UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

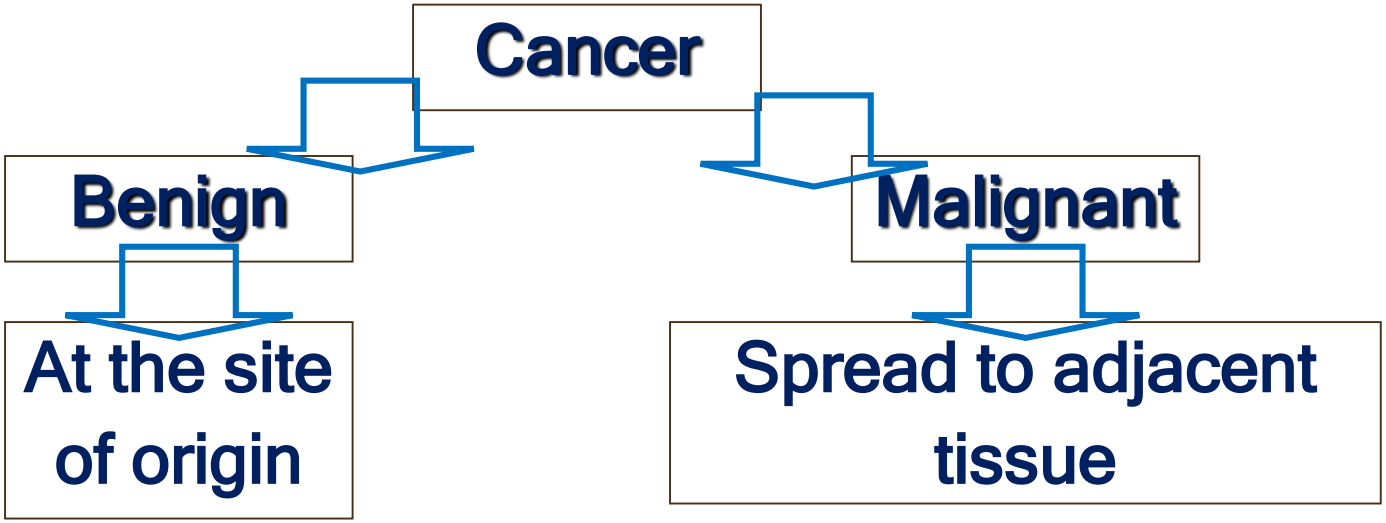
Subject: Virology faculty lectures
Topic: Oncogenic viruses

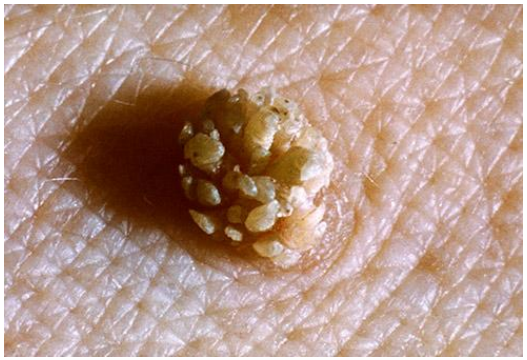
Academic Year 2024/2025

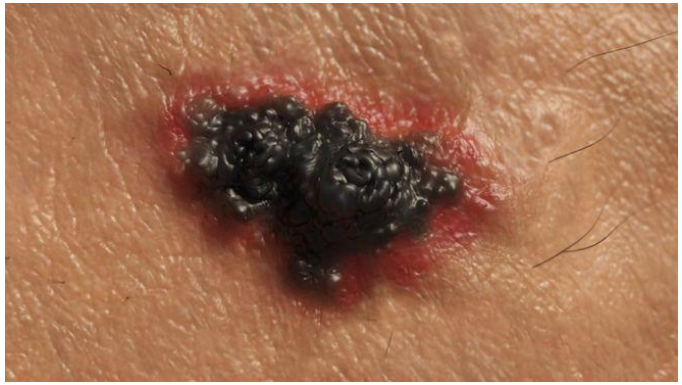
Faculty: Medicine
Field of study: Medicine
Level of study (unif. Master's):
Form of study (full time, part-time):
Year of study: II, III

Academic title/professional title: prof. dr hab.
Name, last name of the lecturer: Beata Sobieszczańska
Position of person conducting classes: professor
Wroclaw Medical University

Cancer = uncontrolled proliferation of cells







There is no single mechanism by which viruses cause tumors

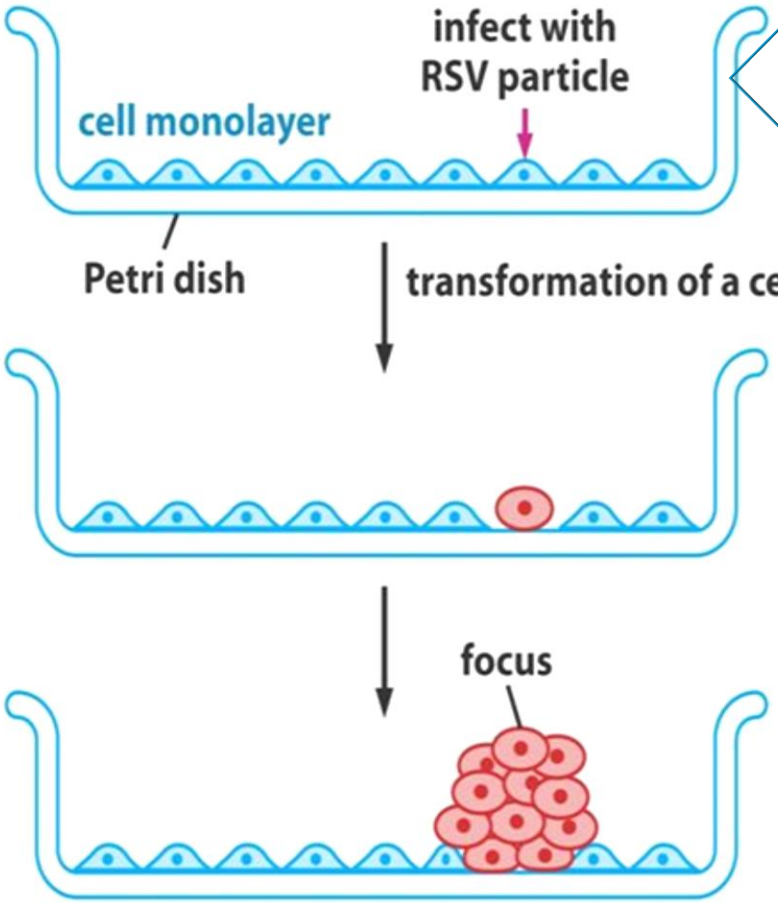
Transformation

- **Transformation** = alteration in a cell's properties that leads to immortalization and different growth

Transformed cells show alterations:

- **growth rate** – loss of contact inhibition; grow and divide indefinitely (immortalization) and more rapidly
- **morphology** – loss of differentiated shape (rounded)
- **chromosomal changes** – the appearance of new antigens
- **biochemical properties** – decreased requirements for growth factors; ECM digesting enzymes

Focus formation by an RNA Tumor Virus



Rous sarcoma virus

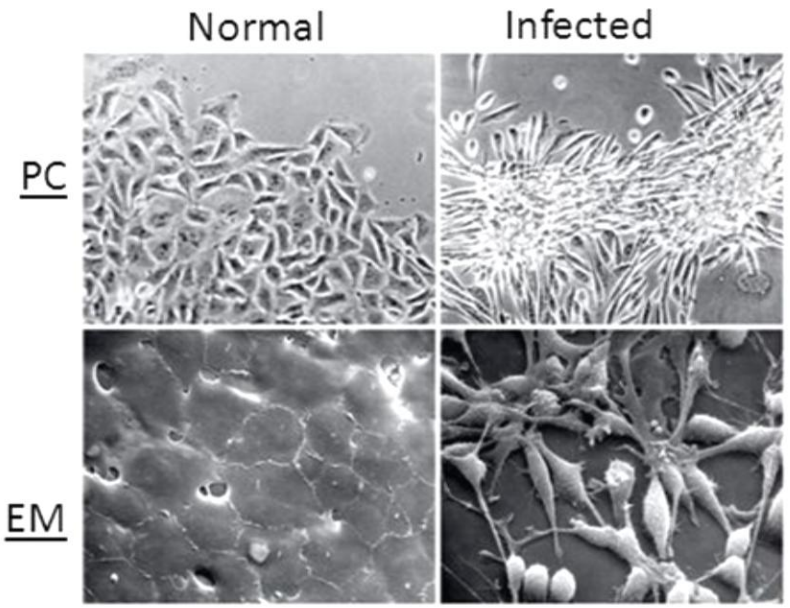
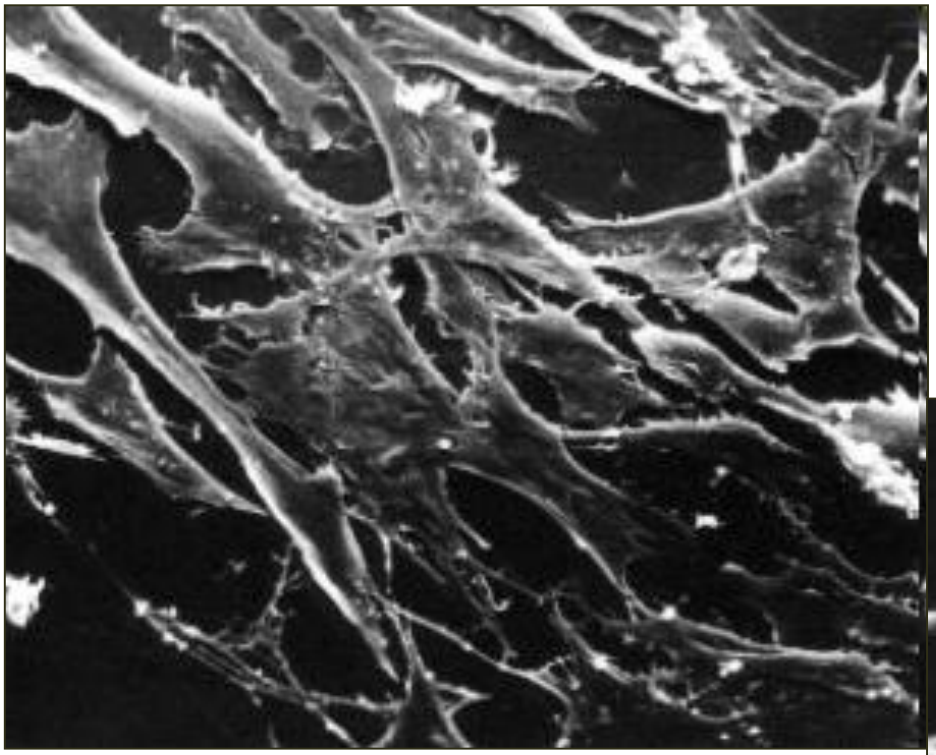
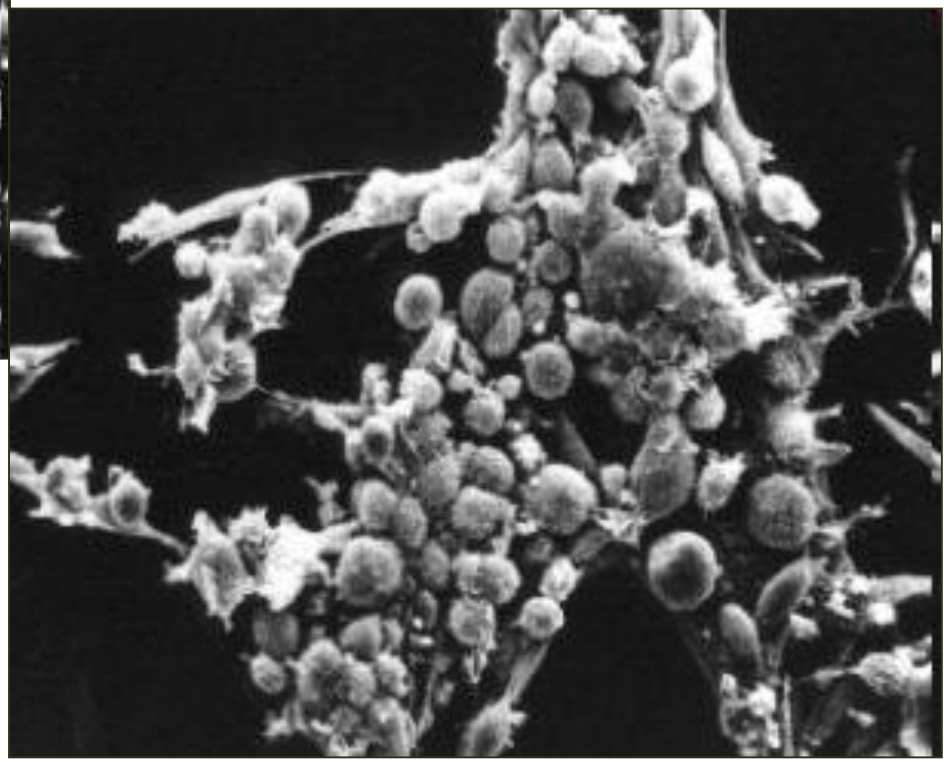


Figure 3.7a *The Biology of Cancer* (© Garland Science 2007)

Transformation



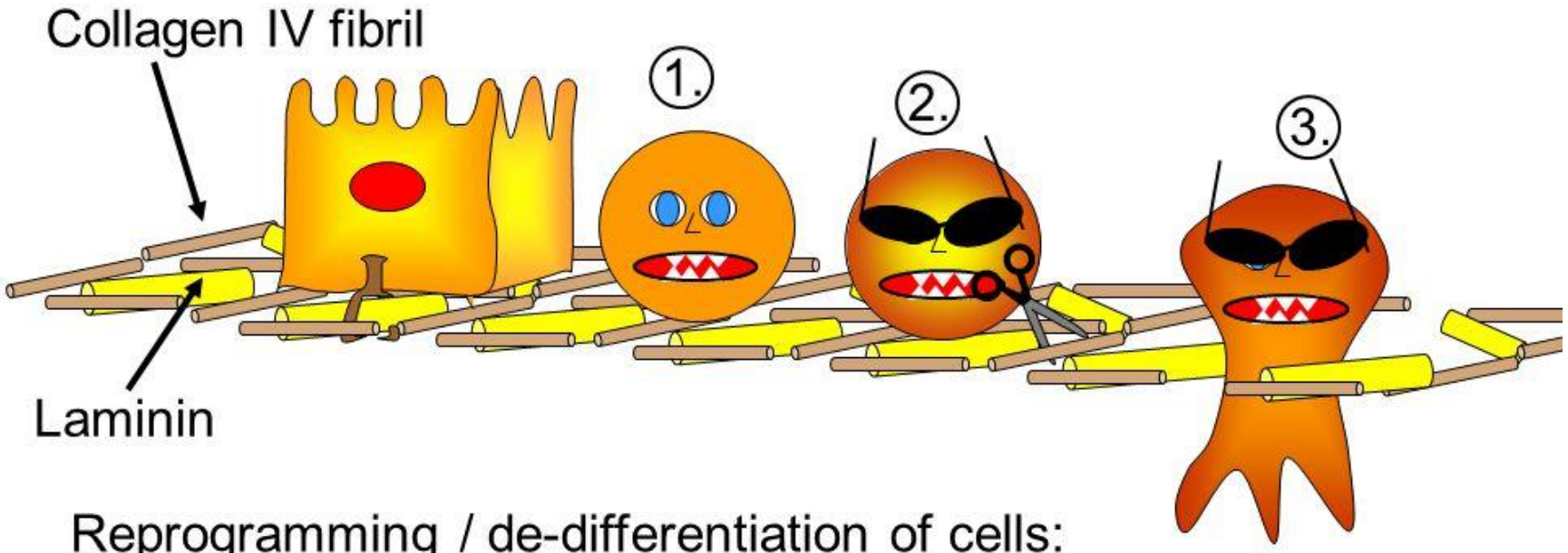
normal cells



transformed cells

Colorectal cancer (CRC) cancerous polyps

6. Penetration of basal lamina



Reprogramming / de-differentiation of cells:

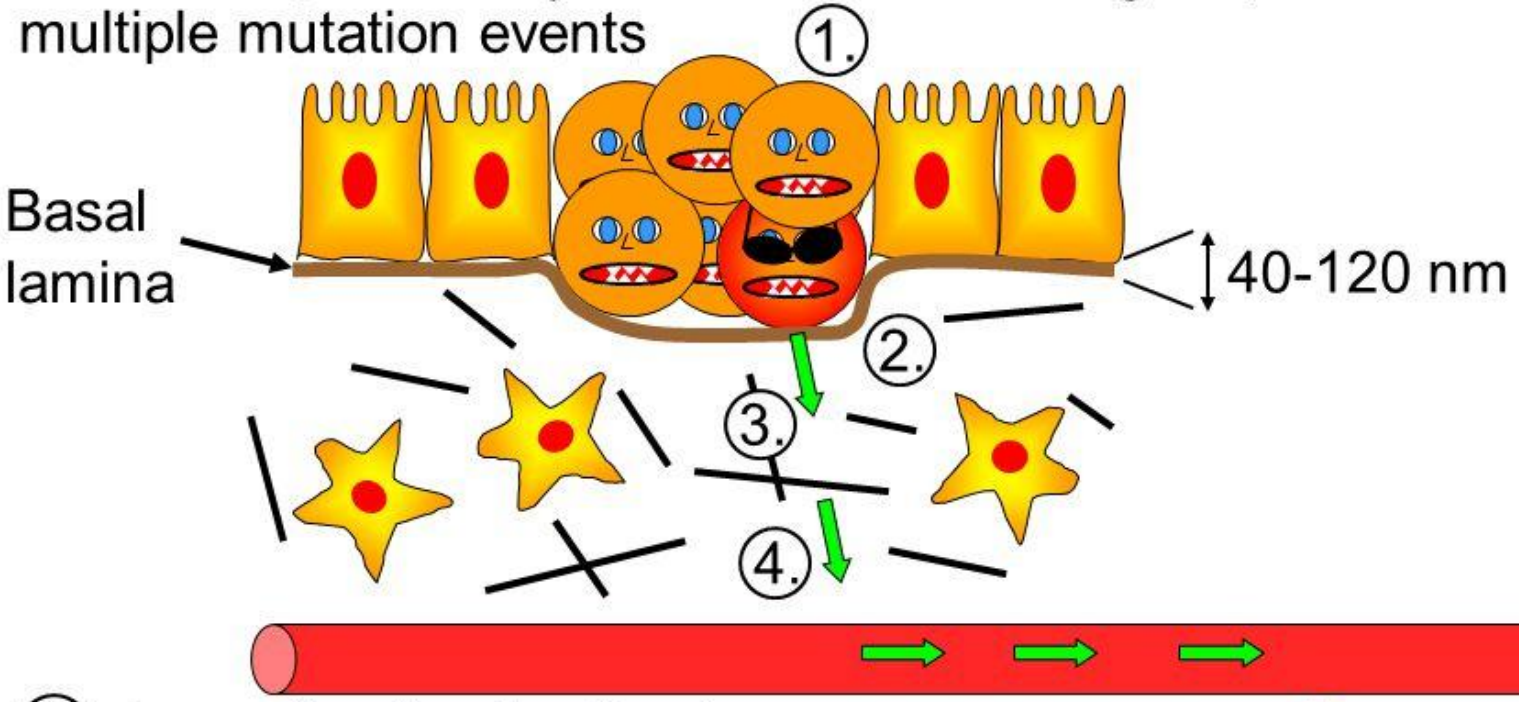
① Loss of hemidesmosomes/laminin receptor (integrin)

② Expression of collagenase

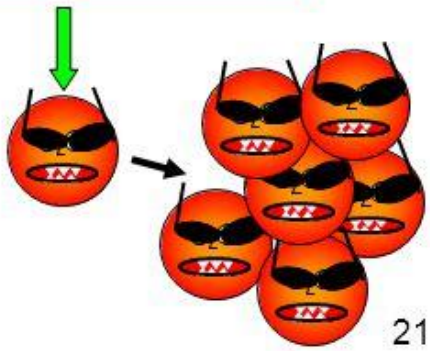
③ Cytoskeletal changes
→ Epithelial–mesenchymal transition (EMT)

