Corso di Oncologia Molecolare AA 2019-2020

VIE DI SEGNALAZIONE DA GF E LORO ALTERAZIONI NEL CANCRO

Fattori che influenzano la transizione G1/S nel cancro

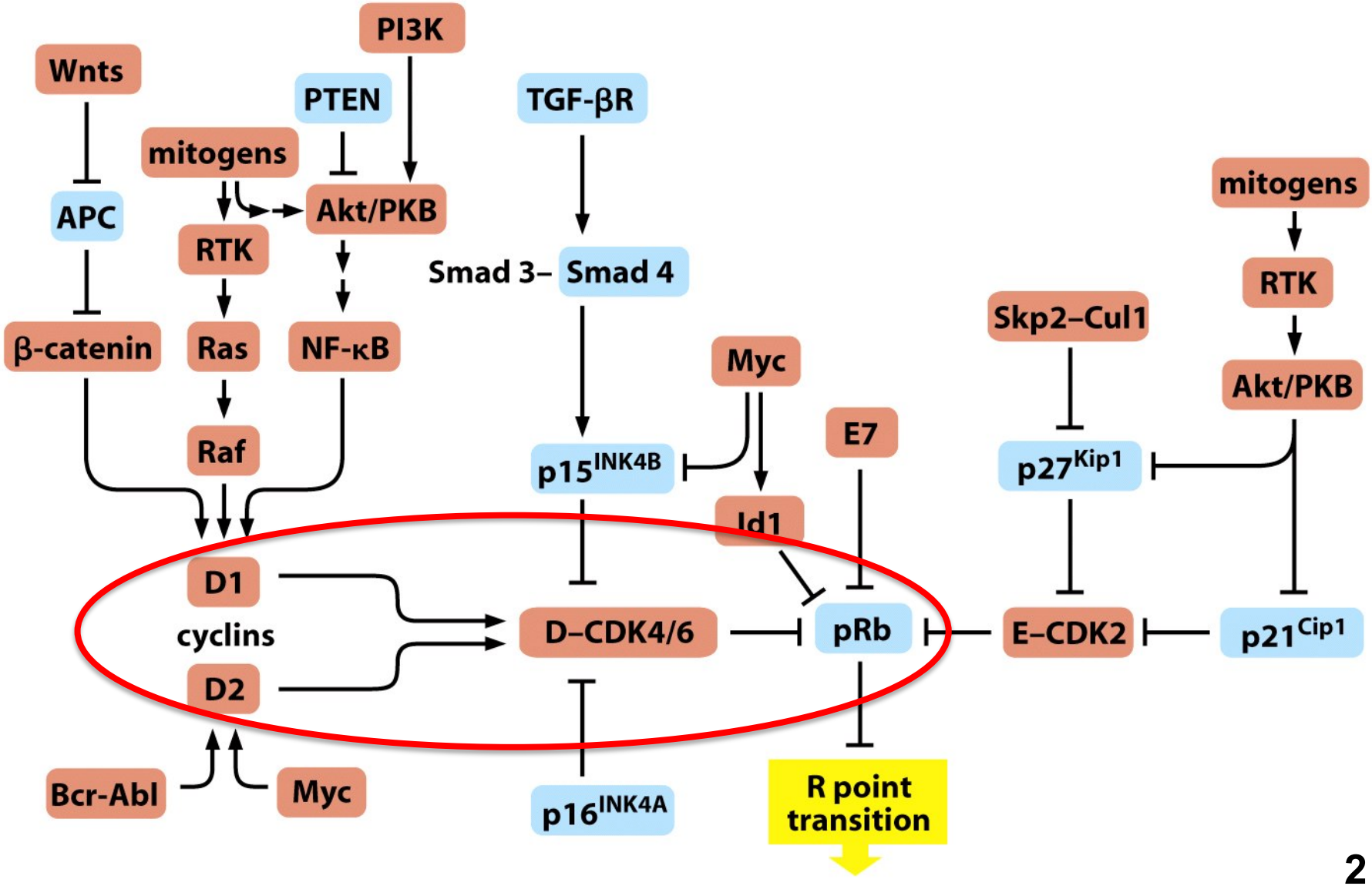


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

Fattori che influenzano la transizione G1/S nel cancro

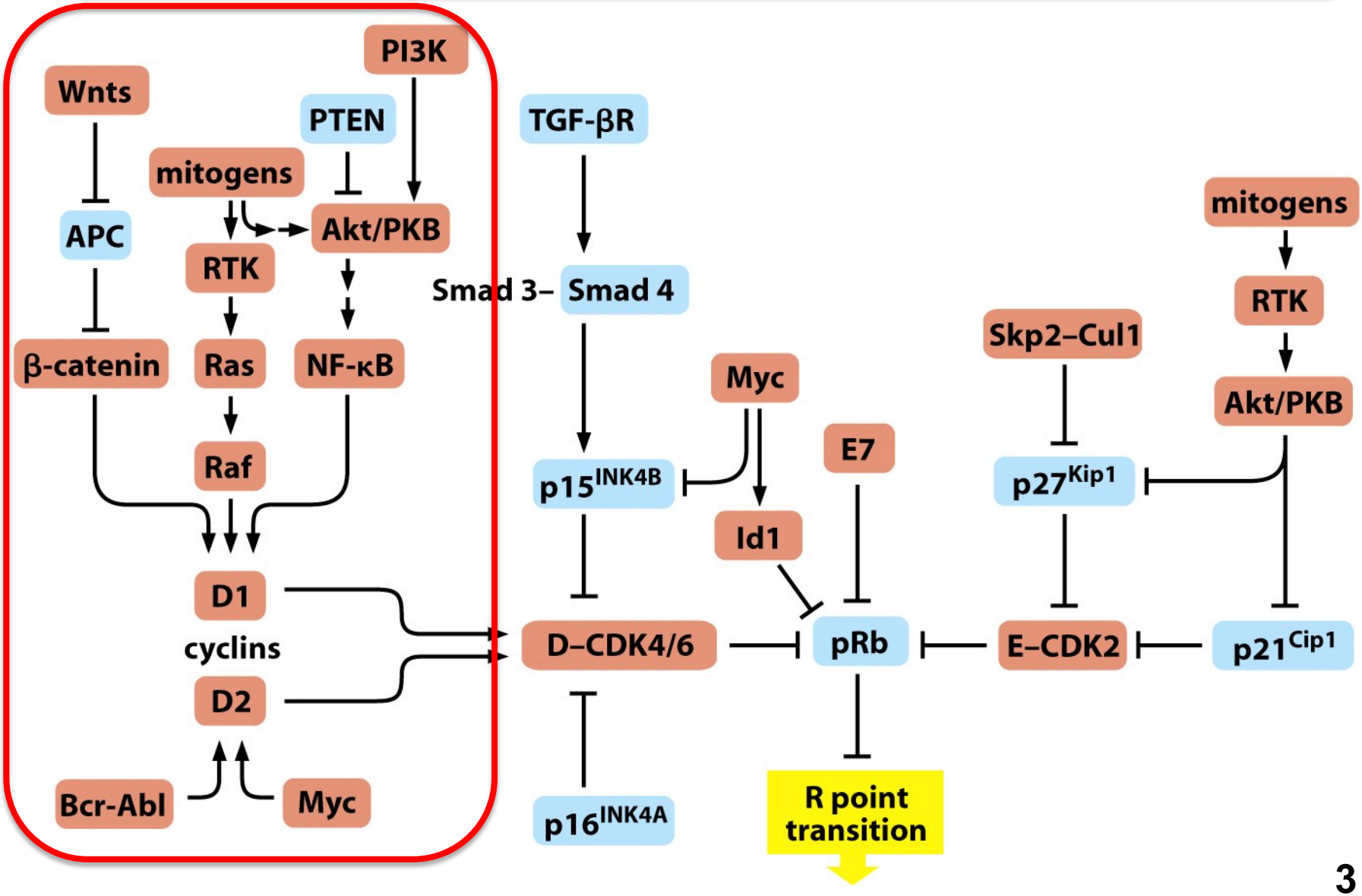
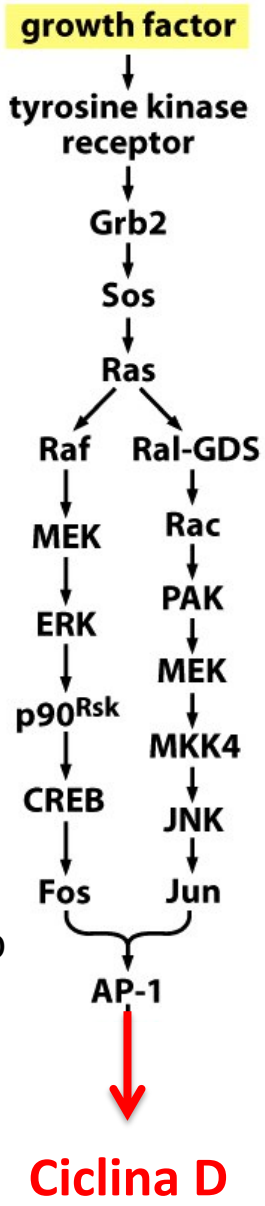


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)



Attivazione di **geni precoci**:
fattori di trascrizione che inducono la trascrizione della **ciclina D**, principale promotore della progressione del ciclo cellulare

Figure 8.11b *The Biology of Cancer* (© Garland Science 2007)

Ras downstream signaling pathways

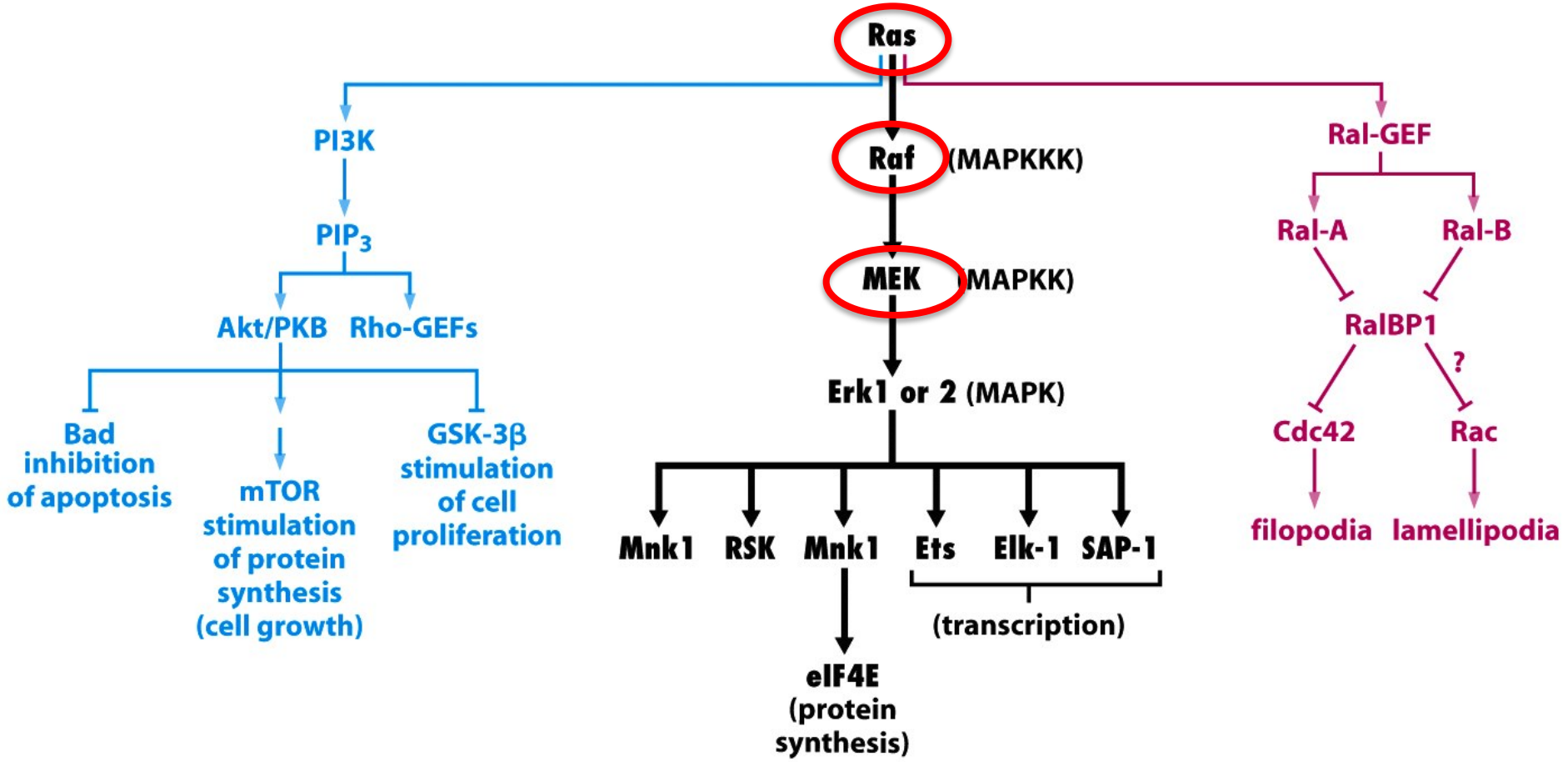
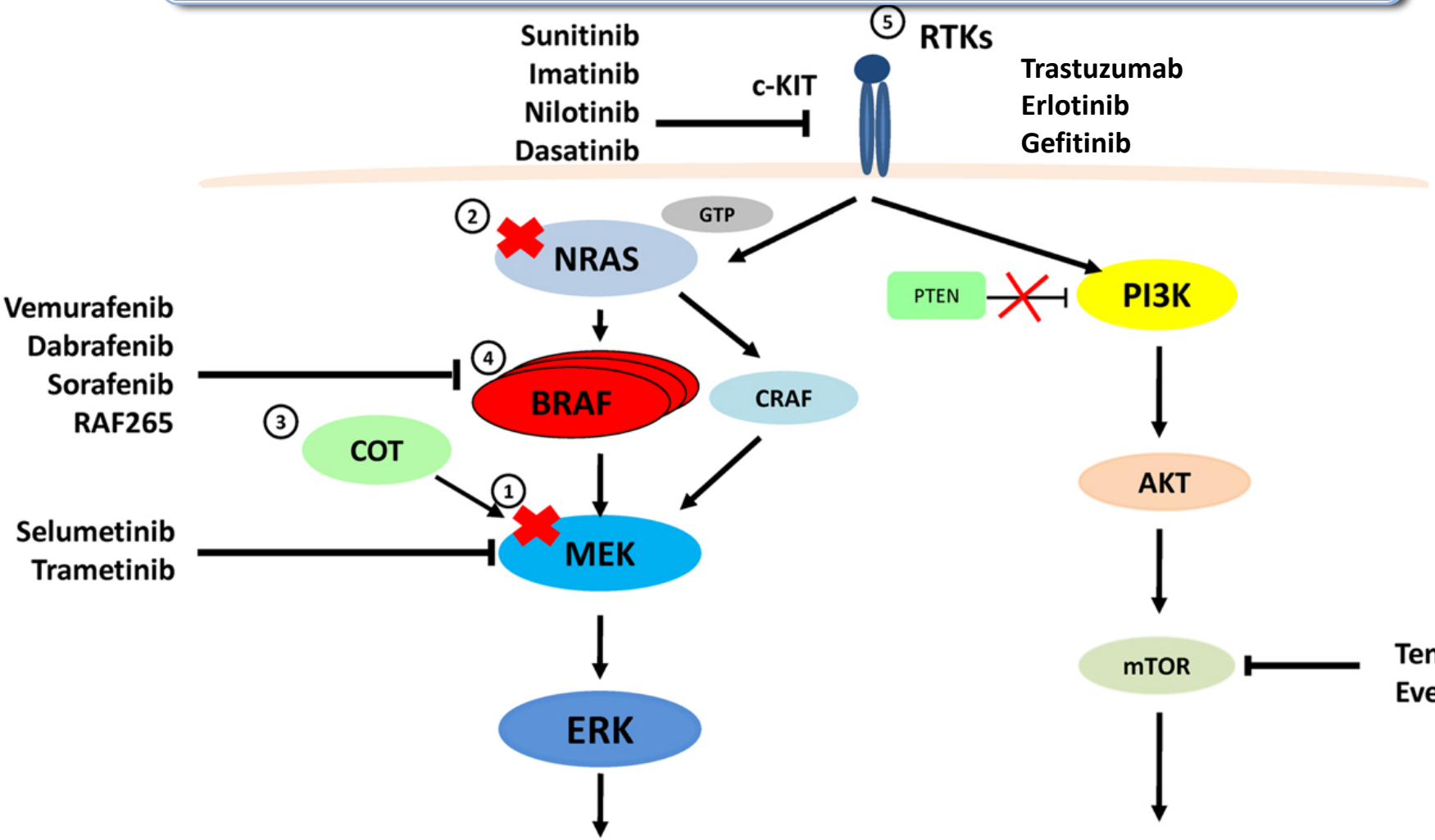


