

Cytopathic–cytoproliferative reaction

Cellular patterns of virus-associated tissue injury and proliferation

Infectious-disease morphology · mechanisms and clinicopathologic interpretation

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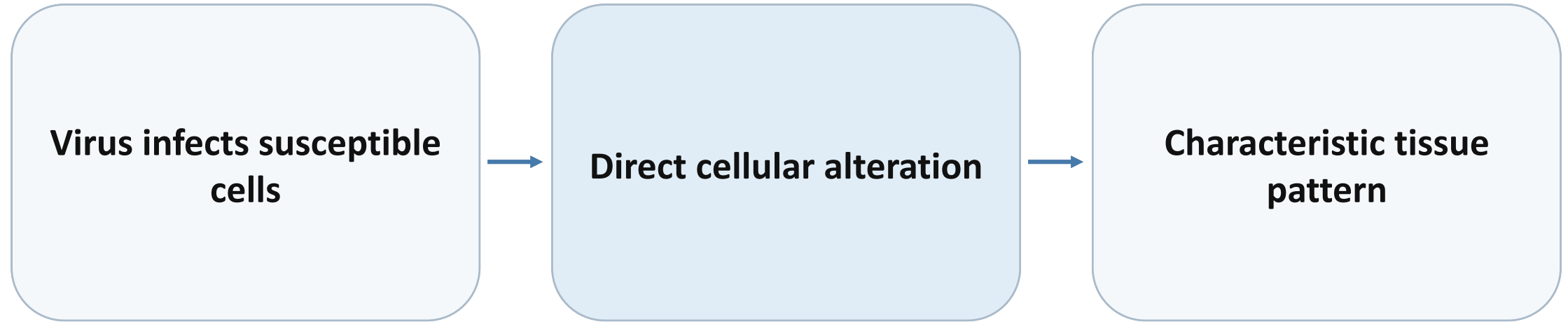
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Learning objectives

- Recognize cytopathic and cytoproliferative reaction patterns as morphologic responses to infection.
- Explain inclusions, cell fusion, epithelial vesiculation, and proliferation from their mechanisms.
- Apply the pattern to HSV, VZV, measles, CMV, HPV, molluscum, and EBV.
- Distinguish direct viral cytopathology from immune-mediated injury and neoplastic transformation.

The pattern is a tissue reaction, not one disease



Several viruses produce overlapping patterns; Morphology narrows, but does not uniquely name, the agent.

Position within the spectrum of infection

Suppurative

Prominent neutrophilic
exudate

Pus / microabscess formation

Cytopathic–proliferative

Altered infected cells;
Often few inflammatory
cells

Necrosis, fusion, or
proliferation

Chronic/scarring

Prolonged inflammation
and tissue remodeling

Loss of normal architecture

Three complementary outcomes of infected cells

Cytolytic injury



Cell-cell fusion



**Epithelial or lymphoid
proliferation**

A single virus can generate more than one of these outcomes, depending on the infected cell and host context.

Cytopathic versus cytoproliferative

Cytopathic

Cell enlargement, inclusions, necrosis

Vesicles or lytic epithelial damage

Cytoproliferative

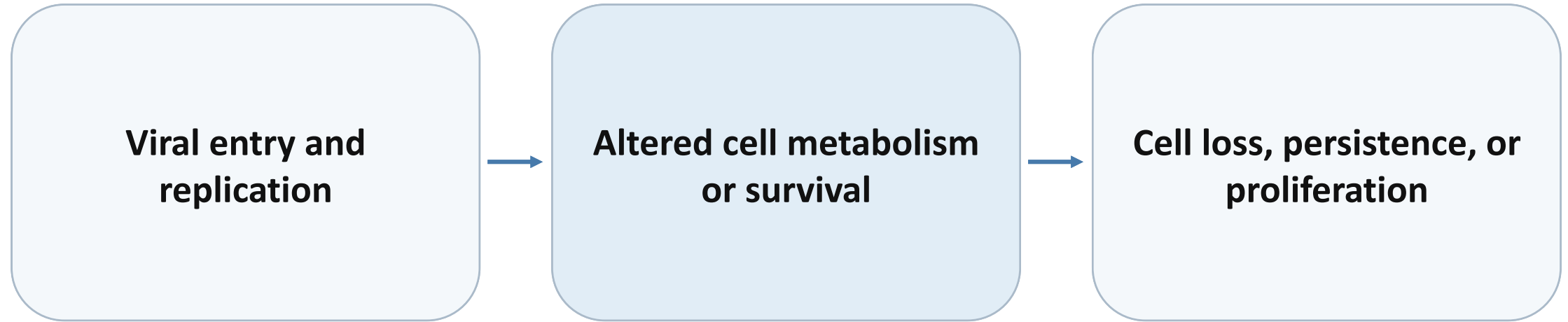
Increased number or expansion of affected cells

Warts, papules, lymphoid proliferation

Morphology begins with the affected cell

- Look first for altered nuclei, cytoplasm, and cell boundaries.
- Then determine whether affected cells die, fuse, or expand.
- Finally assess associated inflammation and the architecture of the lesion.

Virus–host interaction determines injury



Viruses may directly injure host cells; Host immunity can cause additional damage.

Tropism explains selective cellular injury

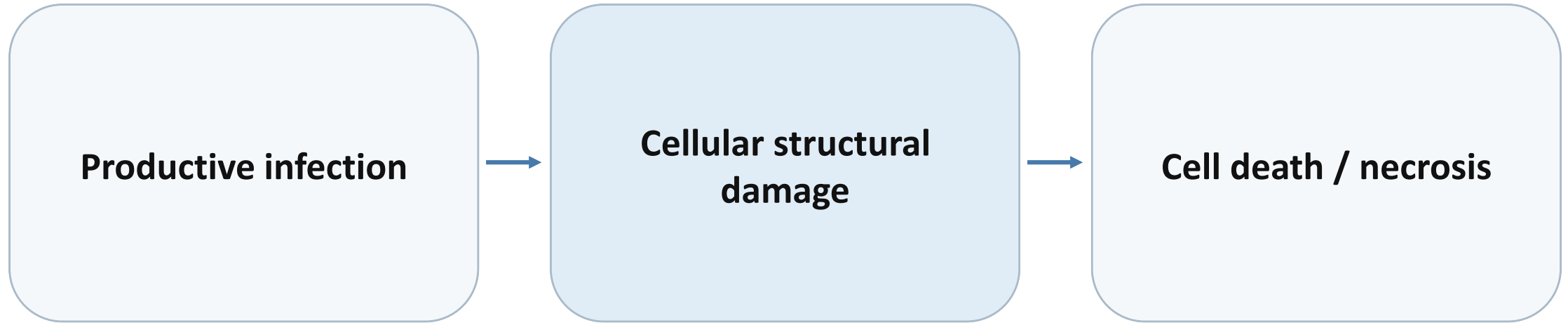


Tropism is the predilection of a virus for particular host cells, not a guarantee that all similarly shaped cells are infected.

Tropism has molecular and cellular determinants

- Host entry receptors as an important determinant of tropism.
- EBV binds CD21 (CR2) on B cells; Other viruses use different receptors.
- Cell lineage–specific factors can further restrict infection.

Direct viral injury can dominate the image



The core Robbins reaction may show conspicuous infected-cell alterations even when inflammatory cells are sparse.

