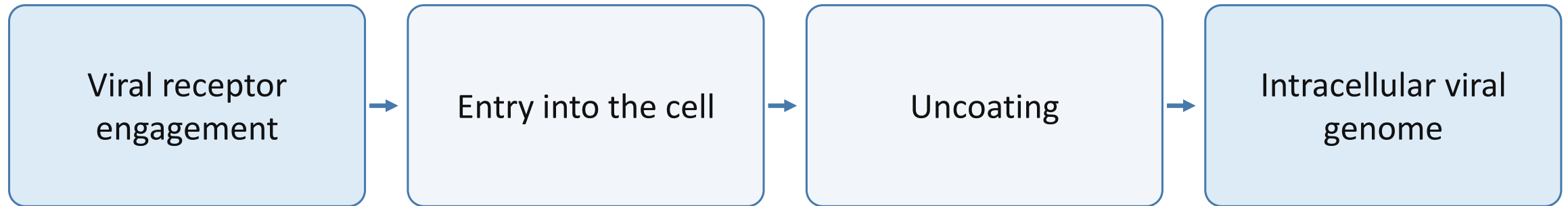
Viral proteins synthesized

Assembly

Viral components accumulate

These replication stages can each be linked to distinct routes of cell injury.

Entry and uncoating give viral genes access



After uncoating, the viral genome becomes available for intracellular processes.

Viral genome replication redirects resources

Viral requirements

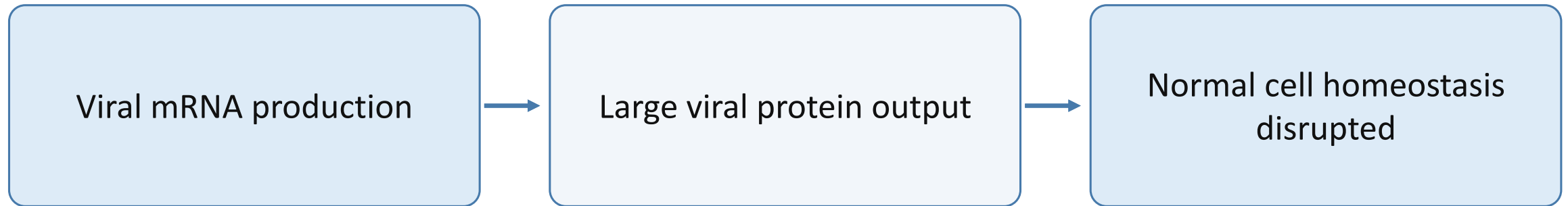
- Genome replication
- Viral mRNA synthesis
- Host metabolic support

Potential host cost

- Competition for cellular machinery
- Disturbed cellular metabolism
- Greater burden during high viral output

Cellular injury arises from the effects of infection, not merely the physical presence of a virion.

Viral protein synthesis can become injurious



Viral protein accumulation also creates stress when folding and processing capacity are exceeded.

Viral assembly is not the only injurious phase

Before assembly

Loss of host biosynthesis; Metabolic disturbance

During protein production

Misfolded proteins and ER stress

After antigen display

Host-cell killing by antiviral lymphocytes

Injury can originate during multiple phases of infection.

Direct cytopathic injury has distinct routes

Biosynthetic shutdown

Essential host DNA, RNA or protein synthesis fails

Viral products

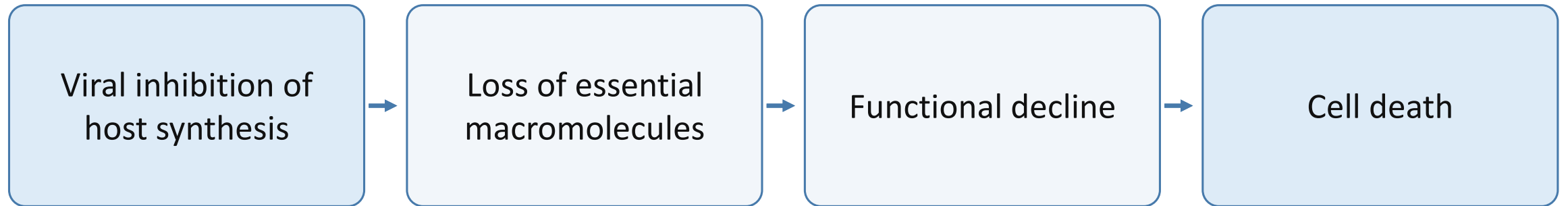
Degradative enzymes or toxic viral proteins

