Virology Lecture Series:

Viral Oncogenesis

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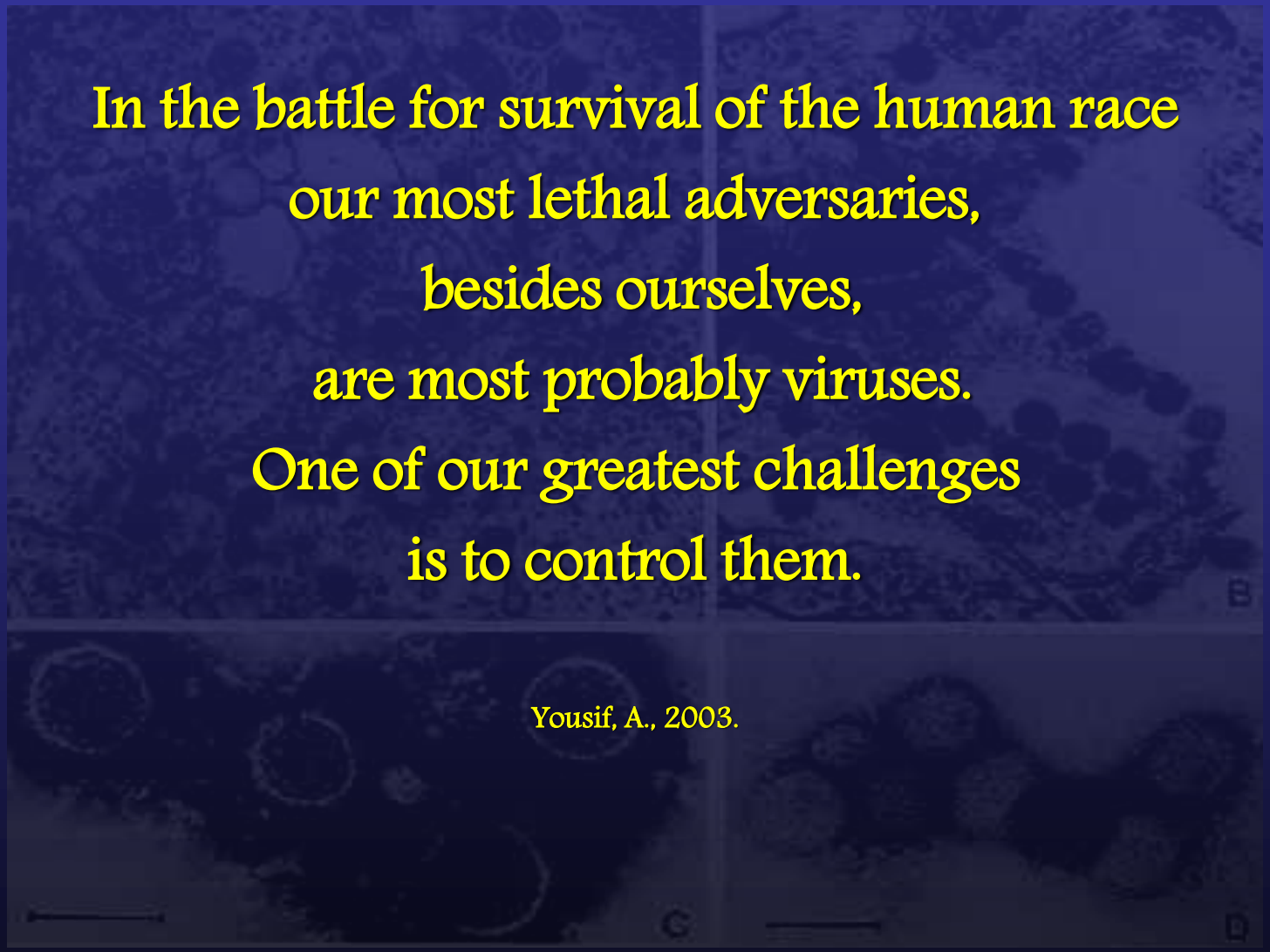


In the battle for survival of the human race
our most lethal adversaries,
besides ourselves,
are most probably viruses.
One of our greatest challenges
is to control them.

Yousif, A., 2003.


Know Your Enemy
Morphology, Pathogenesis, Evasion, Epidemiology
Know Yourself
Social factors, Demography, Geography, Economy,
Know Your Weapons
Diagnostic Technology, Vaccines, Environmental Hygiene
Culture, Education, Institutions, Legistlation
Apply Knowledge
Victory in the battle against Biothreats

Learning Objectives

- Understand how RNA tumor viruses mediate oncogenesis
- Understand how DNA tumor viruses mediate oncogenesis
- Be able to identify viruses that mediate oncogenesis

The cell cycle and its regulation

Cells **2021**, *10*(12), 3327; https://doi.org/10.3390/cells10123327

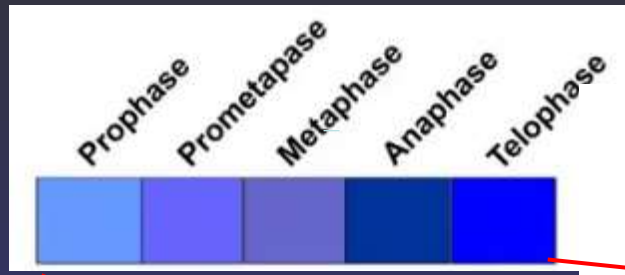
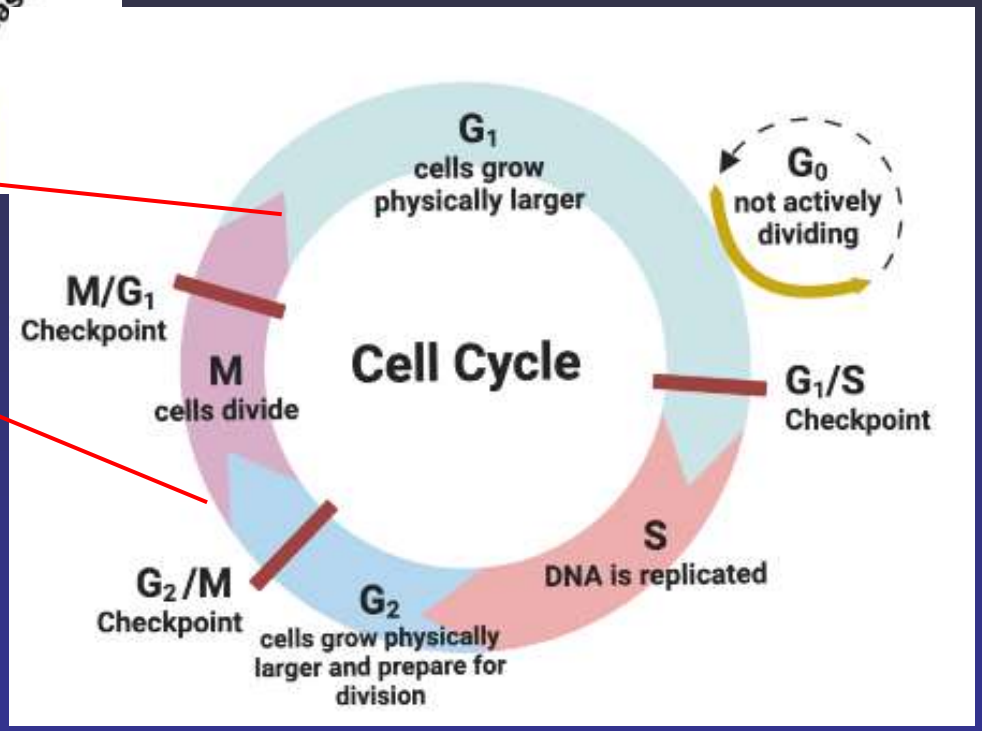


