Cell Cycle Regulation-Part II

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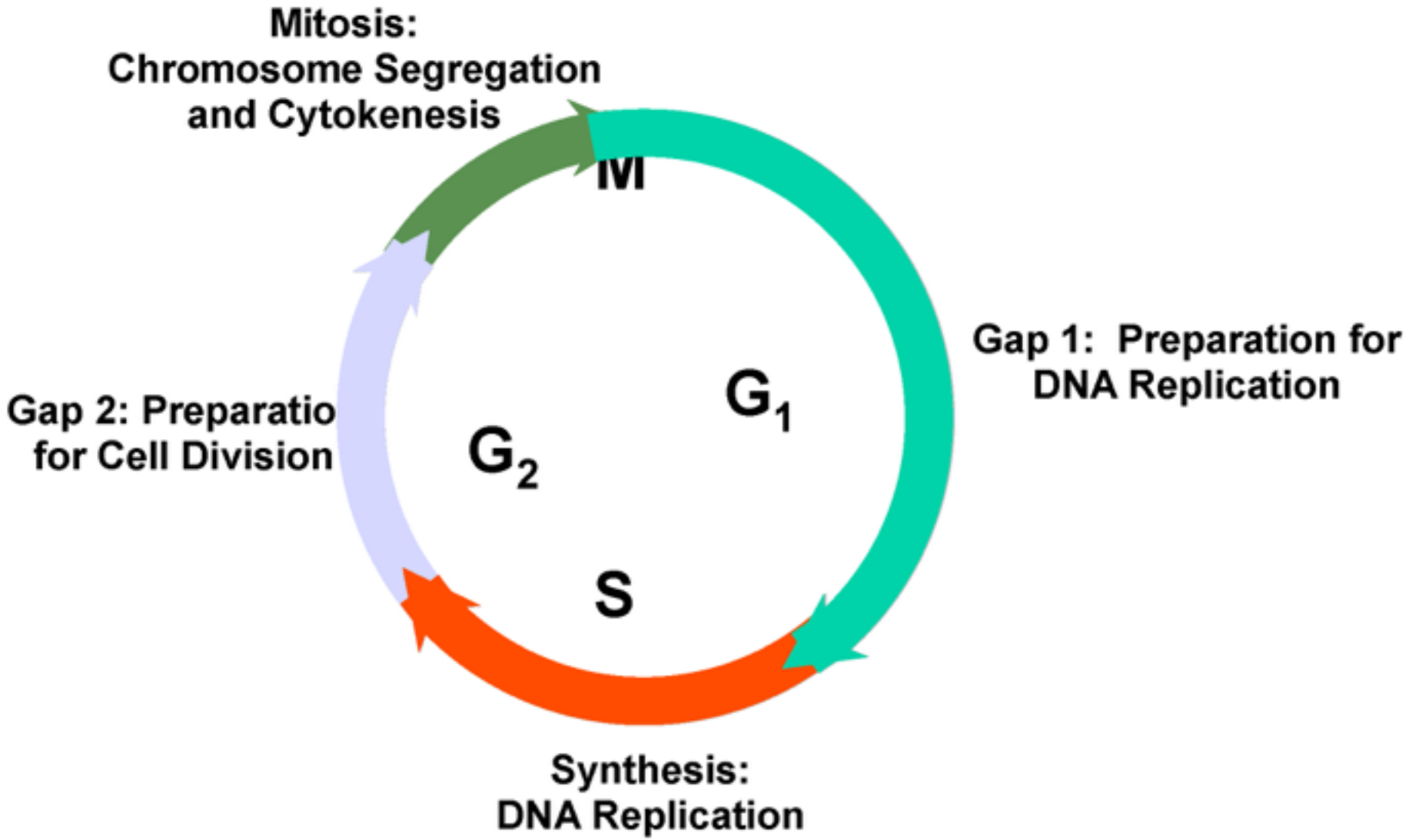
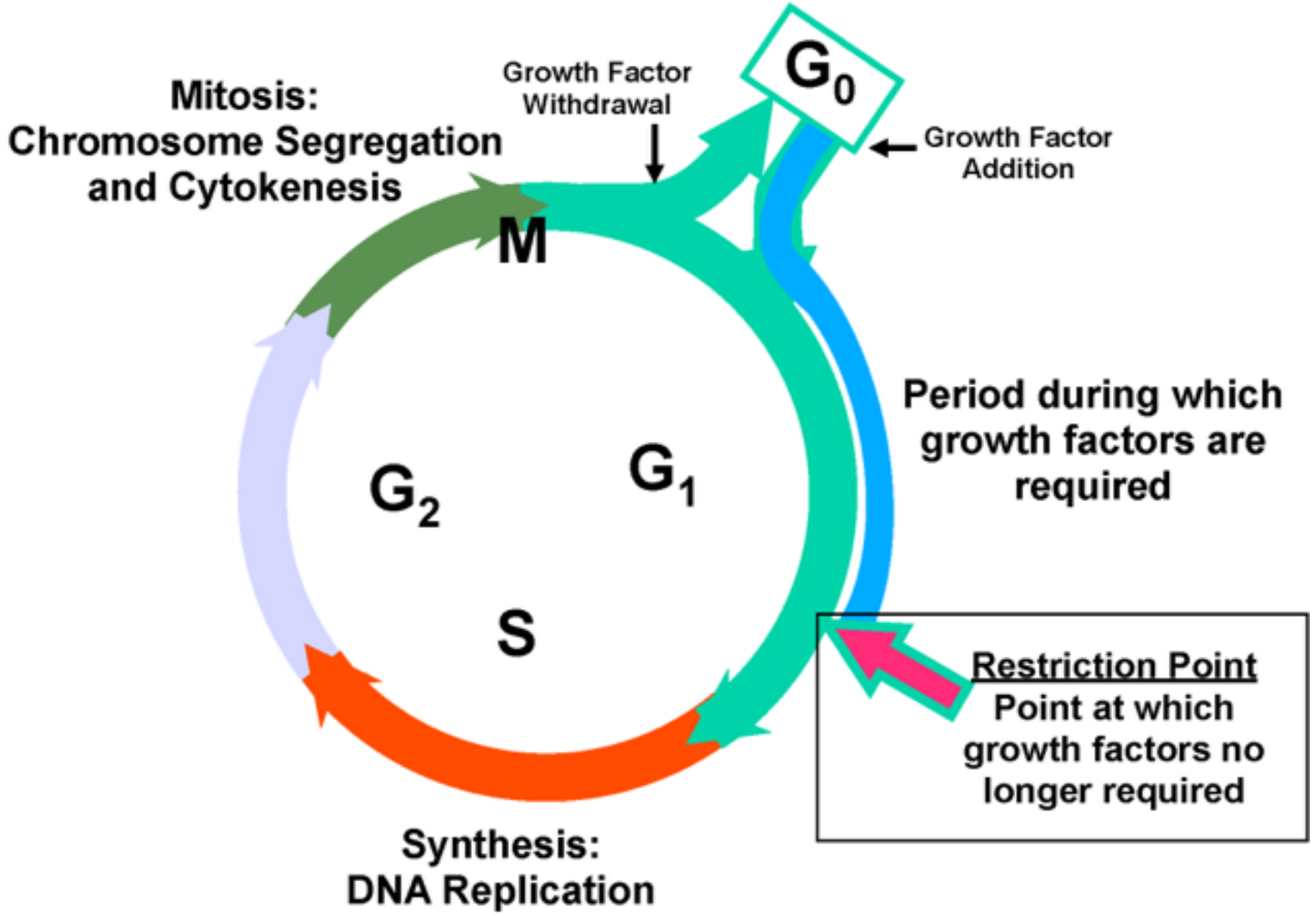
Topics to be discussed

- Recap of the last cell cycle lecture
- Alteration of cellular signaling in cancer
- Cell cycle and apoptosis
- Differences between cancer and normal cells
- Cell cycle regulation in lung carcinogenesis
- The role of ROS in cell cycle

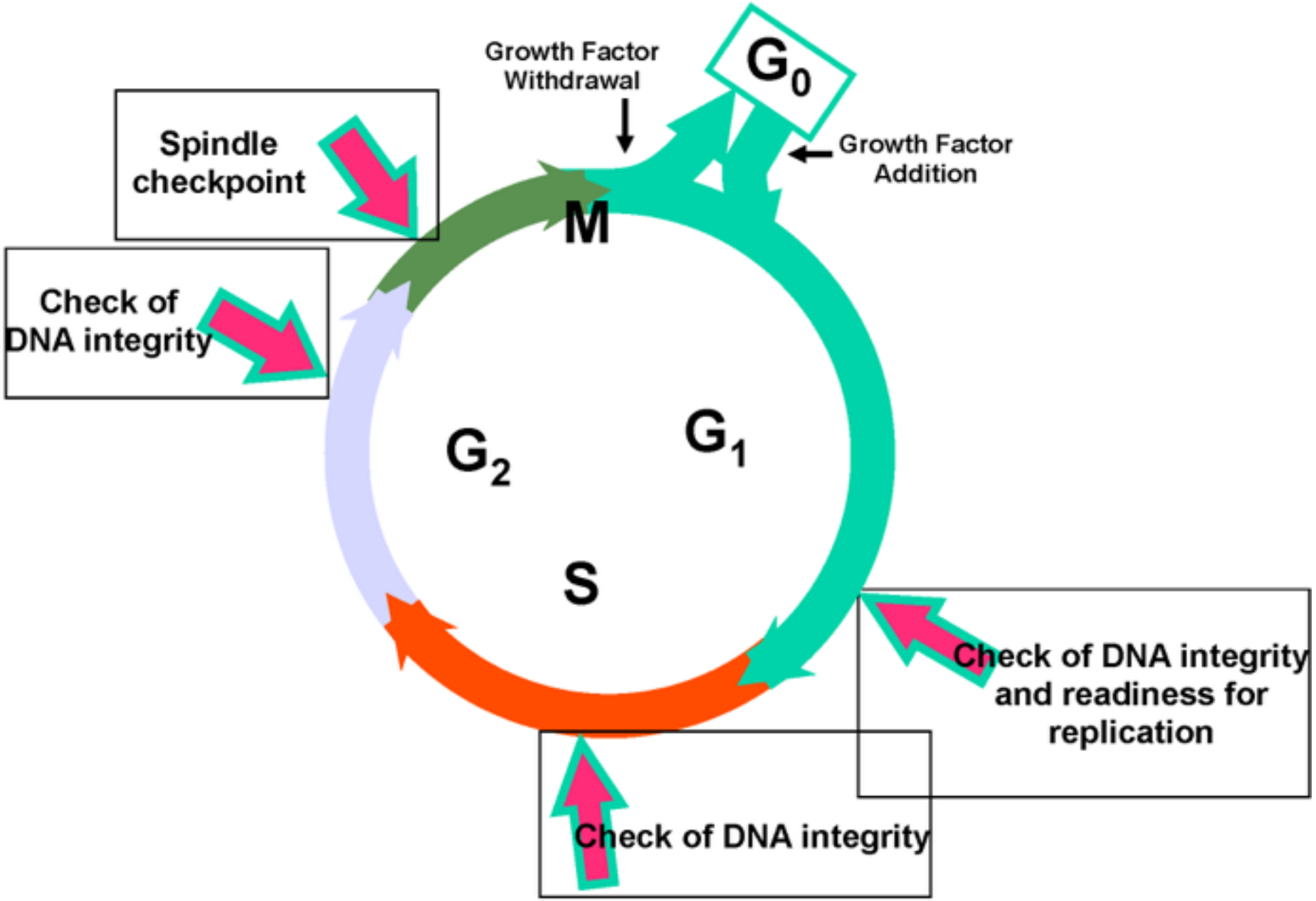
Phases of the cell cycle



Phases of the cell cycle



Cell cycle checkpoints



Cyclins Regulate Cyclin-Dependent Kinases

Cyclin-dependent kinases (cdks)

- Multigene Family [cdk4, cdk6, cdk2, cdk1 (cdc2)]
- Serine/Threonine Kinases
- Require Cyclin Binding for Activity
- Regulated by Phosphorylation
- Regulated by Cyclin-Dependent Kinase Inhibitors (ckis)

Cyclins

- Regulatory Subunits of Cyclin/cdk Complexes
- Main Cell Cycle Regulatory Cyclins:
  cyclin D1-3, cyclin E, cyclin A and cyclin B
- Cyclin/cdk Associations:
  cyclin D/cdk4, cyclin D/cdk6, cyclin E/cdk2,
  cyclin A/cdk2, cyclin A/cdk1 and cyclin B/cdk1
- Expression Oscillates During the Cell Cycle

Cyclin expression during cell cycle

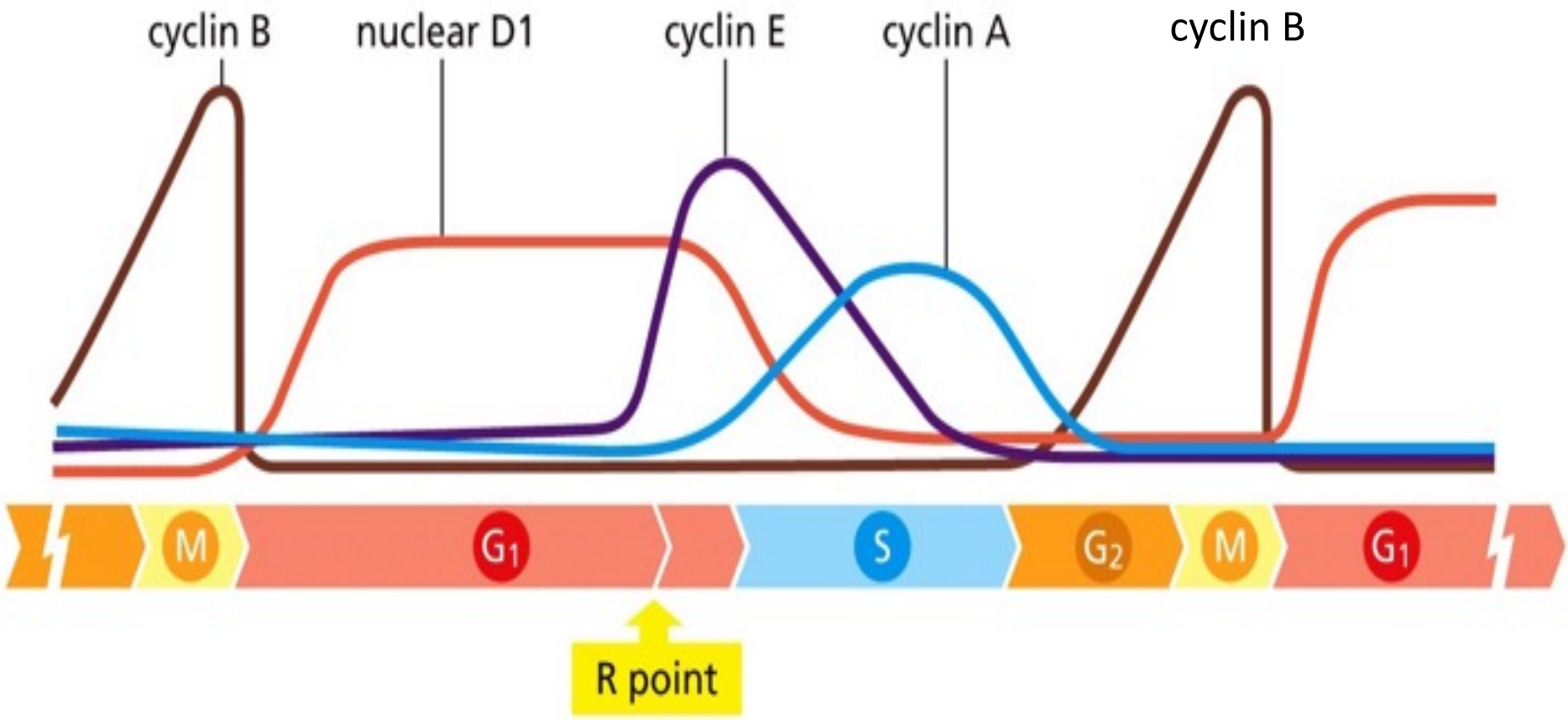


Figure 8.10 The Biology of Cancer (© Garland Science 2014)

Control of cyclin levels during the cell cycle

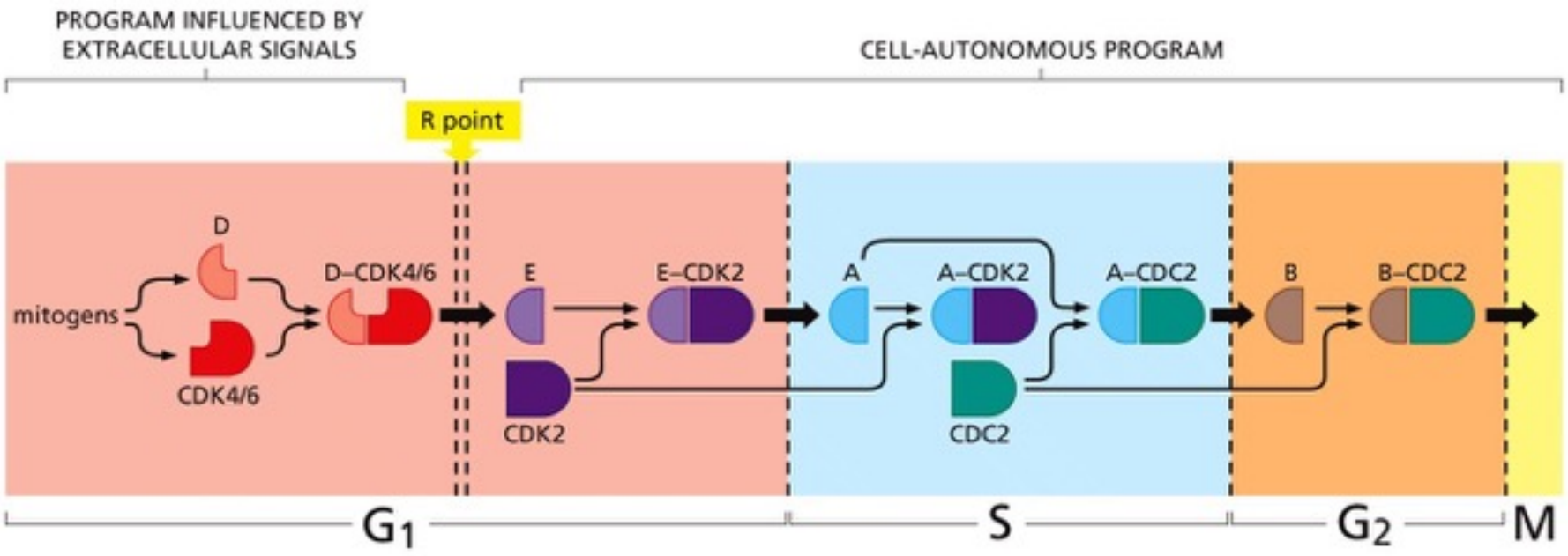


Figure 8.12 The Biology of Cancer (© Garland Science 2014)

