09-18-2007

# Tumor viruses and oncogenes

## References


(1) “The Biology of cancer” (2006) by Weinberg R. , Chapter 3 & 4.

(2) “Principle of Virology” (2000) by Skalka A. et al., Chapter 16

(3) “Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease” (2000), Carcinogenesis, Vol.21, page 405-426.

# Tumor viruses (oncogenic viruses)

1. Tumor viruses: viruses that directly cause cancer in either experimental animals or humans
   - RNA viruses
   - DNA viruses
2. Viruses as etiological factors of human cancer (~15% of all human tumors worldwide are caused by viruses)
3. Tumor viruses contributes to:
   (1) the formation of current concepts of cancer biology
   - molecular mechanisms of cancer formation
   (2) the recognition of the etiology of some human cancers
4. Viruses are usually not complete carcinogens in human cancers; tumor viruses establish long-term persistent infections in human, with cancer an accidental side of viral replication strategy
5. The best-characterized mechanisms of transformation by tumor viruses fall into two major classes
   (1) permanent activation of mitotic signal transduction cascades
   (2) disruption of the circuits that regulate cell cycle progression

# Tumor viruses and human tumors

**Table 4.6** Viruses implicated in human cancer causation

| Virus[a] | Virus family | Cells infected | Human malignancy | Transmission route |
|---|---|---|---|---|
| EBV | Herpesviridae | B cells | Burkitt's lymphoma | saliva |
| | | oropharyngeal epithelial cells | nasopharyngeal carcinoma | saliva |
| | | lymphoid | lymphoma[b] | Hodgkin's disease |
| HTLV-I | Retroviridae | T cells | non-Hodgkin's lymphoma | parenteral, venereal[c] |
| HHV-8[d] | Herpesviridae | endothelial cells | Kaposi's sarcoma, body cavity lymphoma | venereal |
| HBV | Hepadnaviridae | hepatocytes | hepatocellular carcinoma | parenteral, venereal |
| HCV | Flaviviridae | hepatocytes | hepatocellular carcinoma | parenteral |
| HPV | Papovaviridae | cervical epithelial | cervical carcinoma | venereal |
| JCV[e] | Papovaviridae | central nervous system | astrocytoma, glioblastoma | ? |

[a]Most of the viruses carry one or more potent growth-promoting genes/oncogenes in their genomes. However, such genes have not been identified in the genomes of HBV and HCV.
[b]These tumors, which bear copies of EBV genomes, appear in immunosuppressed patients.
[c]Parenteral, blood-borne; venereal, via sexual intercourse.
[d]Also known as KSHV, Kaposi's sarcoma herpesvirus.
[e]JCV (JC virus, a close relative of SV40) infects more than 75% of the population by age 15, but the listed virus-containing tumors are not common. Much correlative evidence supports the role of JCV in the transformation of human central nervous system cells but evidence of a causal role in tumor formation is lacking.

Adapted in part from J. Butel, *Carcinogenesis* 21:405–426, 2000.

A small but significant proportion of human cancers are caused by mechanisms that involve viruses, bacteria or parasites (15%). The main contributors are DNA tumor viruses. Evidence for their involvement comes partly from the detection of viruses In cancer patients and partly from epidemiology

# Transforming retroviruses (oncogenic retroviruses)

1. Identification of first retroviral oncogene from avian Rous sarcoma virus (RSV)

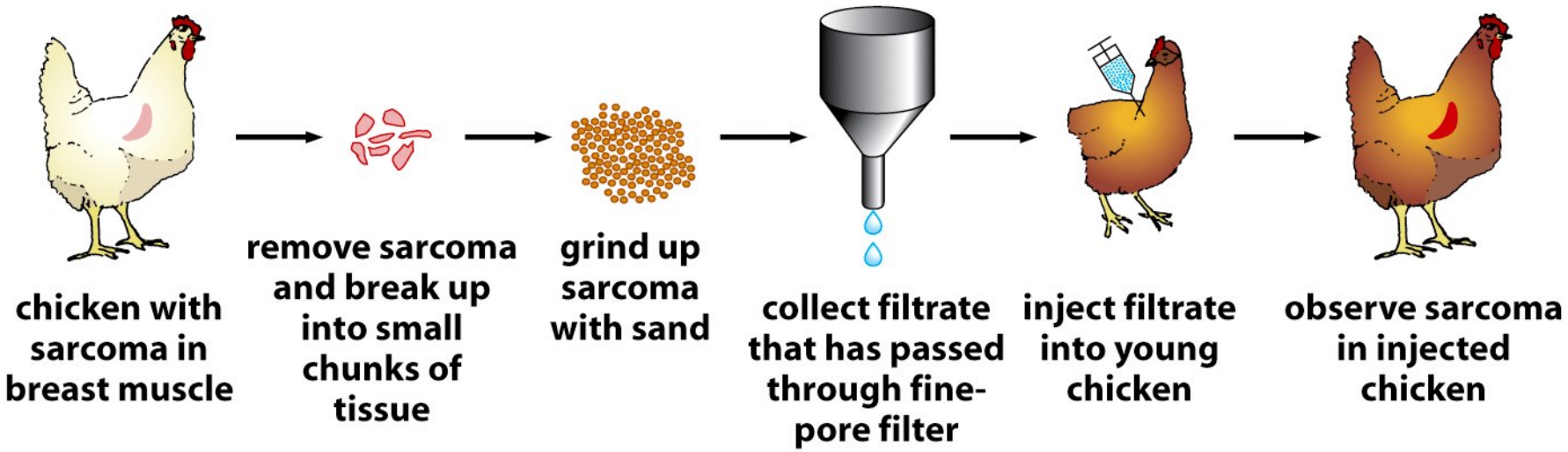
2. Oncogenes in avian or murine retroviruses are not viral genes: they derived from transduction of normal cellular genes → proto-oncogenes (retroviral transduction)

3. Although there are no known human tumor viruses comparable with the acute-transforming viruses that transduce cellular genes, but many oncogenes identified in acute-transforming retroviruses are later found to be involved in human cancers

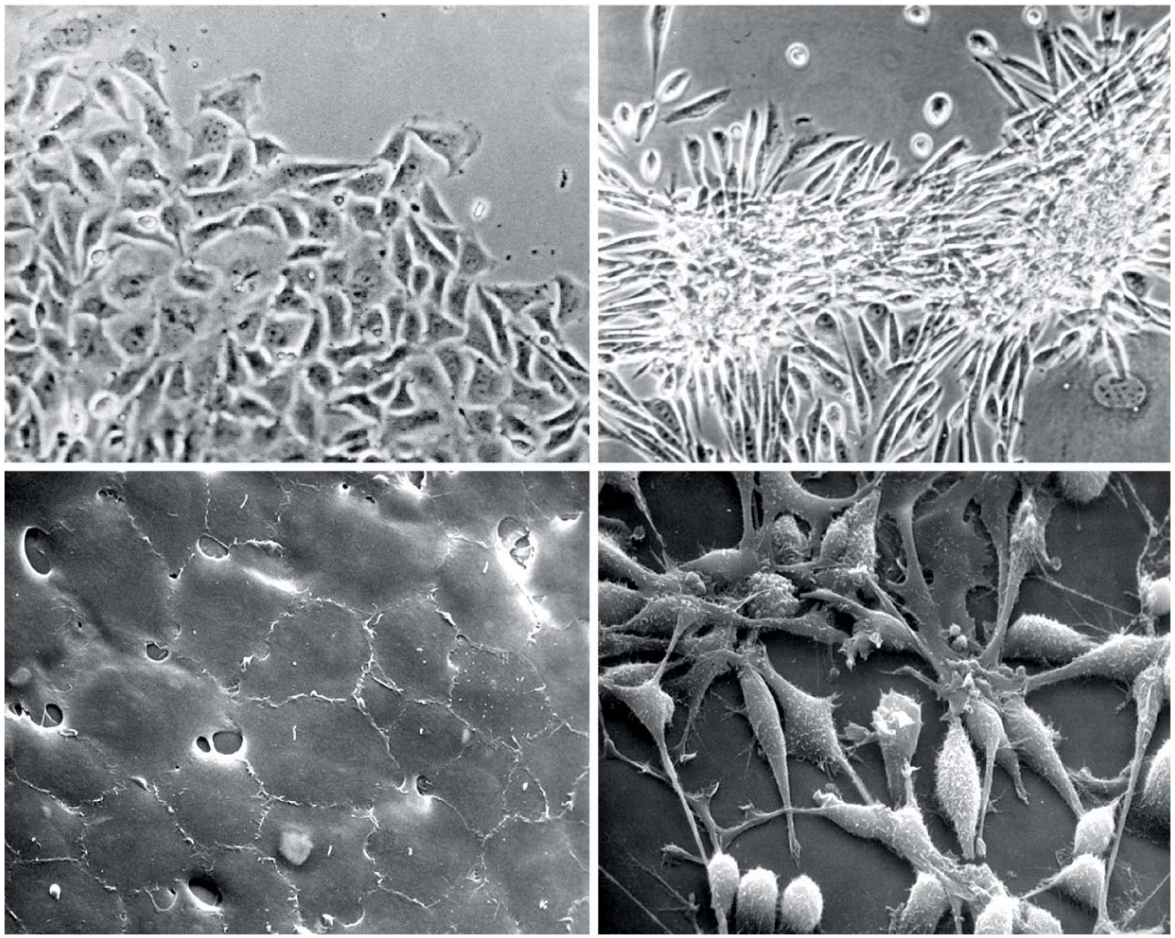
4. Transforming retroviruses carry oncogenes derived from cellular genes that are involved in mitogenic signaling & growth control

5. Retroviruses that associated with human cancers: Human T-cell leukemia virus (HTLV-1), HIV-1

# Peyton Rous discovered a chicken sarcoma virus called Rous sarcoma virus (RSV)



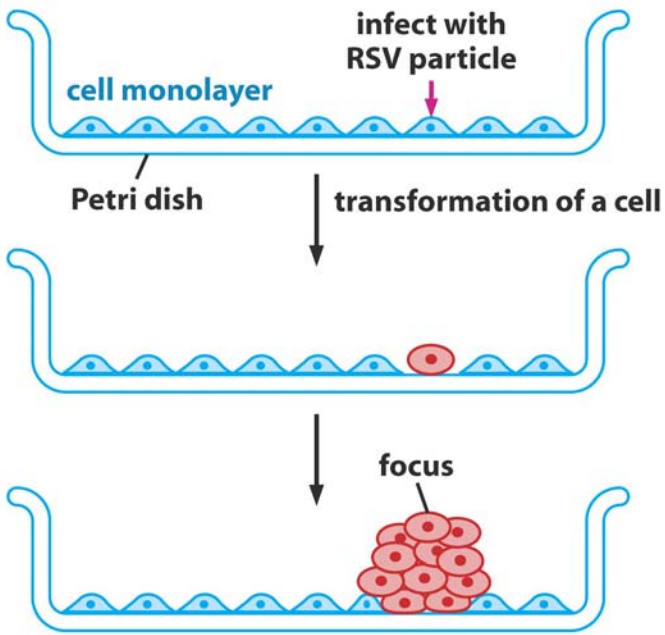
# Rous sarcoma virus is discovered to transform infected cells in culture

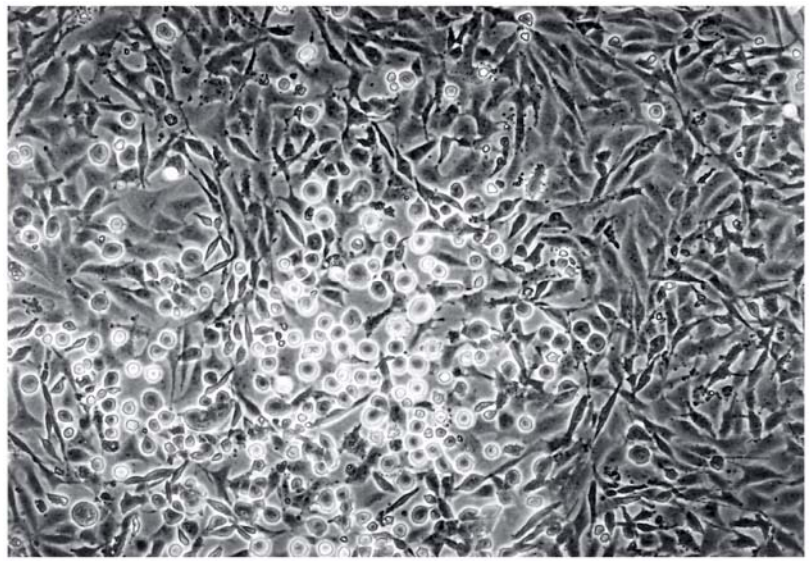


- Transformation: conversion of a normal cell into a tumor cells
- RSV-infected cells exhibit morphological changes

# Rous sarcoma virus is discovered to transform infected cells in culture

Transformed cells forming foci (clusters) due to loss of cell-contact inhibition

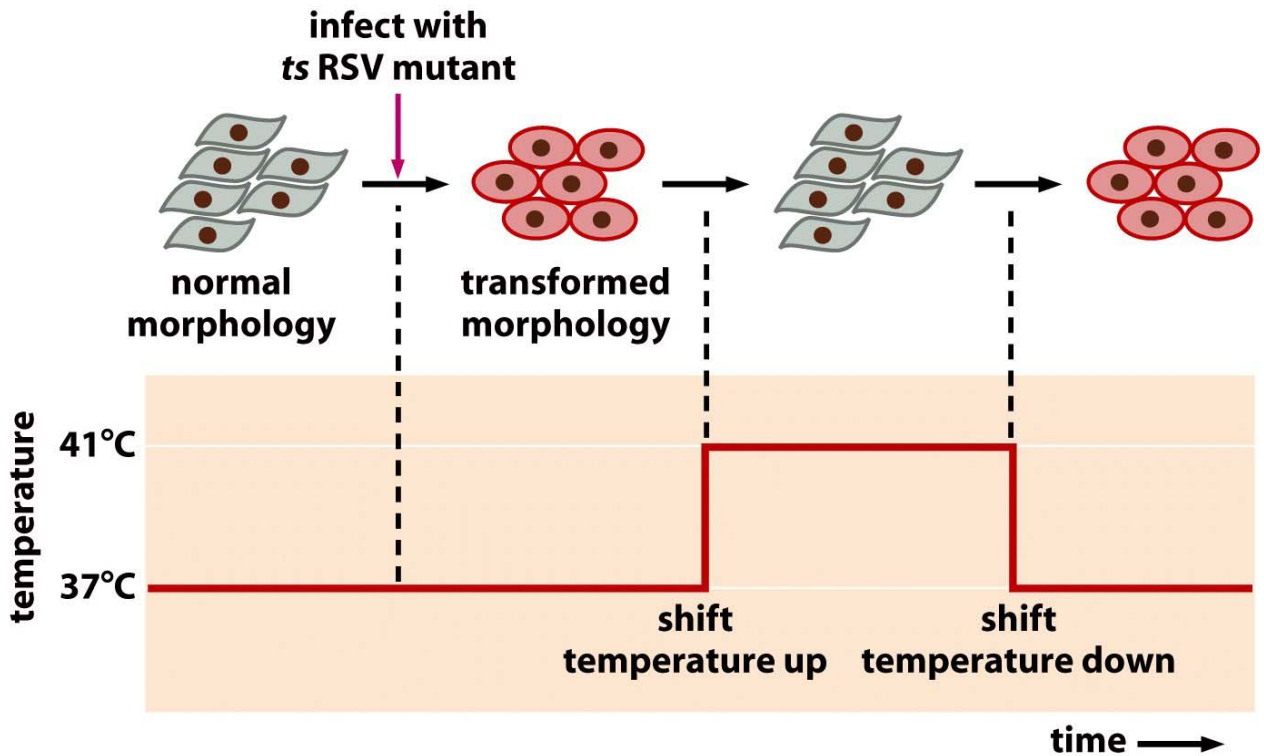


Process of cellular transformation can be accomplished within the confines of a Petri dish

- cancer formation could be studied at the level of individual cells
- cancer is a disease of malfunctioning cells rather than abnormally developing tissues

# The continued presence of a transforming gene is needed to maintain transformation




The viral transforming gene was required to both initiate and maintain the transformed phenotype of virus-infected cells