Table 1. Cell cycle phases

Phase	Description
G_1	Growth and preparation of the chromosomes for replication
S	Synthesis of DNA (centrioles/DNA replication)
G_2	Preparation for mitosis
M	Mitosis
G_0*	Temporary or permanent state of cell cycle exit. Postmitotic/terminally differentiated

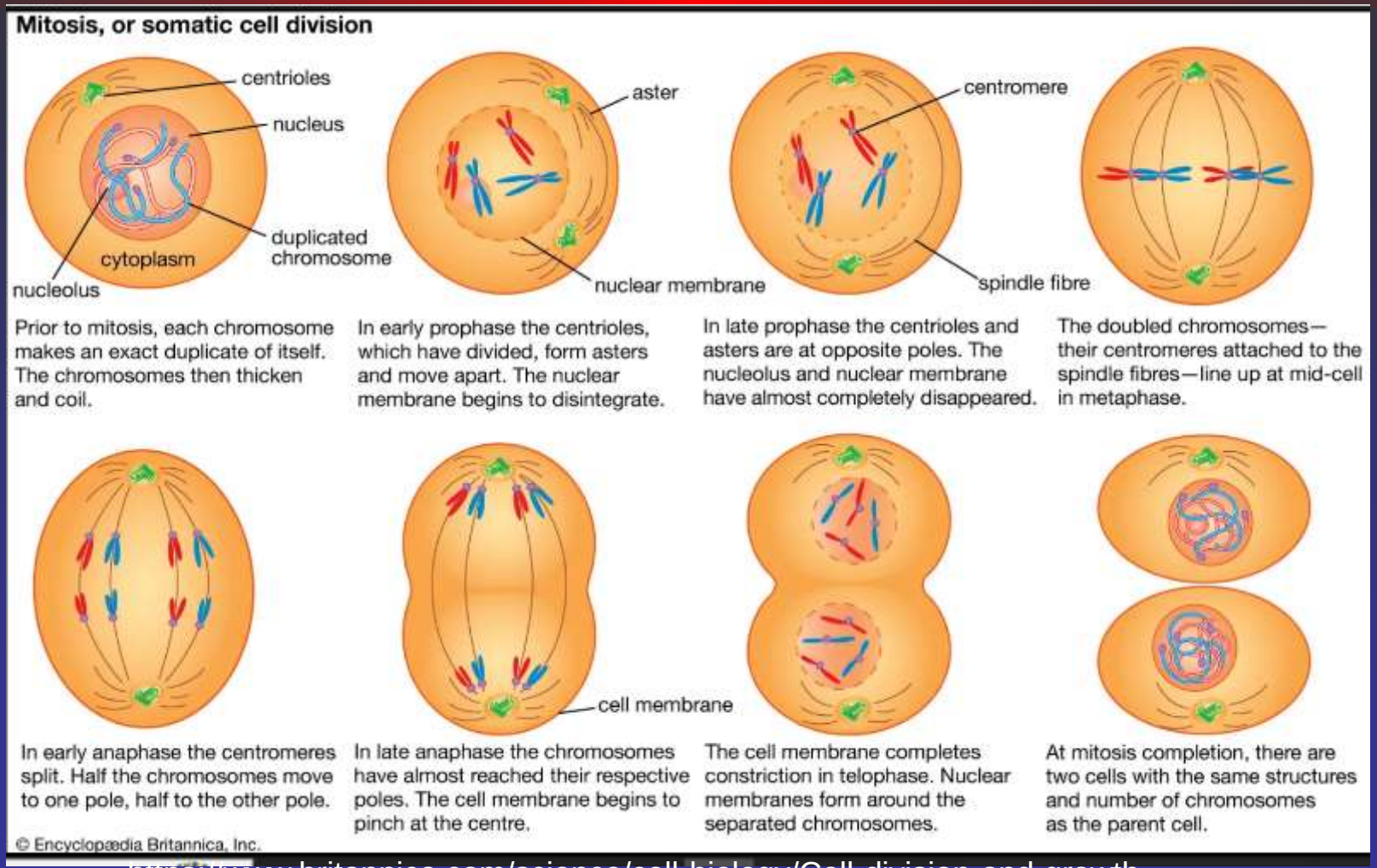
*Exit from the cell cycle at G_1, not occurring in every cell cycle.



https://study.com/skill/practice/analyzing-the-role-of-the-g0-phase-in-the-cell-cycle-questions.html

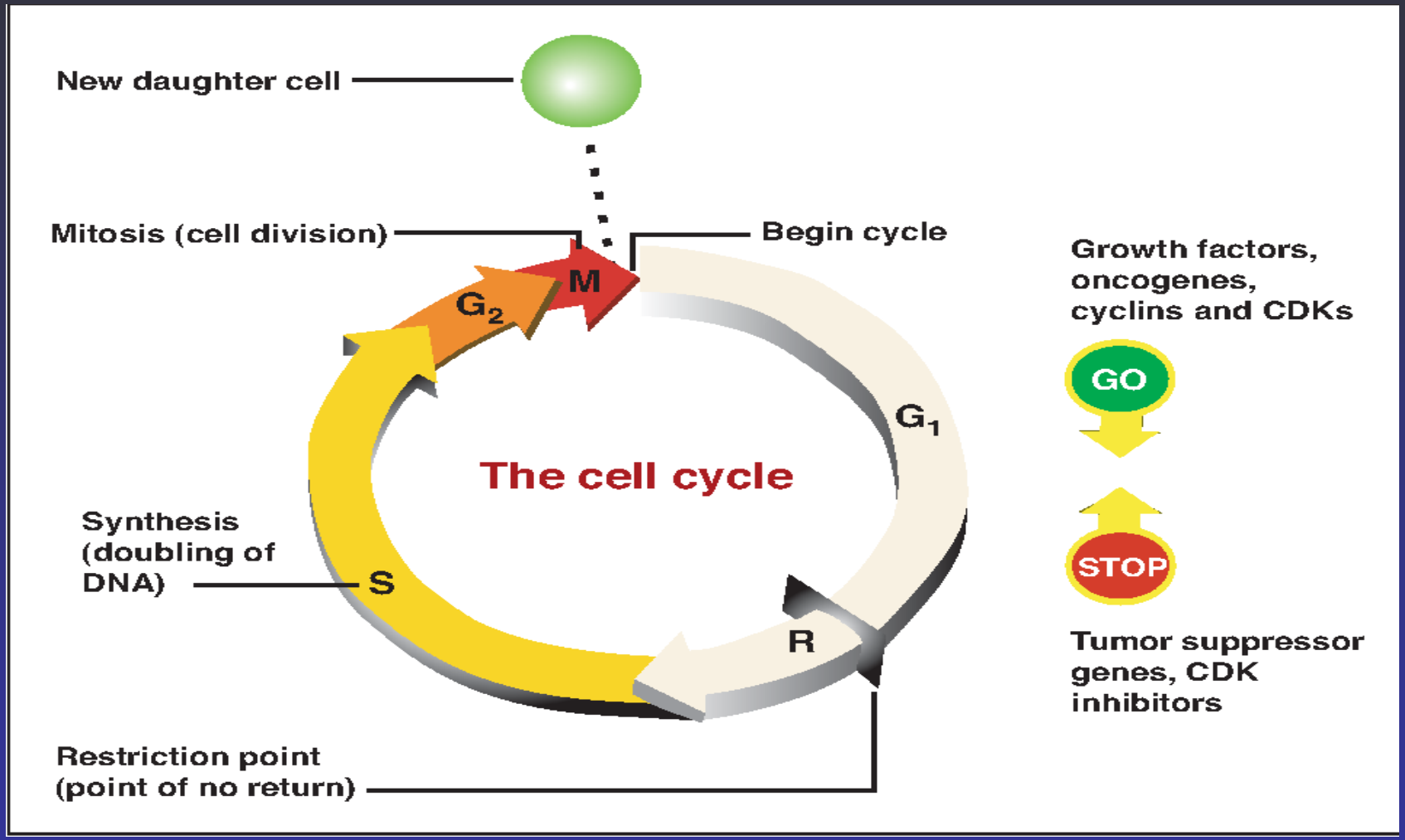
•DOI:10.1634/THEONCOLOGIST.7-1-73 \; Corpus ID: 1435014

