Corso di Oncologia Molecolare AA 2019-2020

L'ACQUISIZIONE DELL'INDIPENDENZA DAI SEGNALI PROLIFERATIVI: IL CICLO CELLULARE

L'ACQUISIZIONE DELLA CAPACITA' REPLICATIVA ILLIMITATA

Eventi che promuovono la proliferazione cellulare nei tumori

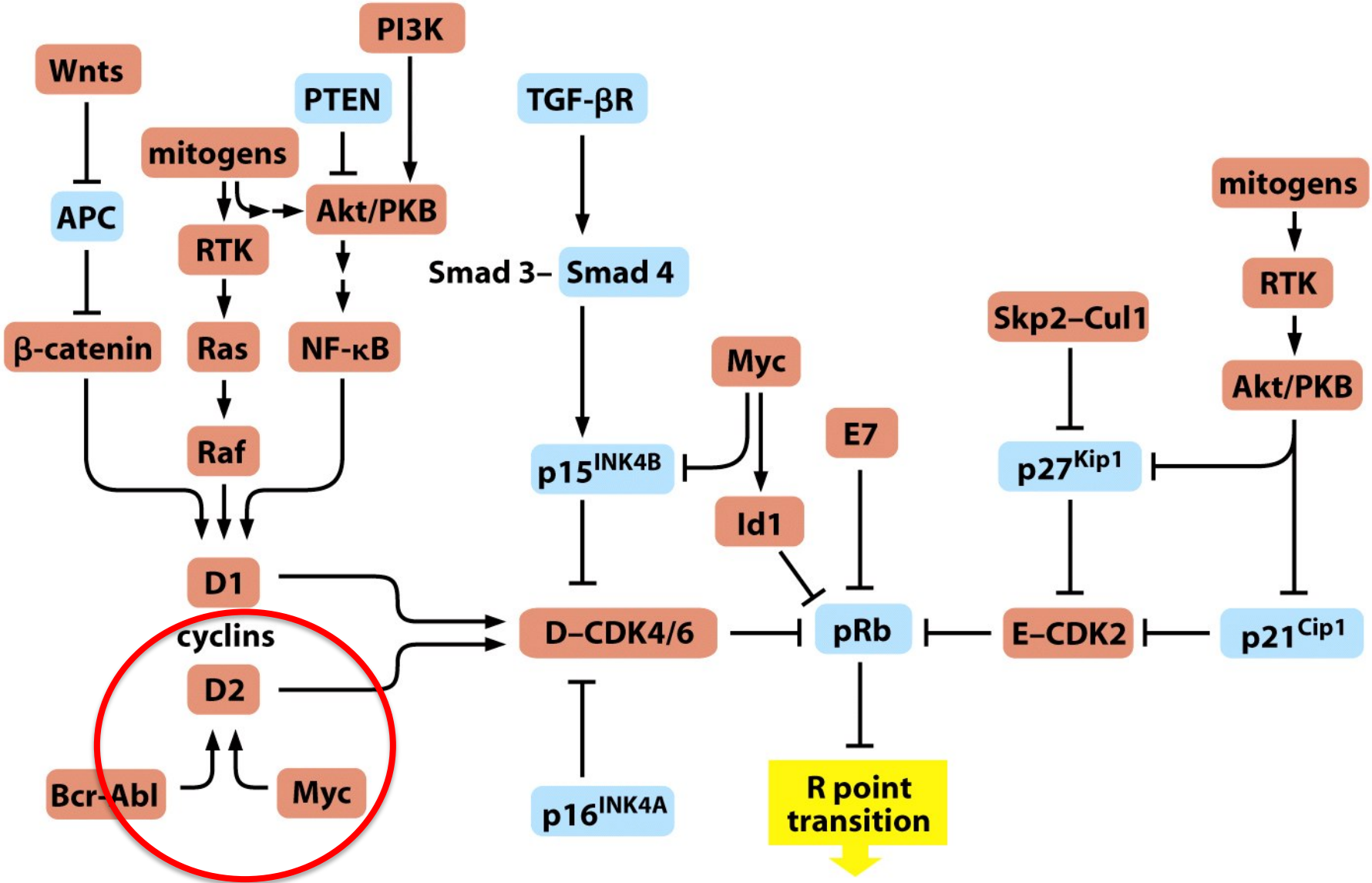
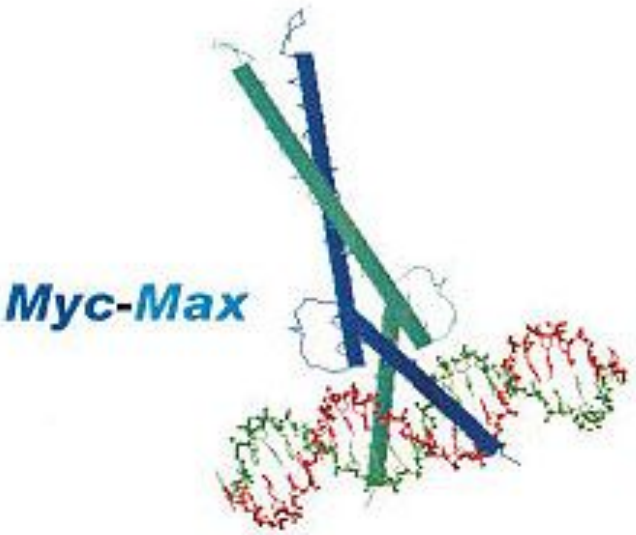


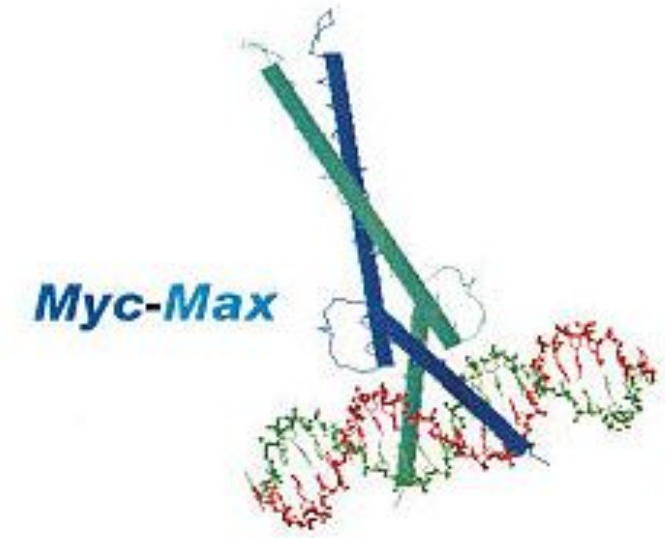
Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

c-Myc



- Cell cycle regulation
- Apoptosis
- Metabolism
- Cell adhesion
- Cellular differentiation

c-Myc



- Cell cycle regulation
- Apoptosis
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- Cell adhesion
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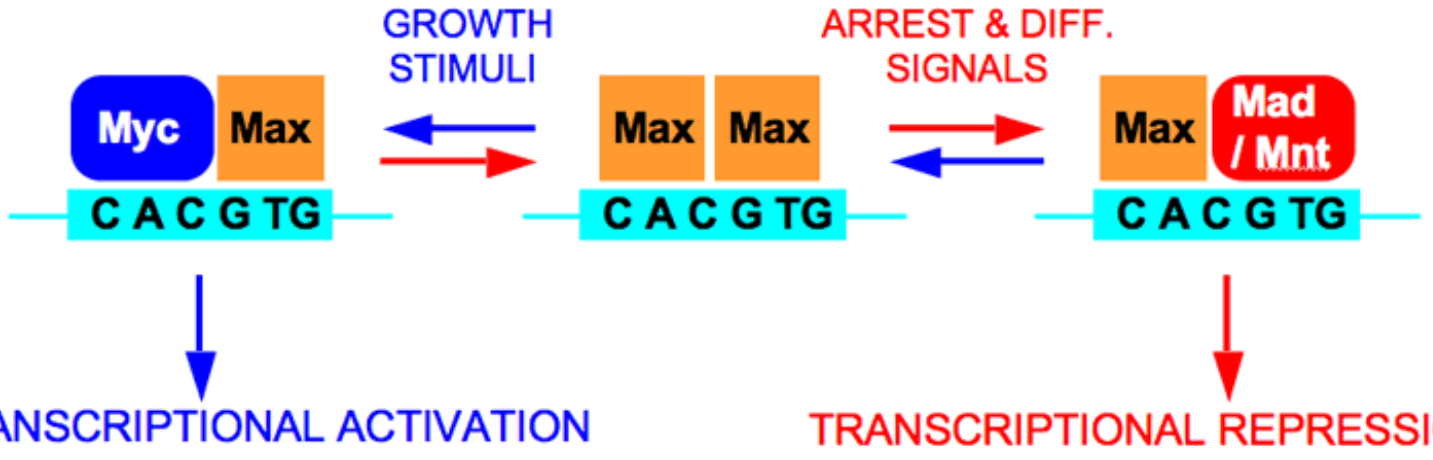


c-Myc induce la trascrizione di CycD2, CDK4 e dei TFs E2F

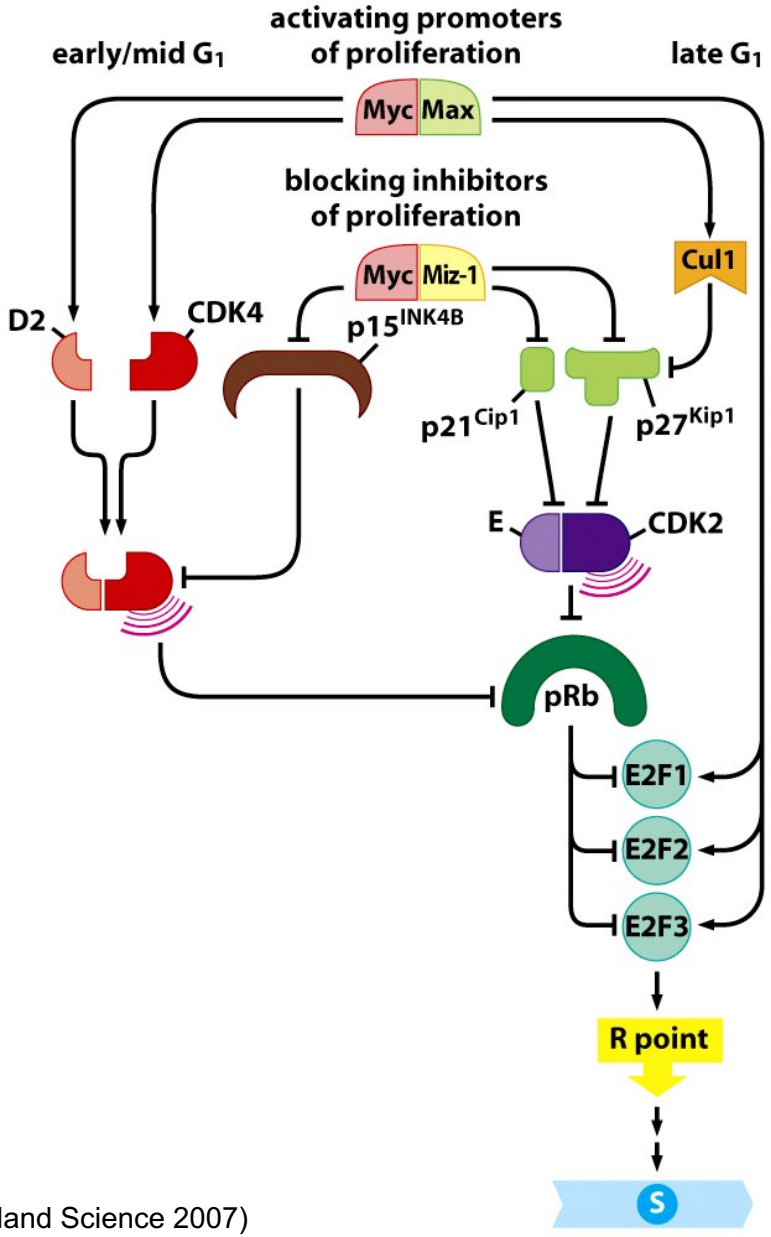
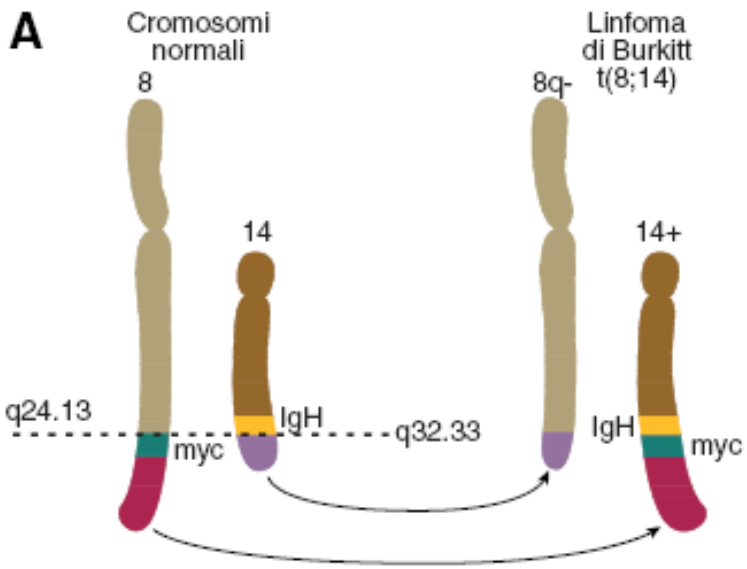
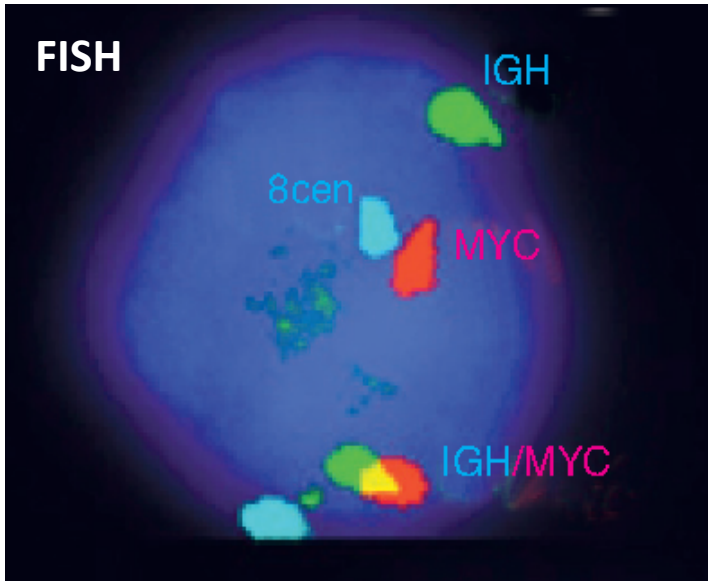
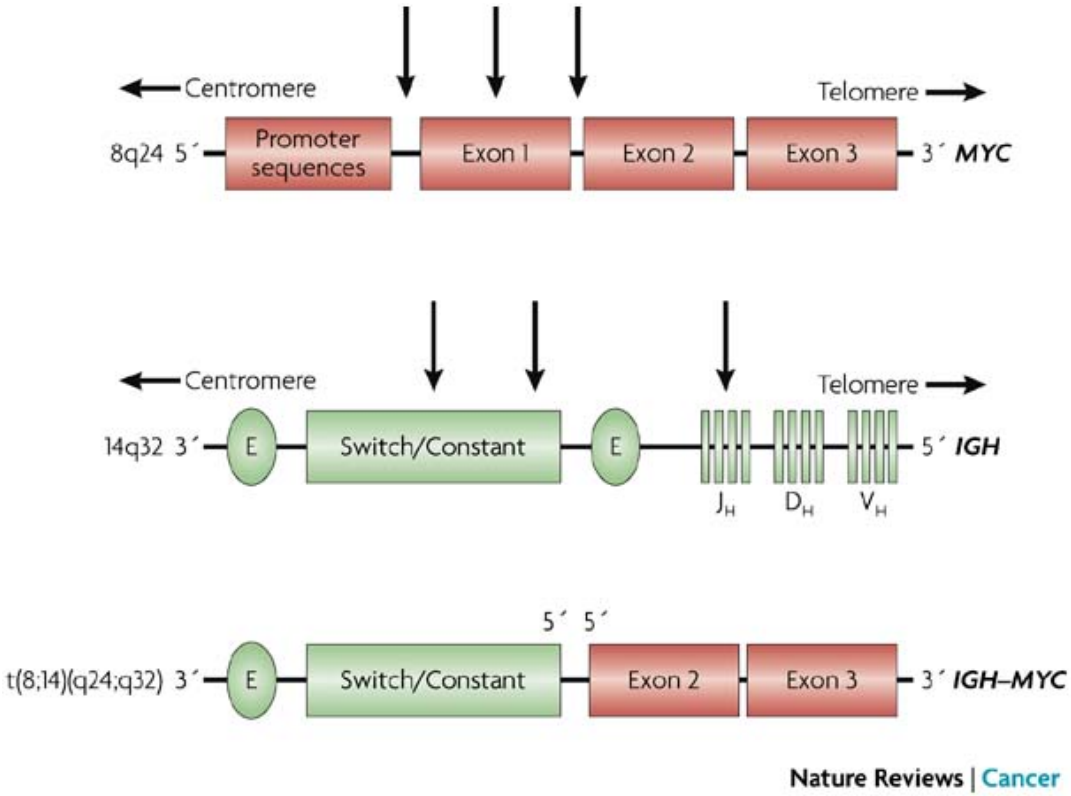


Figure 8.28 *The Biology of Cancer* (© Garland Science 2007)