Proteostasis failure

Misfolded viral proteins trigger ER stress and apoptosis

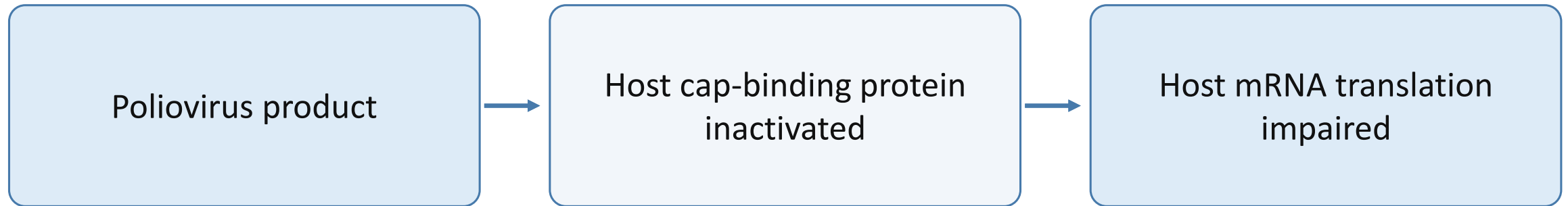
Different viral products can converge on loss of cell viability.

Host macromolecular shutoff disables the cell



Inhibition may affect host DNA, RNA, or proteins, depending on the virus.

Poliovirus disrupts cap-dependent translation



Host translation is selectively inhibited during poliovirus infection.

Poliovirus preserves its own translation

Host-cell mRNAs

- Require host cap-binding function
- Translation markedly reduced

Poliovirus mRNAs

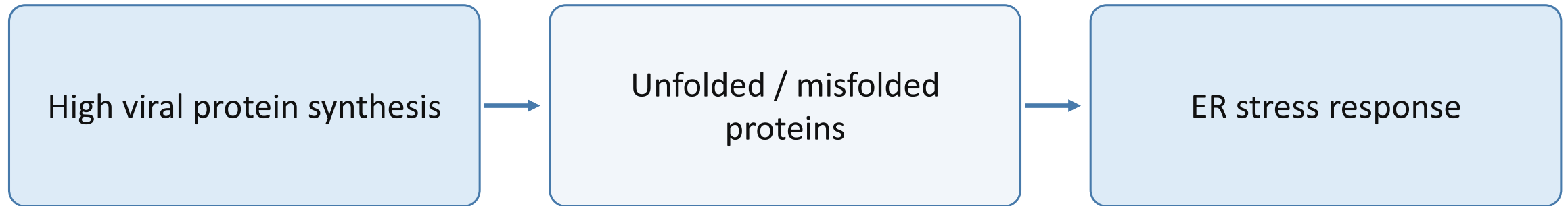
- Translation remains functional
- Viral protein production continues

Selectivity allows viral production while disabling essential host protein synthesis.

Viral enzymes and toxic proteins injure cells

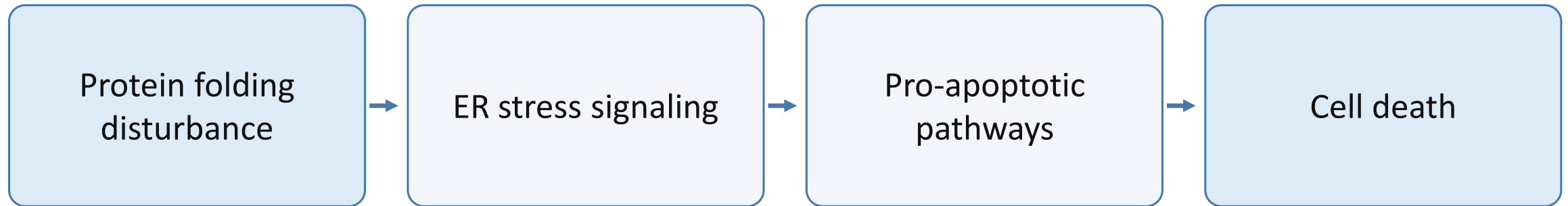
- Some viruses produce degradative enzymes that harm host components.
- Other viral proteins have direct toxic effects within infected cells.
- The result may be loss of cellular integrity or an essential function.