# Discovery of oncogenic viruses from Rous sarcoma viruses (RSV)

RSV: Rous sarcoma virus
(by Peyton Rous, 1911)

acute transforming virus

RNA genome ~ 10 Kba

ALV: avian leukemia virus

weakly transforming virus

RNA genome ~ 8.5 Kb

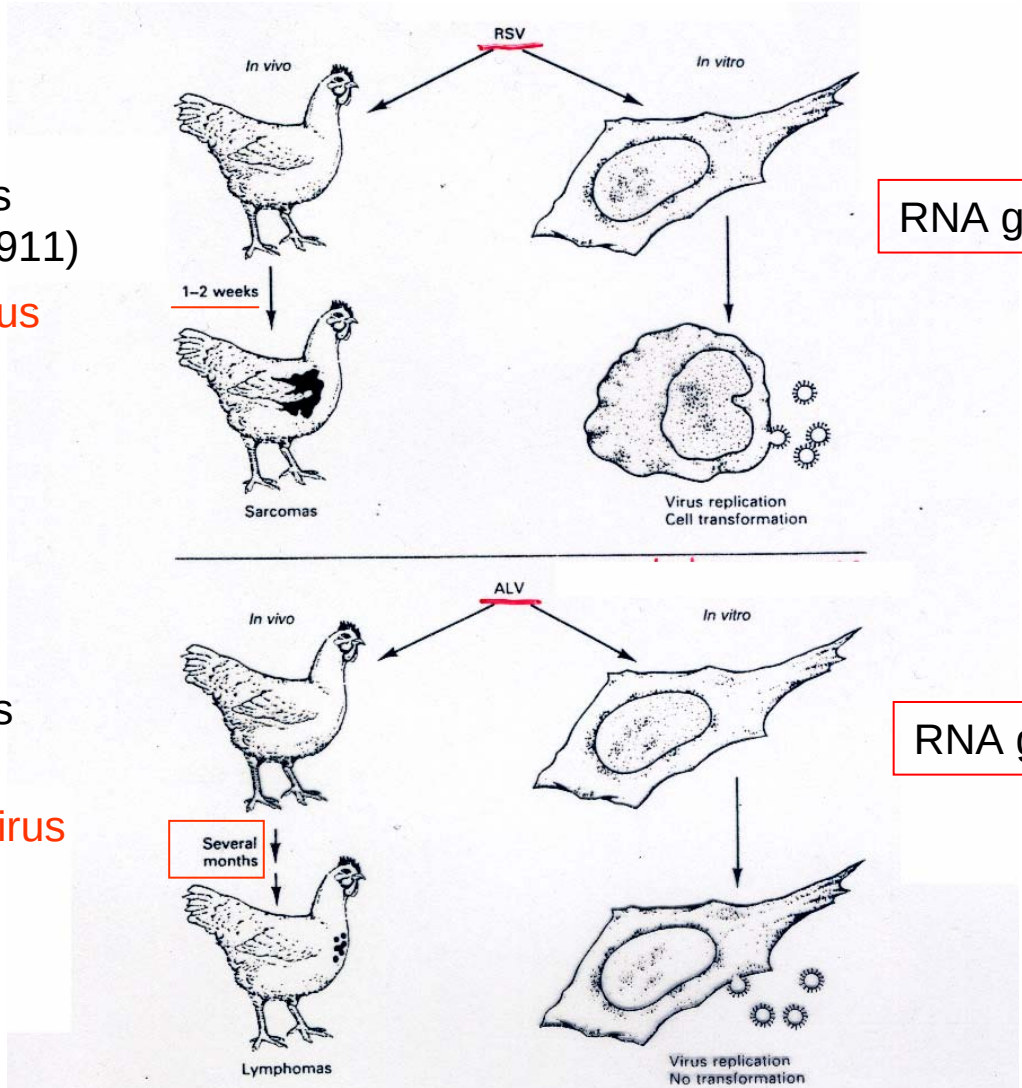
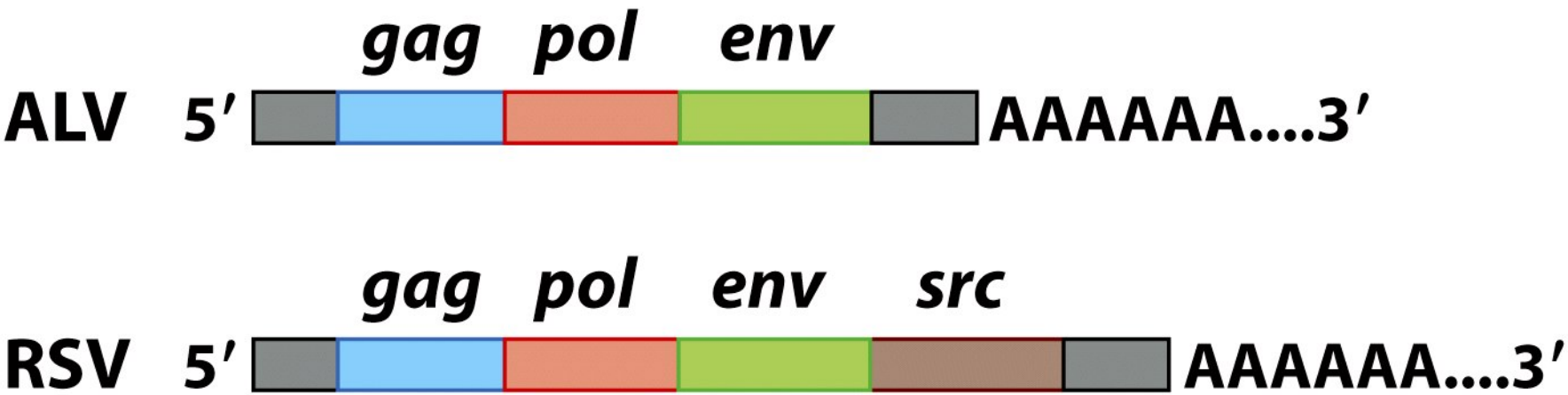
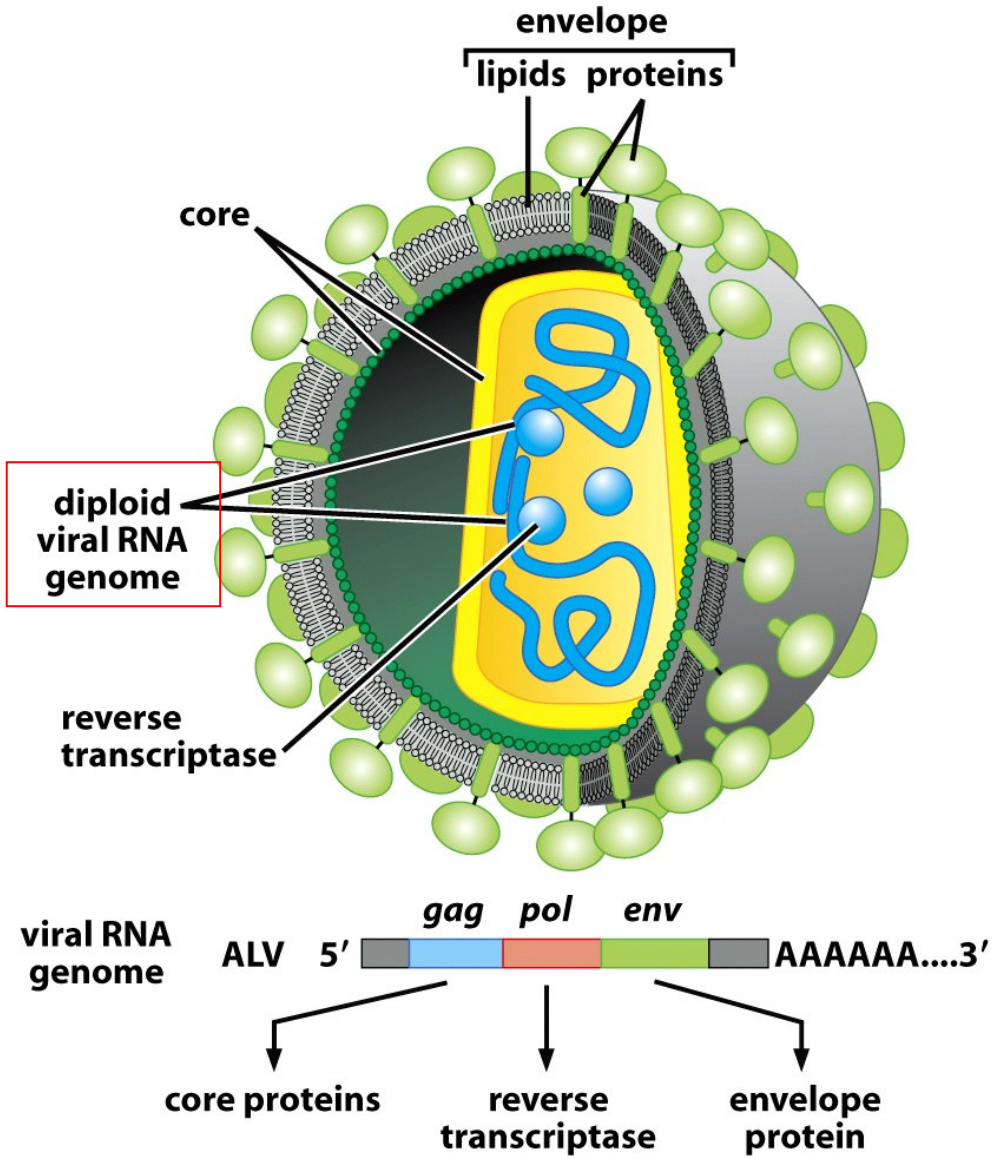



**FIGURE 3.1**
Neoplasm induction and cell transformation by Rous sarcoma virus (RSV) and avian leukosis virus (ALV). RSV induces sarcomas rapidly in infected chickens and efficiently transforms fibroblasts in culture. In contrast, ALV induces lymphomas only after long latent periods in infected birds and does not transform cells in culture.

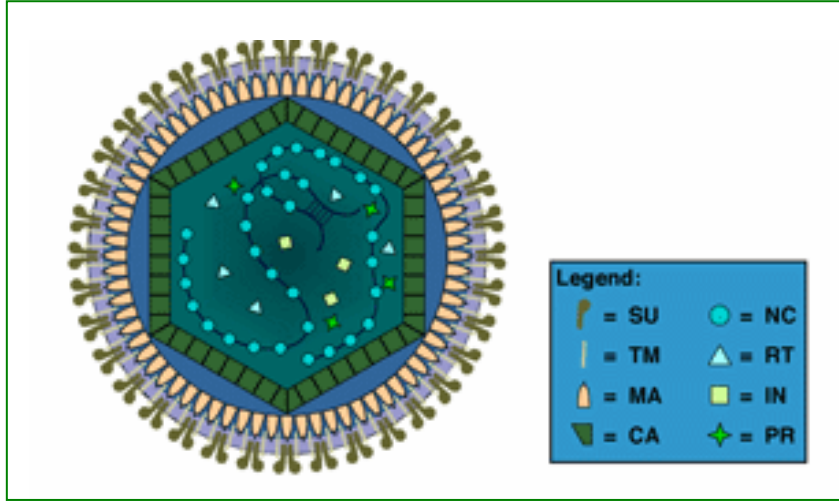
# How RSV acquire additional *src* gene?

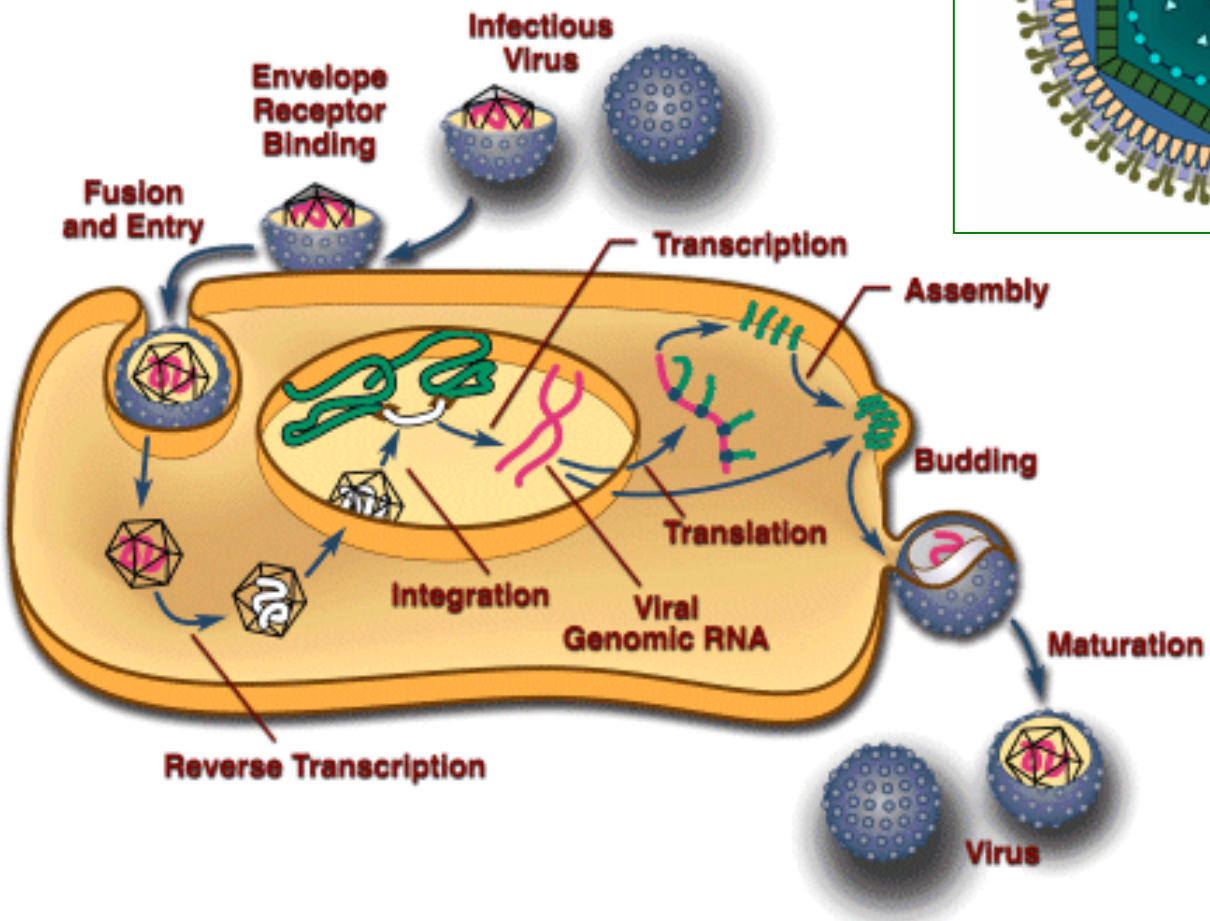


# The structure of a retrovirus



# The life cycle of retrovirus



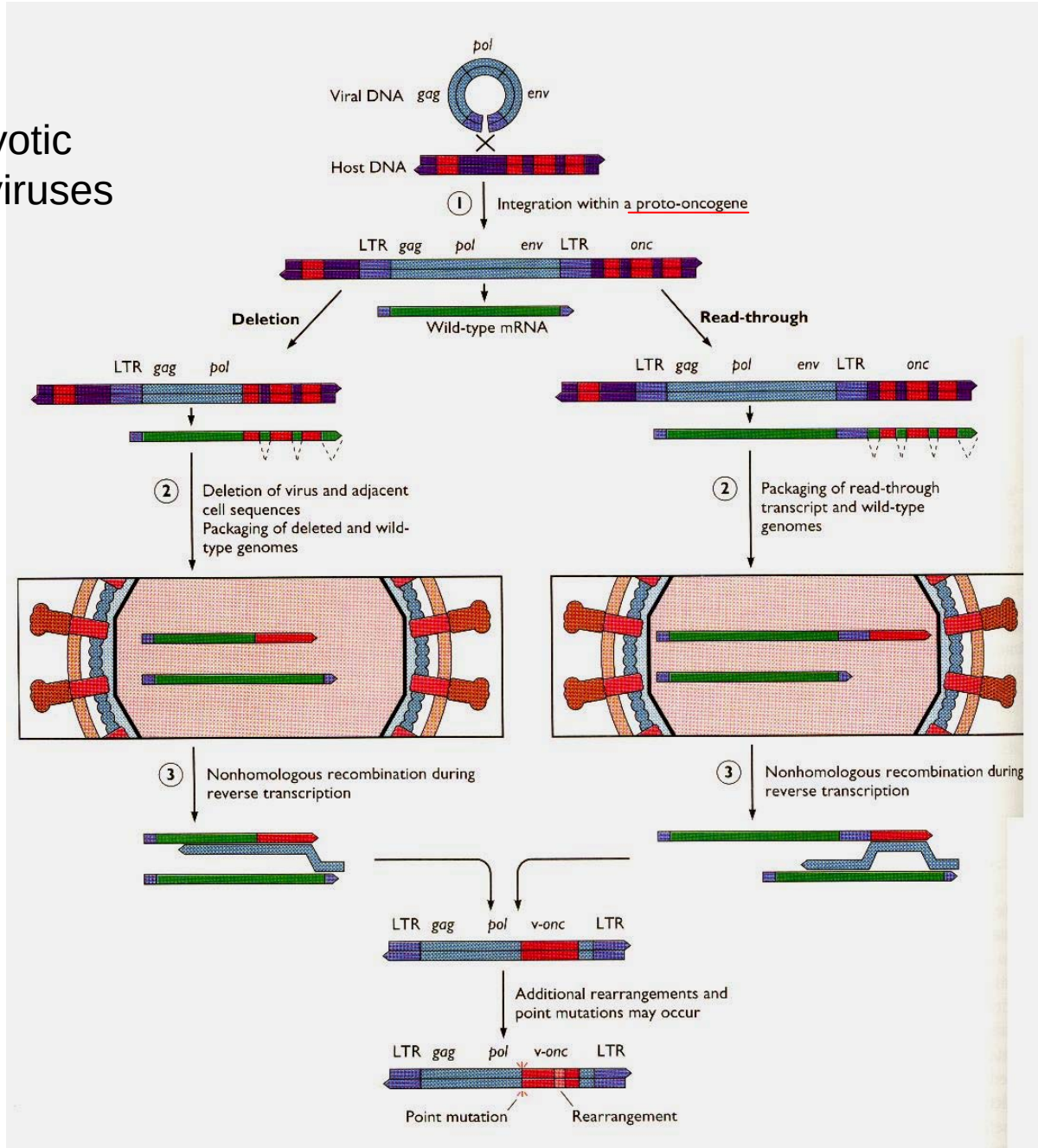




Retroviral genomes become integrated into the chromosomes of infected cells

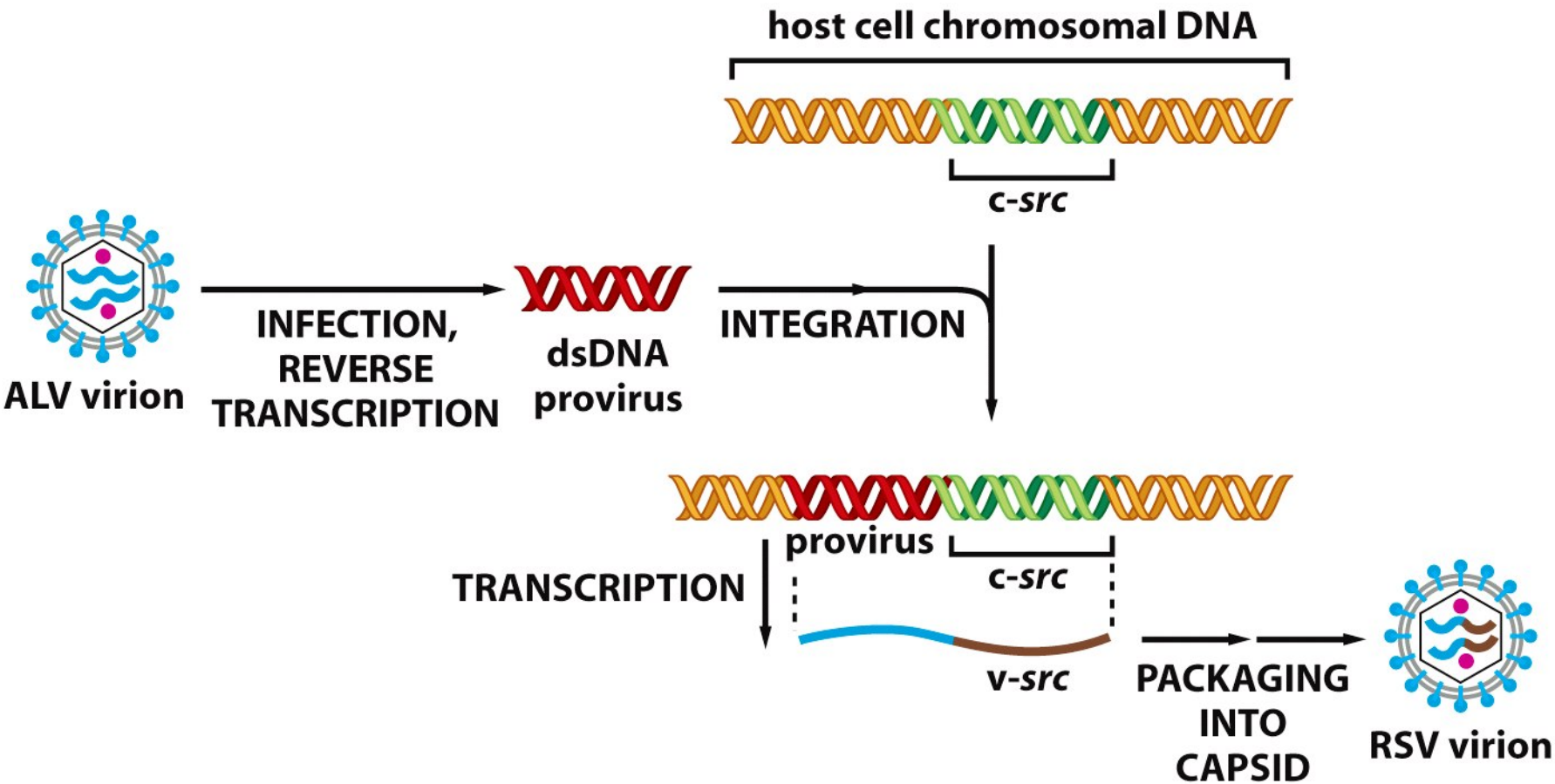
RNA → DNA → Integrated DNA (provirus) → RNA

