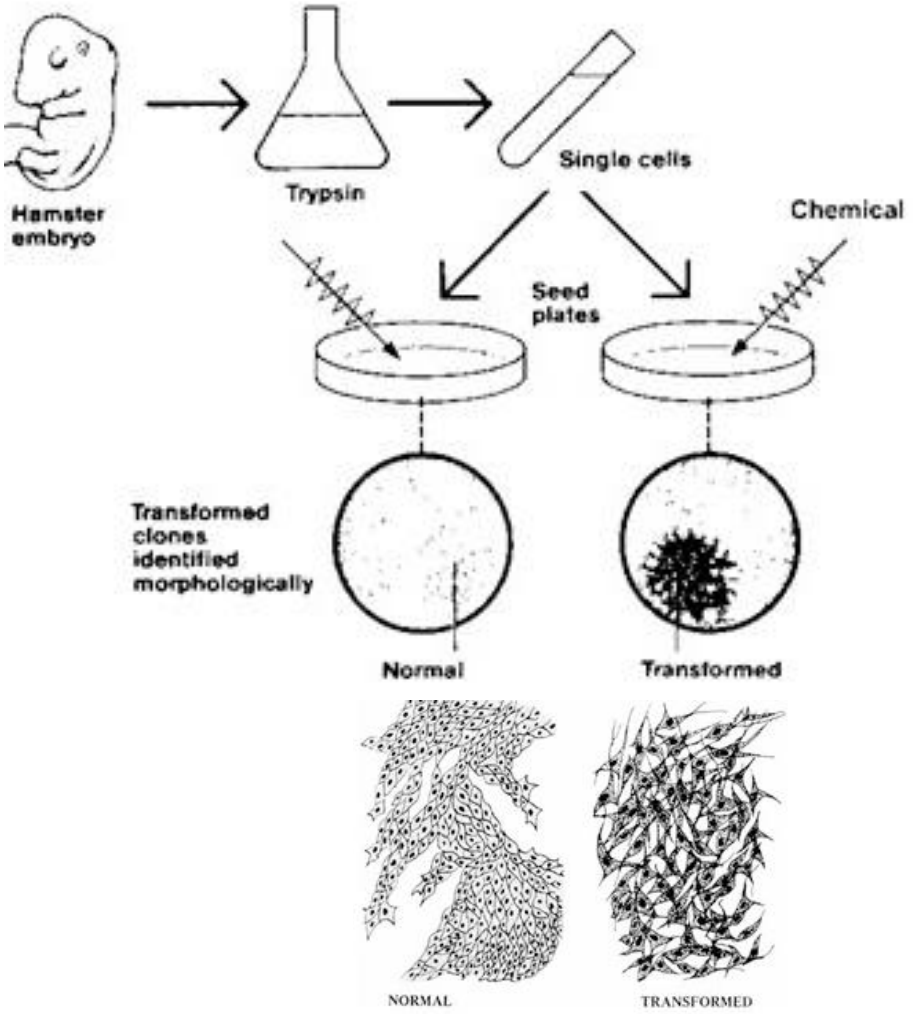
Virusi s onkogenim potencijalom

VIRUSI mogu uzrokovati transformaciju zaraženih stanica koja je preduvjet onkogeneze

TRANSFORMACIJA ≠ ONKOGENEZA

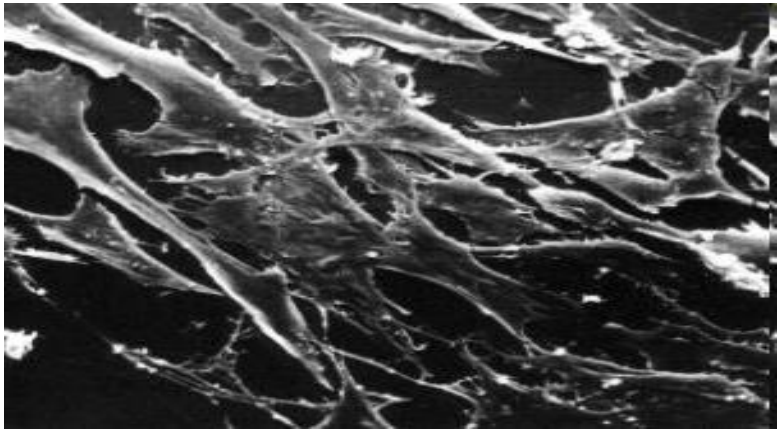
TRANSFORMACIJA (gubitak homeostaze - nekontrolirana dioba)



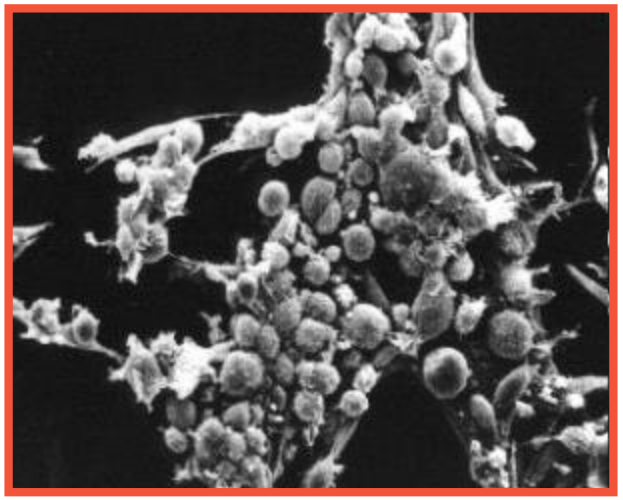
djelovanje mutagena

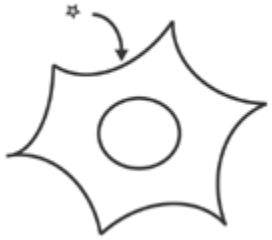
-nekontrolirani rast
-gubitak kontaktne inhibicije
….

