Signal transduction networks in cancer

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How is a cancer cell characterized?

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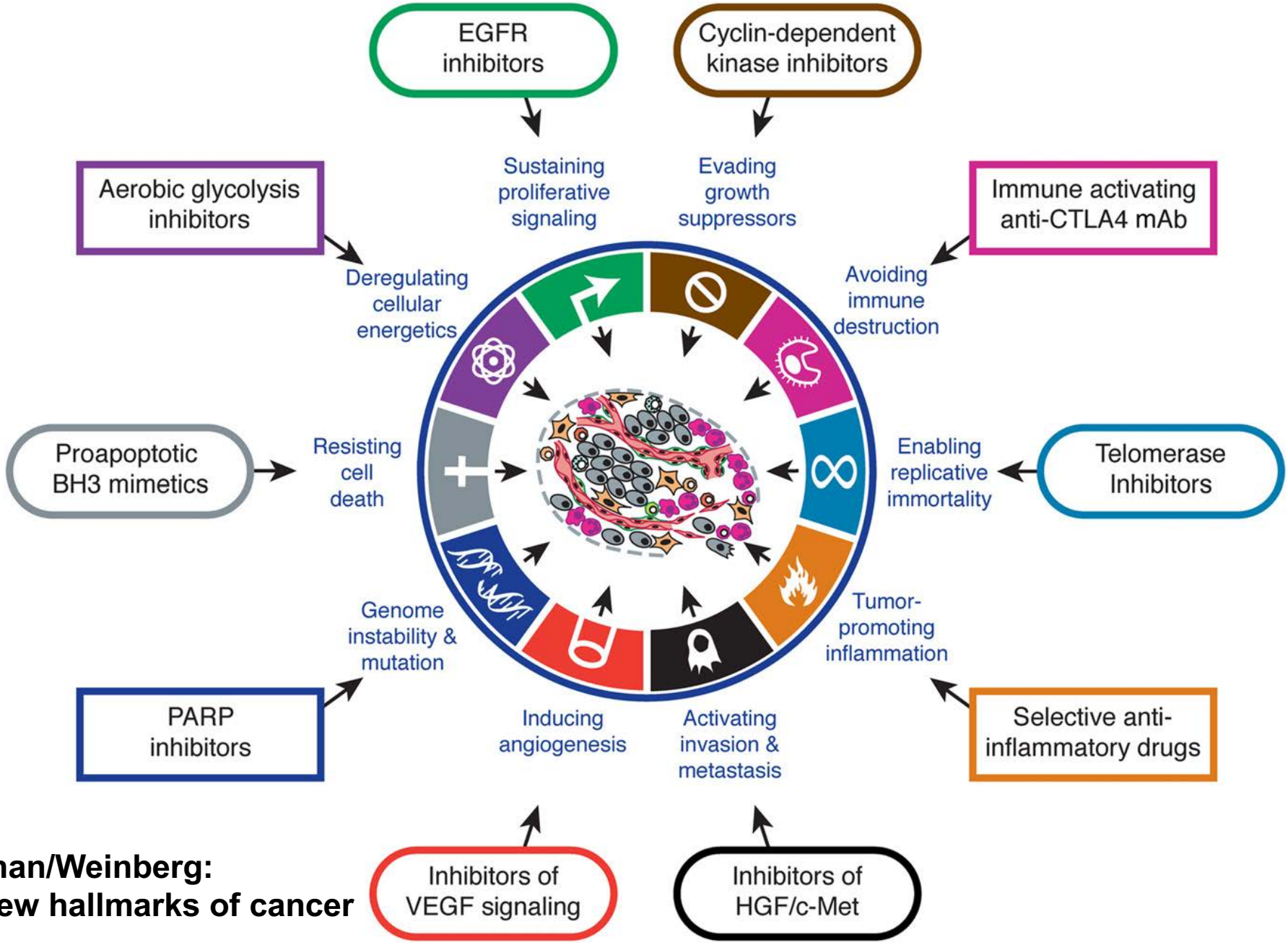

