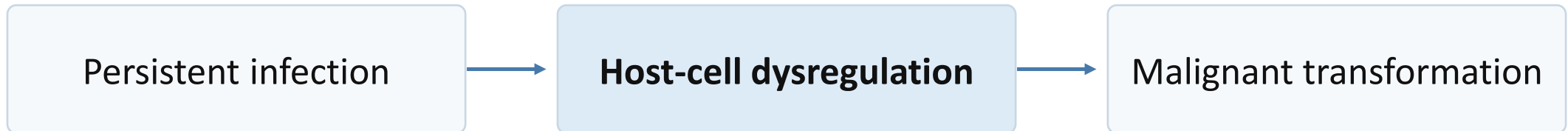


Oncogenic DNA Viruses

Mechanisms of viral carcinogenesis and clinicopathologic associations



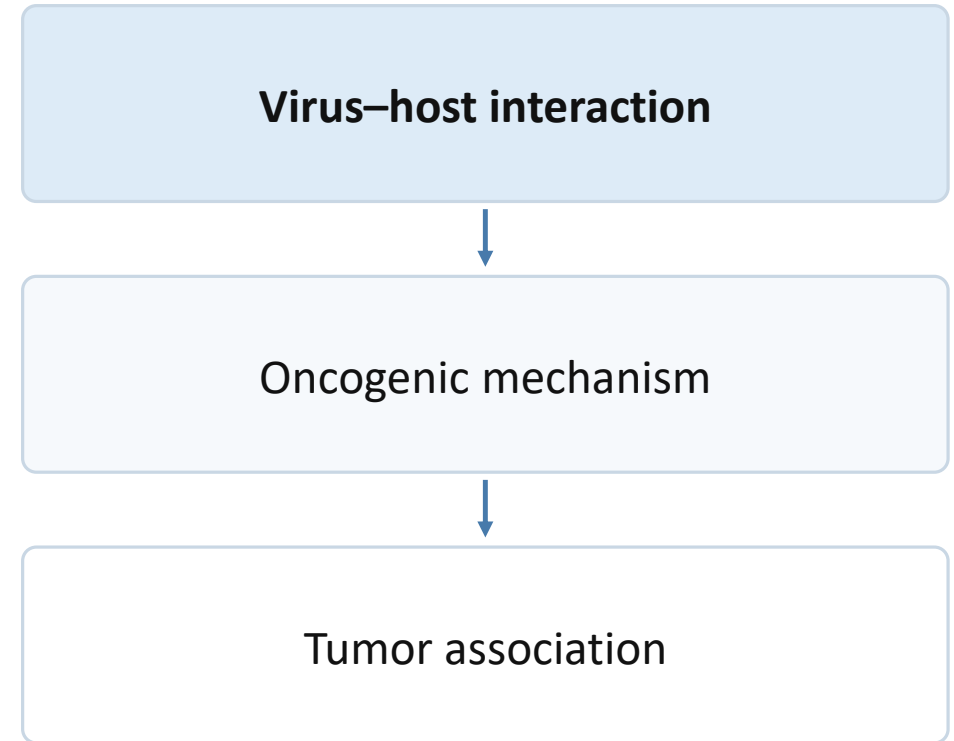
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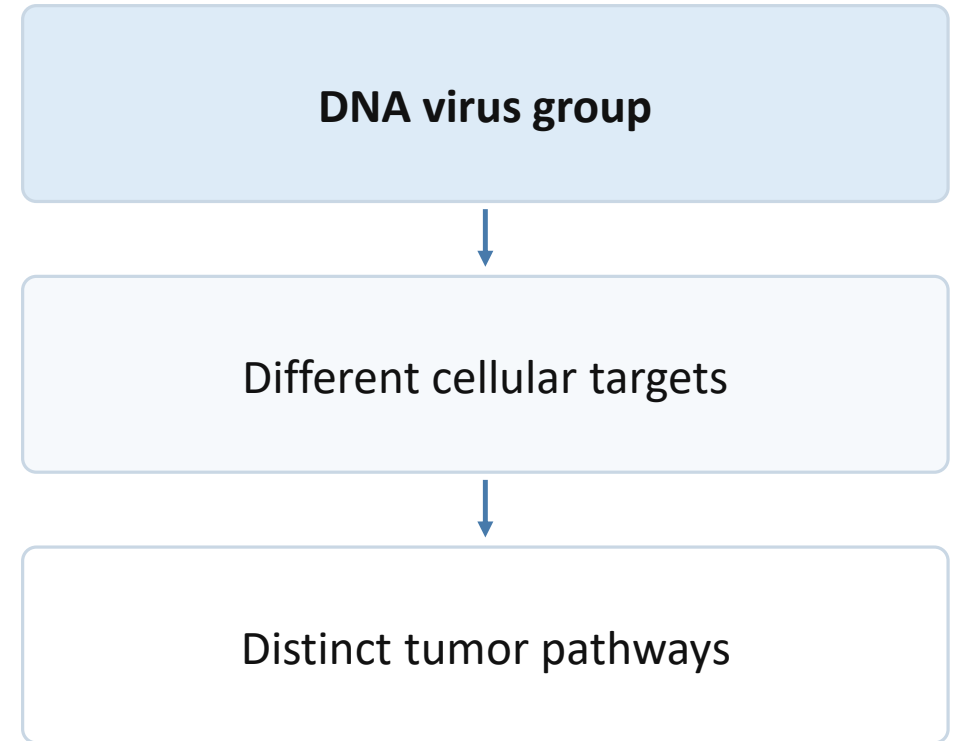
Learning objectives

- Identify the oncogenic human DNA viruses named.
- Explain how persistent infection subverts cell-cycle control or host immunity.
- Differentiate direct viral effects from inflammation-driven carcinogenesis.
- Link major virus–tumor associations to their pathogenic mechanisms.



Five human DNA viruses implicated in cancer

- HPV, EBV, HBV, Merkel cell polyomavirus, and HHV8 are the principal agents listed.
- They differ in target cells, persistence, and tumor spectrum.
- HCV is included for comparison but has an RNA genome.

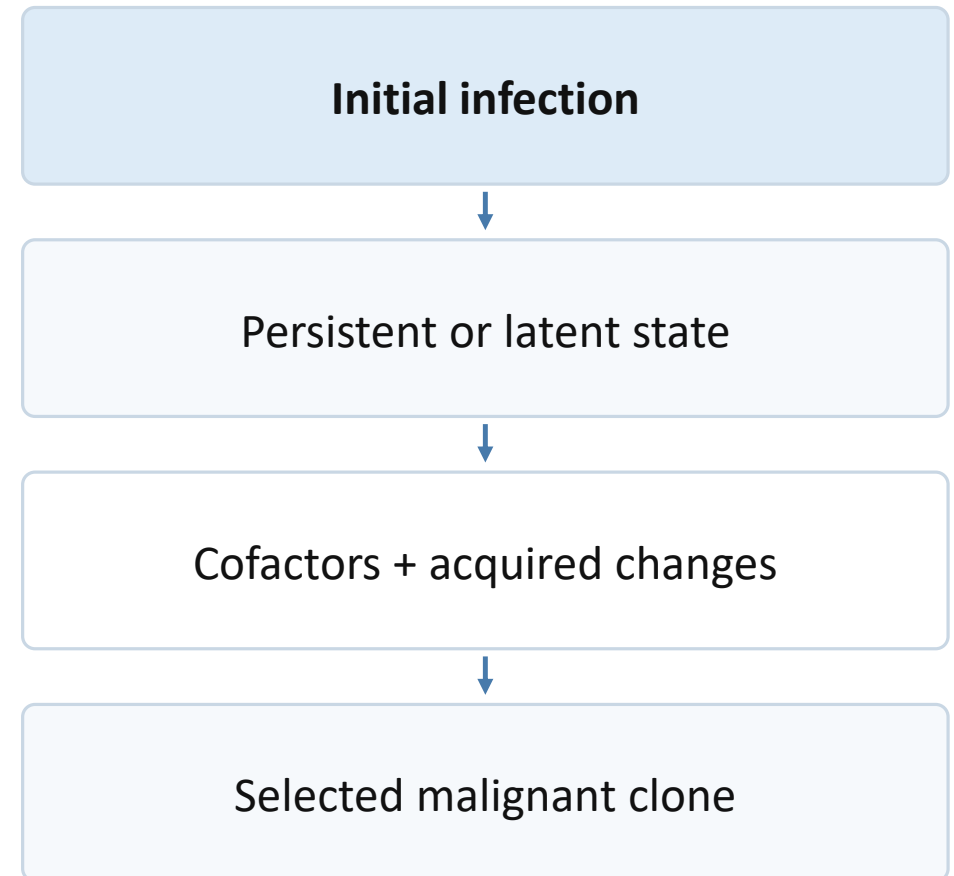


Virus–tumor associations are not interchangeable

Virus	Major tumor association	Dominant teaching mechanism
HPV	Cervical, anogenital, head/neck squamous cancer	E6/p53 and E7/RB
EBV	B-cell lymphomas; nasopharyngeal carcinoma	Latency, signaling, immune context
HBV	Hepatocellular carcinoma	Chronic inflammation; HBx/integration
HHV8 / KSHV	Kaposi sarcoma; selected B-cell disorders	Lytic/latent programs; immune suppression
Merkel polyomavirus	Merkel cell carcinoma	Integrated viral genome; growth-control proteins

An infection is not itself equivalent to malignancy

- Most infections do not culminate in cancer.
- Persistence, permissive host conditions, and additional alterations can be decisive.
- Latency may allow viral genomes to persist without productive cell lysis.



Three mechanistic routes to virus-associated cancer

- Viral proteins can directly impair tumor suppressors and promote proliferation.
- Viral latency may expand an infected cell pool while evading immune elimination.
- Chronic immune-mediated tissue injury can promote regeneration and mutation.

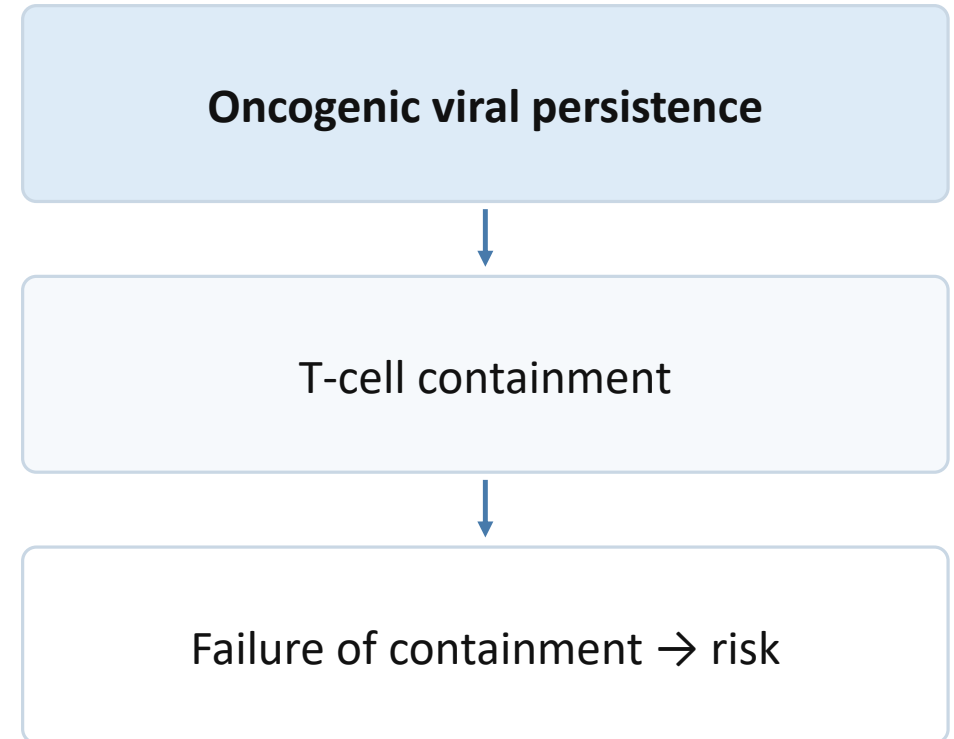
Direct cell-cycle disruption

B-cell immortalization / immune failure

Chronic injury / regeneration

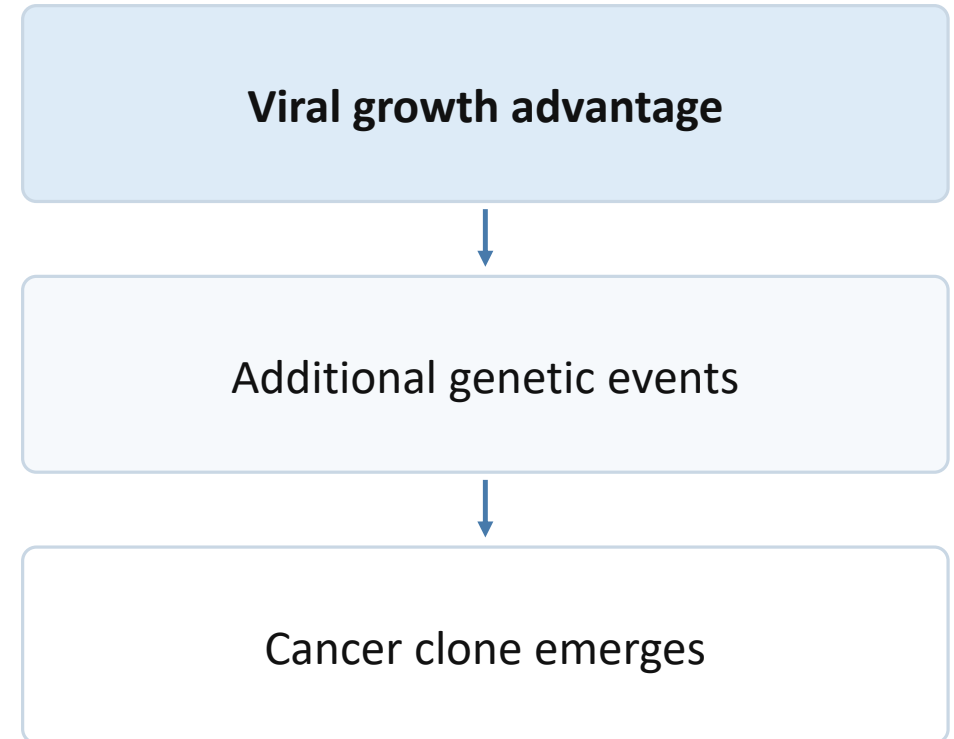
Host T-cell immunity modifies oncogenic risk

- Effective cytotoxic responses restrain EBV-transformed B cells.
- HIV-associated immunodeficiency promotes persistent HPV infection and HHV8-related disease.
- T-cell surveillance may prevent progression of MCV-infected cells.



Genetic collaboration explains delayed transformation

- HPV E6 and E7 can immortalize keratinocytes without making them tumorigenic alone.
- Burkitt lymphoma requires MYC dysregulation in addition to permissive B-cell proliferation.
- Viral infection creates a context in which further alterations become consequential.



Low-risk and high-risk HPV have different outcomes

- Low-risk HPV-6 and HPV-11 predominantly cause genital warts.
- High-risk types, including HPV-16 and HPV-18, are associated with squamous carcinomas.
- Difference in E6/E7 binding activity helps explain differential cancer risk.

**Low risk →
papilloma**

**High risk →
persistent
oncogenic
activity**

Anatomic distribution of high-risk HPV cancers

- Cervical squamous carcinoma is a key HPV-associated malignancy.
- Anogenital squamous cancers are included in the association.
- In the head and neck, tonsillar mucosa is highlighted.

Cervix

Anogenital region

Tonsillar mucosa

HPV genome state differs between warts and cancers

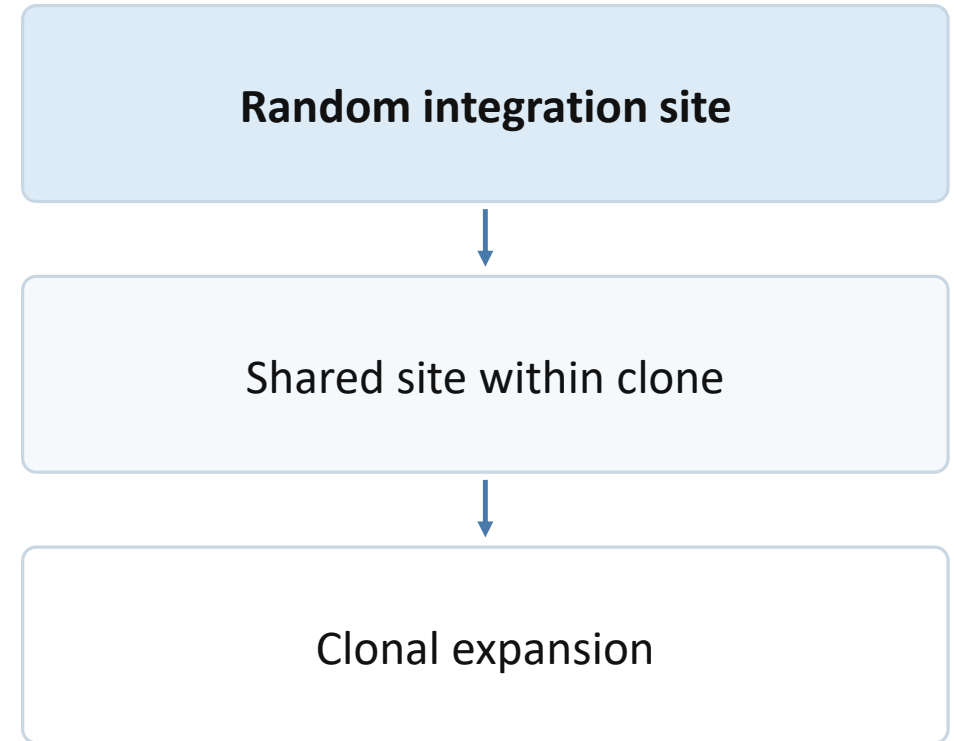
- In benign warts, viral genomes are generally maintained as episomes.
- In cancers, viral DNA is commonly integrated into host chromosomal DNA.
- Integration is implicated in altered expression of oncogenic viral genes.

