Virus Tumorali a DNA: HPV

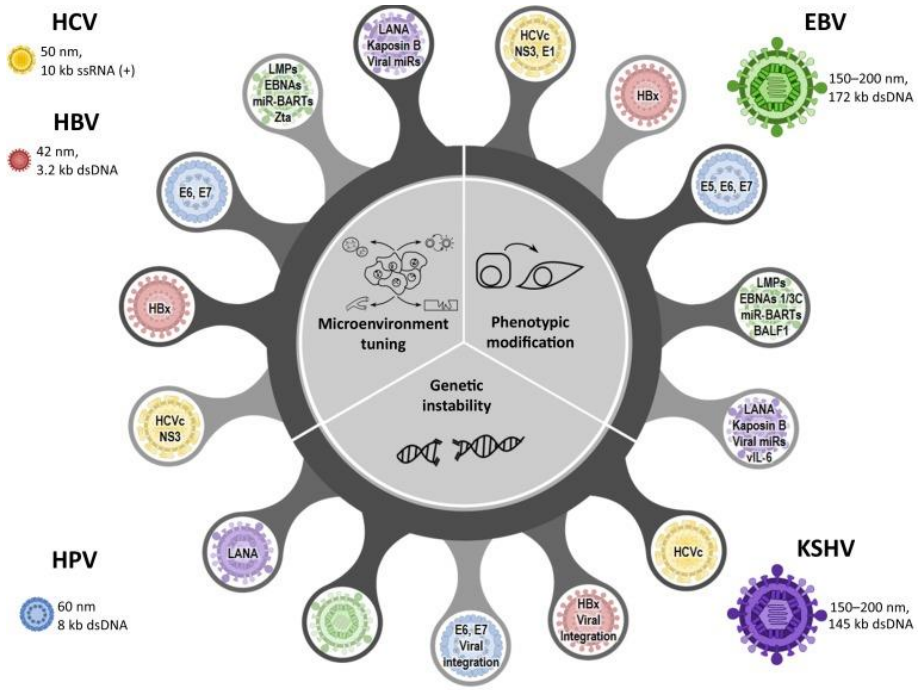
PRINCIPLES *Cellular transformation and oncogenesis*

- Members of DNA and RNA virus families cause or contribute to ~20% of human cancers.
- Cancer is a disease of unregulated cell division, which can be the result of inherited mutations; exposure to environmental carcinogens; or infection with pathogens, including viruses.
- Immortalization, transformation, and oncogenesis are distinct states, but are part of a continuum.
- Transformed cells are distinguished from normal cells by their immortality, loss of contact inhibition, and often production of their own growth factors.
- With few exceptions, transformation is not required for viral reproduction.
- Retroviruses can either encode oncogenes (once derived from host genes) or integrate into the cellular genome and activate adjacent cellular proto-oncogenes.
- Small transforming DNA viruses encode proteins that bind to specific cellular proteins, notably the tumor suppressors Rb and p53, to promote cell cycle progression and block checkpoints.
- Proteins encoded by transforming viruses also can prevent cell death, block immune recognition, and promote blood vessel formation.
- Some viruses associated with human cancers do not transform cells directly, but rather induce a chronic immune response that, with time, results in tissue damage and the emergence of malignant cells.

Virus e Oncogenesi

Table 6.2 Oncogenic viruses and cancer

Family	Associated cancer(s)
RNA viruses	
Flaviviridae	
Hepatitis C virus	Hepatocellular carcinoma
Retroviridae	Hematopoietic cancers, sarcomas, and carcinomas
DNA viruses	
Adenoviridae	Various solid tumors
Hepadnaviridae	Hepatocellular carcinoma
Herpesviridae	Lymphomas, carcinomas, and sarcomas
Papillomaviridae	Papillomas and carcinomas
Polyomaviridae	Various solid tumors
Poxviridae	Myxomas and fibromas



DNA

- Herpesvirus (EBV, KSHV)
- HBV
- HPV
- Merkel cell Polyomavirus

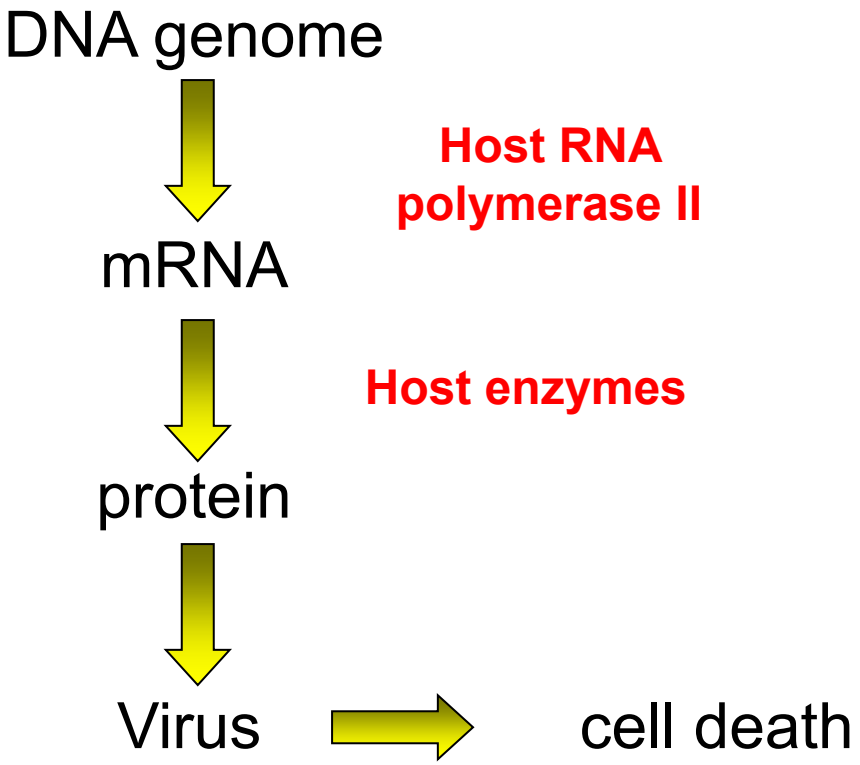
RNA

- HCV
- HTLV-1
- HIV-1

20% dei casi di tumore nell'uomo sono <u>associati</u> a infezioni virali:

Inoltre le proprietà trasformanti sono tipiche anche di Adenovirus, Poxvirus e Retrovirus trasformanti acuti e lenti (non umani)

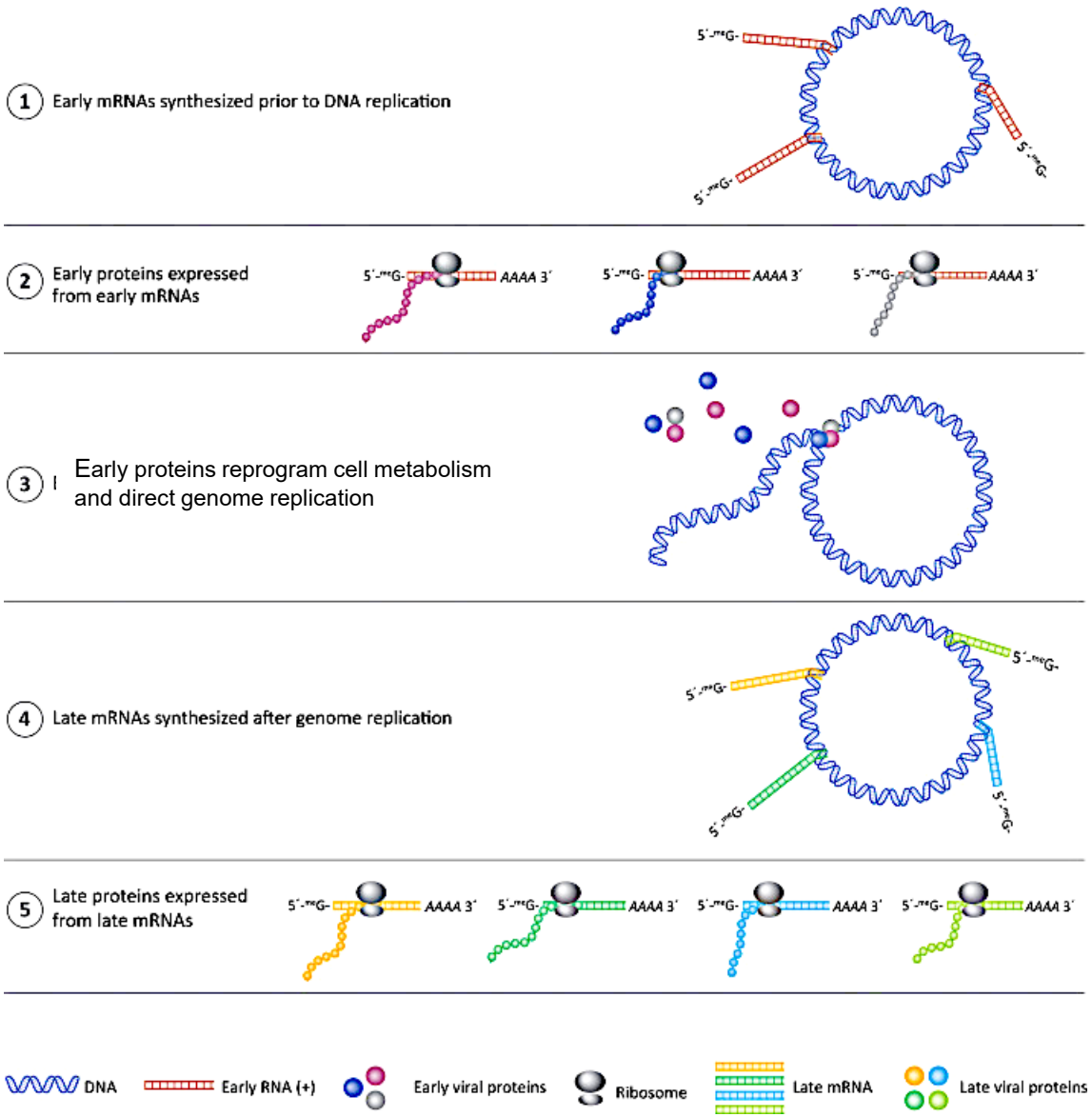
DNA Tumor Viruses
(Adenoviridae, Papillomaviridae, Polyomaviridae)



OR TRANSFORMATION

In transformation usually only EARLY functions are expressed

DNA virus expression timing



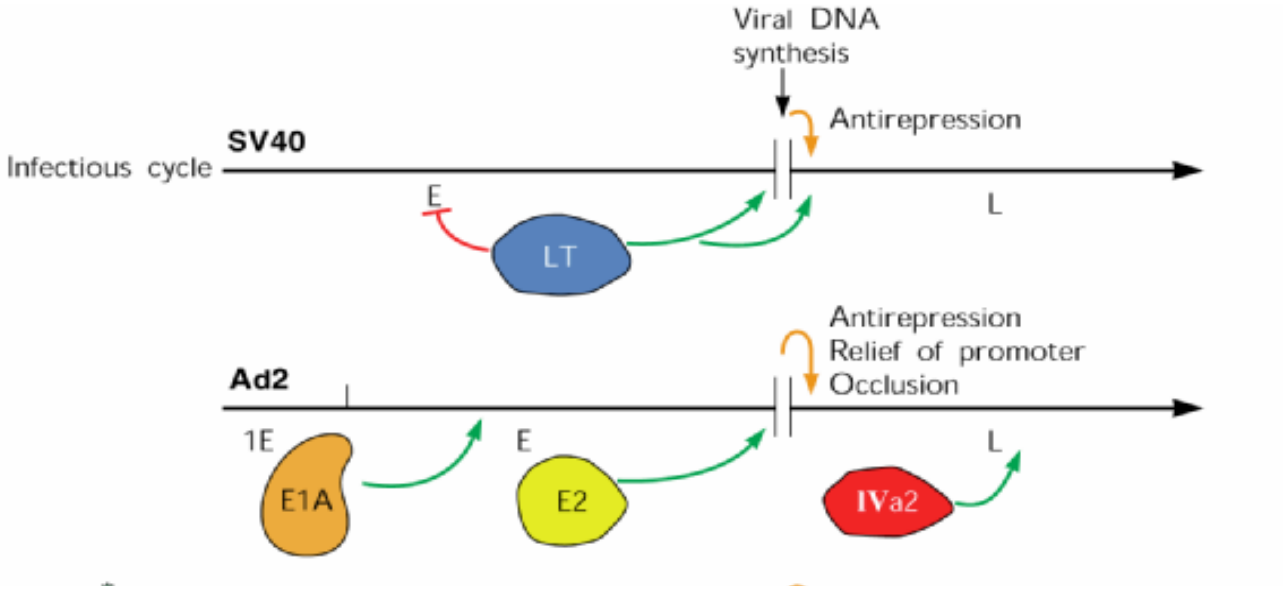
Upon uncoating, the genomes of DNA viruses are transcribed to produce an “early” set of mRNAs. Early mRNAs typically encode for proteins that modulate the host cell environment and/or are required for viral genome replication. After genome replication another set of mRNAs, the “late” mRNAs are expressed. Late genes encode structural proteins (and other proteins that are packaged within virions).

DNA Tumor Viruses

Table 6.4 Some transforming gene products of adenoviruses, papillomaviruses, and polyomaviruses

Virus	Gene product	Activities
Adenoviridae		
Human adenovirus type 2	E1A: 243R and 289R	Cooperate with E1B proteins to transform primary cells; not sufficient for establishment of transformed cell lines
	E1B: 55 kDa and 19 kDa	Necessary for E1A-dependent transformation of primary and established cells; counter apoptosis by different mechanisms
Papillomaviridae		
Human papillomavirus types 16 and 18	E6	Required for efficient immortalization of primary human fibroblasts and keratinocytes
	E7	Cooperates with E6 to transform primary rodent cells; required for efficient immortalization of primary human fibroblasts or keratinocytes
Polyomaviridae		
Polyomavirus	LT	Immortalizes primary cells; required to induce but not to maintain transformation of primary cells
	mT	Transforms established cell lines; required to both induce and maintain transformation of primary cells
Simian virus 40	LT	Immortalizes primary cells; required to induce and maintain transformation of primary and established cells
	sT	Required under many conditions, depending on LT concentration, genetic background of recipient cells, and transformation assay

Early gene expression

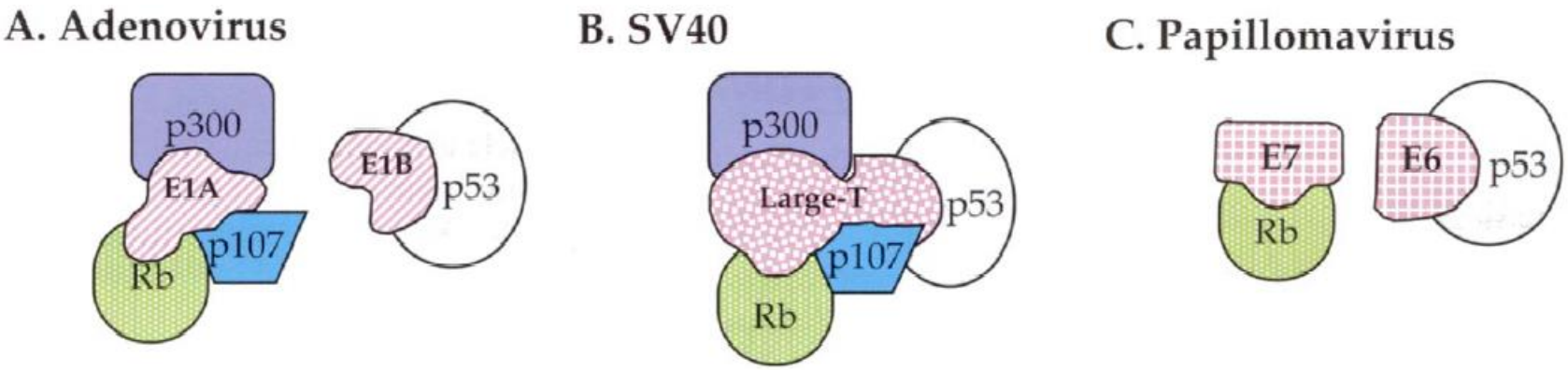


ASM Virology
Fig. 08.15 #815

DNA tumour virus oncoproteins

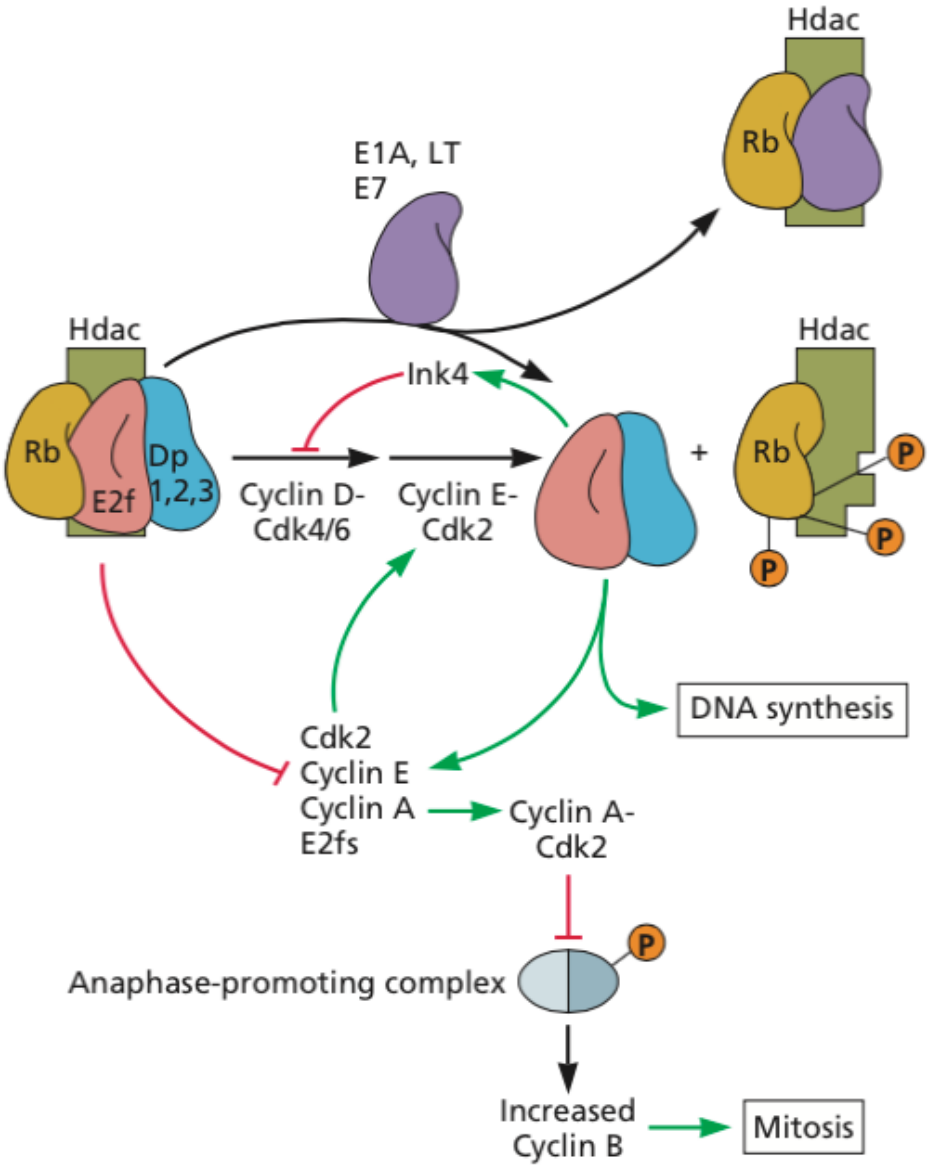
Table 7.5 Transforming proteins of DNA tumour viruses

Virus	Transforming protein(s)	Cellular target
Adenoviruses	E1A + E1B	Rb, p53
Polyomaviruses (SV40)	T antigen	p53, Rb
Papillomaviruses:		
BPV-1	E5	PDGF receptor
HPV-16, 18	E6	p53
	E7	Rb



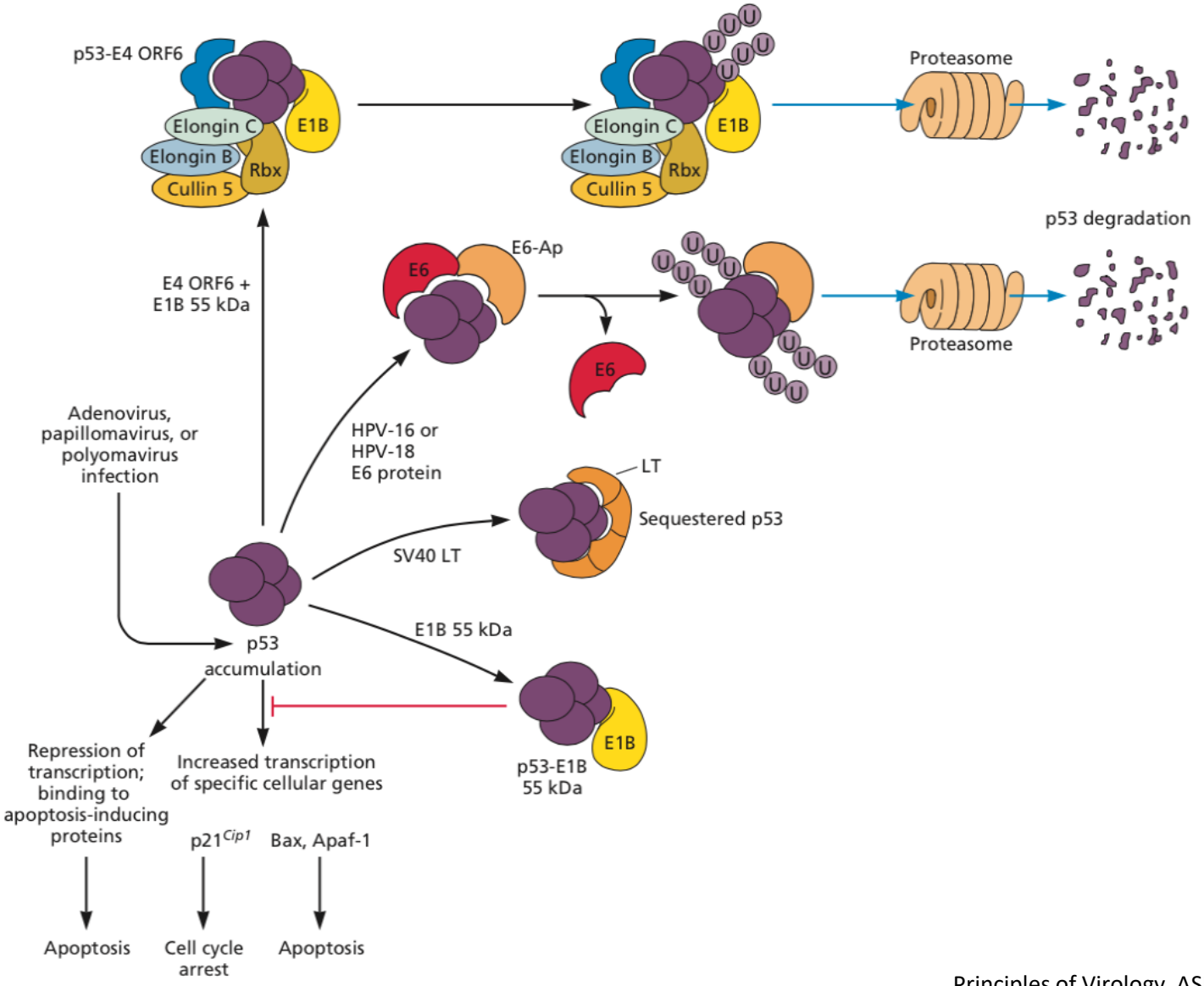
From Cann *Principles of molecular virology* (2001). Academic Press

Interference with Rb protein function



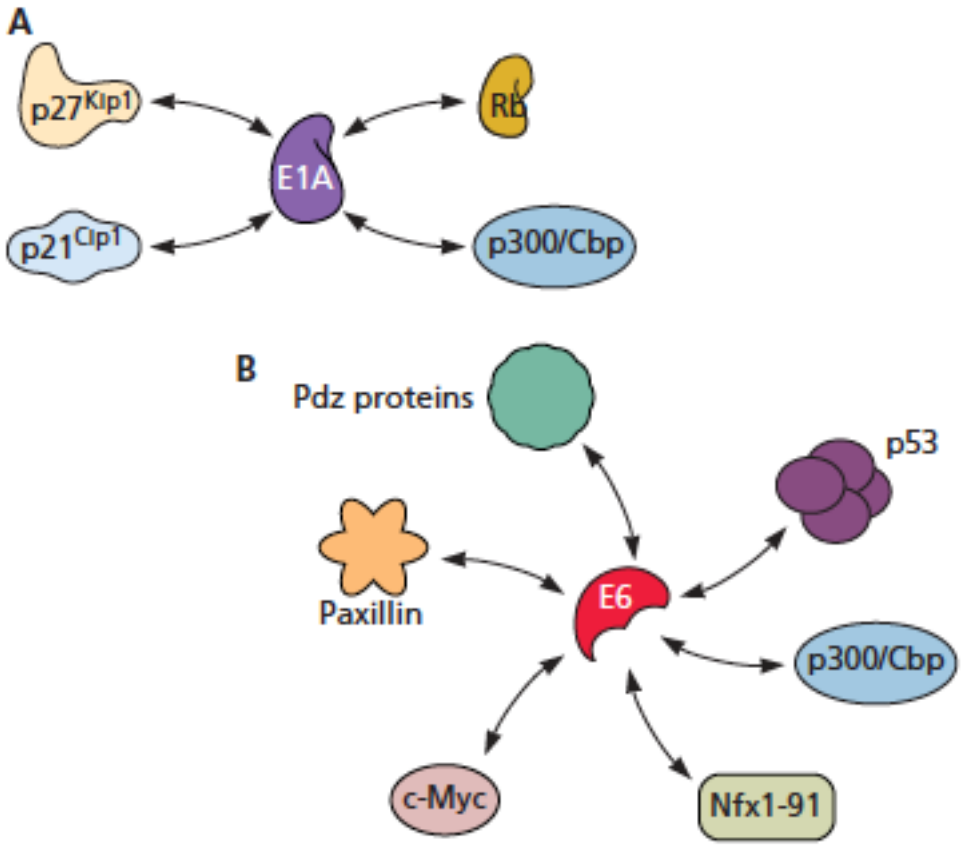
Principles of Virology, ASM Press

Interference with p53 protein function



Principles of Virology, ASM Press

Interactions of DNA virus transforming proteins with multiple cellular proteins

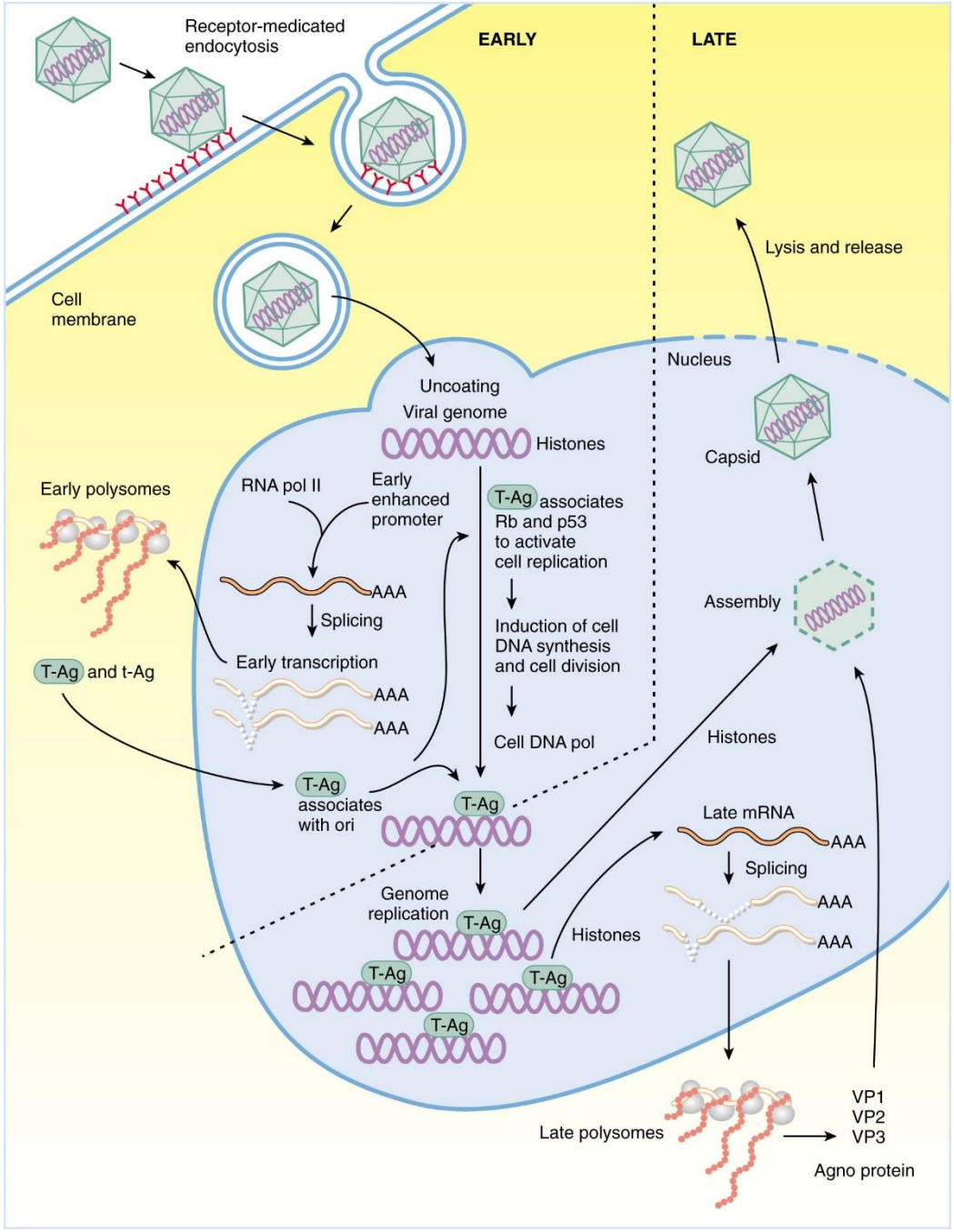


From Flint et al. *Principles of Virology* (2015), ASM Press

Permissive cells: Replication, lysis and death

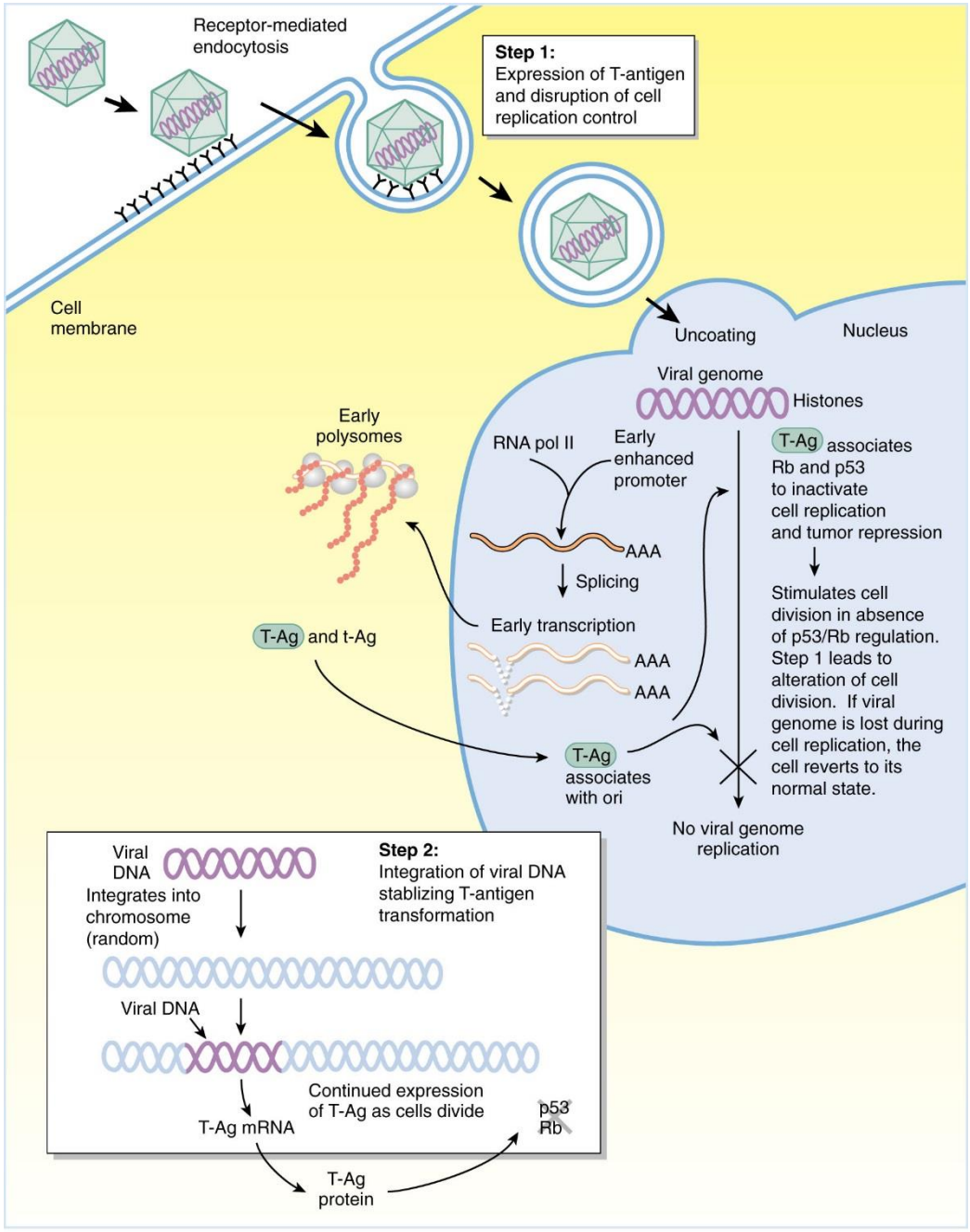
Non-permissive cells: transformation. Usually, DNA is integrated. Early functions only are expressed. Control information, rather than structural proteins