Hanahan/Weinberg:
The new hallmarks of cancer

(Altered) Signaling networks determine cancer cell identity

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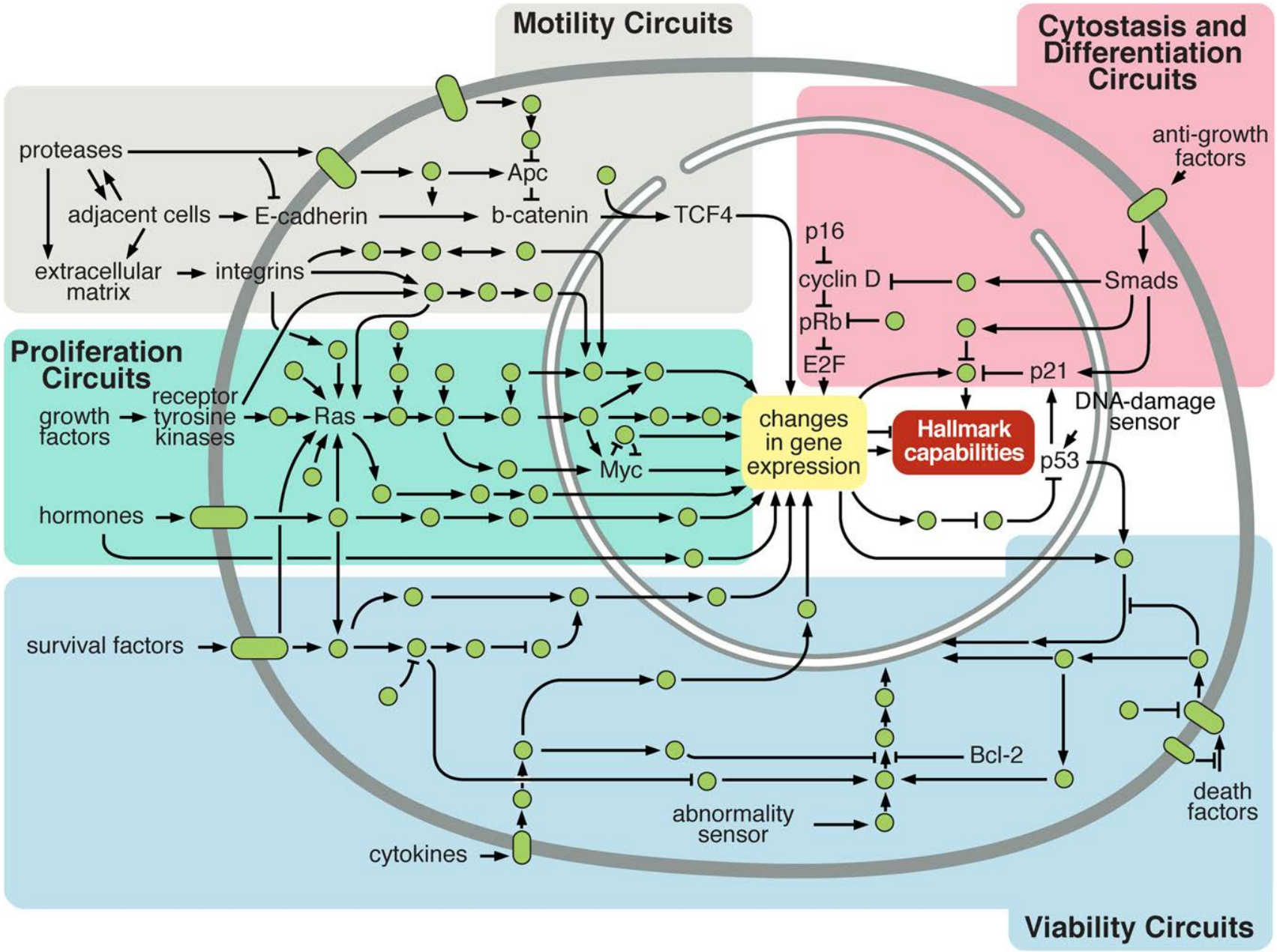

How can signaling networks function?