Direct and immune-mediated injury are distinct

Direct cytopathic damage

Virus replication alters the infected cell

HSV epithelial cytolysis

Host immune injury

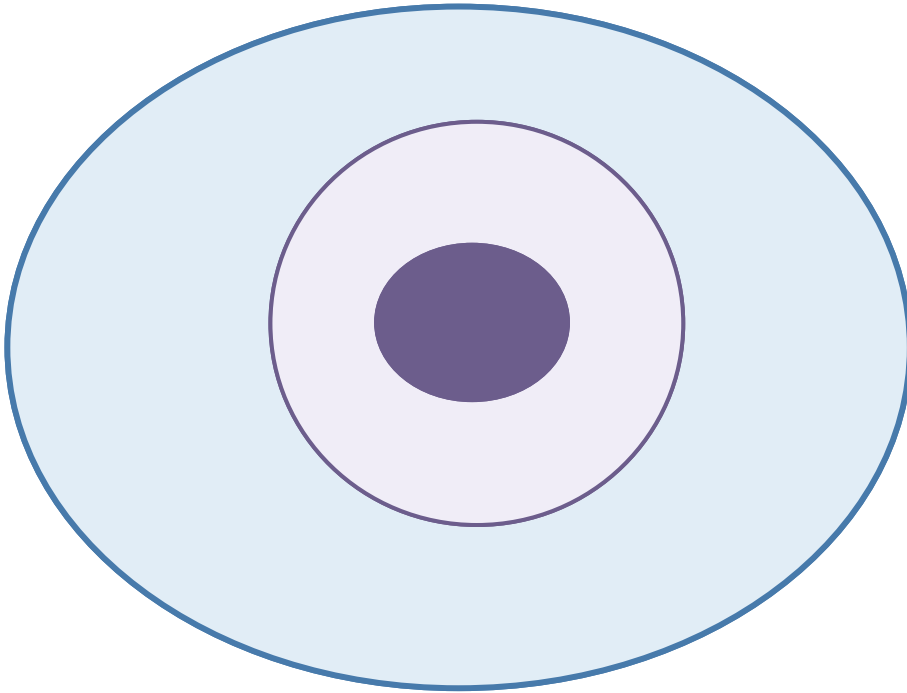
Effector cells attack infected tissues

Inflammatory damage in viral hepatitis or HSV
stromal keratitis

Sparse inflammation is a pattern, not a rule

- Inflammatory cells as “usually” sparse in cytopathic–cytoproliferative lesions.
- Inflammation depends on timing, tissue site, pathogen, and immune competence.
- Concurrent inflammatory or necrotizing reaction patterns can coexist.

Viral inclusions provide a cytologic clue



Nuclear inclusion

Schematic · not a histologic specimen

- A visible aggregate or viral-associated alteration may appear within an infected cell.
- Robbins specifically cites herpesviruses and adenovirus as inclusion-forming examples.

Nuclear and cytoplasmic locations matter

Nuclear

HSV, VZV, CMV and adenovirus are examples with nuclear inclusions.

Assess chromatin and nuclear architecture.

Cytoplasmic

Molluscum produces intracytoplasmic viral inclusions.

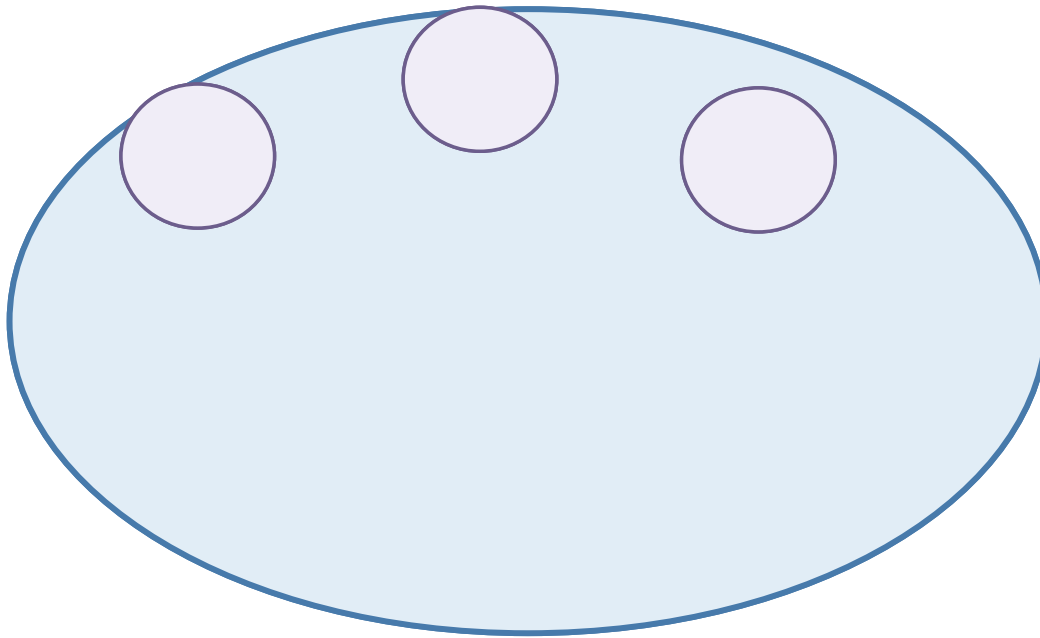
Assess the cytoplasmic compartment.

An inclusion is a clue, not a full diagnosis

- Morphologic inclusions must be interpreted alongside tissue distribution and clinical setting.
- Different viruses can produce nuclear inclusion-like changes.
- Inclusions may be absent in some infected cells or lesions.

Cell fusion creates multinucleated polykaryons

Multiple nuclei



Shared cytoplasm

- Virus-induced fusion preserves several nuclei within a shared cell boundary.
- Robbins gives measles virus and herpesviruses as examples.

Schematic · not a histologic specimen

Polykaryon is not synonymous with granuloma

Virus-associated polykaryon

Fusion of infected cells

Correlate with epithelial or lymphoid infection

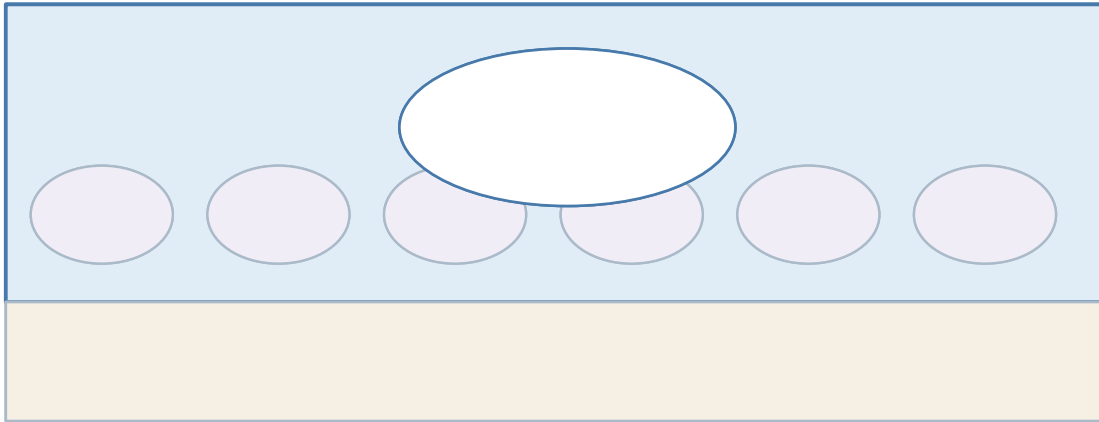
Granulomatous giant cell

Aggregation and fusion of activated
macrophages

Correlate with epithelioid histiocytes /
granuloma

Focal epithelial injury can form a blister

Intraepithelial cleft



Epithelial layer

Schematic · not a histologic specimen

- Injured epithelial cells lose cohesion or detach.
- A fluid-containing cleft develops within the epithelial layer.
- The result is a vesicular lesion rather than a proliferative papule.

Cytopathic damage can progress to ulceration



This sequence is described in the Robbins morphology of herpes simplex lesions.