The cell cycle and its regulation 2



https://www.britannica.com/science/cell-biology/Cell-division-and-growth

The cell cycle and its regulation



•DOI:10.1634/THEONCOLOGIST.7-1-73 \; Corpus ID: 1435014

Cells without control are malignant: Features of Malignant Transformation

Feature	Description
Altered morphology	Loss of differentiated shape Rounded as a result of disaggregation of actin filaments and decreased adhesion to surface More refractile
Altered growth control	Loss of contact inhibition of growth Loss of contact inhibition of movement Reduced requirement for serum growth factors Increased ability to be cloned from a single cell Increased ability to grow in suspension Increased ability to continue growing ("immortalization")
Altered cellular properties	Induction of DNA synthesis Chromosomal changes Appearance of new antigens Increased agglutination by lectins
Altered biochemical properties	Reduced level of cyclic AMP Enhanced secretion of plasminogen activator Increased anaerobic glycolysis Loss of fibronectin Changes in glycoproteins and glycolipids

https://basicmedicalkey.com/tumor-viruses/

A short Historic Perspective

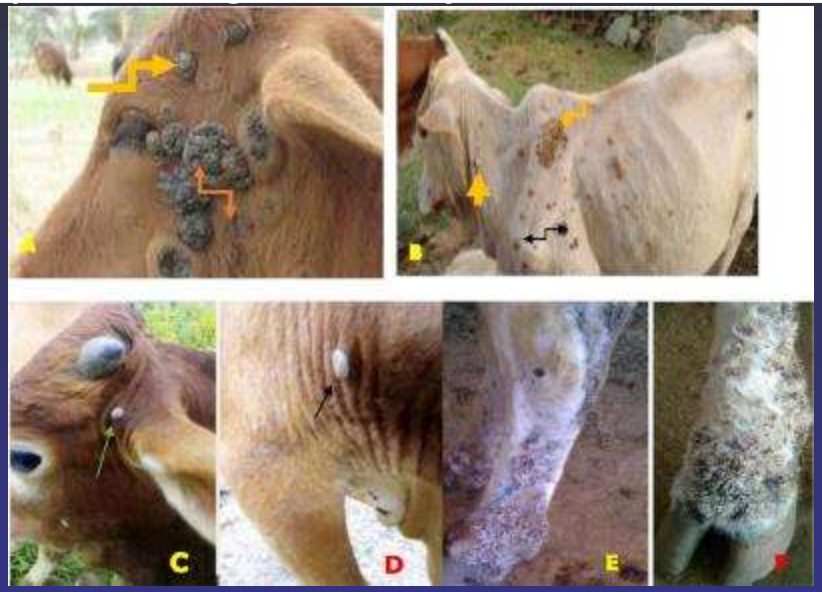
- 1908 Ellerman and Bang 1st showed that avian leukemia could be transmitted by filtered extracts.
- 1911 Peyton Rous demonstrated that sarcomas in chickens had a viral etiology
- 1933 Richard Shope discovered 1st DNA tumor virus (Papilloma in cottontail rabbits)

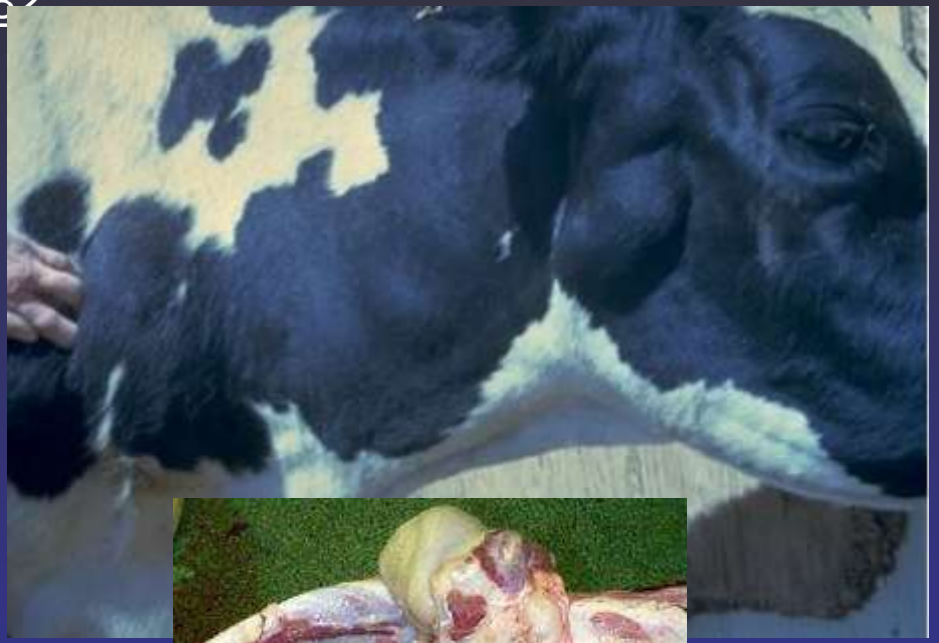
Evidence for classifying a tumor virus

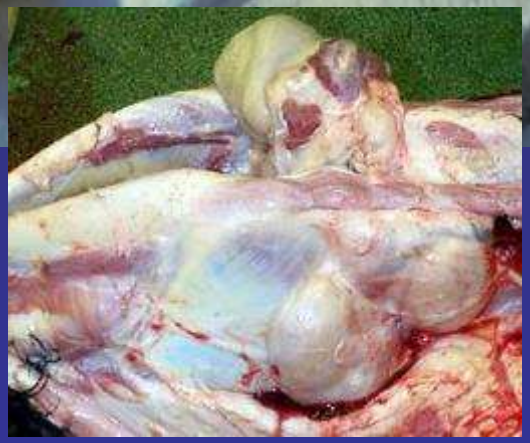
1. Presence of part of viral genome in tumors and expression of some viral genes.
2. In vitro infection of cells leads to transformation
   - Tumorigenic assays:
     1. Growth in low serum (reduced growth factor requirements)
     2. Growth in soft agar (anchorage independent growth)
3. Identification of viral genes that transform cells in culture
4. Infection of animal model system results in tumors
   1. Not possible for human viruses
   2. Vaccination prevents tumor formation