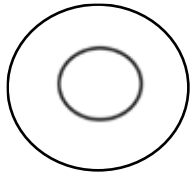
Normalne i transformirane stanice mišjeg vezivnog tkiva u kulturi



RSV







NEKONTROLIRANA DIOBA DOVODI DO NAKUPLJANJA MUTACIJA - ONKOGENEZA

Preduvjeti za virusnu transformaciju stanice:

- citopatogeni efekti moraju biti reducirani ili eliminirani
  (inficirana stanica mora preživjeti)

- virusna replikacija mora biti reducirana ili eliminirana*
  (inficirana stanica ne smije proizvoditi virione – oštećenje/smrt stanice)

- stanica mora nastaviti diobu da bi postala imortalizirana (besmrtna)

Virusi koji uzrokuju transformaciju stanice uglavnom pripadaju:

a) retrovirusima
b) dsDNA virusima

*npr. u semipermisivnim stanicama

Human cancer viruses

Virus	Cancer
RNA viruses	
Human T-lymphotropic virus-1	Adult T cell leukemia
Human immunodeficiency virus-1	Many tissues and organs
Hepatitis C virus	Hepatocellular carcinoma
DNA viruses	
Epstein-Barr virus	Burkitt's lymphoma
Kaposi's sarcoma herpesvirus	Kaposi's sarcoma Primary effusion lymphoma Multicentric Castleman's disease
Hepatitis B virus	Hepatocellular carcinoma
Human papillomavirus	Cervical, penile, anogenital, head and neck cancers
Merkel cell polyomavirus	Merkel cell carcinoma

Contributing factor in ~20% of human cancers

Nastanak tumora u 99,99% slučajeva nije potreban za virusnu replikaciju!!!

Peyton Rous 1911. otkrio da retrovirus uzrokuje sarkome kod kokoši

(*Rous sarcoma virus*, RSV)

On October 1, 1909, Dr. Peyton Rous removed a tumor from an English hen and injected a cell-free filtrate from the tumor into another healthy chicken, which later developed the same type of tumor

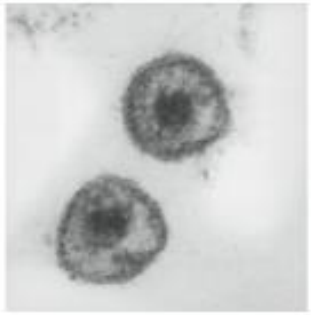
Cancer could be caused by a viral infection!

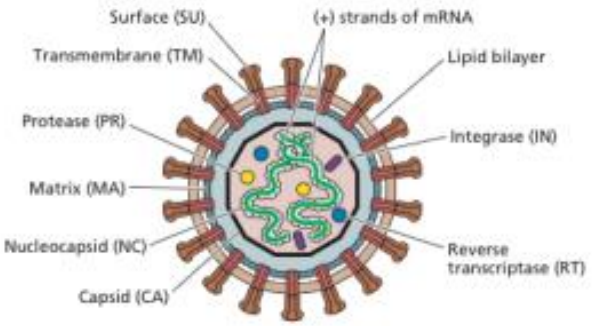
It took the world almost 50 years to accept this idea

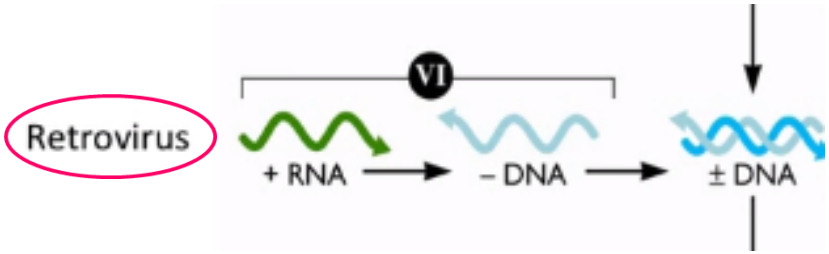
Dr. Rous lived long enough to be awarded the Nobel Prize for Physiology and Medicine in 1966 for his research

Avian leucosis retroviruses (ALV) – endemični kod kokoši

- većina kokoši inficirana unutar prvih mjeseci života
- oko 3% razvija leukemiju, ostali postaju imuni
- kasnije tijekom života razvoj različitih tumora (jedan od njih je i RSV)







Zašto RSV, a ne ALV uzrokuje nastanak sarkoma???

- **virusni genomi izolirani iz tumora kokoši bili su REKOMBINANTE**

- **dio genoma virusa ALV zamijenjen je segmentom domaćinske DNA - ONKOGEN**

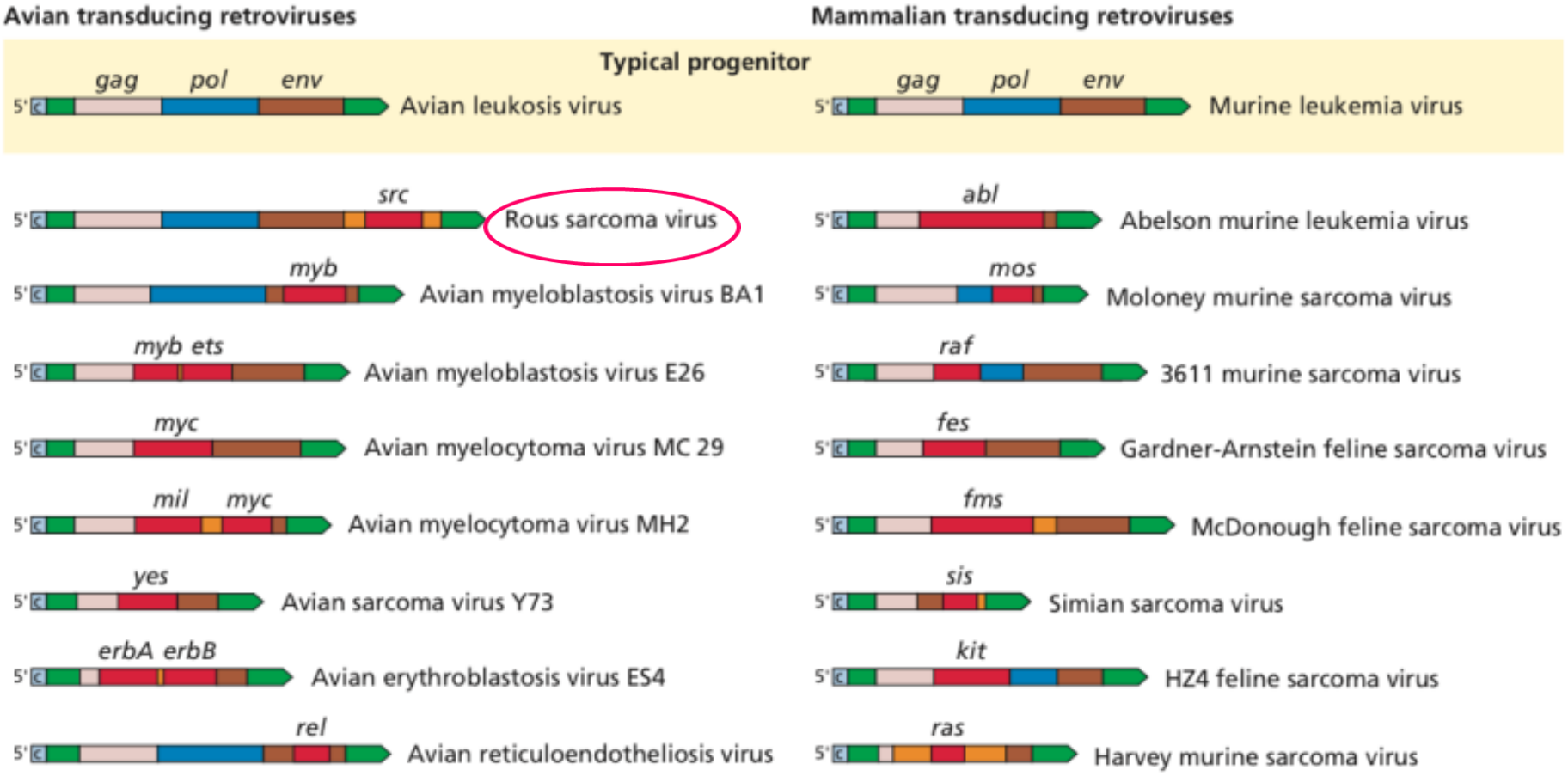
J. Michael Bishop and H. Varmus identified the oncogene (v-SRC) carried by Rous sarcoma virus in 1976