Iper-espressione di c-Myc nel linfoma di Burkitt







Eventi che promuovono la proliferazione cellulare nei tumori

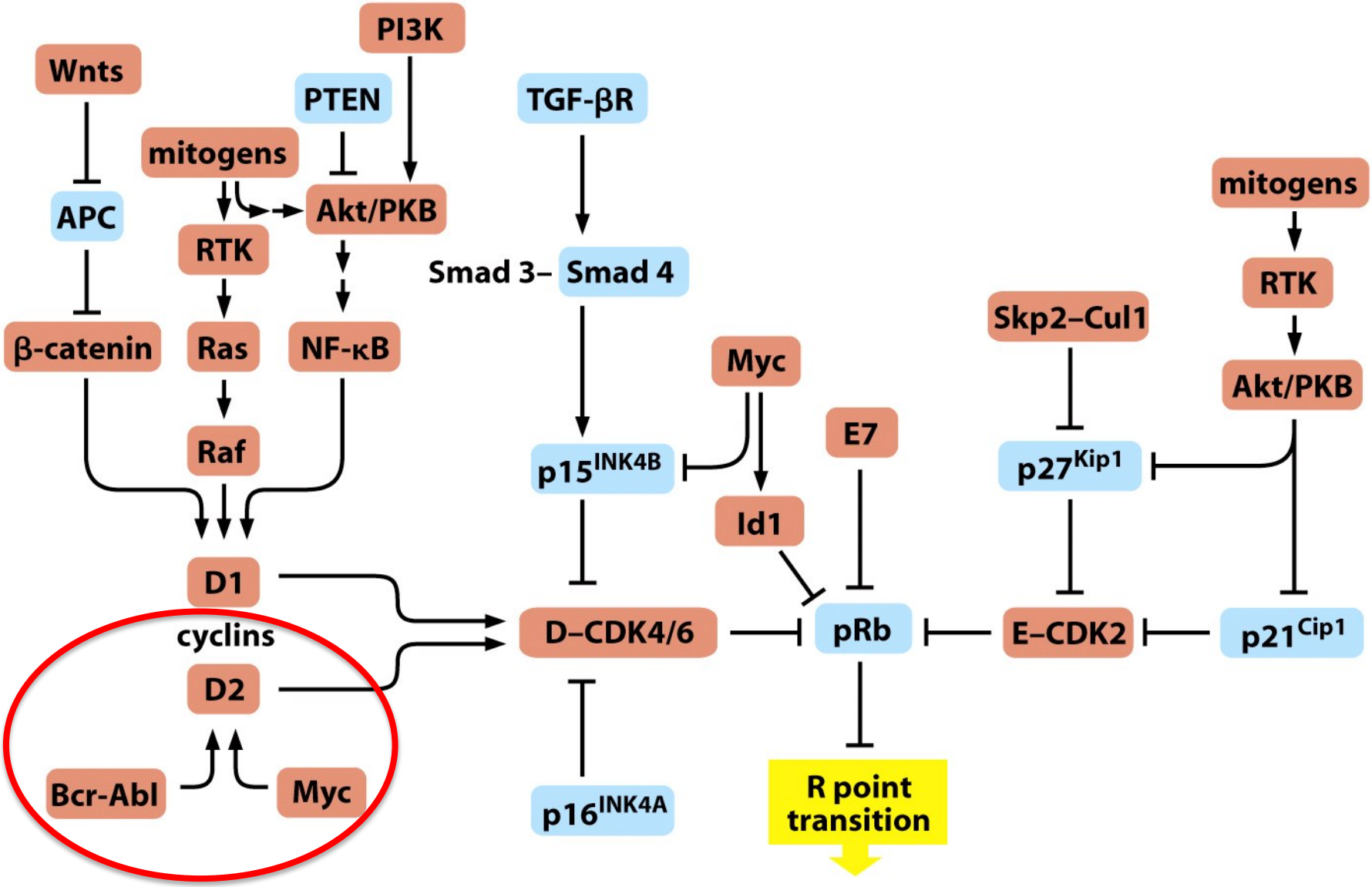


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

La tirosina chinasi Bcr-Abl e la leucemia mieloide cronica

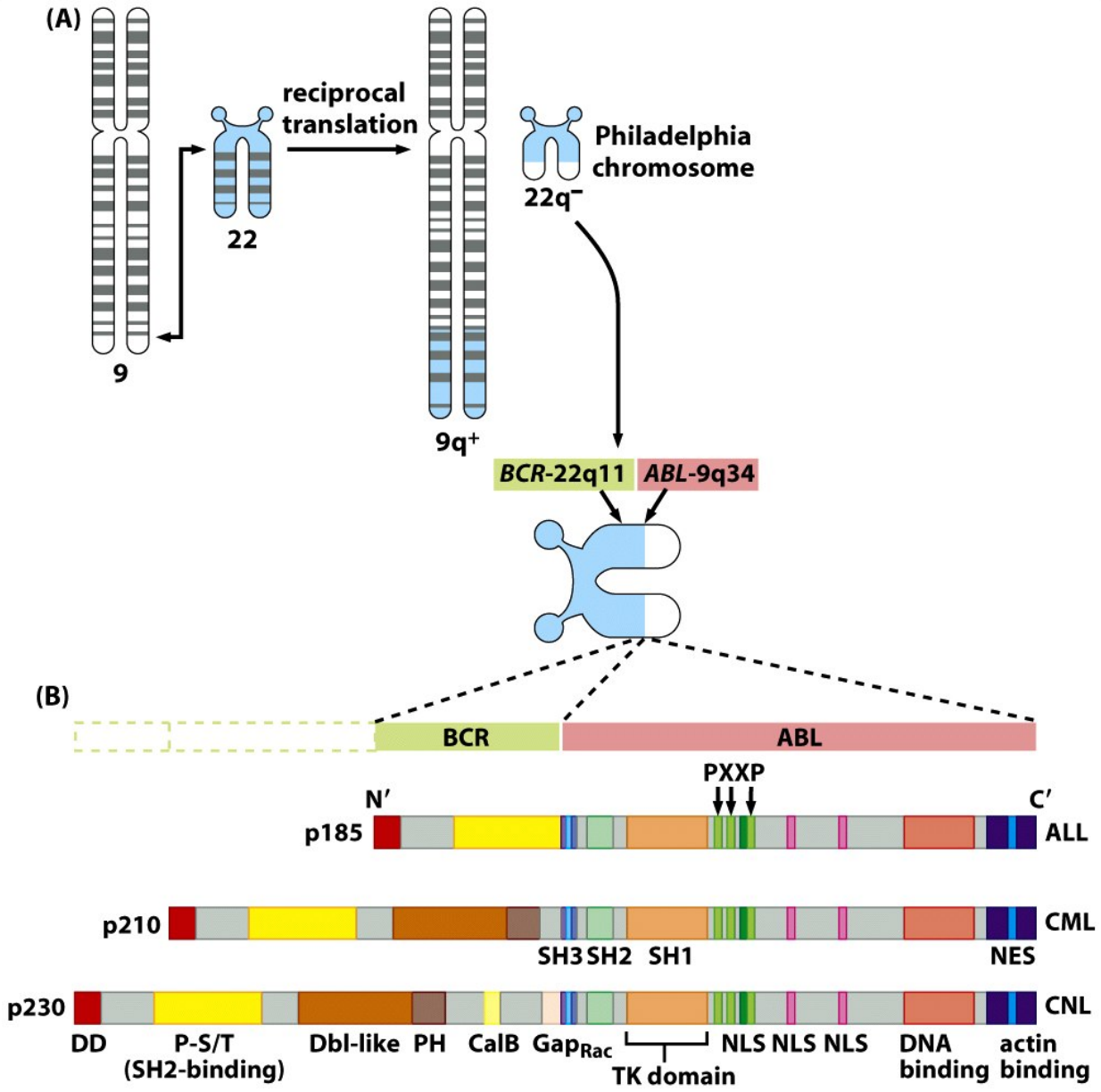
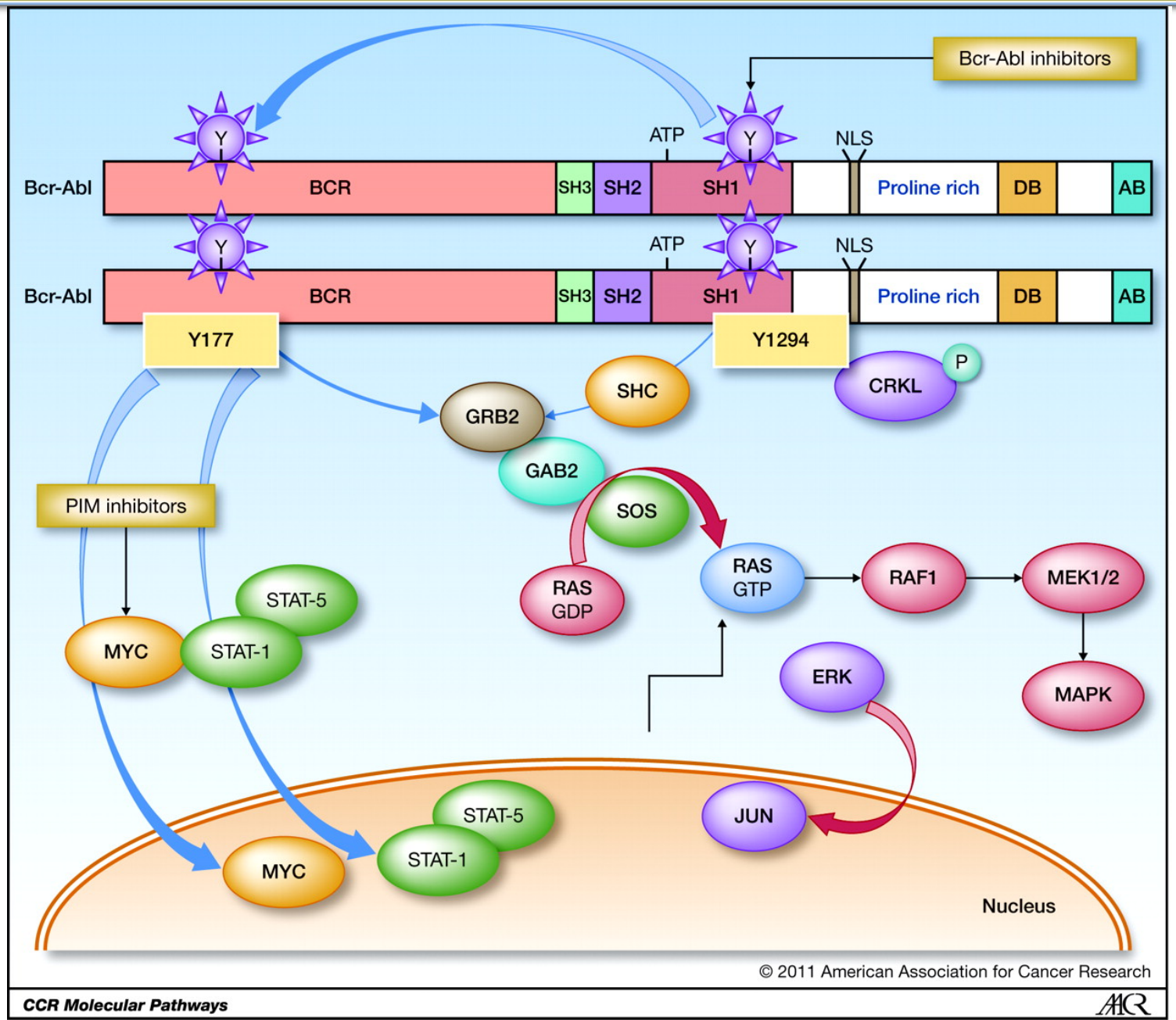
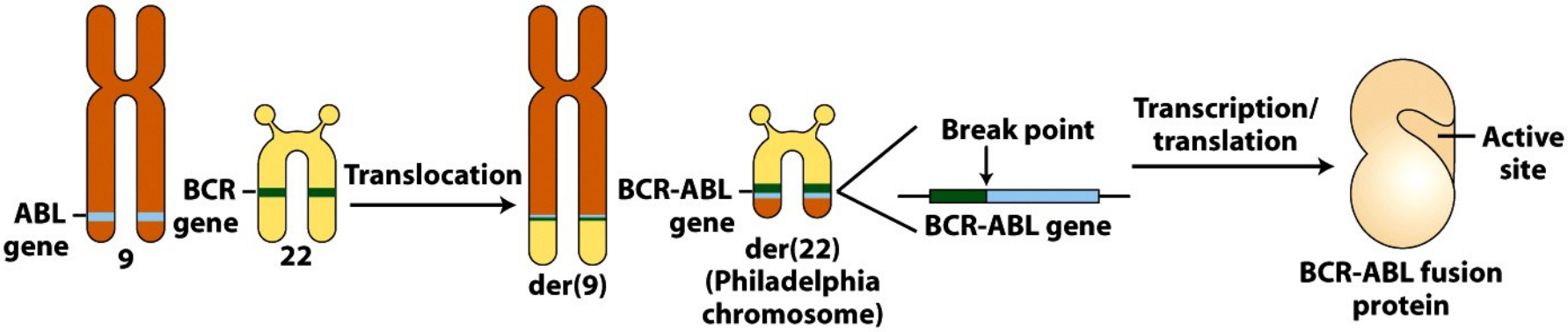


Figure 16.24 *The Biology of Cancer* (© Garland Science 2007)

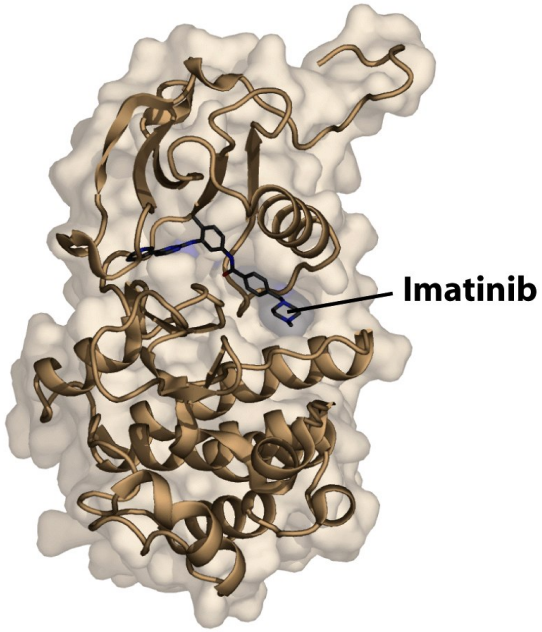
Bcr-Abl: una chinasi chimerica con attività citoplasmatica



L'IMATINIB è un inibitore della chinasi Abl



BCR-ABL fusion protein



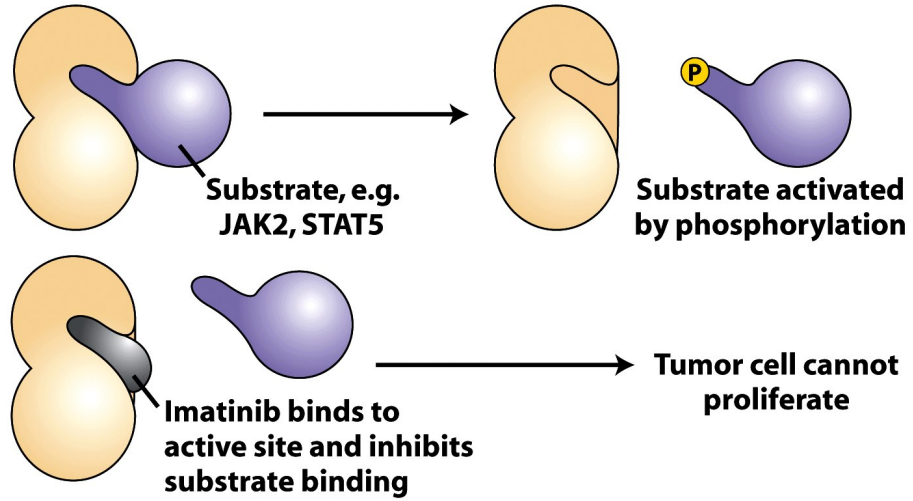
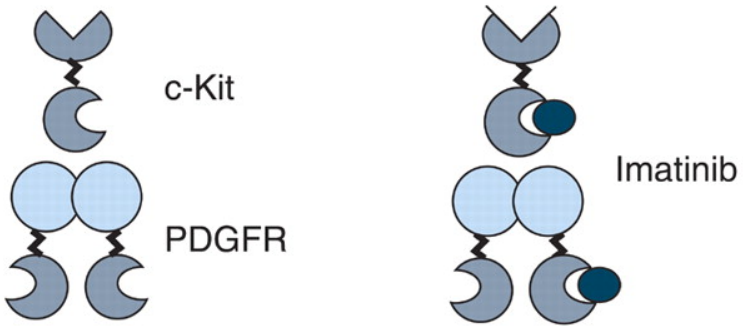


Figure 25-20b
Molecular Cell Biology, Sixth Edition

Binds ATP binding pocket and stabilizes a catalytically inactive form of the kinase

L'imatinib inibisce diverse Tirosina chinasi oncogeniche

Tumor type	Tyrosine-kinase target	Inhibitor
Chronic myelogenous leukemia	BCR-ABL	Imatinib
Gastrointestinal stromal tumors	c-Kit	Imatinib
	PDGFR	
Metastatic medulloblastomas		



Per il trattamento della resistenza all'Imatinib viene impiegato il Dasatinib, Inibitore di Abl e Src

Altre tirosina chinasi non recettoriali sono oncogeni

SRC, YES, FYN,
LYN, LCK, BLK,
HCK, FGR, YRK

FRK (MKK3), BRK
SRM, SAD

BTK, ITK, TEC
MKK2 (BMX)
TXK

CSK,
CTK (MKK1)