# Activation of proto-oncogene by retroviral transduction

Transduction:
acquisition of eukaryotic sequences by retroviruses



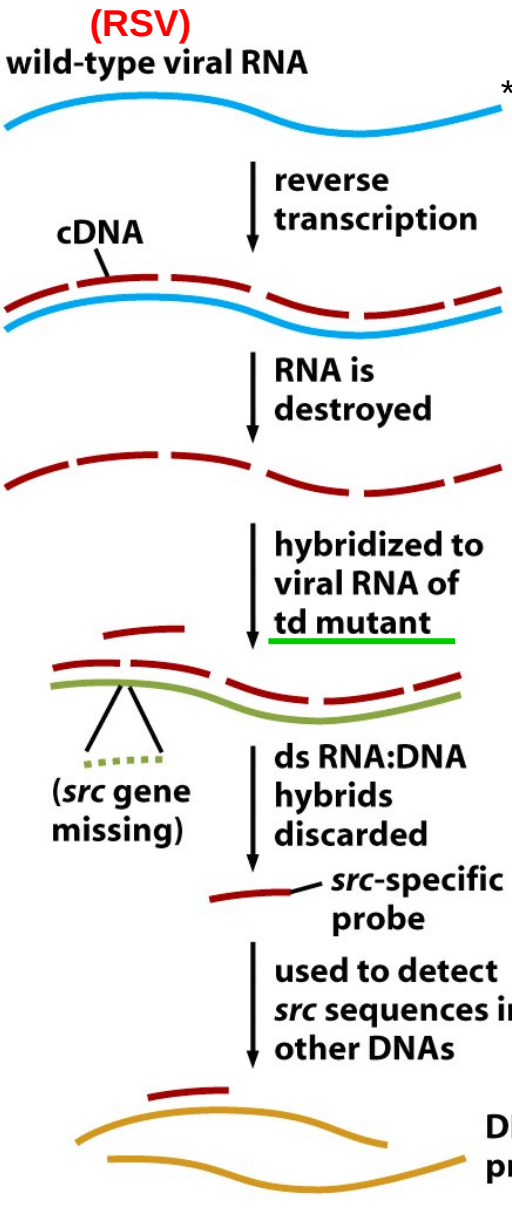
# Capture of *src* by ALV leads to formation of RSV



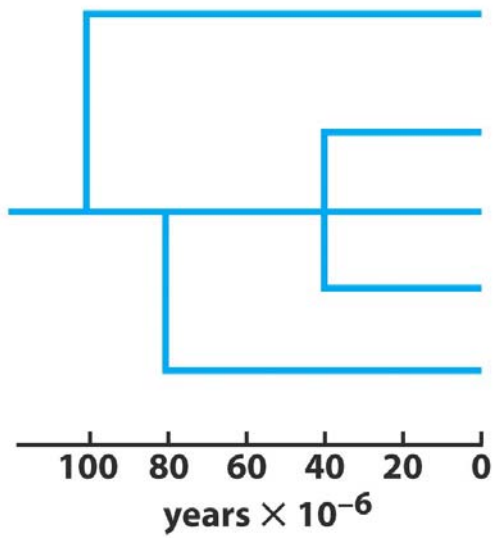

RSV exploits a kidnapped cellular gene to transform cells

# The discovery of proto-oncogenes

A version of the *src* gene carried by RSV is also present in uninfected avian cells




* Some RSV mutants are transformation-defective but replication-competent




| | extent of hybridization | melting temp. |
|---|---|---|
| RSV-rat | 70% | 82° |
| emu | 16% | 75.5° |
| quail | 48% | 78° |
| chicken | 54% | 80° |
| turkey | 53% | 78° |
| duck | 46% | 76° |

- The retroviral oncogenes originated from normal cellular genes (proto-oncogenes)

- Mutation of cellular gene might lead to oncogenecity (many oncogenes identified in oncogeneic retroviruses are later found to be involved in human cancers)

# Most oncogenic transforming viruses are replication-defective

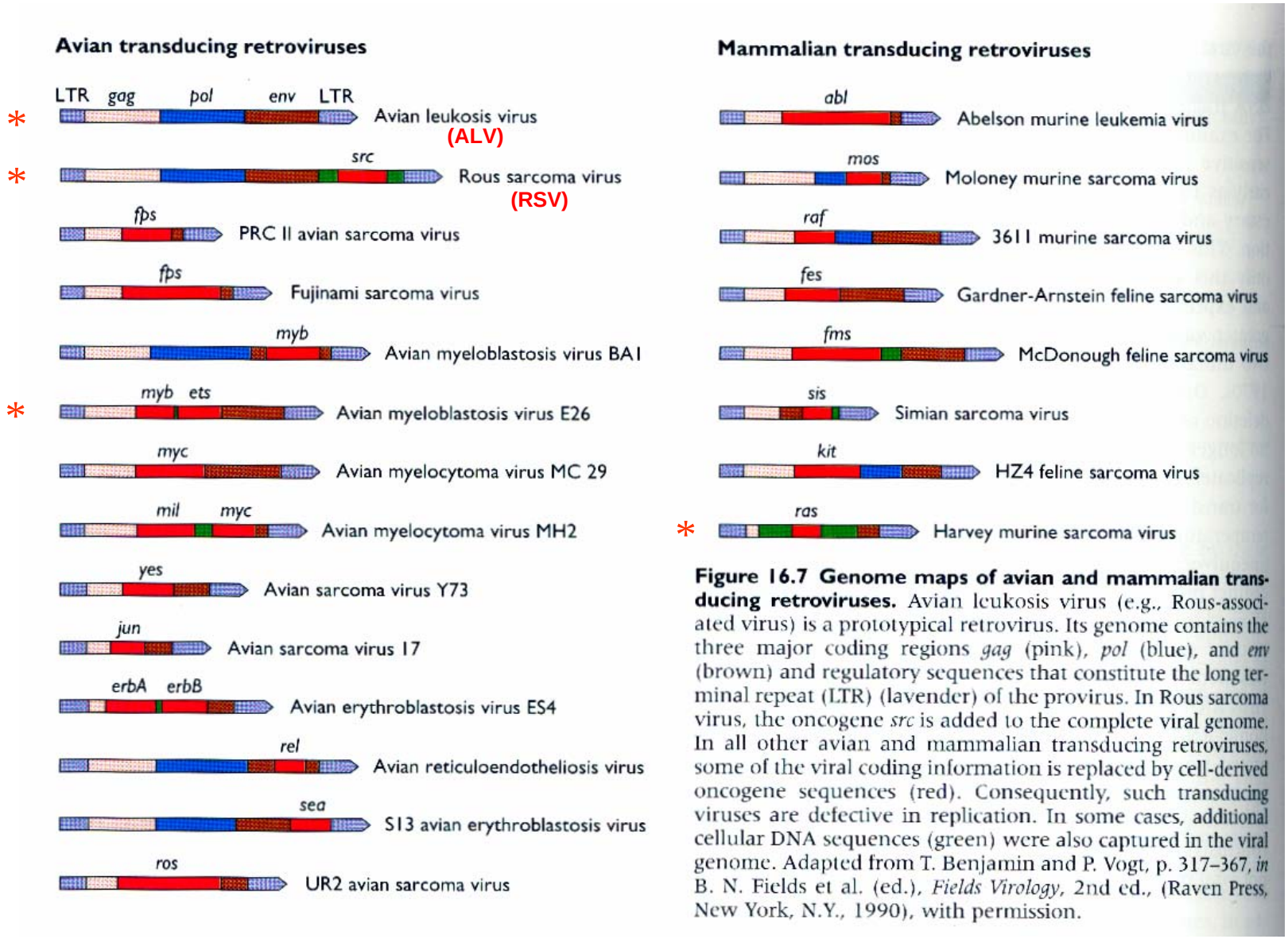
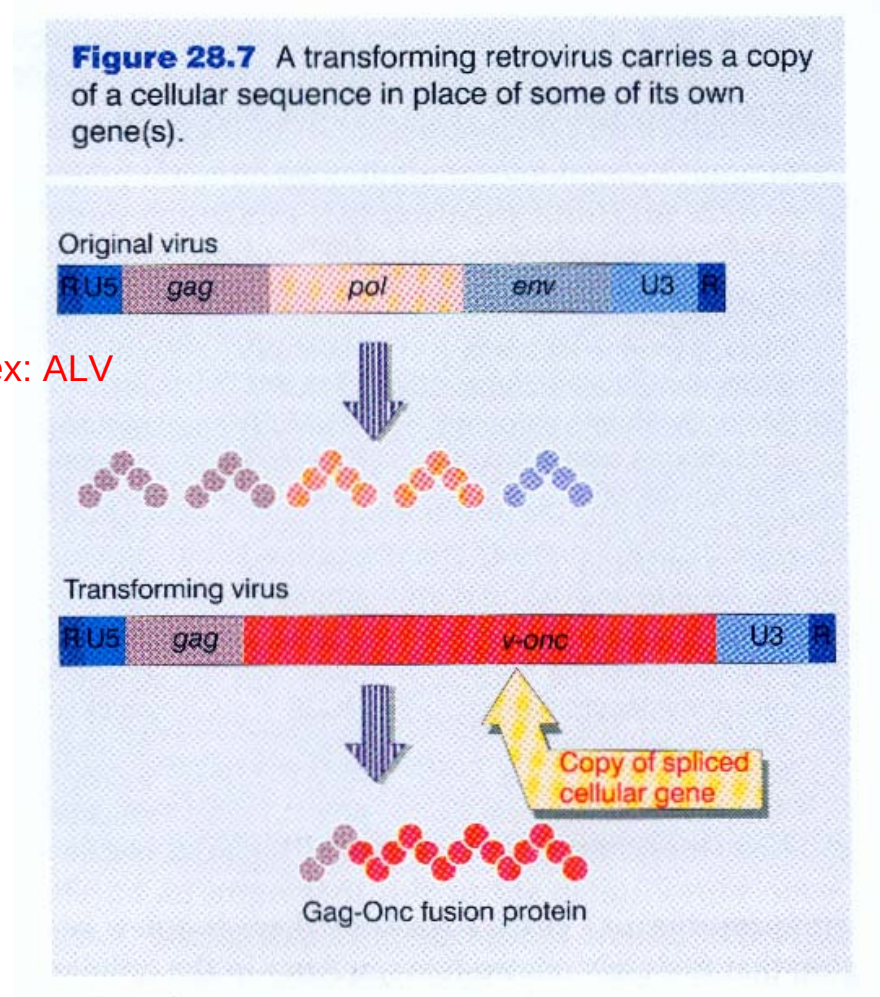



**Figure 16.7 Genome maps of avian and mammalian transducing retroviruses.** Avian leukosis virus (e.g., Rous-associated virus) is a prototypical retrovirus. Its genome contains the three major coding regions *gag* (pink), *pol* (blue), and *env* (brown) and regulatory sequences that constitute the long terminal repeat (LTR) (lavender) of the provirus. In Rous sarcoma virus, the oncogene *src* is added to the complete viral genome. In all other avian and mammalian transducing retroviruses, some of the viral coding information is replaced by cell-derived oncogene sequences (red). Consequently, such transducing viruses are defective in replication. In some cases, additional cellular DNA sequences (green) were also captured in the viral genome. Adapted from T. Benjamin and P. Vogt, p. 317–367, *in* B. N. Fields et al. (ed.), *Fields Virology*, 2nd ed., (Raven Press, New York, N.Y., 1990), with permission.

- Oncogenes in avian or murine retroviruses are not viral genes; they derived from transduction of normal cellular genes (proto-oncogenes)




ex: ALV

Replication-competent viruses
(nontransducing viruses; helper viruses)

Replication-defective viruses
(transducing viruses; transforming viruses)

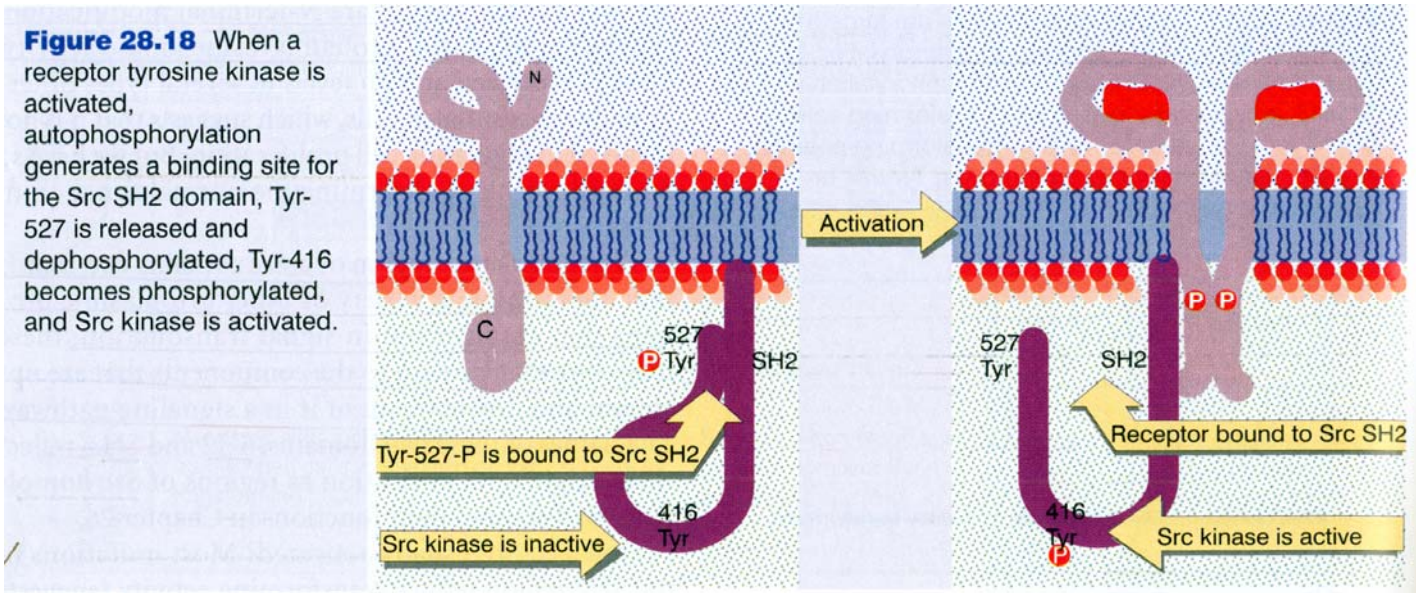
Features of oncogenes activated by retroviral transduction

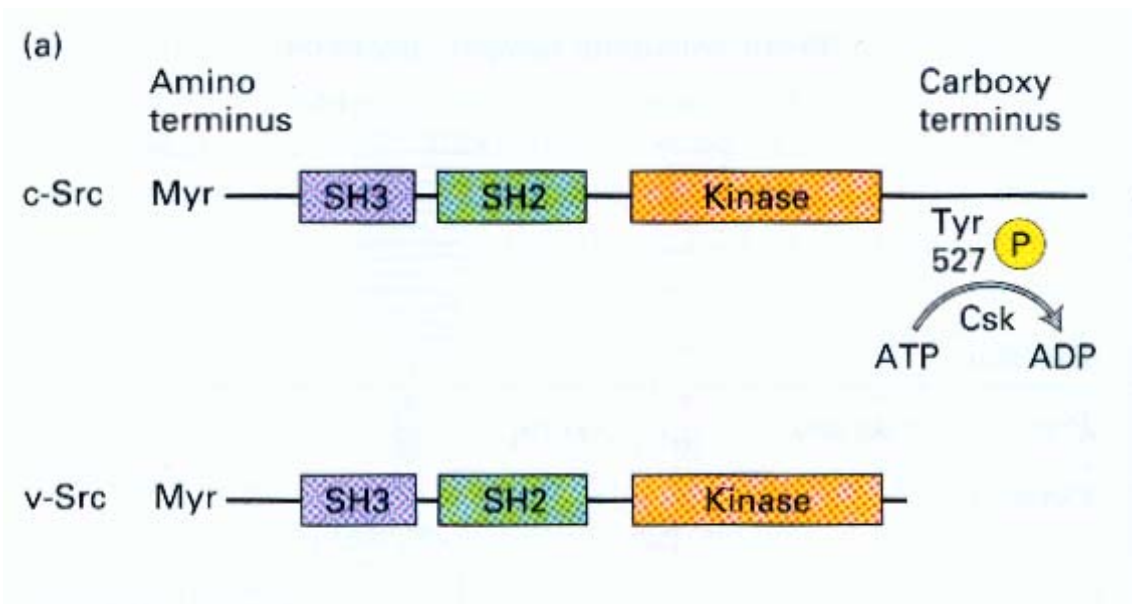
(a) Over-expression

(b) Deletion (truncation)