Nobel Prize to both in 1989 for this discovery

Src family kinases (SFKs) are membrane-associated, non-receptor tyrosine kinases that act as important signaling intermediaries regulating a variety of outputs, such as **cell proliferation, differentiation, apoptosis, migration, and metabolism**.

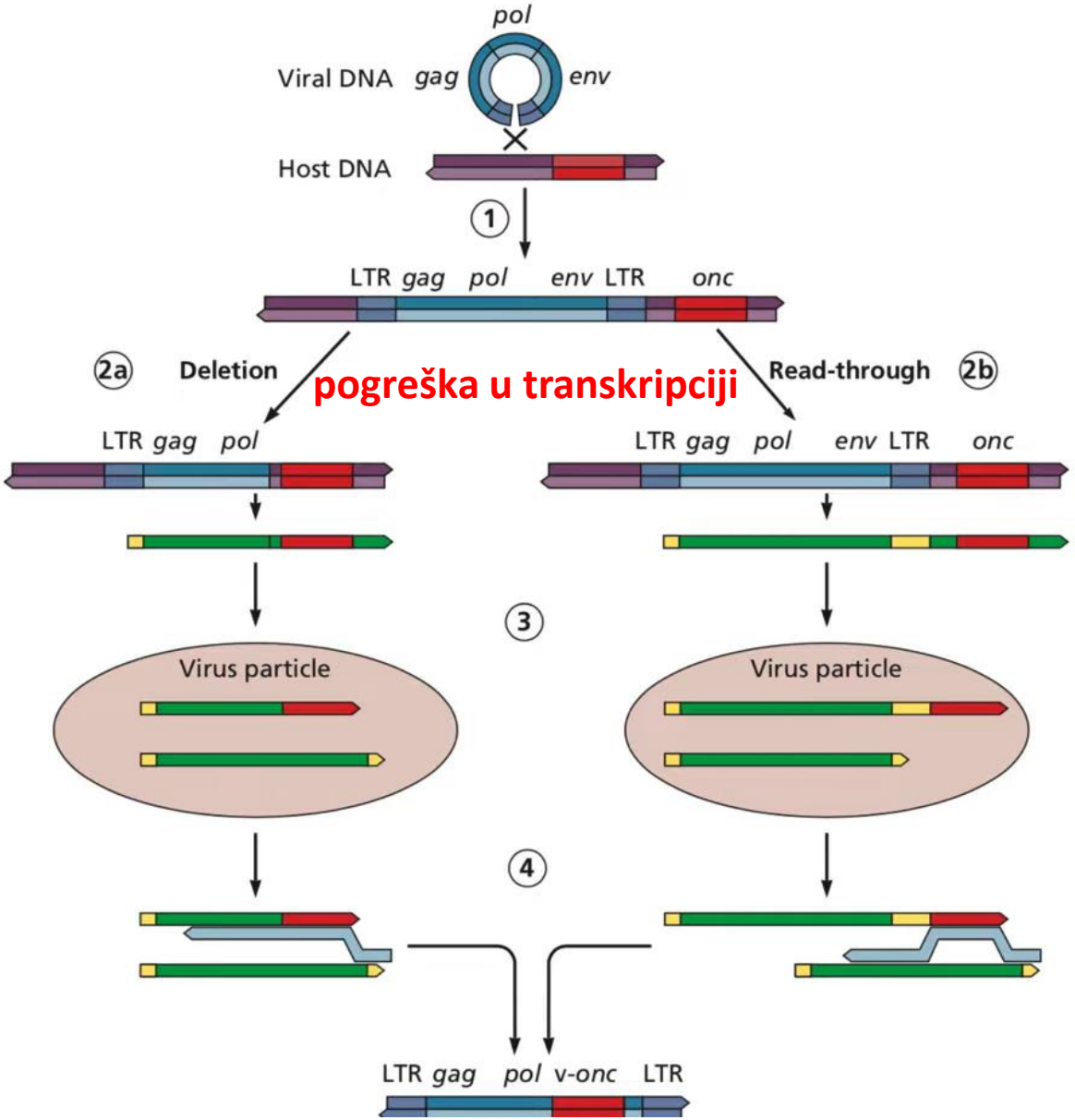
virus uzme dio genoma domaćina i prenese ga u drugu stanicu