ABL, ARG

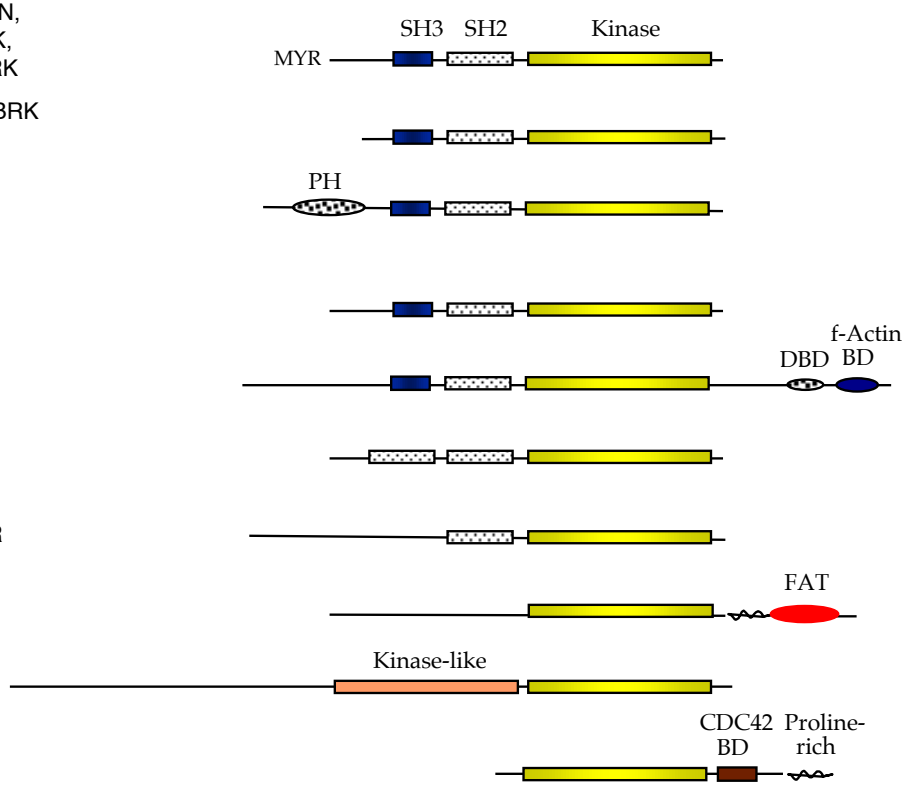
ZAP70, SYK

FES/FPS, FER

FAK, PYK2

JAK1, JAK2,
TYK2, JAK3

ACK, ACK2



SUGEN

Eventi che promuovono la proliferazione cellulare nei tumori

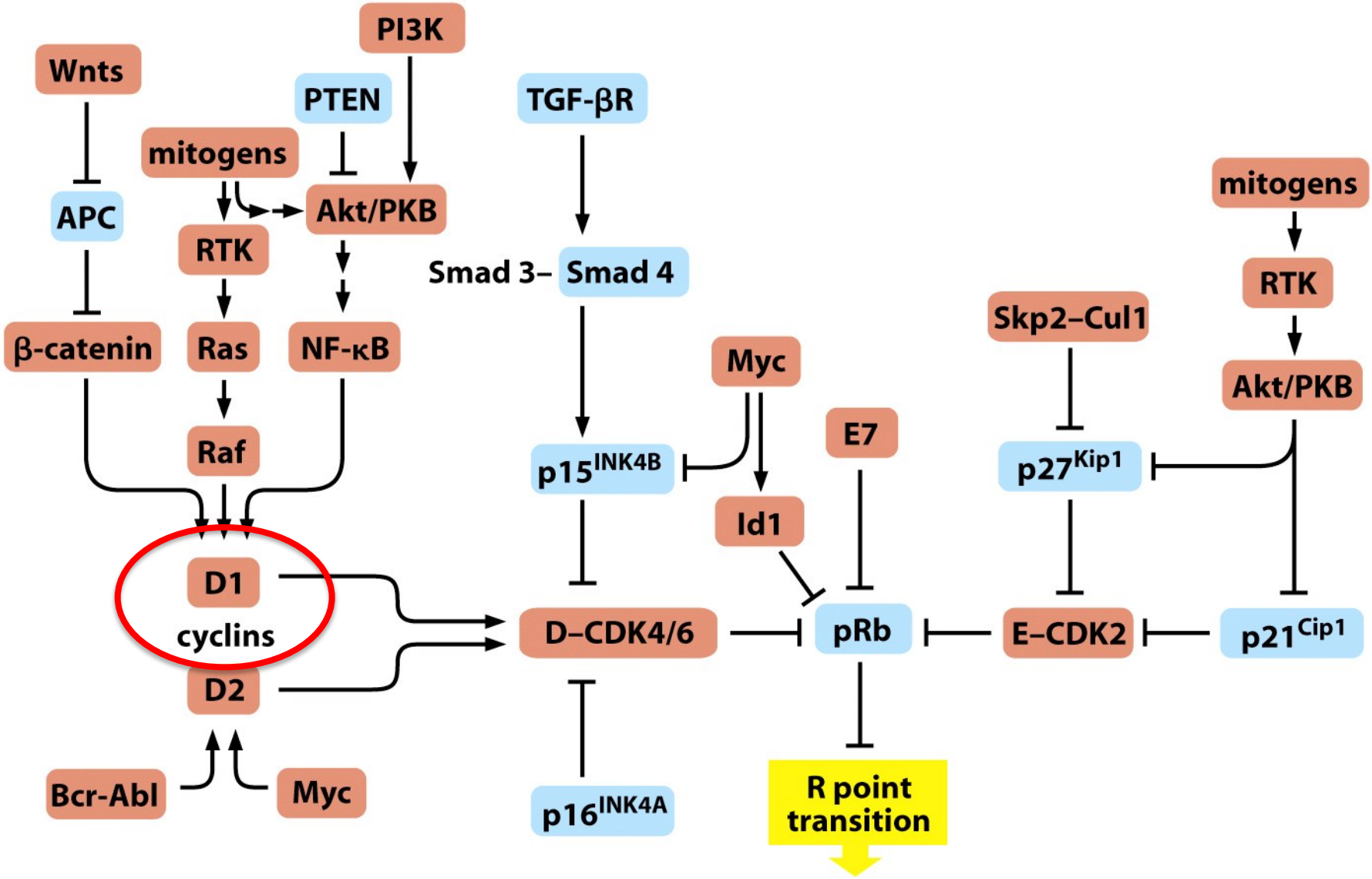
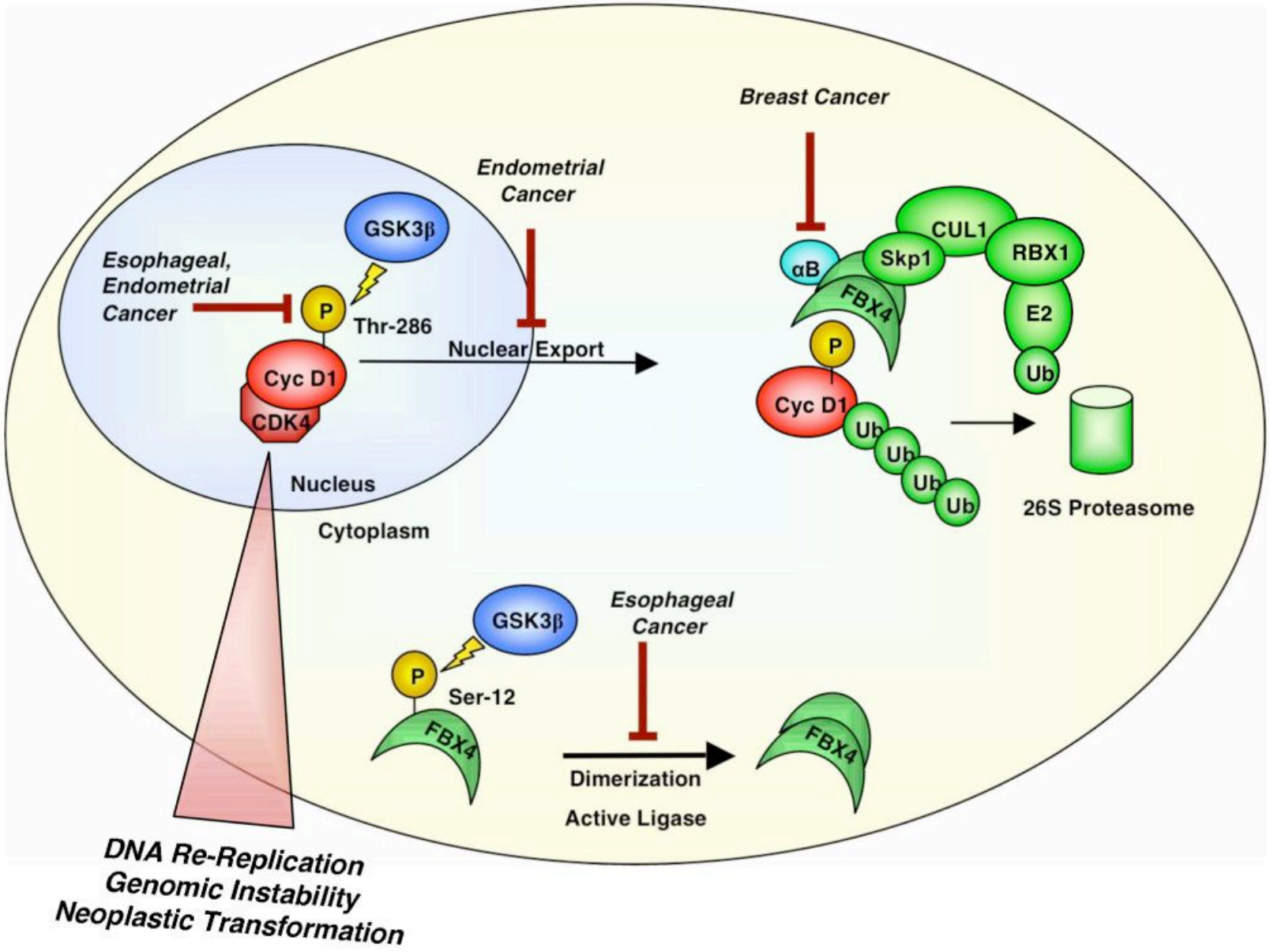


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

La regolazione della stabilità di Ciclina D1 è alterata nei tumori



Eventi che promuovono la proliferazione cellulare nei tumori

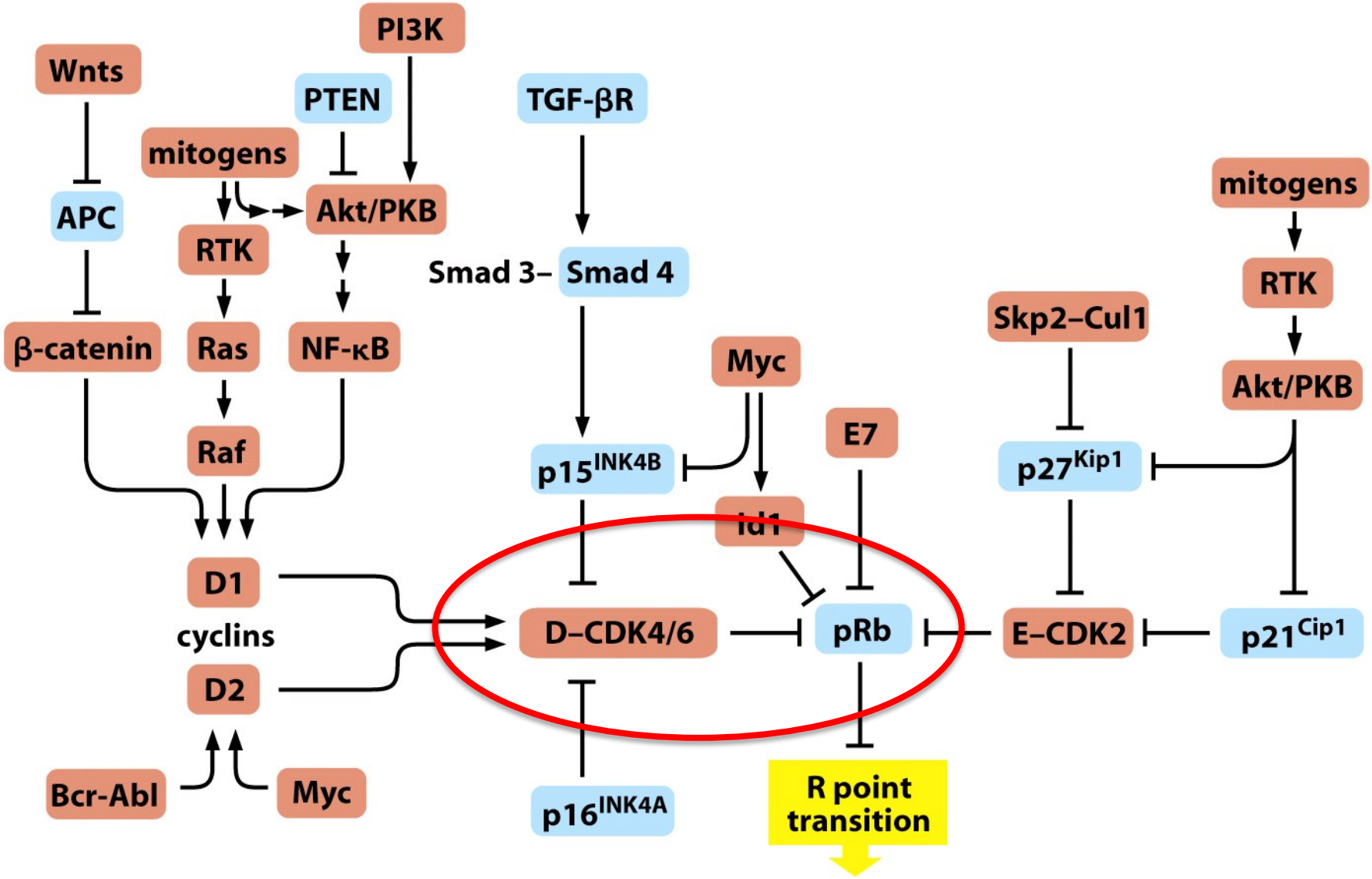
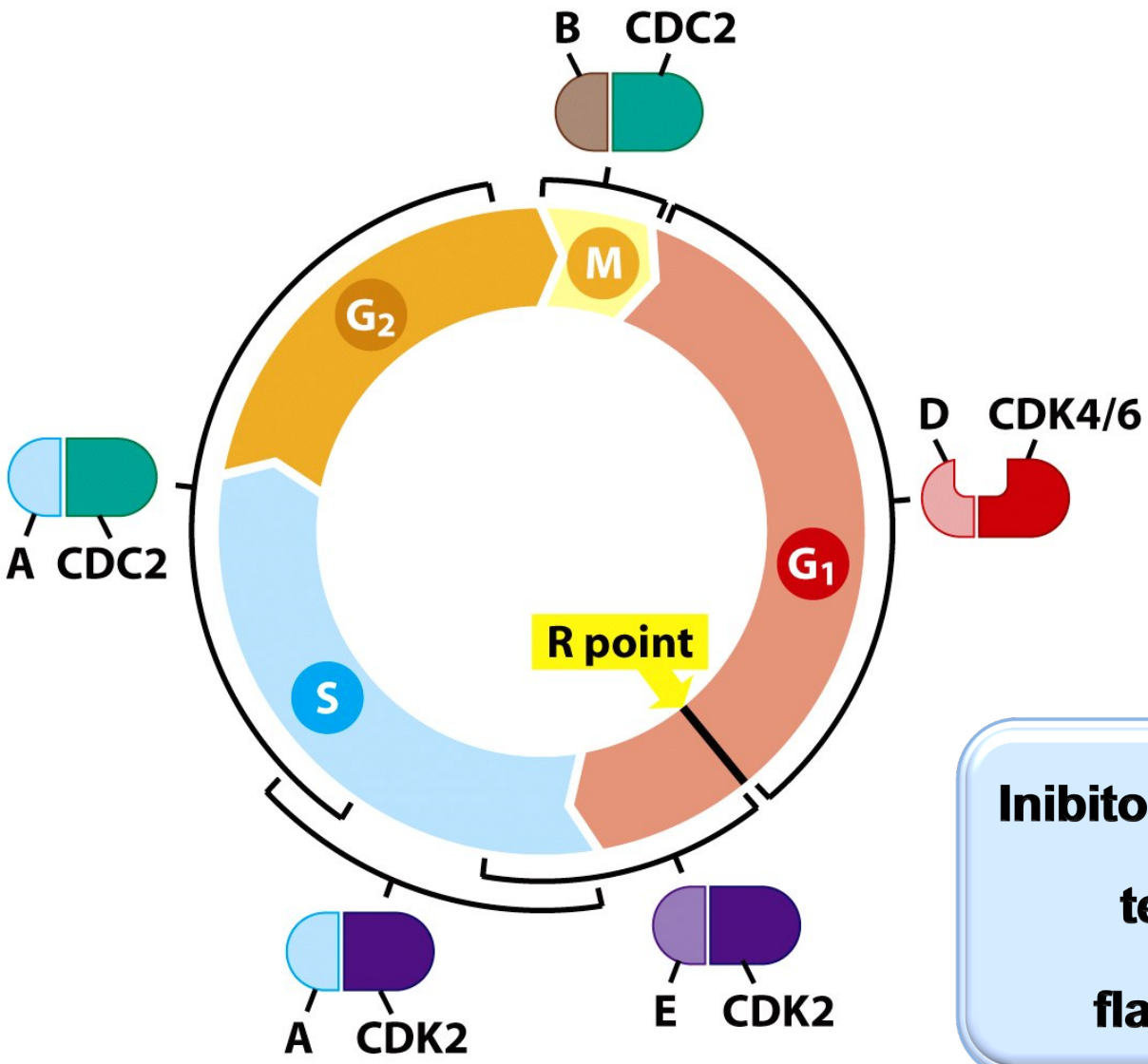


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

La progressione del ciclo cellulare è controllata da complessi Cyc/CDK



Inibitori delle CDK in terapia es. flavopiridolo

Figure 8.8 *The Biology of Cancer* (© Garland Science 2007)

I complessi Cyc/CDK

controllano la fosforilazione di Rb durante il ciclo cellulare

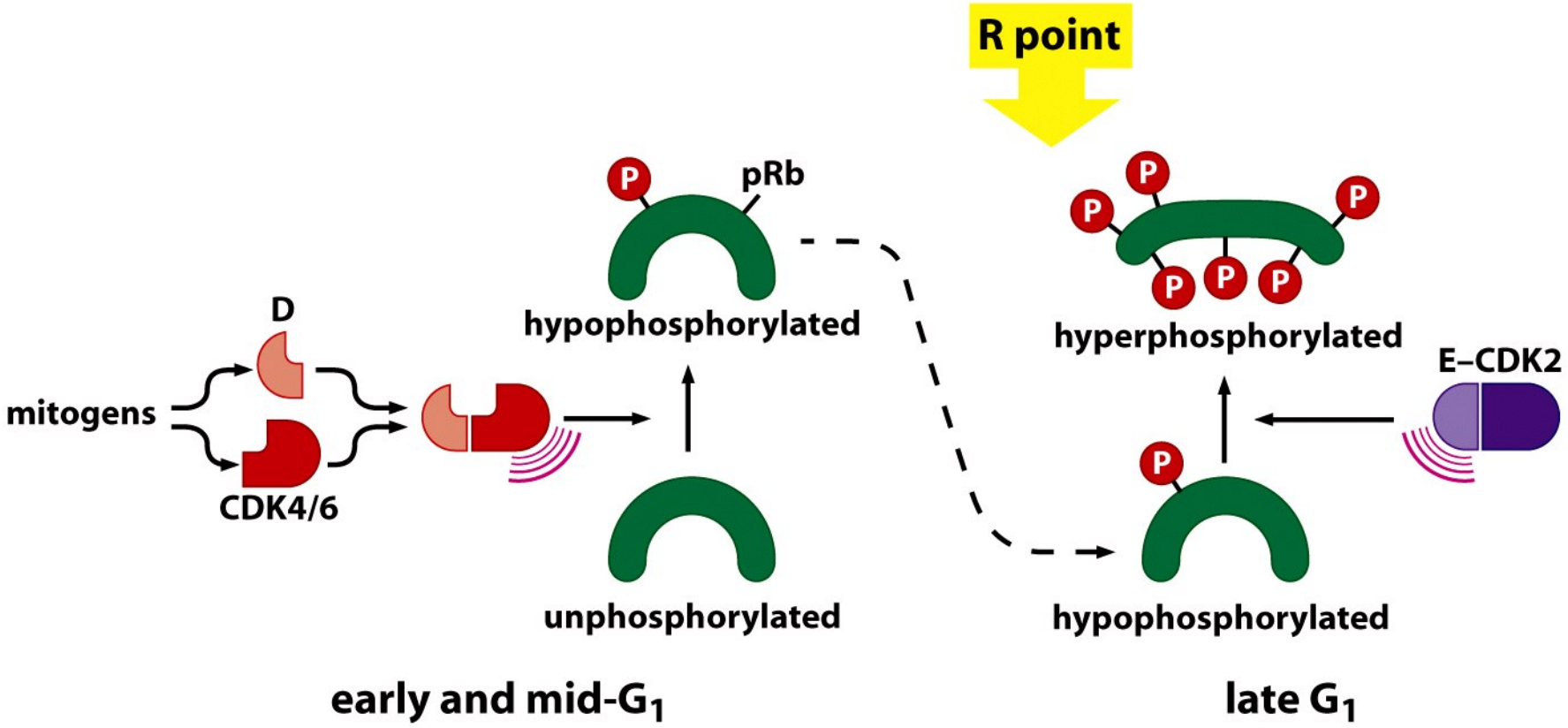


Figure 8.22 *The Biology of Cancer* (© Garland Science 2007)