Viral protein excess challenges proteostasis



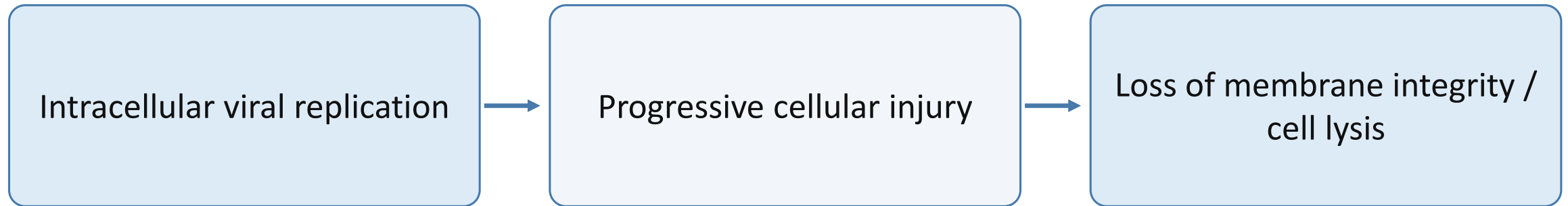
Protein burden is a separate mechanism from inhibition of host translation.

ER stress can activate cell-death programs



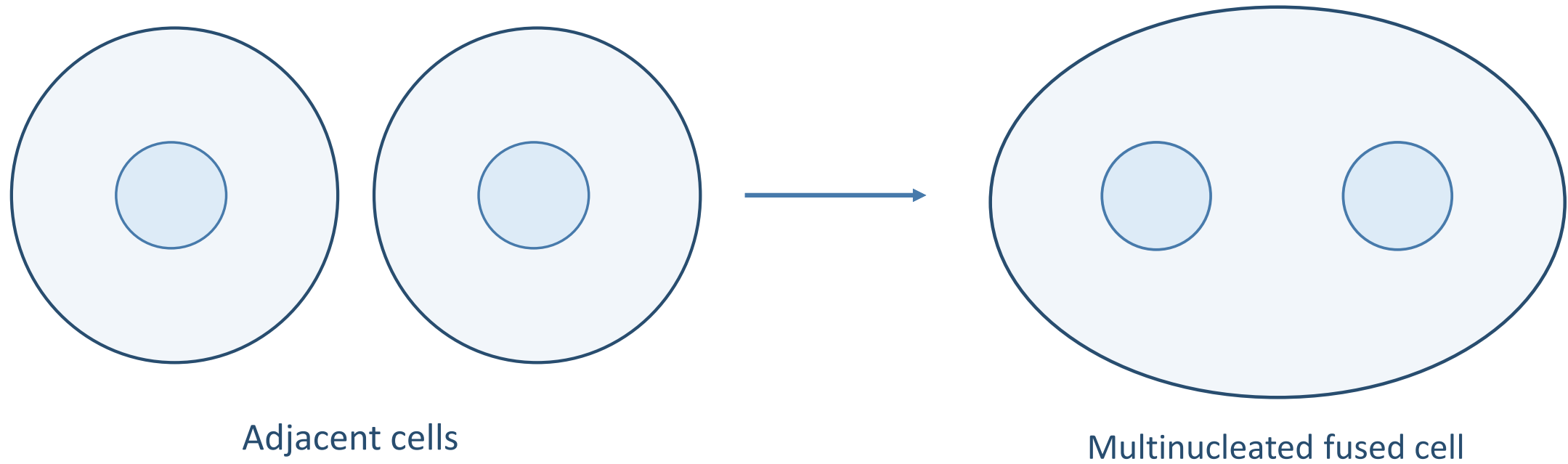
Excessive proteostasis stress can activate apoptotic signaling.

Viral replication may culminate in cell lysis



Cell lysis is one possible cytopathic endpoint, not a property of every virus.

Cell fusion is another cytopathic endpoint



Fusion is a cytopathic alteration that can produce multinucleated cells.