Figure 6.14 *The Biology of Cancer* (© Garland Science 2007)

Targeted therapies against oncogenes in GF response



1. MEK1 mutations
2. NRAS mutations
3. COT overexpression
4. BRAF amplification/ splicing
5. RTKs overexpression/activation (PDGFRβ, IGR1F)

Ras downstream signaling pathways

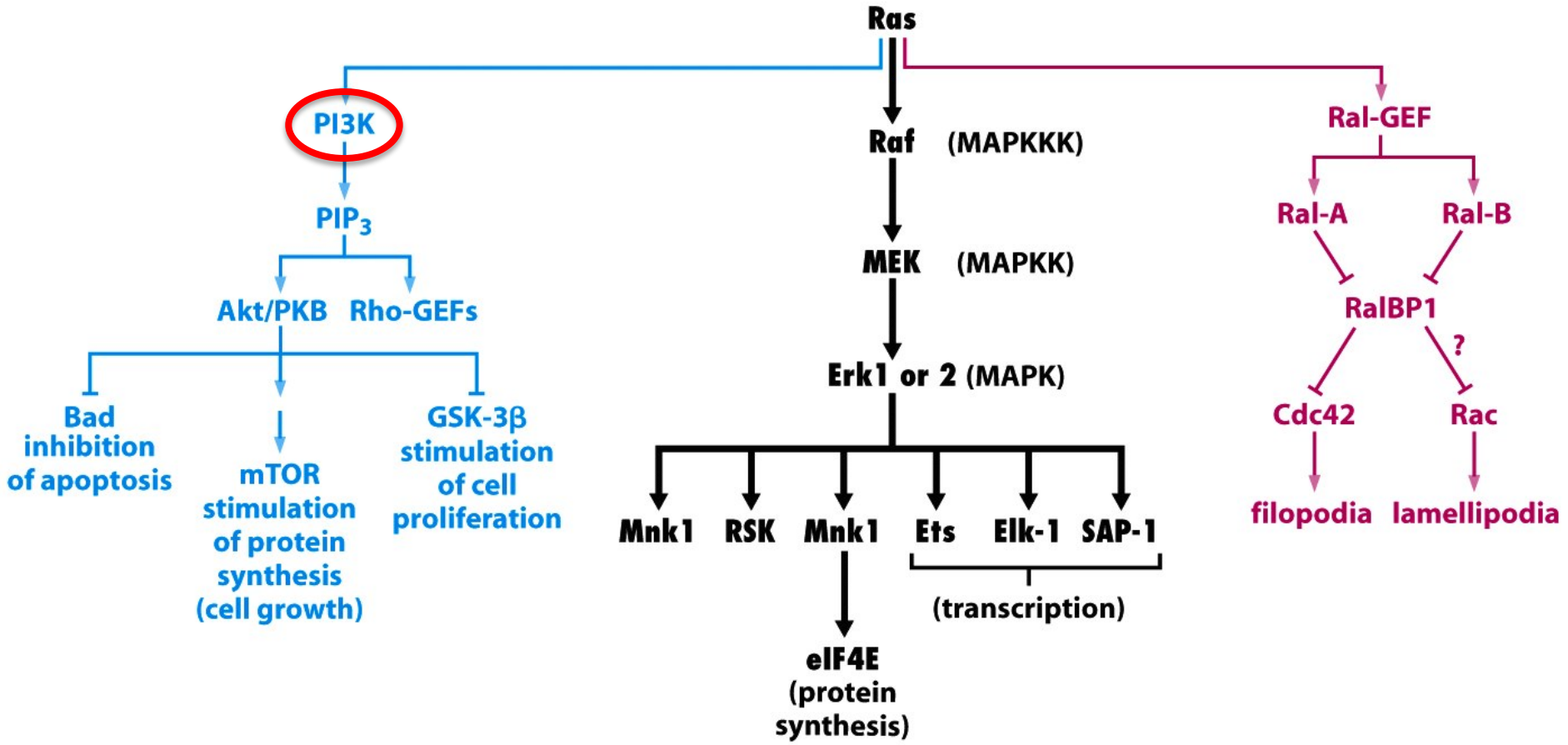
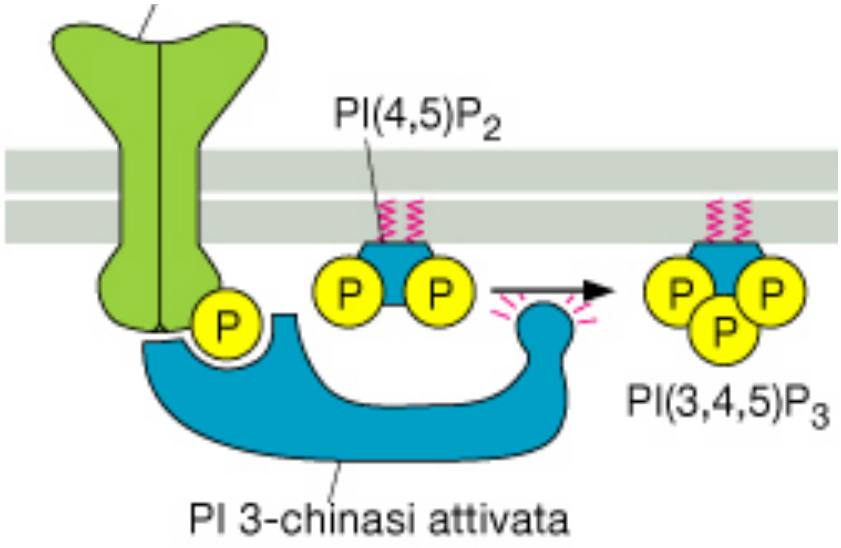
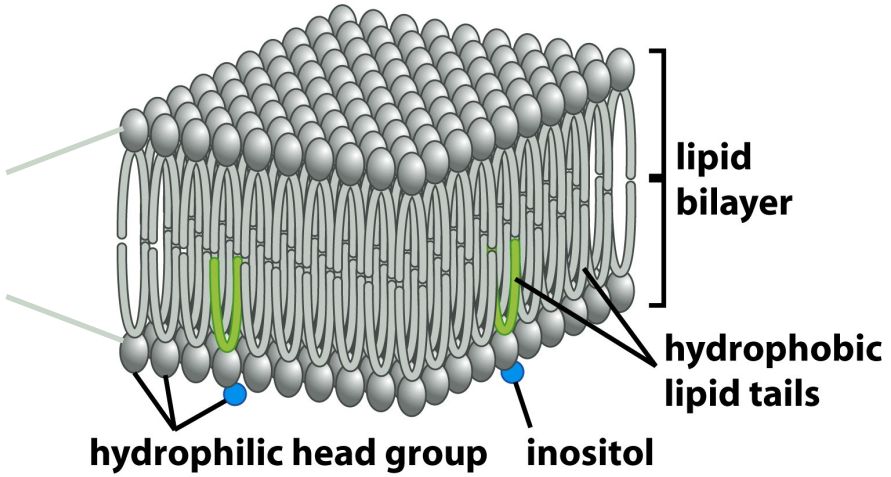


Figure 6.14 *The Biology of Cancer* (© Garland Science 2007)

PI3K: PI 3-kinase

La fosfatidil-inositolo 3 kinasi (PI 3-kinase) genera glicofosfolipidi che sono riconosciuti da proteine di segnalazione (tramite i loro domini PH)





PI3K promuove l'attivazione di Akt/PKB

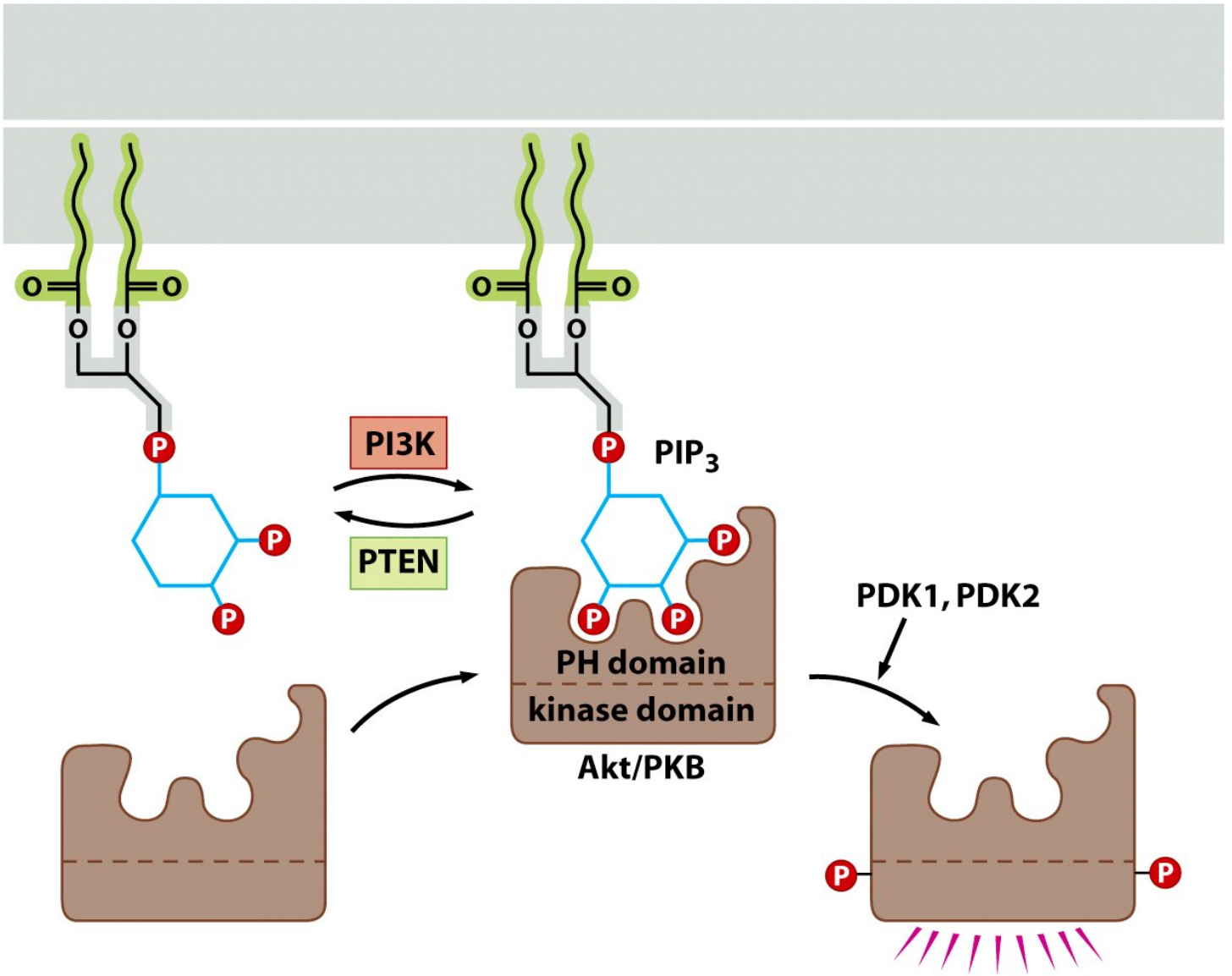


Figure 6.19a *The Biology of Cancer* (© Garland Science 2007)