Fosforilazione di Rb durante il ciclo cellulare

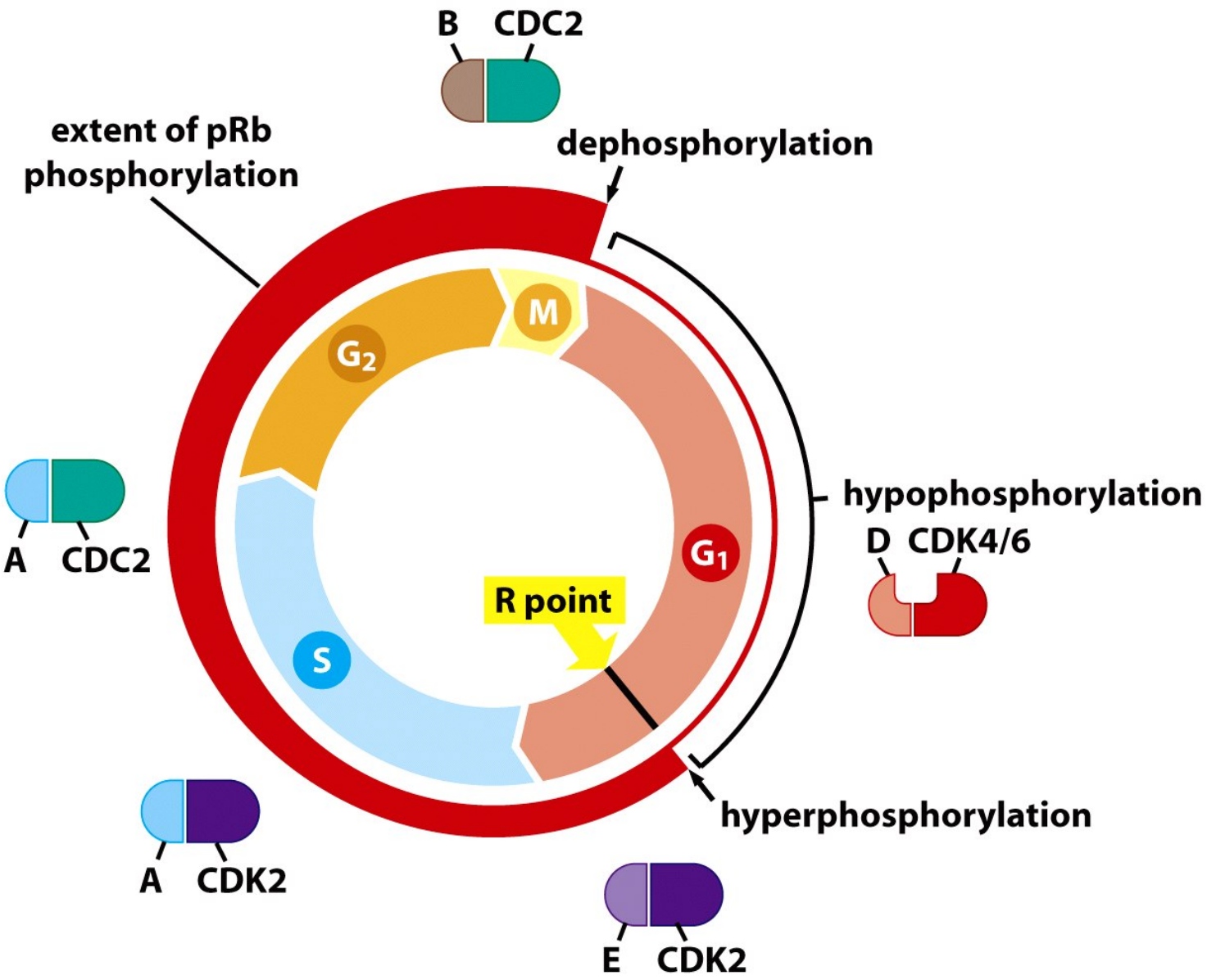
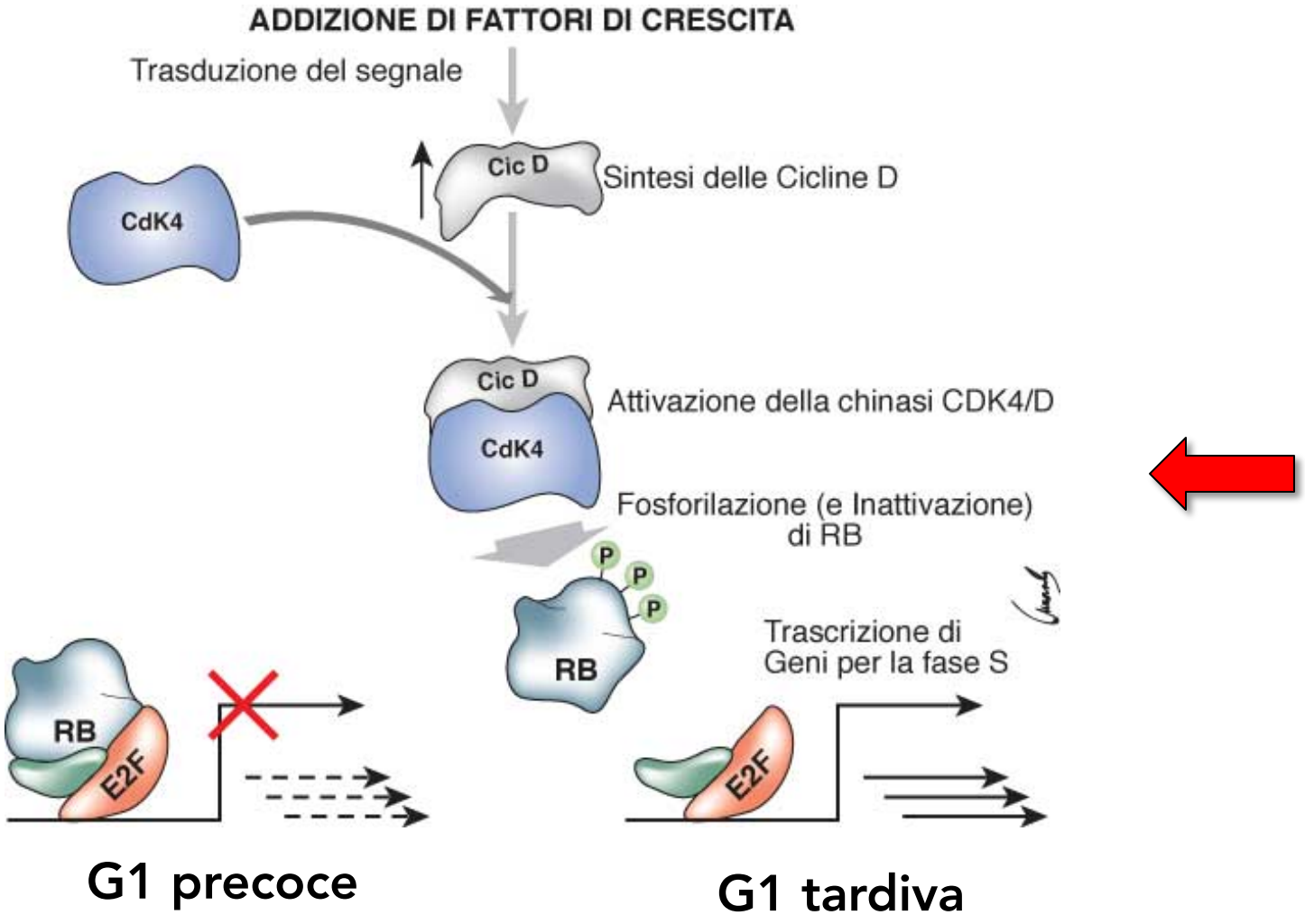


Figure 8.19 *The Biology of Cancer* (© Garland Science 2007)

L'iperfosforilazione di Rb rimuove il blocco della transizione G1/S



Le pocket proteins inibiscono la trascrizione mediata da E2Fs = inibizione della transizione G1/S

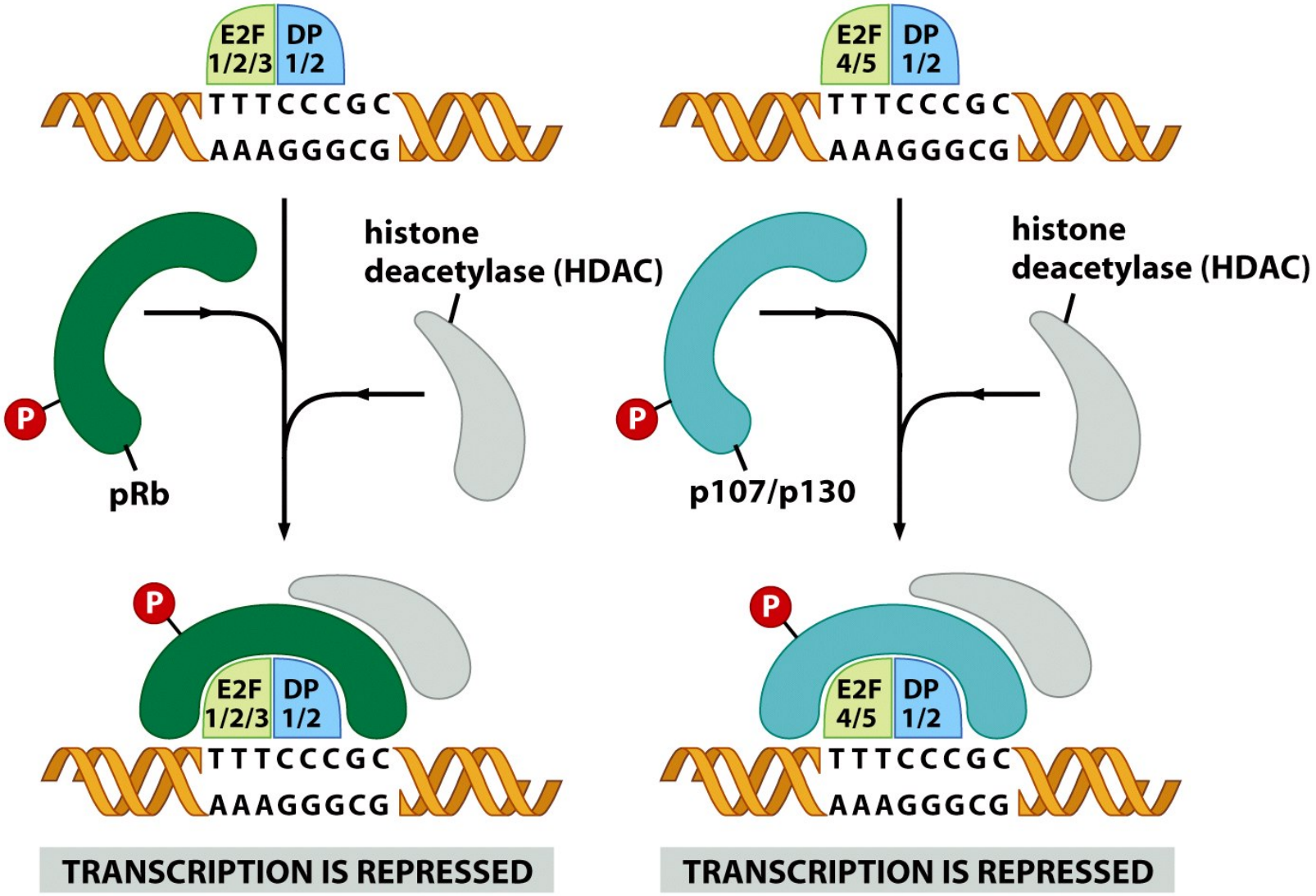


Figure 8.24a *The Biology of Cancer* (© Garland Science 2007)

La rimozione di Rb causa l'attivazione trascrizionale dei geni bersaglio di E2Fs

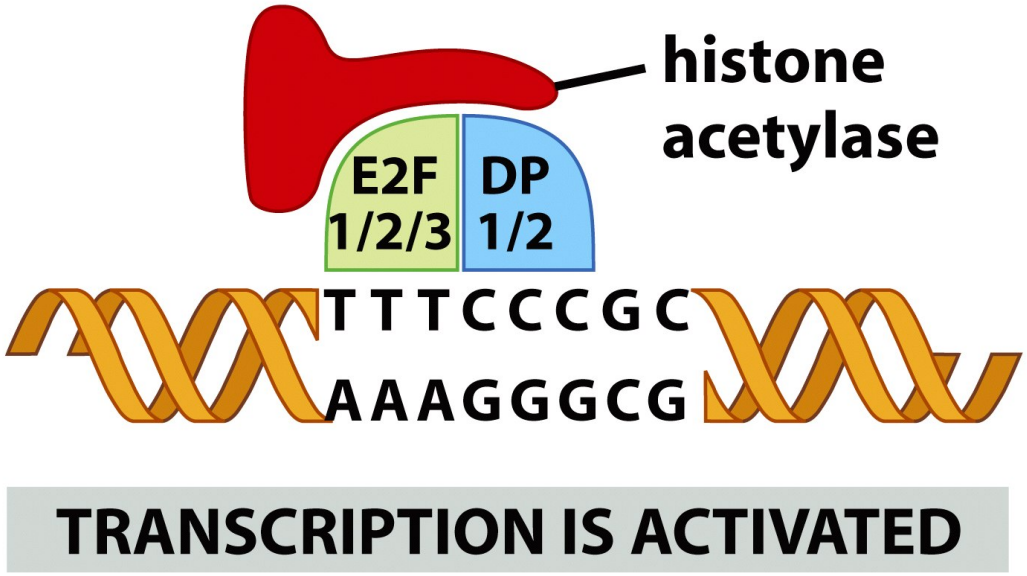


Figure 8.24b *The Biology of Cancer* (© Garland Science 2007)

L'aumento dei livelli delle cicline promuove la transizione G1/S

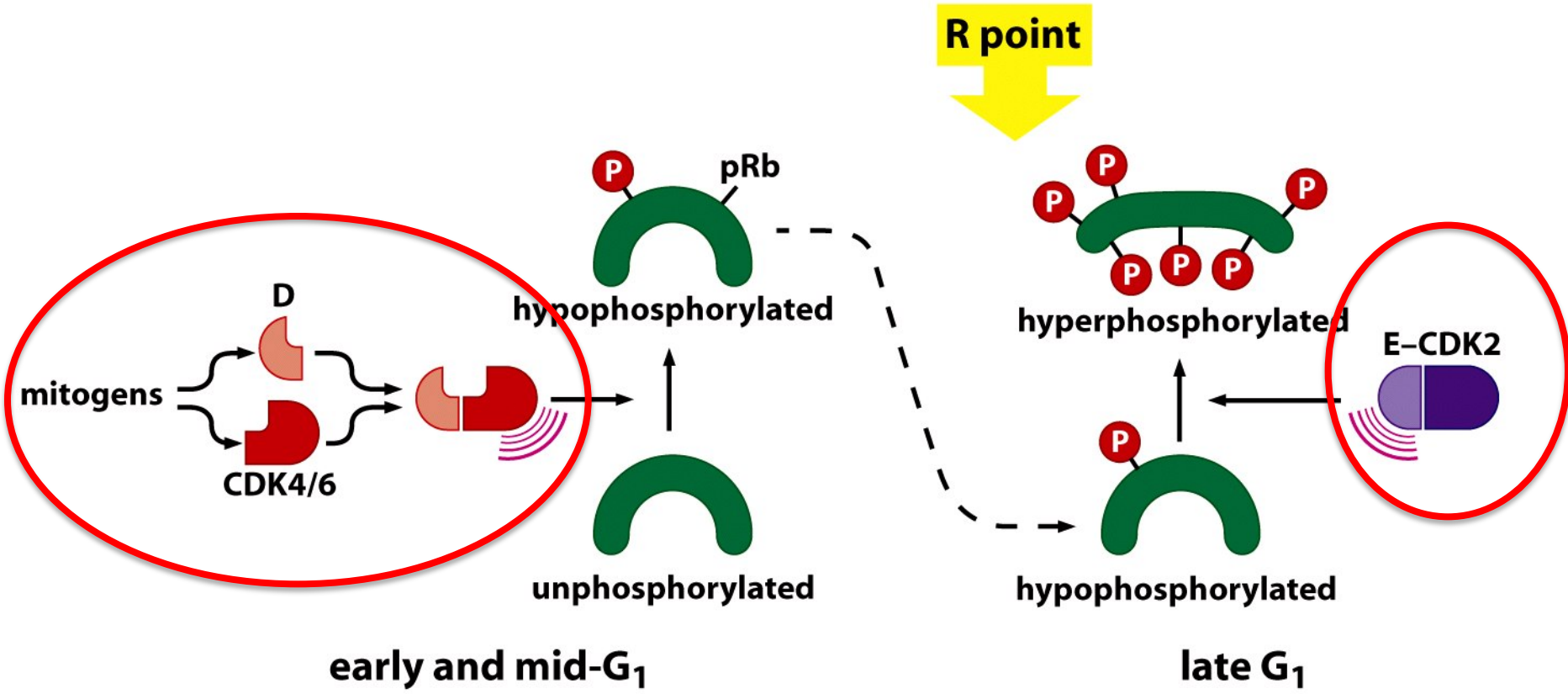


Figure 8.22 *The Biology of Cancer* (© Garland Science 2007)

Mutazioni di Rb promuovono la transizione G1/S

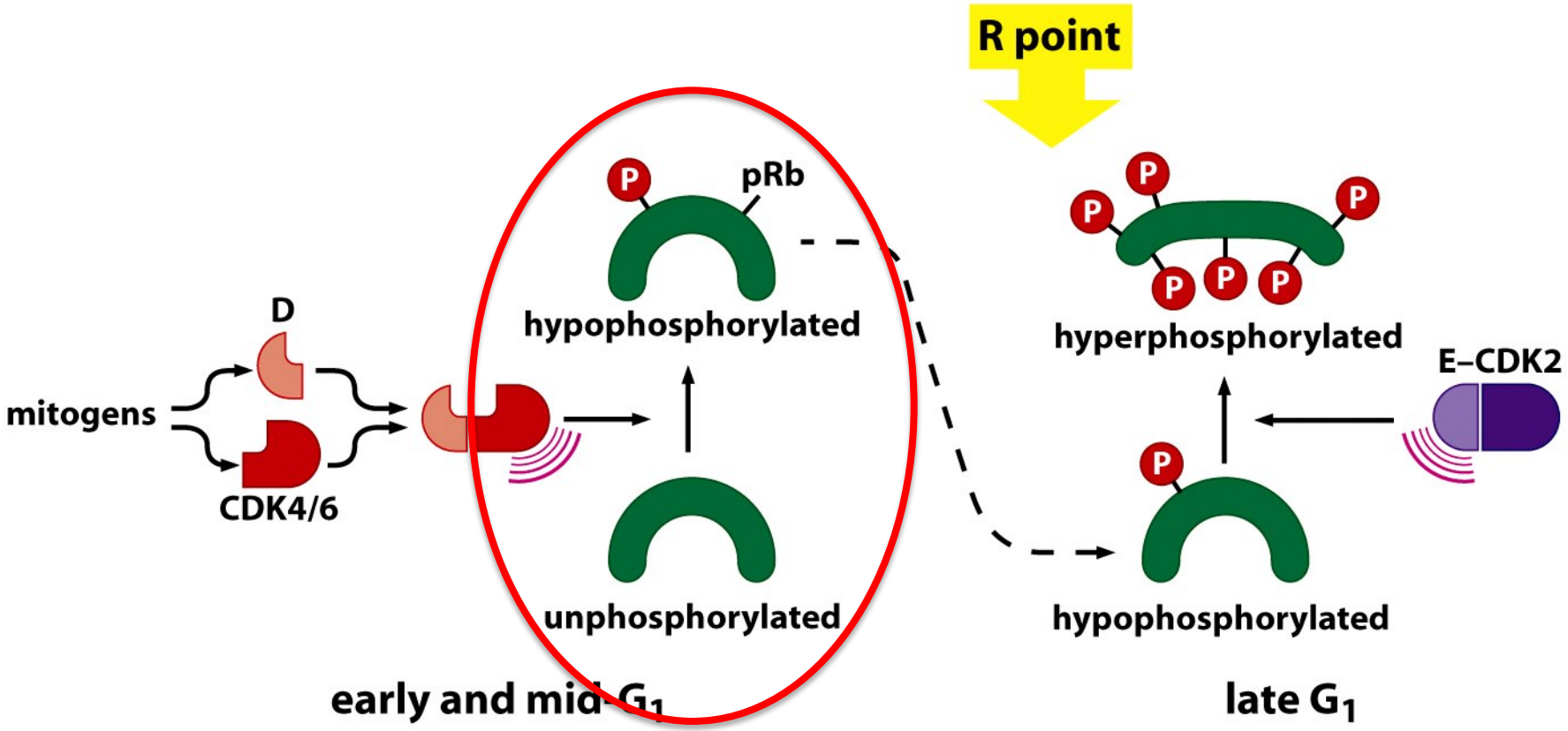


Figure 8.22 *The Biology of Cancer* (© Garland Science 2007)