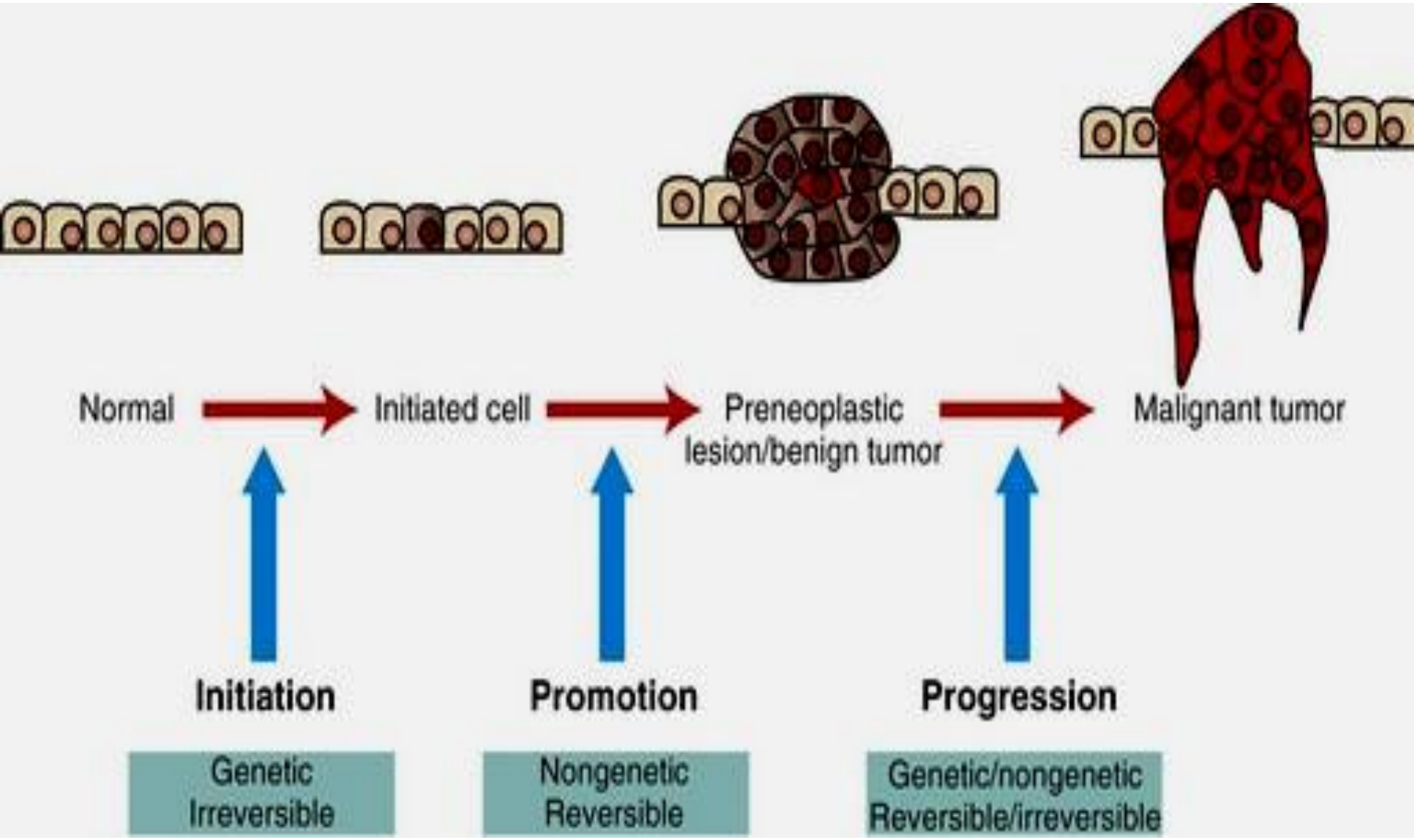
6. Metastasis capability

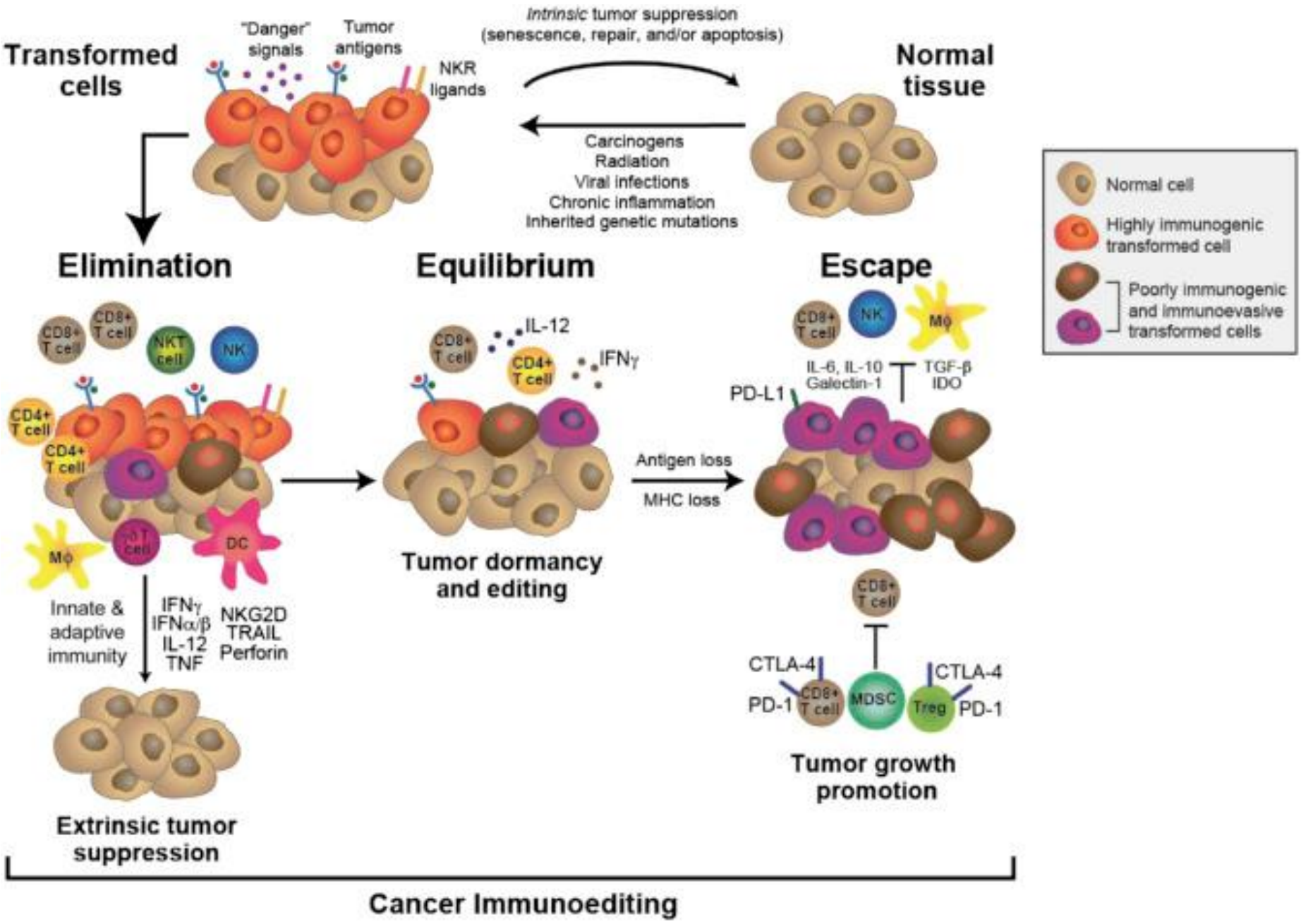
Metastasis, the ability of cancer cells to migrate, results from multiple mutation events



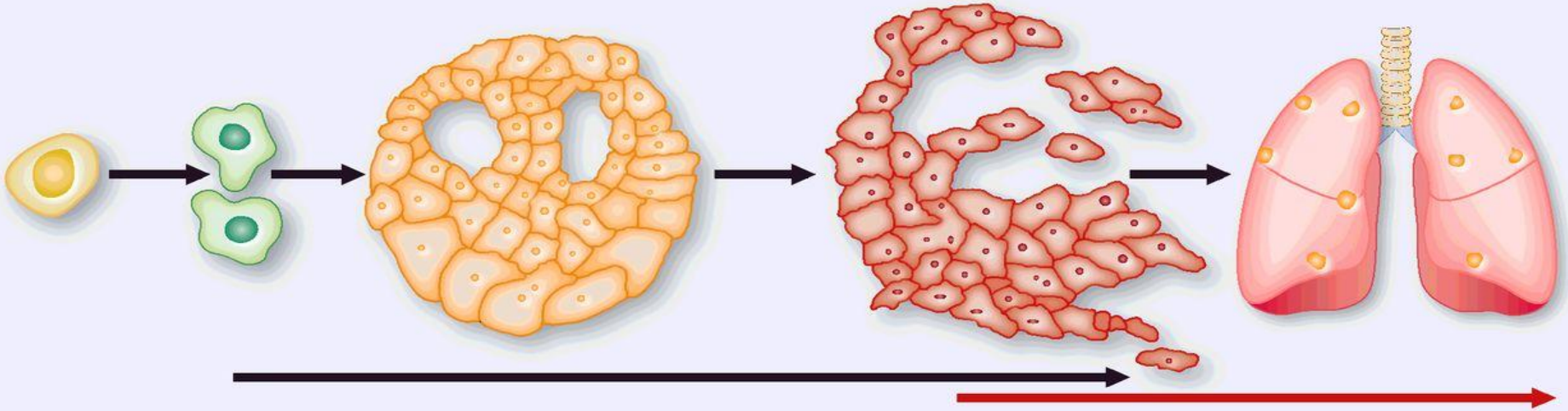
1. Loss of cell-cell adhesion
2. Loss of hemidesmosomes
3. Proteolytic degradation of the ECM
4. Migration through the ECM




Normal
Initiated cell
Preneoplastic lesion/benign tumor
Malignant tumor
Initiation
Promotion
Progression
Genetic
Irreversible
Nongenetic
Reversible
Genetic/nongenetic
Reversible/irreversible


Transformed cells
"Danger" signals
Tumor antigens
NKR ligands
Intrinsic tumor suppression (senescence, repair, and/or apoptosis)
Normal tissue
Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations
Elimination
Equilibrium
Escape
CD8+ T cell
NKT cell
NK
CD4+ T cell
γδ T cell
DC
Mϕ
IL-12
IFNγ
Innate & adaptive immunity
IFNγ
IFNα/β
IL-12
TNF
NKG2D
TRAIL
Perforin
Tumor dormancy and editing
Antigen loss
MHC loss
IL-6, IL-10
Galectin-1
TGF-β
IDO
PD-L1
CTLA-4
PD-1
MDSC
Treg
Tumor growth promotion
Extrinsic tumor suppression
Cancer Immunoediting
Normal cell
Highly immunogenic transformed cell
Poorly immunogenic and immunoevasive transformed cells

Neoplastic progression



Hallmarks of cancer

Immortal
Genetically unstable
Sustained proliferation
Evades apoptosis
Altered metabolism
Inflammation
Evade immune killing
Angiogenic
Resist growth suppression
Invasion

Hallmarks of metastasis

Motility & invasion
Modulate microenvironment
Plasticity
Colonization

Oncovirus, oncogenic virus, transforming virus, tumor virus

=

A virus capable of inducing tumors

or virus that can cause cancer

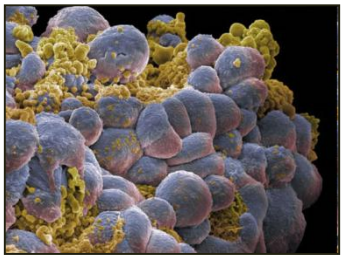
tumor viruses

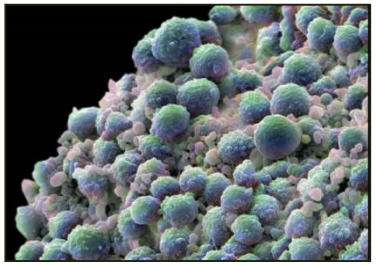
RNA

HTLV-1
HCV

DNA

EBV
HHV-8
HPV
HBV
MCV





- 15% of human cancers are associated with viral infections, but virus is not only factor
- Host immunity and chronic inflammation play an important role in promoting conditions for neoplastic cells development

Virus	Route of Transmission	Human cancer
EBV	saliva	BL, NPC, HL, PTL
HPV	sexual	cervical, oral, anal carcinoma, warts
HCV	sexual post-transfusion IV drug users	hepatocarcinoma
MCPyV	respiratory route	Merkel cell carcinoma
HBV	sexual perinatal	hepatocarcinoma
HHV-8	sexual	Kaposi's sarcoma
HTLV-1	sexual perinatal	ATL

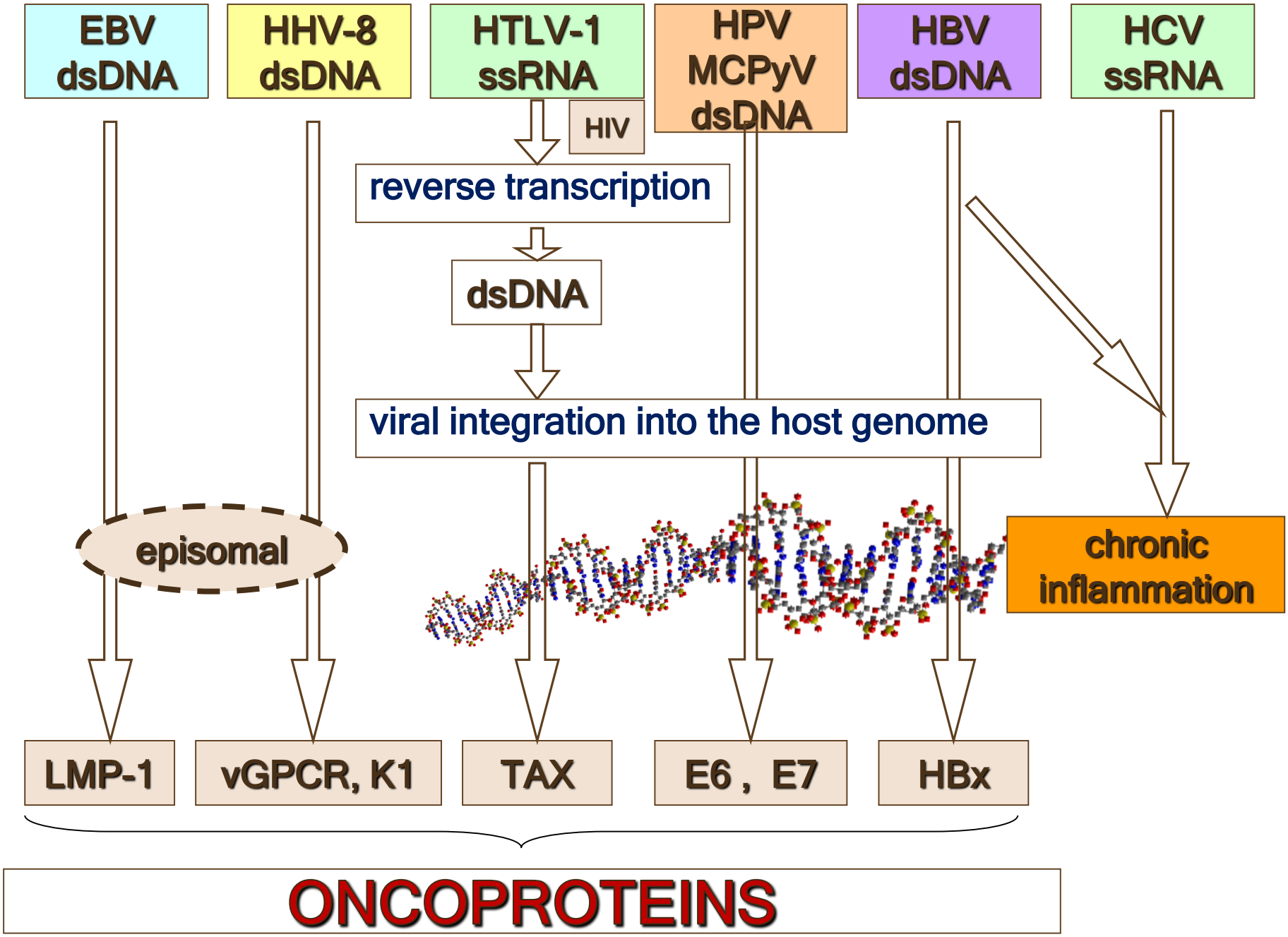
How viruses can transform host cells?

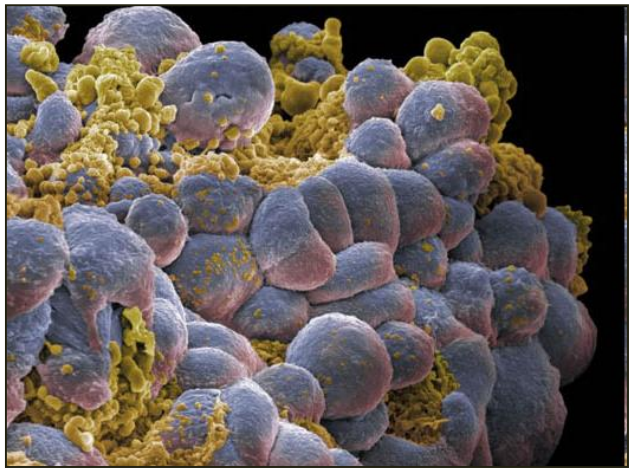
By forcing host non-proliferating cell to proliferate

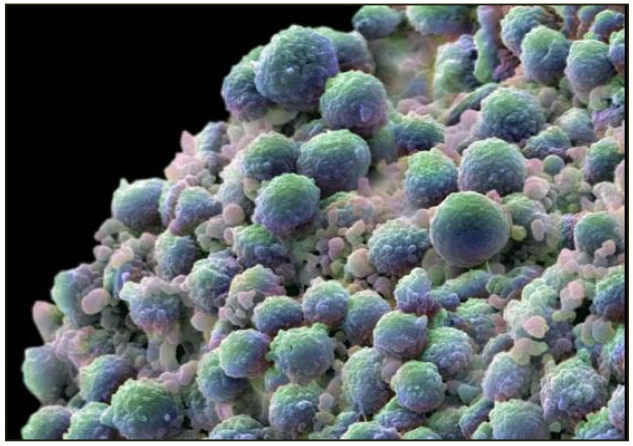
By manipulating the host immune response

Persistent viral infections

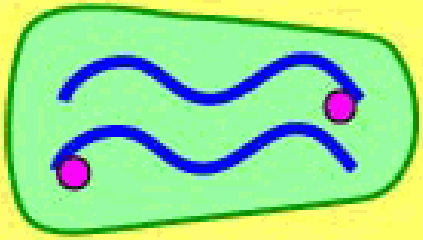
= virus is not cleared following primary infection but remains in specific cells of infected individuals

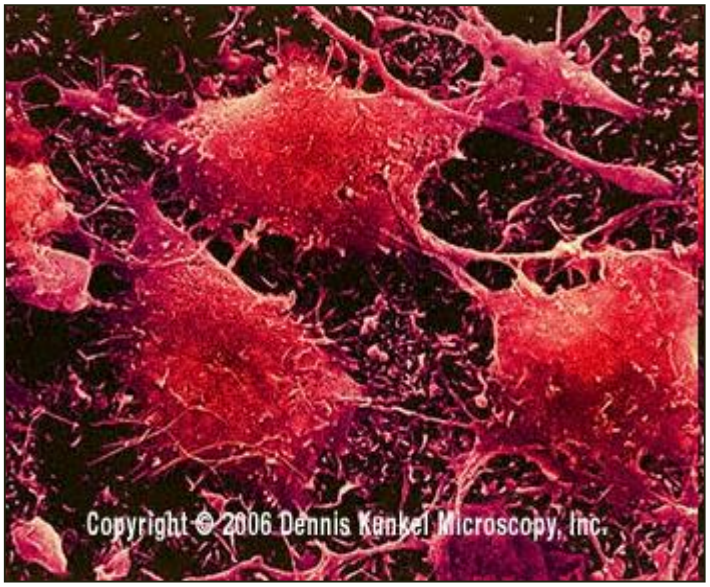

EBV
dsDNA
HHV-8
dsDNA
HTLV-1
ssRNA
HPV
MCPyV
dsDNA
HBV
dsDNA
HCV
ssRNA
HIV
reverse transcription
dsDNA
viral integration into the host genome
episomal
chronic
inflammation
LMP-1
vGPCR, K1
TAX
E6 , E7
HBx
ONCOPROTEINS





Uncoating and Production of a Provirus

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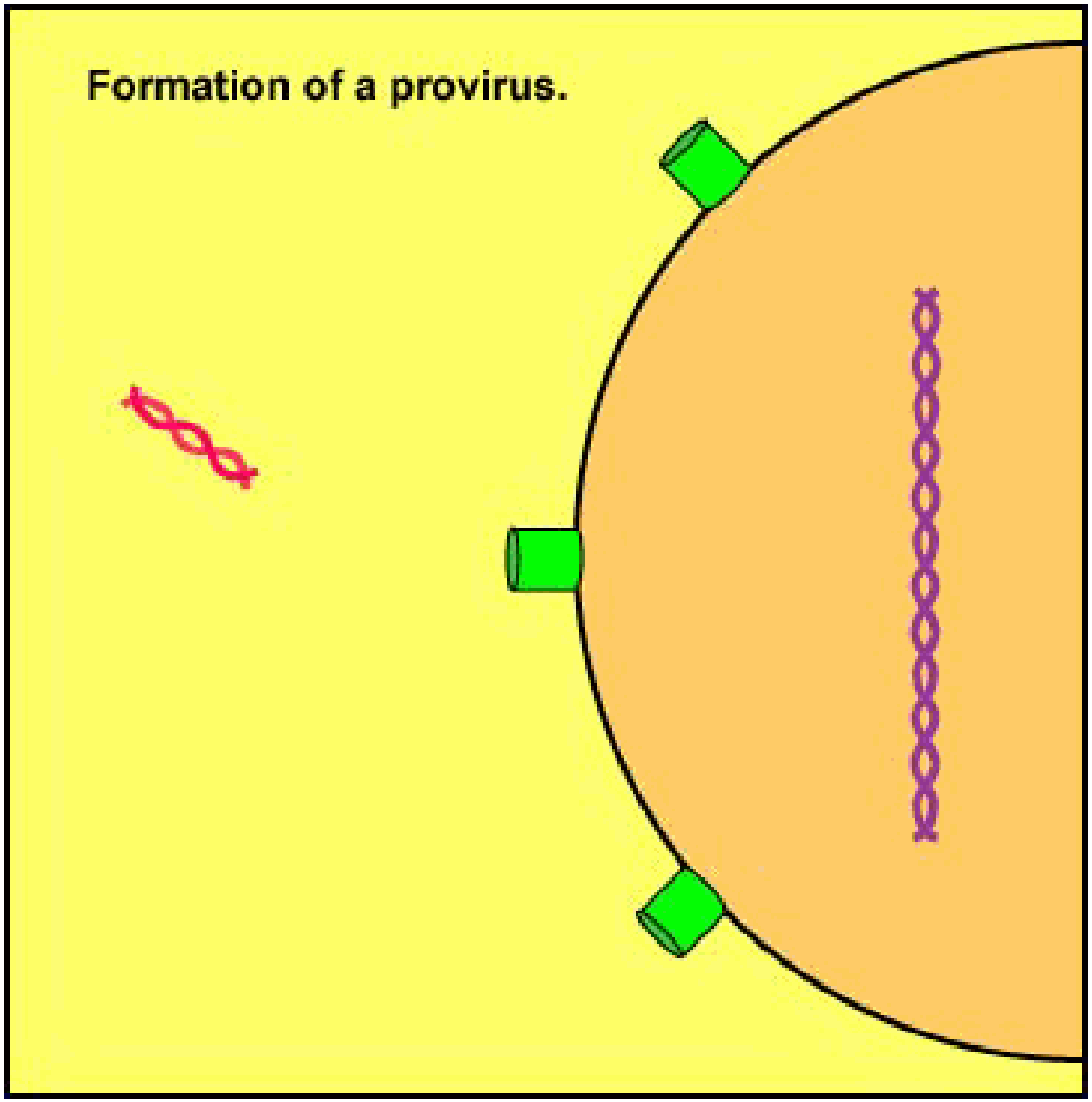
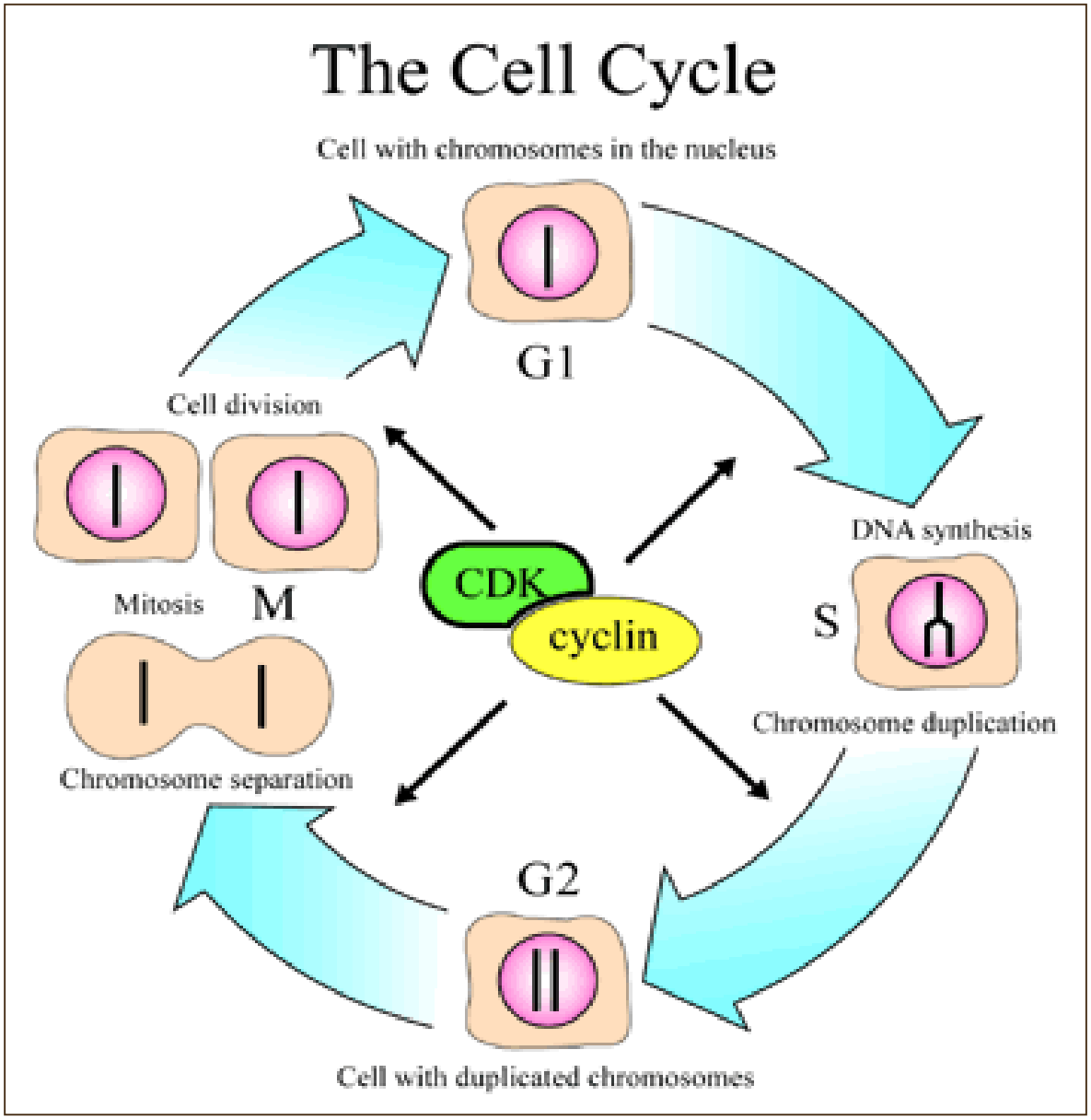

Formation of a provirus.