Cyclin Dependent-Kinase Inhibitors (ckis)

INK Family

- $p15^{INK4b}$, $p16^{INK4a}$, $p18^{INK4c}$, $p19^{INK4d}$
- Bind cyclin D-associating cdks (cdk4 and cdk6)
- Block interaction of cdks with cyclins

CIP/KIP Family

- $p21^{WAF1/CIP1}$, $p27^{KIP1}$, $p57^{KIP2}$
- Inhibit Cyclin A/cdk2 and Cyclin E/cdk2
- Required for assembly of Cyclin D/cdk complexes
- Do not inhibit cyclin D/cdk complexes at physiological levels

Interaction of cdki's with cdks

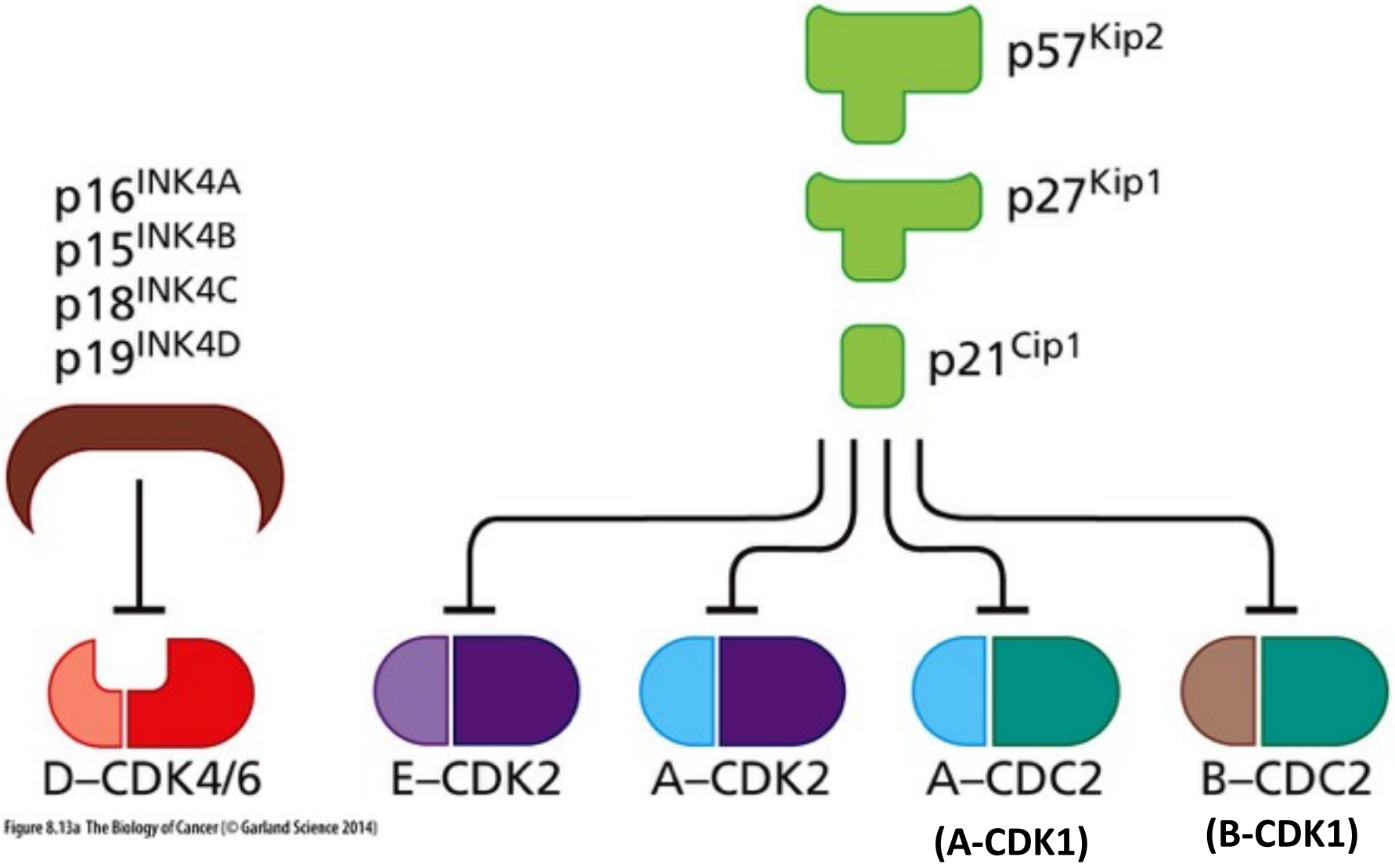


Figure 8.13a The Biology of Cancer (© Garland Science 2014)

Cip/Kip cdki's stimulate cyclin D/cdk association and activity

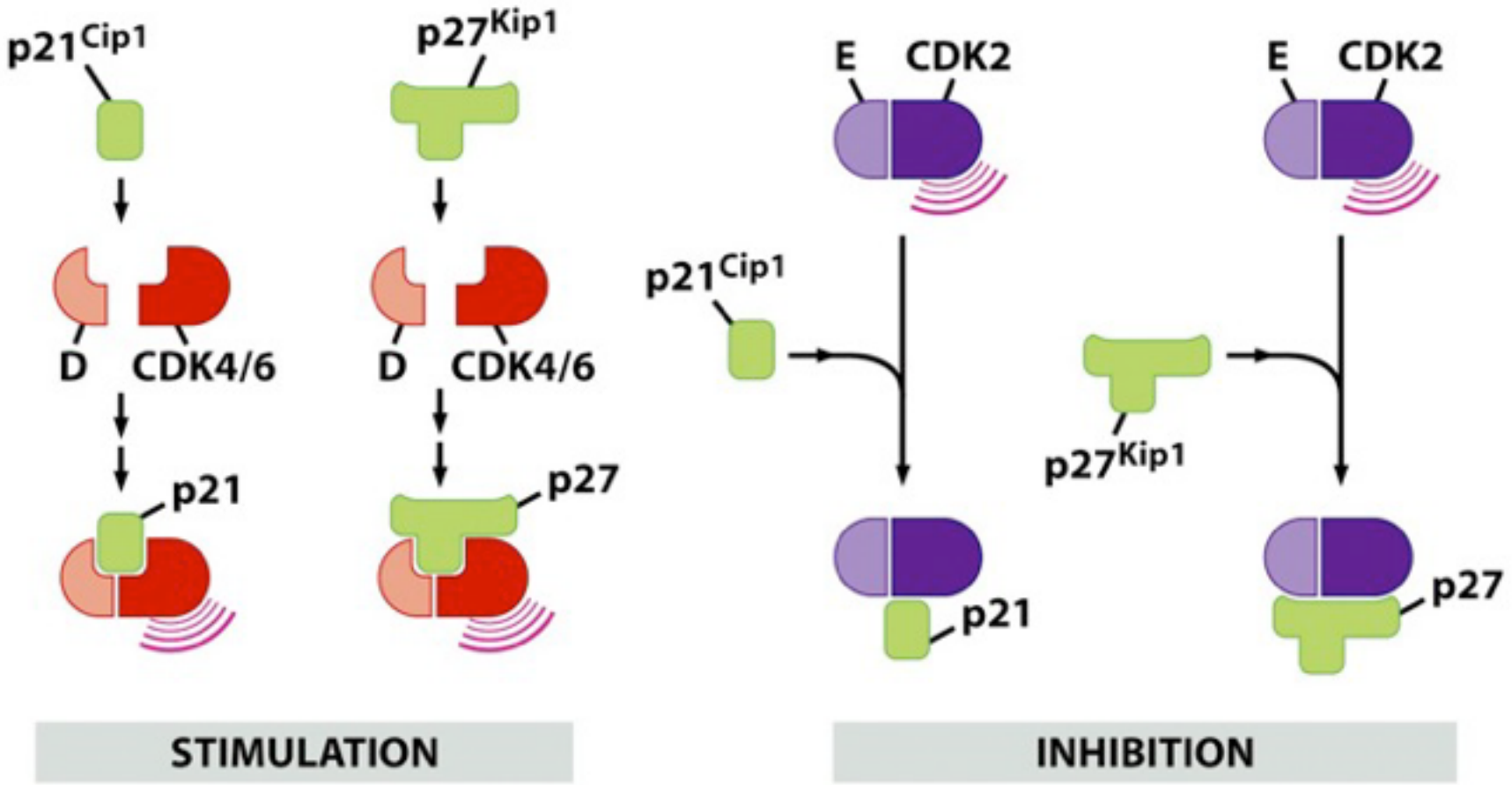


Figure 8.17a *The Biology of Cancer* (© Garland Science 2007)

Cyclin D/cdk complexes sequester cip/kip proteins form cyclin E/cdk2

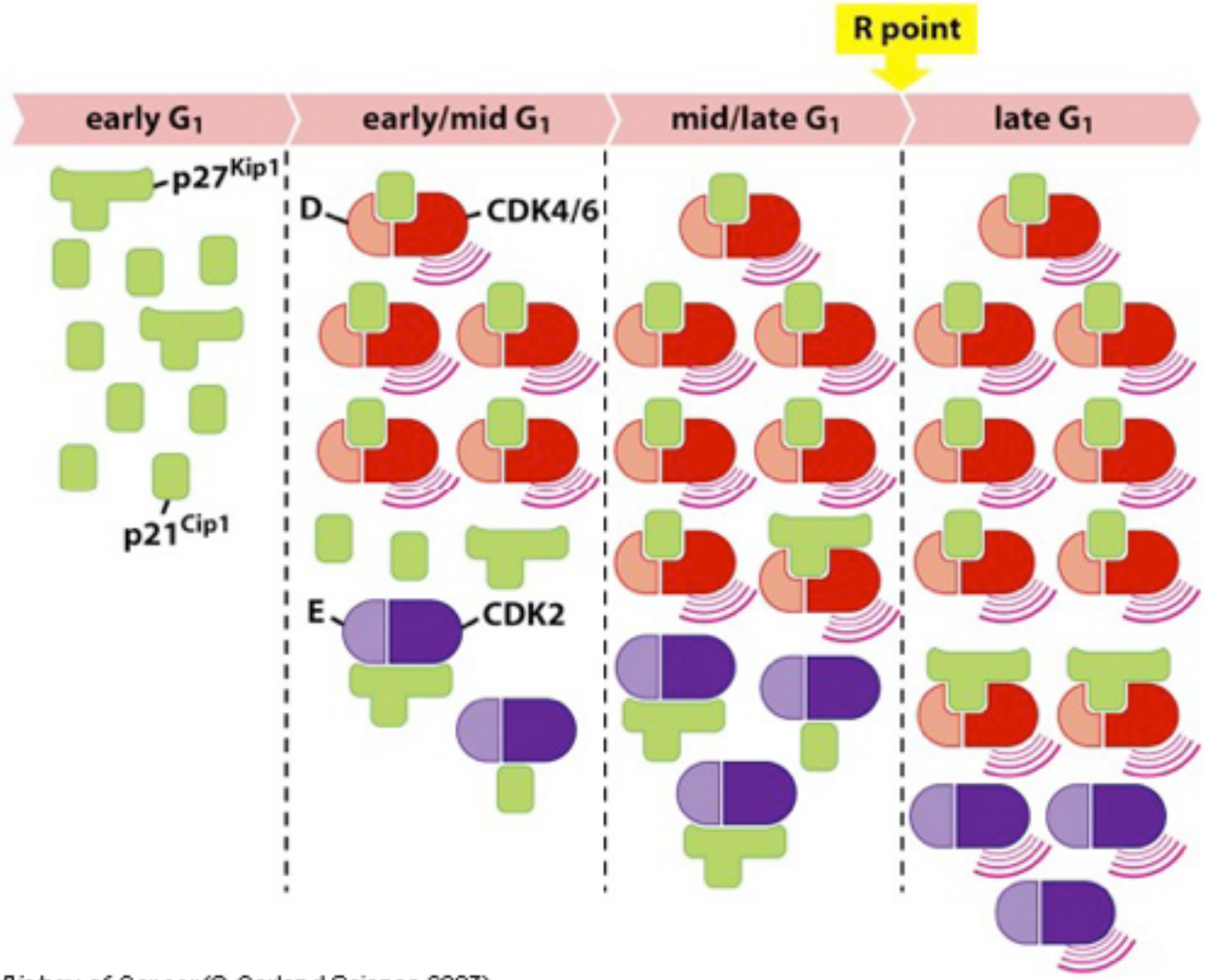
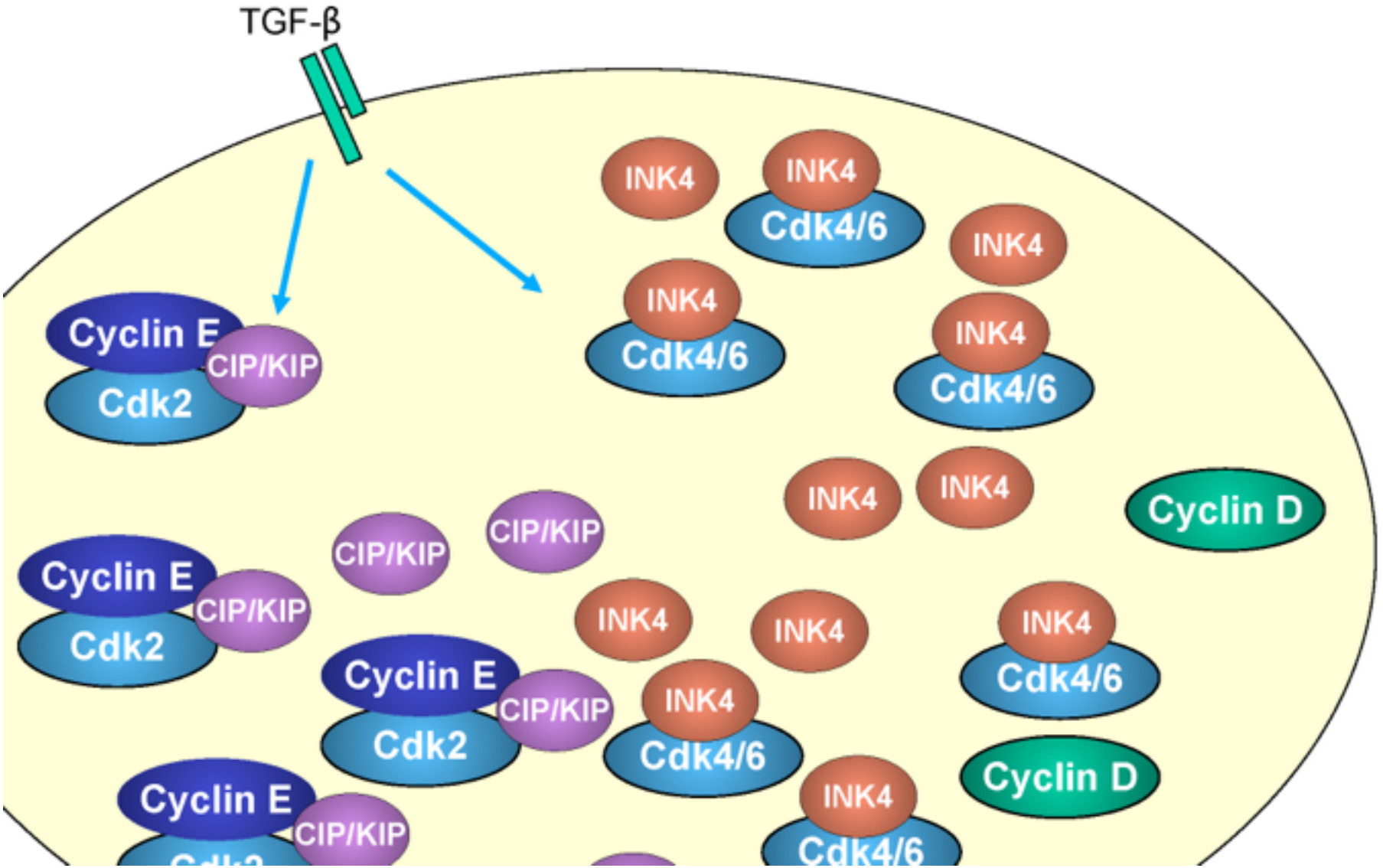
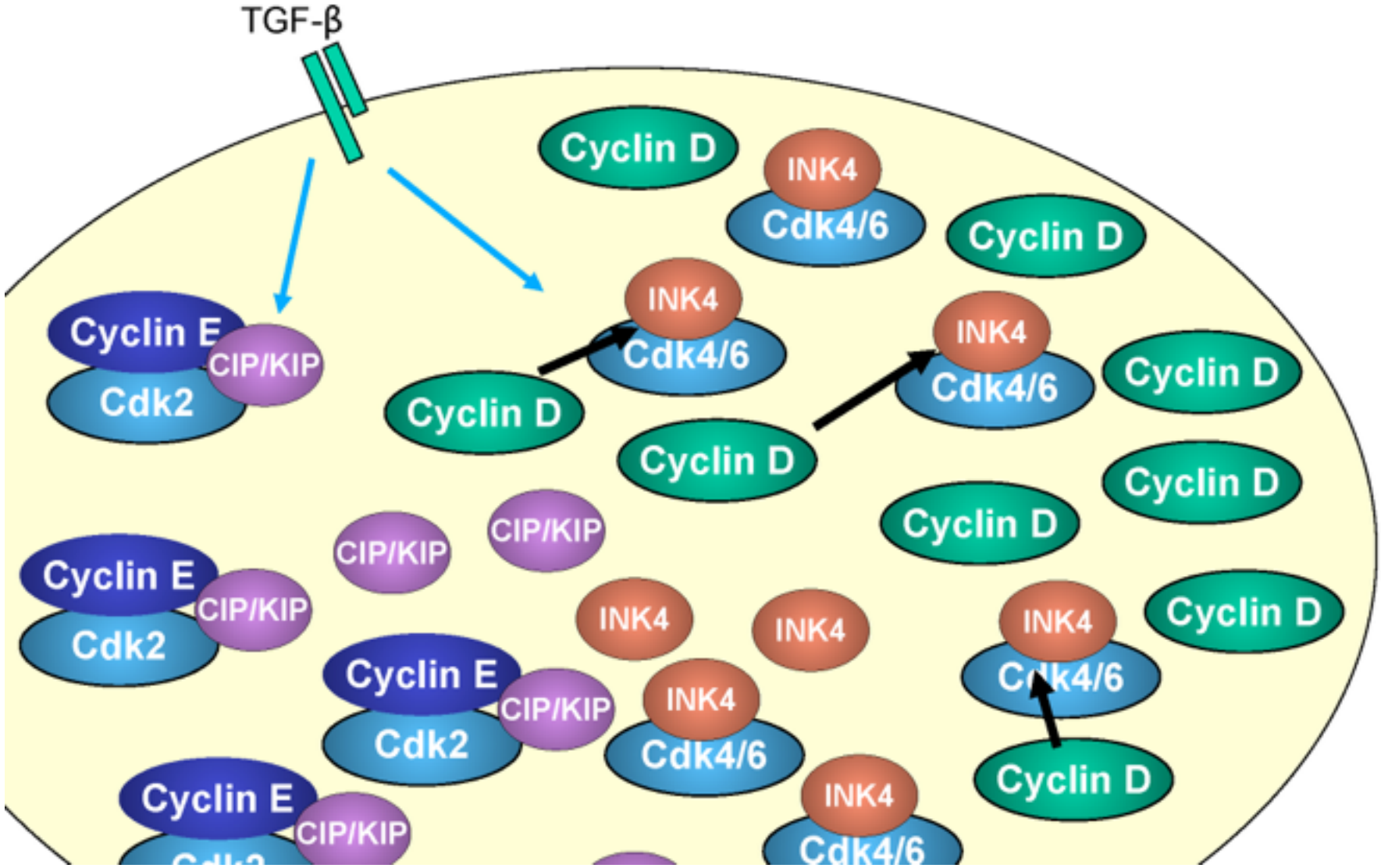