SV40 life cycle, infection of permissive cells



From Wagner and Hewlett *Basic virology* (2003) Blackwell Science Press

SV40 life cycle, infection of non-permissive cells



From Wagner and Hewlett *Basic virology* (2003) Blackwell Science Press

The human cancer viruses

Virus	Genome	Notable cancers	Year first described	Refs
Epstein–Barr virus (EBV; also known as human herpesvirus 4 (HHV4))	Double-stranded DNA herpesvirus	Most Burkitt's lymphoma and nasopharyngeal carcinoma, most lymphoproliferative disorders, some Hodgkin's disease, some non-Hodgkin's lymphoma and some gastrointestinal lymphoma	1964	15
Hepatitis B virus (HBV)	Single-stranded and double-stranded DNA hepadenovirus	Some hepatocellular carcinoma	1965	25
Human T-lymphotropic virus-I (HTLV-I)	Positive-strand, single-stranded RNA retrovirus	Adult T cell leukaemia	1980	20
High-risk human papillomaviruses (HPV) 16 and HPV 18 (some other α-HPV types are also carcinogens)	Double-stranded DNA papillomavirus	Most cervical cancer and penile cancers and some other anogenital and head and neck cancers	1983–1984	29, 30
Hepatitis C virus (HCV)	Positive-strand, single-stranded RNA flavivirus	Some hepatocellular carcinoma and some lymphomas	1989	31
Kaposi's sarcoma herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8))	Double-stranded DNA herpesvirus	Kaposi's sarcoma, primary effusion lymphoma and some multicentric Castleman's disease	1994	33
Merkel cell polyomavirus (MCV)	Double-stranded DNA polyomavirus	Most Merkel cell carcinoma	2008	34

Papillomaviridae

The papillomaviruses (PVs) have been isolated from many mammalian host species, birds, and reptiles, but thus far have not been identified in non-vertebrates

PVs comprise a group of nonenveloped epitheliotropic dsDNA viruses that induce benign lesions of the skin (warts) and mucous membranes (condylomas).

Some PVs have also been implicated in the development of epithelial malignancies, especially cancer of the uterine cervix, other tumors of the urogenital tract, and upper airway cancers.

The recognition that PVs are an important cause of human cancer has led to the development of a preventive virus like Particle (VLP)–based vaccine targeted to the human papillomavirus (HPV) types most often found in the cancers

The study of HPVs is time-honored

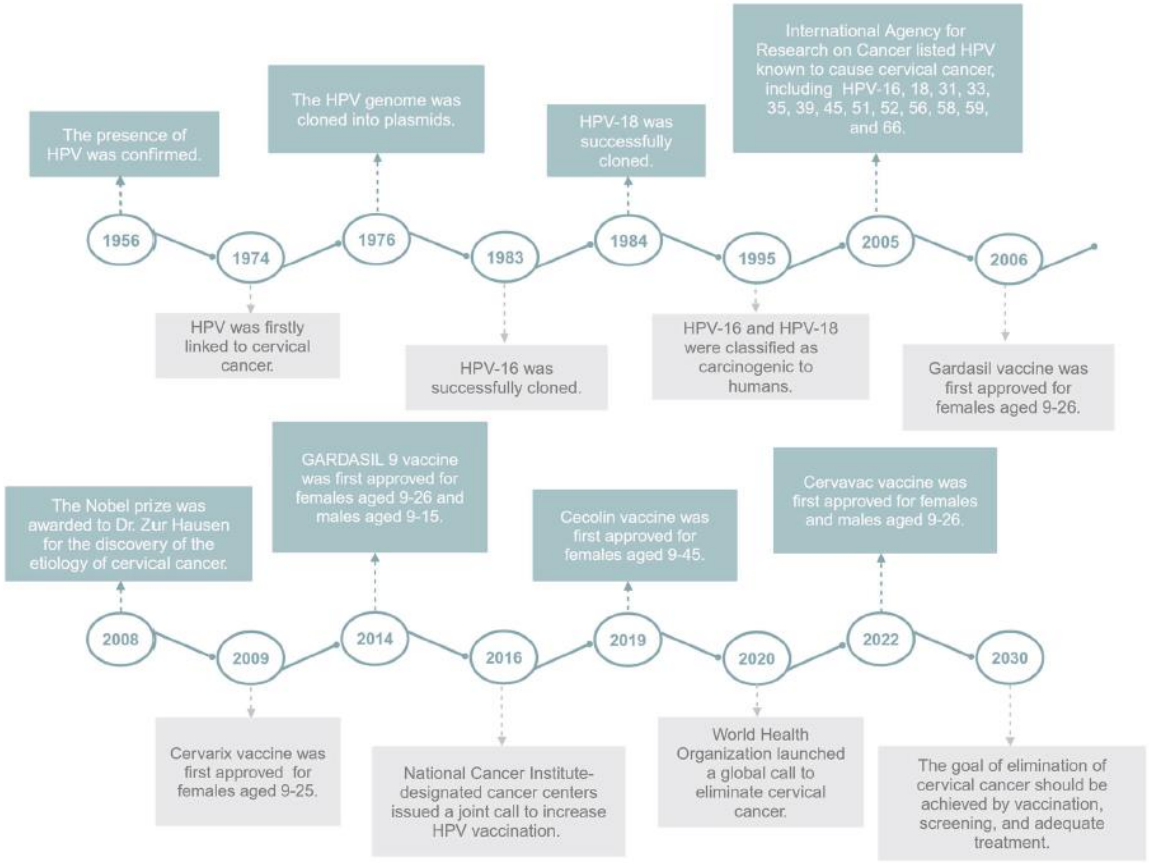
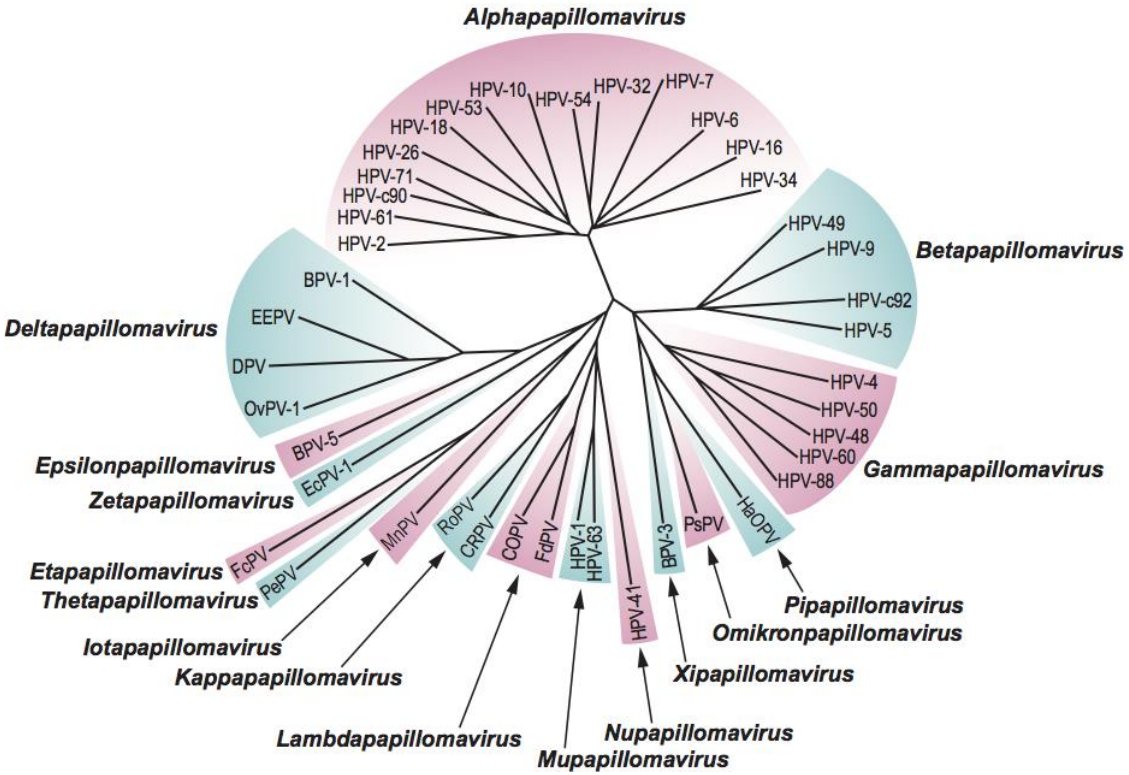


Fig. 1 A timeline of HPV research. Since the presence was identified in 1956, study on HPV has continued to date. Apart from oncogenic mechanisms, vaccines targeting HPV have been developed. Moreover, WHO has launched strategies for worldwide CC elimination. This figure was created with BioRender (www.bioender.com)

Signal Transduction and Targeted Therapy (2025) 10:44 Zhang et al.

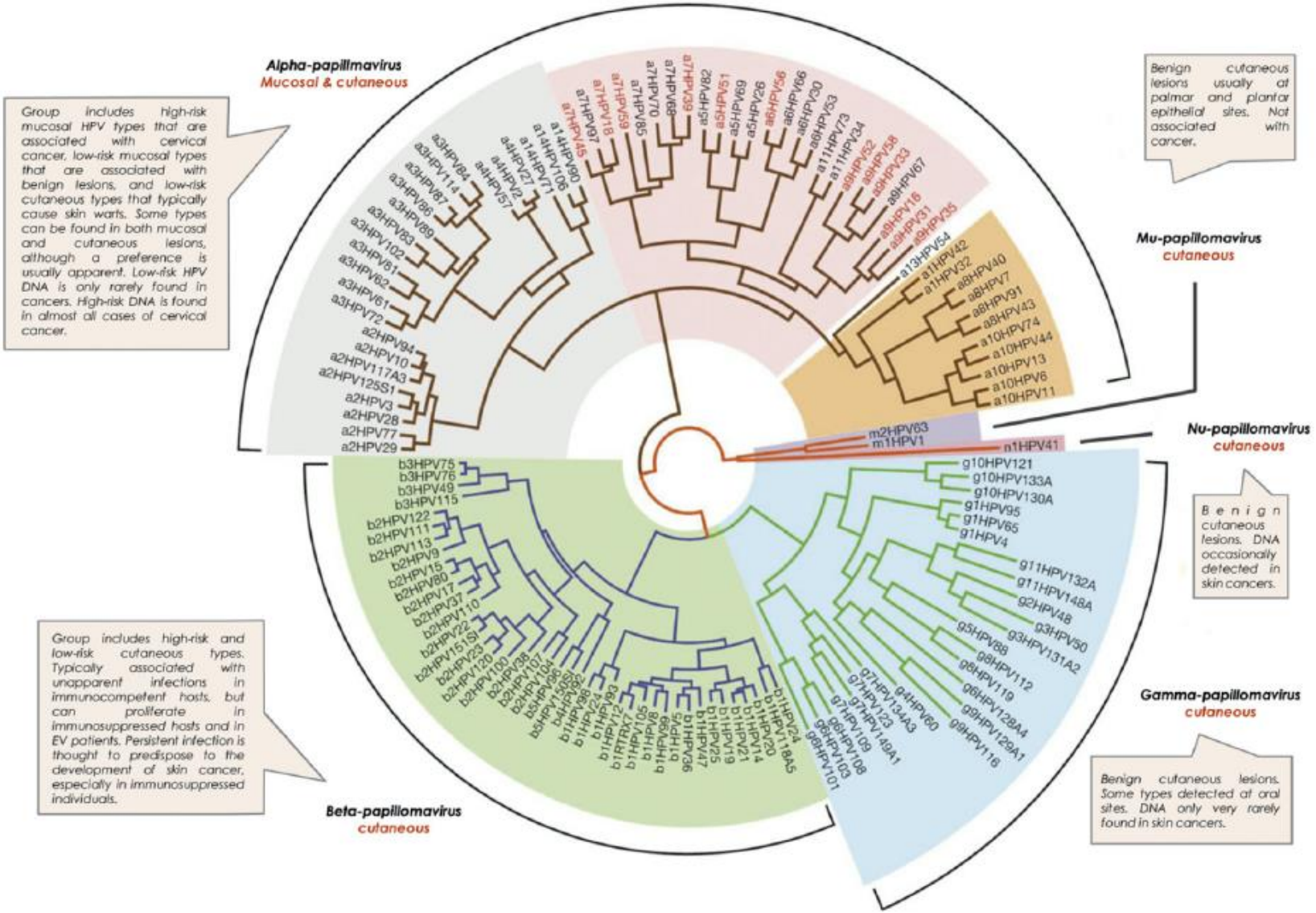
Classification

PVs are classified primarily according to the host species they infect and have been traditionally referred to as types based on their DNA sequence. A distinct type is one whose L1 DNA sequence is at least 10% different from that of other HPV types. PVs appear to have arisen primarily via point mutations scattered throughout the genome, rather than via recombination between PVs.
PVs are divided into 29 genera, each of which is designated by a letter of the Greek alphabet. HPVs cluster in 5 genera: alpha, beta, gamma, mu, and nu



A Viral type within a species has 71% to 89% identity with other types within the species.

Classification



epidermodysplasia verruciformis (EV) specific, because they cause lesions mainly in Patients with EV, a genetic susceptibility to widespread nongenitalHPV lesions.

Classification

Genus + Species	Type	
Alpha 1	HPV 32	More frequent in mucosal lesions than cutaneous (low risk)
Alpha 8	HPV 7	Oral epithelial hyperplasia, cervical intraepithelial neoplasia
Alpha 10	HPV 6 HPV 11	Condylomata acuminata (HPV 6 and HPV 11) Recurrent Respiratory Papillomatosis (HPV 11 and HPV 6)
Alpha 13	HPV 54	Butcher's wart (cutaneous, HPV 7)
Alpha 9	HPV 16 HPV 31	High-risk mucosal lesions Each type shows different carcinogenicity Bowenoid papulosis, Bowen's desease (cutaneous, HPV 16)
Alpha 7	HPV 18 HPV 45	
Alpha 5	HPV 51	
Alpha 6	HPV 56	
Alpha 11	HPV 34	
Alpha 3		Low-risk mucosal lesions
Alpha14		
Alpha 2	HPV 3 HPV 10	More frequent in cutaneous lesions than mucosal (low-risk) Flat warts (Alpha 2)
Alpha 4	HPV 2 HPV 57	Verruca vulgaris (common warts) (Alpha 4)
Beta 1	HPV 5 HPV 8	Most frequently causes cutaneous lesions, DNA is also detected in mucosa A possible role in the development of skin cancer
Beta 2		Commonly assocciated with Epidermodysplasia verruciformis (EV, Beta 1 and 2) or immunosuppressed patients (aquired EV)
Beta 3		
Beta 4		In general immunocompetent population, infection is asymptomatic DNA is detected on plucked hairs, suggesting the hair follicle as a site of infection
Beta 5		
Gamma 1	HPV 4 HPV 65	Gamma-PV DNA is detected from skin and mucosal sample of healthy population Infection is asymptomatic in general immunocompetent population Causes lesions in immunosuppressed paitients
Gamma 4	HPV 60	
other Gammas		Some types are known to cause cutaneous lesions in general population Common warts, Plantar warts, Pigmented warts (HPV 4 and 65), Epidermoid cysts (HPV 60) Histologically distinct intracytoplasmic inclusion bodies
Mu 1	HPV 1	Cutaneous lesion especially in palm and plantar (Myrmecia, HPV 1) Histologically distinct intracytoplasmic inclusion bodies
Mu 2	HPV 63	Eccrine duct is thought to be a site of infection
Nu 1	HPV 41	Isolated from cutaneous lesions

HPVs from the Beta and Gamma genera can elicit inapparent infections of the skin. Alpha-HPVs are associated with various clinical conditions ranging from benign warts to cancers.

Among Alpha-HPVs, only a small part of Alpha-HPVs is oncogenic, which is termed as high-risk HPVs (hr-HPVs)

Table 1. hr-HPVs and associated diseases

Genera	Types	Diseases
α-5	51, 82	Anogenital cancers
α-6	56	Anogenital cancers
α-7	18, 39, 45, 59, 68	Anogenital cancers, oropharyngeal carcinoma
α-9	16, 31, 33, 35, 52, 58	Anogenital cancers, oropharyngeal carcinoma
α-11	73	Anogenital cancers

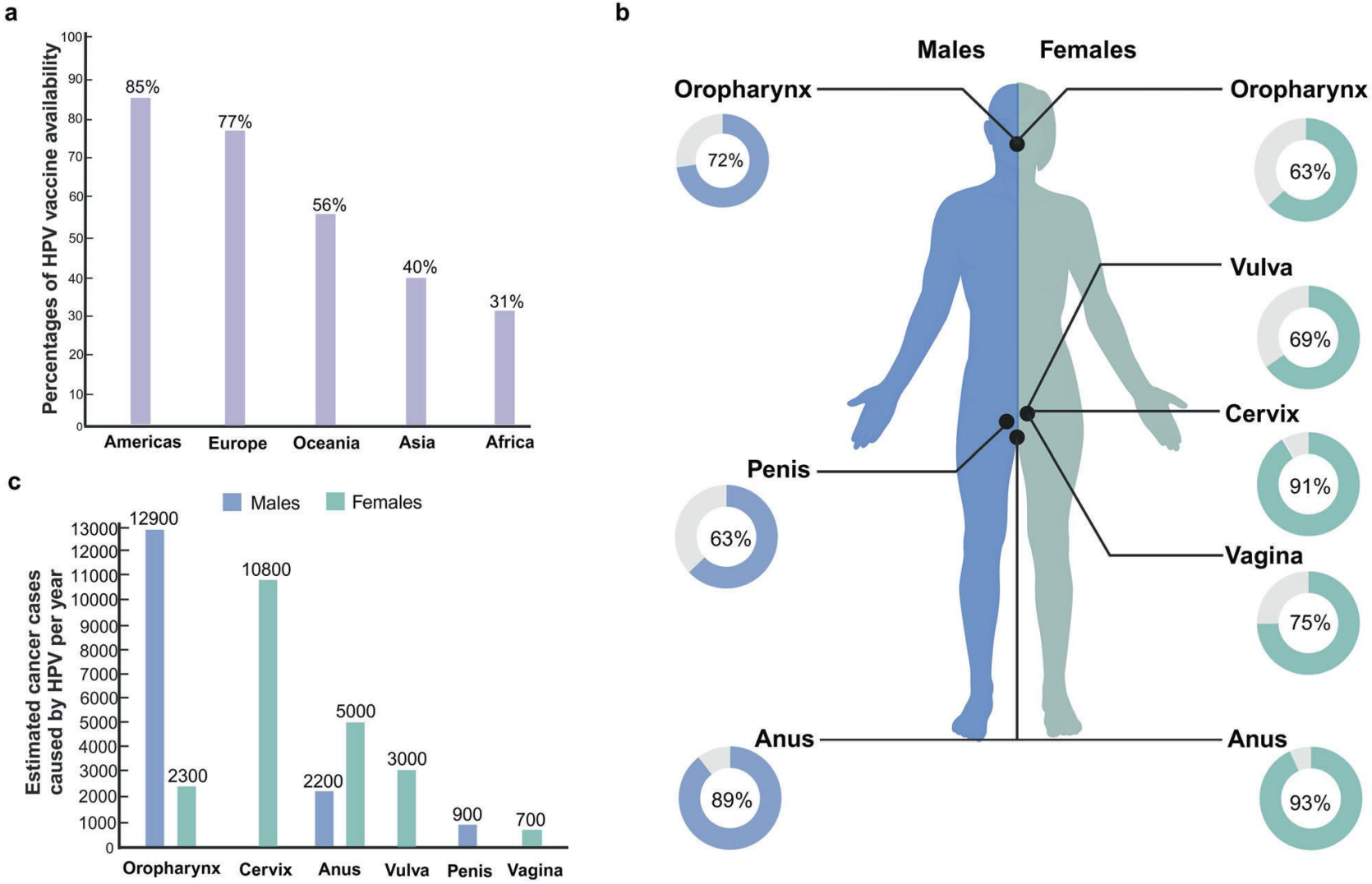
HPVs

More than 200 different HPV types are known, and about 40 of these are sexually transmitted

Human papillomavirus (HPV) are grouped according to their risk to produce cancerous or precancerous lesions (high intermediate or low risk)

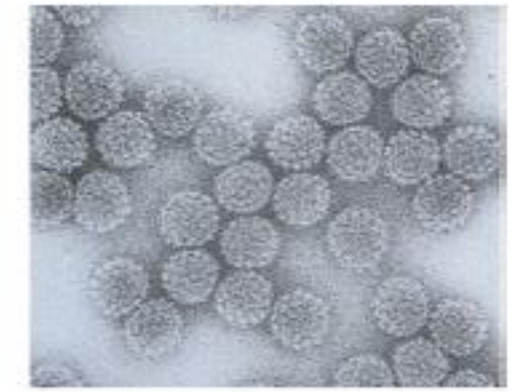
It has been widely recognized that persistent hr-HPV infection contributes to certain types of cancers

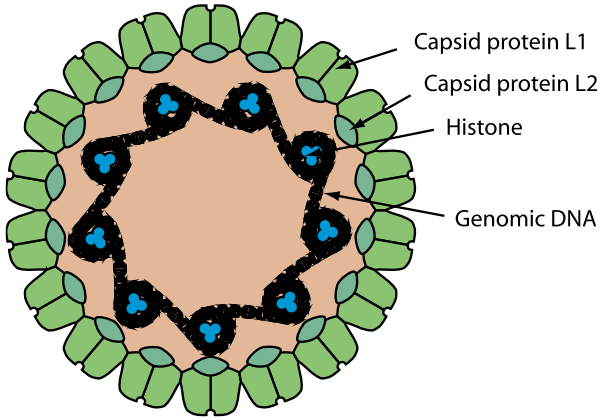
Mentre nelle lesioni benigne (verruche e nei condilomi) il genoma virale si trova in forma episomiale,
nel carcinoma della cervice uterina e in carcinomi squamosi il genoma virale è stato ritrovato integrato nel DNA della cellula tumorale.

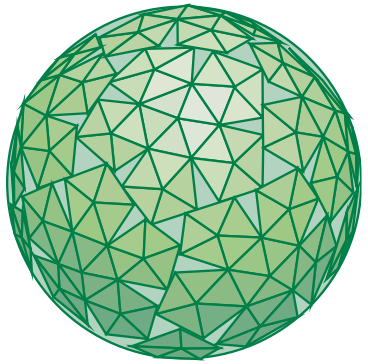


Global HPV vaccine availability and the association between hr-HPVs and cancers:
a Percentage of HPV vaccine availability among different regions. **b** The association between hr-HPVs and cancers. Cervical cancer, oropharyngeal squamous cell carcinoma, anal cancer, vaginal cancer, vulvar cancer, and penile cancer are well recognized as closely associated with hr-HPVs. **c** Number of cancer cases caused by hr-HPV per year.

HPVs



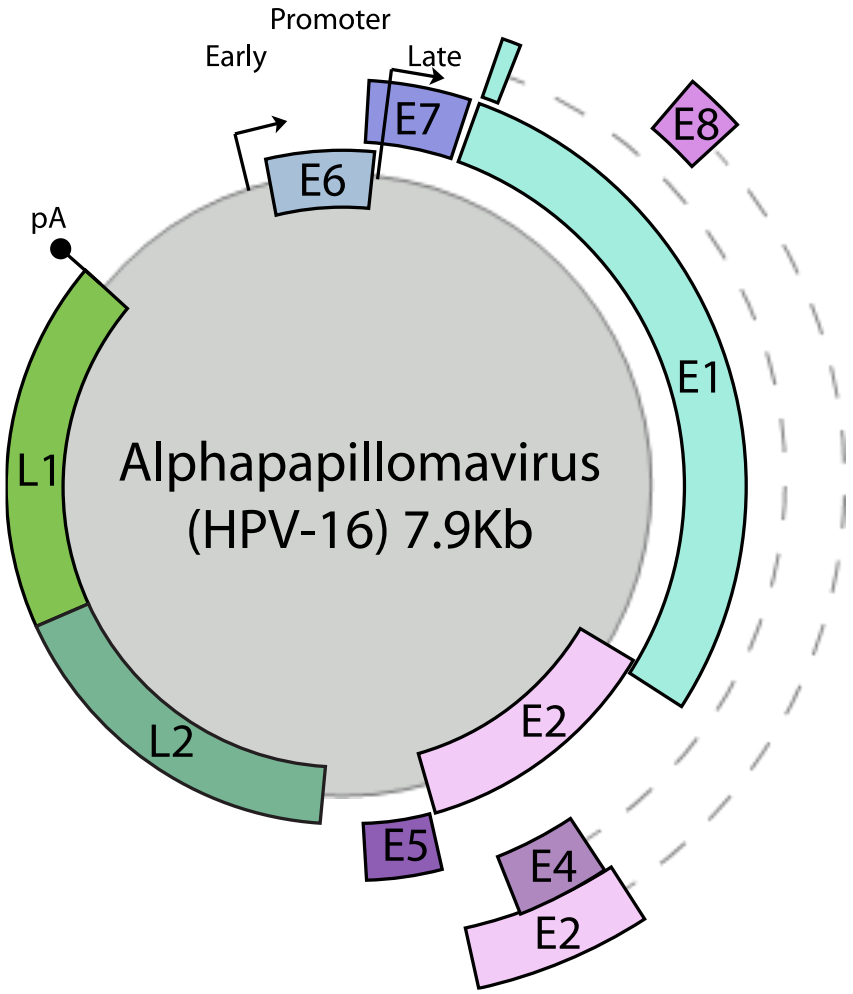




- Family: Papillomaviridae
- Genome: circular dsDNA, 7.9 kb, associated with cellular histones
- Capsid: icosahedra, 52-55 nm (non-enveloped)
- 2 structural proteins: L1 major capsid protein, L2 minor capsid protein (72 capsomers)
- Specie-specific
- Tropism: epithelial cells (skin, mucosa)

From Viralzone website

HPV genome



The HPV genome has three characterized regions: the upstream regulatory region (URR) which is also called the long control region (LCR); the early (E) region; and the late (L) region.