Cell cycle


The Cell Cycle
Cell with chromosomes in the nucleus
G1
DNA synthesis
S
Chromosome duplication
G2
Cell with duplicated chromosomes
Mitosis
M
Chromosome separation
Cell division
CDK
cyclin

Cell cycle regulation:

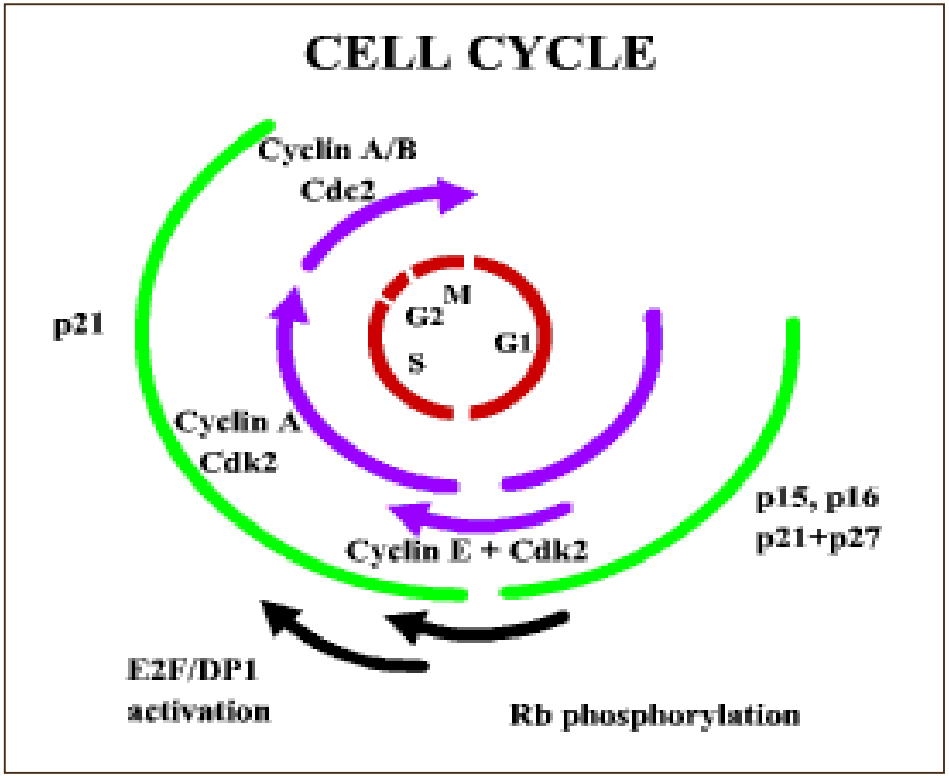
Proto-oncogenes (cellular oncogene *c-onc*) promote normal cell growth (positive growth regulators)

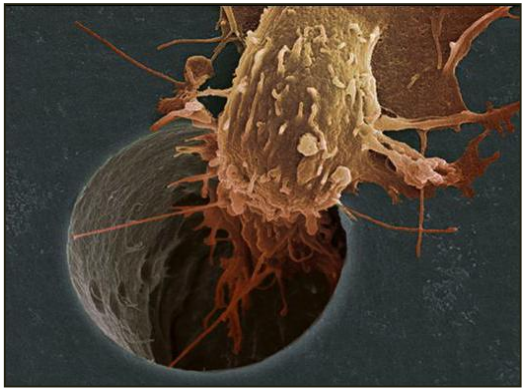
Mutations convert them into **oncogenes**

= **cancer causing genes**

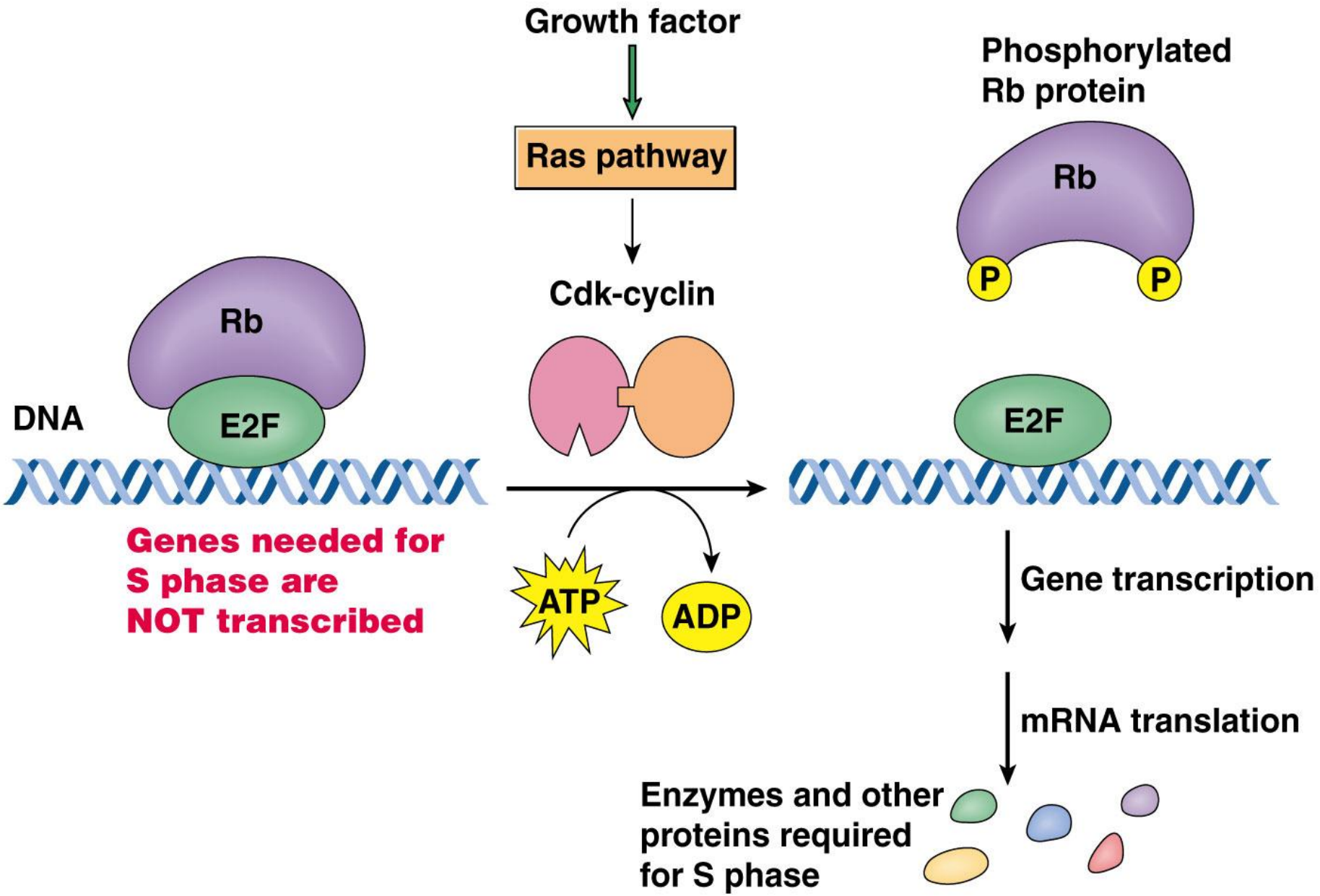
Tumor suppressor genes (pRb, p53) restrain cell growth (upon cellular stress) to give a cell time to repair or trigger apoptosis

Tumor suppressor Rb

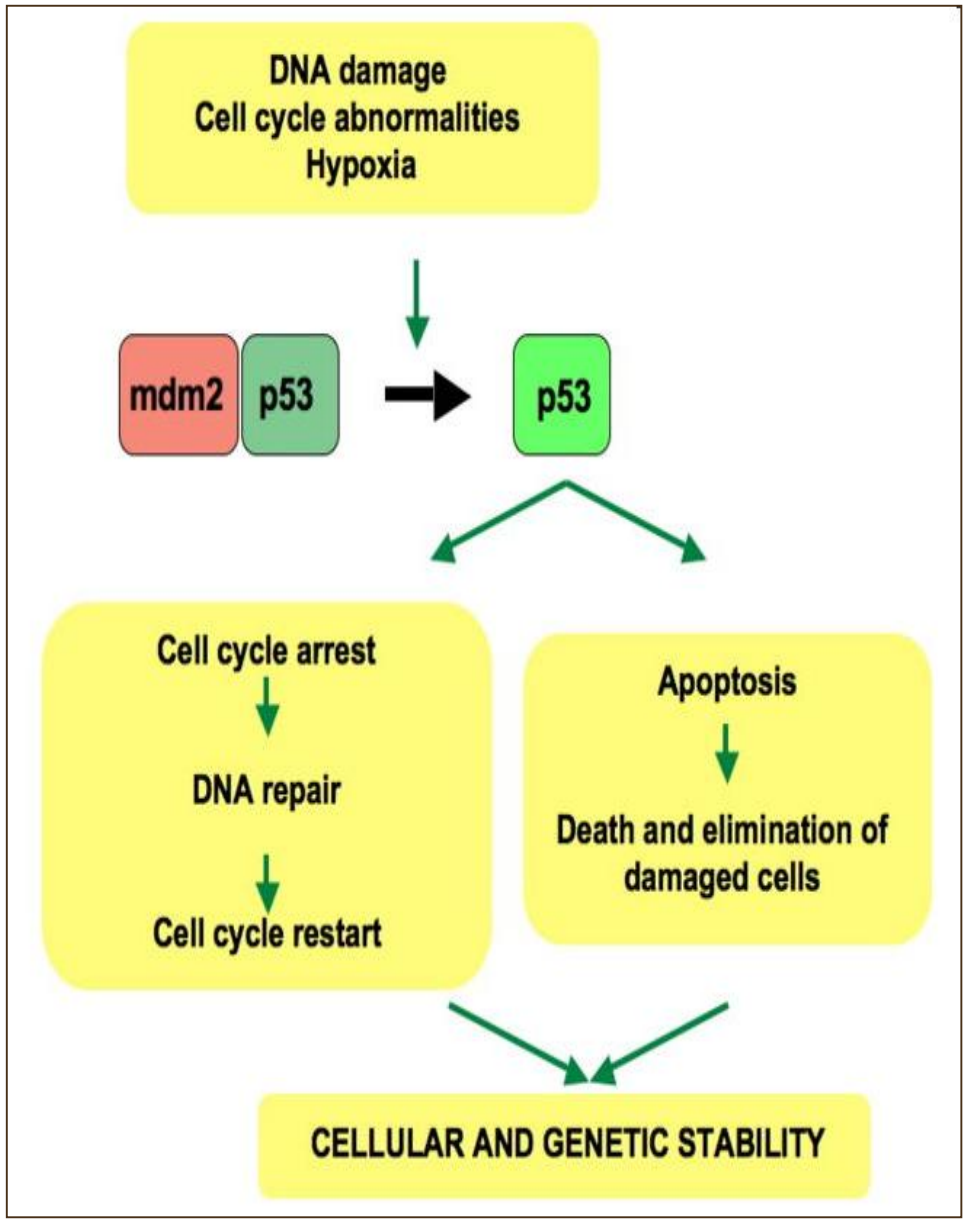




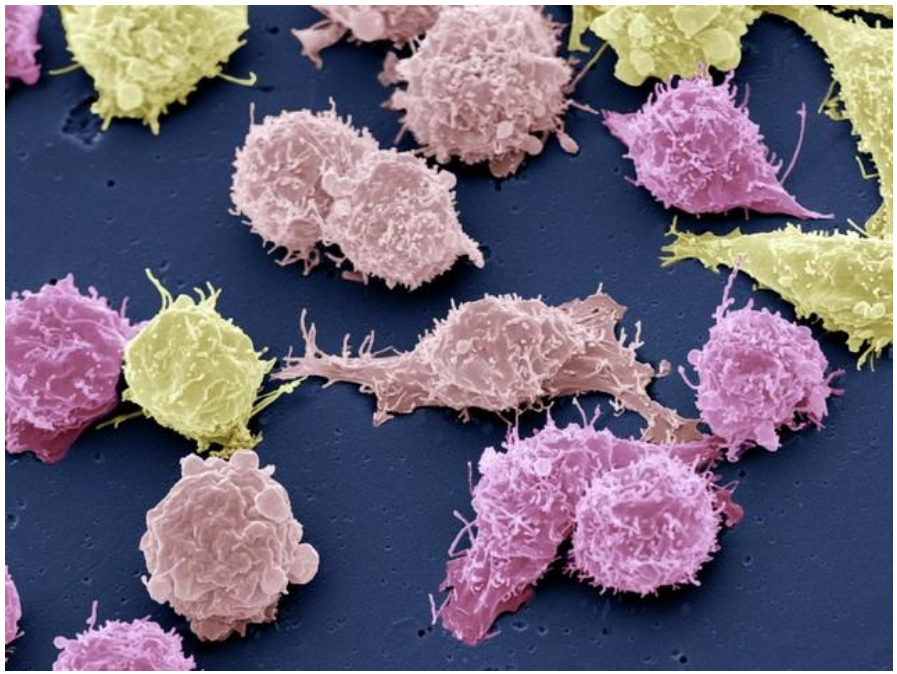
pRB (retinoblastoma gene product) binds to transcription factor E2F and prevents gene expression of proteins needed to go to the S phase



Tumor suppressor p53



P53 halts cell cycle progression when DNA is damaged



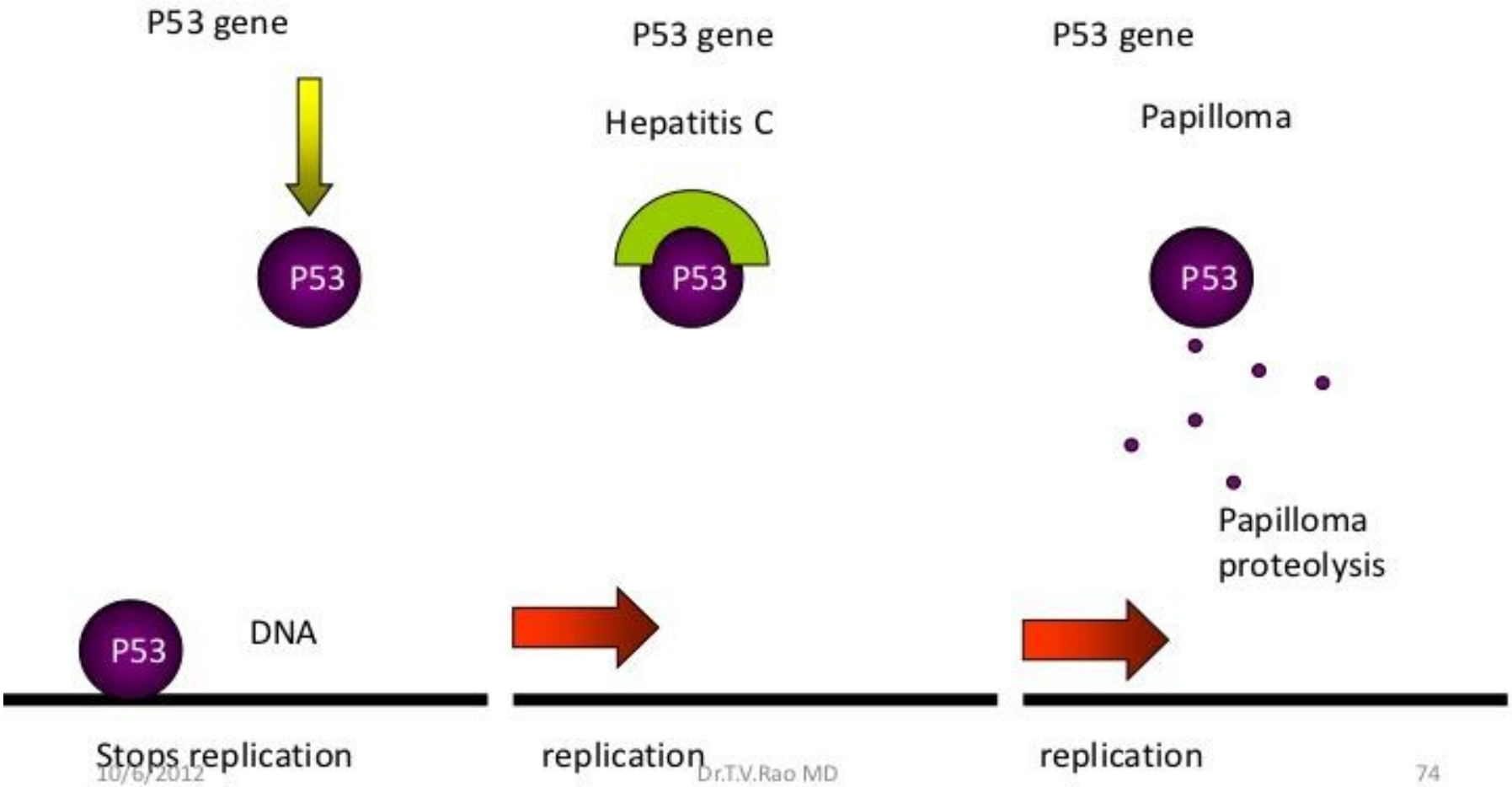
Viral oncogenes

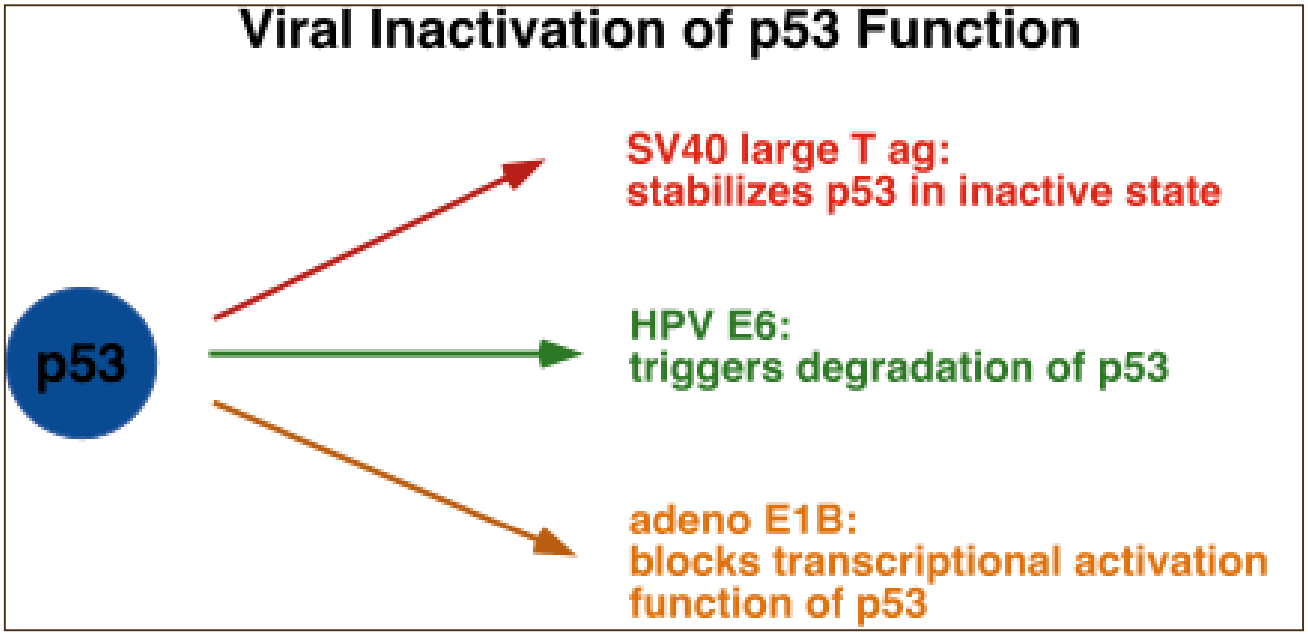
v-onc = altered form of *c-onc*

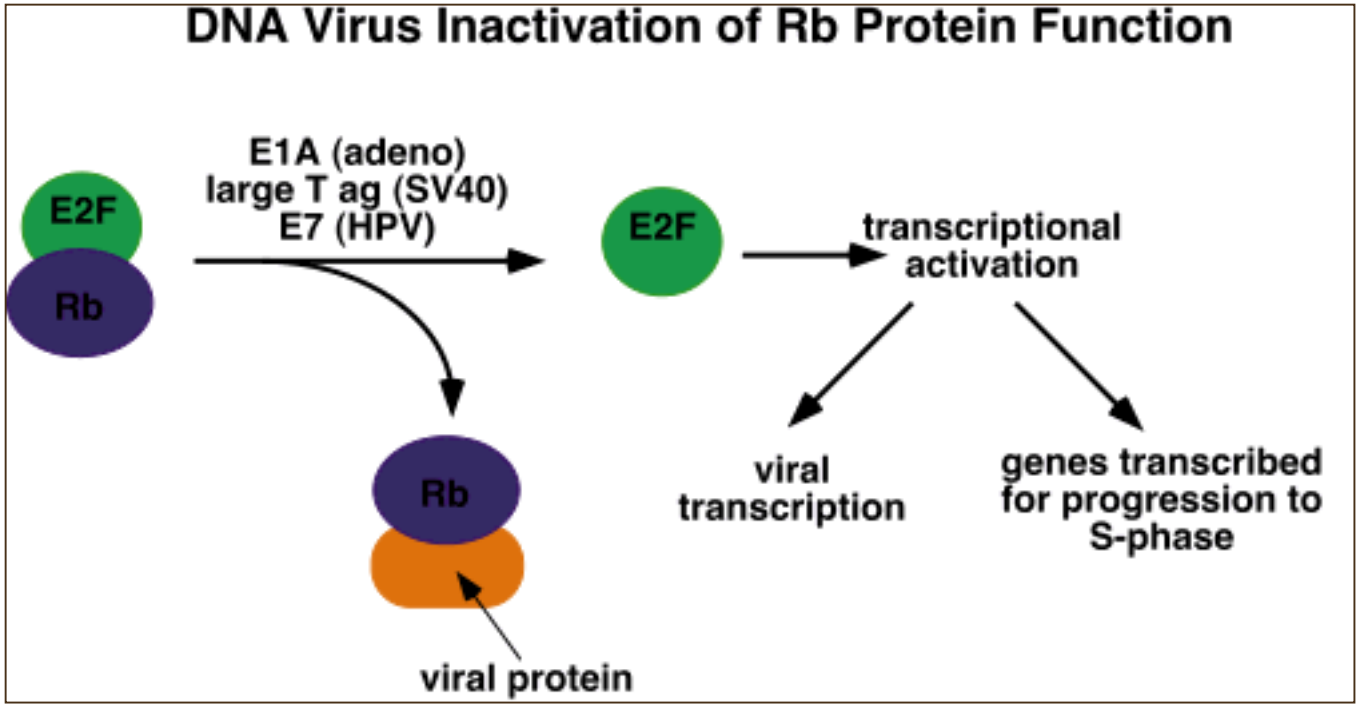
- Oncogenes are normal virus early genes (used in replication)
- Viral oncogenes may:
  - Integrate as part of their cycle (retroviruses)
  - Viral ORI (origin of replication sequences) and genes push cell to S phase (herpes, papilloma)