Figure 8.17b *The Biology of Cancer* (© Garland Science 2007)

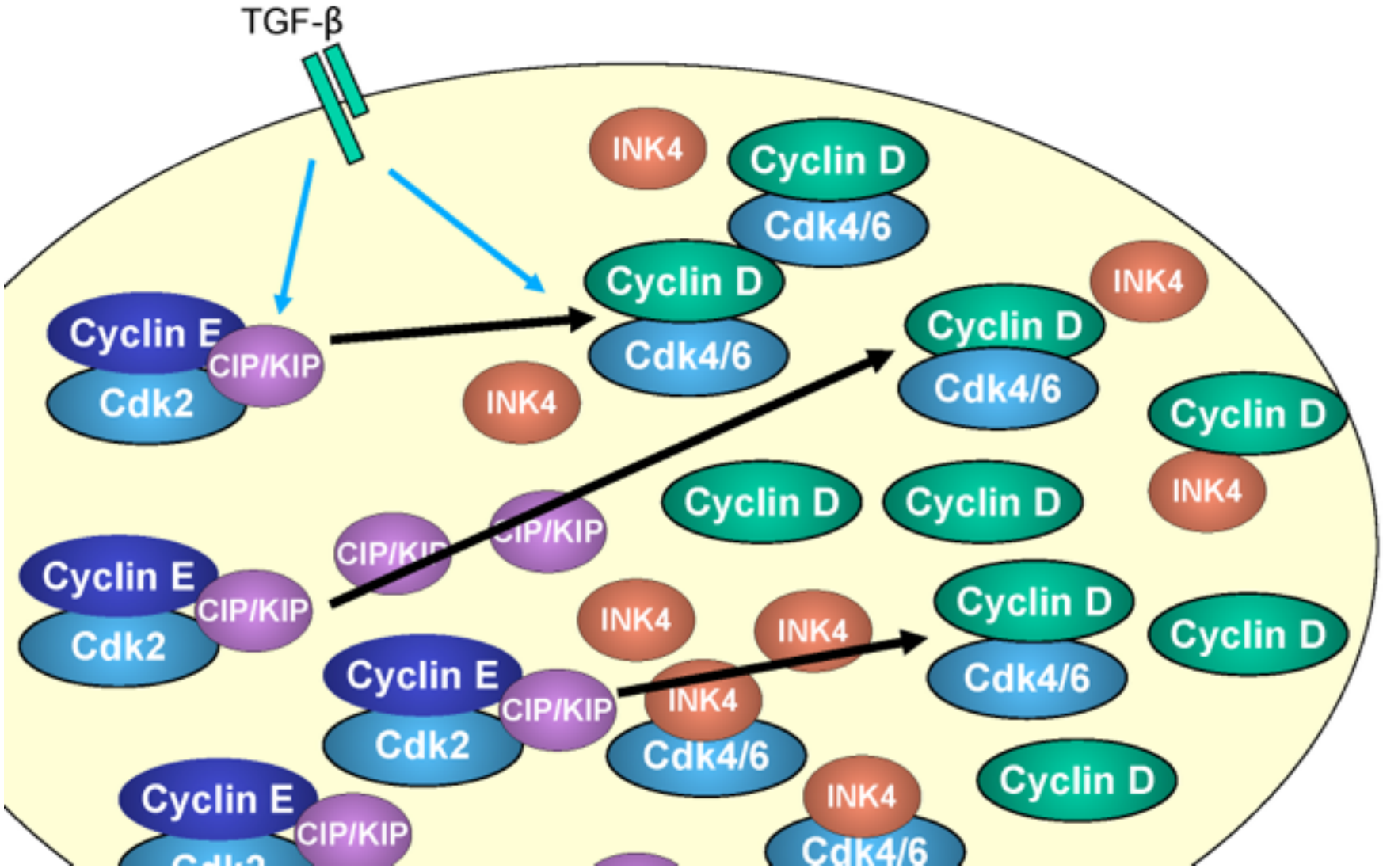
Cyclin D1 and TGF-β



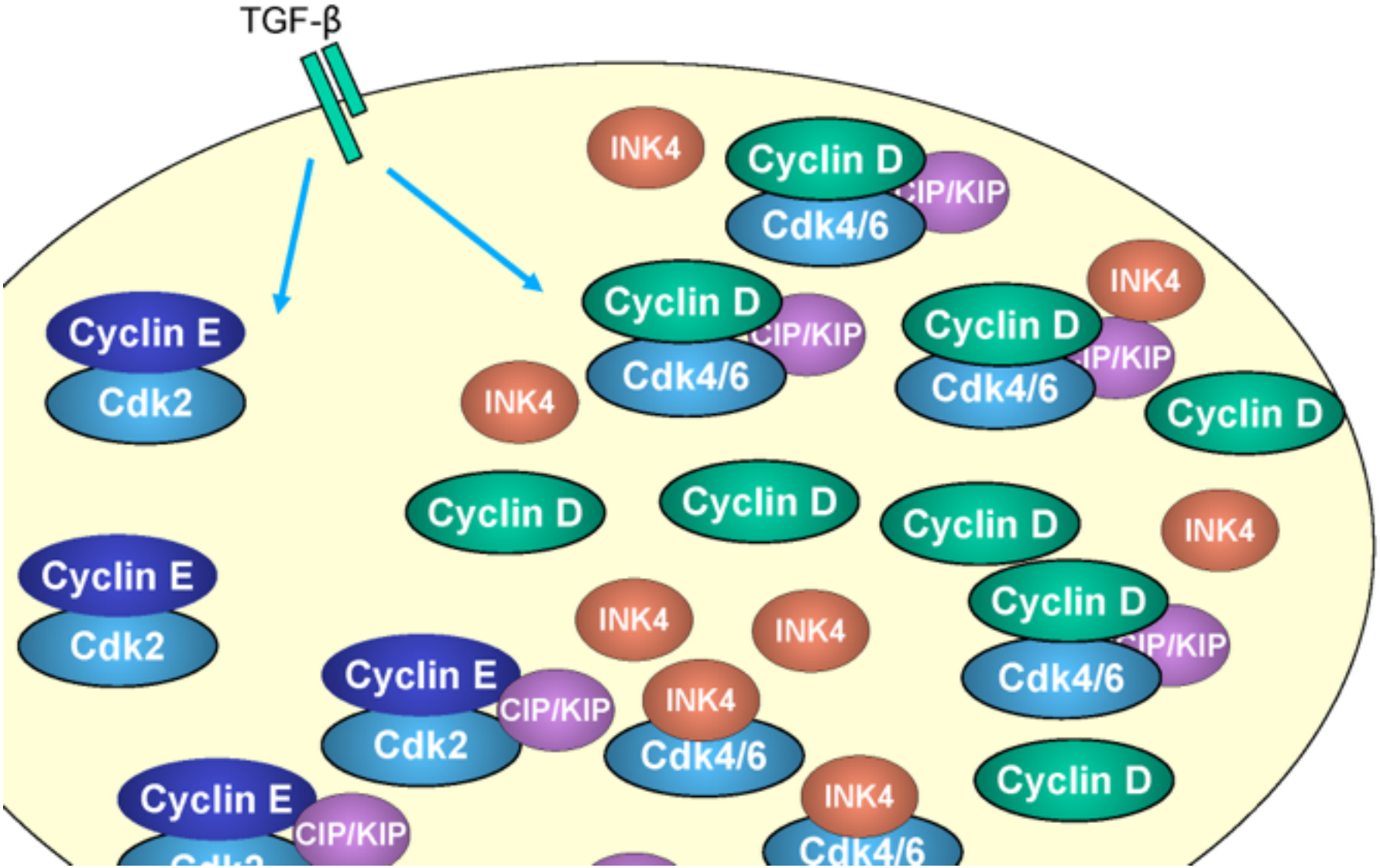
Cyclin D1 and TGF-β

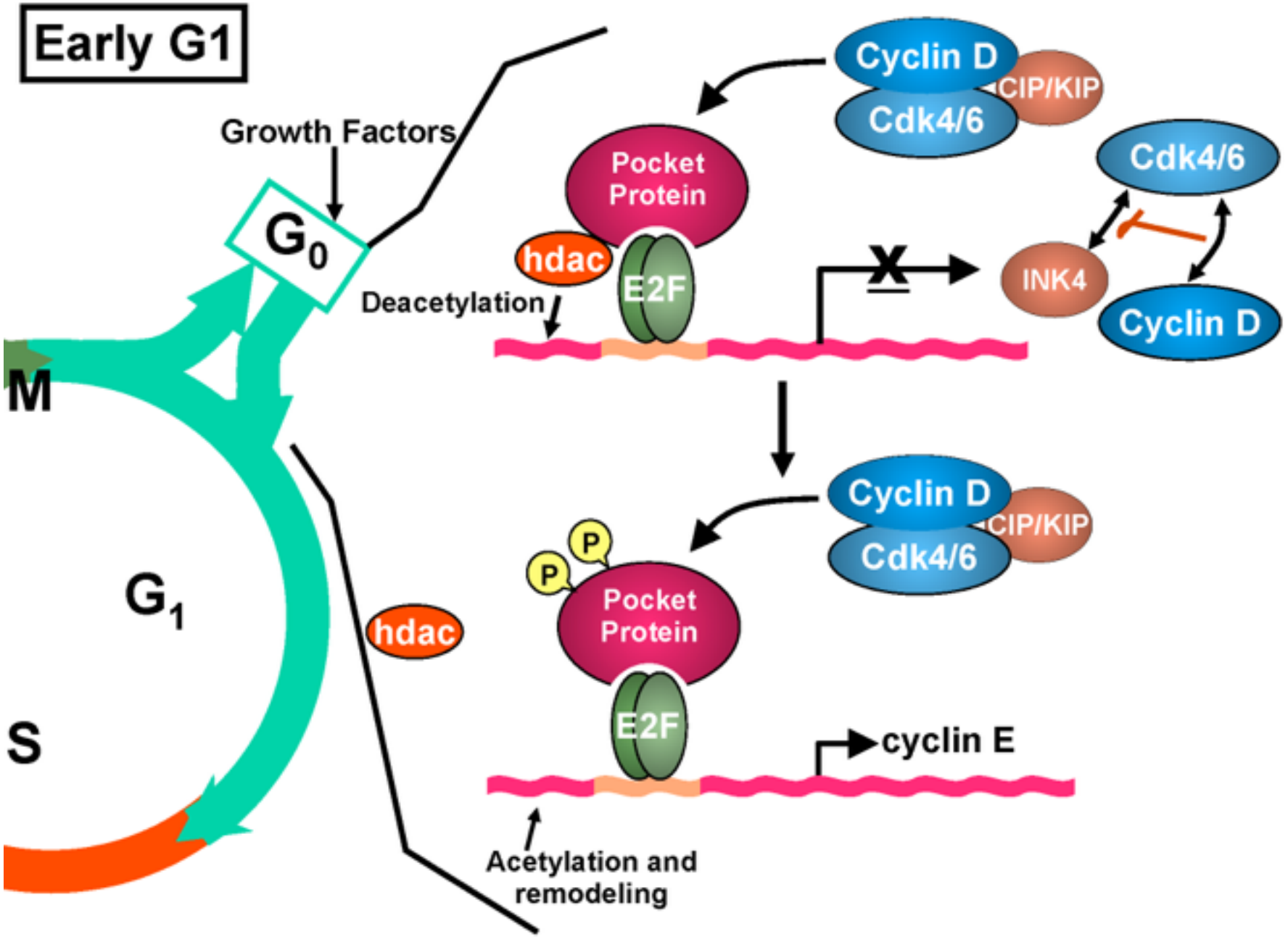


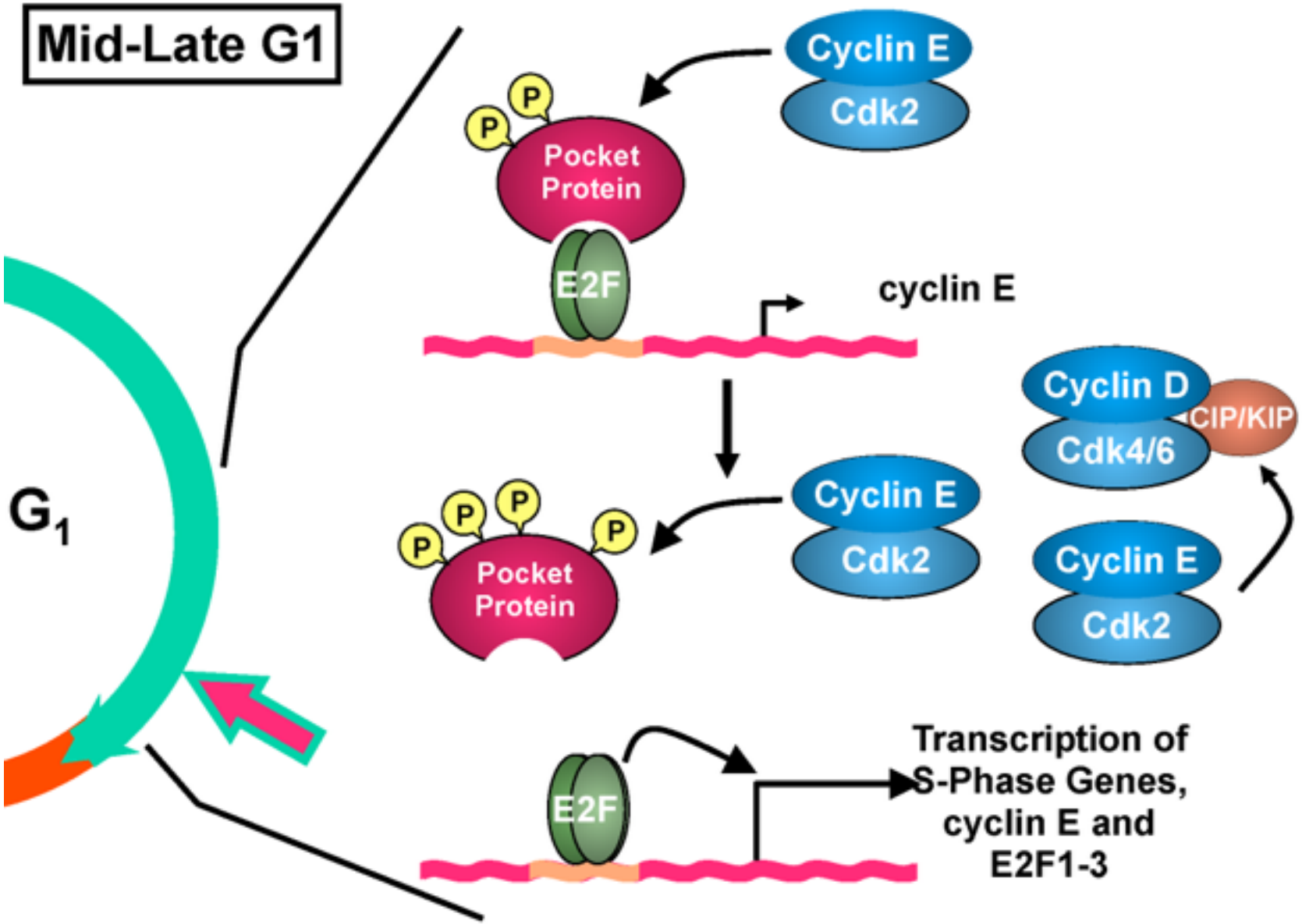
Cyclin D1 and TGF-β

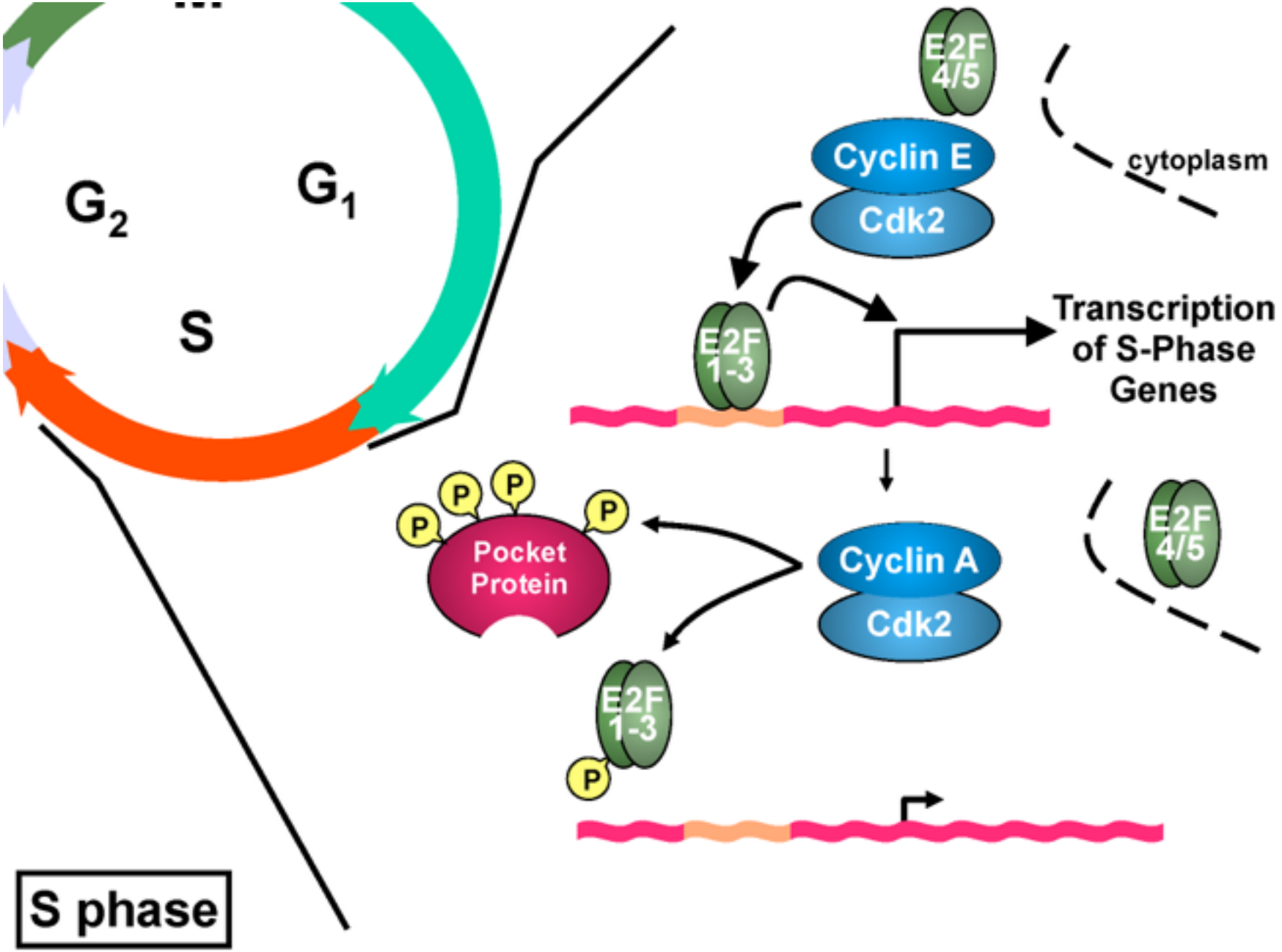


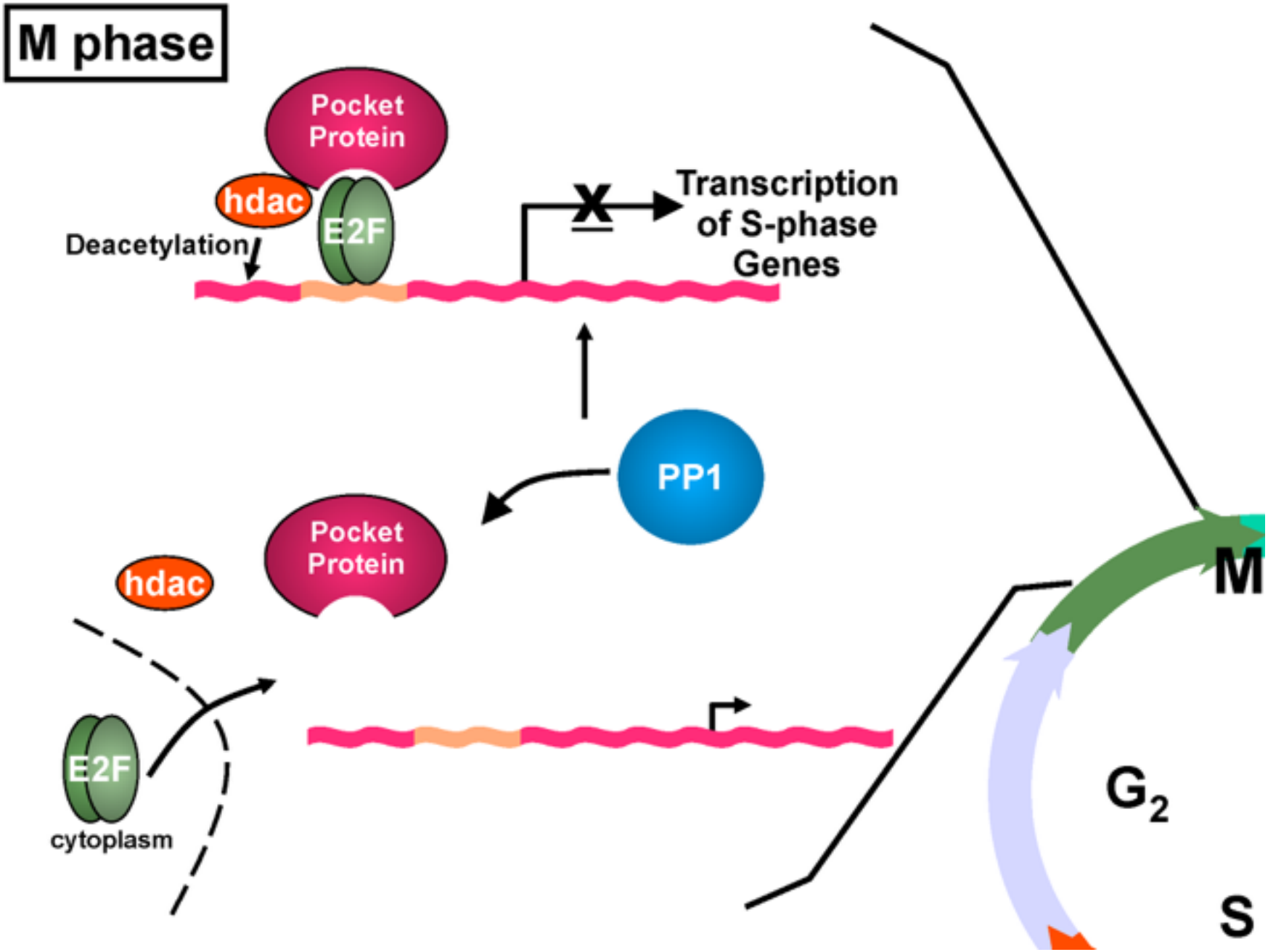
Cyclin D1 and TGF-β

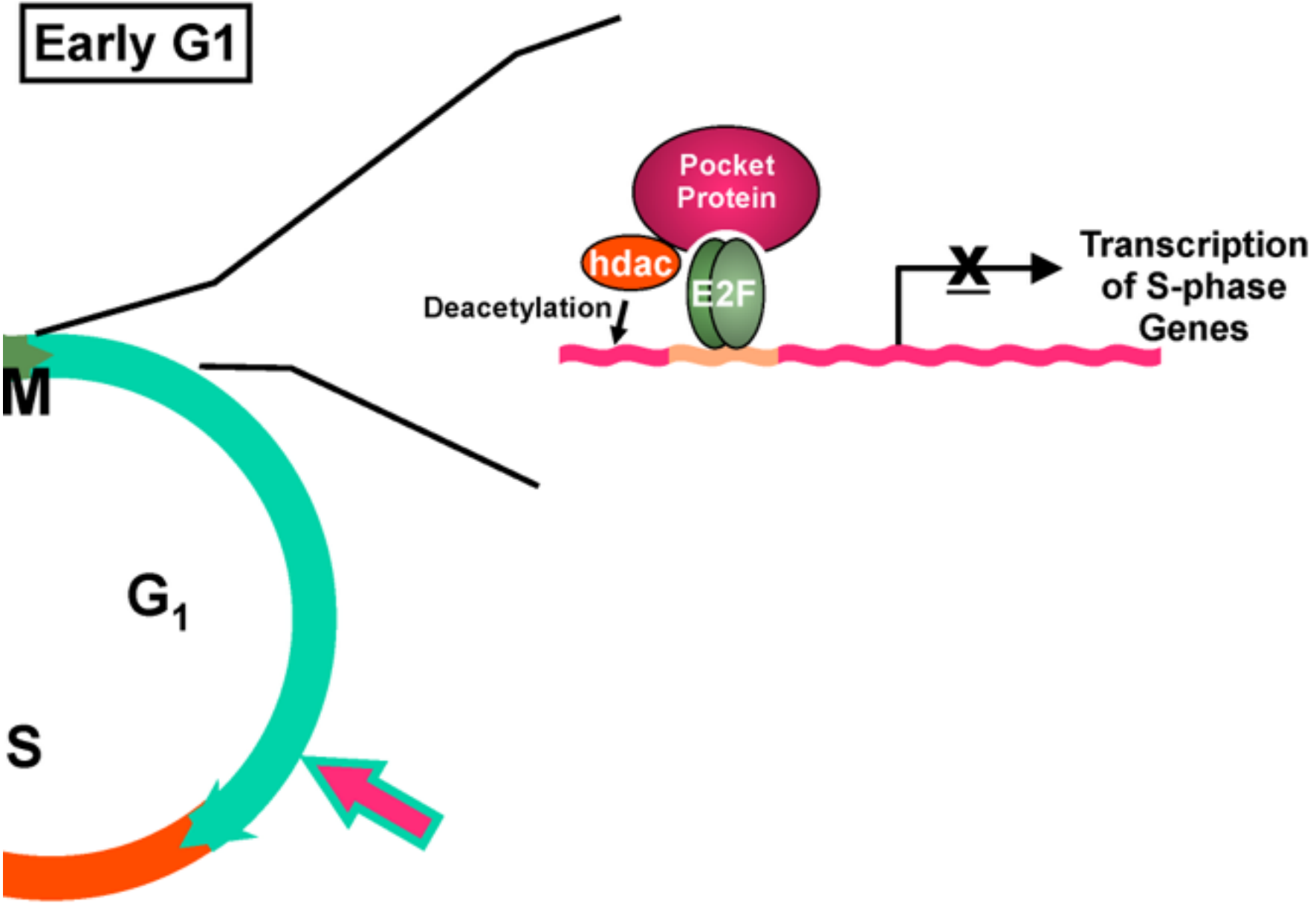



Early G1
Growth Factors
G0
M
G1
S
Cyclin D
CIP/KIP
Cdk4/6
Pocket Protein
hdac
E2F
Deacetylation
X
Cdk4/6
INK4
Cyclin D
Cyclin D
CIP/KIP
Cdk4/6
P
P
Pocket Protein
hdac
E2F
cyclin E
Acetylation and remodeling

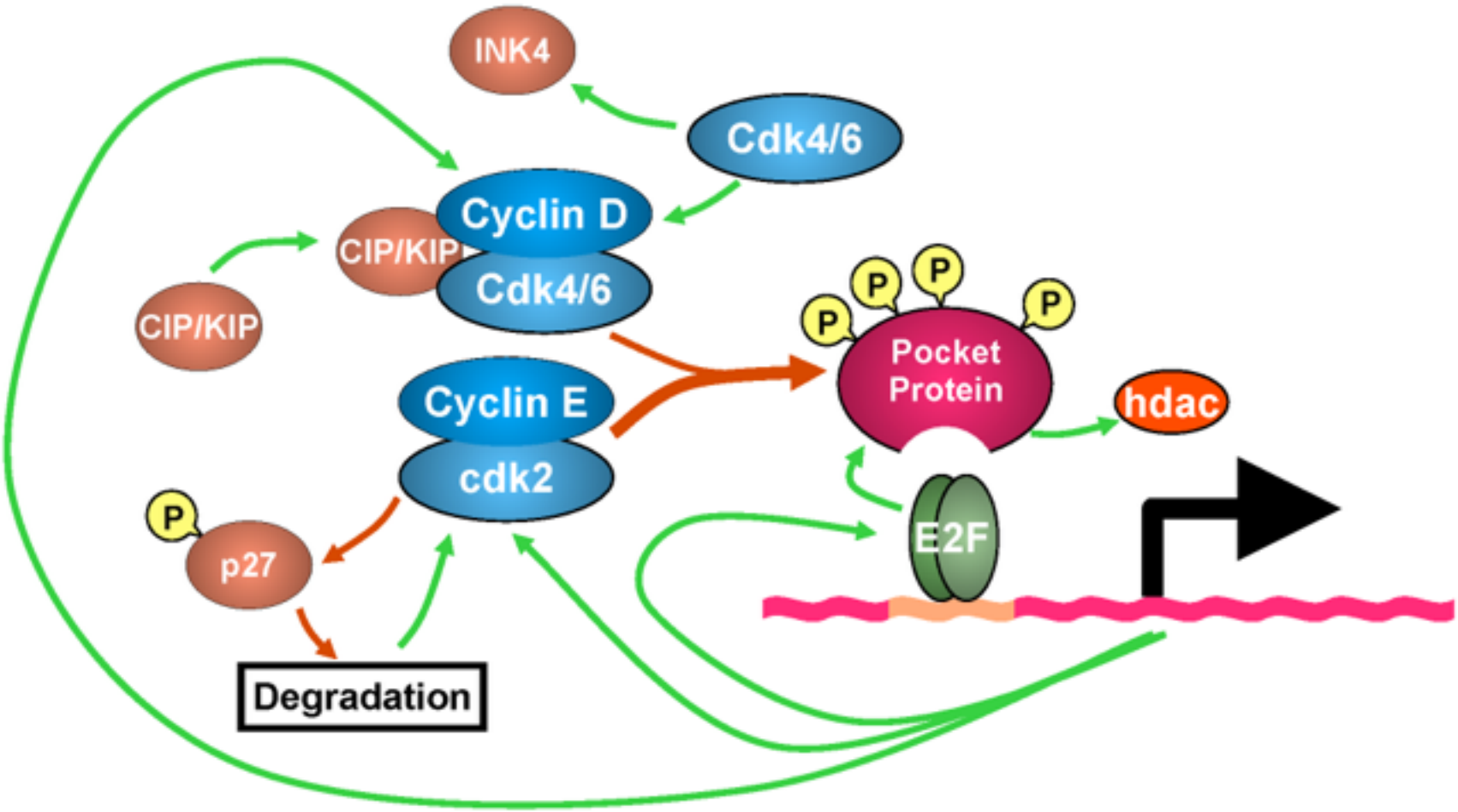

Mid-Late G1
Cyclin E
Cdk2
P
