Tumour Suppressor Genes and Oncogenes

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Aims

- Become more insightful about cancer as a disease of cell biology

- Understand the difference between an oncogene and a tumour suppressor gene (TSG)

- Provide the basis to understand mechanisms underlying carcinogenesis

Learning Outcomes

By the end of this lecture you will be able to:

- **Define gene, oncogene and tumour suppressor gene**
- **Give examples of different oncogenes and enumerate cancers in which they play key roles**
- **Understand how important it is for cells to 'communicate properly with each other'…**

Today's Menu

- Proto-oncogenes and oncogenes
- Tumour suppressor genes
- Signal transduction pathways activated by oncogenes
- Cell cycle regulation by TSGs

Introduction

- 1960s: viruses were shown to be "packets of the genetic material (DNA or RNA)
    - * RSV = RNA
    - * SV 40 = DNA
- Small number of genes (3 to 5 in tumour viruses)
- 3 to 5 genes are enough to induce cancer!

How do viruses induce cancer?

- **How do so few genes 'impose' on our ~30,000 genes?**

Option 1

Virus enters the cell – viral genes irreversibly alter cell – virus (and its genes) leaves the cell

Option 2

Virus enter cell – viral genes alter cell – viral genome integrates in cell genome and stays

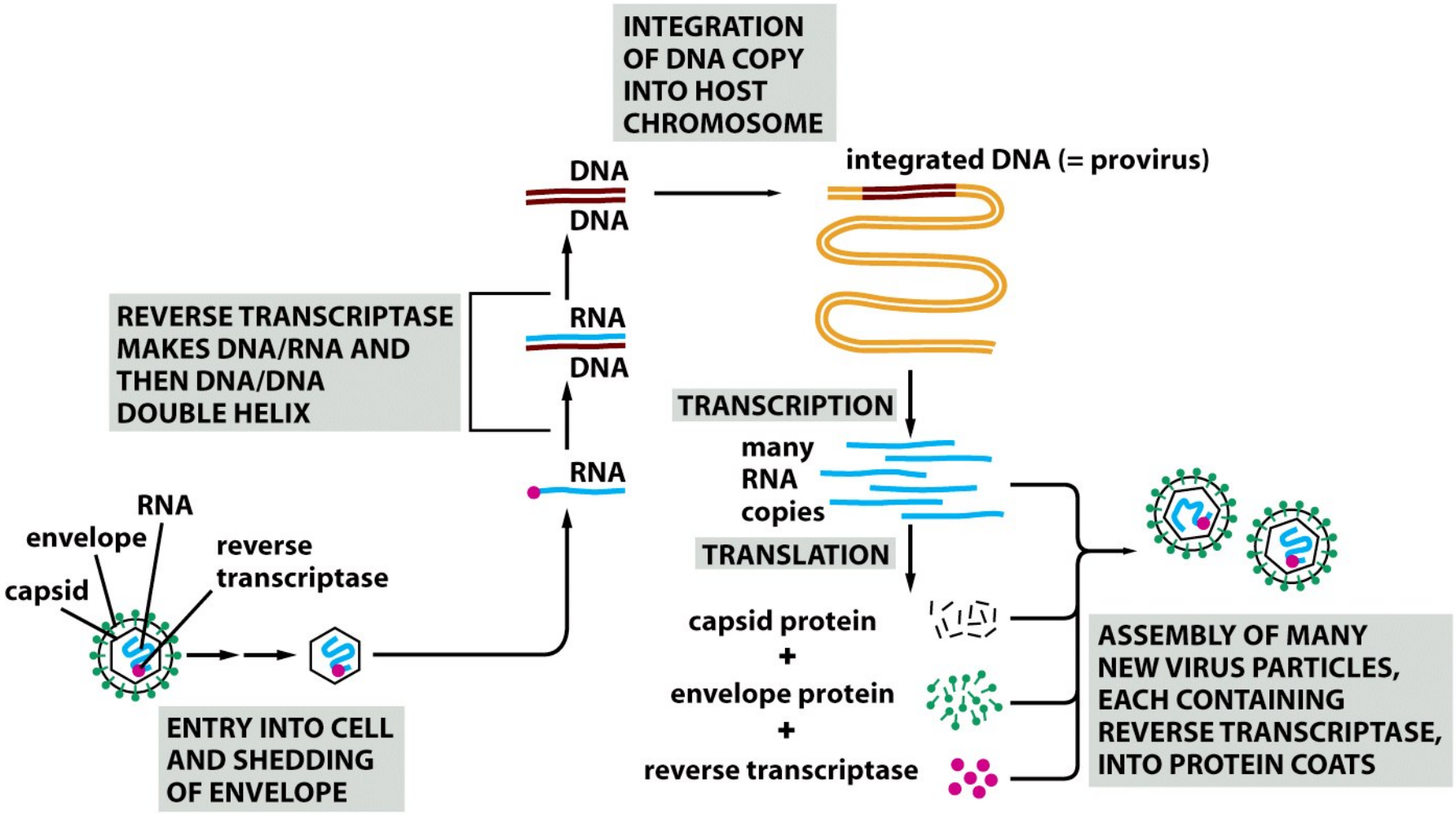

Figure 3-17 The Biology of Cancer (© Garland Science 2007)

Weinberg (2007). The Biology of Cancer, 1st ed. Garland Science, New York, USA

A bit of history…

- DNA structure was unveiled in 1953 – before that there was no way of knowing what a gene was…

- Tumour cells had "weird" chromosomes that could be seen under the light microscope – but which "bits" (genes) were "affected" (mutated)?

The early days…

- **Inspection of chromosomes (using a light microscope, not fluorescence as shown here!)**

  * each chr. 2,000-10,000 genes

Figure 1-11c The Biology of Cancer (© Garland Science 2007)

- **Use of cancer-causing viruses from lab animals**

  • isolated from most vertebrates, induce ≠ types of tumours and belong to ≠ virus families

  * RNA: retroviruses; DNA: polyomaviruses, papillomaviruses, adenoviruses, herpesviruses

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.

Weinberg (2007). The Biology of Cancer, 1st ed. Garland Science, New York, USA

Proto-oncogenes and Oncogenes

oncogene | ˈä ng kəˌjēn |

noun Medicine

a gene that dominates the behaviour of the cell in which it acts and that, in certain circumstances can transform a cell into a tumour cell.

- **What makes a gene become an oncogene?**
- **What genes serve as targets for mutations that predispose towards cancer?**
- **What are the normal functions of these targets?**

The *src* Gene of Rous Sarcoma Virus

- Initial experiments helped by a mutant *src* sensitive to temperature shifts

- RSV has 1 gene (v-*src*) whose protein (src) is required to maintain the transformed phenotype

- In 1970 it was shown that mammalian cells have a v-*src* homologue: c-*src*.