Four morphologic signs to recognize

Inclusion

Altered nuclear or
cytoplasmic
material

Cell-level

Multinucleation

Several nuclei in
fused cytoplasm

Cell-level

Vesicle

Cleft from
epithelial
destruction

Tissue-level

Papillomatous growth

Expanded
epithelium /
papules

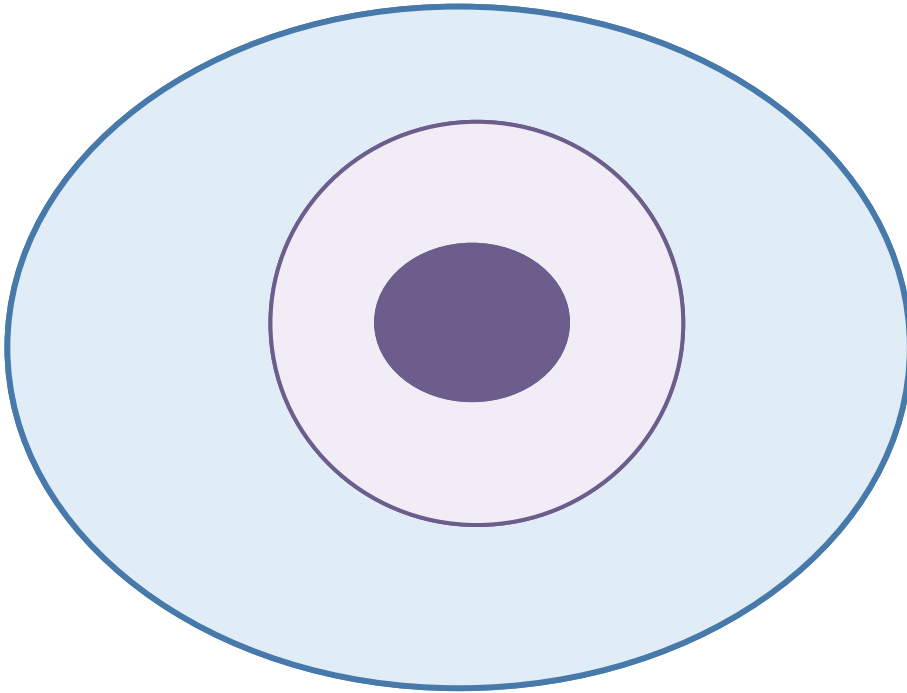
Tissue-level

HSV: Epithelial infection and cytolysis



HSV-1 and HSV-2 produce similar cytopathic patterns, despite differing clinical distributions.

HSV: Intranuclear Cowdrey type A inclusions



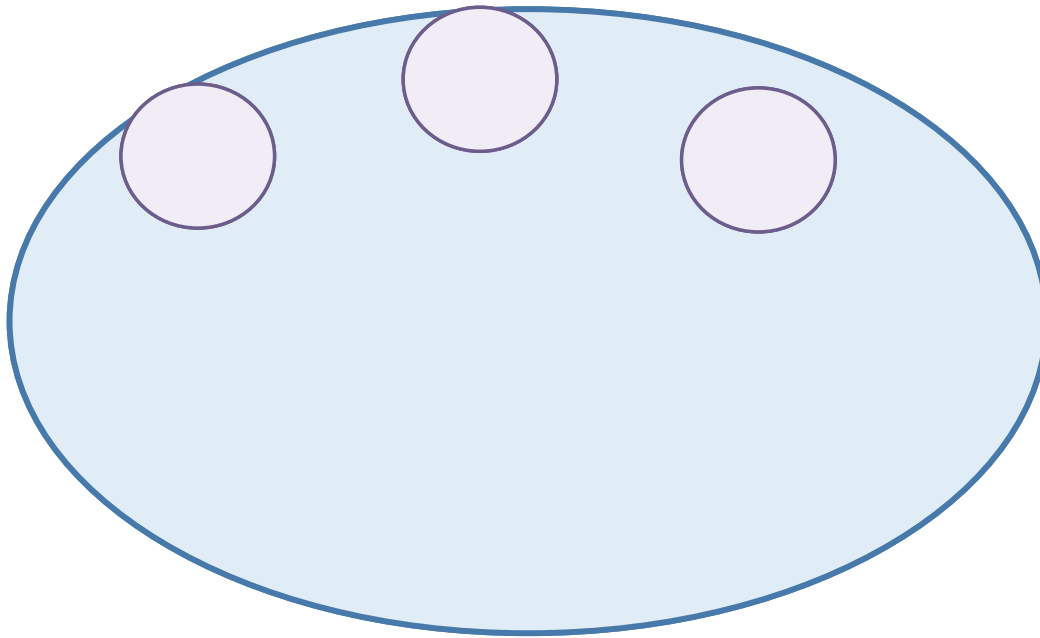
Nuclear inclusion

Schematic · not a histologic specimen

- Large pink-to-purple intranuclear inclusions appear in infected epithelial cells.
- Peripheral displacement of host chromatin accompanies inclusion formation.

HSV: Viral-induced multinucleated syncytia

Multiple nuclei



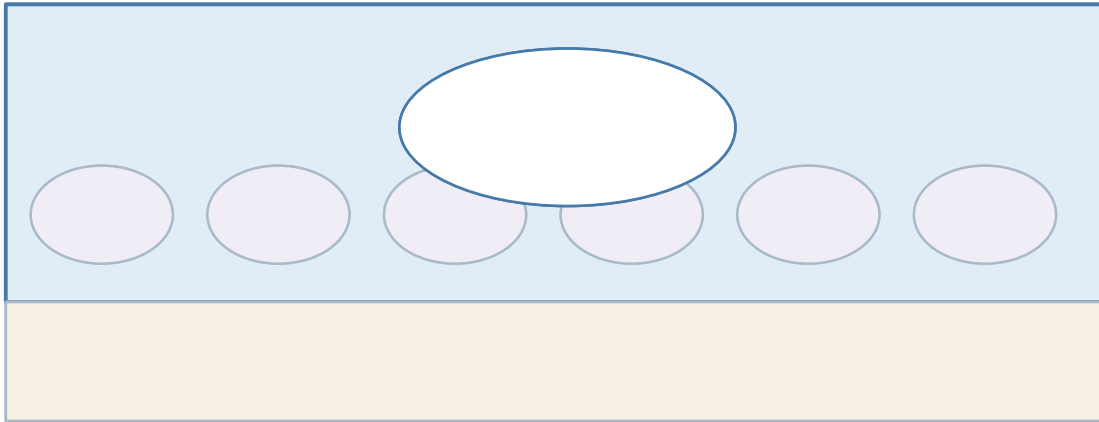
Shared cytoplasm

- Fusion produces multinucleated epithelial cells.
- The same lesion can show both nuclear inclusions and syncytial cells.

Schematic · not a histologic specimen

HSV: Ballooning degeneration and vesicles

Intraepithelial cleft

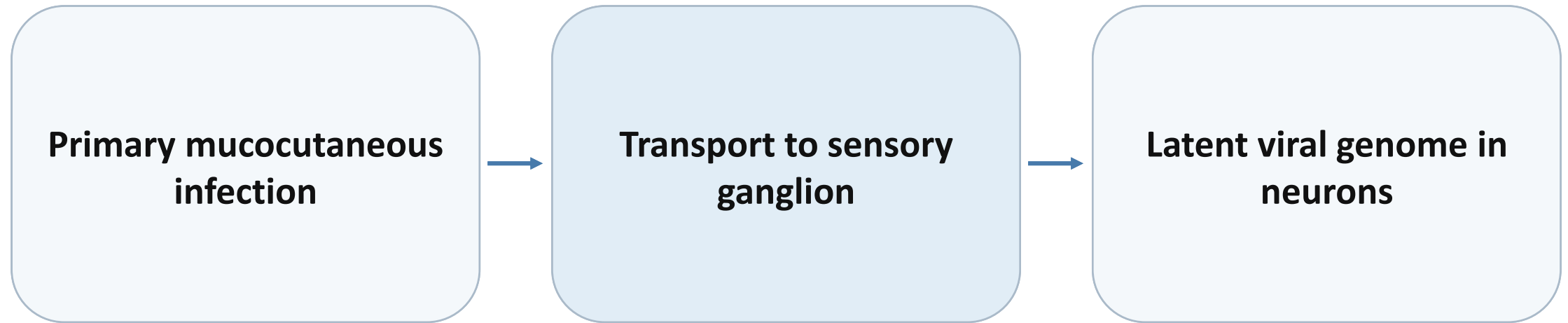


Epithelial layer

Schematic · not a histologic specimen

- Intracellular edema and ballooning degeneration disrupt epithelial integrity.
- Intraepithelial vesicles may burst, crust, or create superficial erosions.

HSV latency changes the site of persistence



Visible cytopathic damage characterizes epithelial replication, not necessarily neuronal latency.

HSV reactivation reconnects ganglion and skin

**Neuronal viral
reactivation**



Axonal spread outward



**Recurrent skin /
mucosal lesion**

A recurrent vesicular eruption reflects viral return to the peripheral site of infection.