P
Pocket Protein
E2F
cyclin E
G1
Cyclin D
CIP/KIP
Cdk4/6
Cyclin E
Cdk2
P
P
P
P
Pocket Protein
Cyclin E
Cdk2
E2F
Transcription of S-Phase Genes, cyclin E and E2F1-3


G2
G1
S
S phase
E2F 4/5
Cyclin E
Cdk2
cytoplasm
E2F 1-3
Transcription of S-Phase Genes
P
P
P
P
Pocket Protein
Cyclin A
Cdk2
E2F 4/5
E2F 1-3
P


M phase
Pocket Protein
hdac
E2F
Deacetylation
Transcription of S-phase Genes
PP1
Pocket Protein
hdac
E2F
cytoplasm
M
G2
S


Early G1
Pocket Protein
hdac
E2F
Deacetylation
Transcription of S-phase Genes
M
G1
S

Positive Feedback Loop for E2F activation



Control of cyclin advance by extracellular signals

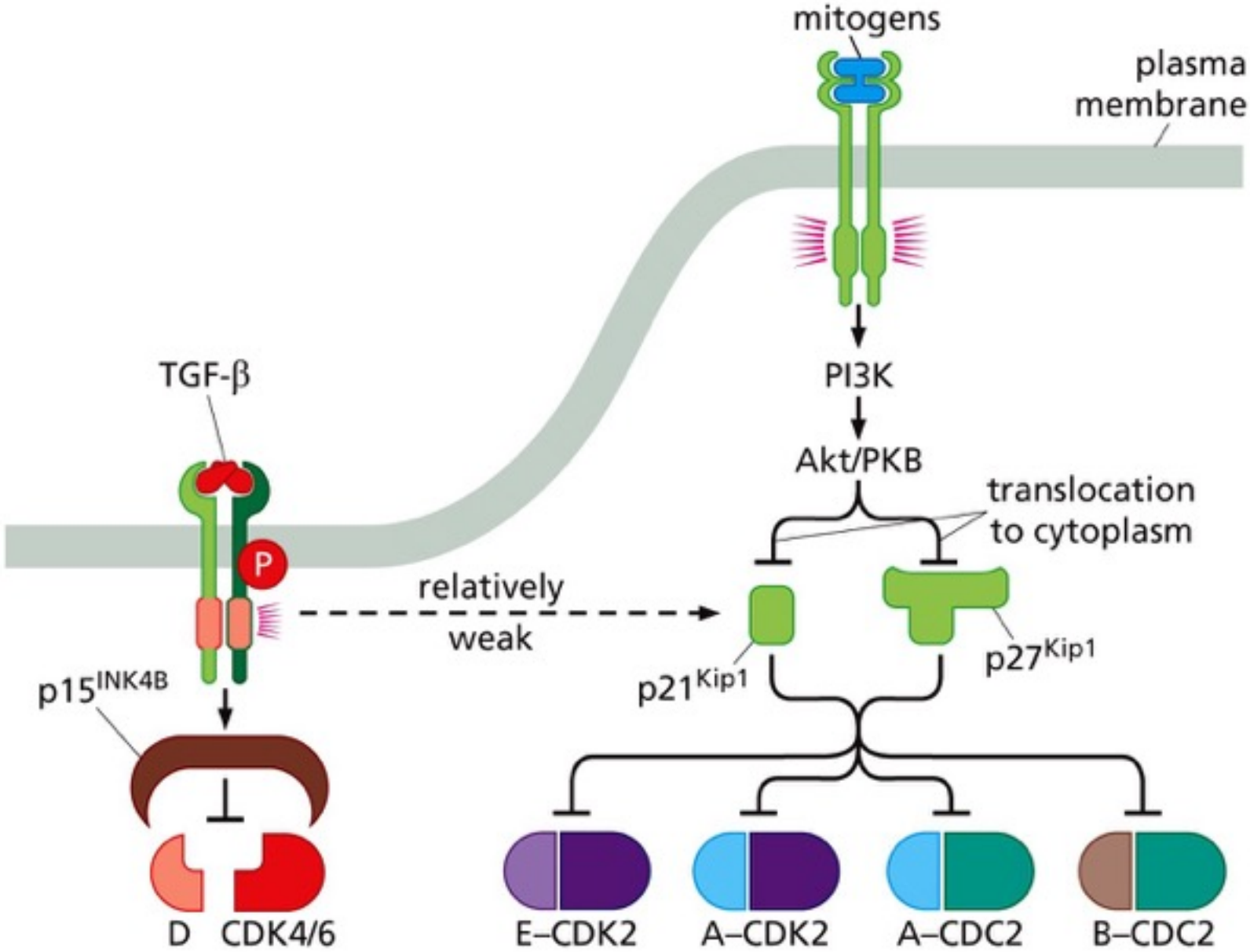


Figure 8.15a The Biology of Cancer (© Garland Science 2014)