**Episomal viral
DNA**

**Integrated viral
DNA**

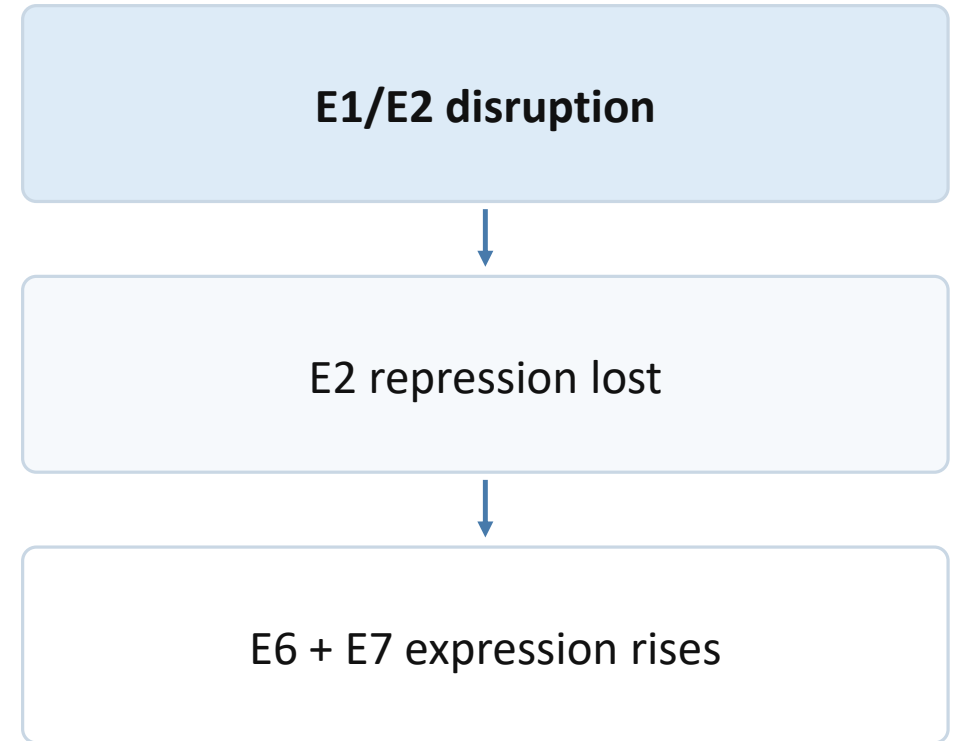
Clonal integration is evidence of early viral involvement

- Integration sites vary across tumors; No single host locus is required.
- Within a tumor, integration patterns are clonal.
- Clonality supports expansion of a progenitor bearing the viral event.



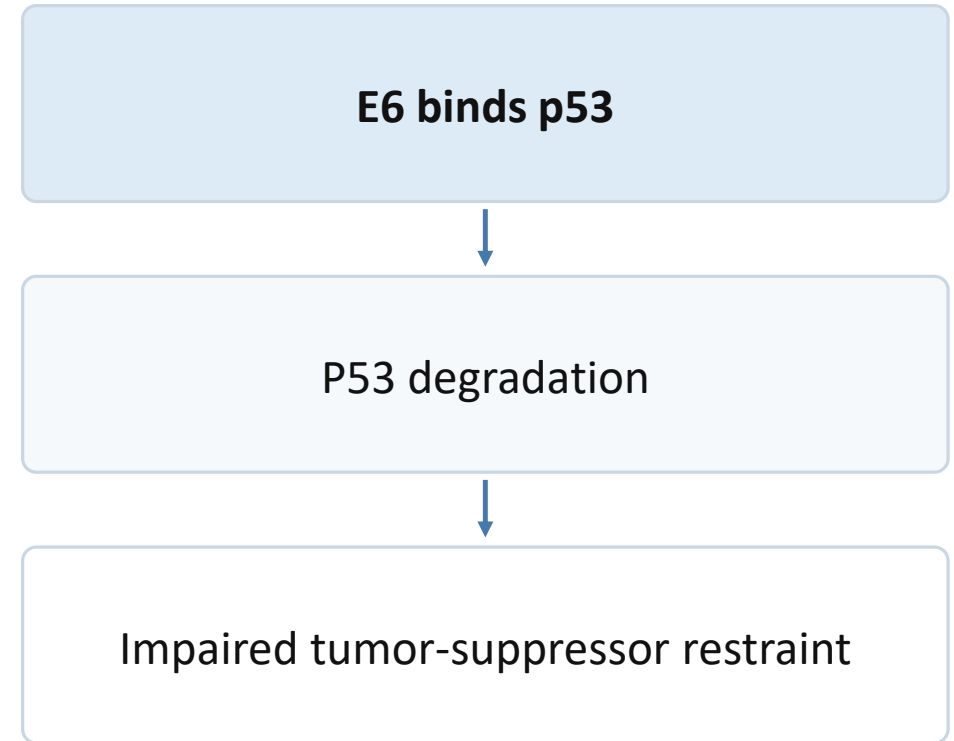
E2 loss derepresses the E6/E7 oncogenes

- Integration disrupting the E1/E2 region.
- Loss of the E2 repressor increases expression of E6 and E7.
- The consequence is sustained interference with host growth checkpoints.



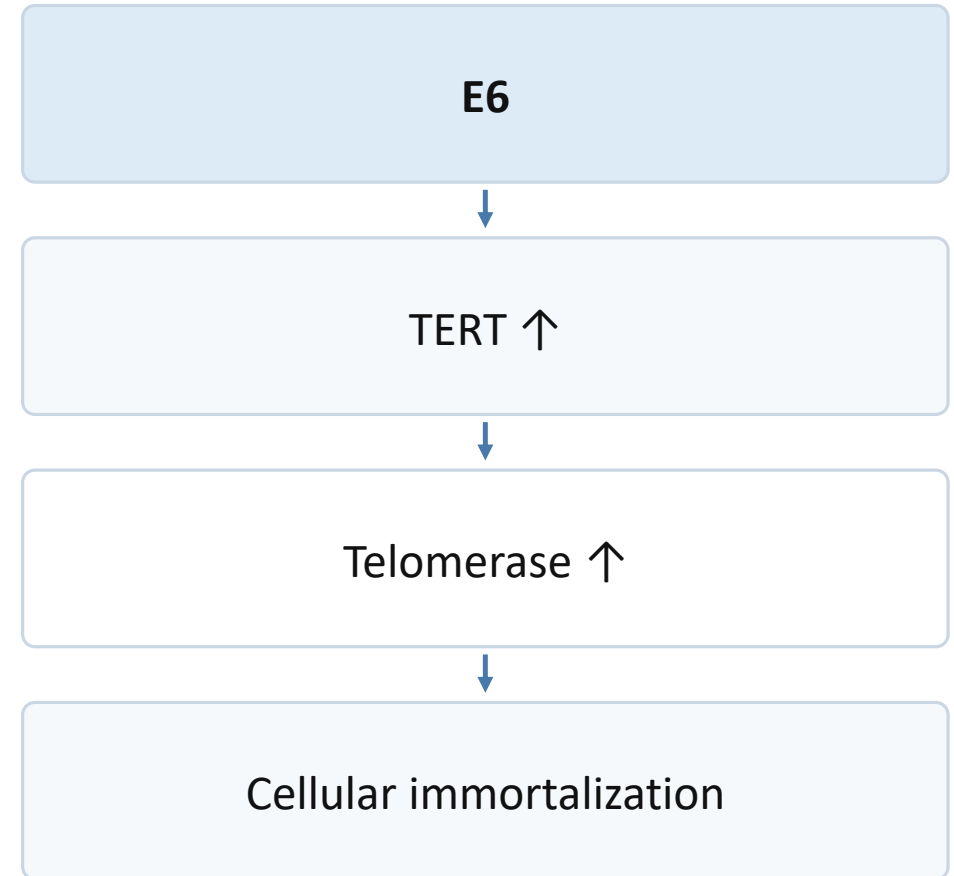
E6 accelerates degradation of p53

- E6 binds p53 and facilitates its destruction.
- Loss of p53 impairs damage-response restraints on abnormal cells.
- High-risk HPV E6 binds p53 more avidly than low-risk E6.



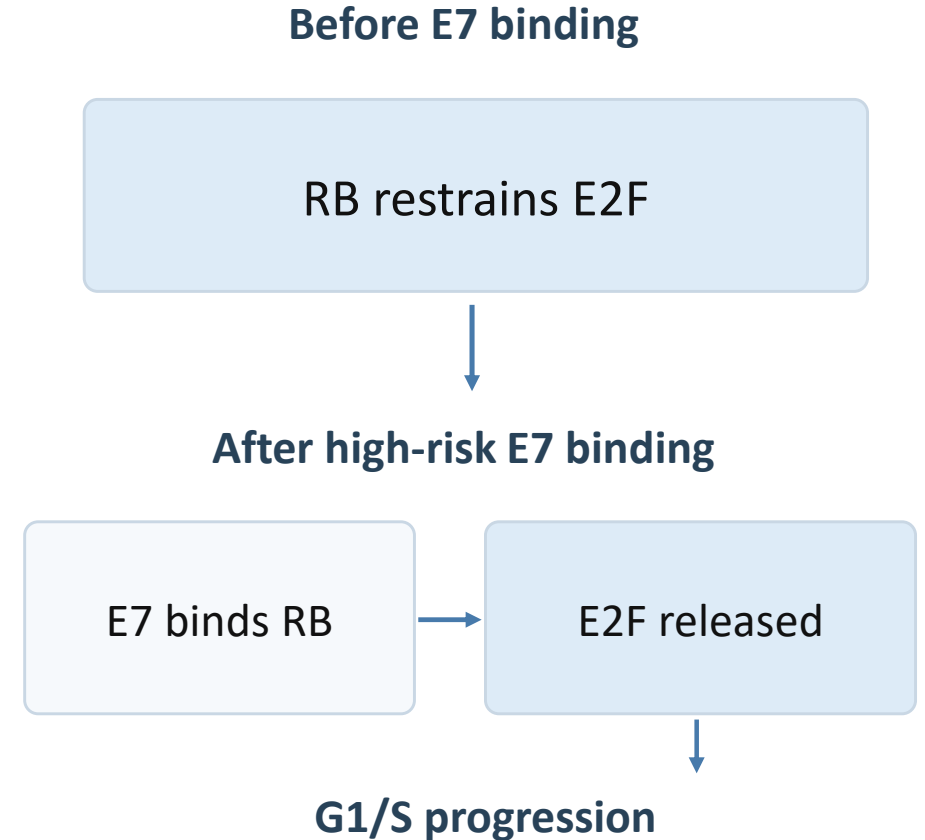
E6 also supports replicative immortality

- E6 stimulates expression of telomerase reverse transcriptase (TERT).
- TERT is the catalytic subunit of telomerase.
- Telomerase activity helps infected cells bypass senescence.



E7 releases the RB–E2F cell-cycle brake

- RB normally sequesters E2F transcription factors.
- E7 binds RB and releases E2F.
- Available E2F promotes transcription required for G1/S progression.



High-risk E7 binds RB with greater affinity

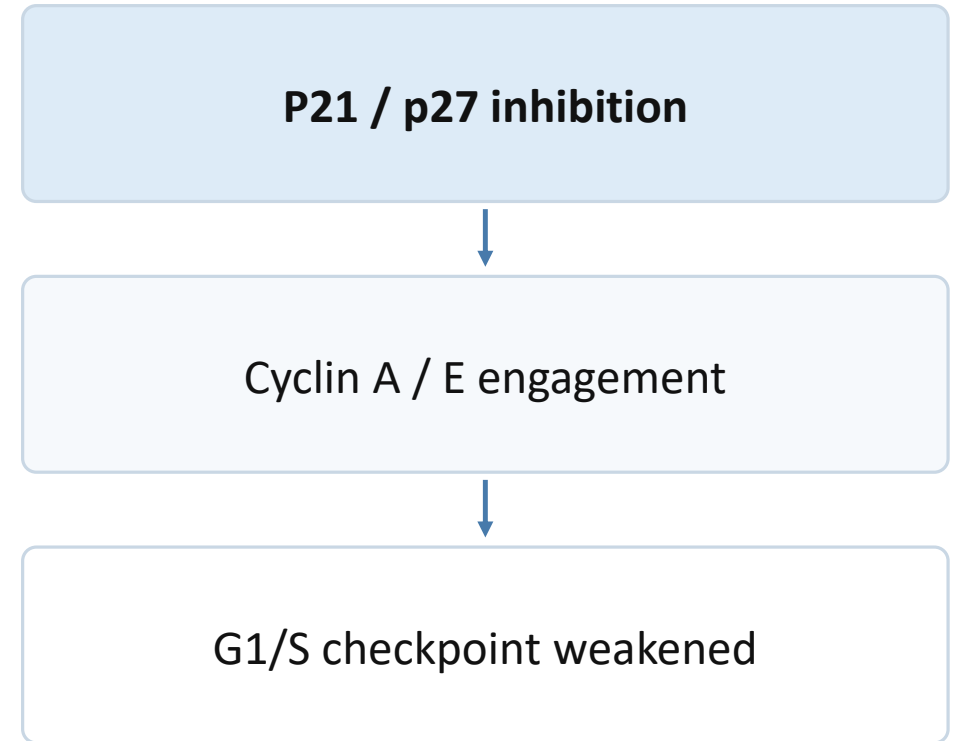
- The E7 proteins of high-risk HPVs bind RB more strongly than low-risk E7.
- This strengthens the proliferative impact of a persistent infection.
- Oncogenic potential is related to functional properties, not just presence of viral DNA.

Low-risk E7 / RB

High-risk E7 / RB

E7 removes additional G1/S restraints

- E7 inactivates the CDK inhibitors p21 and p27.
- High-risk E7 can bind and probably activate cyclins A and E.
- These combined actions favor progression through the cell cycle.

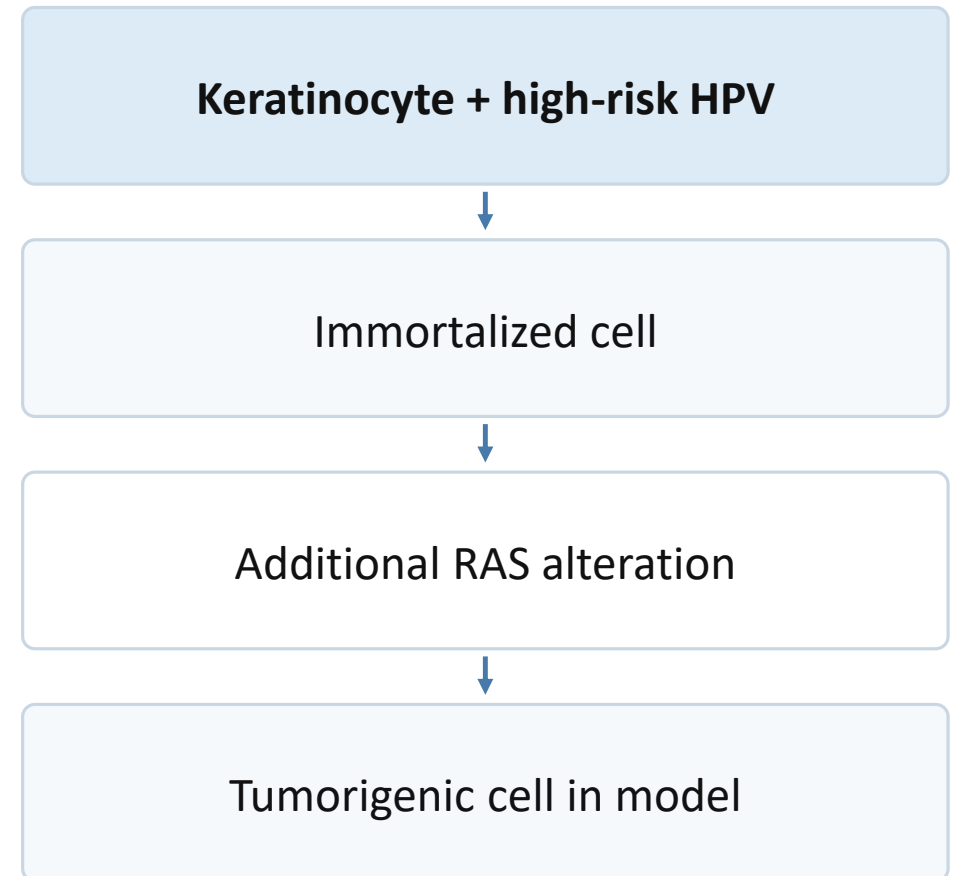


E6 and E7 attack complementary safeguards

Oncoprotein	Principal host target	Pathologic consequence
E6	p53 degradation	Reduced damage-dependent restraint
E6	TERT expression	Maintenance of telomeres / immortalization
E7	RB binding, E2F release	G1/S progression
E7	p21 / p27 inhibition; cyclins A/E	Additional cell-cycle acceleration

Cell-cycle deregulation is not full transformation

- HPV-16, -18 or -31 DNA can immortalize human keratinocytes in vitro.
- That tumor formation requires an additional altered RAS gene in this model.
- Transformation therefore has a multistep genetic requirement.



Persistent infection distinguishes many high-risk cases

- A high proportion of women clear high-risk HPV infections.
- The subgroup with persistent infection bears greater cervical-cancer risk.
- The long interval between infection and cancer supports additional events.