Only one strand of the genome is transcribed and yield two classes of proteins expressed by alternative splicing :

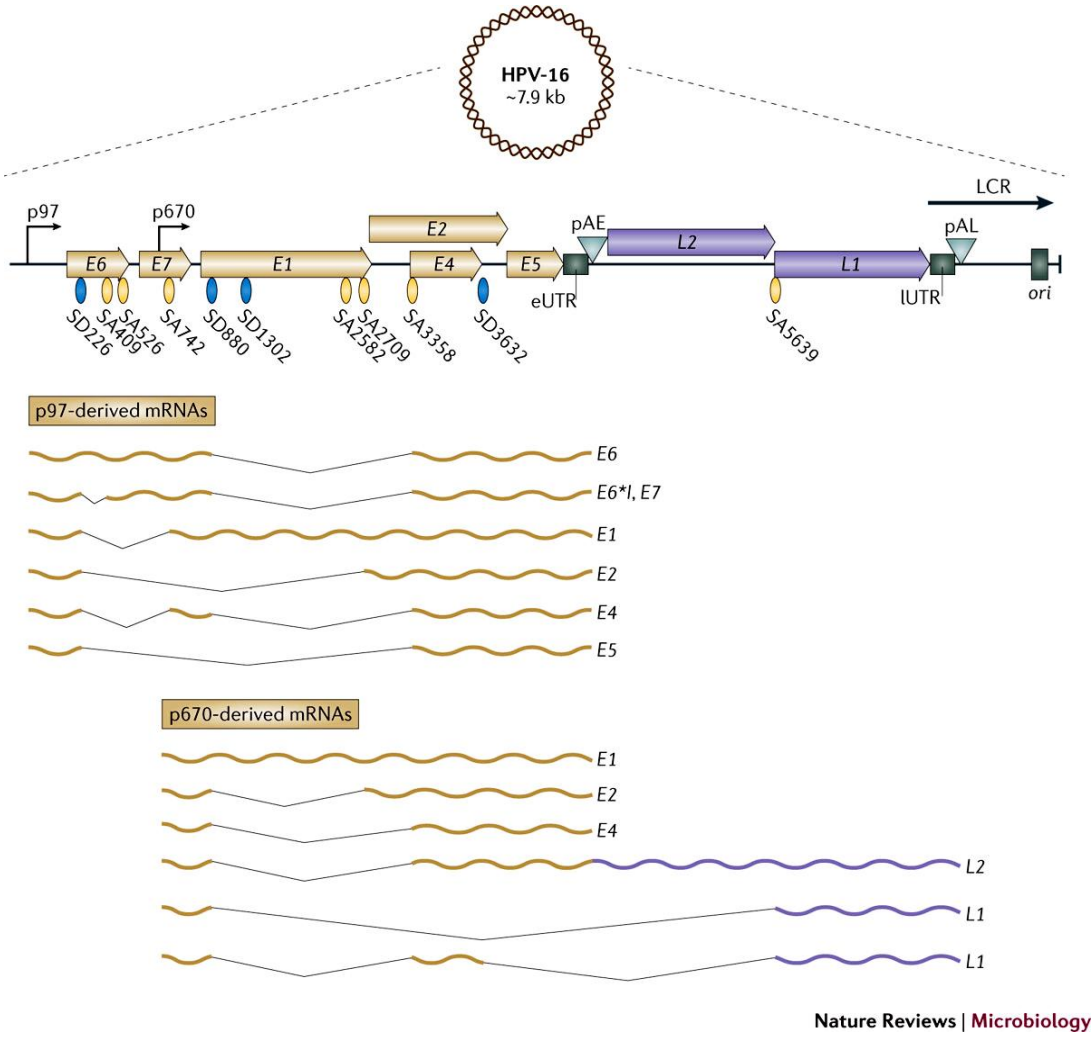
a) Early Proteins: non-structural regulatory proteins (E1-E7).

b) Late Proteins: the structural proteins L1 and L2. E7 can be expressed by leaky scanning from the E6 mRNA.

From Viralzone website

HPV genome

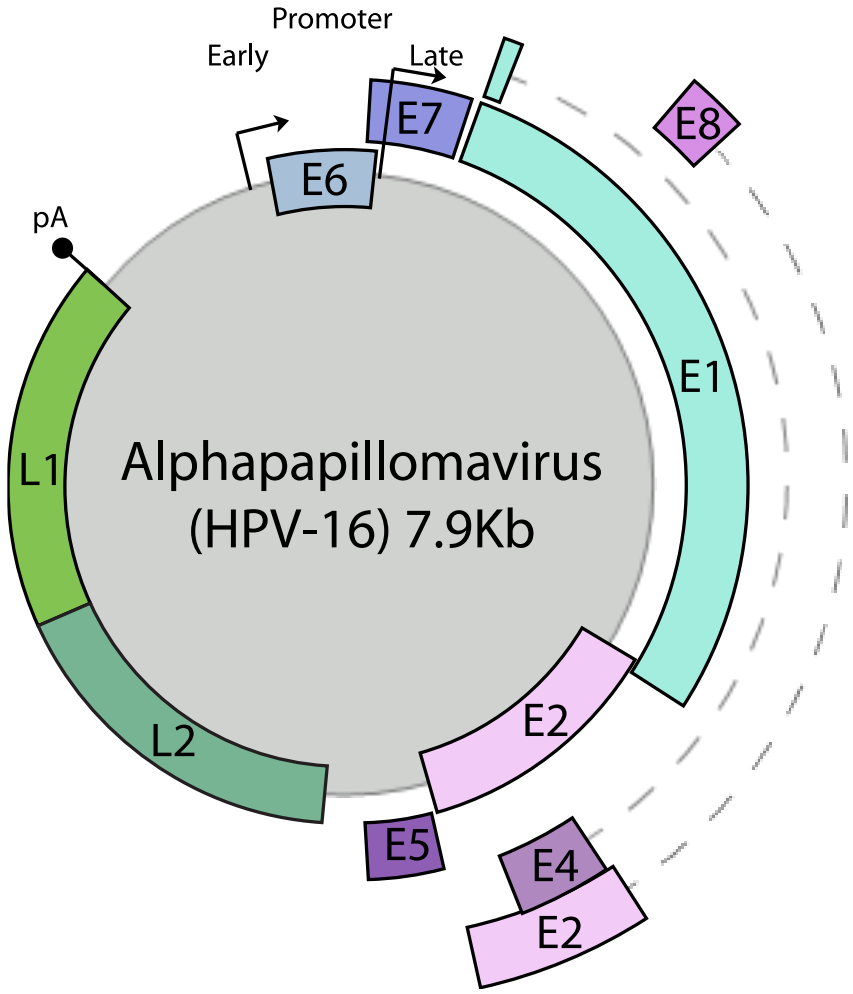
The non-protein-coding sequence between the ***L1*** stop codon and the ***E6*** AUG is termed the long control region (LCR) and contains the origin of DNA replication (***ori***) and the early viral promoter,p97.
The late, differentiation-dependent promoter, p670, is located in the ***E7*** coding region. Two polyadenylation signals are present in the HPV genome. The early polyadenylation signal (pAE) is located downstream of ***E5*** and preceded by the early 3′ UTR (eUTR). The late polyadenylation signal (pAL) is located downstream of ***L1*** and preceded by the late 3′ UTR (lUTR).
Known 5′ splice sites (splice donor 226 (SD226), SD880, SD1302 and SD3632) and known 3′ splices sites (splice acceptor 409 (SA409), SA526, SA742, SA2582, SA2709, SA3358 and SA5639) are indicated. A subset of the alternatively spliced, p97- and p670-derived HPV-16 mRNAs is indicated. Each mRNA represents the likeliest candidate mRNA for production of the corresponding proteins.



E6 and E7 genes of the “low risk” HPVs such as HPV6 and HPV11 are expressed from two independent promoters

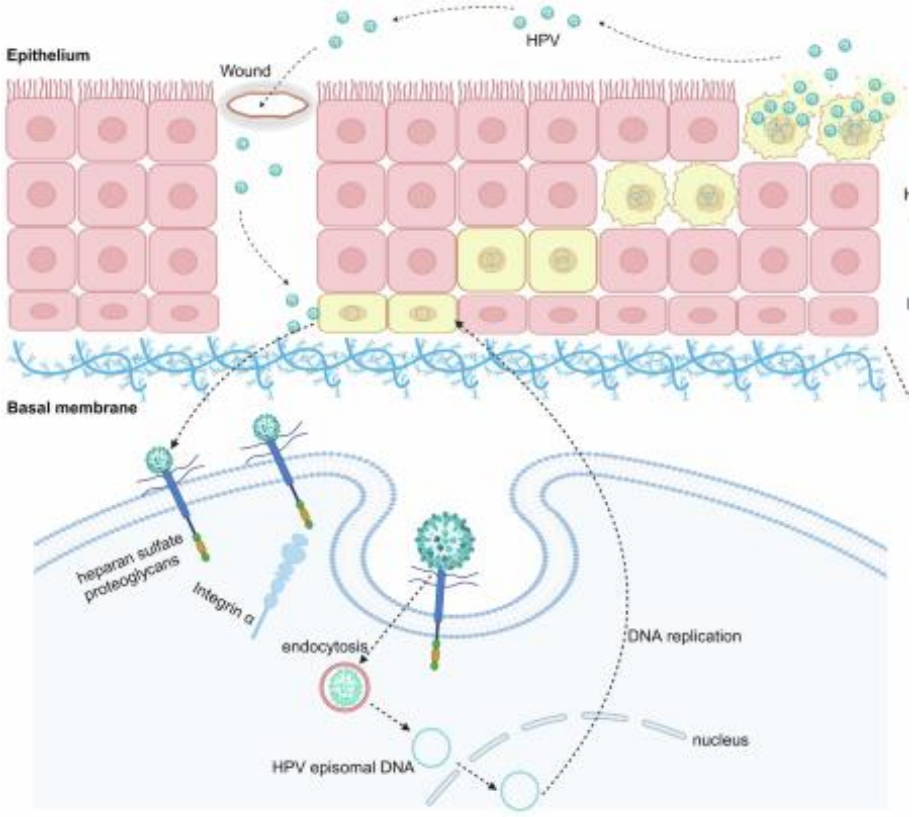
HPV genome

LCRs contain constitutive enhancer elements that have some tissue or cell-type specificity.
These elements are important for the initial expression of the viral genes and in the maintenance of viral latency.
A number of transcription factor binding sites have been identified in the LCRs of the various HPV. Included sites that bind AP1, SP1, Oct-1, among others. The HPV16 LCR also contain nuclear matrix attachment sites that may be important for controlling viral gene expression. the LCR contains binding sites for the virally encoded E2 regulatory proteins and the origin of DNA replication that binds the E1 replication factor.



E1	DNA helicase activity, DNA-dependent ATP-binding, ATPase activity. Role in replication and replication repression.
E2	Regulator of viral transcription and replication, control of early region viral gene expression, necessary for efficient viral DNA replication together with E1, and long-term plasmid maintenance.
E4	Expressed as a late gene primarily in differentiating epithelium, role in productive infection, associated with the keratin cytoskeleton of cultured epithelial cells, role in viral egress.
E5	Transforming activity in HPV-16 *in vitro* (EGFR binding). Presumably stimulates benign cell proliferation *in vivo* but might have a role in the initiation of carcinogenesis
E6	Role in transformation process together with E7. Transcriptional activation properties. E6 of high-risk HPVs inactivates p53 by inducing its degradation. Together with E7 provides a cellular environment for viral DNA replication
E7	Transactivating properties, induces DNA synthesis in quiescent cells. E7 binds to the hypophosphorylated form of the retinoblastoma protein (pRB) resulting in its functional inactivation permitting cell progression to S phase of the cell cycle. E7 proteins from the low-risk HPV types 6 and 11 bind pRB less efficiently than the E7 proteins from high-risk HPVs (types 16 and 18).
L1	Major capsid protein.
L2	Minor capsid protein.

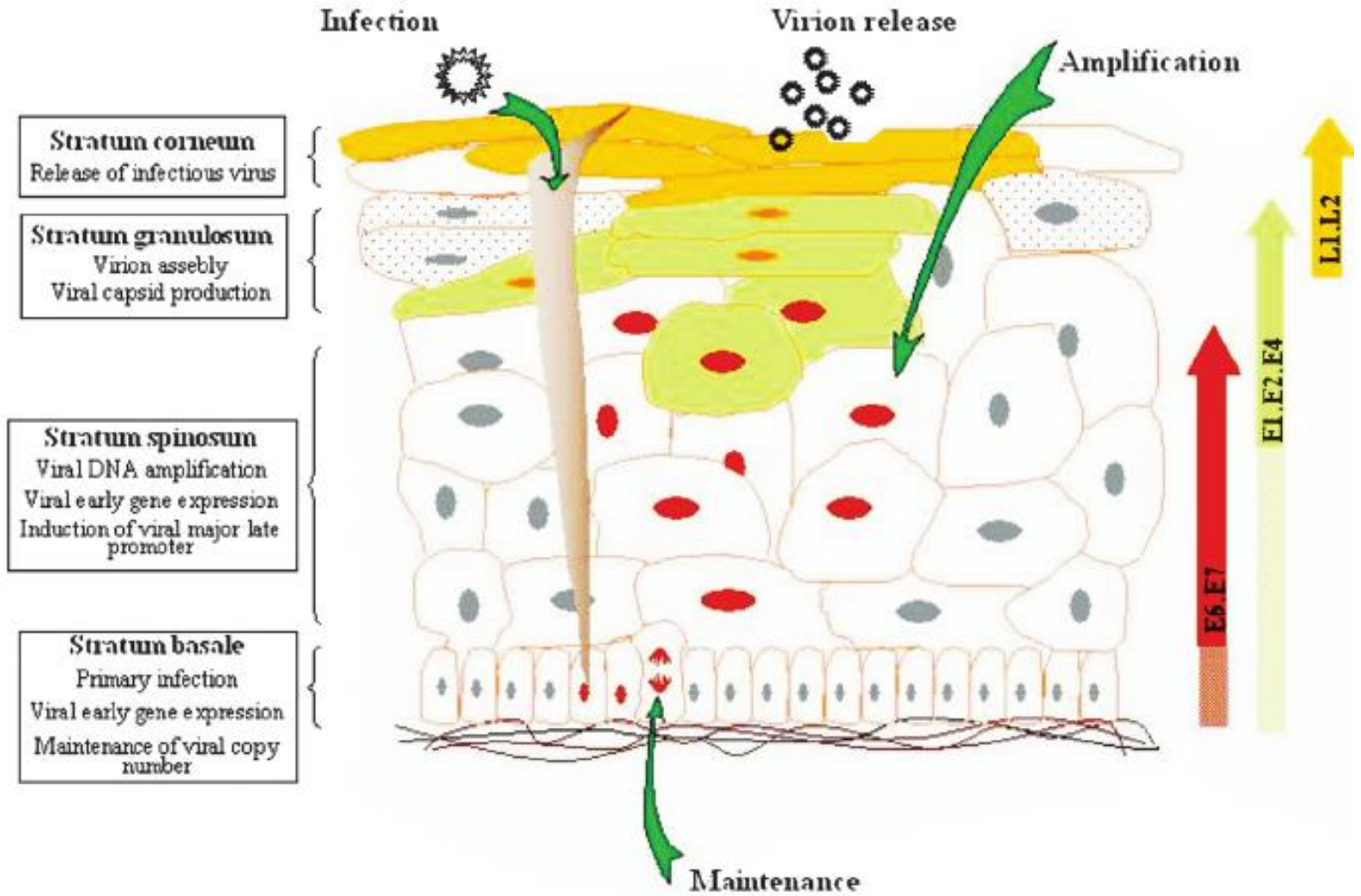
HPV life cycle



HPV particles enter the basal layer of the epithelium via minuscule abrasion or wound of epidermis. Then, HPV particles attach to heparan sulfate proteoglycans and secondary receptors such as α_6-Integrin, which facilitate HPV particles entering into host cells.
HPV infection undergoes four stages once entering the basal cells: initial, maintenance, vegetative amplification, virus assembly and release

HPV life cycle:

the close link of the papillomavirus life cycle with the differentiation program of the squamous epithelium



HPV life cycle: model of entry

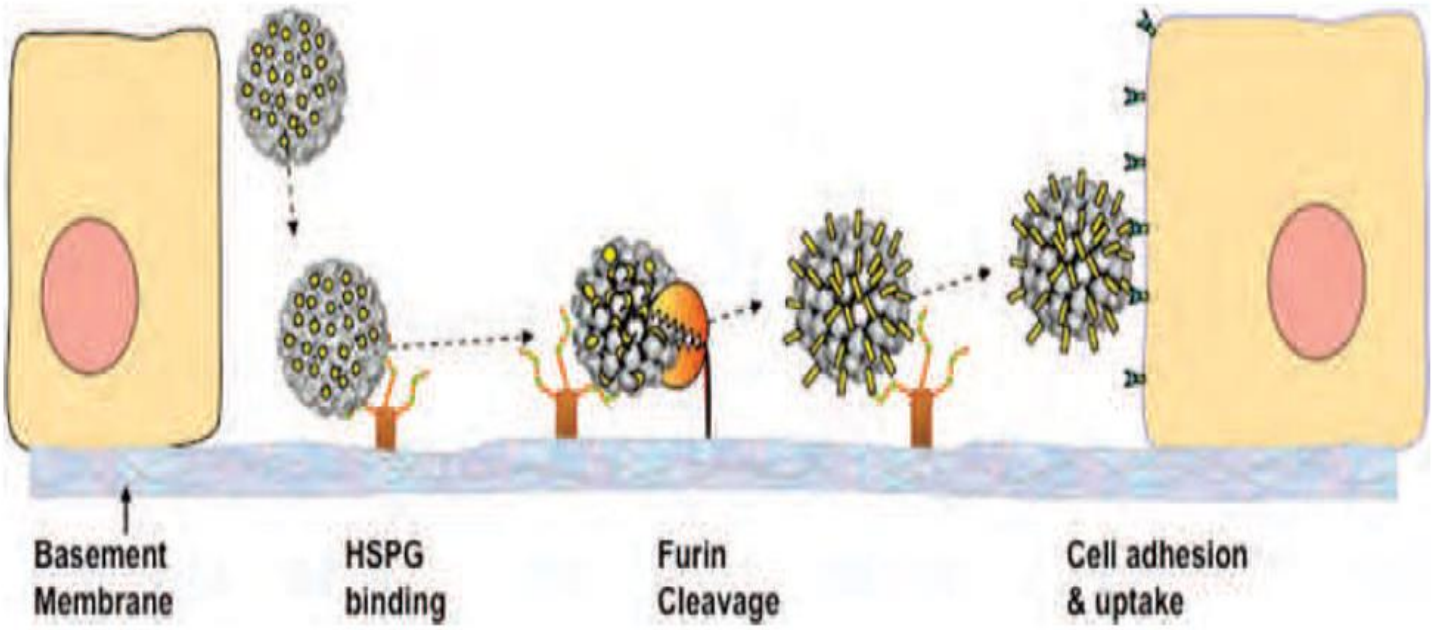


FIGURE 54.6. Model of in vivo papillomavirus infection. The virion first binds to heparan sulphate proteoglycans (HSPGs) on the basement membrane exposed after disruption. This induces a conformational change exposing a site on L2 (depicted in yellow) susceptible to proprotein convertase (furin or PC5/6) cleavage. After L2 cleavage, an L2 neutralizing epitope is exposed and a previously unexposed region of L1 binds to an unidentified secondary receptor on the invading edge of the epithelial cells.

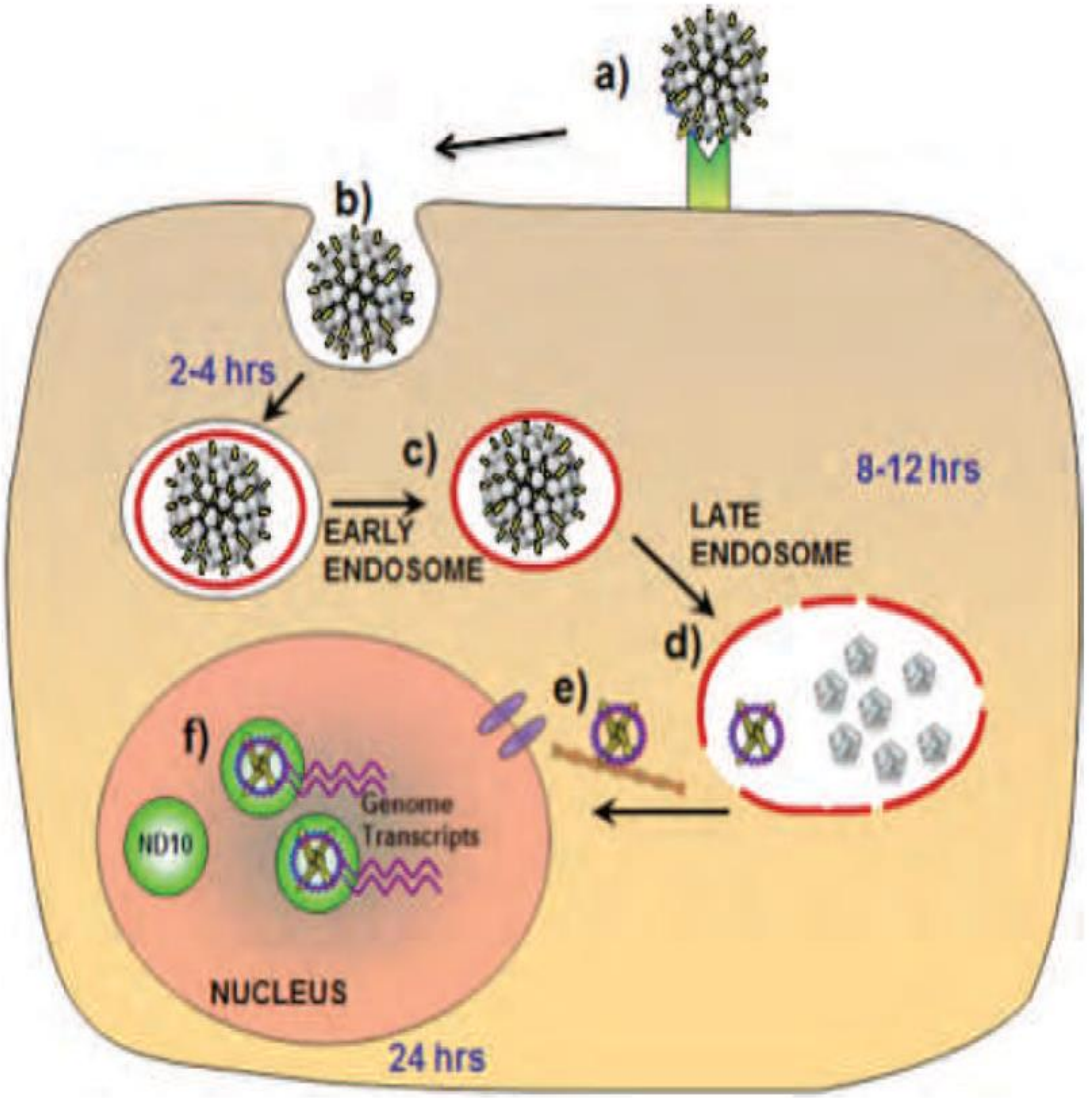


FIGURE 54.7. Infectious process after cell binding. After binding to a cell surface receptor (a), the virus enters the cell via an endocytic pathway (b) and within 4 hours localizes in the early endosome (c). By 12 hours the virus uncoats within the late endosome and the viral genome complexed with L2 is released (d). The L2–genome complex traffics through the cytoplasm, perhaps via microtubules, and enters the nucleus by 24 hours (e). After nuclear entry, the complex co-localizes with ND10 and viral genome transcription begins (f).

HPV life cycle

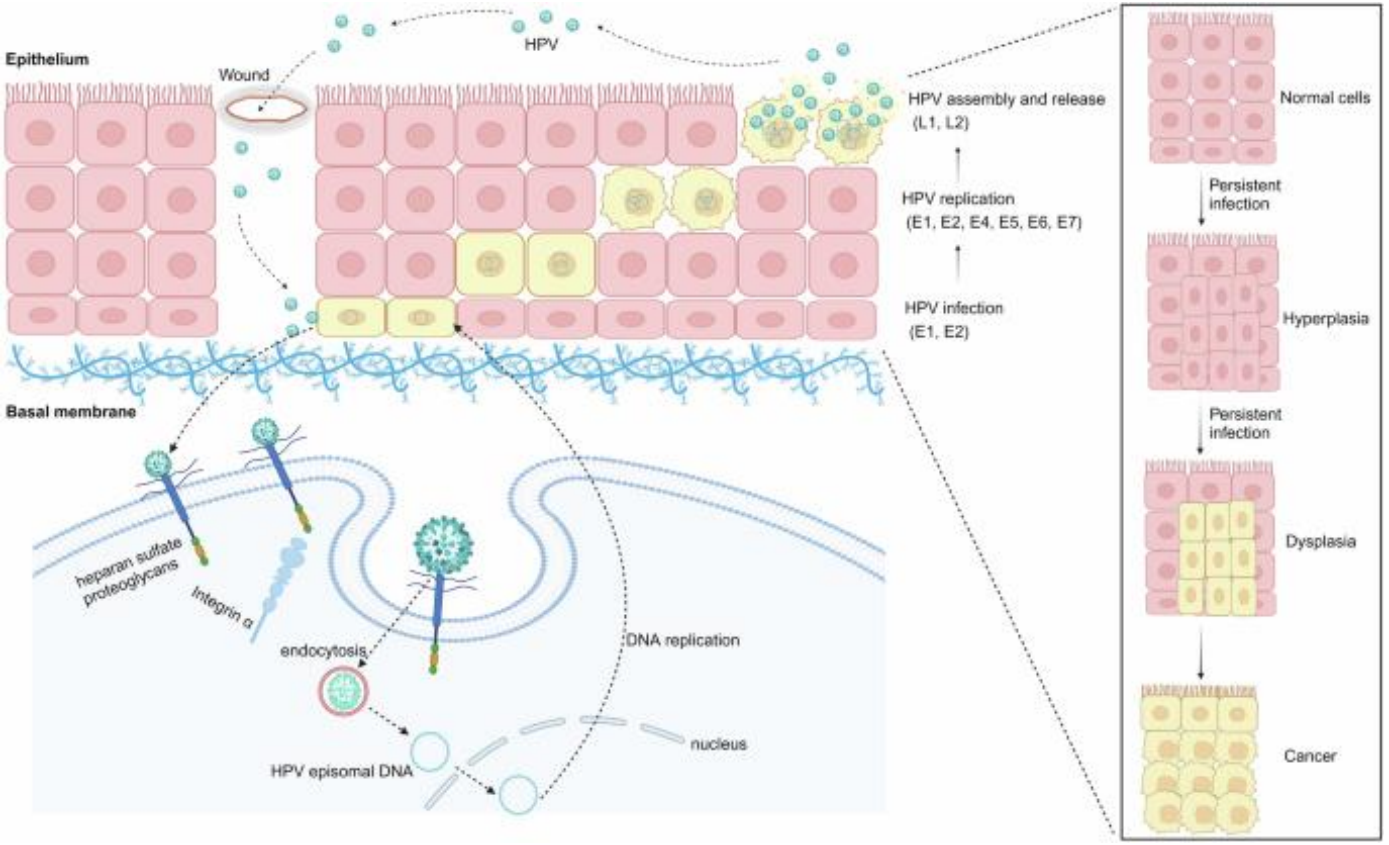
Through endocytosis, HPV particles have access to basal cells. Then, the L1 protein separates from the L2 protein.

The L2 protein forms a complex with the HPV genome in the vesicle form, transports to the trans-Golgi and resides until HPV particles enter the nucleus when the nuclear envelope breaks down during mitosis

Upon getting into the nucleus, the E1 and E2 proteins are expressed and cooperatively connect to the replication origin to initiate DNA replication.
HPVs infect the proliferating basal cells of the epithelium to construct the maintenance stage, during which HPV genomes exist in the form of extrachromosomal plasmids and replicate along with the host genome in the S-phase.