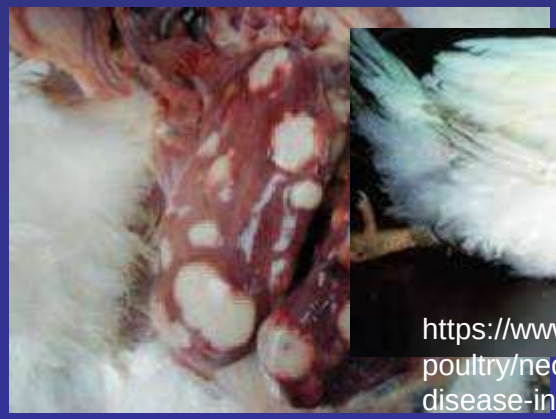
How can viruses cause transformation?

https://doi.org/10.1016/j.sciaf.2021.e00882









https://www.msdvetmanual.com/poultry/neoplasms/marek-s-disease-in-poultry

https://nwdistrict.ifas.ufl.edu/phag/2023/01/06/are-you-familiar-with-the-signs-of-bovine-leukosis-virus/

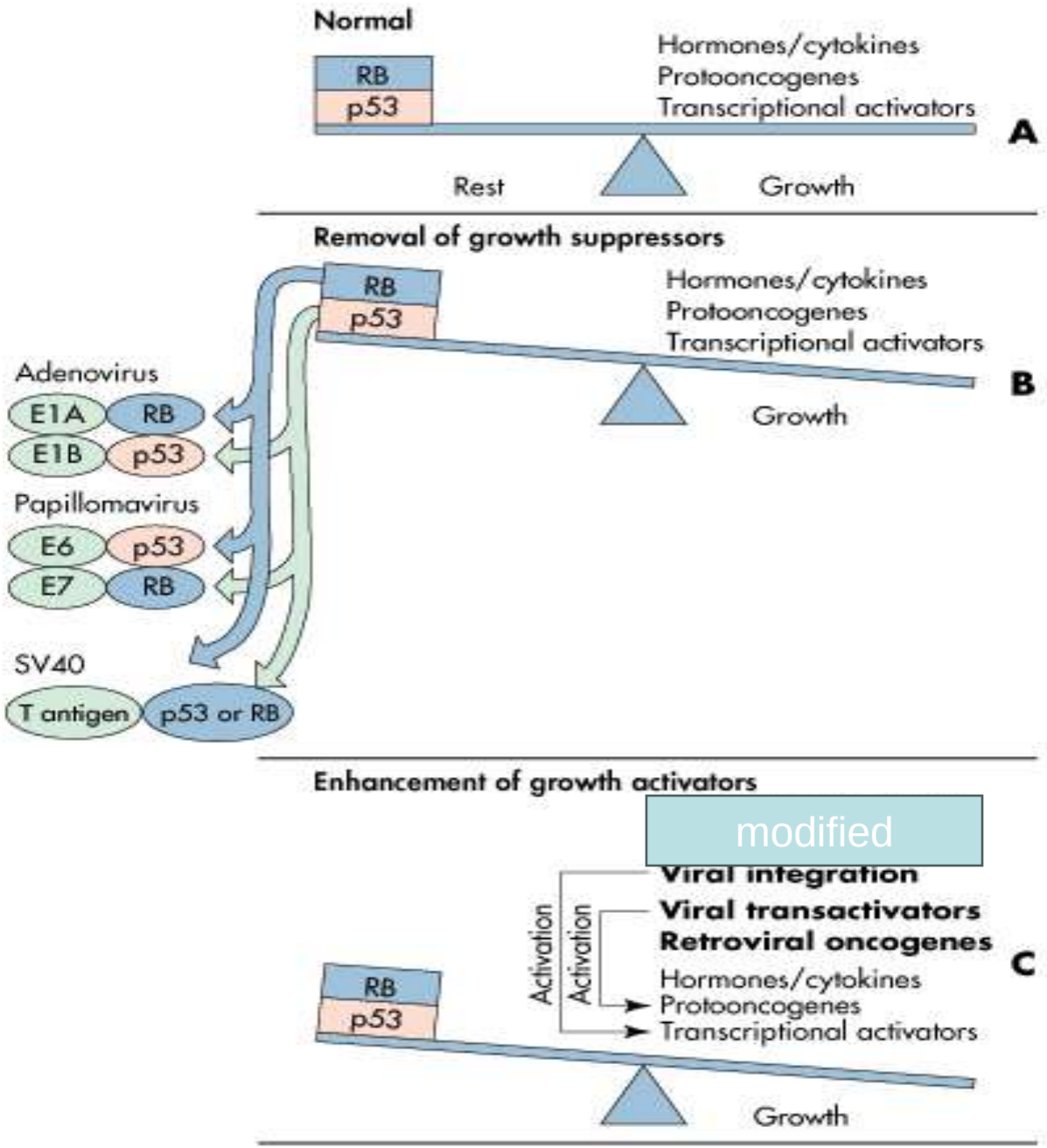
Select Virus Families that Induce Tumors

- **DNA viruses:**
  - Papillomaviruses.
  - Polyomaviruses (SV40).
  - Hepadnaviruses.
  - Herpesviruses.
  - Adenoviruses.
  - Poxviruses (Yaba monkey Tumor virus).

- **RNA viruses:**
  - Retroviruses.
  - Flaviviruses (HCV).