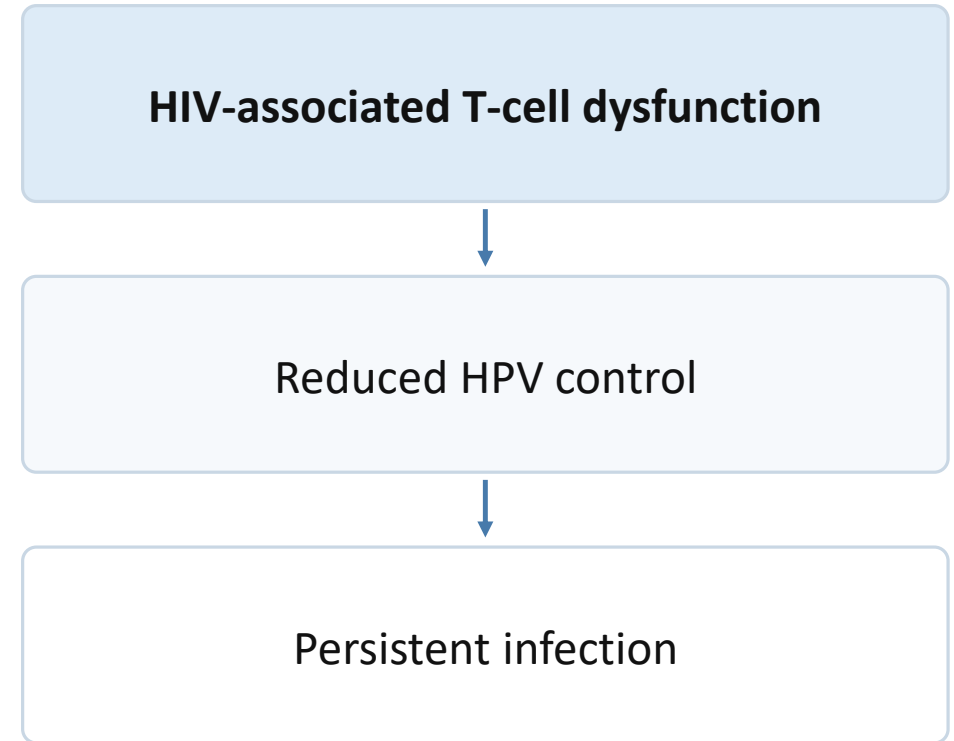
High-risk infection

Clearance → lower risk

Persistence → continuing risk

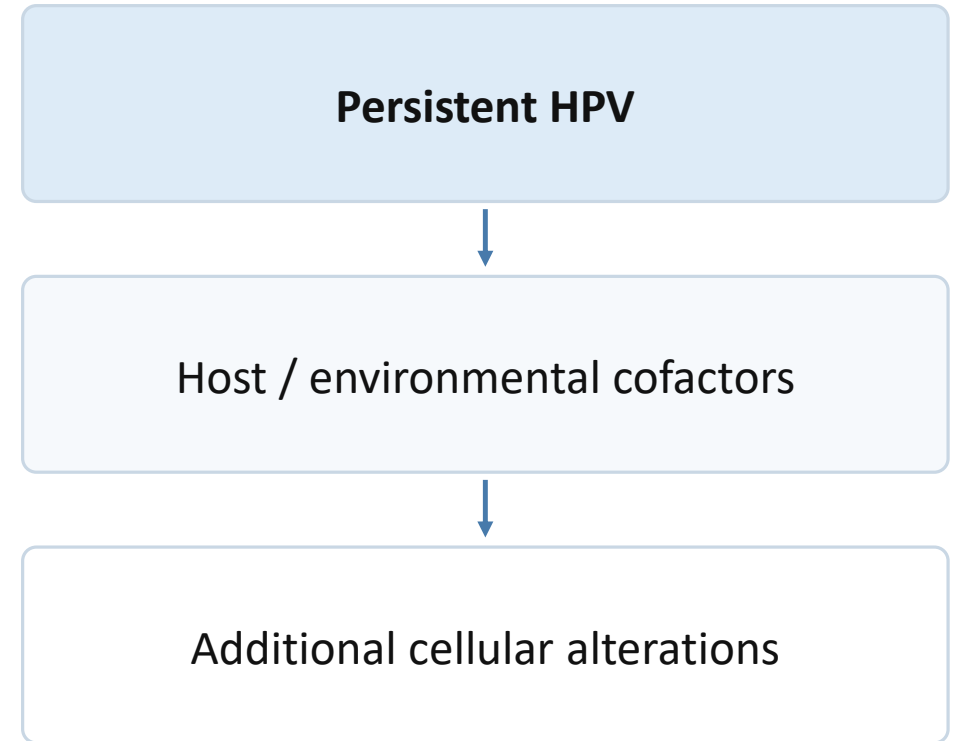
HIV co-infection increases persistence risk

- HIV co-infection as an important predictor of persistence.
- The proposed explanation is defective T-cell immune control.
- The relevant pathway is prolonged high-risk viral exposure, not HIV as a DNA virus.



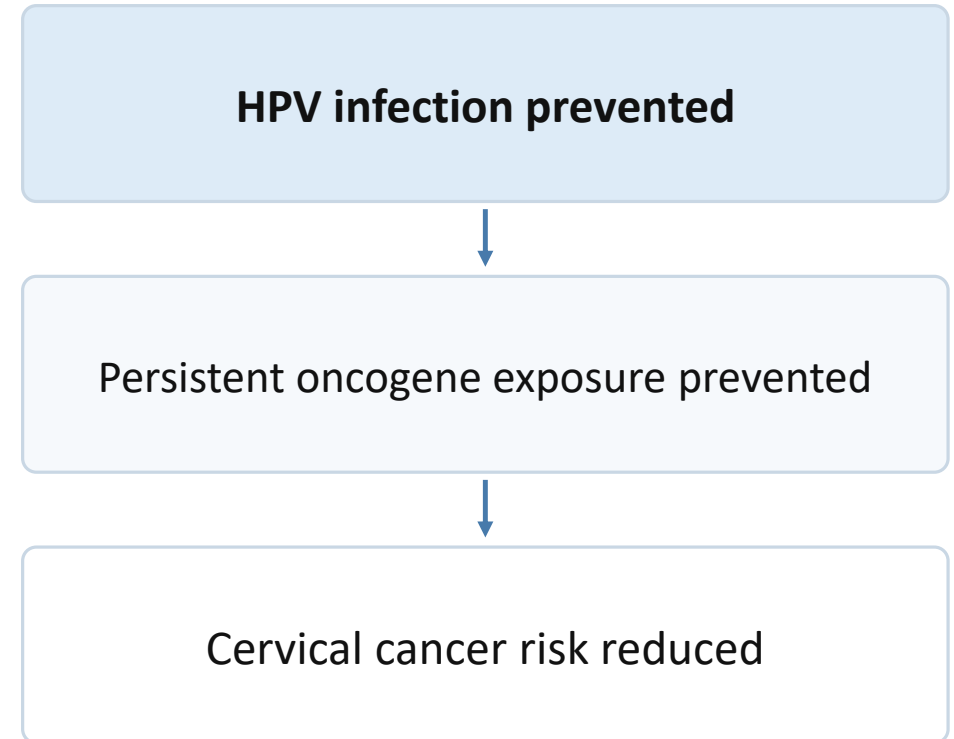
Nonviral cofactors influence HPV carcinogenesis

- Cigarette smoking and coexisting microbial infections.
- Dietary deficiencies and hormonal changes are also noted.
- These factors modify risk but do not replace the etiologic role of high-risk HPV.



Why HPV vaccination prevents cancer

- Preventing high-risk HPV infection interrupts the initiating viral exposure.
- Vaccine effectiveness as strong causal evidence for cervical cancer.
- Vaccination illustrates prevention upstream of somatic transformation.



Apply the HPV mechanism to a cervical lesion

- A lesion contains integrated high-risk HPV DNA and abundant E6/E7 expression.
- Predict the status of p53 regulation, RB-bound E2F, and telomerase.
- Which finding reflects viral oncogene activity rather than an inherited TP53 mutation?

E6 → p53 degradation

E7 → RB/E2F release

E6 → TERT ↑

EBV-associated tumors involve several lineages

- B-cell lymphomas and nasopharyngeal carcinoma.
- Other EBV-related lymphomas, carcinomas, and rare sarcomas are described.
- Tumor phenotype and immune context shape the mechanism.

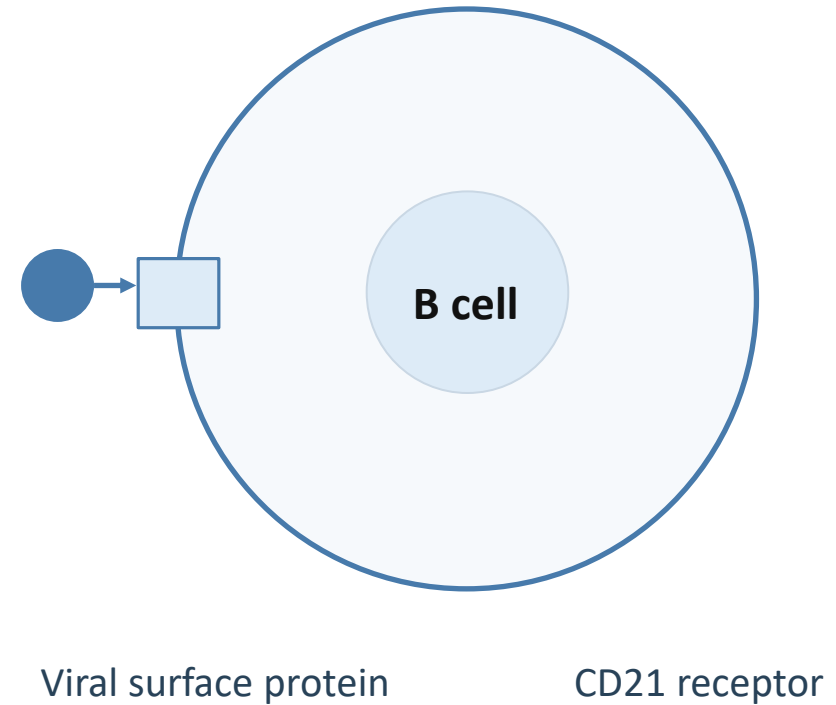
B-cell proliferations

Epithelial carcinomas

Other rare neoplasms

EBV enters B cells through CD21

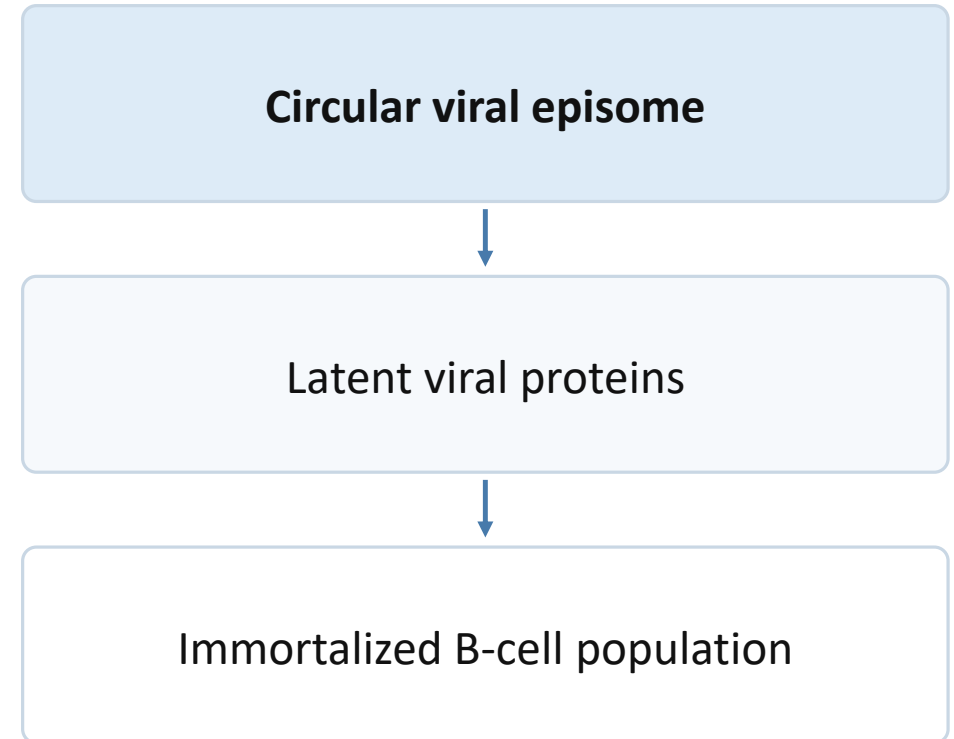
- EBV surface glycoproteins recognize complement receptor CD21.
- Binding facilitates B-cell infection, likely in the tonsils after salivary exposure.
- The initially infected B cell provides a long-lived latent reservoir.



Schematic — receptor-mediated B-cell entry

EBV latency persists as a circular episome

- The latent EBV genome remains extrachromosomal.
- Latent infection does not require ongoing productive viral replication.
- Viral gene expression supports prolonged survival and proliferation of infected cells.



LMP1 mimics constitutive CD40 signaling

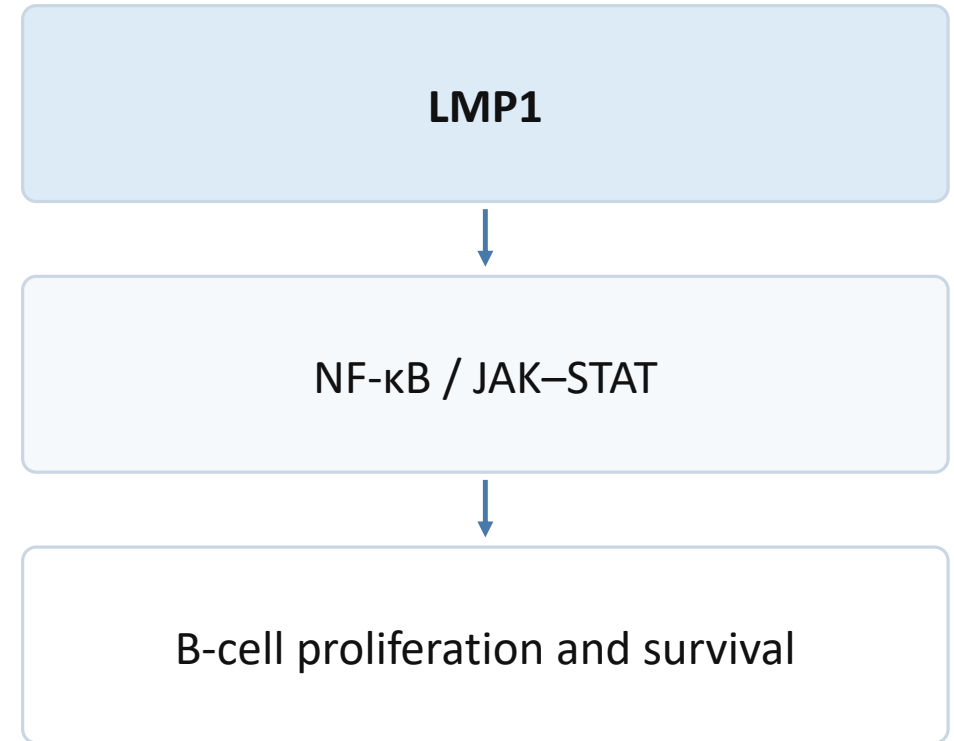
- Latent membrane protein 1 (LMP1) behaves like an active CD40 receptor.
- Normally, helper T-cell CD40 signals support B-cell growth.
- LMP1 supplies an autonomous growth and survival signal.

**Physiologic CD40
ligation**

**LMP1
constitutive
mimic**

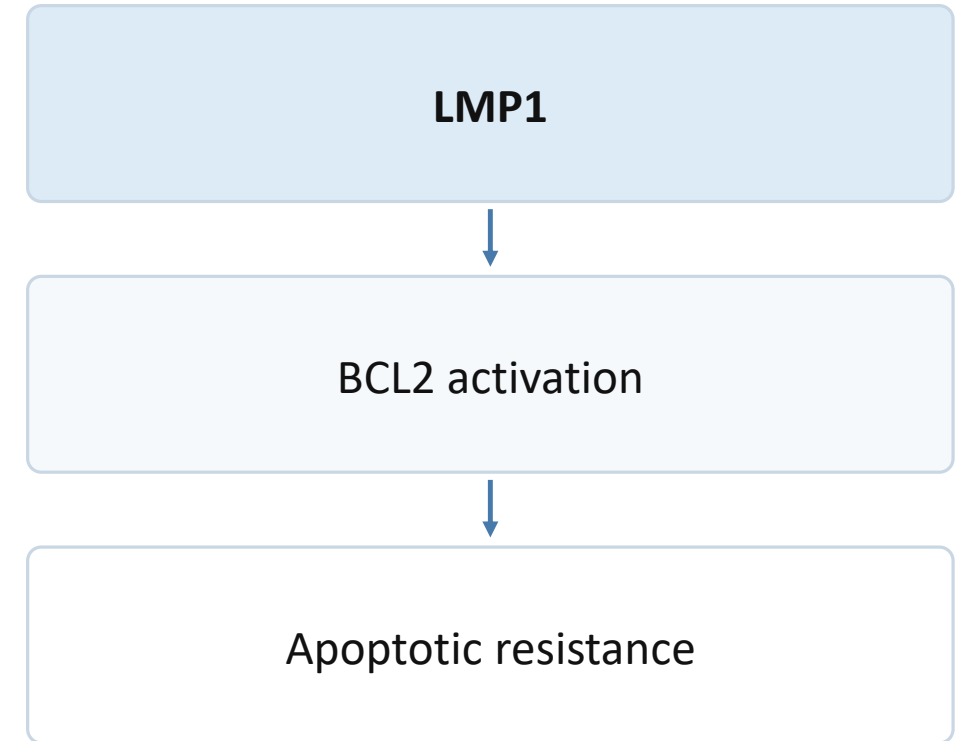
LMP1 activates NF- κ B and JAK/STAT

- These pathways normally transmit growth and survival cues.
- In EBV-infected cells they can operate without external helper T-cell stimulation.
- The result is autonomous B-cell expansion and survival.