Anti-Oncogenes

p53

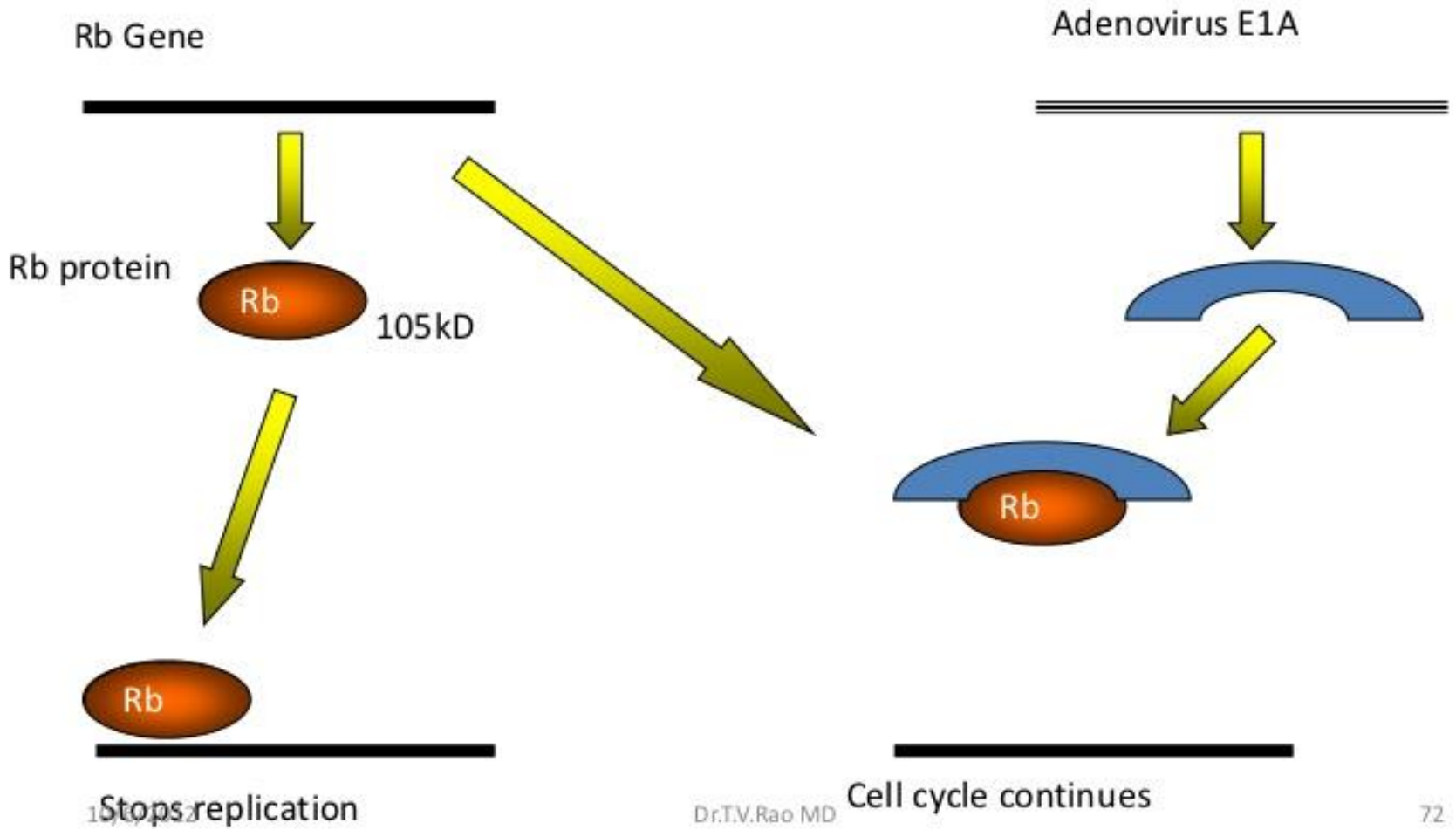



Viral Inactivation of p53 Function
p53
SV40 large T ag:
stabilizes p53 in inactive state
HPV E6:
triggers degradation of p53
adeno E1B:
blocks transcriptional activation
function of p53


DNA Virus Inactivation of Rb Protein Function
E2F
Rb
E1A (adeno)
large T ag (SV40)
E7 (HPV)
E2F
transcriptional
activation
Rb
viral protein
viral
transcription
genes transcribed
for progression to
S-phase

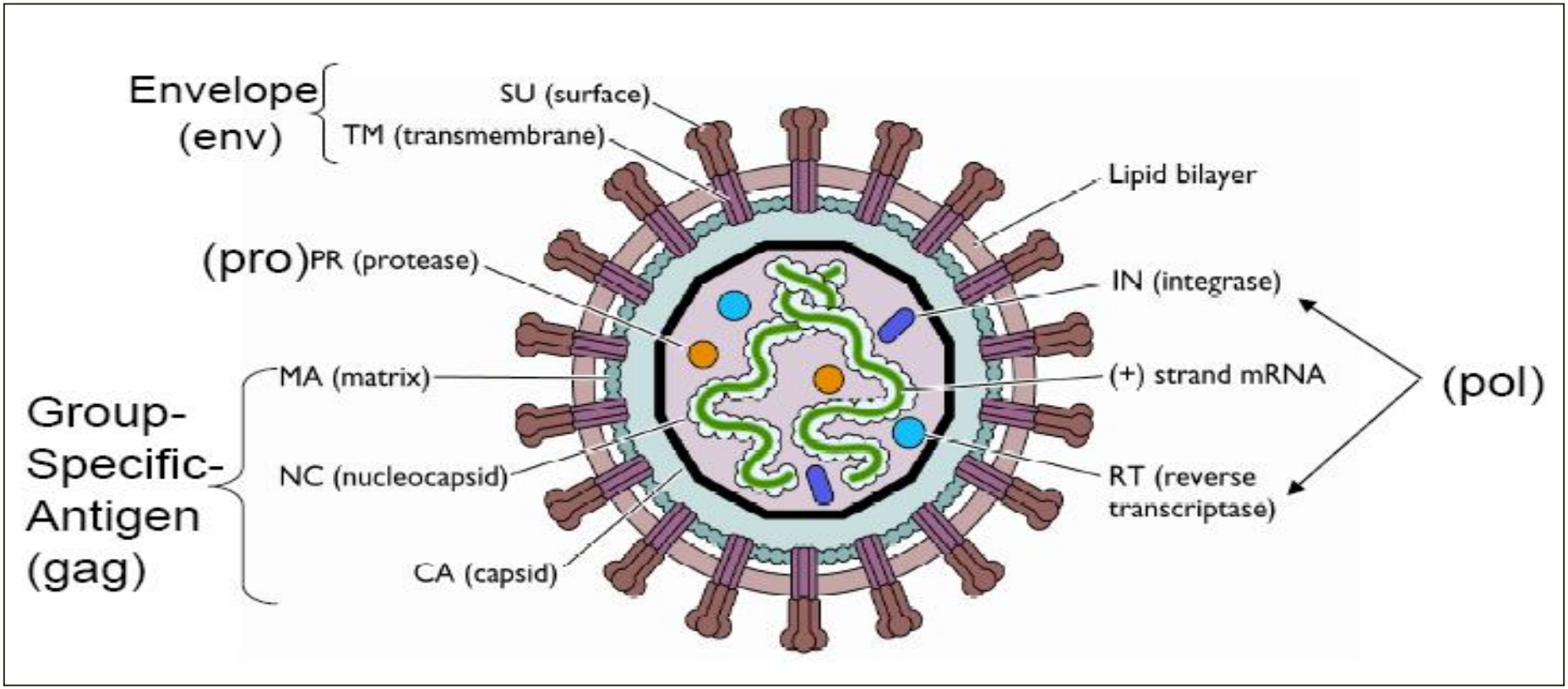
Anti-Oncogenes

Retinoblastoma



Retroviruses

Retroviruses may transform cells into three different mechanisms



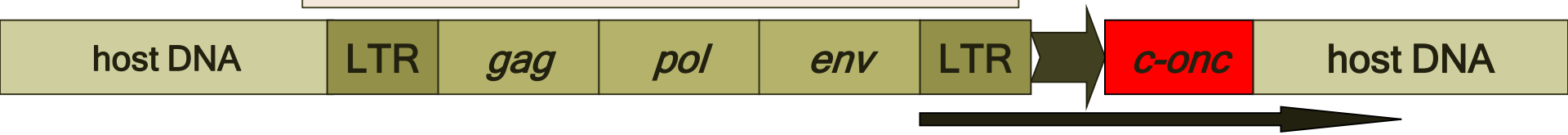
Retroviruses

	HIV-1	HTLV-1
Prevalence	35 million people	20 million people
Transmission	· Sexual transmission · Parenteral transmission (blood transfusions, organ transplantation, and via infected sharp objects) · Mother to child (breast-feeding and during delivery)	· Sexual transmission · Parenteral transmission (blood transfusions, organ transplantation, and via infected sharp objects) · Mother to child (breast-feeding and during delivery)
Endemic areas	Africa, Eastern Europe, South Asia, and China	Caribbean region, Central Africa, and South Japan

LTR (long terminal repeats) = virus LTR is a strong promotor

Transformation by Retroviruses

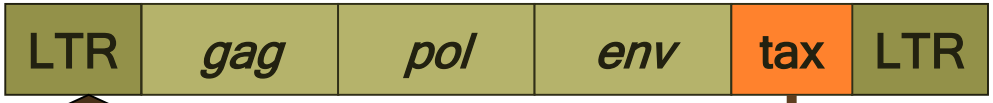
Insertional mutagenesis

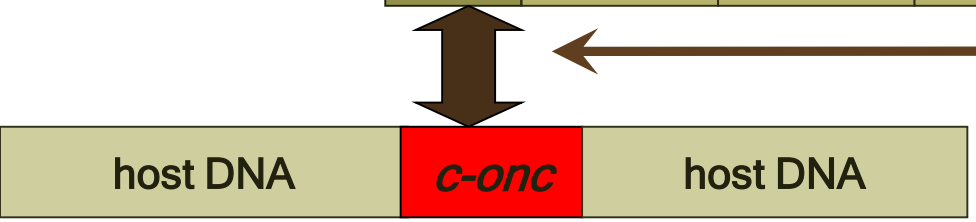


Transductional mutagenesis

GROWTH SUPPRESSORs INACTIVATION

Oncogene transactivation





Retroviruses

HTLV-1 (Human T-cell Leukemia Virus-1) is a T-cell tropic virus (promotes T-cell activation and proliferation)

Causes: adult T-cell leukemia (ATL) and progressive myelopathy (HAM)

ssRNA with retroviral genes encoding for:

- the core proteins (*gag*)
- reverse transcriptase (*pol*)
- surface glycoprotein for receptor binding (*env*)
- transcriptional activator (tax)

Retroviruses

HTLV-1, after reverse transcription into a dsDNA, is integrated (provirus) randomly into the host chromosome

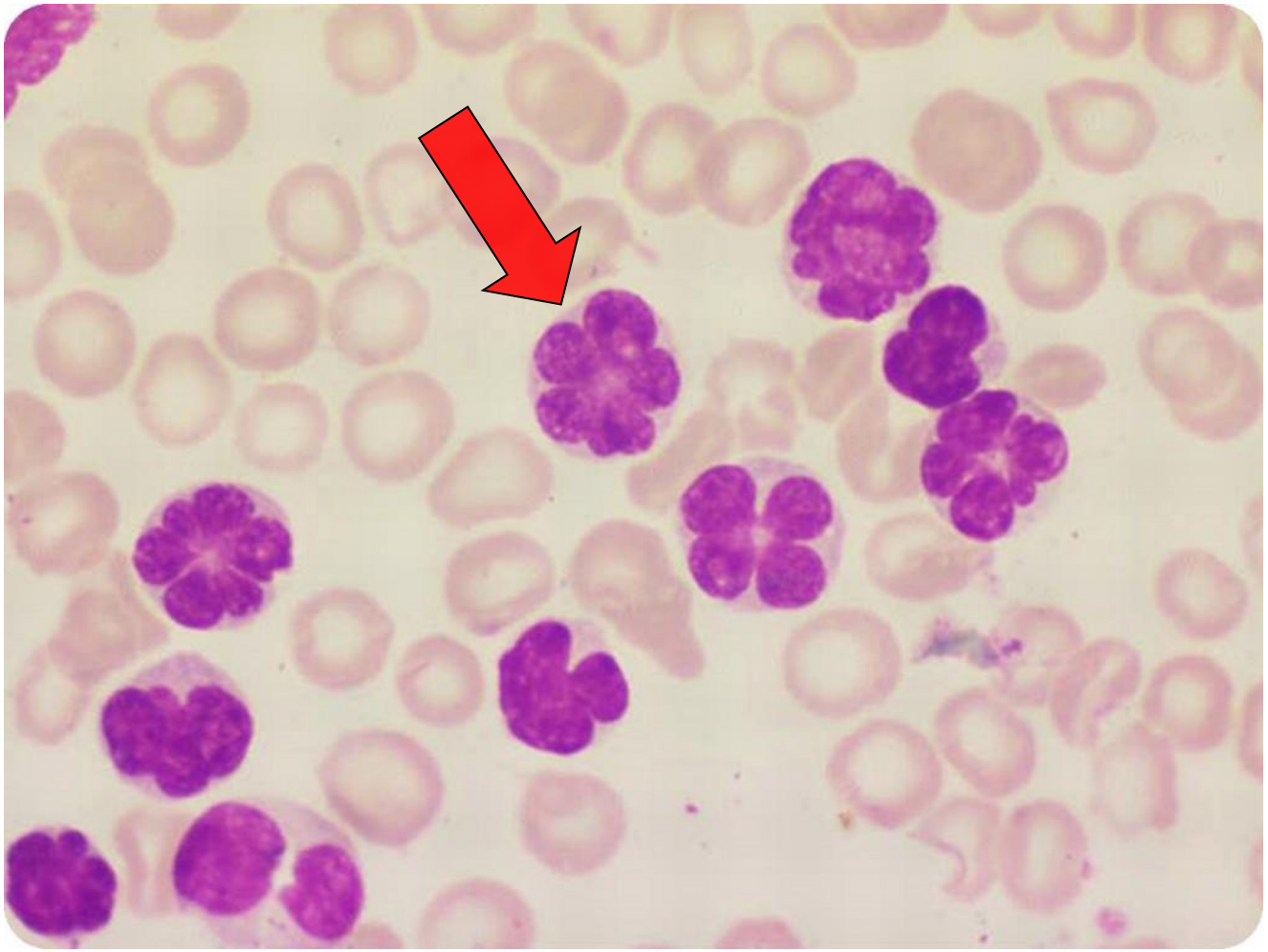
HTLV-1 contains a unique region (pX) encoding the Tax protein

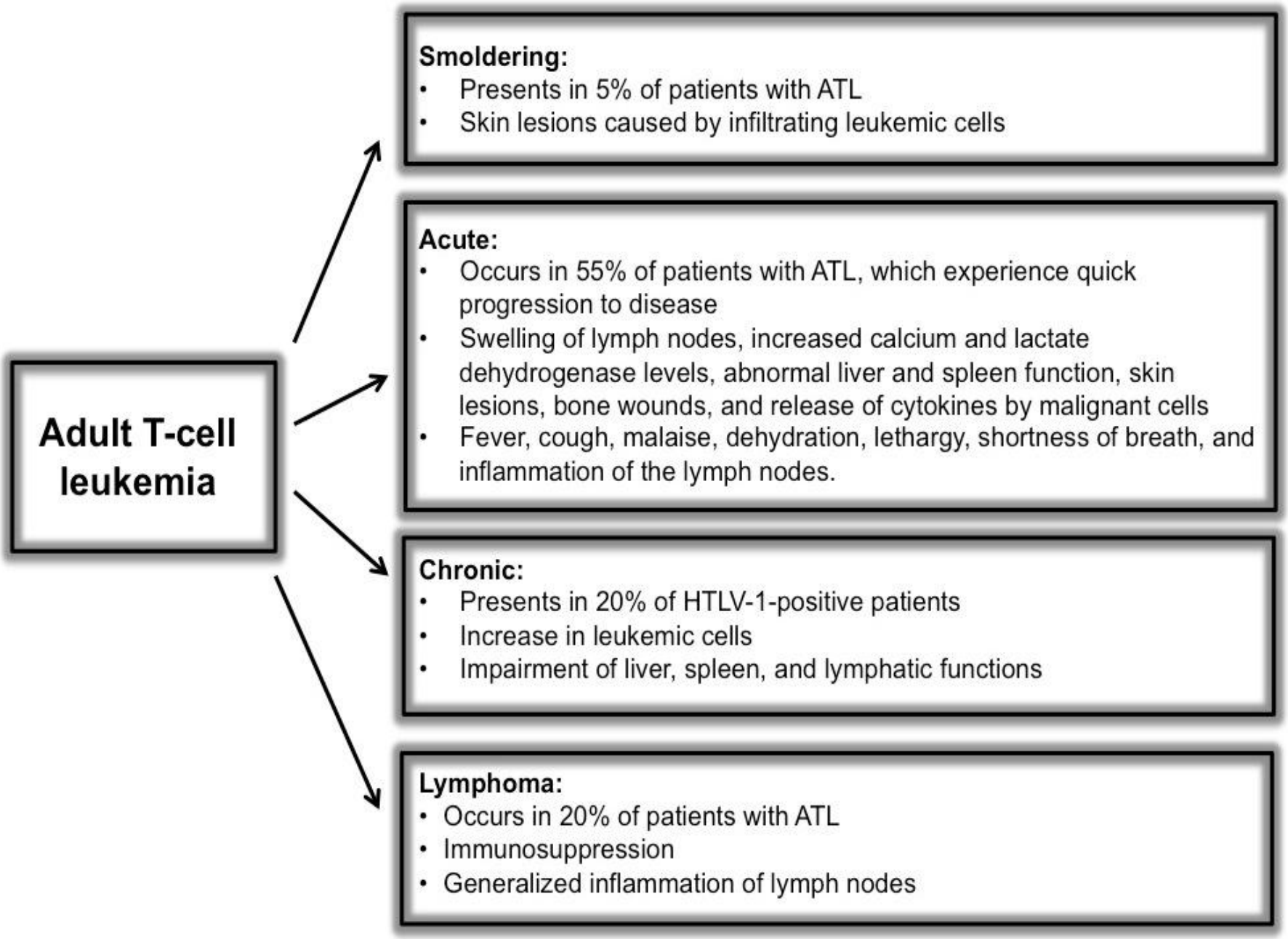
Tax promotes viral and cellular gene expression through the activation of transcriptional factors with further modification of the signal transduction