Positive-feedback loops and irreversibility of cell cycle advance

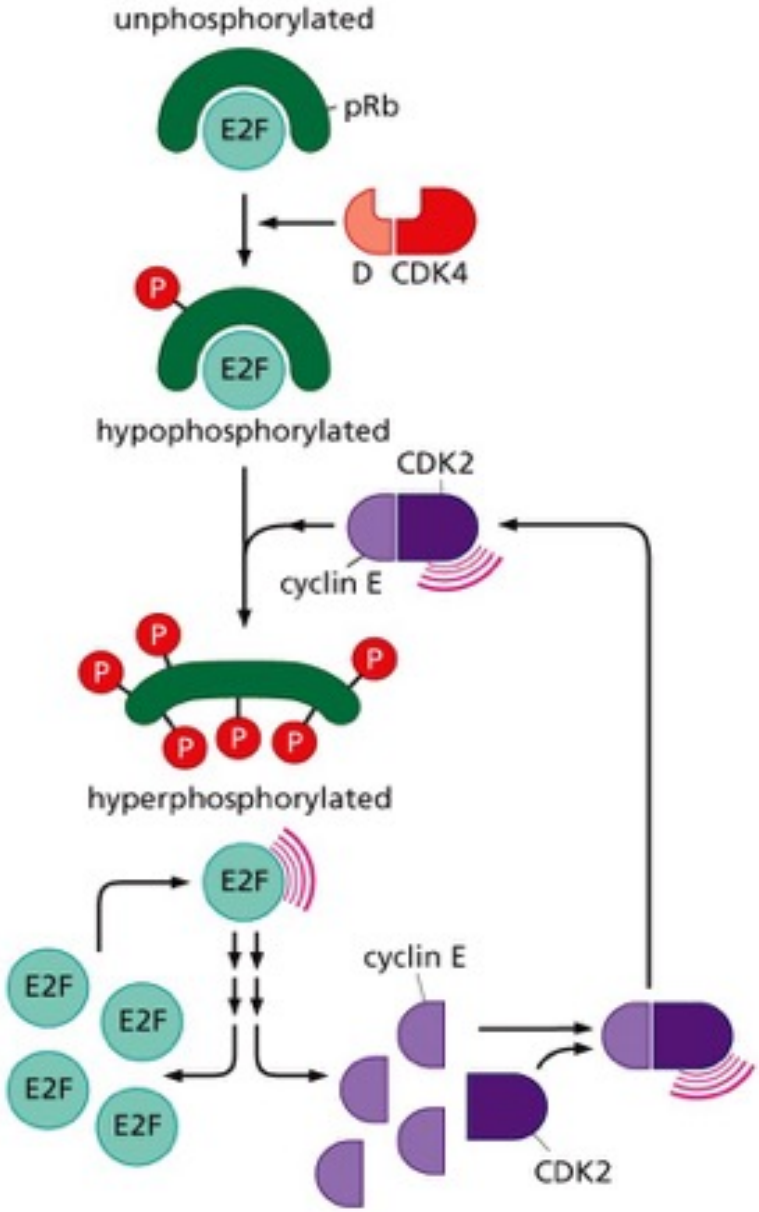


Figure 8.25a The Biology of Cancer (© Garland Science 2014)

Positive-feedback loops and irreversibility of cell cycle advance

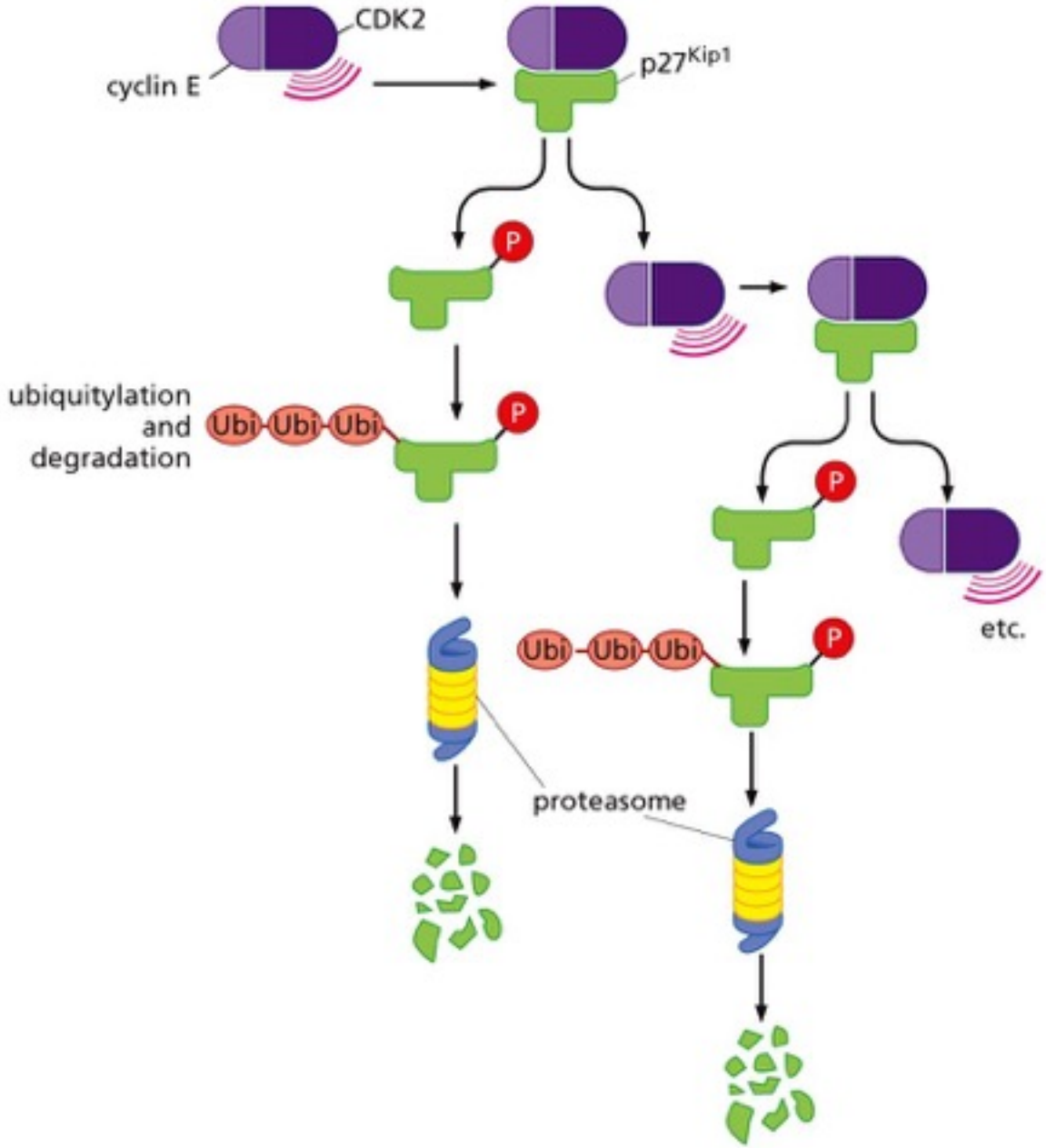


Figure 8.25b The Biology of Cancer (© Garland Science 2014)

Alteration of cellular signaling in cancer

Components of the E2F-pRB pathway disrupted in cancer

pRB.....**mutated or deleted**

p130.....**mutated (rare?)**

Cyclin D1.....**overexpressed (amplification/transcriptional)**

Cyclin E (rare).....**overexpressed**

cdk4.....**overexpressed**

mutated to disrupt $p16^{INK4a}$ binding

$p16^{INK4a}$..... **deleted or transcriptionally repressed**

$p27^{KIP1}$..... **downregulated**

Table 8.4 Alteration of the cell cycle clock in human tumors A plus sign indicates that this gene or gene product is altered in at least 10% of tumors analyzed. Alteration of gene product can include abnormal absence or overexpression. Alteration of gene can include mutation and promoter methylation. More than one of the indicated alterations may be found in a given tumor.

Tumor type	Gene product or gene						% of tumors with 1 or more changes
	Rb	Cyclin E1	Cyclin D1	$p16^{INK4A}$	$p27^{Kip1}$	CDK4/6	
Glioblastoma	+	+		+	+	+/+	>80
Mammary carcinoma	+	+	+	+	+	+/	>80
Lung carcinoma	+	+	+	+	+	+/	>90
Pancreatic carcinoma			[a]		+		>80
Gastrointestinal carcinoma	+	+	+[b]	+	+	+/[c]	>80
Endometrial carcinoma	+	+	+	+	+	+/	>80
Bladder carcinoma	+	+	+	+	+		>70
Leukemia	+	+	+	+[d]	+	+/	>90
Head and neck carcinomas	+		+	+	+	+/	>90
Lymphoma	+	+	+[e]	+[d]	+	/+	>90
Melanoma		+	+	+	+	+/	>20
Hepatoma	+	+	+	+[d]	+	+/[c]	>90
Prostate carcinoma	+	+	+	+	+		>70
Testis/ovary carcinomas	+	+	+[b]	+	+	+/	>90
Osteosarcoma		+		+		+/	>80
Other sarcomas		+	+	+	+	/+	>90

[a]Cyclin D3 (not cyclin D1) is present and is up-regulated in some tumors.
[b]Cyclin D2 also is up-regulated in some tumors.
[c]CDK2 is also found to be up-regulated in some tumors.
[d]$p15^{INK4B}$ is also found to be absent in some tumors.
[e]Cyclin D2 and D3 are also found up-regulated in some lymphomas.
Adapted from M. Malumbres and M. Barbacid, *Nat. Rev. Cancer* 1:222–231, 2001.

Control of cyclin D levels

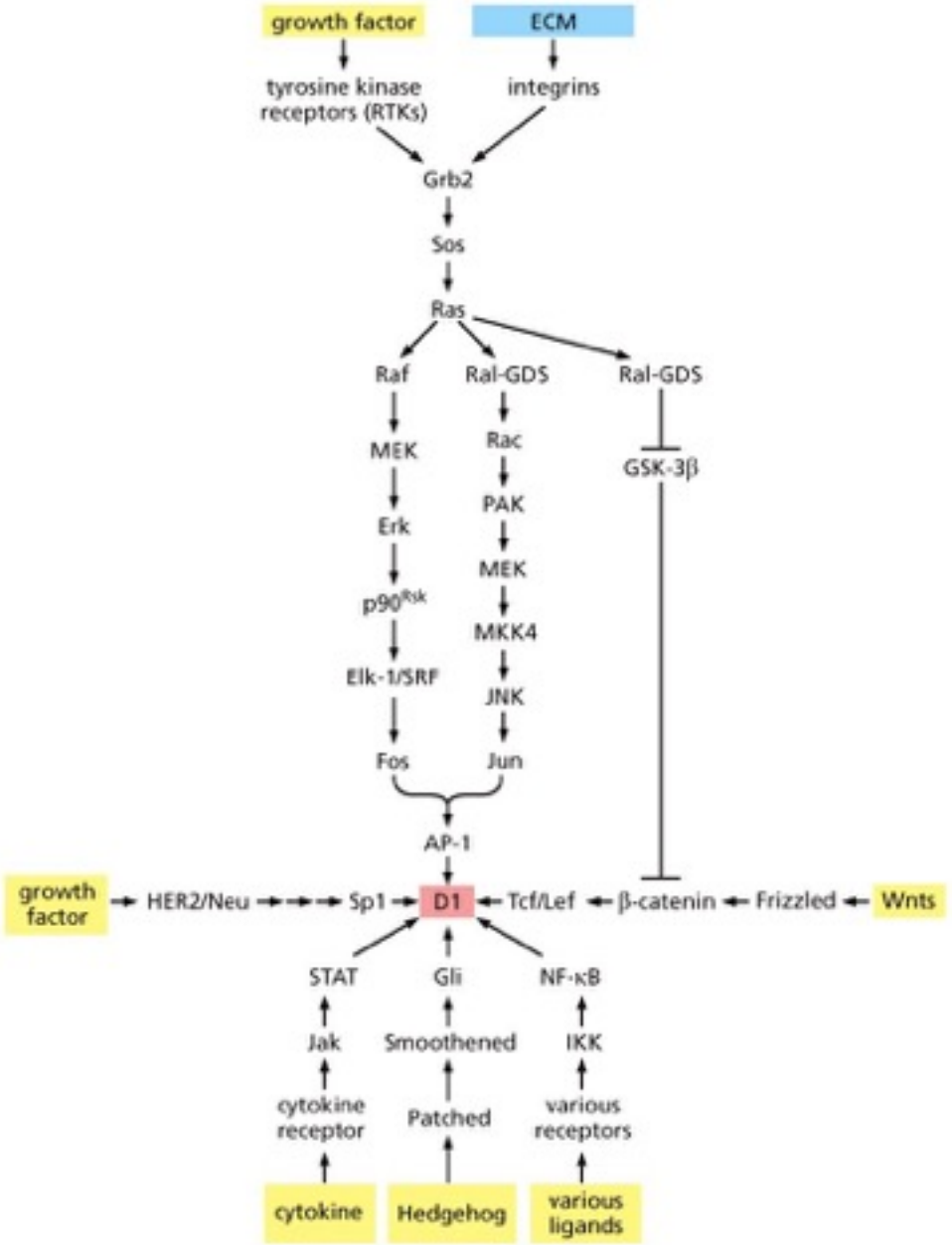


Figure 8.11b The Biology of Cancer (© Garland Science 2014)

Table 8.1 Induction of D-type cyclin expression by extracellular signals

Source of signal	Signaling intermediaries	Type of cyclin
RANK receptor	NF-κB pathway	D1
Prolactin receptor	Jak/STAT	D1
Estrogen receptor	AP-1 TF (?)	D1
Focal adhesion kinase		D1
HER2/Neu receptor	E2F and Sp1 TFs	D1
Wnts–Frizzled receptor	β-catenin and Tcf/Lef TFs	D1
Bcr/Abl		D2
FSH receptor	cyclic AMP	D2
Various mitogens	Myc	D2
Interleukin-4, 7 receptor		D2
Interleukin-5 receptor	STAT3/5	D3
Mitogens	E2A TF	D3

Abbreviations: RANK, receptor activator of NF-κB; FSH, follicle-stimulating hormone.

Control of cyclin D1 levels by Ras

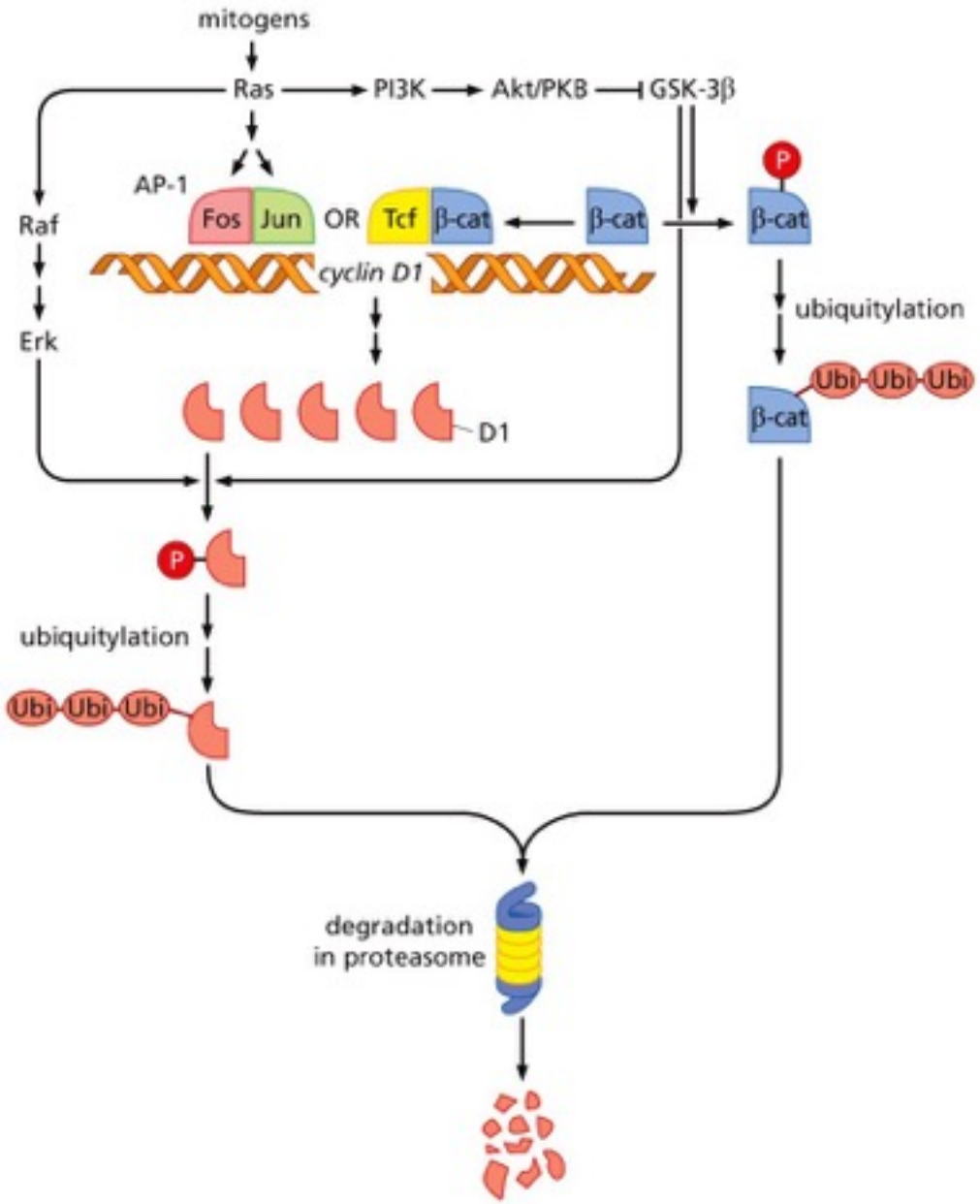


Figure 8.26 The Biology of Cancer (© Garland Science 2014)

Action of Myc on cell cycle

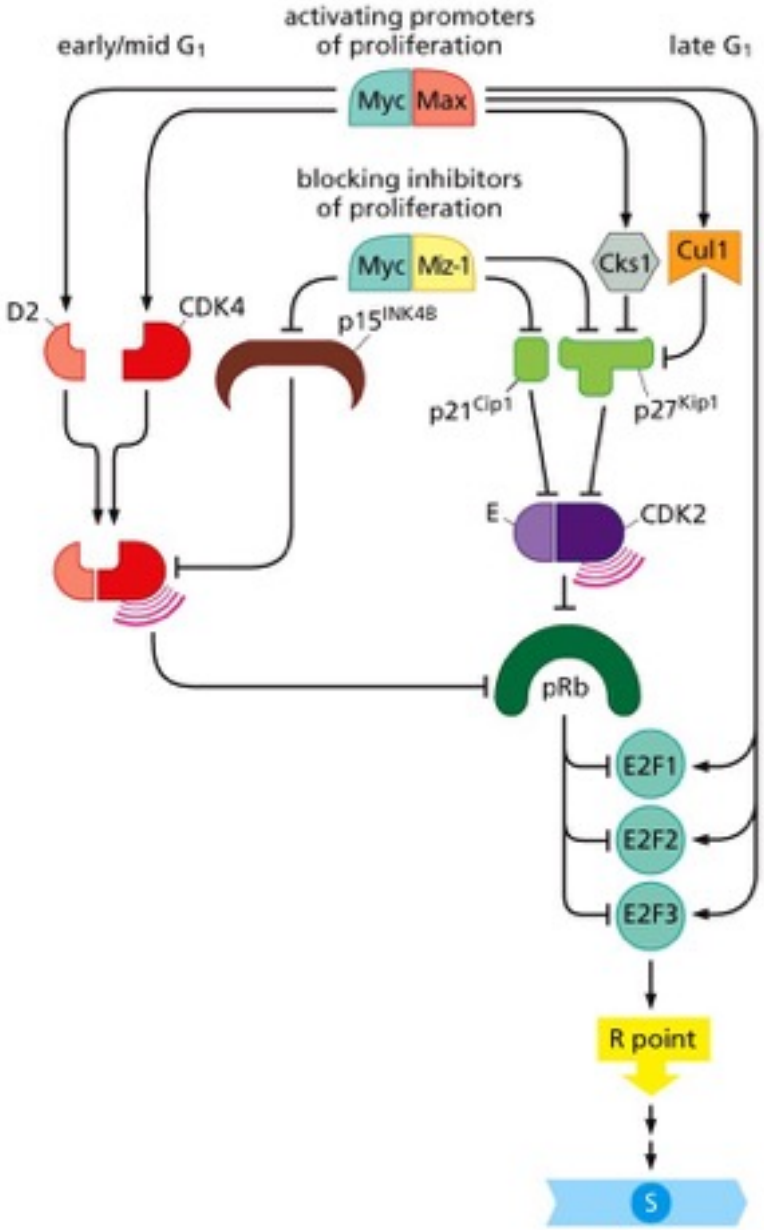


Figure 8.28 The Biology of Cancer (© Garland Science 2014)

