Landmarks in animal virus research: The early period (From Virology- Fields 2002)

DATA	Virologist	DISCOVERY
1898	Loeffler F. Frosch P.	First filterable animal virus
1898	Sanarelli G.	Myxomatous virus
1901	Reed W.	First human virus (YFV)
1903	Remingler P. , Riffat-Bay	Rabies virus
1903	Negri A.	The body inclusion of rabies virus
1908	Ellerman V., Bang O.	First leukemia-causing virus
1909	Landsteiner K., Popper E.	Poliovirus
1911	Rous P.	First solid tumor-causing virus

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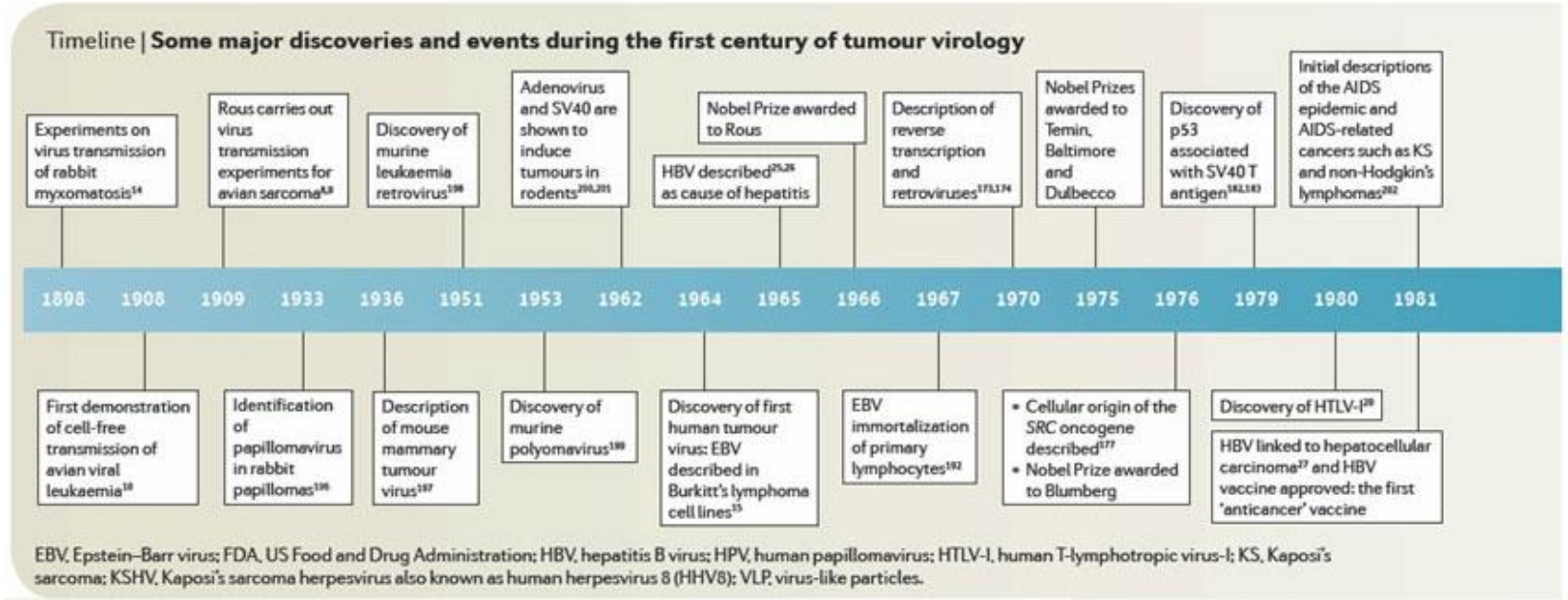


NATURE REVIEWS | **CANCER** 2010

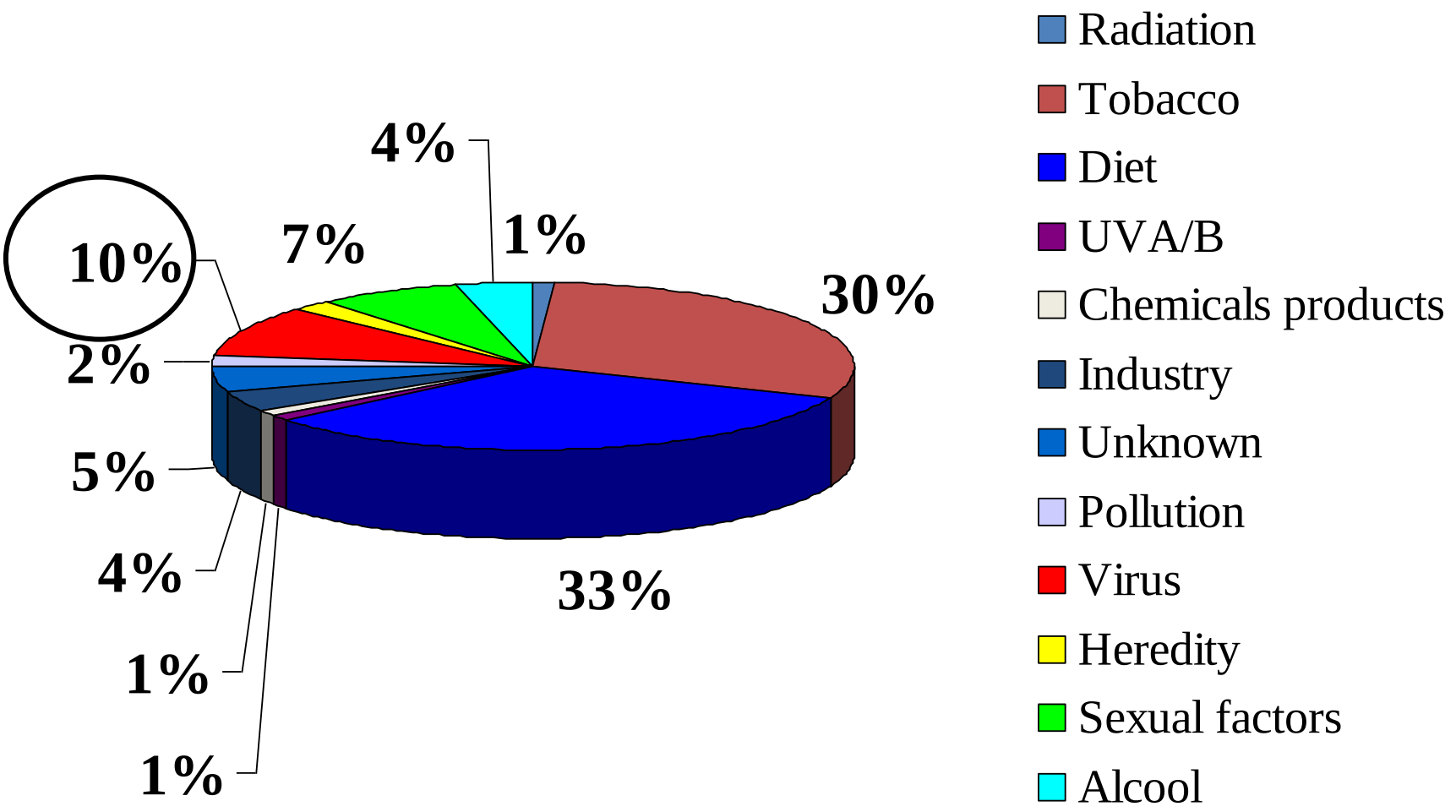
Peyton Rous
Born: 5 October 1879, Baltimore, MD, USA
Died: 16 February 1972, New York, NY, USA
Affiliation at the time of the award:
Rockefeller University, New York, NY, USA
Prize motivation: "for his discovery of tumour-inducing viruses"

Nobel Lecture
Nobel Lecture, December 13, 1966
The Challenge to Man of the Neoplastic Cell

Renato Dulbecco
Born: 22 February 1914, Catanzaro, Italy
Died: 19 February 2012, La Jolla, CA, USA
Affiliation at the time of the award: Imperial Cancer Research Fund Laboratory, London, United Kingdom
Prize motivation: "for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell"

1975, The Nobel Prize in Physiology or Medicine

Etiology of cancer in man



Etiology of cancer in man: role of infectious diseases

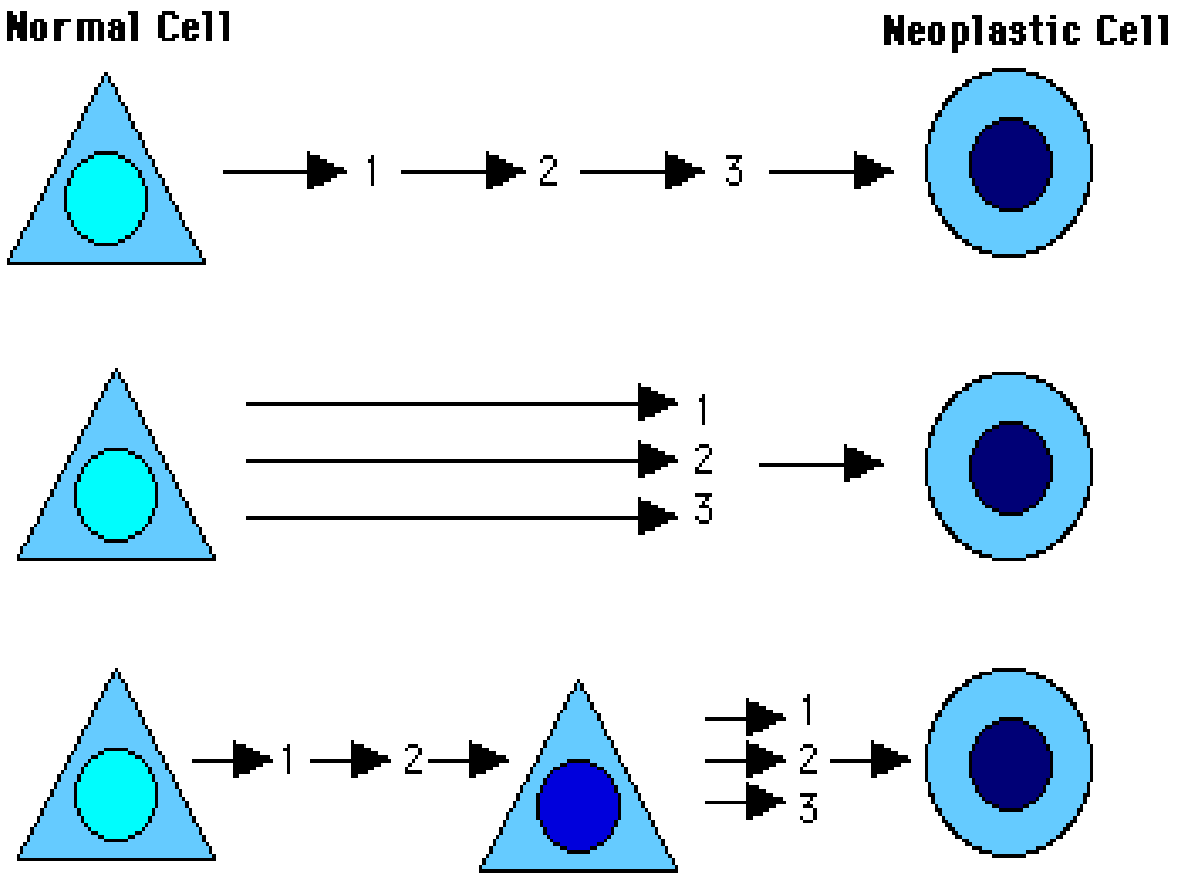
Total	**15-16%**	
	9%	Westerns countries
	21%	Developing countries

Infectious agents may induce the development of cancer

Mechanism	Trasforming action	Example
Genetic	Modifications on cellular DNA expression	carcinoma uterine cervix (HPV)
Inflammatory	Chronic inflammatory response	epatocarcinoma (HBV)
Immunodepressive	No response to cancer development	Kaposi sarcoma (HHV-8)

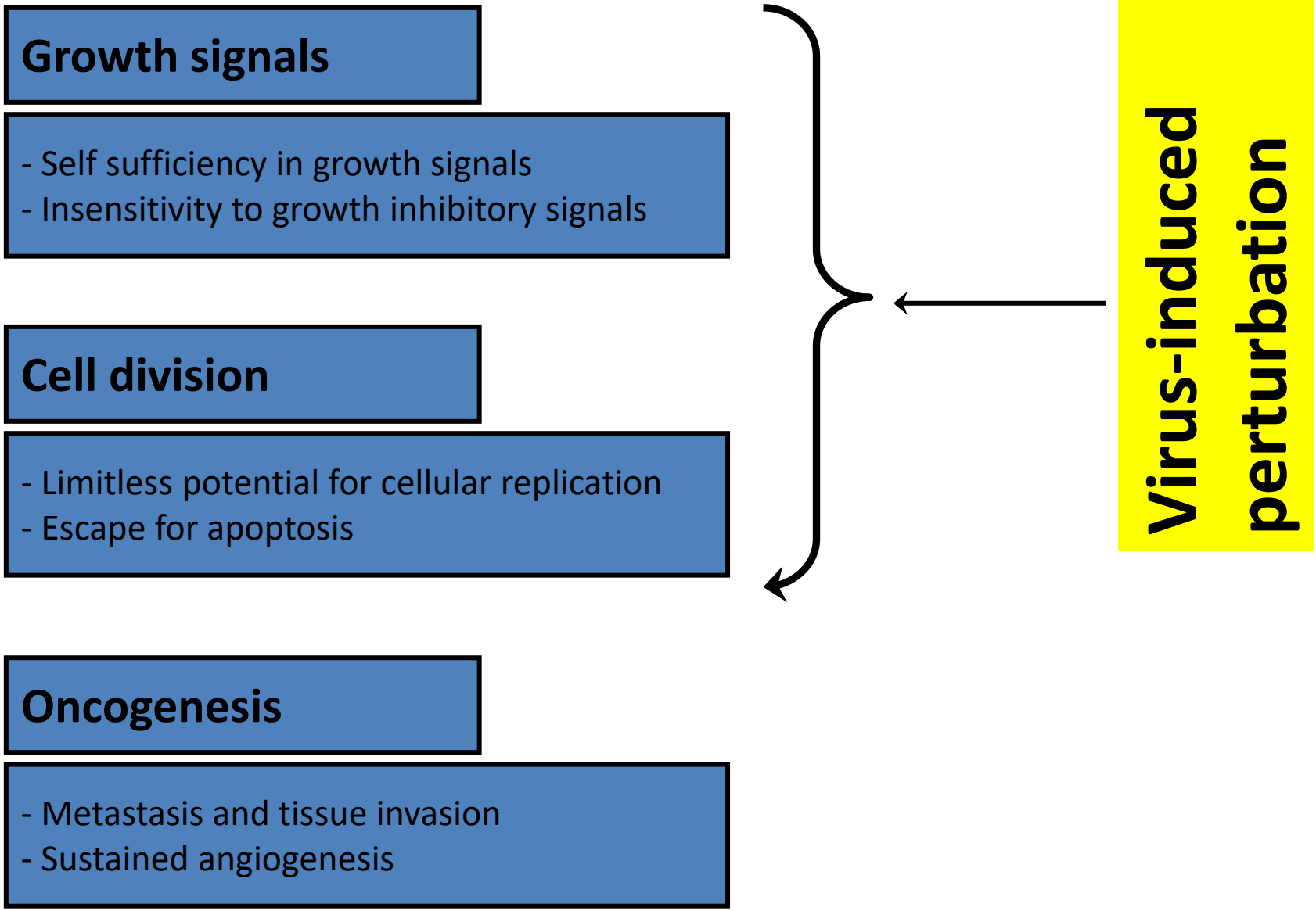
Mechanism of transformation

In vivo and epidemiological studies indicate that transformation is a **multi-step process** involving: **initiation**, **promotion** and **progression**