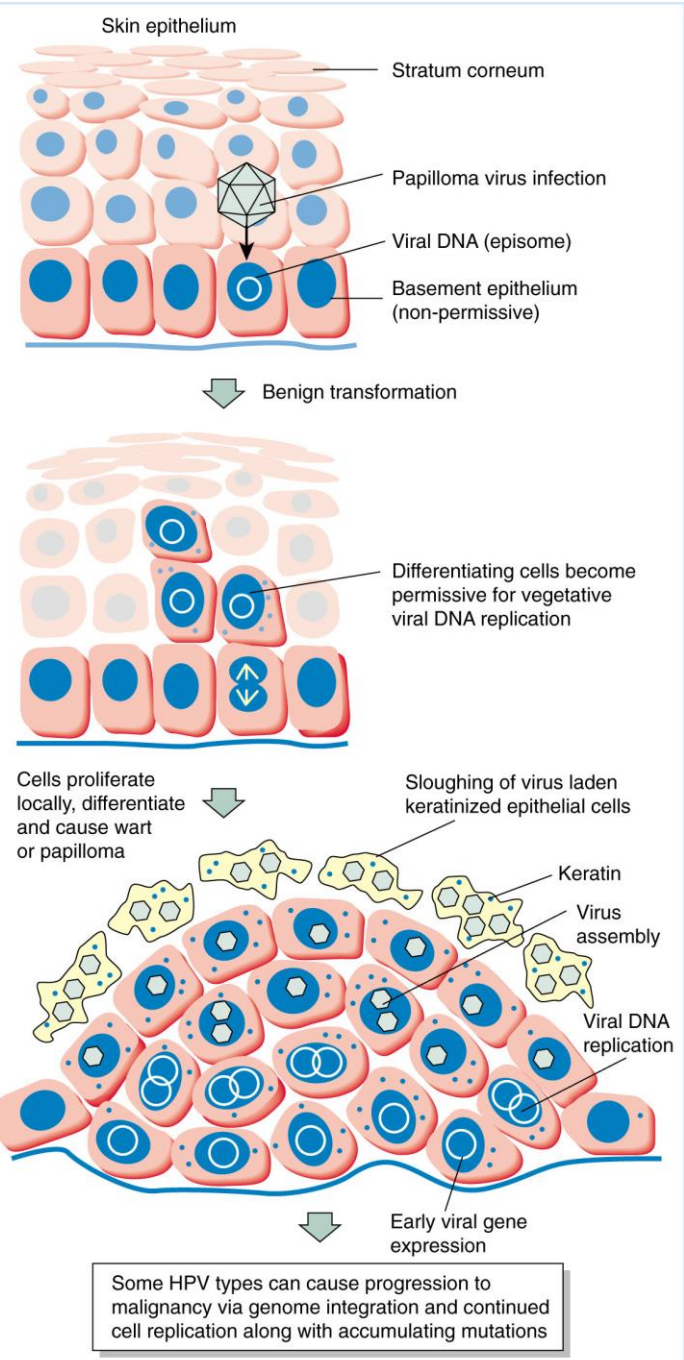
Notably, hr-HPVs have the ability to drive cell proliferation in the basal and parabasal layers, distinguishing them from other types of HPV

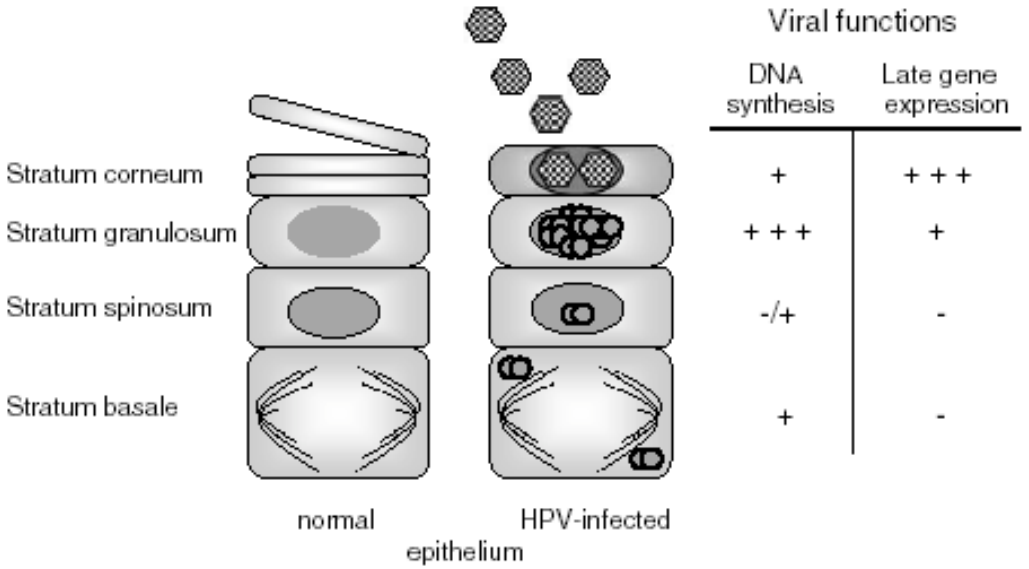
HPV life cycle



DNA amplification occurs in the differentiated cells of the upper layers of the epithelium. Then the viral genome can be packaged and released from the surface of the epithelium. HPV triggers the DNA damage response (DDR) and employs the DDR mechanism to obtain materials necessary for viral DNA synthesis in the G2-like phase

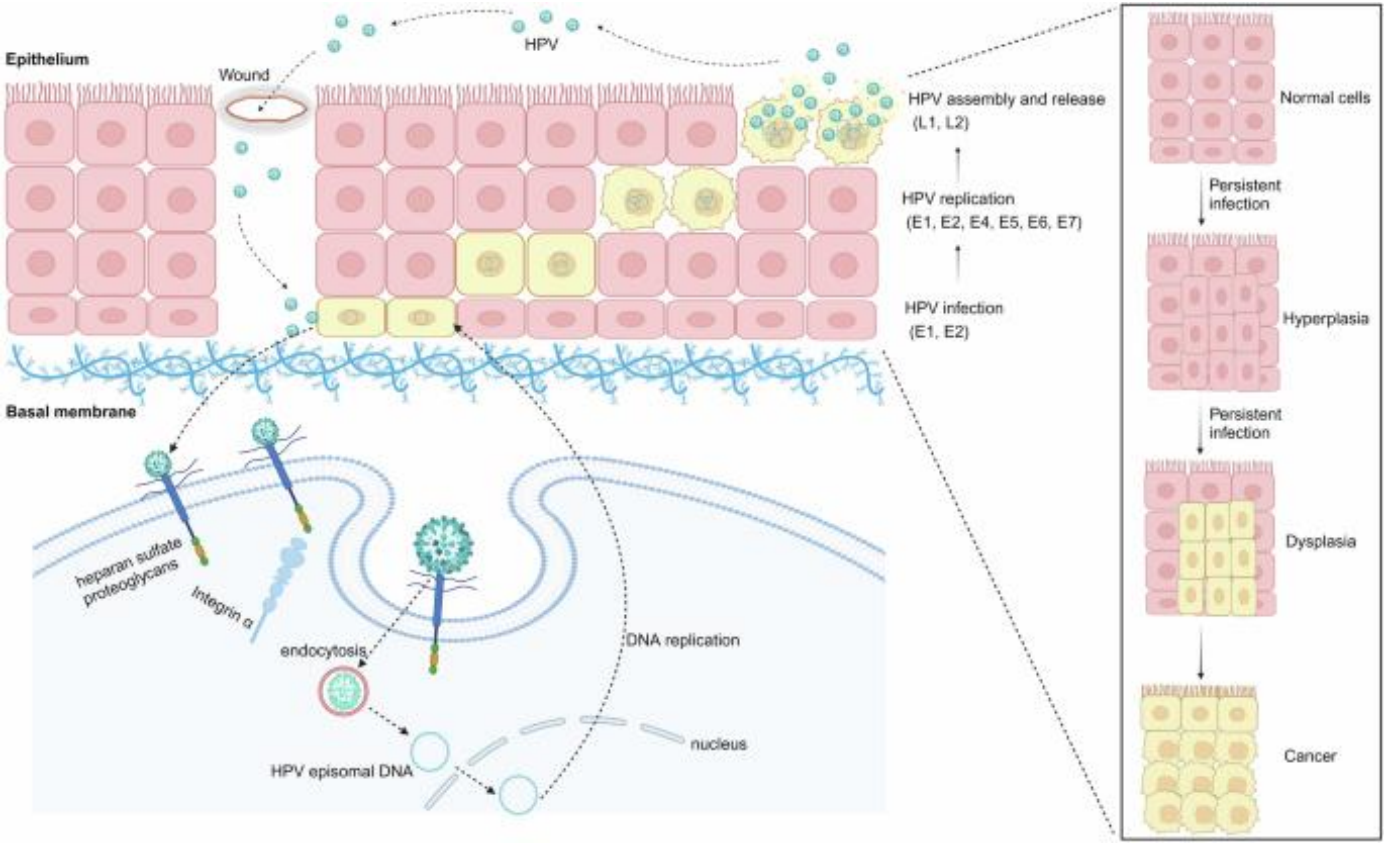
HPV life cycle





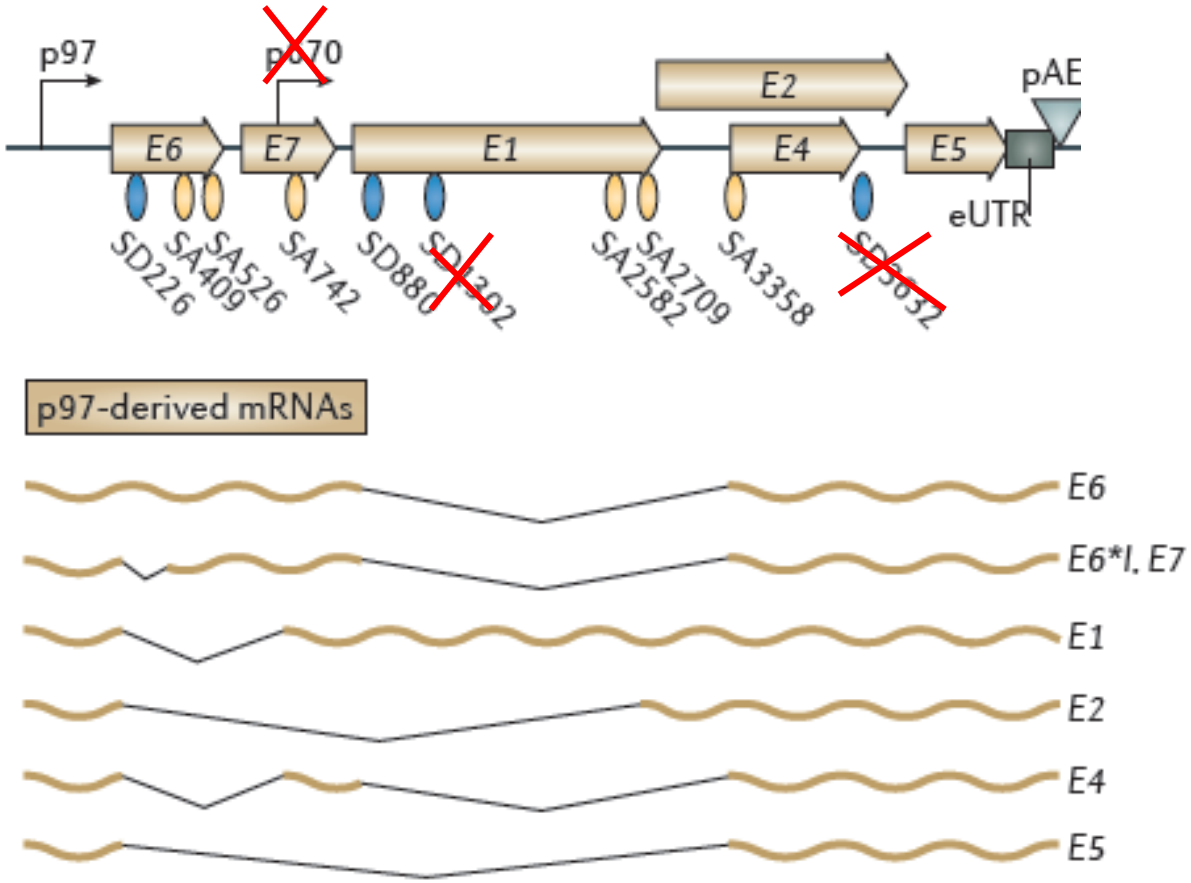
From Wagner and Hewlett *Basic virology* (2003) Blackwell Science Press

HPV life cycle



Persistent infection results in hyperplasia and dysplasia. Without intervention, dysplasia has a great possibility to evolve into cancers

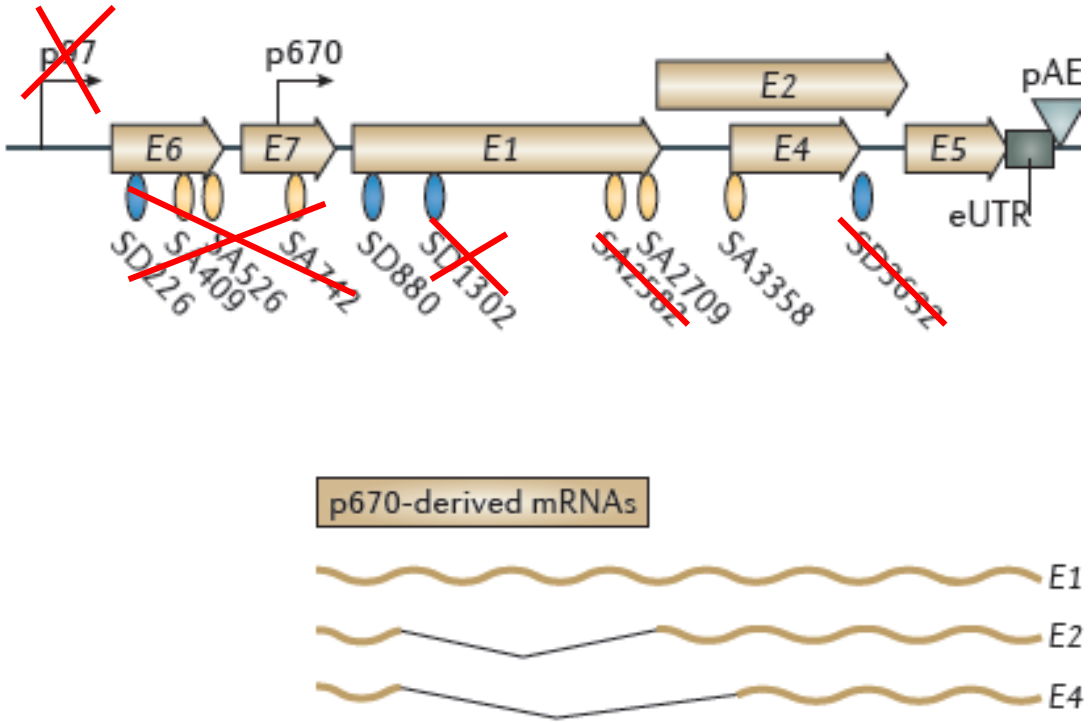
Papillomavirus very early gene expression



In the early stages of the viral life cycle, transcription from the early promoter p97 generates mRNAs encoding all of the early genes, which are polyadenylated at the early polyadenylation signal (pAE). These polycistronic mRNAs are subjected to alternative splicing through the differential use of various early splice sites (splice donor 226 (SD226), splice acceptor 409 (SA409), SA526, SA742, SD880, SA2582, SA2709 and SA3358.

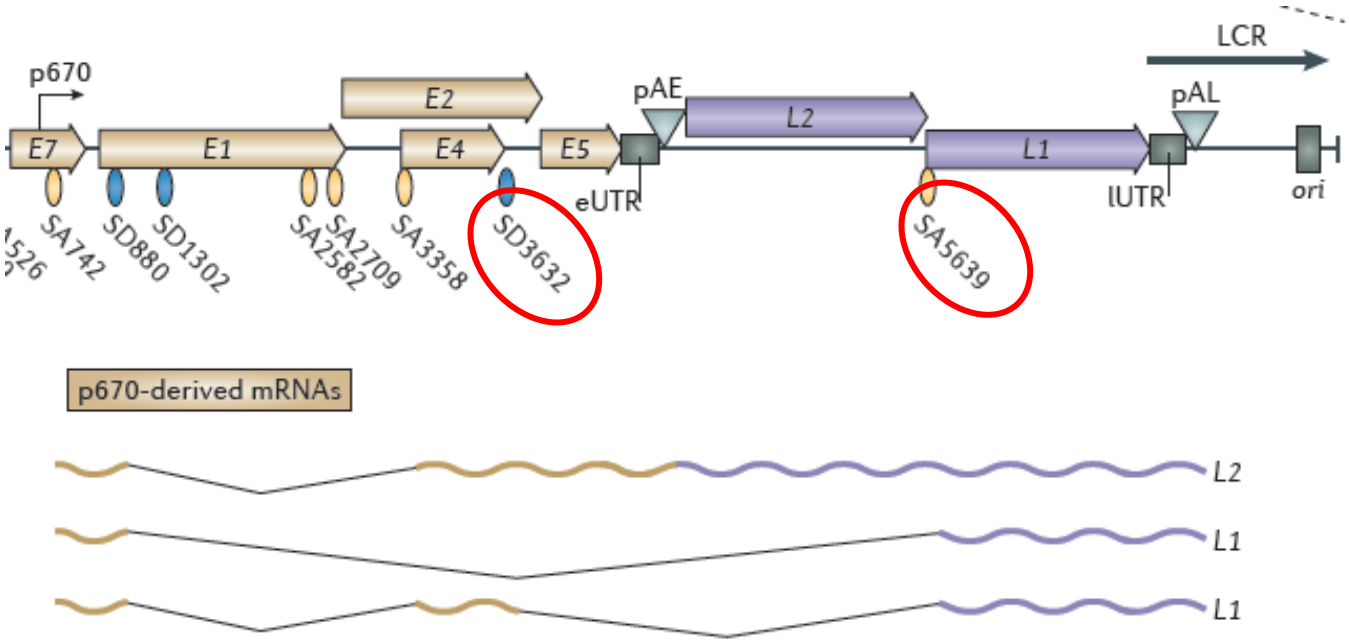
NATURE REVIEWS | MICROBIOLOGY

Papillomavirus early-late gene expression



As the infected cells undergo into differentiation program, the late promoter p670 is activated, and expression from this promoter bypasses the *E6* and *E7* genes and induces high expression of *E1*, *E2* and *E4* mRNAs using primarily the early splice sites SD880, SA2709 and SA3358. These mRNAs are also polyadenylated at pAE.

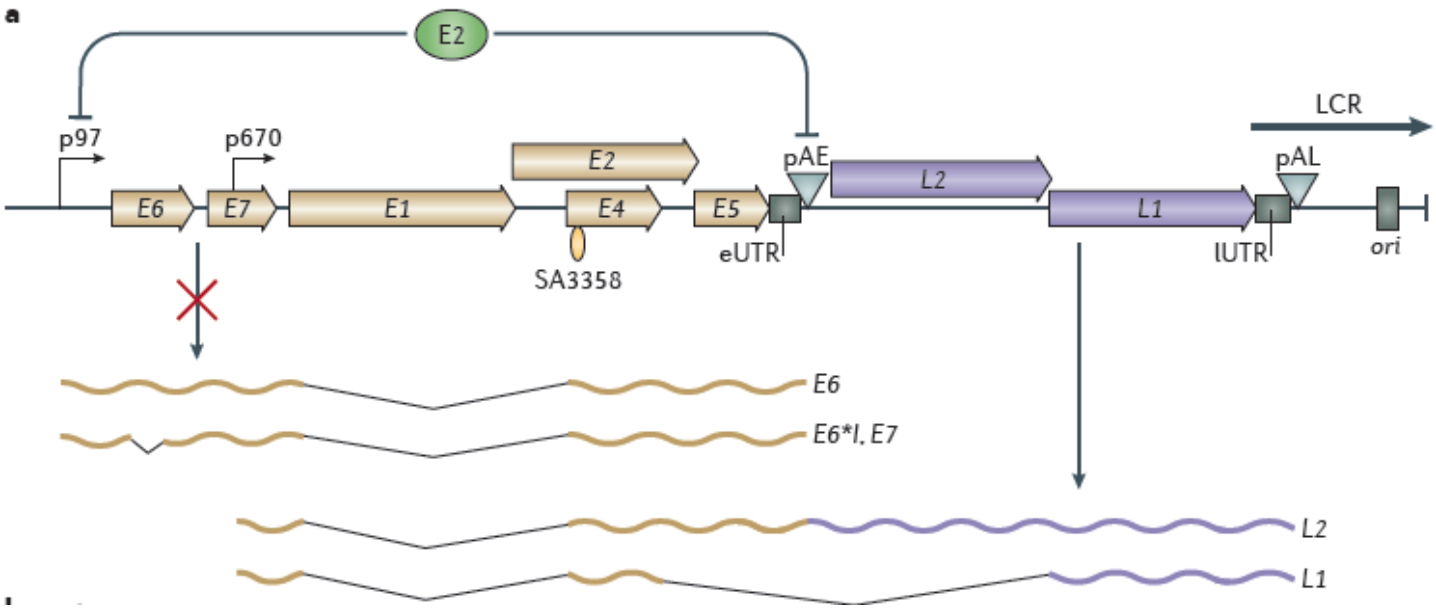
Papillomavirus late gene expression



The E1 and E2 proteins bind to the origin of replication (*ori*), which is located in the LCR, to replicate the viral DNA genome.
Terminal differentiation of the host cell downregulates the activity of pAE, resulting in readthrough into the true late region of the genome (encoding L1 and L2) followed by polyadenylation at the late polyadenylation signal (pAL) to generate *L2* mRNAs. Derepression of the exclusively late splice sites SD3632 and SA5639 generates *L1* mRNAs in addition to the *L2* mRNA.

NATURE REVIEWS | MICROBIOLOGY

HPV 16 E2 protein inhibits the early polyadenylation signal to induce late gene expression



HPV-16 produces two early (E) gene *E2* mRNAs, one produced from the early promoter, p97, and one produced from the late promoter, p670. Activation of the differentiation-dependent promoter, p670, drives the expression of high levels of *E2* mRNAs. An increase in the level of the E2 protein inhibits p97 and thereby shuts down E6 and E7 expression to pave the way for cell differentiation and entry into the late stage of the viral life cycle. High levels of E2 also inhibit use of the early polyadenylation signal (pAE), allowing readthrough into the late region of the HPV-16 genome, followed by production of the late (L) mRNAs encoding L1 and L2.

NATURE REVIEWS | MICROBIOLOGY

One of the major differences that mark the low-risk HPV types from high-risk, is that the former do not typically use their E6 and E7 gene products to drive extensive cell proliferation in the basal and parabasal cell layers

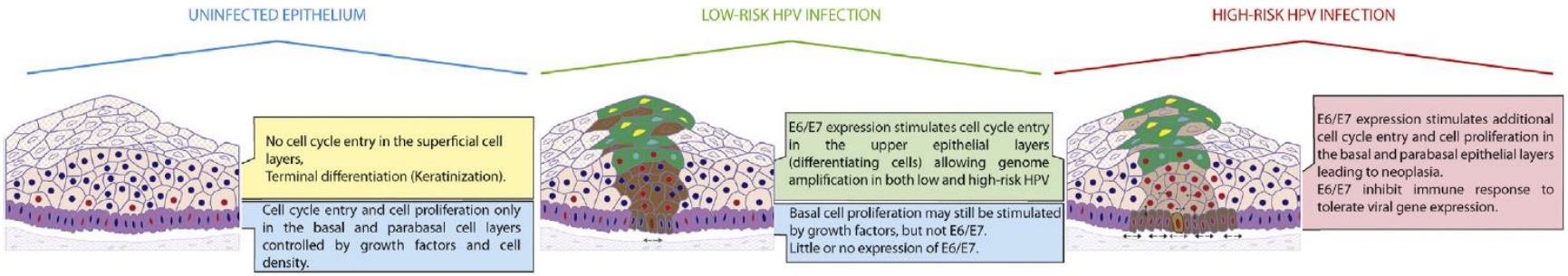


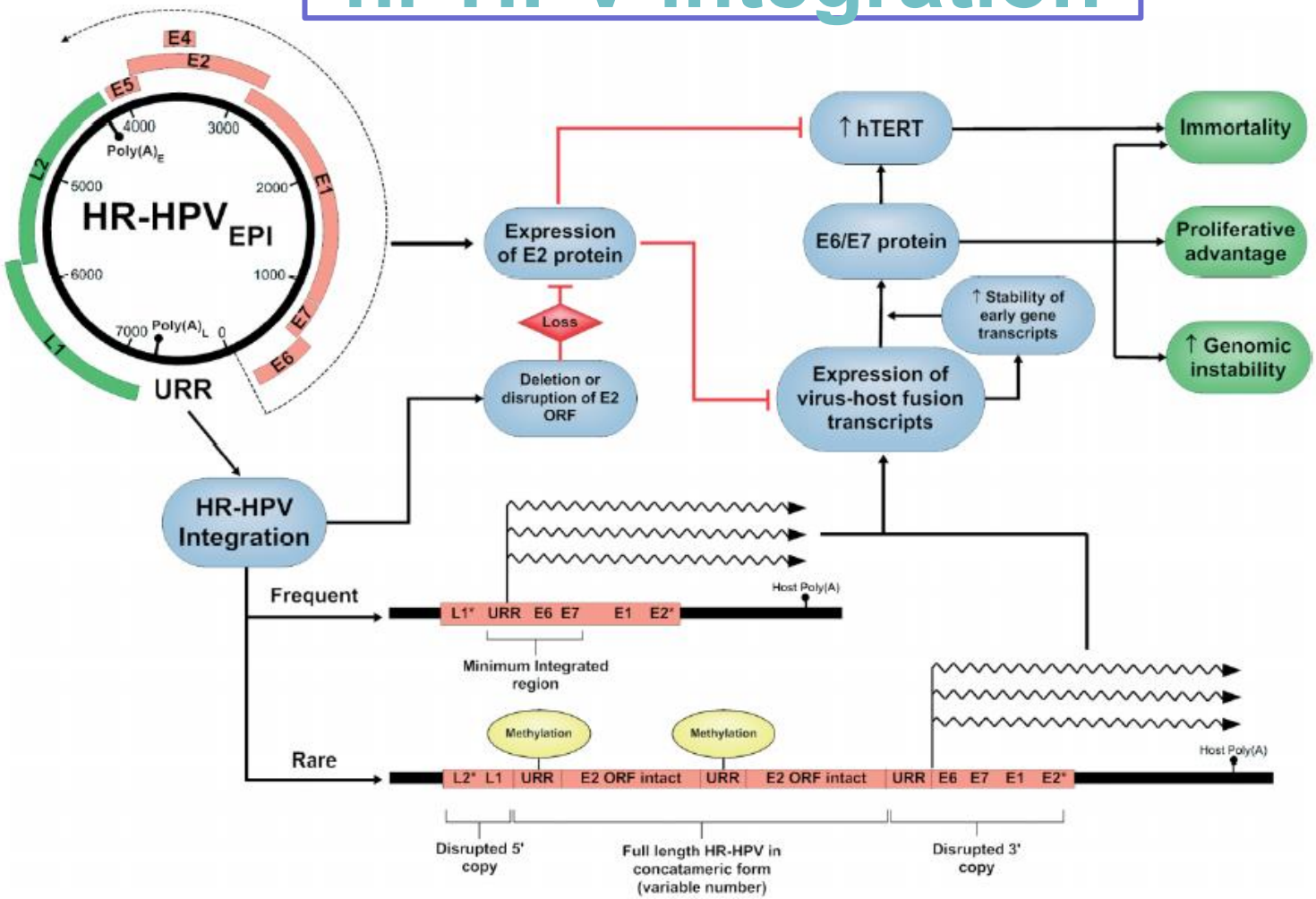
Fig. 3. The different function and expression of viral proteins underlies disease phenotype. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
(A) In uninfected epithelium, cell cycle entry (red nuclei) and cell division in the basal/parabasal cell layers is controlled by cell density and growth factors. In the suprabasal layer, cells exit the cell cycle and start to terminally differente (keratinization). (B) In lesions caused by low-risk Alpha HPV types, it is thought that basal cell proliferation is largely regulated by the presence of growth factors. The primary role of the HPV E6/E7 proteins in these lesions is to drive cell cycle entry above the basal layer in order to facilitate HPV genome amplification (red nuclei in mid epithelial layers). This is thought to be dependent on the ability of E7 to bind the Rb family member p130. Little or no E6/E7 expression is thought to occur in the basal layer, and the precise role of these proteins in basal cells is not known. E6/E7 may limit keratinocyte differentiation in the basal layer, or increase the population of infected cells to drive "Papillomatosis" and to retain the reservoir of infection. (C). In high-risk Alpha HPV infections, expression of the high-risk E6/E7 proteins in the basal layer leads to cell proliferation and evasion from host immune surveillance. In these cell populations, malignant transformation is may develop.

hr-HPV carcinogenesis

The progressive E6-mediated loss of p53 and the activationof hTERT, accompanied by a comparable degree of E7-mediated pRb inhibition, underlies many of the hrHPV's transformation and oncogenic properties.

In addition, a wide range of important biological and biochemical activities are associated with the hr E6 and E7 proteins, including the modulation of PDZ protein functions involved in cell–cell communication, the induction of chromosomal instability, and the evasion of the adaptive and innate immune responses that contribute to persistence and carcinogenesis

hr-HPV integration



HPV integration mainly occurs in fragile sites that provide clonal selection advantages. HPV integration can be classified into two types. One copy is integrated in type 1 integration, while in type 2 integration, several tandem repeats are noticed.