(c) Point mutations

# v-Src is a dominant active form of c-Src




**proto-oncogene**

A normal gene have the intrinsic potential to become oncogene

**viral oncogene**

An abnormal gene with ability to induce transformation and tumorigenicity

Table 3.3 Acutely transforming retroviruses and the oncogenes that they have acquired[a]

| Name of virus | Viral oncogene | Species | Major disease | Nature of oncoprotein |
|---|---|---|---|---|
| Rous sarcoma | *src* | chicken | sarcoma | non-receptor TK |
| Y73/Esh sarcoma | *yes* | chicken | sarcoma | non-receptor TK |
| Fujinami sarcoma | *fps*[b] | chicken | sarcoma | non-receptor TK |
| UR2 | *ros* | chicken | sarcoma | RTK; unknown ligand |
| Myelocytomatosis 29 | *myc* | chicken | myeloid leukemia[c] | transcription factor |
| Mill Hill virus 2 | *mil*[d] | chicken | myeloid leukemia | ser/thr kinase |
| Avian myeloblastosis E26 | *myb* | chicken | myeloid leukemia | transcription factor |
| Avian myeloblastosis E26 | *ets* | chicken | myeloid leukemia | transcription factor |
| Avian erythroblastosis ES4 | *erbA* | chicken | erythroleukemia | thyroid hormone receptor |
| Avian erythroblastosis ES4 | *erbB* | chicken | erythroleukemia | EGF RTK |
| 3611 murine sarcoma | *raf*[e] | mouse | sarcoma | ser/thr kinase |
| SKV770 | *ski* | chicken | endothelioma (?) | transcription factor |
| Reticuloendotheliosis | *rel* | turkey | immature B-cell lymphoma | transcription factor |
| * Abelson murine leukemia | *abl* | mouse | pre-B-cell lymphoma | non-receptor TK |
| Moloney murine sarcoma | *mos* | mouse | sarcoma, erythroleukemia | ser/thr kinase |
| Harvey murine sarcoma | H-*ras* | rat, mouse | sarcoma | small G protein |
| Kirsten murine sarcoma | K-*ras* | mouse | sarcoma | small G protein |
| FBJ murine sarcoma | *fos* | mouse | osteosarcoma | transcription factor |
| Snyder–Theilen feline sarcoma | *fes*[f] | cat | sarcoma | non-receptor TK |
| McDonough feline sarcoma | *fms* | cat | sarcoma | CSF-1 RTK |
| Gardner–Rasheed feline sarcoma | *fgr* | cat | sarcoma | non-receptor TK |
| Hardy–Zuckerman feline sarcoma | *kit* | cat | sarcoma | steel factor RTK |
| Simian sarcoma | *sis* | woolly monkey | sarcoma | PDGF |
| AKT8 | *akt* | mouse | lymphoma | ser/thr kinase |
| Avian virus S13 | *sea* | chicken | erythroblastic leukemia[g] | RTK; unknown ligand |
| Myeloproliferative leukemia | *mpl* | mouse | myeloproliferation | TPO receptor |
| Regional Poultry Lab v. 30 | *eyk* | chicken | sarcoma | RTK; unknown ligand |
| Avian sarcoma virus CT10 | *crk* | chicken | sarcoma | SH2/SH3 adaptor |
| Avian sarcoma virus 17 | *jun* | chicken | sarcoma | transcription factor |
| Avian sarcoma virus 31 | *qin* | chicken | sarcoma | transcription factor[h] |
| AS42 sarcoma virus | *maf* | chicken | sarcoma | transcription factor |
| Cas NS-1 virus | *cbl* | mouse | lymphoma | SH2-dependent ubiquitylation factor |

-The vertebrate genome carries a large group of proto-oncogenes
- More than thirty distinct vertebrate proto-oncogenes have been discovered through this route

# RNA viruses contribute to the formation of current concepts of cancer biology

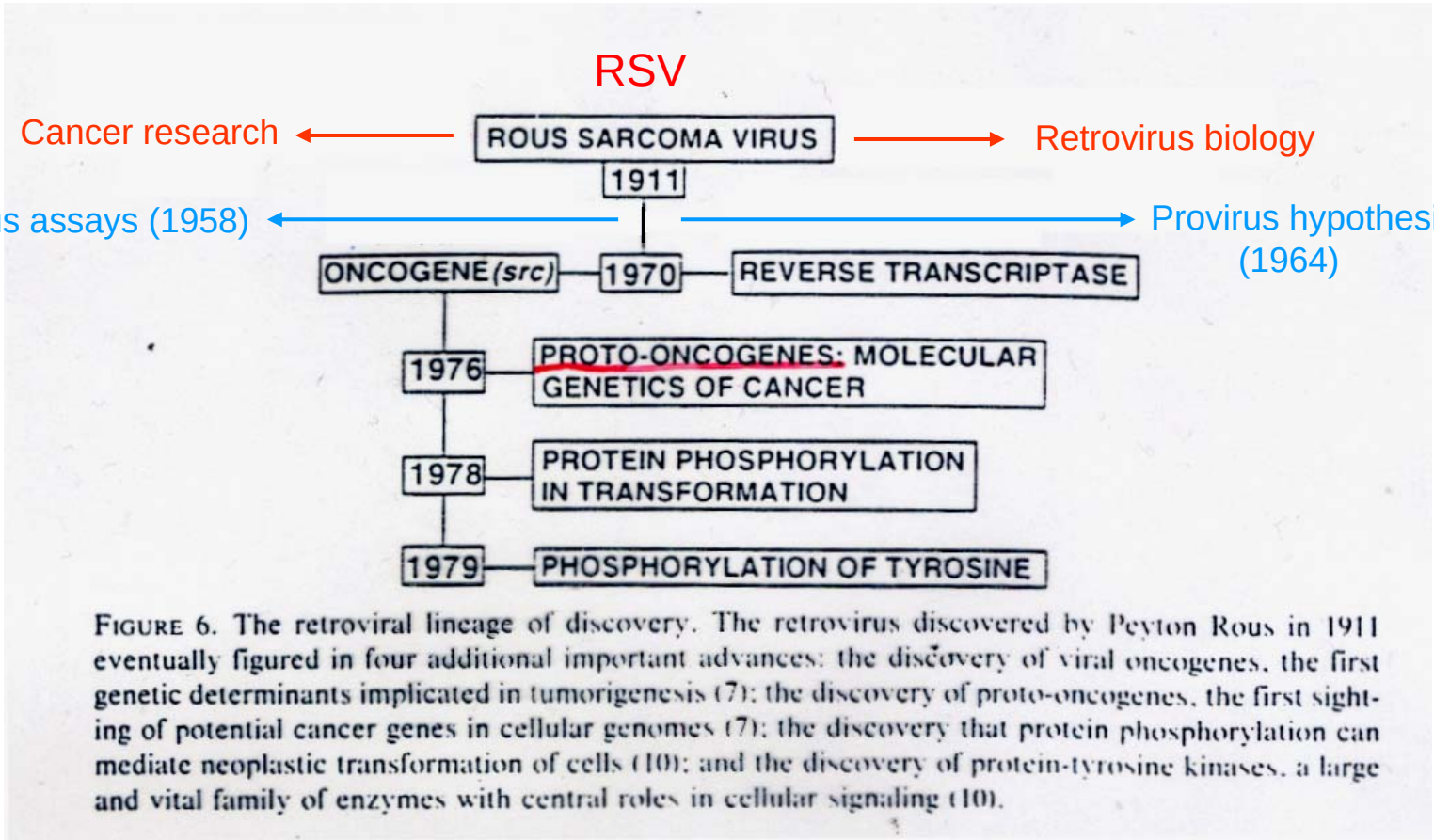



FIGURE 6. The retroviral lineage of discovery. The retrovirus discovered by Peyton Rous in 1911 eventually figured in four additional important advances: the discovery of viral oncogenes, the first genetic determinants implicated in tumorigenesis (7); the discovery of proto-oncogenes, the first sighting of potential cancer genes in cellular genomes (7); the discovery that protein phosphorylation can mediate neoplastic transformation of cells (10); and the discovery of protein-tyrosine kinases, a large and vital family of enzymes with central roles in cellular signaling (10).

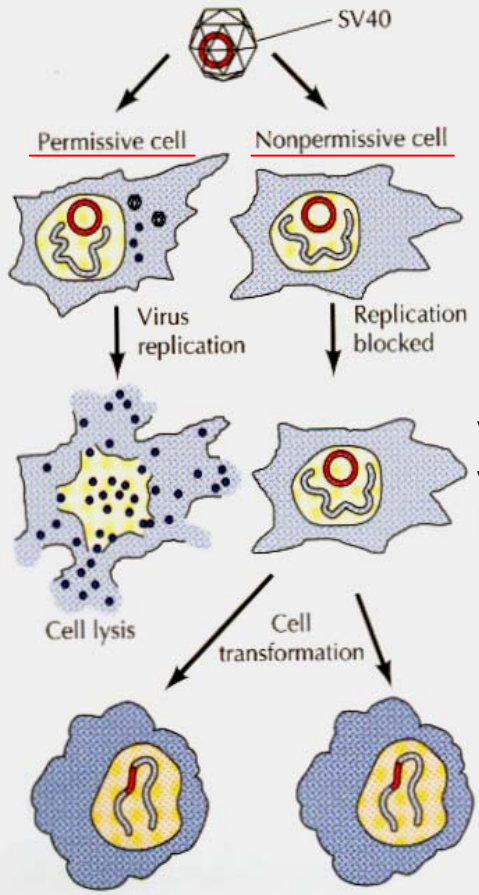
# Viruses containing DNA molecules are also able to induce cancer

**Table 3.1** Tumor virus genomes

| | Virus family | Approximate size of genome (kb) |
|---|---|---|
| *DNA viruses* | | |
| Hepatitis B virus (HBV) | hepadna | 3 |
| * SV40/polyoma | papova | 5 |
| * Human papilloma 16 (HPV) | papova | 8 |
| Human adenovirus 5 | adenovirus | 35 |
| Human herpesvirus 8 (HSV-8; KSHV) | herpesviruses | 165 |
| Shope fibroma virus | poxviruses | 160 |
| *RNA viruses* | | |
| * Rous sarcoma virus (RSV) | retrovirus | 9 |
| * Human T-cell leukemia virus (HTLV-I) | retrovirus | 9 |

# Permissive vs. nonpermissive cells

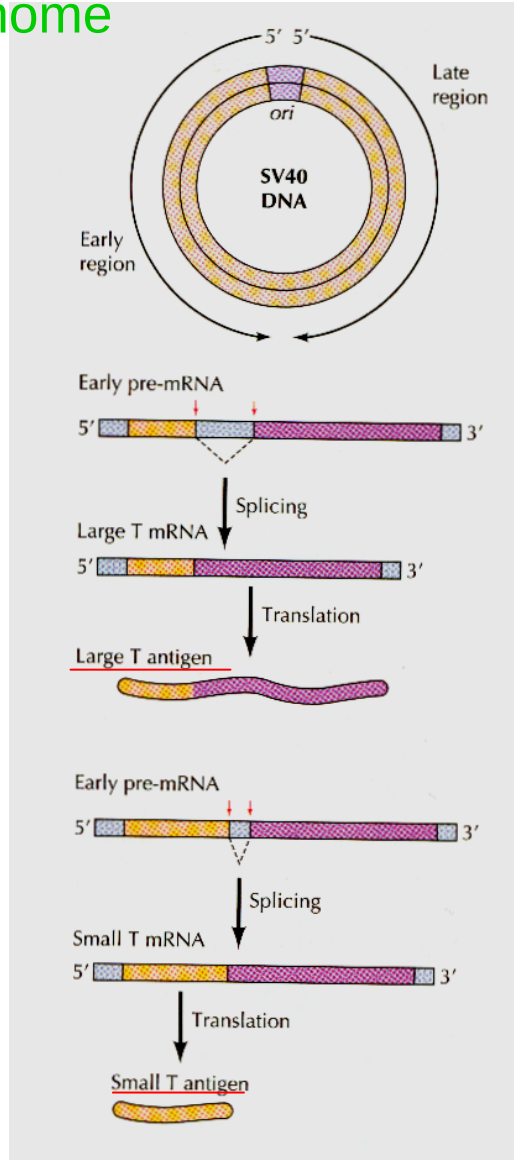
*Figure 15.13*
**SV40 replication and transformation**
Infection of a permissive cell results in virus replication, cell lysis, and release of progeny virus particles. In a non-permissive cell, virus replication is blocked, allowing some cells to become permanently transformed.




Viral genomes persist in virus-transformed cells by becoming part of host genome (<0.1%)

SV40 and polyomavirus serve as models to study DNA tumor virus-induced cellular transformation

# Oncogenic proteins in DNA tumors are viral proteins encoded by viral genome




Large T antigens bind and inactivate Rb and p53

# DNA tumor viruses

1. Encode oncogenes of viral origin that are essential for both viral replication and cellular transformation; study of DNA tumor viruses lead to the discovery of cellular tumor suppressor genes

2. Induce transformation by

(1) Disruption of the circuits that regulate cell cycle progression

*ex: large T antigen from SV40 virus interacts with Rb and p53.

*ex: in adenoviruses, E1A interacts with Rb, and E1B interacts with p53

(2) Activation of cellular mitogenic signal transductuin pathways by altering activity or expression level

*ex: LMP-1 of Epstein-Barr virus acts as constitutively active receptor to alter cellular gene expression

*ex: The human papillomavirus E5 protein increase concentration of the cell surface EGF receptor

*ex: Polymavirus middle T protein can function as virus-specific adaptor to activate abnormal signal transduction

*ex: SV40 virus small T antigen inhibit activity of protein phosphatase 2A

# Tumor viruses induce multiple changes in cell phenotypes including acquisition of tumorigenicity

**Table 3.2 Properties of transformed cells**

| | |
|---|---|
| | Altered morphology (rounded shape, refractile in phase-contrast microscope) |
| * | Loss of contact inhibition (ability to grow over one another) |
| * | Ability to grow without attachment to solid substrate (anchorage independence) |
| * | Ability to proliferate indefinitely (immortalization) |
| | Reduced requirement for mitogenic growth factors |
| | High saturation density (ability to accumulate large numbers of cells in culture dish) |
| | Inability to halt proliferation in response to deprivation of growth factors |
| | Increased transport of glucose |
| * | Tumorigenicity |

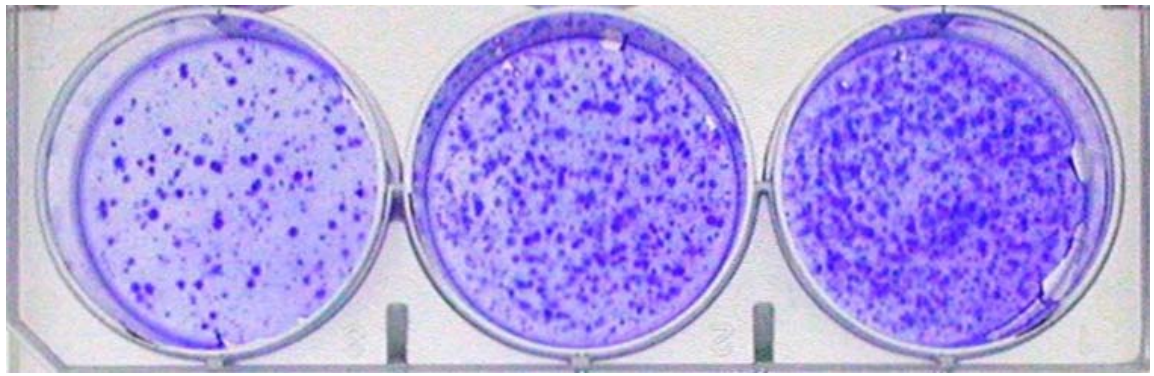
Transformation: conversion of a normal cell into a tumor cells

Tumorigenicity: tumor formation in host animals

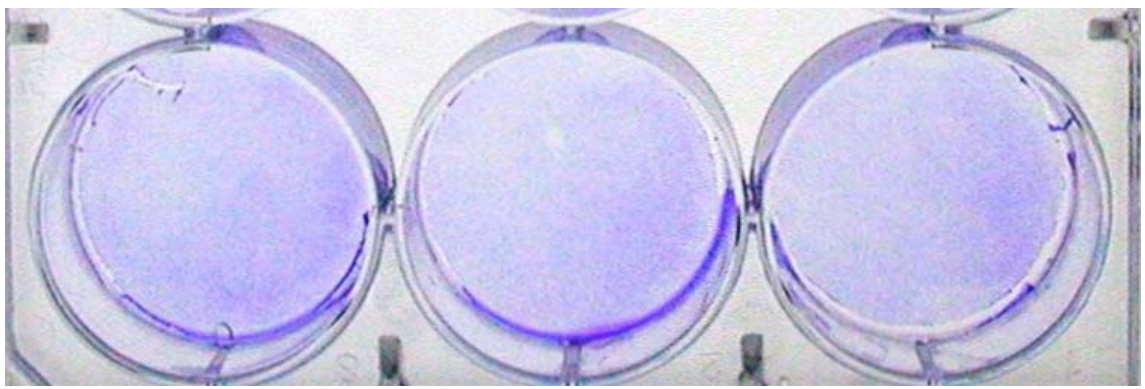
# Focus assays

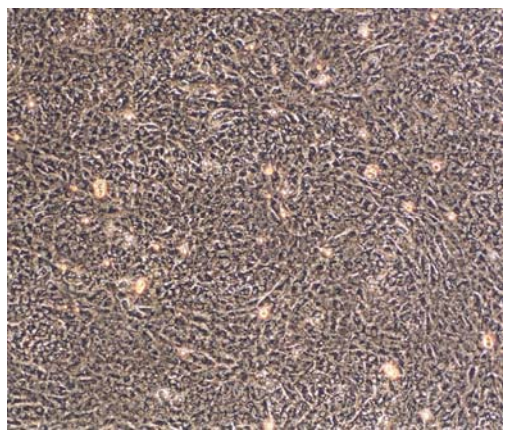
- To detect loss of cell-contact inhibition

v-Src



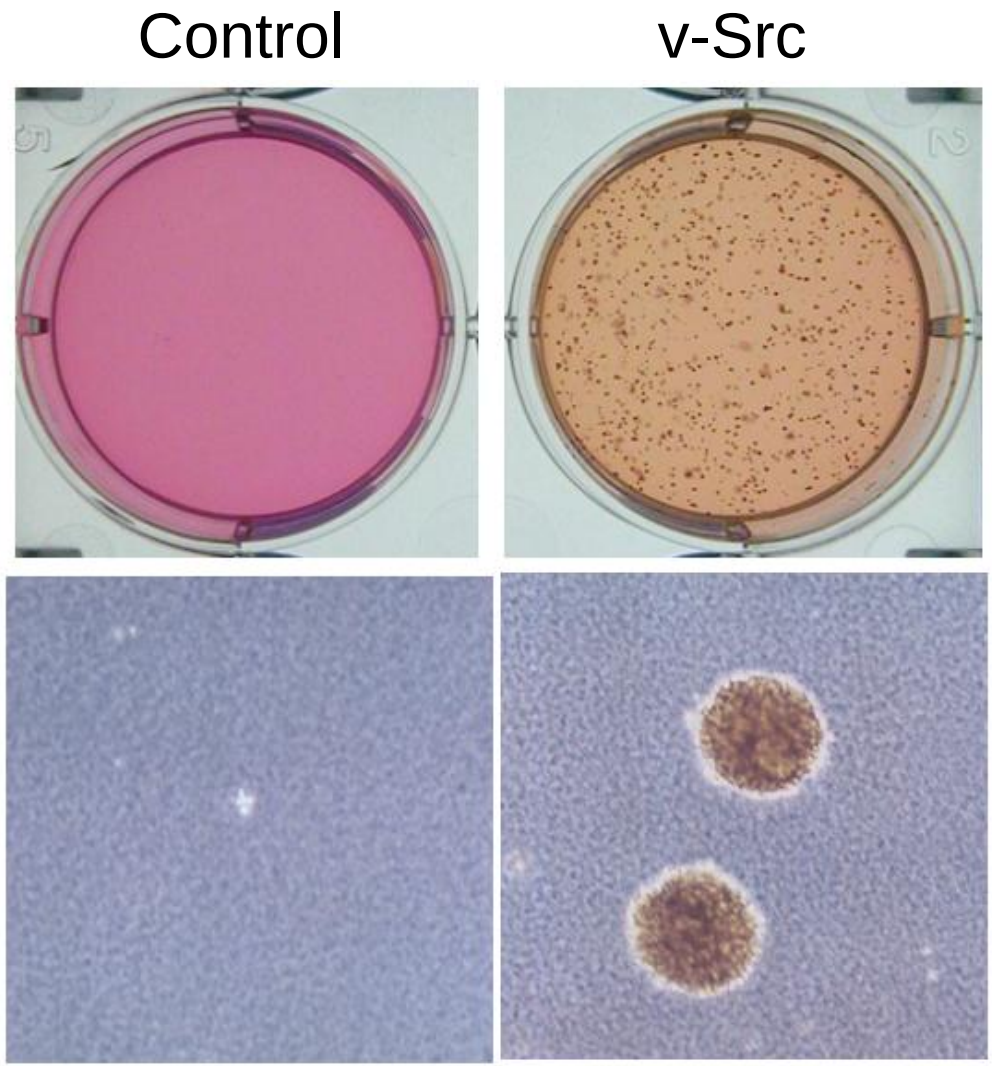
Control





# Soft agar assays

- To detect loss of anchorage-independence



# *In vivo* tumorigenesis assays

Immunocompromised host

syngeneic host

# Activation of proto-oncogenes

## RNA virus-related

Retroviral transduction

Promoter/enhancer insertion

Trans-activation

## DNA virus-related

Altering activity/expression of host growth-related genes through protein-protein interaction