Effect: resistance to apoptosis (interaction with pRb) and cell proliferation

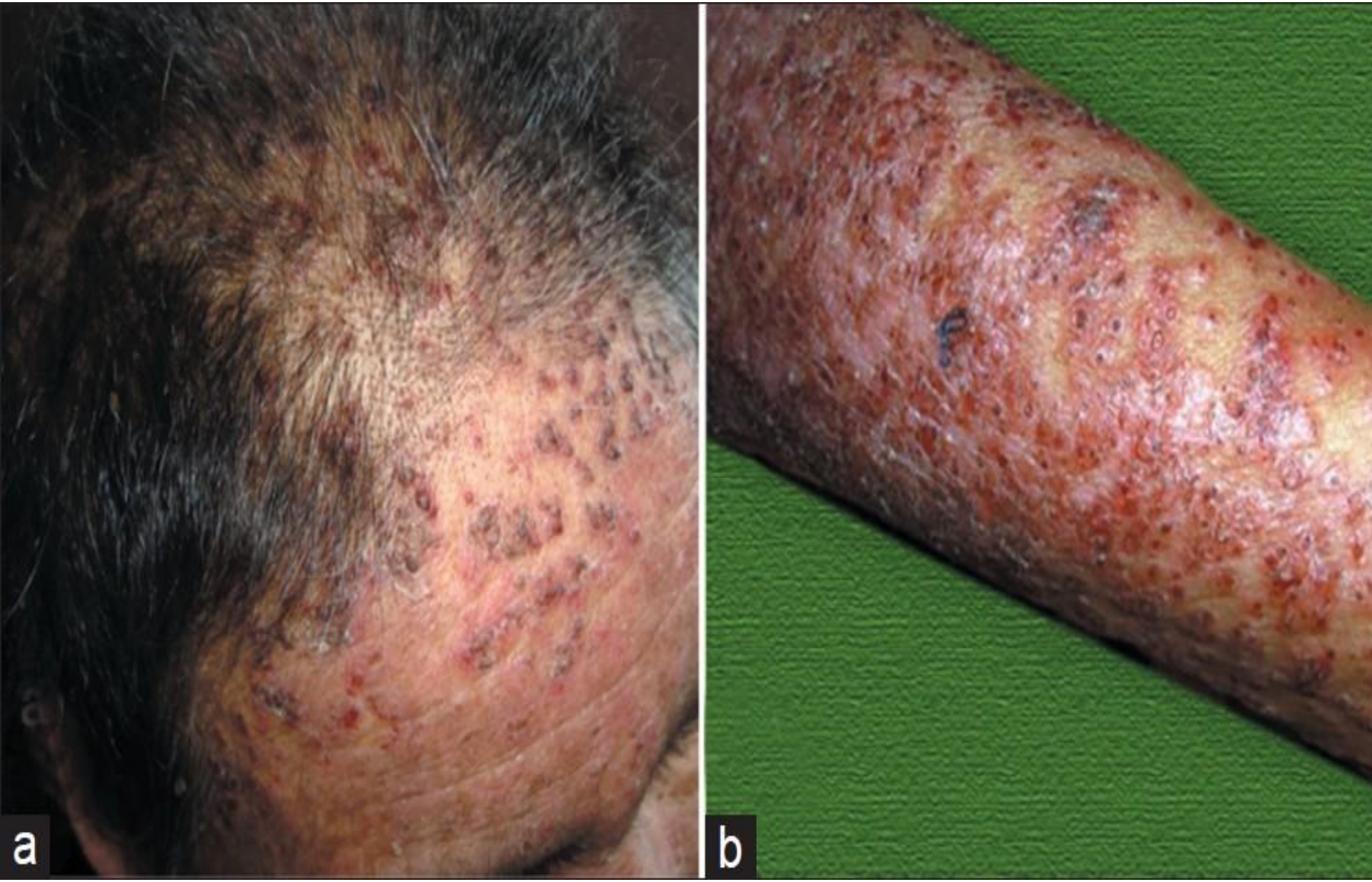
Retroviruses

HTLV-1: adult T-cell leukemia blood smear showing a typical flower cell



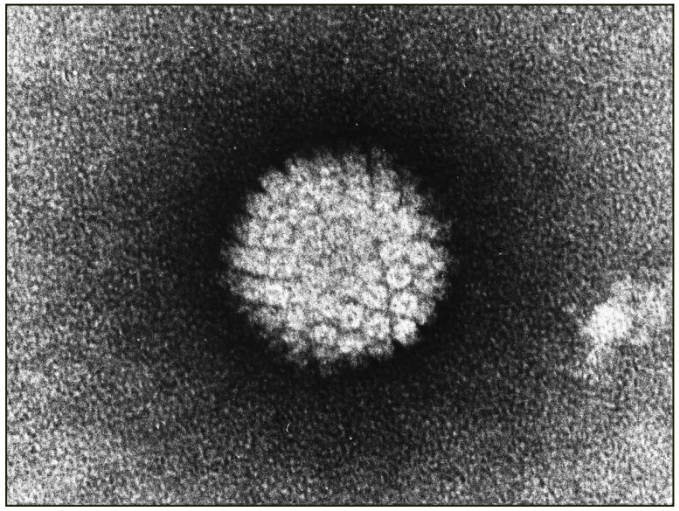

Adult T-cell leukemia
Smoldering:
• Presents in 5% of patients with ATL
• Skin lesions caused by infiltrating leukemic cells
Acute:
• Occurs in 55% of patients with ATL, which experience quick progression to disease
• Swelling of lymph nodes, increased calcium and lactate dehydrogenase levels, abnormal liver and spleen function, skin lesions, bone wounds, and release of cytokines by malignant cells
• Fever, cough, malaise, dehydration, lethargy, shortness of breath, and inflammation of the lymph nodes.
Chronic:
• Presents in 20% of HTLV-1-positive patients
• Increase in leukemic cells
• Impairment of liver, spleen, and lymphatic functions
Lymphoma:
• Occurs in 20% of patients with ATL
• Immunosuppression
• Generalized inflammation of lymph nodes

Retroviruses



Papovaviridae

- Genus: Papillomavirus
- Genus: Polyomavirus: JC i BK (human)
  SV40 (simian)
  MCPyV human cancer



Icosahedral non-enveloped
dsDNA

Papillomavirus (HPV)

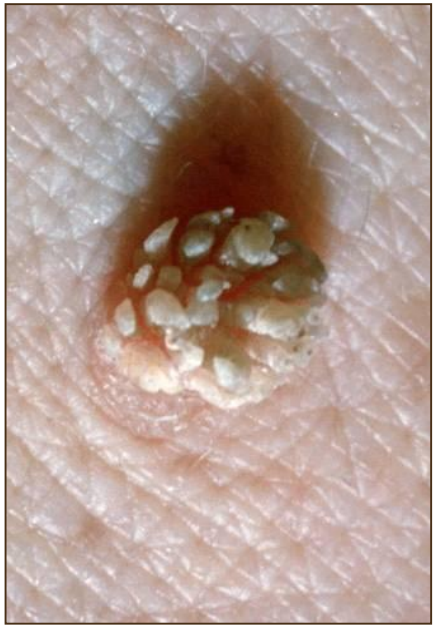
- **Permissive cell** = virus replication, cell lysis, cell transformation rare (defective virus particle)
- **Non-permissive cell** = no virus replication, cell transformation possible
- Over 200 different types of HPV have been identified
- 40 types **mucosotropic** = preferentially infect mucosal stratified epithelia of the anogenital tract (anus, cervix, vagina) and oral cavity
- HPV responsible for ca. 5% of worldwide cancers

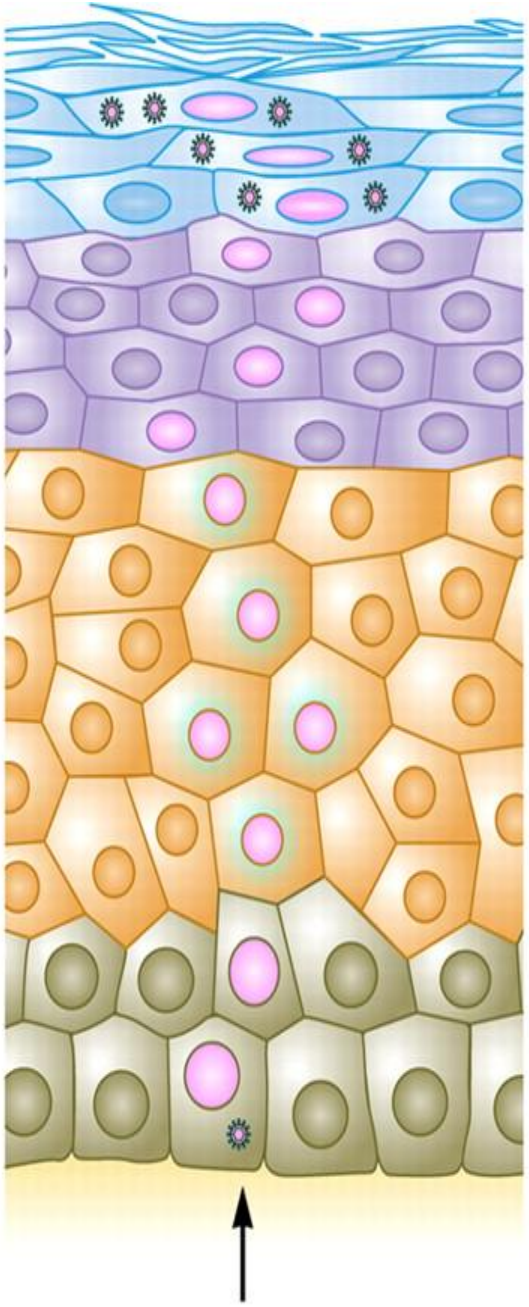
Papillomavirus (HPV)

HPV-16, HPV-18 = high risk
(oncogenic potential)
(70% of cervical and anal cancers)

HPV-6, HPV-11 = low risk
(90% of genital warts)

>90% of HPV infections are naturally cleared





Virus particles assembled

Differentiated cells
E and L viral
genes expressed

Dividing cells
Only E genes expressed
Very low levels of
protein made

Virus laden cells ready for desquamation and infection of naive individual **L1/L2, L1, L2, E4**

Viral genomes at 1000's per cell
E6, E7, E1, E2, E5

Viral DNA amplification in non-dividing cells

Virus and cell replicate together
E1, E2

Virus infects a primitive basal keratinocyte
E1, E2, ?, E5, E6, E7

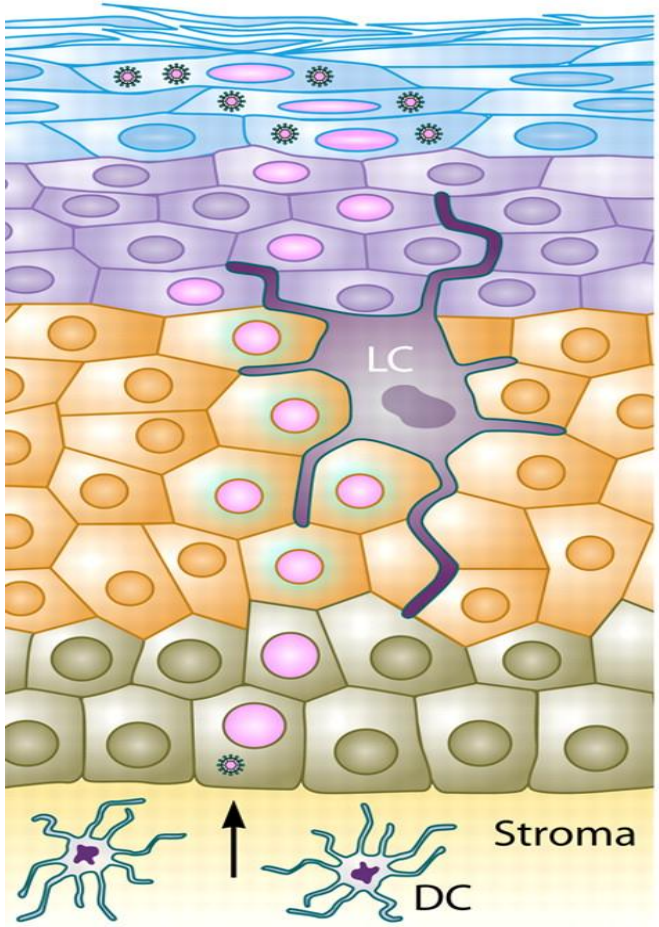
6–12 weeks

0 weeks

Infectious Cycle of High Risk HPVs

Very low levels of protein, no viremia
No cell death, no inflammation

HPV globally downregulates innate immune sensors in keratinocytes
HPV E6 and E7 genes down-regulate type 1 interferon response



In the absence of inflammation

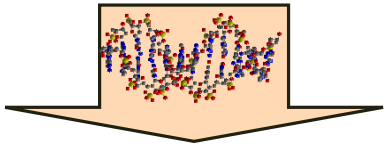
- Keratinocytes do not release pro-inflammatory cytokines
- No activation of Langerhans cells and/or stromal dendritic cells
- No stimulus for dendritic cell activation, migration, antigen processing and presentation

HPVs evade the innate immune response and delay activation of adaptive immunity

HPV

NONPERMISSIVE CELL

Early genes expression



early mRNA E1-E7

E7 protein

E6 protein

Rb bypassing cell arrest

cell proliferation mutations accumulation

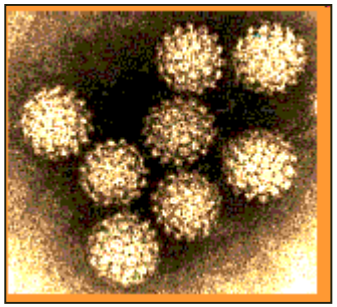
malignant

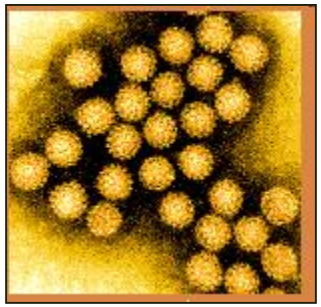
TRANSFORMATION

nucleus - p53

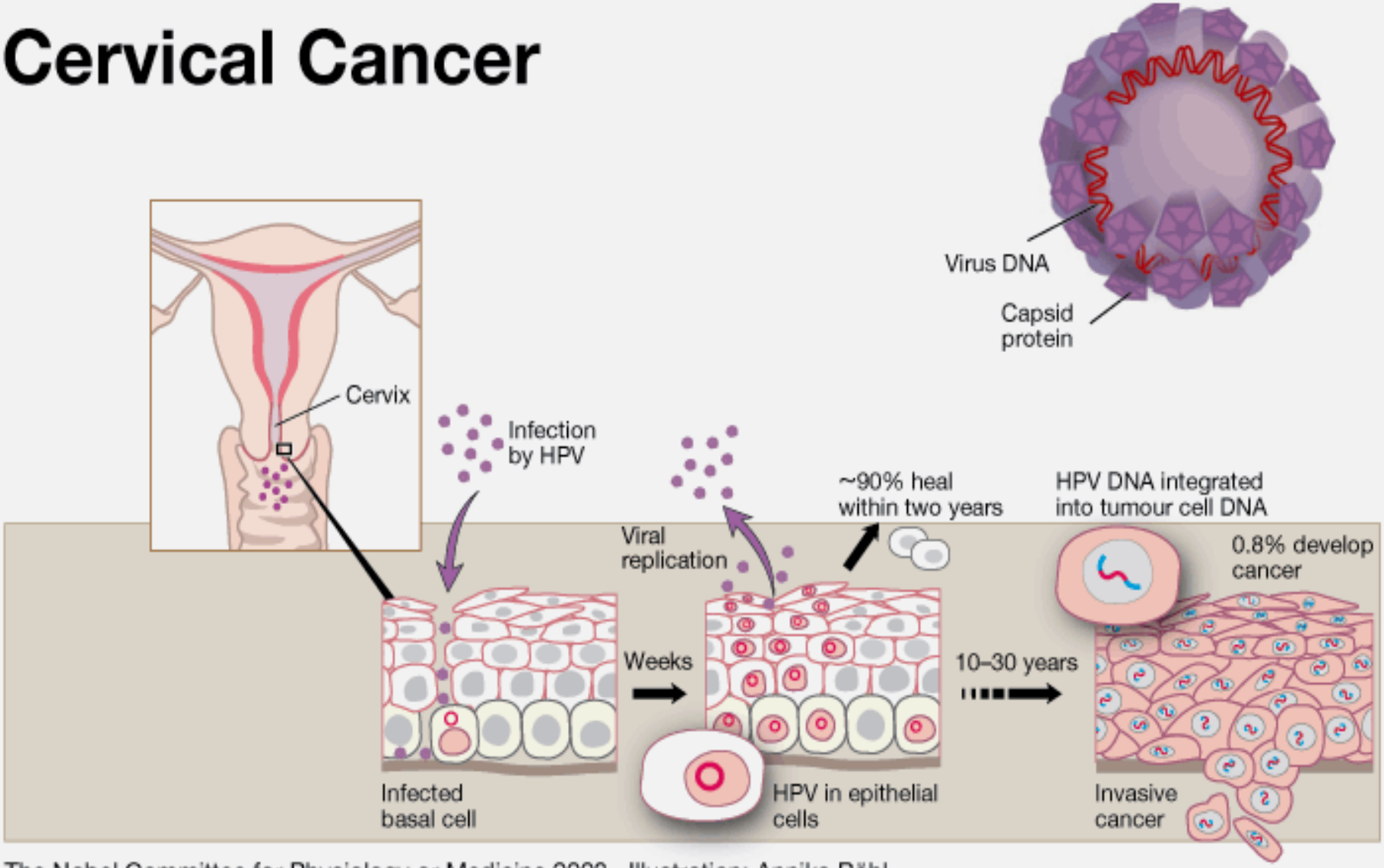
apoptosis inhibition

benign



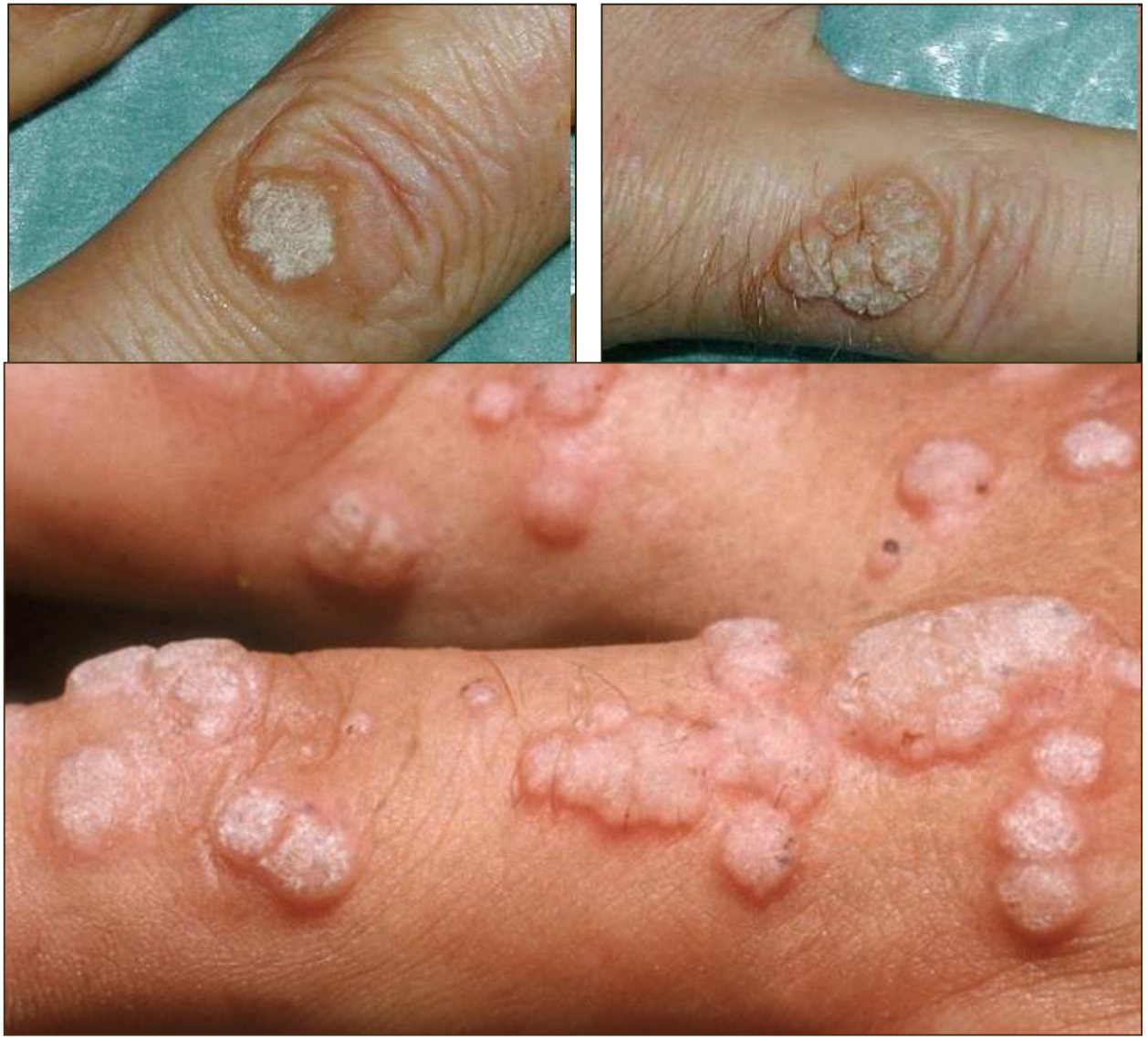


Cervical Cancer

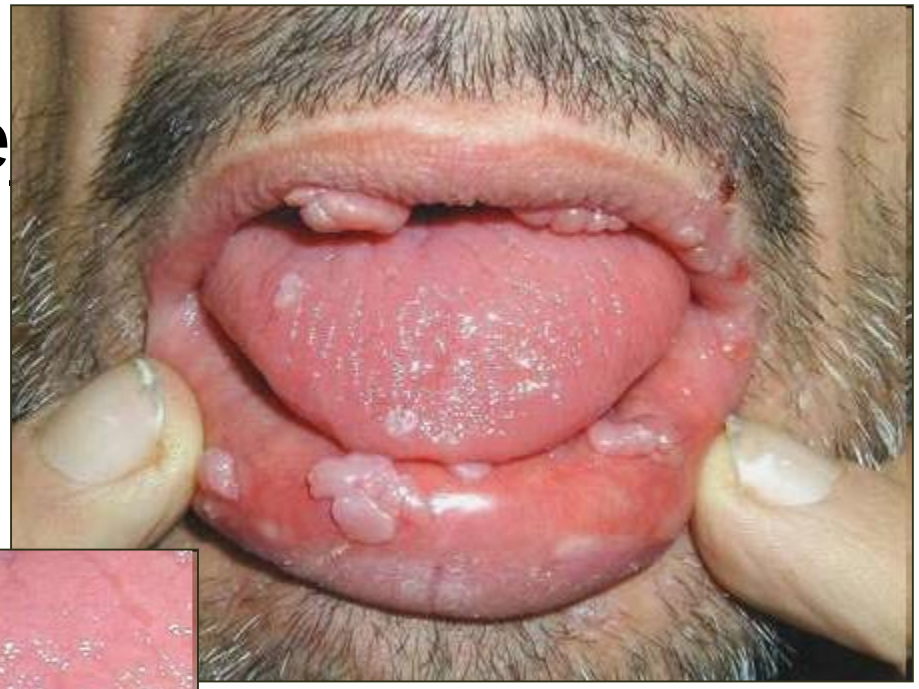


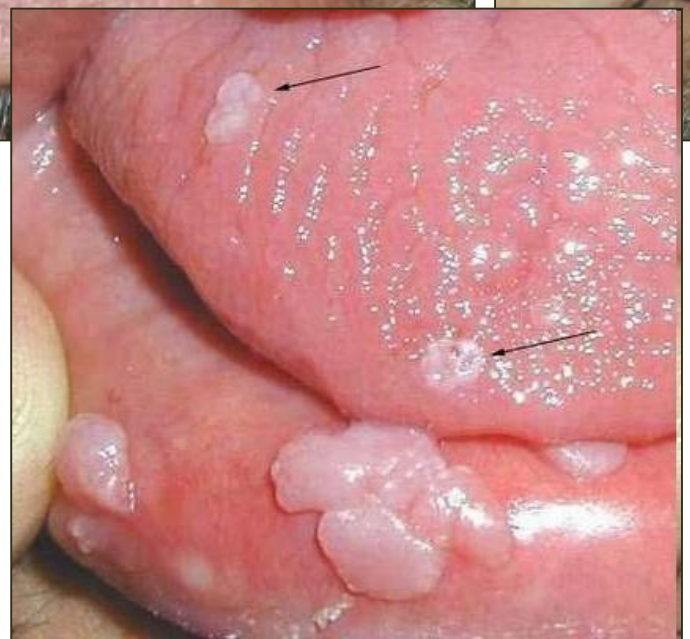
The Nobel Committee for Physiology or Medicine 2008 Illustration: Annika Röhl