How do viruses transform cells? Examples

Proto-oncogenes are genes that normally **help cells grow and divide to make new cells, or to help cells stay alive**. When a proto-oncogene mutates (changes) or there are too many copies of it, it can become turned on (activated) when it is not supposed to be, at which point it's now called an oncogene.Aug 31, 2022 https://www.cancer.org/cancer/understanding-cancer/genes-and-cancer/oncogenes-tumor-suppressor-genes.html

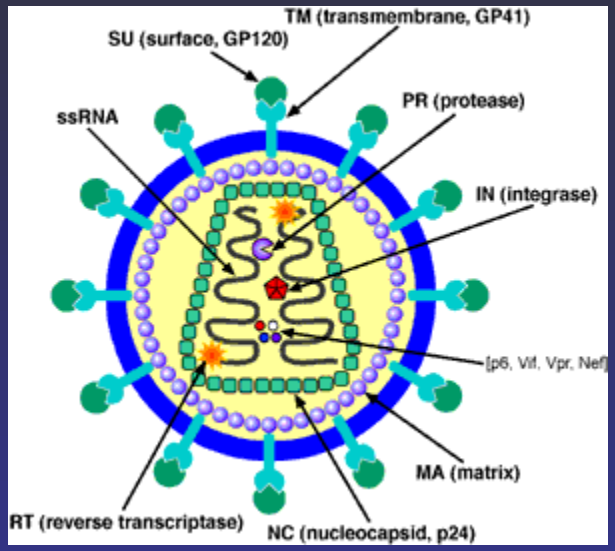


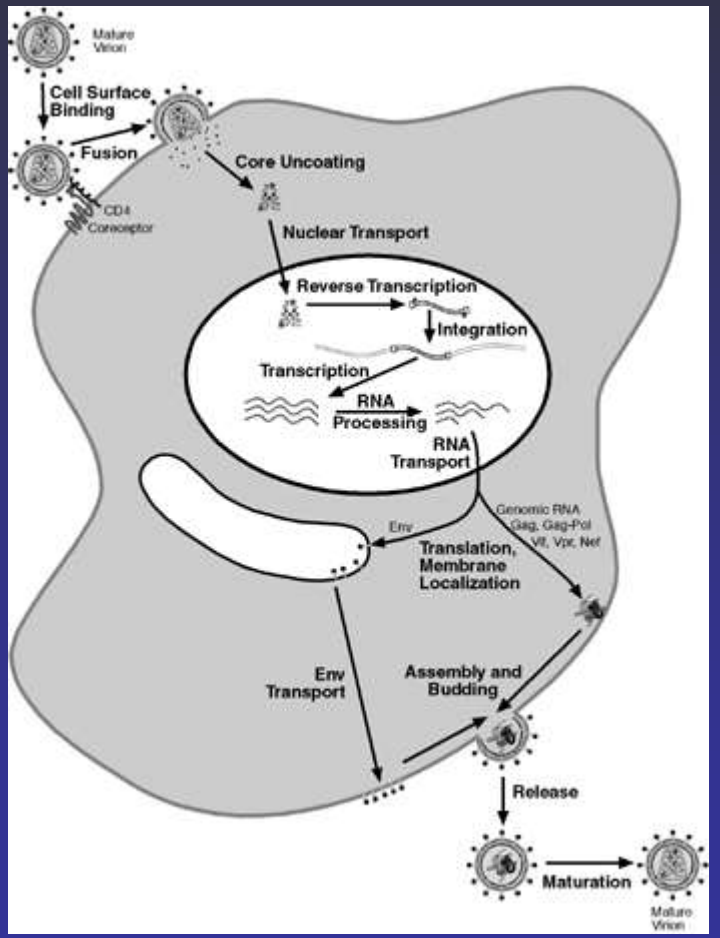
Generalization about Viral Transformation (which is not always good) !!!!

- RNA viruses activate oncogenes
- DNA viruses negate tumor suppressors

RNA TUMOR VIRUSES

Retrovirus Lifecycle (FYI)





Simple retrovirus

•*LTR*-*gag*-*pol*-*env*-*LTR*

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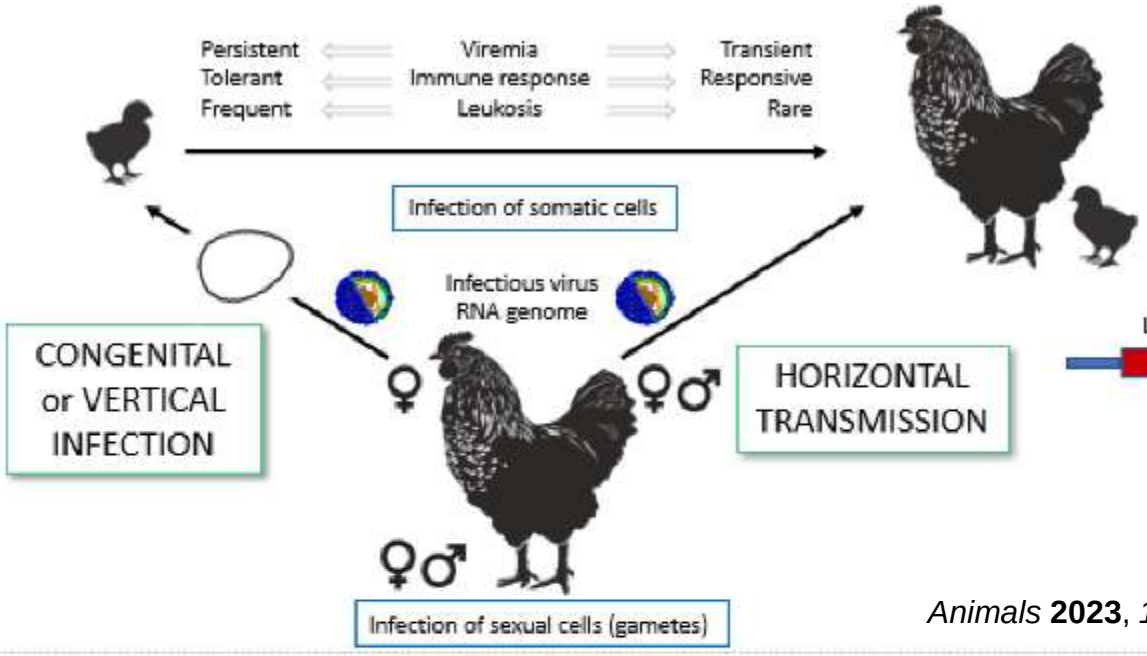
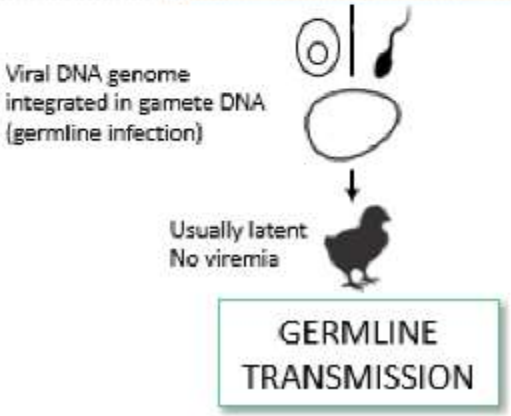
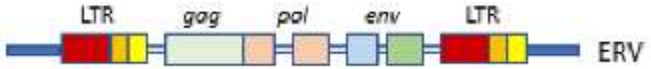


EXOGENOUS

Animals **2023**, *13*(14), 2358; https://doi.org/10.3390/ani13142358





ENDOGENOUS

Retroviruses

- RNA tumor viruses “create” oncogenes by acquiring, modifying, deregulating cellular genes (proto-oncogenes)

- v-onc not essential viral gene & unrelated to strategy of viral replication

- Replication of RNA viruses is not cytocidal nor is it required for tumorigenesis.