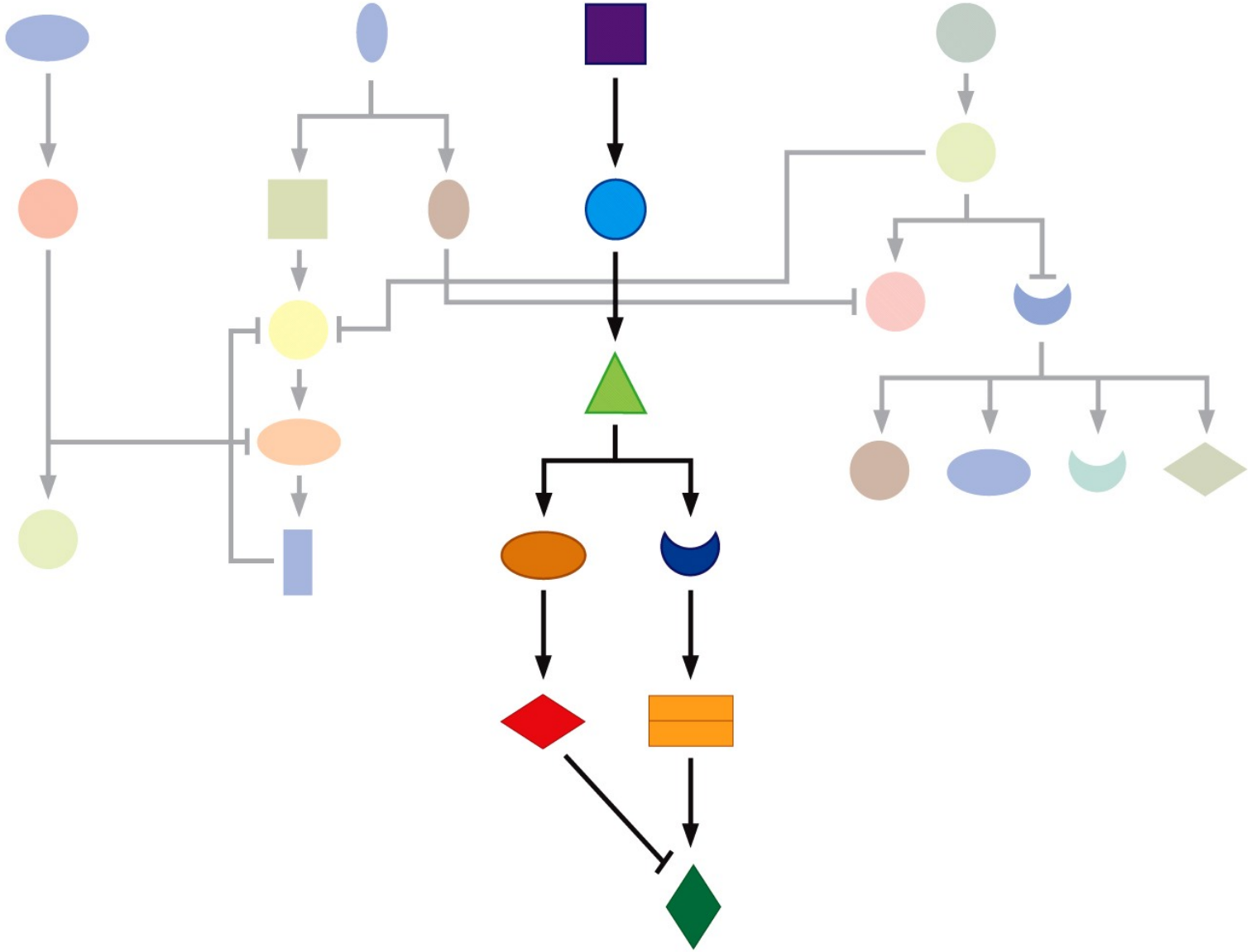

Figure 6.1 The Biology of Cancer (© Garland Science 2014)

Stimulation of a cell to proliferate induces an orchestrated gene expression program.

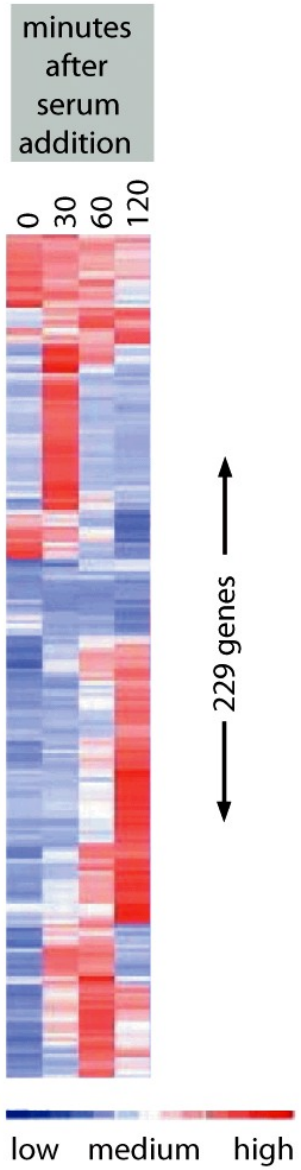

Figure 6.2 The Biology of Cancer (© Garland Science 2014)

Different patterns of gene expression

**Some genes stay up, some down,
some are induced rapidly and stay a while,
others are induced only for a brief period of time,
yet others show a delayed response**

**Immediate early gene expression vs
delayed gene expression**

Note: this complex pattern is achieved with a single defined mitogenic stimulus (e.g. PDGF, EGF)!!

Immediate early genes

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Table 6.1 A sampling of immediate early genes[a]

Name of gene	Location of gene product	Function of gene product
fos[b]	nucleus	component of AP-1 TF
junB	nucleus	component of AP-1 TF
egr-1	nucleus	zinc finger TF
nur77	nucleus	related to steroid receptors
Srf-1[c]	nucleus	TF
myc	nucleus	bHLH TF
β-*actin*	cytoplasm	cytoskeleton
γ-*actin*	cytoplasm	cytoskeleton
tropomyosin	cytoplasm	cytoskeleton
fibronectin	extracellular	extracellular matrix
glucose transporter	plasma membrane	glucose import
JE	extracellular	cytokine
KC	extracellular	cytokine

[a]The genes listed here represent only a small portion of the immediate early genes (IEGs; see Figure 6.2).

[b]Expression of a group of fos-related genes is also induced as IEGs. These include *fosB*, *fra-1*, and *fra-2*.

[c]Srf is a TF that binds to the promoters of other immediate early genes such as *fos*, *fosB*, *junB*, *egr-1*, and *egr-2*, *nur77*, and cytoskeletal genes such as actins and myosins.

Adapted in part from H.R. Herschman, *Annu. Rev. Biochem.* 60:281–319, 1991; and from B.H. Cochran, in R. Grzanna and R. Brown (eds.), Activation of Immediate Early Genes by Drugs of Abuse. Rockville, MD: National Institutes of Health, 1993, pp. 3–24.

