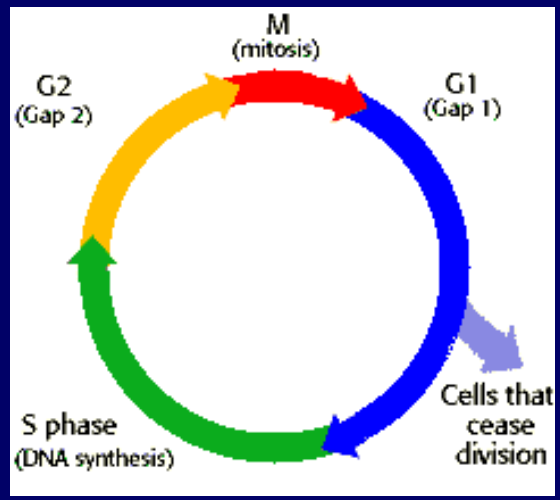
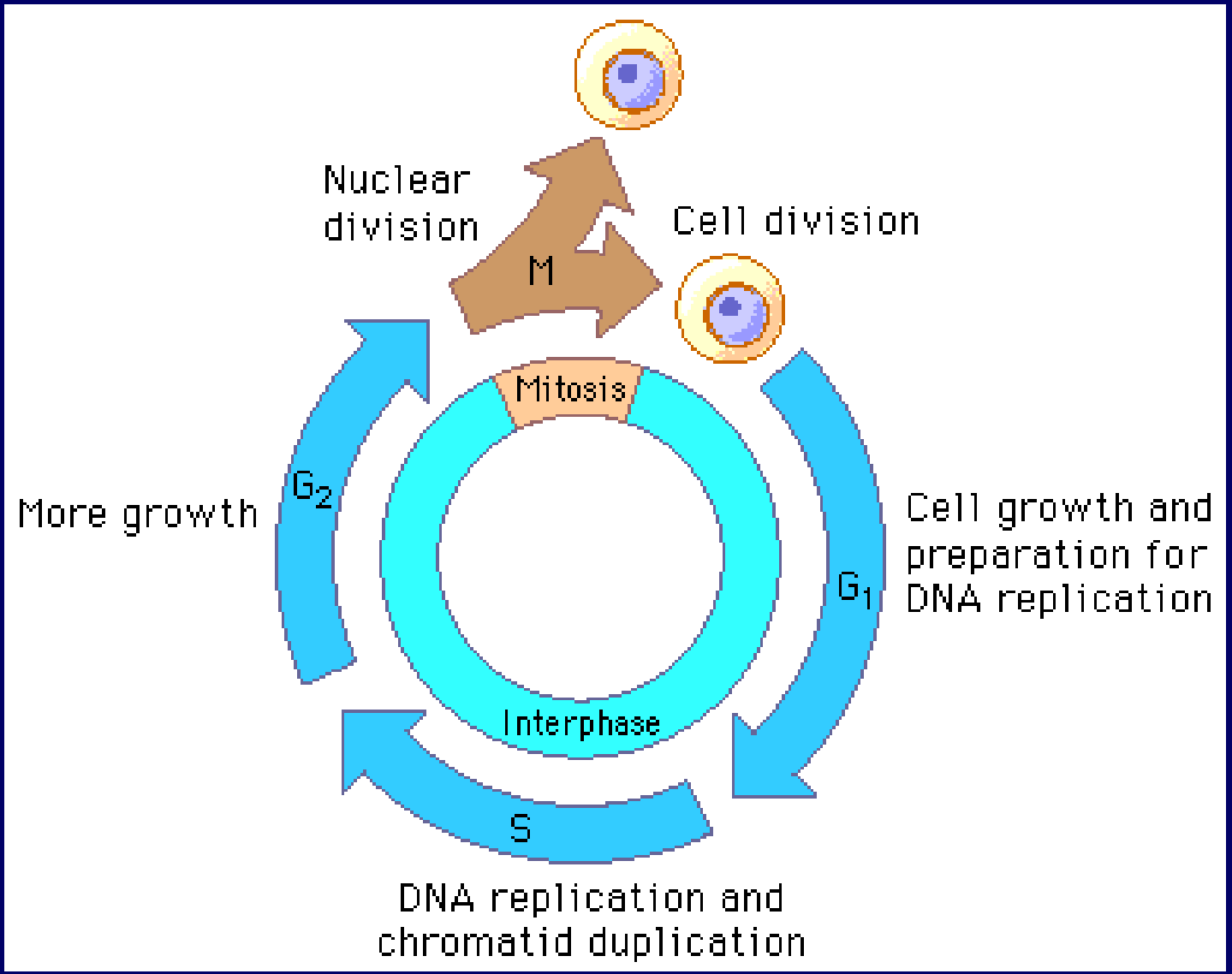
Ciclo celular y su regulación



Ciclo celular



UMBRAL ⟶ Decisión crucial

Proliferación ⟷ Quiescencia

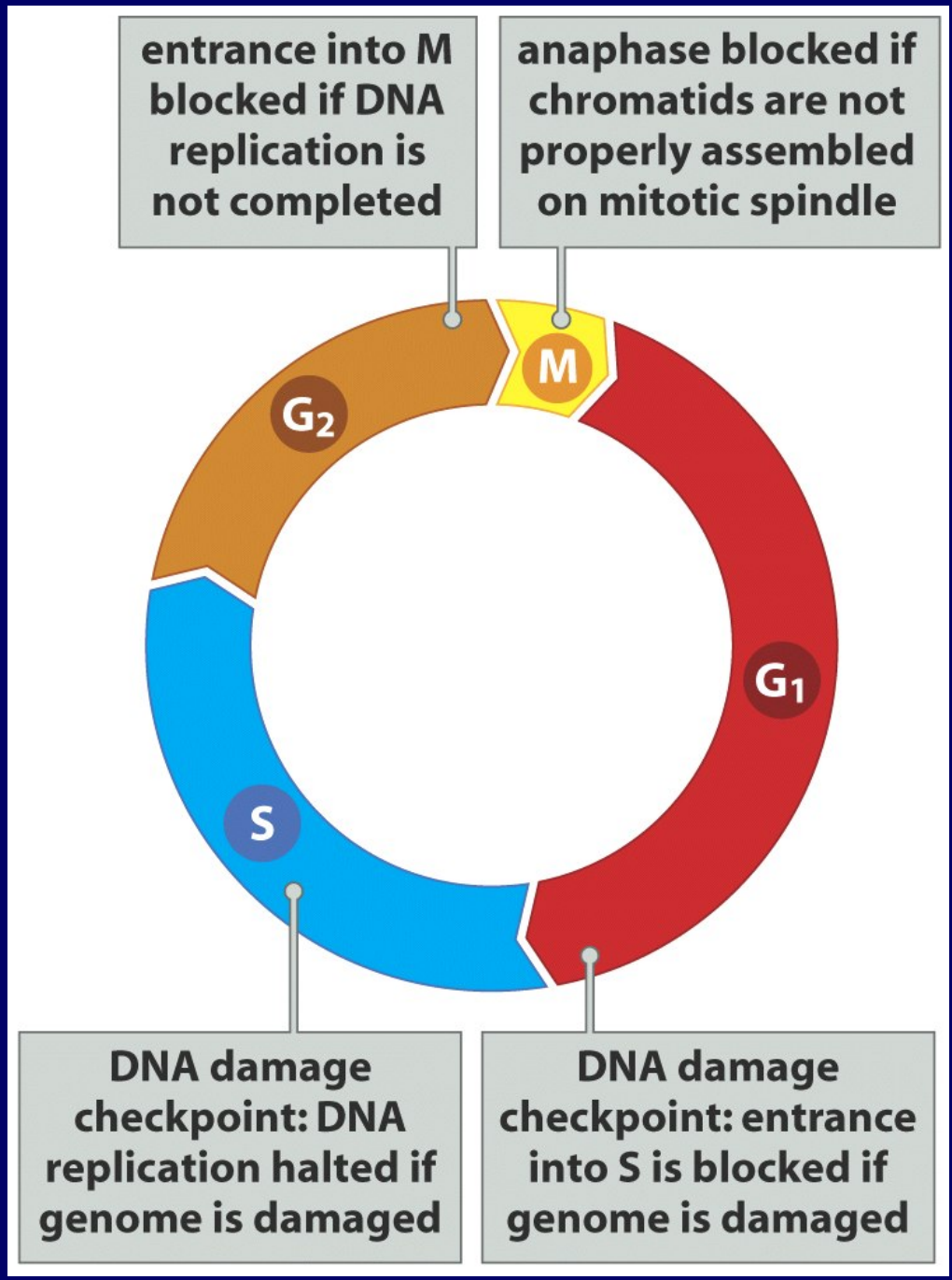
Desarrollo embrionario = proliferación

Organismo adulto = quiescencia

Todas las células conservan su capacidad para proliferar o sea para reentrar al ciclo, entonces...

...cuáles son los mecanismos que controlan estas decisiones?

Puntos de control (*checkpoints*)


entrance into M blocked if DNA replication is not completed
anaphase blocked if chromatids are not properly assembled on mitotic spindle
M
G2
G1
S
DNA damage checkpoint: DNA replication halted if genome is damaged
DNA damage checkpoint: entrance into S is blocked if genome is damaged

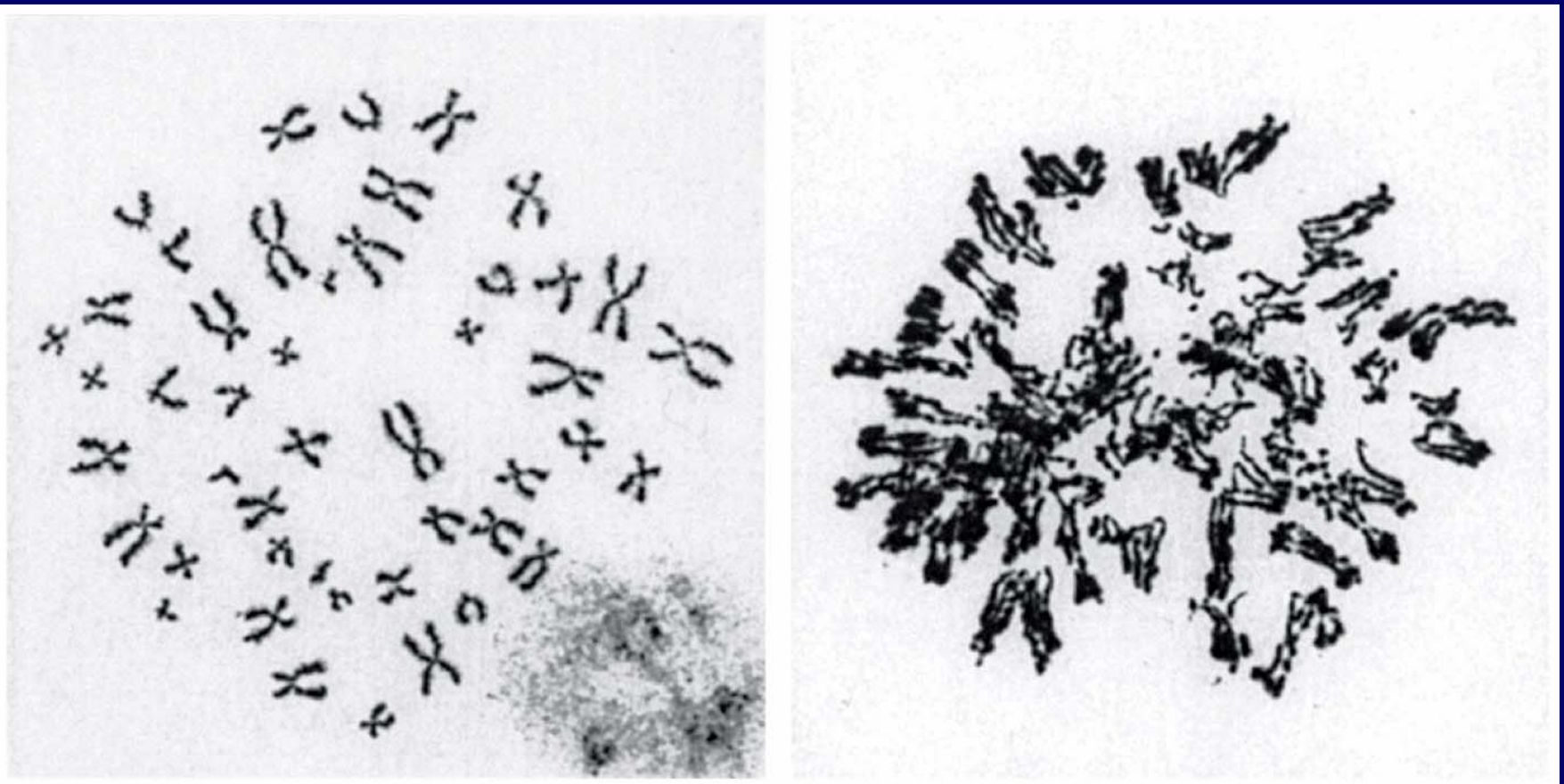


Figure 8-5a The Biology of Cancer (© Garland Science 2007)

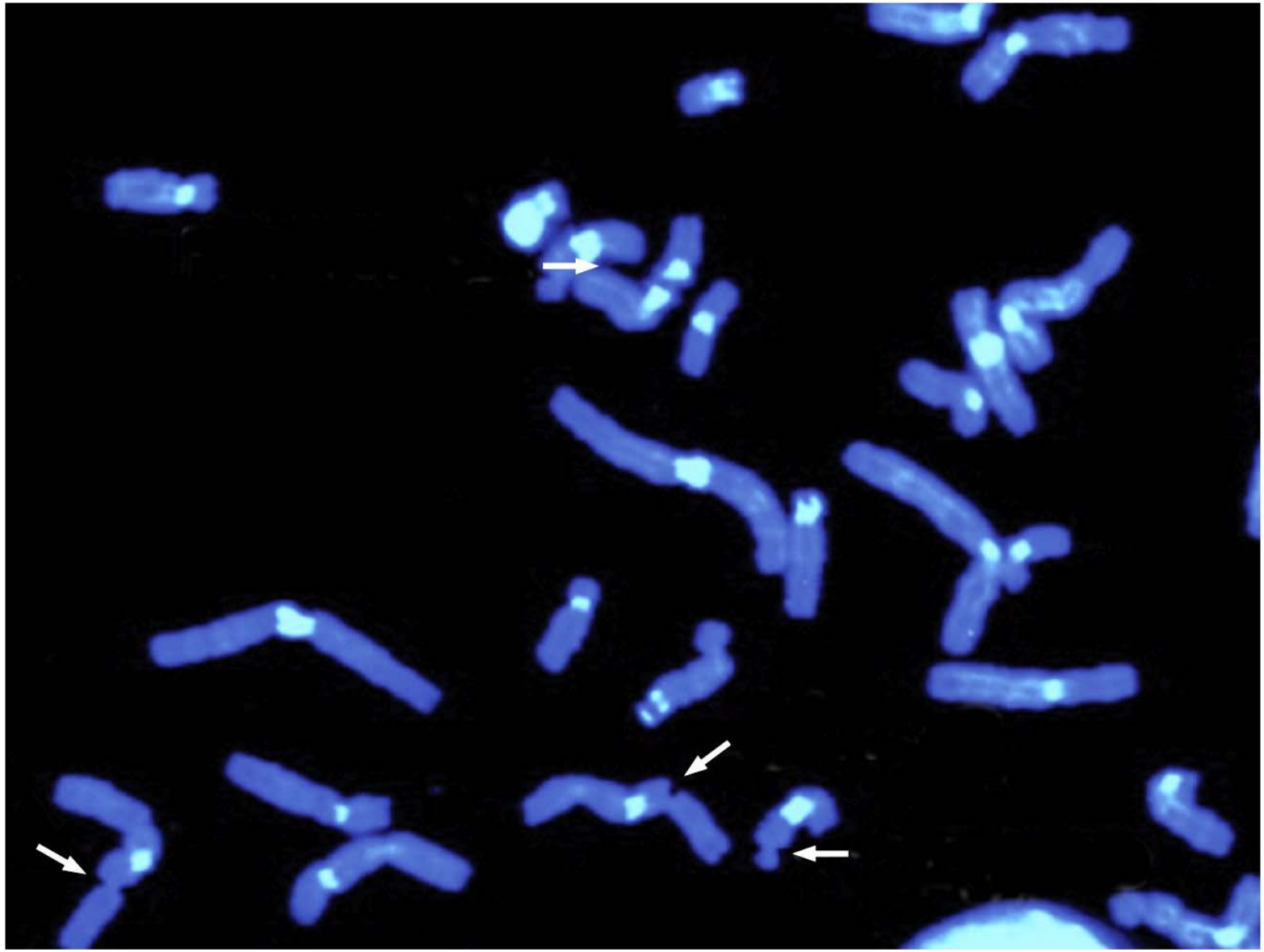


Figure 8-5c The Biology of Cancer (© Garland Science 2007)