## Non-viral

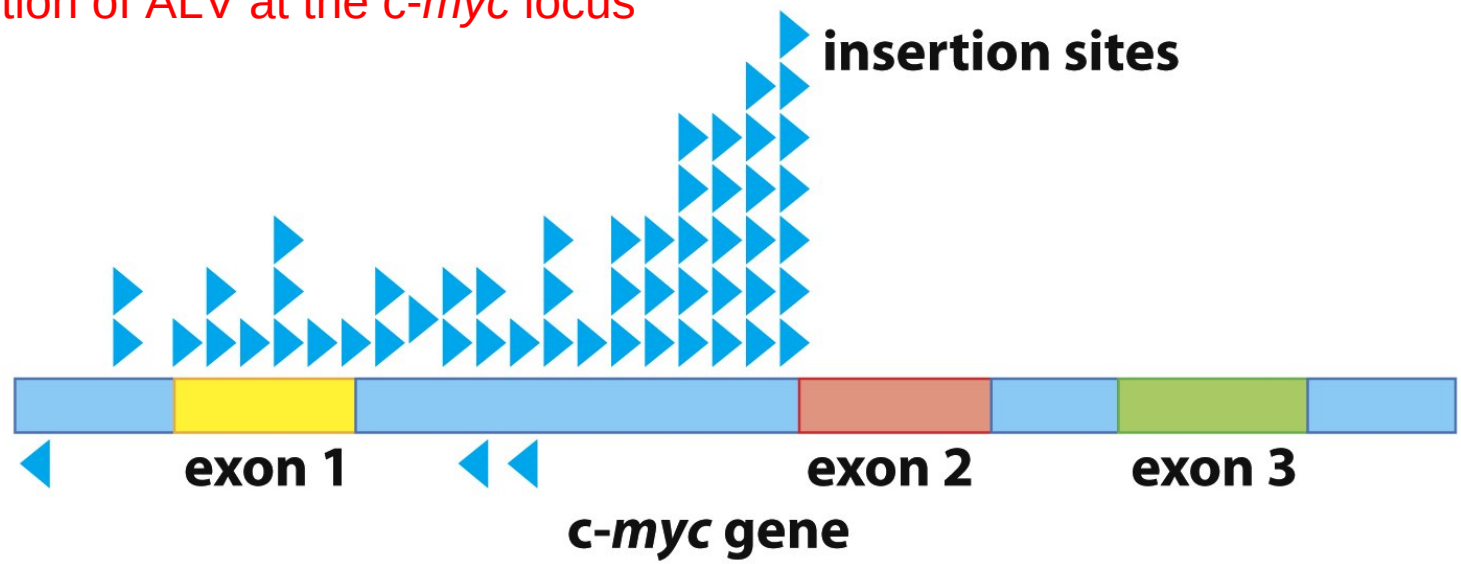
Point mutation

Amplification

Chromosomal translocation

# Promoter/enhancer insertion by retroviruses

Insertion of ALV at the c-*myc* locus



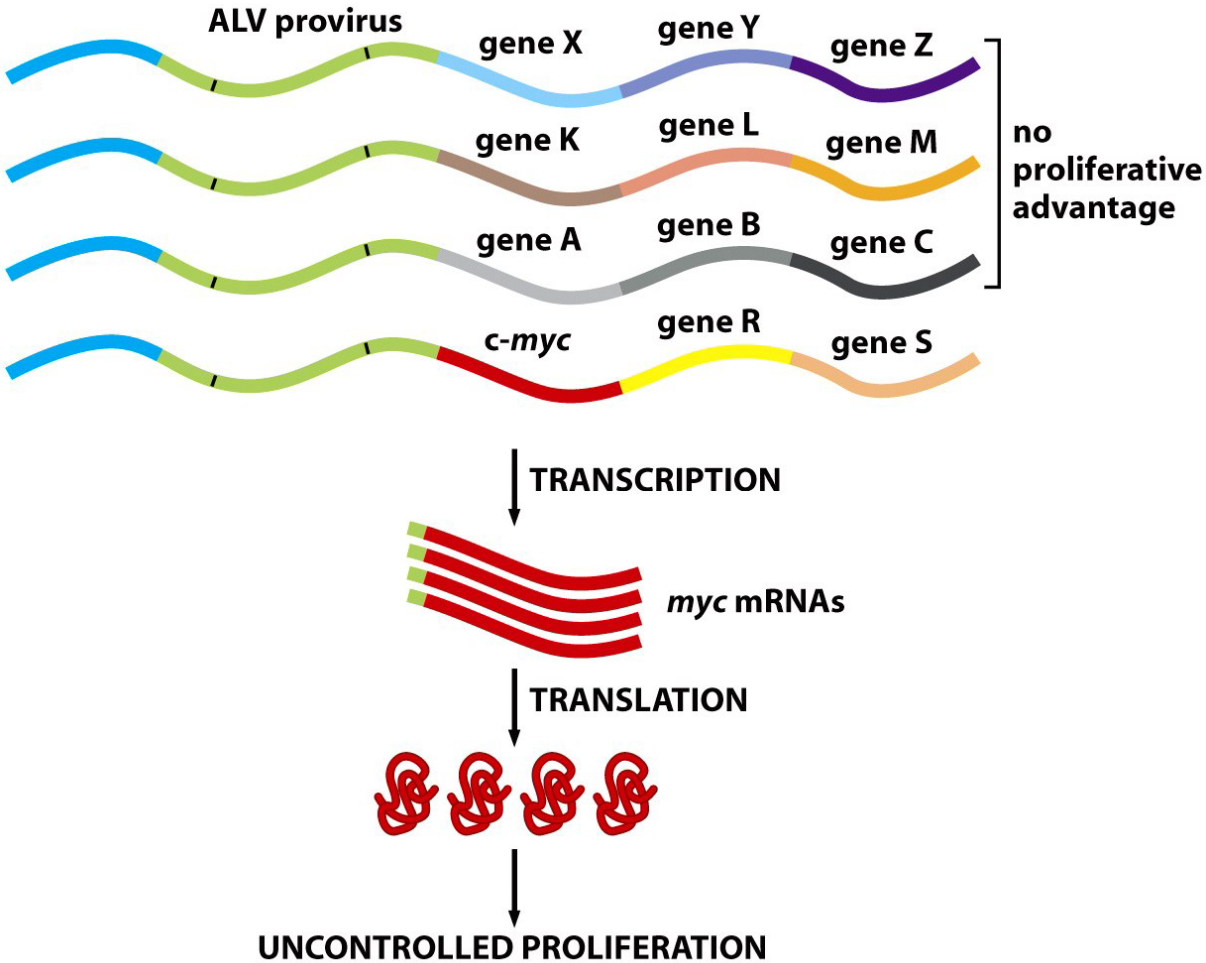

- Slowly transforming retroviruses (ex: ALV) activate proto-oncogenes by inserting their genomes adjacent to these cellular genes

- This insertion places the *myc* under the control of the viral transcriptional promoter, which leads to over-expression of *myc* gene

**Insertional mutagenesis:

Insertion of the viral genome adjacent to into cellular genes in cellular chromosomes

# Conversion of c-*myc* gene into an oncogene by insertional mutagenesis




Insertion of ALV at the c-*myc* locus leads to overexpression of Myc protein

**Table 3.4** Examples of cellular genes found to be activated by insertional mutagenesis

| Gene | Insertional mutagen | Tumor type | Species | Type of oncoprotein |
|---|---|---|---|---|
| *myc* | ALV | B-cell lymphoma | chicken | transcription factor |
| *myc* | ALV, FeLV | T-cell lymphoma | chicken, cat | transcription factor |
| *nov* | ALV | nephroblastoma | chicken | growth factor |
| *erbB* | ALV | erythroblastosis | chicken | receptor TK |
| *mos* | IAP | plasmacytoma | mouse | ser/thr kinase |
| *int-1*[a] | MMTV | mammary carcinoma | mouse | growth factor |
| *int-2*[b] | MMTV | mammary carcinoma | mouse | growth factor |
| *int-3* | MMTV | mammary carcinoma | mouse | receptor[c] |
| *int-H/int-5* | MMTV | mammary carcinoma | mouse | enzyme[d] |
| *pim-1* | Mo-MLV | T-cell lymphoma | mouse | ser/thr kinase |
| *pim-2* | Mo-MLV | B-cell lymphoma | mouse | ser/thr kinase |
| *bmi-1* | Mo-MLV | T-cell lymphoma | mouse | transcription repressor |
| *tpl-2* | Mo-MLV | T-cell lymphoma | mouse | non-receptor TK |
| *lck* | Mo-MLV | T-cell lymphoma | mouse | non-receptor TK |
| *p53* | Mo-MLV | T-cell lymphoma | mouse | transcription factor |
| *GM-CSF* | IAP | myelomonocytic leukemia | mouse | growth factor |
| *IL2* | GaLV | T-cell lymphoma | gibbon ape | cytokine[e] |
| *IL3* | IAP | T-cell lymphoma | mouse | cytokine |
| K-*ras* | F-MLV | T-cell lymphoma | mouse | small G protein |
| *CycD1* | F-MLV | T-cell lymphoma | mouse | G1 cyclin |
| *CycD2* | Mo-MLV | T-cell lymphoma | mouse | G1 cyclin |

[a]Subsequently renamed *Wnt-1*.
[b]Subsequently identified as a gene encoding a fibroblast growth factor (FGF).
[c]Related to notch receptors.
[d]Enzyme that converts androgens to estrogens.
[e]Cytokines are GFs that largely regulate various types of hematopoietic cells.

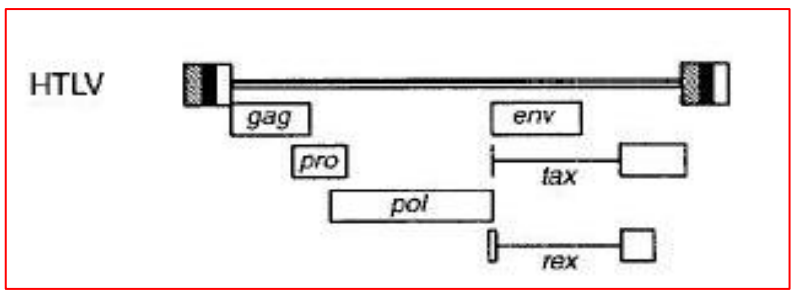
Abbreviations: ALV, avian leukosis virus; FeLV, feline leukemia virus; F-MLV, Friend murine leukemia virus; GaLV, gibbon ape leukemia virus; GF, growth factor; IAP, intracisternal A particle (a retrovirus-like genome that is endogenous to cells); Mo-MLV, Moloney murine leukemia virus; MMTV, mouse mammary tumor virus; ser/thr, serine/threonine; TK, tyrosine kinase.

Adapted in part from J. Butel, Viral carcinogenesis: Revelation of molecular mechanisms and etiology of human disease, *Carcinogenesis* 21:405–426, 2000; and from N. Rosenberg and P. Jolicoeur, Retroviral pathogenesis, in J.M. Coffin, S.H. Hughes and H.E. Varmus (eds.), Retroviruses. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1997. Also in part from G.M. Cooper, Oncogenes, 2nd ed. Boston: Jones and Bartlett Publishers, 1995.

# Human retroviruses

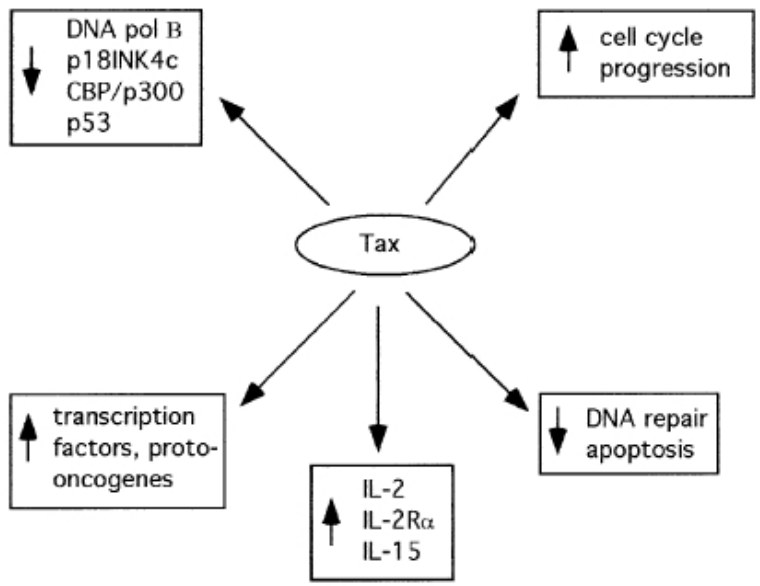
## HTLV-1 (human T-cell leukemia virus 1)

- The only currently accepted human tumor virus from the retrovirus family
- Associated with adult T cell leukemia/lymphoma (ATL)
- This virus carries oncogene “tax”
- Tax protein: a transcription factor, function in viral replication, also responsible for enhanced transcription of viral and cellular genes that promote cell growth factor and dysfunction of cellular regulatory tumor suppressor genes




p.s:
Other host factors and virus-host interactions also contribute to genesis of ALT, ex: virus strain, HLA haplotype, route of infection, and immune response to HTLV-I

Mechanisms of HTLV-I-induced cellular transformation

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# Activation of proto-oncogenes

## RNA virus-related

Retroviral transduction ex: RSV

Promoter/enhancer insertion ex: ALV

Trans-activation ex: HTLV-1

## DNA virus-related

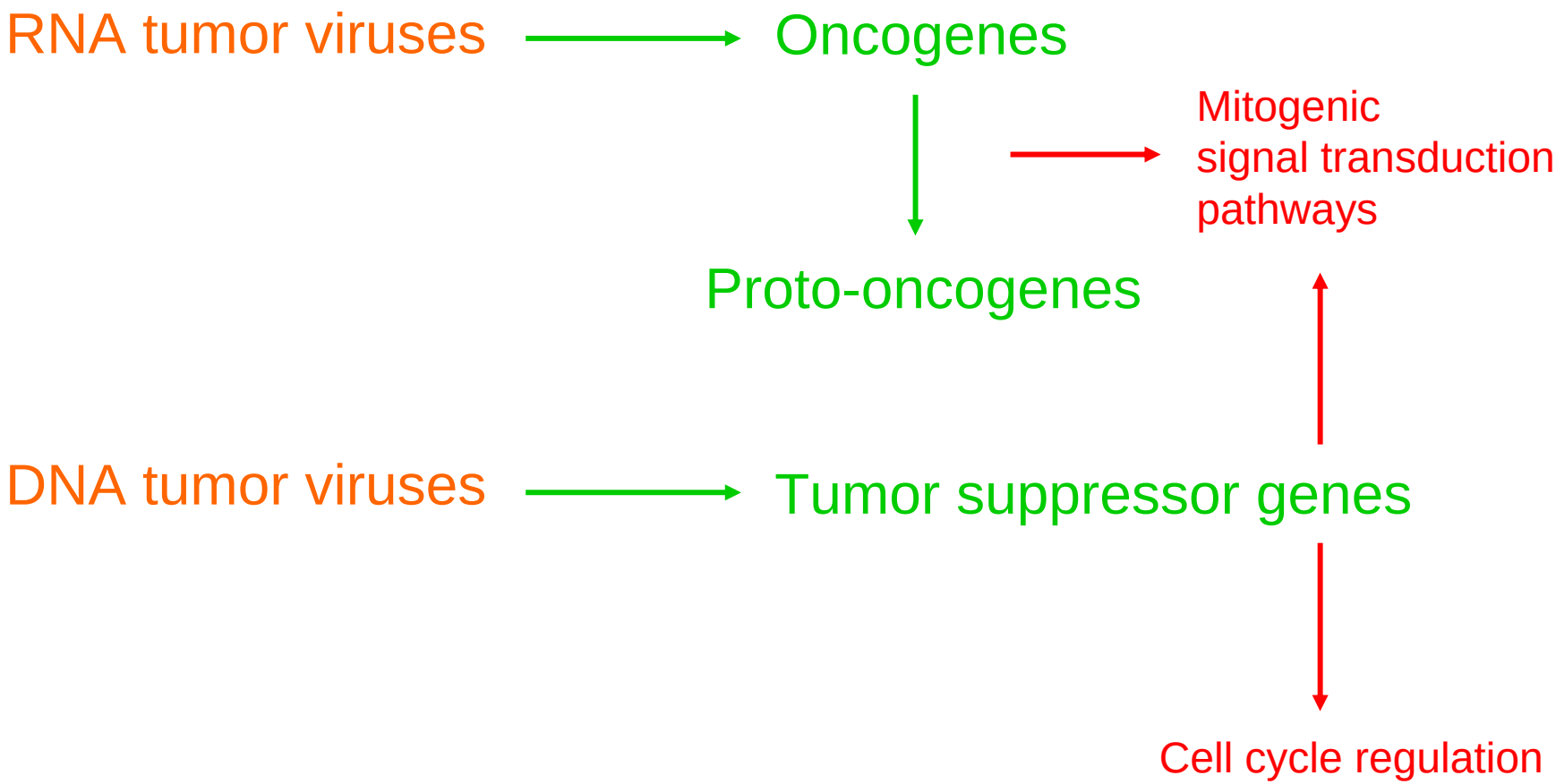
Altering activity/expression of host growth-related genes through protein-protein interaction