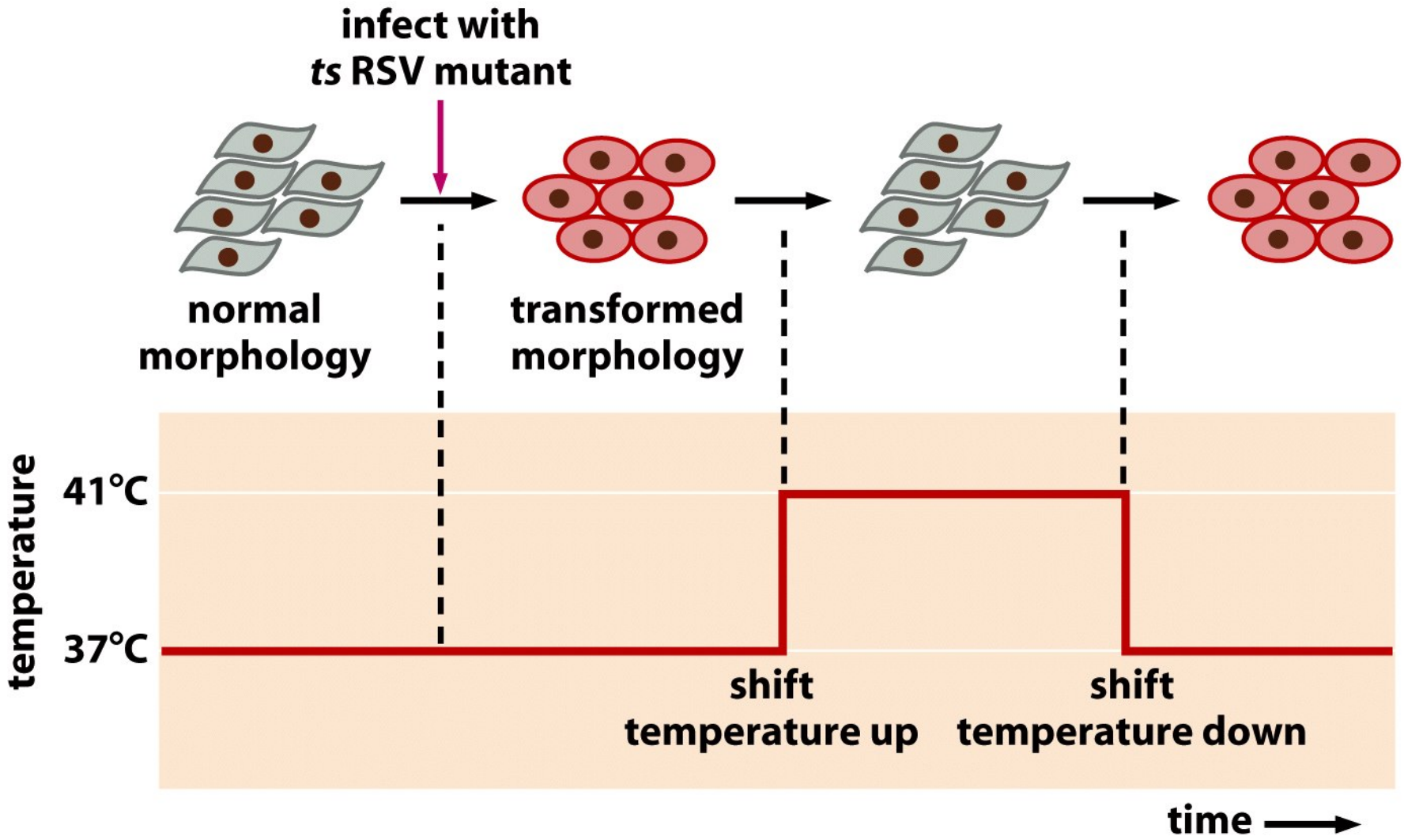

Figure 3-8 The Biology of Cancer (© Garland Science 2007)

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src

- **Highly conserved so must be beneficial to the cell…**

- **Many other retroviruses carry oncogenes and each is also derived from a ≠, normal precursor**
  - * MC29 virus – myeloid leukaemia in chickens – v-*myc*
  - * MS virus – murine sarcoma – Ha-*ras* and Ki-*ras*

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.

Table 4-1 The Biology of Cancer (© Garland Science 2007)

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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.

Table 4-6 The Biology of Cancer (© Garland Science 2007)

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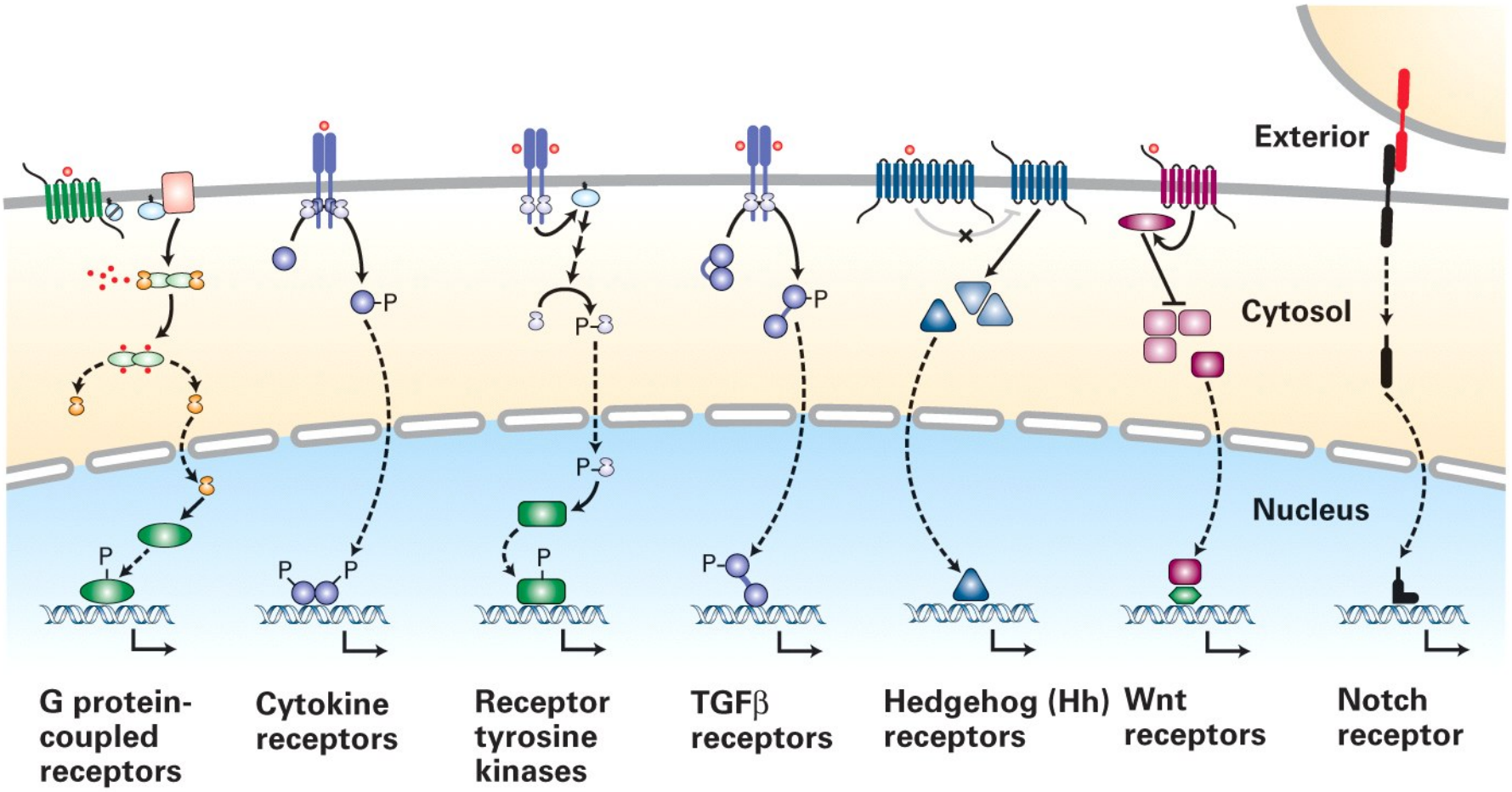
Major Types of Cell Surface Receptors



Lodish *et al.* (2004). Molecular Cell Biology, 5th ed, W.H. Freeman & Co., NY, USA.