The oncogenic virus may be necessary but not sufficient to produce neoplasia

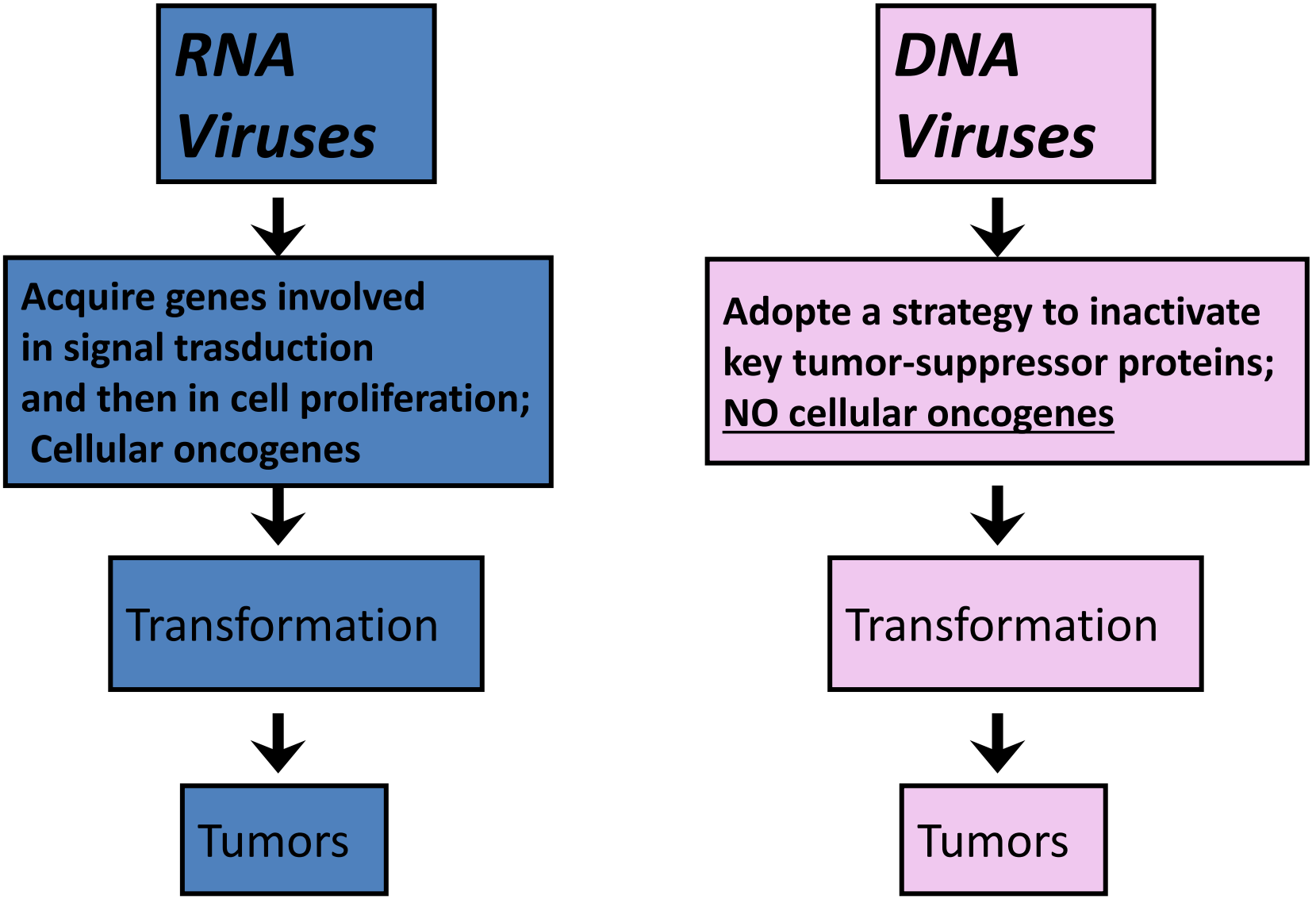
Multifactorial induction of cancer: Molecular determinants



Common characteristics of viral oncogenic transformation

- A single infectious virus particle is sufficient for transformation
- Virus induced transformation is a “single hit” process
- All or part of the viral genome persist in the trasformed cell. In virtually all cases of virus-induced transformation at least part of the viral genome is expressed in the transformed cells
- Transformation results from corruption of normal cell growth and cell-division signals
- Reversion of the transformed cellular phenotype can be achieved by specific interference with the function of viral effector

Oncogenic viruses



Oncogenic viruses

RNA viruses

- The replication is not cytocidal. Transformation is compatible with the production of infectious progeny
- Virus production is not a prerequisite of oncogenesis
- Virus oncogenes are not essential for viral replication
- Only one virus family does exist

DNA viruses

- The synthesis of infectious progeny is linked to cell death
- Transformation can occur only if the viral cycle is aborted
- The oncogenic potential is linked to the genetic strategy of virus replication
- Seven different groups do exist

Tabella 38.1 **Virus associati a tumori dell'uomo.**

DEOSSIRIBOVIRUS		
Famiglia	**Virus**	**Tumori associati**
Herpesviridae	Virus Epstein-Barr	Linfoma di Burkitt Linfomi a cellule B, carcinoma nasofaringeo
	HSV-2	Carcinoma della cervice uterina
	HHV-8	Sarcoma di Kaposi, linfomi cavitari
Papillomaviridae	Papilloma	Papillomi e carcinomi cutanei, genitali e laringei
Polyomaviridae	JC e BK	Tumori in modelli animali
	MCPyV	Carcinoma a cellule di Merkel
Hepadnaviridae	HBV	Carcinoma epatocellulare primario
Poxviridae	Mollusco contagioso	Iperplasia nodulare epidermica
RIBOVIRUS		
Famiglia	**Virus**	**Tumori associati**
Retroviridae	HTLV-1	Linfomi e leucemia a cellule T dell'adulto
	HIV-1, HIV-2	Sarcoma di Kaposi, linfoma non-Hodgkin, cancro cervicale; tumori non-AIDS correlati
Flaviviridae	HCV	Carcinoma epatocellulare primario