J Pathol 2007; **212**: 356–367

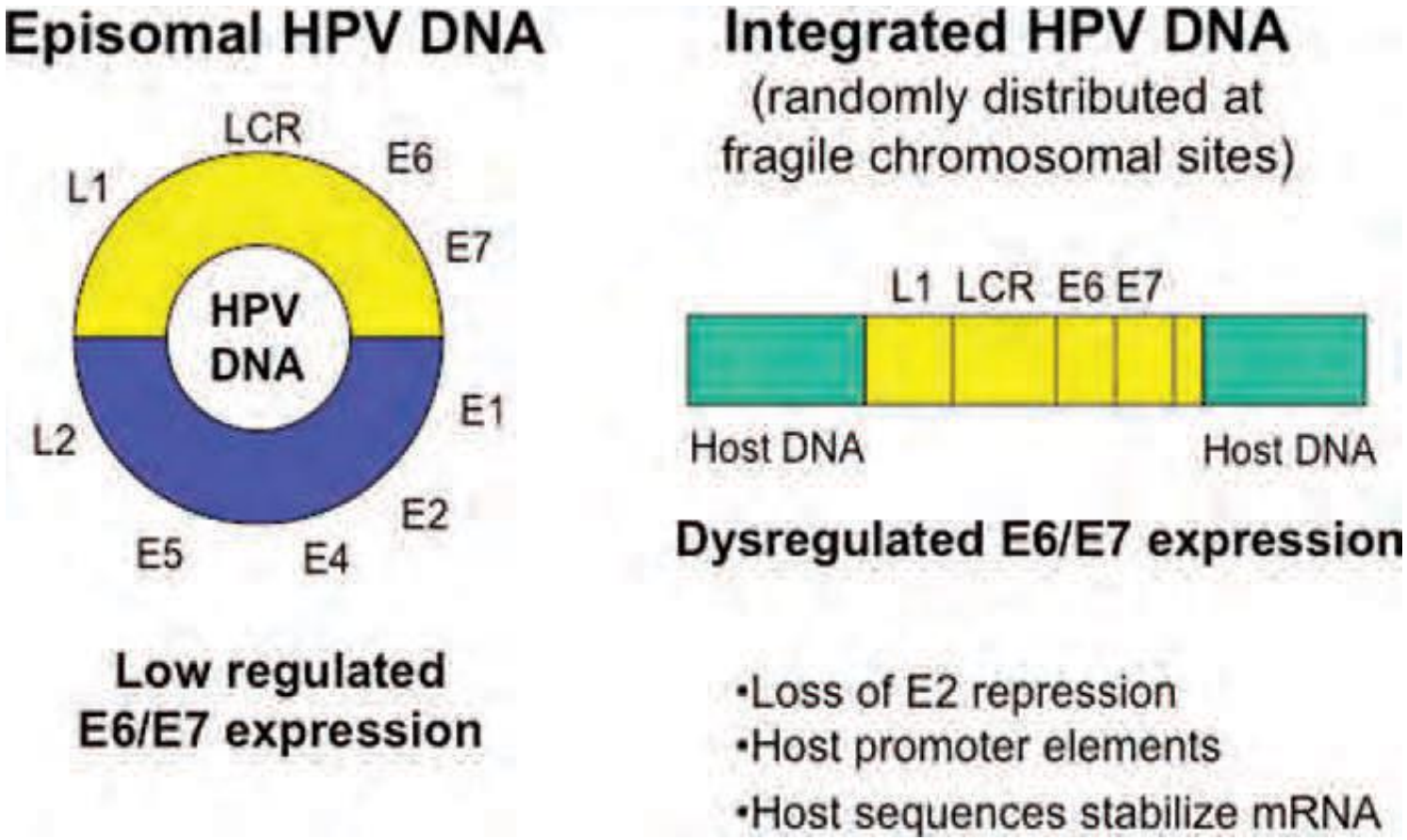
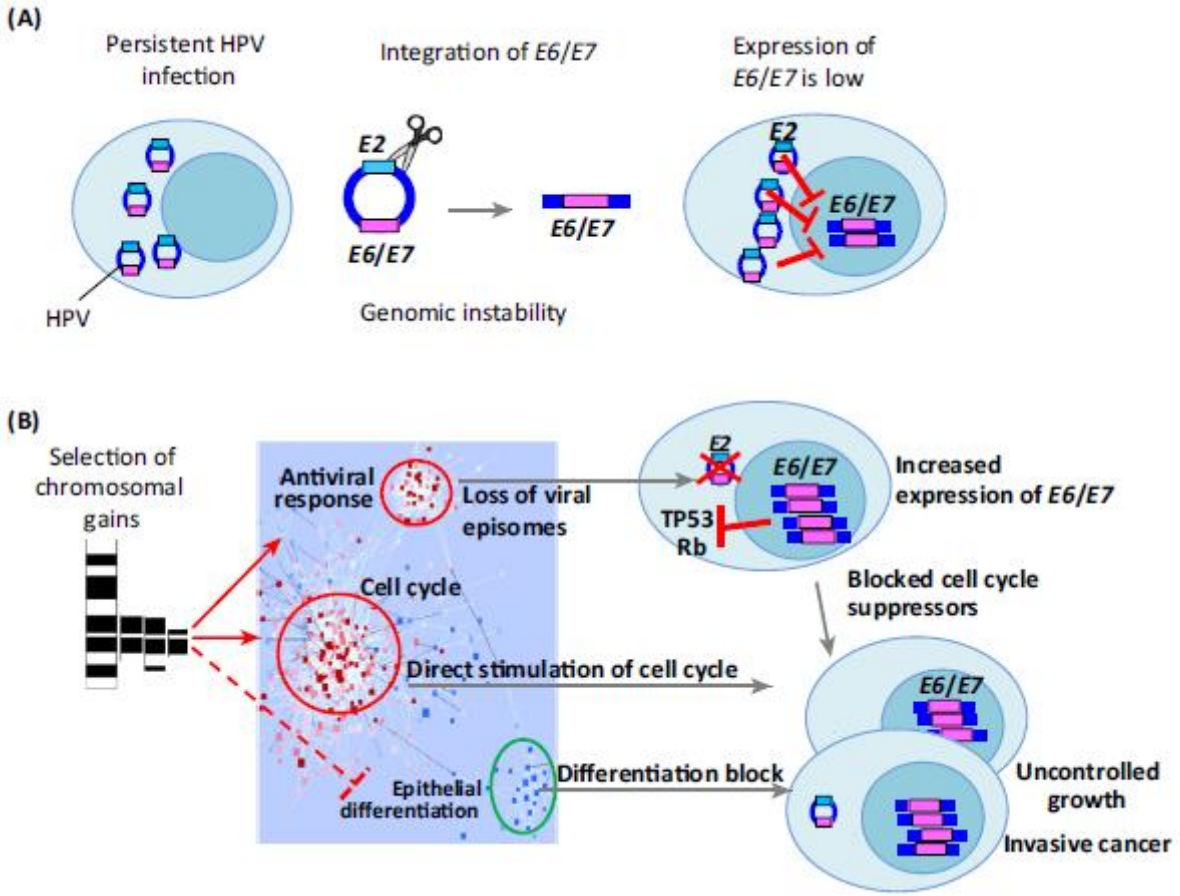


FIGuRe 54.24. Integration of HPV DNA results in high level expression of E6 and E7. In low-grade lesions, the viral genome is maintained as an episome, which is associated with low level expression of E6 and E7. Viral DNA integration into the host DNA, which occurs in high-grade dysplasia or cancer, is usually associated with deletion of portions of the viral genome, with preferential retention of the long control region (LCR) E6-E7 region and the higher levels of expression of E6 and E7, attributable to multiple factors.

A model of cervical carcinogenesis



(A) Persistent high-risk human papillomavirus (HPV) infection may result in the integration of virus into the host genome upon which E2 is disrupted. The integration leads to the increased genomic instability, however, the expression of E6/E7 oncogenes is still controlled by episomal E2. (B) Frequent chromosomal aberrations (gains) occur in the regions containing antiviral genes, which will induce the elimination of inhibitory episomal E2 and the release of E6/E7 that will block suppressors of the cell cycle [tumor protein 53 (TP53) and retinoblastoma (Rb)]. The same chromosomal gains contain drivers of the cell cycle that directly induce cell proliferation and miRNAs that may inhibit cell differentiation. All three processes act synergistically allowing the dysplastic cell to become a malignant tumor.

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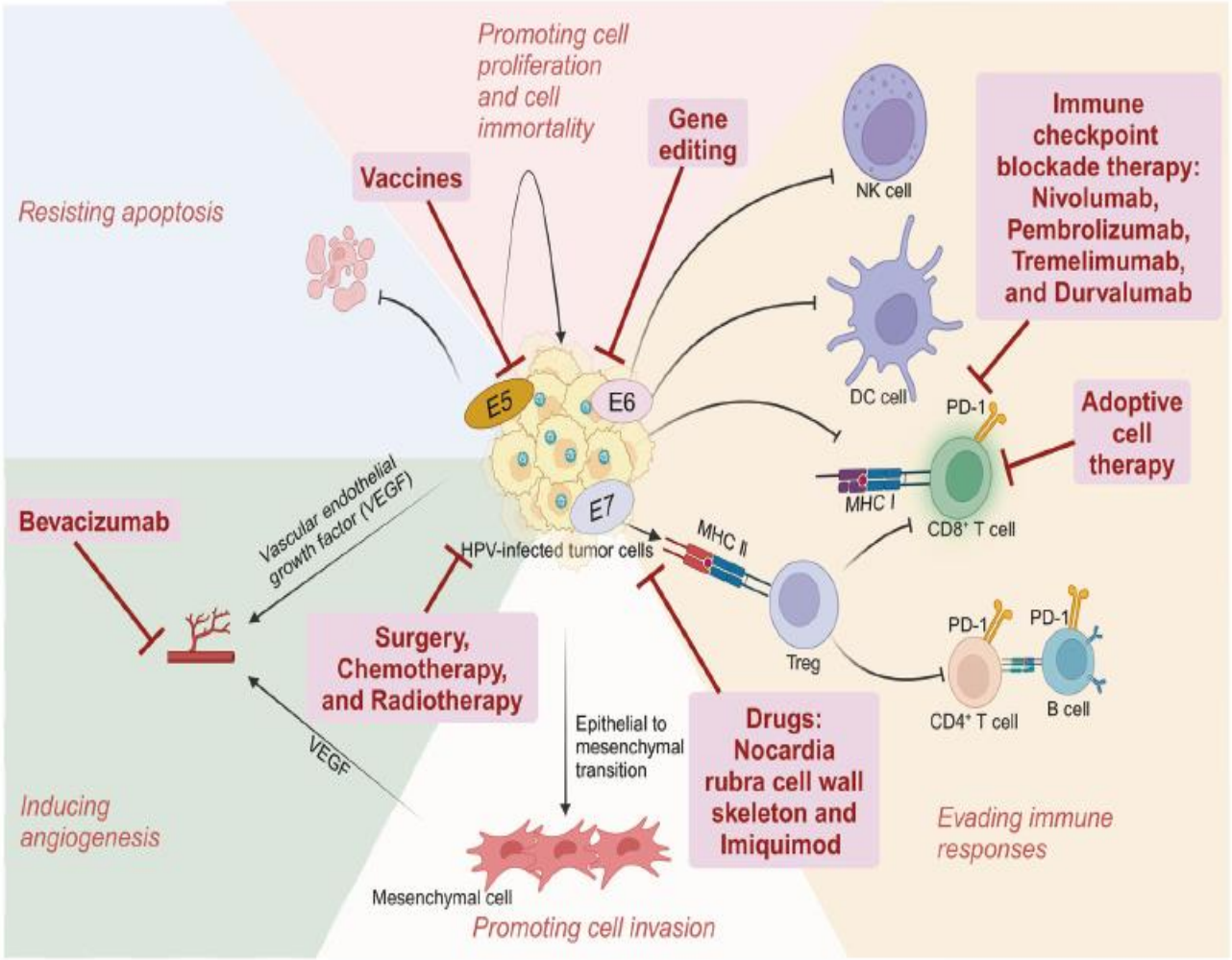
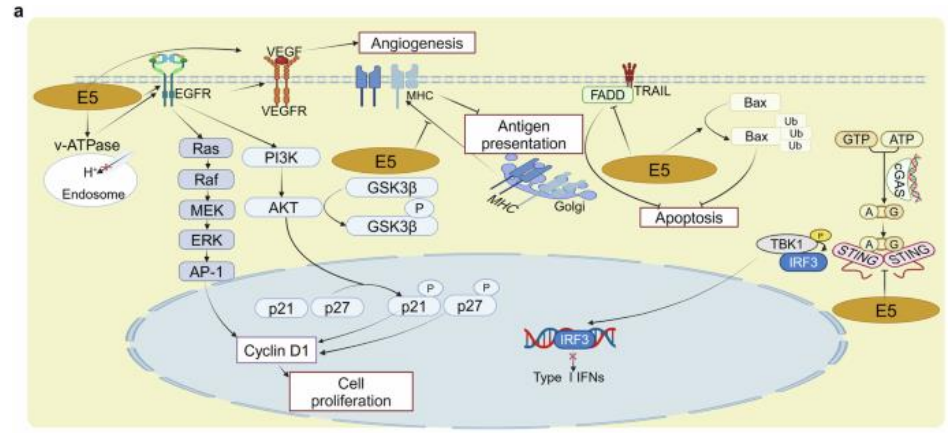
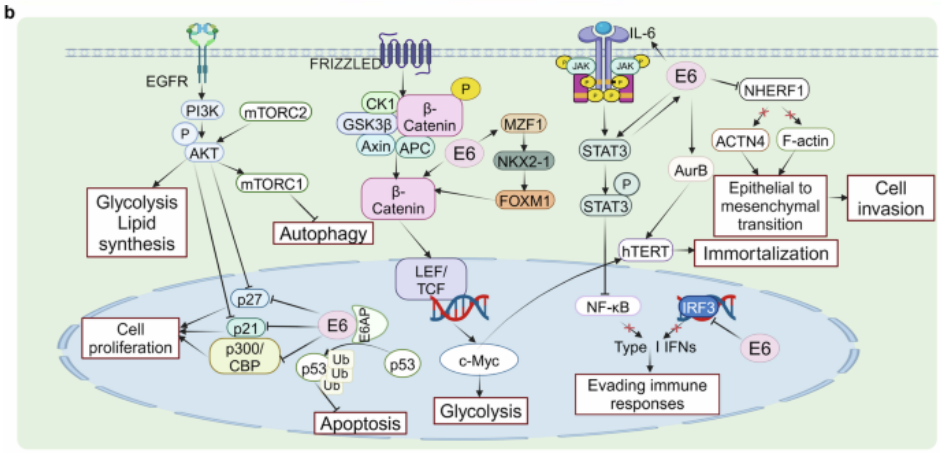


Fig. 4 Oncogenic mechanisms of hr-HPVs and therapeutic strategies for hr-HPV-related cancers. hr-HPVs contribute to the oncogenesis through various ways, including evading immune responses, promoting cell proliferation, resisting apoptosis, inducing cell immortality, fostering angiogenesis, and promoting cell invasion. Different types of therapies treating hr-HPV-related cancers have been widely applied in clinic, aiming to gain better efficacy and prognosis. This figure was created with BioRender (www.bioender.com)

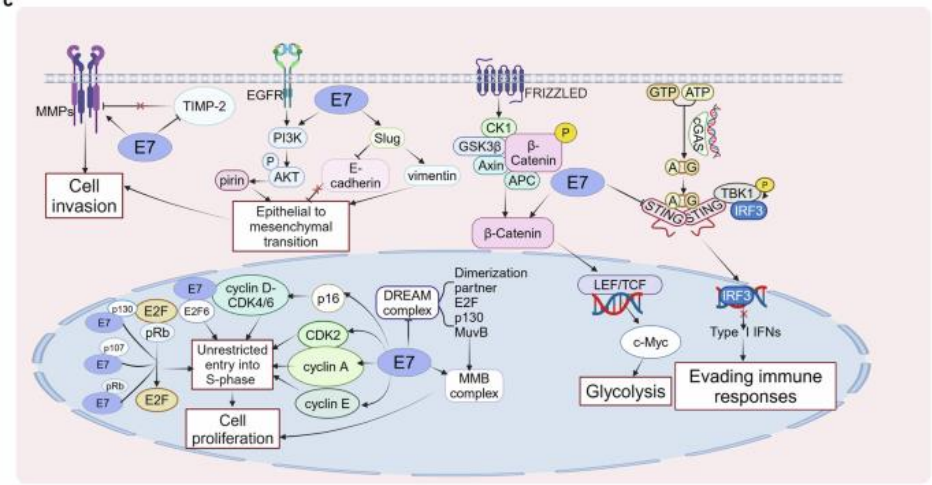
Oncogenic signaling pathways of hr-HPVs E5/E6/E7



E5 can activate epidermal growth factor receptor (EGFR) signaling. Through EGFR, E5 activates the PI3K/AKT and MAPK/ERK pathways to promote uncontrolled cell proliferation. Moreover, E5 facilitates cell migration and inhibits apoptosis and immune responses

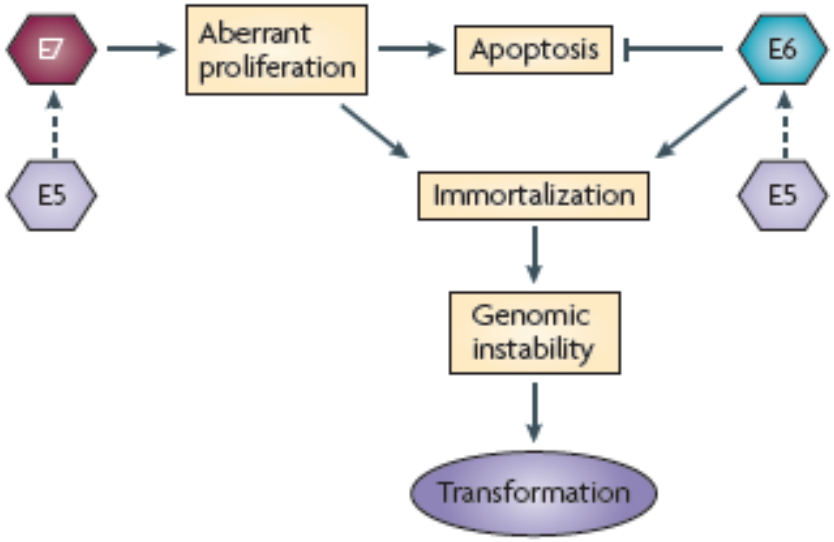


E6 Degradation of p53 promotes cell proliferation and inhibits apoptosis. E6 inhibit autophagy and immune responses and facilitate cell immortalization



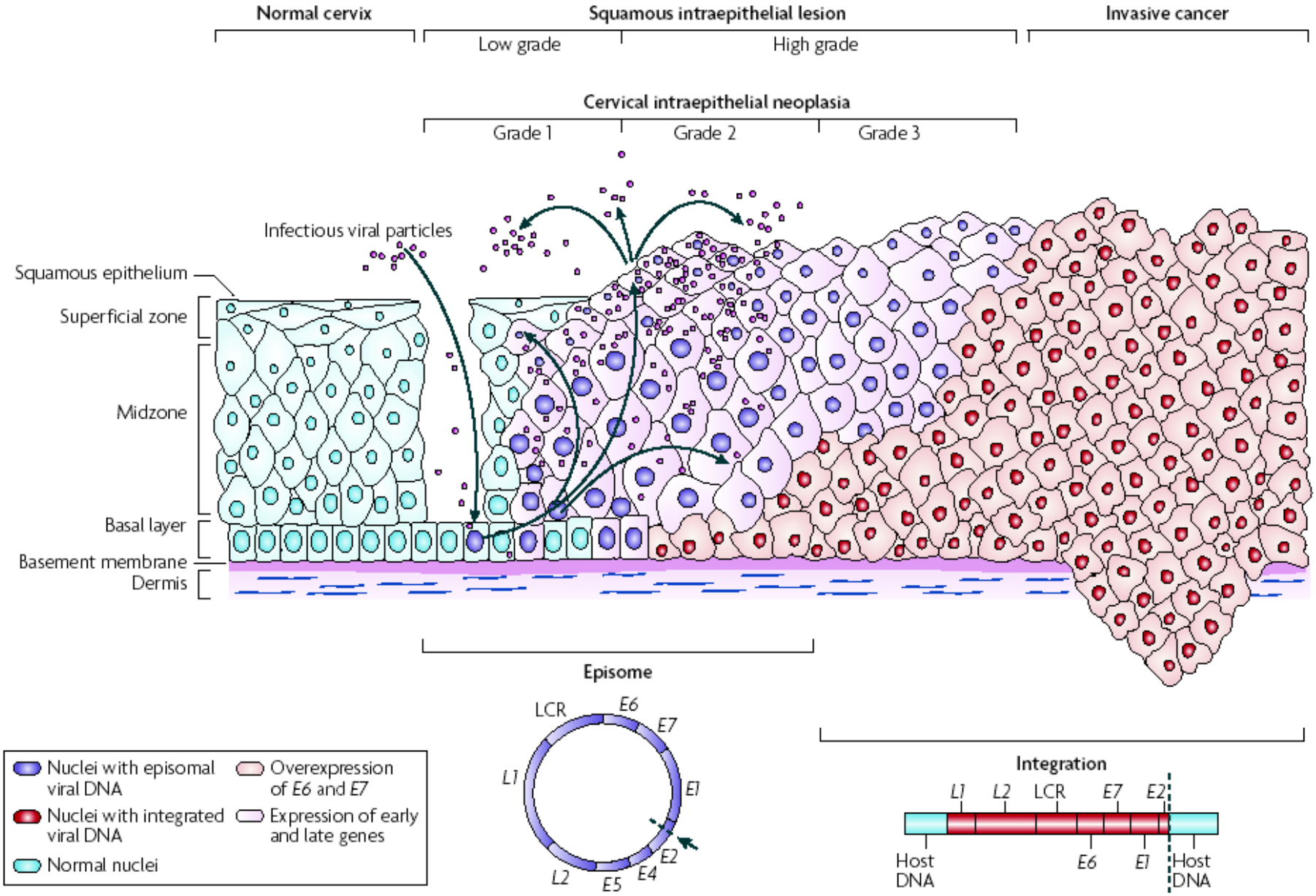
E7 binds with pRb and increase the expression of cyclins to enable cells to enter S-phase resulting in uncontrolled cell proliferationE7 boosts cell migration and hinders immune responses

Molecular mechanisms by which the human papillomavirus oncoproteins cooperate to induce cervical carcinogenesis.



The induction of hyperproliferation by the E7 protein triggers apoptosis, which is blocked by the actions of the E6 protein. The cooperative actions of E6 and E7 efficiently immortalize cells and this process is augmented by the actions of the E5 protein. The ability of E6 and E7 to target crucial regulators of proliferation, apoptosis, immortalization and genomic stability collectively promotes the emergence of a clonal population of cells with a growth advantage and an increased propensity for transformation and malignant progression

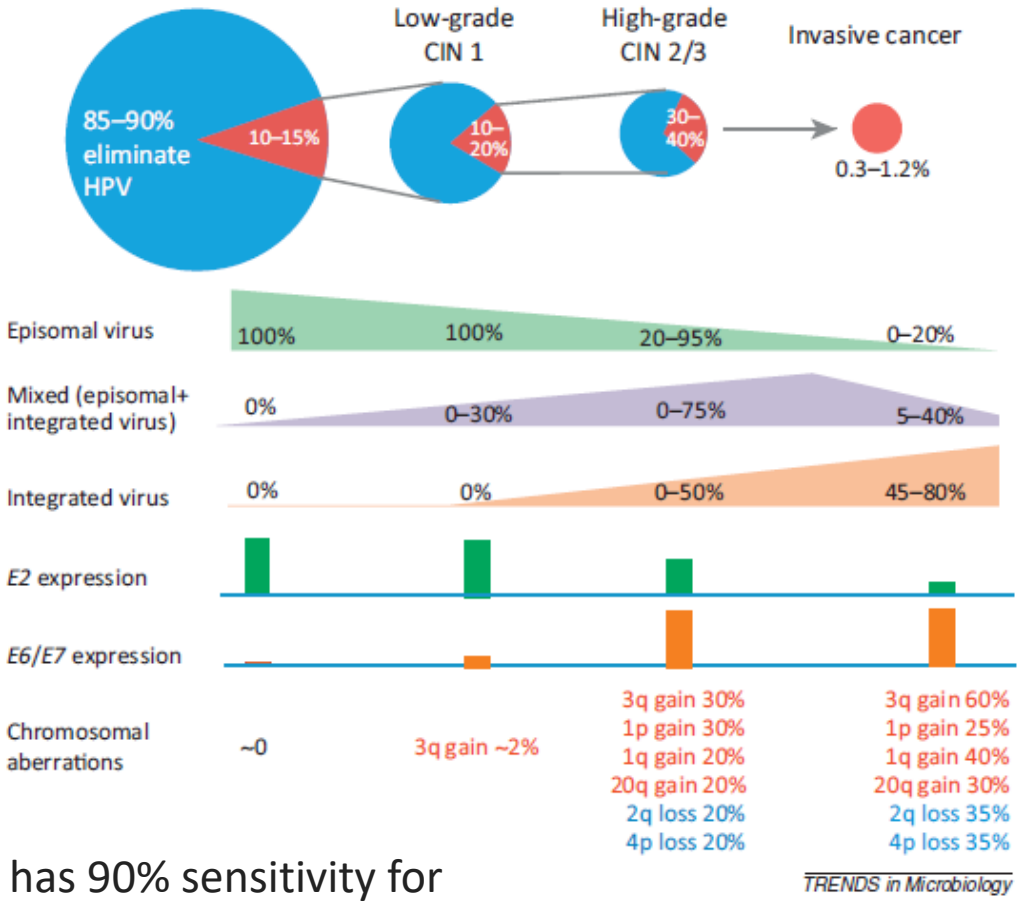
NATURE REVIEWS | CANCER



CIN: Cervical intraepithelial neoplasia

NATURE REVIEWS | CANCER

Progression of human papillomavirus (HPV) cervical infection to cancer



The cervical HPV test has 90% sensitivity for detecting precancer. HPV screening combined with cytology test is recommended once every 5 years for individuals aged 30–65 years

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HPV vaccines

2.2 Human papillomavirus vaccines

There are currently three HPV vaccines licensed in Europe: the bivalent vaccine Cervarix (GlaxoSmithKline Biologicals) that contains virus-like-particles (VLPs) of HPV types 16 and 18, the quadrivalent HPV vaccine Gardasil (Merck Sharp & Dohme – MSD) that includes VLPs of HPV types 6, 11, 16 and 18 and the nonavalent vaccine (MSD), that contains VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. All vaccines contain VLPs of HPV types 16 and 18 which are associated with 71% of all cervical cancer cases worldwide (i.e. those attributable to HPV types 16 and 18), while the nonavalent vaccine contains VLPs of additional high-risk HPV types cumulatively responsible for 89% of cervical cancer cases [23, 35].

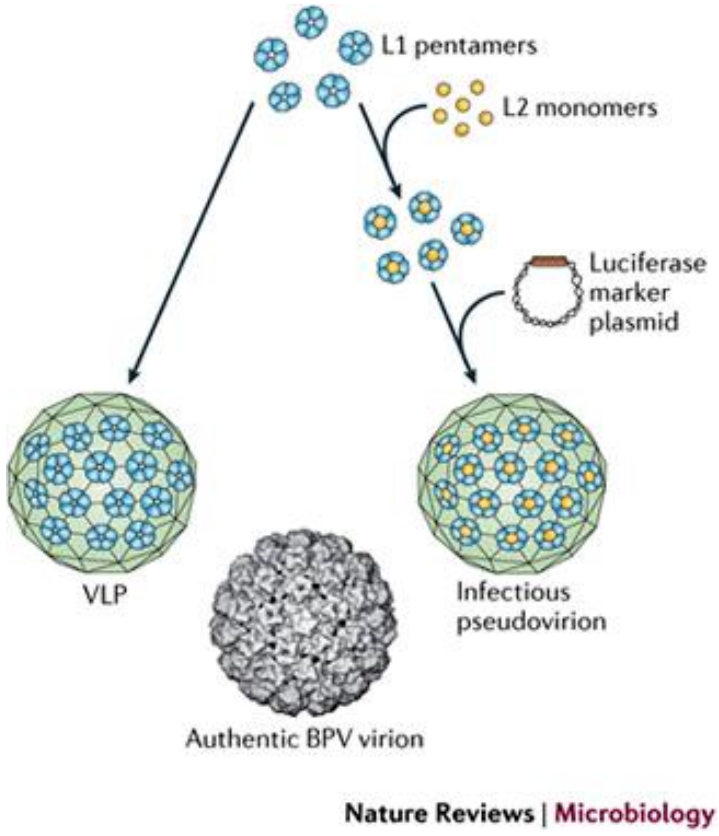
The bivalent vaccine is licensed for protection against cancer of the cervix (neck of the womb) or anus, and precancerous lesions (abnormal cell growth) in the genital area (cervix, vulva, vagina or anus), caused by certain types of human papillomavirus [36]. The quadrivalent vaccine is licensed for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic human papillomavirus (HPV) types; and for the prevention of genital warts causally related to specific HPV types [37]. The 9-valent vaccine is licensed for protection against precancerous lesions (growths) and cancers in the cervix, vulva or vagina and anus, and genital warts, caused by nine types of the human papillomavirus (HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) [38]. All vaccines are approved from the age of nine years with a recommended schedule of two doses (0–6 months) up to and including the age of 14 years for the bivalent and nonavalent vaccines, and up to and including the age of 13 years for the quadrivalent vaccine. In individuals older than the above indicated ages (15 years of age for the bivalent and 9-valent vaccines, 14 years of age for the quadrivalent vaccine), the recommended schedule is three doses administered at 0, one (or two) and six months [18, 39-41].