Table 5.1 Growth factors (GFs) and tyrosine kinase receptors that are often involved in tumor pathogenesis

Name of GF	Name of receptor	Cells responding to GF
PDGF[a]	PDGF-R	endothelial, VSMCs, fibroblasts, other mesenchymal cells, glial cells
EGF[b]	EGF-R[c]	many types of epithelial cells, some mesenchymal cells
NGF	Trk	neurons
FGF[d]	FGF-R[e]	endothelial, fibroblasts, other mesenchymal cells, VSMCs, neuroectodermal cells
HGF/SF	Met	various epithelial cells
VEGF[f]	VEGF-R[g]	endothelial cells in capillaries, lymph ducts
IGF[h]	IGF-R1	wide variety of cell types
GDNF	Ret	neuroectodermal cells
SCF	Kit	hematopoietic, mesenchymal cells

[a]PDGF is represented by four distinct polypeptides, PDGF-A, -B, -C, and -D. The PDGF-Rs consist of at least two distinct species, α and β, that can homodimerize or heterodimerize and associate with these ligands in different ways.
[b]The EGF family of ligands, all of which bind to the EGF-R (ErbB1) and/or heterodimers of erbB1 and one of its related receptors (footnote c), includes—in addition to EGF—TGF-α, HB-EGF, amphiregulin, betacellulin, and epiregulin.
[c]The EGF-R family of receptors consists of four distinct proteins, ErbB1 (EGF-R), ErbB2 (HER2, Neu), ErbB3 (HER3), and ErbB4 (HER4). They often bind ligands as heterodimeric receptors, for example, ErbB1 + ErbB3, ErbB1 + ErbB2, or ErbB2 + ErbB4; ErbB3 is devoid of kinase activity and is phosphorylated by ErbB2 when the two form heterodimers. ErbB3 and ErbB4 bind neuregulins, a family of more than 15 ligands that are generated by alternative splicing. Because ErbB3 has no intrinsic kinase activity, it becomes phosphorylated in heterodimeric complexes by ErbB2, which has no ligand of its own but does have strong tyrosine kinase activity.
[d]FGFs constitute a large family of GFs. The prototypes are acidic FGF (aFGF) and basic FGF (bFGF); in addition there are other known members of this family.
[e]There are four well-characterized FGF-Rs.
[f]There are four known VEGFs. VEGF-A and -B are involved in angiogenesis, while VEGF-C and -D are involved predominantly in lymphangiogenesis.
[g]There are three known VEGF-Rs: VEGF-R1 (also known as Flt-1) and VEGF-R2 (also known as Flk-1/KDR), involved in angiogenesis; and VEGF-R3, involved in lymphangiogenesis.
[h]The two known IGFs, IGF-1 and IGF-2, both related in structure to insulin, stimulate cell growth (i.e., increase in size) and survival; they also appear to be mitogenic.

Abbreviation: VSMC, vascular smooth muscle cell.

Adapted in part from B. Alberts et al., Molecular Biology of the Cell, 4th ed. New York: Garland Science, 2002.

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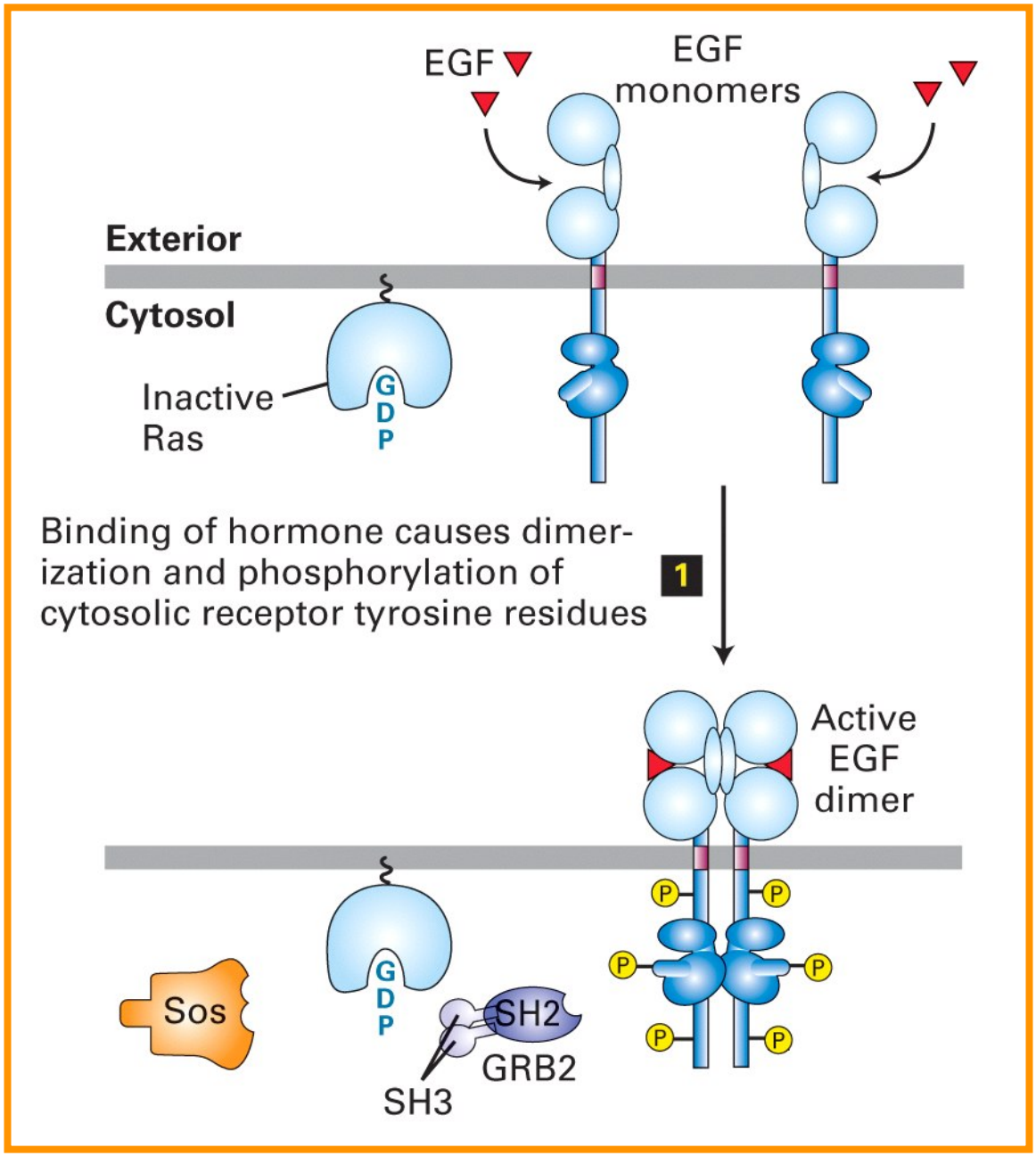
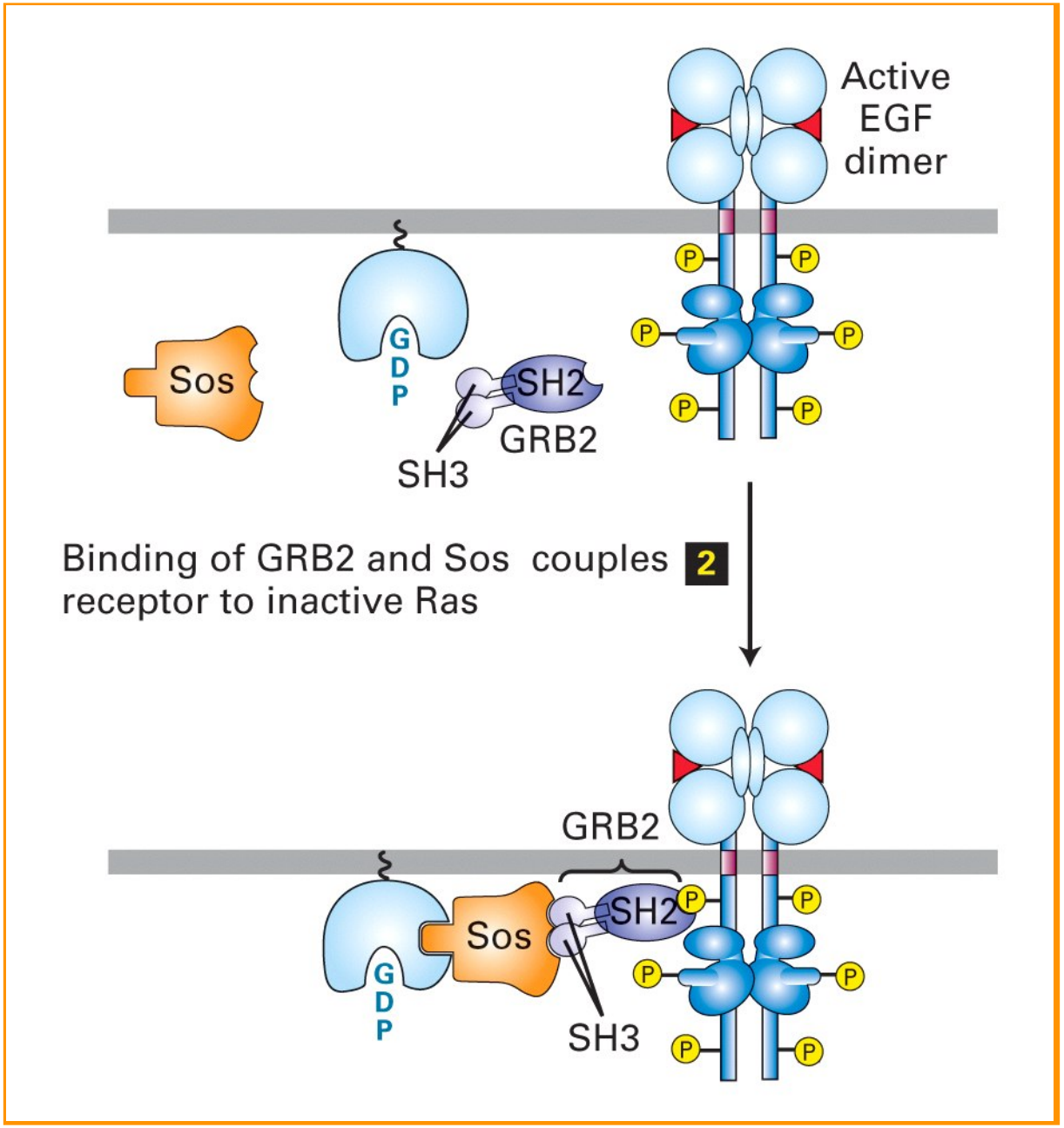