Mechanisms of cell transformation by retroviruses

Virus category	Tumor latency period	Efficiency of tumor formation	Oncogenic effector	Infecting viral Genome	Transform cultured cells?
Transducing retrovirus	Short (days)	High (can reach 100% of animals)	Cell-derived oncogene carried in viral genome	Viral-cellular chimera, replication defective	Yes
Cis-acting/ nontransducing	Intermediate (wk, mo)	High to intermediate	Cellular oncogene activated in situ by provirus insertion	Intact, replication competent	No
Trans-activating/ nontransducing long latency	Long (mo, yr)	Very low (<5%)	Virus-coded Transcriptional regulatory protein	Intact, replication competent	No

Mechanisms of cell transformation by retroviruses

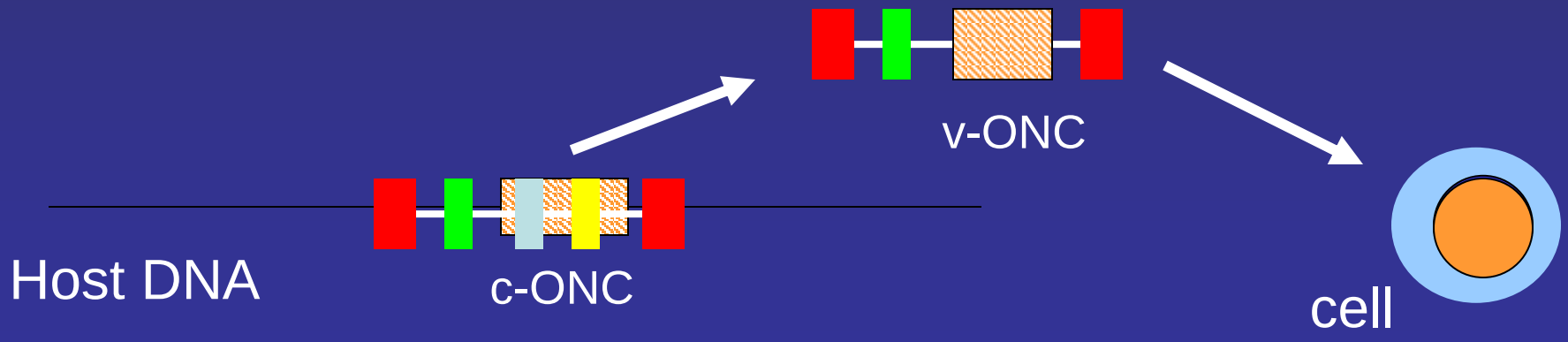
1) Retroviral transduction of oncogene (transducing retrovirus)

2) Oncogene activation by retroviral insertion (*cis*-acting / nontransducing retrovirus)

3) Oncogenesis mediated by essential retrovirus proteins (*trans*-activating / nontransducing long-latency retrovirus)

Transducing retroviruses

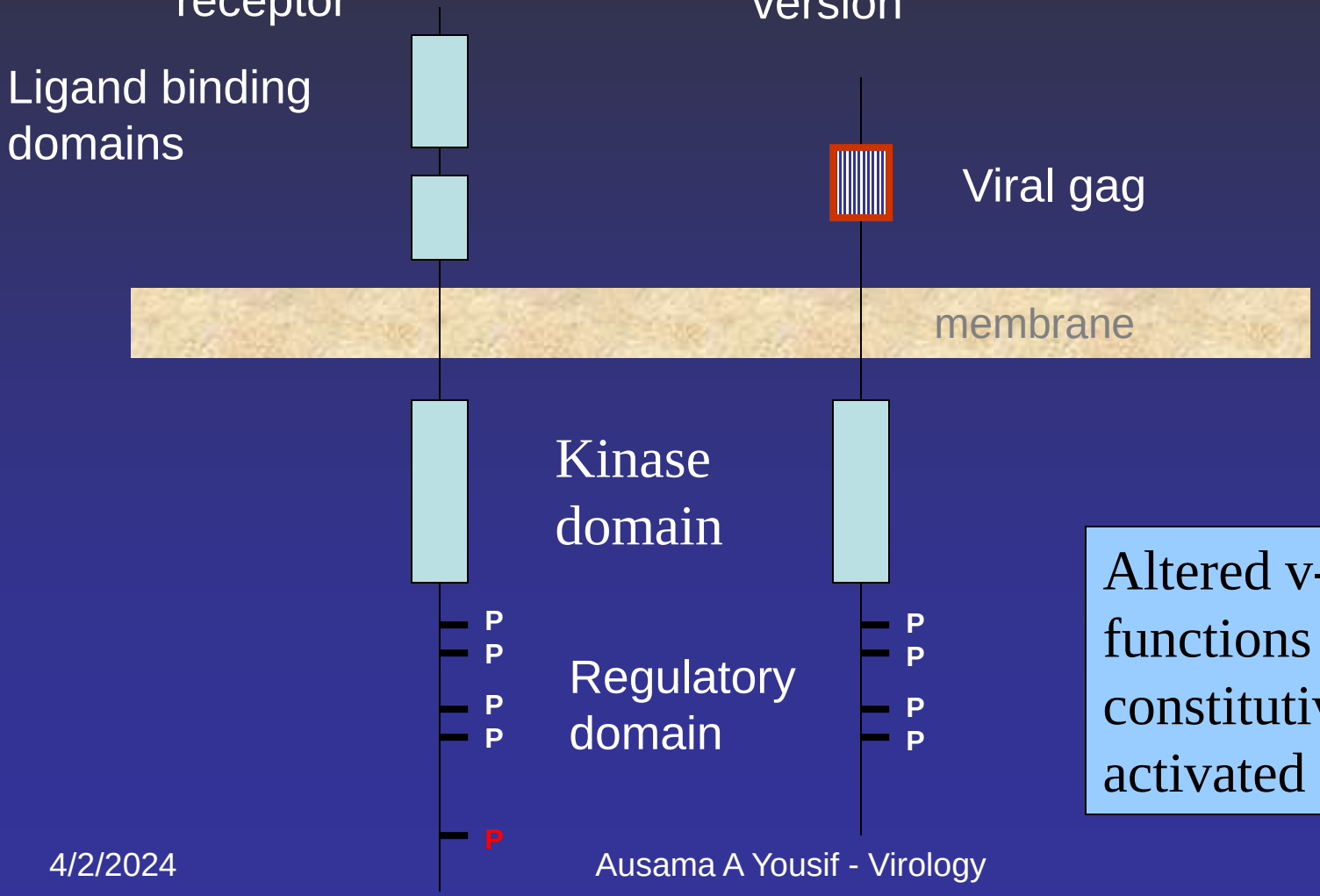
- Viral acquisition of cellular proto-oncogene with capacity to transform if deregulated, usually replacing viral coding sequences (exception is RSV=src oncogene).
- Becomes replication defective, secondary to the loss of viral coding information; requires helper virus