***checkpoints* rígidos**

↓

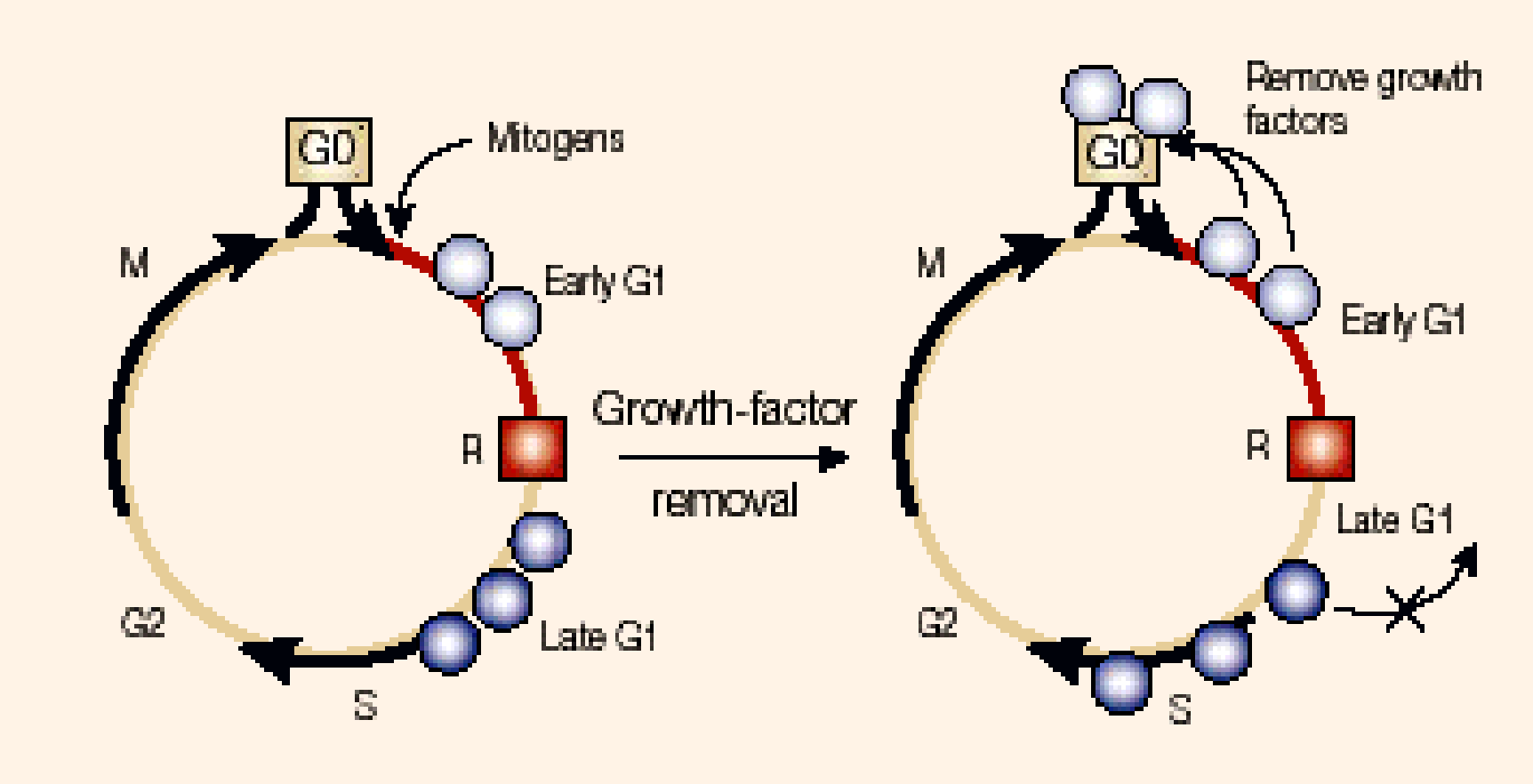
Incapacidad de proliferar

***checkpoints* lábiles**

↓

proliferación descontrolada

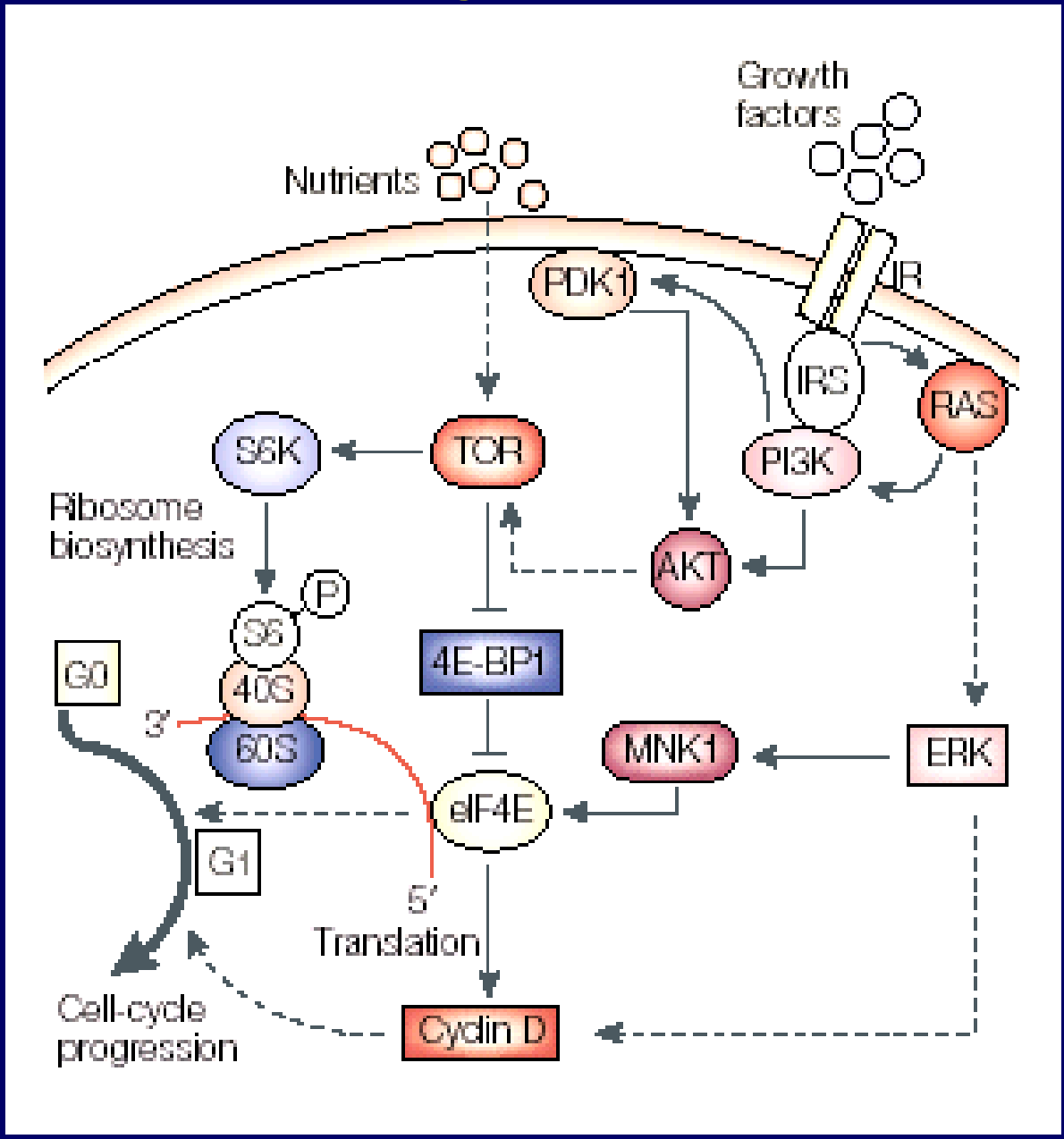
Punto de restricción (R)



Nat. Rev. Cancer 1 (2001), 222

Crecimiento celular

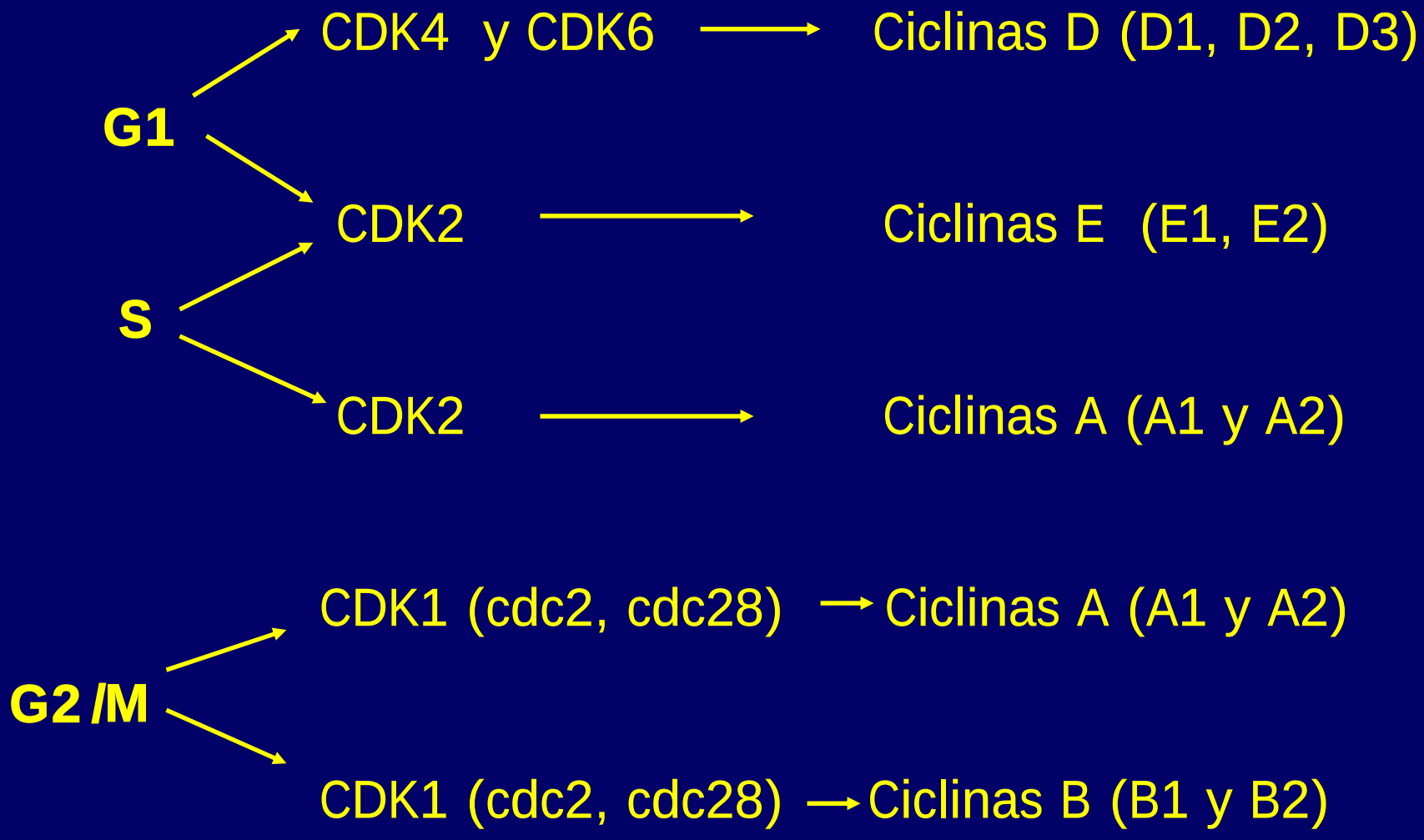
Crecimiento y división celular



Imposibilidad de crecimiento y proliferación autónomo de las células.

Excepción ES cells

Ciclinas y CDKs



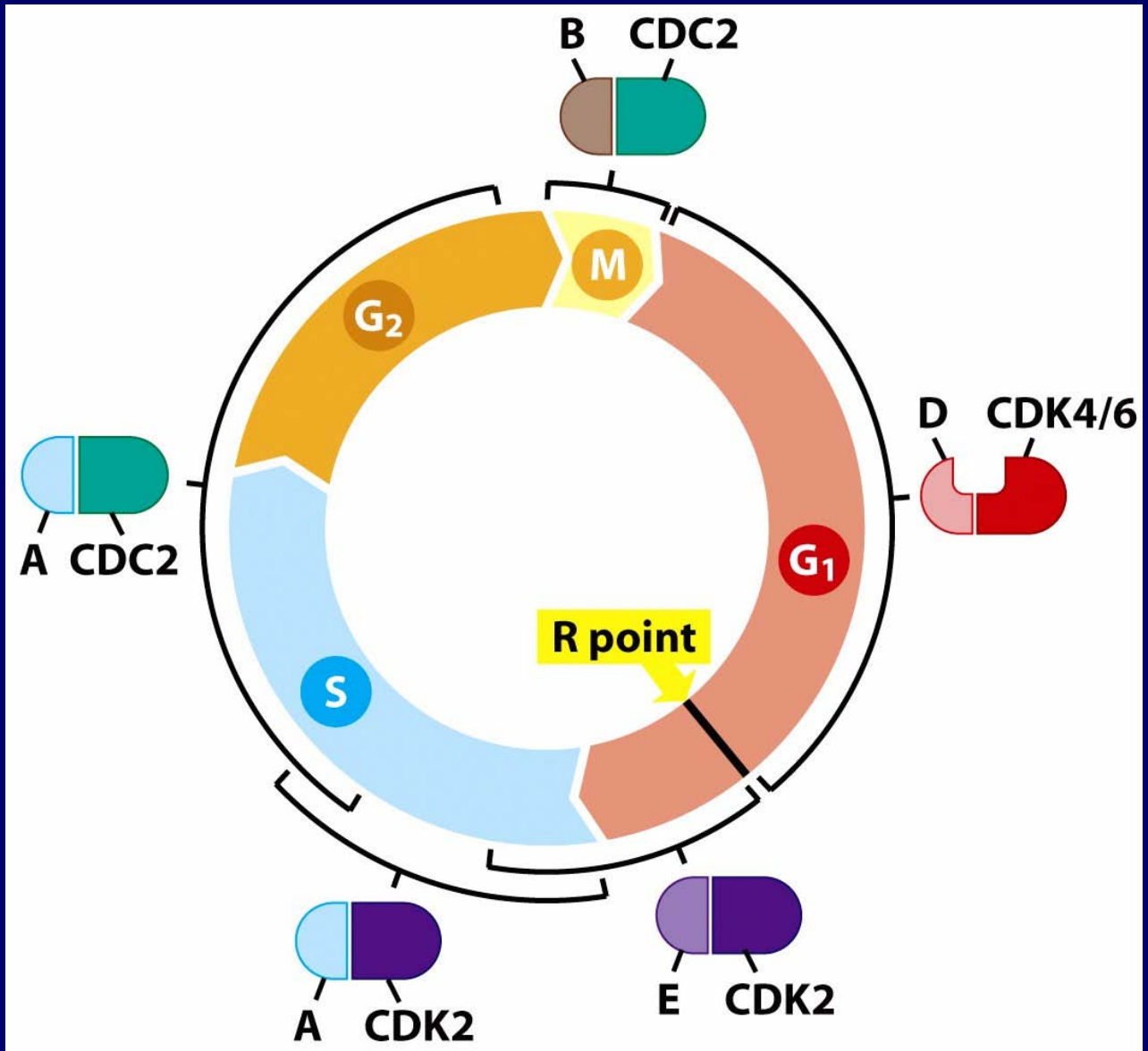


Figure 8-8 The Biology of Cancer (© Garland Science 2007)