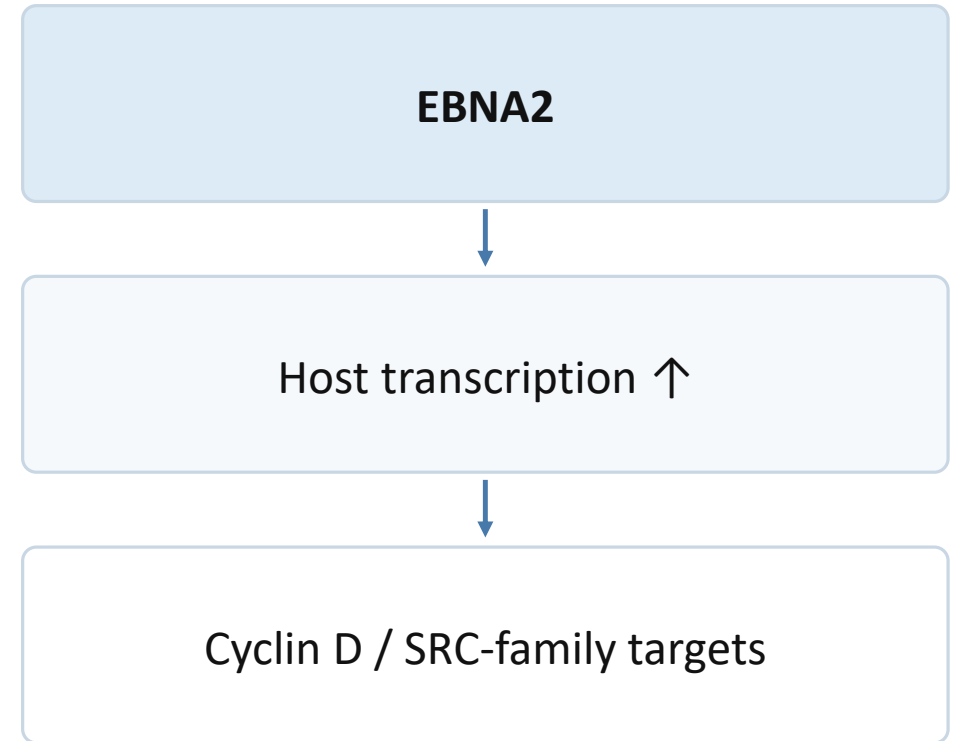
LMP1 promotes resistance to apoptosis

- LMP1 activates the antiapoptotic factor BCL2.
- Survival signals allow an enlarged pool of infected B cells to persist.
- Persistence creates opportunities for secondary oncogenic alterations.



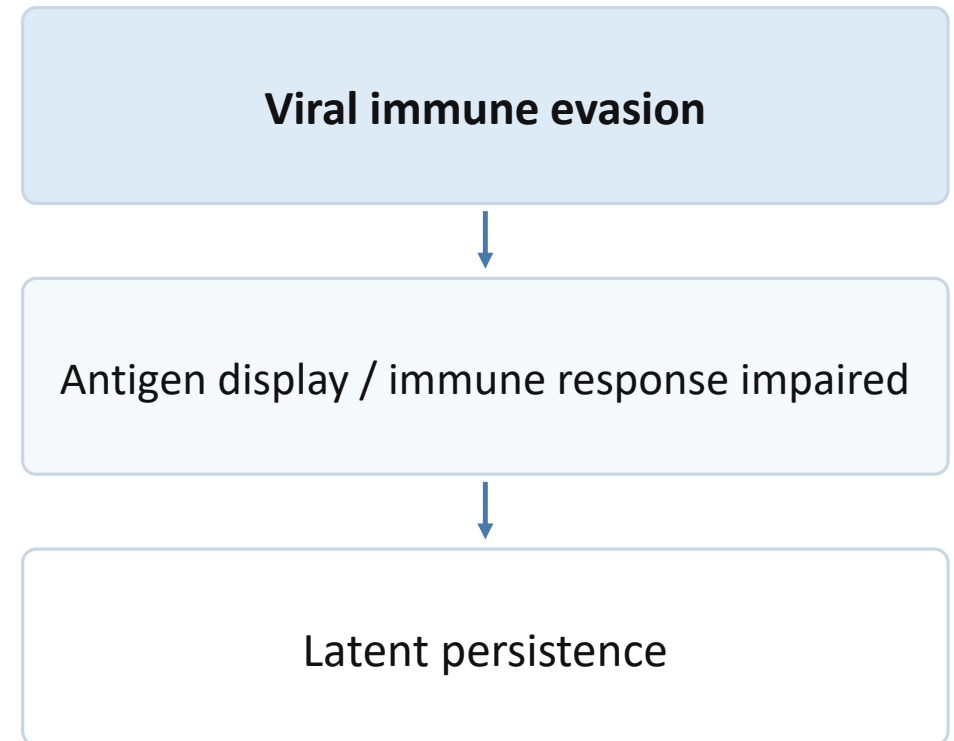
EBNA2 mimics activated Notch signaling

- Epstein–Barr nuclear antigen 2 (EBNA2) behaves like activated Notch.
- It changes host transcription rather than acting as a host DNA mutation.
- Robbins specifically names cyclin D and SRC-family genes among its targets.



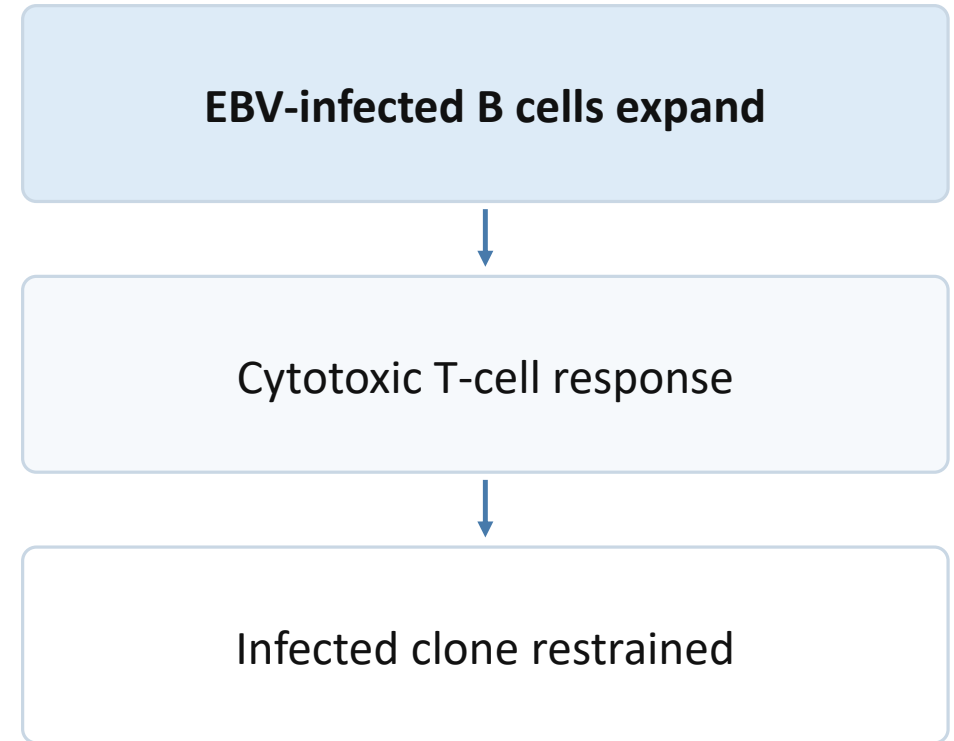
EBV immune evasion sustains latency

- Some EBV genes limit antigen presentation.
- Other products blunt NK-cell and T-cell responses.
- Reduced recognition favors the establishment of a persistent infected-cell reservoir.



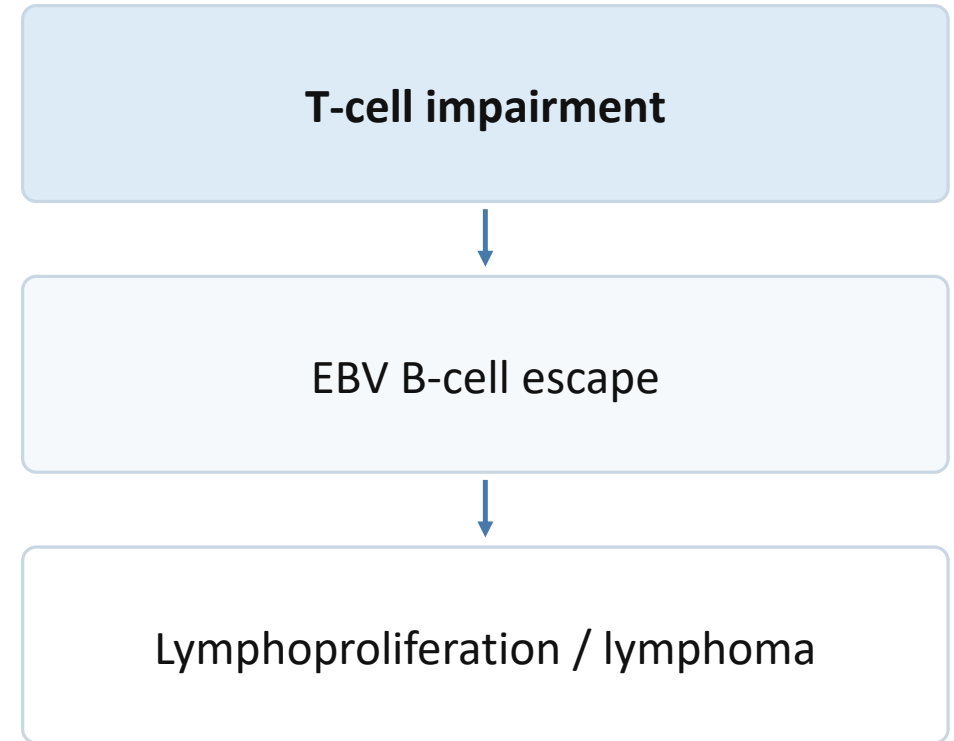
Normal T cells control EBV-driven B-cell expansion

- EBV growth-driving proteins are strongly immunogenic.
- Cytotoxic T cells usually contain the resulting polyclonal B-cell proliferation.
- The clinical outcome may be asymptomatic infection or infectious mononucleosis.



T-cell failure permits uncontrolled B-cell growth

- When T-cell immunity is defective, EBV-transformed B cells may proliferate rapidly.
- This mechanism is important in AIDS and in transplant immunosuppression.
- Immune context is therefore causally central, not merely associated.



Burkitt lymphoma: EBV association depends on setting

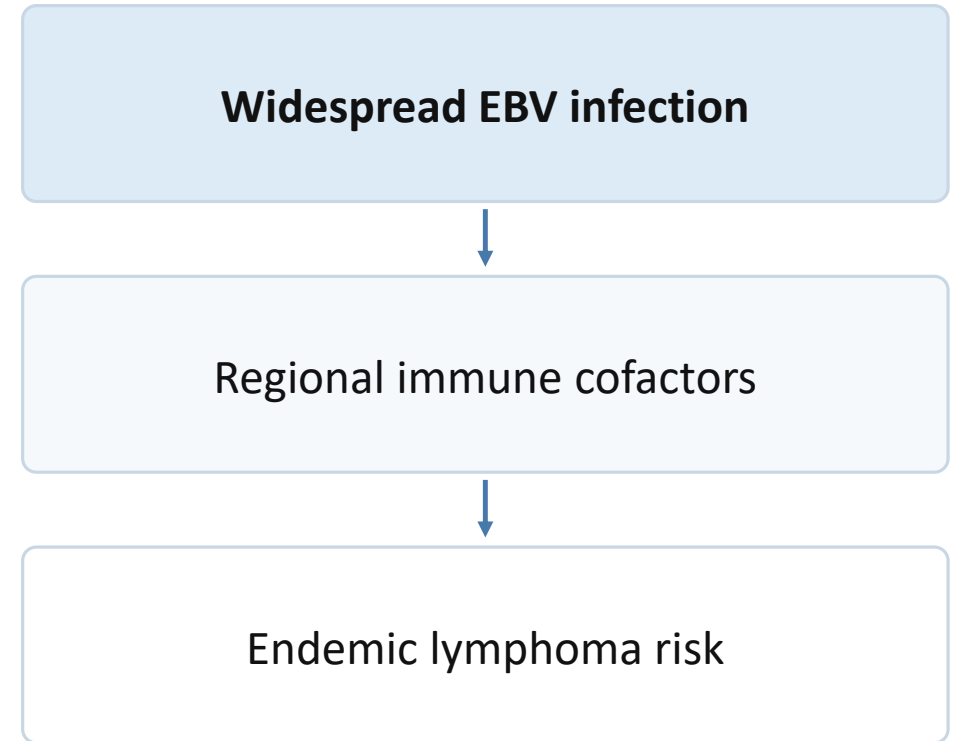
- More than 90% of endemic Burkitt lymphomas are EBV positive.
- Only 15%–20% of tumors outside endemic regions harbor EBV.
- Morphologically similar tumors can therefore have different viral associations.

**Endemic: >90%
EBV+**

**Outside endemic
areas: 15–20%
EBV+**

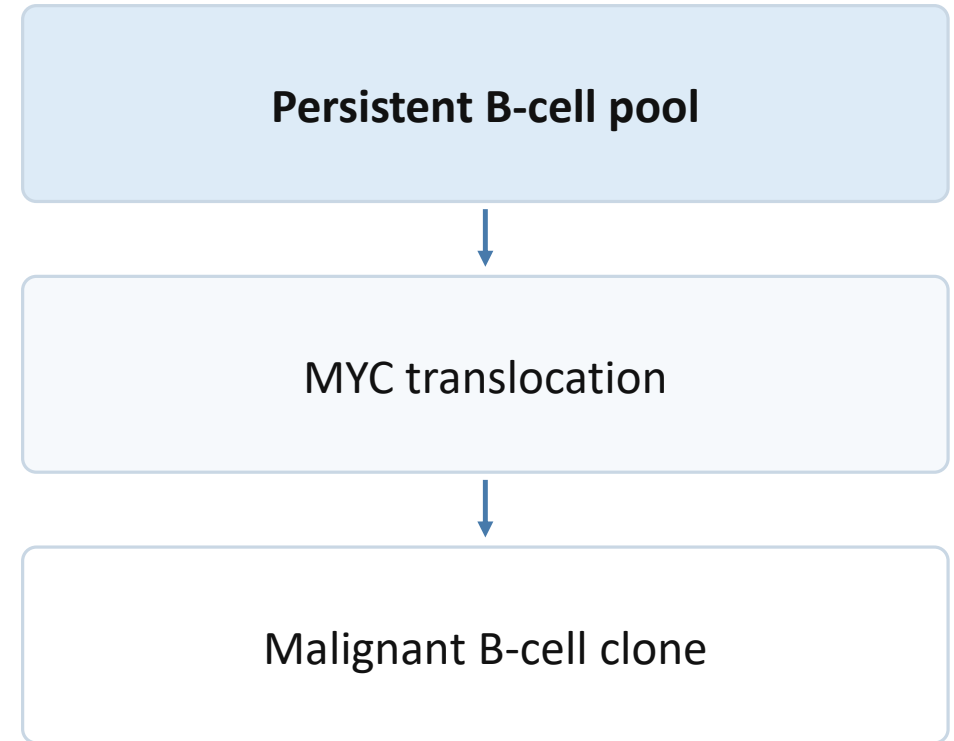
Geography points to cofactors in endemic Burkitt lymphoma

- Endemic Burkitt lymphoma is described in central Africa and New Guinea.
- EBV itself is nearly ubiquitous, whereas the tumor is geographically clustered.
- Concomitant infections such as malaria as cofactors.



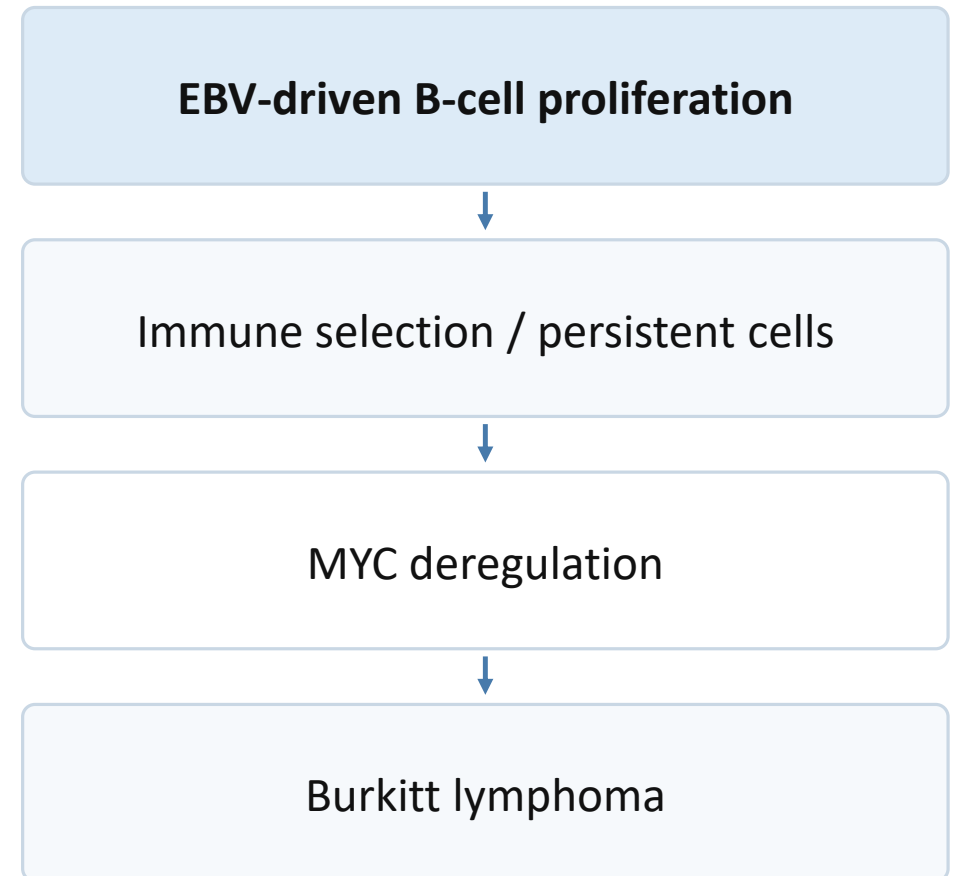
MYC dysregulation is crucial in Burkitt lymphoma

- Nearly all Burkitt lymphomas have an MYC-associated translocation.
- The classic event is t(8;14); Alternative MYC translocations occur.
- MYC dysregulation drives transformation beyond EBV-induced proliferation.