Table 6.1 The Biology of Cancer (© Garland Science 2014)

Immediate changes after cell stimulation

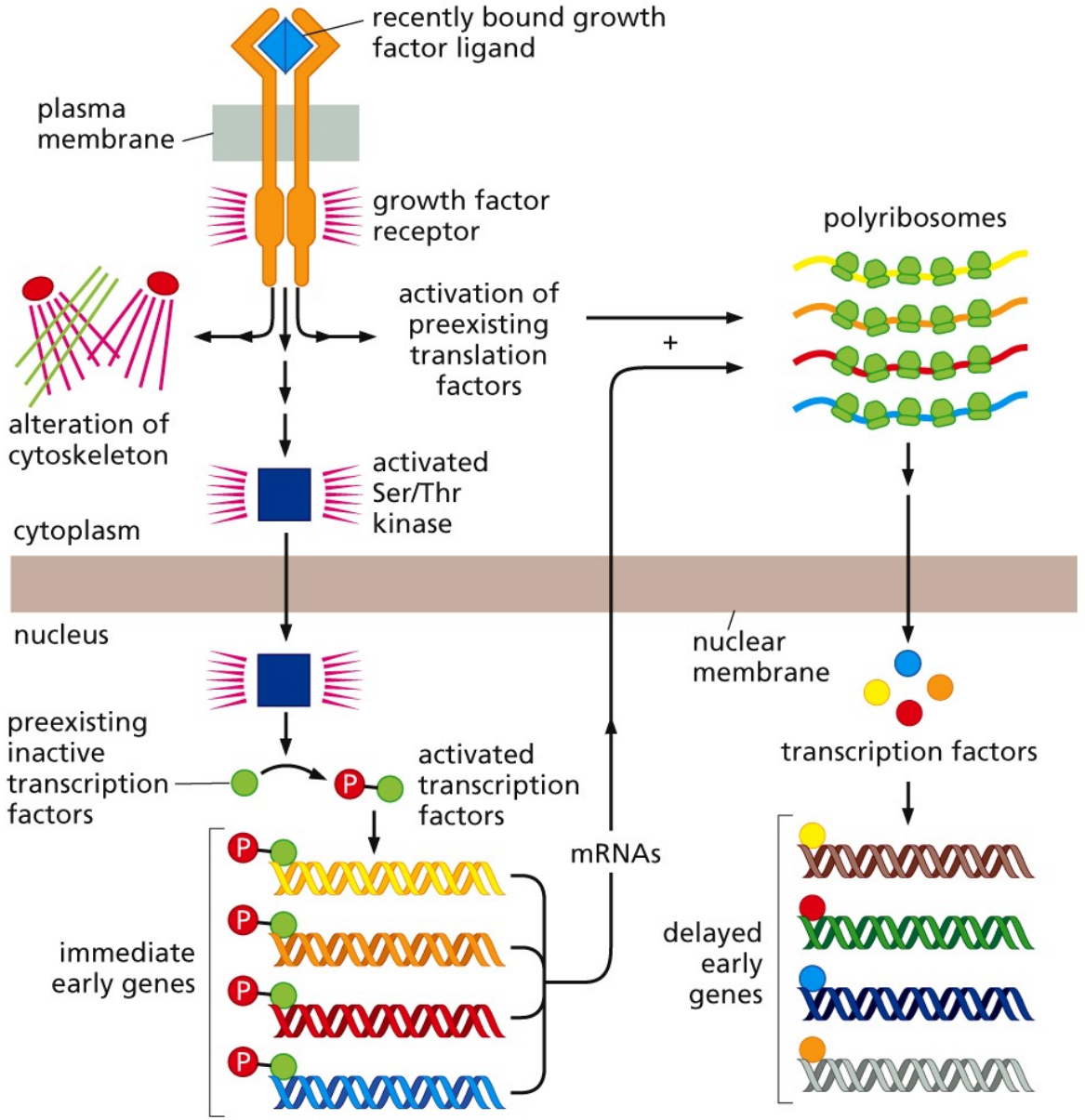

Figure 6.3 The Biology of Cancer (© Garland Science 2014)