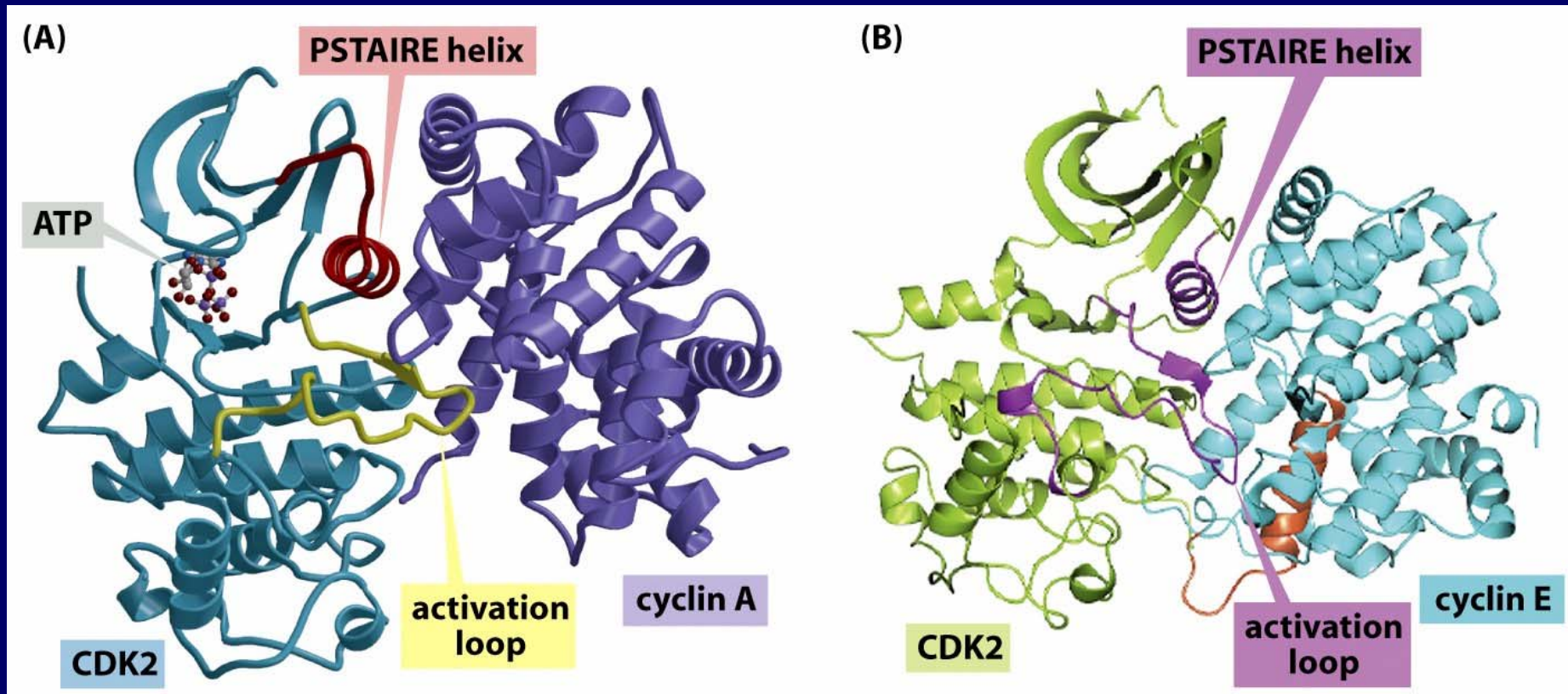
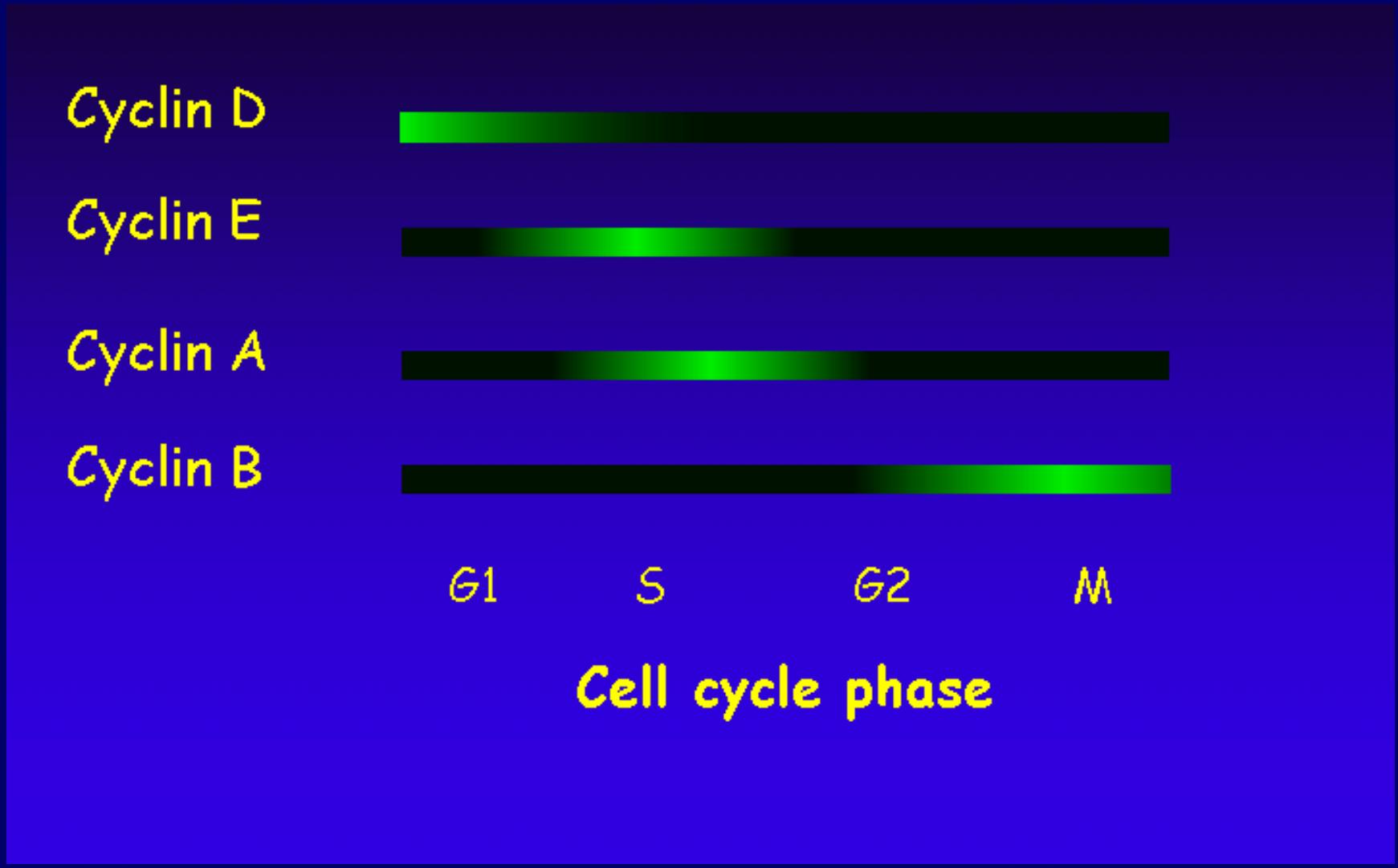


Figure 8-7 The Biology of Cancer (© Garland Science 2007)

Expresión temporal de las ciclinas



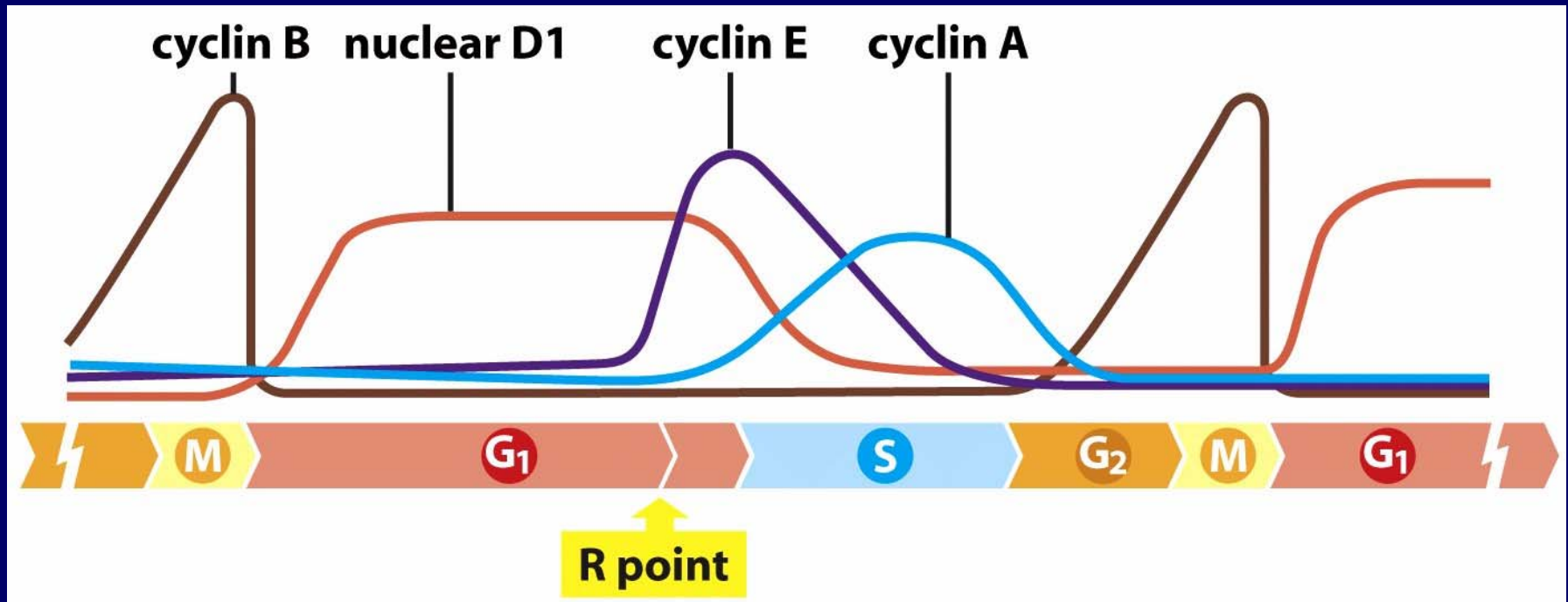
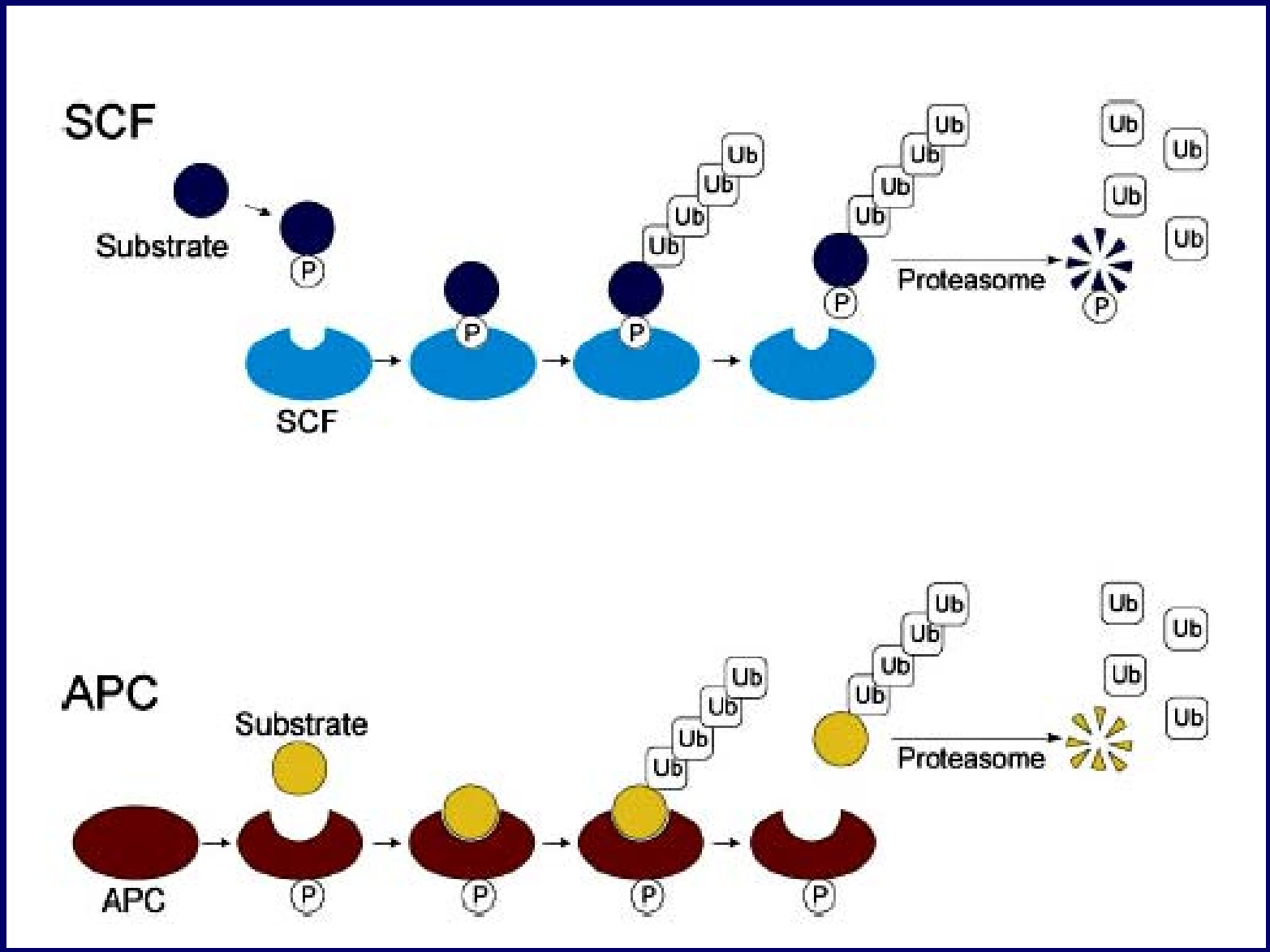


Figure 8-10 The Biology of Cancer (© Garland Science 2007)