Risposte biologiche a valle della chinasi Akt/PKB

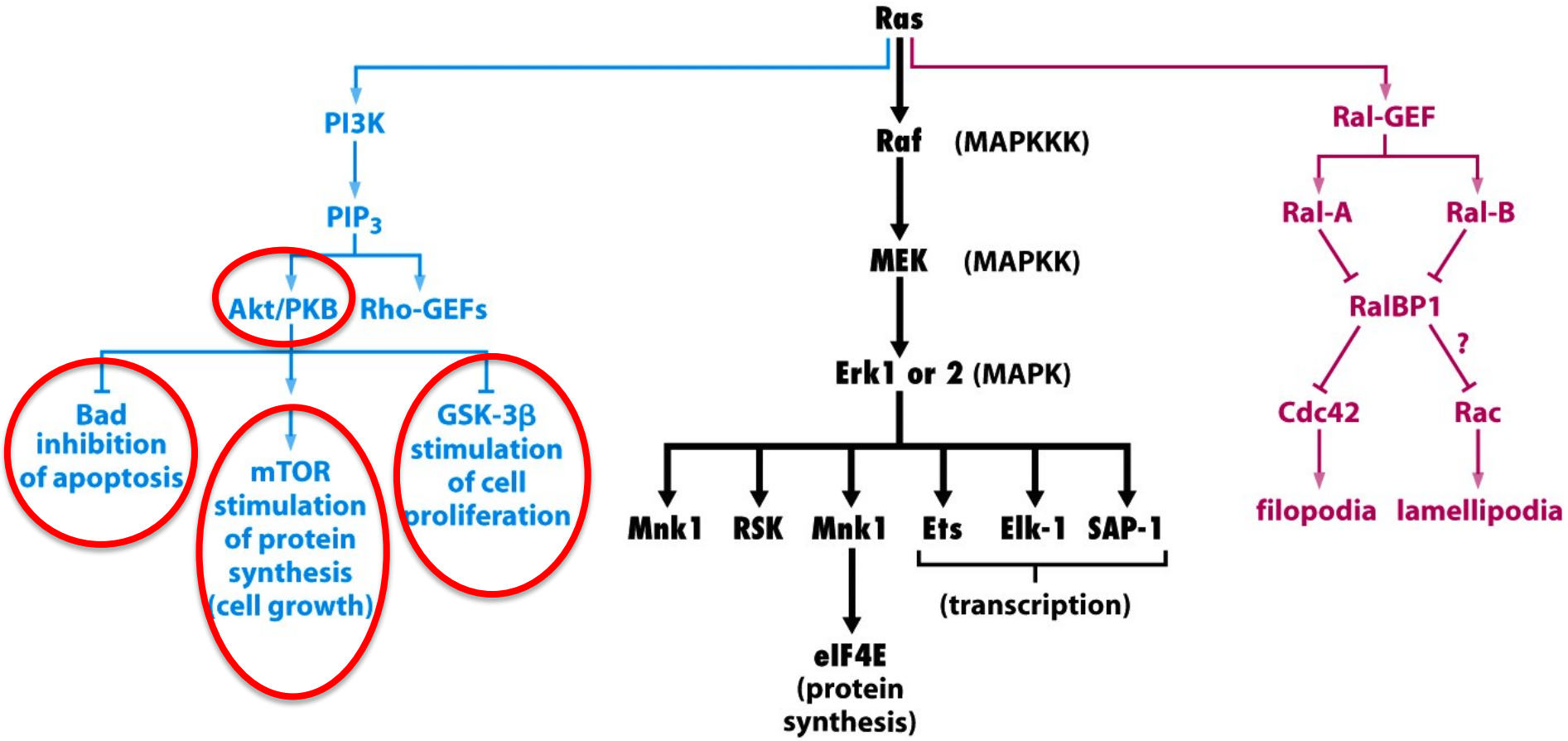
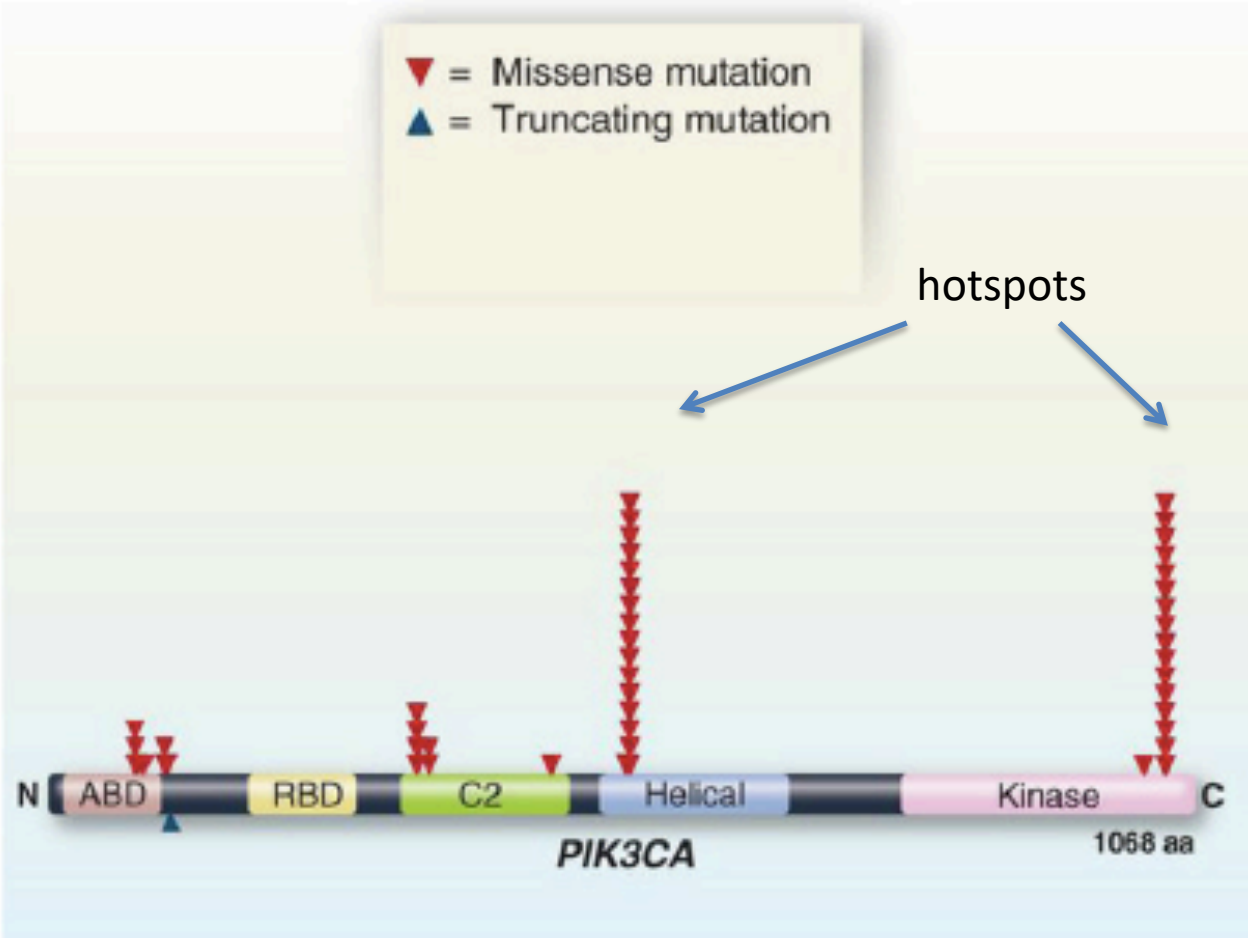


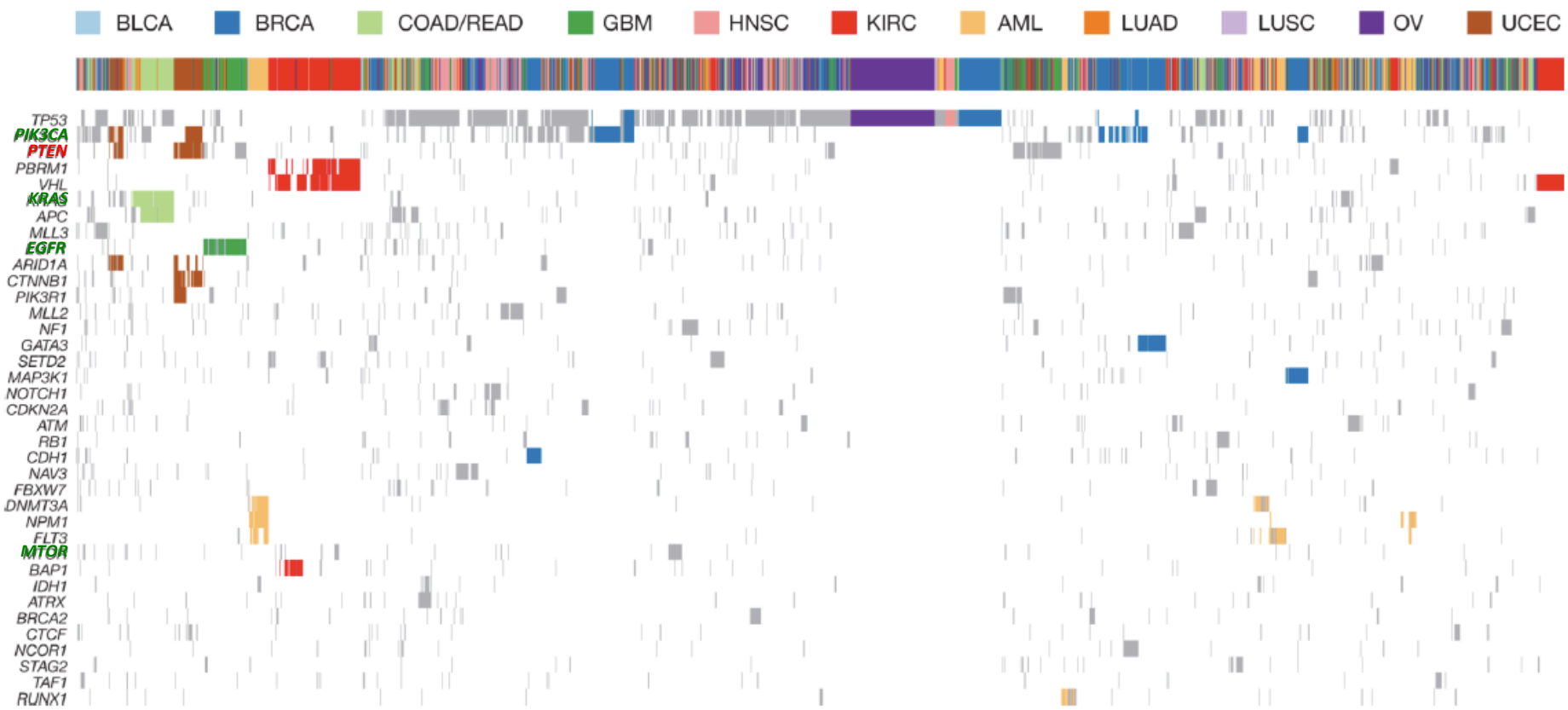
Figure 6.14 *The Biology of Cancer* (© Garland Science 2007)

Mutazioni nel gene per la subunità catalitica di PI3K p110α causano iperattivazione dell'oncogene in 1/3 dei carcinomi colorettali