Table 8.3 Molecular changes in human cancers leading to deregulation of the cell cycle clock

Specific alteration	Clinical result
Alterations of pRb	
Inactivation of the *Rb* gene by mutation	retinoblastoma, osteosarcoma, small-cell lung carcinoma
Methylation of *Rb* gene promoter	brain tumors, diverse others
Sequestration of pRb by Id1, Id2	diverse carcinomas, neuroblastoma, melanoma
Sequestration of pRb by the HPV E7 viral oncoprotein	cervical carcinoma
Alteration of cyclins	
Cyclin D1 overexpression through amplification of *cyclin D1* gene	breast carcinoma, leukemias
Cyclin D1 overexpression caused by hyperactivity of *cyclin D1* gene promoter driven by upstream mitogenic pathways	diverse tumors
Cyclin D1 overexpression due to reduced degradation of cyclin D1 because of depressed activity of GSK-3β	diverse tumors
Cyclin D3 overexpression caused by hyperactivity of *cyclin D3* gene	hematopoietic malignancies
Cyclin E overexpression	breast carcinoma
Defective degradation of cyclin E protein due to loss of hCDC4	endometrial, breast, and ovarian carcinomas
Alteration of cyclin-dependent kinases	
CDK4 structural mutation	melanoma
Alteration of CDK inhibitors	
Deletion of 15^{INK4B} gene	diverse tumors
Deletion of 16^{INK4A} gene	diverse tumors
Methylation of $p16^{INK4A}$ gene promoter	melanoma, diverse tumors
Decreased transcription of $p27^{Kip1}$ gene because of action of Akt/PKB on Forkhead transcription factor	diverse tumors
Increased degradation of $p27^{Kip1}$ protein due to Skp2 overexpression	breast, colorectal, and lung carcinomas, and lymphomas
Cytoplasmic localization of $p27^{Kip1}$ protein due to Akt/PKB action	breast, esophagus, colon, thyroid carcinomas
Cytoplasmic localization of $p21^{Cip1}$ protein due to Akt/PKB action	diverse tumors
Multiple concomitant alterations by Myc, N-myc or L-myc	
Increased expression of Id1, Id2 leading to pRb sequestration	diverse tumors
Increased expression of cyclin D2 leading to pRb phosphorylation	diverse tumors
Increased expression of E2F1, E2F2 E2F3 leading to expression of cyclin E	diverse tumor
Increased expression of CDK4 leading to pRb phosphorylation	diverse tumors
Increased expression of Cul1 leading to $p27^{Kip1}$ degradation	diverse tumors
Repression of $p15^{INK4B}$ and $p21^{Cip1}$ expression allowing pRb phosphorylation	diverse tumors

Table 8.3 *The Biology of Cancer* (© Garland Science 2007)

Mutazioni di Rb sono frequenti in retinoblastoma e osteosarcoma

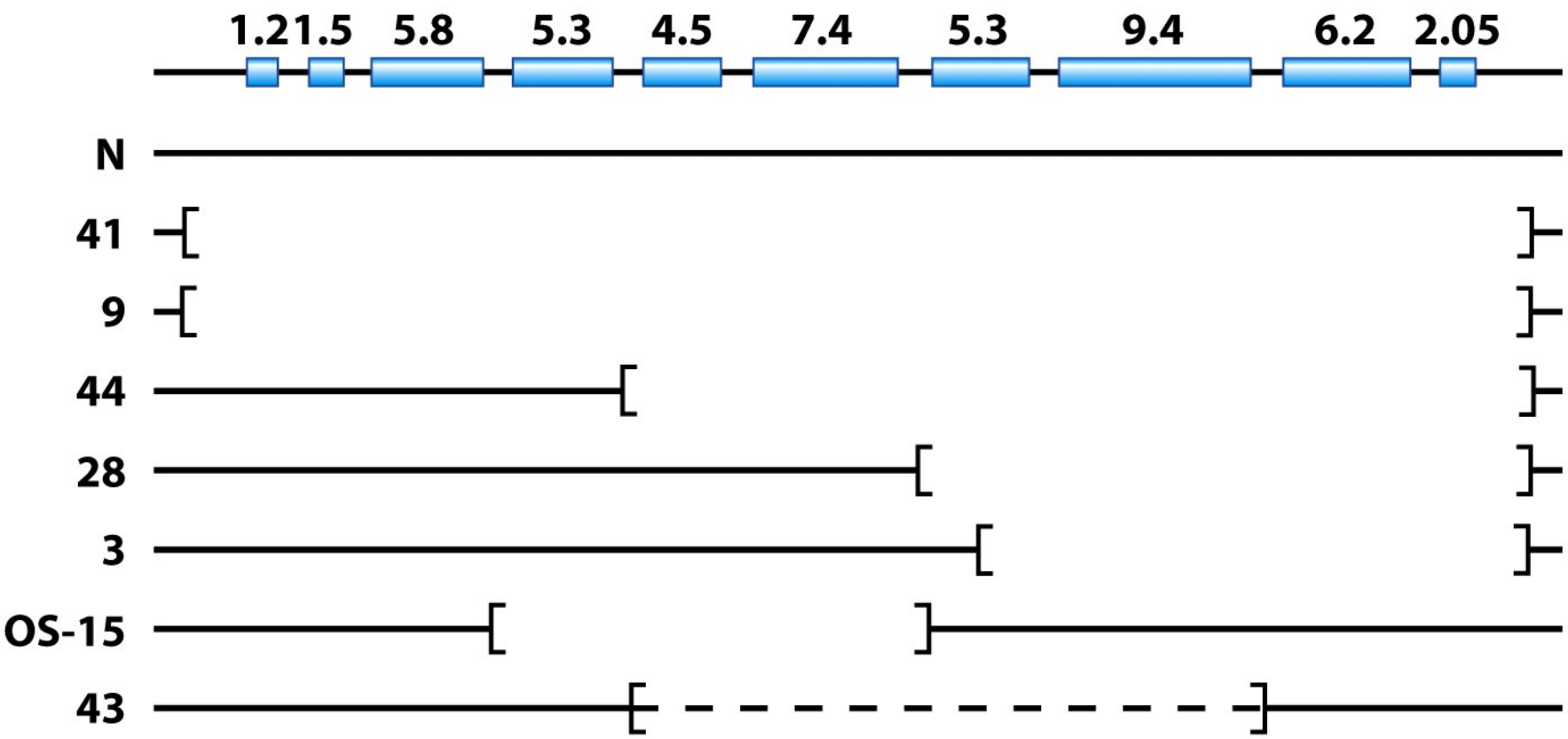
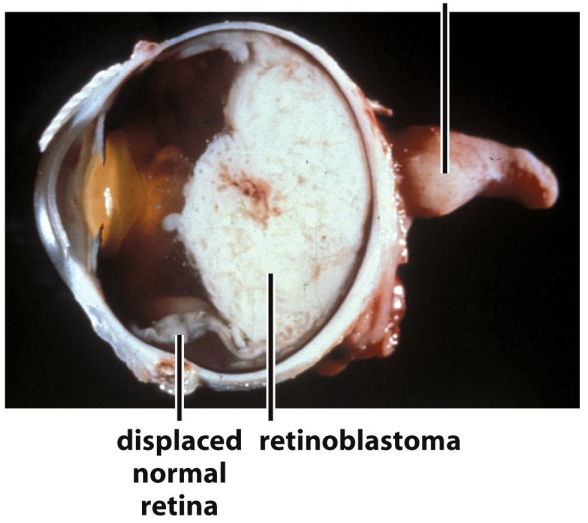


Figure 7.12 *The Biology of Cancer* (© Garland Science 2007)

Mutazioni di Rb causano il retinoblastoma familiare e sporadico



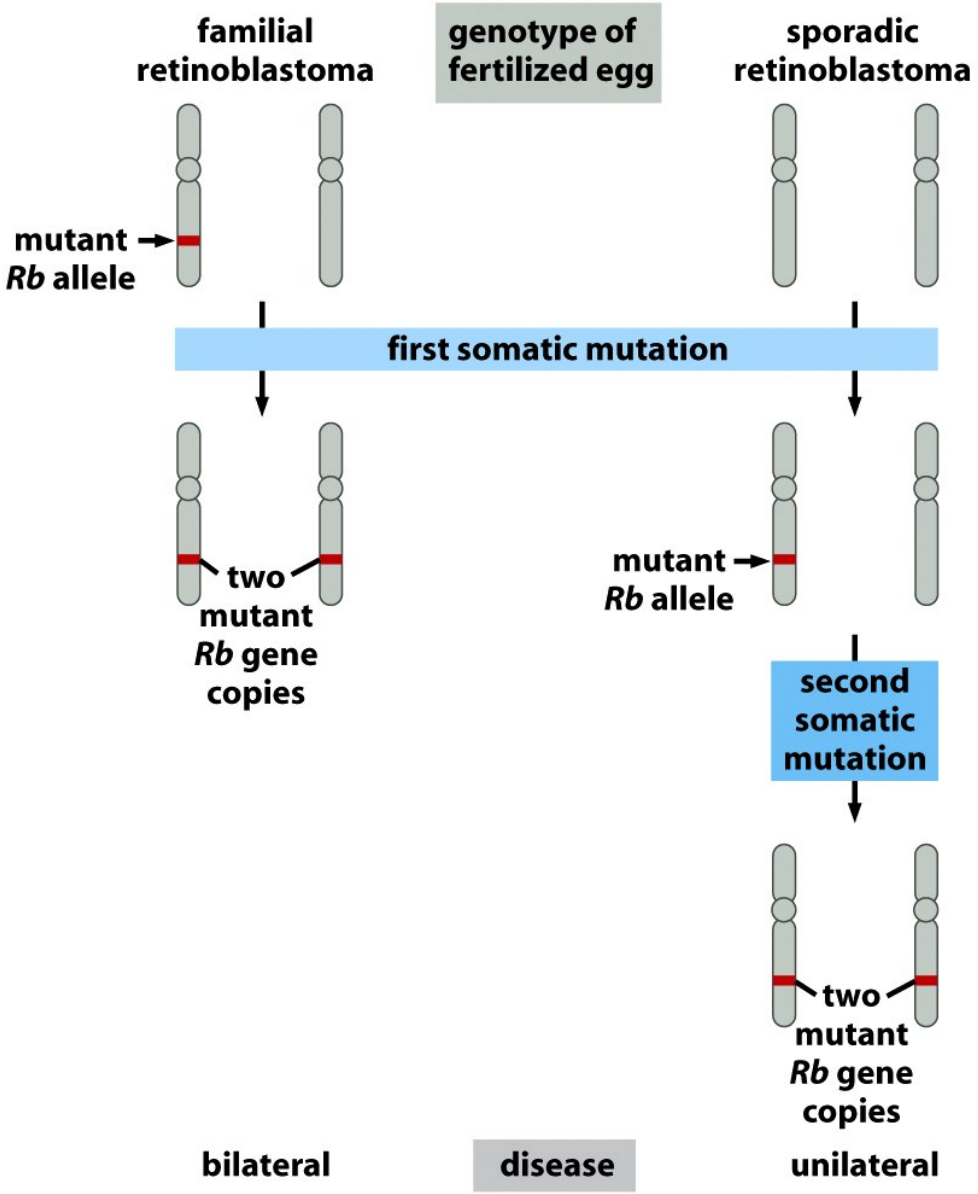


Figure 7.7 *The Biology of Cancer* (© Garland Science 2007)

Meccanismo di perdita di eterozigosi di Rb: ricombinazione mitotica

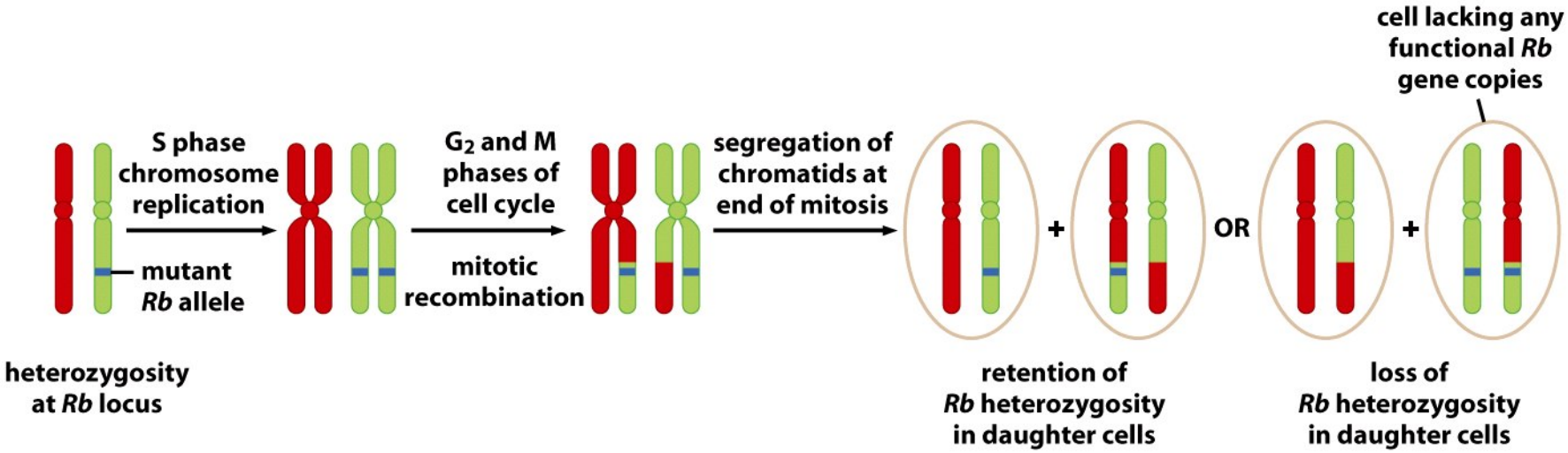


Figure 7.8 *The Biology of Cancer* (© Garland Science 2007)

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Sequestration of pRb by the HPV E7 viral oncoprotein	cervical carcinoma
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Cyclin D1 overexpression caused by hyperactivity of *cyclin D1* gene promoter driven by upstream mitogenic pathways	diverse tumors
Cyclin D1 overexpression due to reduced degradation of cyclin D1 because of depressed activity of GSK-3β	diverse tumors
Cyclin D3 overexpression caused by hyperactivity of *cyclin D3* gene	hematopoietic malignancies
Cyclin E overexpression	breast carcinoma
Defective degradation of cyclin E protein due to loss of hCDC4	endometrial, breast, and ovarian carcinomas
Alteration of cyclin-dependent kinases	
CDK4 structural mutation	melanoma
Alteration of CDK inhibitors	
Deletion of 15^{INK4B} gene	diverse tumors
Deletion of 16^{INK4A} gene	diverse tumors
Methylation of $p16^{INK4A}$ gene promoter	melanoma, diverse tumors
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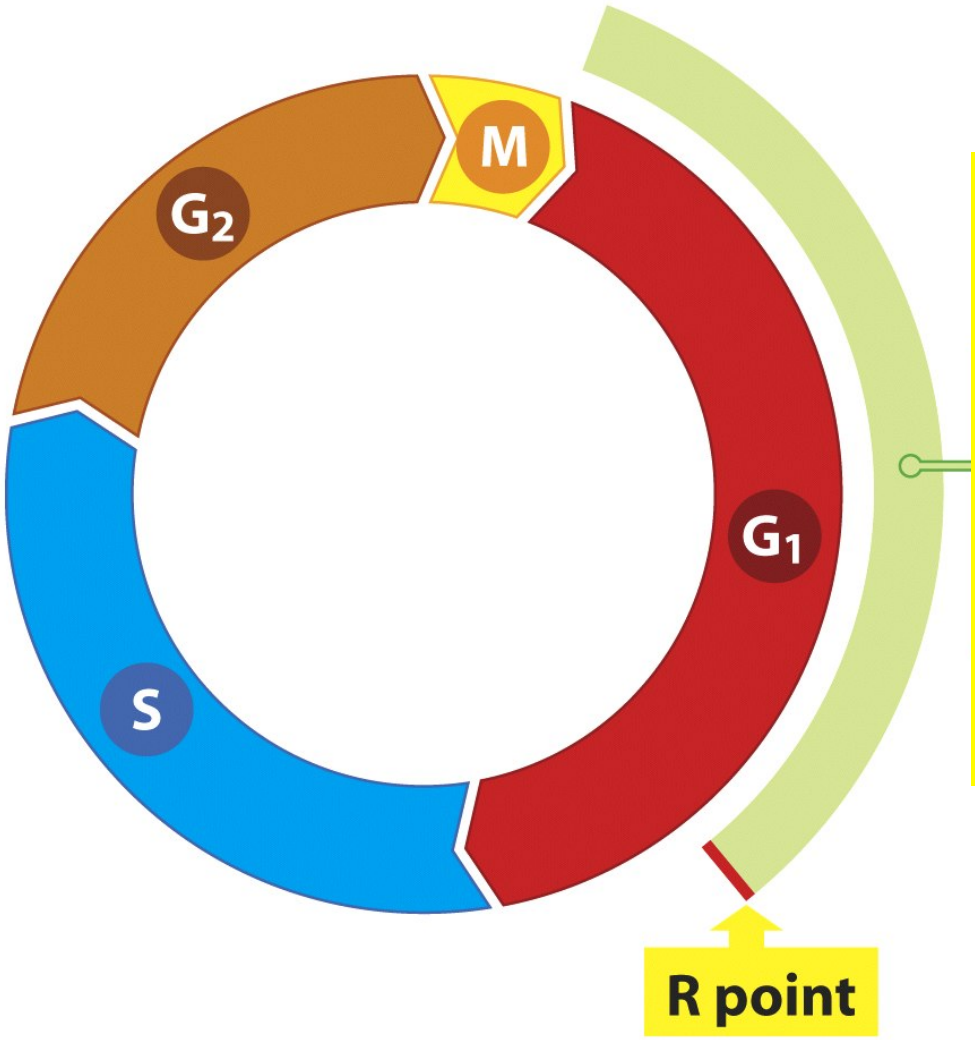
Increased expression of E2F1, E2F2 E2F3 leading to expression of cyclin E	diverse tumor
Increased expression of CDK4 leading to pRb phosphorylation	diverse tumors
Increased expression of Cul1 leading to $p27^{Kip1}$ degradation	diverse tumors
Repression of $p15^{INK4B}$ and $p21^{Cip1}$ expression allowing pRb phosphorylation	diverse tumors

Table 8.3 *The Biology of Cancer* (© Garland Science 2007)