Lodish *et al.* (2004). Molecular Cell Biology, 5th ed, W.H. Freeman & Co., NY, USA.



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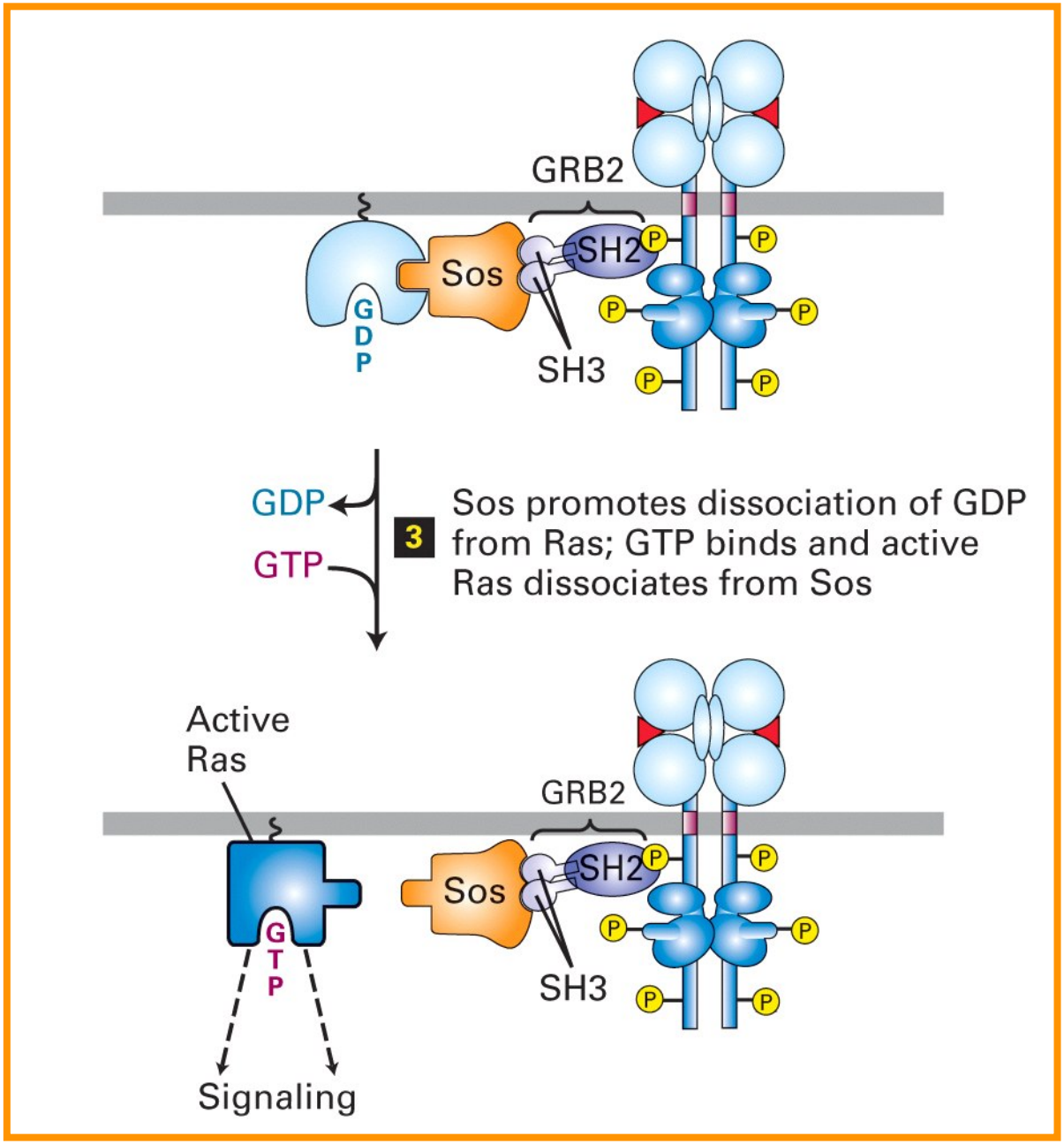

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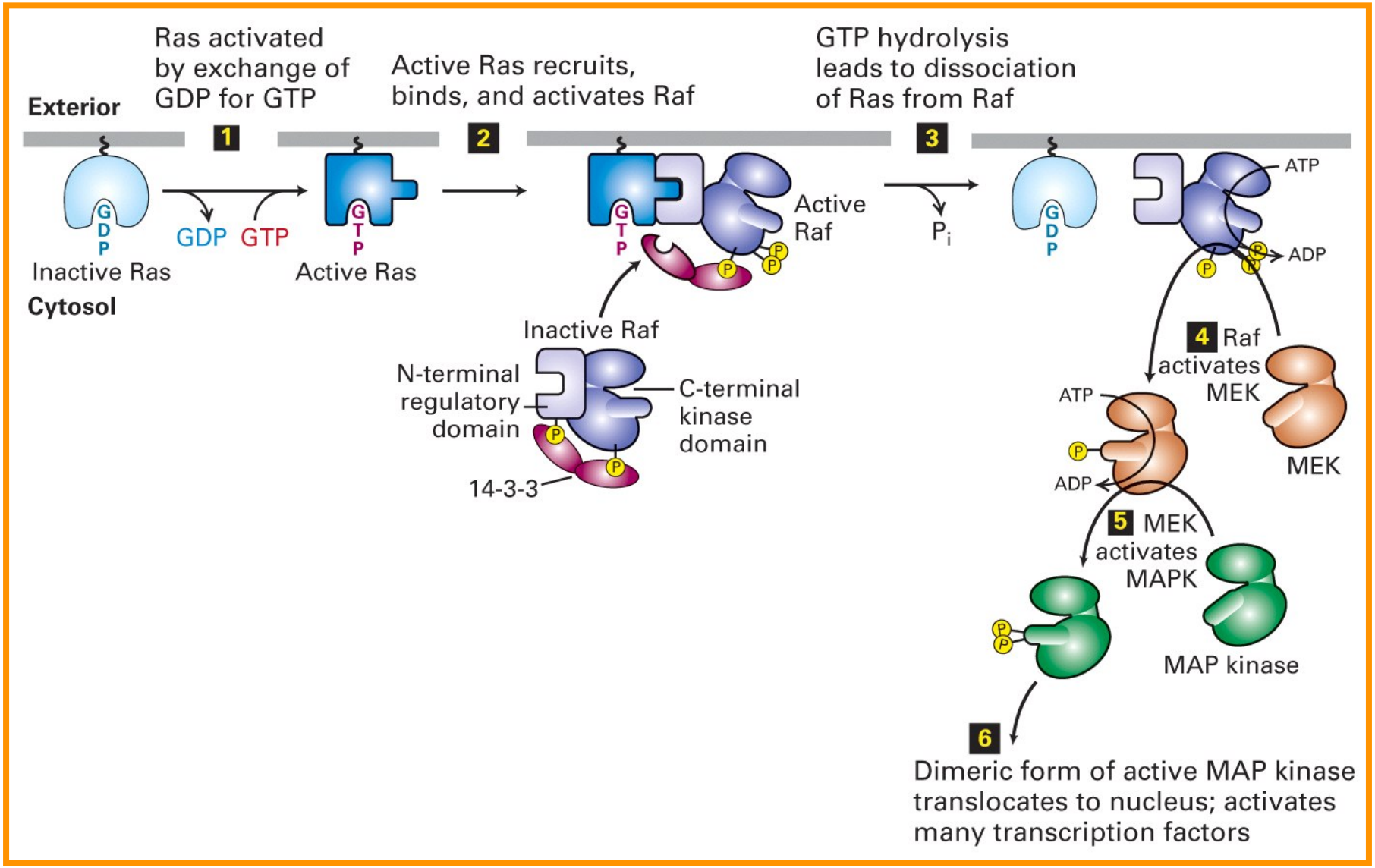