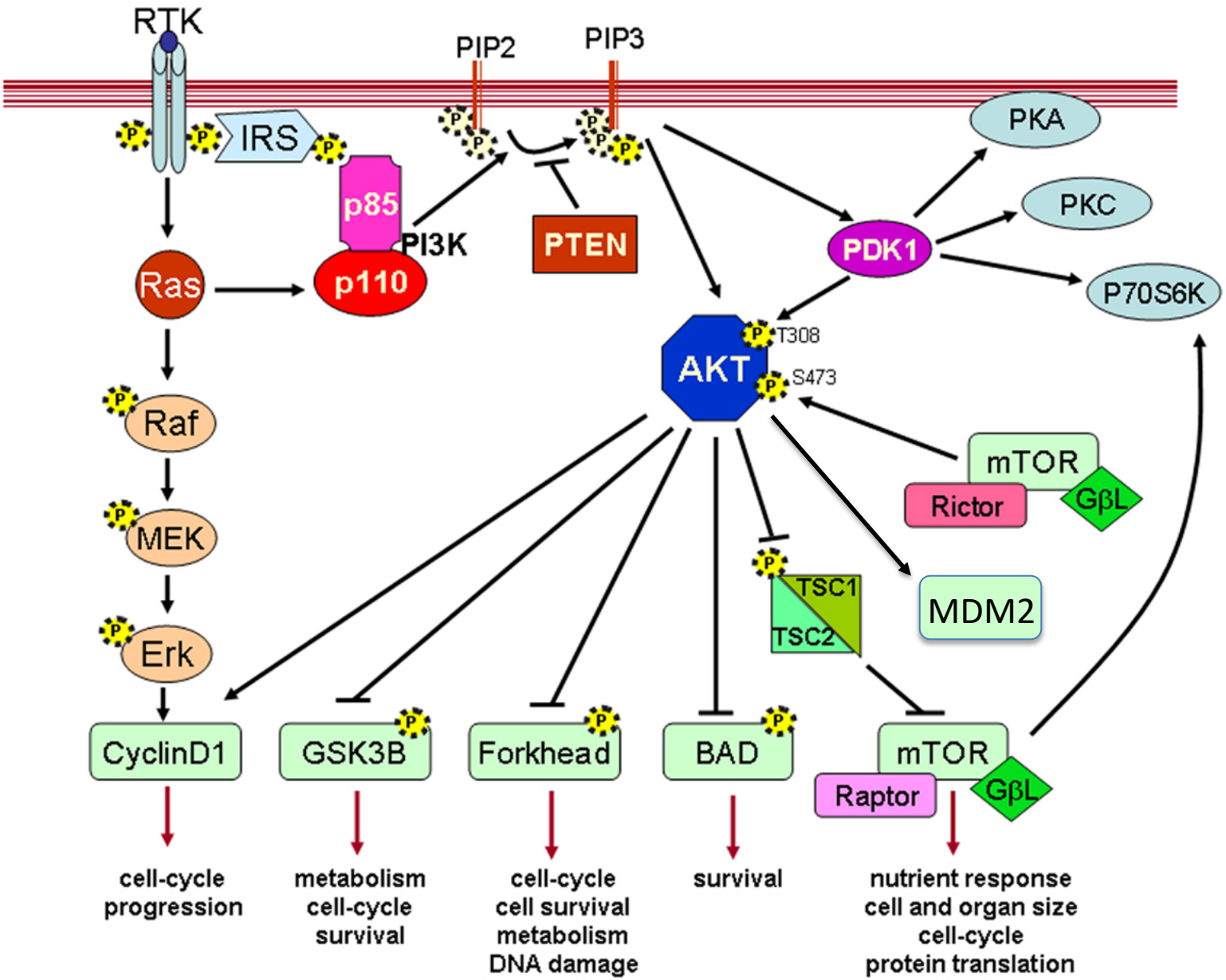
Vogelstein et al *Science,* 2013

Principali geni mutati in diversi tumori umani

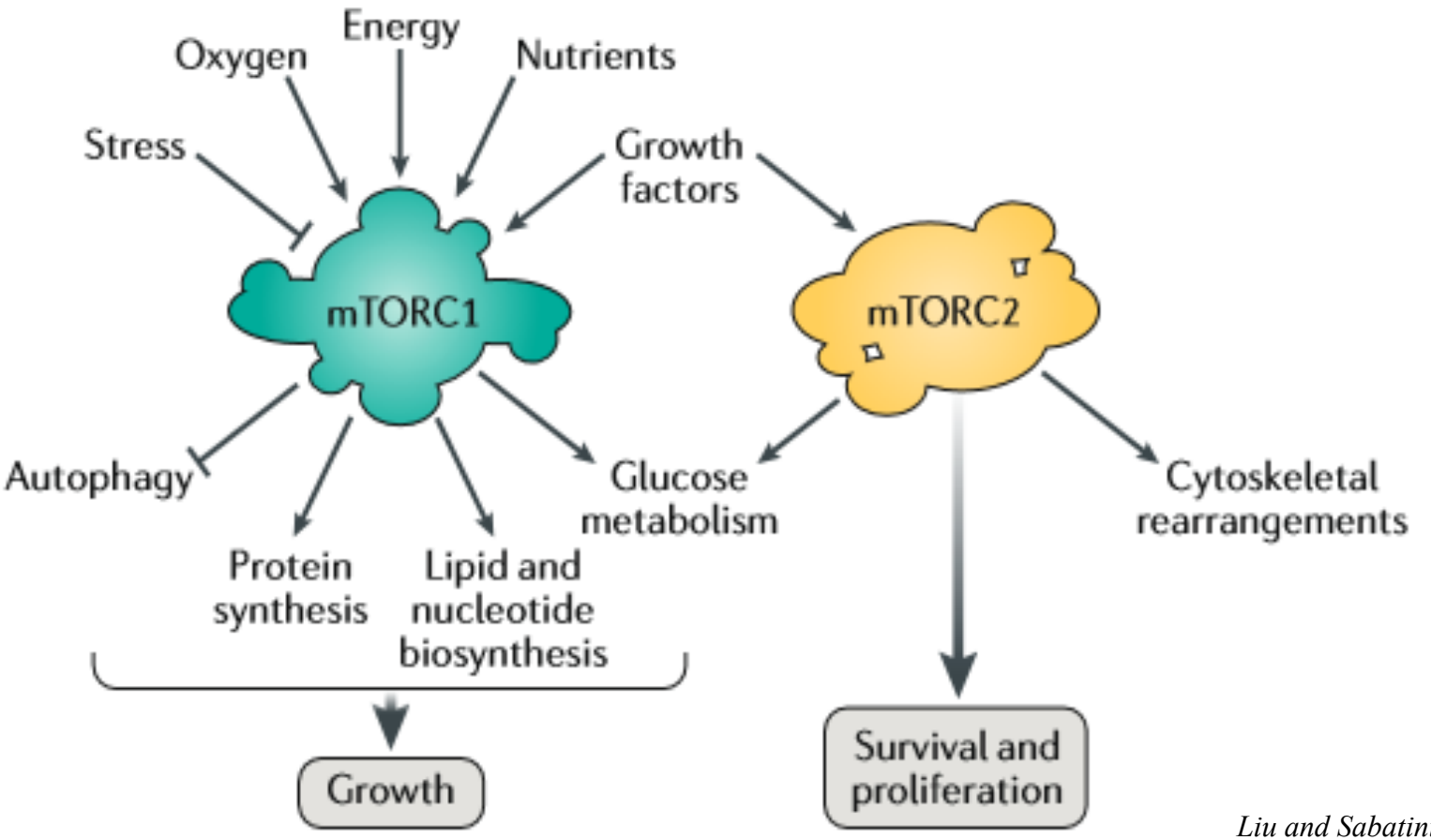


Kandoth et al *Nature,* 2013

Regulation and pleiotropic activities of Akt/PKB



Roles of mTOR kinase in cell growth and survival



Liu and Sabatini, 2020

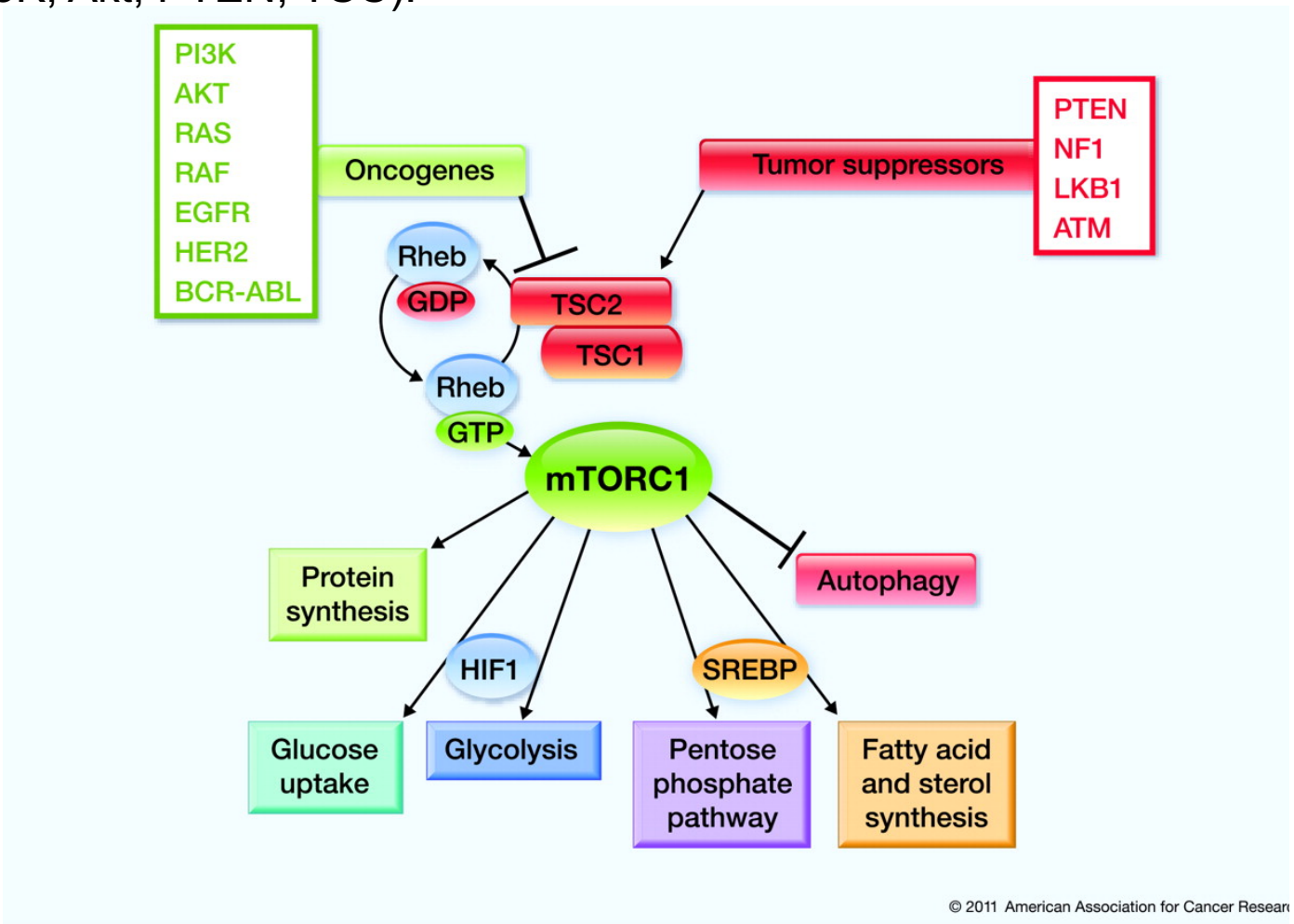
- mTOR è una serin/treonin chinasi presente in due complessi:

  mTORC1 e mTORC2.

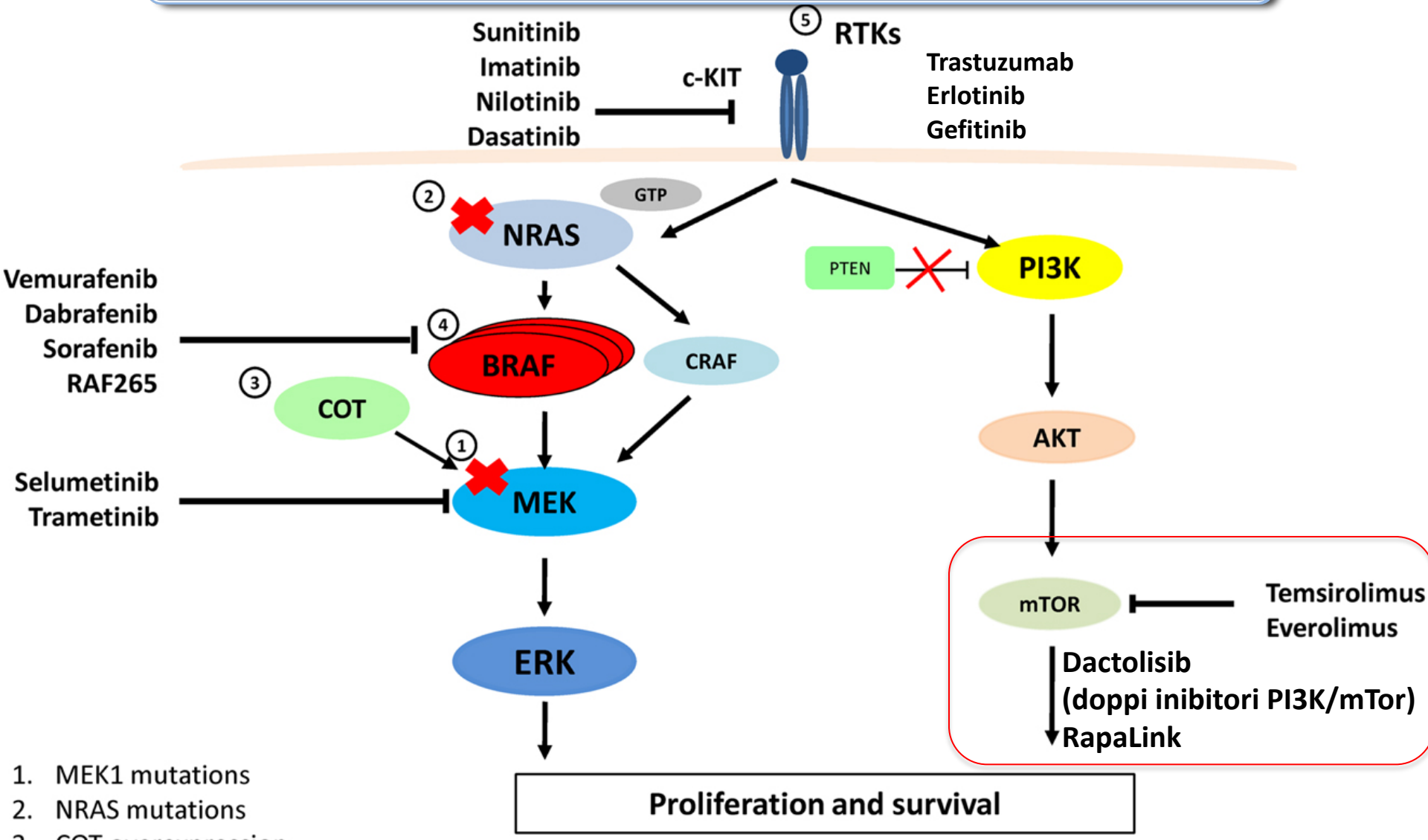
- mTORC1 è il principale **sensore di stimoli nutrizionali** ed energetici e attiva **processi di biosintesi** per la crescita cellulare.

mTOR pathway is hyperactivated in tumors

- La via di segnalazione di mTOR è **iper attivata** nell'80% dei tumori.
- L'iper attivazione di mTORC1 è dovuta a **mutazioni** del gene o dei regolatori (PI3K, Akt, PTEN, TSC).