Il controllo del ciclo cellulare

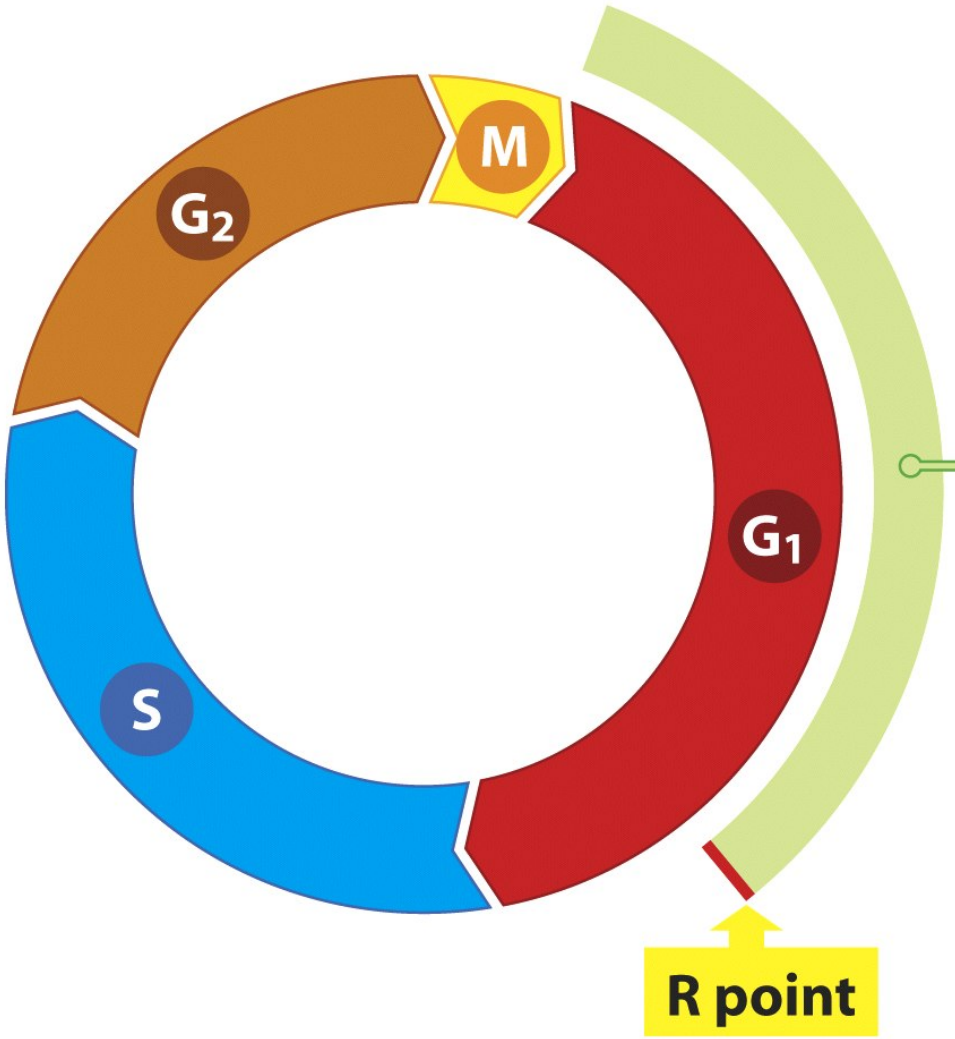


Integrazione di

- **segnali estrinseci (fattori di crescita-citostatici/adesione cell-cell e cell-matrice) con**
- **stimoli intrinseci (stato metabolico, integrità del genoma)**

Figure 8.6 *The Biology of Cancer* (© Garland Science 2007)

Blocco della progressione del ciclo cellulare



- segnali estrinseci citostatici (es. TGFb, inibizione da contatto)
- stimoli intrinseci (danni al DNA, erosione dei telomeri)

inducono produzione di CDKi

Figure 8.6 *The Biology of Cancer* (© Garland Science 2007)

CDKi sono indotti da stimoli intrinseci ed estrinseci

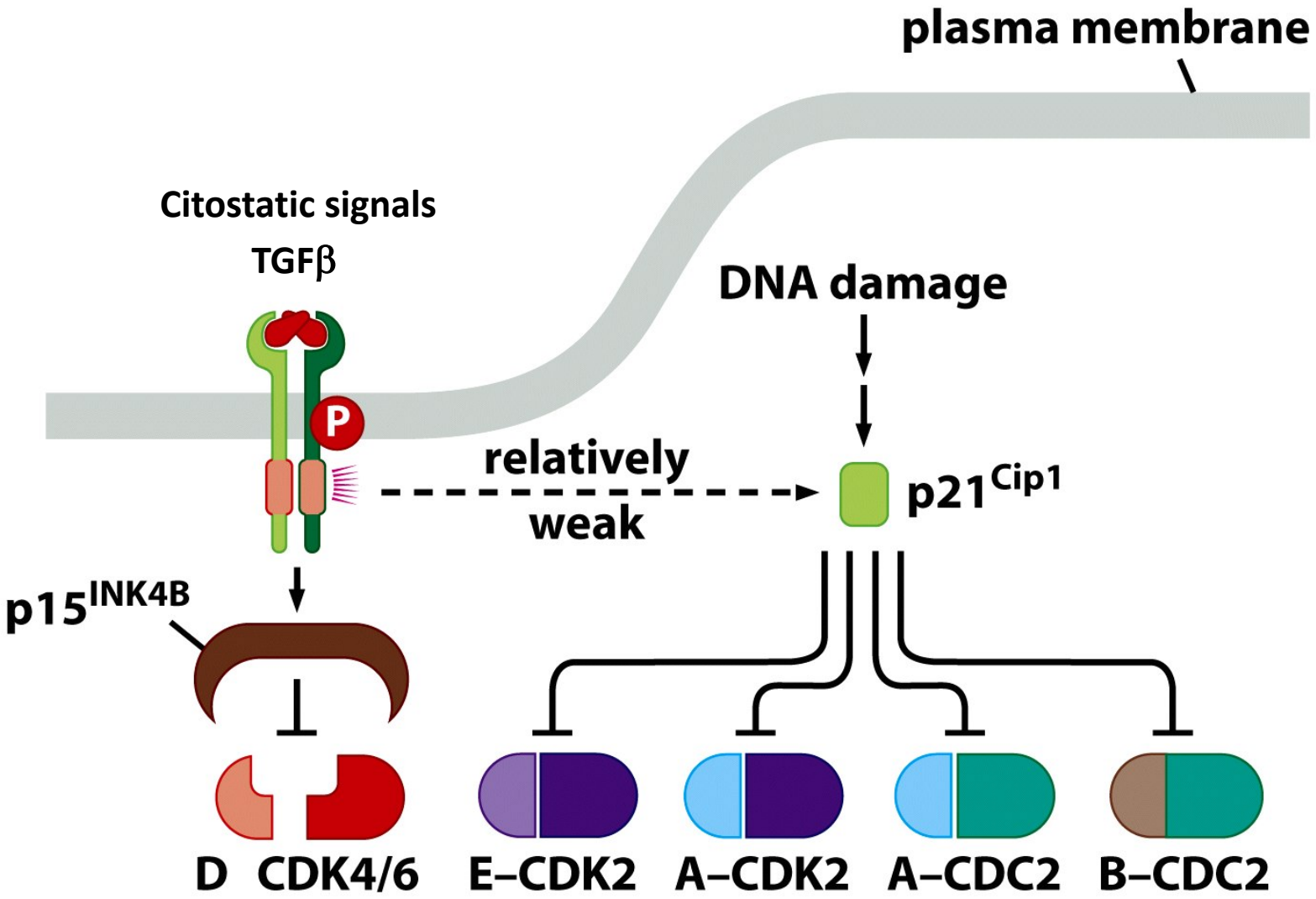


Figure 8.14a *The Biology of Cancer* (© Garland Science 2007)

Gli inibitori stechiometrici delle CDK Inibiscono la transizione G1/S

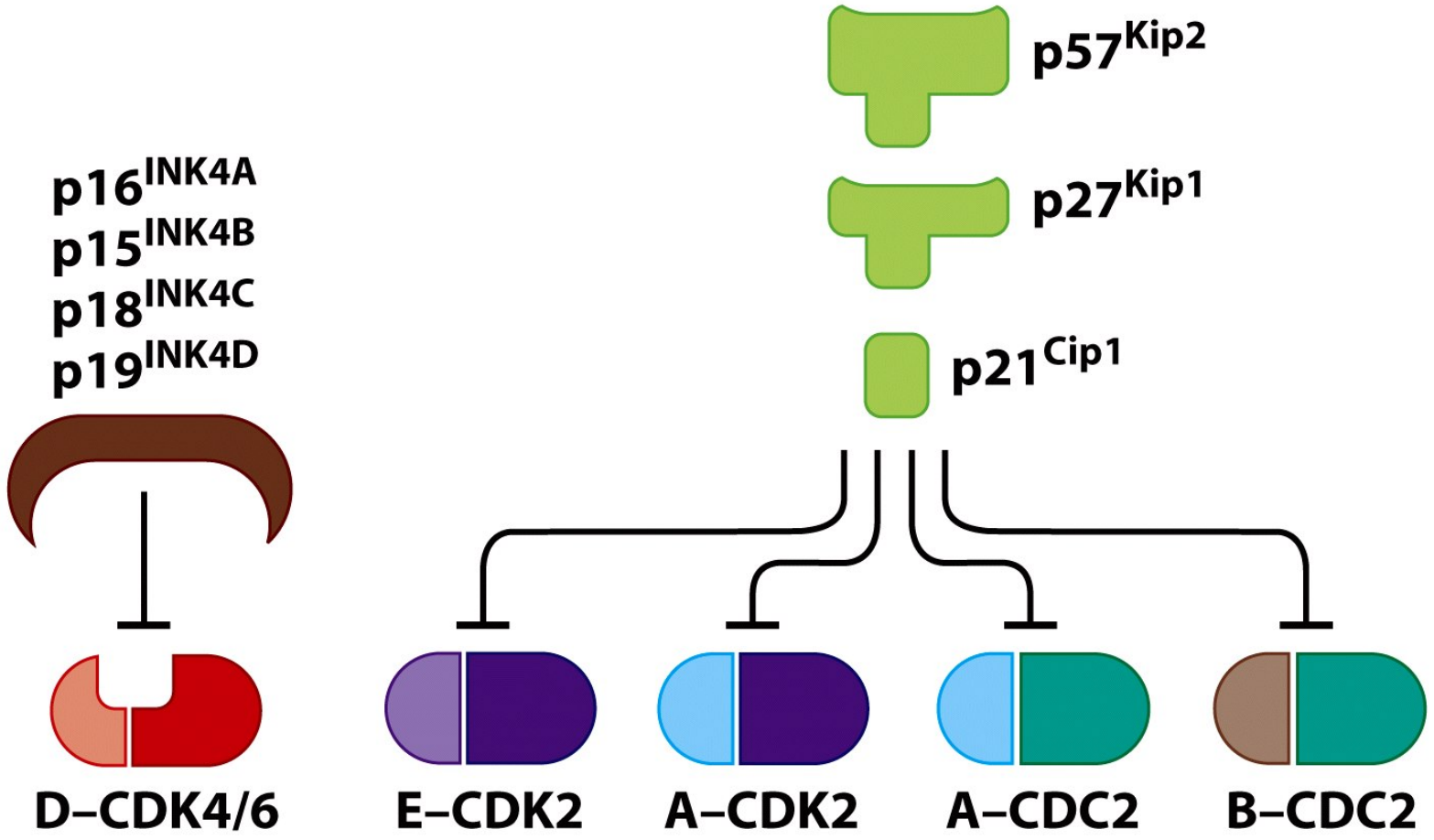


Figure 8.13a *The Biology of Cancer* (© Garland Science 2007)

Alterazioni degli inibitori stechiometrici delle CDK promuovono la transizione G1/S

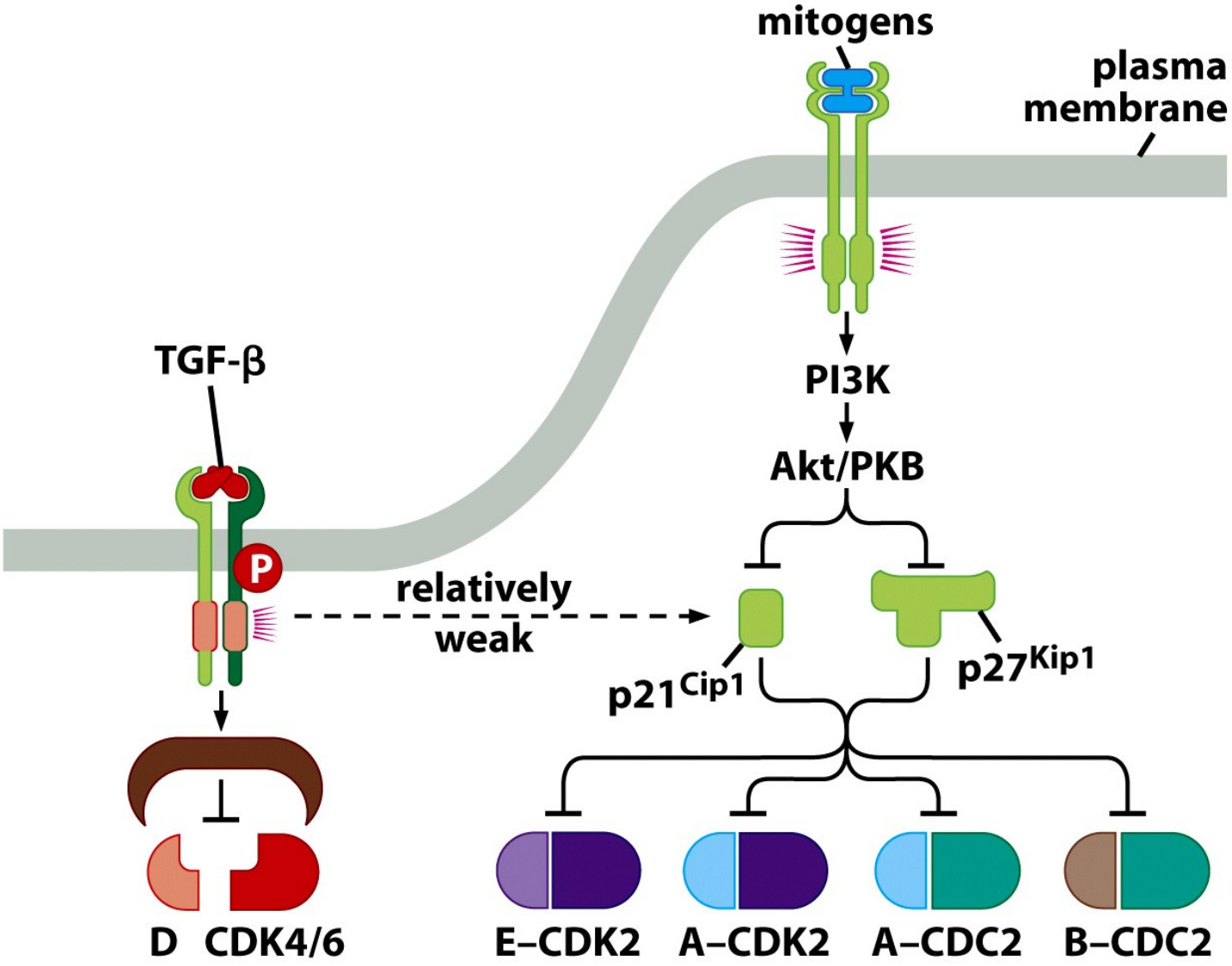


Figure 8.15a *The Biology of Cancer* (© Garland Science 2007)