Mecanismos de degradación de ciclinas



Cell 116 (2004), 221

Señal de degradación de ciclinas mitóticas

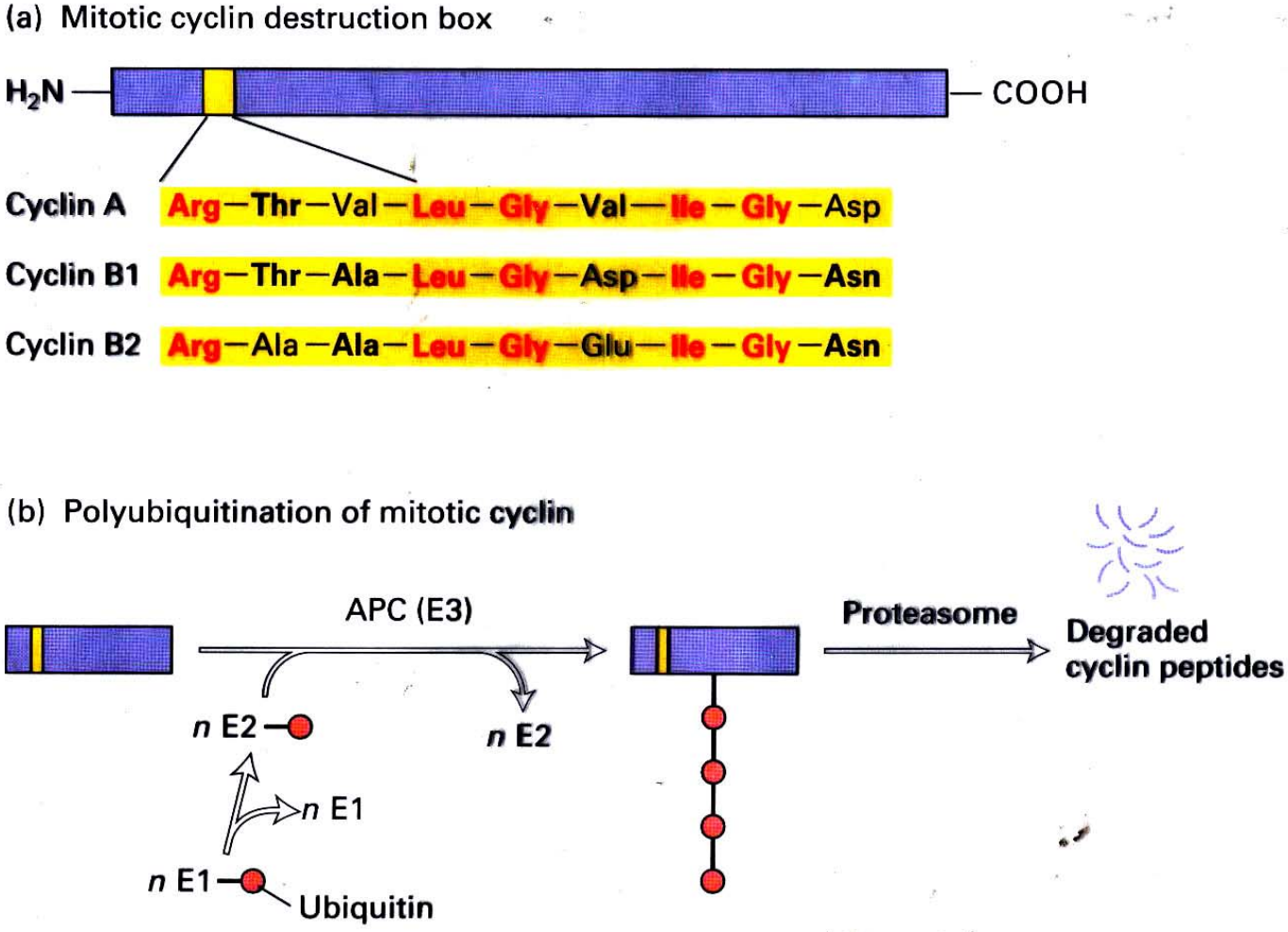
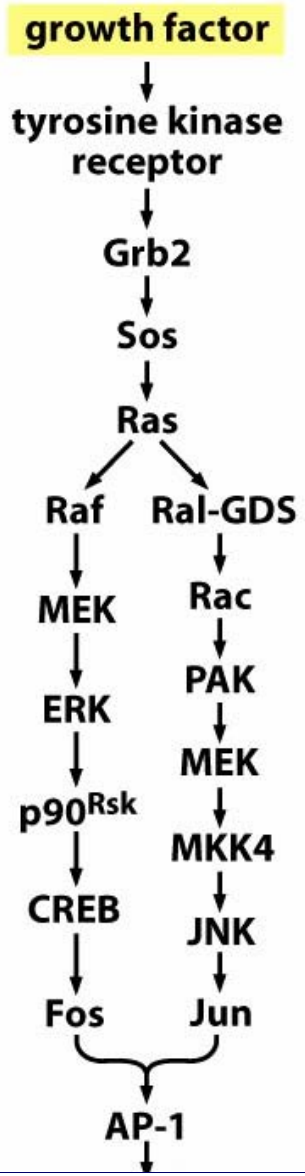
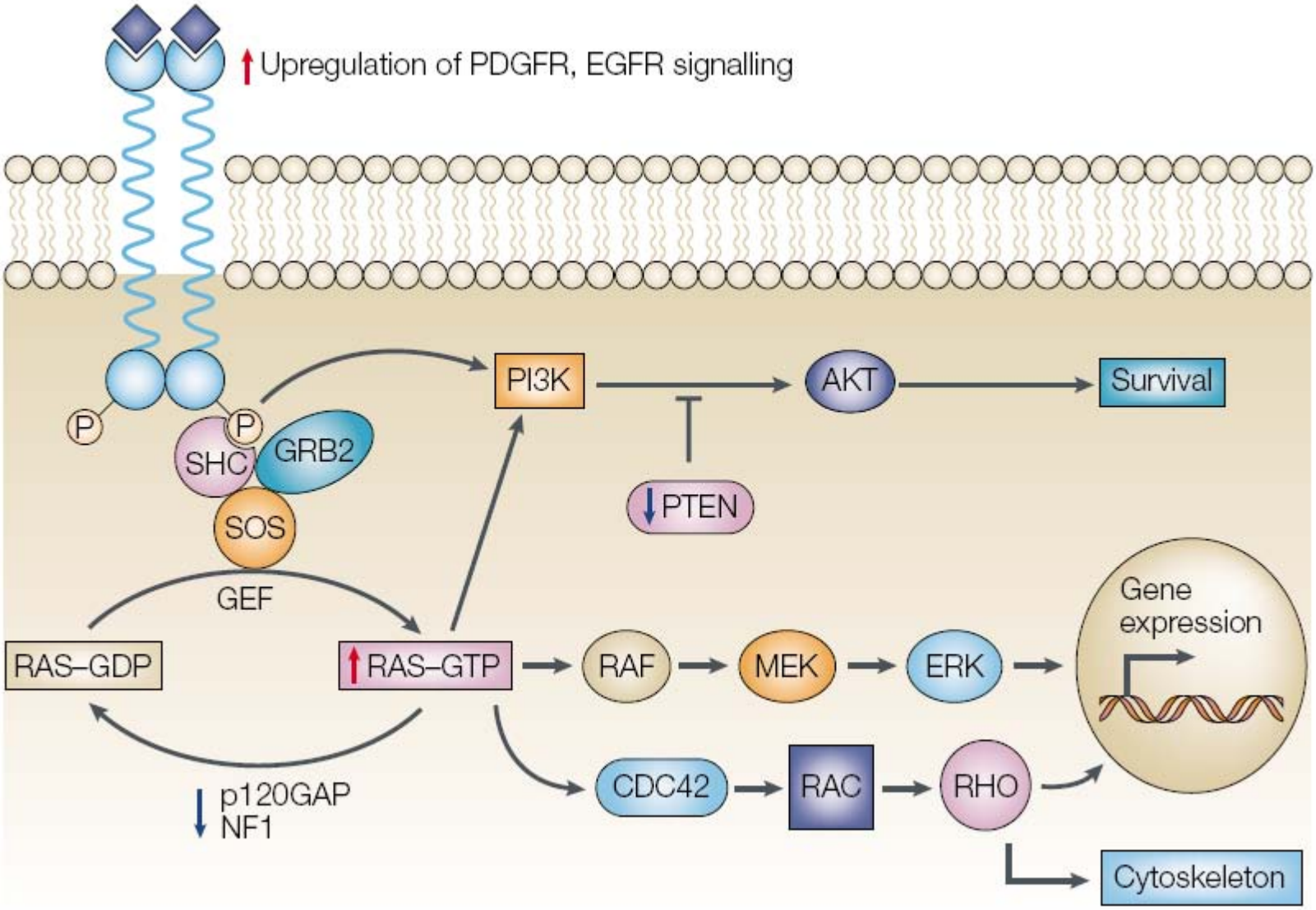


Figure 13-8
Lodish et al. MOLECULAR CELL BIOLOGY, Fourth Edition


growth factor
tyrosine kinase receptor
Grb2
Sos
Ras
Raf
Ral-GDS
MEK
Rac
ERK
PAK
p90Rsk
MEK
CREB
MKK4
Fos
JNK
Jun
AP-1

D1

Transducción de señales mitogénicas



Nat. Rev. Cancer **2** (2002), 616

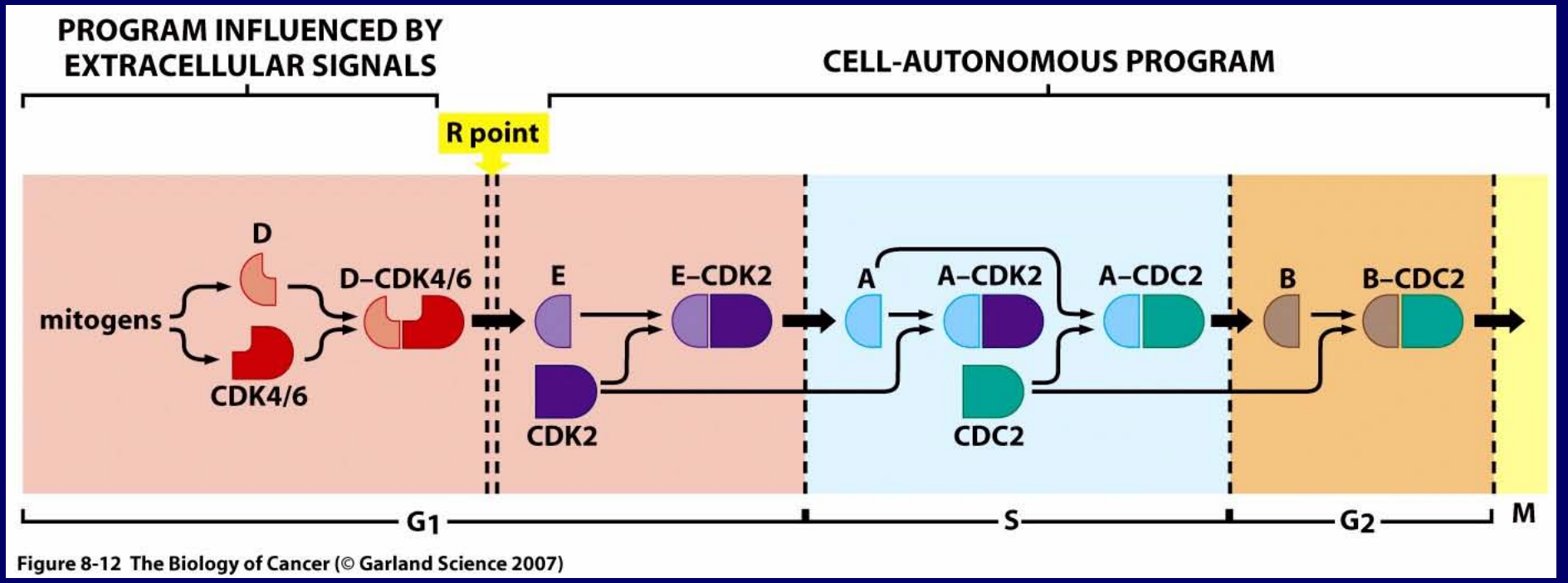
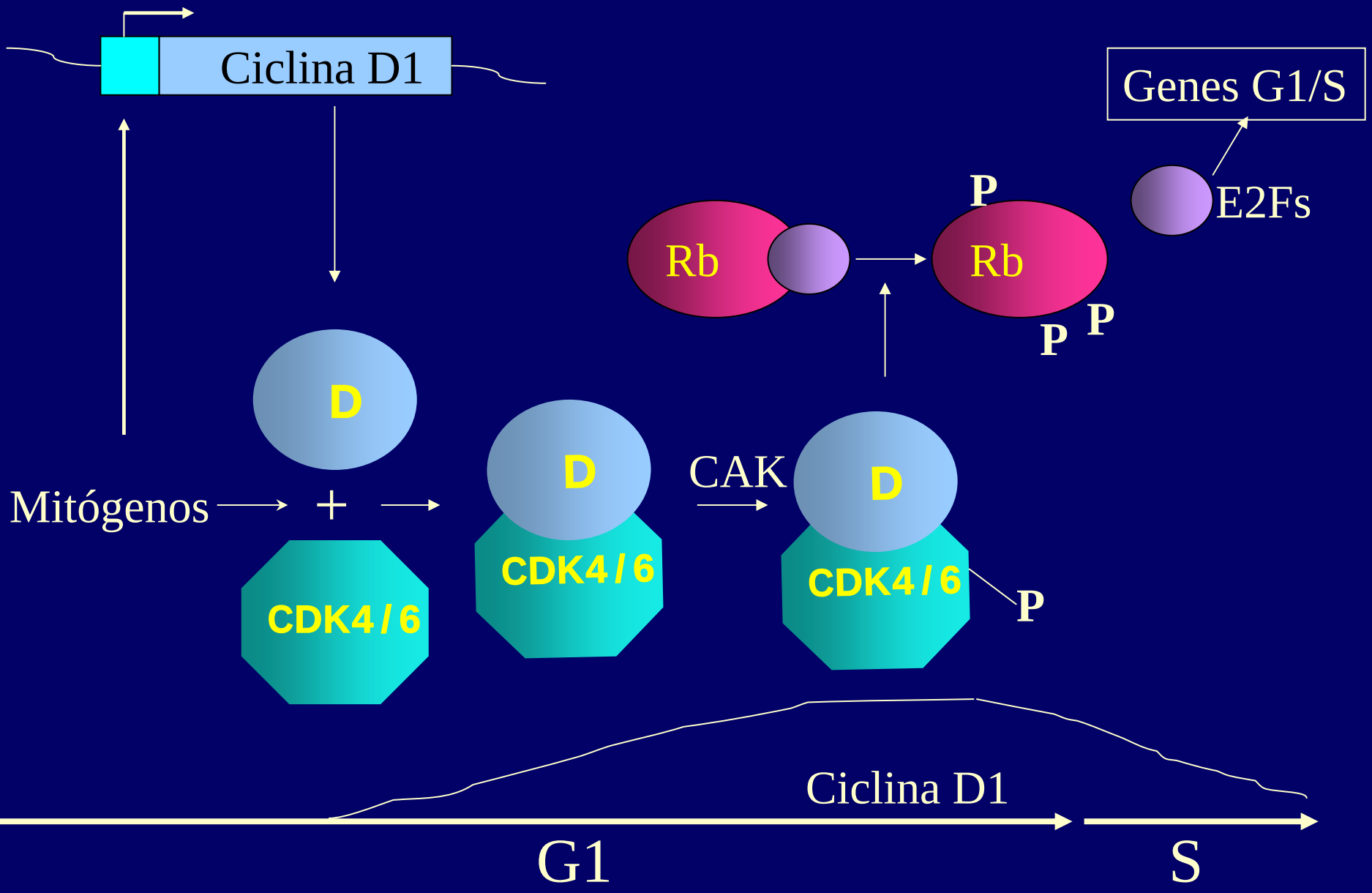
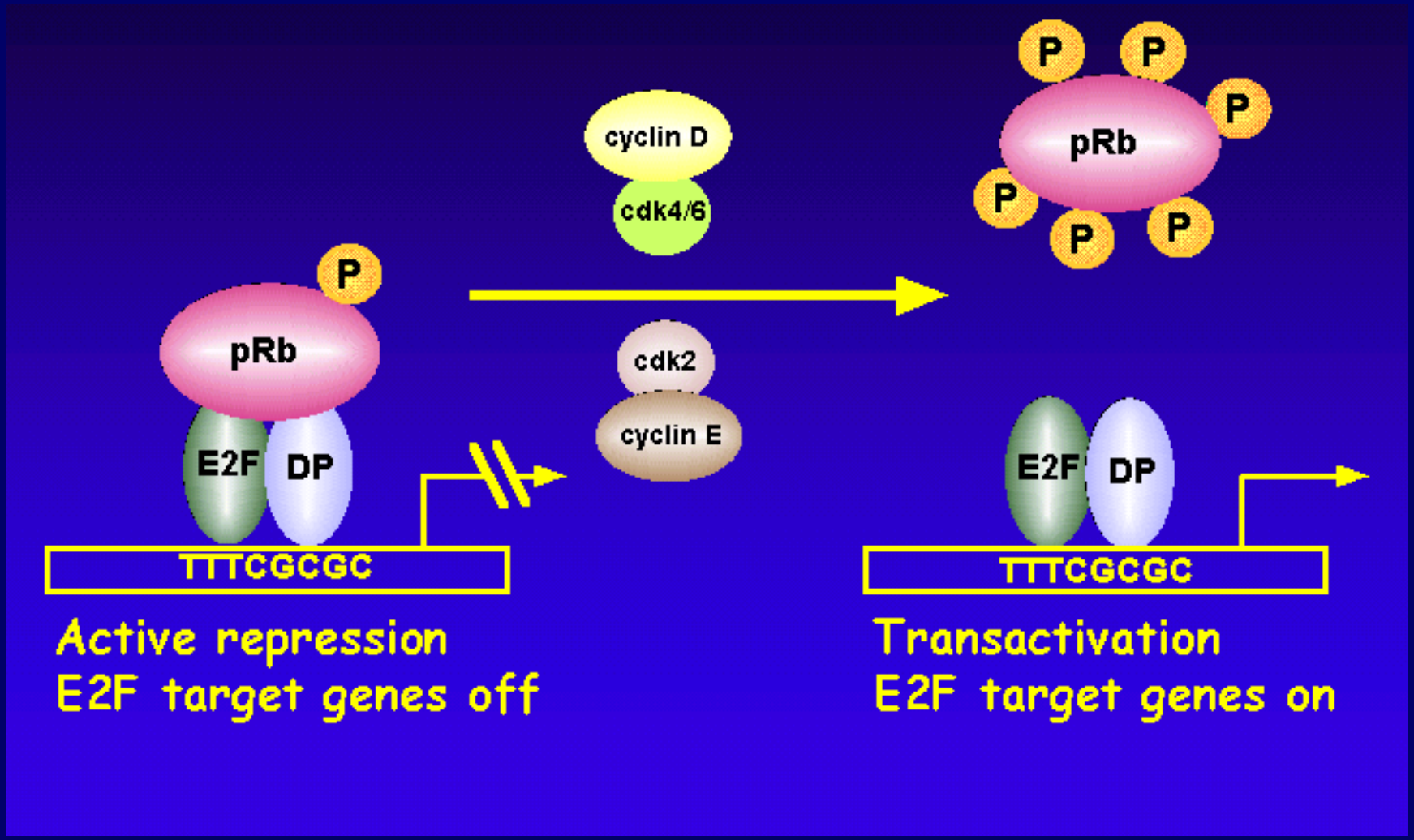