HSV corneal disease: Two injury mechanisms

Epithelial keratitis

Virus-induced epithelial cytolysis

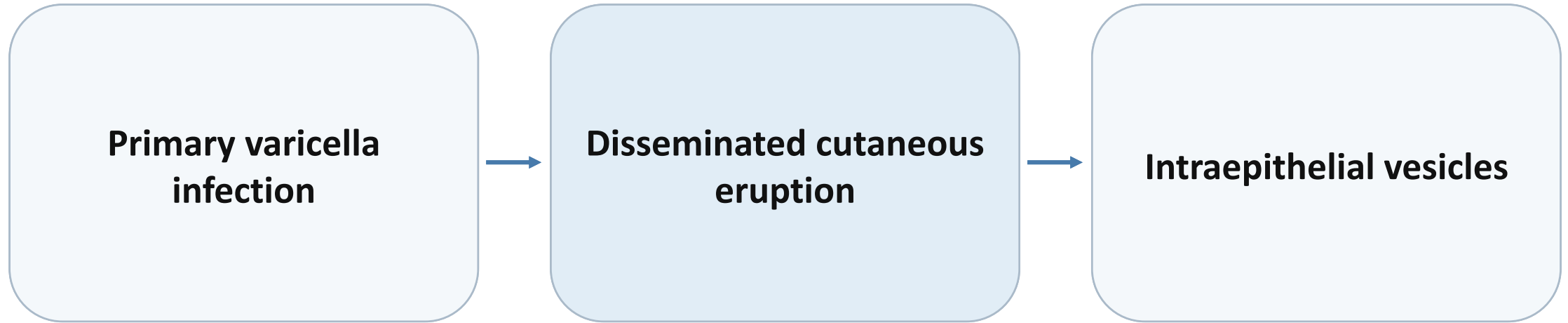
Direct cytopathic injury

Stromal keratitis

Mononuclear infiltrates, neovascularization
and scarring

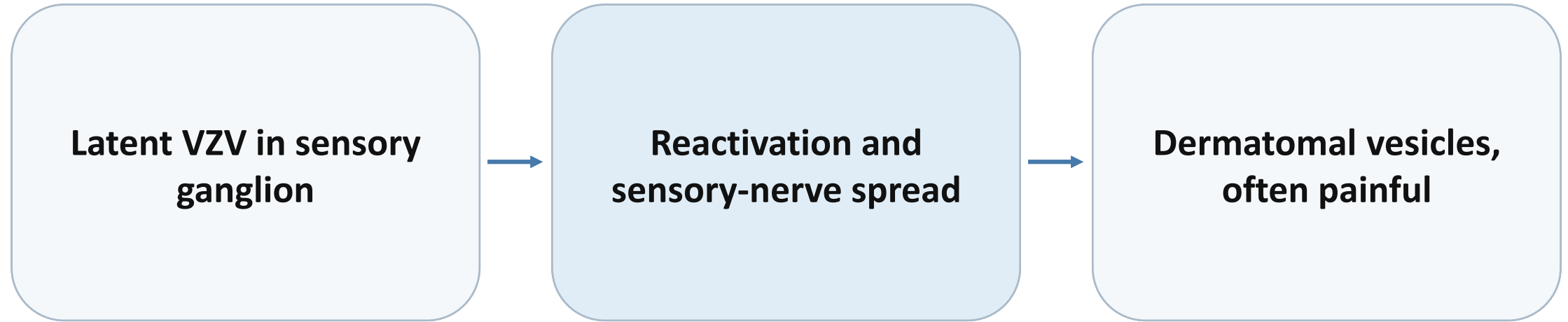
Immune-mediated tissue damage

VZV primary infection creates widespread vesicles



Chickenpox lesions that evolve from macules to vesicles and then crusts.

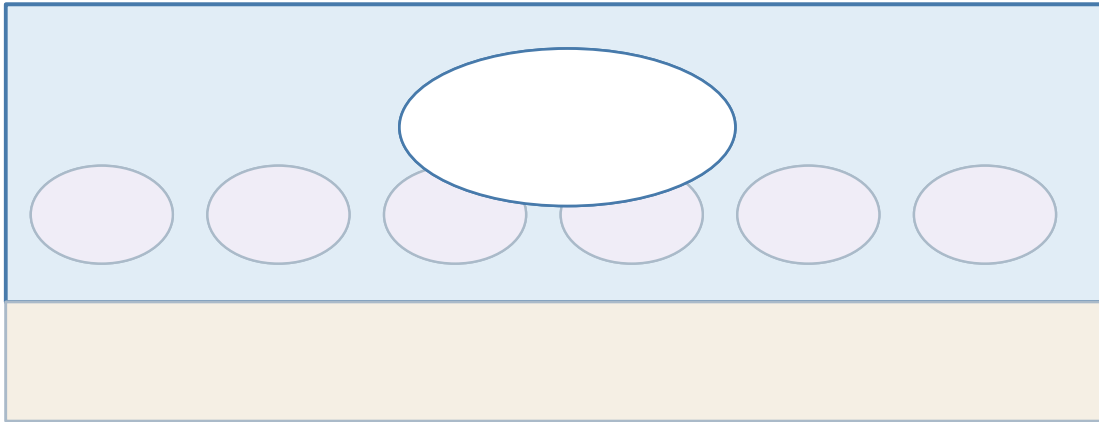
VZV reactivation produces dermatomal shingles



The epithelial cytopathic effect coexists with radiculoneuritis-related pain.

VZV histology links inclusion and vesicle

Intraepithelial cleft



Epithelial layer

Schematic · not a histologic specimen

- Chickenpox lesions show intraepithelial vesicles.
- Intranuclear inclusions occur in cells at the vesicle base.
- Rupture may be followed by crusting and regeneration.

HSV and VZV share a cell-injury pattern

Shared morphology

Vesicular epithelial injury; Intranuclear inclusions

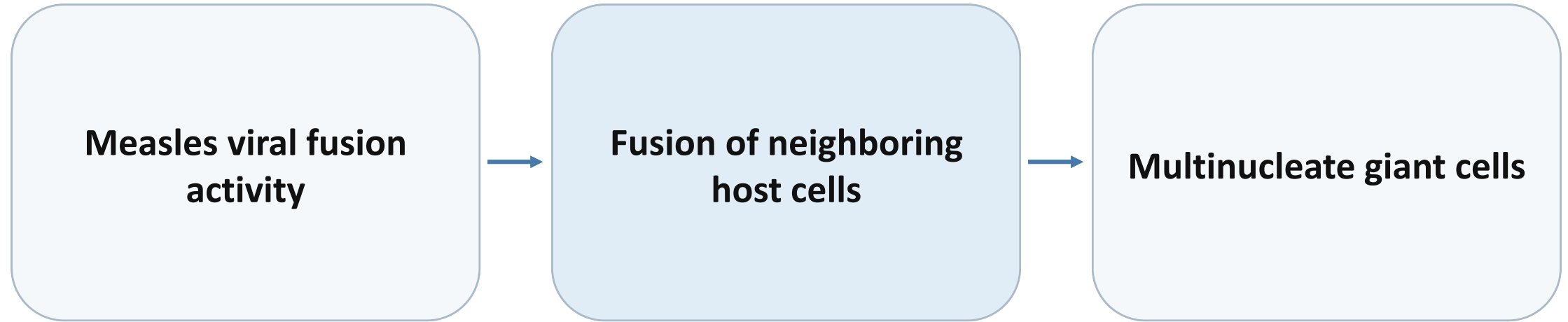
Histology alone may not settle viral type

Clinical context differs

HSV mucocutaneous recurrences; VZV varicella or dermatomal zoster

Distribution helps focus etiologic testing

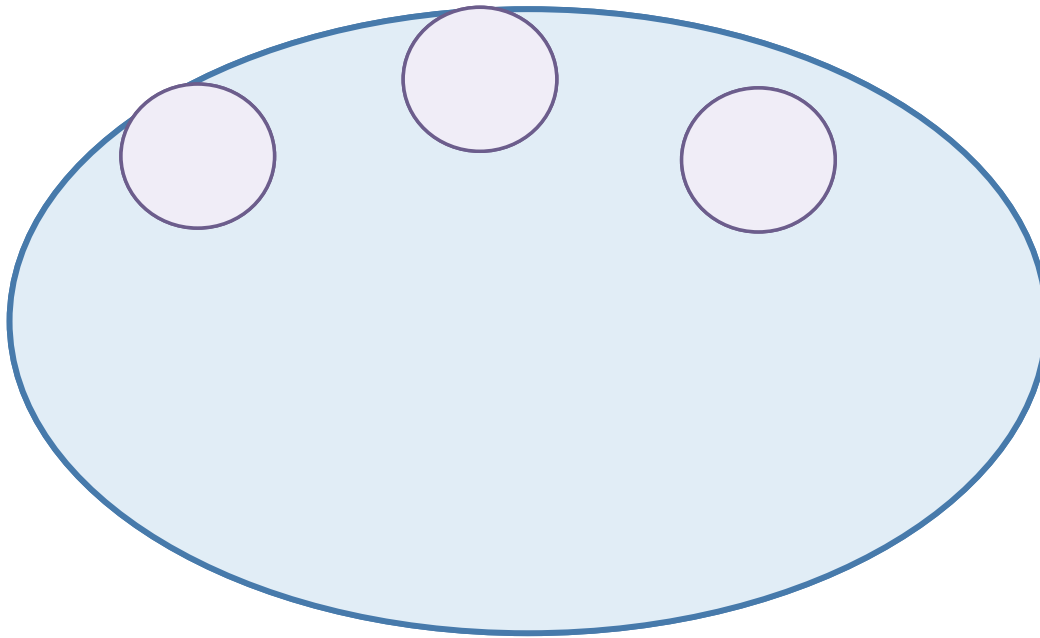
Measles is a prototype of virus-induced fusion



Cell fusion to the measles fusion (F) protein.