Action of Myc-ER (estrogen receptor) on cell cycle

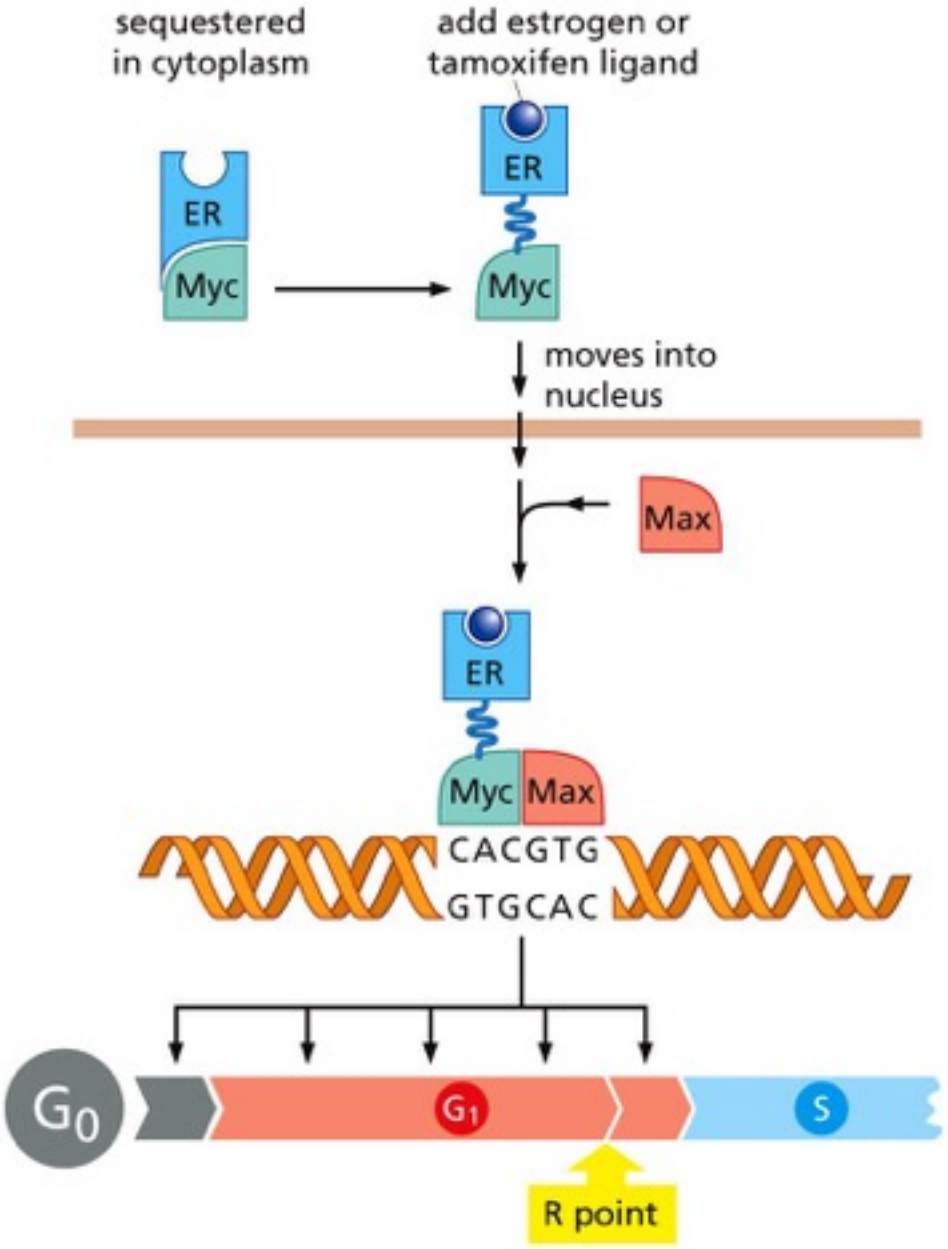


Figure 8.29 The Biology of Cancer (© Garland Science 2014)

Myc inhibits cell differentiation by ID (inhibitor of differentiation)

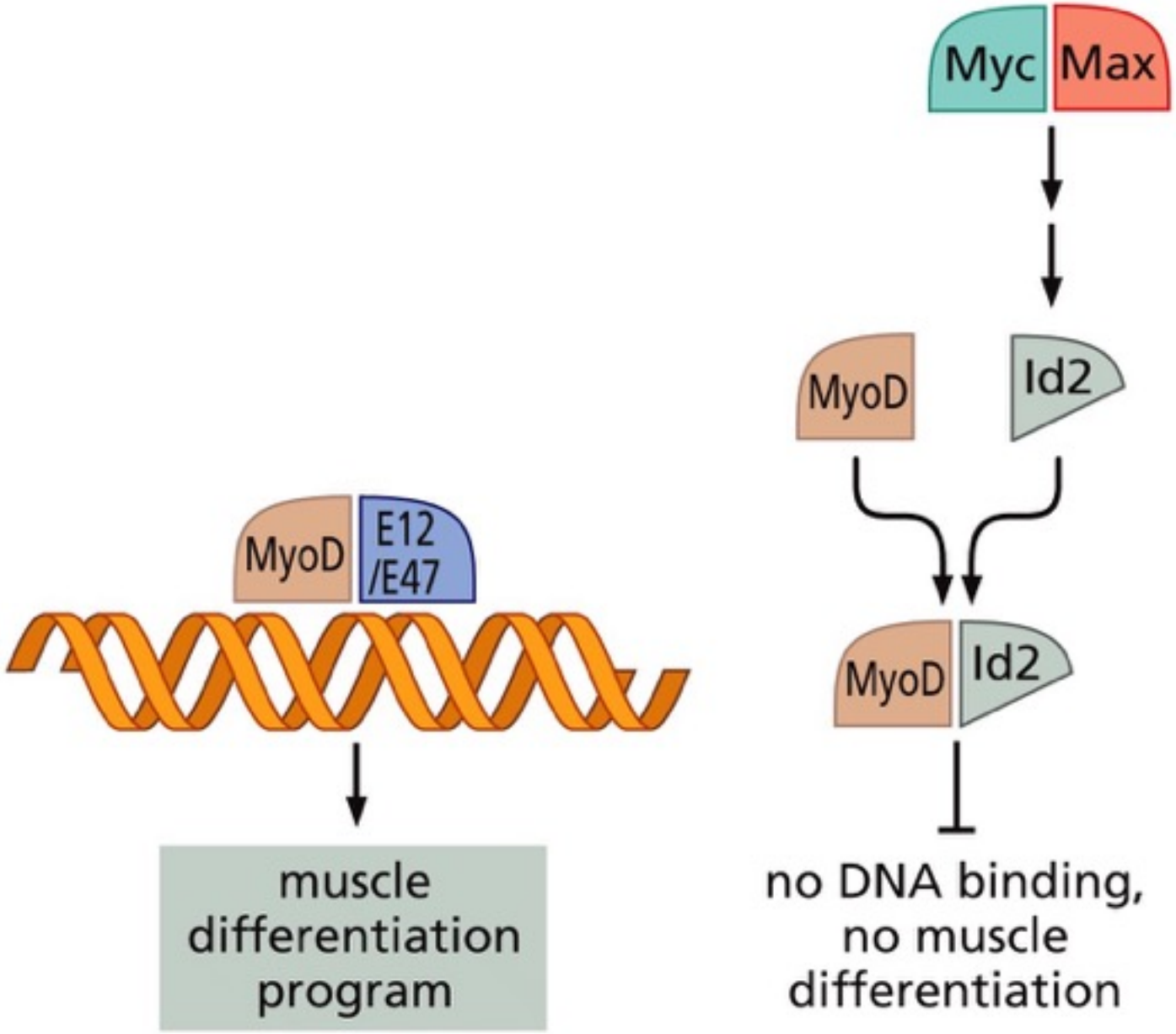


Figure 8.34 The Biology of Cancer (© Garland Science 2014)

Perturbation of the R-point transition in human tumors

Red: favors cell cycle Blue: inhibits cell cycle Gray: not known to change cell cycle

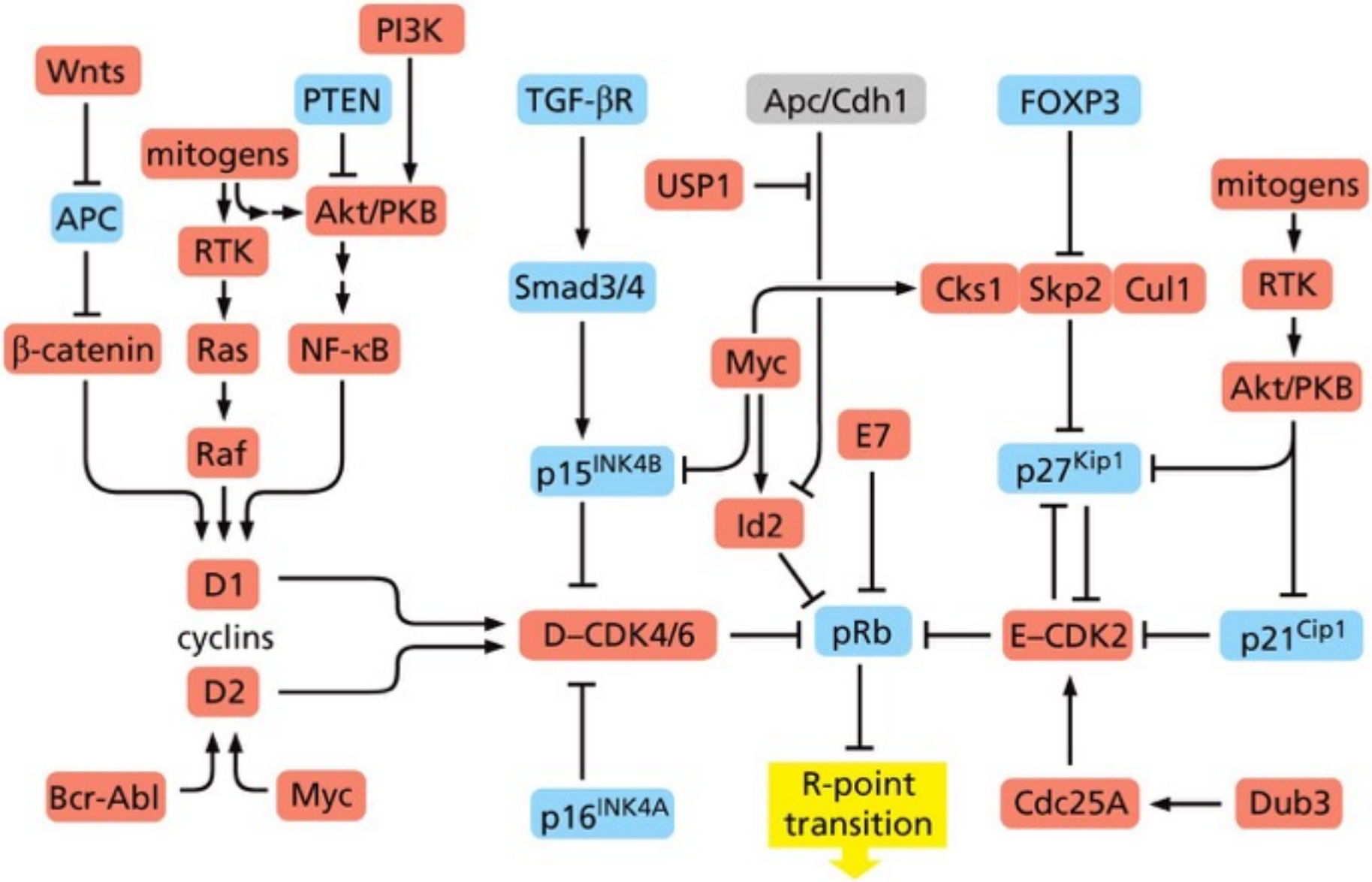
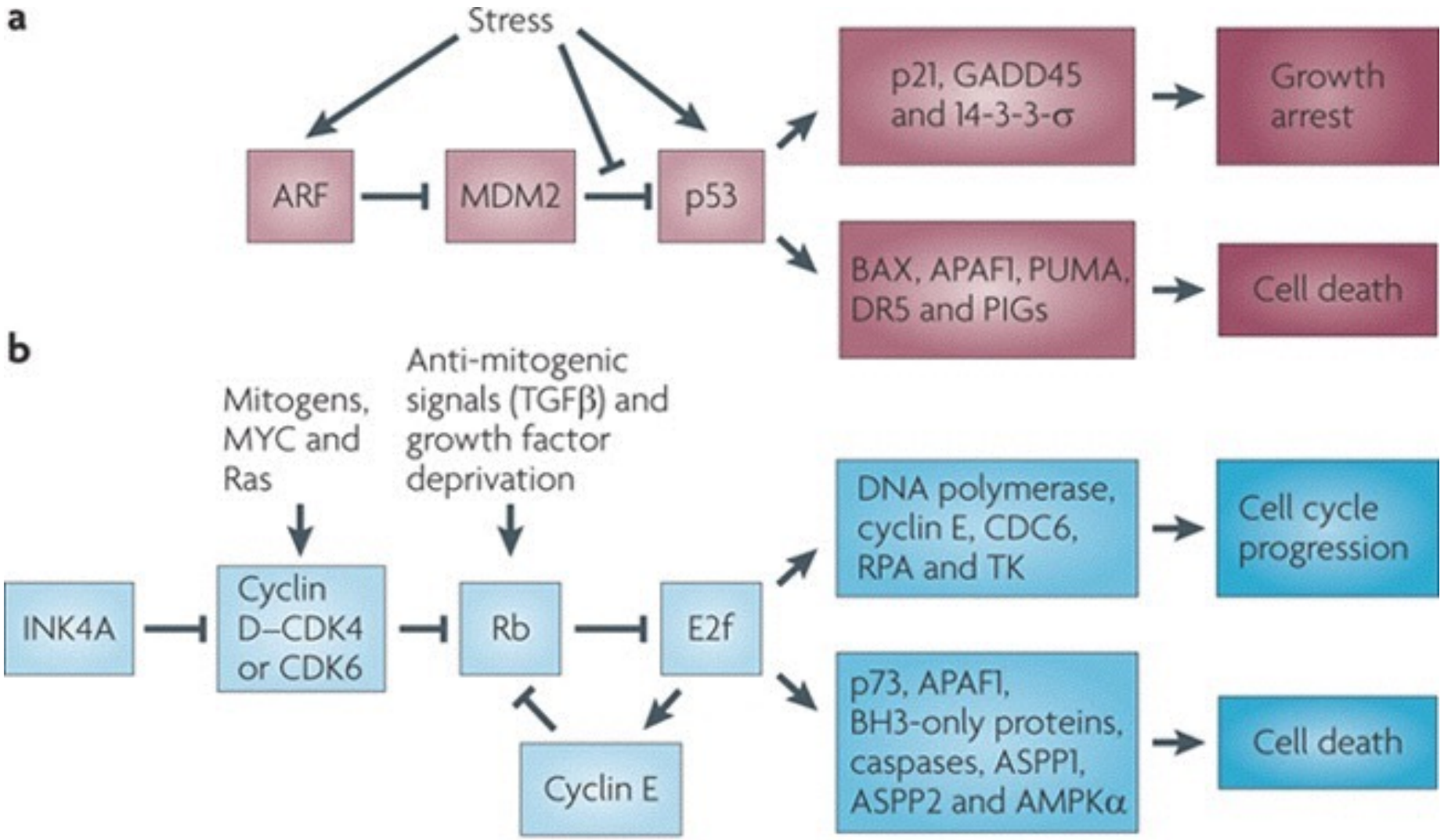


Figure 8.35 The Biology of Cancer (© Garland Science 2014)