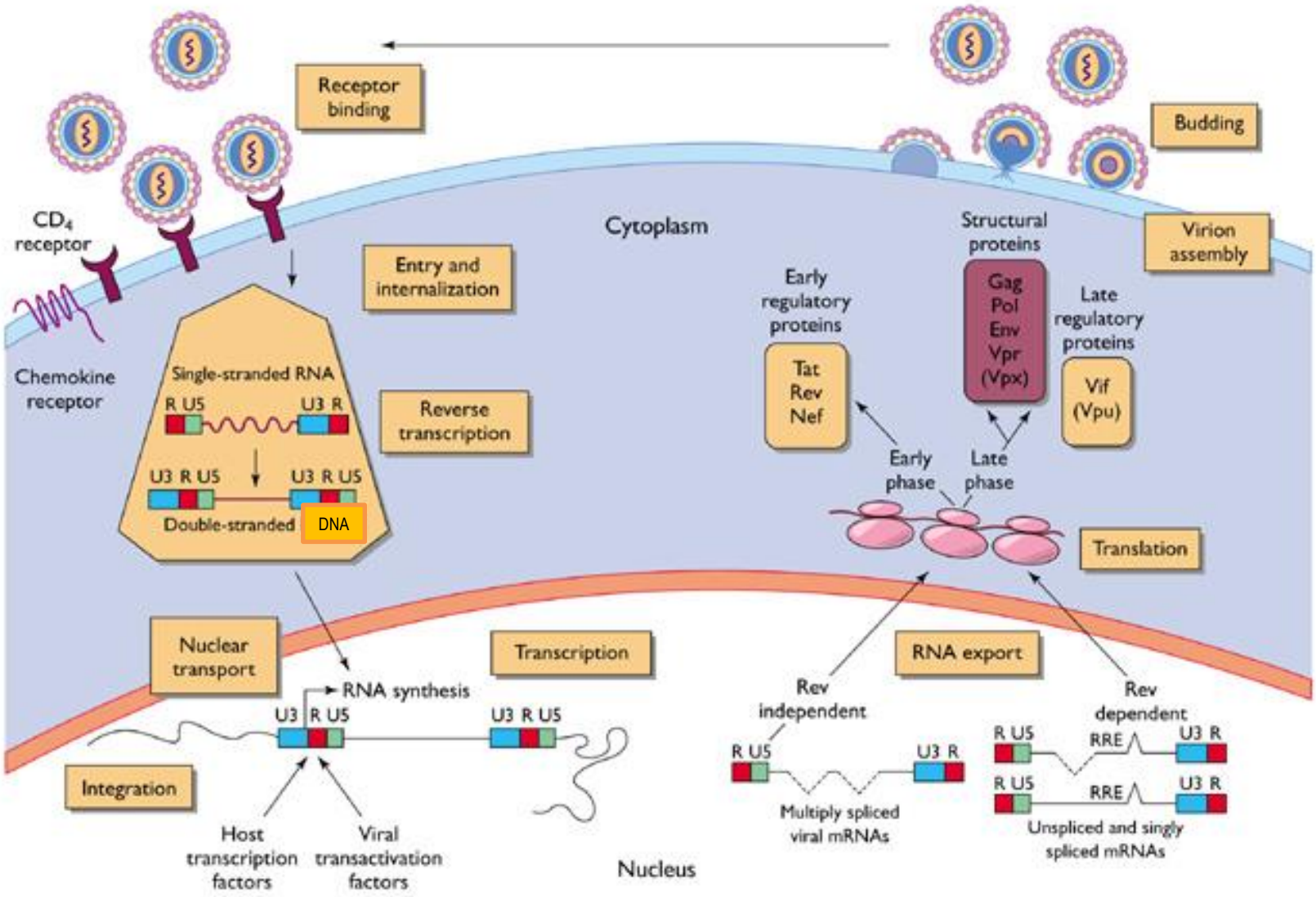
Oncogenic RNA viruses: RETROVIRUS

Oncogenic RNA viruses

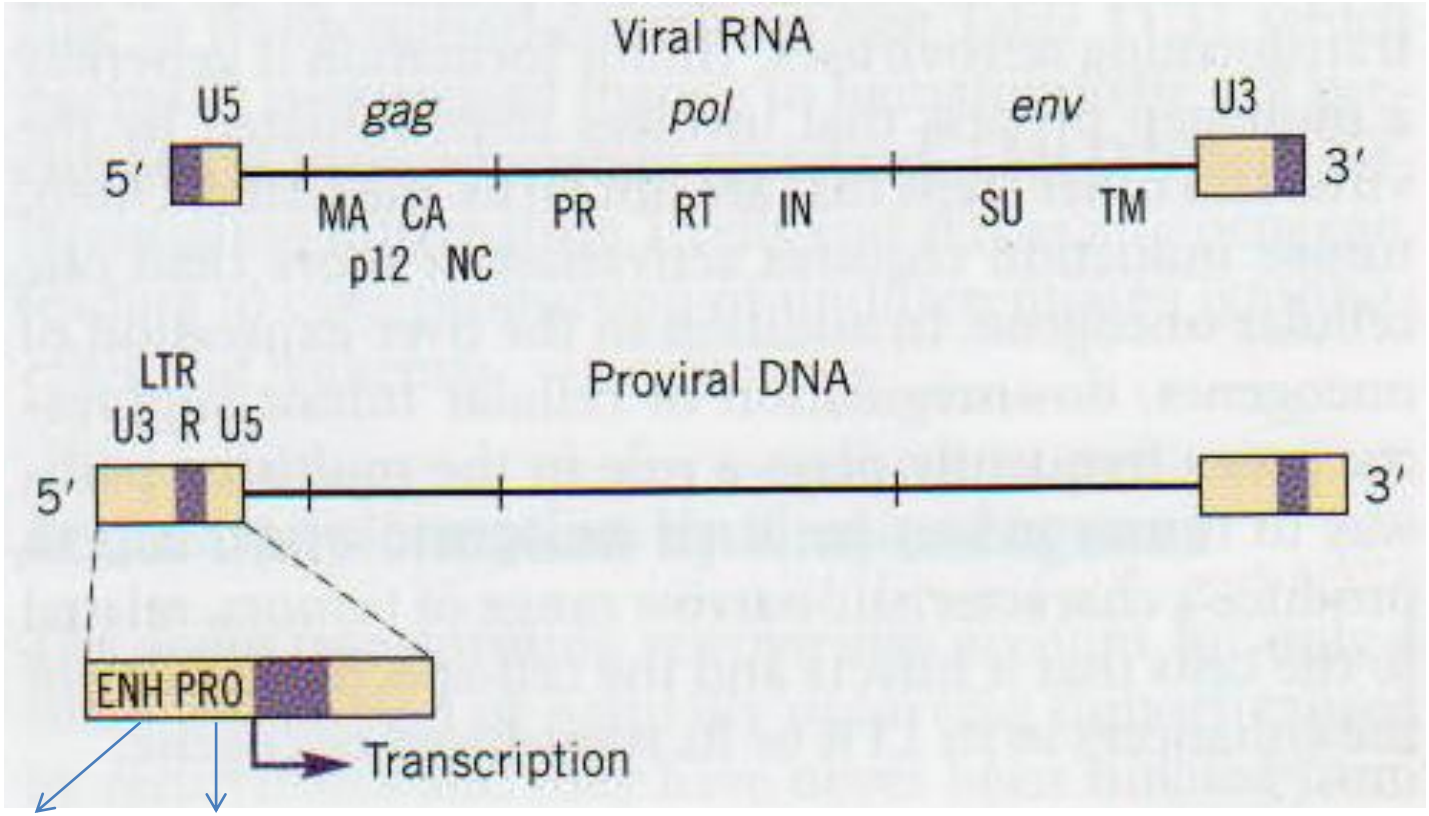
Taxonomic grouping	Examples	Tumor Types
Retroviridae		
Mammalian B type		
	Mouse mammary tumor virus	Mammary carcinoma, T-cell lymphoma, Leukemia
Mammalian C type	Murine leukemia viruses Gross leukemia virus Moloney leukemia virus Graffi leukemia virus Friend leukemia virus Moloney sarcoma virus Kirsten sarcoma virus Harvey sarcoma virus Feline leukemia viruses Gardner-Amstein feline sarcoma virus McDonough feline sarcoma virus Simian sarcoma virus	Leukemia, lymphoma, sarcoma, various other malignancies and pathologic conditions
Avian C type	Avian leukosis and sarcoma viruses Rous sarcoma virus Rous-associated viruses (RAV) Avian leukosis viruses Avian myeloblastosis virus Avian erythroblastosis virus Mill-Hill 2 virus Myelocytoma virus MC29	Sarcoma, B-cell lymphoma, myeloid and erythroid leukemia, various carcinomas and other tumors
HTLV-BLV	Human T-lymphotropic virus Bovine leukemia virus	T-cell leukemiaa B-cell lymphoma

Fields Virology, V ed., Lippincott Williams and Wilkins - 2012

RETROVIRUS replication



RETROVIRUS genome



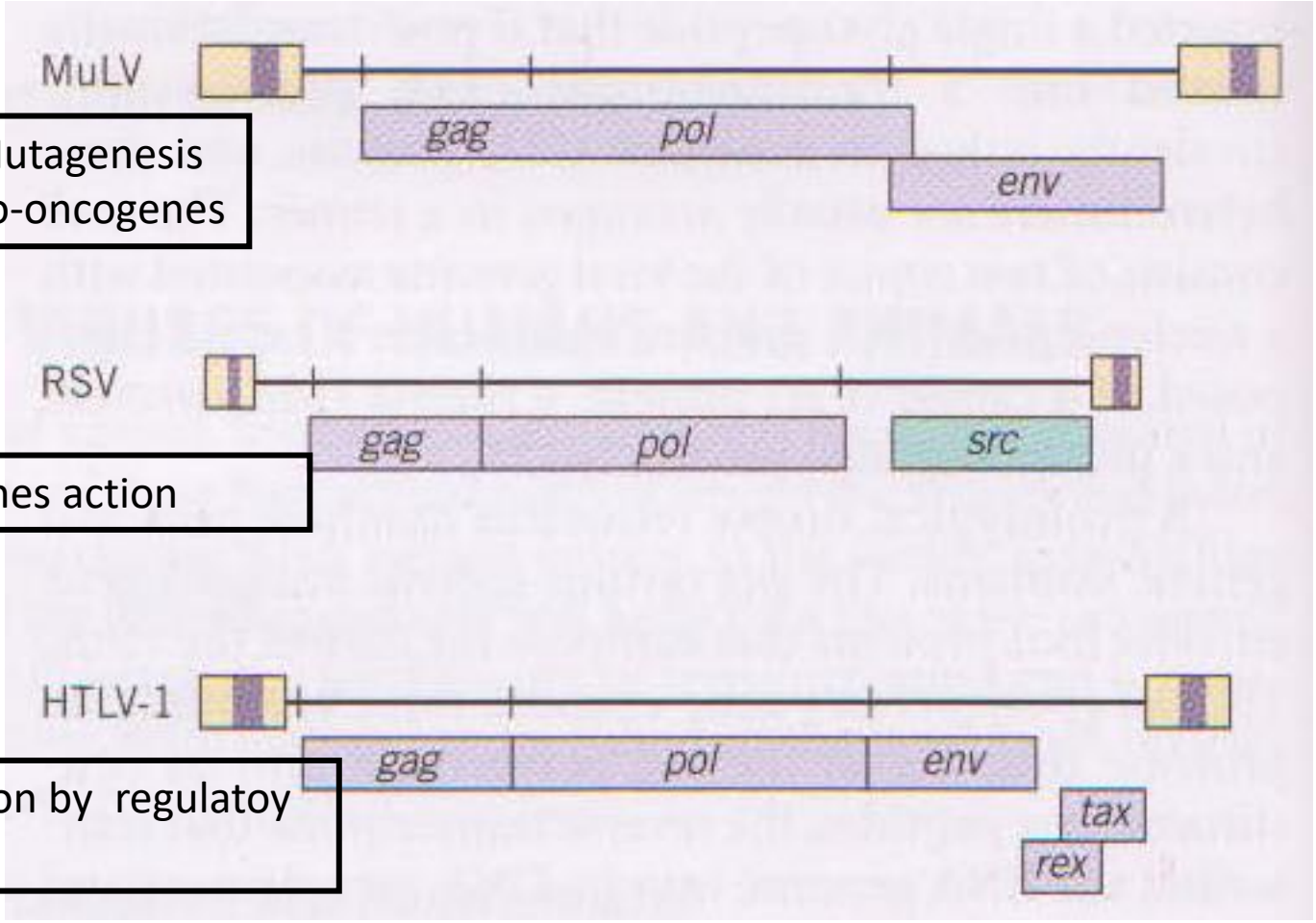
Nathanson N, Viral Pathogenesis and iMis and Immunity , Academic Press Elsevier, 2007

RETROVIRUS genomes : DIFFERENT MECHANISMS OF ONCOGENESIS

Insertional Mutagenesis
Cellular proto-oncogenes

Viral oncogenes action

Transactivation by regulatoy viral genes



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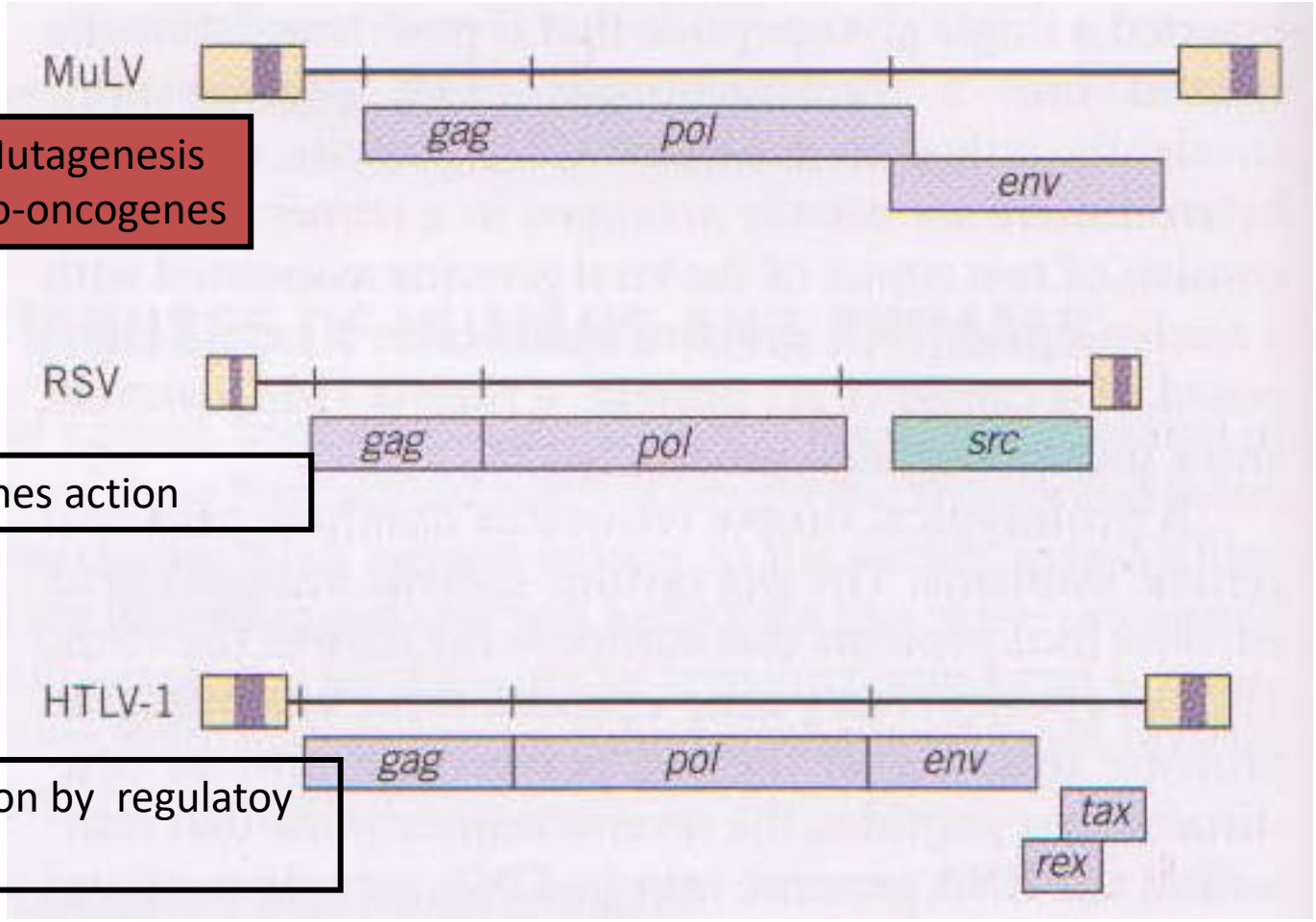
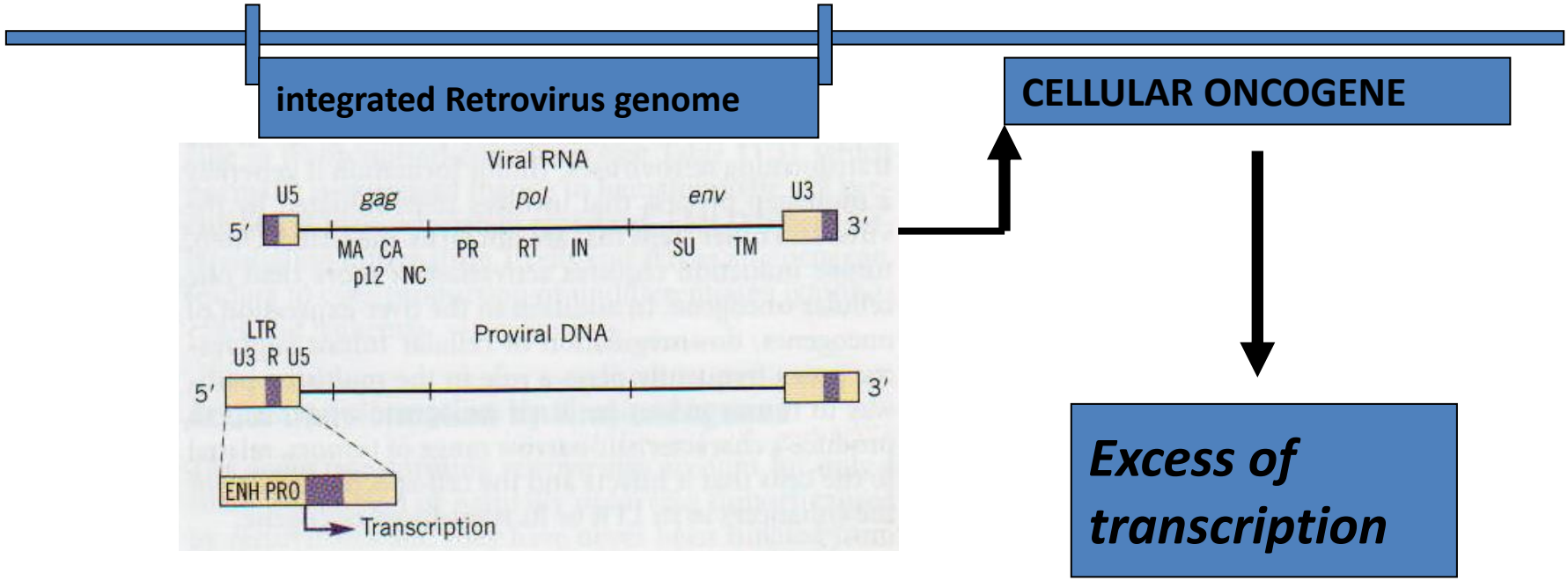