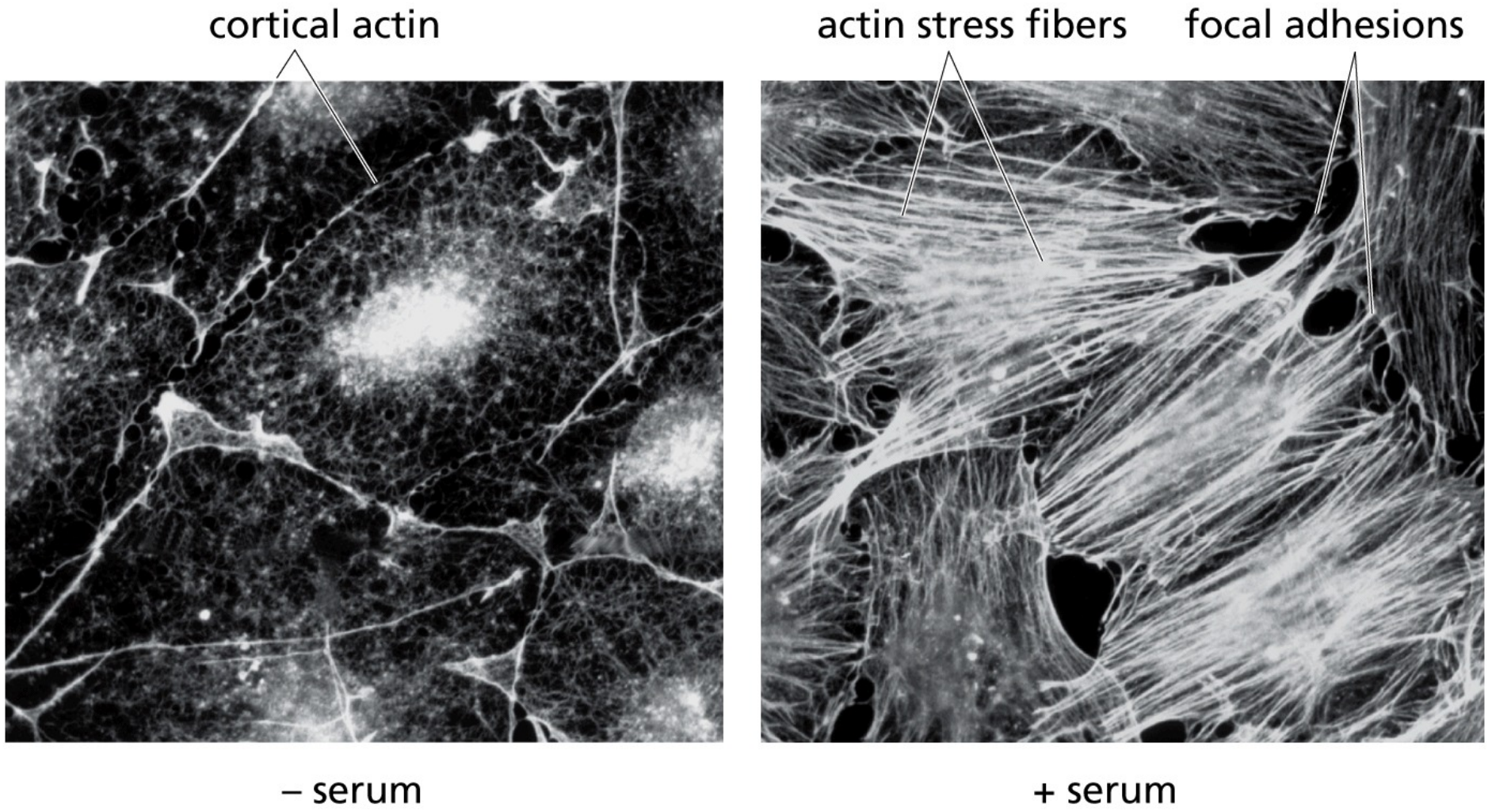

Figure 6.4 The Biology of Cancer (© Garland Science 2014)