Genomes of transducing retroviruses

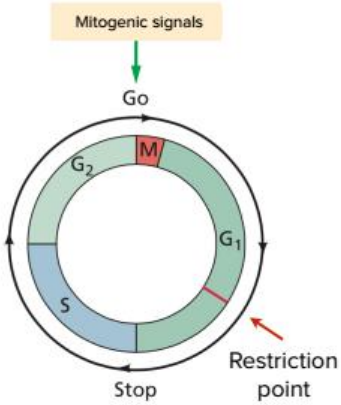


defektni virusi trebaju „helper” viruse za replikaciju

Mechanism for oncogene capture



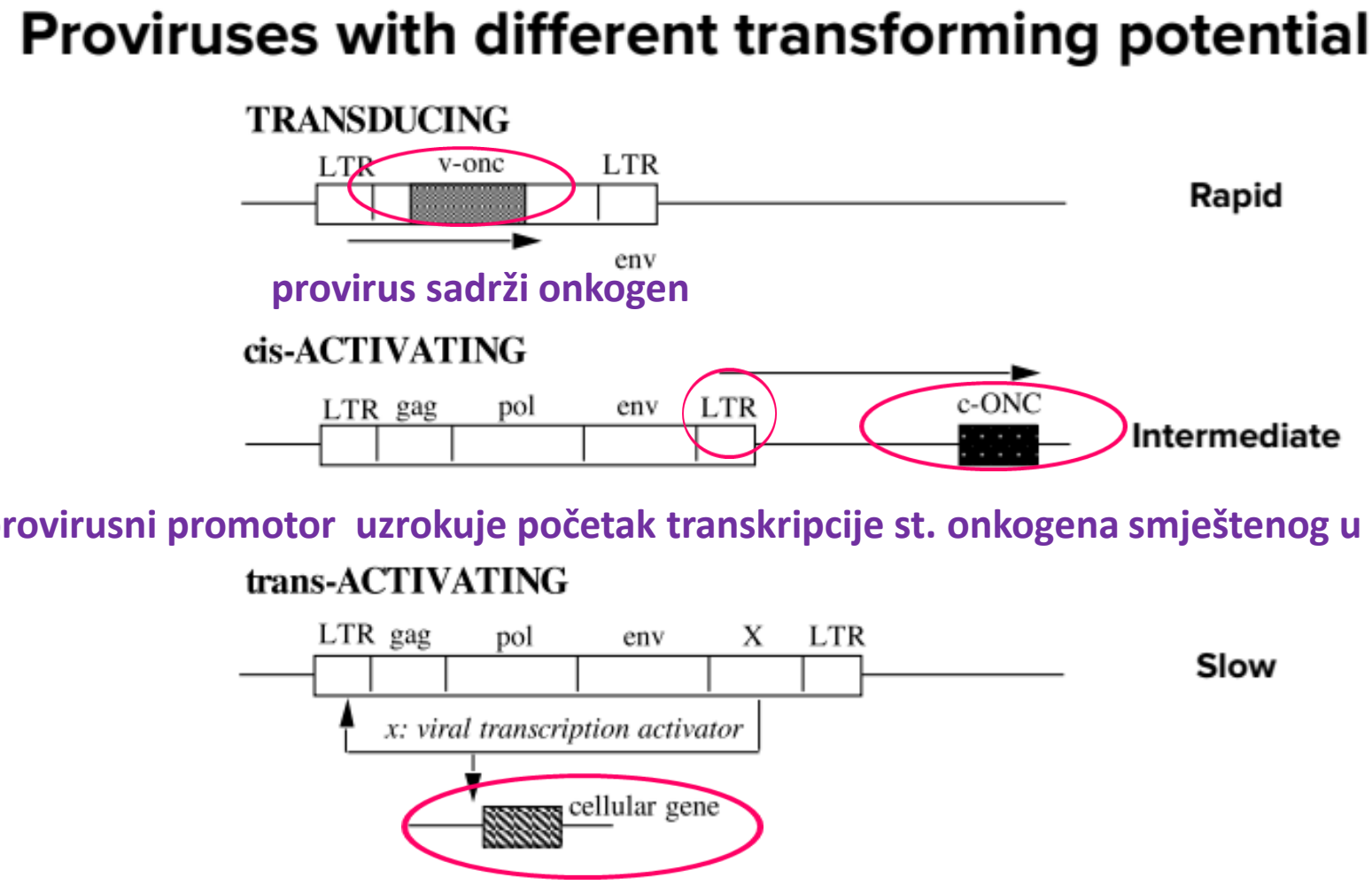
PROTOONKOGENI



- >60 staničnih gena
- prisutni u svim stanicama, kontroliraju staničnu diobu
- normalni stanični geni imaju kraticu c (cellular), pr. c-SRC, c-MYC.....
- retrovirusi izolirani iz tumora nose kopije staničnih protoonkogena koje imaju kraticu v (viral), pr. v-SRC, v-MYC.... ONKOGENI

Retrovirusni genomi integrirani u domaćinski genom – PROVIRUSI

PROVIRUSI transformiraju stanice različitim mehanizmima:



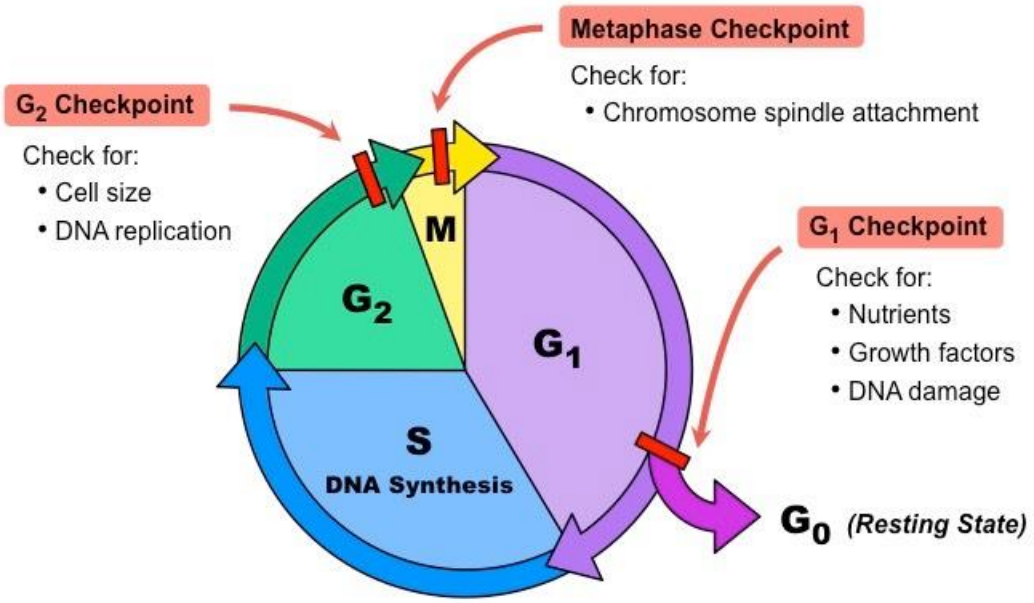
TRANSFORMACIJA POSREDOVANA DNA VIRUSIMA

Za replikaciju virusnog DNA genoma, domaćinska stanica mora biti u S-fazi staničnog ciklusa!