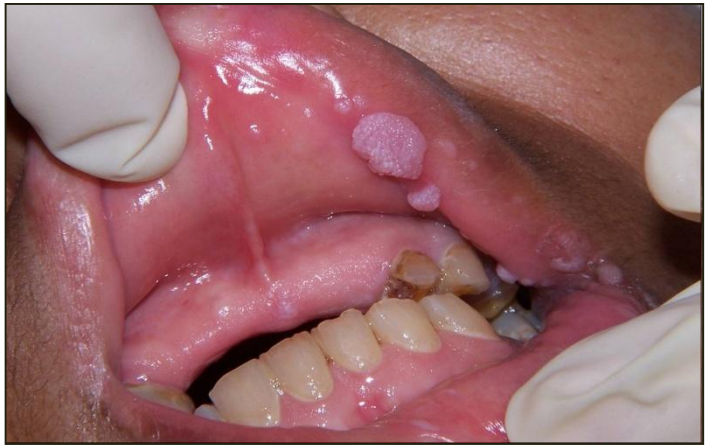
Common warts



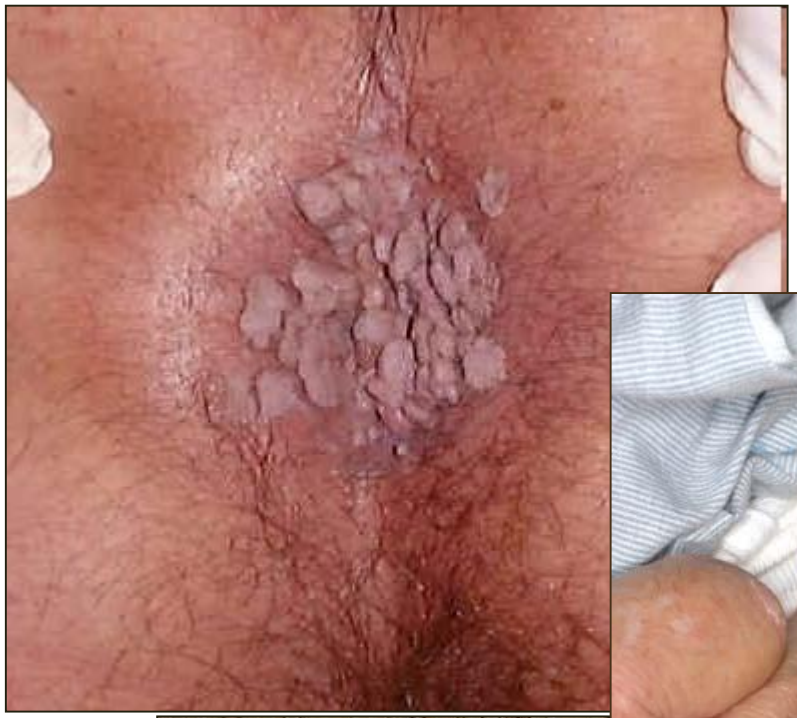
Oral warts

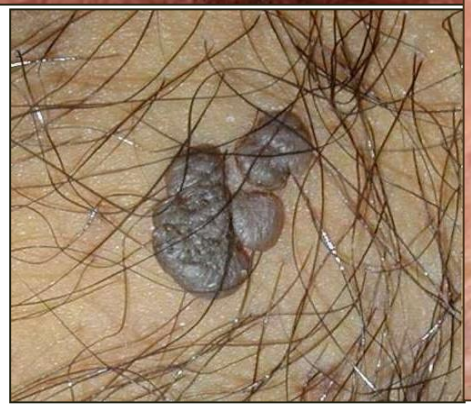


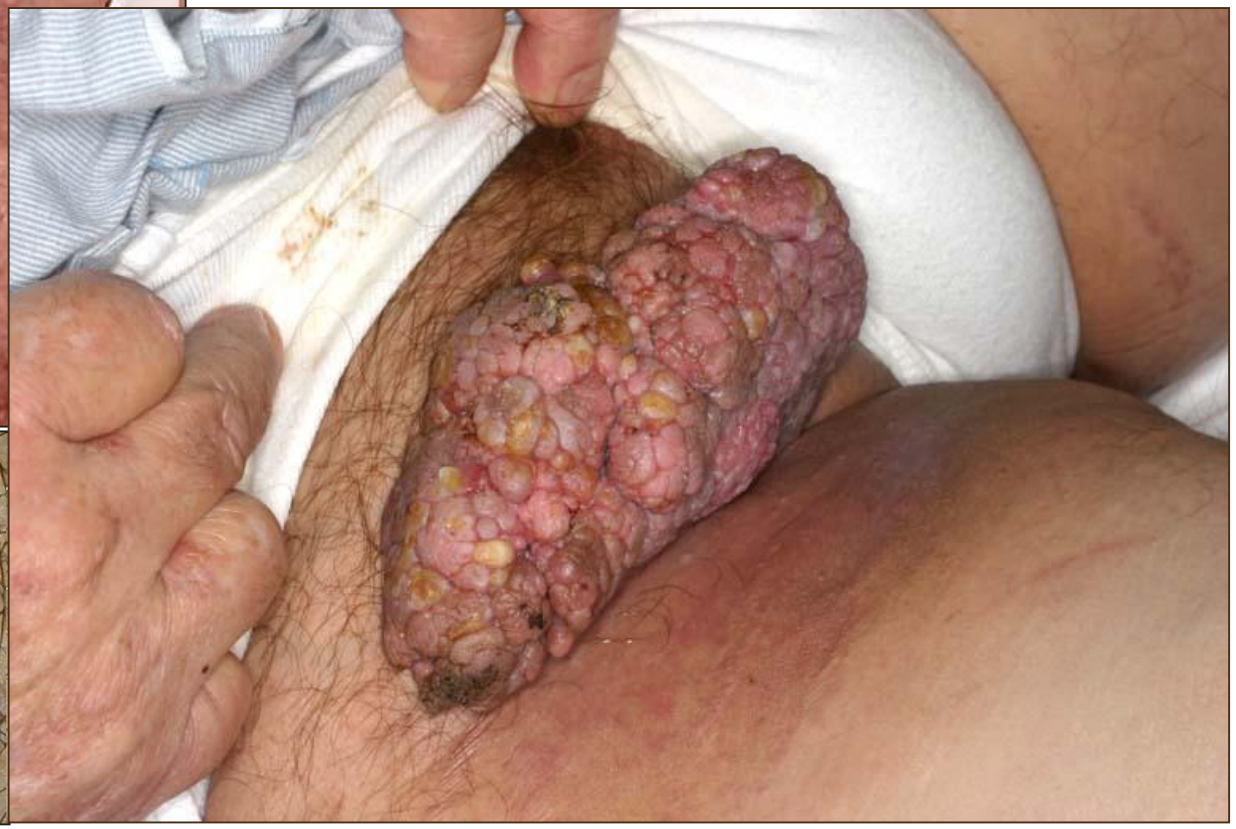




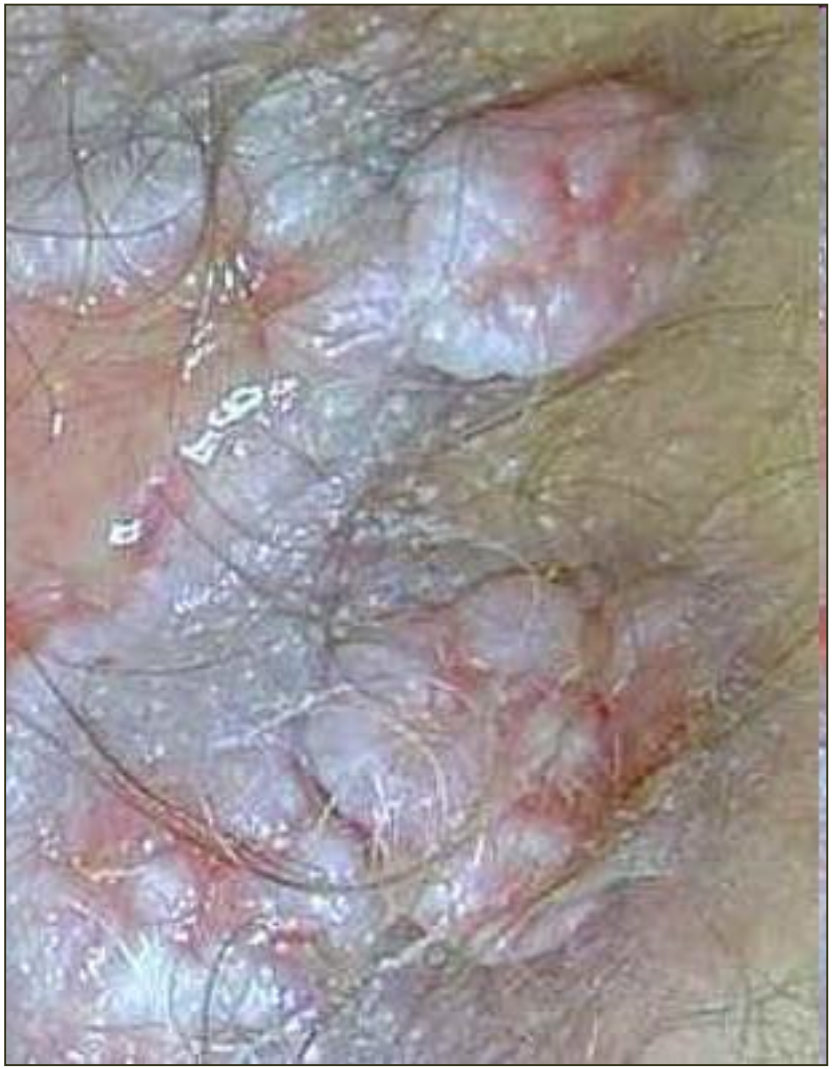
Anogenital warts

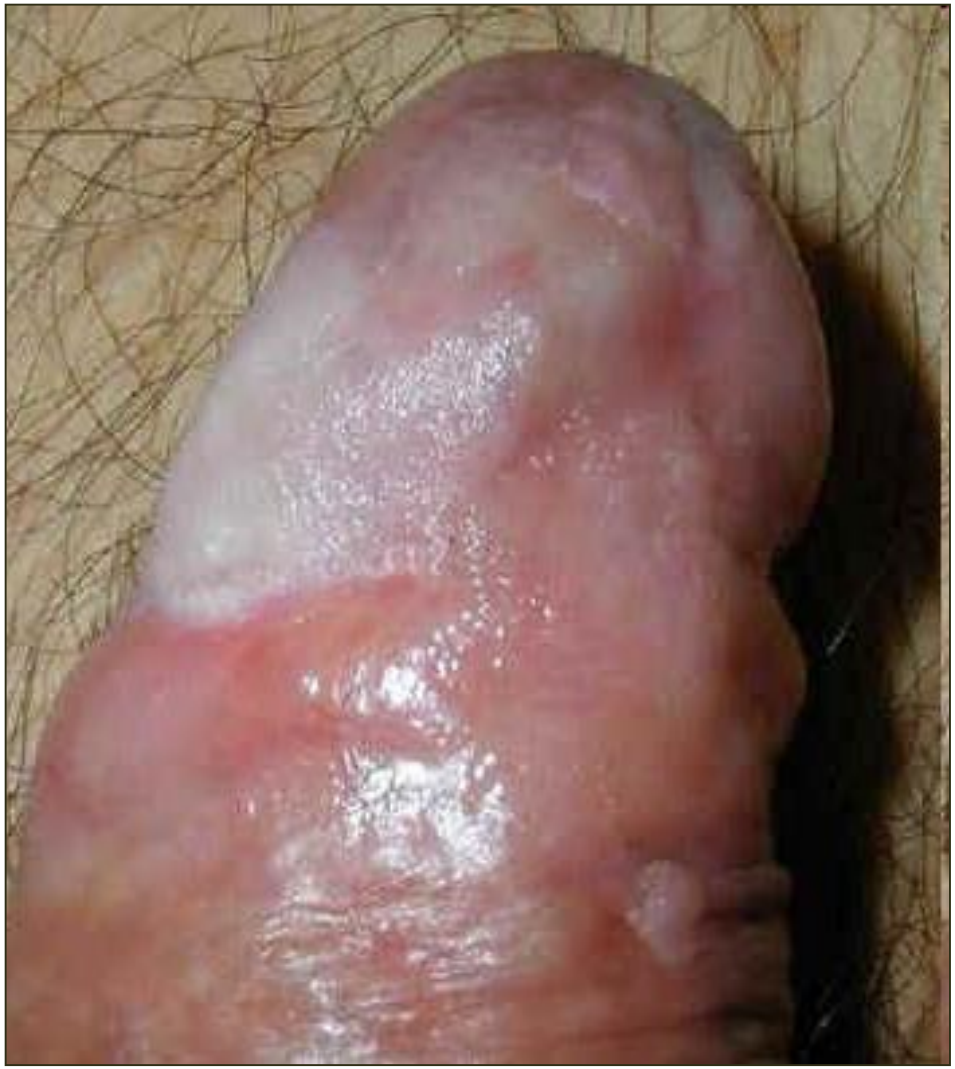




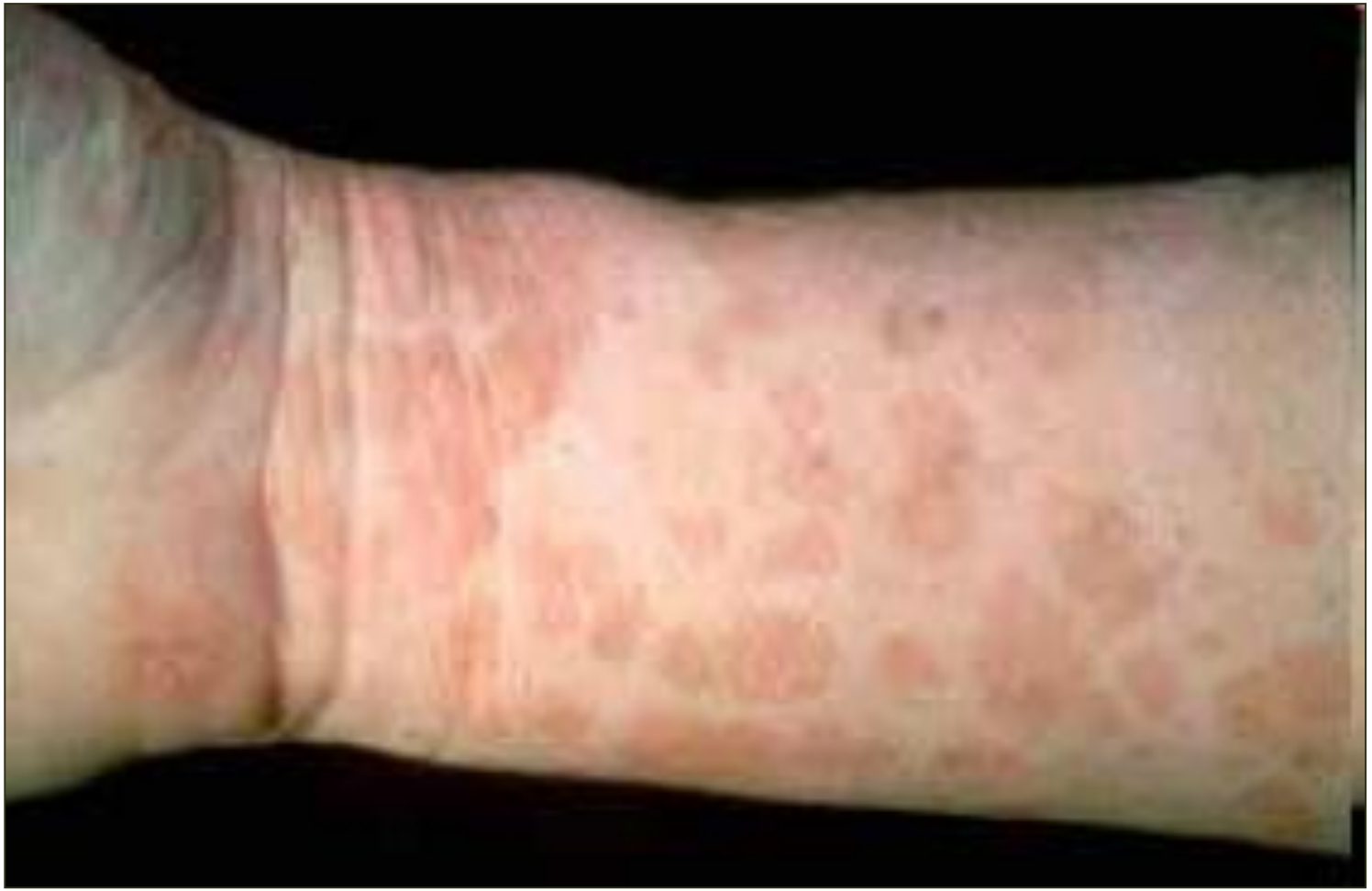


Epithelioma (benign cancer)





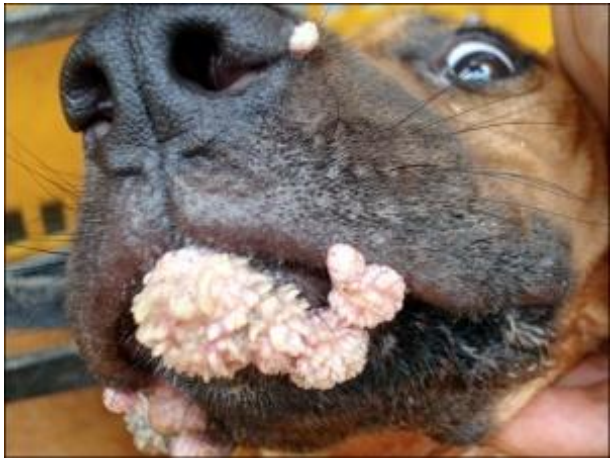
Epidermodysplasia (malignant cancer)

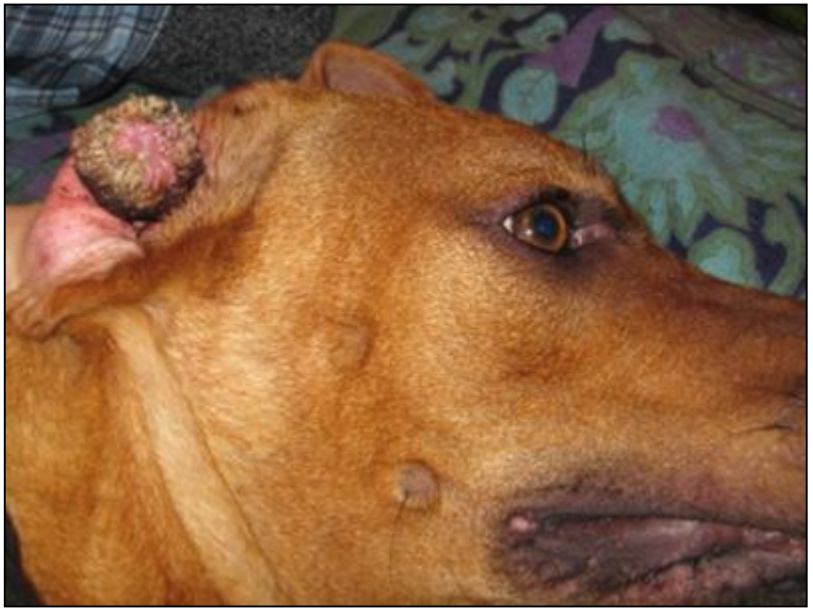


Epidermodysplasia verruciformis

abnormal susceptibility to HPVs of the skin

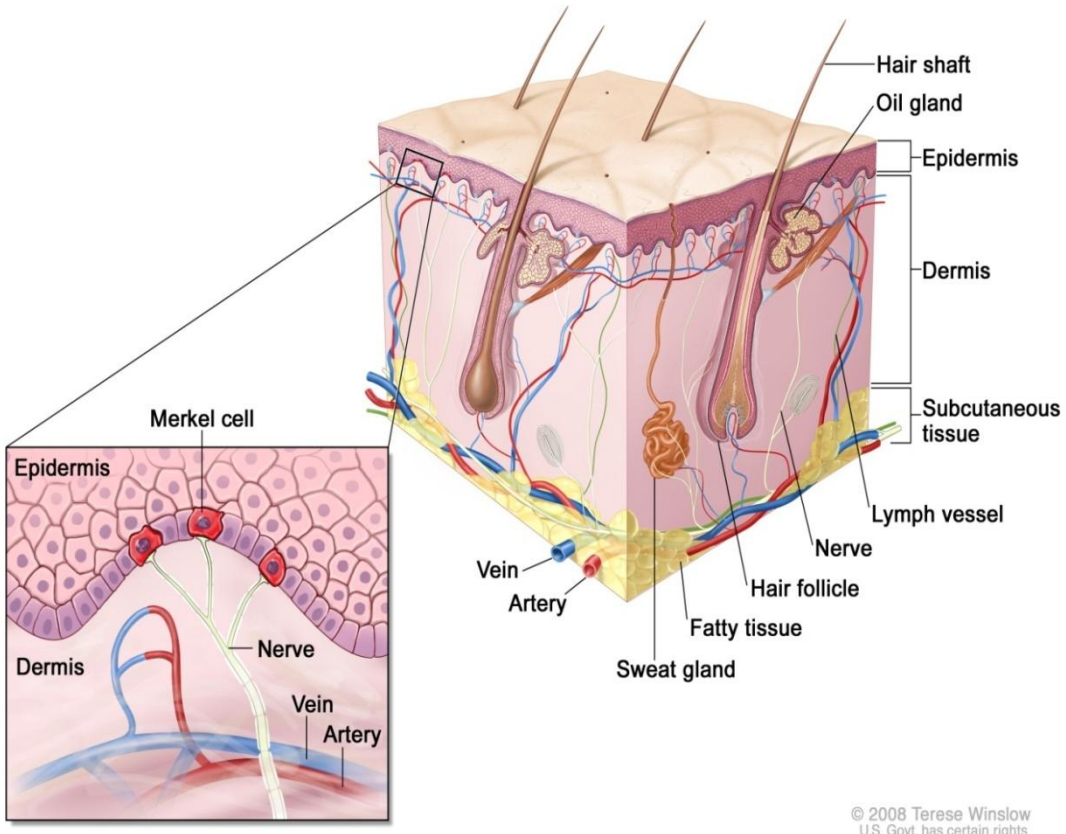
Papillomaviruses infection in aminals



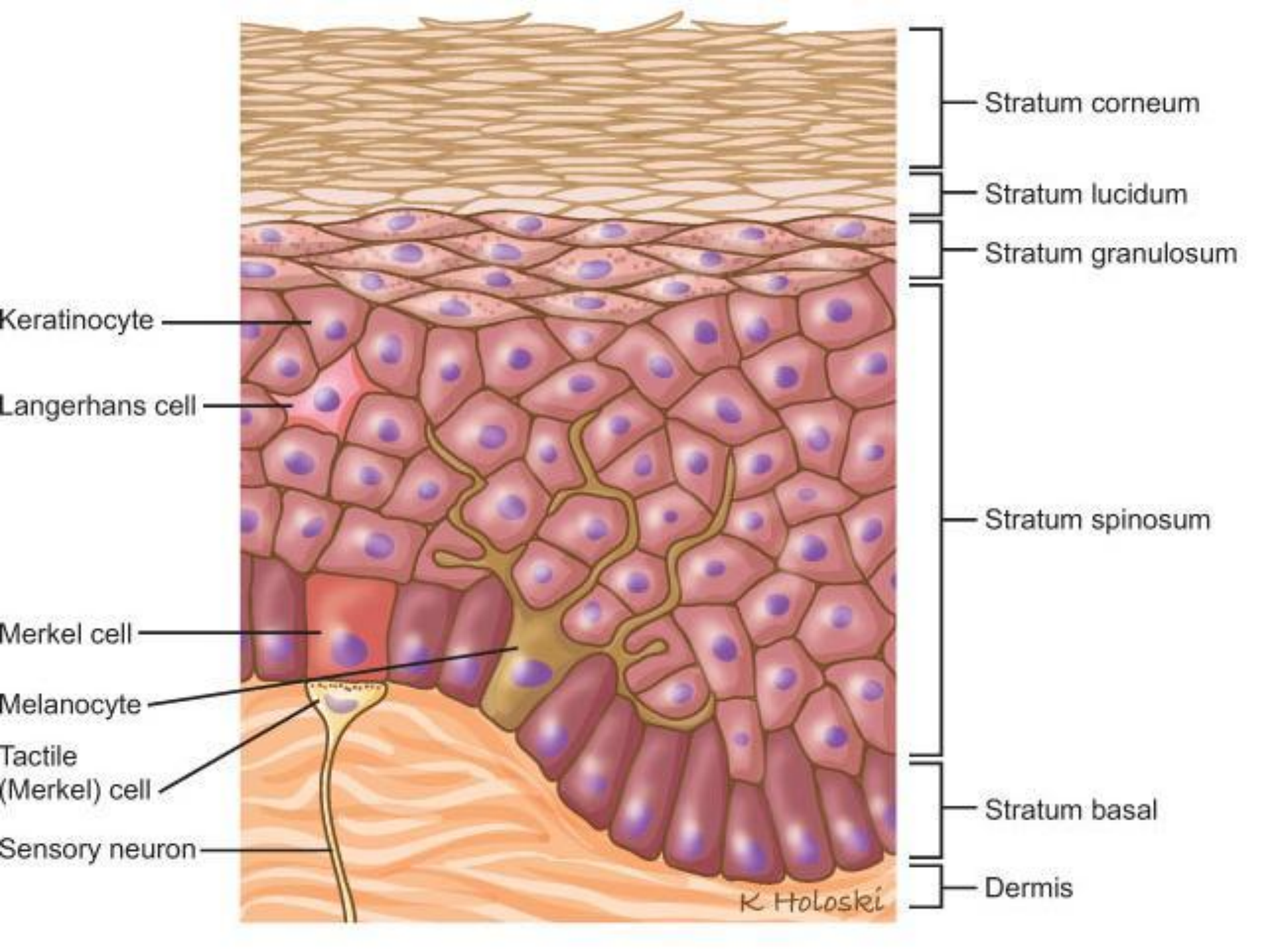


Merkel carcinoma - polyomavirus

- MCPyV (**M**erkel **c**arcinoma **P**olyoma**v**irus)
- MCC – Merkel cell carcinoma