Viral inclusions indicate altered intracellular content

Inclusion formation

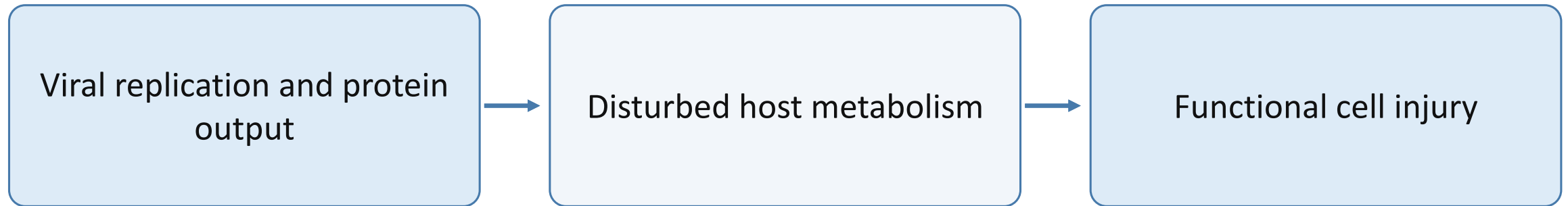
- Accumulated viral components or altered host material
- Recognizable intracellular change

Pathologic interpretation

- A morphologic clue in some infections
- Not proof of one universal injury mechanism

Inclusions are morphologic clues that require pathogen-specific interpretation.

Metabolic derangements link replication to dysfunction



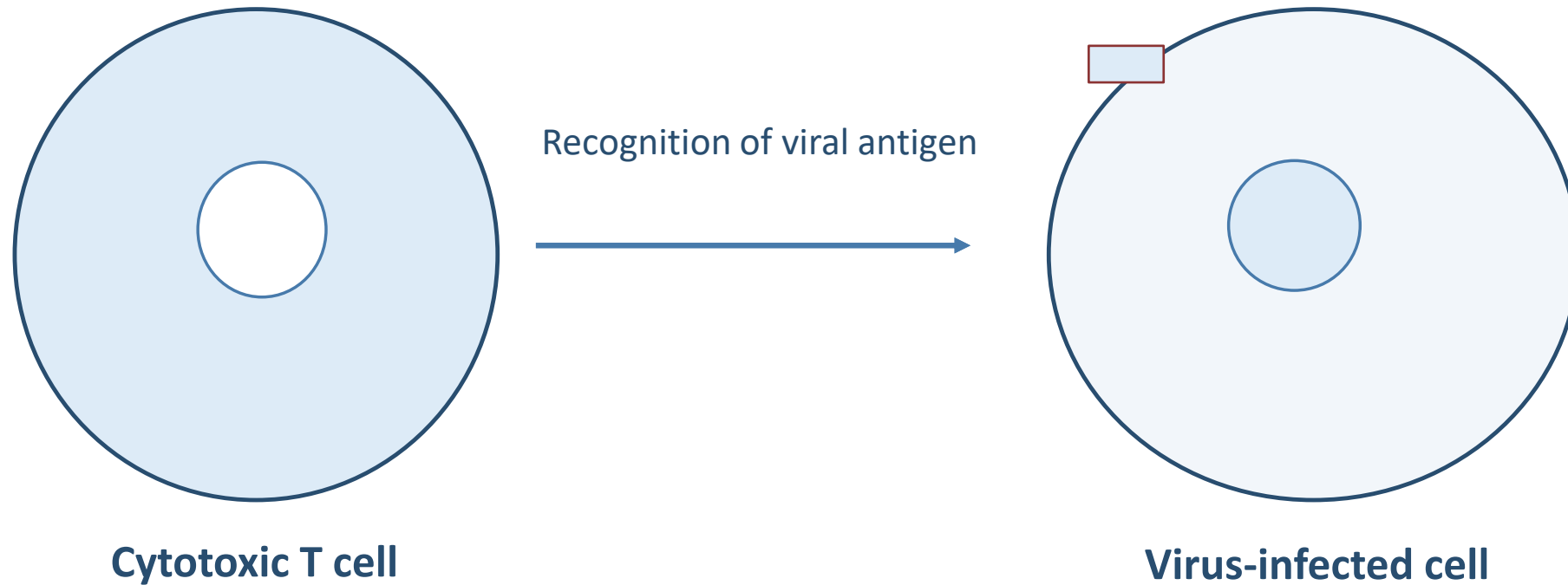
Host metabolic alterations provide another route from replication to cellular dysfunction.

Direct cytopathy: Mechanism-to-effect map

Mechanism	Primary host disturbance	Possible consequence
Macromolecular shutoff	Reduced host synthesis	Cell failure / death
Viral toxic products	Host component damage	Cytopathic injury
Misfolded protein burden	ER stress	Pro-apoptotic signaling
Lysis / fusion	Membrane integrity altered	Loss of cell structure

“Possible” matters: No single outcome applies to all viruses.