Many growth factor receptors have intrinsic tyrosine kinase activity

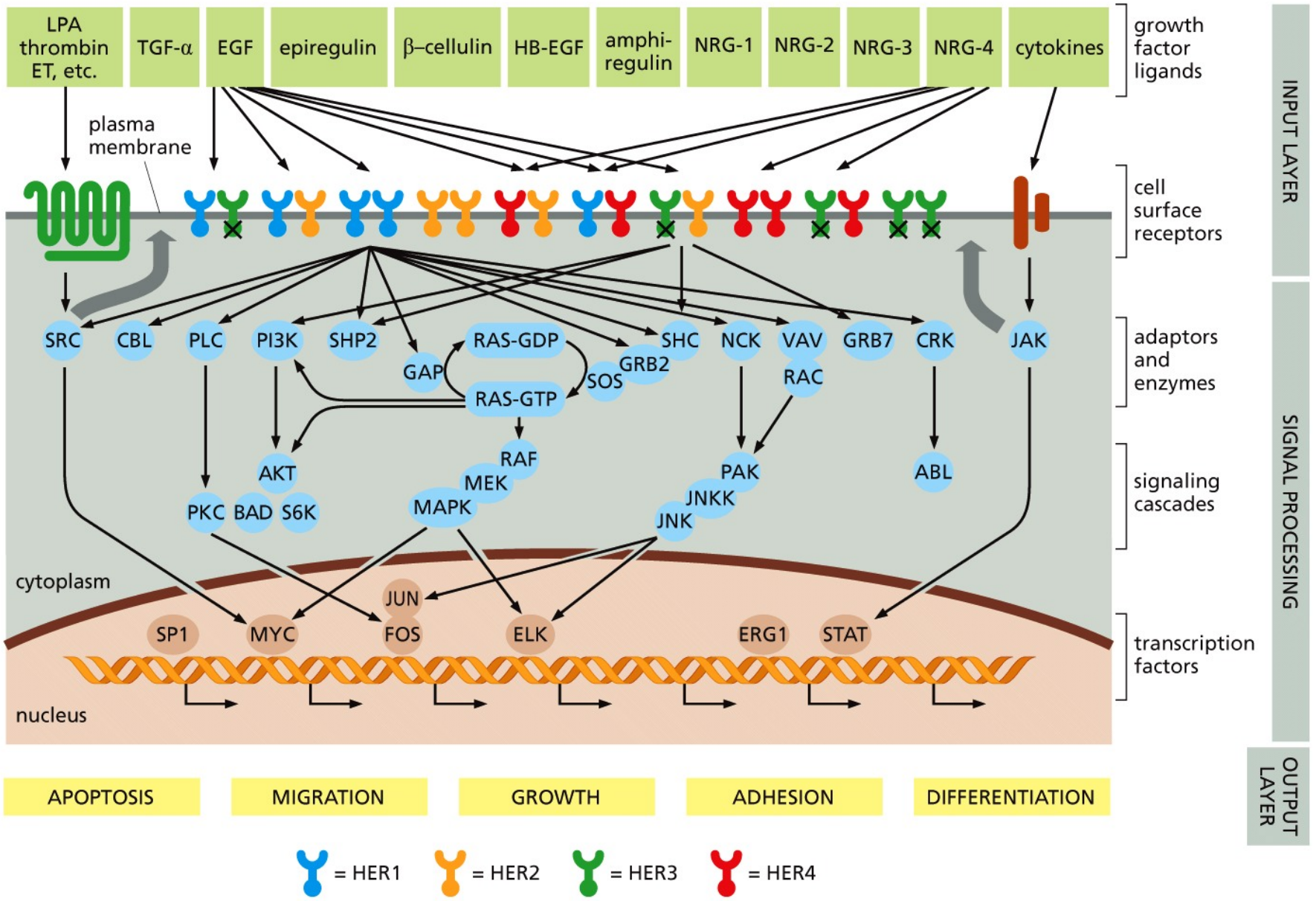

Figure 5.1 The Biology of Cancer (© Garland Science 2014)