Eventi che promuovono la proliferazione cellulare nei tumori

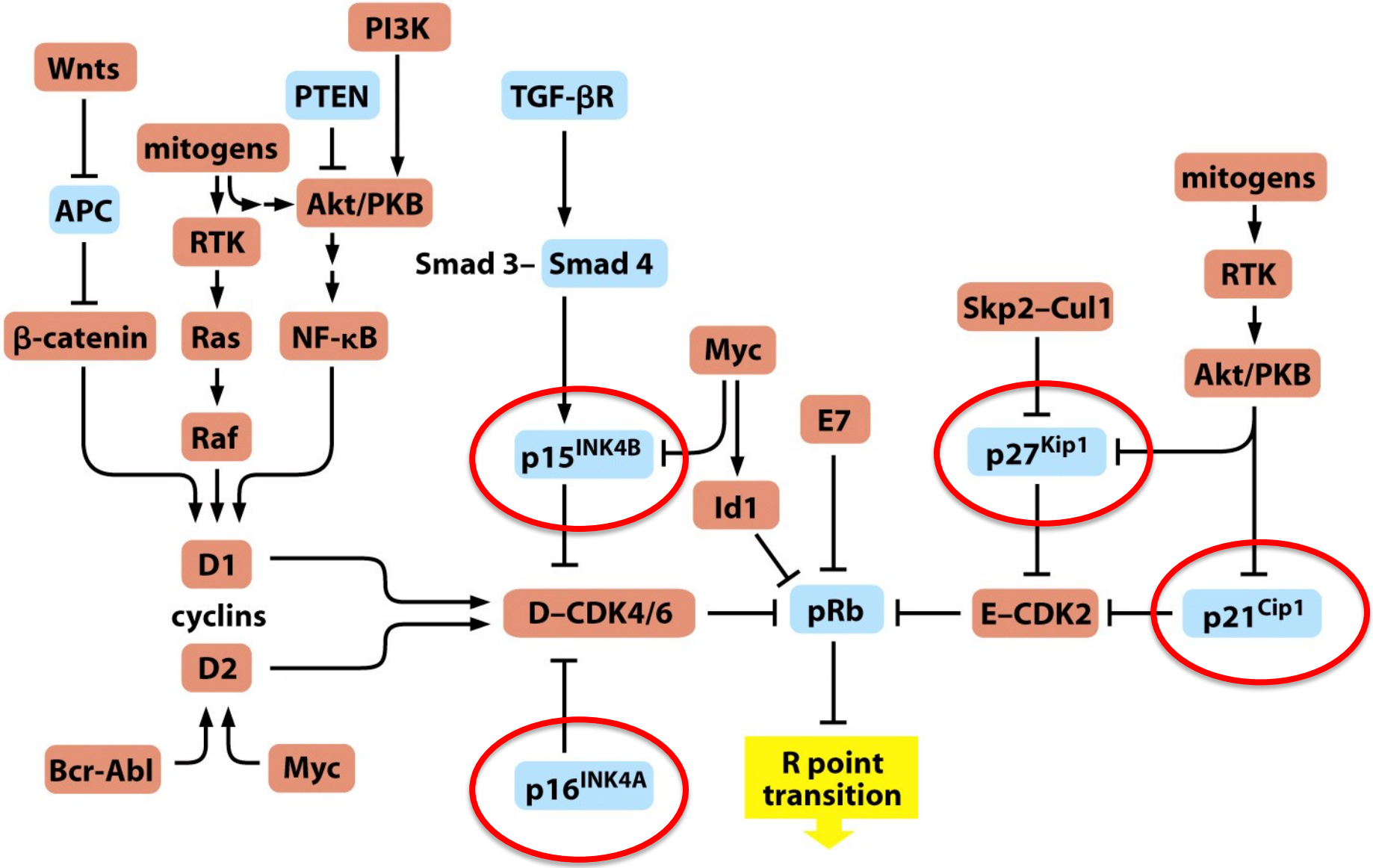


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

Il locus Ink4a/Arf codifica per gli oncosoppressori p16 e ARF

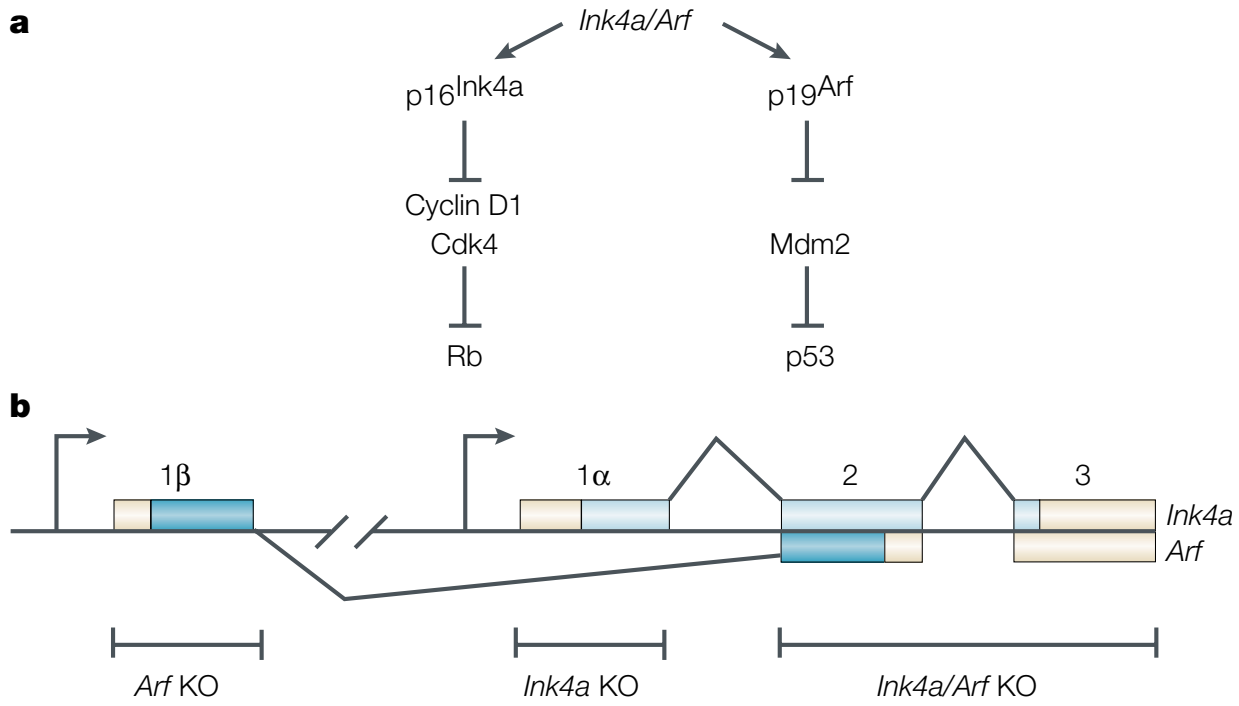


Figure 1 | **The *Ink4a/Arf* locus. a** | The two products of the mouse *Ink4a/Arf* locus, $p16^{Ink4a}$ and $p19^{Arf}$ ($p14^{ARF}$ in human) indirectly regulate the retinoblastoma protein (Rb) and p53, respectively. **b** | Alternative first exons (1α and 1β) that are transcribed from different promoters (arrows) specify the 5' ends of the *Ink4a* and *Arf* transcripts, respectively. These are spliced to the same acceptor site in exon 2, which is translated in alternative frames. *Ink4a* coding sequences in exons 1α, 2 and 3 are denoted by light shading, and *Arf* coding sequences in exons 1β and 2 are indicated by dark blue shading. The regions that are disrupted in the different knockout (KO) mouse strains are indicated below the figure. The schematic is not drawn to scale, and in both the human and mouse genomes, exons 1α and 1β are separated by >15 kb. (**b** is adapted from REF. 14.)

Scherr C., Nat. Rev. Mol. Cell. Biol., 2001

Acquisizione dell'immortalità replicativa

Indipendenza dai segnali di crescita

Resistenza ai segnali inibitori della crescita

Riprogrammazione del metabolismo cellulare

Evasione dal sitema immunitario

Evasione dai meccanismi oncosoppressivi intrinseci

Potenziale replicativo illimitato

Mutazione e instabilità genomica

Infiammazione pro-tumorale

Angiogenesi

Invasione e metastasi

Le cellule di un tumore effettuano un elevato numero di divisioni

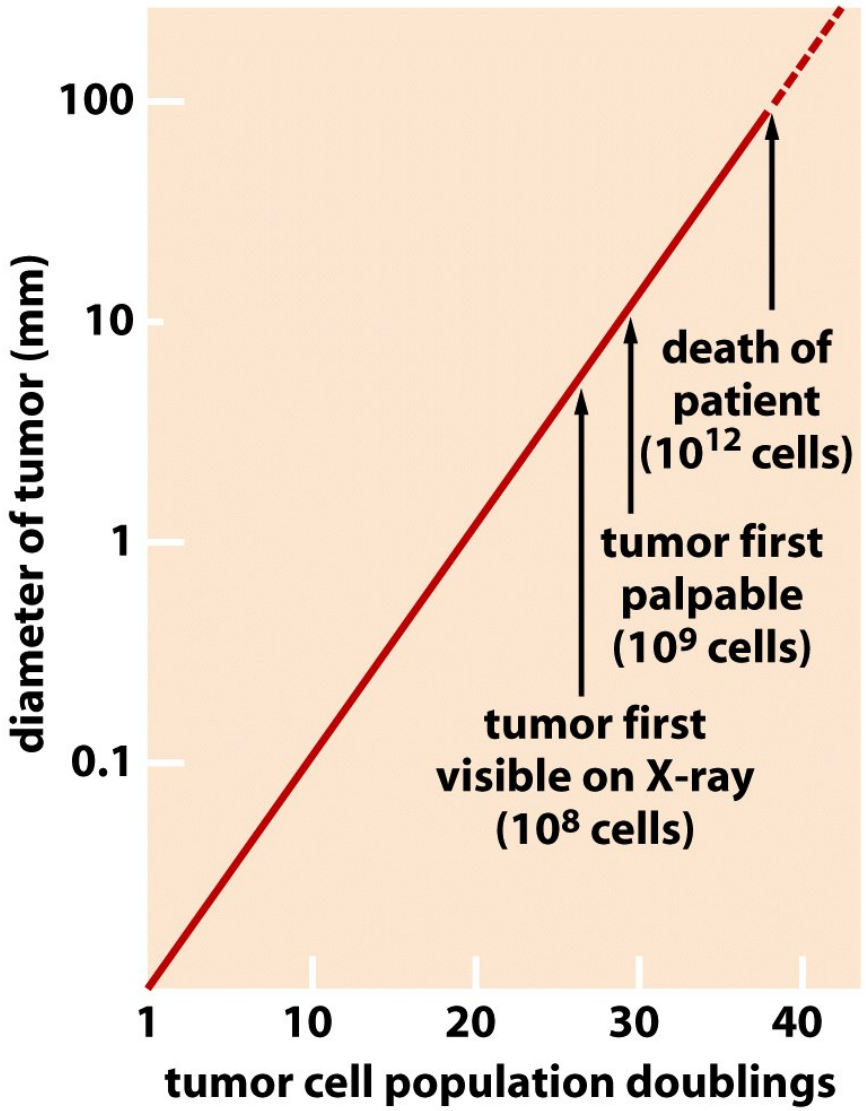
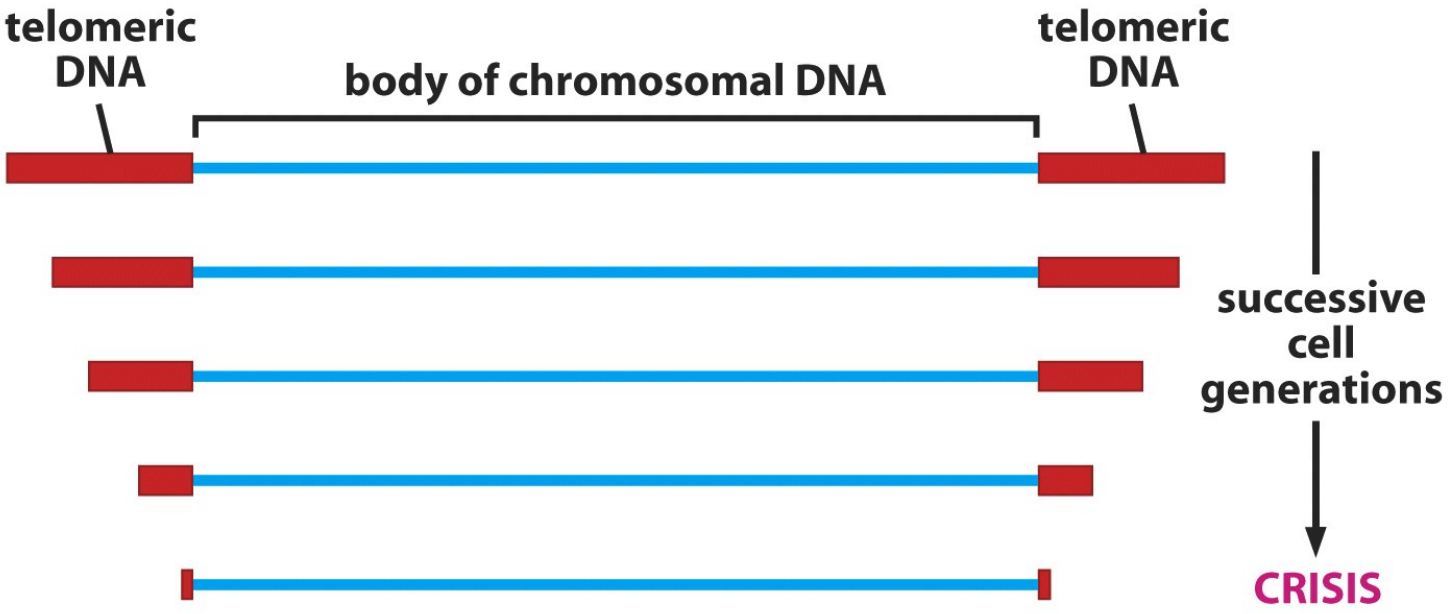


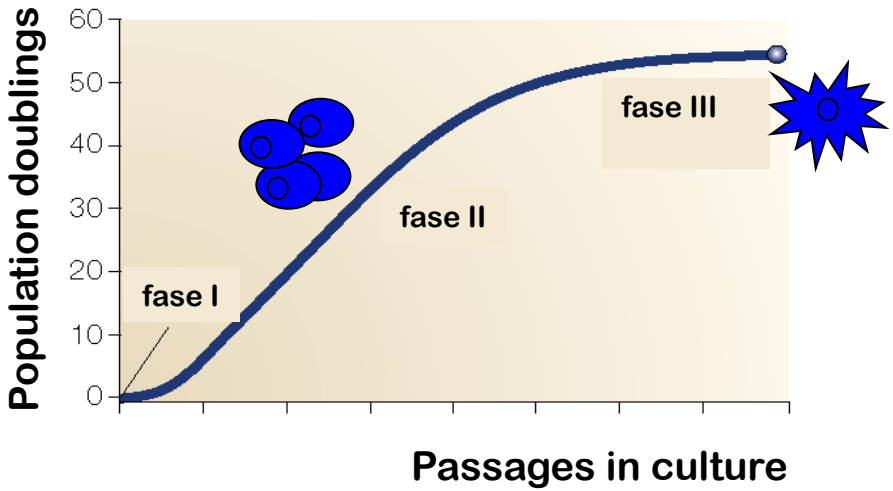
Figure 10.5a *The Biology of Cancer* (© Garland Science 2007)

Cellule somatiche normali subiscono il progressivo accorciamento dei telomeri ad ogni divisione cellulare

End-replication problem:
cells lose 50-200 bp of telomeric DNA
during each S phase



L'accorciamento dei telomeri può causare alterazioni strutturali e induce l'arresto permanente della proliferazione



Hayflick's limit

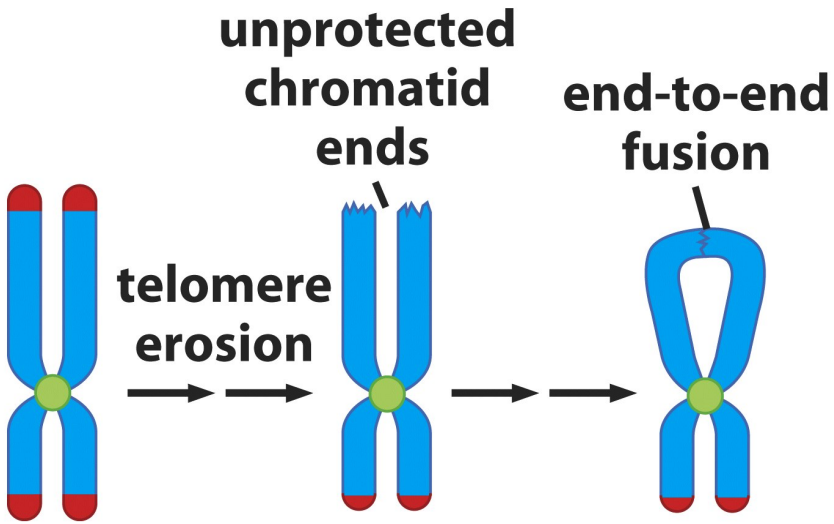


Figure 10.14a *The Biology of Cancer* (© Garland Science 2007)

La struttura dei telomeri protegge le estremità dei cromosomi

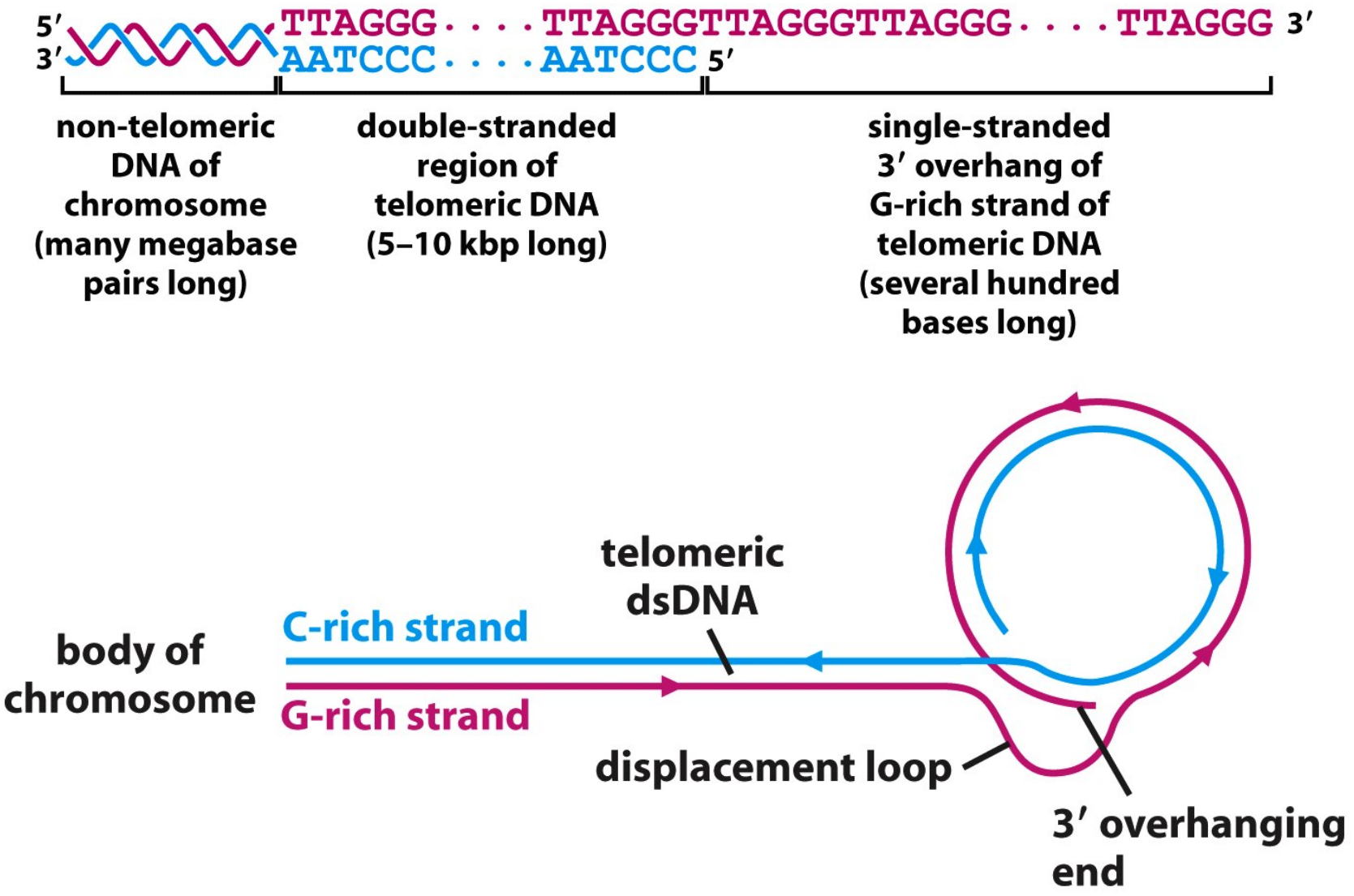
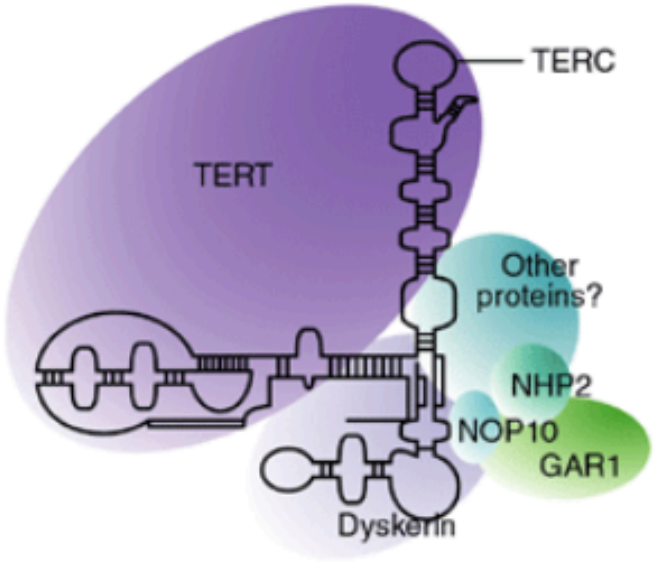


Figure 10.13b *The Biology of Cancer* (© Garland Science 2007)