Figure 8-12 The Biology of Cancer (© Garland Science 2007)

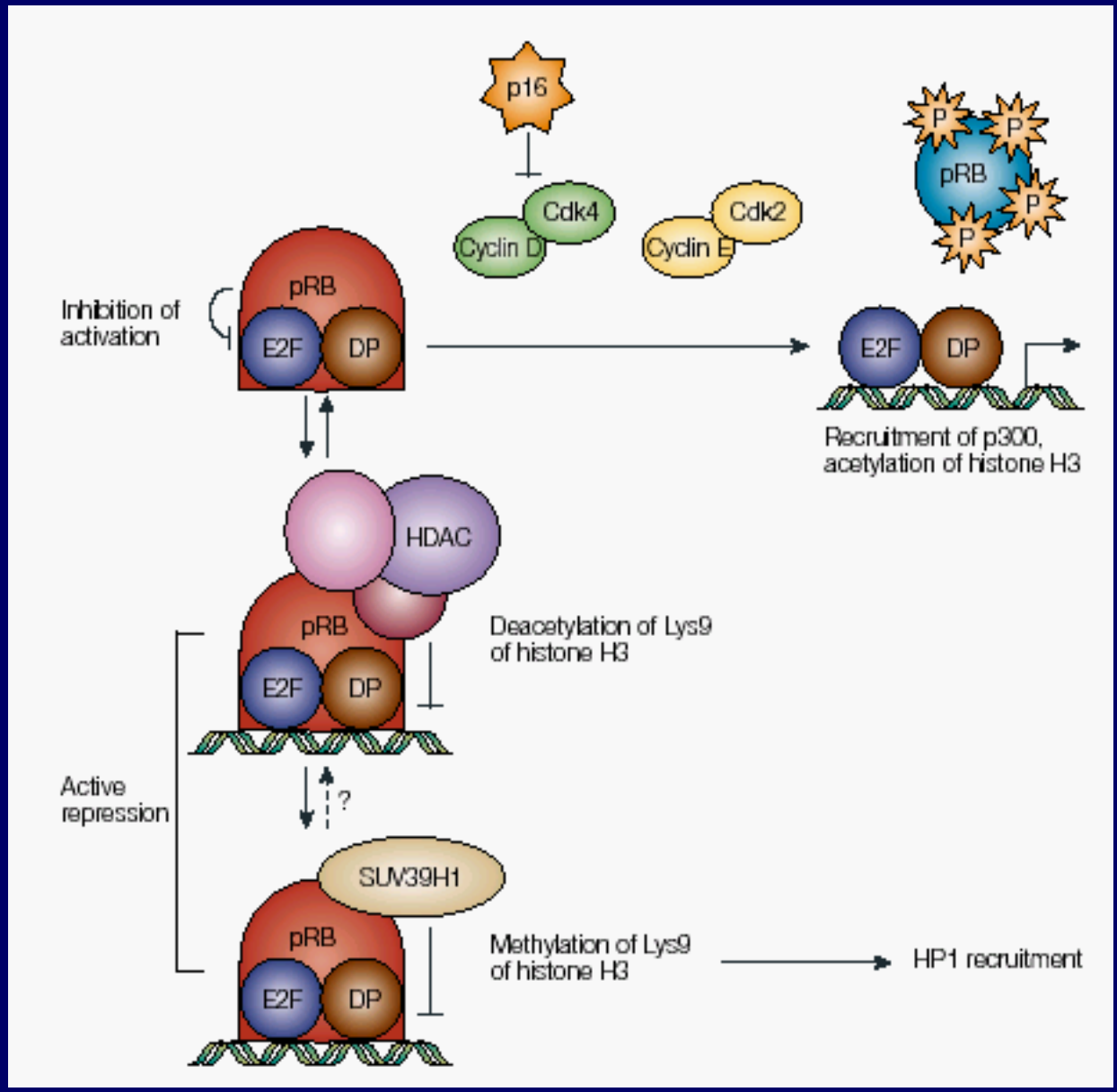
Ciclina D y fosforilación del Retinoblastoma



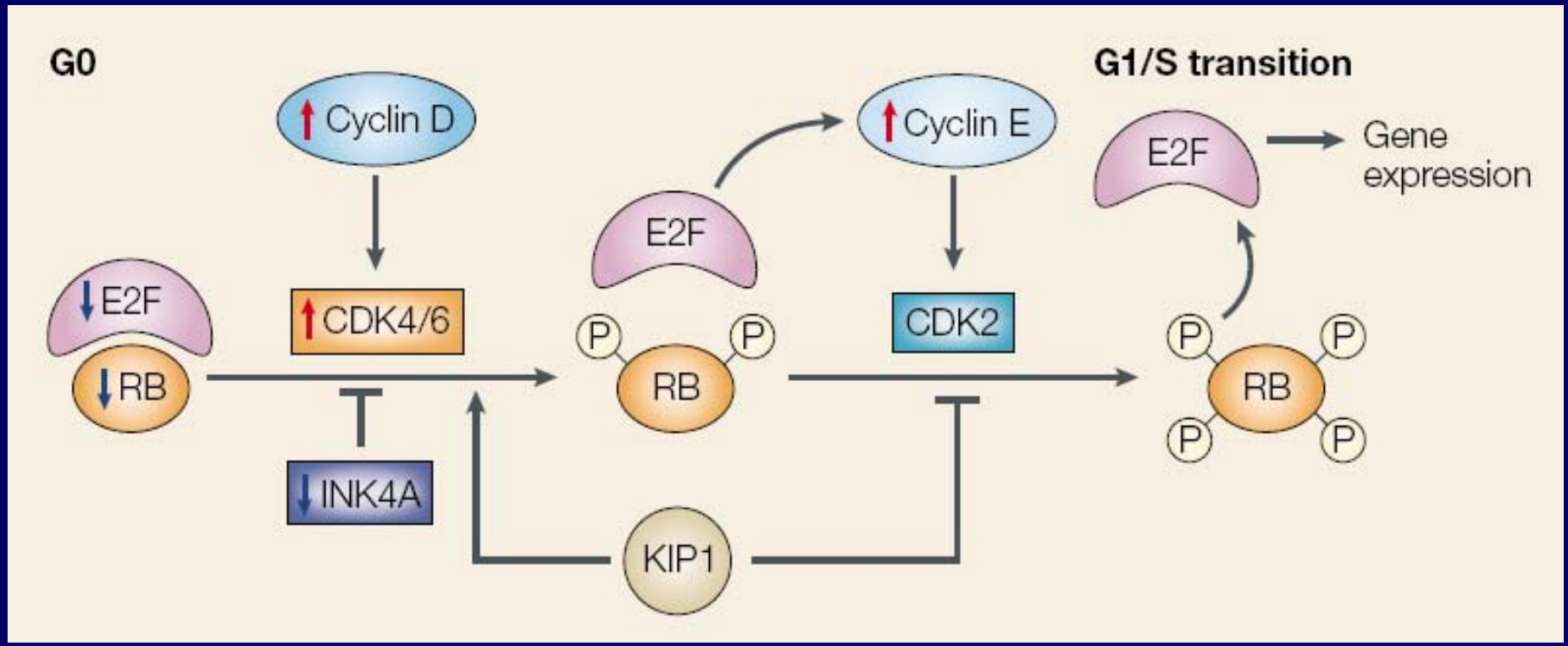
Activación del factor E2F



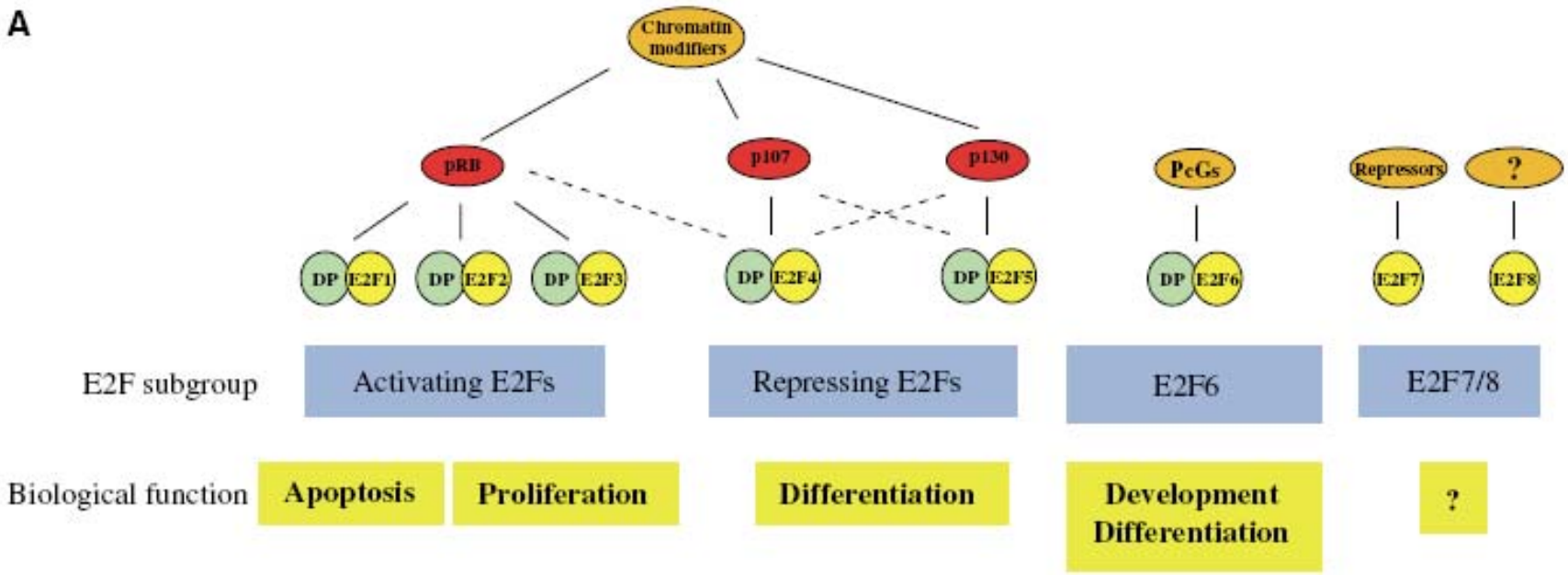
Mecanismos de represión de Rb sobre E2F



Nat. Rev. Mol. Cell Biol. 3 (2002), 11


G0
G1/S transition
Cyclin D
Cyclin E
E2F
Gene expression
E2F
CDK4/6
CDK2
RB
P
INK4A
KIP1

Familia de factores de transcripción E2F



EMBO J **23** (2004), 4709

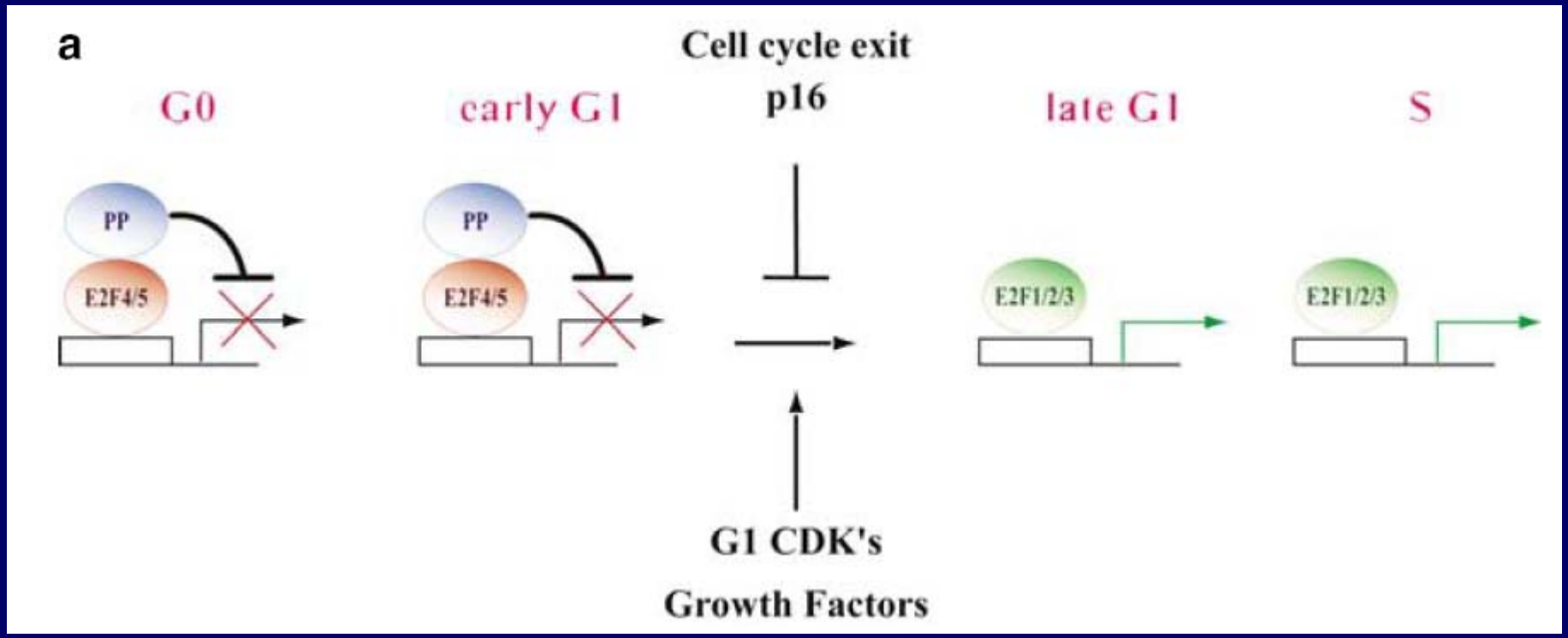


Figure 2 (a) Current molecular model for E2F/RB function. E2F4/pocket protein (PP) or E2F5/pocket-protein complexes are present at cell cycle-regulated promoters in G0 and early G1 cells and function to repress transcription. Upon mitogenic stimulation G1, Cdks phosphorylate pocket proteins and disrupt E2F/pocket protein interactions. In late G1 and early S phase, activator E2Fs (E2F1–3) bind to cell cycle-regulated promoters and activate transcription. Cell cycle exit and differentiation signals block this transition. (b) The