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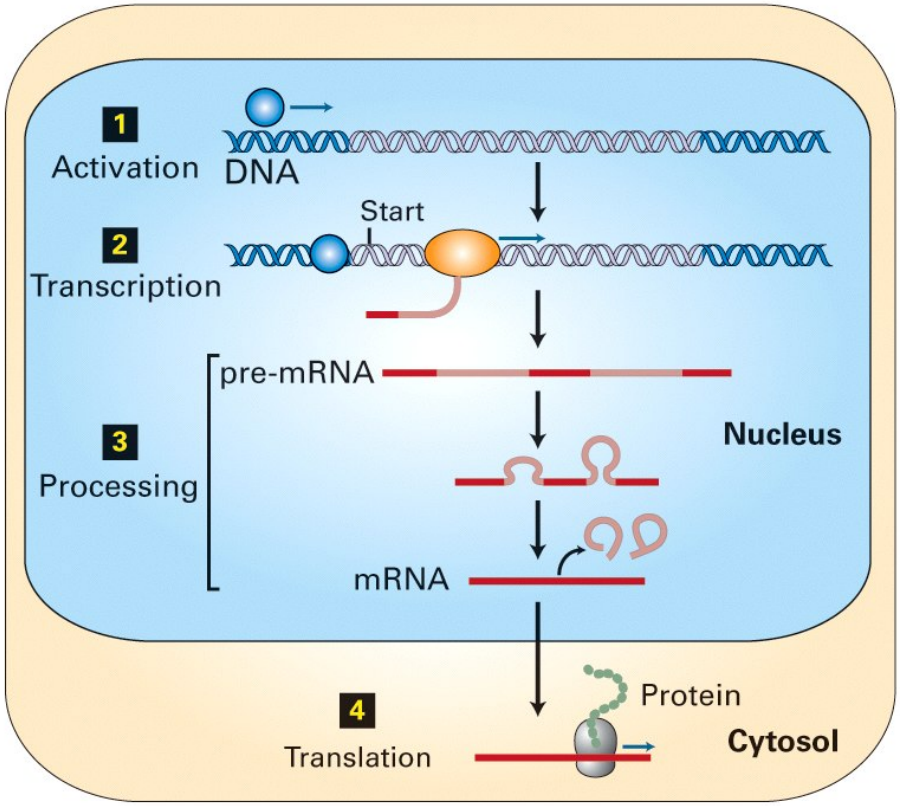
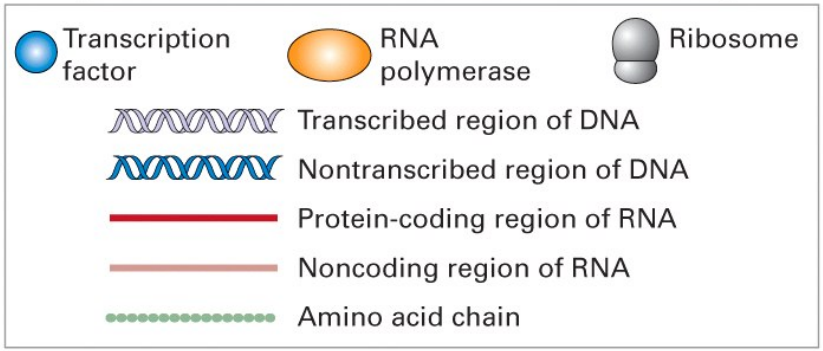
Gene Transcription





- Each cell has instructions to make all proteins
- Only a small subset is thought to be produced
- **Some genes are read; some are silenced**
- Different sets of genes are expressed in different cells
- Quantities expressed can vary by many fold

Incredibly complex!!!

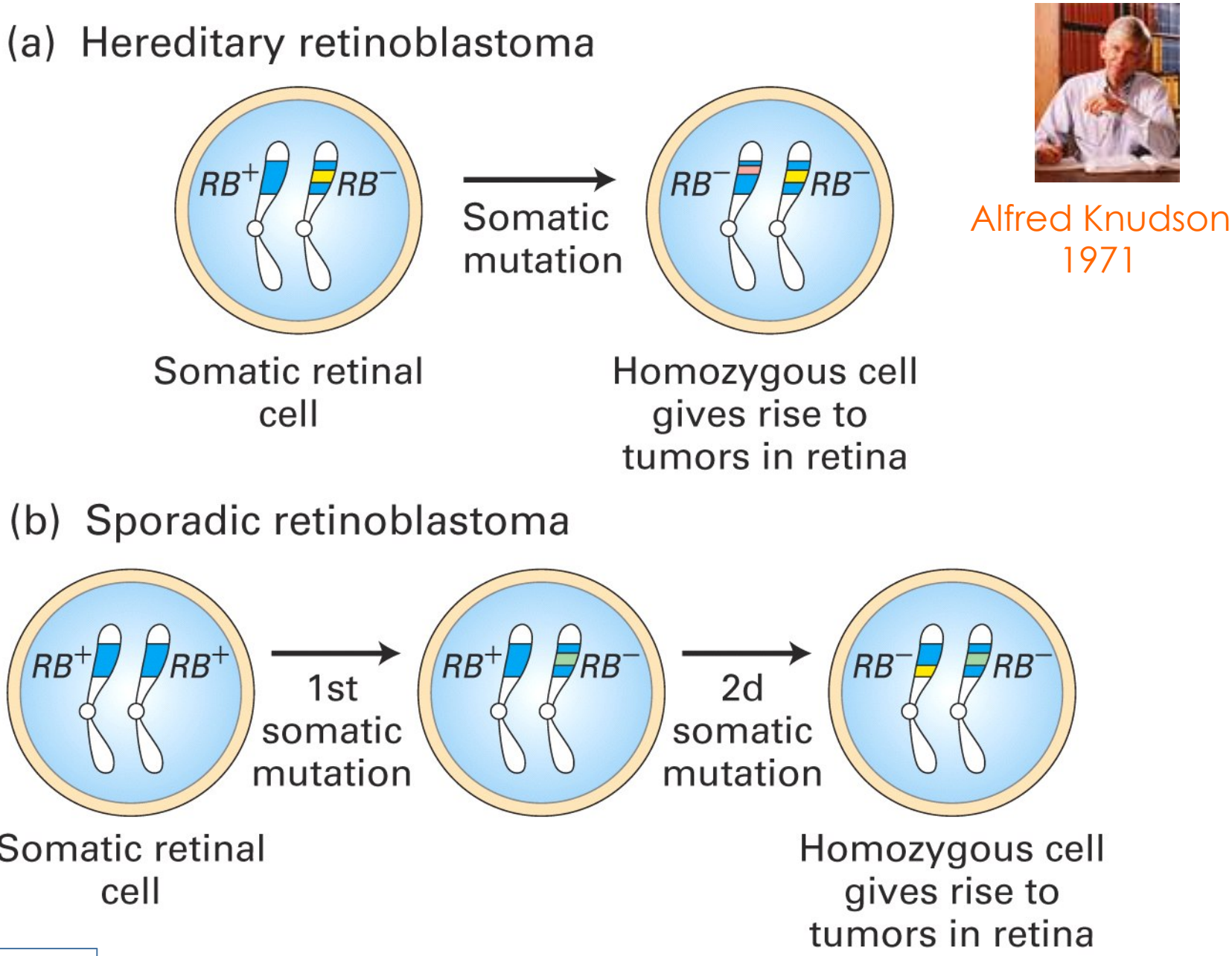
Lodish *et al.* (2004). Molecular Cell Biology, 5th ed, W.H. Freeman & Co., NY, USA.