L'allungamento dei telomeri è effettuato dall'enzima telomerasi



TERT: protein component

TERC: non-coding RNA component

core components

Dyskerin, NOP10, NHP2, GAR1

improve activity

Elisabeth Blackburn
Carol Greider
Jack Szostak
Nobel Price 2009

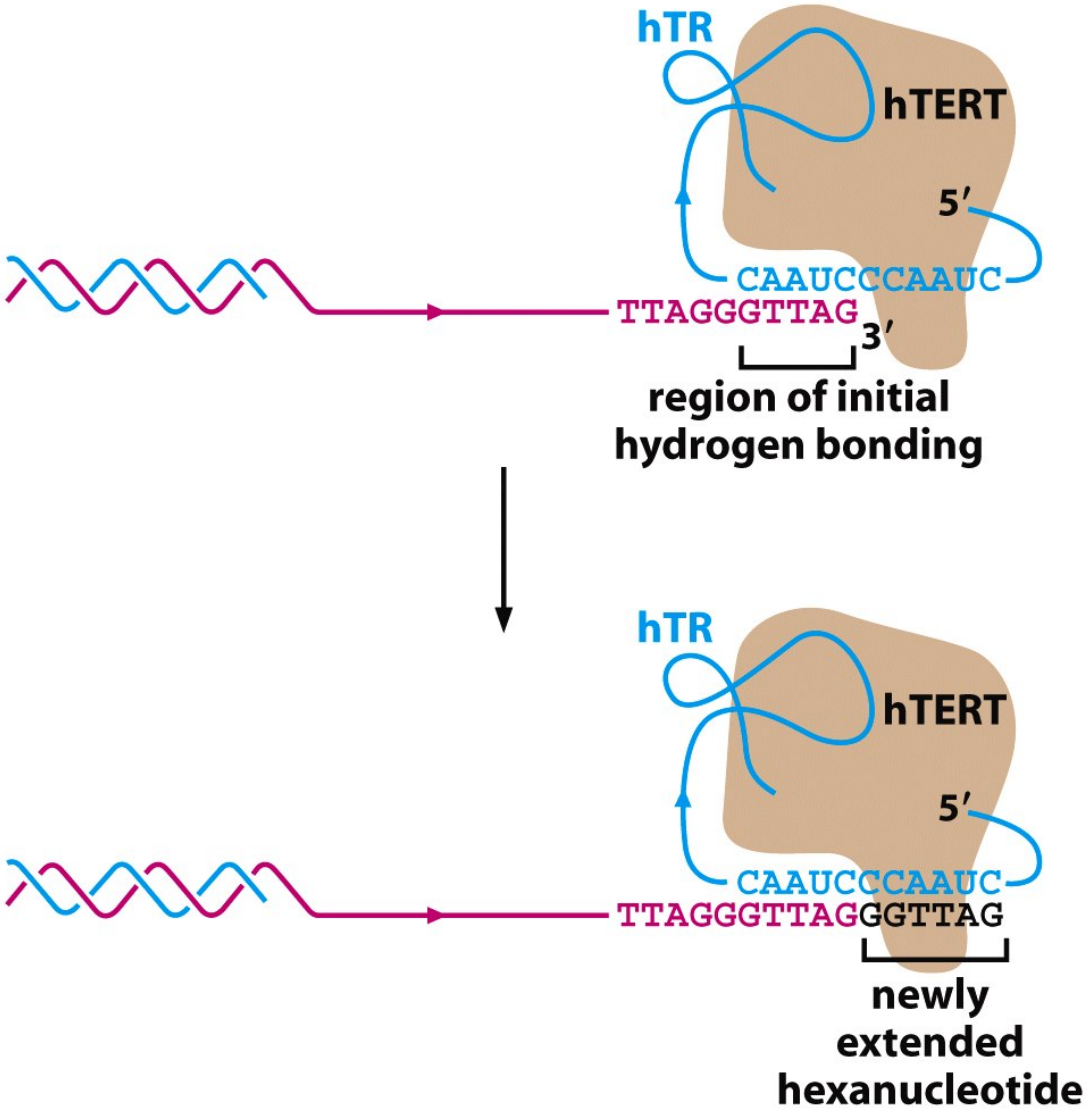
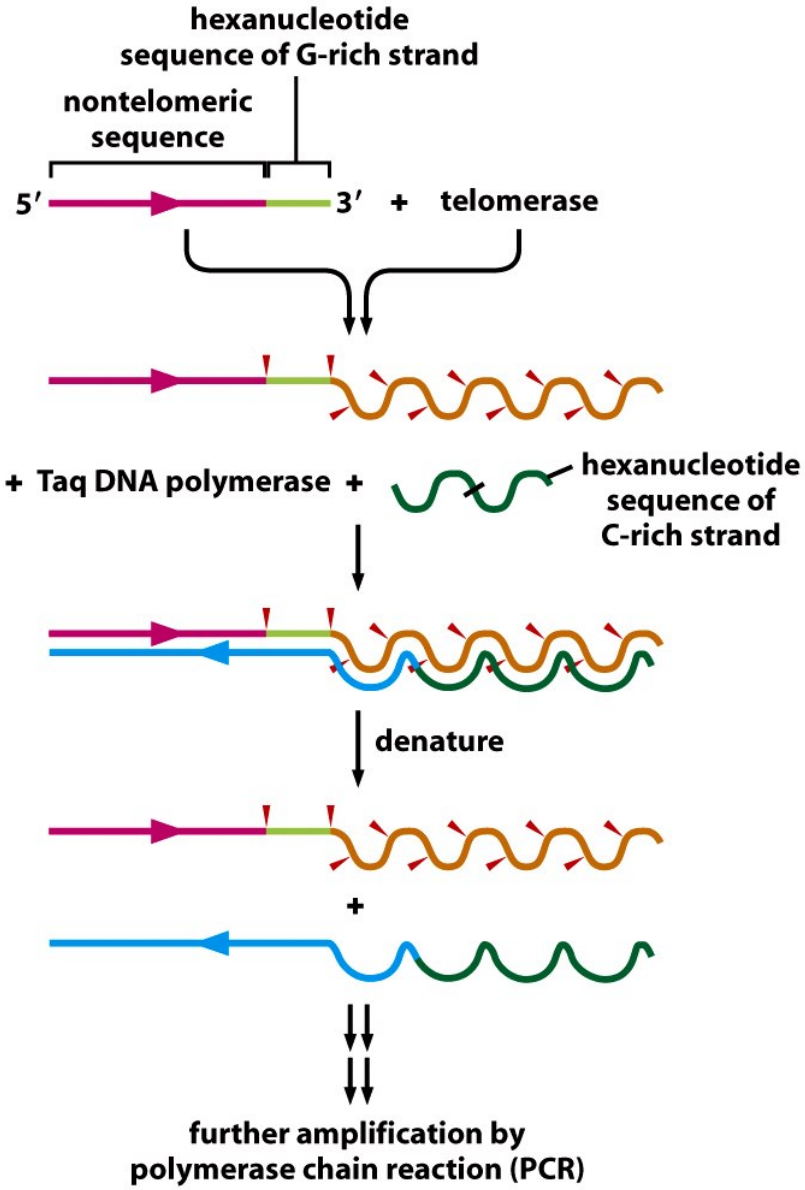
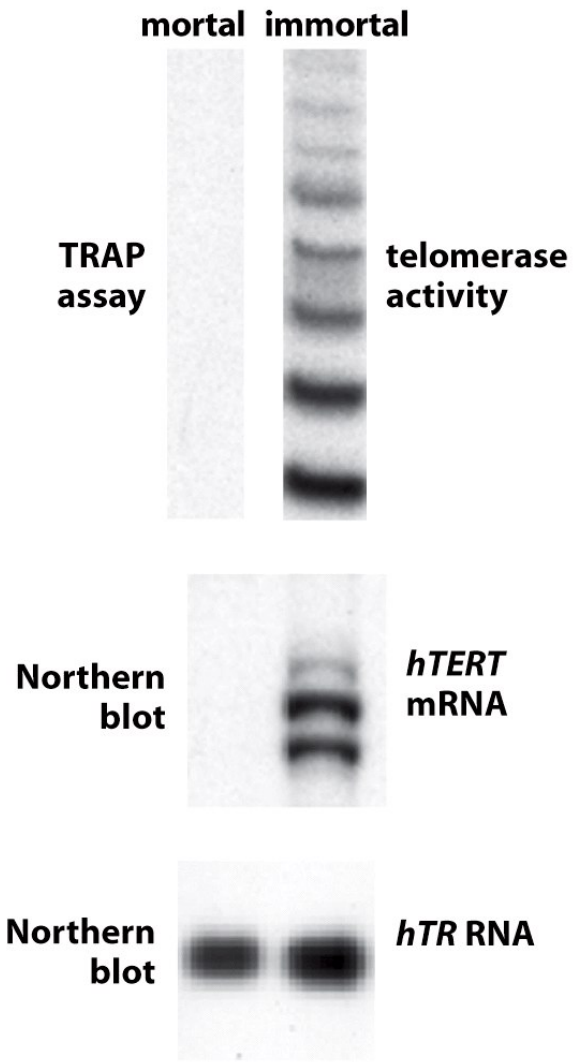


Figure 10.23a *The Biology of Cancer* (© Garland Science 2007)

Telomerase activity (TRAP) assay





La sovraespressione della telomerasi immortalizza cellule normali

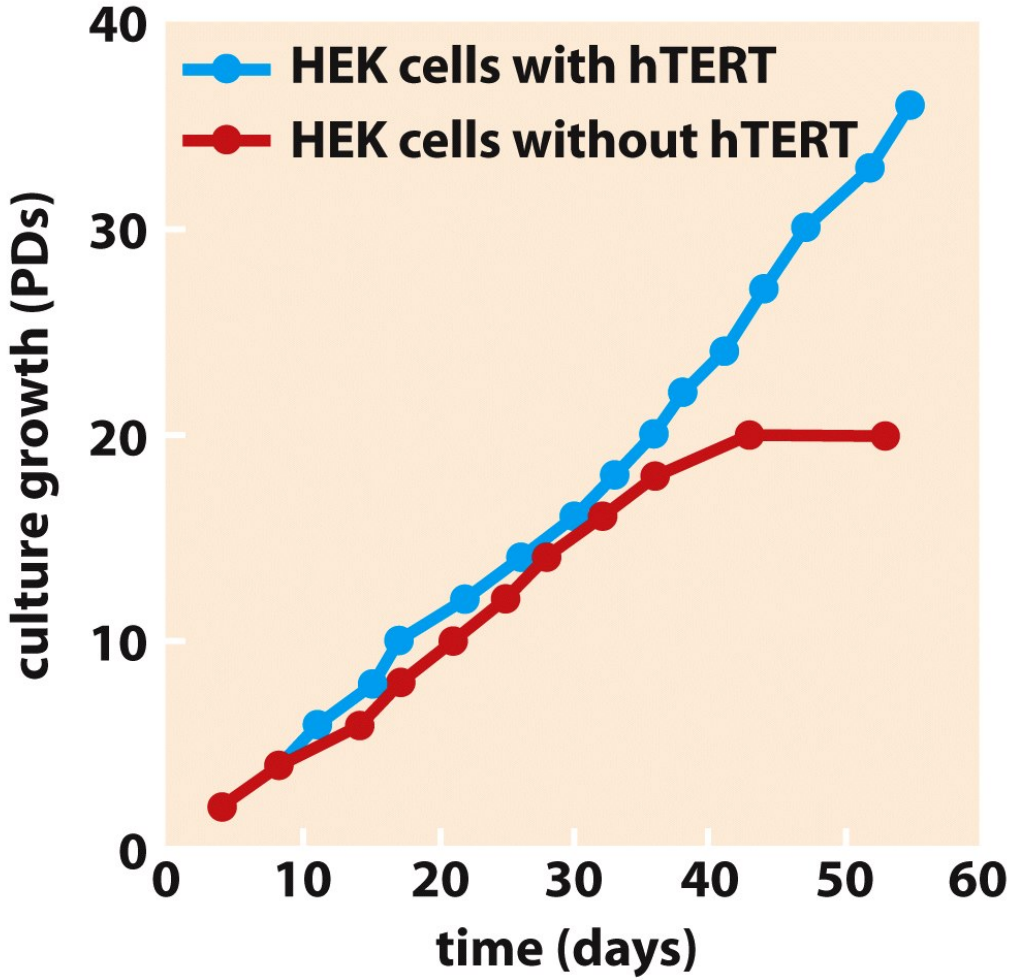


Figure 10.25b *The Biology of Cancer* (© Garland Science 2007)

La riattivazione della telomerasi nei tumori è associata a prognosi negativa

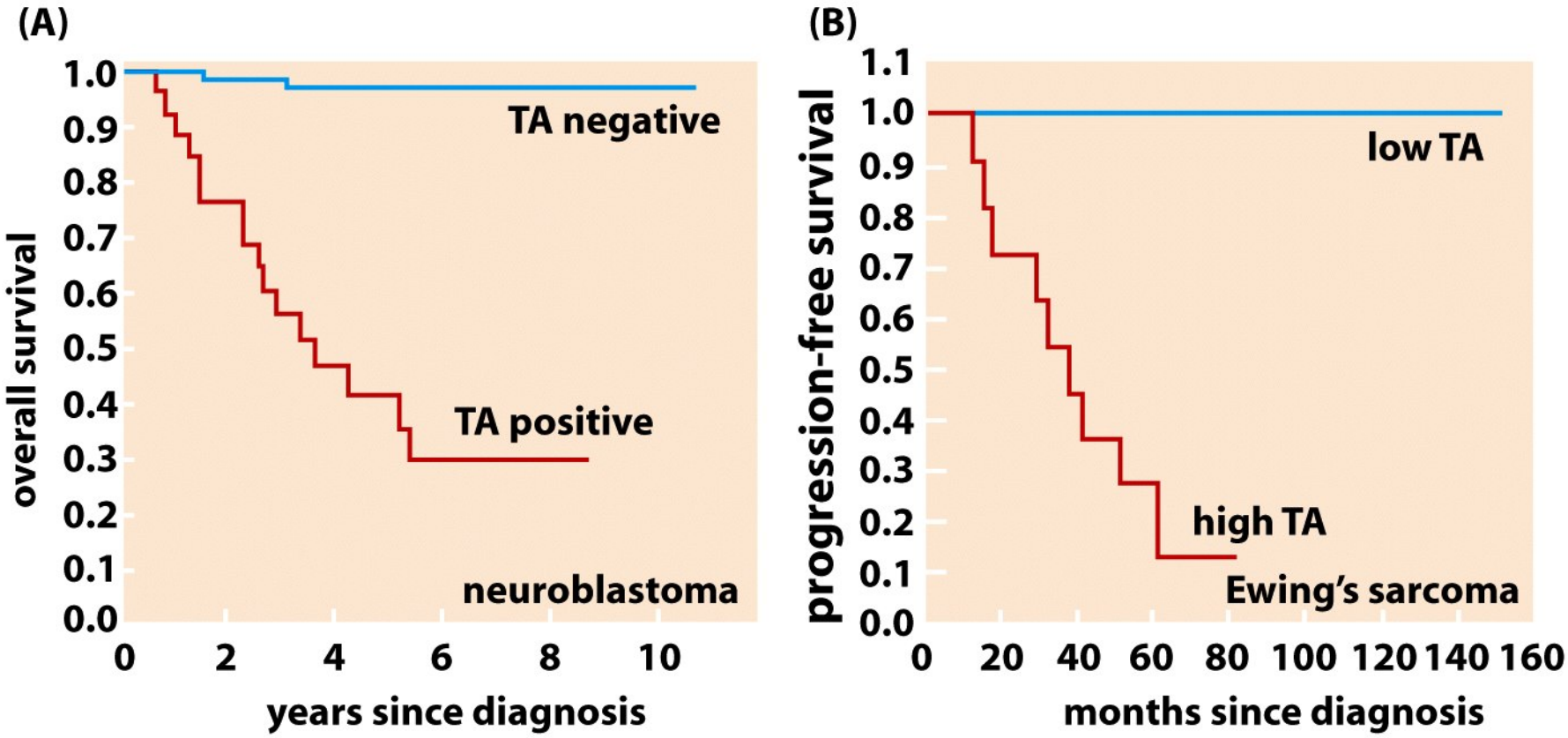


Figure 10.28 *The Biology of Cancer* (© Garland Science 2007)

Re-activation of telomerase is a hallmark of human cancer (90%)

Tissue	Incidence
Head/neck and lung	78-100%
GI and pancreas	85-100%
Hepatic tissue	86%
Breast	75-88%
Cervical/endometrial/vaginal/ovarian	91-100%
Prostate	90%
Kidney/urinary	83-100%
Neural*	50-100%
Skin	83-95%
Hematological tissue	73-100%

Or: Alternative lengthening of telomeres (ALT) via recombination (10% of cancers)

*retinoblastoma, meningioma, neuroblastoma,

Shay 1997

Alternative lengthening of telomeres (ALT)

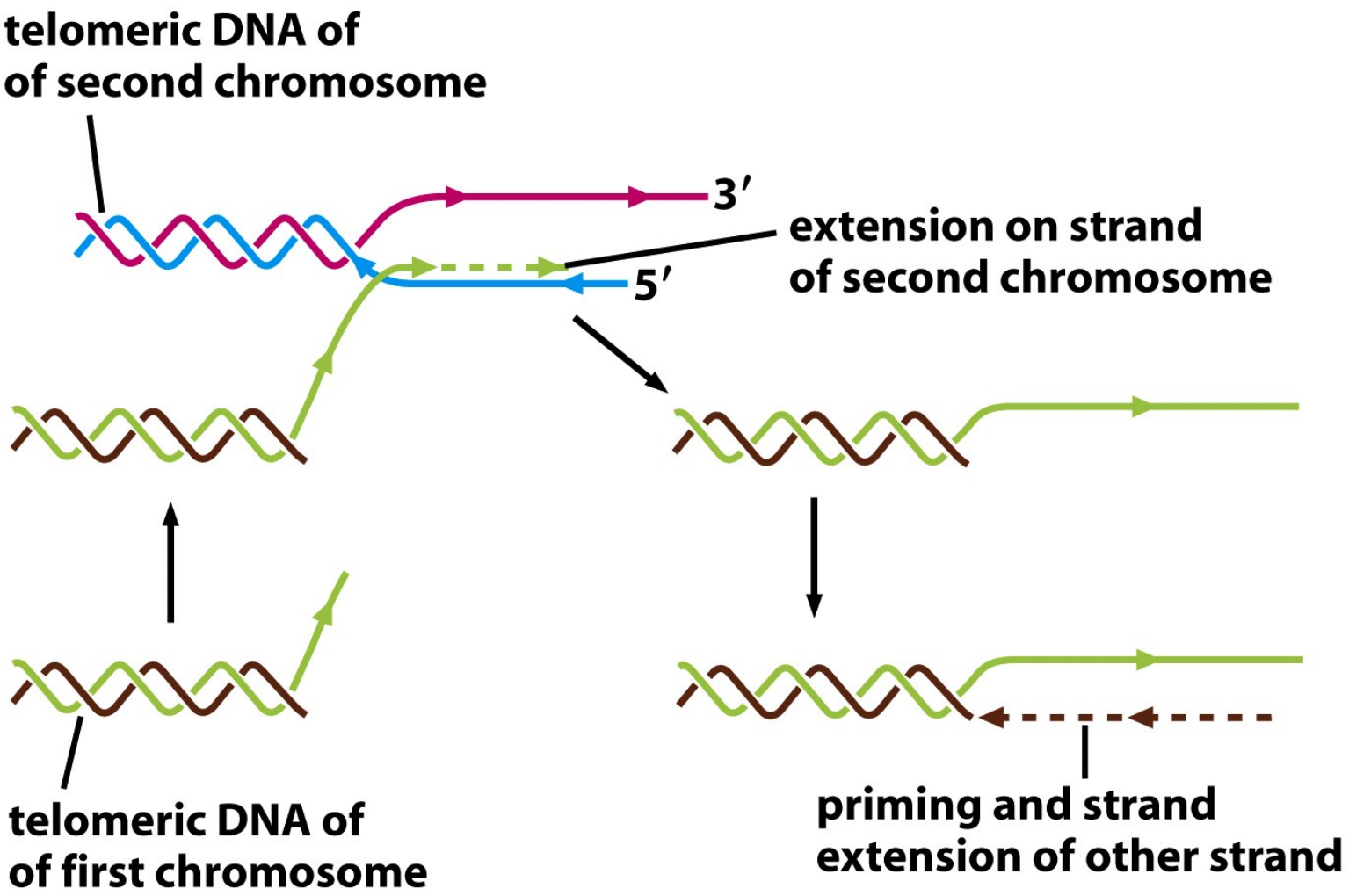


Figure 10.30 *The Biology of Cancer* (© Garland Science 2007)