The duration of protection from HPV-related cervical and genital disease attributable to HPV serotypes is reported by the WHO position paper on human papillomavirus vaccines and by the EMA's Summaries of Product Characteristics (SmPC) and European Public Assessment Reports (EPAR) [18, 36-38].

https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-on-HPV-vaccination-in-EU-countries2020-03-30.pdf

HPV vaccines

Prophylactic vaccines are based on virus-like particles derived from the L1 protein and can prevent infection through the generation of L1-specific neutralizing antibodies

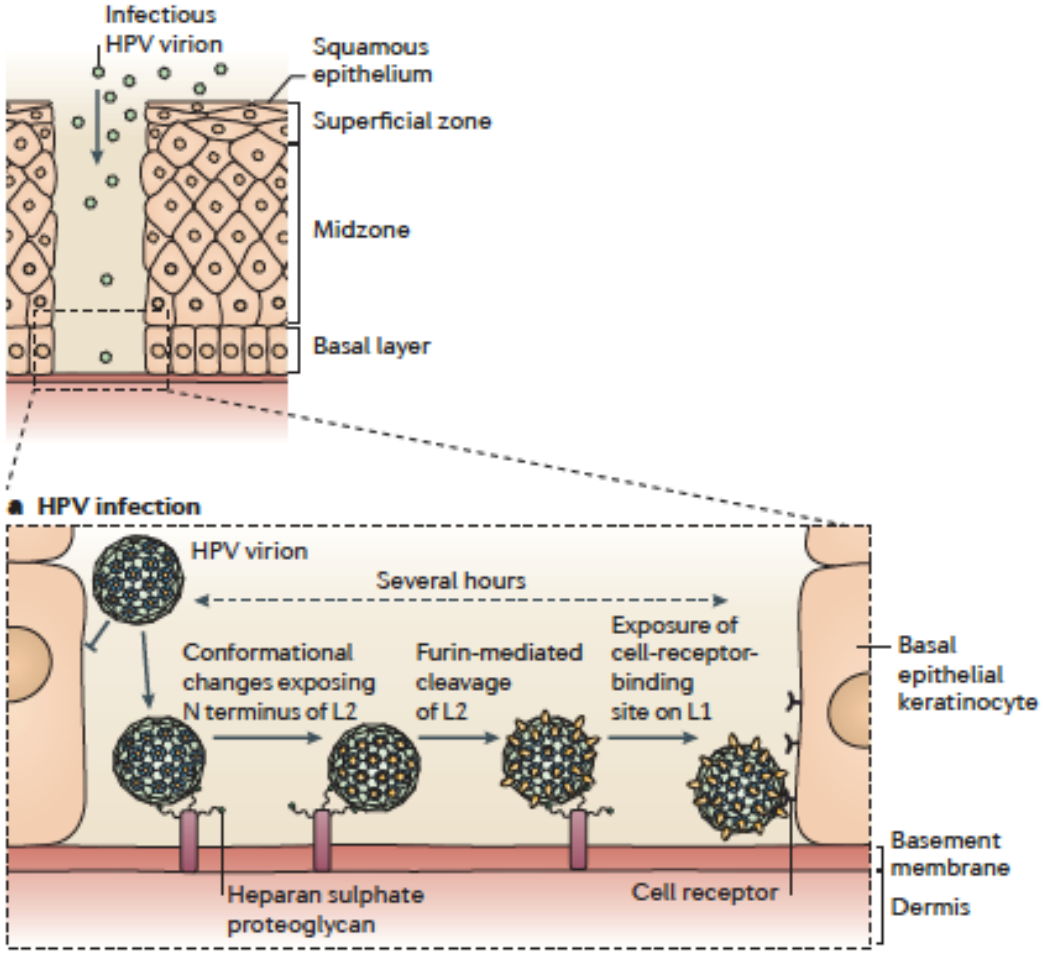


All over the world the majority of cervical cancers are related to two types, HPV 16 (~55%) and HPV 18 (~15%). The contributions of HPV 16 and HPV 18 to high-grade CIN and to HPV-related vulvar, vaginal and anal cancers are similar to those found in cervical cancer. HPV 6, 11, 16 and 18 together cause ~35% of CIN 1 cases. HPV 6 and HPV 11 cause approximately 90% of genital warts and RRP (recurrent respiratory papillomatosis) and 10% and 20% of CIN 1 lesions, respectively, but are not associated with cervical or anal carcinoma

HPV vaccines

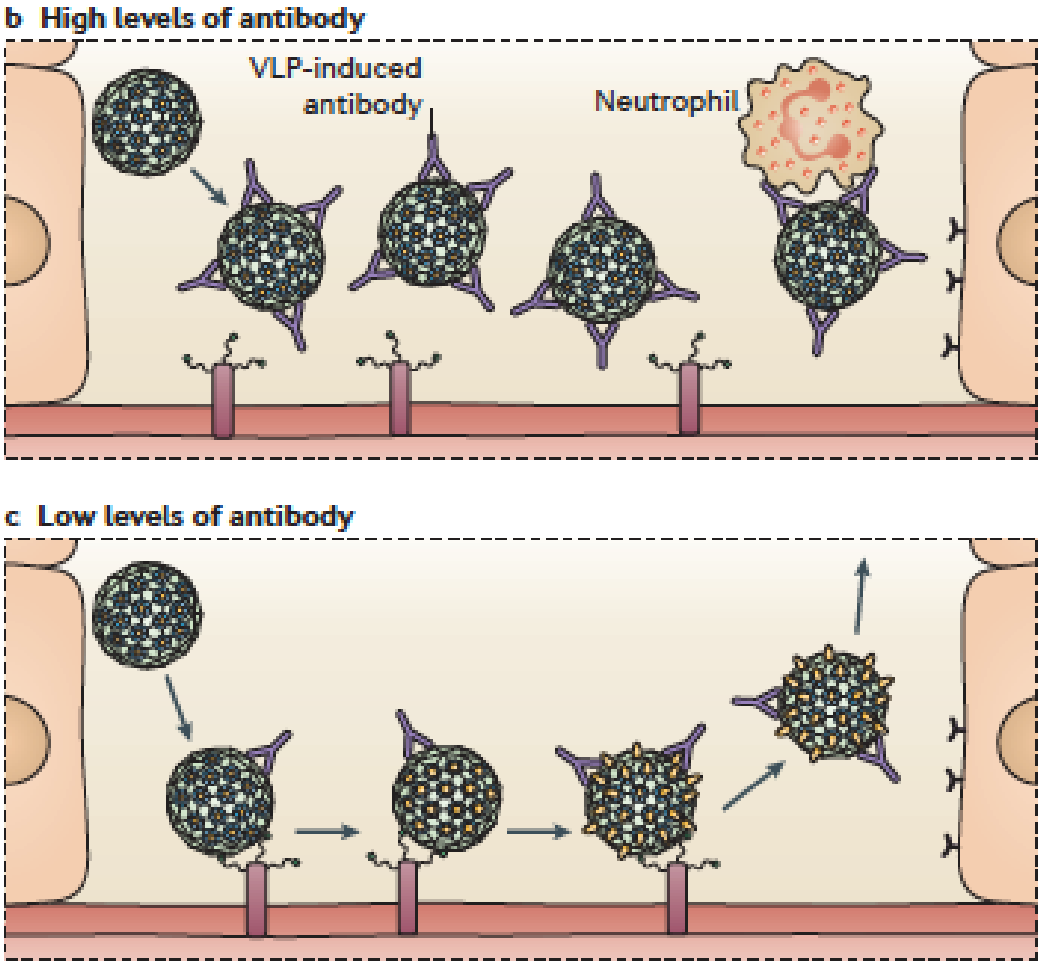
Name	Valents	Targets	Adjuvants	Expression system	Current progress	Eligible age and sex	References
Gardasil	4	HPV-16/18/6/11	Amorphous aluminum hydroxy phosphate sulfate	Recombinant Saccharomyces cerevisiae, Yeast	Approved in 2006	Females aged 9–26	211
Cervarix	2	HPV-16/18	3-0-Desacyl-4′-monophosphoryl lipid A, Aluminum hydroxide salt	Trichoplusia ni insect cells, Baculovirus	Approved in 2009	Females aged 9–25	216
Gardasil-9	9	HPV-16/18/31/33/45/52/58/6/11	Amorphous aluminum hydroxy phosphate sulfate	Recombinant Saccharomyces cerevisiae, Yeast	Approved in 2014	Females aged 9–45	212

HPV vaccines



a | Human papillomavirus (HPV) virions cannot bind or infect intact squamous epithelium.
They must first bind the basement membrane via heparan sulphate proteoglycans. Then, in a process that takes several hours, they must undergo a series of conformational changes, beginning with furin-mediated cleavage of the minor capsid protein, L2 (yellow), to expose their receptor-binding site on the major capsid protein, L1 (blue), followed by binding to the cell surface receptor and infection of basal epithelial keratinocytes.

HPV vaccines



b | High levels of virus-like particle (VLP)-induced antibodies prevent attachment of the virus to the basement membrane, and this in turn prevents the conformational changes required for cell surface binding. Virus–antibody complexes associate with neutrophils in the cervicovaginal mucus.

c | Low levels of VLP-induced antibodies permit basement membrane attachment and the conformational changes leading to furin-mediated L2 cleavage, but they prevent a stable association of the virion with the cell surface.

HPV VACCINAZIONE E PREVENZIONE - COSA SAPERE

L'HPV (Human Papilloma Virus) è un virus ad altissima diffusione che si trasmette per via sessuale attraverso la cute e le mucose. L'infezione è assai comune nei giovani sessualmente attivi, è asintomatica e nella maggior parte dei casi regredisce da sola entro un paio di anni.

I problemi insorgono, sia negli uomini che nelle donne, quando l'infezione persiste e il virus permane nelle mucose rischiando di dar luogo a differenti patologie: da malattie benigne, come i **condilomi genitali**, sino a **tumori che si possono presentare in sede genitale (vulva, vagina, pene), extra genitale (orofaringe e ano) o nella cervice uterina.**

L'infezione da HPV è molto comune, soprattutto fra le persone giovani, e **il preservativo non garantisce una protezione al 100%, seppure riduca molto i rischi di contagio da questa come da altre infezioni a trasmissione sessuale**. Infatti, il profilattico non protegge completamente poiché il virus può infettare anche la cute non protetta dal preservativo.

L'unico metodo per prevenire l'infezione da HPV è la vaccinazione.

È importante sapere che la vaccinazione è offerta gratuitamente a tutti i ragazzi e le ragazze a partire dal compimento dell'undicesimo anno d'età.

Nel Lazio, per contrastare la diffusione del Papilloma virus, è stato introdotto nel 2007-2008 **un vaccino anti HPV che viene offerto gratuitamente presso i Centri Vaccinali delle ASL, con le seguenti modalità**:

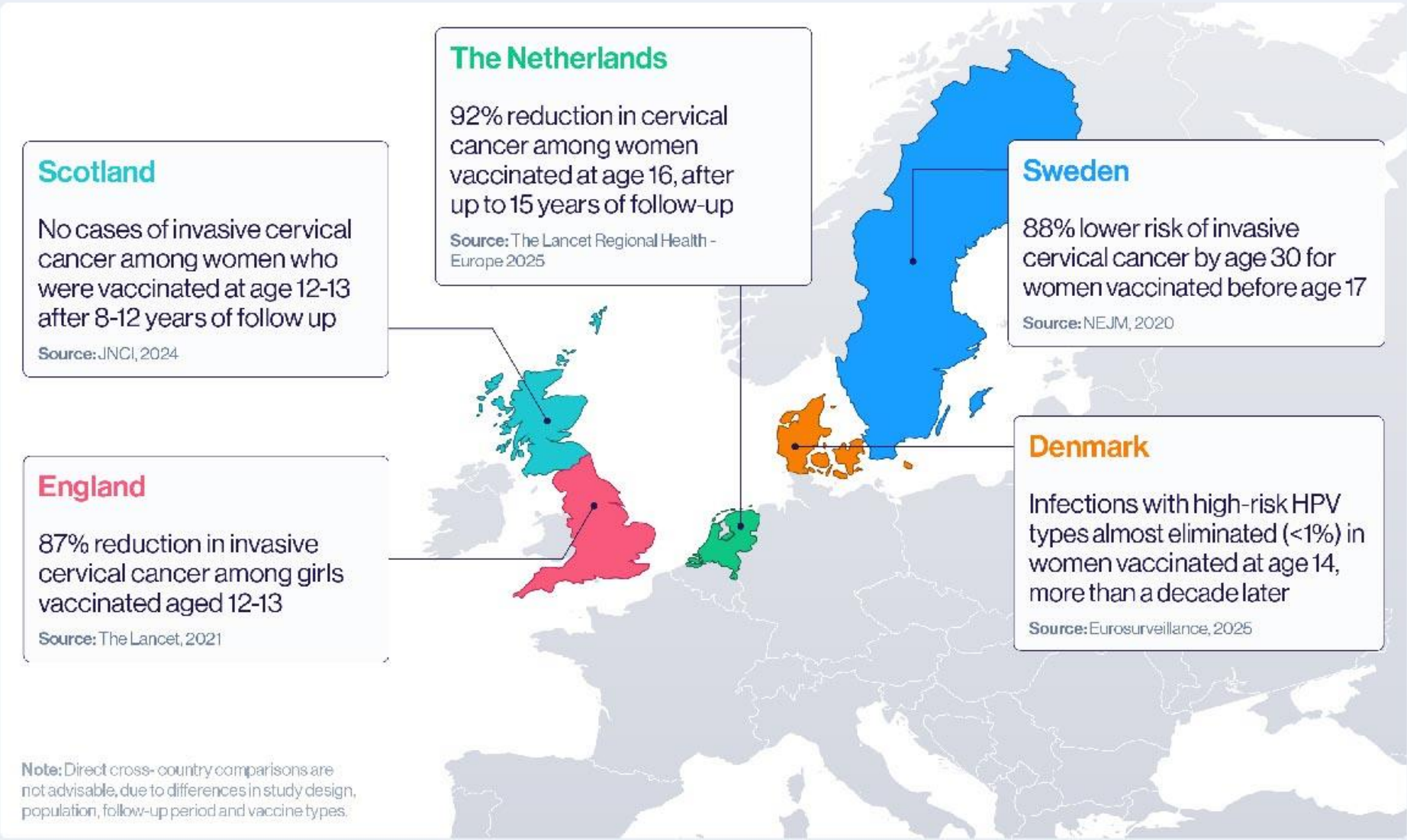
- a maschi e femmine al compimento degli 11 anni. Per i maschi l'offerta gratuita è valida per i nati a partire dal 2006. Il diritto all'offerta gratuita si mantiene fino ai 26 anni;
- ai soggetti con infezione da HIV;
- a tutte le 25enni non vaccinate, in occasione della chiamata attiva per l'offerta dello screening per la diagnosi precoce del carcinoma della cervice uterina;
- a tutte le donne già trattate per lesioni pre-cancerose;
- ai soggetti a rischio per determinati comportamenti o condizioni, includendo gli uomini che fanno sesso con uomini, ai soggetti immunocompromessi e a coloro che devono iniziare una terapia con immunomodulatori e immunosoppressori.

Per uomini e donne che non rientrano nell'offerta gratuita, è possibile comunque effettuare la vaccinazione presso i Centri Vaccinali delle ASL, pagando il ciclo vaccinale (3 dosi) a prezzo agevolato e non al prezzo di vendita al pubblico, con uno sconto superiore al 60%.

Il vaccino utilizzato nel Lazio è il vaccino 9-valente che protegge da 9 tipi di HPV. Ad esempio dai tipi 6 e 11 (a basso rischio oncogeno) che causano oltre il 90% dei condilomi (verruche genitali) ma anche dai tipi 16 e 18 responsabili di oltre il 70% dei tumori del collo dell'utero nelle casistiche di tutto il mondo.

Real-world efficacy of HPV vaccines

Across countries with long-running HPV vaccination programmes, real-world data show strong reductions in cervical cancer and precancer – particularly when vaccination occurs before age 17.



Scotland

No cases of invasive cervical cancer among women who were vaccinated at age 12-13 after 8-12 years of follow up

Source: JNCI, 2024

The Netherlands

92% reduction in cervical cancer among women vaccinated at age 16, after up to 15 years of follow-up

Source: The Lancet Regional Health - Europe 2025

Sweden

88% lower risk of invasive cervical cancer by age 30 for women vaccinated before age 17

Source: NEJM, 2020

England

87% reduction in invasive cervical cancer among girls vaccinated aged 12-13

Source: The Lancet, 2021

Denmark

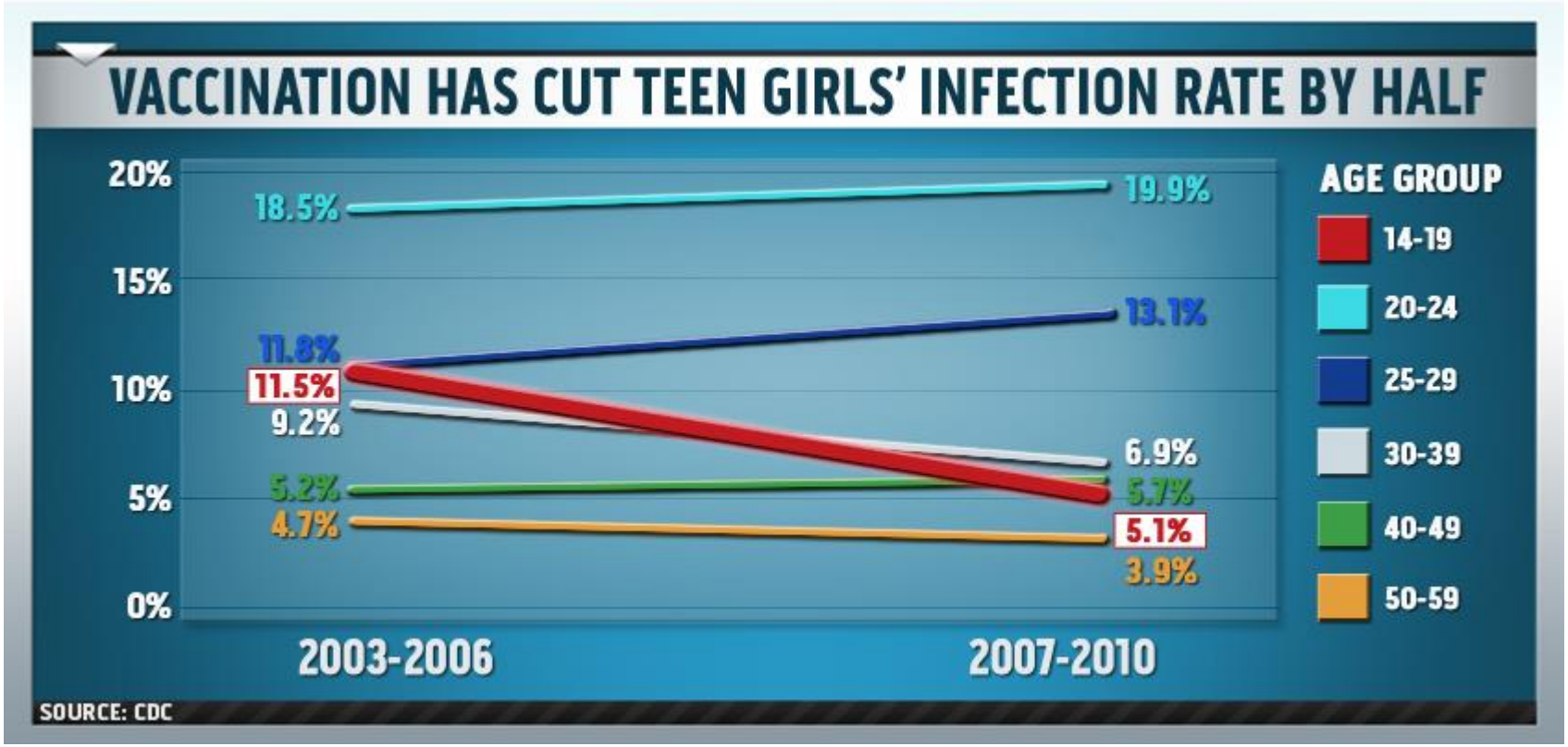
Infections with high-risk HPV types almost eliminated (<1%) in women vaccinated at age 14, more than a decade later

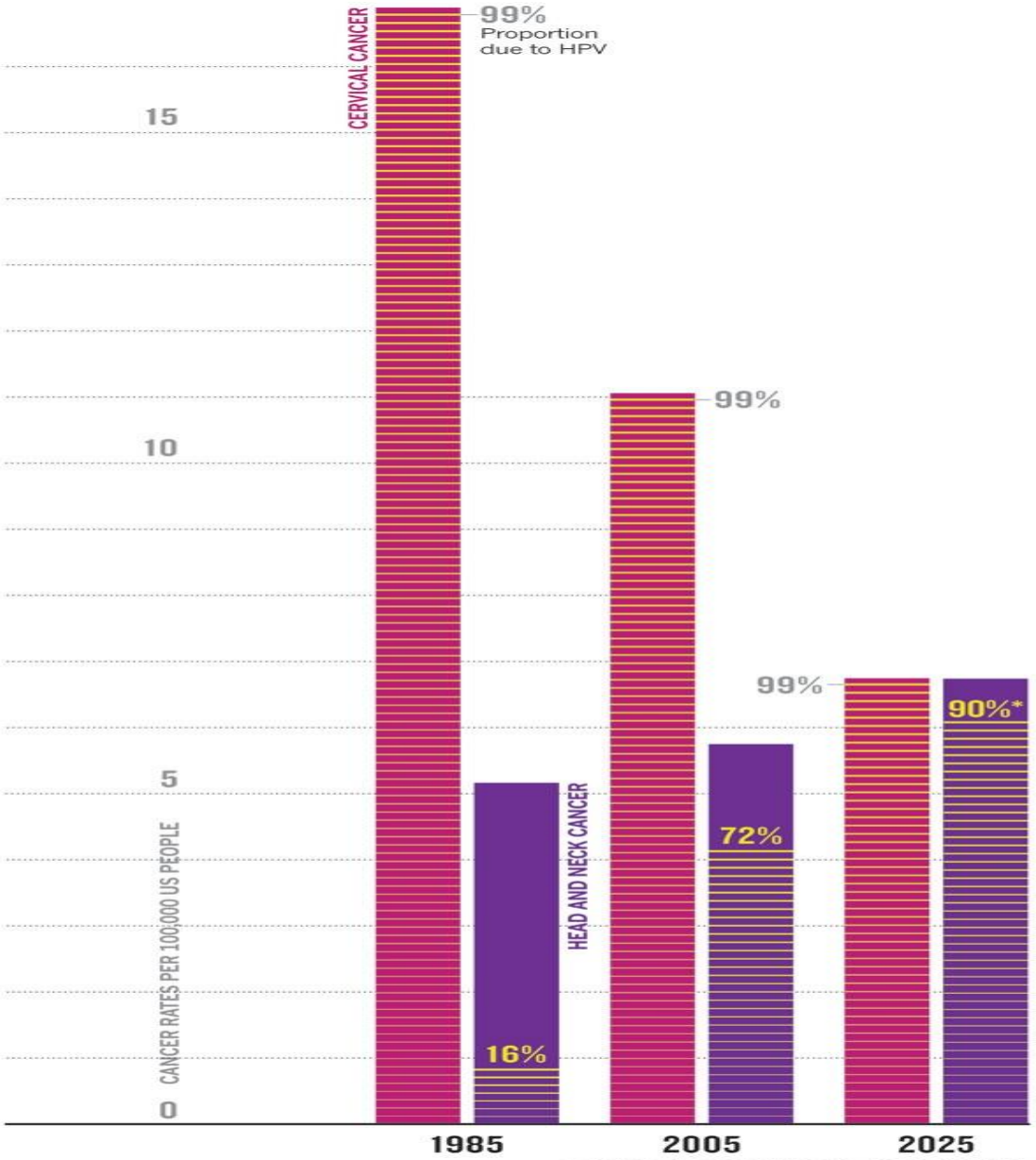
Source: Eurosurveillance, 2025

Note: Direct cross- country comparisons are not advisable, due to differences in study design, population, follow-up period and vaccine types.

Gardasil HPV types 6, 11, 16, and 18

Cervix HPV types 16, and 18





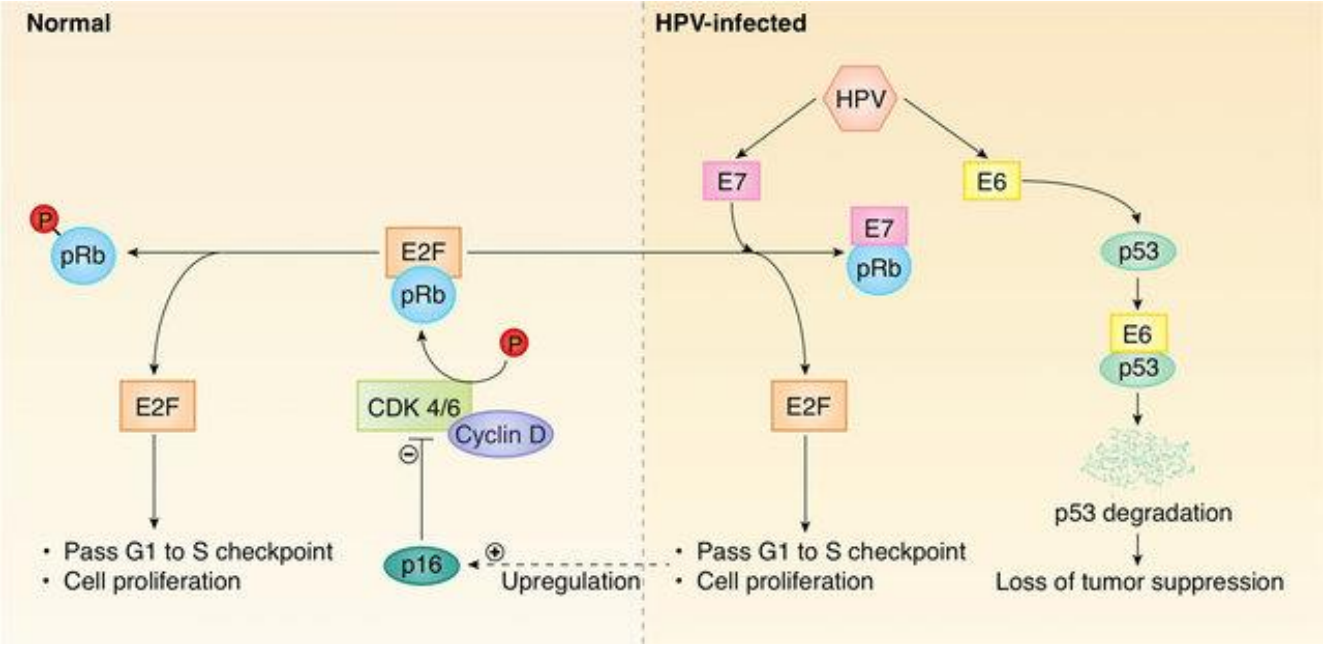
EMERGING THREAT

Rates of head and neck cancer (purple) have risen — and they are set to grow further. An increasing proportion of cases is caused by human papillomavirus (HPV, yellow). At the same time, rates of cervical cancer (red; nearly all caused by HPV) have declined, owing to increased screening.

*Estimate based on clinical observations

	HPV-positive HNSCC	HPV negative SCC
Epidemiology		
Incidence	Increasing	Decreasing
Demographic background		
Age	Younger	Older
Socioeconomic status	Higher	Lower
Risk factors	High-risk sexual practices, marijuana exposure	Tobacco and alcohol exposure
Molecular etiology		
P53 pathway	E6-mediated degradation of cellular p53	TP53 genetic mutation
RB pathway	E7-mediated degradation of Rb	17p LOH, hypermethylation of p16INK4A promoter
P16 expression	Overexpression	Decreased expression
Clinical characteristics		
Location of primary tumor	Oropharynx (palatal and lingual tonsils)	All head and neck sites
Survival	Better	Worse
Response to chemoradiation	Better	Worse
Tumor recurrence	Lower risk	Higher risk

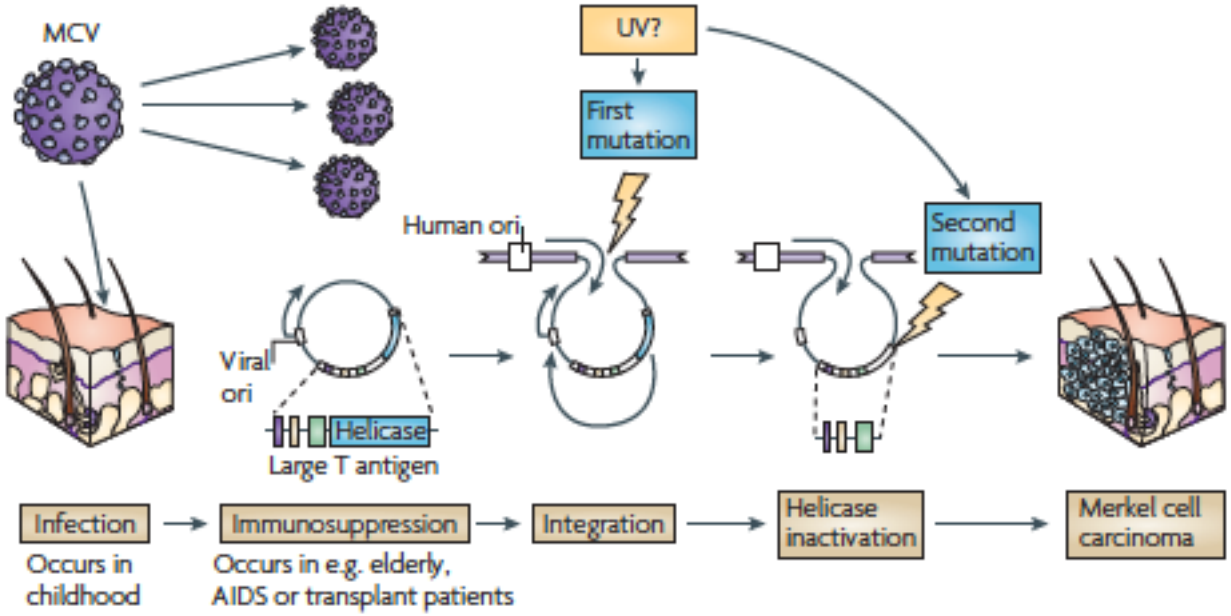
Human papillomavirus (HPV)+ cancer increases expression of p16



Left panel: Normal, uninfected cell. Cyclin D-cyclin dependent kinase (CDK) 4/6 complex initiates phosphorylation of the tumor suppressor protein, pRb. The hyperphosphorylation of pRb leads to release of the transcription factor E2F into its active state, which drives the expression of downstream gene products allowing the cell to transition from the G1 to S phase. As a cyclin kinase inhibitor, p16 is a tumor suppressor and negative regulator of the cyclin D-CDK 4/6 complex. Right panel: HPV infected cell. When the transcription factor E2F is bound to pRb, it remains inactive. The overexpression of the E7 oncoprotein by high-risk HPV subtypes disrupts the E2F-pRb complex by displacing E2F and binding to pRb. The subsequent release of E2F into its active state drives the expression of downstream gene products, allowing the cell to transition from the G1 to S phase. In a regulatory feedback attempt to inhibit further cell proliferation, p16 is upregulated, and thus can be a surrogate for HPV+ tumors. The overexpression E6 oncoprotein acts via a separate mechanism. E6 binds to the tumor suppressor protein, p53, and ultimately leads to degradation of p53. Loss of the regulatory function of p53 causes aberrant propagation of the cell cycle and prevents apoptosis.