Virusni proteini (tzv. T-antigeni) stanice iz mirovanja (G_0 faza) „guraju" u replikaciju (S faza)!

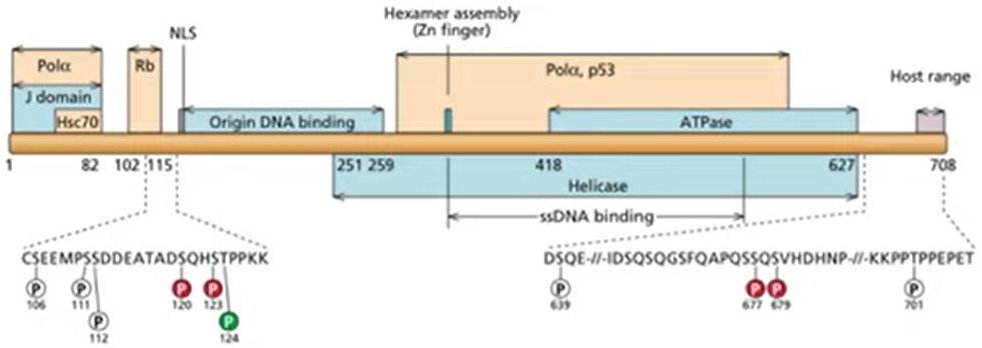
Kako???

Interakcija virusnih proteina sa staničnim proteinima koji kontroliraju stanični ciklus



T-antigene kod različitih virusa predstavljaju različiti proteini!

Key finding: Viral T antigens in tumors and transformed cells



- SV40: Large T, small T
- Polyomaviruses: Large T, middle T, small T
- Papillomaviruses; T encoded by E6, E7 genes
- Adenoviruses: T antigens are E1A, E1B

All different proteins!

Radi se o esencijalnim virusnim proteinima (replikacija, transkripcija…)!

Izolirani T-antigen sposoban je samostalno transformirati stanicu!

Proces transformacije:

- DNA virusi moraju inicirati ulazak stanice u S-fazu kako bi osigurali vlastitu replikaciju

- zbog toga virusni T-antigeni inaktiviraju stanične proteine važne za regulaciju staničnog ciklusa

  tumor supresor Rb (retinoblastoma protein) – kontrolira ulazak stanice u S-fazu
  tumor supresor protein p53 – važan za inicijaciju apoptoze u stanica s oštećenjem DNA
  ...

Ukoliko ne dođe do raspada inficirane stanice, T-antigen se zajedno sa staničnim genomom nastavlja replicirati što dovodi do TRANSFORMACIJE i eventualno ONKOGENEZE!

Transformacija kod ove skupine virusa je relativno rijetka!

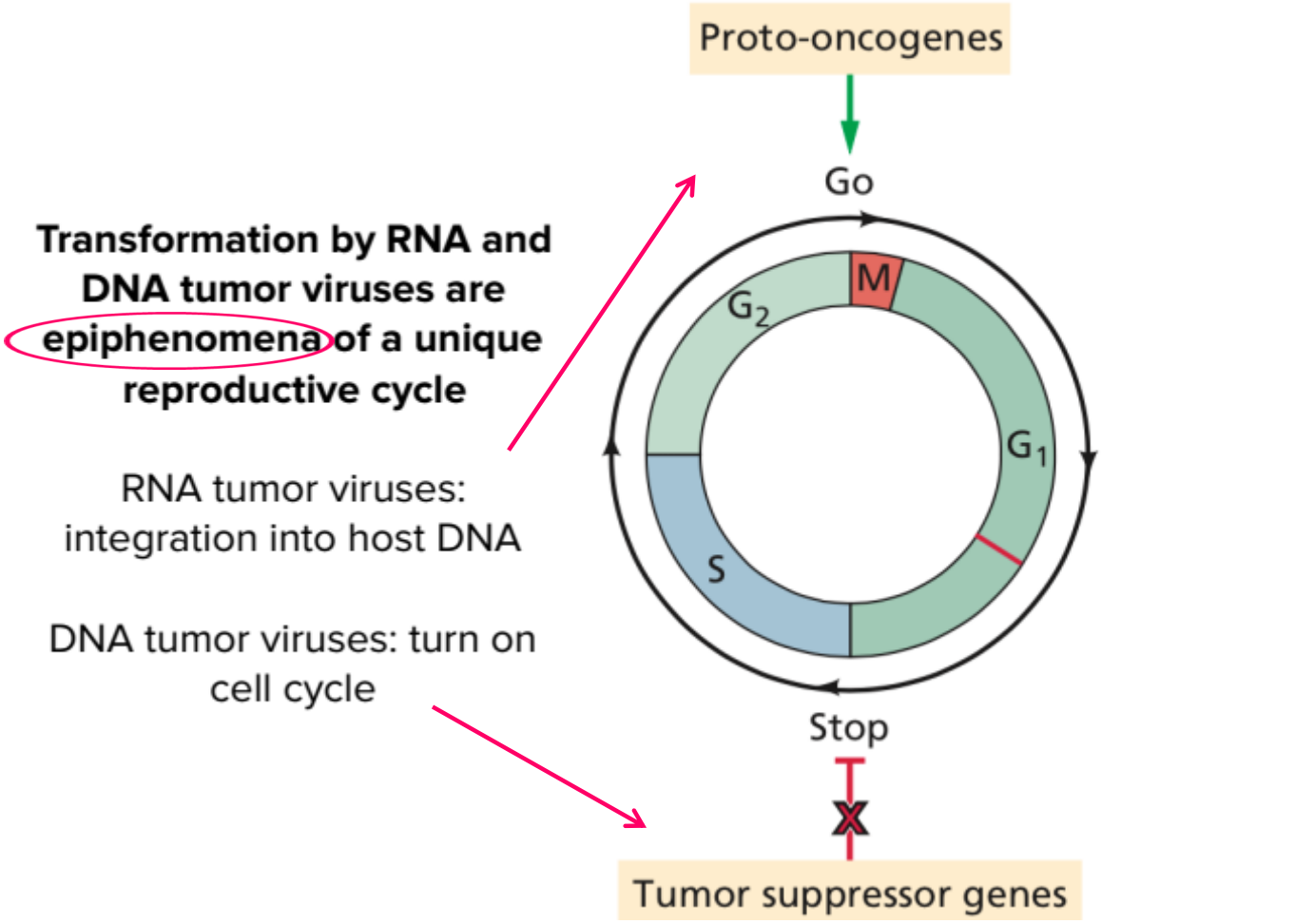
Razlozi:

- **geni odgovorni za letalnost ne smiju biti eksprimirani u domaćinskoj stanici (prirodne spontane delecije ovih gena su rijetke)**

  Infekcija semipermisivnih stanica češće vodi do transformacije (nema ekspresije kasnih gena niti izlaska virusa iz stanice)!!!

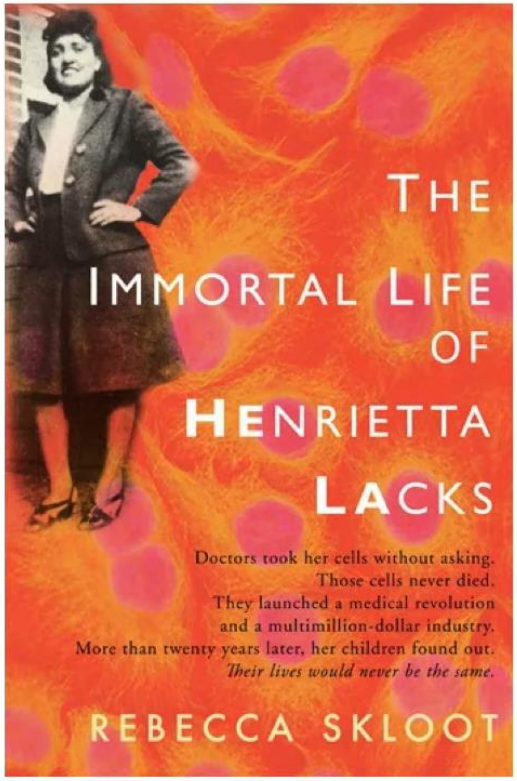
- **virusna DNA koja kodira T-antigen mora biti integrirana u domaćinski genom i prenositi se na novonastale stanice (najagresivniji HPV-genotipovi 16 i 18)**

PROTOONKOGENI
- potiču napredovanje kroz stanični ciklus



TUMOR SUPRESOR GENI
- zaustavljaju napredovanje kroz stanični ciklus

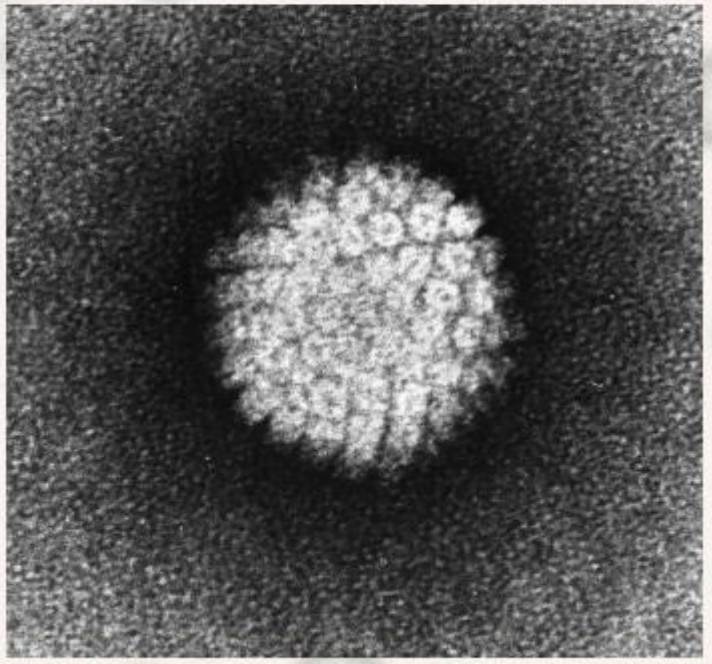
Henrietta Lacks' cervical cancer and Hela cells explained



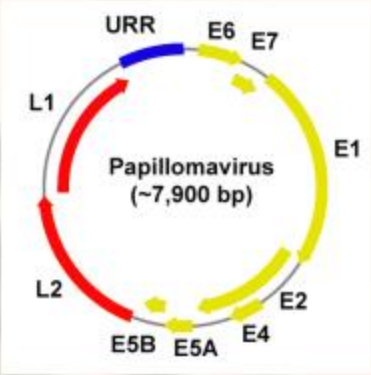
- Genome sequence of Hela cells reveals integration of HPV 18 in chromosome 18
- Only E6 (binds Rb), E7 (degrades p53) intact genes present
- Integration of viral DNA rare event in infected individuals

Ljudski papiloma virus (HPV)