## Non-viral

Point mutation

Amplification

Chromosomal translocation

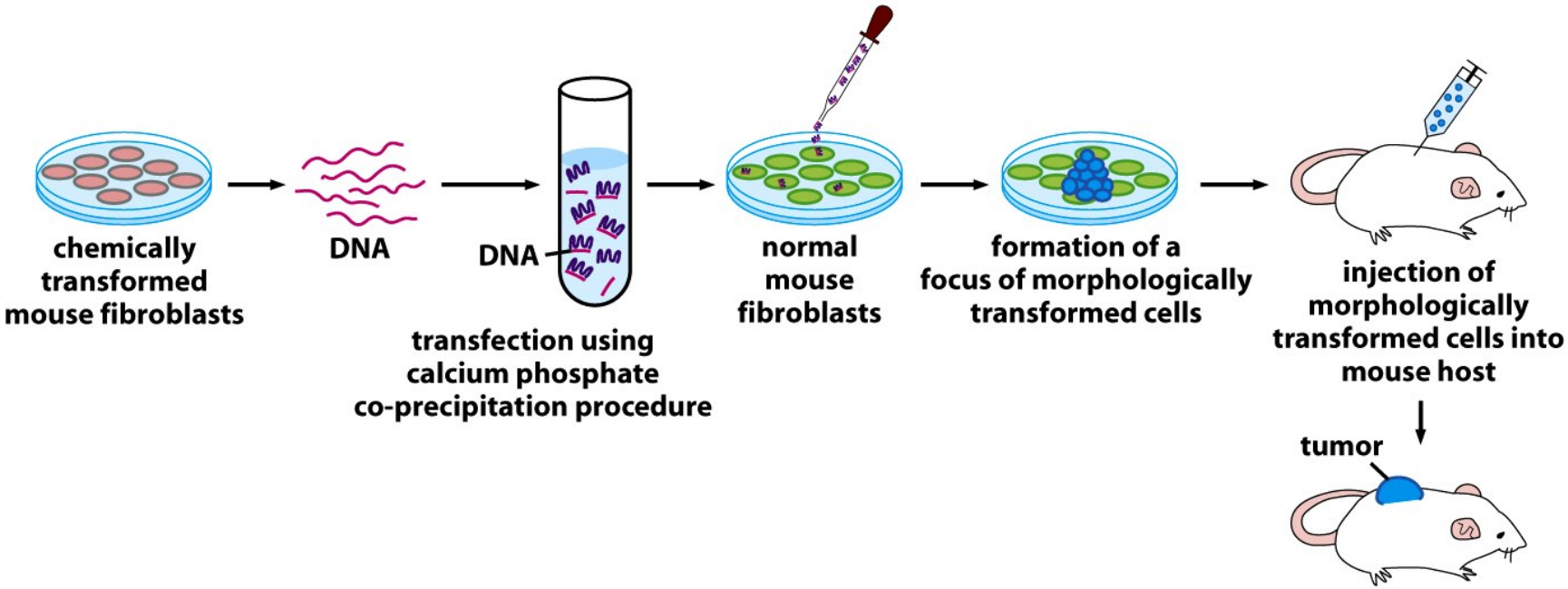



- Most types of human cancer clearly did not spread from one individual to another as an infectious diseases

- By studying tumor viruses and their mechanisms of action, research found that cancer is a disease of genes and thus a condition that was susceptible to analysis by the tools of molecular biology and genetics

The inability o find tumor viruses in the majority of human cancers in the mid-1970s left researchers with one main theory of how most human cancers arises: that carcinogens act as mutagens and function by mutating normal growth-controlling genes into oncogenes

# Transfection of DNA provides a strategy for detecting non-viral oncogenes




- The donor tumor DNA carried one or several genetic elements that were able to convert non-tumorigenic NIH3T3 recipient cell into a cell that was strongly tumorigenic

- DNA extracted from cell lines derived from human bladder, lung, and colon carcinomas were found capable of transforming recipient NIH3T3 cells.

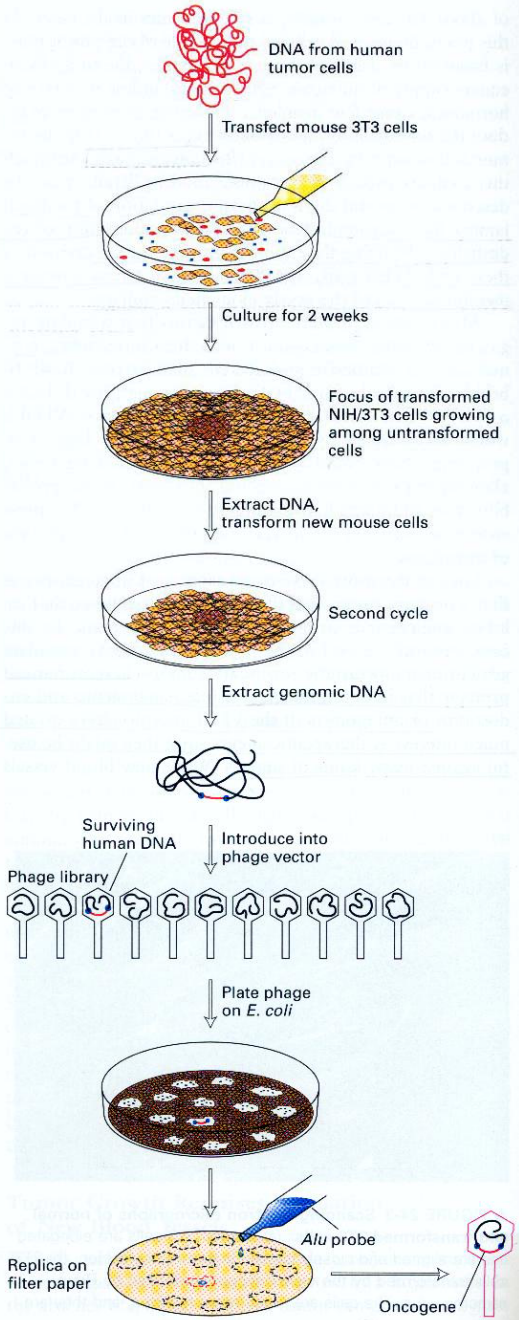
# Molecular cloning of cellular oncogene *ras* from human cancer cells by gene transfer assays (Robert Weinberg, 1981)

- Direct evidence to show the involvement of cellular oncogene in human cancers

- Ras sequence identified from this method contains point mutation, and is homologous to oncogenic Ras carried by transforming murine sarcoma viruses.

- The same cellular proto-oncogene could be affected by viruses, by chemical carcinogenesis, or by non-viral somatic mutations

- Proto-oncogene vs. viral oncogene vs. cellular oncogene




▶ **FIGURE 24-4 The identification and molecular cloning of the *ras*$^{D}$ oncogene.** Addition of DNA from a human bladder carcinoma to a culture of mouse 3T3 cells causes about one cell in a million to divide abnormally and form a focus, or clone of transformed cells. To clone the oncogene responsible for transformation, advantage is taken of the fact that most human genes have nearby repetitive DNA sequences called *Alu* sequences. DNA from the initial focus of transformed mouse cells is isolated, and the oncogene is separated from adventitious human DNA by secondary transfer to mouse cells. The total DNA from a secondary transfected mouse cell is then cloned into bacteriophage λ; only the phage that receives human DNA hybridizes with an *Alu* probe. The hybridizing phage should contain part or all of the transforming oncogene. This expected result can be proved by showing either that the phage DNA can transform cells (if the oncogene has been completely cloned) or that the cloned piece of DNA is always present in cells transformed by DNA transfer from the original donor cell.

# Mutation responsible for H-Ras oncogene activation

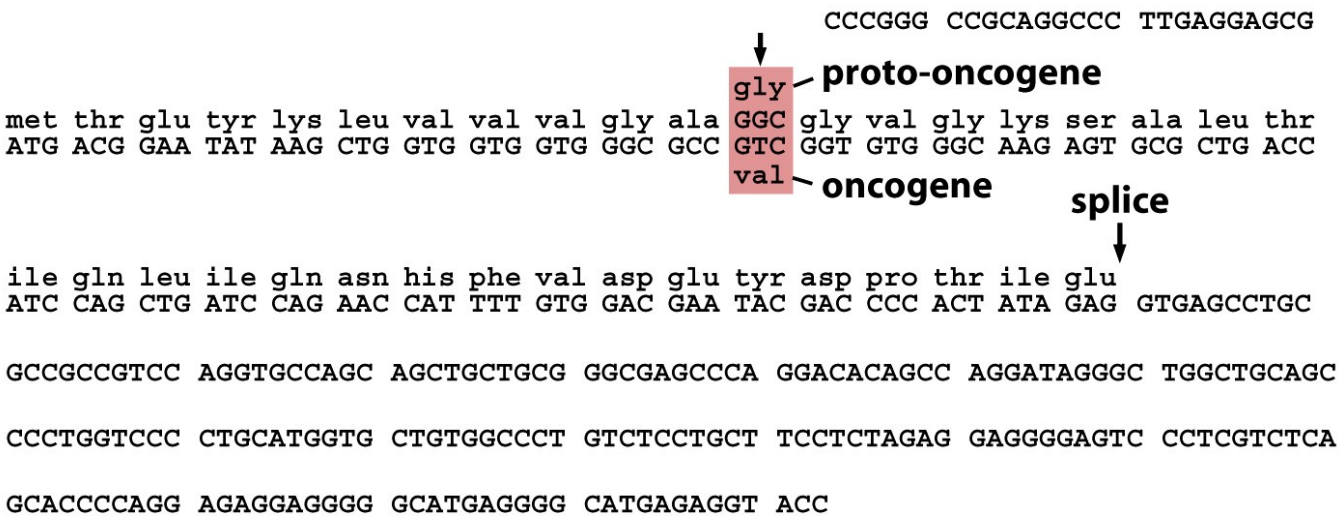



Table 4.2 A list of point-mutated *ras* oncogenes carried by a variety of human tumor cells

| Tumor type | Proportion (%) of tumors carrying a point-mutated *ras* gene[a] |
|---|---|
| Pancreas | 90 K |
| Thyroid (papillary) | 60 (H, K, N) |
| Thyroid (follicular) | 55 (H, K, N) |
| Colorectal | 45 (K) |
| Seminoma | 45 (K, N) |
| Myelodysplasia | 40 (N, K) |
| Lung (non-small-cell) | 35 (K) |
| Acute myelogenous leukemia | 30 (N) |
| Liver | 30 (N) |
| Melanoma | 15 (K) |
| Bladder | 10 (K) |
| Kidney | 10 H |

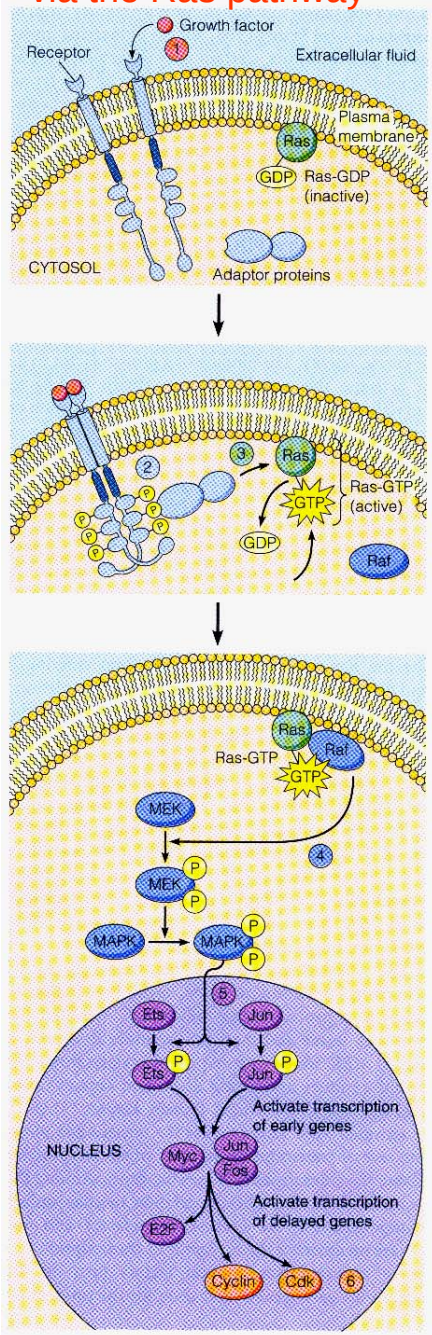
# Constitutive activation of Ras oncogenes in cancer cells

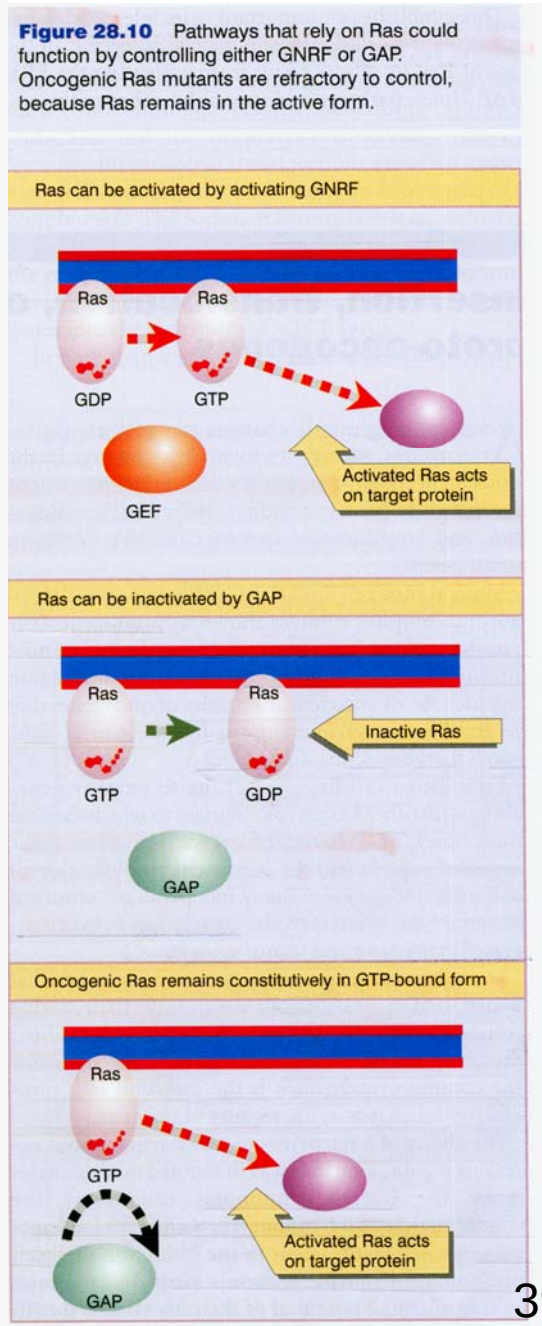
- The first human transforming oncogene
- Ras mutation are found in 20% of human cancers
- Position 12, 13 and 61 are most frequently mutated amino acid in Ras gene found in retroviruses and various types of human cancers

GEF: guanine nucleotide-exchange factor

GAP: GTPase-activating proteins

Growth factor signaling via the Ras pathway



# Oncogenes originally discovered in transforming retroviruses could be found in human tumor cell genomes

**Table 4.1** Examples of retrovirus-associated oncogenes that have been discovered in altered form in human cancers

| | Name of virus | Species | Oncogene | Type of oncoprotein | Homologous oncogene found in human tumors |
|---|---|---|---|---|---|
| * | Rous sarcoma | chicken | *src* | receptor TK | colon carcinoma[a] |
| | Abelson leukemia | mouse | *abl* | nonreceptor TK | CML |
| * | Avian erythroblastosis | mouse | *erbB* | receptor TK | gastric, lung, breast[b] |
| | McDonough feline sarcoma | cat | *fms* | receptor TK | AML[c] |
| | H-Z feline | cat | *kit* | receptor TK[d] | gastrointestinal stromal |
| | Murine sarcoma 3611 | mouse | *raf* | Ser/Thr kinase[e] | bladder carcinoma |
| | Simian sarcoma | monkey | *sis* | growth factor (PDGF) | many types[f] |
| * | Harvey sarcoma | mouse/rat | H-*ras*[g] | small G protein | bladder carcinoma |
| | Kirsten sarcoma | mouse/rat | K-*ras*[g] | small G protein | many types |
| | Avian erythroblastosis | chicken | *erbA* | nuclear receptor[h] | liver, kidney, pituitary |
| | Avian myeloblastosis E26 | chicken | *ets* | transcription factor | leukemia[i] |
| * | Avian myelocytoma | chicken | *myc*[j] | transcription factor | many types |
| | Reticuloendotheliosis | turkey | *rel*[k] | transcription factor | lymphoma |

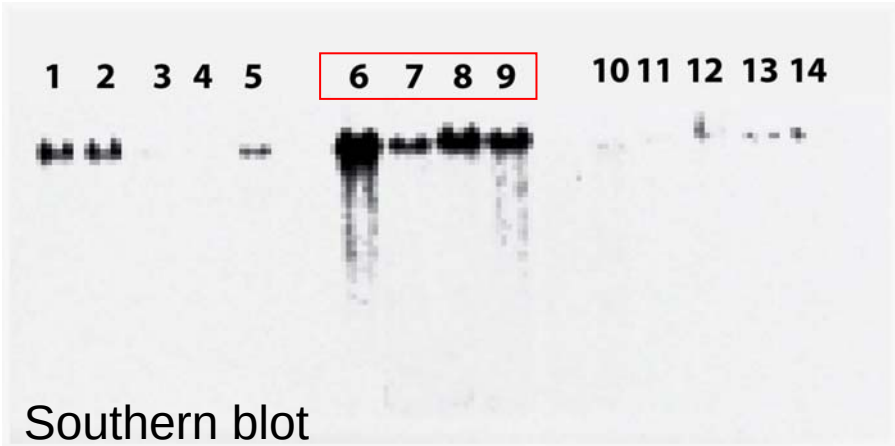
[a]Mutant forms found in a small number of these tumors.
[b]Receptor for EGF; the related erbB2/HER2/Neu protein is overexpressed in 30% of breast cancers.
[c]Fms, the receptor for colony-stimulating factor (CSF-1), is found in mutant form in a small number of AMLs; the related Flt3 (Fms-like tyrosine kinase-3) protein is frequently found in mutant form in these leukemias.
[d]Receptor for stem cell factor.
[e]The closely related B-Raf protein is mutant in the majority of melanomas.
[f]Protein is overexpressed in many types of tumors.
[g]The related N-*ras* gene is found in mutant form in a variety of human tumors.
[h]Receptor for thyroid hormone.
[i]27 distinct members of the Ets family of transcription factors are encoded in the human genome. Ets-1 is overexpressed in many types of tumors; others are involved in chromosomal translocations in AML and in Ewing sarcomas.
[j]The related N-*myc* gene is overexpressed in pediatric neuroblastomas and small-cell lung carcinomas.
[k]Rel is a member of a family of proteins that constitute the NF-κB transcription factor, which is constitutively activated in a wide range of human tumors.