Warthin–Finkeldey cells in measles

Multiple nuclei



Shared cytoplasm

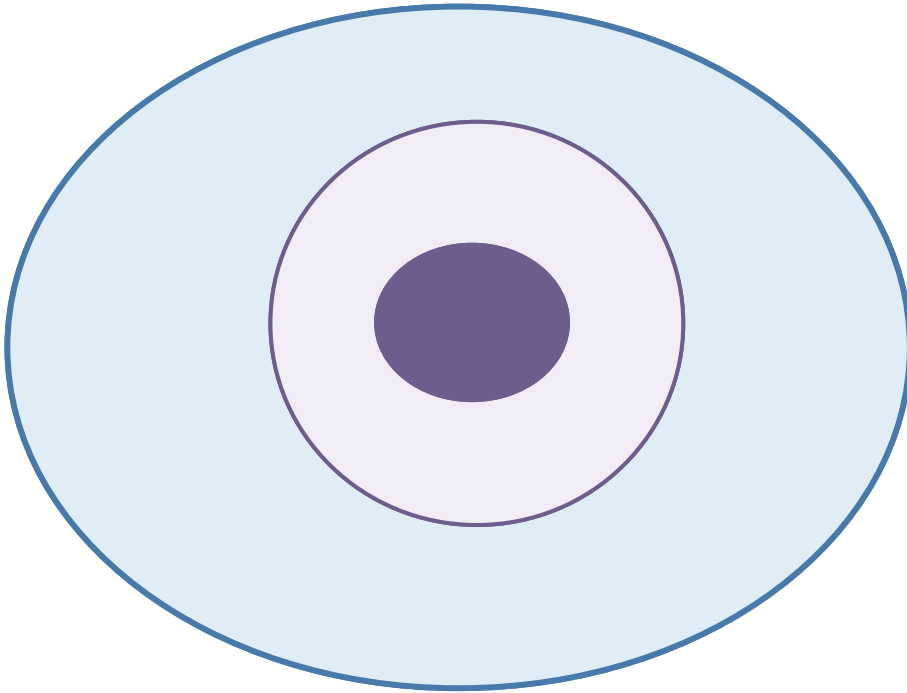
- Multinucleated giant cells can be distributed in lymphoid organs.
- Eosinophilic nuclear and cytoplasmic inclusions.

Schematic · not a histologic specimen

Measles rash also has immune morphology

- Vascular dilation, edema, and mononuclear perivascular cells accompany the rash.
- T-cell-mediated immunity helps control measles and contributes to the cutaneous eruption.
- Thus, a virus with a syncytial cytopathic signature can also produce a conspicuous host reaction.

Adenovirus is a nuclear-inclusion example

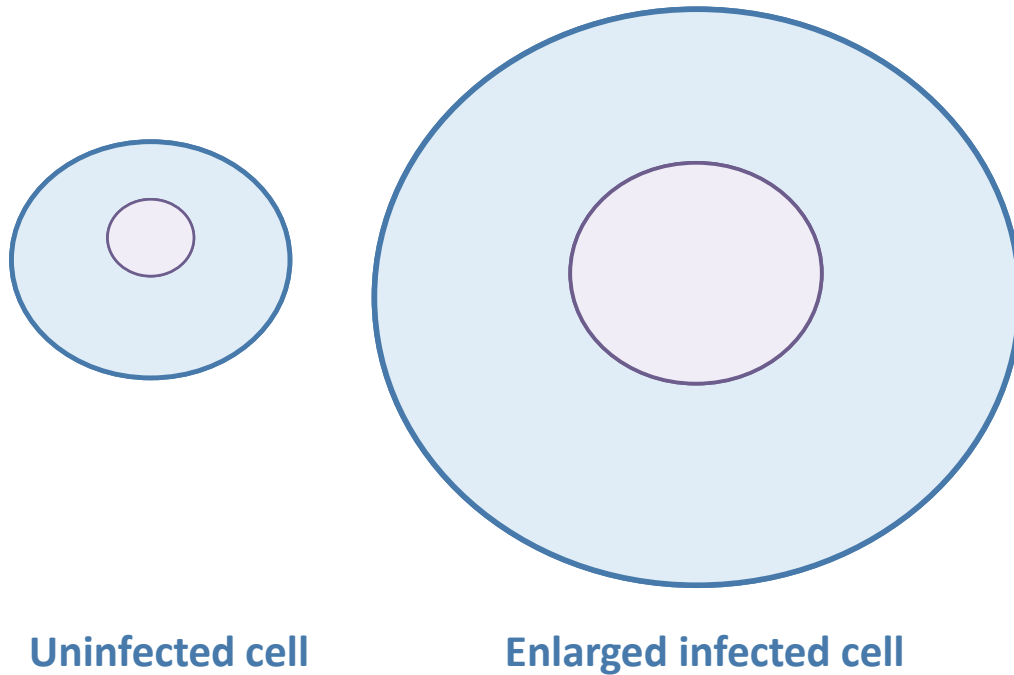


Nuclear inclusion

Schematic · not a histologic specimen

- The cytopathic–cytoproliferative heading explicitly includes adenovirus among inclusion-forming viruses.
- This fact identifies a morphologic category; It does not establish adenovirus from inclusions alone.

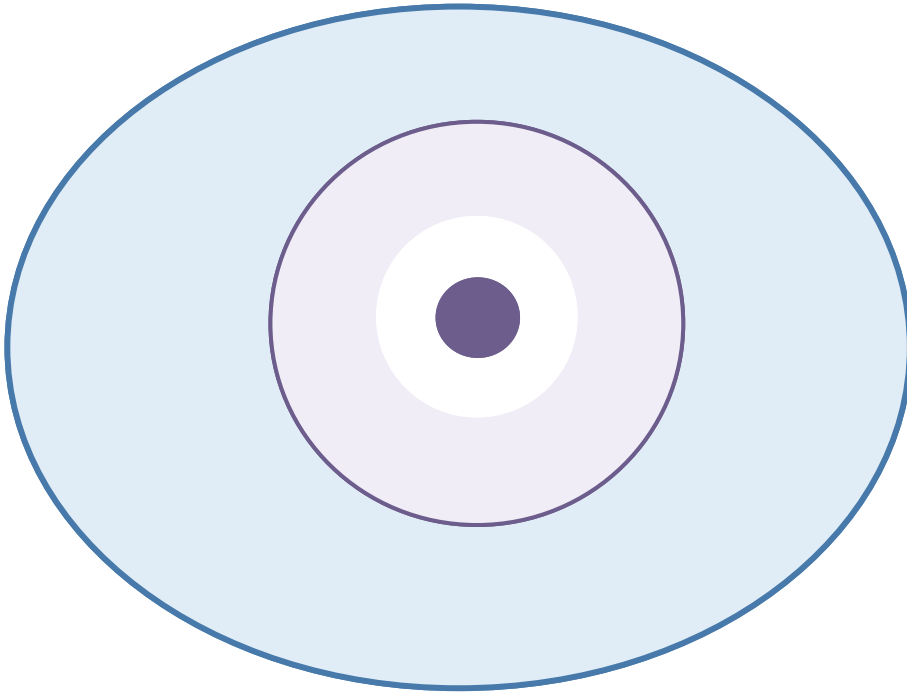
CMV characteristically enlarges infected cells



- CMV-infected cells may show marked enlargement of the whole cell and nucleus.
- The name “cytomegalovirus” reflects this distinctive cellular enlargement.