Cells 2020, 9, 500; doi:10.3390/cells9020500

The molecular evolution of a human tumour virus



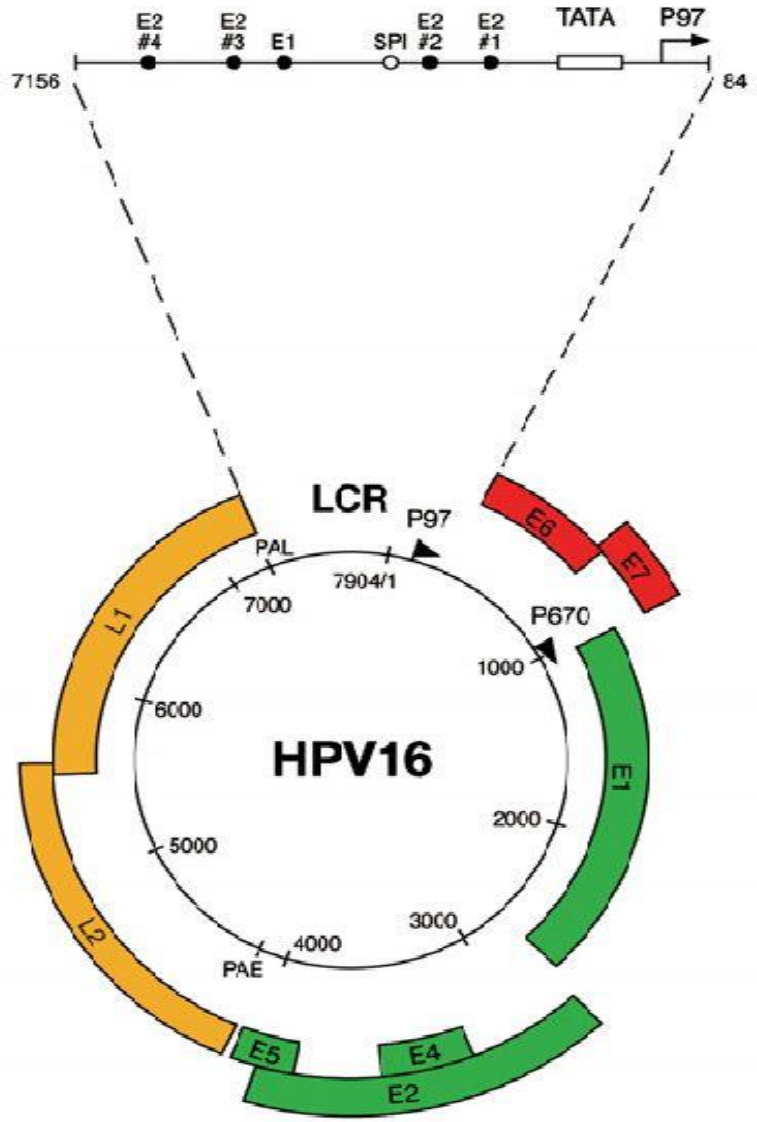
Merkel cell polyomavirus (MCV), which has tumour-specific truncation mutations, illustrates common features among the human tumour viruses involving immunity, virus replication and tumour suppressor targeting. Although MCV is a common infection, loss of immune surveillance through ageing, AIDS or transplantation and subsequent treatment with immunosuppressive drugs may lead to resurgent MCV replication in skin cells. If a rare integration mutation into the host cell genome occurs, the MCV T antigen can activate independent DNA replication from the integrated viral origin that will cause DNA strand breaks in the proto-tumour cell. A second mutation that truncates the T antigen, eliminating its viral replication functions but sparing its RB1 tumour suppressor targeting domains, is required for the survival of the nascent Merkel tumour cell. Exposure to sunlight (possibly ultraviolet (UV) irradiation) and other environmental mutagens may enhance the sequential mutation events that turn this asymptomatic viral infection into a cancer virus.

NATURE REVIEWS | CANCER 2010

P R I N C I P L E S
Cellular transformation and oncogenesis

- Members of DNA and RNA virus families cause or contribute to 20% of human cancers.
- Cancer is a disease of unregulated cell division, which can be the result of inherited mutations; exposure to environmental carcinogens; or infection with pathogens, including viruses.
- Immortalization, transformation, and oncogenesis are distinct states, but are part of a continuum.
- Transformed cells are distinguished from normal cells by their immortality, loss of contact inhibition, and often production of their own growth factors.
- Usually, transformation is not required for viral reproduction.

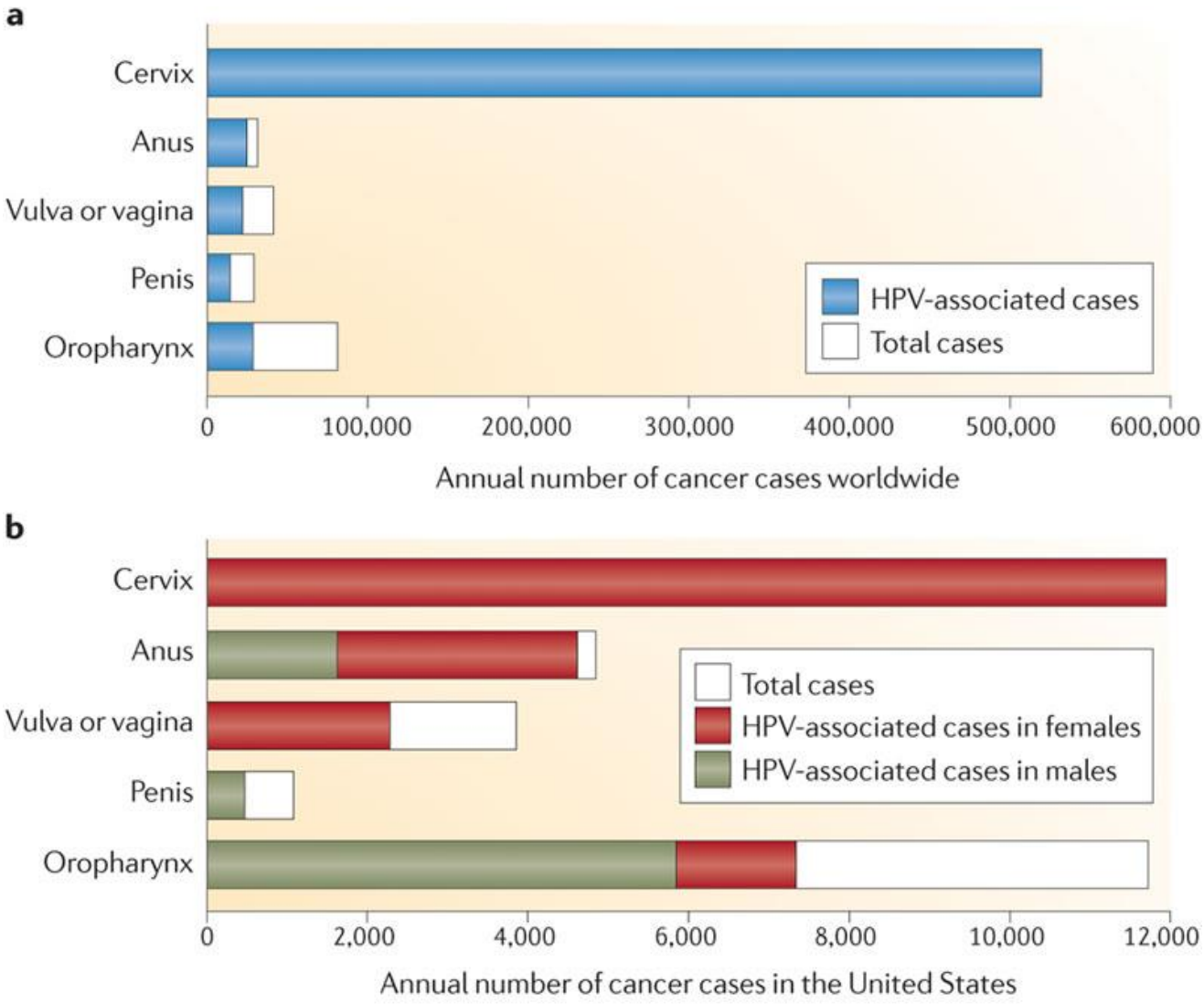
Papillomavirus genome



The human papillomavirus type 16 (HPV-16) genome is nearly 8 kb in size and exists as a circular episome in the nucleus of the infected cell. The viral genome encodes the so-called early (E) genes, designated ***E1***–***E7***, and the late (L) genes ***L1*** and ***L2***. The non-protein-coding sequence between the ***L1*** stop codon and the ***E6*** AUG is termed the long control region (LCR) and contains the origin of DNA replication (***ori***) and the early viral promoter, p97

Clinical Science (2006)

Prevalence of human papillomavirus-associated cancers



Nature Reviews | Microbiology

Significance of HR-HPV integration events detected in cervical carcinomas. The majority of integrants that derive from insertion of HR-HPV episomes (HR-HPVEPI) into the host genome are detected at low copy number and retain at least the E6 and E7 oncogenes together with the viral upstream regulatory region (URR). Integrant copy number is often increased through amplification of viral and flanking host DNA. Typical integrants also have complete or partial disruption of the open reading frame (ORF) for E2, the viral gene that regulates viral replication and which, by binding sites in the URR, can inhibit expression from integrated virus. Disruption of the viral genome also dissociates viral early (E) gene transcription from the viral early polyadenylation signal, leading to use of host poly(A) signals and transcription of virus–host fusion transcripts with a longer half life. These events lead to increased levels of E6 and E7 proteins, which, together with loss of additional inhibitory effects of E2, result in cellular immortalization, deregulated proliferation, and increased genomic instability.
More rarely, concatameric integrants are observed, where viral copies (including intact E2) are arranged in a head-to-tail fashion with partially deleted copies at the 5 and 3 ends.
The dashed line in the figure represents transcription from the early promoter of HR-HPVEPI (P97 in HPV16)

Cancer Hallmark Activation by Human Oncoviruses

A

Human Oncovirus Replication and Persistence Strategies

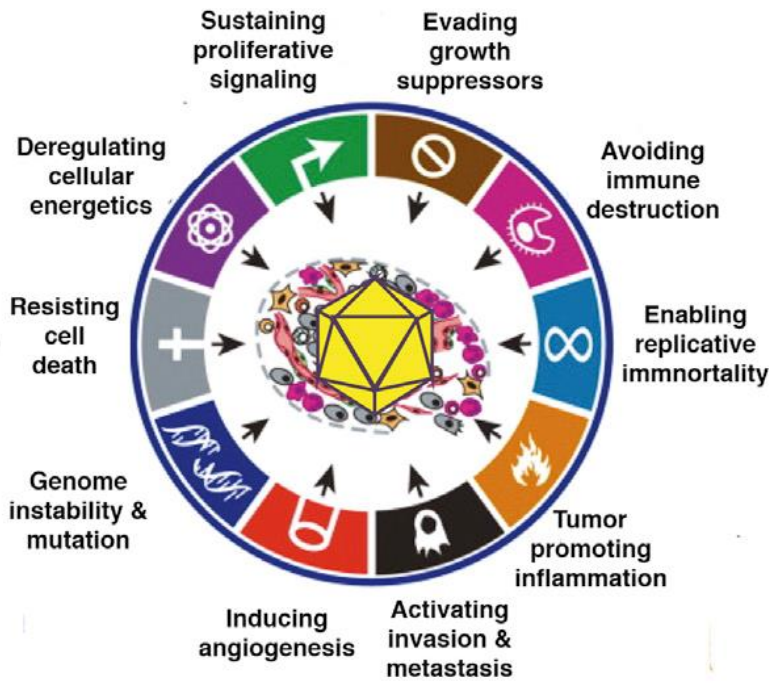
Find/ Create conditions for replication
- Induce the Cell cycle
- Metabolic reprogramming
- Inducing angiogenesis

Ensure correct replication
- Recruit or inhibit DDR

Maximize virus production
- prevent apoptosis until virion matures
- Immune evasion

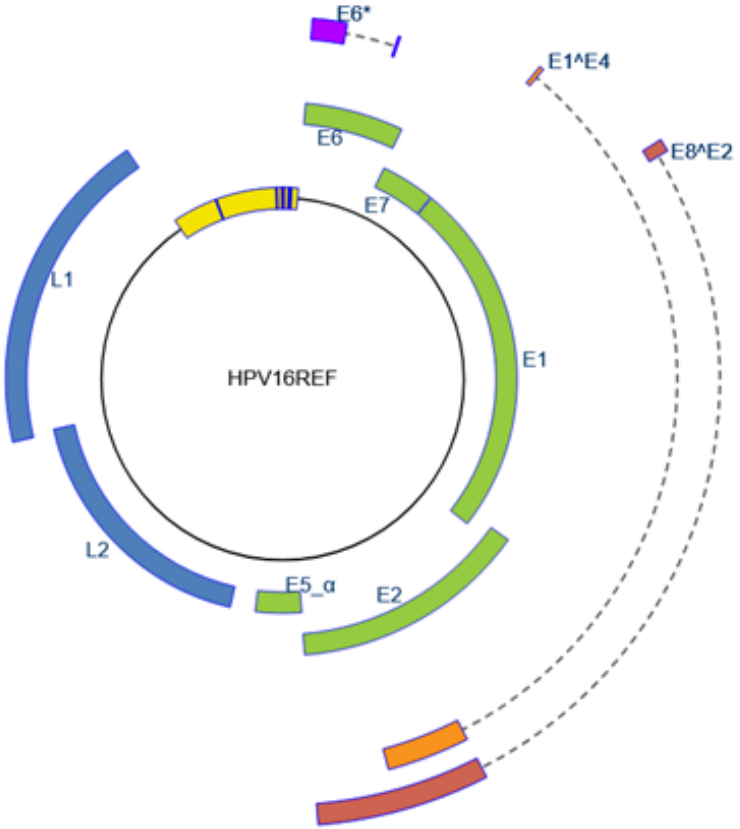
Multiply latent episomes or provirus
- Cell survival
- Cell immortalization
- Cell proliferation

Hallmarks of Cancer



Cell Host & Microbe 15, March 12, 2014

HPV16 genome



E8^E2 protein plays a role in limiting the replication of viral DNA in keratinocytes. Recruits the host NCoR/SMRT complex to viral replication foci to mediate repression of both viral replication and transcription.

The HPV E8^E2 mRNA is generated from a separate promoter within the E1 gene with transcriptional start sites located 70–150 nt upstream of the E8 ATG start codon. Transcript analyses of HPV16 suggest that the main function of this promoter is to drive E8^E2 expression.

P R I N C I P L E S
Cellular transformation and oncogenesis

- Retroviruses can either encode oncogenes (once derived from host genes) or integrate into the cellular genome and activate adjacent cellular proto-oncogenes.

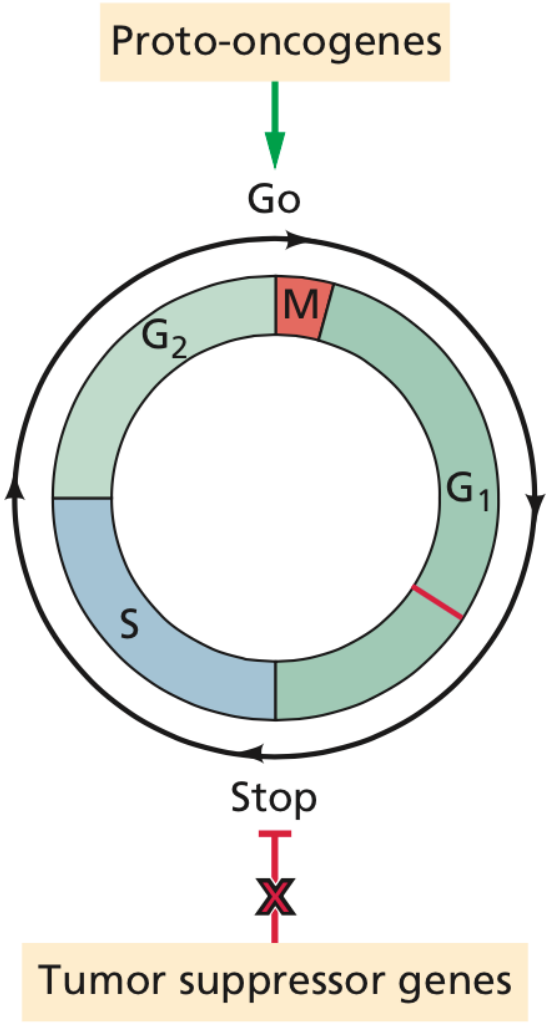
- Small transforming DNA viruses encode proteins that bind to specific cellular proteins, notably the tumor suppressors Rb and p53, to promote cell cycle progression and block checkpoints.

- Proteins encoded by transforming viruses also can prevent cell death, block immune recognition, and promote blood vessel formation.

- Some viruses associated with human cancers do not transform cells directly, but rather induce a chronic immune response that, with time, results in tissue damage and the emergence of malignant cells.

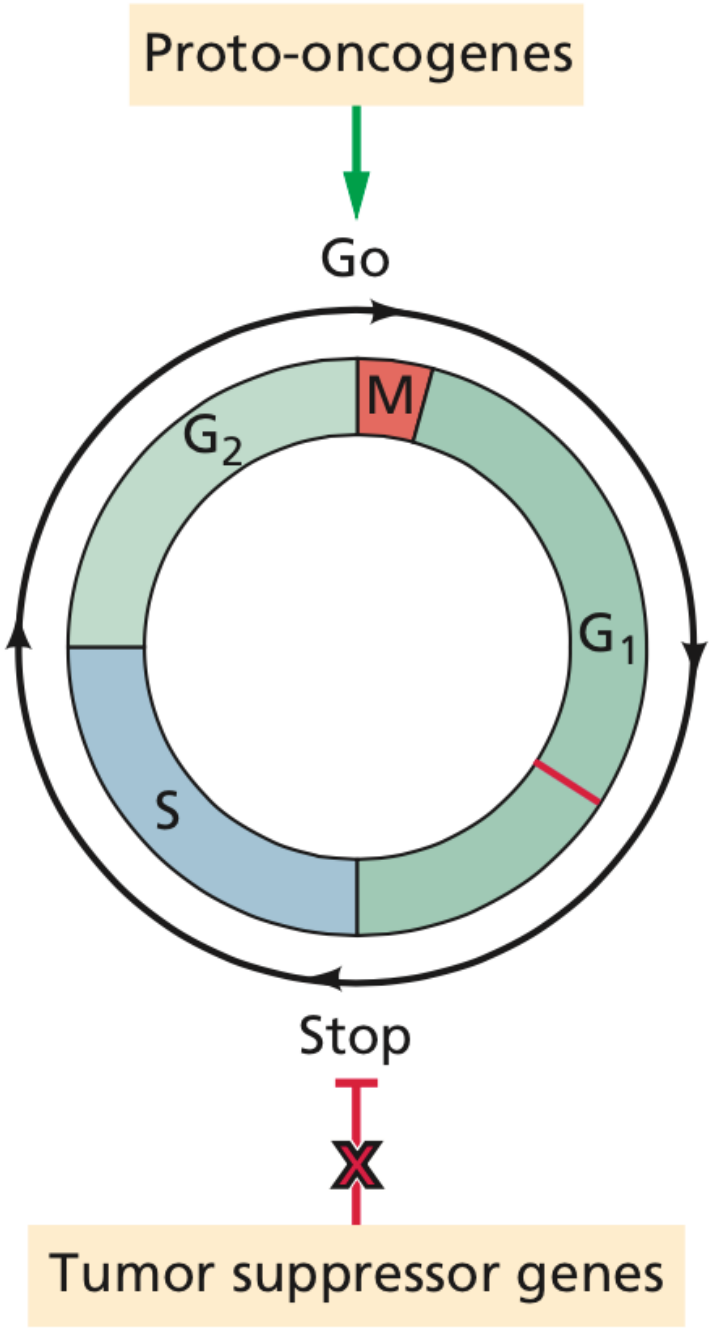
A genetic paradigm for cancer

(Cancer is a disease of unregulated cell division)



The pace of the cell cycle can be modulated both positively and negatively by different sets of gene products. Cancer arises from a combination of dominant, gain-of function mutations in proto-oncogenes and recessive, loss-of-function mutations in tumor suppressor genes, which encode proteins that block cell cycle progression at various points. The function of either type of gene product can be affected by oncogenic viruses.

From Flint et al. *Principles of Virology* (2015), ASM Press

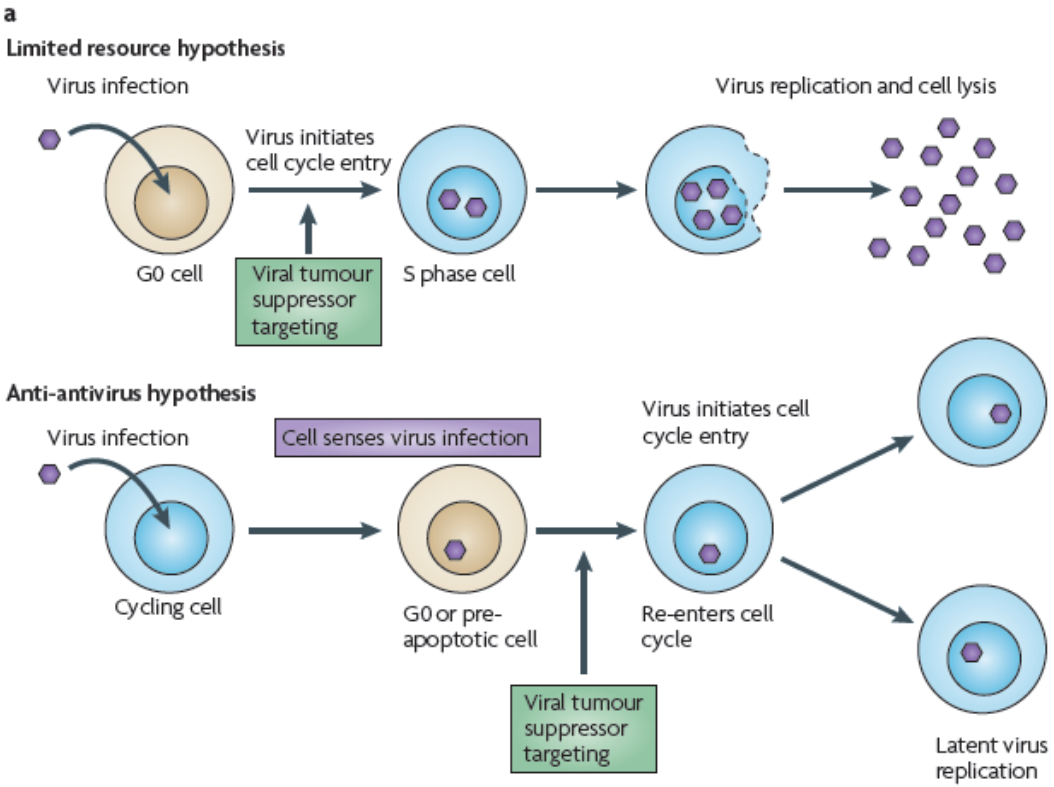


Revealed by studying transforming retroviruses
Dominant oncogenes

Revealed by studying DNA tumor viruses
Recessive oncogenes

From Flint et al. *Principles of Virology* (2015), ASM Press

Two views for the origins of viral oncoproteins



The tumour virus proteins target RB1 and p53 to drive a quiescent G0 cell into S phase of the cell cycle, allowing viral access to the nucleotide pools and replication machinery that are needed for replication and transmission. Viral tumourigenesis is a by-product of the molecular parasitism by viruses to promote their own replication. Cells respond to virus infection by activating RB1 and p53 to inhibit virus replication as part of the innate immune response. To survive, tumour viruses have evolved the means for inactivating these and other immune signalling pathways that place the cell at risk for cancerous transformation. This view holds that many tumour suppressor proteins have dual functions in preventing cancer formation and virus infection.

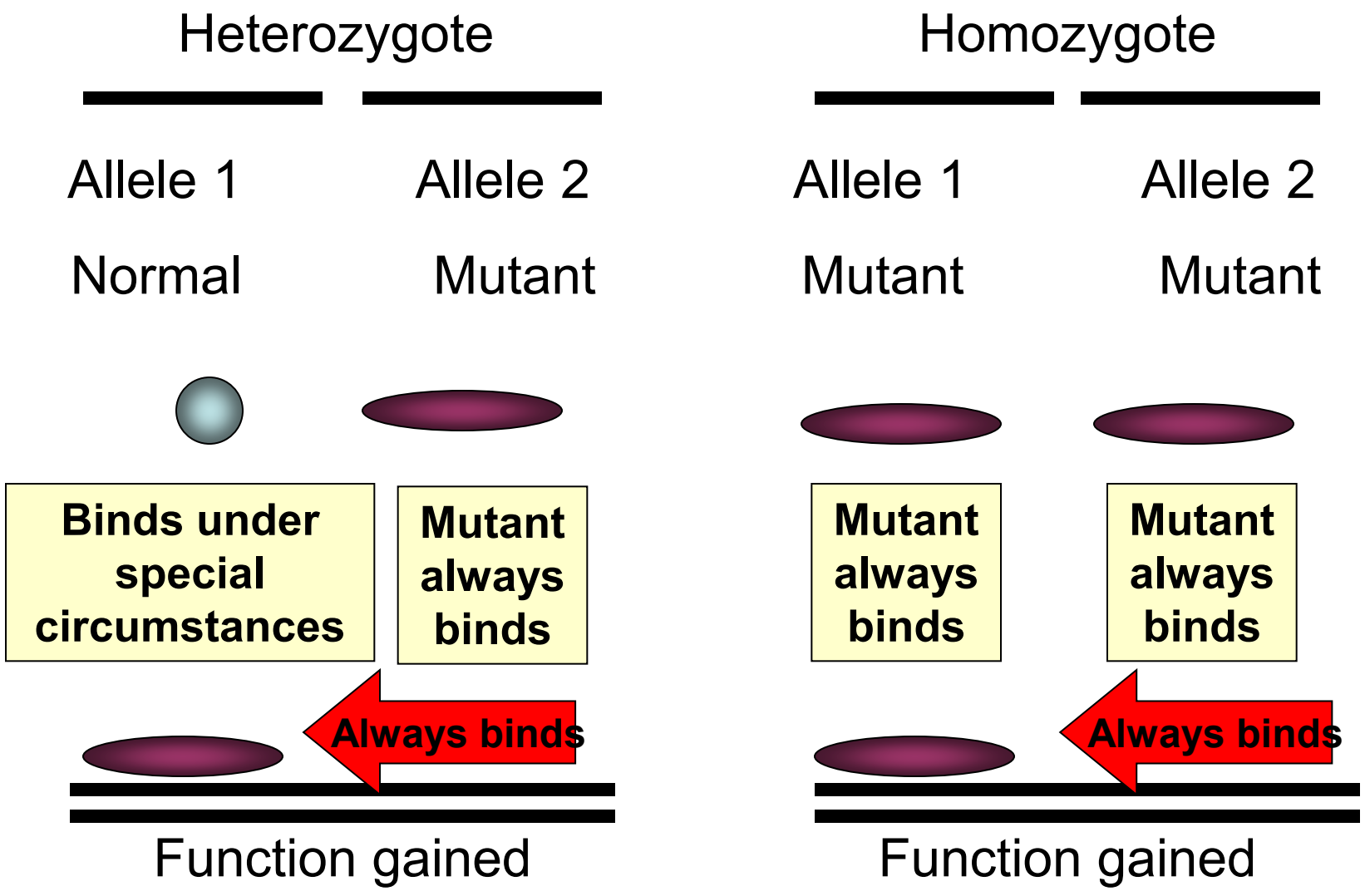
Human papillomavirus (HPV) grouping according to their risk to produce cancerous or precancerous lesions

More than 120 different HPV types are known, and about 40 of these are sexually transmitted

HPV group	HPV types
High risk	HPV-16, HPV-18, HPV-45, HPV-56
Intermediate risk	HPV-31, HPV-33, HPV-35, HPV-51, HPV-52, HPV-58
Low risk	HPV-6, HPV-11, HPV-42, HPV-43, HPV-44