Adapted in part from J. Butel, *Carcinogenesis* 21:405–426, 2000; and G.M. Cooper, Oncogenes, 2nd ed. Boston and London: Jones and Bartlett, 1995.

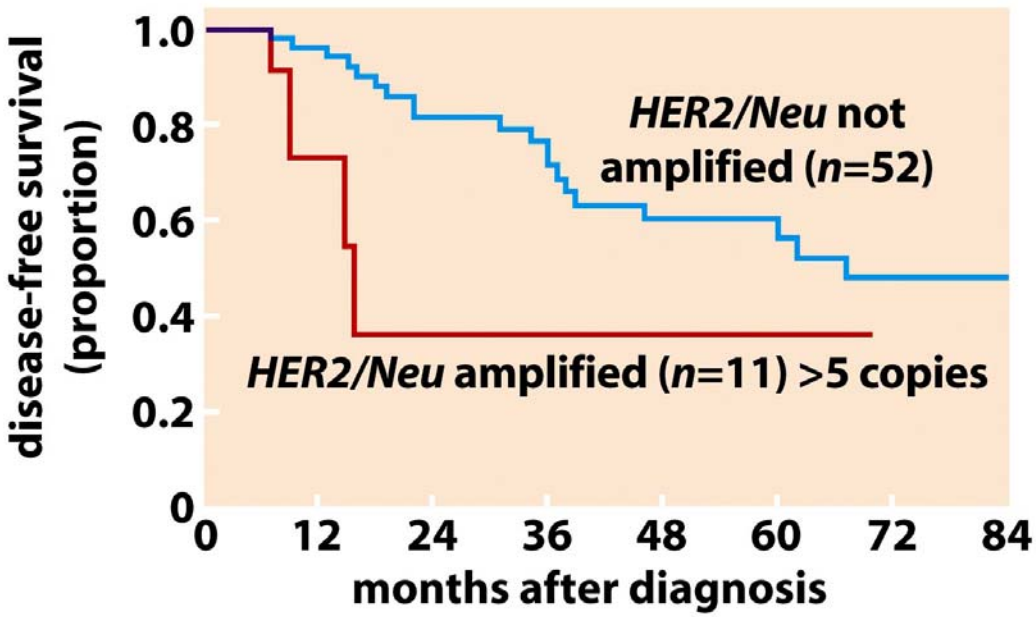
# Oncogenes（致癌基因）

1. Defined by their ability to transform cells in culture or induce cancer in animals
2. Gain-of-function mutations of proto-oncogenes (cellular counterpart of oncogenes)
3. Dominant effect: mutations in only one of the two alleles is sufficient for inducing oncogenesis
4. Originally identified from transforming retroviruses (viral oncogenes)
5. Identification of cellular oncogenes in human cancers by gene transfer assays
6. Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure
7. Actions of oncogenes: uncontrolled growth-promoting signals
   - (a) production of hyperactive products (qualitative changes)
     - * example: constitutive Ras activity in cancer cells
   - (b) over-expression of protein products (quantitative change)
     - * example: overexpression of Myc
8. Mechanisms to activate proto-oncogenes
   - (a) retroviral transduction : v-*src*
   - (b) promoter/enhancer insertion (insertional mutagenesis): *myc*
   - (c) point mutation: *ras* oncogene
   - (d) amplification: *erbB*, *myc*
   - (e) chromosomal translocation: *myc*

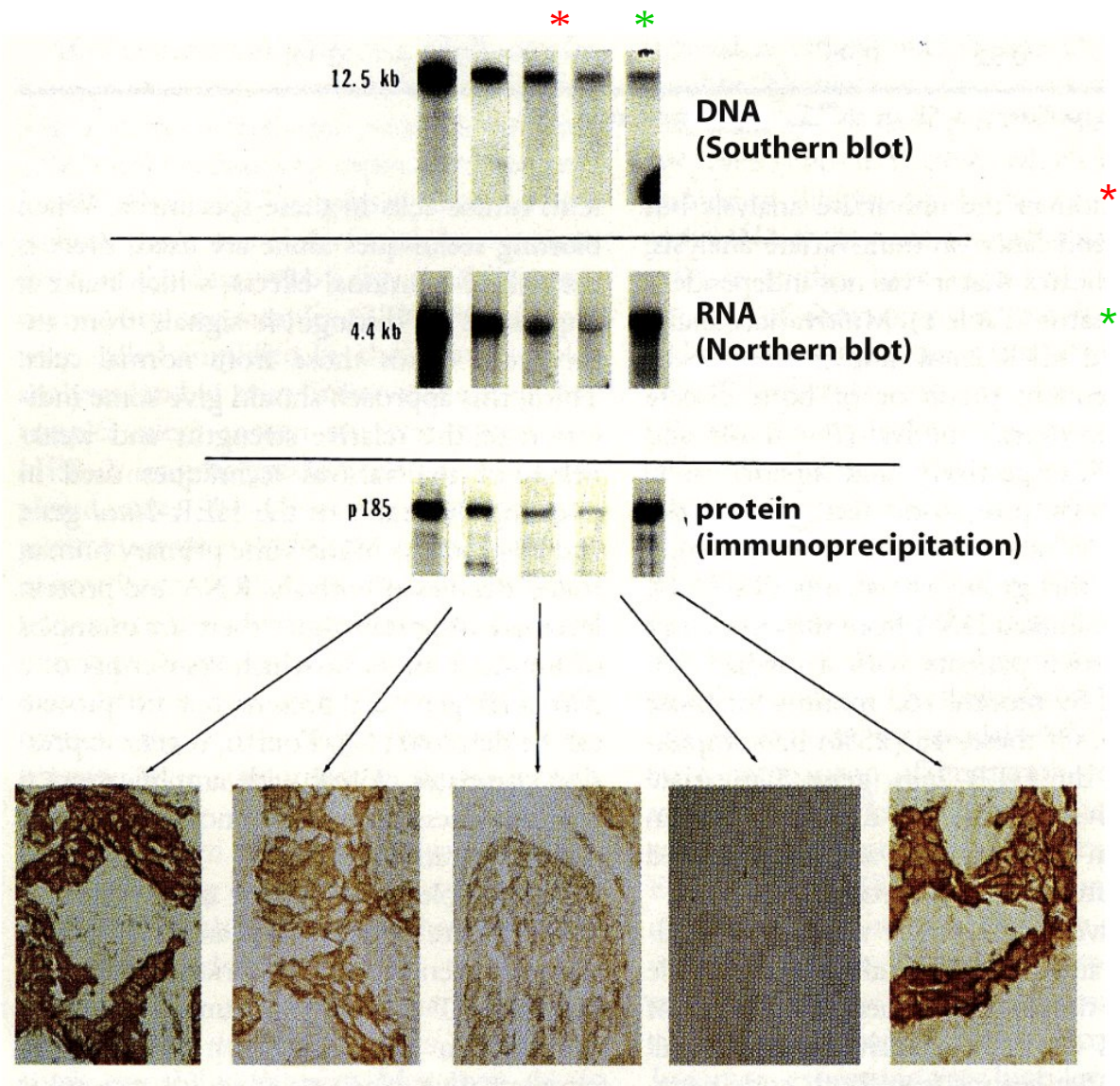
# Amplification of the erB2/*neu* oncogene in breast cancers




Southern blot



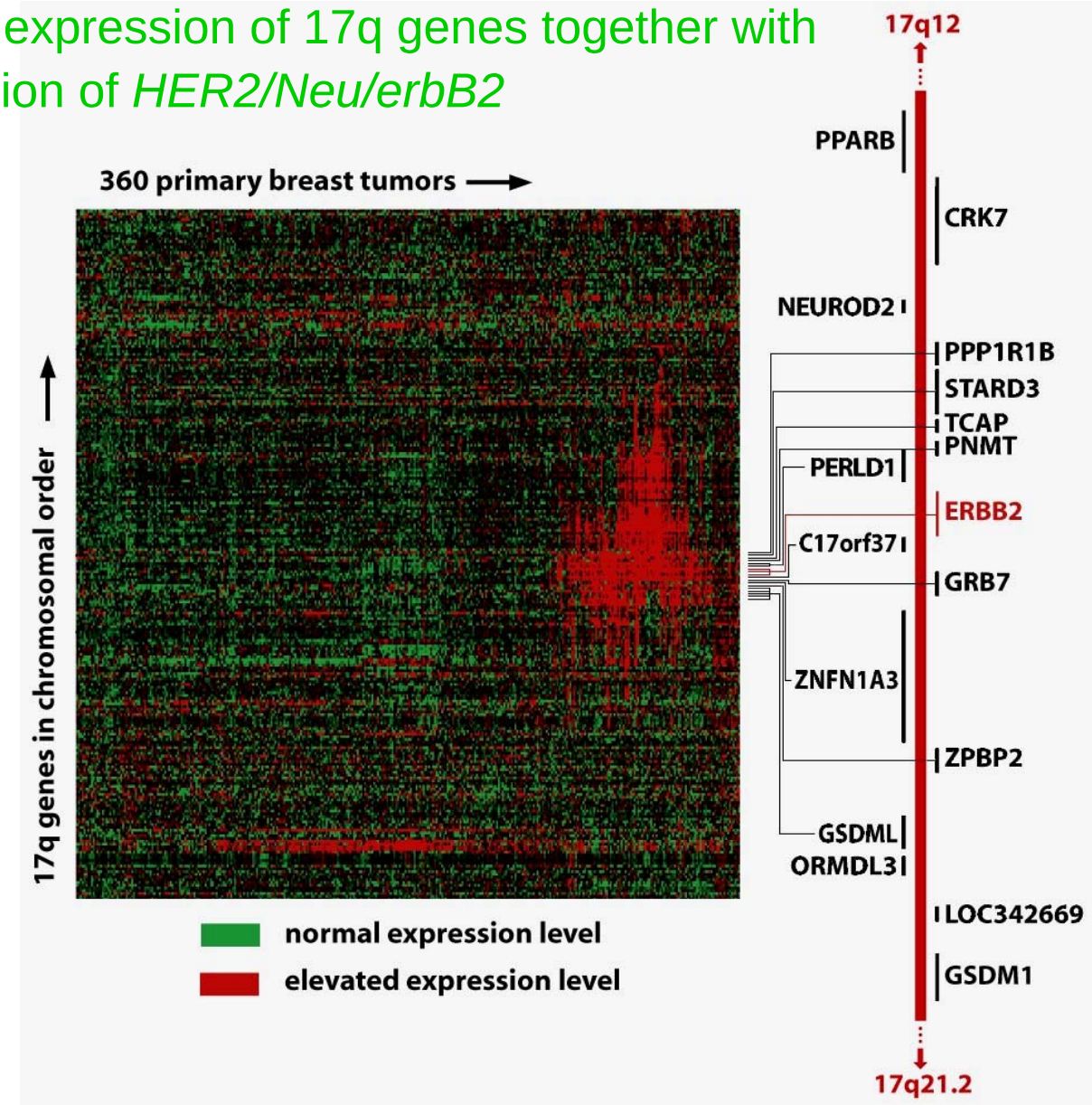
# Amplification of the erB2/*neu* oncogene in breast cancers




* : gene amplification

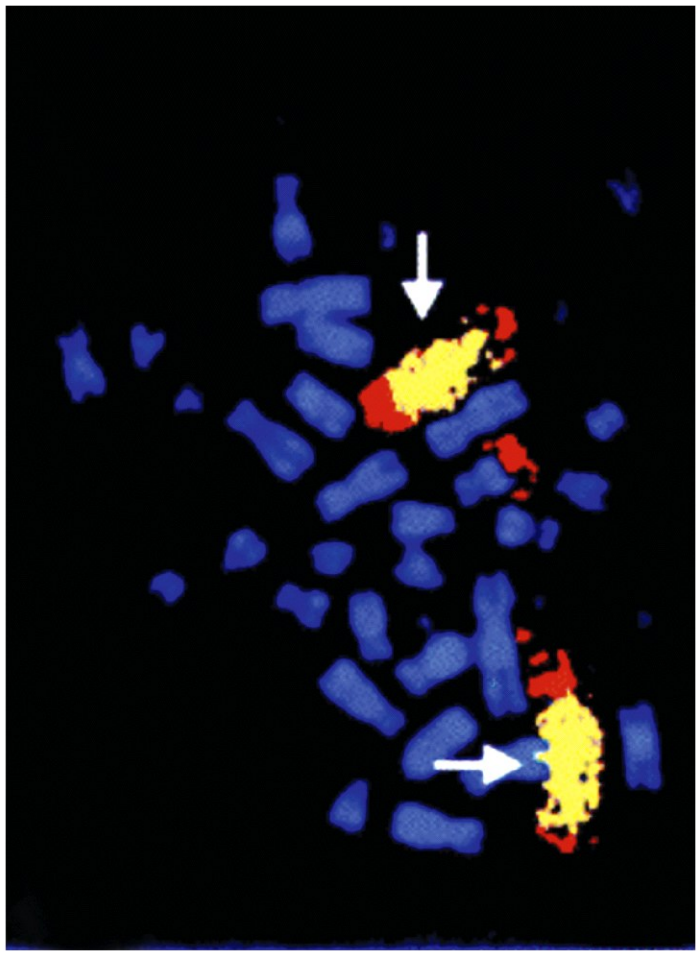
* : aberrant transcriptional activation

Elevation of expression of 17q genes together with overexpression of *HER2/Neu/erbB2*




*Genes flanking HER2 were also over-expressed in a number of these tumors

# N-myc amplification and childhood neuroblastomas



- Amplification of the N-*myc* gene occurs in about 40% of advanced pediatric neuroblastomas

HSRs:
homogeneous staining regions

The increased gene copy numbers result in corresponding increase in the level of gene products

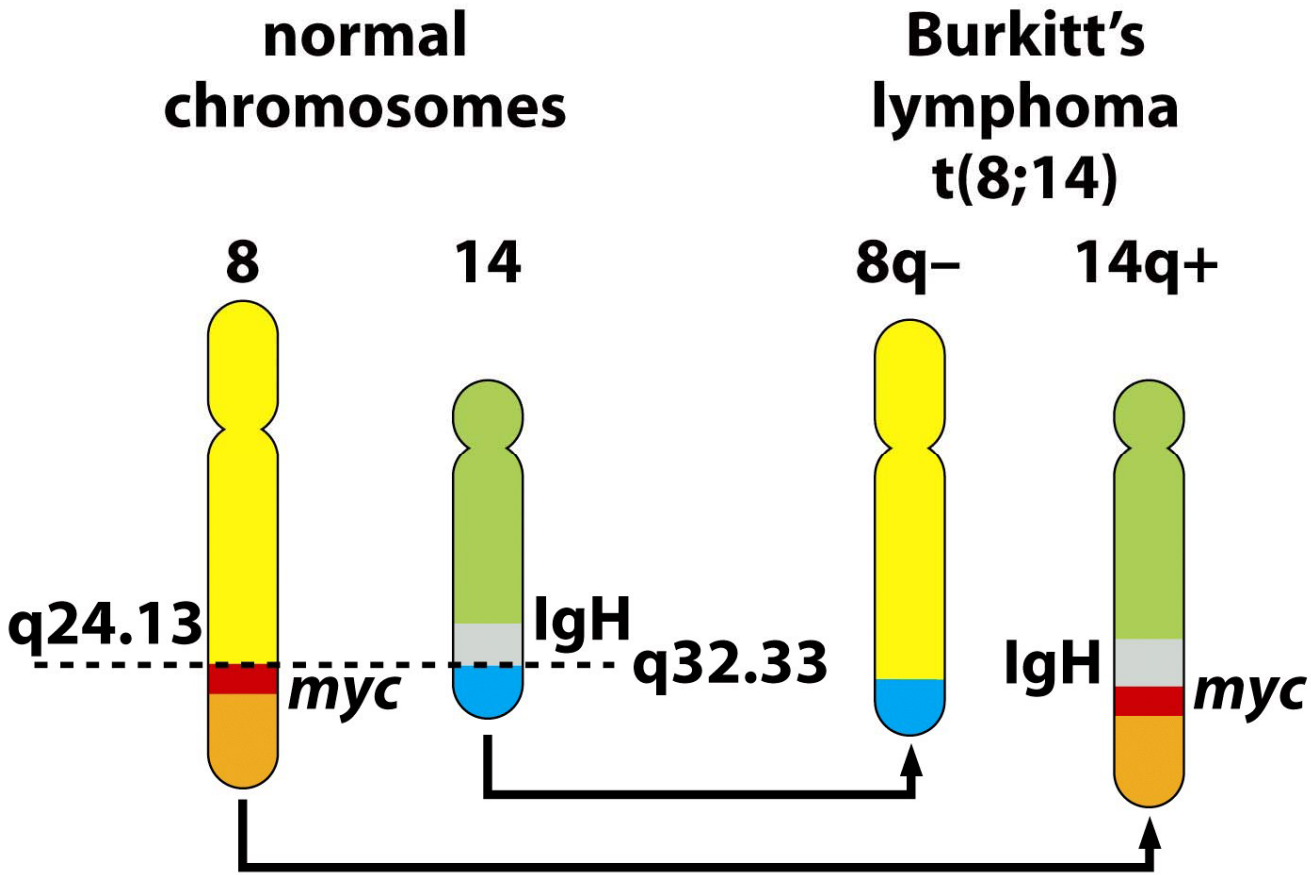
**Table 4.3** Some frequently amplified chromosomal regions and the genes they are known to carry

| Name of oncogene[a] | Human chromosomal location | Human cancers | Nature of protein |
|---|---|---|---|
| *erbB1* | 7q12–13 | glioblastomas (50%); squamous cell carcinomas (10–20%) | RTK |
| *cab1–erbB2–grb7* | 17q12 | gastric, ovarian, breast carcinomas (10–25%) | RTK, adaptor protein |
| *k-sam* | 7q26 | gastric, breast carcinomas (10–20%) | RTK |
| *FGF-R1* | 8p12 | breast carcinomas (10%) | RTK |
| *met* | 7q31 | gastric carcinomas (20%) | RTK |
| K-*ras* | 6p12 | lung, ovarian, bladder carcinomas (5–10%) | small G protein |
| N-*ras* | 1p13 | head and neck cancers (30%) | TF |
| c-*myc* | 8q24 | various leukemias, carcinomas (10–50%) | TF |
| L-*myc* | 1p32 | lung carcinomas (10%) | TF |
| N-*myc–DDX1* | 2p24–25 | neuroblastomas, lung carcinomas (30%) | TF |
| *akt-1* | 14q32–33 | gastric cancers (20%) | ser/thr kinase |
| *cyclin D1–exp1–hst1–ems1* | (11q13) | breast and squamous cell carcinomas (40–50%) | G1 cyclin |
| *cdk4–mdm2–sas–gli* | 12q13 | sarcomas (40%) | CDK, p53 antagonist |
| *cyclin E* | 19q12 | gastric cancers (15%) | cyclin |
| *akt2* | (19q13) | pancreatic, ovarian cancers (30%) | ser/thr kinase |
| *AIB1, BTAK* | (20q12–13) | breast cancers (15%) | receptor co-activator |
| *cdk6* | (19q21–22) | gliomas (5%) | CDK |
| *myb* | 6q23-24 | colon carcinoma, leukemias | TF |
| *ets-1* | 11q23 | lymphoma | TF |
| *gli* | 12q13 | glioblastomas | TF |
| *FGFR2* | 10q26 | breast carcinomas | RTK |