Oncogene **24 (2005), 2810**

Fosforilación de pRb a través del ciclo celular

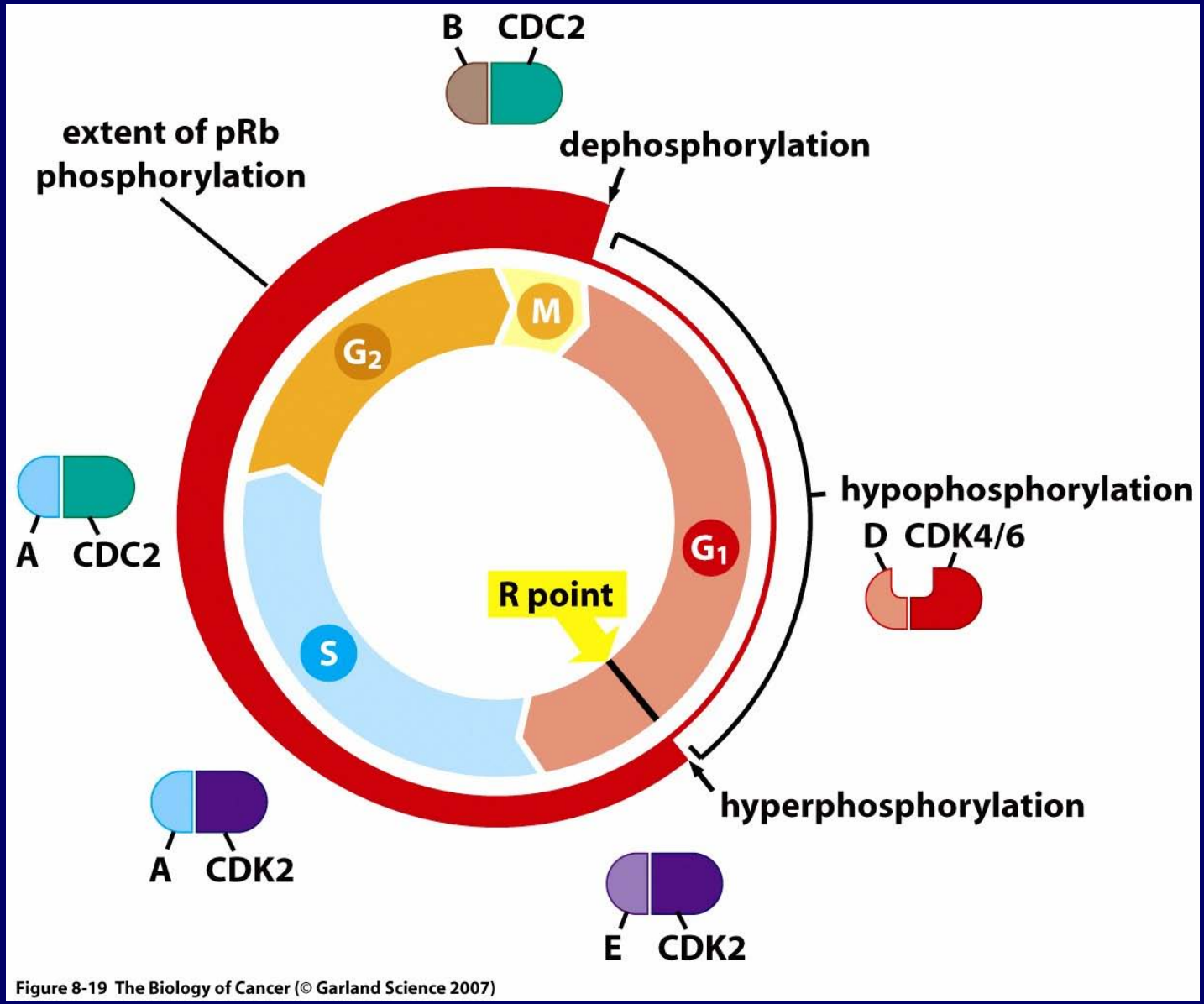


Figure 8-19 The Biology of Cancer (© Garland Science 2007)

Inhibidores de CDKs (CKIs)

Familia Cip/Kip

p21 Cip1/Waf1 (CDKN1A)

p27 Kip1 (CDKN1B)

p57 Kip2 (CDKN1C)

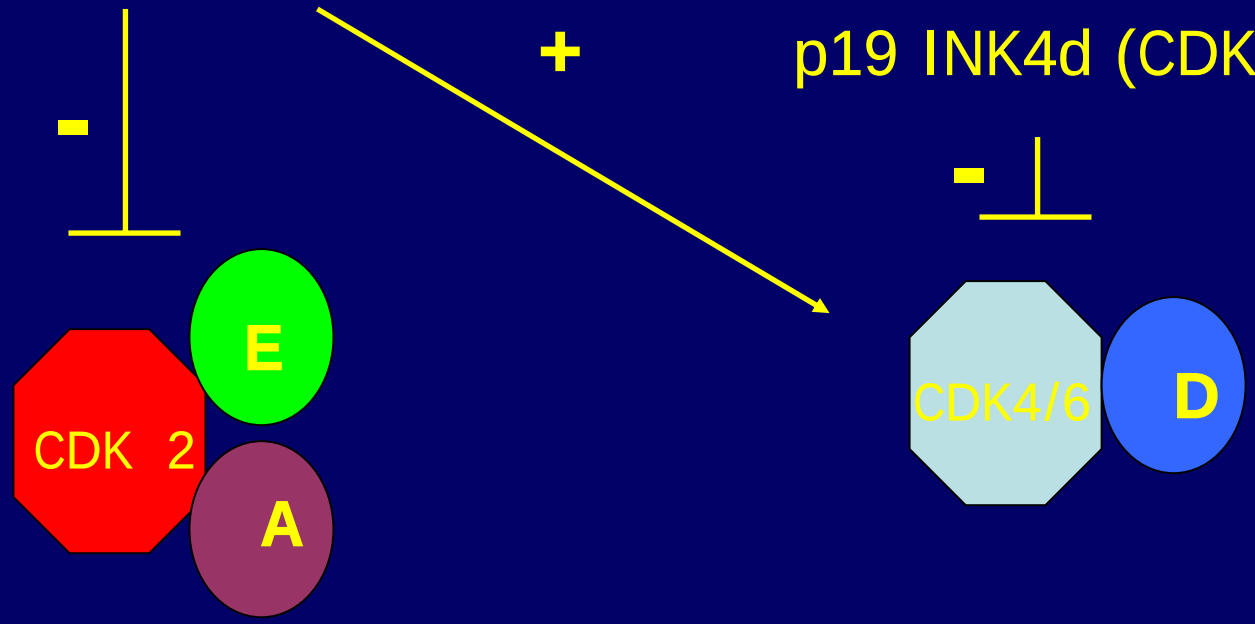
Familia INK4

p16 INK4a (CDKN2A)

p15 INK4b (CDKN2B)

p18 INK4c (CDKN2C)

p19 INK4d (CDKN2D)



Inhibidores de CDKs (CKIs)

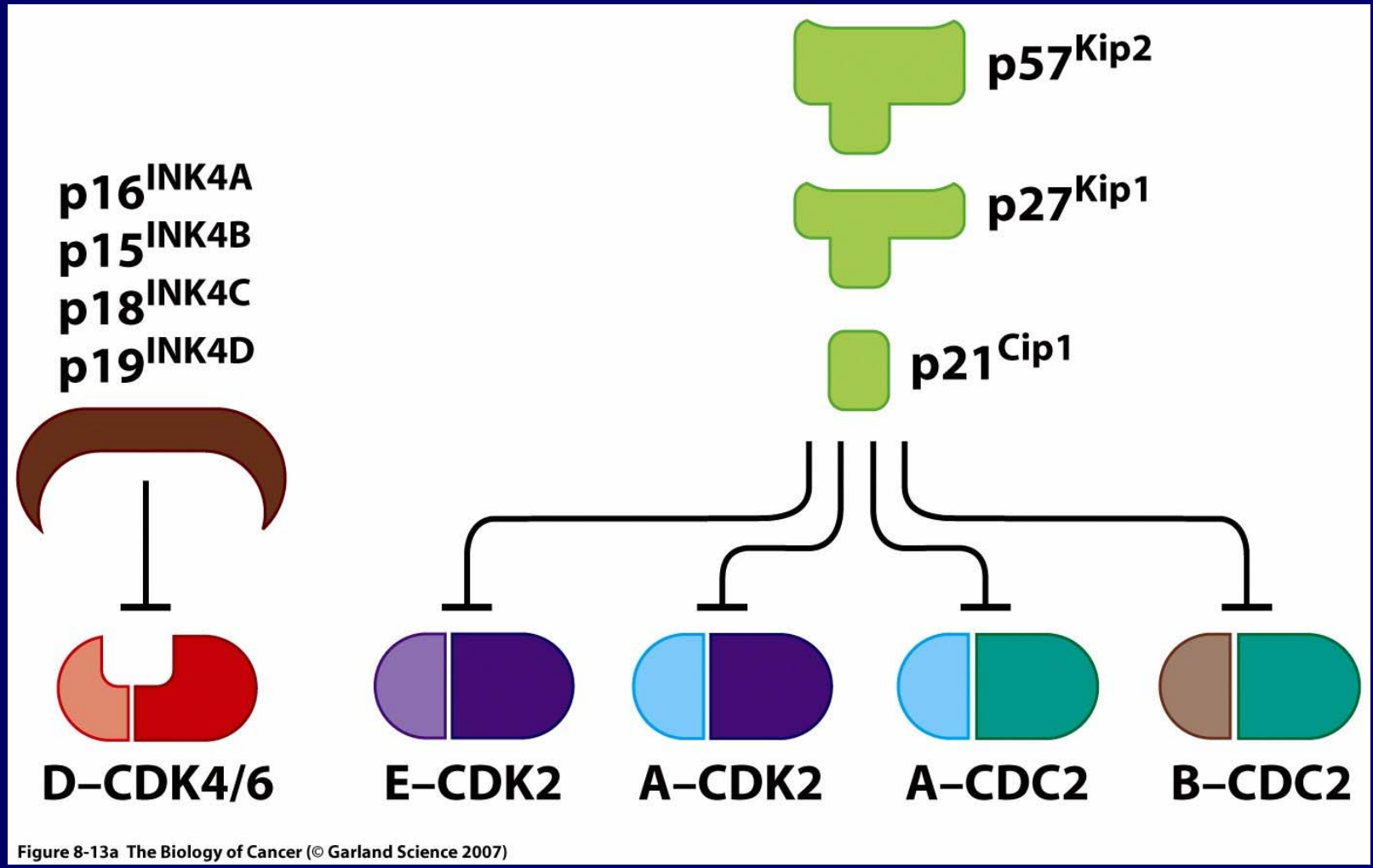
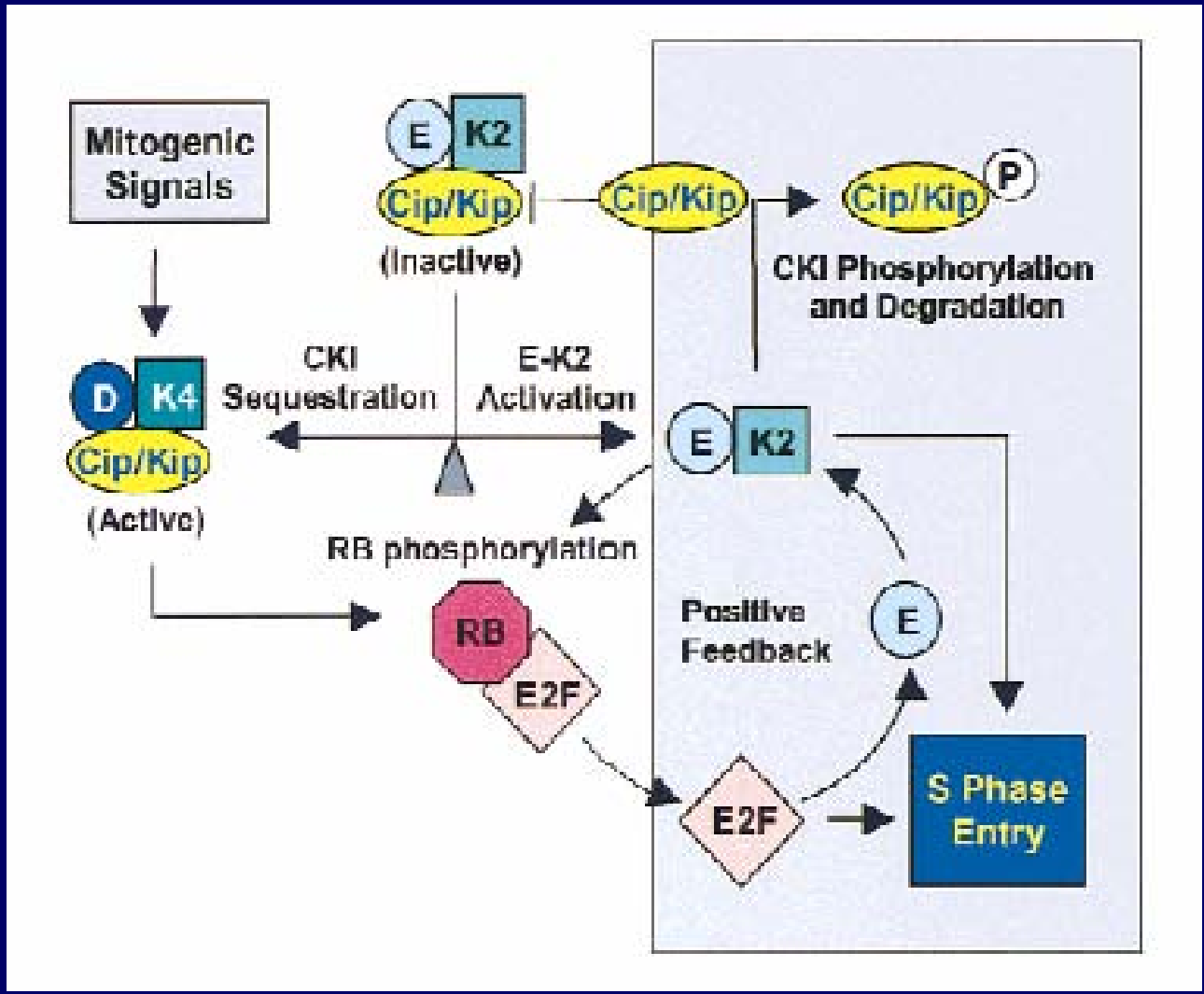


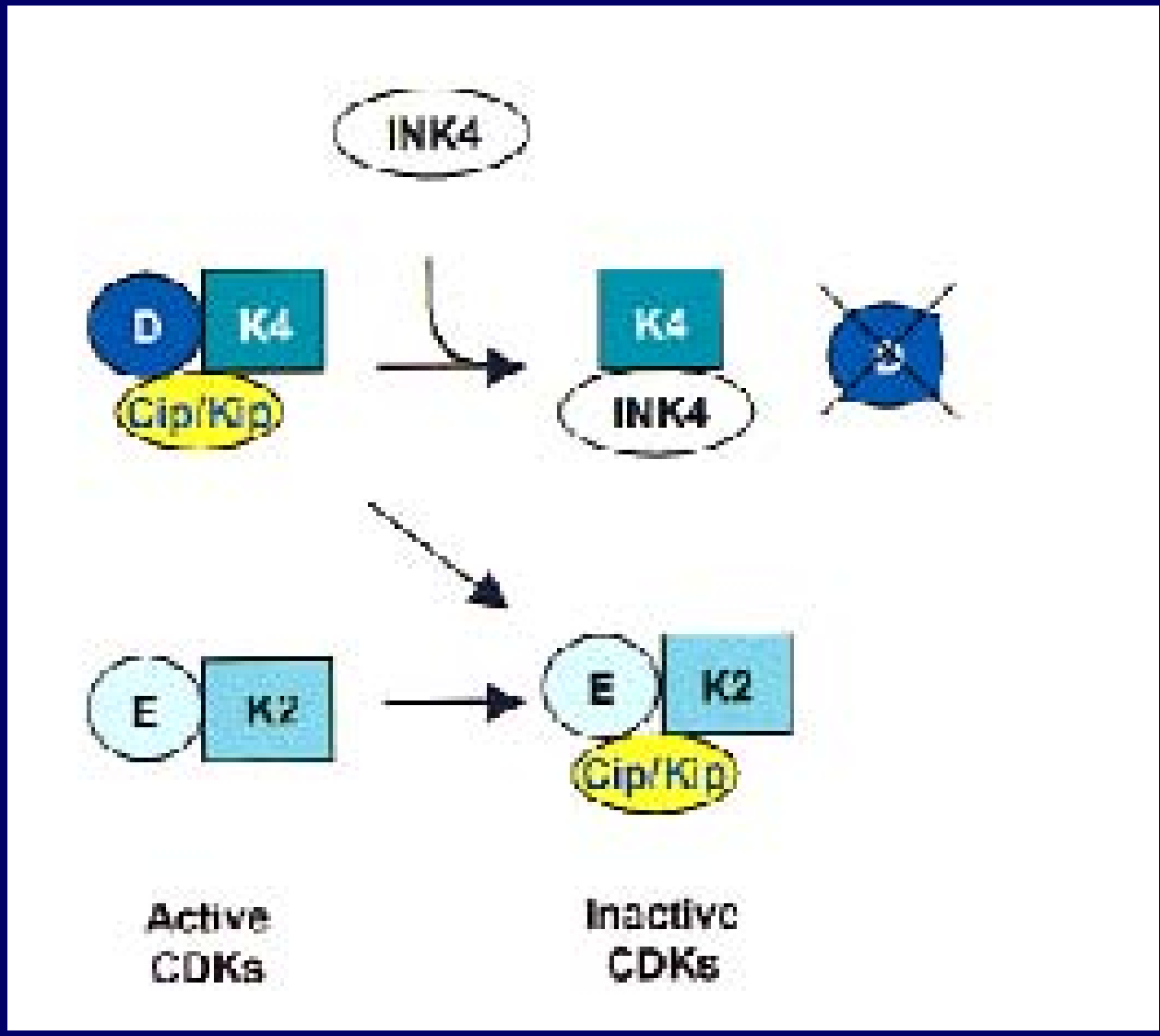
Figure 8-13a The Biology of Cancer (© Garland Science 2007)