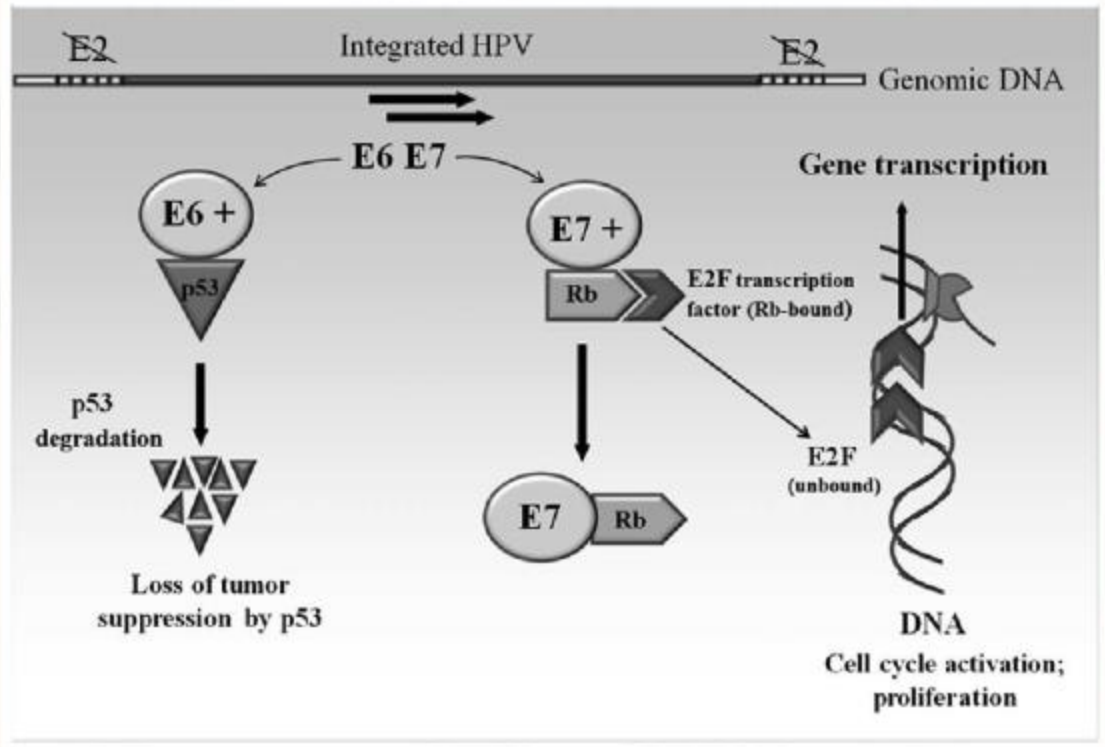
- dsDNA (I grupa)
- Mnogo tipova, uzrokuju benigne bradavice i maligne tumore (primarno genitalne)
- Replikacija u bazalnim i epitelnim stanicama
- Papa-test
- Cjepivo je dostupno unatrag zadnjih 10 godina



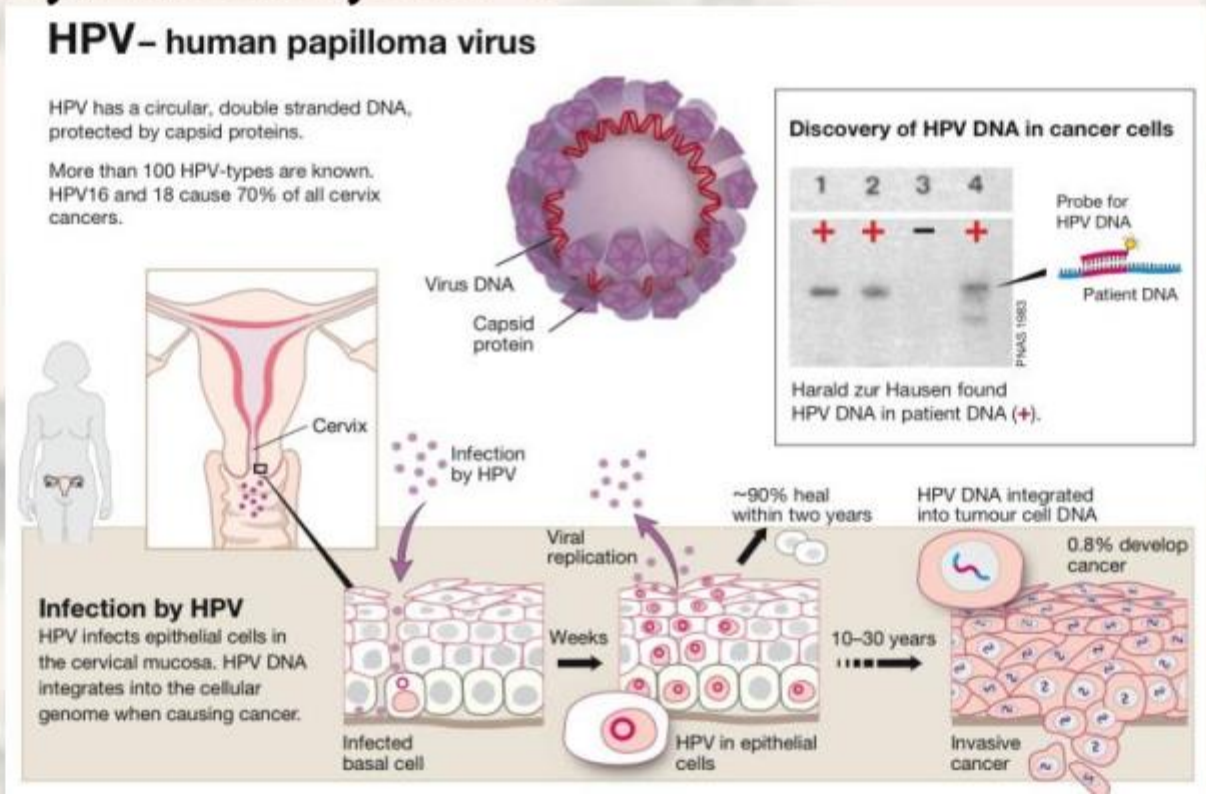
Maligna transformacija: proteini E6 i E7