Targeted therapies against mTOR



1. MEK1 mutations
2. NRAS mutations
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4. BRAF amplification/ splicing
5. RTKs overexpression/activation (PDGFRβ, IGR1F)

PTEN (Phosphatase and Tensin homolog) agisce come antagonista di PI3K

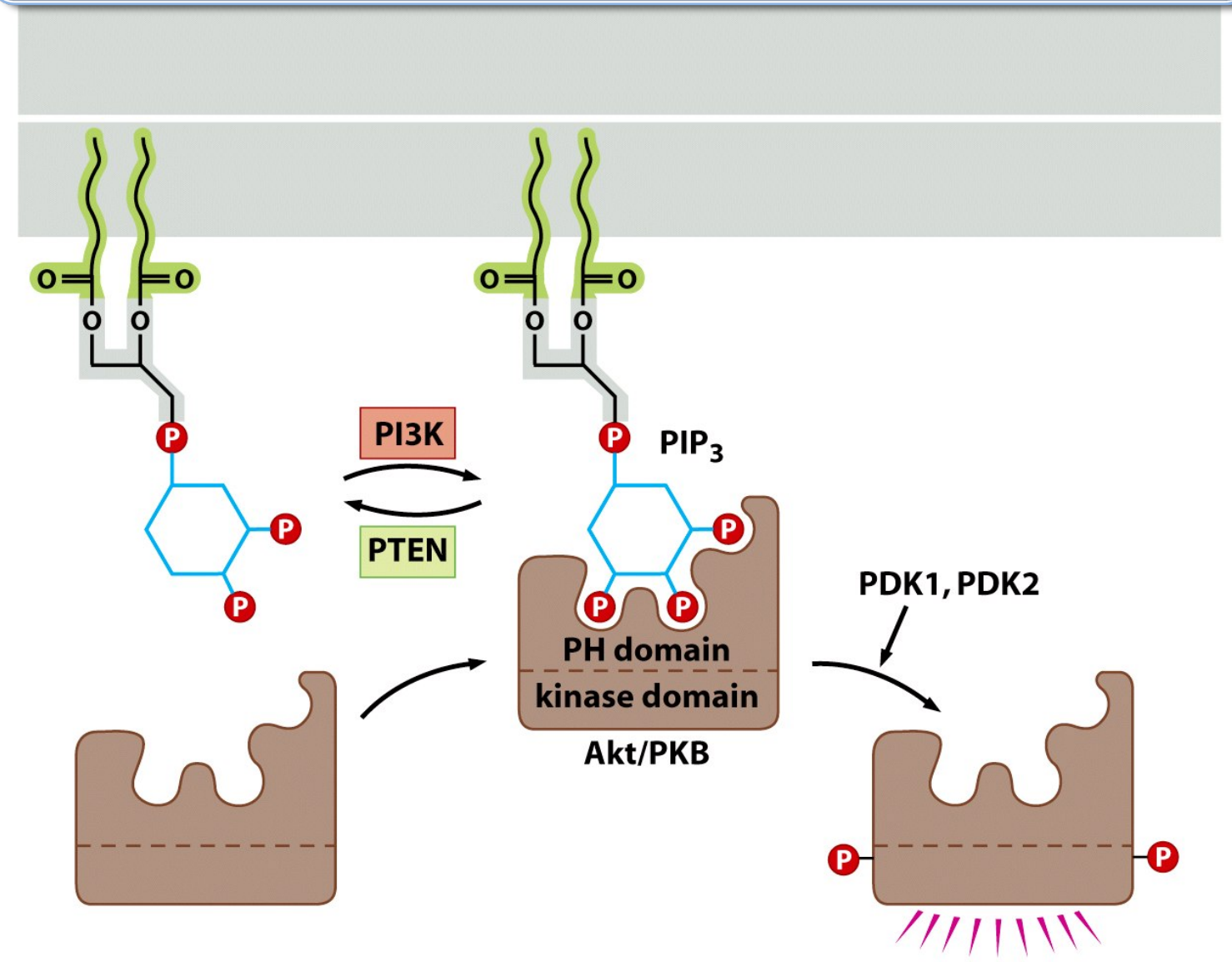


Figure 6.19a *The Biology of Cancer* (© Garland Science 2007)

L'attività di PTEN è persa nel 30-40% di tutti i tumori

Cancer type	Type of alteration
Glioblastoma (25–50%)	*PTEN* mutation
Ovarian carcinoma	*PTEN* mutation; *AKT2* amplification; *PI3K* amplification; PI3K *p85α* mutation
Breast carcinoma	increased Akt1 activity; *AKT2* amplification; *PTEN* mutation
Endometrial carcinoma (35%)	*PTEN* mutation; *PTEN* methylation[a]
Hepatocellular carcinoma	*PTEN* mutation
Melanoma	*PTEN* mutation; *PTEN* methylation[a]
Lung carcinoma	*PTEN* mutation
Renal cell carcinoma	*PTEN* mutation
Thyroid carcinoma	*PTEN* mutation; Akt/PKB overexpression
Lymphoid	*PTEN* mutation
Prostate carcinoma (40–50%)	*PTEN* mutation
Colon carcinoma (>30%)	Akt/PKB overexpression; *PI3K* mutation

[a]Methylation refers to repression of transcription of a gene through methylation of cytidines in its promoter; see Section 7.8.

Adapted from I. Vivanco and C.L. Sawyers, The phosphatidylinositol 3-kinase-AKT pathway in human cancer, *Nat. Rev. Cancer* 2:489–501, 2002.

Table 6.4 *The Biology of Cancer* (© Garland Science 2007)

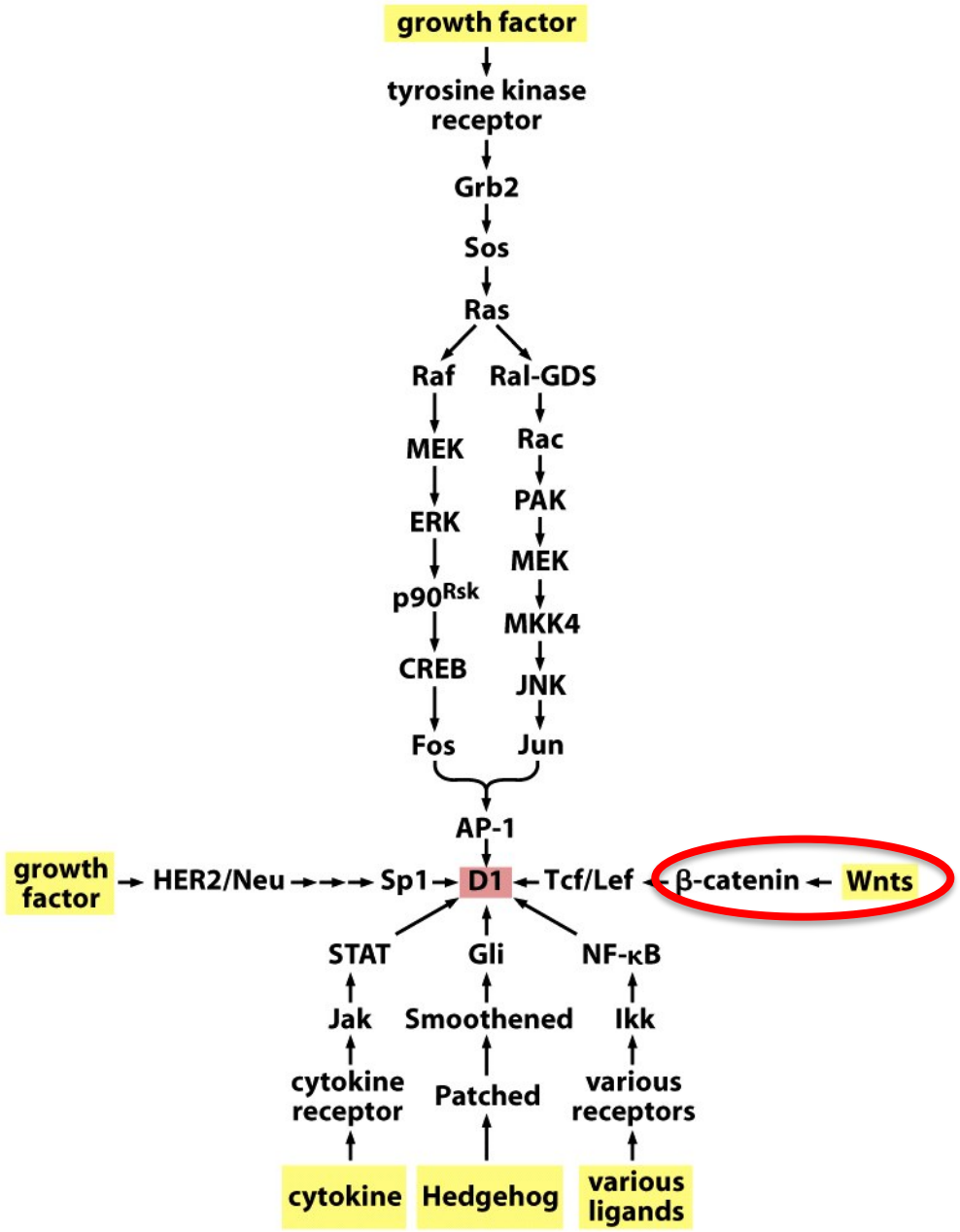


Figure 8.11b *The Biology of Cancer* (© Garland Science 2007)

Eventi che promuovono la proliferazione cellulare nei tumori

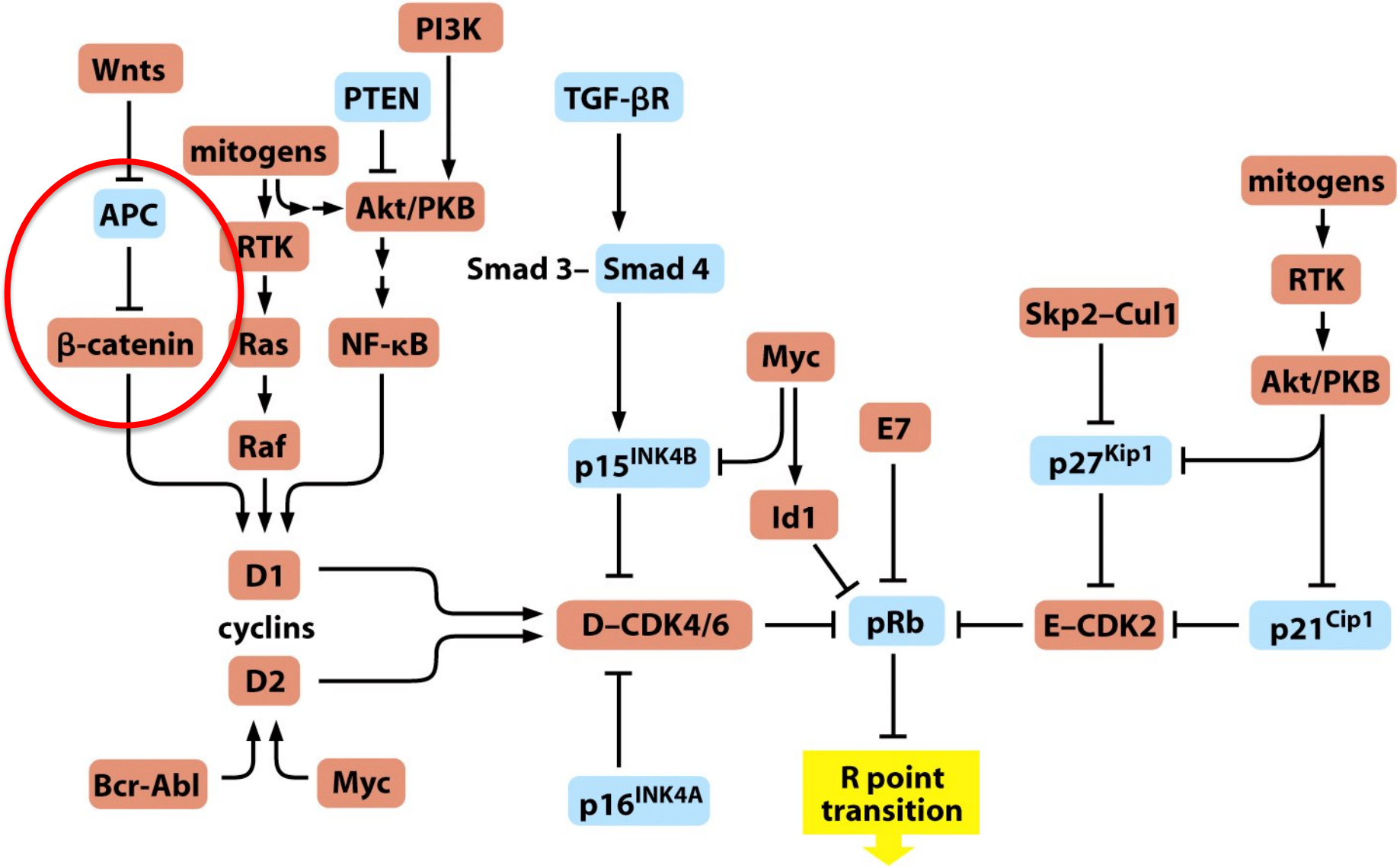
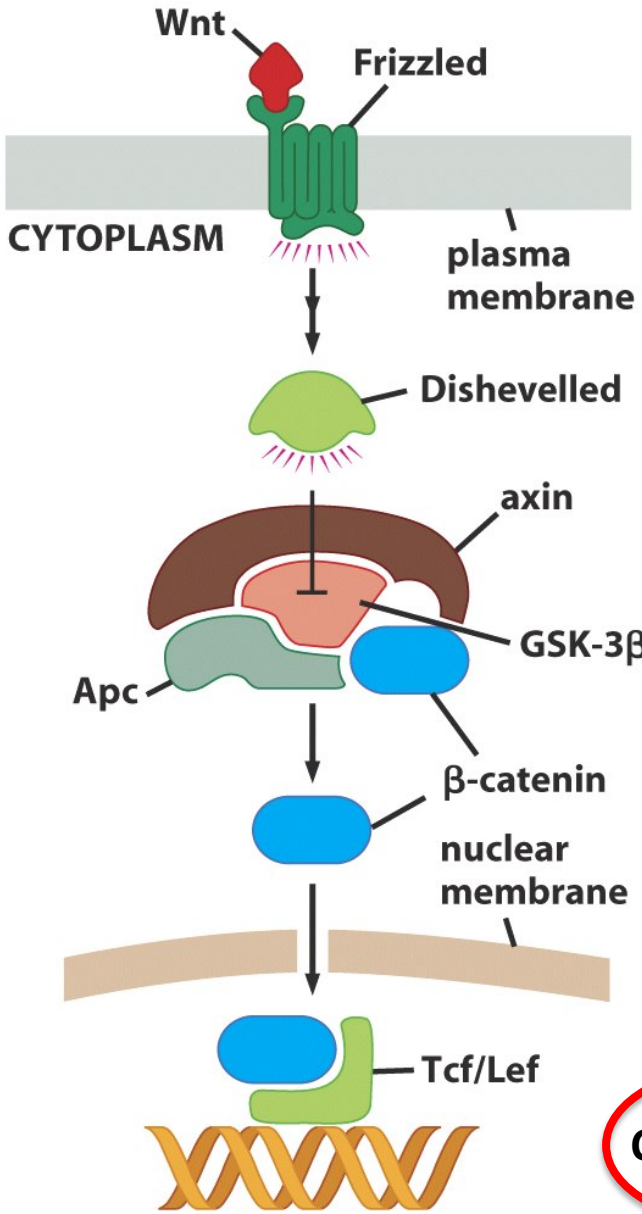