Schematic · not a histologic specimen

CMV: Large inclusion with a clear halo



**Intranuclear inclusion
And surrounding halo**

Schematic · not a histologic specimen

- A prominent intranuclear basophilic inclusion is separated from the nuclear envelope by a clear halo.
- This is conventionally described as the “owl’s eye” appearance.

CMV disease depends strongly on immune status

Preserved immunity

Often asymptomatic or mononucleosis-like illness

Cellular injury may be clinically limited

Impaired cellular immunity

Reactivation and systemic tissue infection may occur

Greater clinical impact across organs

Mixed infection may produce mixed tissue reactions

CMV in lung

Cytologic alterations of infected alveolar lining cells

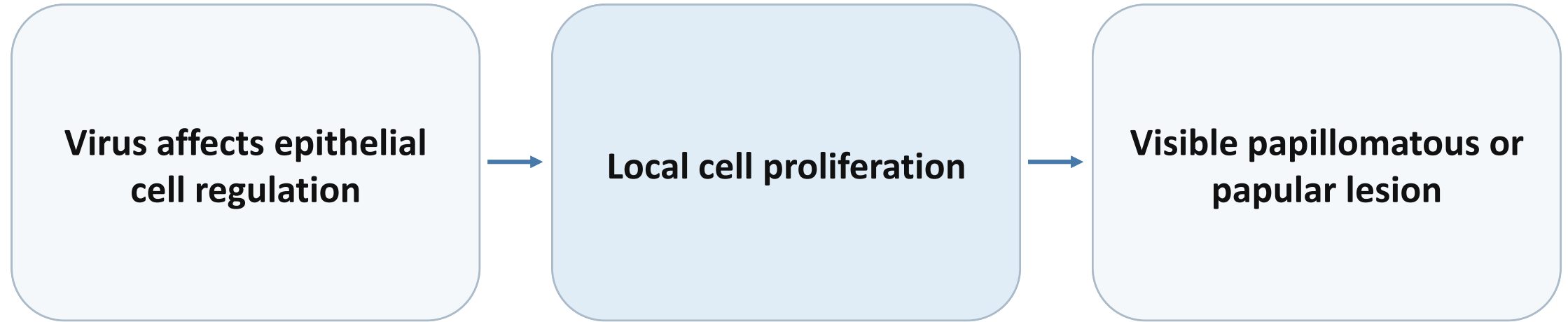
Cytopathic morphology

Pneumocystis in lung

Interstitial inflammation

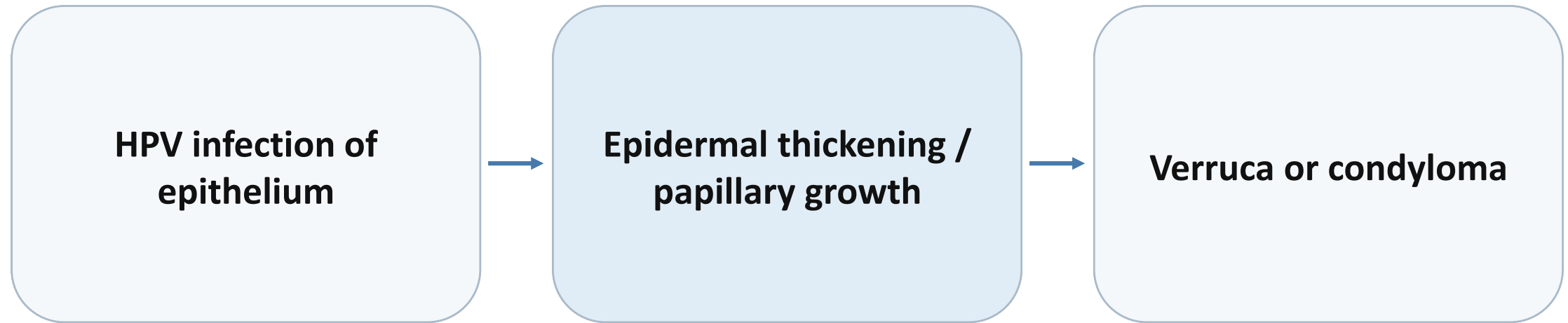
Distinct simultaneous reaction pattern

Cytoproliferation means altered growth



HPV-associated warts and poxvirus-associated molluscum papules as characteristic examples.

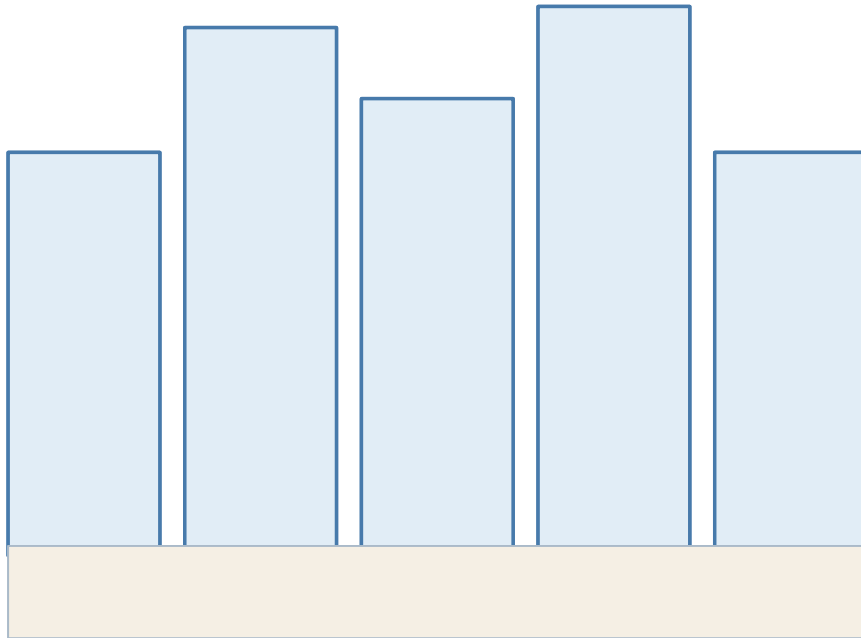
HPV: Proliferating squamous epithelium forms warts



The macroscopic growth pattern reflects epithelial proliferation rather than simply inflammation.

A wart has a papillomatous architecture

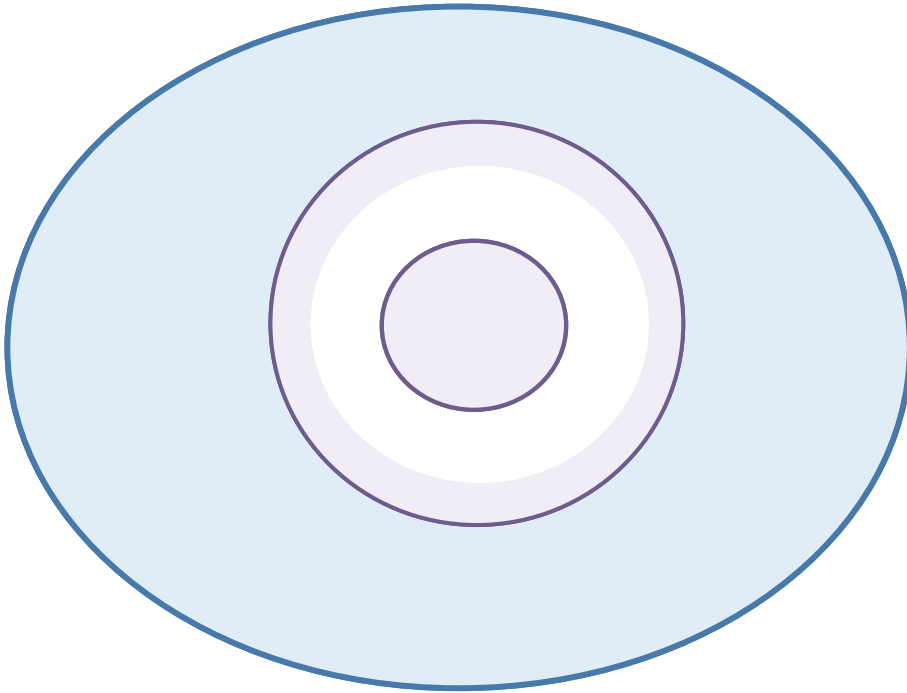
Papillomatous projections



- Common warts show undulant or spire-like epidermal proliferation.
- Papillomatous hyperplasia describes the architectural change.