Structural Changes in an Acquired vOnc

c-Erb B (EGFR)
Epidermal growth factor receptor

v-Erb B
Transduced retroviral version



Altered v-Erb B functions as a constitutively activated EGFR

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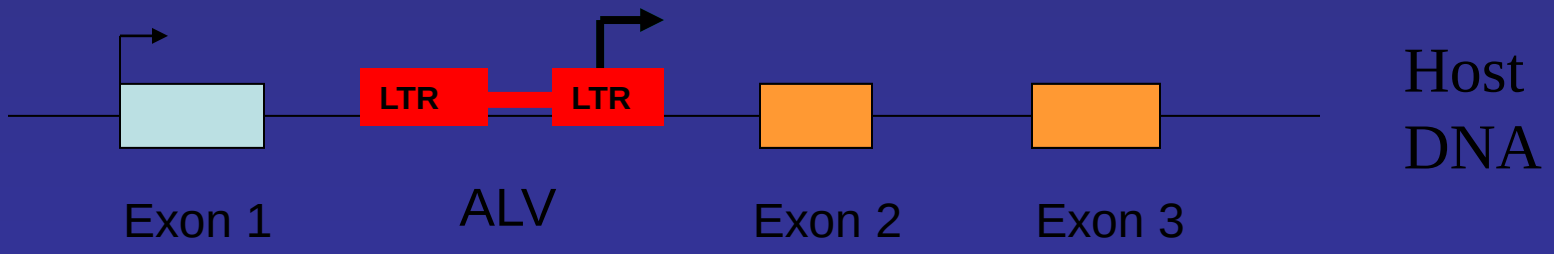
Cis-acting retroviruses

- Do not carry oncogenes
- Retain all viral genes
- Are replication-competent

Mechanism of cell transformation for cis-acting retroviruses

- Random retroviral integration into cell DNA
- Insertional activation (or inactivation)
- Cis activation by promoter or enhancer insertion next to proto-oncogene (encoded by exons 1-3)



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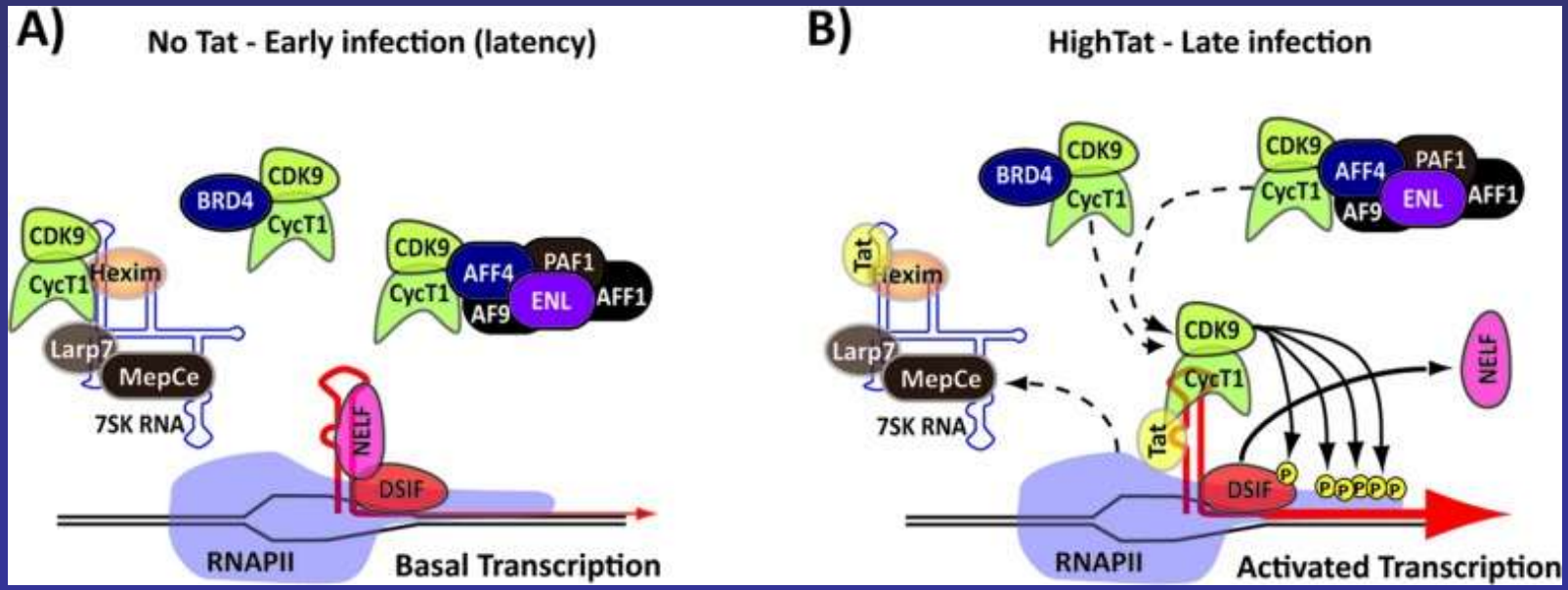
Oncogenesis mediated by essential retrovirus proteins (*trans*-activating / nontransducing long-latency retrovirus)

- **The Tat protein is a potent transactivator of transcription from the viral LTR**. Acts by binding to a hairpin structure, the TAR element, and recruiting host factors cyclinT and Cdk9 to the RNA (to continue the replication cycle).
- Is secreted by the infected cells, accumulates in the extracellular environment and is up taken by neighboring cells, affecting their gene expression and functions.
- Interact with the host cell genome, cellular messengers, transcription factors and several proteins to alter expression of cellular genes and generate a permissive environment for viral replication.



Oncotarget. 2017 Apr 18; 8(16): 27569–27581. Published online 2017 Feb 7. doi: 10.18632/oncotarget.15174