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

La pathway di Wnt promuove proliferazione cellulare e staminalità



Ser/Thr kinase

CycD1, Myc

Figure 6.26b
The Biology of Cancer
(© Garland Science 2007)

La fosforilazione di β-catenina ne induce la degradazione via ubiquitina-proteasoma

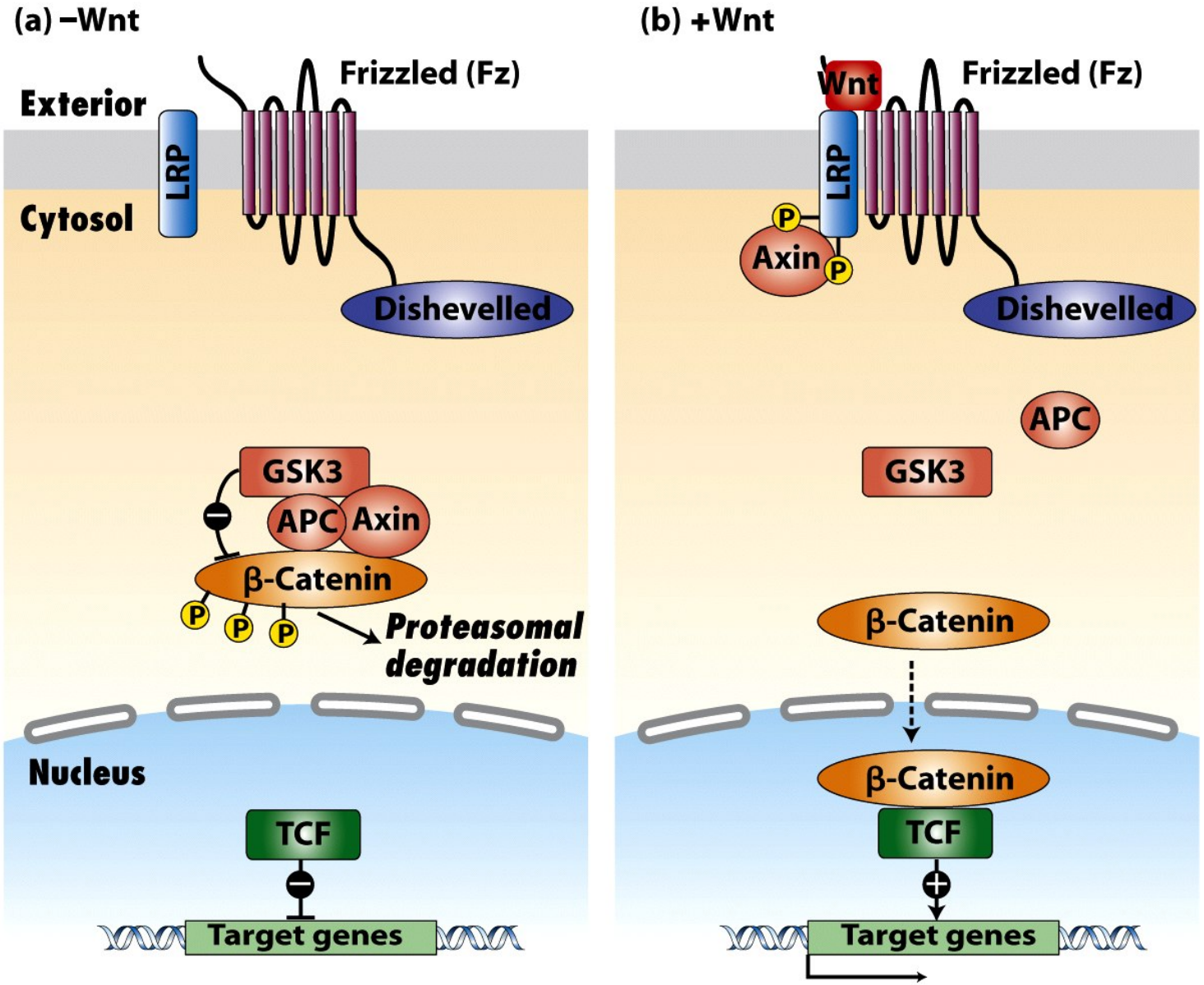
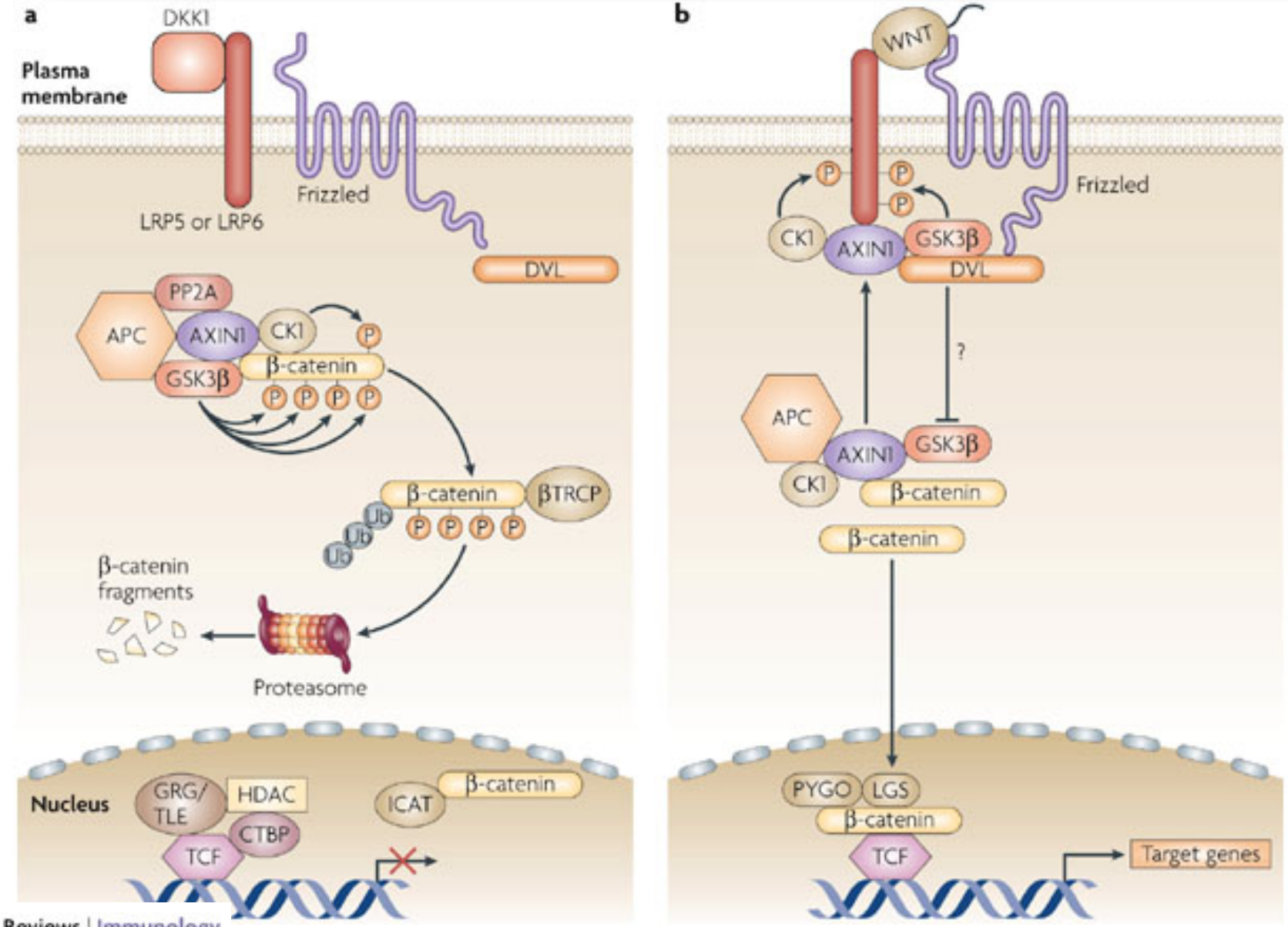


Figure 16-32
Molecular Cell Biology, Sixth Edition

La fosforilazione di beta-catenina ne induce la degradazione via ubiquitina-proteasoma



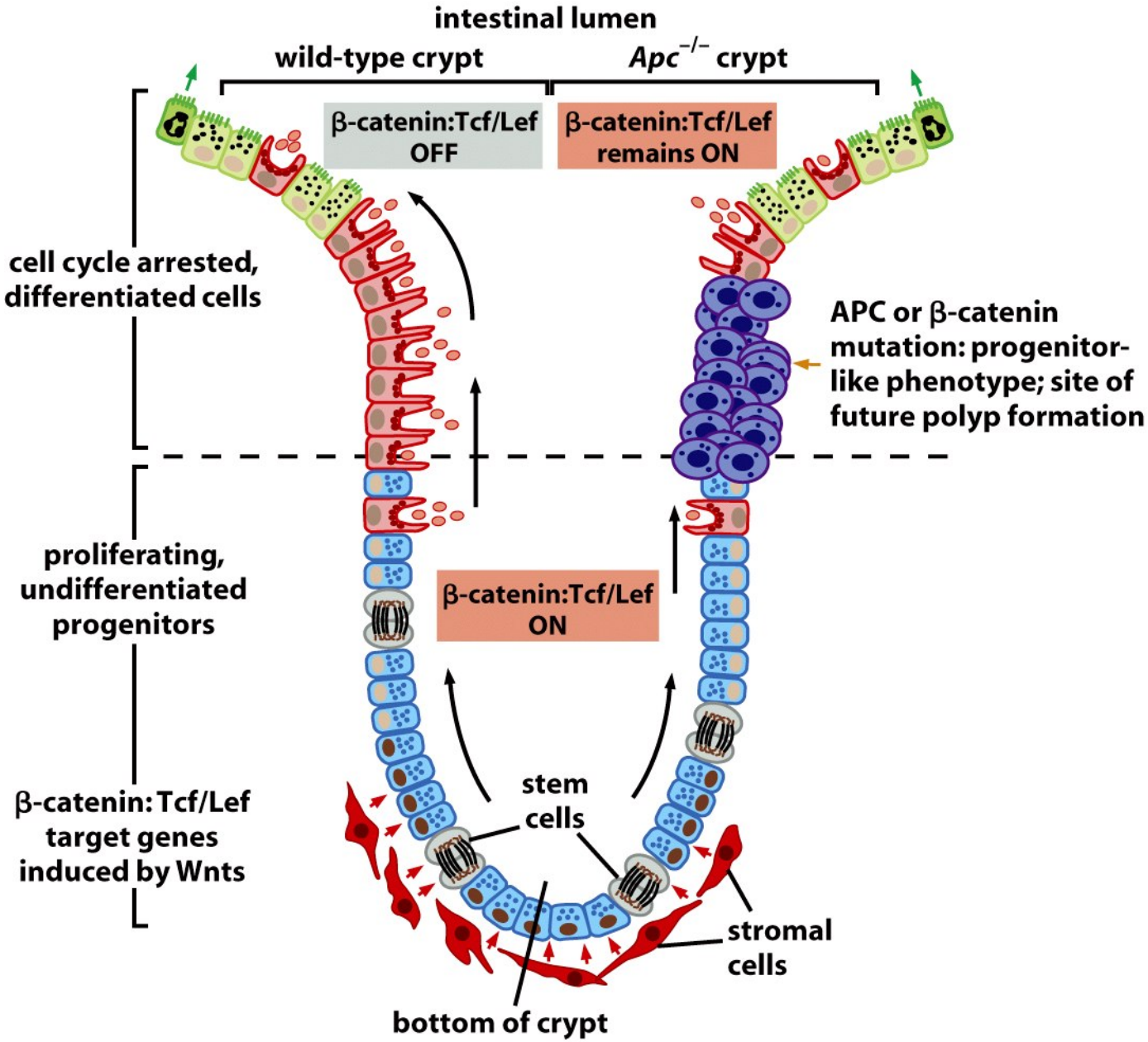
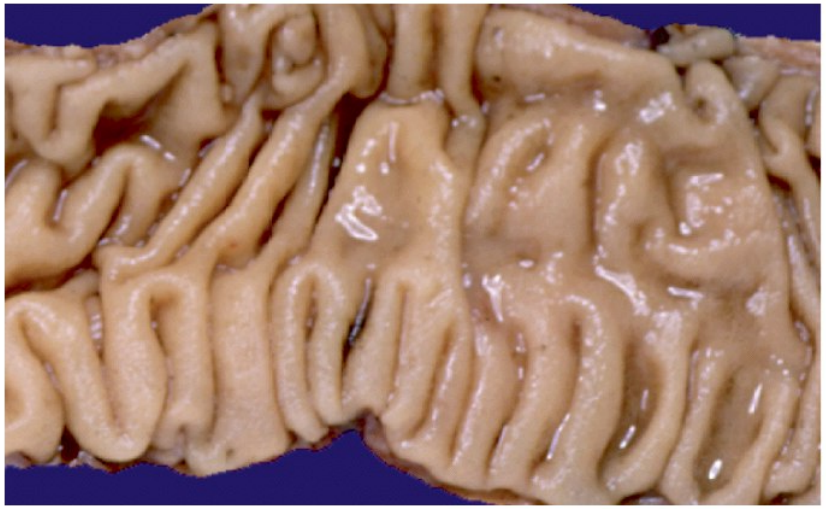


Figure 7.24a *The Biology of Cancer* (© Garland Science 2007)