Many growth factor receptors have intrinsic tyrosine kinase activity

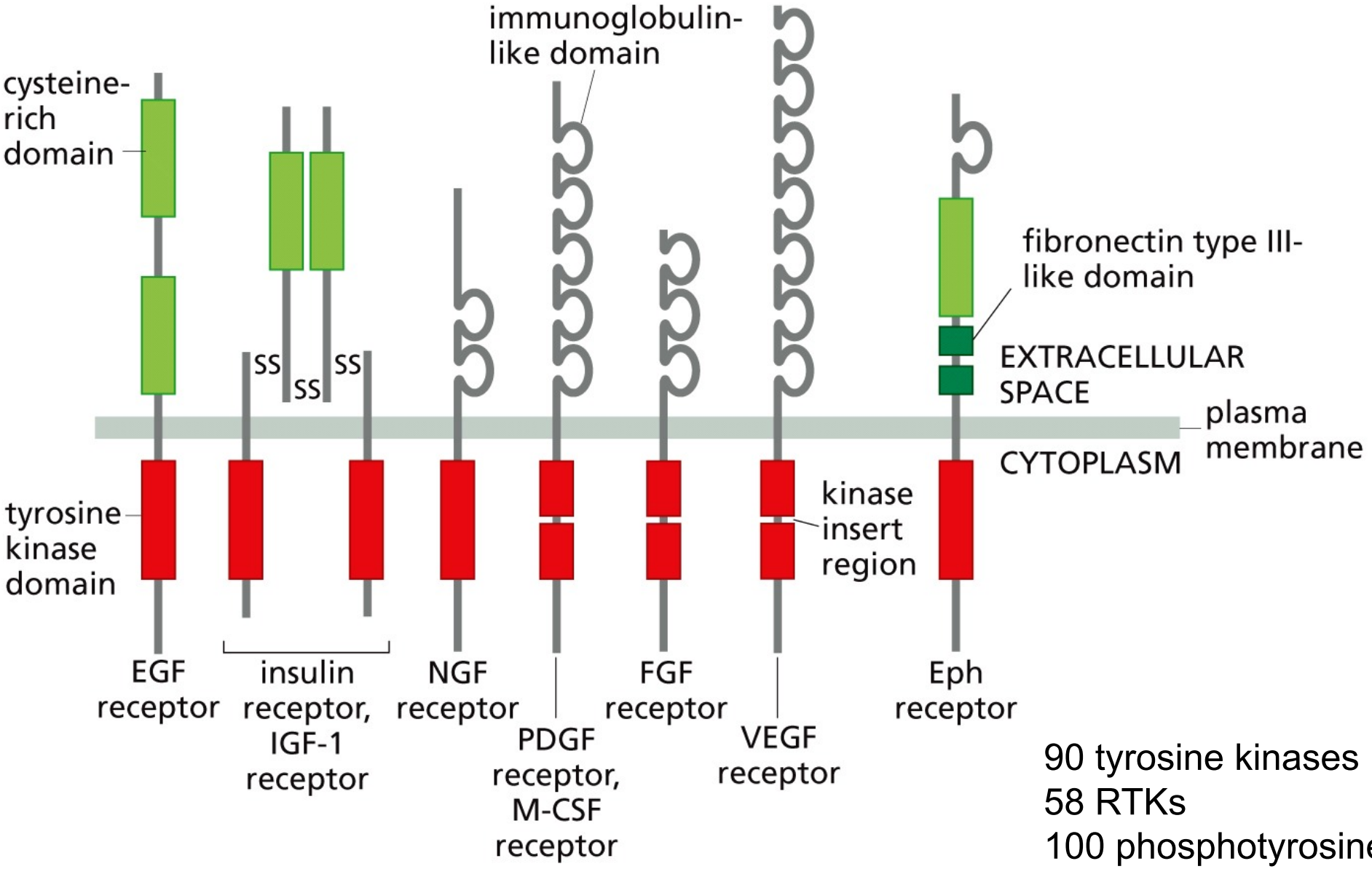

Figure 5.9 The Biology of Cancer (© Garland Science 2014)

90 tyrosine kinases
58 RTKs
100 phosphotyrosine phosphatases

Initial RTK signaling

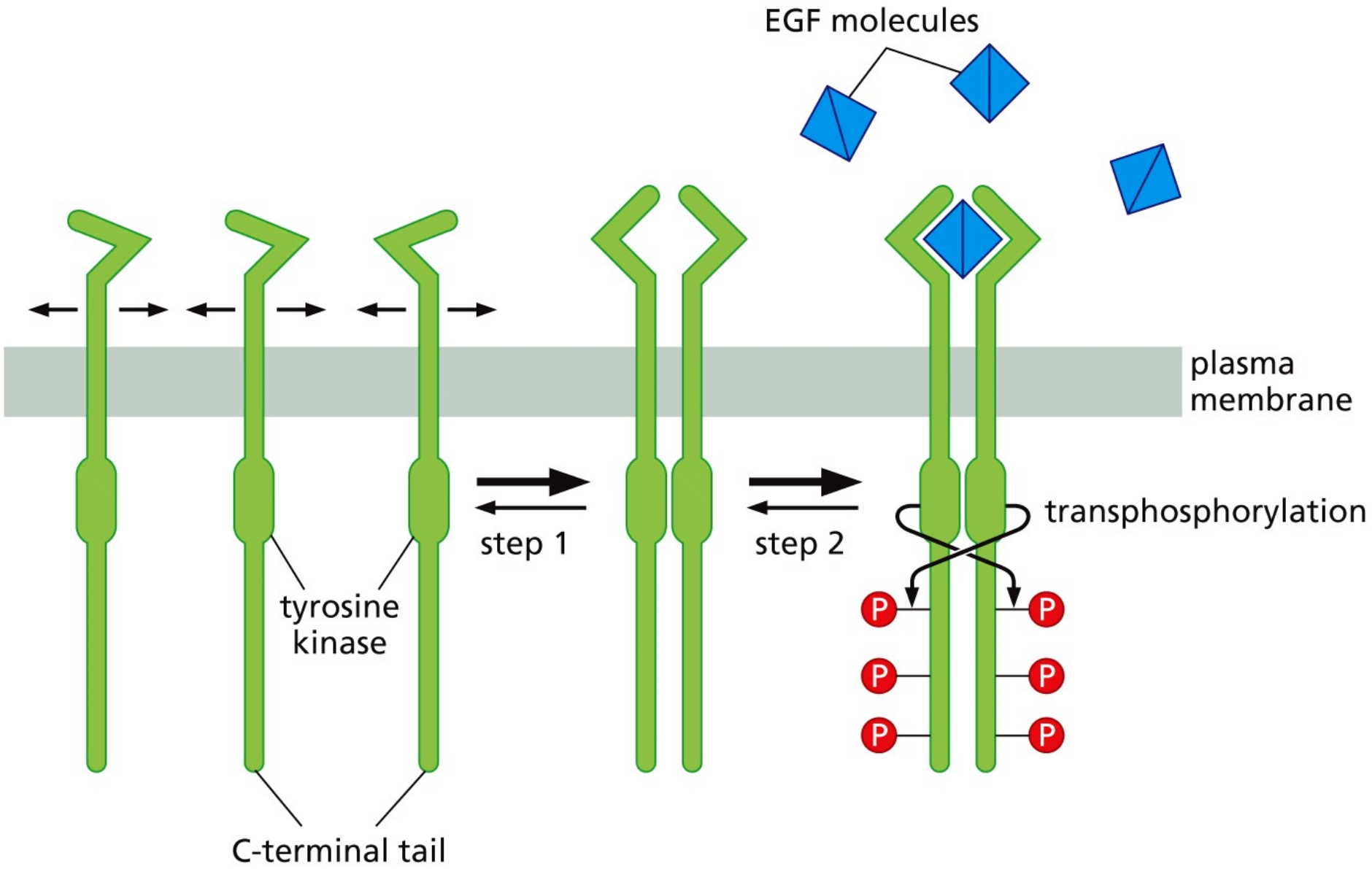

Figure 5.14a The Biology of Cancer (© Garland Science 2014)