Proposed sequence for endemic Burkitt lymphoma

- EBV infection expands B cells; Malaria-associated immune impairment can prolong expansion.
- Cells that reduce immunogenic viral proteins may survive immune selection.
- A subsequent MYC event can generate overt lymphoma.



Why Burkitt lymphoma lacks growth-driving viral antigens

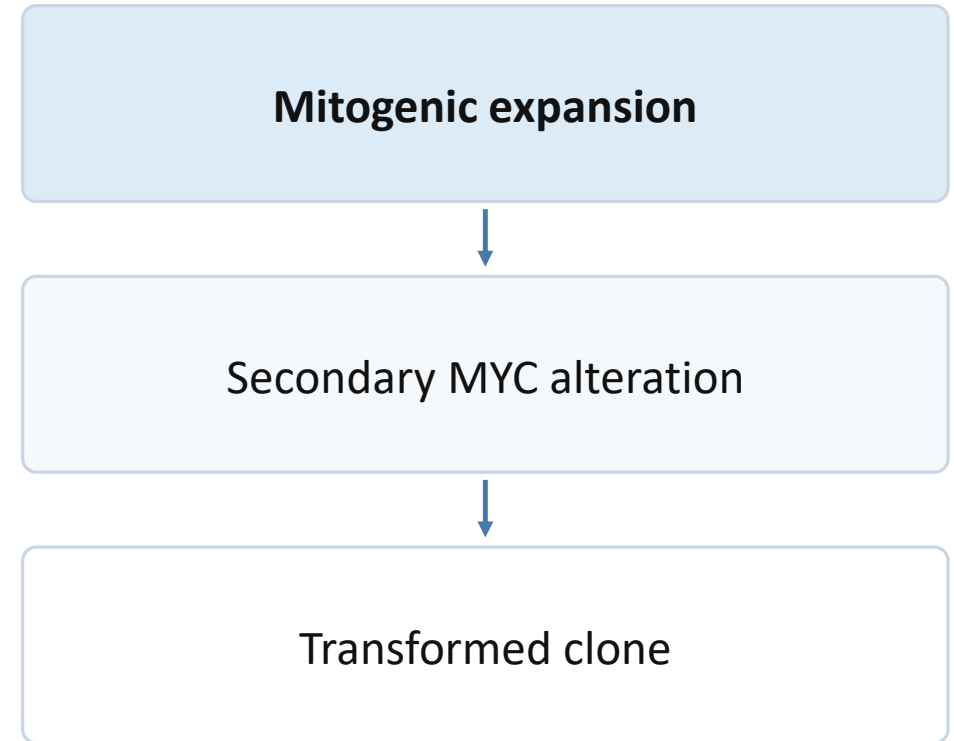
- Burkitt lymphoma cells generally do not express LMP1 or EBNA2.
- These antigens are expressed in EBV-immortalized B-cell lines.
- This contrast supports immune selection plus acquired host oncogenic changes.

**Immortalized B
cell: LMP1 /
EBNA2**

**Burkitt cell: Low
growth-antigen
expression**

EBV contributes indirectly to Burkitt transformation

- Robbins characterizes EBV primarily as a polyclonal B-cell mitogen in this setting.
- An expanded precursor pool favors acquisition and selection of MYC alterations.
- The same MYC pathway is implicated in EBV-negative sporadic disease.



Immunosuppression-related tumors use a different route

- Post-transplant and AIDS-associated EBV lymphoproliferations often express LMP1/EBNA2.
- They usually lack the MYC translocations characteristic of Burkitt lymphoma.
- Some arise in extranodal sites, including gut or central nervous system.

Loss of T-cell surveillance



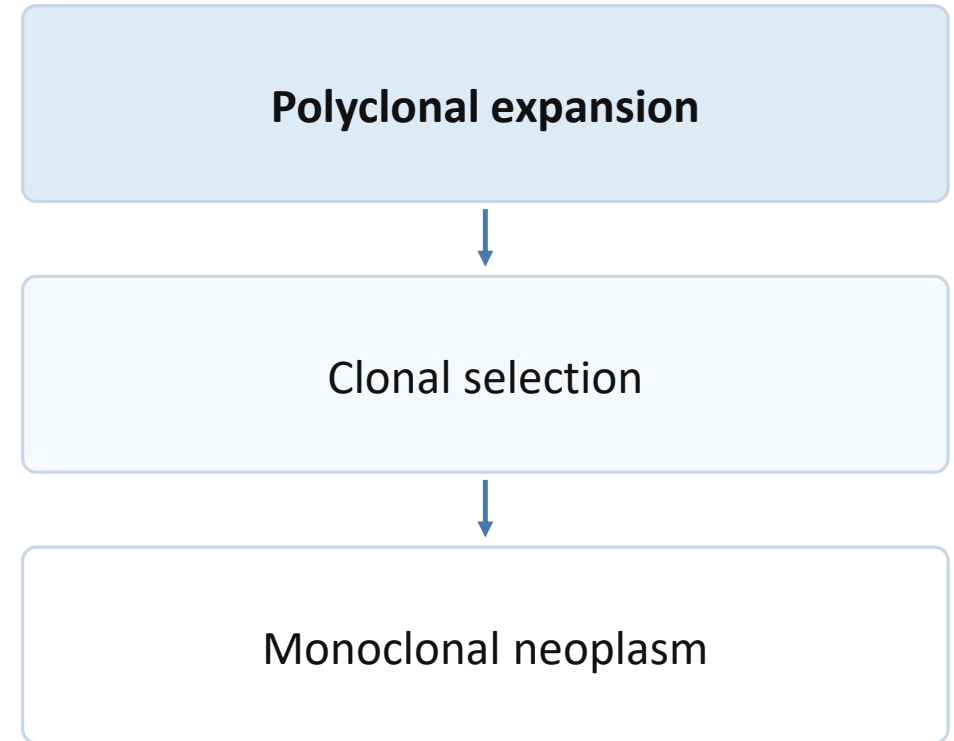
Viral growth proteins retained



B-cell lymphoproliferation

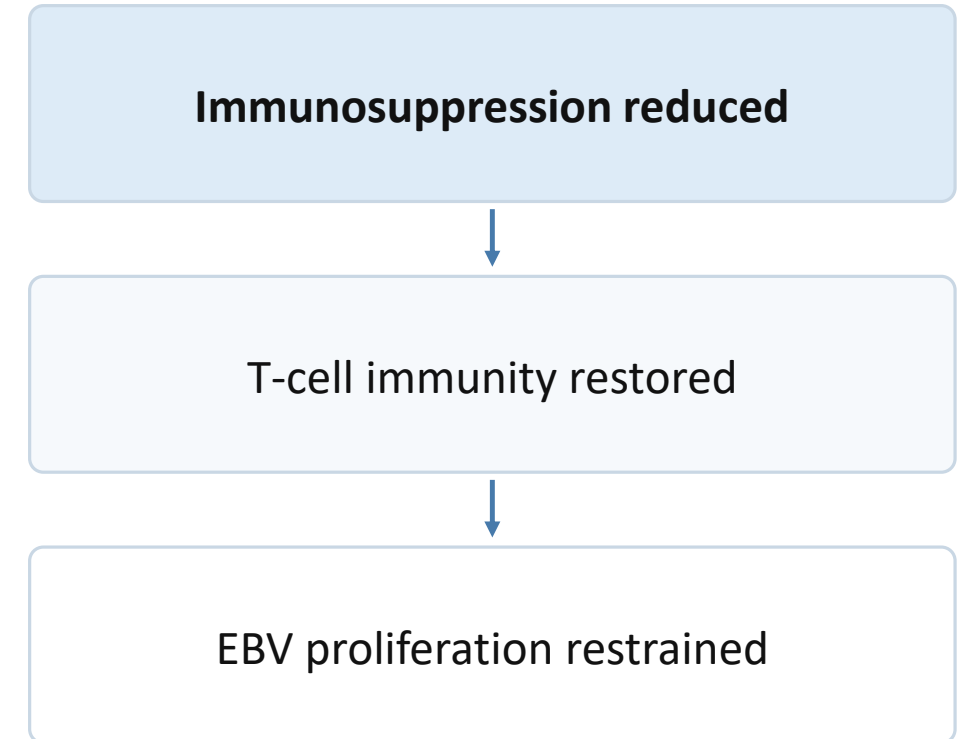
Early EBV lymphoproliferation may be polyclonal

- The earliest immunodeficiency-associated expansions may involve many B-cell clones.
- Some progress to a monoclonal neoplasm.
- Polyclonality does not guarantee a harmless clinical course.



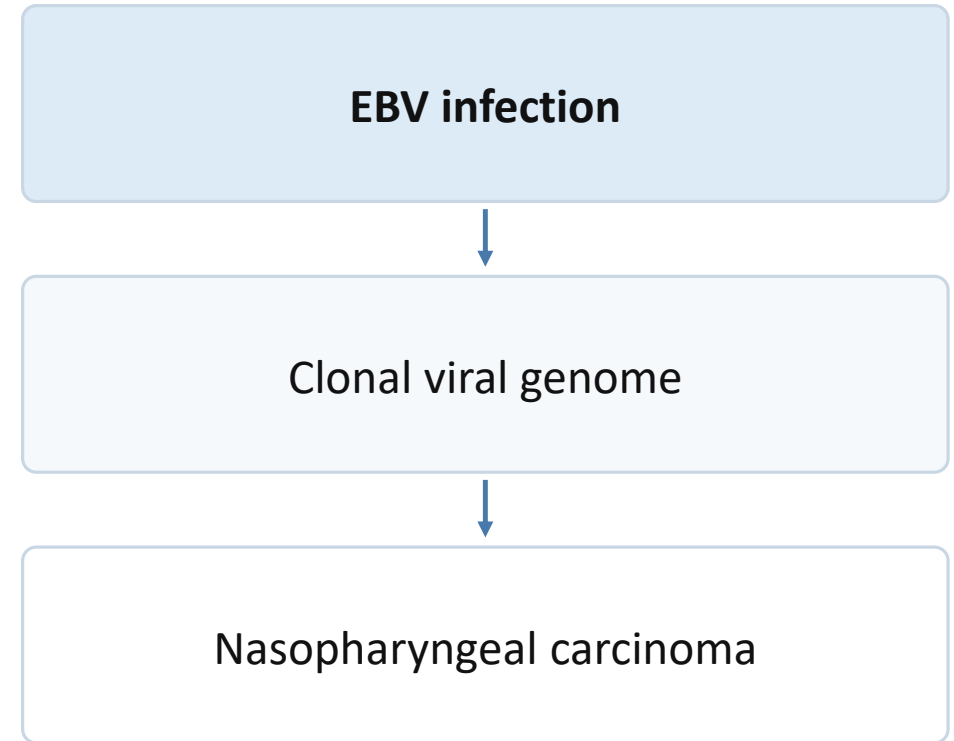
Immune restoration can suppress EBV-driven growth

- Reducing immunosuppression after transplant may restore T-cell restraint.
- EBV lymphoproliferations can regress when immunity returns.
- This directly demonstrates the role of host immune surveillance.



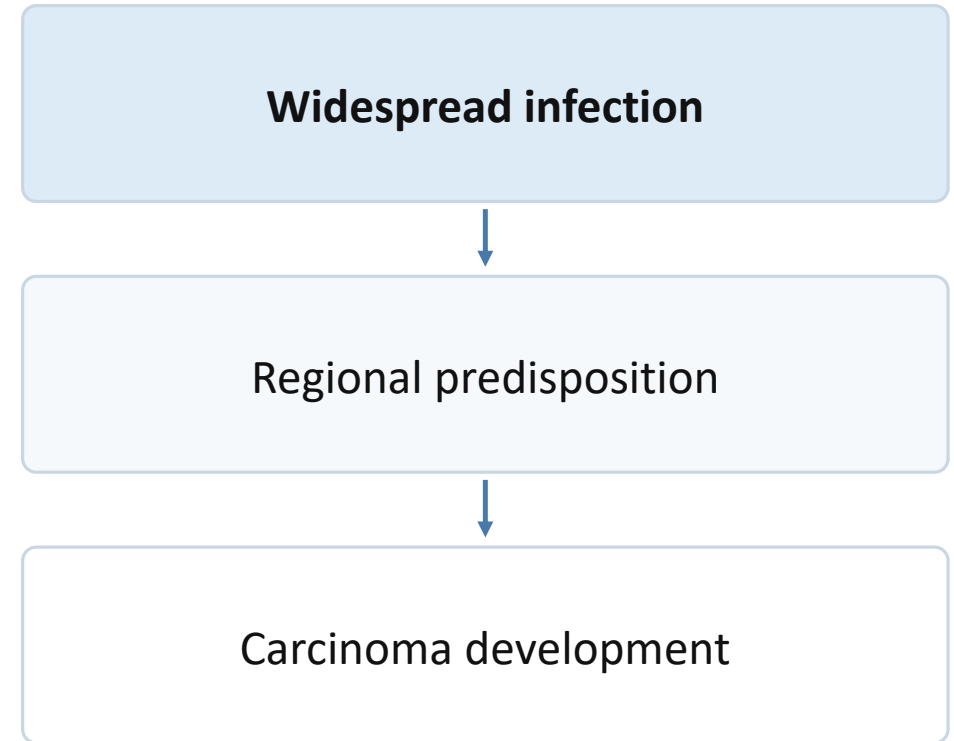
Nasopharyngeal carcinoma has a strong EBV link

- EBV in virtually all nasopharyngeal carcinomas studied.
- Within a tumor the viral genome has a clonal configuration.
- Clonality indicates infection preceded expansion of the malignant population.



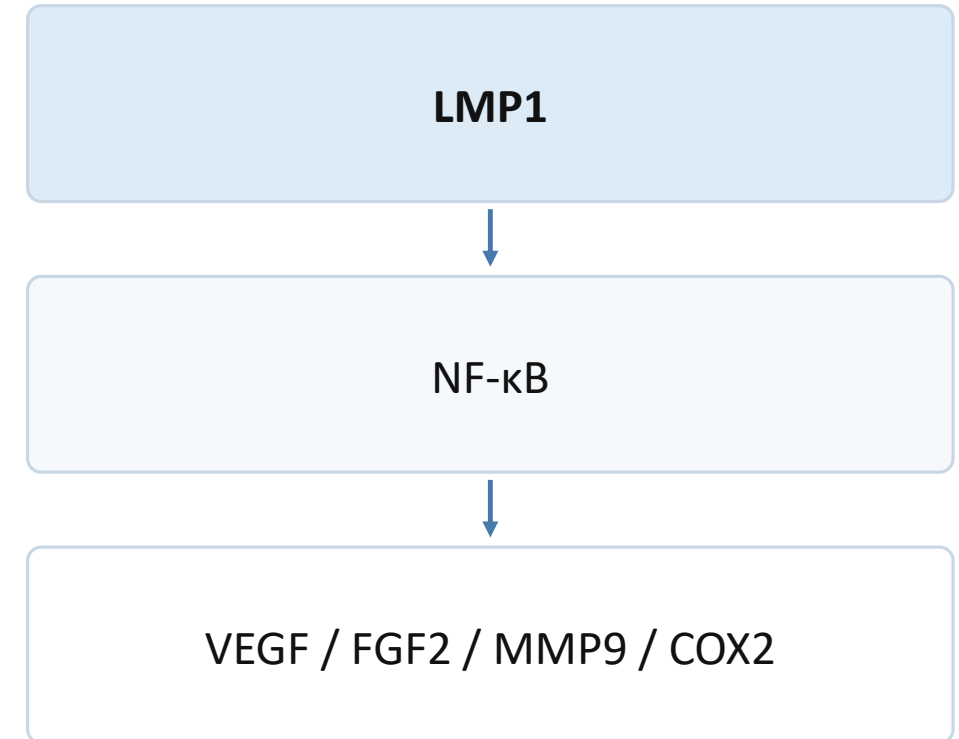
Nasopharyngeal carcinoma still needs cofactors

- The cancer is endemic in southern China, parts of Africa, and Inuit populations.
- Geographic clustering is not explained by widespread EBV infection alone.
- Host genetics or environmental exposures likely modify risk.



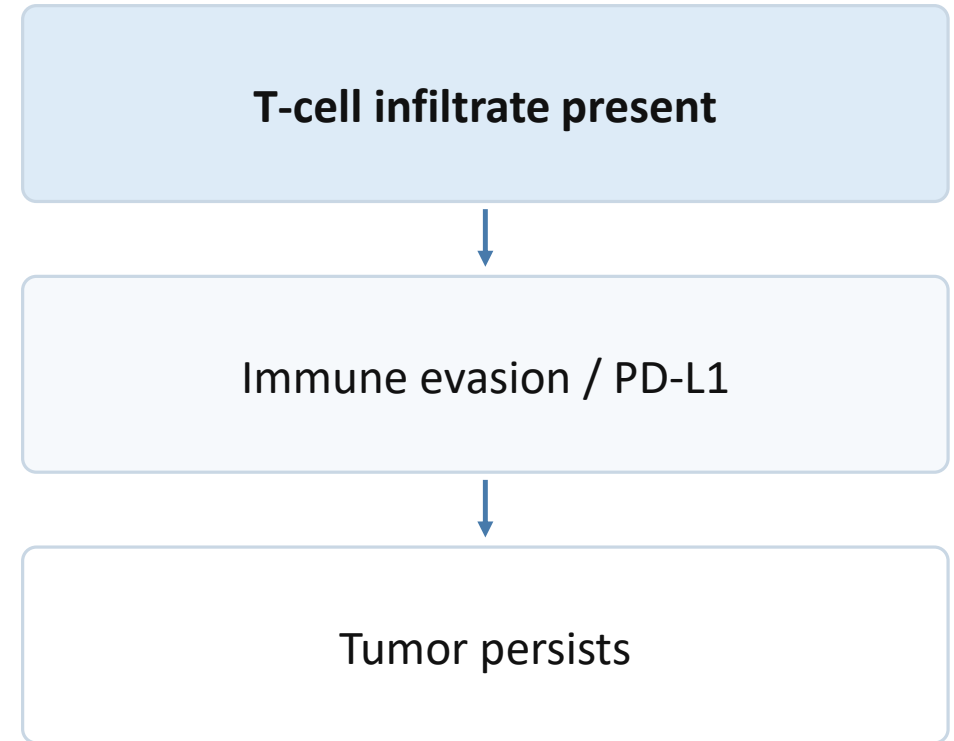
LMP1 changes signaling in epithelial tumors

- LMP1 is expressed in nasopharyngeal carcinoma.
- Activation of NF- κ B can increase VEGF, FGF2, MMP9, and COX2.
- These products are implicated in the supportive oncogenic microenvironment.