Tumour Suppressor Genes

- Cell growth must be tightly regulated
  - * limitation of mitogenic signals
  - * Inhibitors of proliferation

- The inhibitors and controllers of proliferation are the tumour suppressor genes (sometimes called anti-oncogenes)

- When inactivated can lead to cancer

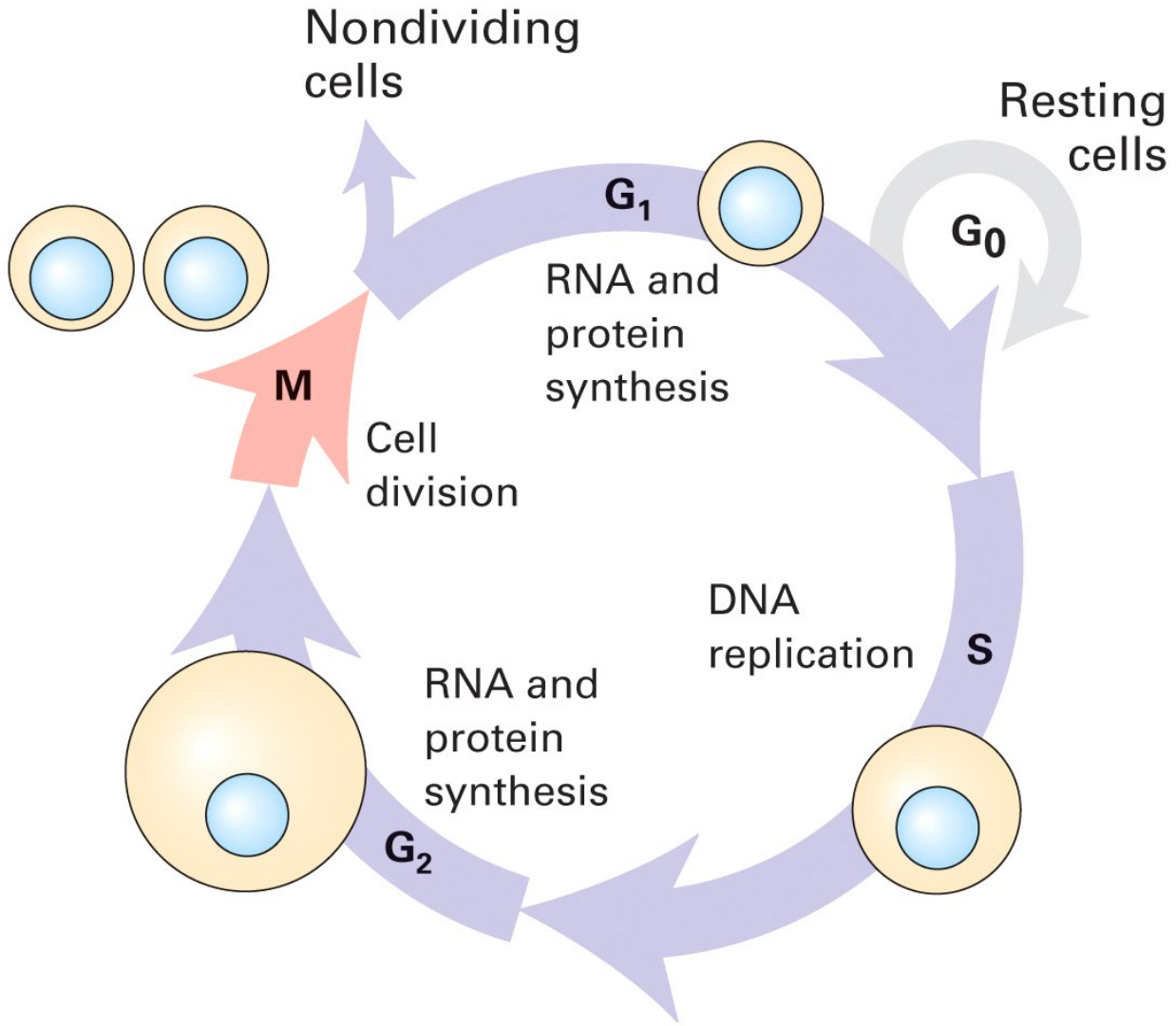


Alfred Knudson
1971

Chr. 13, q14

Lodish *et al.* (2004). Molecular Cell Biology, 5th ed, W.H. Freeman & Co., NY, USA.

TSGs Work During Cell Cycle



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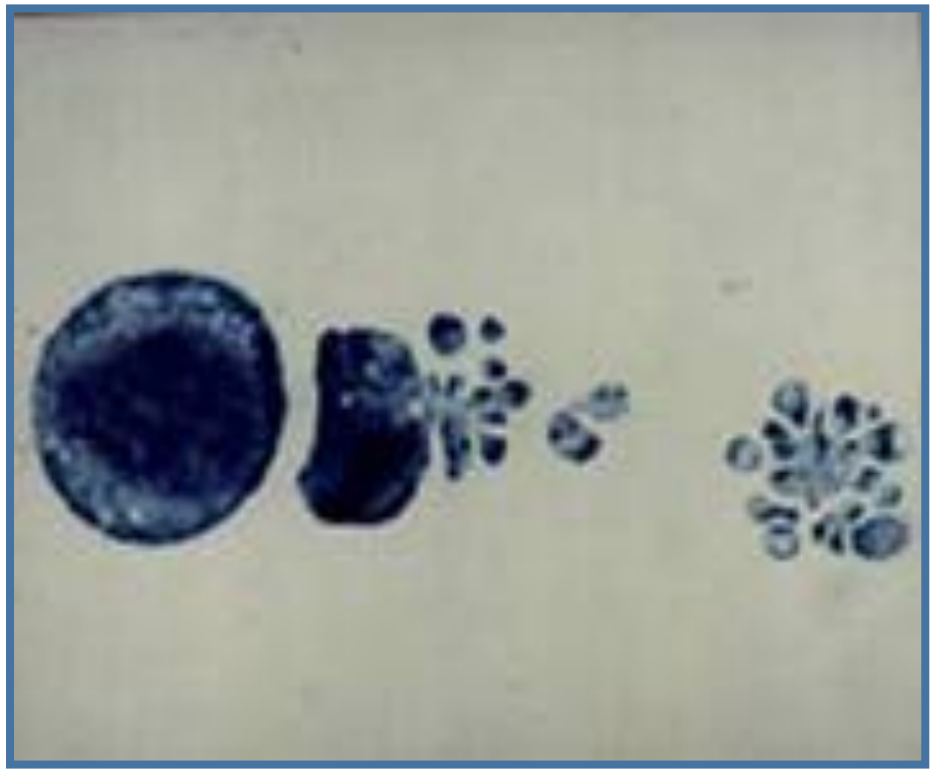
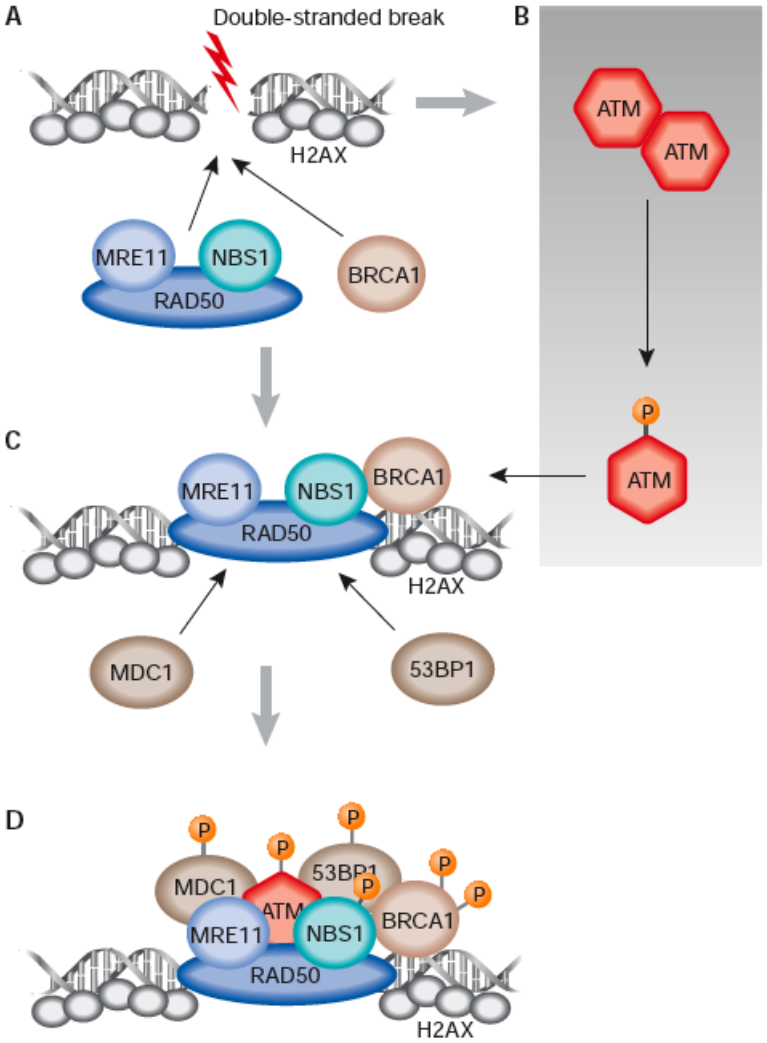
TSGs Induce Apoptosis