Non acute trasformation by RNA tumor viruses: insertional mutagenesis

cellular genome



CATEGORY OF ONCOGENE (EXAMPLE)	FUNCTION OF c-onc	ALTERATION IN v-onc RELATIVE TO c-onc	ACTION OF v-onc
PTK protein tyrosine kinase (*src*)	Tyrosine phosphorylation activates intracellular signaling proteins	Loss of C terminal tyrosine or loss of receptor binding domain	Increase tyrosine phosphorylation causes sustained intracellular signaling
Serine-threonine kinase(*mos*)	Phosphorylation activates cell cycle proteins	Deletion of N terminal regulatory sequences	Increase phosphorylation activates cell cycle
G-protein (*ras*)	Cycles between GTP/GDP forms regulating signaling	Change in amino acid at codon 12	High GTP/GDP ratio causes sustained activation signals
Transcription factor (*myb*)	Interactions with transcription complex to enhance or reduce transcription	Deletion of regulatory domains or increase of mRNA or protein accumulation	Increase transcription of growth factors or cell cycle genes or reduction of anti-oncogene expression

RETROVIRUS genomes : DIFFERENT MECHANISMS OF ONCOGENESIS

Insertional Mutagenesis
Cellular proto-oncogenes

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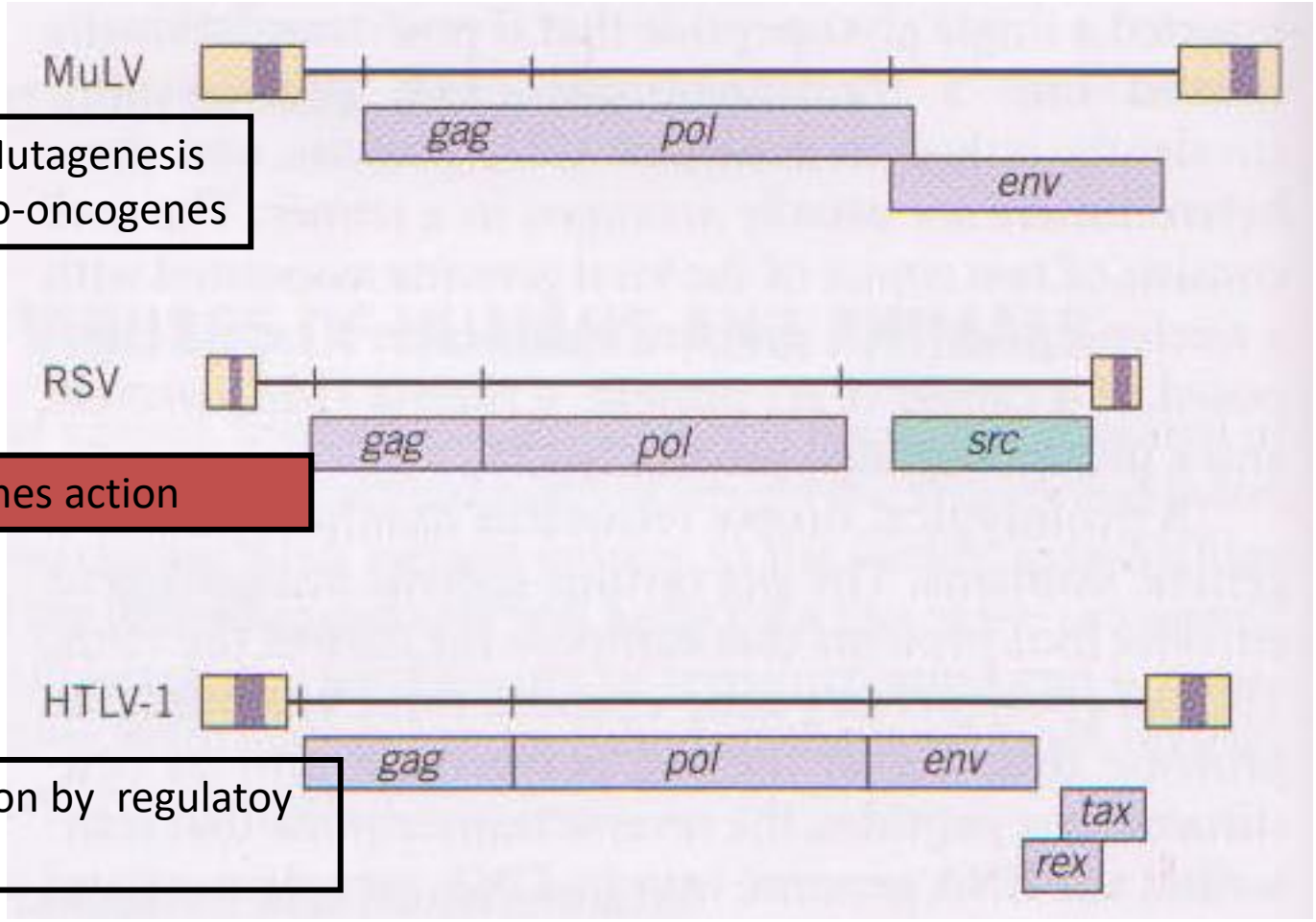
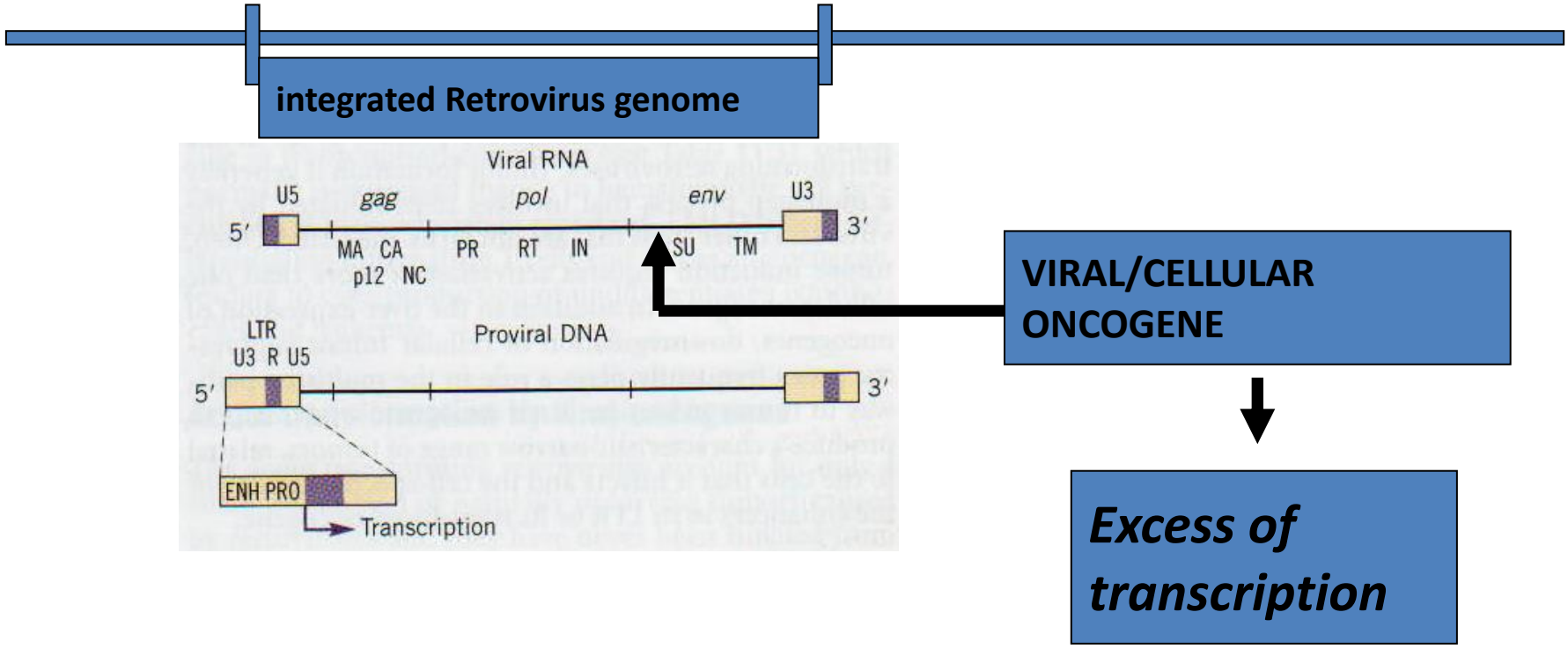


Acute trasformation by RNA tumor viruses: expression of viral/cellular oncogene

cellular genome



Oncogeni di Retrovirus a trasformazione acuta

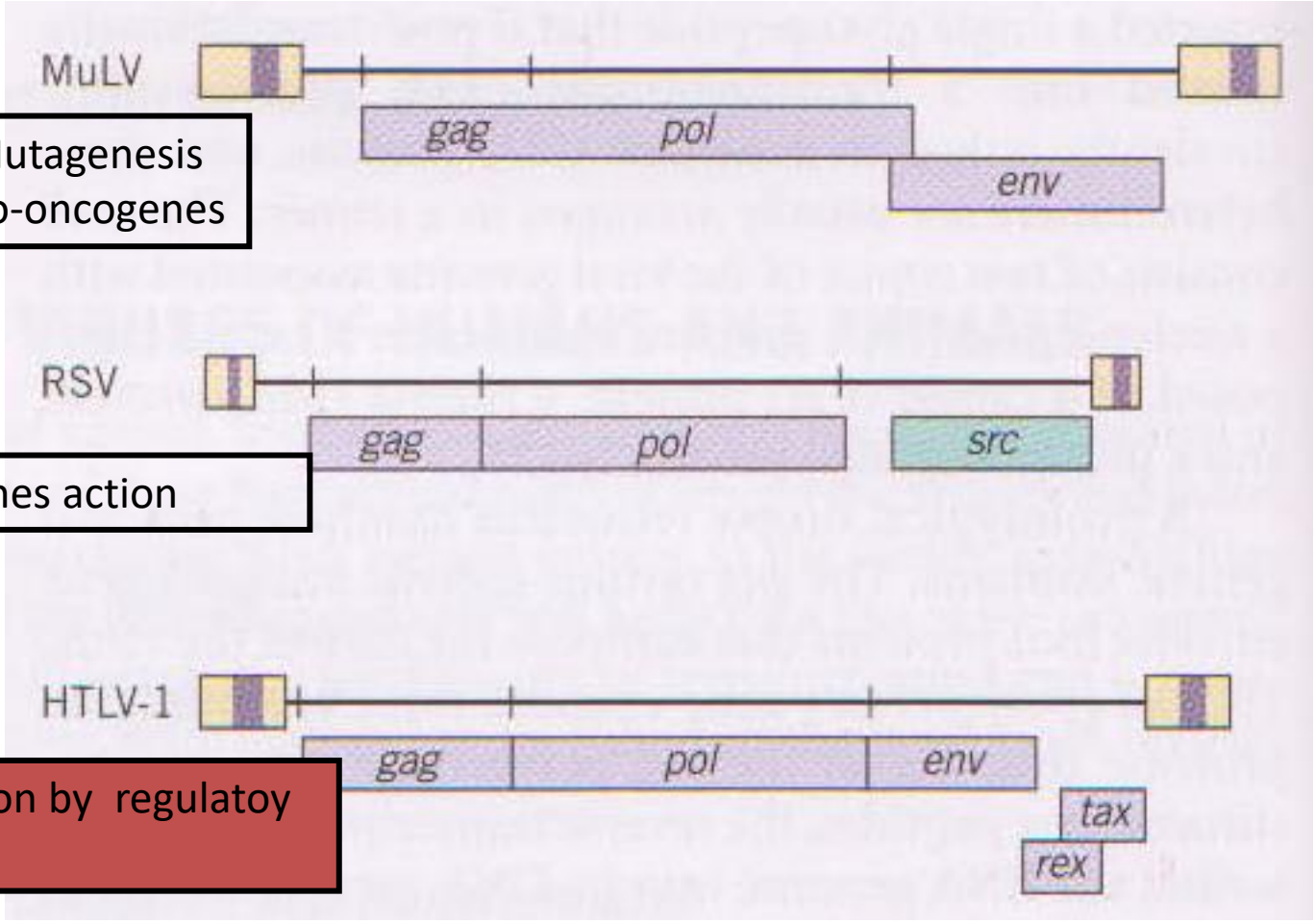
src	Rous sarcoma virus	Chicken
myc	Avian myelocytomatosis virus	Chicken
erb A, erb B	Avian erythroblastosis virus	Chicken
myb	Avian myeloblastosis virus	Chicken
ets	Avian erythroblastosis virus	Chicken
rel	Avian reticuloendotheliosis virus	Turkey
H-ras	Harvey rat sarcoma virus	Rat
K-ras	Kirsten murine sarcoma virus	Mouse
abl	Abelson murine leukemia virus	Mouse
raf	Murine sarcoma virus	Mouse
fos	Mouse osteosarcoma virus	Mouse
fms	Feline sarcoma virus	Cat
fes	Feline sarcoma virus	Cat
sis	Simian sarcoma virus	Monkey