Proto-oncogenes

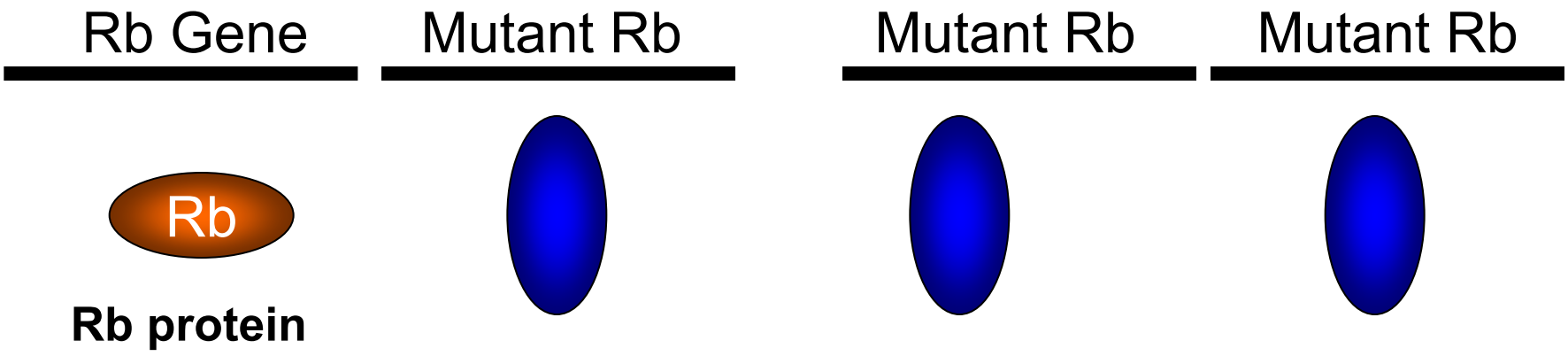
Dominant mutations



Anti-Oncogenes/tumour suppressor genes

Recessive mutations

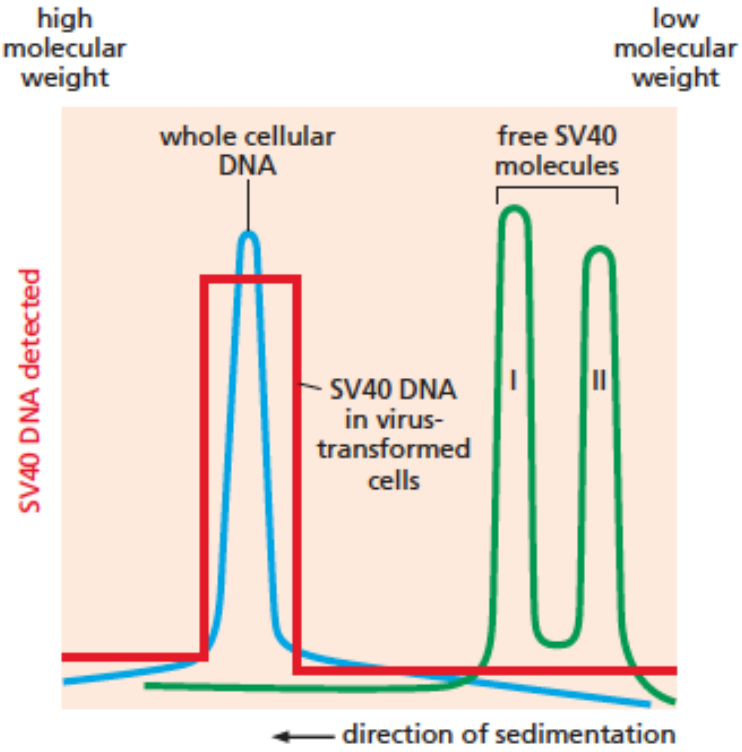
Mutation → growth



Binds and controls cell cycle
Turns off DNA replication

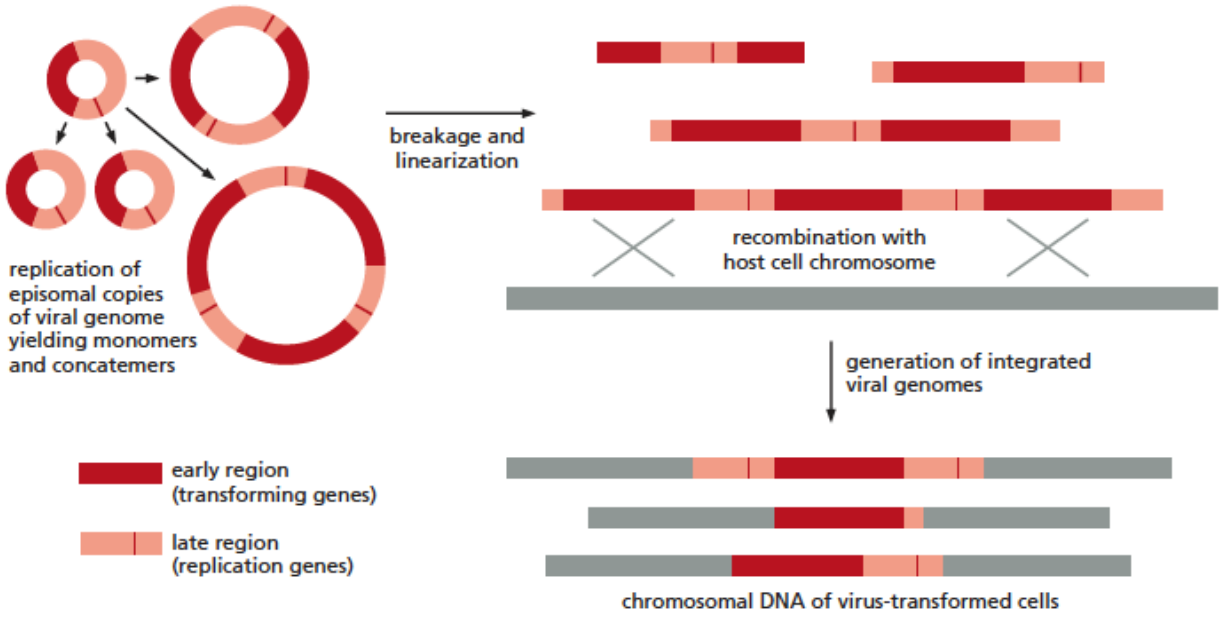
No binding - Growth continues

Integration of SV40 DNA



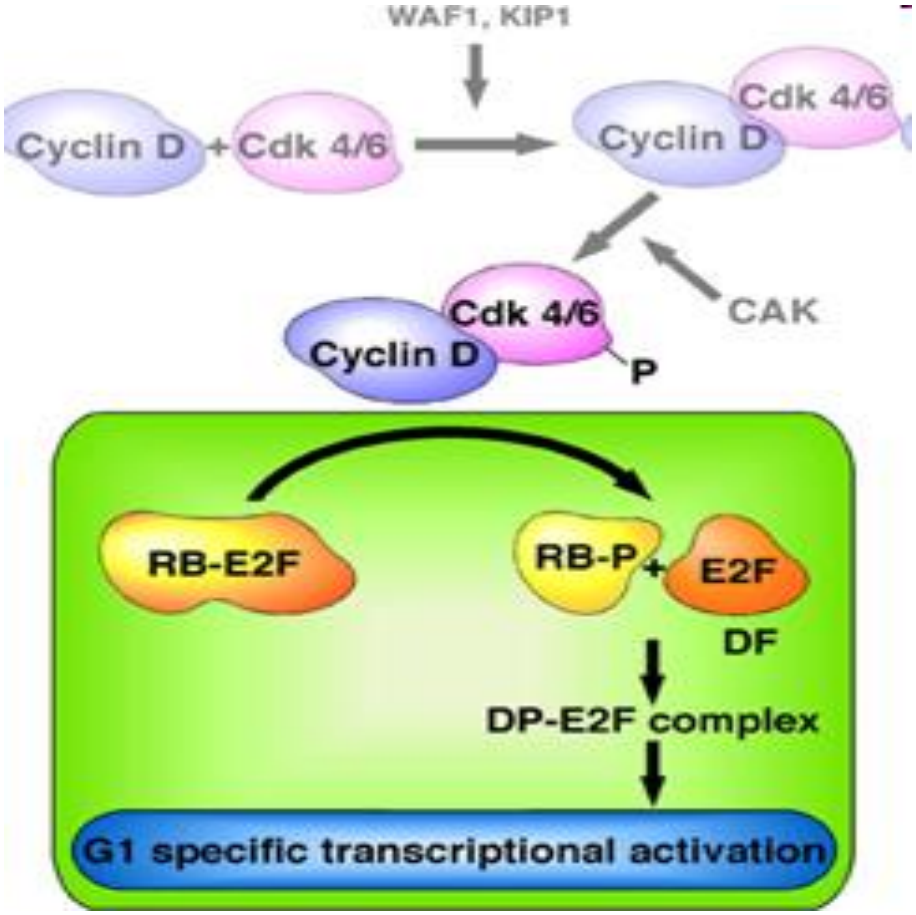
DNA molecules from SV40- transformed cells were isolated and sedimented by centrifugation through an alkaline solution stabilized by a sucrose gradient (used to prevent mixing of different fluid strata within the centrifuge tube).
Under these conditions, the high–molecular-weight cellular DNA (blue) sedimented a substantial distance down the sucrose gradient (left side of graph). In contrast, the SV40 DNA isolated from virus particles (green) sedimented more slowly, indicative of its lower molecular weight. Forms I and II viral DNA refer to the closed circular and nicked circular DNAs of SV40, respectively. Use of nucleic acid hybridization revealed that the SV40 DNA sequences in SV40 virus–transformed cells co-sedimented with the high–molecular-weight chromosomal DNA of the virus-transformed cells, indicating covalent association of the viral genome with that of the host cell (red).

Formation of integrated SV40 genomes

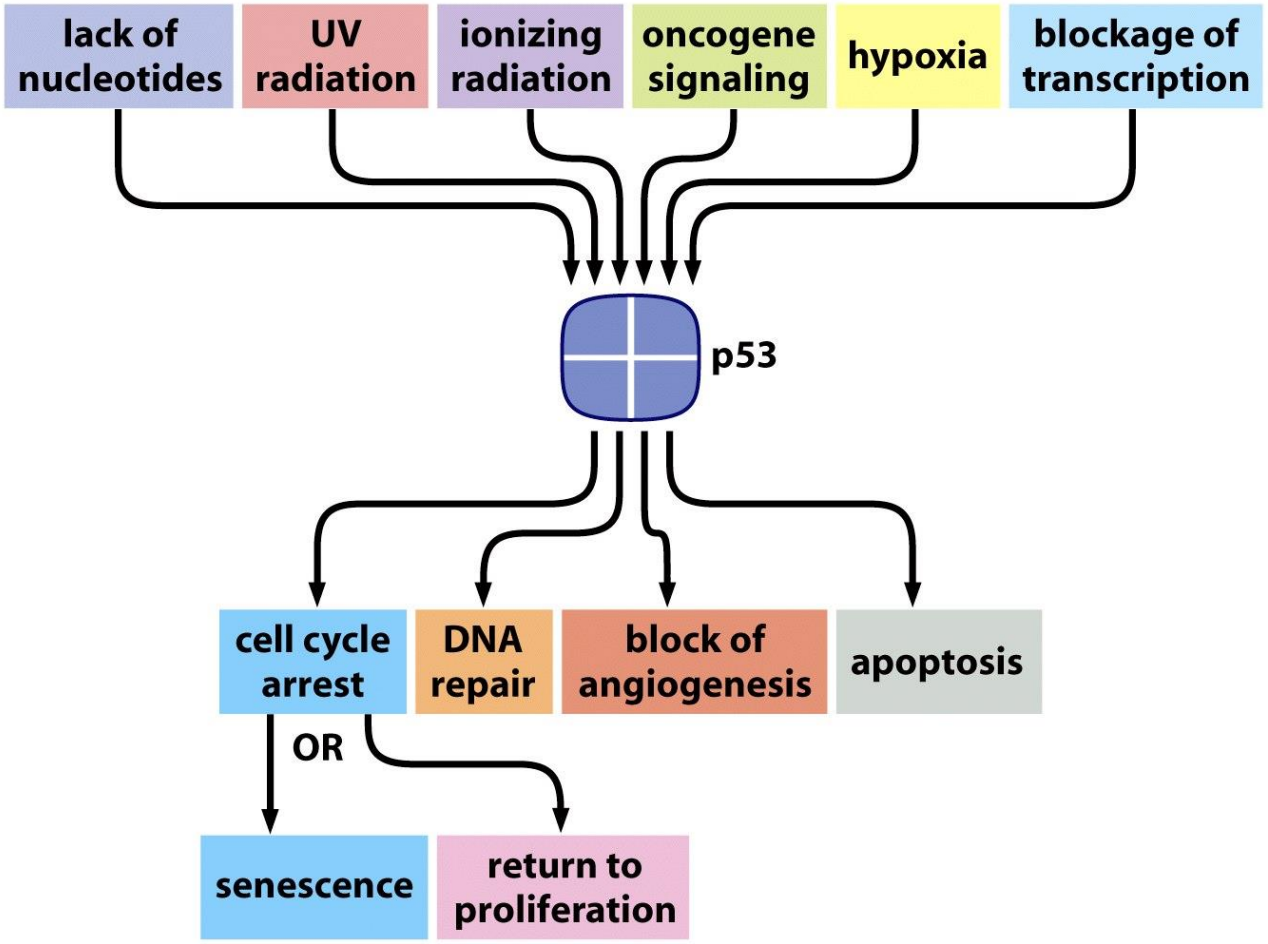


When unintegrated (that is, episomal) SV40 genomes (top leftmost circle) replicate, they often generate large, tandemly repeated genomes termed concatemers. Monomeric and concatemerized SV40 DNA genomes can undergo linearization and then recombine at low efficiency with the host-cell chromosomal DNA (gray), doing so at random sites in the host genome; this leads to the covalent linkage of viral and cellular DNA sequences. Since the viral and host-cell genomes lack significant sequence identity, this type of recombination is termed nonhomologous or illegitimate recombination. Use of restriction enzyme cleavage-site mapping revealed the configurations of SV40 genomes integrated into the chromosomal DNA of virus-transformed cells. In some cells, only a portion of the viral genome was present; in others, full, multiple, head-to-tail tandem arrays were present. Cell transformation by SV40 requires only the genes in the “early region” of the viral genome (dark red). Consequently, all virus-transformed cells contained at least one uninterrupted copy of this early region but often lacked segments of the viral late region (pink), which is unimportant for transformation.

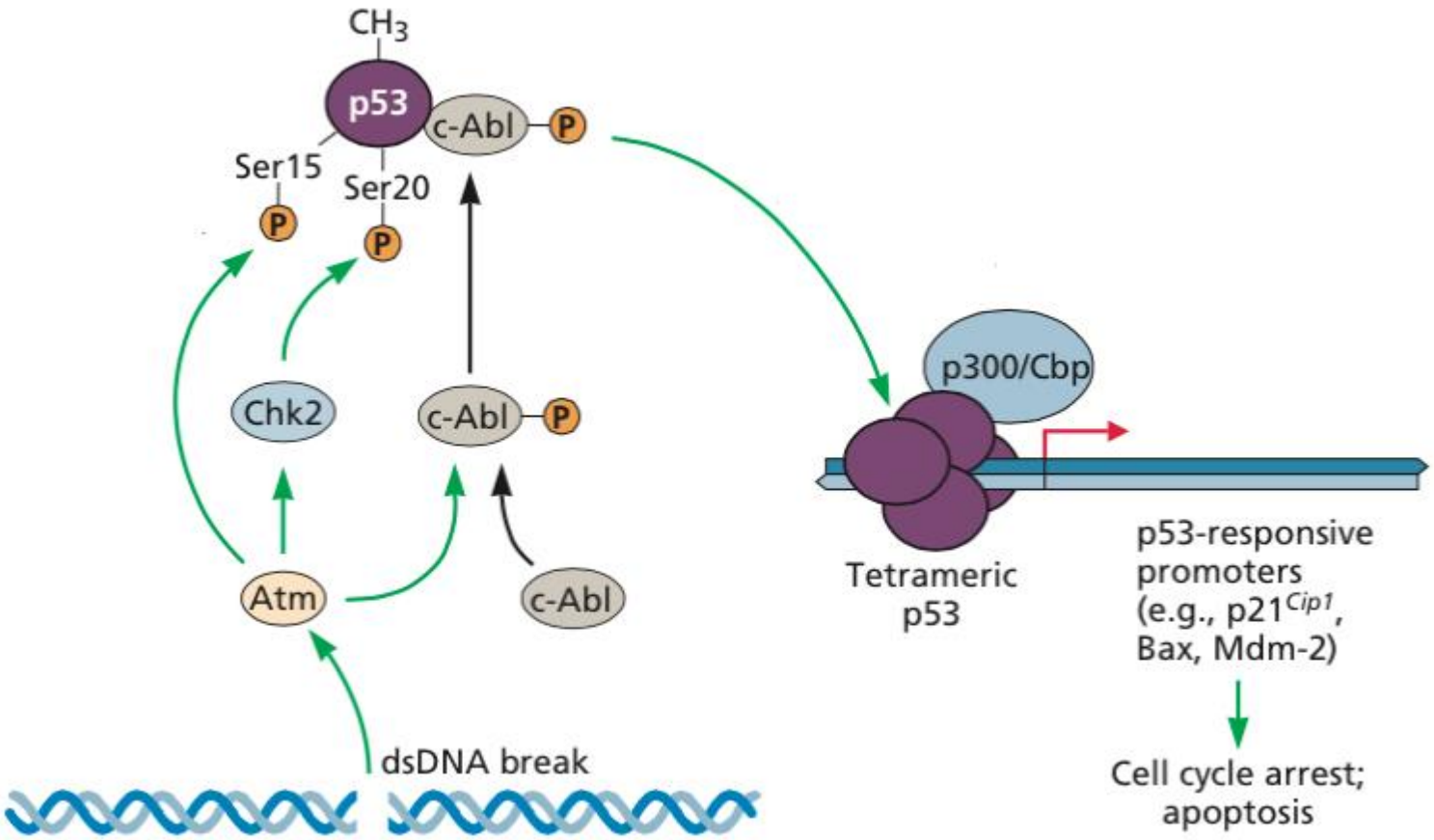
Schematic view of Rb activity



Schematic view of p53 activity

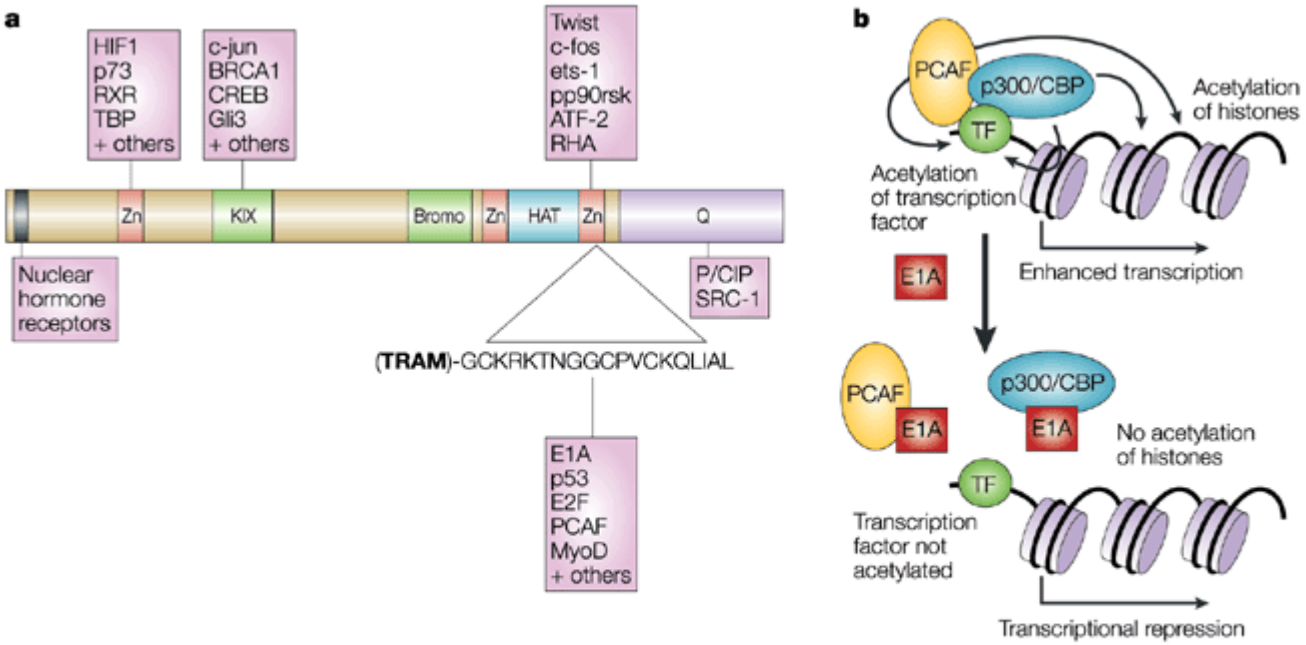


The entry into S decision is under MORE control

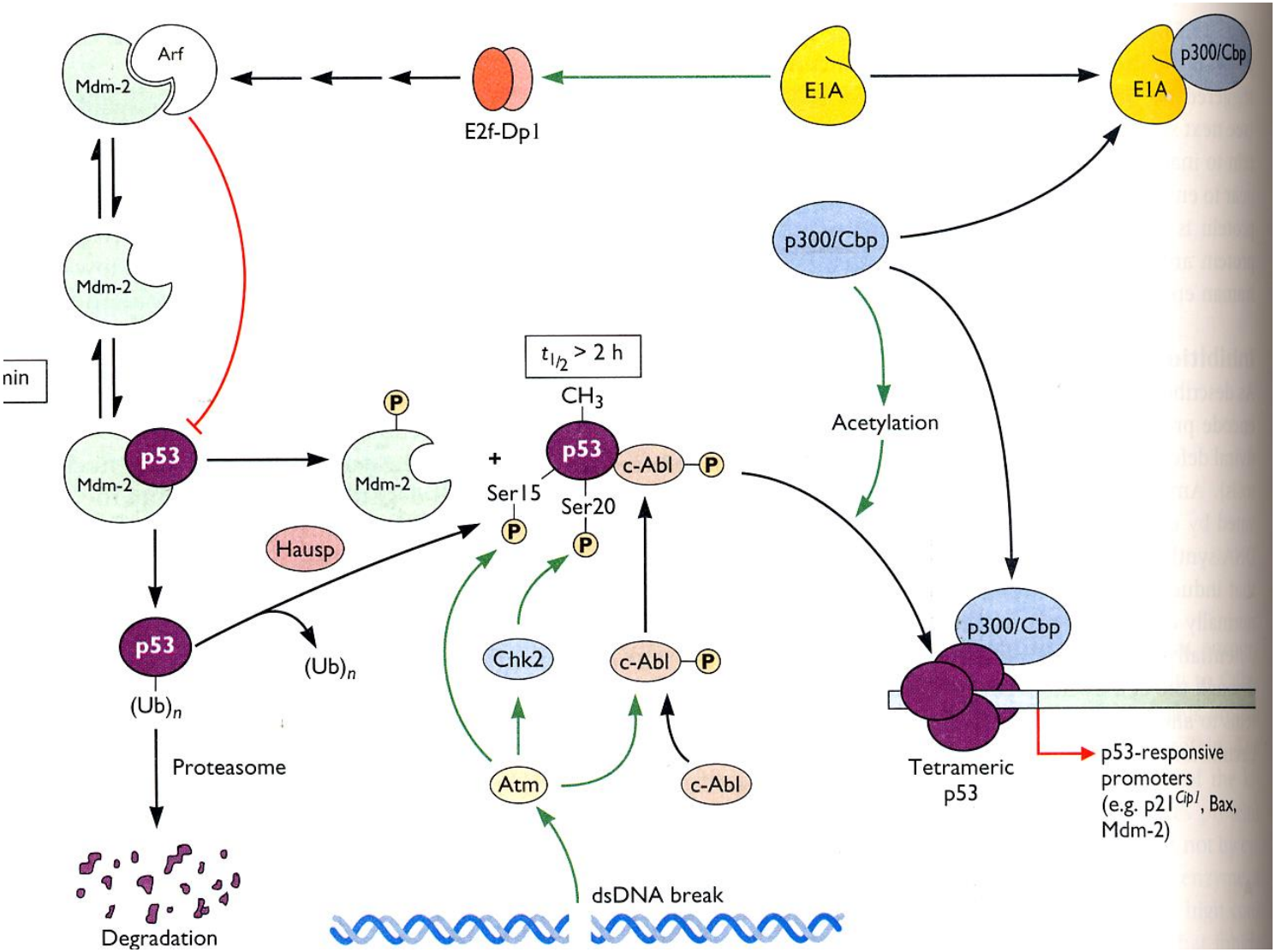


DNA damage or *unscheduled* DNA synthesis is monitored by p53

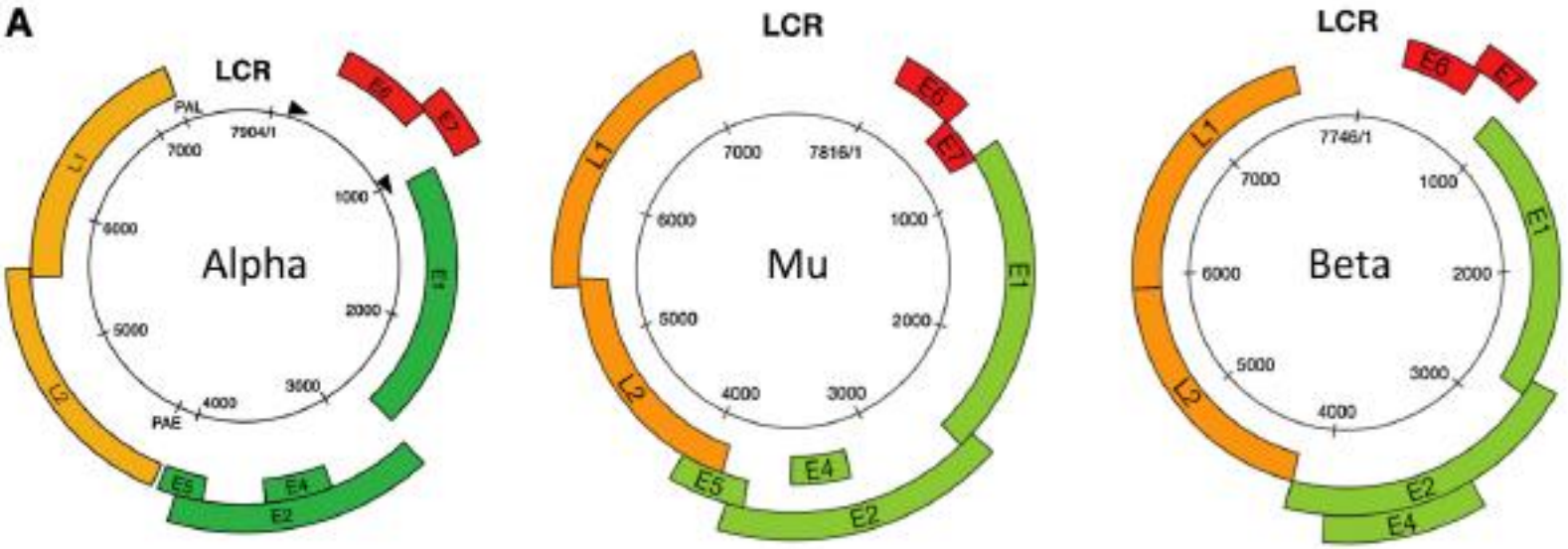
Principles of Virology, ASM Press



Nature Reviews | Molecular Cell Biology

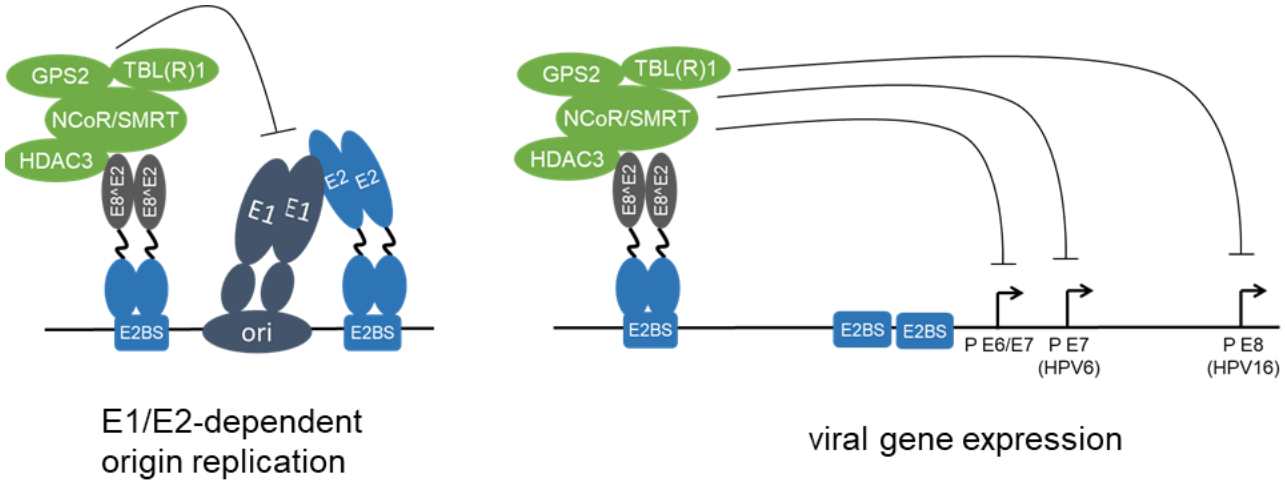


Principles of Virology, ASM Press



Typical genome organization of the high-risk Alpha, Mu, and Beta HPV genomes. Although all share a common genetic organization, the size and position of the major ORFs can vary, with Beta HPV types lacking an E5 ORF. The positions of the major promoters are marked with arrows on the high-risk Alpha HPV genome map, with early and late polyadenylation sites marked as polyadenylation late and polyadenylation early,

HPV E8^E2 proteins repress viral replication and transcription.



E1/E2-dependent origin replication

viral gene expression

HPV E8^E2 proteins bind to E2BS via the DNA binding domain within the C-terminal part shared by full-length E2 and E8^E2. The E8 domain recruits NCoR/SMRT corepressor complexes composed of GPS2, HDAC3, NCoR, SMRT, TBL1, and TBLR1, and this inhibits both E1/E2-dependent replication of the viral origin and the transcription from different viral promoters.

Viruses 2022, 14, 953. https://doi.org/10.3390/v14050953

High-Risk Alpha	Low-Risk Alpha	Beta
Core Genes Essential funcions in viral genome replication and genome packaging Conserved between types		
E1 ATP-dependent helicase, role in papillomavirus genome replication. E2 Coactivator of viral genome replication by the recruitment of E1 to the viral replication origin. Transcription factor of E6 and E7, also important for viral genome segregation. E4 Abundantly expressed as an E1–E4 fusion protein during the late phase of the virus life cycle. Accumulates as cytoplasmic inclusion granules in Beta, Gamma and Mu HPV types. Binds to cytokeratin filaments and disrupts cell structure.		L1 Major capsid protein. Assembles into pentomeric capsomeres, which are the primary components of the icosahedral virion shell. L2 Minor capsid protein, also involved in encapsidation of viral DNA and in viral uncoating after infection

	Accessory Genes Modify the cellular environmrnt to support and tolerate viral genome replication Maximize the viral-fitness to complete viral life cycle in the site of infection Differ between types		
	High-Risk Alpha	**Low-Risk Alpha**	**Beta**
E6	Encodes E6* products	Does not encodes E6* products	
	Binds E6AP		
	Degradation of p53 and PDZ-proteins	No degradation of p53 and PDZ proteins	
	Inhibition of p53 transactivation and acetylation		Inhibition of transactivation following DNA damage*1
	Inhibits Notch pathway via p53	Not known	Binds MAML1 and inhibits Notch pathway
	Inhibition of interferon response	Weak inhibition of interferon response	Decreases MHC class I via down regulation of STAT-1*2
	Degradation of BAK		
	Activation of telomerase	No activation of telomerase	Activation of telomerase
E7	Destabilizes pRB (p105), p107 and p130	Destabilizes p130	Targeting pRB with low efficiency
	Induction of cell cycle entry and DNA synthesis, role in genome amplification		Induction of cell cycle entry and proliferation in suprabasal layer in raft culture
	Supression of STAT-1 function	No supression of STAT-1 function	Not known
	Immortalization and transformation	No immortalization and transformation	
E5	Stimulation of EGFR signaling pathways	Not known	No E5 gene
	Downregulation of MHC		