An infected cell can become an immune target



Successful host antiviral defense can itself produce tissue injury.

Cytotoxic T cells are both protective and injurious

Protective action

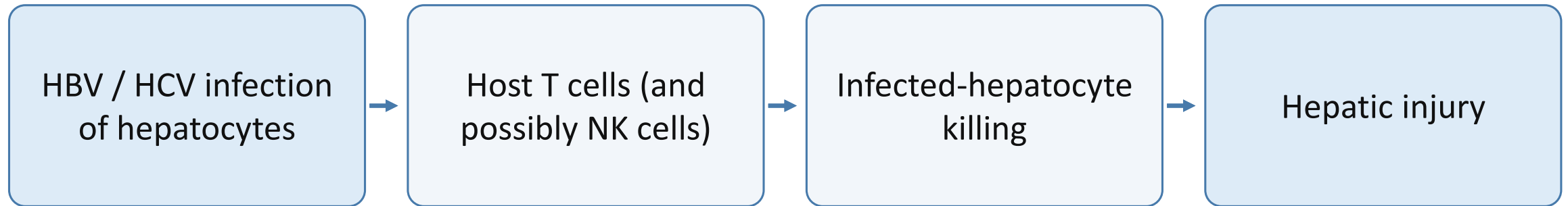
- Recognize infected cells
- Eliminate sites of viral replication

Pathologic consequence

- Loss of infected functional cells
- Tissue inflammation and injury

The same effector response can clear infection and damage an organ.

HBV and HCV: Hepatocyte injury is largely host-mediated



Host immune killing is a major driver of hepatocyte damage in viral hepatitis.

Direct cytopathy and immune injury are not synonyms

Question	Direct cytopathy	Antiviral immune injury
Primary effector	Virus-induced intracellular damage	Host antiviral effectors
Cell loss arises from	Replication / toxic effects / stress	Immune recognition and killing
Interpretive pitfall	Assume every infection is lytic	Assume inflammation reflects only viral toxicity

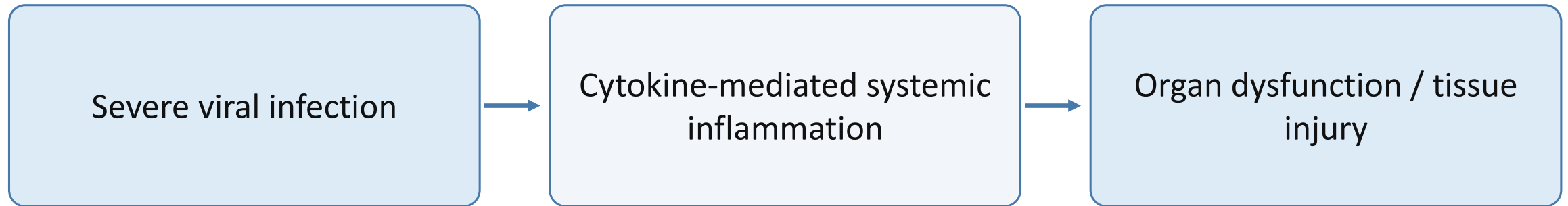
Both mechanisms may operate together.

Inflammation can amplify damage beyond infected cells



Inflammatory damage is a consequence of protective immunity when excessive or prolonged.

Systemic cytokine effects in severe viral infection



Cytokine-mediated inflammation contributes to some severe cases of COVID-19.

Receptor-defined targets and immune effectors differ

Where infection begins

- Receptor expression
- Cell-lineage permissivity
- Local physical environment

Where injury develops

- Direct viral effects
- Immune-cell killing
- Inflammatory amplification

Targeting the infected cell and causing tissue damage are distinct causal questions.