Prof. Thomas G Cotter, UCC, Cork, Ireland

TSGs Are Involved in DNA Repair



Ataxia Telangiectasia
(telos+angeion+ektasis)

Degenerative disease

- Cerebellar degeneration
- Radiosensitivity
- Predisposition to cancer
- Immunodeficiency

EMBO reports (2004) 5, 772–776. doi:10.1038/sj.embor.7400210

Table 7.1 Human tumor suppressor genes that have been cloned

Name of gene	Chromosomal location	Familial cancer syndrome	Sporadic cancer	Function of protein
RUNX3	1p36	—	gastric carcinoma	TF co-factor
HRPT2	1q25–32	parathyroid tumors, jaw fibromas	parathyroid tumors	chromatin protein
FH	1q42.3	familial leiomyomatosis[a]	—	fumarate hydratase
FHIT	3p14.2	—	many types	diadenosine triphosphate hydrolase
RASSF1A	3p21.3	—	many types	multiple functions
TGFBR2	3p2.2	HNPCC	colon, gastric, pancreatic carcinomas	TGF-β receptor
VHL	3p25	von Hippel–Lindau syndrome	renal cell carcinoma	ubiquitylation of HIF
hCDC4	4q32	—	endometrial carcinoma	ubiquitin ligase
APC	5p21	familial adenomatous polyposis coli	colorectal, pancreatic, and stomach carcinomas; prostate carcinoma	β-catenin degradation
NKX3.1	8p21	—	prostate carcinoma	homeobox TF
$p16^{INK4A}$ [b]	9p21	familial melanoma	many types	CDK inhibitor
$p14^{ARF}$ [c]	9p21	—	all types	p53 stabilizer
PTC	9q22.3	nevoid basal cell carcinoma syndrome	medulloblastomas	receptor for hedgehog GF
TSC1	9q34	tuberous sclerosis	—	inhibitor of mTOR[f]
BMPR1	10q21–22	juvenile polyposis	—	BMP receptor
PTEN[d]	10q23.3	Cowden's disease, breast and gastrointestinal carcinomas	glioblastoma; prostate, breast, and thyroid carcinomas	PIP_3 phosphatase
WT1	11p13	Wilms tumor	Wilms tumor	TF
MEN1	11p13	multiple endocrine neoplasia	—	histone modification, transcriptional repressor

[a]Familial leiomyomatosis includes multiple fibroids, cutaneous leiomyomas, and renal cell carcinoma. The gene product is a component of the tricarboxylic cycle.
[b]Also known as *MTS1*, *CDKN2*, and *p16*.
[c]The human homolog of the murine $p19^{ARF}$ gene.
[d]Also called *MMAC* or *TEP1*.
[e]*SDHS* encodes the succinate–ubiquinone oxidoreductase subunit D, a component of the mitochondrial respiratory chain complex II.
[f]mTOR is a serine/threonine kinase that controls, among other processes, the rate of translation and activation of Akt/PKB. TSC1 (hamartin) and TSC2 (tuberin) control both cell size and cell proliferation.
[g]The *CBP* gene is involved in chromosomal translocations associated with AML. These translocations may reveal a role of a segment of CBP as an oncogene rather than a tumor suppressor gene.
[h]Also termed Carney complex.
[i]Encodes the Smad4 TF associated with TGF-β signaling; also known as *MADH4* and *SMAD4*.
[j]The human SNF5 protein is a component of the large Swi/Snf complex that is responsible for remodeling chromatin in a way that leads to transcriptional repression through the actions of histone deactylases. The rhabdoid predisposition syndrome involves susceptibility to atypical teratoid/rhabdoid tumors, choroid plexus carcinomas, medulloblastomas, and extra-renal rhabdoid tumors.

Adapted in part from E.R. Fearon, *Science* 278:1043–1050, 1997; and in part from D.J. Marsh and R.T. Zori, *Cancer Lett.*181:125–164, 2002.

Table 7-1 part 1 of 2 The Biology of Cancer (© Garland Science 2007)

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Table 7.1 Human tumor suppressor genes that have been cloned

Name of gene	Chromosomal location	Familial cancer syndrome	Sporadic cancer	Function of protein
BWS/CDKN1C	11p15.5	Beckwith–Wiedemann syndrome	—	$p57^{Kip2}$ CDK inhibitor
SDHD	11q23	familial paraganglioma	pheochromocytoma	mitochondrial protein[e]
RB	13q14	retinoblastoma, osteosarcoma	retinoblastoma; sarcomas; bladder, breast, esophageal, and lung carcinomas	transcriptional repression; control of E2Fs
TSC2	16p13	tuberous sclerosis	—	inhibitor of mTOR[f]
CBP	16p13.3	Rubinstein–Taybi	AML[g]	TF co-activator
CYLD	16q12–13	cylindromatosis	—	deubiquitinating enzyme
CDH1	16q22.1	familial gastric carcinoma	invasive cancers	cell–cell adhesion
BHD	17p11.2	Birt–Hogg–Dube syndrome	kidney carcinomas, hamartomas	unknown
TP53	17p13.1	Li–Fraumeni syndrome	many types	TF
NF1	17q11.2	neurofibromatosis type 1	colon carcinoma, astrocytoma	Ras-GAP
BECN1	17q21.3	—	breast, ovarian, prostate	autophagy
PRKAR1A	17.q22–24	multiple endocrine neoplasia[h]	multiple endocrine tumors	subunit of PKA
DPC4[i]	18q21.1	juvenile polyposis	pancreatic and colon carcinomas	TGF-β TF
LKB1/STK11	19p13.3	Peutz–Jegher syndrome	hamartomatous colonic polyps	serine/threonine kinase
RUNX1	21q22.12	familial platelet disorder	AML	TF
SNF5[j]	22q11.2	rhabdoid predisposition syndrome	malignant rhabdoid tumors	chromosome remodeling
NF2	22q12.2	neurofibroma-position syndrome	schwannoma, meningioma; ependymoma	cytoskeleton–membrane linkage