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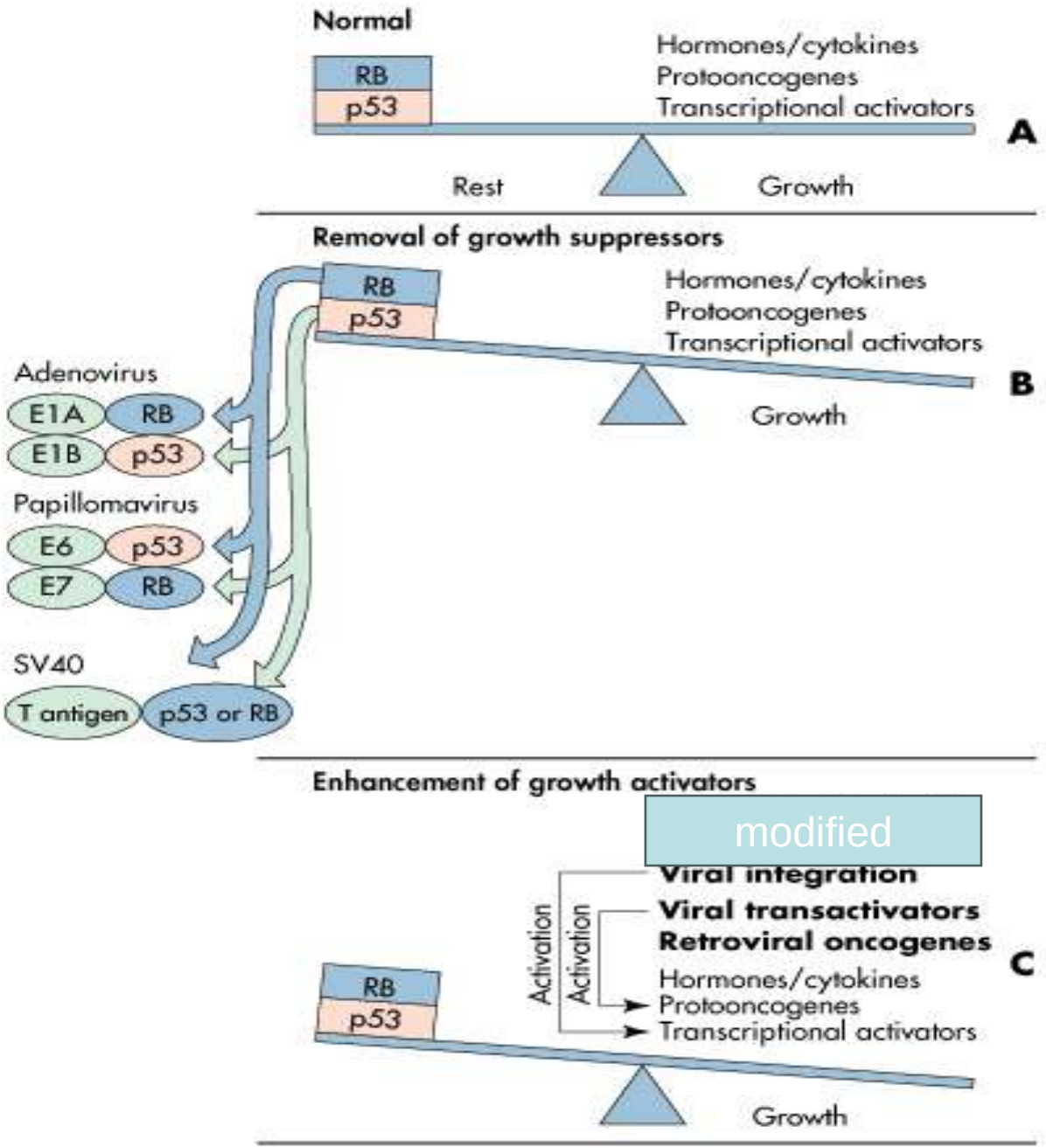
DNA TUMOR VIRUSES

DNA Tumor viruses

- DNA tumor viruses transform cells by
  - Altering cell cycle progression
    - Negate Rb and p53 cell cycle blocks to induce proliferation.
  - Encode cellular mimics to activate signal transduction pathways that enhance cell proliferation.

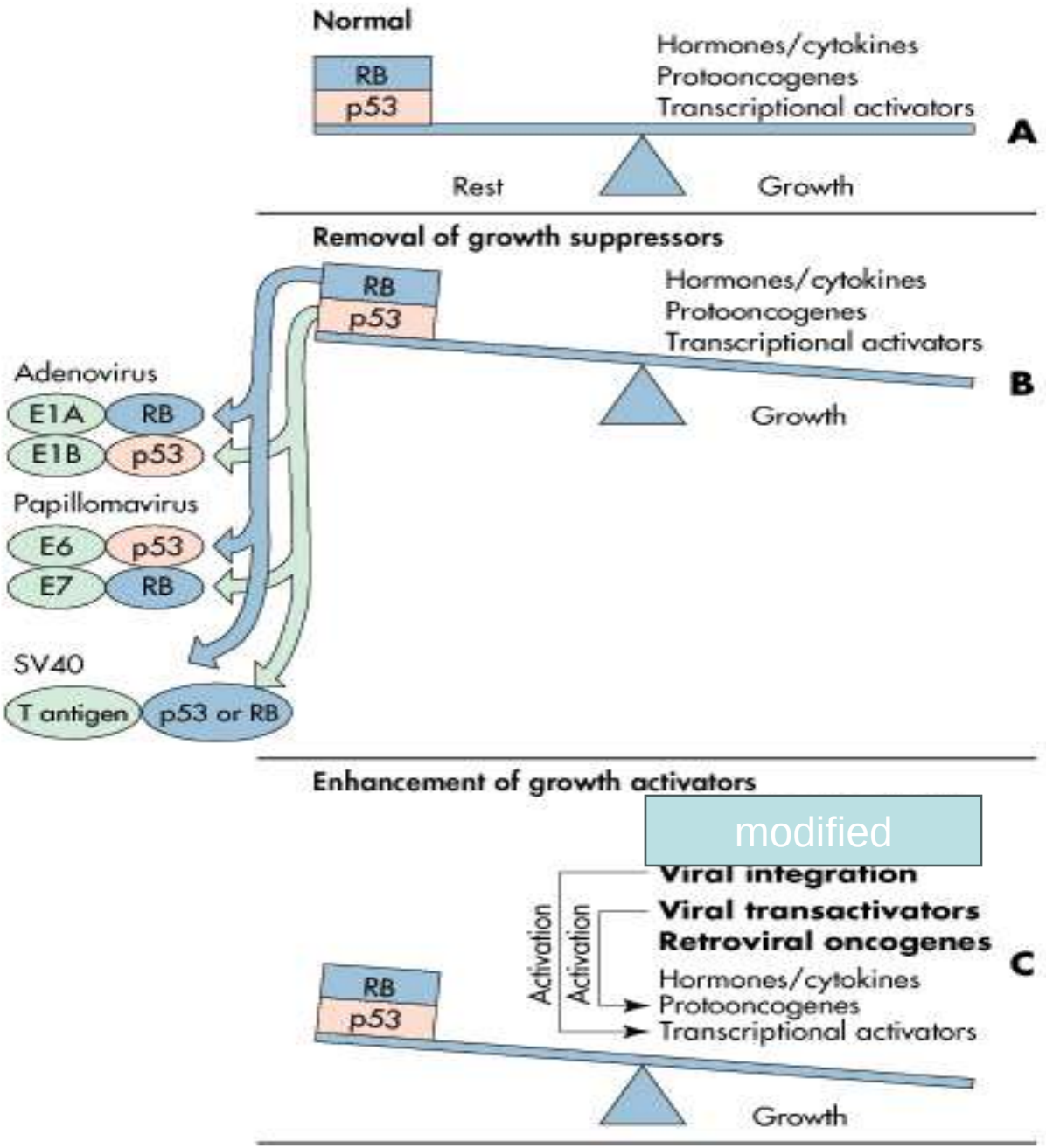
How do viruses transform cells? Examples



DNA tumor viruses target tumor suppressors

Virus	Gene Product	Cellular target
Adenovirus	E1A	Rb
	E1B	p53
SV40	Large T antigen	Rb, p53
Polyomavirus	Middle T antigen	Src, PI3K
Papillomavirus	E7	Rb
	E6	p53
	E5	PDGF receptor

How do viruses transform cells? Examples



”هذا خلق الله، فأروني ماذا خلق الذين من دونه“

لقمان 11


Biosheild Egypt
مصر الخير و البركة

Acknowledgements

- Mechanisms of Transformation by Retroviruses. Virology 324A. Dept. of Microbiology and Immunology. McGill University. I used many of the slides they prepared. However, I did some modifications based on the references listed within. Many thanks to all the scientists that made this information available to humanity.