Immune evasion affects the trajectory of infection

Reduced recognition

MHC presentation altered

Weakened antiviral signaling

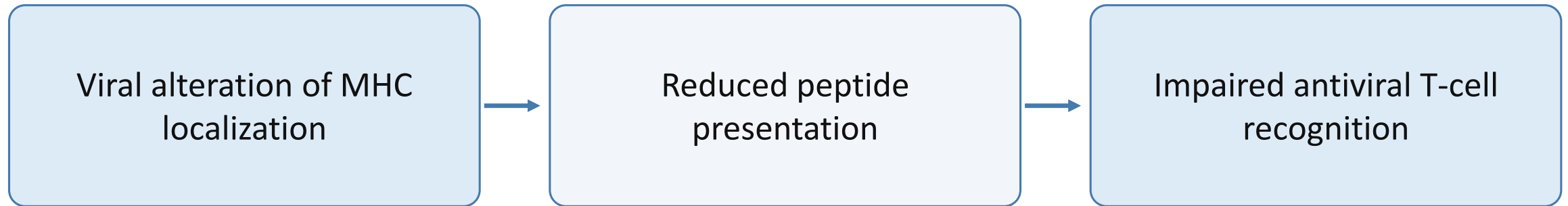
Interferon pathways inhibited

Extended persistence

Apoptosis suppressed or latency established

These mechanisms provide necessary context for chronic infection and tissue injury.

Viral interference with MHC limits T-cell recognition



HSV, CMV and EBV exemplify interference with antigen-presentation pathways.

Some viruses inhibit interferon pathways

Decoy receptors

Soluble homologues neutralize
IFN activity

JAK/STAT inhibition

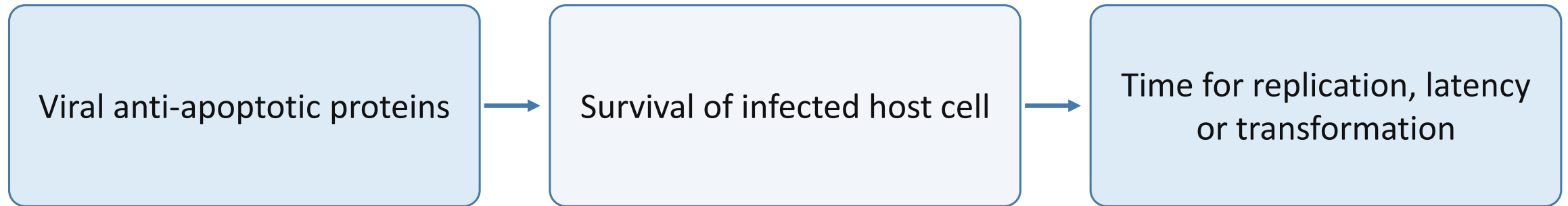
Cytokine receptor signals
interrupted

PKR antagonism

IFN-induced antiviral effect
weakened

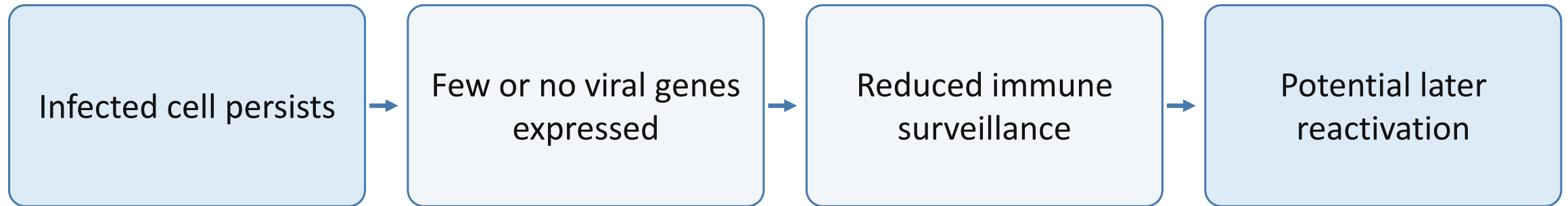
Interferon resistance can arise at distinct molecular checkpoints.

Preventing apoptosis may extend viral survival



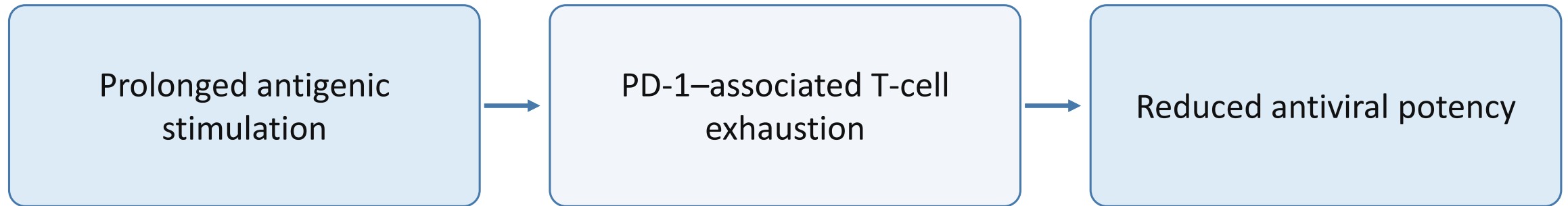
A virus may delay death even when later injury remains possible.