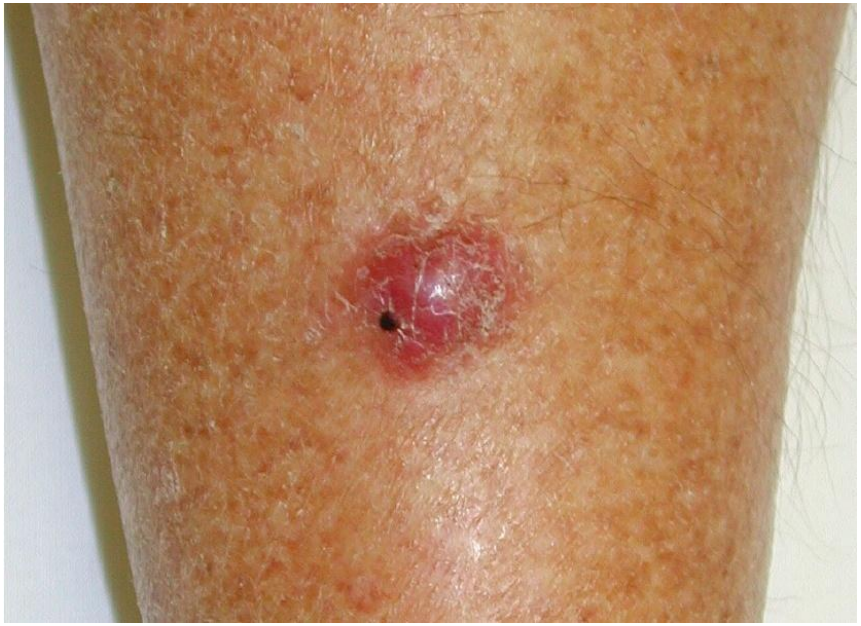
- Rare but aggressive cancer of skin neuroendocrine cells
- Incidence has increased over the past 30 years
- 80% MCC – viral DNA detected
- Mostly affects light-skinned elderly immunosuppressed

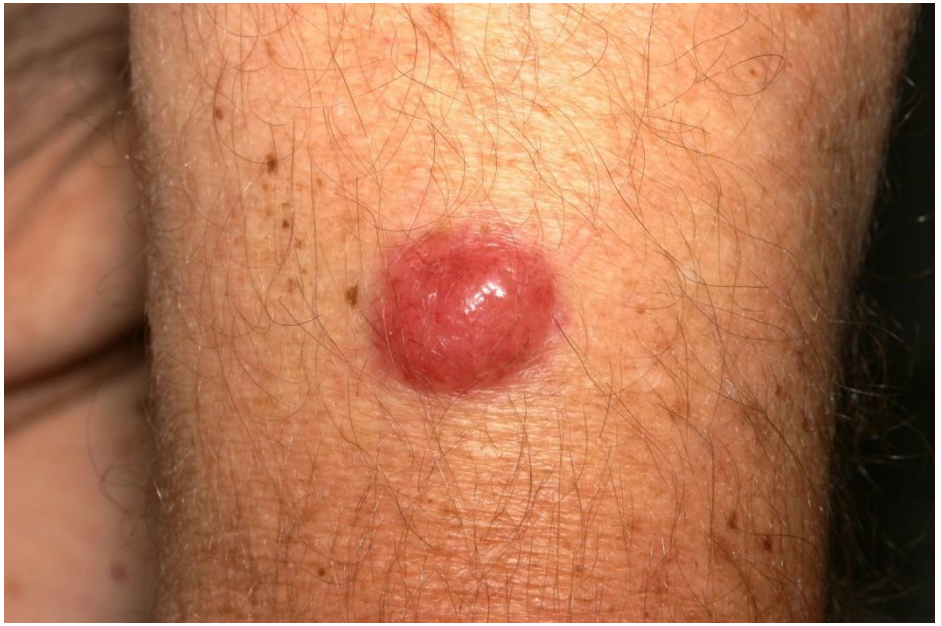

Stratum corneum
Stratum lucidum
Stratum granulosum
Keratinocyte
Langerhans cell
Stratum spinosum
Merkel cell
Melanocyte
Tactile
(Merkel) cell
Sensory neuron
Stratum basal
Dermis
K Holoski

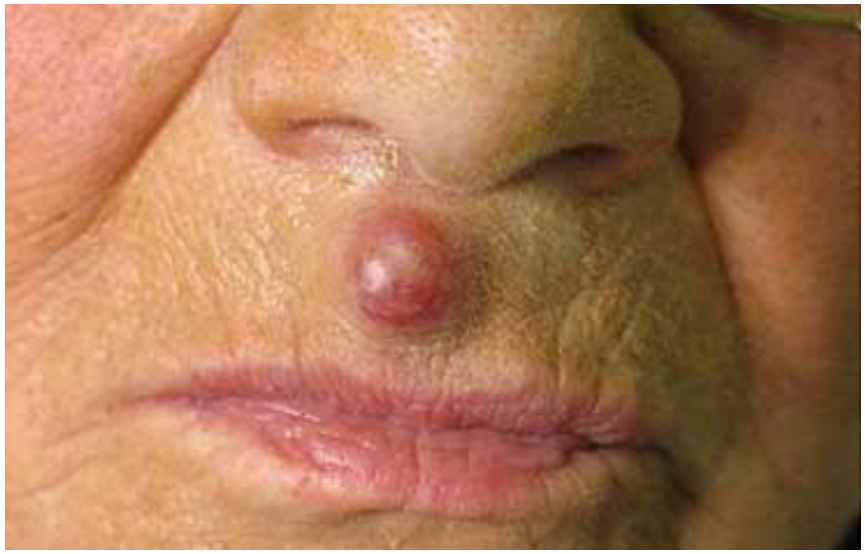
Merkel carcinoma

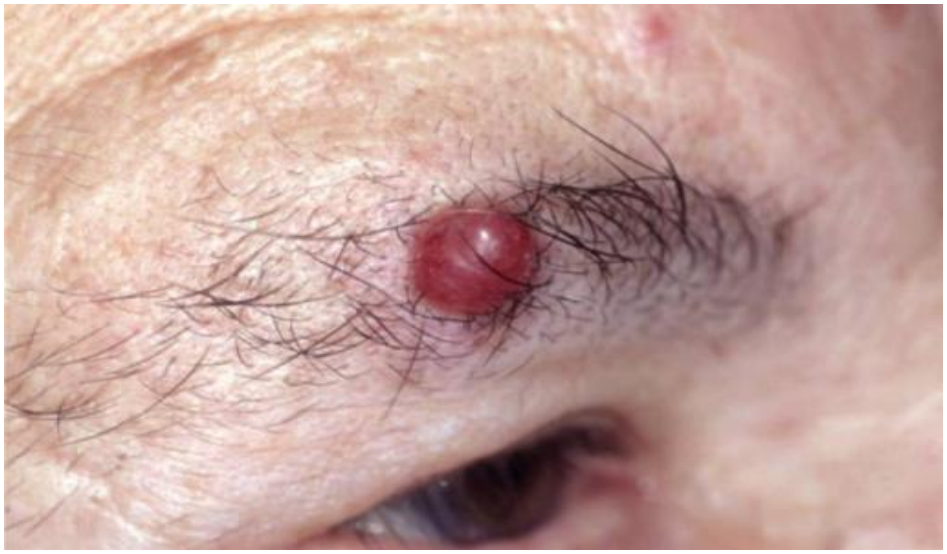
- It appears as firm, painless nodule or tumor
- MCC metastasizes quickly and spreads towards regional lymph nodes (liver, lungs, brain, bones)
- Primary infection with MCPyV asymptomatic
- Transmitted via respiratory route

Merkel carcinoma

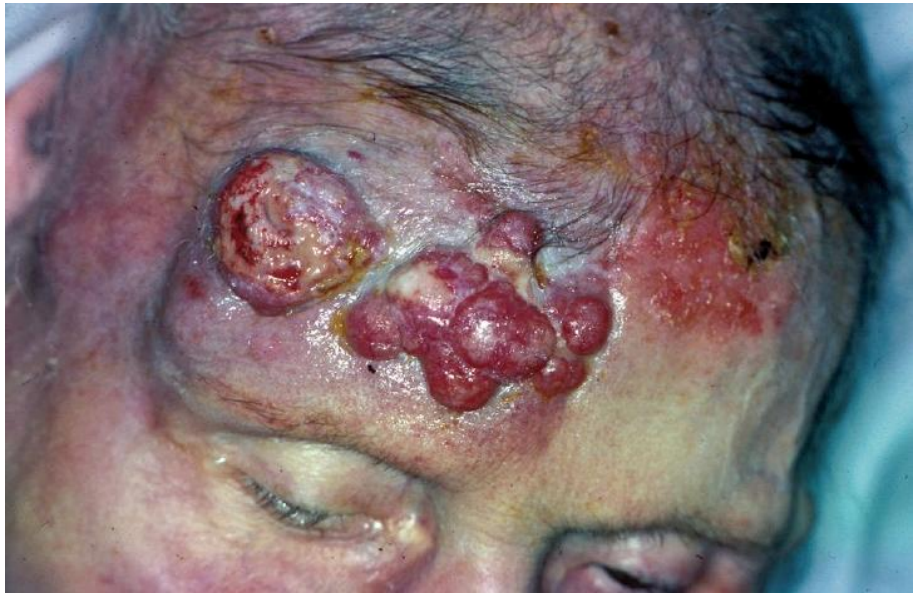


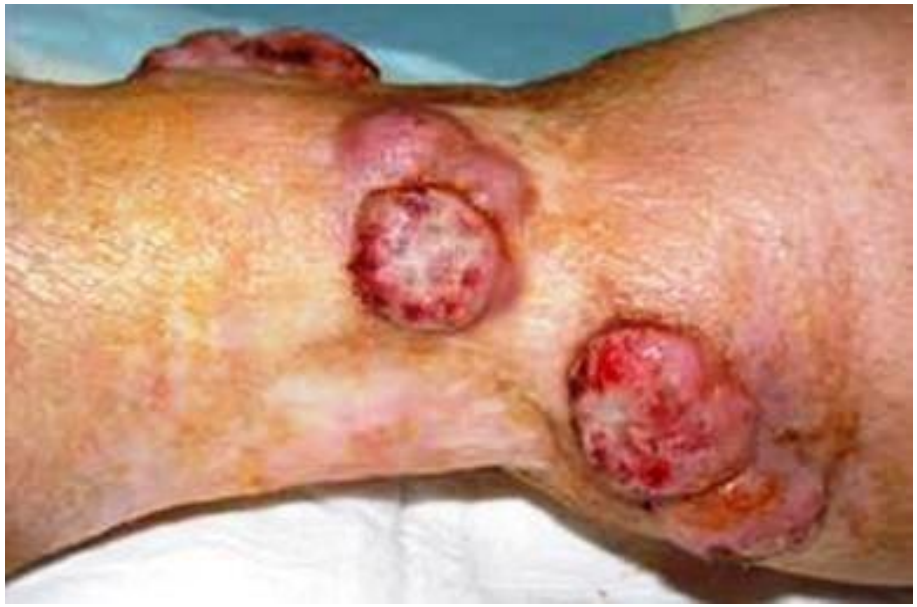


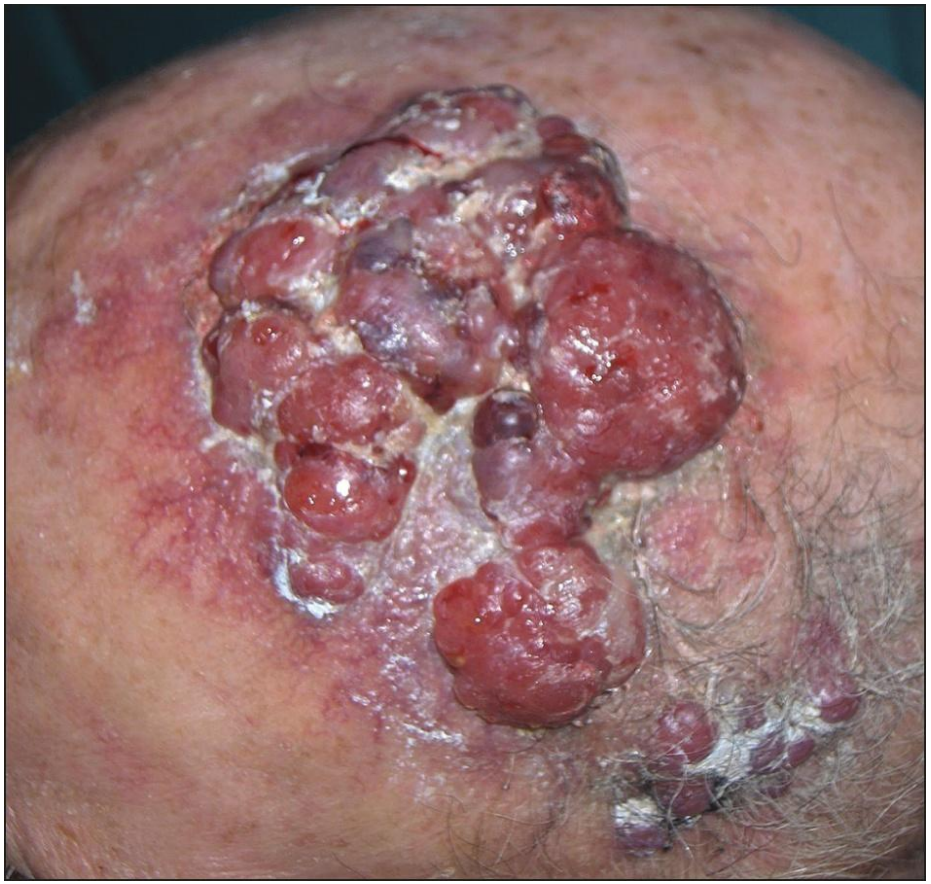




Merkel carcinoma







Herpesviridae

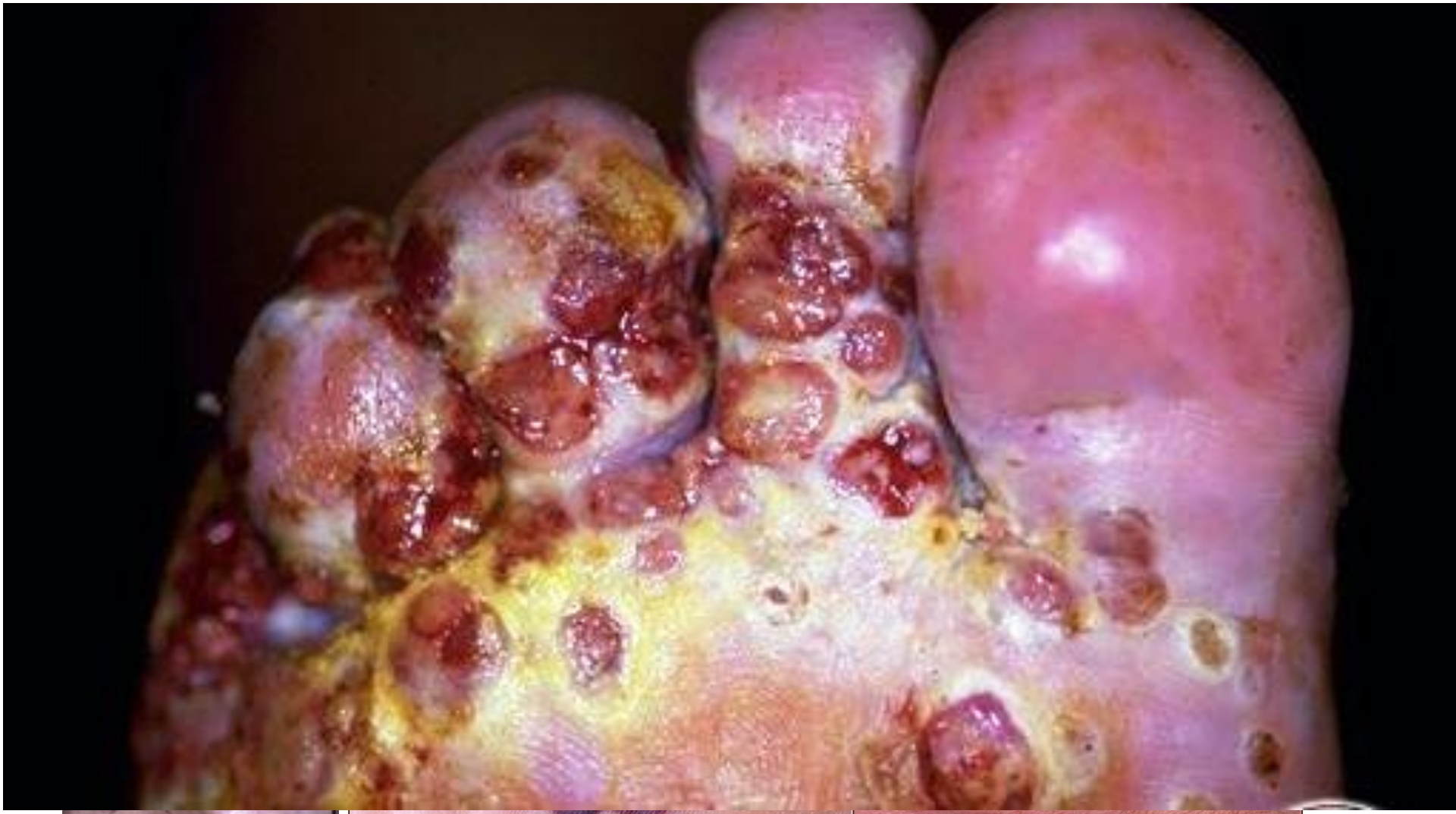
- **HHV-8 (KSHV)**, Kaposi's sarcoma-associated virus
- Sexually transmitted remains latent with the possibility of reactivation in immunosuppressed individuals
- Disorders: **Kaposi 's sarcoma (KS)**, primary effusion lymphoma (PEL; B-cell lymphoma), multicentric Castleman's disease (MCD; B-cells hyperproliferation)

KSHV has stolen from the host cell genes that shut off defense mechanisms (molecular piracy)

Herpesviridae

- KSHV produces a variety of immunomodulatory proteins and contains several gene products with transforming properties
- Most important: **viral G-protein coupled receptor** vGPCR (IL-8 and IL-6 analog receptor) and **K1 protein** = activates pathways controlling cellular growth, angiogenesis, and inhibition of apoptosis

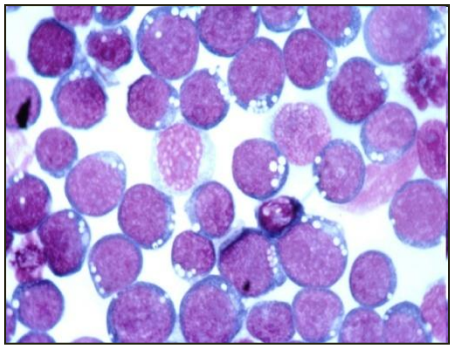
Kaposi's sarcoma

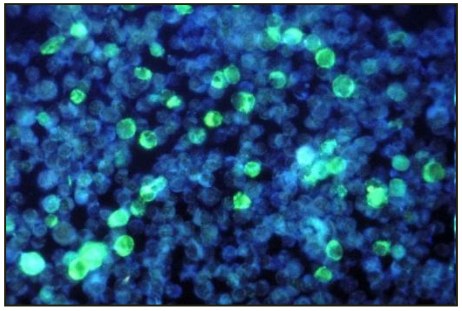


Epstein-Barr virus (EBV)

Disorders:

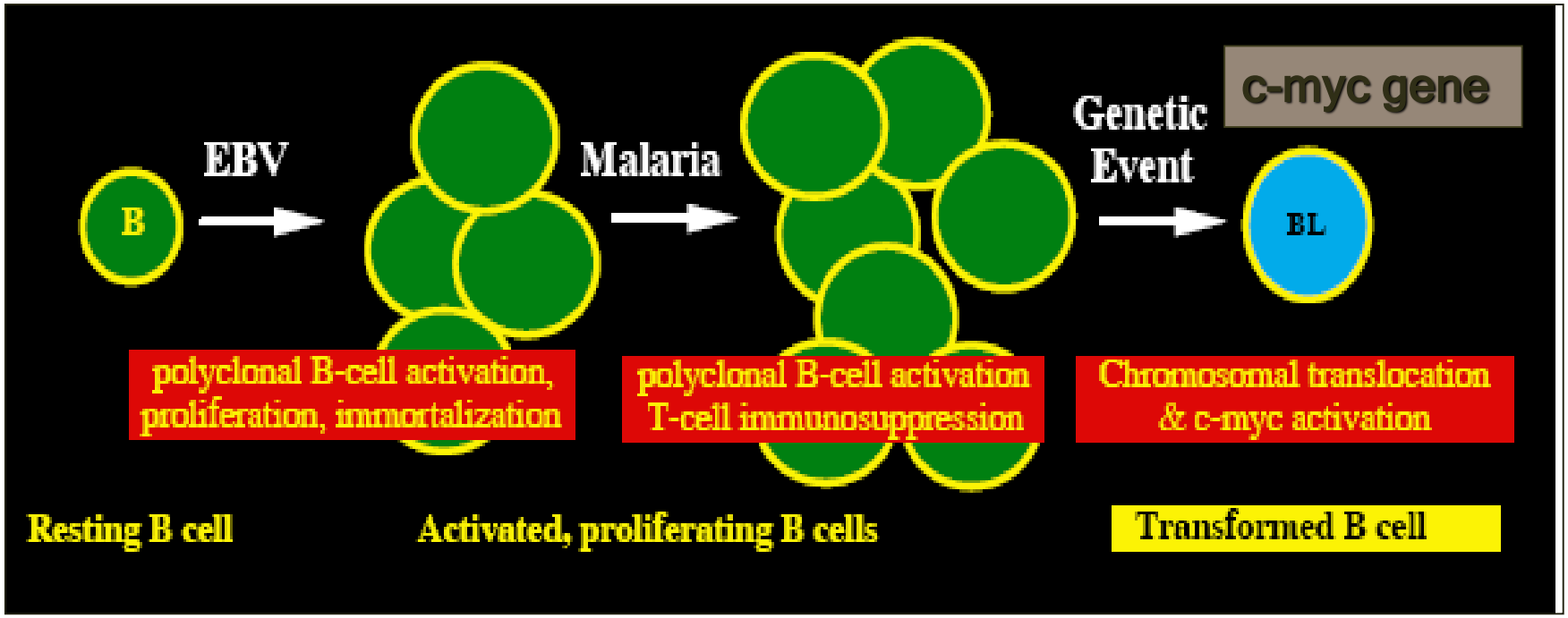
- **Burkitt's lymphoma (BL)** - higher incidence in areas with endemic malaria (co-carcinogen) - AFRICA
- **Nasopharyngeal carcinoma** (NPC) - higher incidence among smoked fish (contain **nitrosamines – well-known carcinogen**) consumers - CHINA
- **Post-transplant lymphomas**
- **Hodgkin's lymphoma**
- Genes encoding proteins: EBNA-1, EBNA-2, EBNA3A, 3B, 3C, EBNA-LP; **LMP-1 (viral oncogene)**, 2A, 2B; early RNAs (EBERs) - abundant in latent cells (markers to detect EBV infection) = apoptosis inhibition, B-cell proliferation



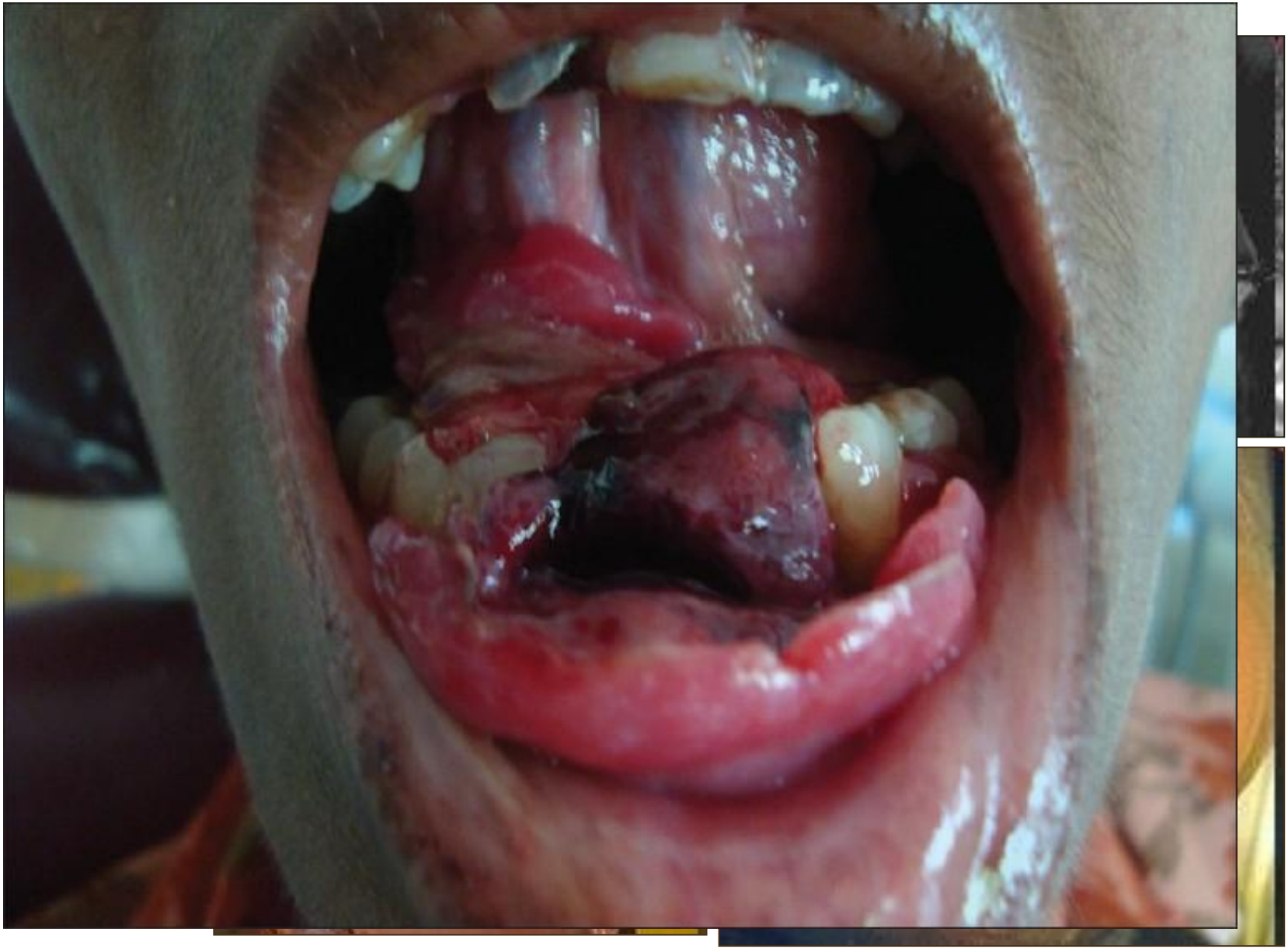


EBV infected B-cells

EBV- immortalizes B cells
Malaria – reduces immune surveillance of B cells infected with EBV
Result: an excessive number of B cells infected with EBV and an increased likelihood of unchecked mutations



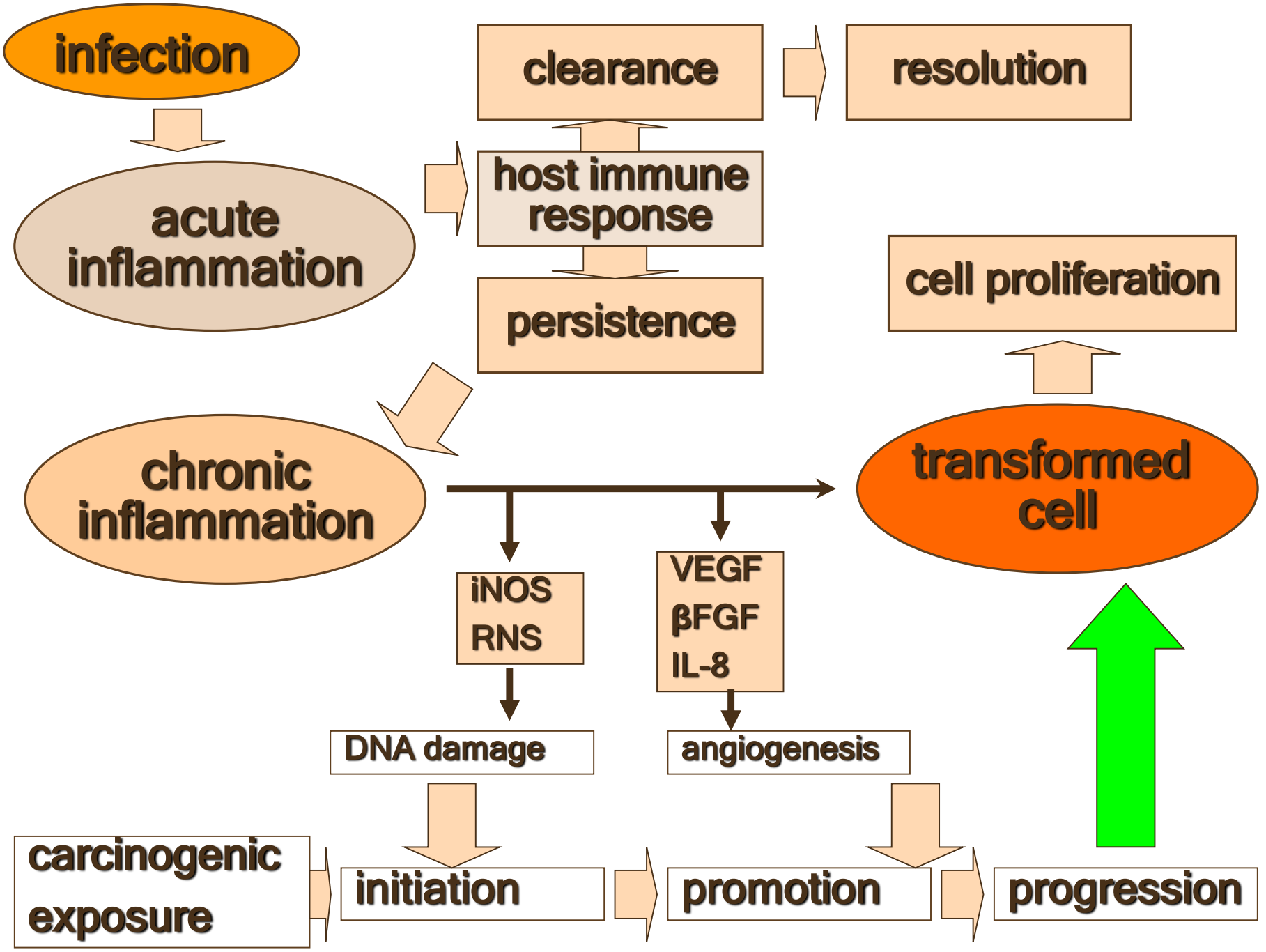
Burkitt's lymphoma (BL)



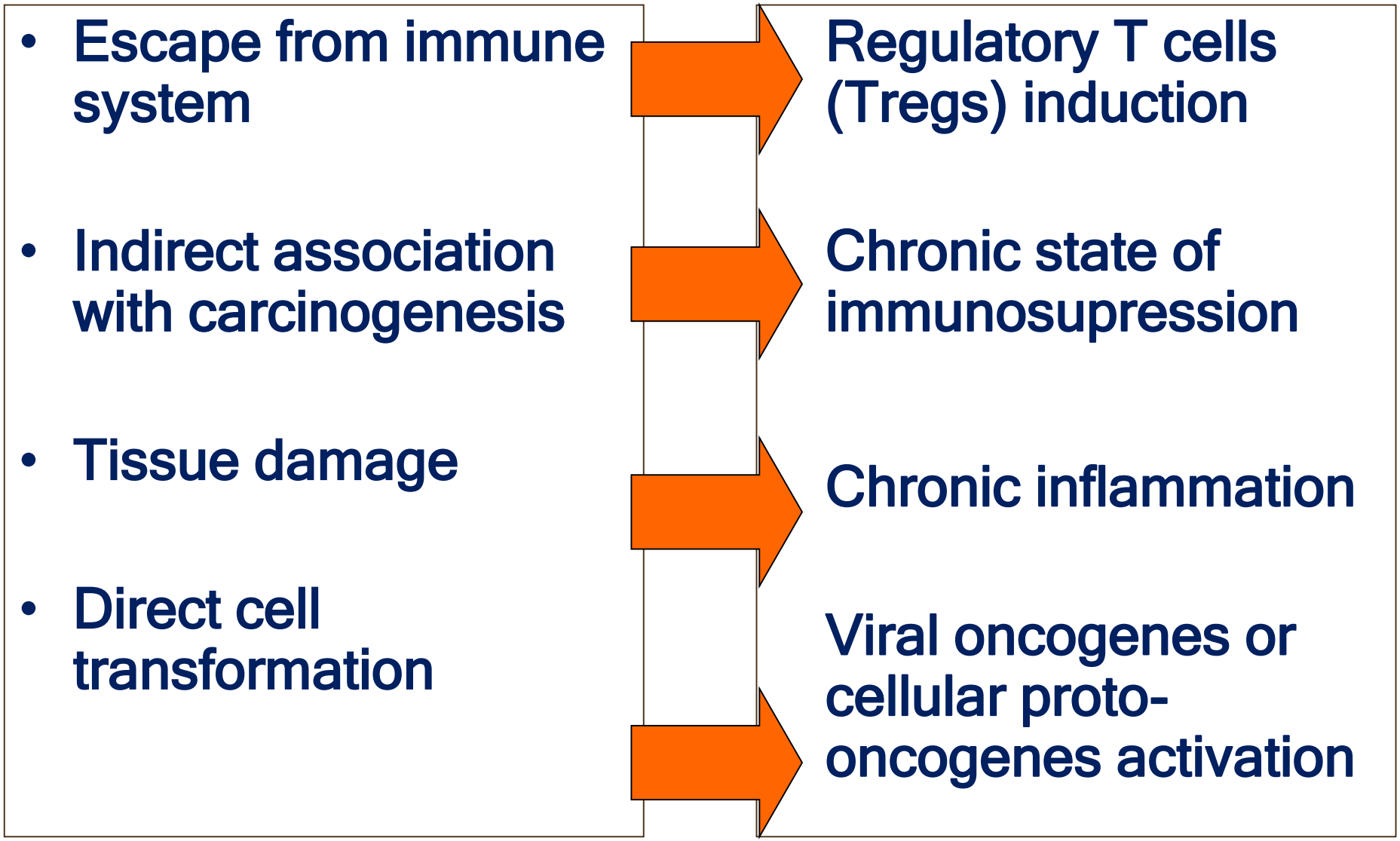
How viruses can transform host cells?

By forcing host non proliferating host cell to proliferate

By manipulating the host immune response

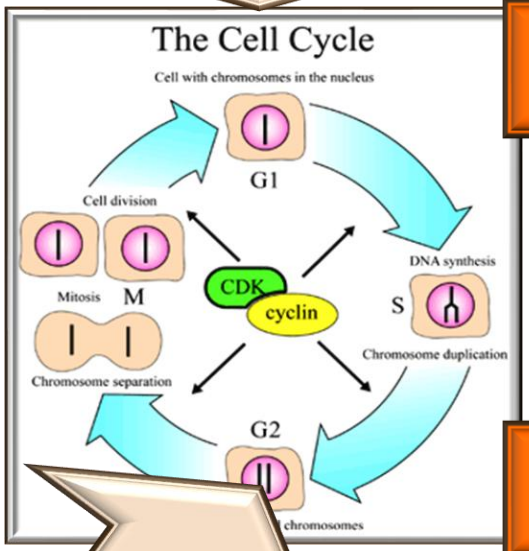

infection
acute inflammation
clearance
resolution
host immune response
persistence
cell proliferation
chronic inflammation
transformed cell
iNOS
RNS
VEGF
βFGF
IL-8
DNA damage
angiogenesis
carcinogenic exposure
initiation
promotion
progression

Latent / chronic viral infection



Stress (UV, hypoxia), DNA damage

IMMUNE SYSTEM



REPAIR

MUTATION

TRANSFORMATION

APOPTOSIS

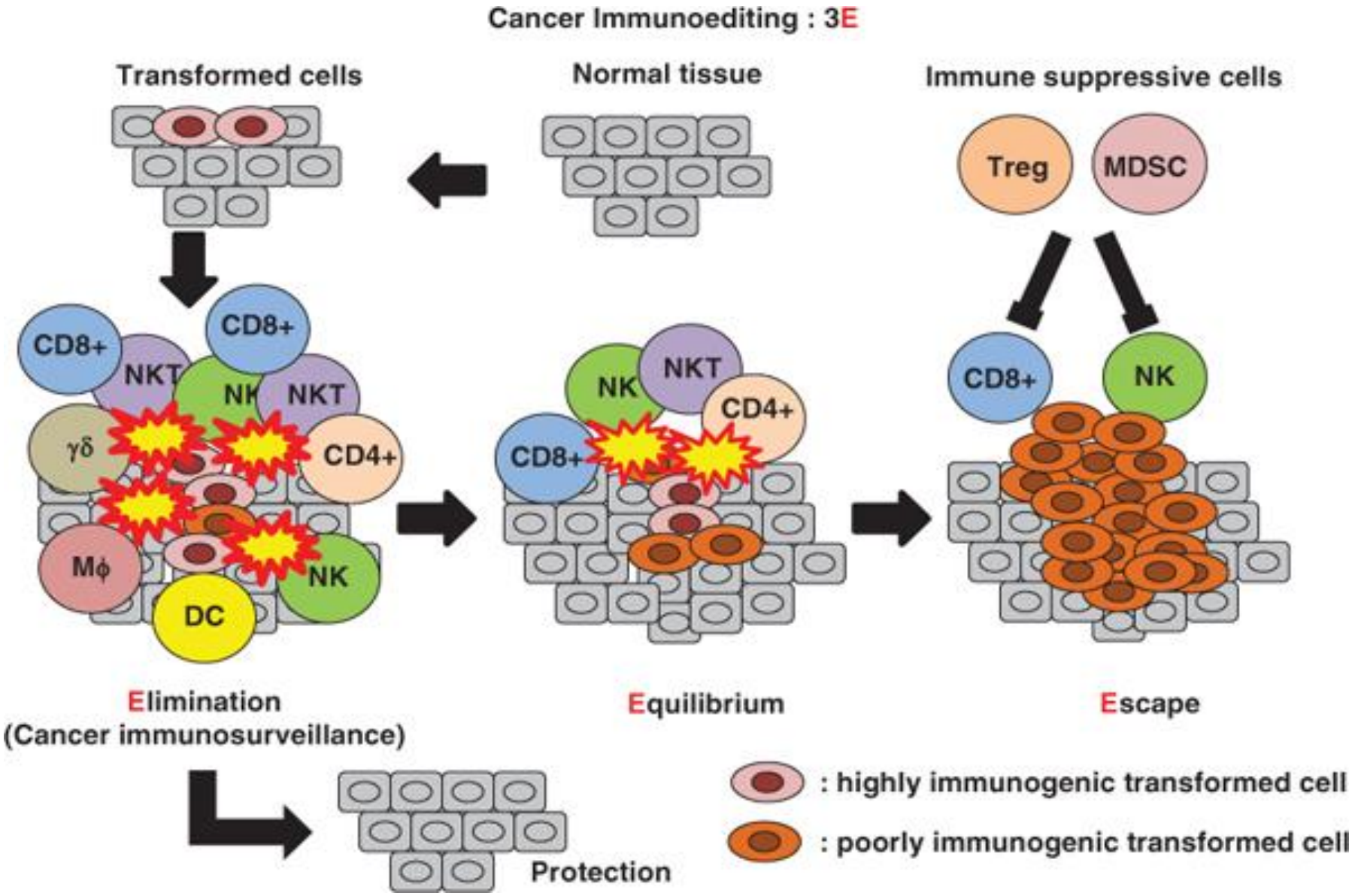
UNCONTROLLED GROWTH

STOP

Suppressors pRB, p53

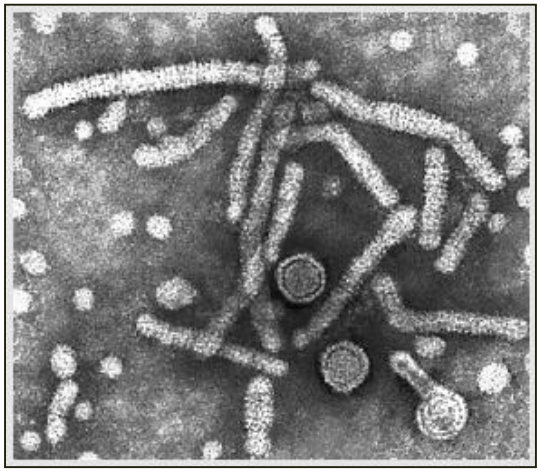
MUTATION

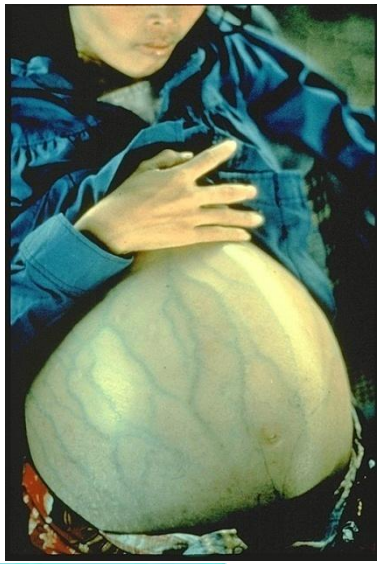
Role of the immune system in oncogenesis

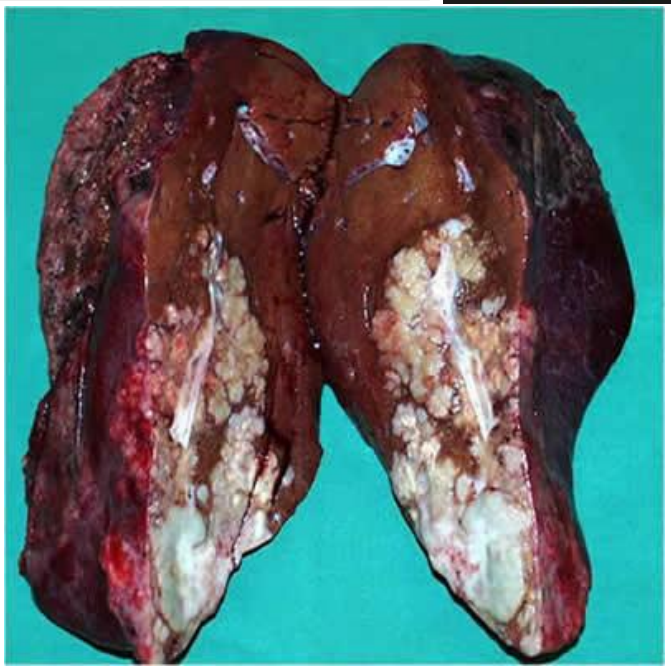


Hepatitis B & C

- DNA virus with RNA intermediate
- In tumors, the virus is integrated with little gene expression
- HCV (RNA virus) p53 binding by NS5A
- Both bypass immune response
- Believed to be from chronic liver damage/loss and replacement/ causing increased mutations







Answer questions

- List cancers associated with RNA viruses
- List cancers linked to DNA viruses
- What host factor plays an essential role in viral oncogenesis?
- What host cel genes are the most common targets for oncogenic viruses?

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Thank you for your attention!

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beata.sobieszczanska@umw.edu.pl