Schematic · not a histologic specimen

HPV: Koilocytosis is a cytopathic change



Perinuclear halo

Schematic · not a histologic specimen

- Superficial squamous cells show perinuclear clearing (“halo”).
- Associated nuclear enlargement and hyperchromasia make the cell abnormal.

HPV combines proliferation and cytopathic injury

Architectural finding

Papillomatous epithelial expansion

Cytoproliferative component

Cellular finding

Koilocytotic perinuclear halo and nuclear atypia

Cytopathic component

Condyloma and common wart: Shared biology

Verruca vulgaris

Rough hyperkeratotic / papillomatous cutaneous lesion

Koilocytosis can be conspicuous

Condyloma acuminatum

Soft anogenital cauliflower-like growth

Diagnosis draws on papillary architecture and koilocytosis

Benign HPV proliferation differs from cancer

Low-risk types

HPV 6 and 11 commonly produce genital warts

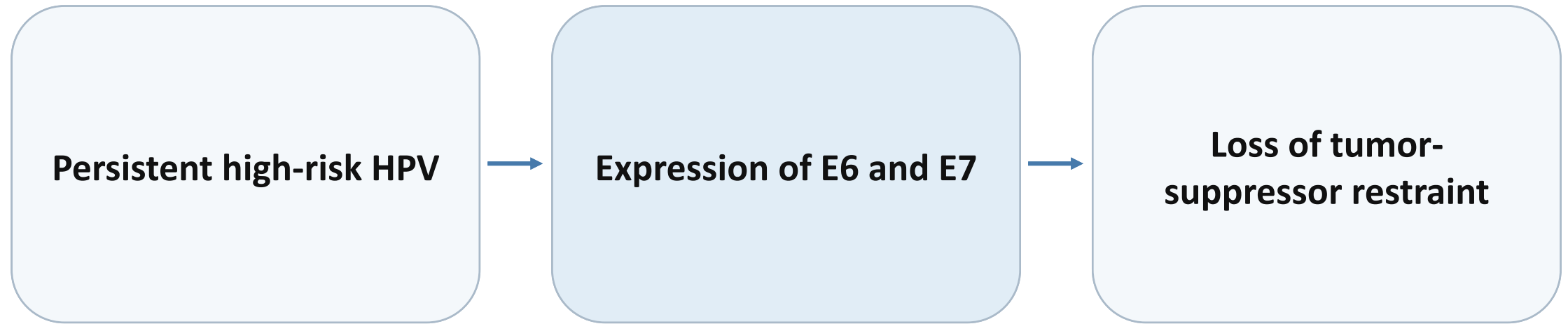
Low malignant potential

High-risk types

HPV 16 and 18 are implicated in multiple squamous carcinomas

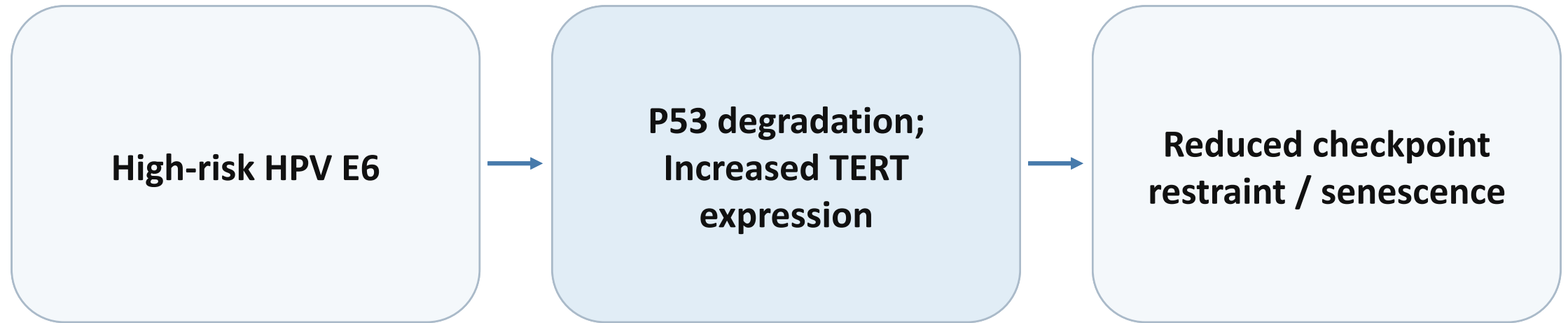
Cancer risk associated with persistent infection and molecular changes

High-risk HPV shifts cell-cycle control



Viral oncogenic action from the visible papillomatous growth of a benign wart.

HPV E6 undermines p53 function



E6 is a molecular mechanism of HPV-associated oncogenesis, not a histologic inclusion body.

HPV E7 undermines RB function

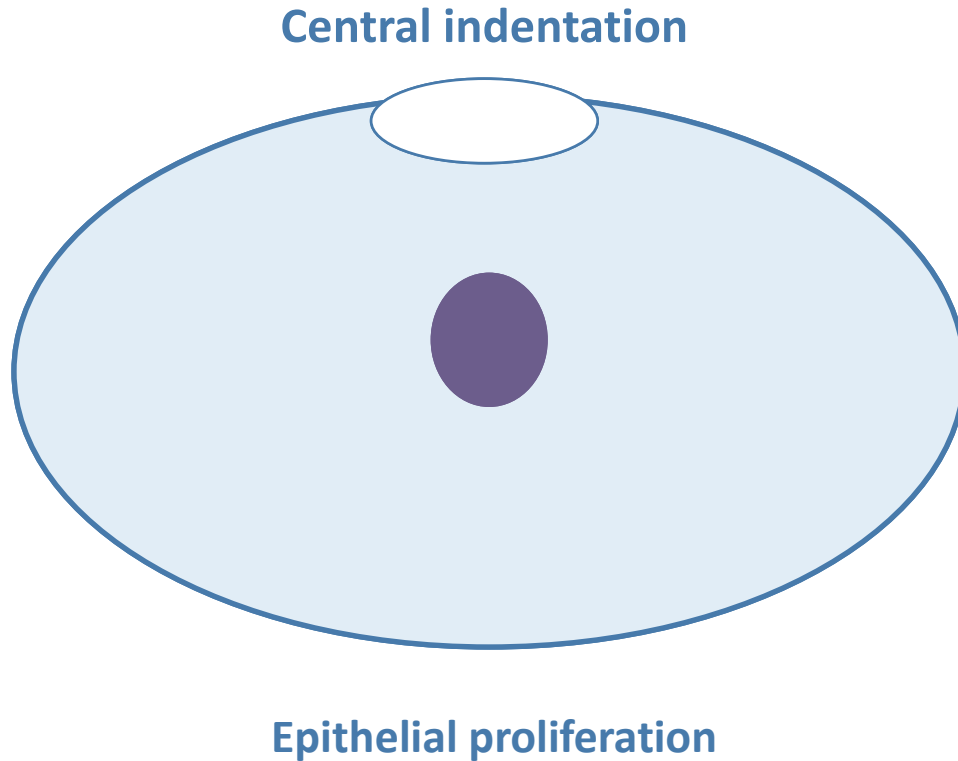


Robbins also notes inhibition of p21 and p27 and modulation of cyclin activity.

HPV infection alone does not ensure carcinoma

- High-risk HPV is causally important, but progression usually requires additional genetic or epigenetic alterations.
- The relevant distinction is productive benign epithelial growth versus transformed malignant growth.
- A virus-associated proliferation is not automatically a cancer.