A lymphocyte-rich tumor can still evade immunity

- Nasopharyngeal carcinoma often has a conspicuous T-cell infiltrate.
- The infiltrate does not necessarily eliminate EBV-positive tumor cells.
- Tumor PD-L1 expression and responses to PD-1/PD-L1 blockade.

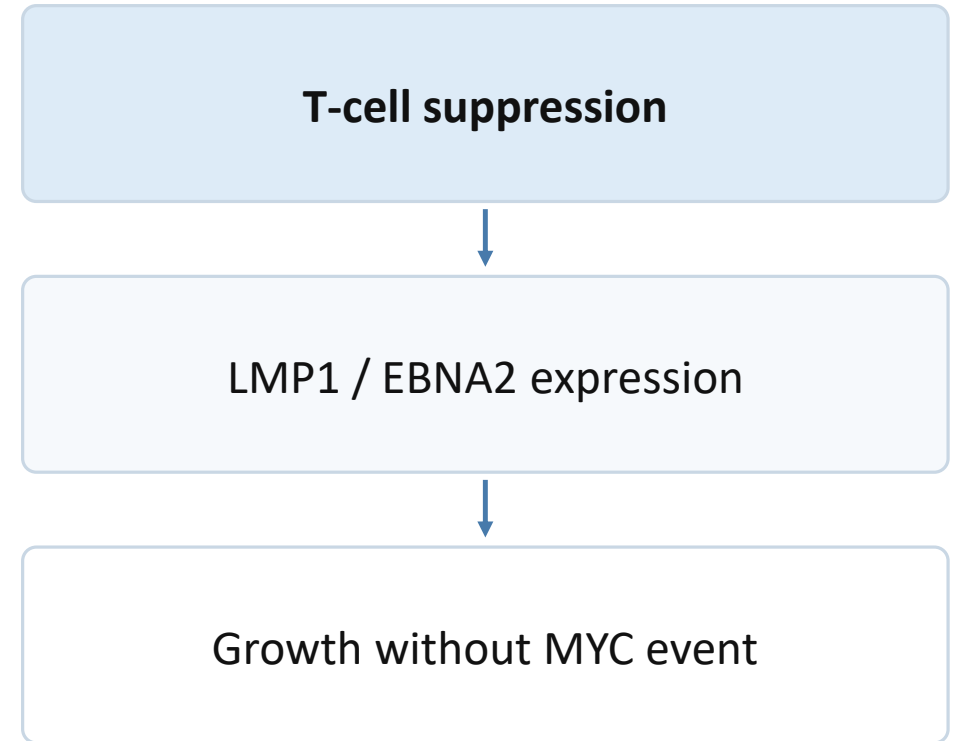


EBV-associated B-cell and epithelial cancers differ

Tumor setting	Key EBV relationship	Additional determinant
Endemic Burkitt lymphoma	EBV-positive in most; LMP1/EBNA2 not expressed by tumor	MYC translocation; regional cofactors
Immunodeficiency-associated B-cell tumors	LMP1/EBNA2 often retained	Defective T-cell surveillance
Nasopharyngeal carcinoma	Clonal EBV; epithelial LMP1 signaling	Geographic / host cofactors; immune evasion

Apply immune surveillance to an EBV-positive mass

- A transplant recipient develops an extranodal EBV-positive B-cell proliferation.
- LMP1 and EBNA2 are expressed; No MYC translocation is detected.
- Which mechanism distinguishes this from endemic Burkitt lymphoma?



HBV and HCV strongly associate with hepatocellular carcinoma

- 70%–85% of HCC worldwide to HBV or HCV infection.
- HBV is a DNA virus; HCV is an RNA virus discussed as a comparator.
- Neither infection makes malignant transformation inevitable.

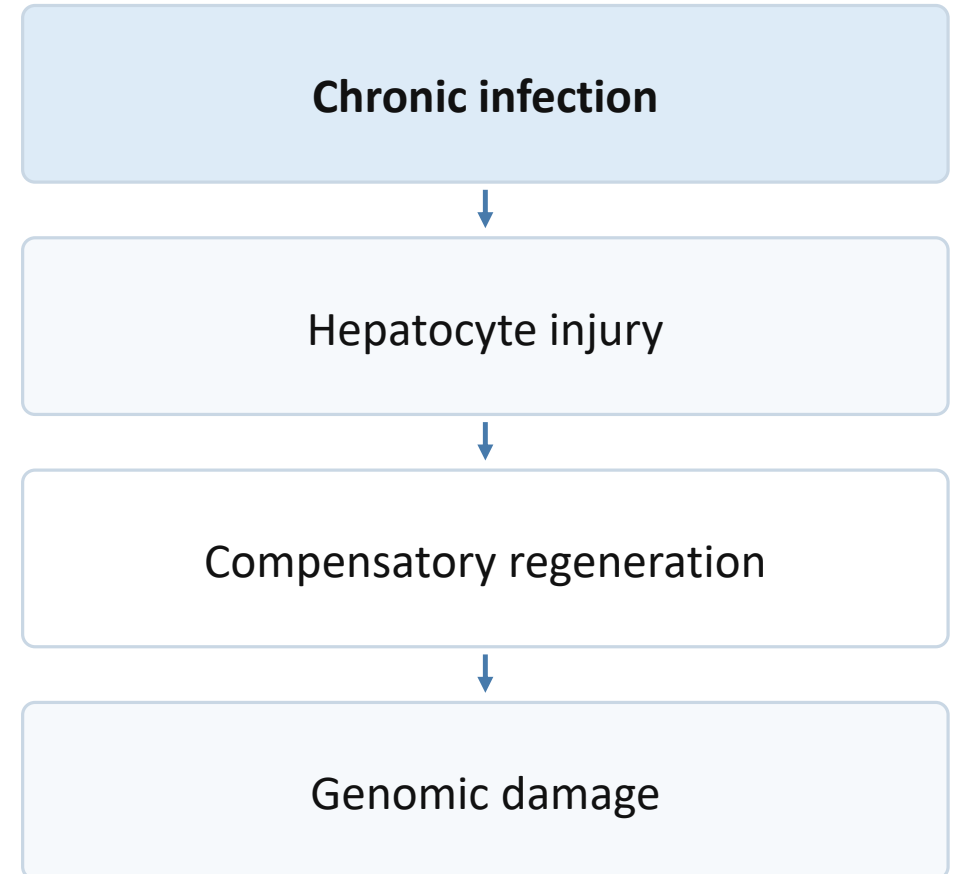
HBV: DNA

HCV: RNA

Shared HCC outcome

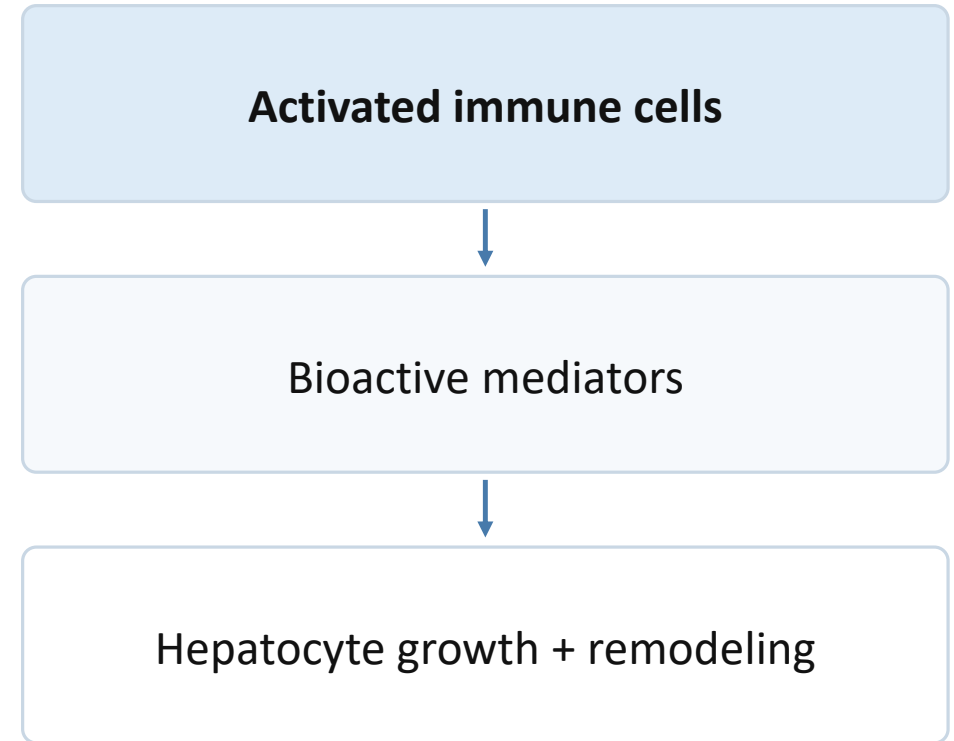
Chronic injury is the dominant carcinogenic route

- Persistent viral hepatitis causes cycles of hepatocyte death and regeneration.
- Inflammatory mediators sustain compensatory cell division.
- Proliferating cells accumulate opportunities for genomic injury.



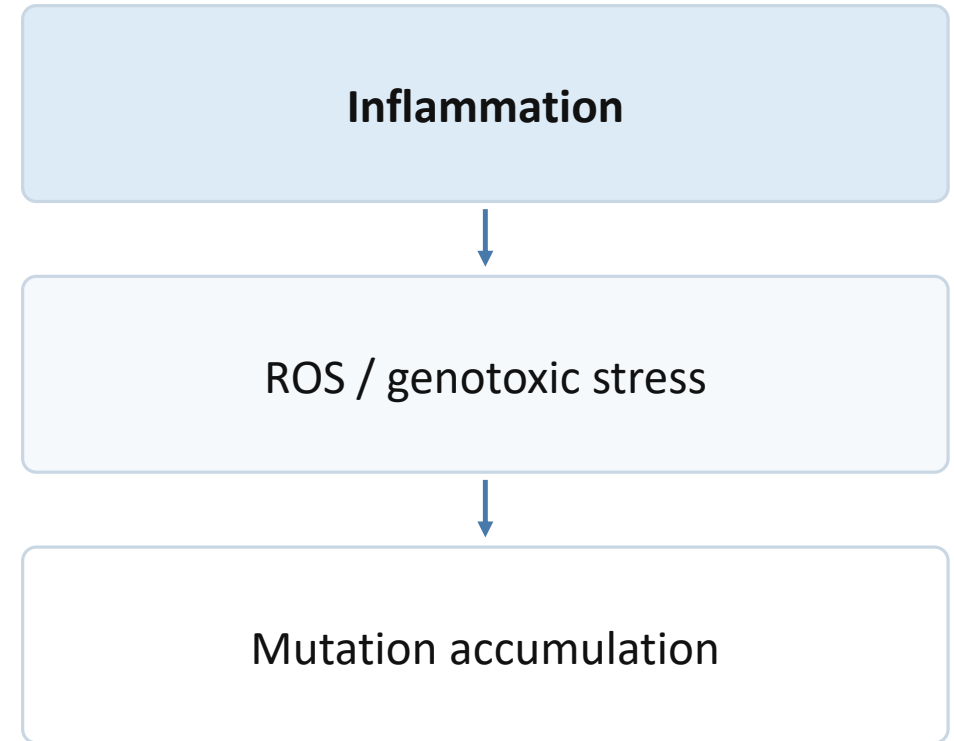
Immune-derived factors support liver cell proliferation

- Activated immune cells produce cytokines, growth factors, and chemokines.
- These mediators promote survival, remodeling, and angiogenesis.
- A response intended for repair can sustain pro-oncogenic regeneration.



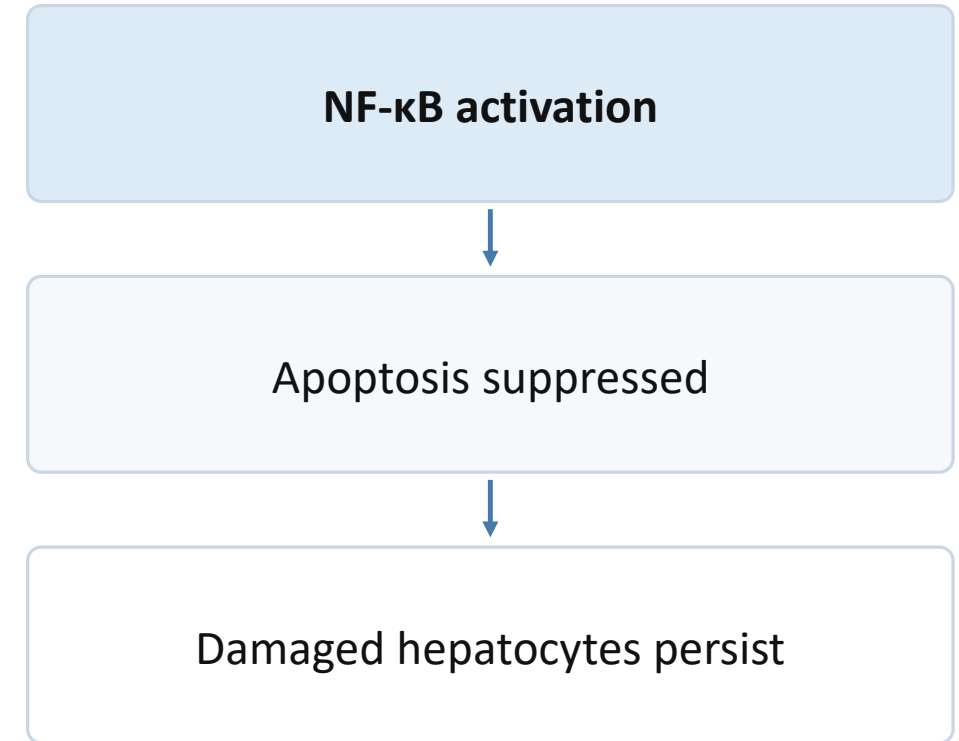
Inflammatory reactive oxygen species damage DNA

- Chronic inflammatory cells can generate reactive oxygen species.
- Oxidative stress is genotoxic and mutagenic.
- Sustained turnover increases the probability that altered hepatocytes will expand.



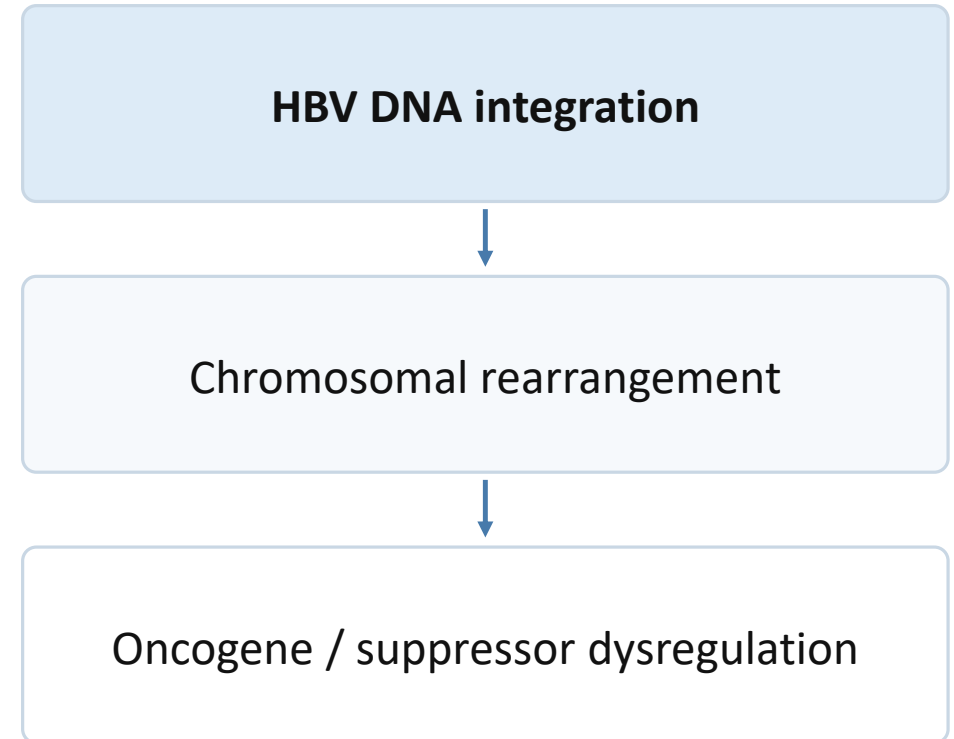
NF- κ B permits survival under genotoxic stress

- NF- κ B activation as a key molecular event.
- Its antiapoptotic effects allow proliferating hepatocytes to survive damage.
- Survival plus regeneration favors accumulation of genetic changes.



HBV integration is not a universal insertion-site mechanism

- HBV DNA can integrate into human chromosomal DNA.
- No consistent single integration site in HCC.
- Insertion can nevertheless produce structural chromosomal changes affecting cancer genes.



HBx provides an additional direct viral contribution

- HBV encodes the HBx protein.
- HBx can activate transcription factors and signal-transduction pathways.
- These effects supplement, rather than replace, inflammation-mediated injury.