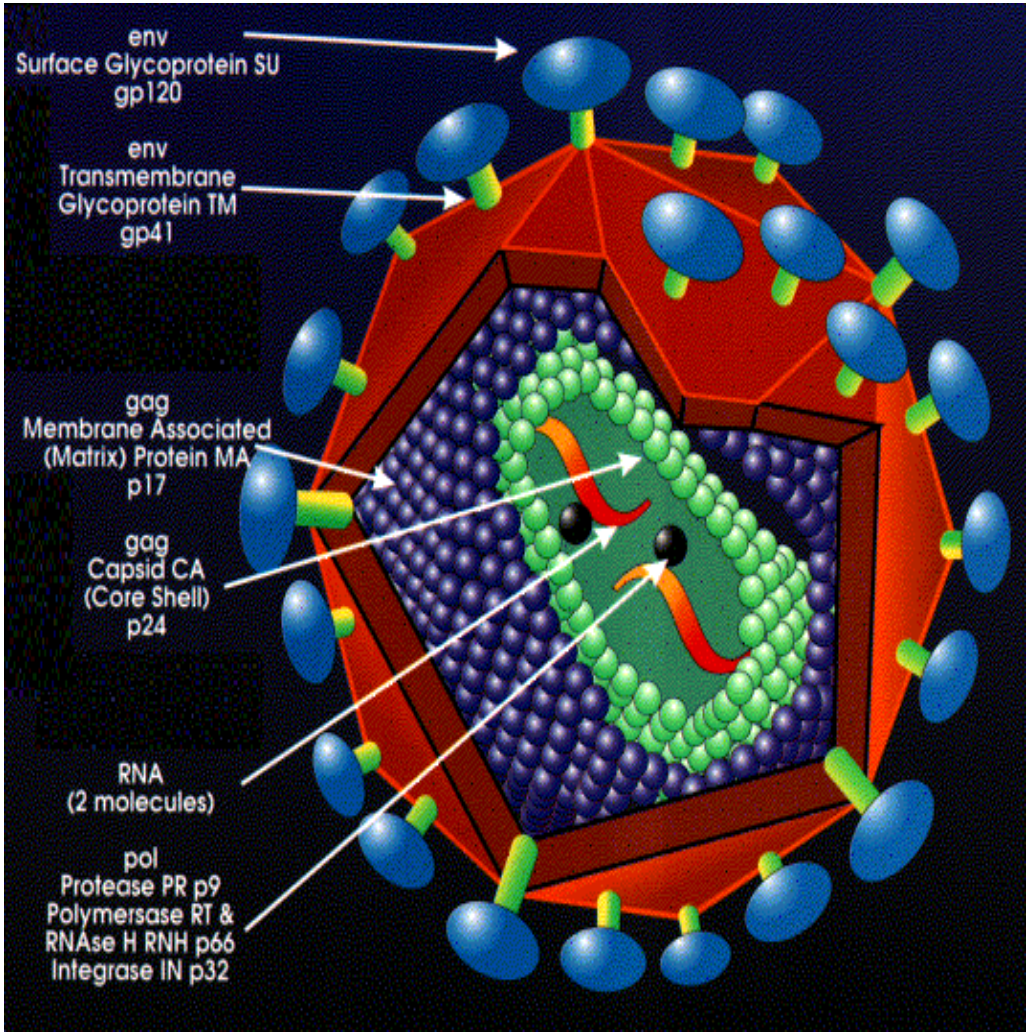
E2 suprimira ekspresiju E6 i E7; integracijom virusnog genoma u genom stanica domaćina može doći do promjene u E2 ORF-u → gubitak funkcije E2



Progresija infekcije HPV



Struktura HIV-a



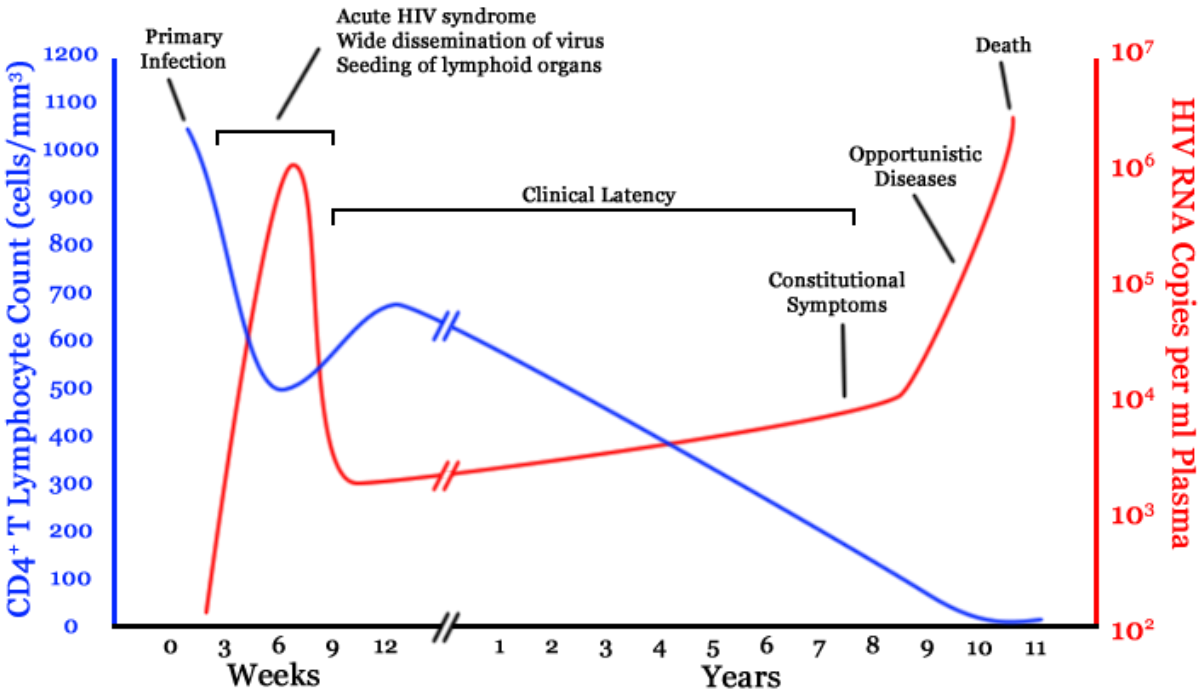
- Nukleokapsida:

  - protein p24
    - 2 molekule **RNA**
    - Enzimi: reverzna transkriptaza, integraza i proteaza

- Matrix: protein p17

- Ovojnica: proteini gp120 i gp41

- prenosi se spolnim putem, preko krvi ili krvnih pripravaka te s majke na dijete
- umnožavanje u $CD4^+$ pomoćničkim limfocitima, makrofagima i dendritičkim stanicama



Tijek infekcije

- U akutnoj fazi pada broj $CD4^+$ limfocita, a nakon nekoliko tjedana počinje proizvodnja specifičnih protutijela
- U fazi latencije održava se ravnoteža između HIV-a i imunosnog odgovora
- SIDA=AIDS – kolaps stanične imunosti i razvoj oportunističkih bolesti

Oportunističke bolesti

- Plućne infekcije (Pneumocystis jirovecii, Mycobacterium tuberculosis)
- Gastrointestinalne infekcije (Candida, Salmonella, Shigella...)
- Neurološke smetnje (Toxoplasma gondii, Cryptococcus neoformans...)
- Tumori (Kaposijev sarkom, Burkittov limfom, Hodgkinsova bolest)