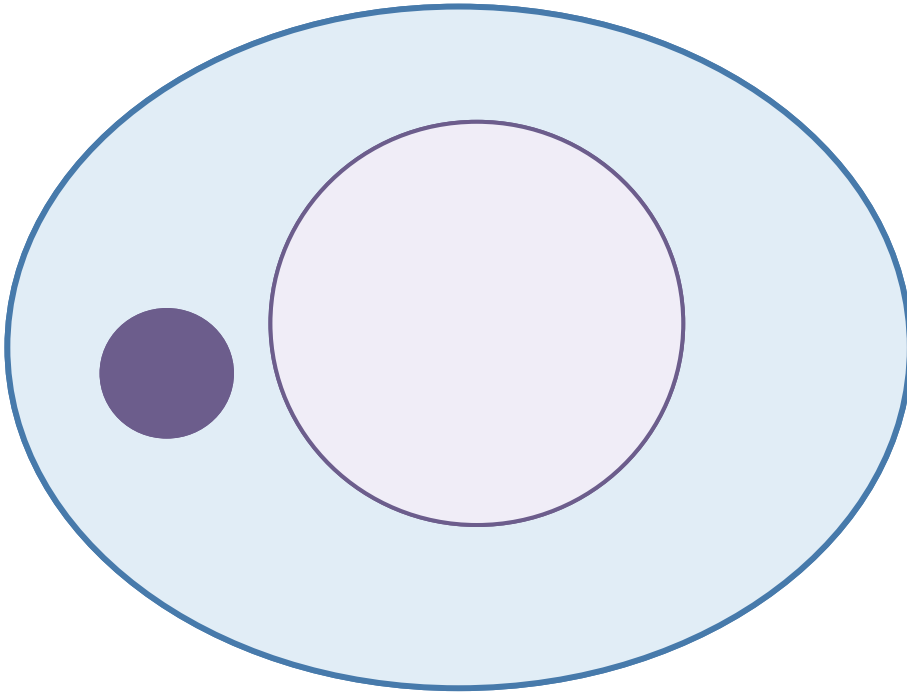
Molluscum: Proliferative umbilicated papules



- Poxvirus infection creates characteristic pearly dome-shaped papules with a depressed center.
- The lesion is an epithelial proliferation with a recognizable clinical architecture.

Schematic · not a histologic specimen

Molluscum: Inclusions are cytoplasmic



Cytoplasmic inclusion

Schematic · not a histologic specimen

- The central core of a papule contains infected cells with intracytoplasmic viral inclusions.
- Compartment location contrasts with the classic herpesvirus nuclear inclusion.

HPV and molluscum: Two types of papules

HPV wart

Papillomatous / verruciform epithelial growth

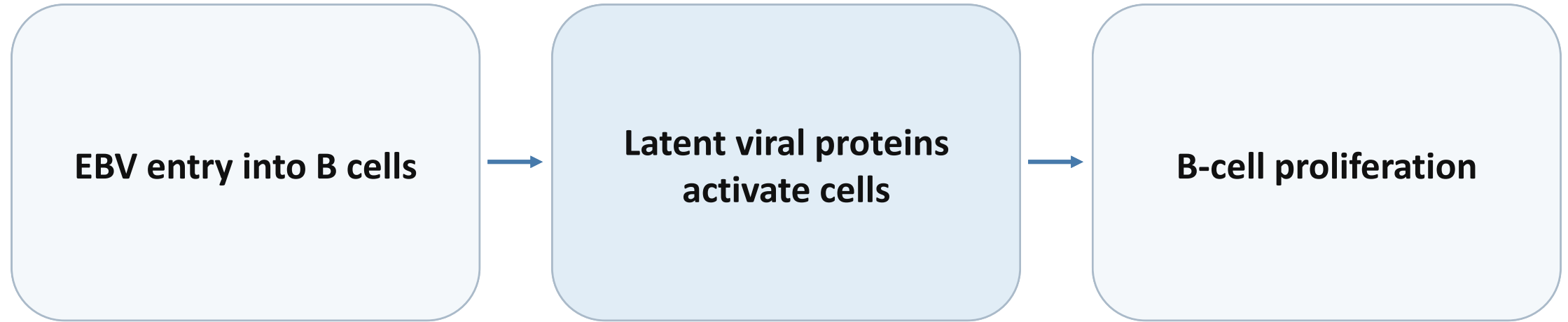
Koilocytosis in upper layers

Molluscum contagiosum

Dome-shaped umbilicated papule

Cytoplasmic inclusions

EBV produces a proliferative B-cell response



LMP1 and EBNA2 as proteins that promote infected B-cell activation and expansion.

EBV mononucleosis is not just B-cell expansion

EBV-infected B cells

A proliferating, virally infected cell population

Latent viral proteins in a minority of nodal cells

Reactive T cells

Expanded antiviral CD8+ response

Atypical lymphocytes; Paracortical expansion

EBV links benign lymphoproliferation and cancer

- EBV causes a benign, often self-limited infectious mononucleosis syndrome.
- It also contributes to the pathogenesis of some lymphomas and nasopharyngeal carcinoma.
- A viral association does not mean every expanded lymphoid population is malignant.

Reaction pattern by exemplar

Virus	Signature cytopathic / proliferative feature
HSV / VZV	Intranuclear inclusions; Epithelial vesicles; Fusion
Measles	Multinucleated giant cells / syncytia
CMV	Cytomegaly with prominent nuclear inclusion
HPV	Papillomatous proliferation and koilocytosis
Molluscum	Umbilicated papule; Cytoplasmic inclusions
EBV	Infected B-cell proliferation; Reactive lymphoid expansion

Suppuration and cytopathic injury differ

Purulent reaction

Numerous neutrophils and pus

Classically prominent in pyogenic bacterial infections

Cytopathic reaction

Affected cells may dominate despite little inflammation

Classically viral inclusions, fusion or vesiculation

Tissue necrosis can eclipse specific inclusions

Cytopathic pattern

Individual infected cells show inclusions, fusion or architectural effects

Cell-level clues may be preserved

Necrotizing pattern

Extensive destruction becomes the dominant feature

HSV brain or HBV liver cited as severe examples

Mixed patterns challenge single-label diagnosis

- Robbins cautions that host tissue responses rarely occur in pure form.
- One lesion can combine cytopathic change, necrosis, and inflammation.
- A mixed pattern can also reflect simultaneous infections, particularly in immunosuppressed hosts.

Interpret the lesion in a fixed sequence

**Identify cell-level
alteration**



**Characterize tissue
architecture**



**Integrate inflammation
and clinical context**

Choose targeted etiologic confirmation when morphology is compatible but nonspecific.

Case: Painful recurrent grouped mucosal vesicles

A patient develops recurrent localized vesicles near the lip. Biopsy shows intraepithelial vesiculation and inclusion-bearing multinucleated epithelial cells.

What reaction pattern is demonstrated, and which virus is favored?

Interpretation: Cytopathic reaction with epithelial injury, syncytia, and nuclear inclusions; HSV is favored by the recurrent localized mucocutaneous setting.

Case: Unilateral painful dermatomal eruption

A person develops painful vesicles restricted to one sensory dermatome. Infected keratinocytes contain intranuclear inclusions.

How do distribution and cellular findings complement one another?

Interpretation: Intranuclear inclusion—associated epithelial cytopathy indicates a viral reaction; The dermatomal, painful recurrence points toward VZV reactivation.

Case: Papule with epithelial viral inclusions

A small, pearly umbilicated skin papule has an epithelial core of cells containing cytoplasmic inclusions.

Which pattern and etiologic group are suggested?

Interpretation: Cytoproliferative papule with intracytoplasmic inclusions, characteristic of molluscum contagiosum (poxvirus).

Case: Papillary growth with koilocytosis

An anogenital exophytic lesion shows papillary epithelial hyperplasia and koilocytosis in superficial cells.

What mechanism explains the tissue architecture and nuclear/cytoplasmic change?

Interpretation: HPV-associated epithelial proliferation and cytopathic koilocytosis; Benign condyloma is favored by this combined pattern.

Synthesis: Follow the cells, then the tissue

- Inclusions and multinucleation indicate virus-associated alterations of infected cells.
- Vesicles reflect epithelial injury; Papillomas and some papules reflect epithelial proliferation.
- Specific viral examples must be interpreted in clinical and tissue context.
- The reaction may coexist with inflammation, necrosis, or neoplastic transformation.

Primary references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Ch. 8: Infectious Diseases, esp. pp. 308–325.
- Related source sections: Ch. 7 (HPV / viral oncogenesis); Ch. 22 (molluscum in genital tract); Ch. 25 (viral skin lesions).
- All diagrams in this lecture are original, editable schematics; no textbook figures or authentic photomicrographs were reproduced.