Mutazioni del gene APC nella sindrome FAP (poliposi adenomatosa familiare) e nei tumori sporadici del colon, pancreas, stomaco e prostata

normale



FAP

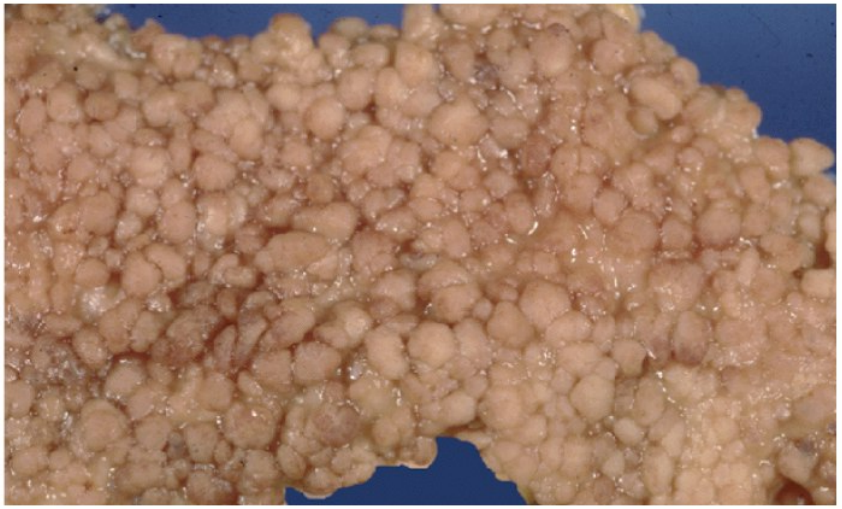


Figure 7.22 *The Biology of Cancer* (© Garland Science 2007)

Struttura e mutazioni tumorigeniche del gene APC

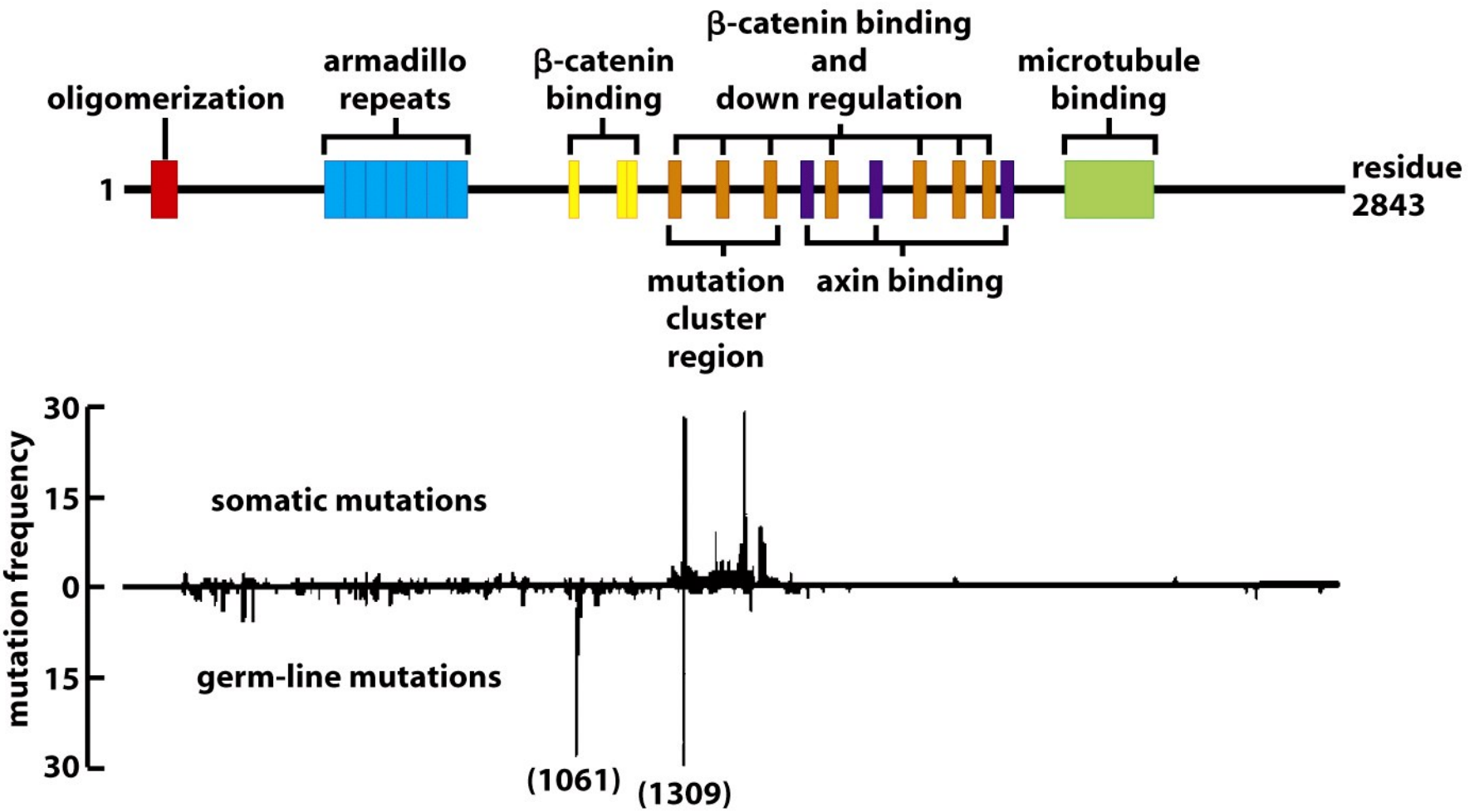
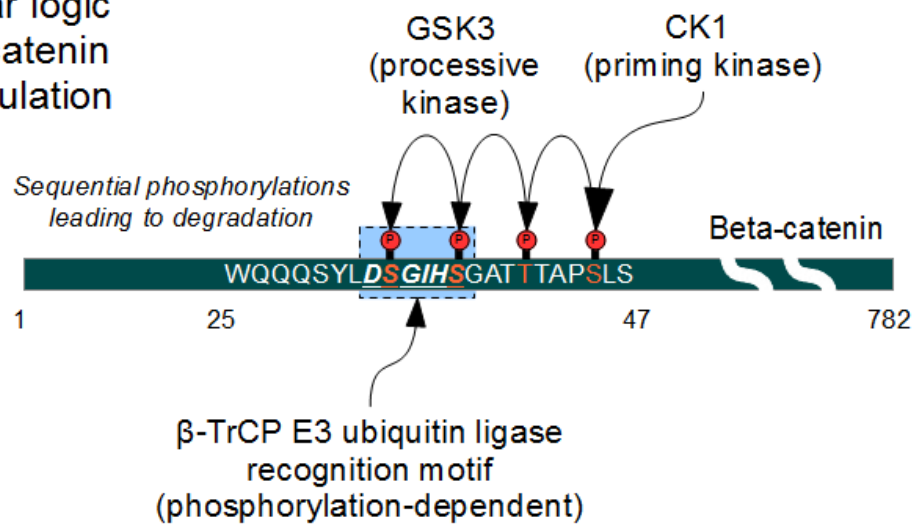
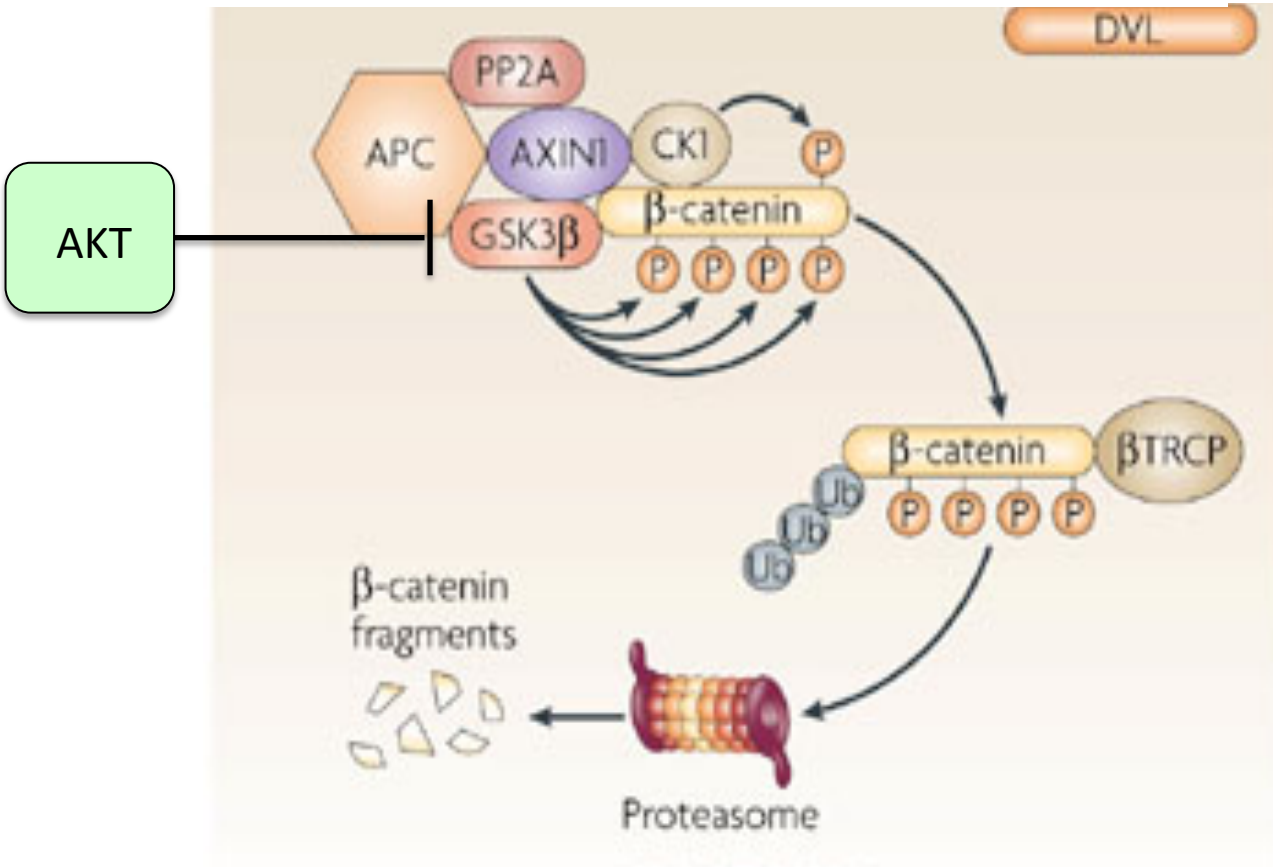


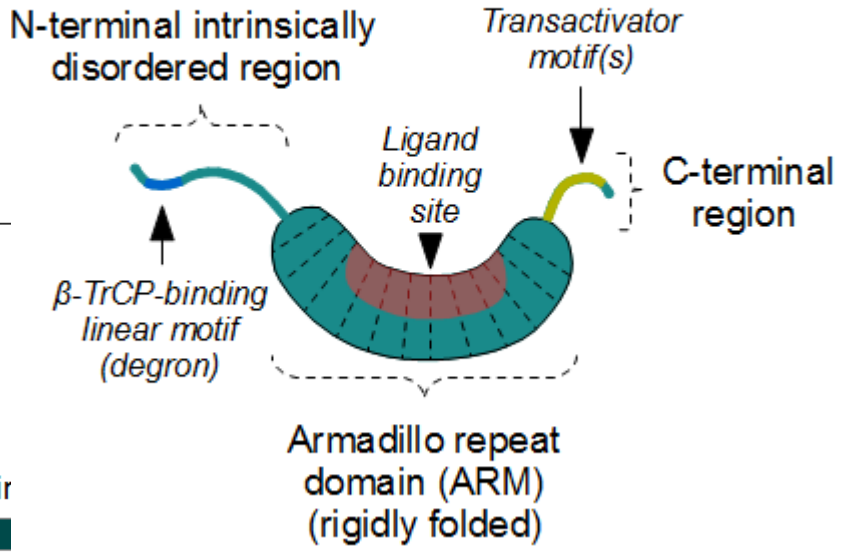
Figure 7.25a *The Biology of Cancer* (© Garland Science 2007)

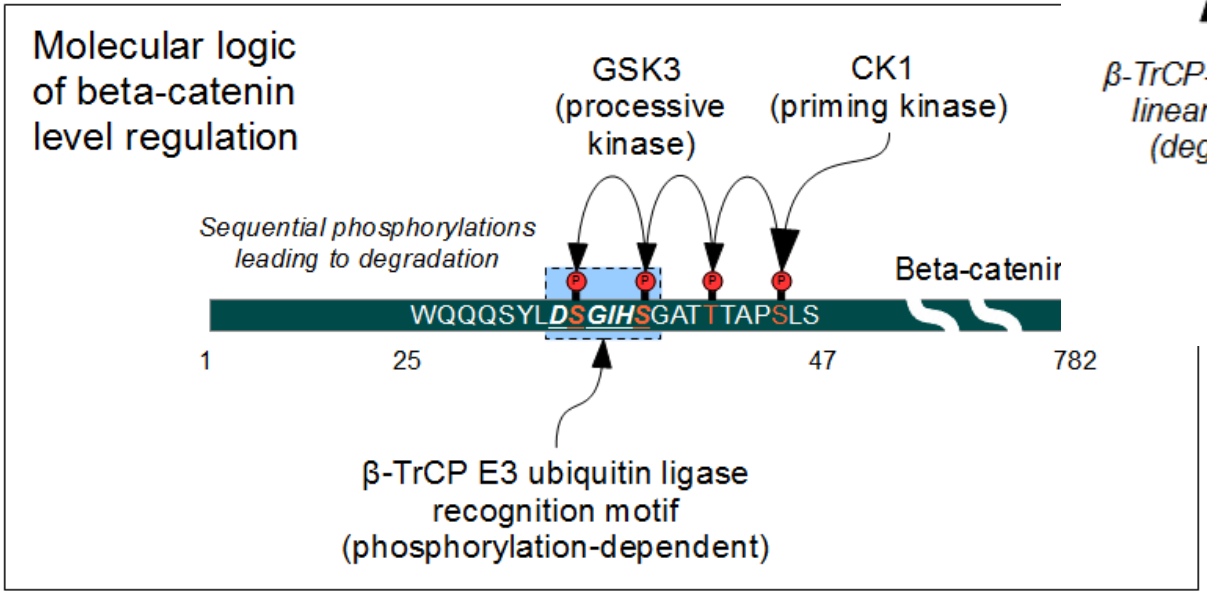
Molecular logic of beta-catenin level regulation