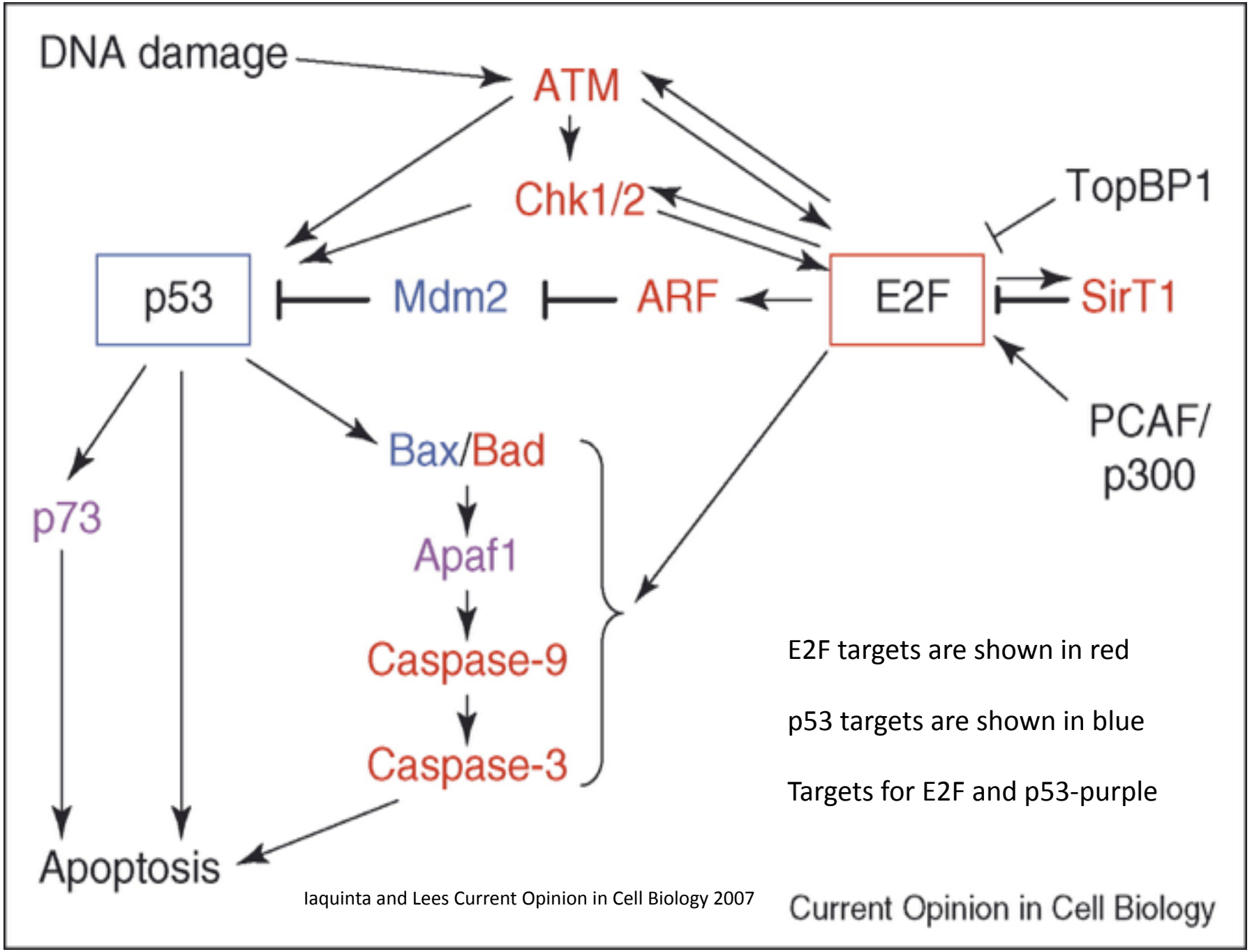
E2F1 and Apoptosis

- Overexpression of E2F1 induces apoptosis
- Apoptotic effects of E2F1 blocked by pRB
- Induces p53-dependent and -independent apoptosis
- p53-Dependent
    - a) E2F upregulates p53 levels (through ARF)
    - b) enhances apoptotic function of p53 (e.g. by competition for p300)
- p53-Independent
    - a) enhanced by p300
    - b) blocks antiapoptotic pathways (e.g. NFkB activity, IAP expression)
    - c) inhibition of E2F1 phophorylation in S-phase enhances apoptosis
    - d) May involve p73

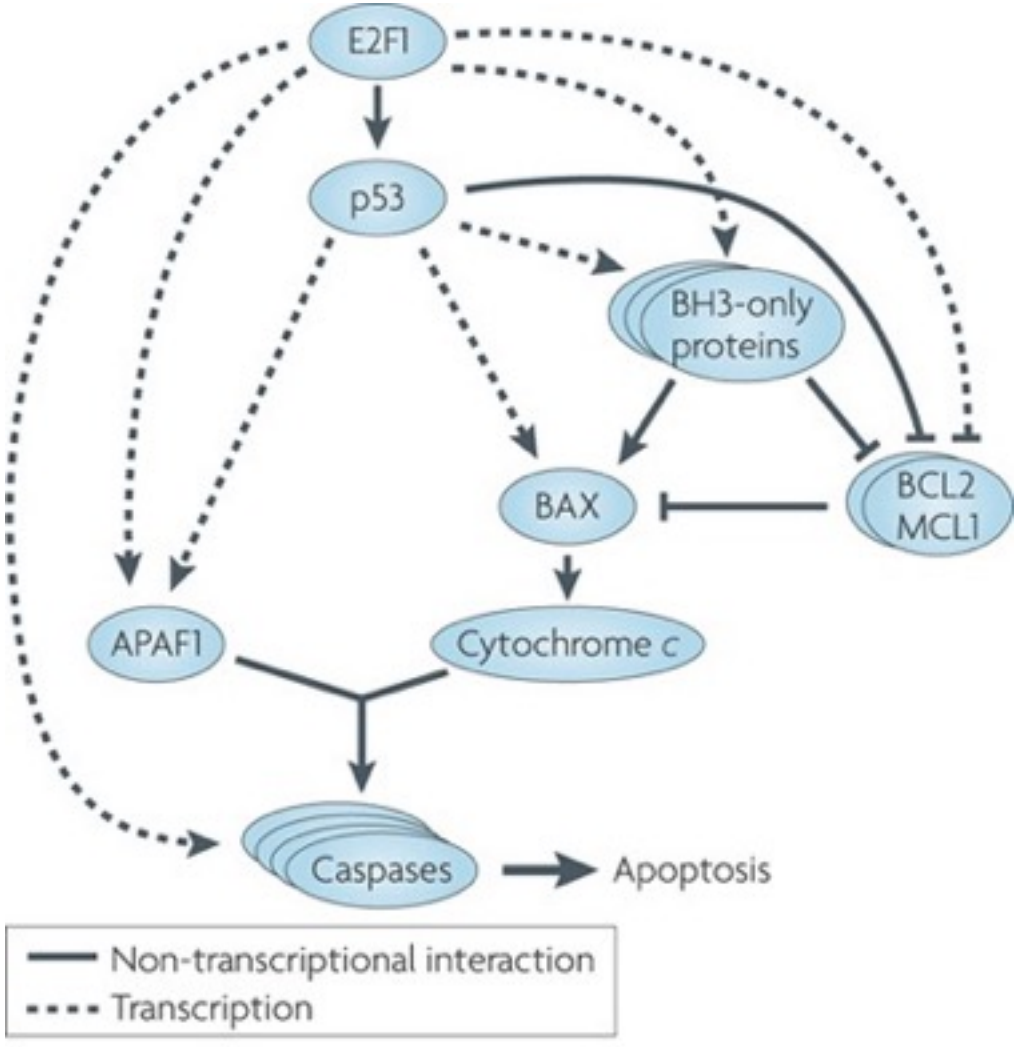
Regulation and activities of p53 and E2F



Nature Reviews | Cancer


DNA damage
ATM
Chk1/2
TopBP1
p53
Mdm2
ARF
E2F
SirT1
PCAF/
p300
p73
Bax/Bad
Apaf1
Caspase-9
Caspase-3
Apoptosis
E2F targets are shown in red
p53 targets are shown in blue
Targets for E2F and p53-purple
Iaquinta and Lees Current Opinion in Cell Biology 2007
Current Opinion in Cell Biology

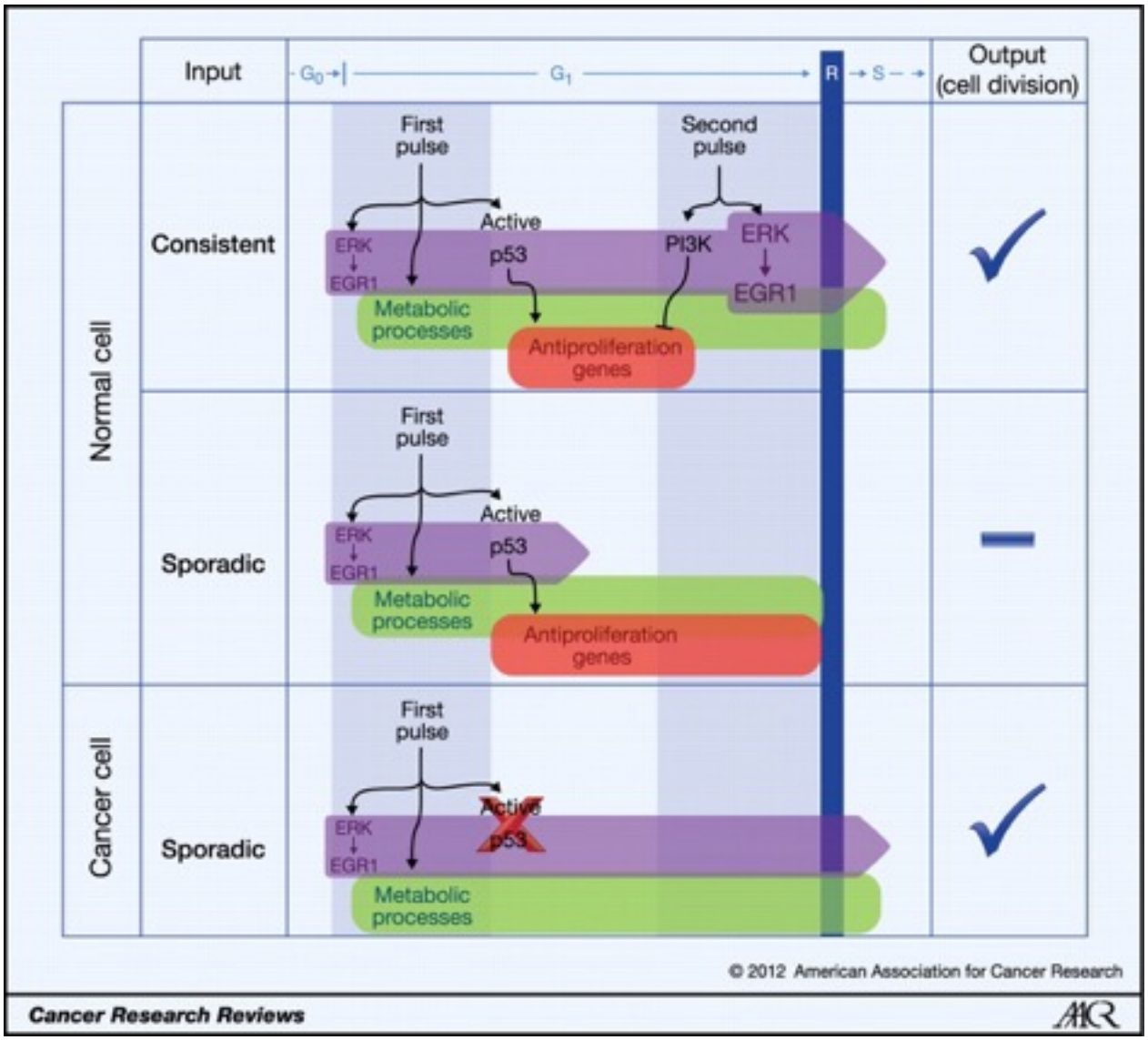
E2F1 regulates p53 and thus apoptosis



Nature Reviews | Cancer

Differences between cancer and normal cells

Contrasting schemes of the proposed response of normal and cancer cells to mitogens.

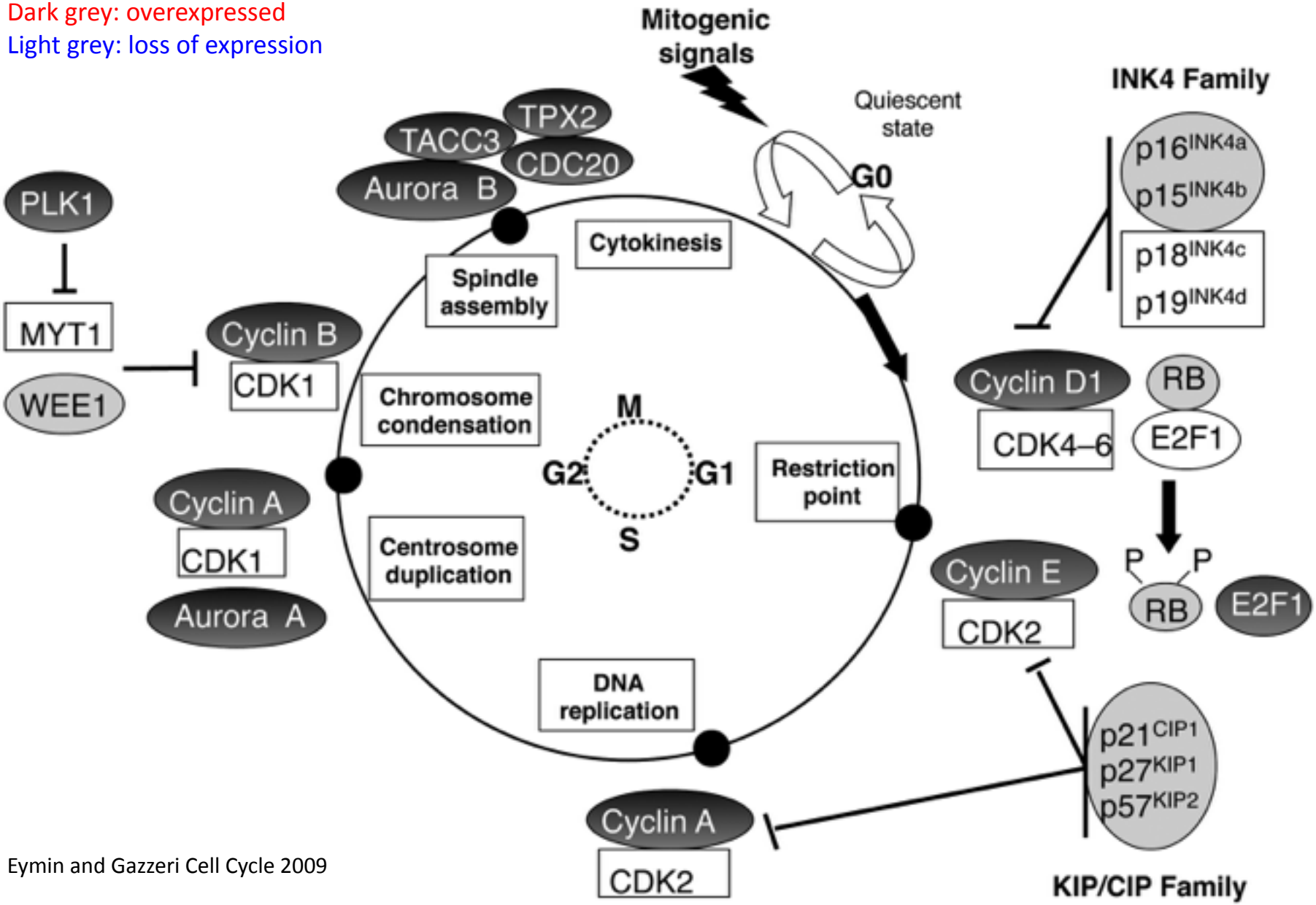


Zwang Y et al. Cancer Res 2012;72:1051-1054

Cell cycle regulation in lung carcinogenesis

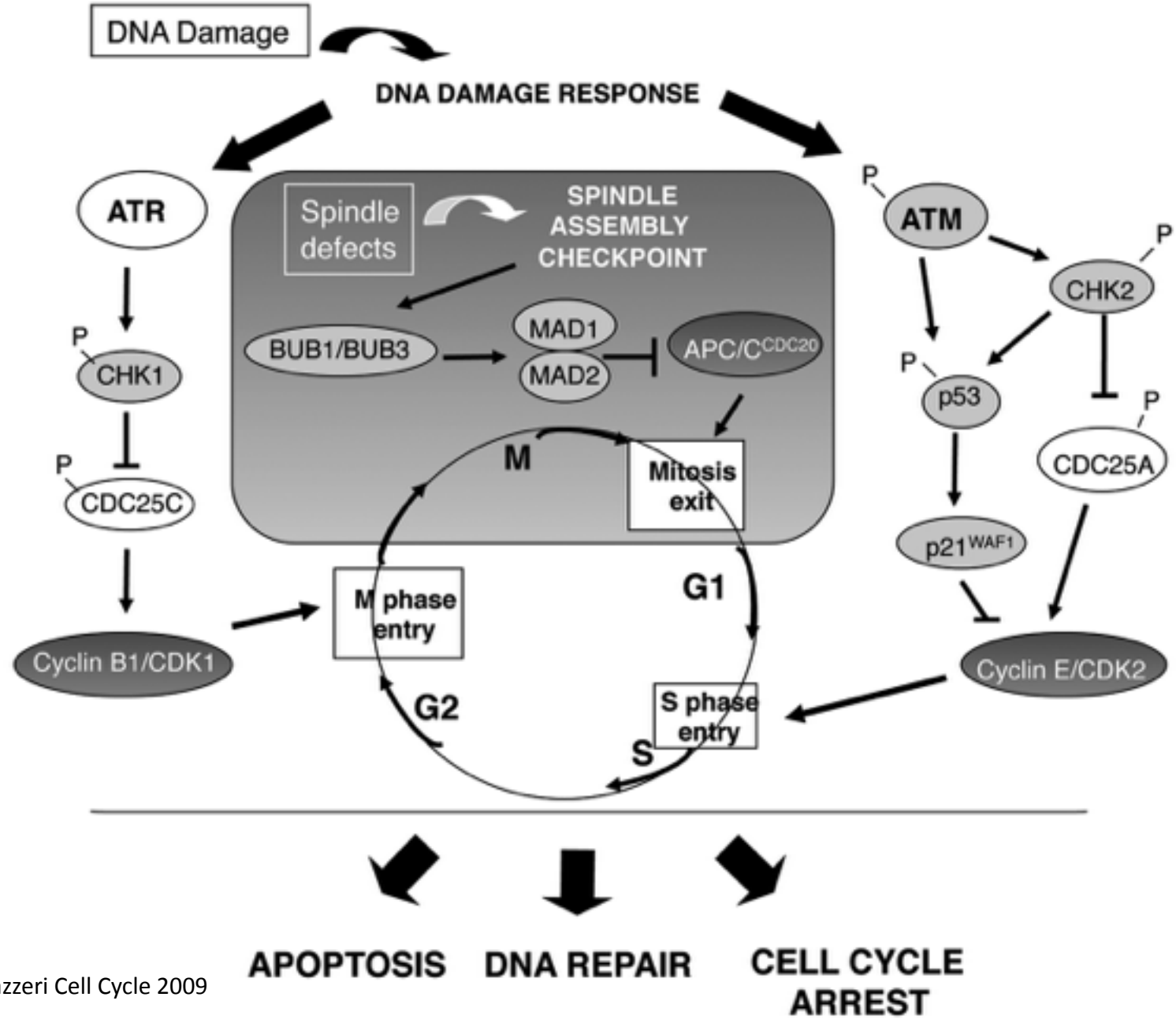
Abnormalities of cell cycle regulators in human lung tumors