Transición G1 / S



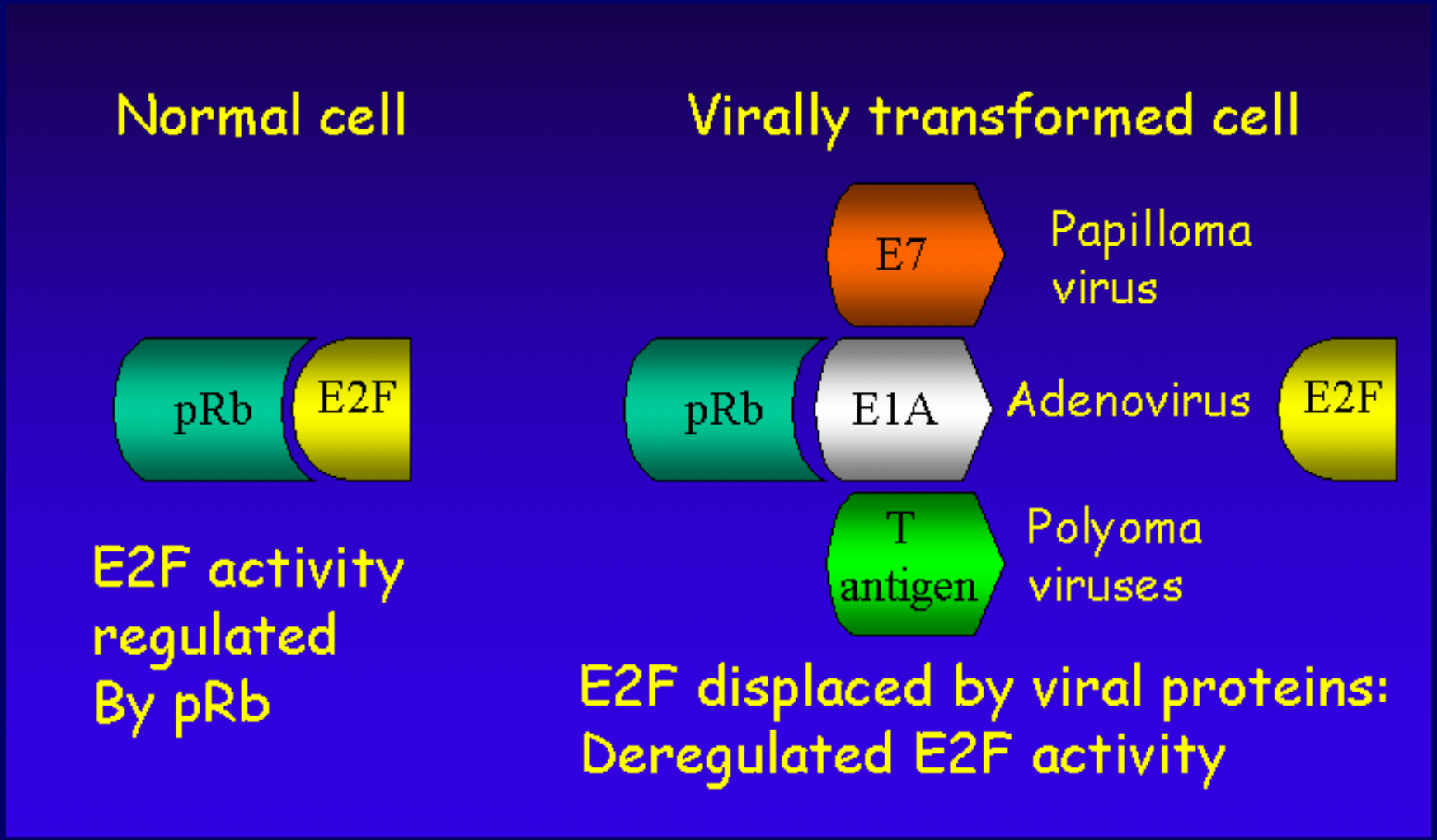
Genes Dev. 13 (1999), 1501

INK4 antagoniza la proliferación

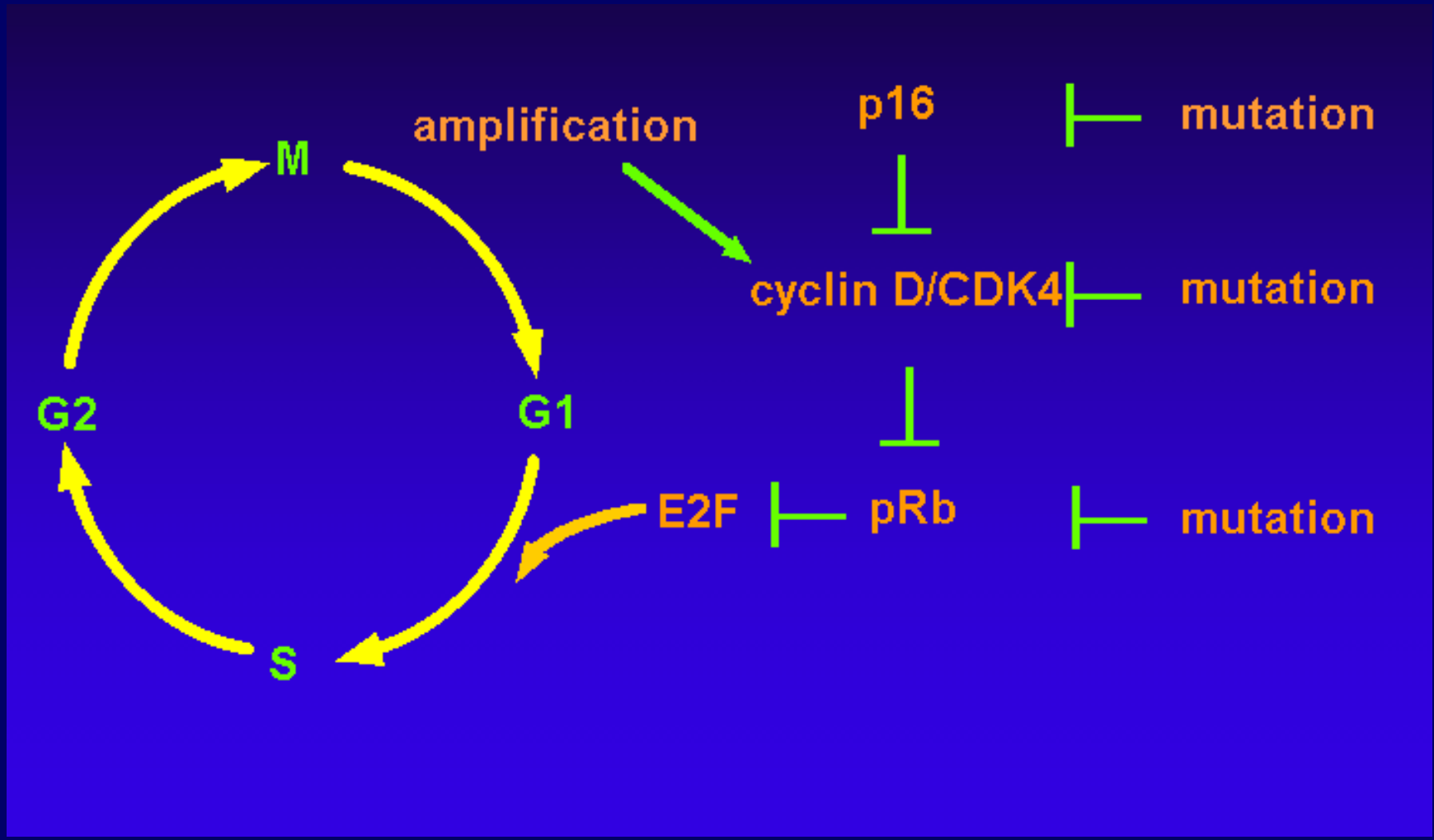


Genes Dev. 13 (1999), 1501

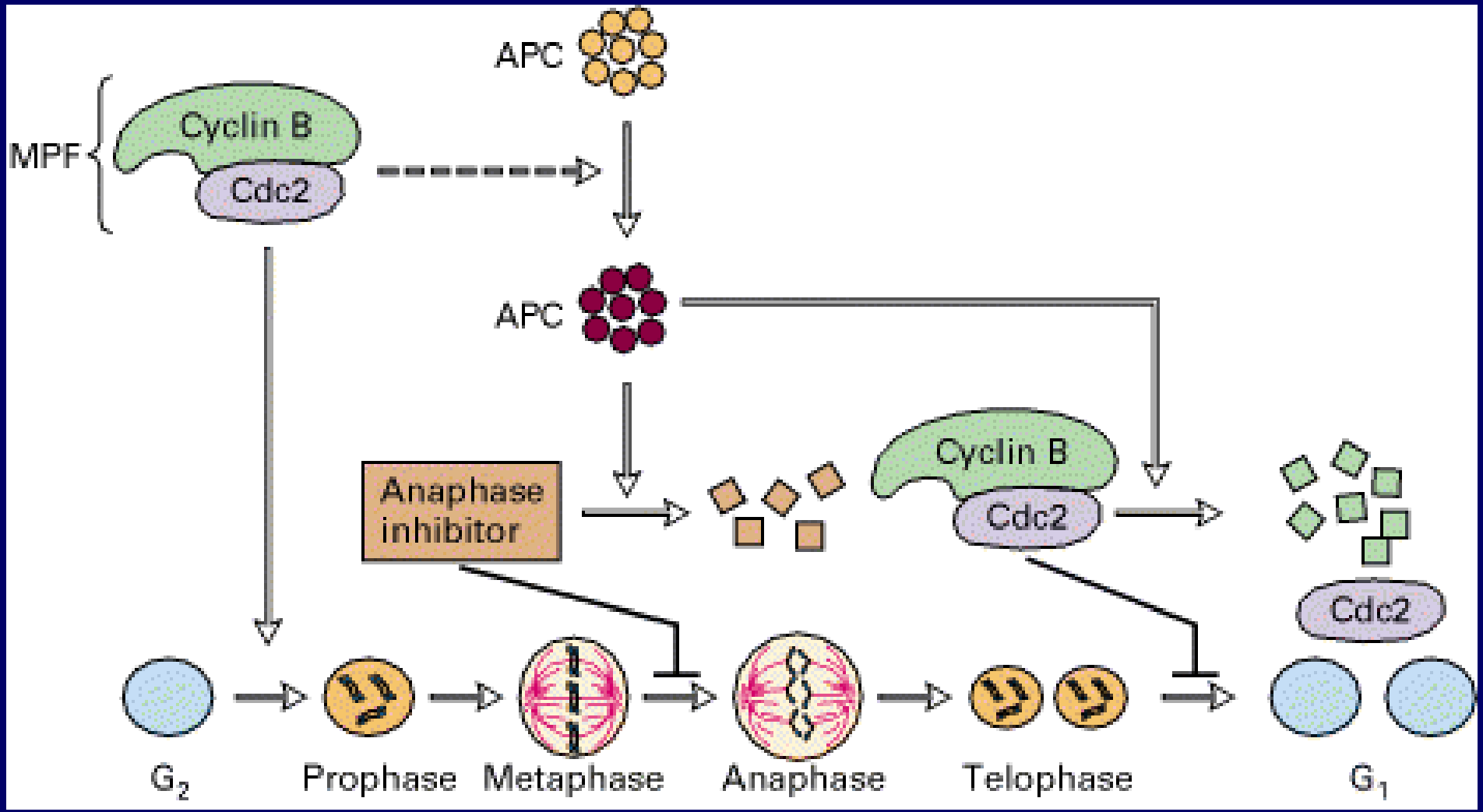
Oncoproteínas virales interaccionan con la proteína retinoblastoma



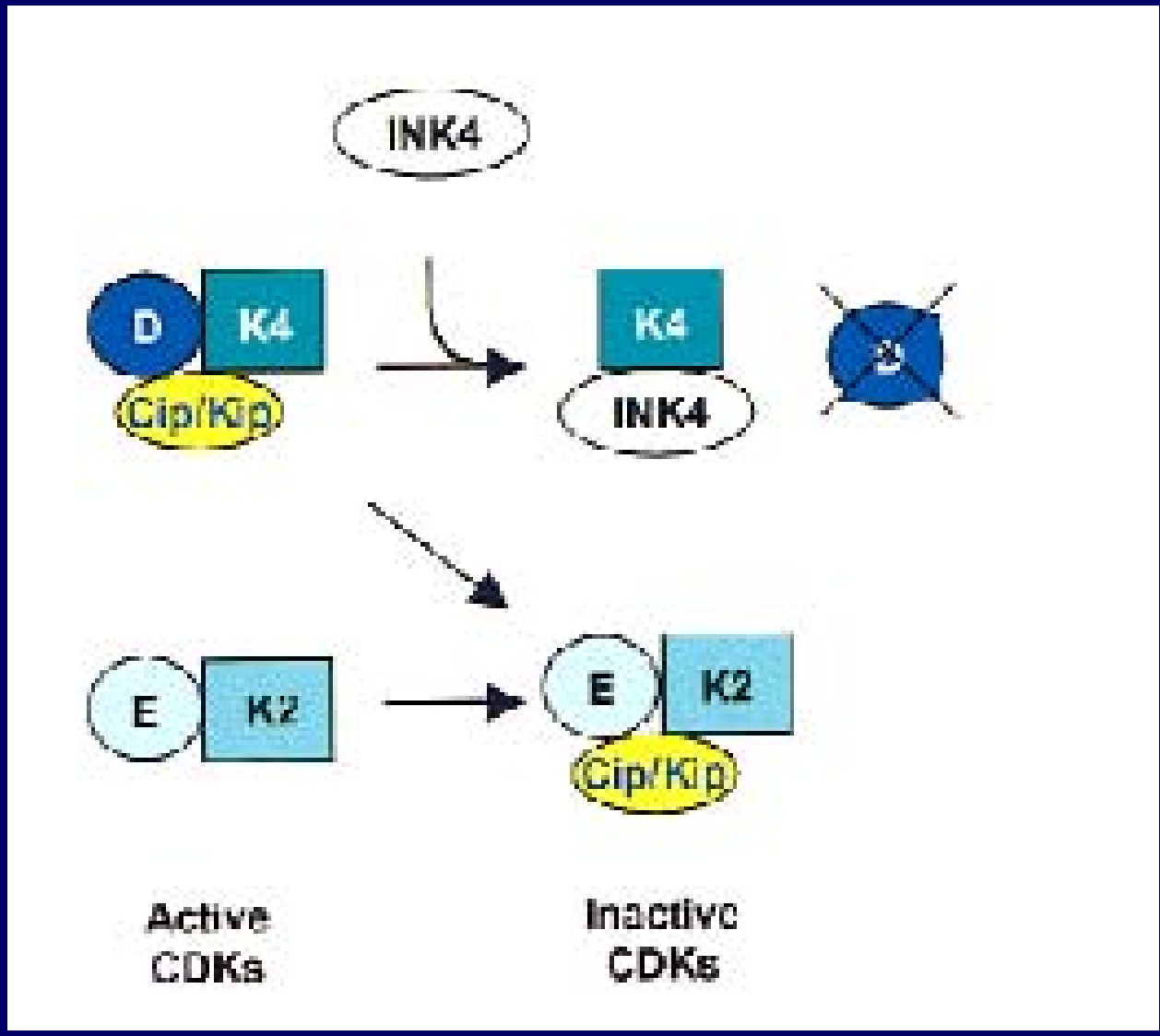
La vía p16-ciclina D-Rb es un blanco frecuente en cánceres humanos