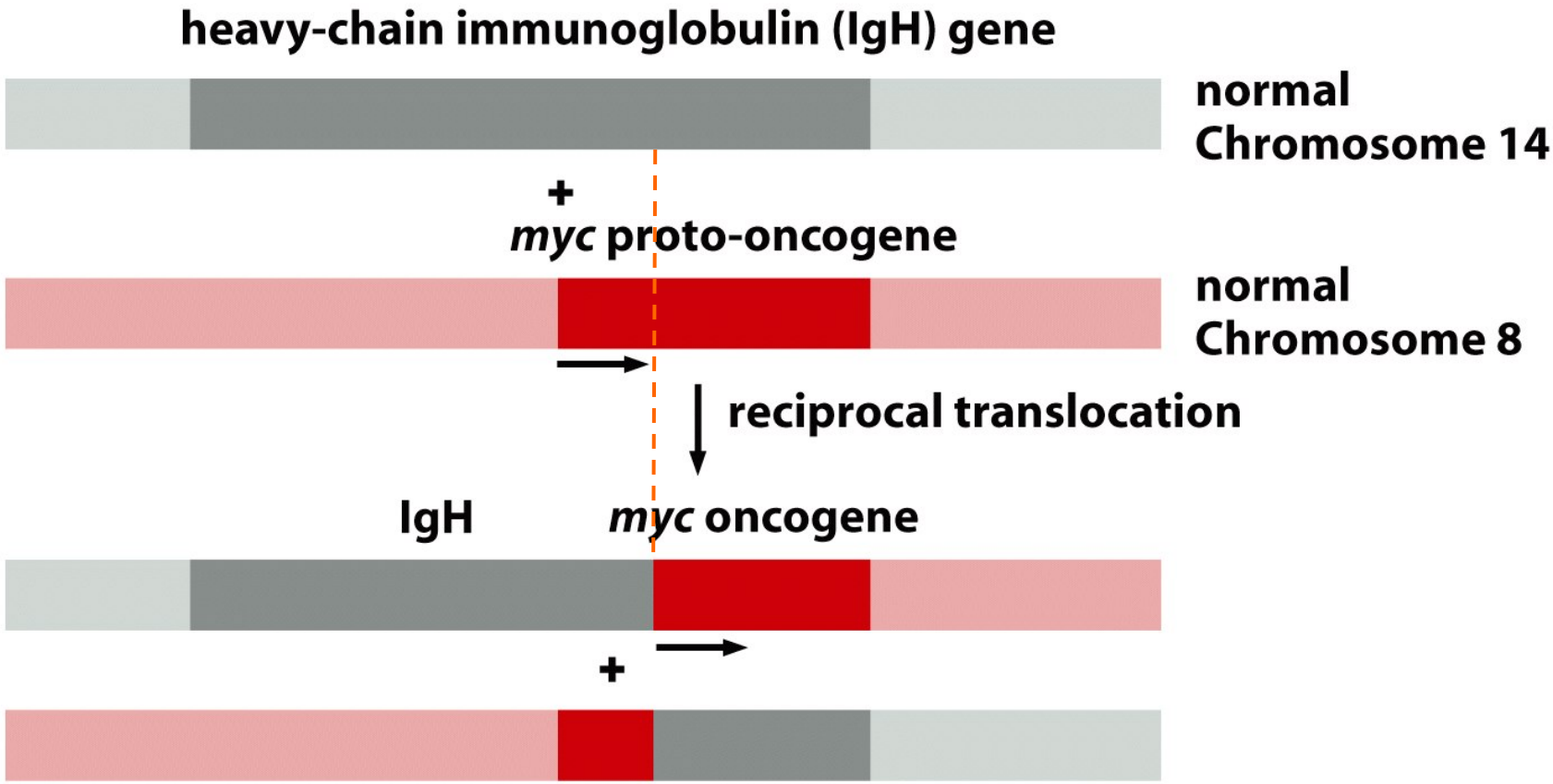
[a]The listing of several genes indicates the frequent co-amplification of a number of closely linked genes; only the products of the most frequently amplified genes are described in the right column.

Courtesy of M. Terada, Tokyo, and adapted from G.M. Cooper, Oncogenes, 2nd ed. Boston and London: Jones and Bartlett, 1995.

# Chromosomal translocations in Burkitt's lymphomas



# Chromosomal translocation in Burkitt's lymphomas



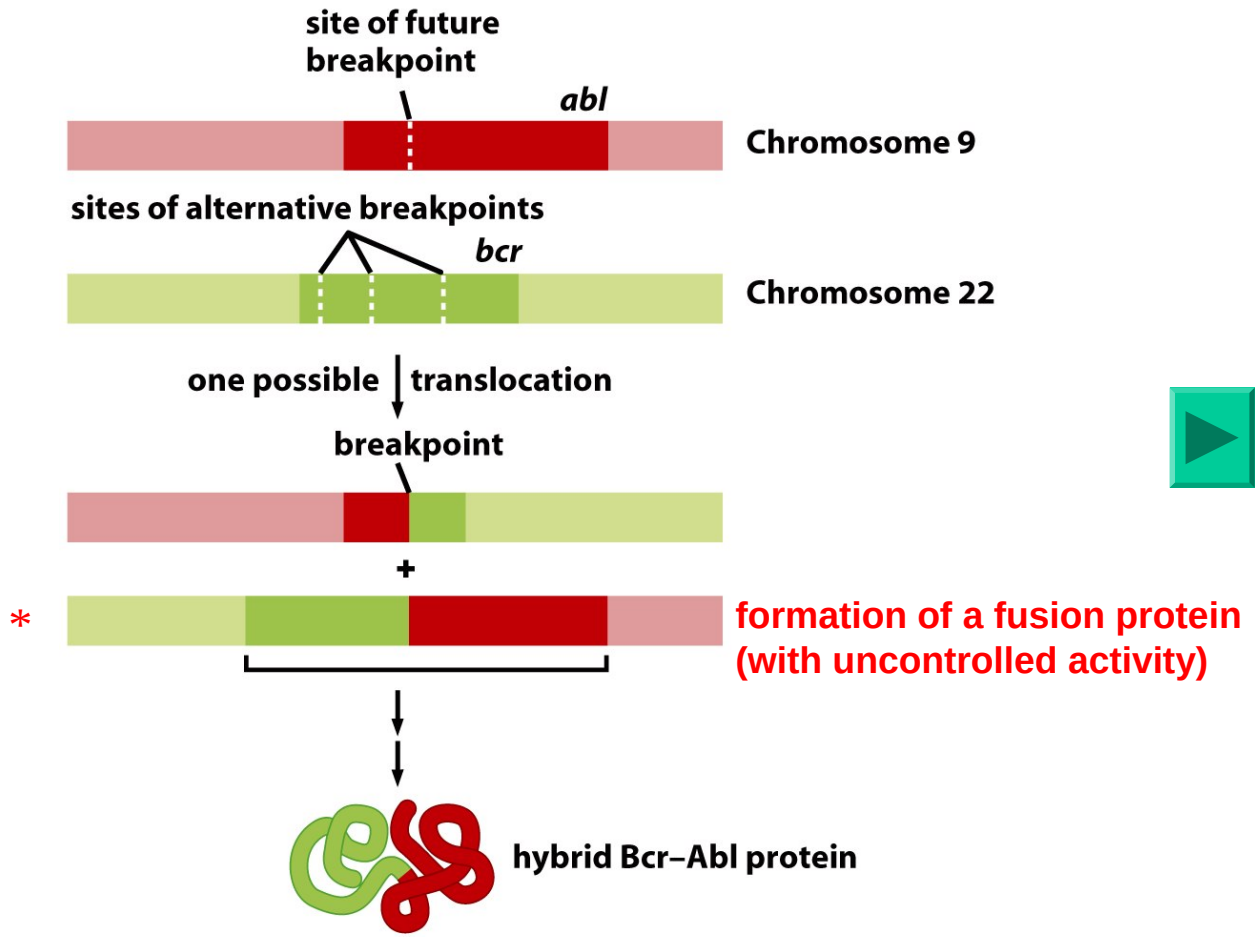

This translocation places *c-myc* gene under the control of IgH promoter/enhancer, and leads to overexpression of *myc* gene

**Table 4.4** Translocations in human tumors that deregulate proto-oncogene expression and thereby create oncogenes

| Oncogene | Neoplasm |
|---|---|
| *myc* | Burkitt's lymphoma; other B- and T-cell malignancies |
| *bcl-2* | follicular B-cell lymphomas |
| *bcl-3* | chronic B-cell lymphomas |
| *bcl-6* | diffuse B-cell lymphomas |
| *hox1* | acute T-cell leukemia |
| *lyl* | acute T-cell leukemia |
| *rhom-1* | acute T-cell leukemia |
| *rhom-2* | acute T-cell leukemia |
| *tal-1* | acute T-cell leukemia |
| *tal-2* | acute T-cell leukemia |
| *tan-1* | acute T-cell leukemia |

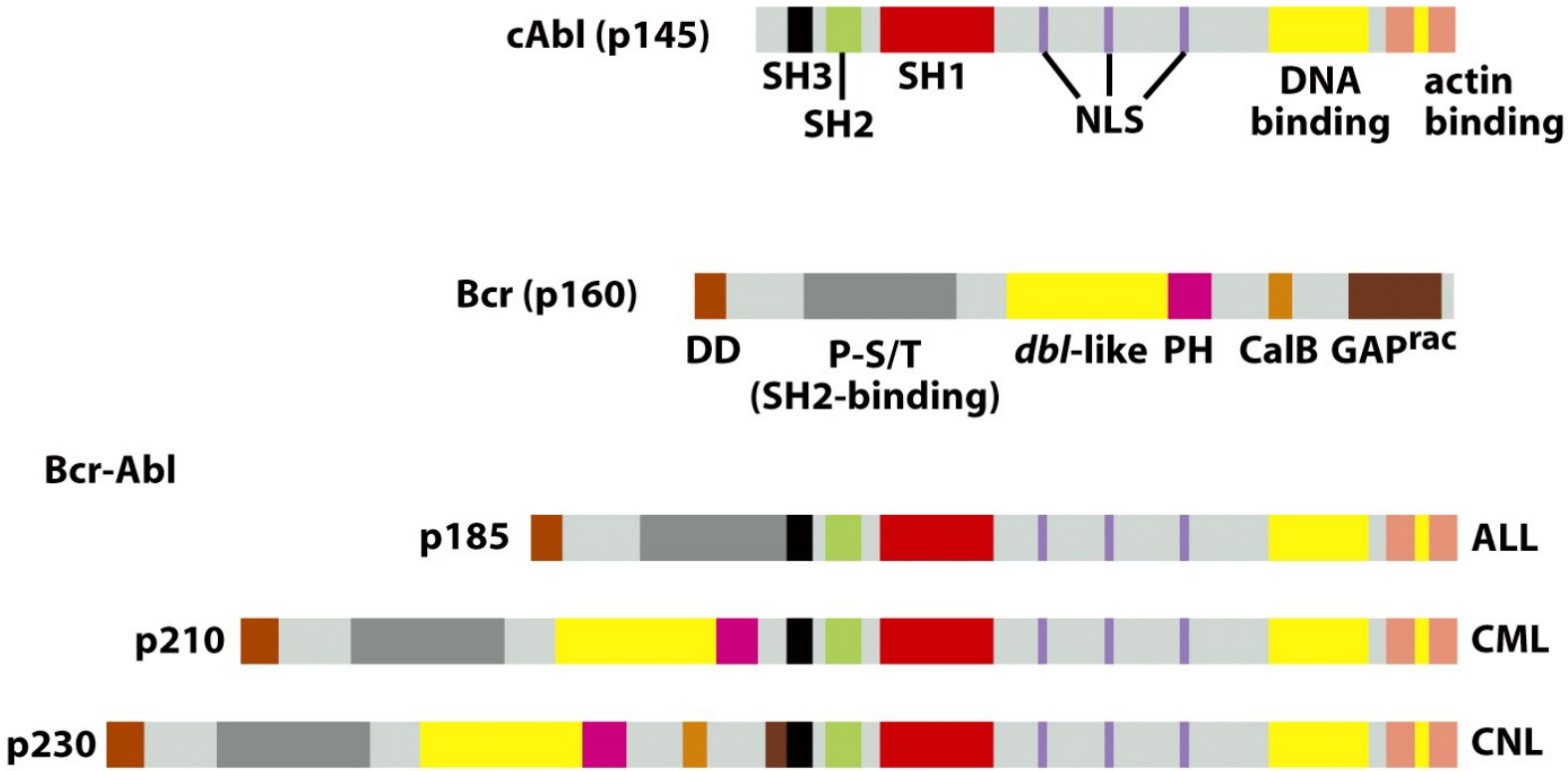
Adapted from G.M. Cooper, Oncogenes, 2nd ed. Boston and London: Jones and Bartlett, 1995.

# Formation of the *bcr-abl* oncogene by chromosomal translocation




Structural changes in proto-oncogenes can also lead to oncogenic activation

# Formation of the *bcr-abl* oncogene by chromosomal translocations were found in different types of human leukemia




Different breakpoints in *bcr* are observed in the chromosomal translocations encountered in different types of human leukemia

**Table 4.5** Translocations in human tumors that cause the formation of oncogenic fusion proteins of novel structure and function

| Oncogene | Neoplasm |
|---|---|
| *bcr/abl* | chronic myelogenous leukemia; acute lymphocytic leukemia |
| *dek/can* | acute myeloid leukemia |
| *E2A/pbx1* | acute pre-B-cell leukemia |
| *PML/RAR* | acute promyelocytic leukemia |
| *?/erg* | myeloid leukemia |
| *irel/urg* | B-cell lymphoma |
| *CBFβ/MYH11* | acute myeloid leukemia |
| *aml1/mtg8* | acute myeloid leukemia |
| *ews/fli* | Ewing sarcoma |
| *lyt-10/Cα1* | B-cell lymphoma |
| *hrx/enl* | acute leukemias |
| *hrx/af4* | acute leukemias |
| *NPM/ALK* | large-cell lymphomas |

Adapted from G.M. Cooper, Oncogenes, 2nd ed. Boston and London: Jones and Bartlett, 1995.

Almost all of these have been found in leukemias and lymphomas

## Proto-oncogenes can be activated by genetic changes affecting protein expression

c-*myc* proto-oncogene can be activated by retroviral transduction, provirus insertion, gene amplification, and chromosomal translocation. All of these mechanisms lead to overexpression of *myc* gene.

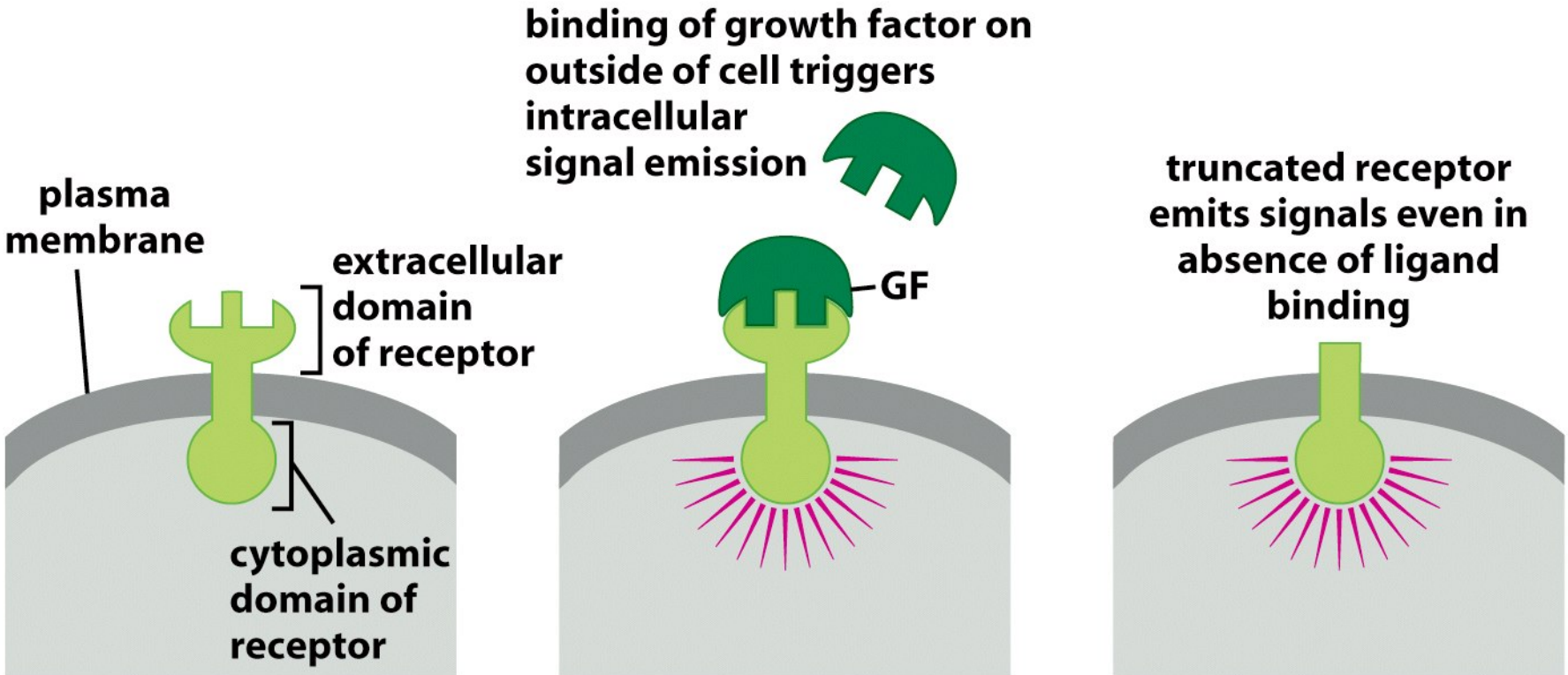
## Structural changes in proto-oncogenes can also lead to oncogenic activation

c-*ras* proto-oncogene can be activated by retroviral insertion and somatic mutations. Both mechanisms result in oncogenic *ras* with point mutations

## Both activation mechanisms (regulatory and structural alterations) might collaborate to create an active oncogene

*H-ras* carries by Harvey sarcoma virus contains a point mutation and is over-expressed

# Deregulated signaling of growth factor receptors




Structural changes in proto-oncogenes can also lead to oncogenic activation