RETROVIRUS genomes : DIFFERENT MECHANISMS OF ONCOGENESIS

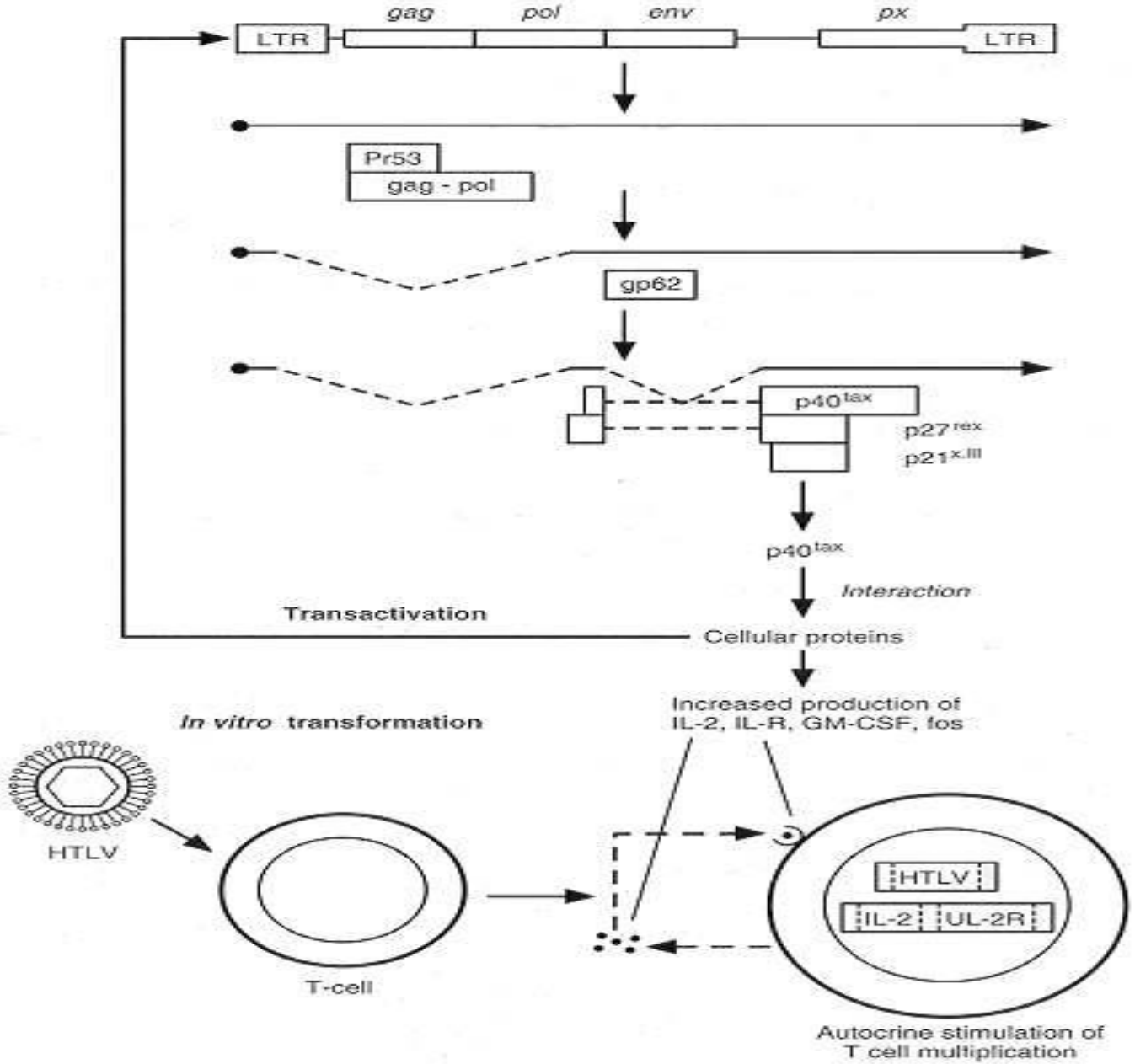
Insertional Mutagenesis
Cellular proto-oncogenes

Viral oncogenes action

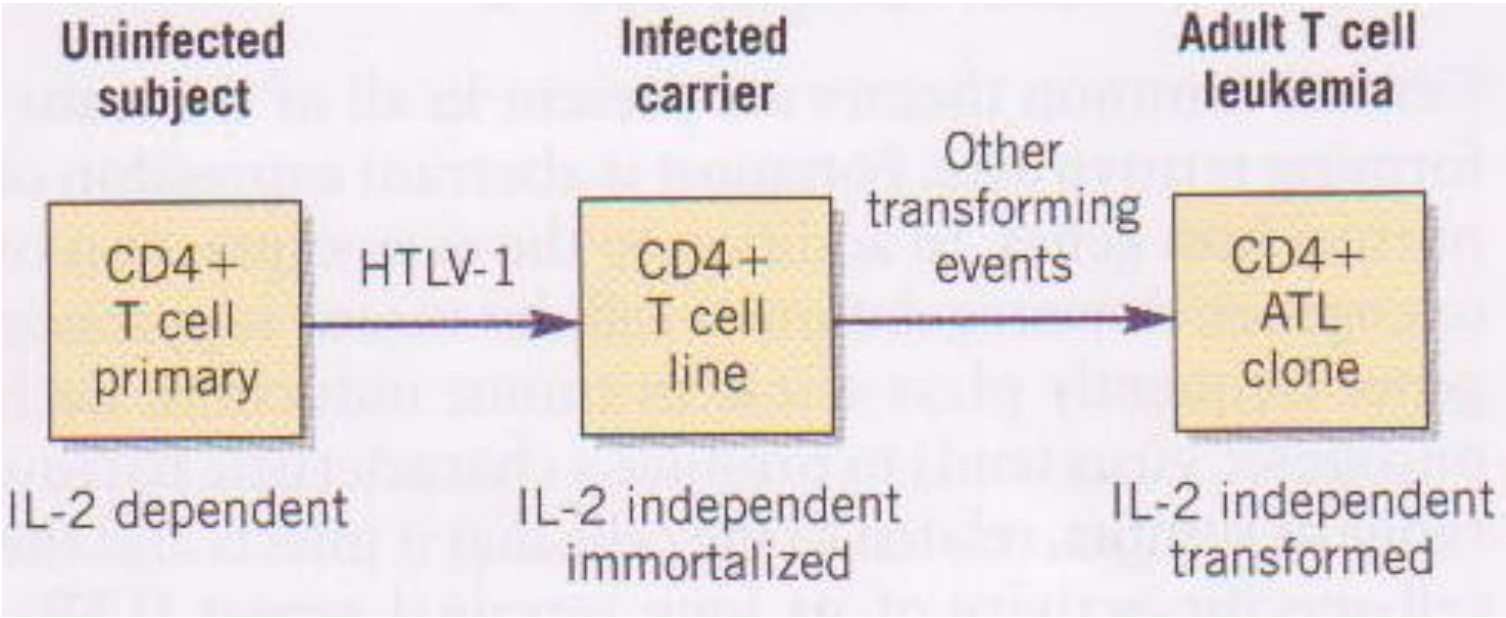
Transactivation by regulatoy viral genes



Transactivation by regulatory viral genes



PUTATIVE TRANSFORMING ACTION OF HTLV-I



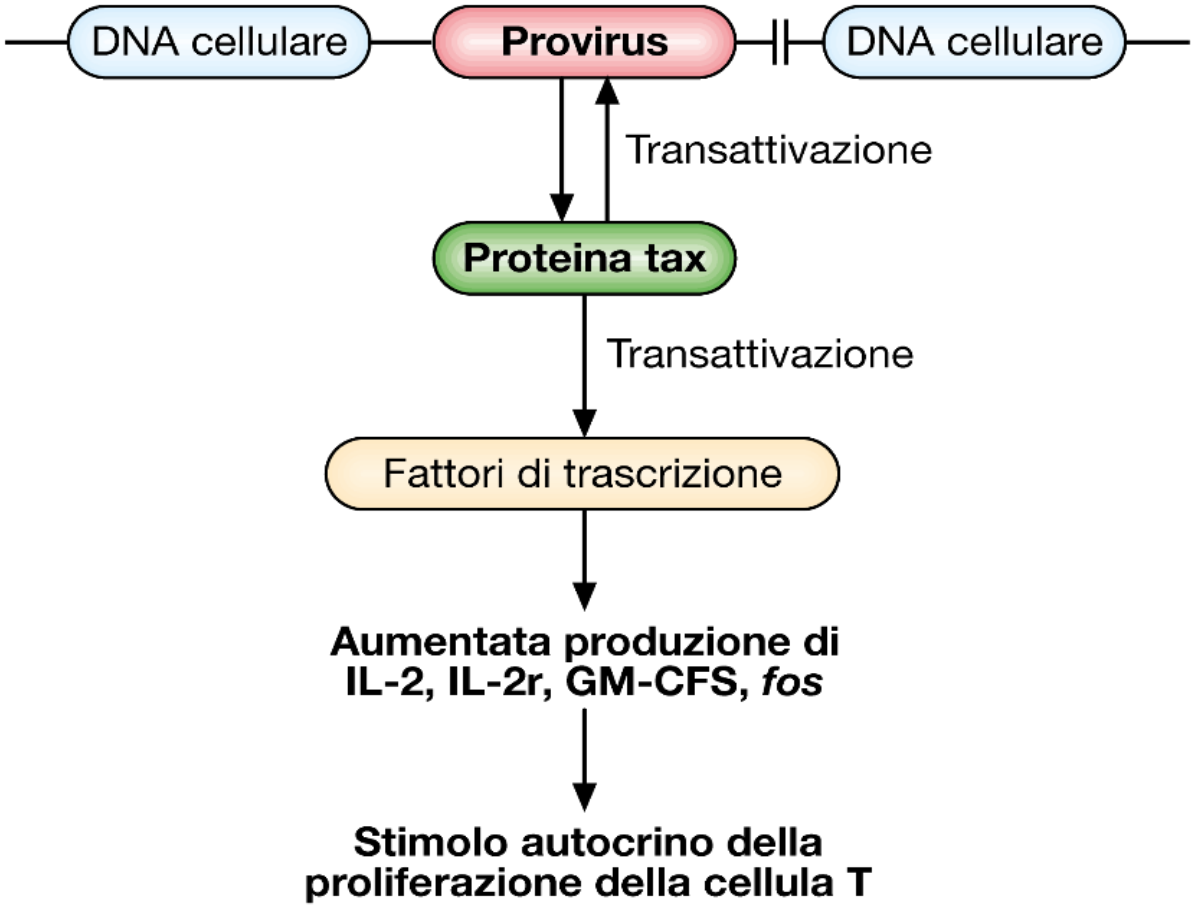


Figura 38.4 Schema del meccanismo trasformante di HTLV-1. Il prodotto del gene *tax* di HTLV-1 è in grado di transattivare non solo geni virali ma anche geni cellulari fra cui quelli codificanti l'IL-2 e il suo recettore. L'attivazione di IL-2 è responsabile della proliferazione e immortalizzazione dei linfociti T.

978-88-08-18705-5

CARACHETISTICS OF ONCOGENIC RETROVIRUSES

CATEGORY	Incubation period	MECHANISM	REPLICATION	EXAMPLE
Acute transforming	Weeks Uncommon	Viral oncogens	Defective	ASV MSV FeSV
Non-acute transforming	Years Common	Insertional mutagenesis and up-regulation of cellular oncogenes	Replication Competent	MuLV ALV FeLV
Trans-acting transforming	Years Uncommon	Transactivation of viral regulatory genes	Replication competent	**HTLV 1** BLV

Oncogenic RETROVIRUS:

in human pathology only

Human T cell Leukemia Virus type I (HTLV-I)

HTLV-1

- The first human retrovirus to be discovered, isolated from a patient with cutaneous T cell lymphoma in 1980
- Infects 10-20 million people worldwide from seroprevalence studies
- Disease only manifests in approx 5% of infected patients
- Primarily transmitted by breast feeding, although spread via blood transfusion, sharing of needles, and sexual intercourse also occurs
- Endemic in southern Japan, the Caribbean, South America, the Melanesian islands, Papua New Guinea, the Middle East and central/southern Africa
- Seroprevalence increases with age, women are twice as likely to be infected as men in endemic areas (only seen after 30 yrs of age and probably 2/2 sexual transmission)
- In non-endemic areas like US and Europe the seroprevalence is less than 1%
- Human T-lymphotropic virus type-1 (HTLV-1) is the causative agent of adult T-cell leukaemia/lymphoma (ATL), an aggressive CD4+ T-cell malignancy (and neurological disorders including myelopathy/Tropical spastic paraparesis).

Tabella 38.1 **Virus associati a tumori dell'uomo.**

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Flaviviridae	HCV	Carcinoma epatocellulare primario

Other oncogenic RNA viruses

- HIV
  - DIRECT - Tat protein
  - INDIRECT - Immunosuppression
- HCV
  - INDIRECT - Liver regeneration

DNA VIRUSES (1)

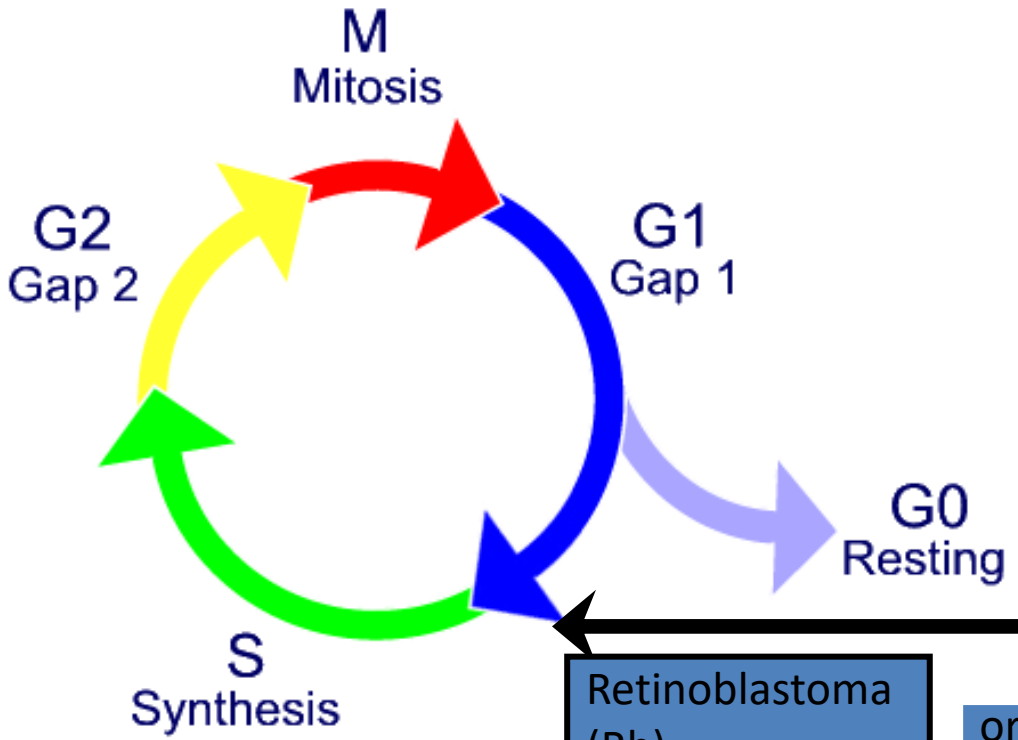
- Most DNA viruses of eukaryotes transcribe and replicate their genomes and assemble progeny **in the nucleus**, the site of cellular DNA transcription and replication. The exceptions are the poxviruses, iridoviruses, and African swine fever virus, which replicate their DNA genomes partly or completely in the cytoplasm.
- DNA virus use **host cell enzymes for transcription**
- **Early in infection, a subset of so-called immediate early viral genes is expressed to produce mostly catalytic amounts of the nonstructural proteins required for DNA replication and modulation of the intracellular environment**
- **Sometimes these early events can lead to neoplastic transformation**
- Most viruses with small DNA genomes use host cell enzymes for **DNA replication**; those with intermediate and large size genomes have sufficient genetic capacity to encode DNA polymerases
- After genome replication, a different subset of genes is expressed (**late genes**) that directs synthesis of stoichiometric amounts of the **structural proteins** required for progeny virus assembly

DNA VIRUSES (2)

- **Because cellular DNA synthesis occurs only during the S-phase of the cell cycle and not at all in terminally differentiated G0 cells, viruses that depend on the DNA polymerases of the host must either wait for infected cells to enter S-phase spontaneously, as do parvoviruses, or early in infection they must express one or more viral oncogenes to override the regulation imposed by the cell cycle control proteins p53 and pRb and thereby stimulate infected cells to enter S-phase prematurely, as do polyoma- and papillomaviruses, among others.**

- **Viruses with large DNA genomes** (e.g., **herpes-** and **poxviruses**) **encode some of these enzymes themselves**, **and can thus replicate in nondividing cells** and other environments that would otherwise be inhospitable for DNA replication, such as terminally differentiated cells of the nervous system (some herpesviruses) or even the cytoplasm (poxviruses).