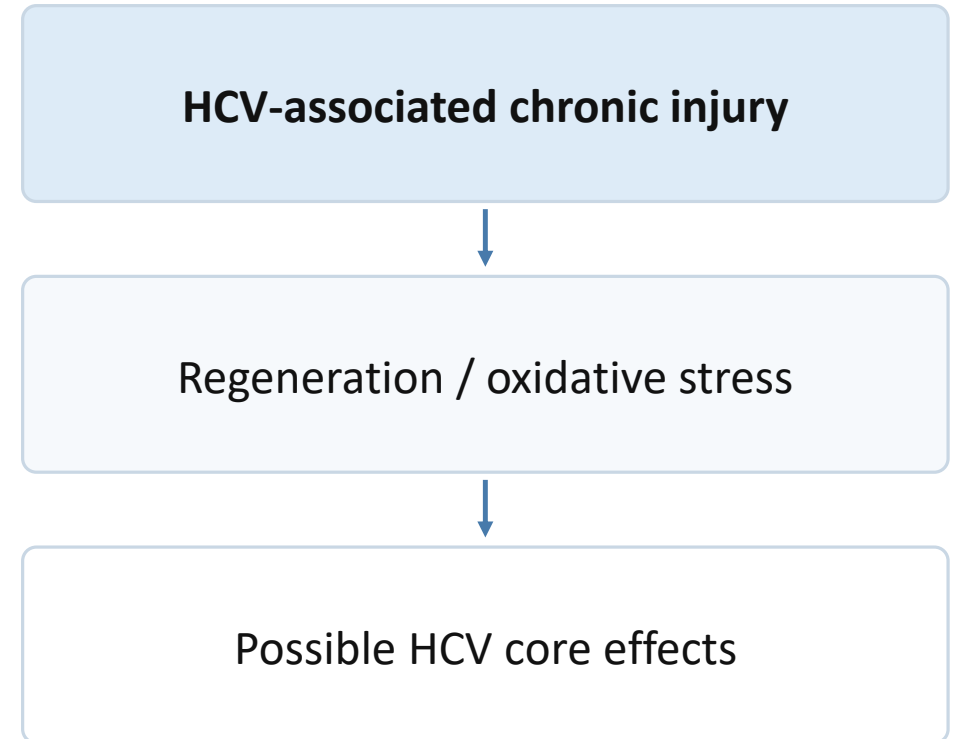
Chronic liver injury

HBx pathway activation

Combined pro-oncogenic effects

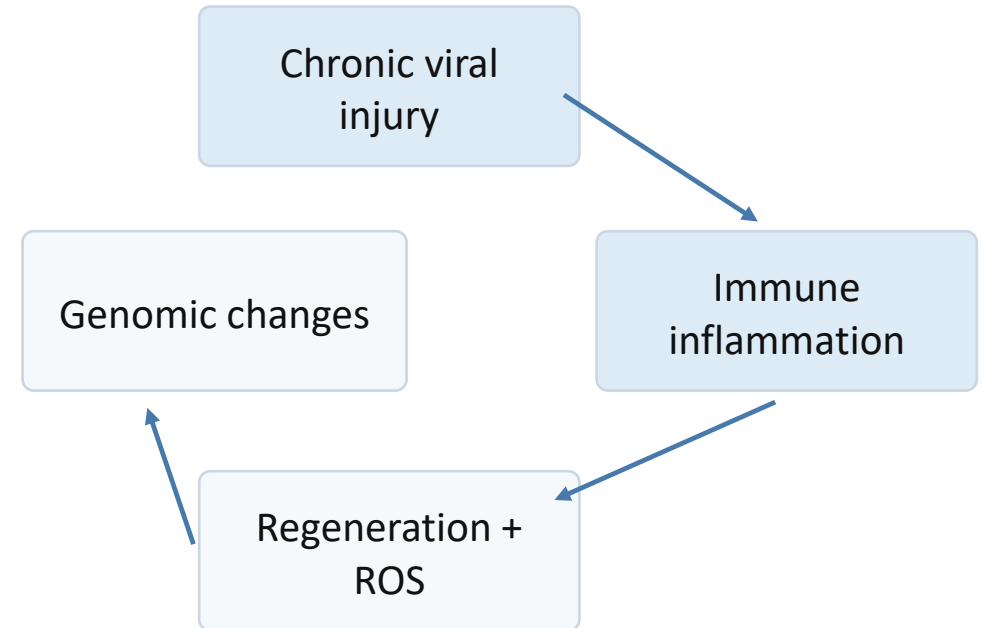
HCV-associated HCC occurs without viral DNA integration

- HCV has an RNA genome and is not among the five DNA viruses.
- Chronic injury and compensatory regeneration remain central.
- HCV core protein may also activate growth-promoting signaling; Mechanism remains uncertain.



The viral hepatocarcinogenesis cycle

- Hepatocyte injury recruits and activates inflammatory responses.
- Inflammation increases regeneration while adding mutagenic stress.
- The resulting altered cells can be positively selected during repeated injury.



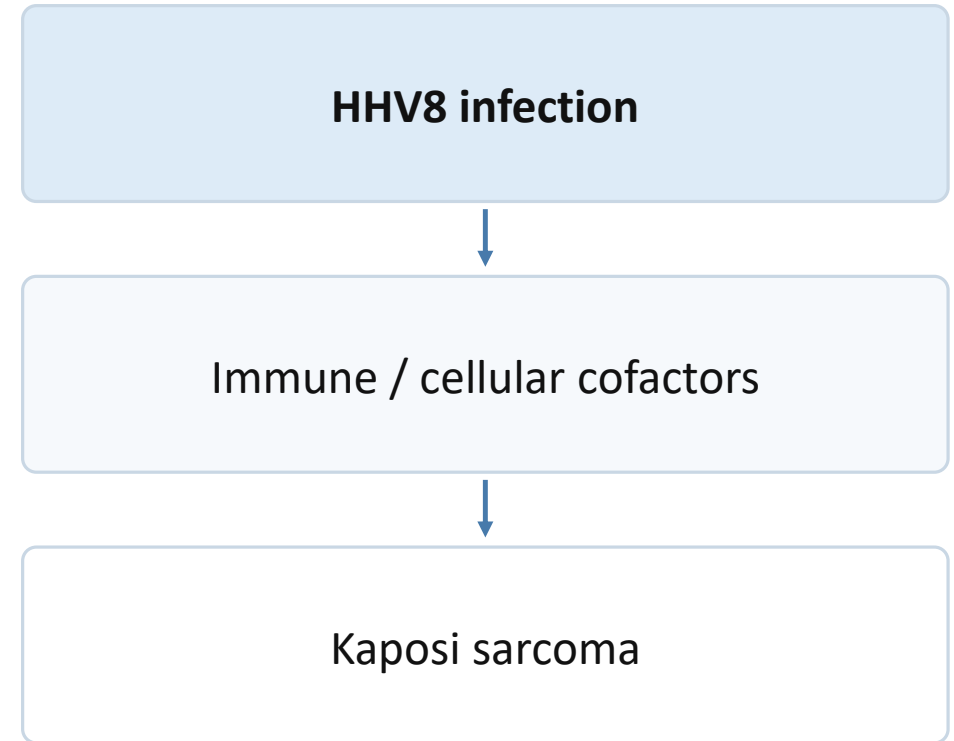
Repeated injury selects altered hepatocytes

HBV, HPV and EBV use integration differently

Virus	Viral genome state	Oncogenic inference
High-risk HPV	Episomal in benign warts; integrated in many cancers	E2 disruption → increased E6/E7
EBV	Extrachromosomal circular episome during B-cell latency	Latent proteins hijack growth/survival signals
HBV	Integration possible; no consistent insertion site	Chronic injury dominant; integration/HBx also contribute

HHV8 links Kaposi sarcoma to viral oncogenesis

- HHV8 is also called Kaposi sarcoma-associated herpesvirus (KSHV).
- Robbins finds HHV8 in virtually all Kaposi sarcoma lesions.
- Viral infection is necessary but not sufficient; Immune and cellular cofactors matter.



Lytic and latent programs both promote Kaposi sarcoma

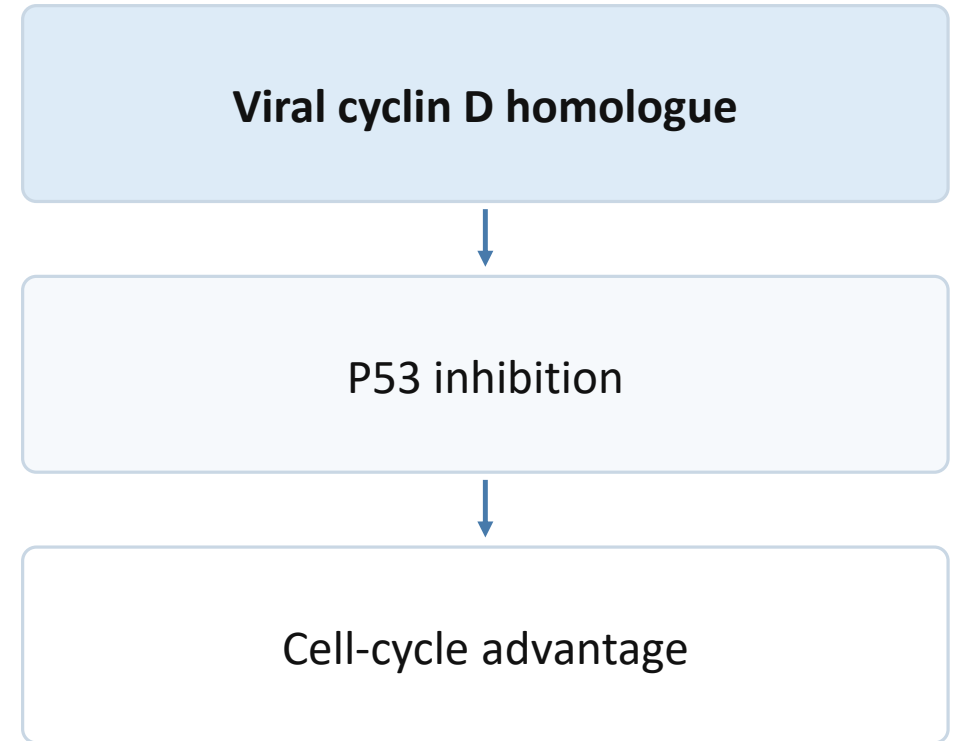
- Lytic infection recruits inflammatory cells and local growth signals.
- Latent viral proteins favor proliferation and resistance to apoptosis.
- These complementary programs help create the angioproliferative lesion.

**Lytic:
Inflammation /
VEGF**

**Latent: Growth /
survival**

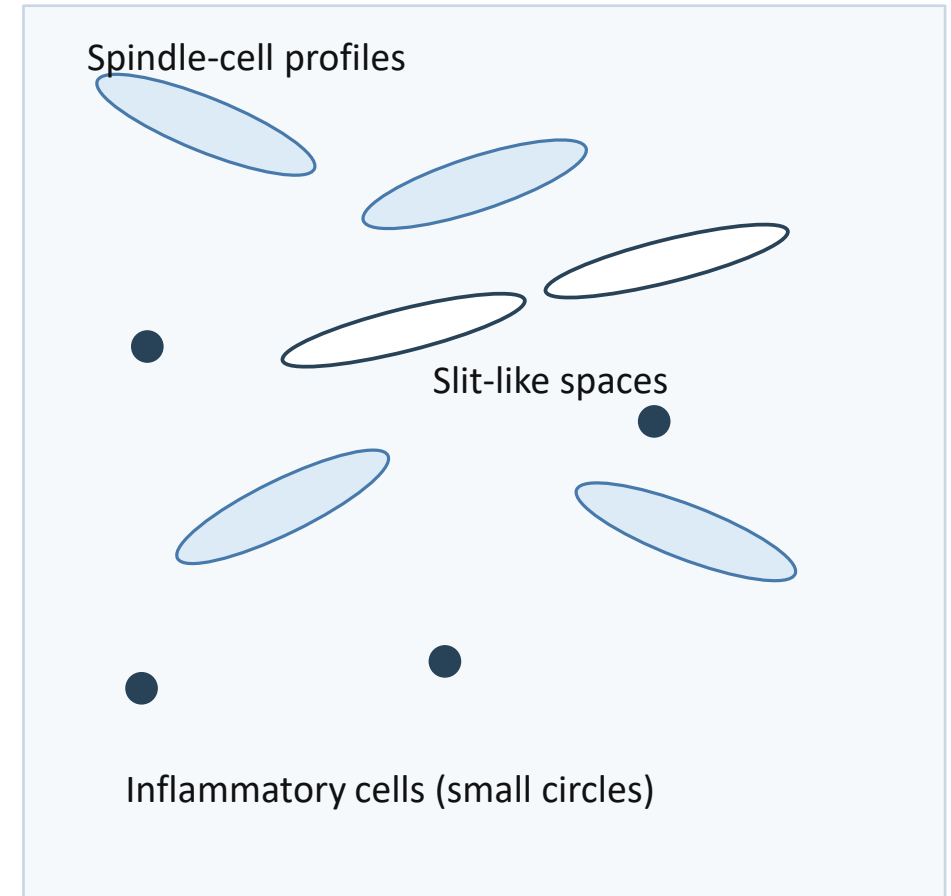
HHV8 encodes cell-cycle and survival modulators

- A viral cyclin D homologue.
- Viral proteins can inhibit p53-mediated tumor suppression.
- The effects make infected spindle-cell populations more likely to persist.



Kaposi sarcoma is a vascular–inflammatory proliferation

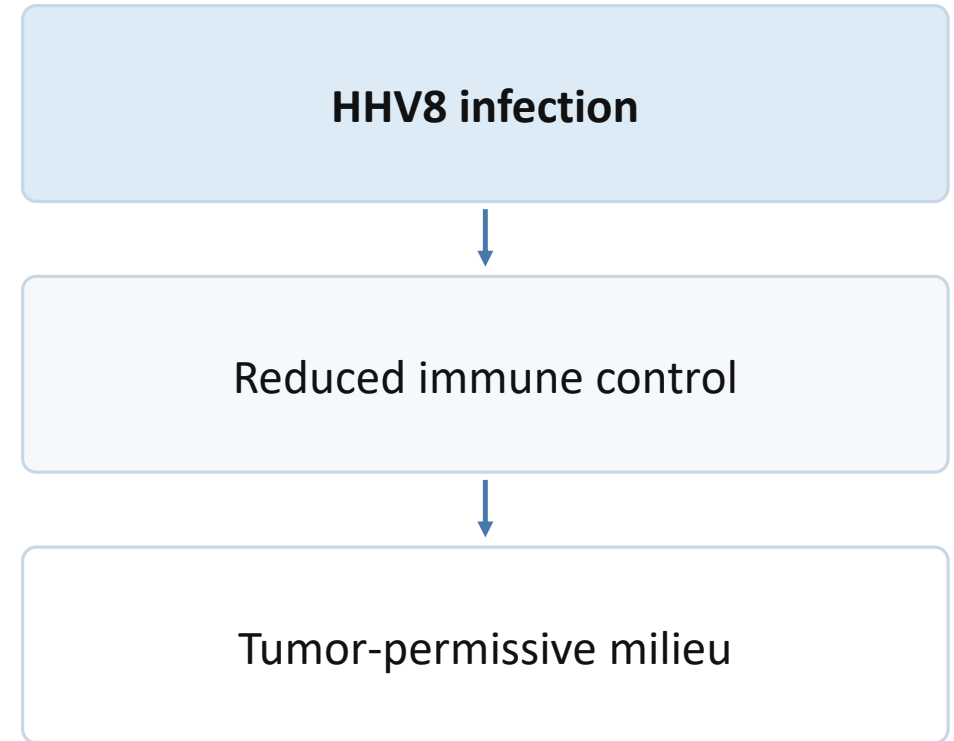
- Lesions contain spindle-shaped cells and slit-like vascular spaces.
- Chronic inflammatory cells are intermingled with the lesion.
- The microscopic pattern reflects angiogenesis and tumor–microenvironment interactions.



Schematic — not a histologic specimen

Altered T-cell immunity is a critical cofactor

- HHV8 infection alone generally does not cause Kaposi sarcoma.
- AIDS-related immune suppression facilitates HHV8 persistence and dissemination.
- Aging-related decline in T-cell immunity is relevant in some non-HIV cases.



HHV8 is also linked to B-cell disorders

- HHV8 with primary effusion lymphoma.
- Multicentric Castleman disease is another linked B-cell lymphoproliferation.
- A single virus can participate in endothelial and lymphoid pathology.

Kaposi sarcoma

Primary effusion lymphoma

Multicentric Castleman disease

Merkel cell carcinoma has two pathogenetic settings

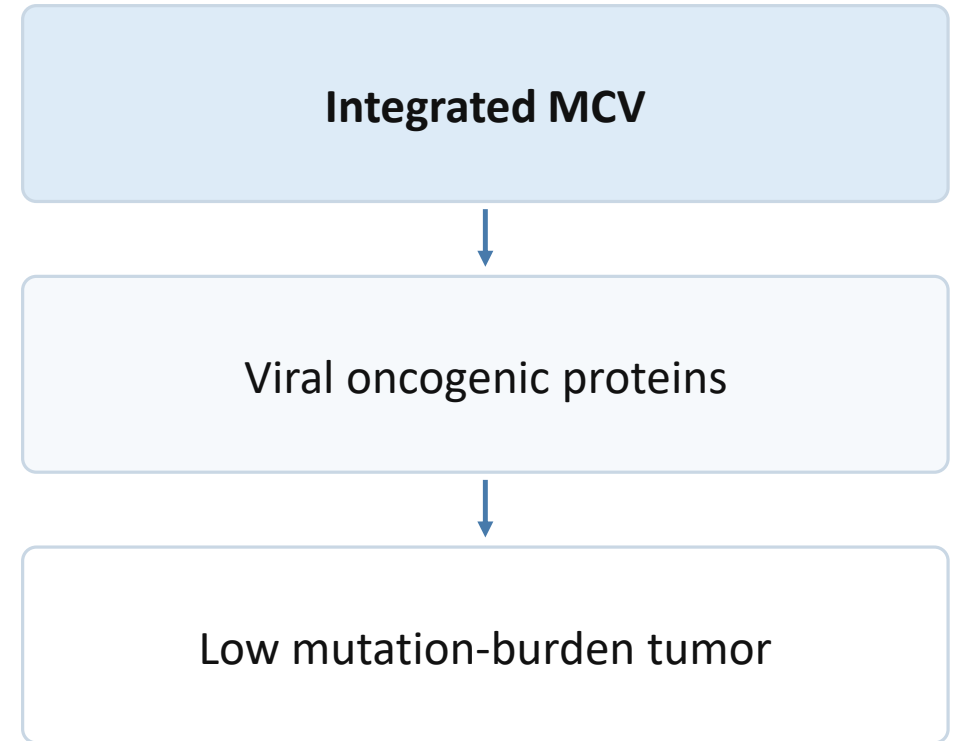
- MCV-related tumors are emphasized in immunosuppressed patients.
- Virus-independent tumors occur in sun-exposed older patients.
- These pathways can converge on a similar aggressive neuroendocrine skin cancer.