Dark grey: overexpressed
Light grey: loss of expression



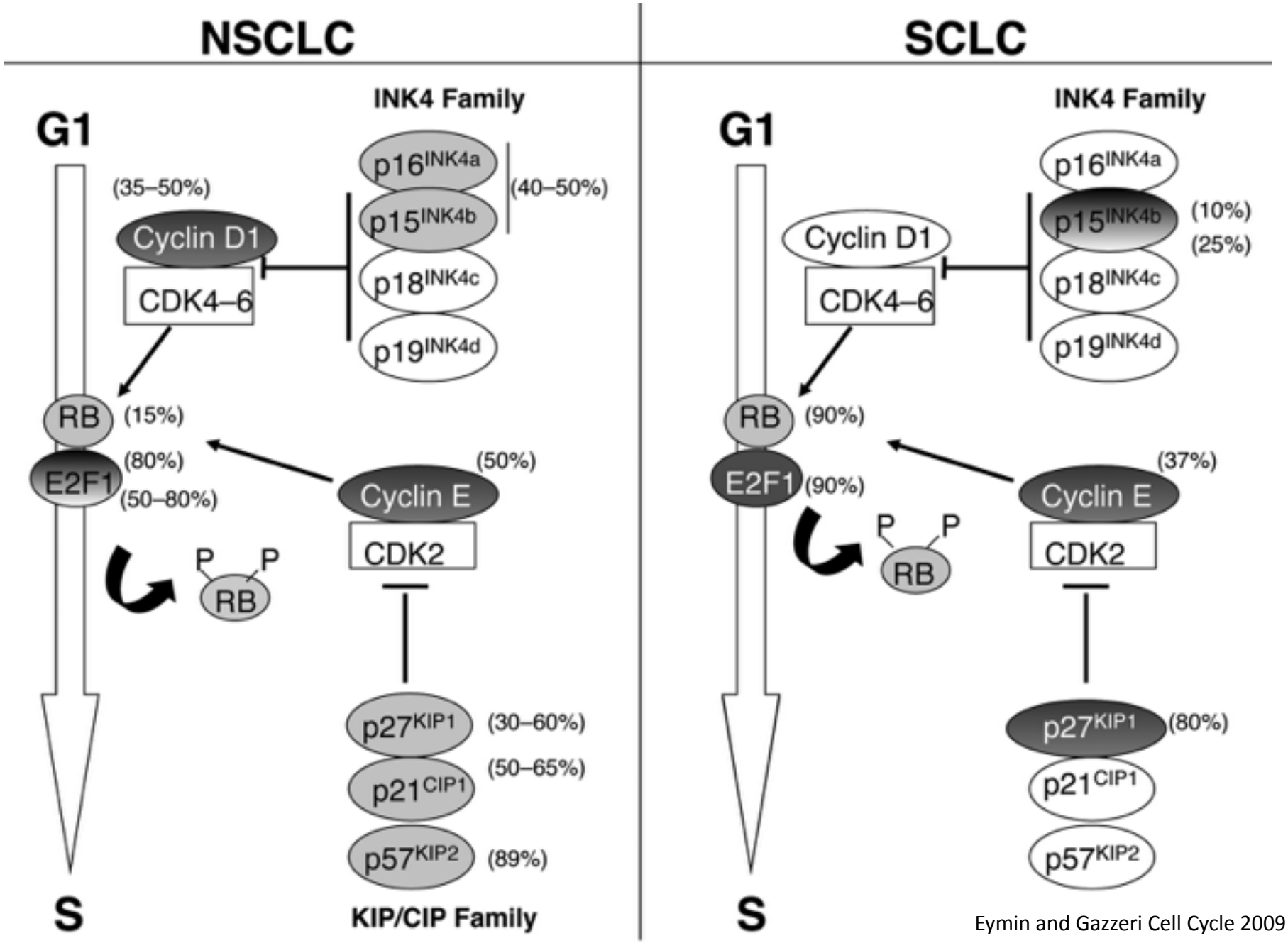
Eymin and Gazzeri Cell Cycle 2009

Alterations in components of cell cycle checkpoints in lung tumors



Eymin and Gazzeri Cell Cycle 2009

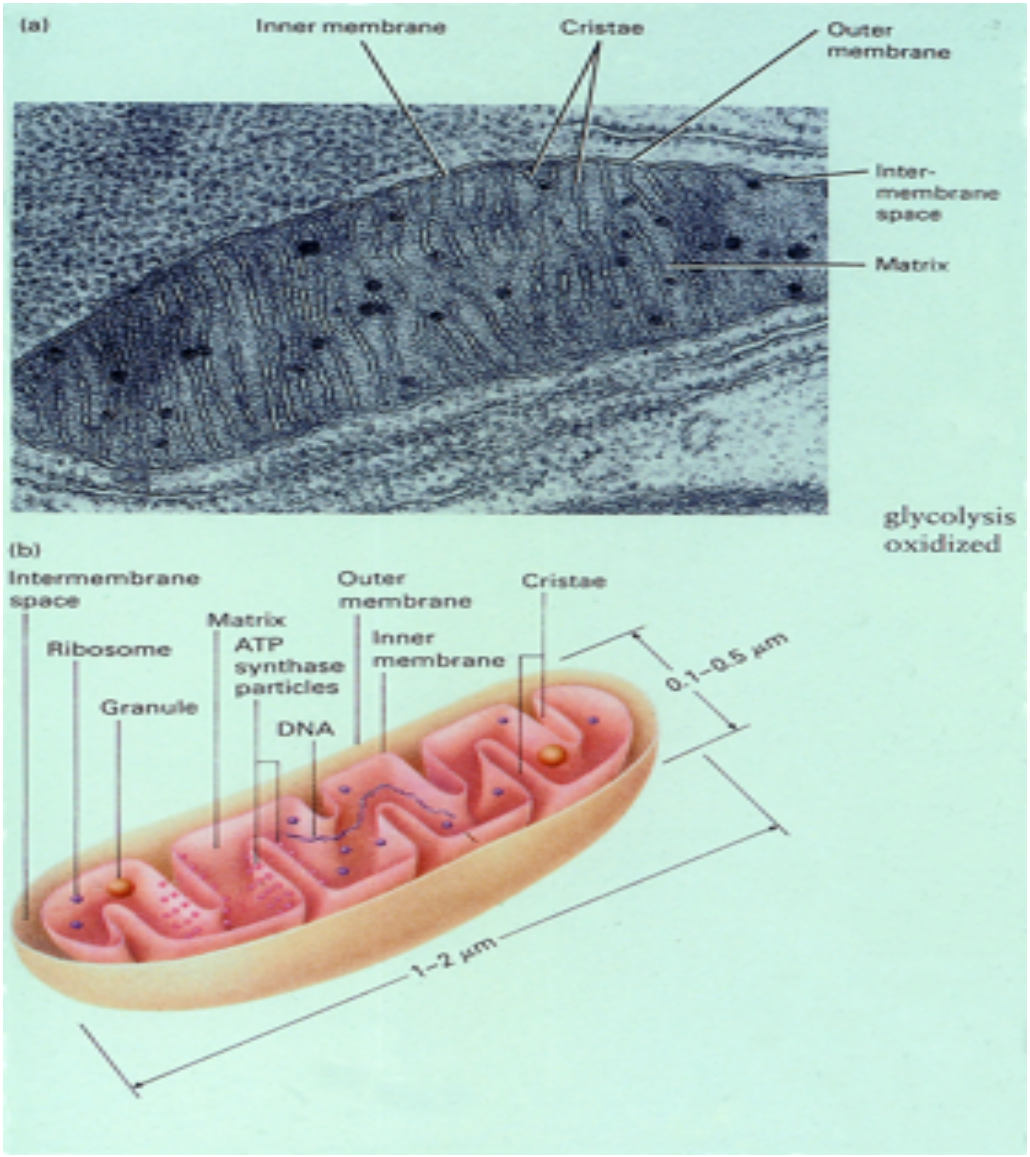
Alterations of the G1/S transition regulators in NSCLC vs SCLC



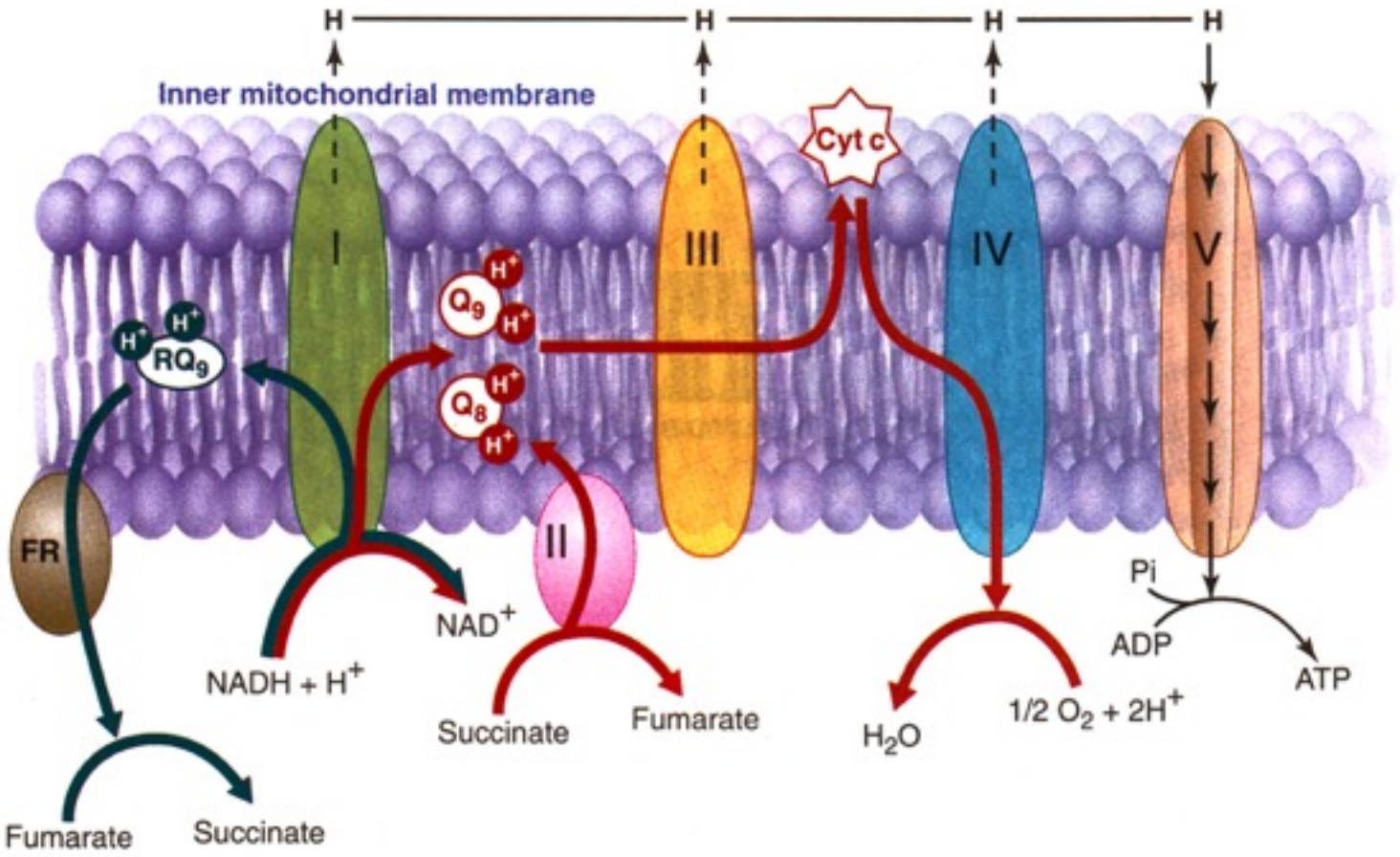
Eymin and Gazzeri Cell Cycle 2009

The role of ROS in cell cycle

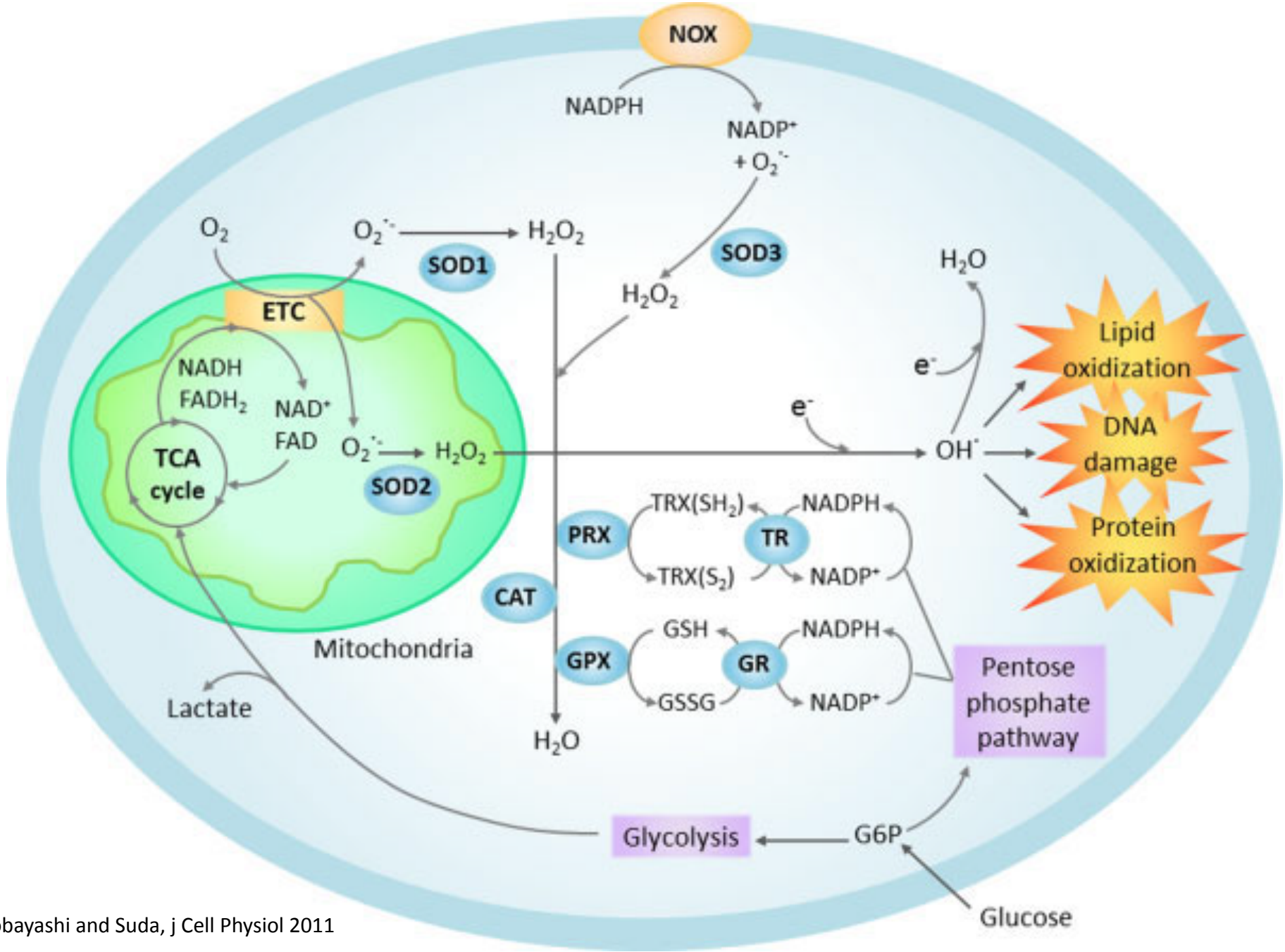
Mitochondria



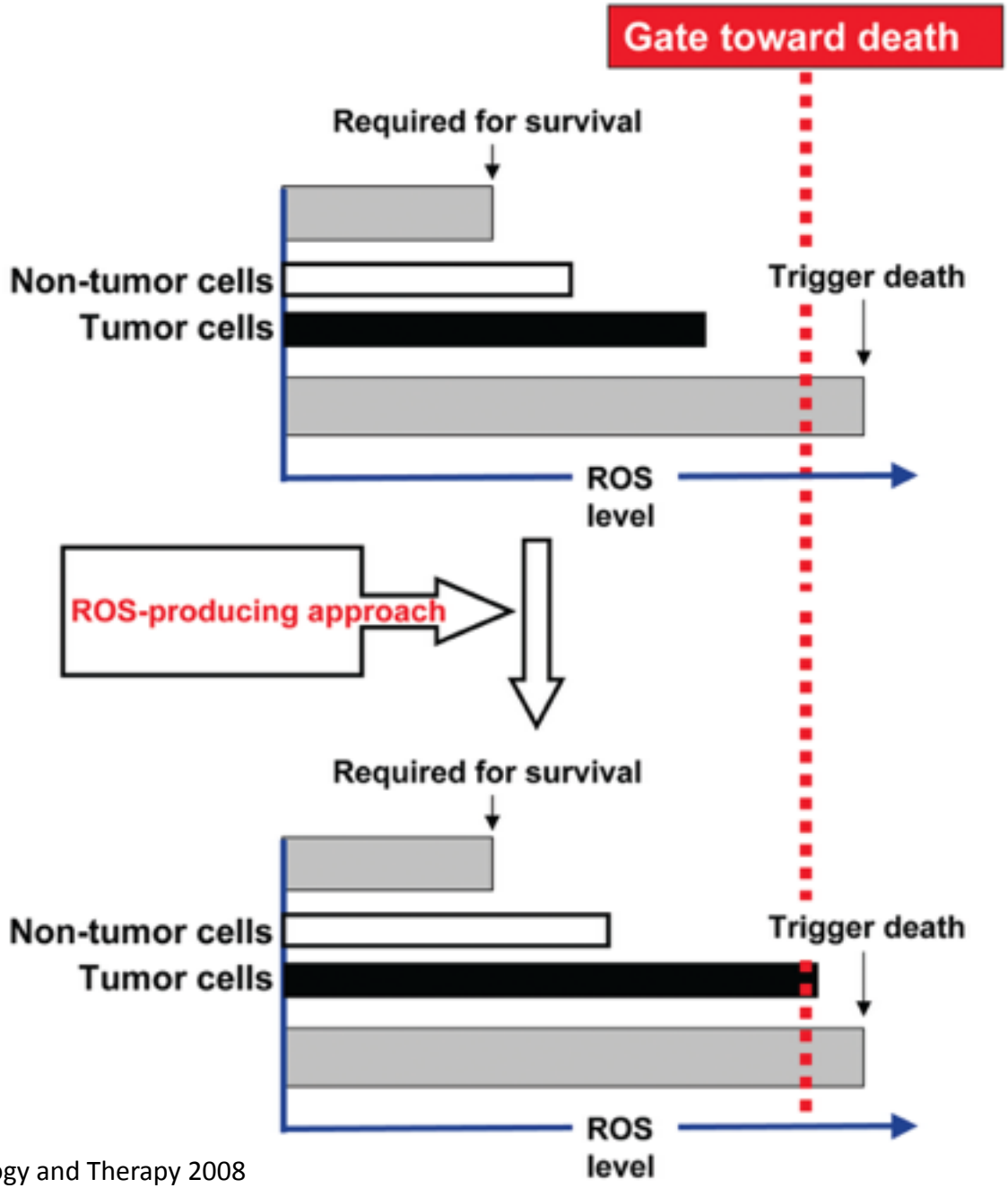
Mitochondrial respiratory chain



www.sciencemag.org SCIENCE VOL 295 4 JANUARY 2002



Kobayashi and Suda, j Cell Physiol 2011



Wang and Yi, Cancer Biology and Therapy 2008