Tumor DNA viruses



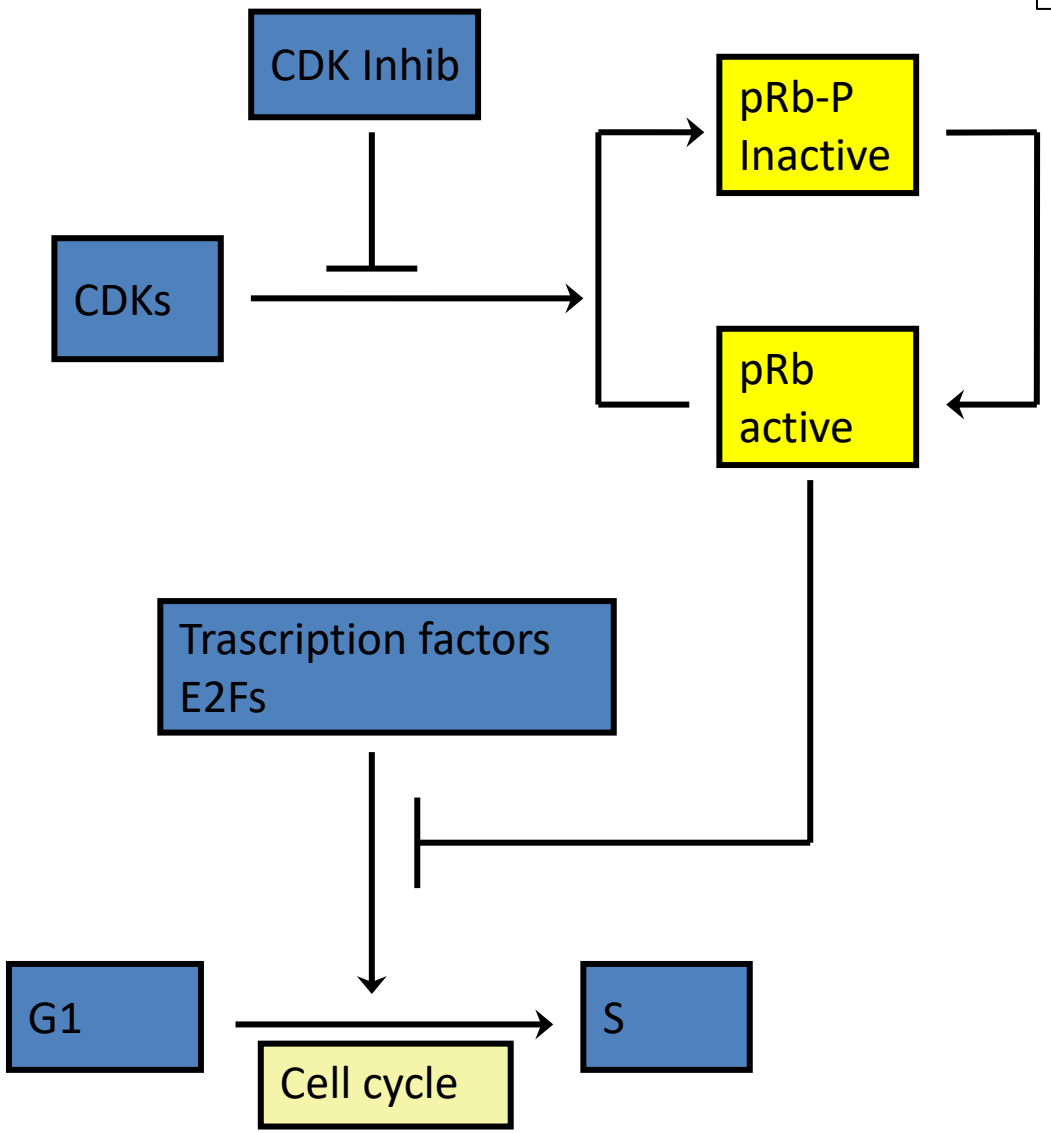
Retinoblastoma (Rb) or p53

Tumor suppressor genes

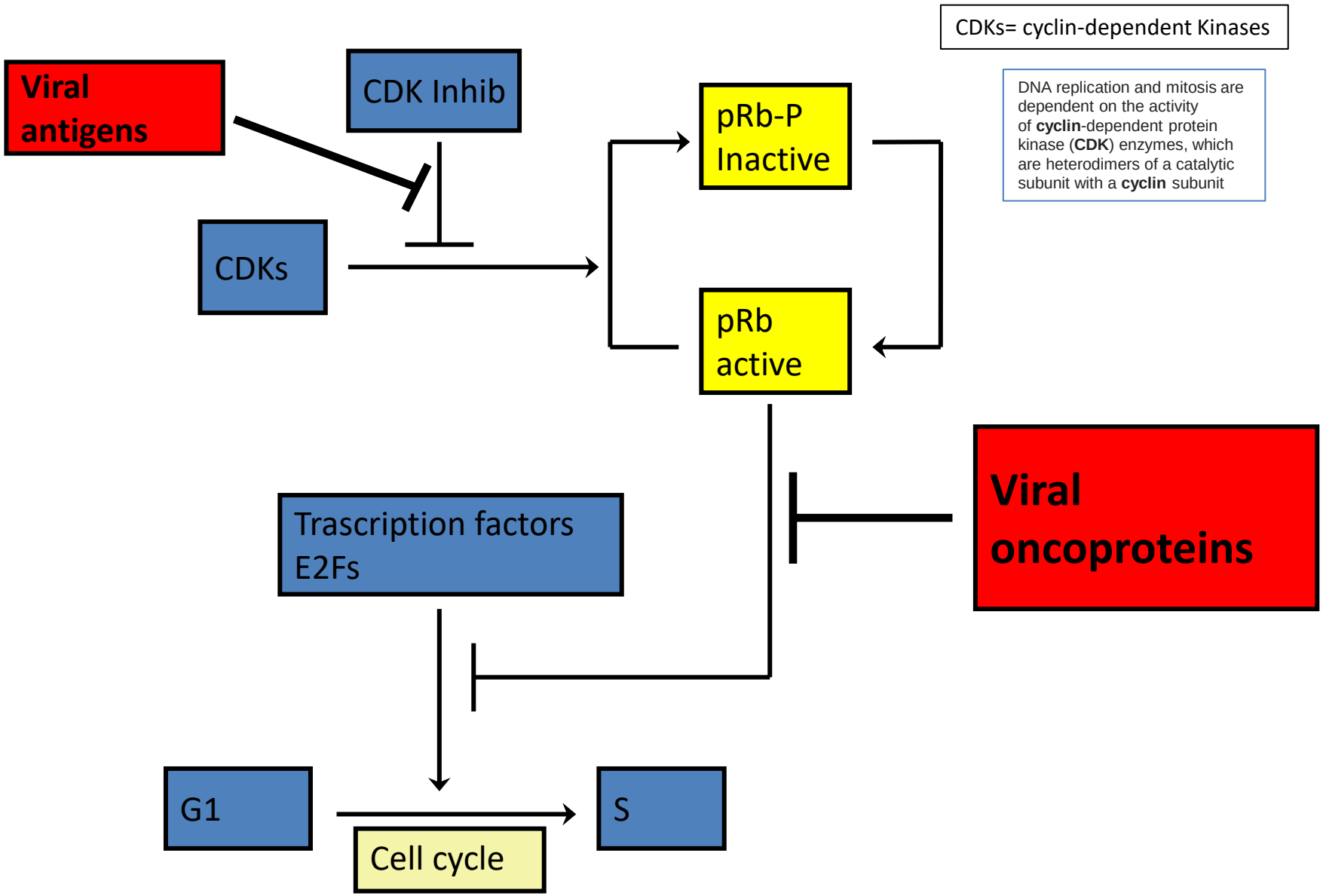
ACTION OF THE RETINOBLASTOMA PROTEIN (Rb)

CDKs= cyclin-dependent Kinases

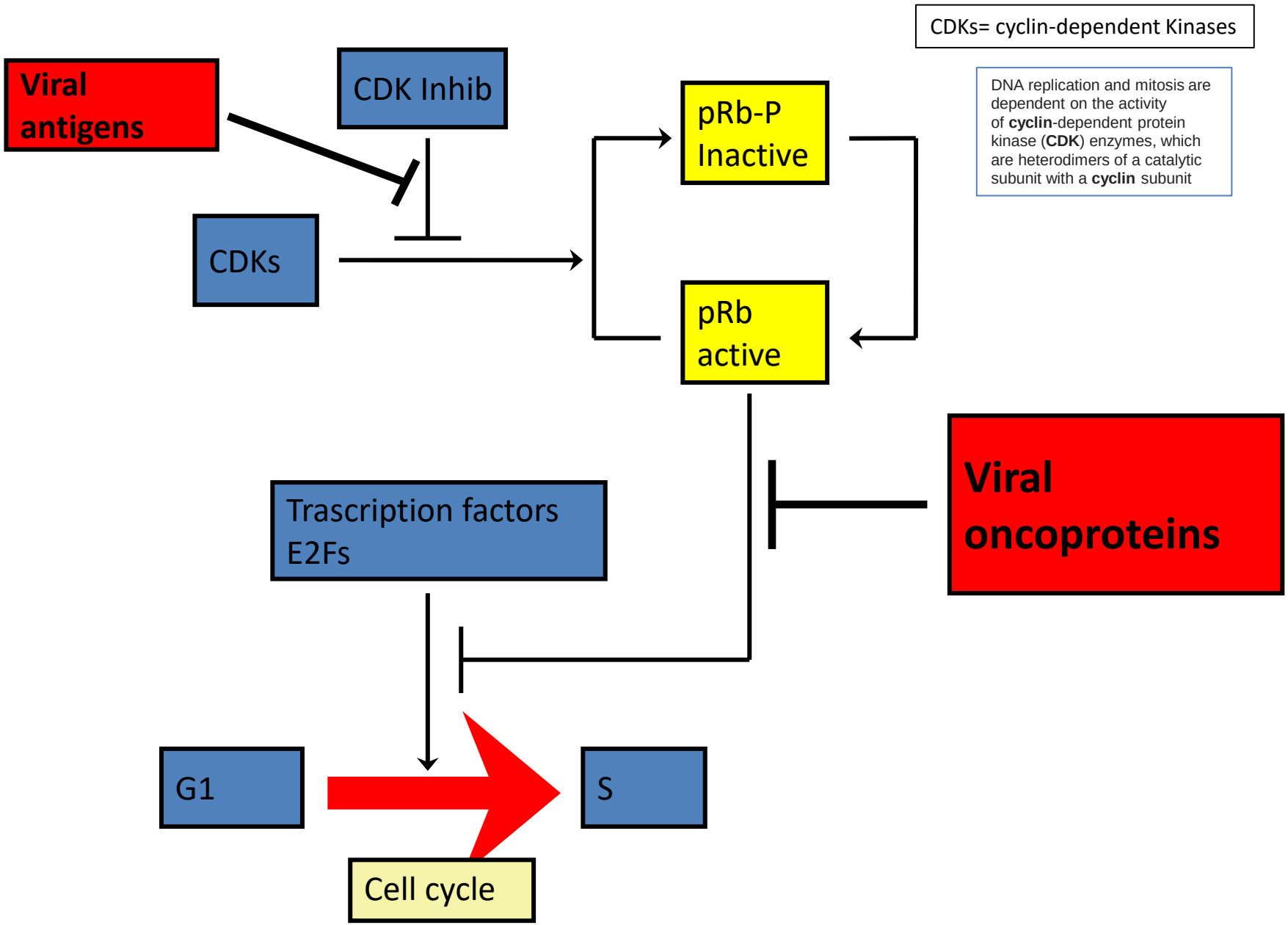
DNA replication and mitosis are dependent on the activity of **cyclin**-dependent protein kinase (**CDK**) enzymes, which are heterodimers of a catalytic subunit with a **cyclin** subunit



ACTION OF THE RETINOBLASTOMA PROTEIN (Rb)