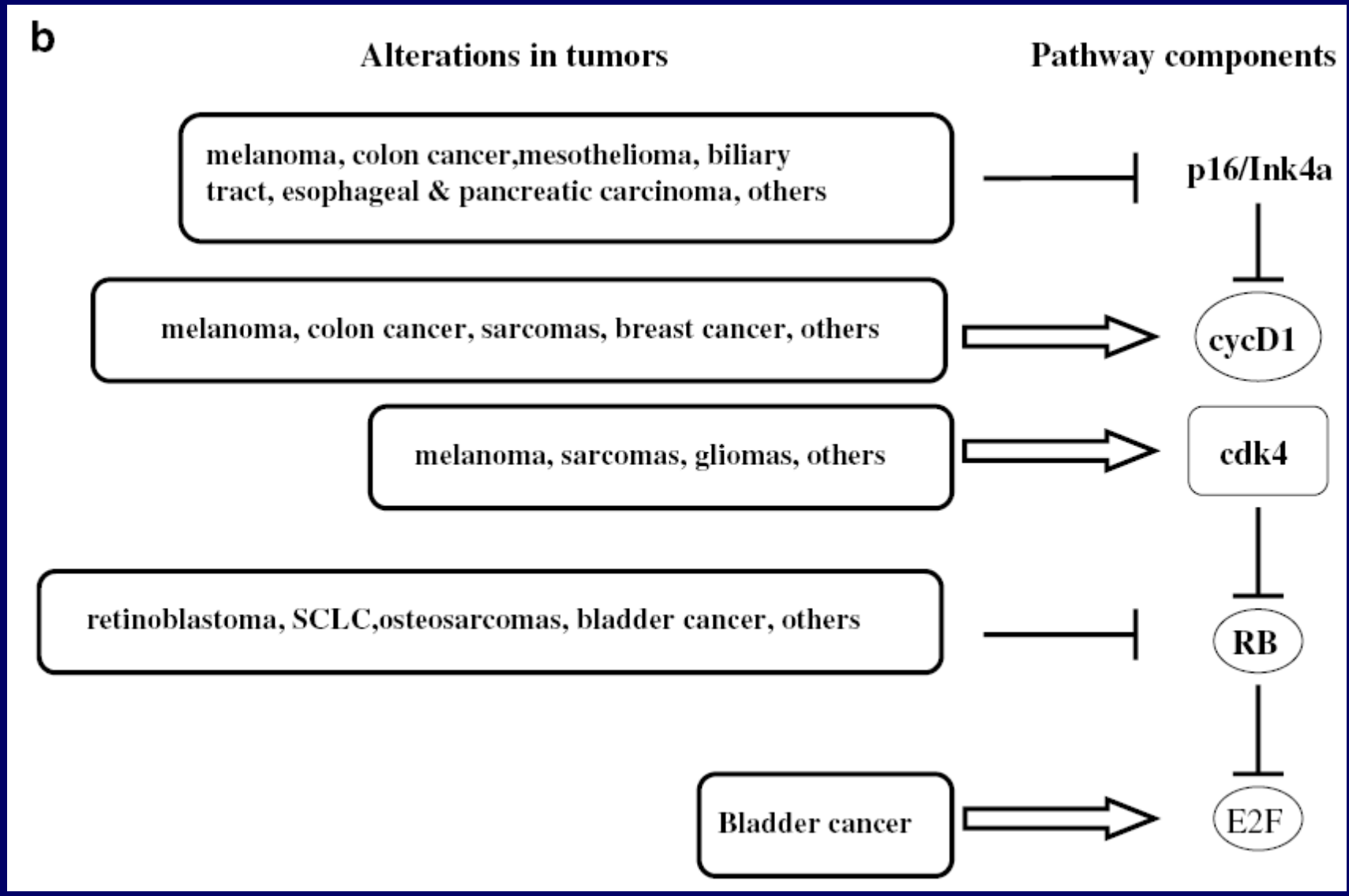
Mecanismo de acción de APC



INK4 antagoniza la proliferación



Genes Dev. 13 (1999), 1501



bind to cell cycle-regulated promoters and activate transcription. Cell cycle exit and differentiation signals block this transition. (**b**) The RB pathway in human tumors. Human tumors often contain alterations such as point mutations, deletions, amplifications or promoter methylation in components of the RB pathway. This alterations can be either inactivating or activating. Most frequently, they occur in upstream regulators of RB. Examples of the types of human cancer where such alterations occur are given next to each component of the pathway

Oncogene **24 (2005), 2810**

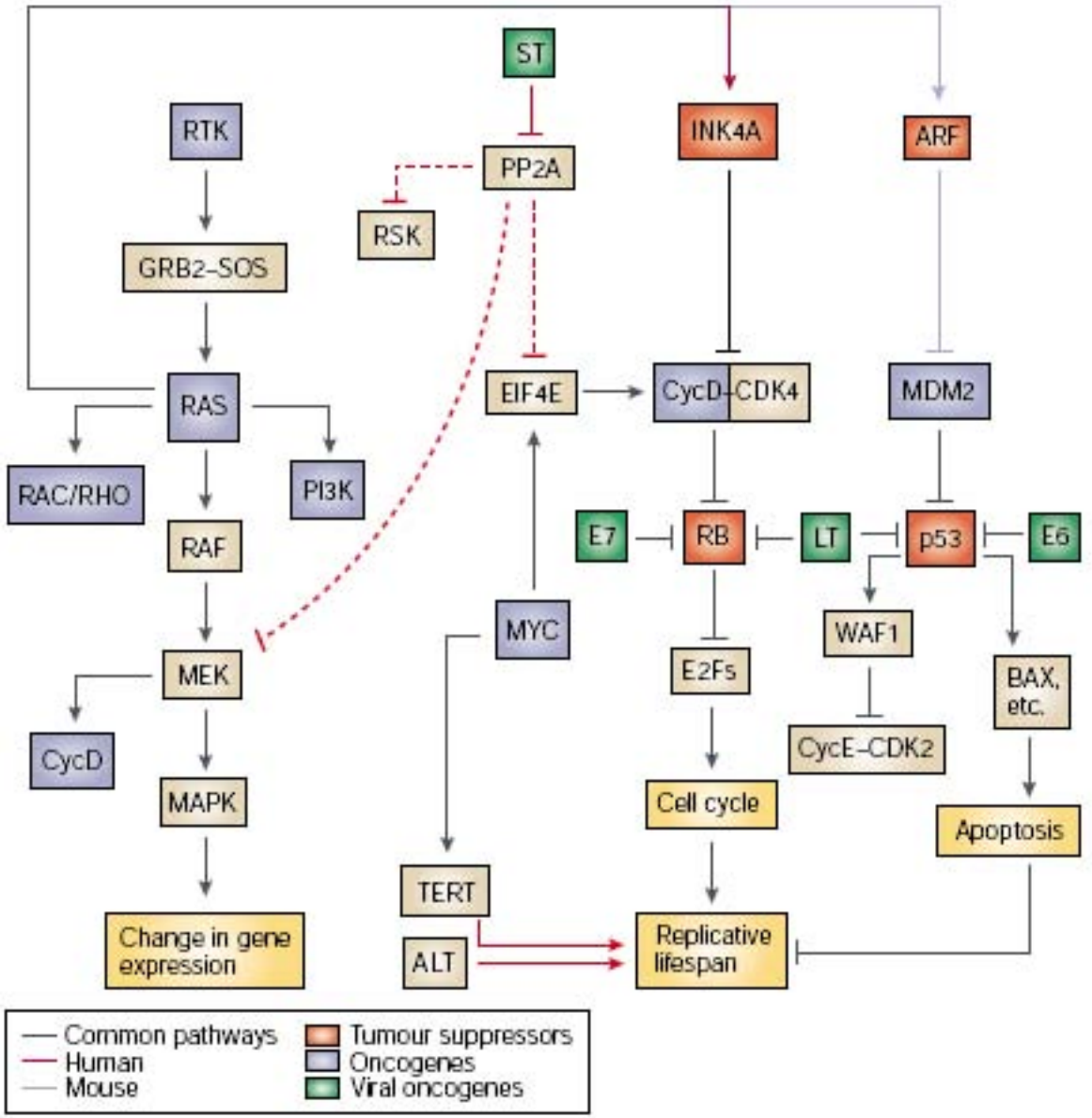
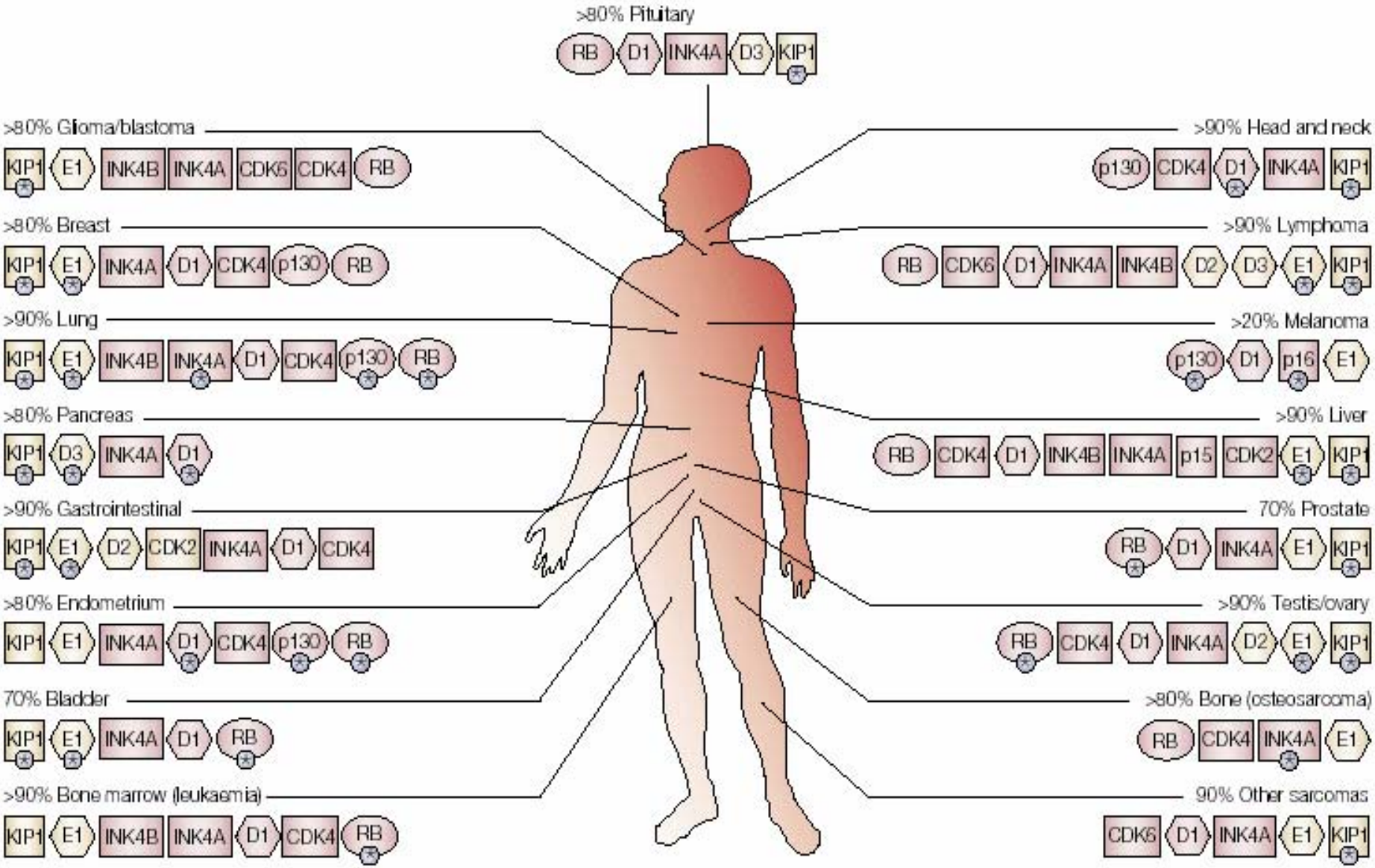


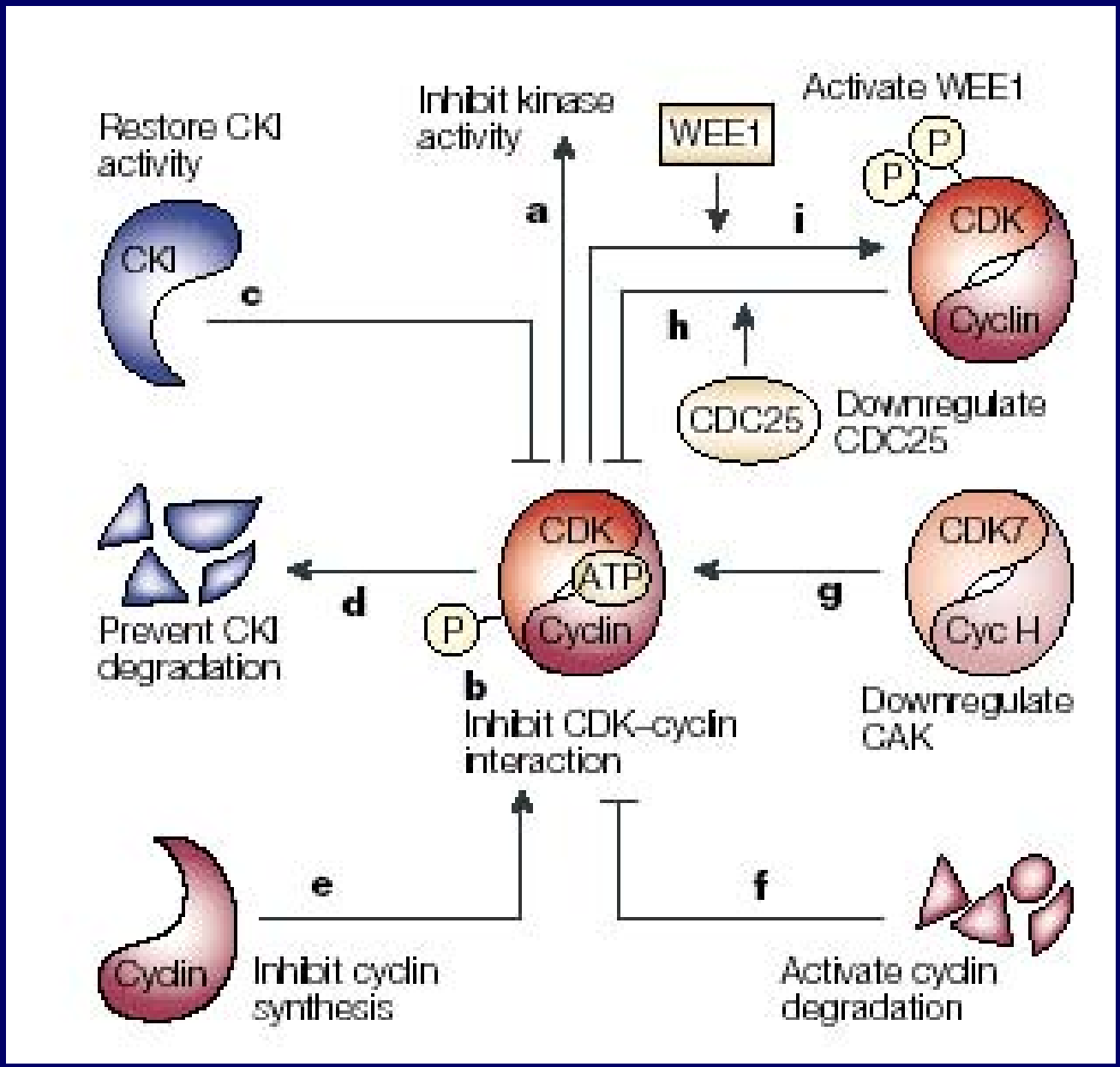
Figure 2 | **The molecular circuitry of cancer.** Although countless differences between normal

Nature Rev. Cancer **2** (2002), 331

Mutaciones de reguladores G1/S en tumores humanos



Potenciales estrategias terapéuticas



Nat. Rev. Cancer 1 (2001), 222