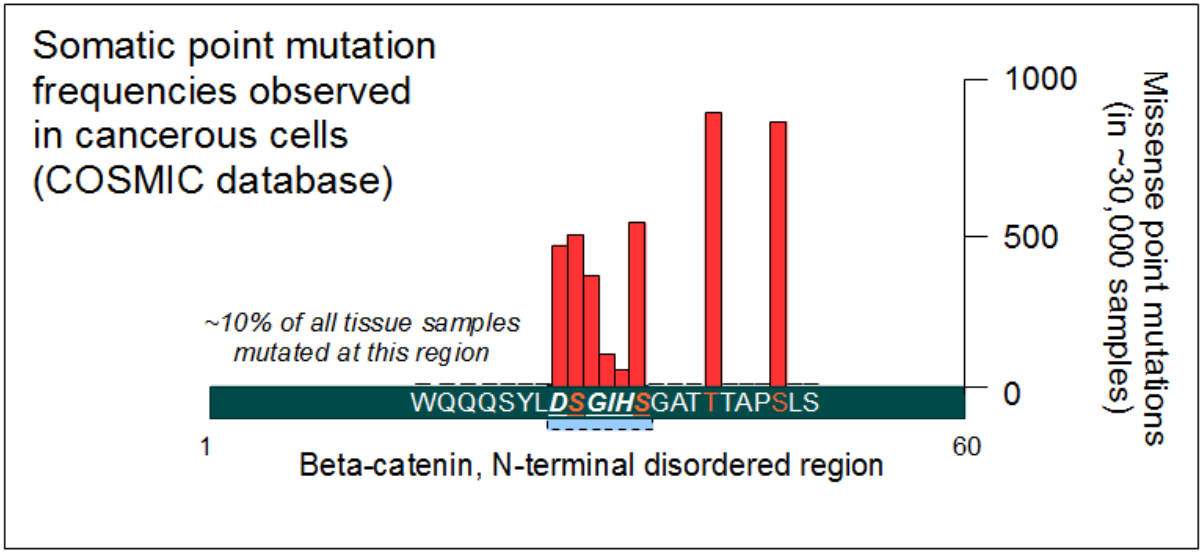




Struttura e mutazioni di β-catenina

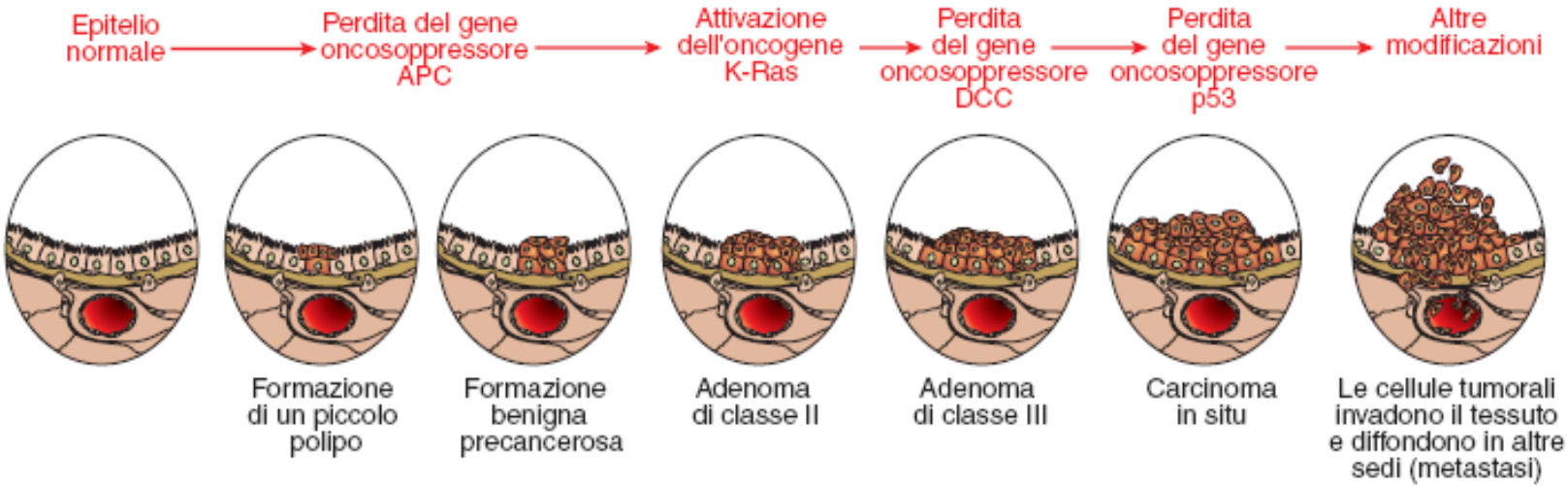


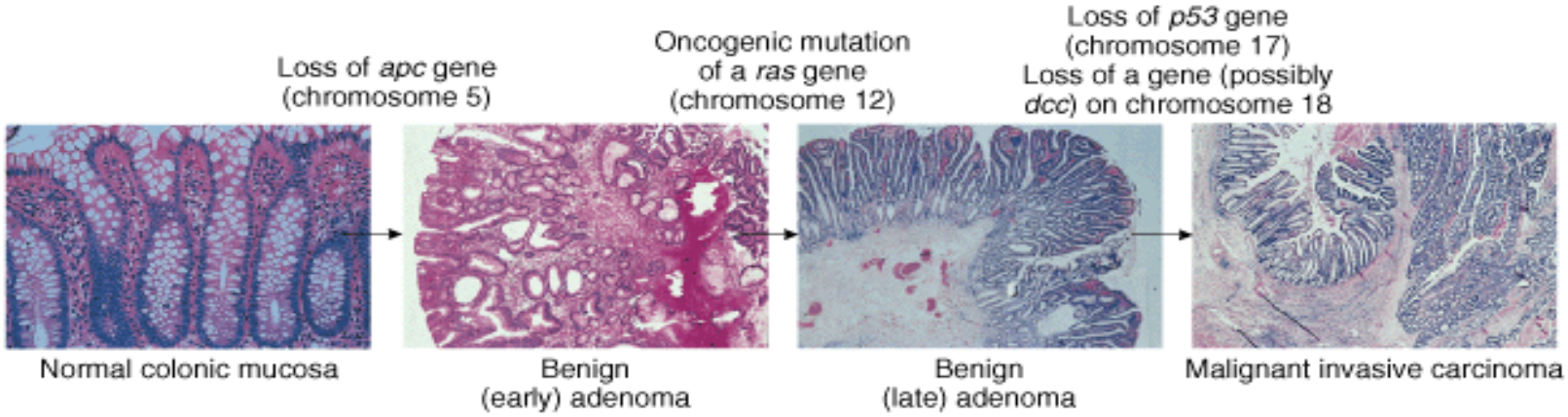




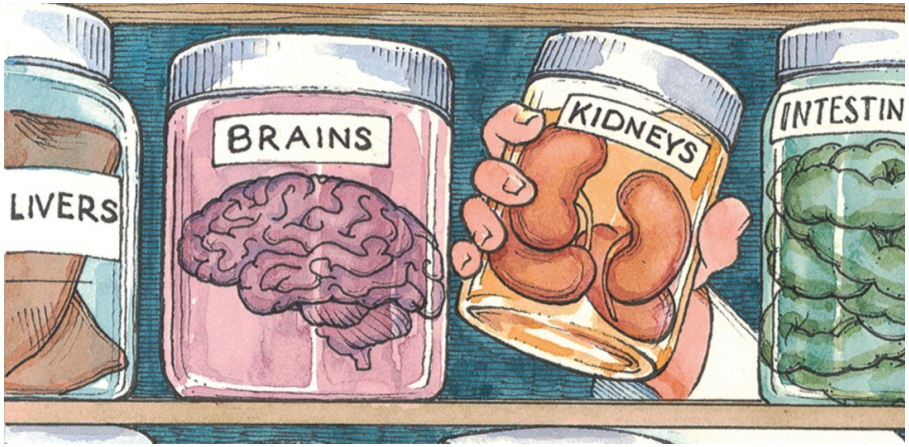
Evoluzione del cancro al colon

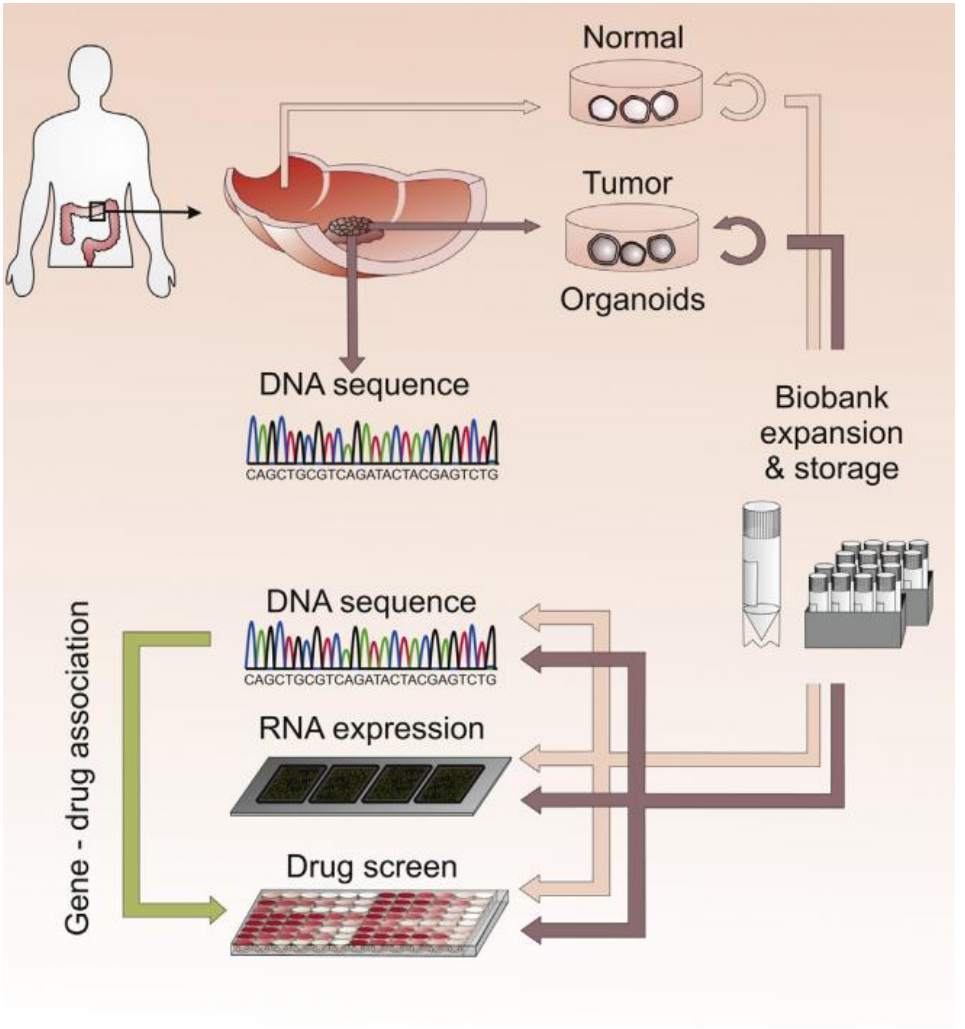
initiation → **promotion** → **progression**





Applicazioni: biobanche di organoidi tumorali da pazienti





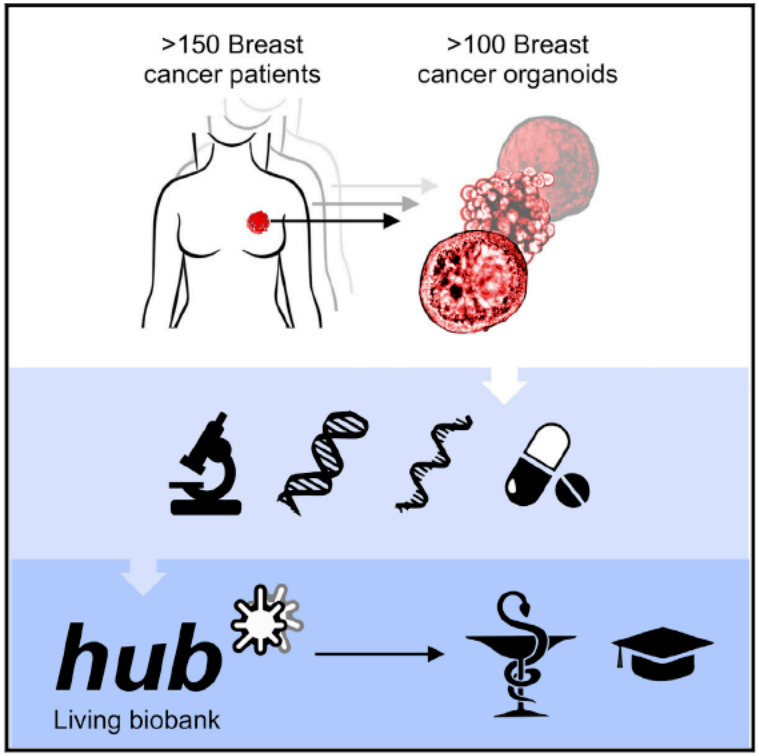
Van de Wetering et al., Cell 2015

Resource

Cell

A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity

Graphical Abstract



Authors

Norman Sachs, Joep de Ligt, Oded Kopper, ..., Robert Gerhardus Jacob Vries, Edwin Cuppen, Hans Clevers

Correspondence

h.clevers@hubrecht.eu

In Brief

The heterogeneity of breast cancer subtypes can be captured using organoid cultures that can facilitate drug screens that corroborate with patient responses.