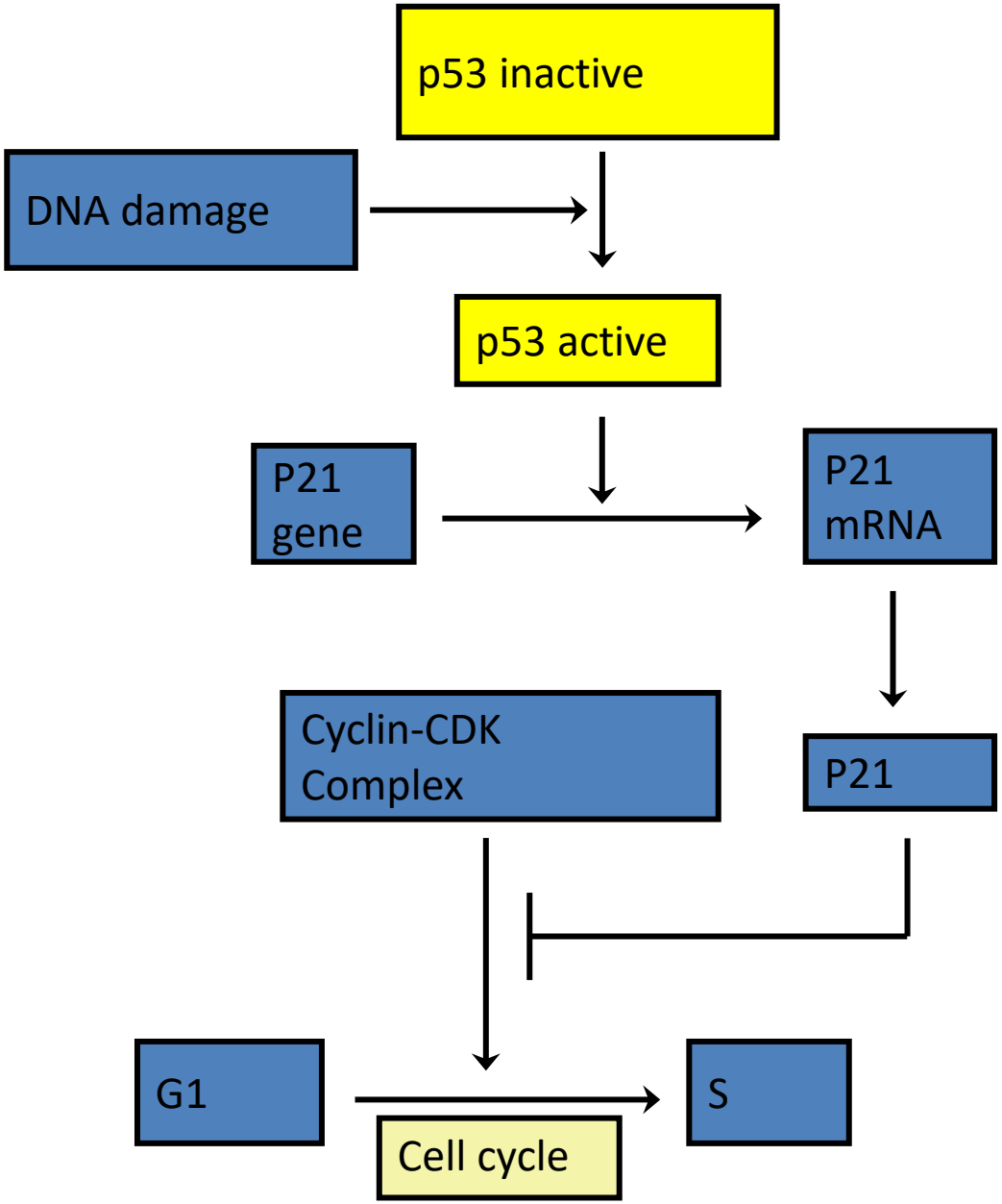
ACTION OF THE RETINOBLASTOMA PROTEIN (Rb)



DNA tumor viruses: Viral proteins that inactivate cellular oncogenes (pRb)

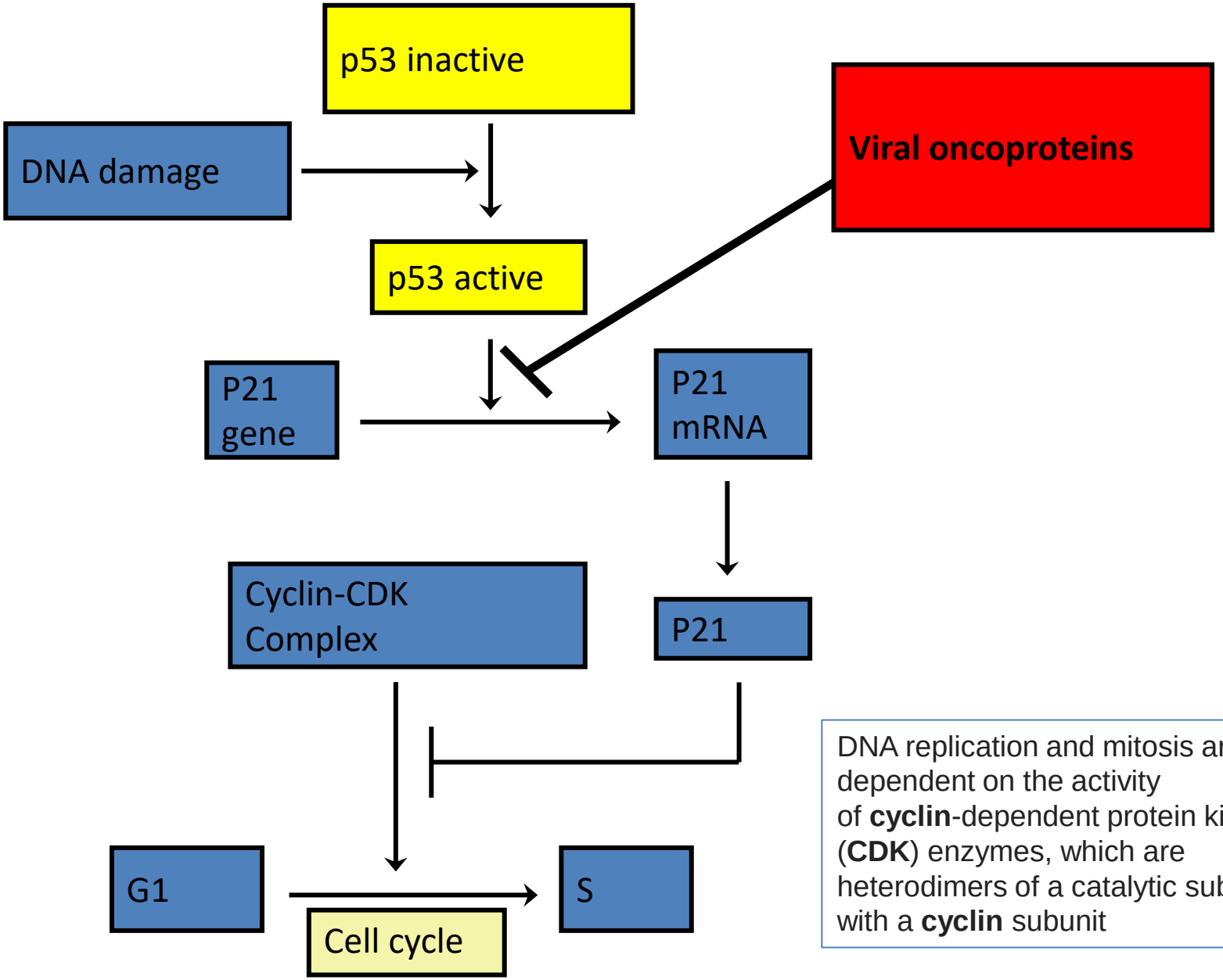
Virus	Viral protein that complexes with **pRb** cellular anti-oncoprotein
Simian virus 40	Large T antigen
Human papillomavirus	E7
Adenovirus	E1A
Human herpes virus 8	LANA
Epstein-Barr virus	EBNA 3C

ACTION OF THE p53 PROTEIN



DNA replication and mitosis are dependent on the activity of **cyclin**-dependent protein kinase (**CDK**) enzymes, which are heterodimers of a catalytic subunit with a **cyclin** subunit

ACTION OF THE p53 PROTEIN



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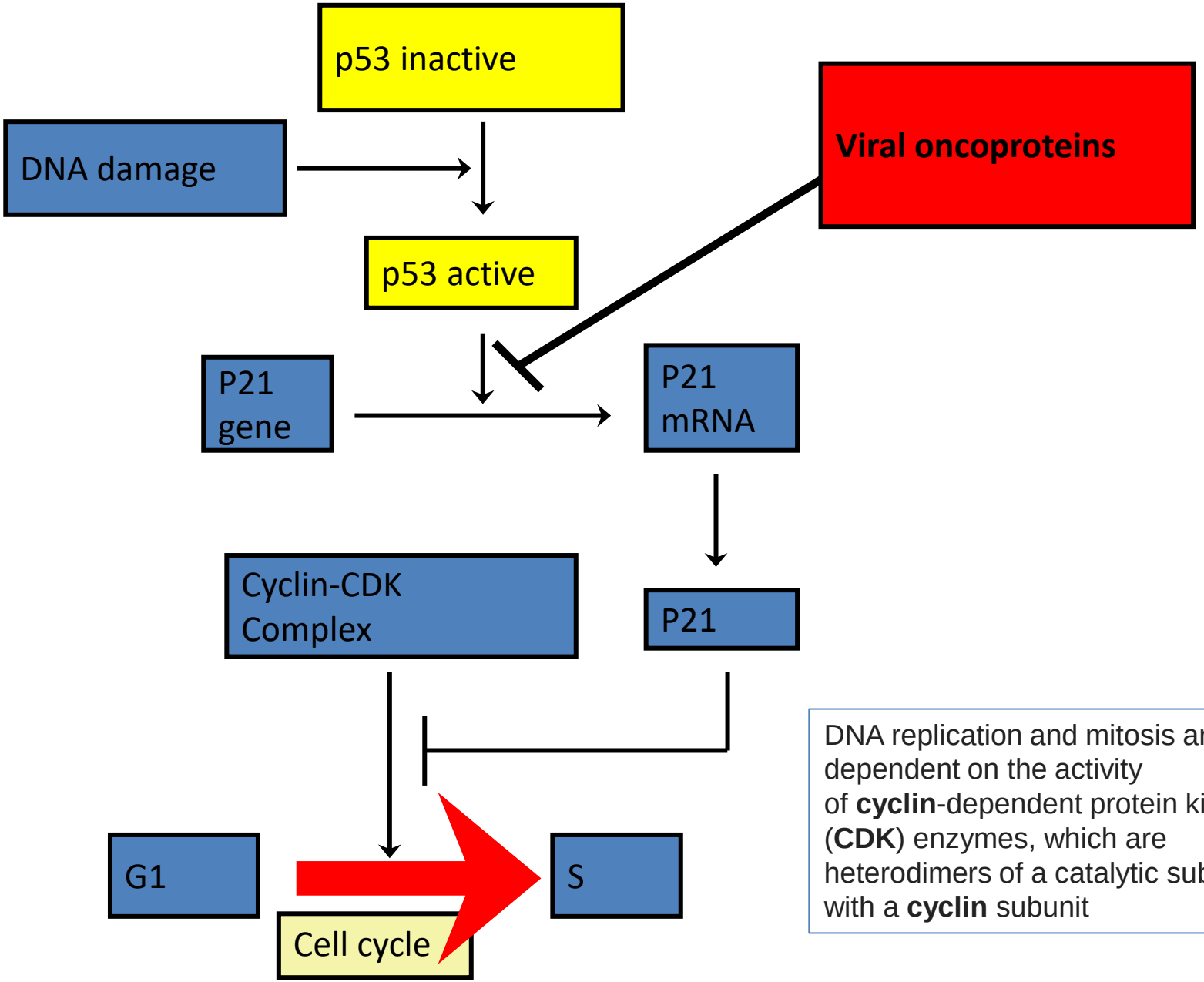
ACTION OF THE p53 PROTEIN



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DNA tumor viruses: Viral proteins that inactivate cellular oncogenes (p53)

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Human papillomavirus	E6
Adenovirus	E1B
Human herpes virus 8	LANA

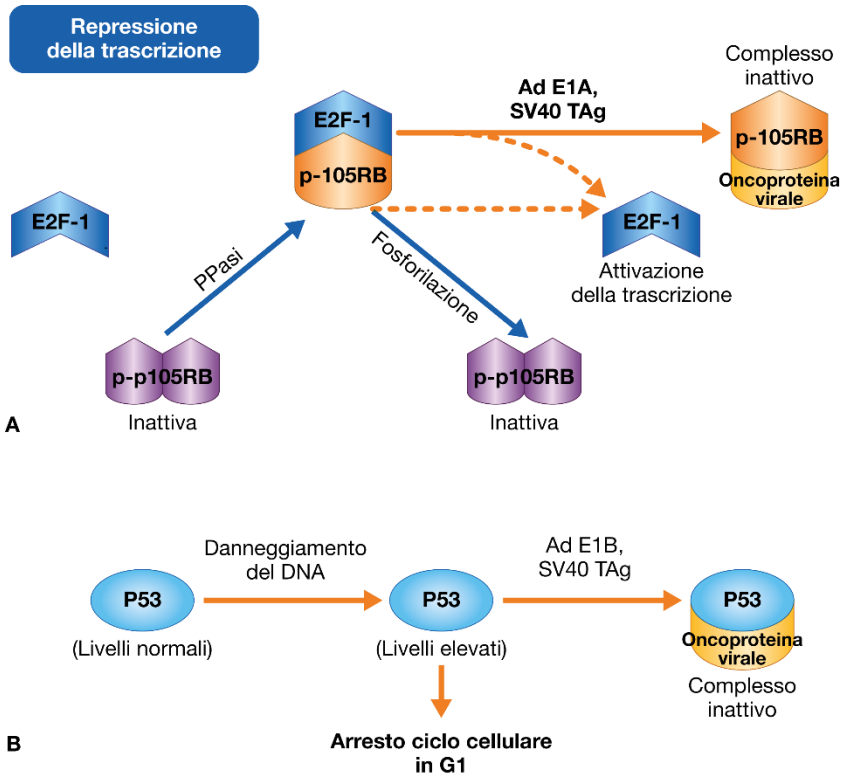


Figura 38.1 A. Interazione di oncoproteine prodotte da alcuni deossiribovirus con la proteina p105RB. Le proteine precoci E1A di adenovirus (Ad E1A) e T-grande del poliomavirus SV40 (SV40 TAg) possono interagire con la forma attiva ipofosforilata della proteina p105RB formando un complesso che porta alla liberazione del fattore di trascrizione E2F-1, il quale può così attivare la trascrizione di geni specifici che permettono alla cellula di entrare nella fase S. **B. Interazione di oncoproteine prodotte con la proteina p53.** Le proteine E1B di adenovirus (Ad E1B) e T-grande del poliomavirus SV40 (SV40 TAg) si legano alla proteina p53 inattivando la sua funzione.