[a]Familial leiomyomatosis includes multiple fibroids, cutaneous leiomyomas, and renal cell carcinoma. The gene product is a component of the tricarboxylic cycle.
[b]Also known as *MTS1, CDKN2,* and *p16.*
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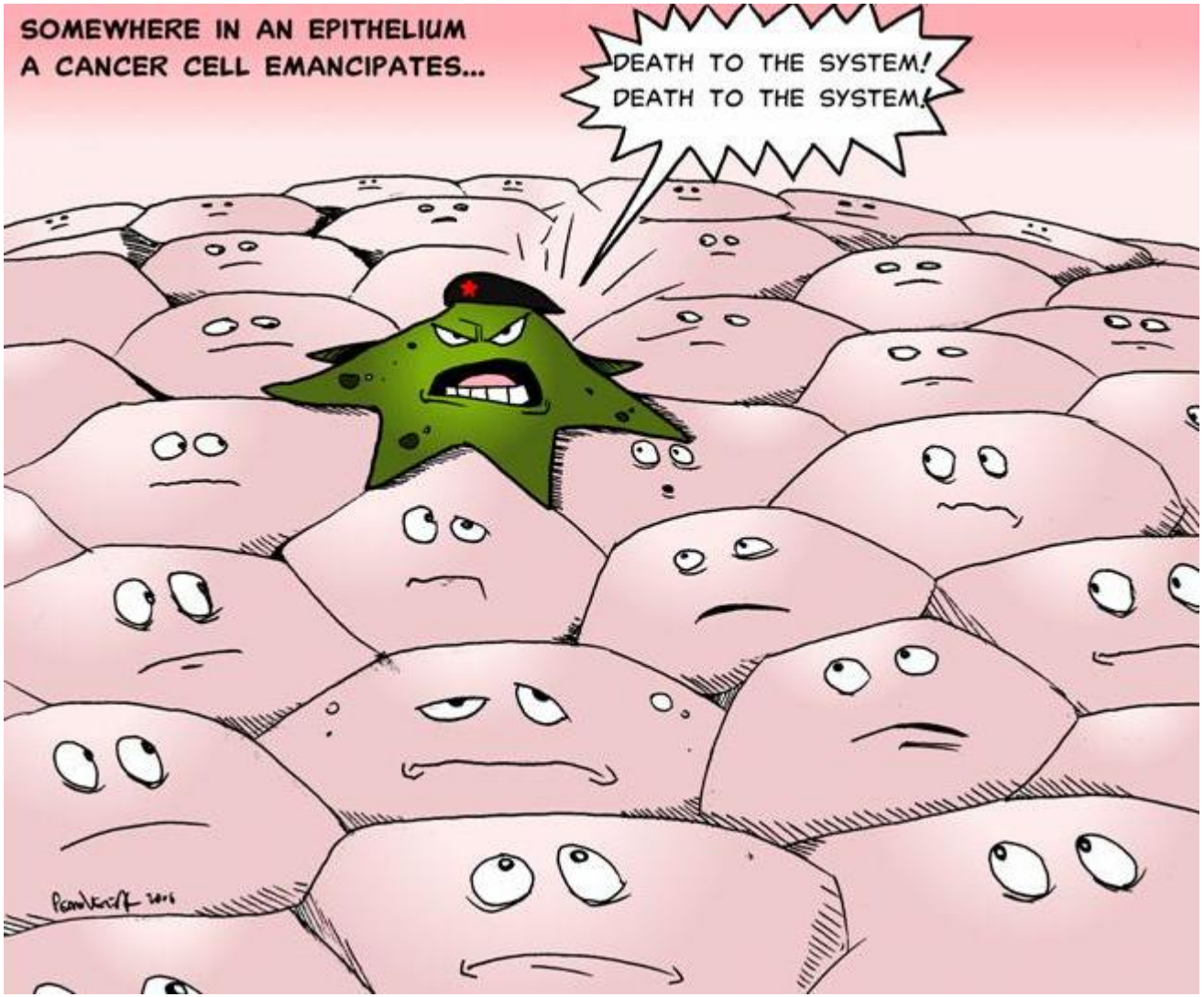
Conclusions

- Proto-oncogenes can lead a cell astray
- Oncogenes dominate the WT gene
- TSGs protect cells from uncontrolled growth
- Only 1 copy of the TSG is required – 2 exist as a safeguard – thus need 2 hits on both TSGs for a cell to become cancerous


SOMEWHERE IN AN EPITHELIUM
A CANCER CELL EMANCIPATES...
DEATH TO THE SYSTEM!
DEATH TO THE SYSTEM!

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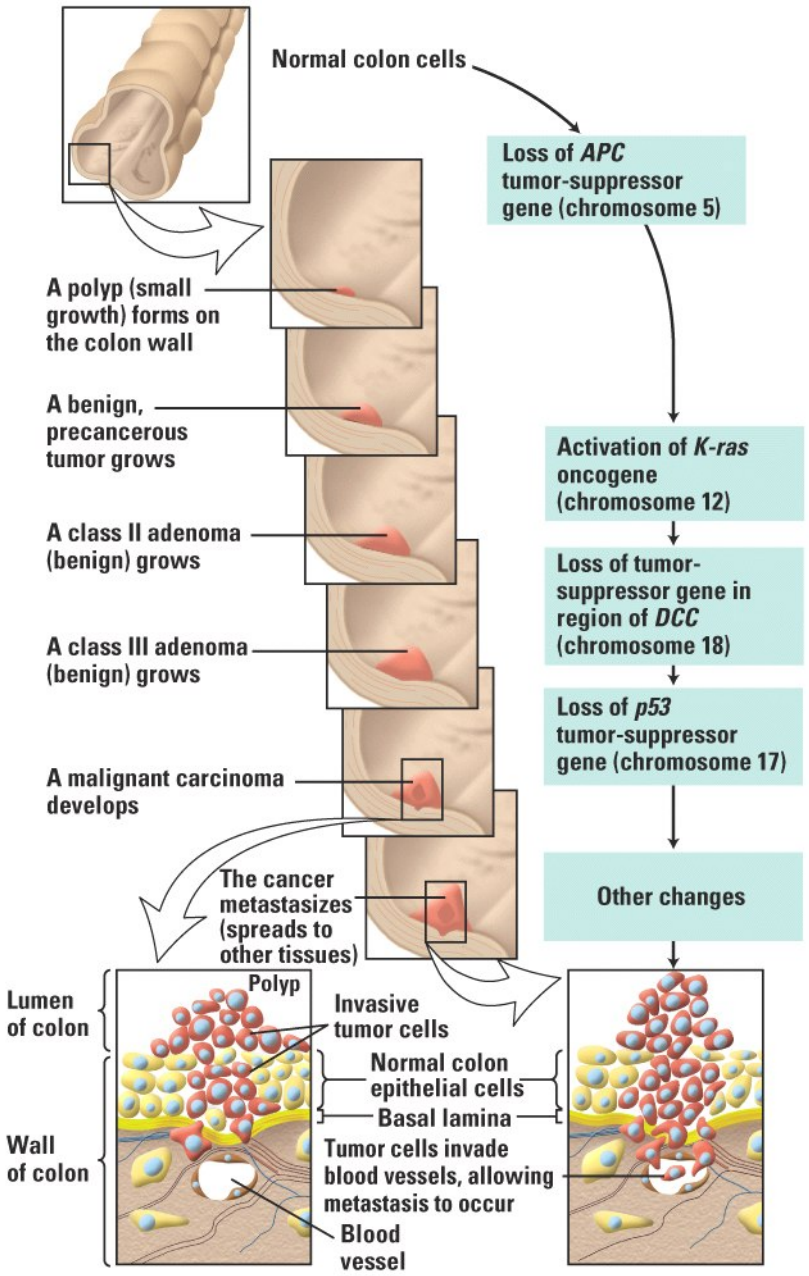

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