**MCV-associated
route**

**UV-associated
route**

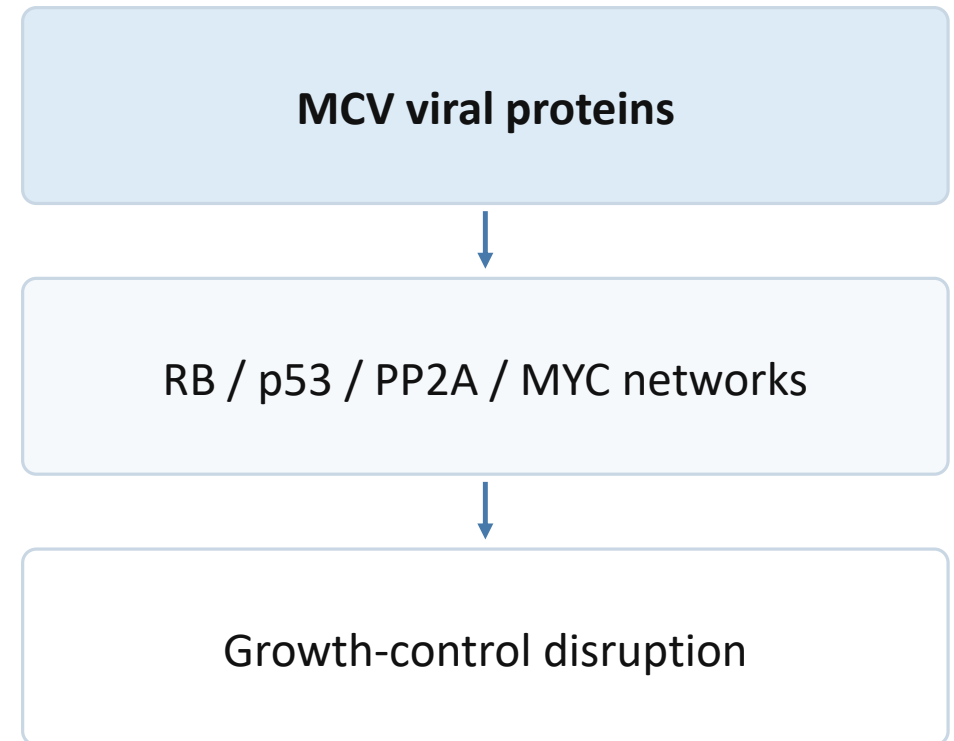
MCV-associated Merkel cell carcinoma integrates viral DNA

- In MCV-associated tumors, viral DNA is integrated into the tumor genome.
- Relatively few acquired mutations and usually diploid genomes.
- Viral oncoproteins influence key host growth-control pathways.



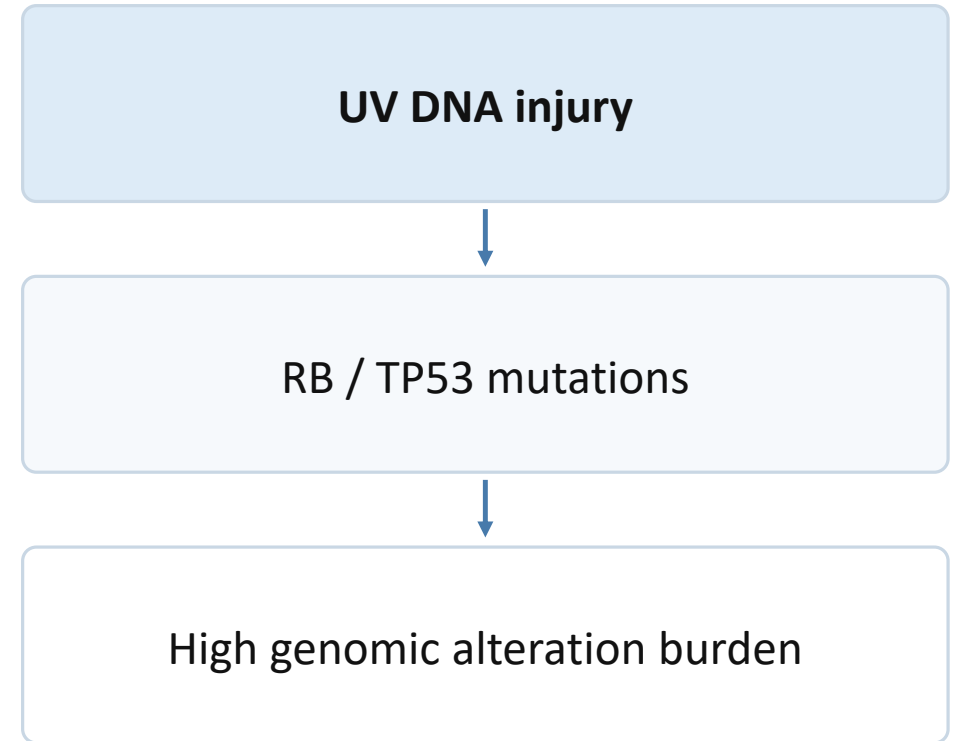
MCV proteins perturb tumor-suppressive networks

- Effects involving RB, p53, PP2A, and MYC.
- These pathways regulate cell-cycle entry, survival, or growth.
- Viral oncoprotein expression can substitute for some host genomic lesions.



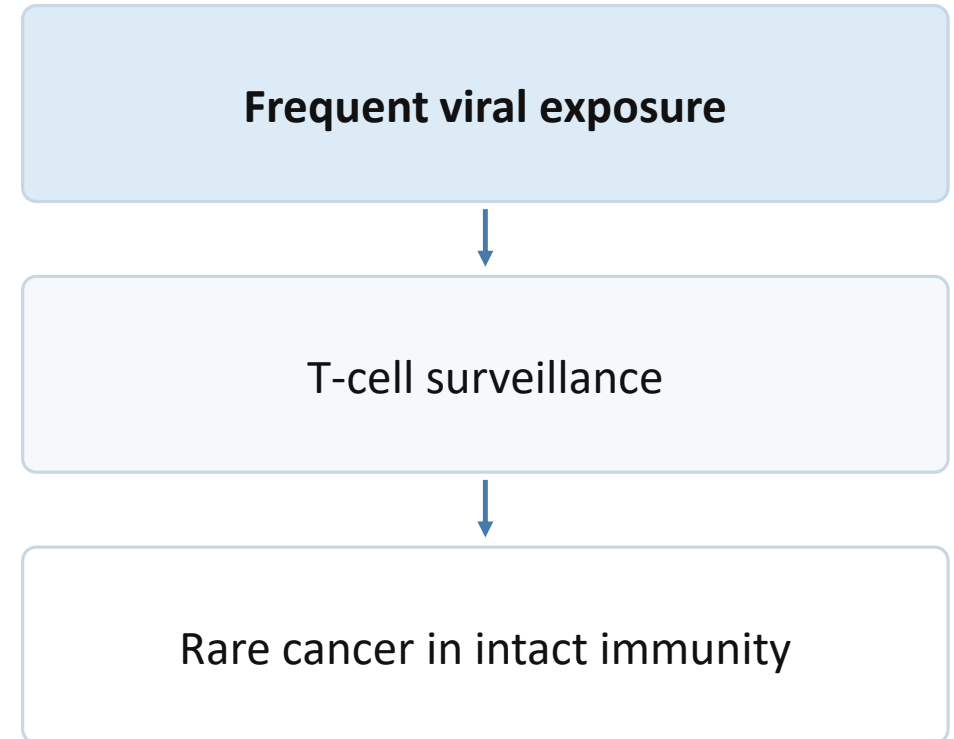
UV-associated tumors have a different genomic profile

- Virus-independent tumors can carry many UV-signature mutations.
- Acquired RB and TP53 loss-of-function changes are often present.
- Copy-number gains and losses contrast with the usually diploid MCV-related group.



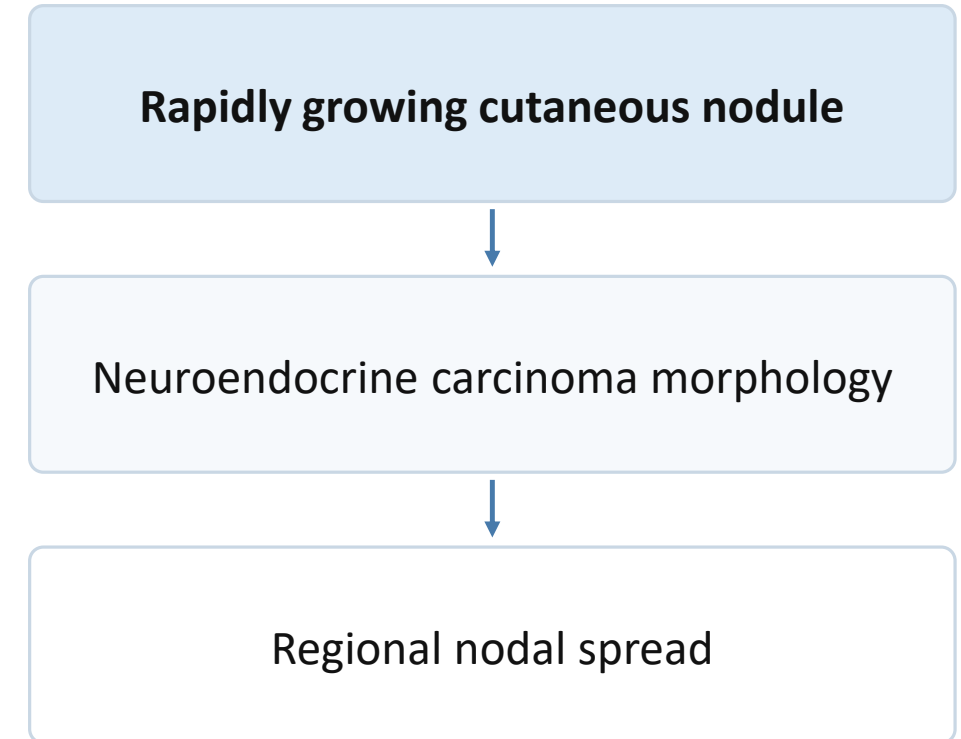
Immune surveillance explains rarity despite exposure

- MCV infection is widespread, but Merkel cell carcinoma is rare.
- Protective MCV-specific T-cell responses.
- Immunosuppression shifts the balance toward MCV-associated cancer.



Morphology and clinical course remain important

- Merkel cell carcinoma often presents as a rapidly enlarging skin nodule.
- Microscopically it resembles an aggressive neuroendocrine carcinoma.
- Regional lymph-node spread is common; The viral and UV pathways differ biologically.



Comparison of the five oncogenic DNA viruses

DNA virus	Principal cell or tissue	Illustrative malignancy	Pathogenic route
HPV	Squamous epithelium	Cervical carcinoma	E6/E7
EBV	B cells; epithelium	Burkitt / nasopharyngeal	Latent signaling / cofactors
HBV	Hepatocytes	Hepatocellular carcinoma	Inflammation ± HBx
HHV8	Vascular / B cells	Kaposi sarcoma	Angiogenesis / immune
MCV	Skin	Merkel cell carcinoma	Viral oncoproteins

Direct viral oncoproteins versus tissue-injury carcinogenesis

- HPV E6/E7 directly impair p53 and RB checkpoints.
- EBV and HHV8 use latent growth/survival programs under immune selection.
- HBV-associated HCC prominently involves chronic inflammatory injury and regeneration.

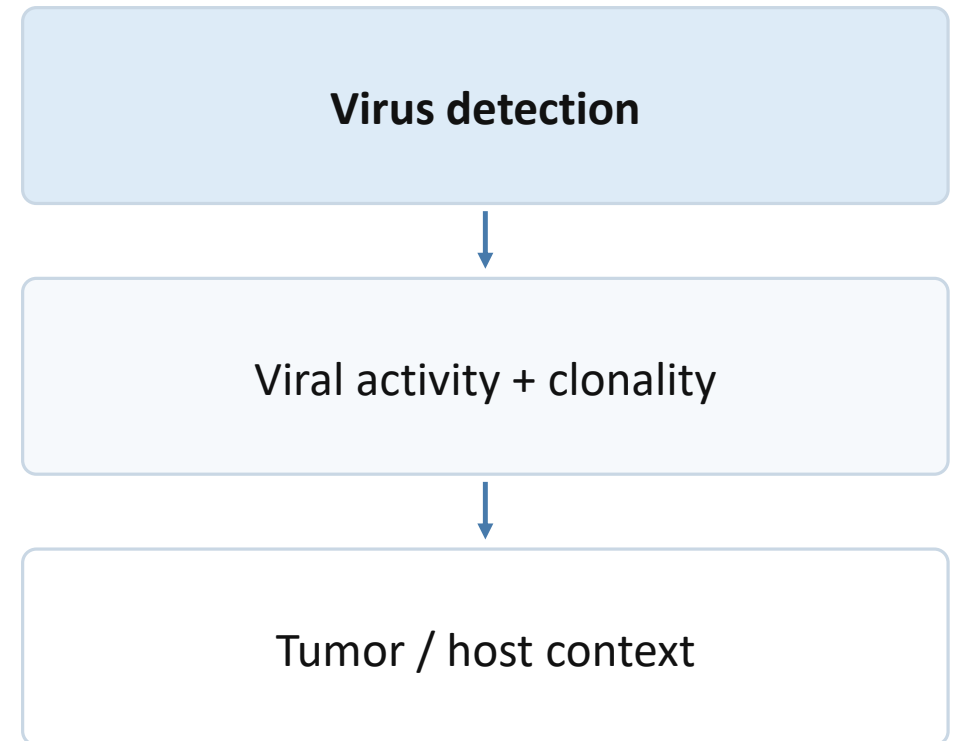
Tumor suppressor antagonism

Latent cell survival

Inflammation / regeneration

Interpret viral detection in the correct context

- A tumor-associated virus may be causal, a cofactor, or simply present in a host.
- Clonal viral genome patterns provide evidence about timing of infection.
- Mechanistic inference requires tumor type, host immunity, and additional lesions.



Clinical challenge: Tumor biology and host context

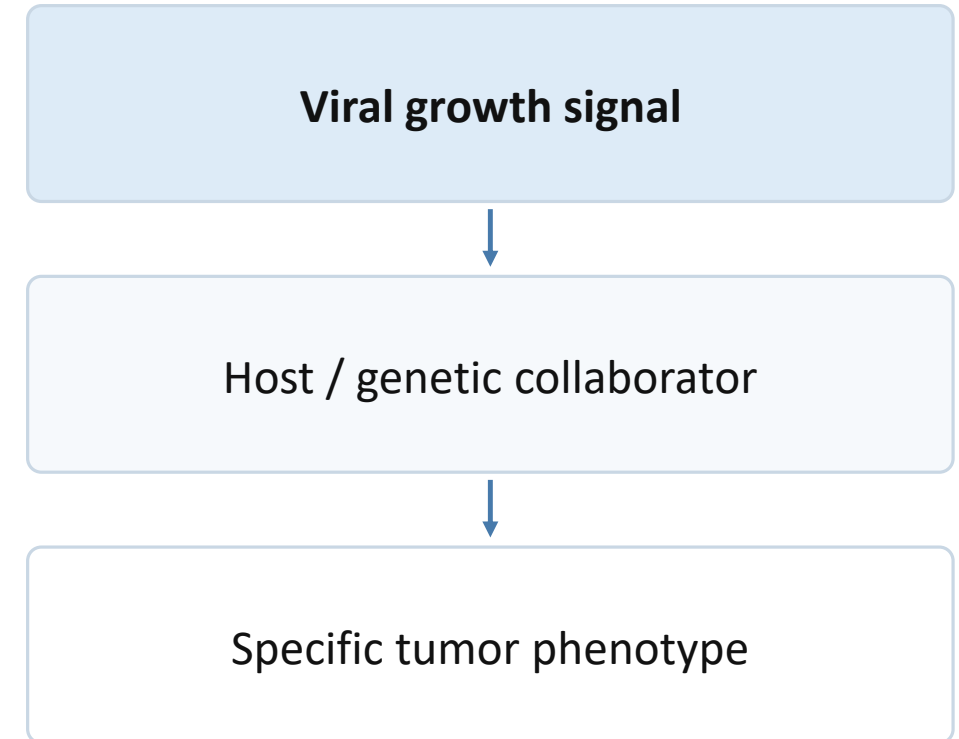
- A patient receiving transplant immunosuppression develops an EBV-positive B-cell mass.
- Another patient has HPV-associated cervical dysplasia with HIV coinfection.
- Compare how impaired T-cell surveillance changes progression risk in each case.

**EBV:
Uncontrolled B-
cell expansion**

**HPV: Persistent
epithelial
infection**

Five mechanism-to-disease pairings

- HPV E6/E7 → impaired p53 and RB pathways → squamous carcinomas.
- EBV B-cell latency plus MYC dysregulation → Burkitt lymphoma.
- HBV/HCV chronic liver injury → hepatocellular carcinoma.
- HHV8 vascular growth programs → Kaposi sarcoma; MCV oncoproteins → Merkel cell carcinoma.



Conceptual checkpoints

- Which two viral proteins target p53 and RB, and what is the consequence?
- Why do EBV-linked Burkitt lymphoma and post-transplant lymphoma arise by different routes?
- How can HBV and HCV both drive hepatocellular carcinoma despite different genomes?
- What distinguishes MCV-associated from UV-associated Merkel cell carcinoma?

Viral protein mechanism



Host immune context



Tissue injury and genomic collaboration