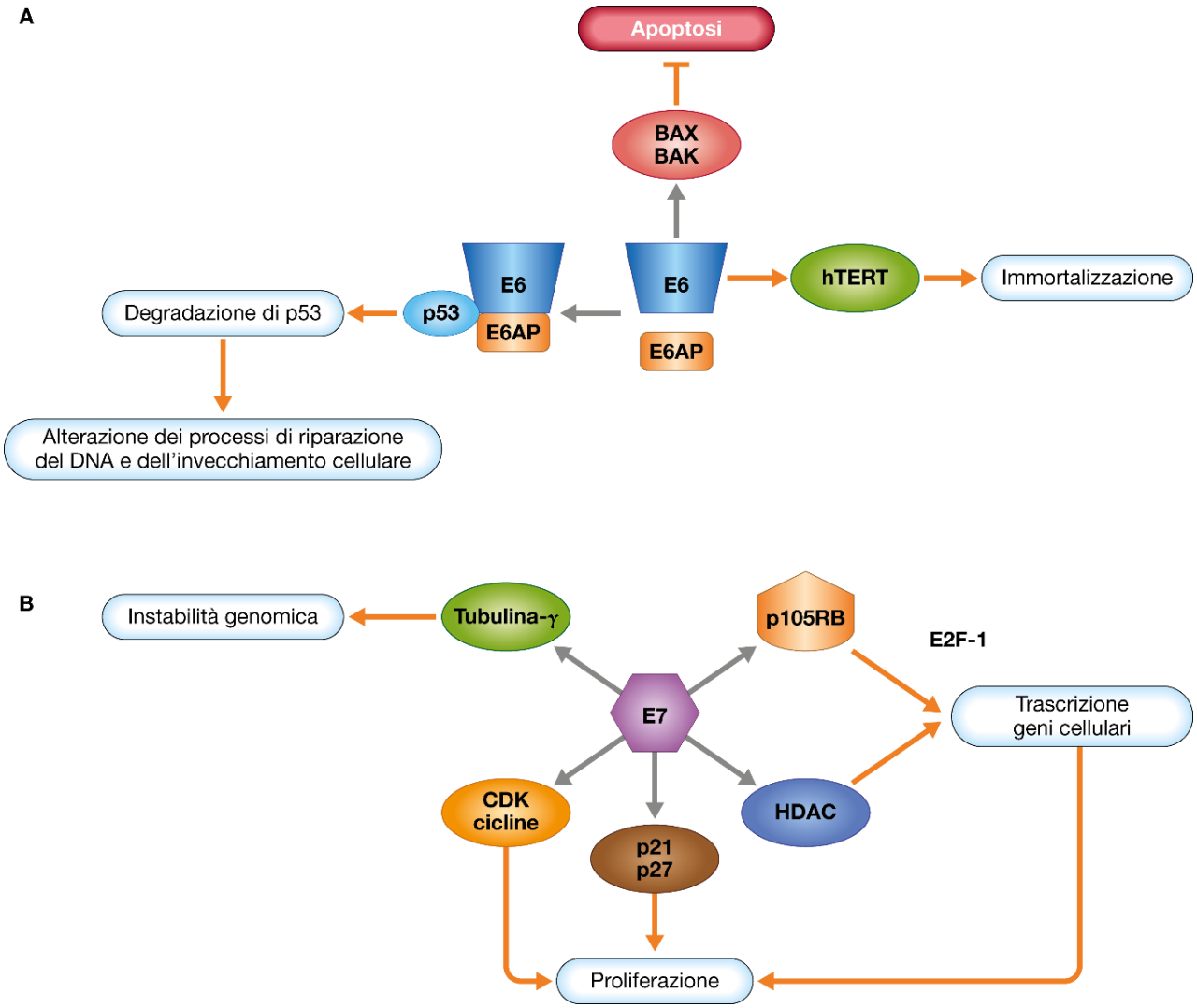


Figura 38.2 **A.** Interazione della oncoproteina E6 di papilloma virus con prodotti cellulari. La proteina precoce E6 può portare alla degradazione di p53 dopo formazione del complesso trimerico con E6AP e p53. E6 è anche in grado di interagire con hTERT e di bloccare l'apoptosi mediante interazione con BAX e BAK. **B.** Interazione della oncoproteina E7 di papillomavirus con prodotti cellulari. La proteina precoce E7 può interagire con la forma attiva ipofosforilata della proteina p105RB portando alla liberazione del fattore di trascrizione E2F-1, il quale può così attivare la trascrizione di geni coinvolti nella proliferazione cellulare. Inoltre E7 deregola il ciclo cellulare inibendo gli inibitori delle chinasi ciclino-dipendenti come p21 e p27 o interagendo direttamente con CDK2. E7 induce anche instabilità genomica interagendo con la tubulina-γ e attivando la trascrizione di geni cellulari mediante interazione con gli istoni deacetilasi (HDAC).

Other oncogenic DNA viruses

- HHV-8
  - DIRECT
    Sequence homology with cellular genes involved in apoptosis, cell proliferation and immune response
- HSV-1
- HSV-2
  - DIRECT
    Insertional mutations, cis-activation of protooncogenes
- HBV
  - DIRECT
    Insertional mutations, cis-activation of protooncogenes
  - INDIRECT
    Liver regeneration

In most (approximately 90%) of the cases of Burkitt's lymphoma, a reciprocal translocation has moved the proto-oncogene c-myc from its normal position on chromosome 8 to a location close to the immunoglobulin (Ig) heavy-chain gene enhancer on chromosome 14. ENHANCEMENT OF GROWTH ACTIVATORS

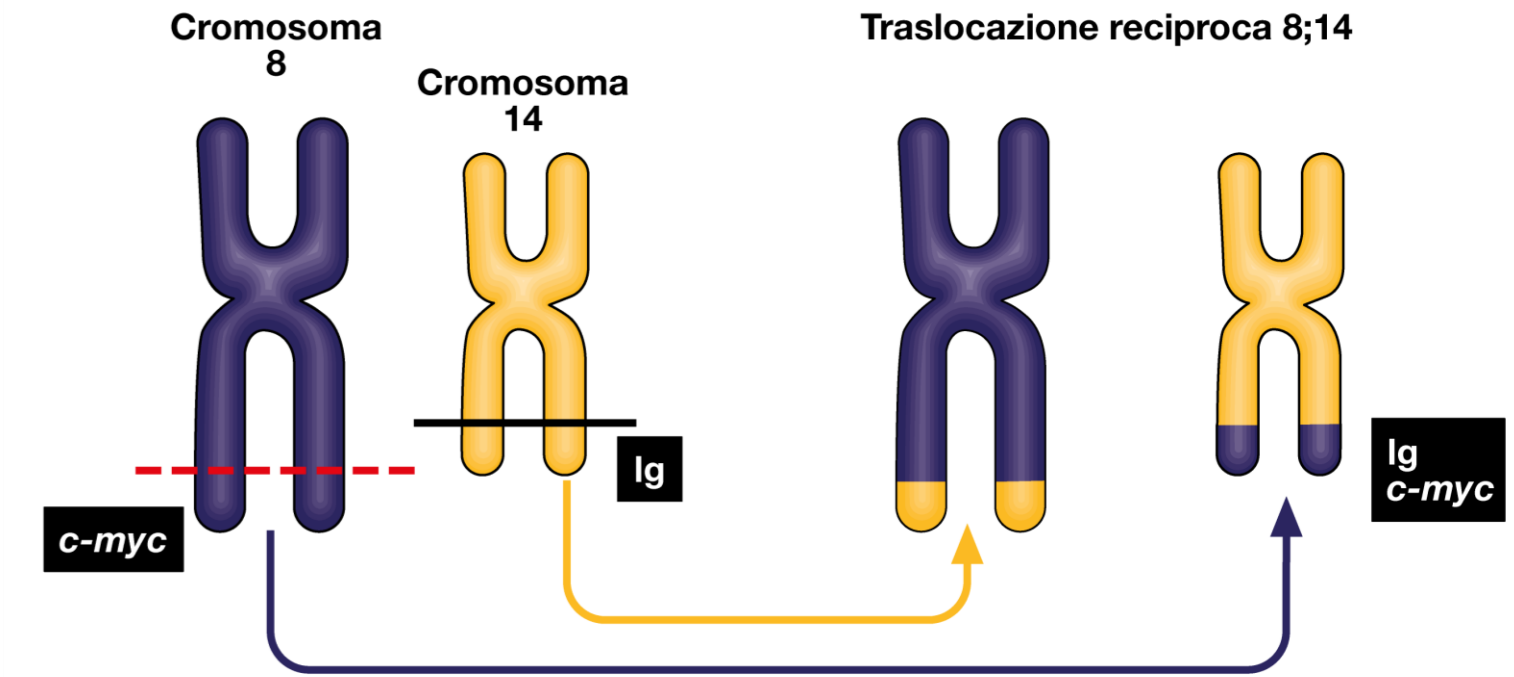
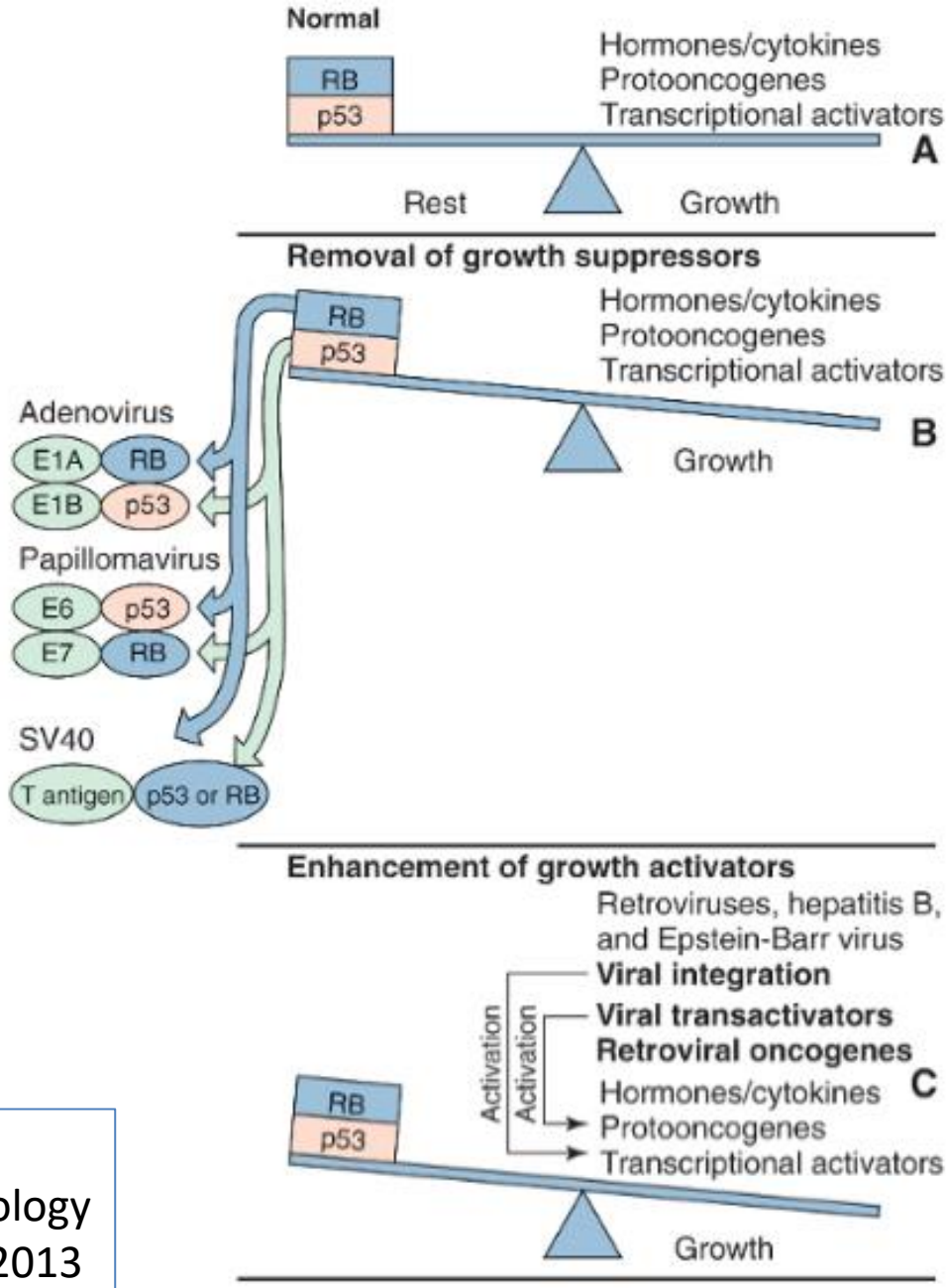


Figura 38.3 Traslocazione cromosomica nel linfoma di Burkitt. Nella traslocazione più frequente osservata in questo linfoma (8;14) l'oncogene *c-myc* presente sul cromosoma 8 viene portato sul cromosoma 14 in prossimità dei geni che codificano per la porzione costante delle catene pesanti delle immunoglobuline.



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