Latency minimizes viral gene expression



Latent HSV/VZV may persist in neurons; Latent EBV persists in B cells.

Chronic infection can produce T-cell exhaustion



Exhausted antiviral T-cell responses are described in HIV, HBV and HCV infection.

Immune escape and injury can coexist

Immediate viral advantage

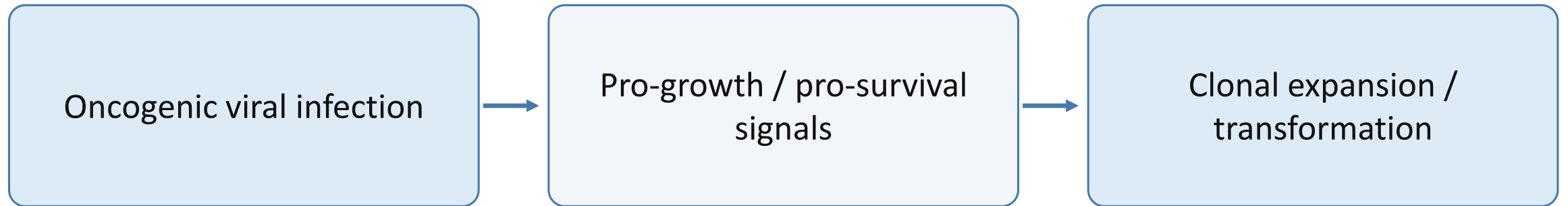
- Less elimination of infected cells
- Opportunity for persistence

Potential host cost

- Prolonged infection
- Ongoing immune activation and tissue damage

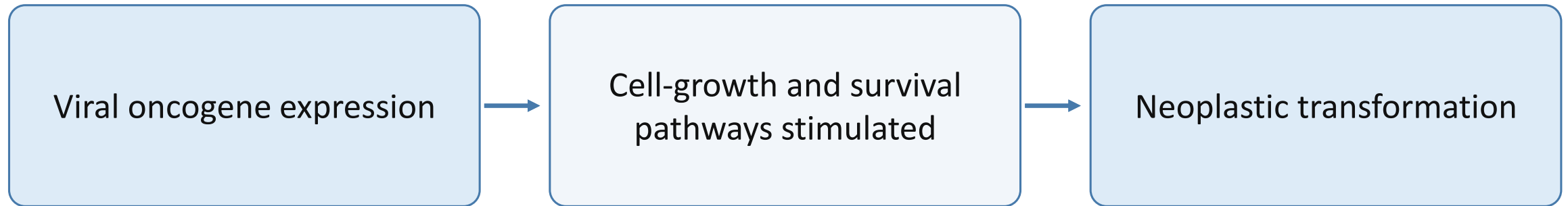
Reduced immune clearance can coexist with persistent, injurious inflammation.

Oncogenic viruses alter growth and survival



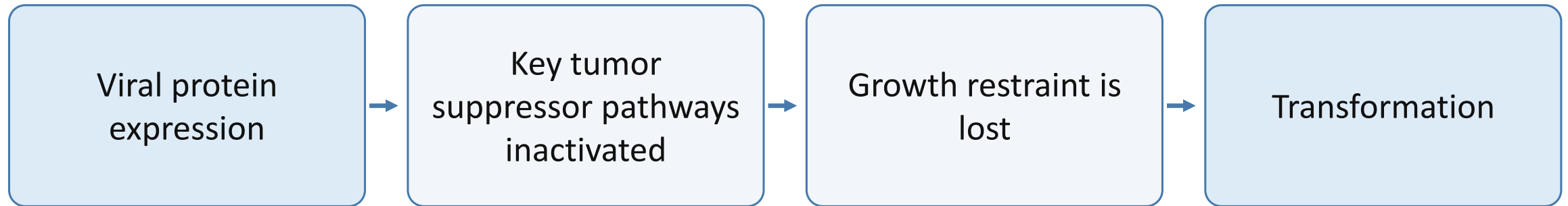
Viral transformation is the third principal injury category in this section.

Virus-encoded oncogenes can drive proliferation



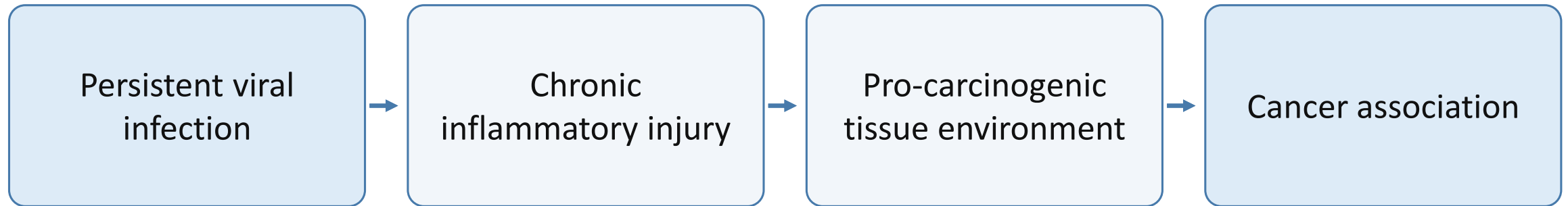
The key concept is direct stimulation of cell growth and survival pathways.

Viral proteins may disable tumor suppressors



Loss of tumor-suppressor function removes an important restraint on proliferation.

Chronic inflammation provides another cancer route



Inflammation-associated cancer risk does not require a virus-encoded oncogene.

Separate direct transformation from indirect risk

Pathway	Immediate driver	Interpretation
Virus-directed transformation	Oncogenes or suppressor inactivation	Directly alters growth/survival
Inflammation-associated carcinogenesis	Chronic immune-mediated inflammation	Fosters tumor development
Important distinction	Oncogenic association $\neq$ one mechanism	Do not infer a viral oncogene for HBV/HCV

Cancer associations cannot be interpreted without specifying the causal route.

Injury phenotype depends on timing and mechanisms

Early infection

Entry and permissive
replication

Active infection

Direct stress and
immune recognition

Persistent infection

Latency or exhausted
host responses

Long-term consequence

Chronic injury or
altered growth

This is an integrative teaching schematic; Stages are possible routes, not a universal natural history.

Integrated mechanisms of viral injury

Layer	Question	Representative consequence
Tropism	Which cells can support infection?	Selective tissue targeting
Direct cytopathy	How does replication impair cells?	Shutdown / ER stress / lysis
Host immunity	How are infected cells cleared?	CTL-mediated damage
Transformation	How are growth controls altered?	Neoplastic potential

Determine tissue targeting before attributing the pattern of cellular injury.

Applied example: Interpret HIV receptor use

A virus binds CD4 but also requires a chemokine receptor for efficient cellular entry.

1

Which two chemokine receptors are identified for HIV gp120?

2

How can different host-cell receptor patterns contribute to tropism?

Applied example: Explain poliovirus cytopathy

An infected cell loses translation of most host mRNAs, yet viral protein synthesis continues.

1

Identify the host factor that poliovirus inactivates.

2

Explain why the effect favors viral replication at host-cell expense.

Applied example: Explain JC virus targeting

Viral surface attachment does not fully explain oligodendroglial disease.

1

Identify the intracellular host determinant responsible for restricted replication.

2

Explain why permissive gene expression matters after entry.

Applied example: Interpret viral hepatitis injury

An HBV-infected liver shows injured hepatocytes and host inflammatory activity.

1

Which effector mechanism is emphasized for hepatocyte loss?

2

Why is it incorrect to equate the amount of injury with direct viral toxicity?

Morphologic and functional consequences are distinct

Observation	Mechanistic inference	Interpretive limit
Cell lysis or fusion	Possible cytopathic effect	Not universal among viruses
Viral inclusions	Altered intracellular viral/host content	Not a unique diagnosis without context
Immune-cell injury	Host response damages tissue	Virus may not directly lyse cells
Transformation	Growth regulation altered	Requires pathway-specific support

Do not mistake a consequence for evidence of only one cause.

Synthesize: Five questions about viral tissue injury

Where?

Which cells and tissues are permissive?

How entry?

Which receptor or cofactor is used?

Direct damage?

Is host synthesis or proteostasis disrupted?

Host damage?

Are immune effectors injuring infected cells?

Long-term?

Could infection persist or alter growth?

Use these questions to structure a clinicopathologic explanation.

References

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition. Elsevier; 2026.