RTKs are overexpressed/mutated in tumors

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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. In addition, other related ligands bind to heterodimers of ErbB2 and ErbB3 or ErbB4; these include epigen and a variety of proteins generated by alternatively spliced neuregulin (NRG) mRNAs, including heregulin (HRG), glial growth factor (GGF), and less well-studied factors such as sensory and motor neuron–derived factor (SMDF).
[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. ErbB2 has no ligand of its own but does have strong tyrosine kinase activity. ErbB3 and ErbB4 bind neuregulins, a family of more than 15 ligands that are generated by alternative splicing.
[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 (that is, increase in size) and survival; they also appear to be weakly mitogenic.

Abbreviation: VSMC, vascular smooth muscle cell.
Adapted in part from B. Alberts et al., Molecular Biology of the Cell, 5th ed. New York: Garland Science, 2008.

Table 5.1 The Biology of Cancer (© Garland Science 2014)

Normal vs oncogenic RTK-signaling

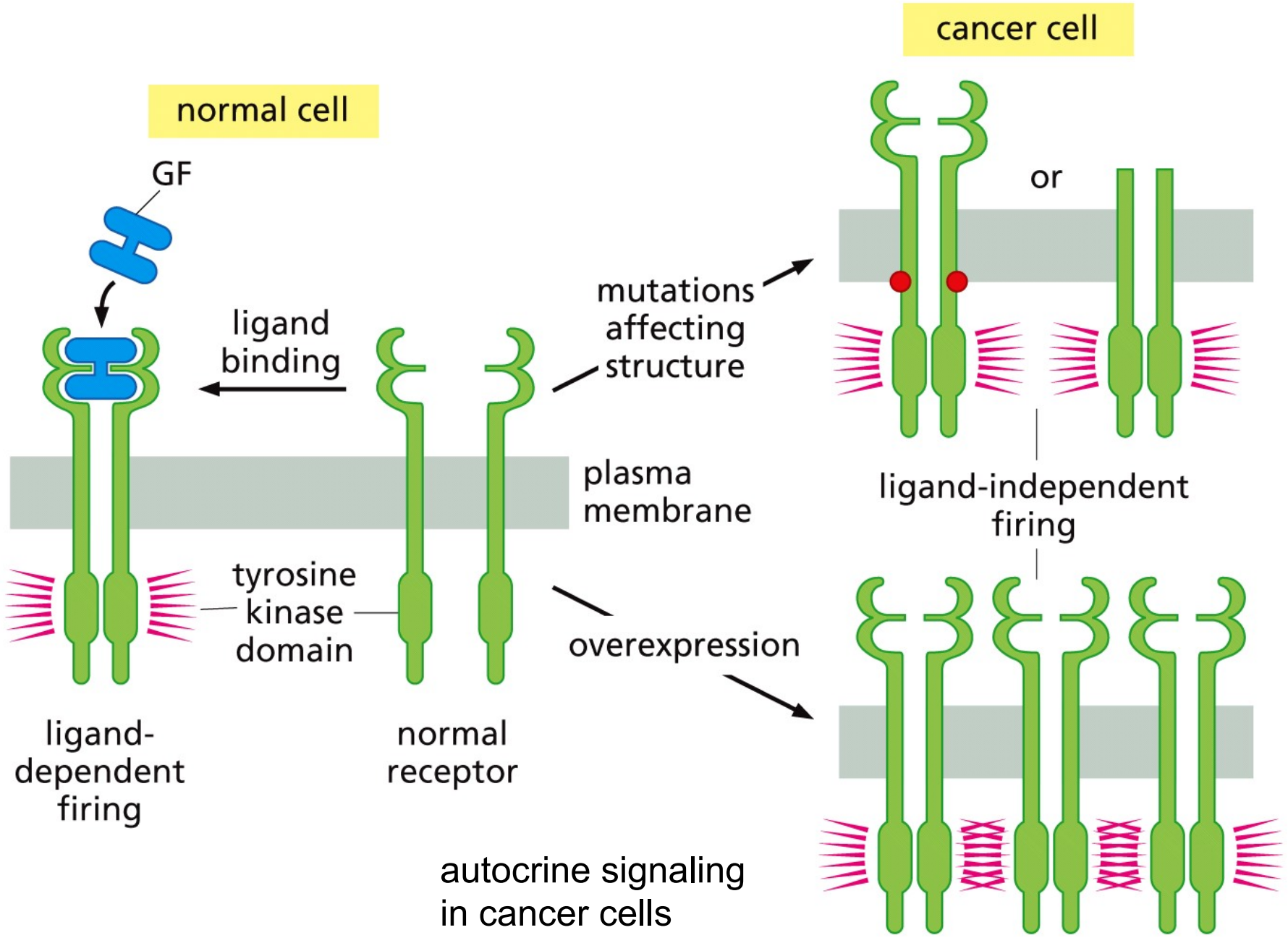
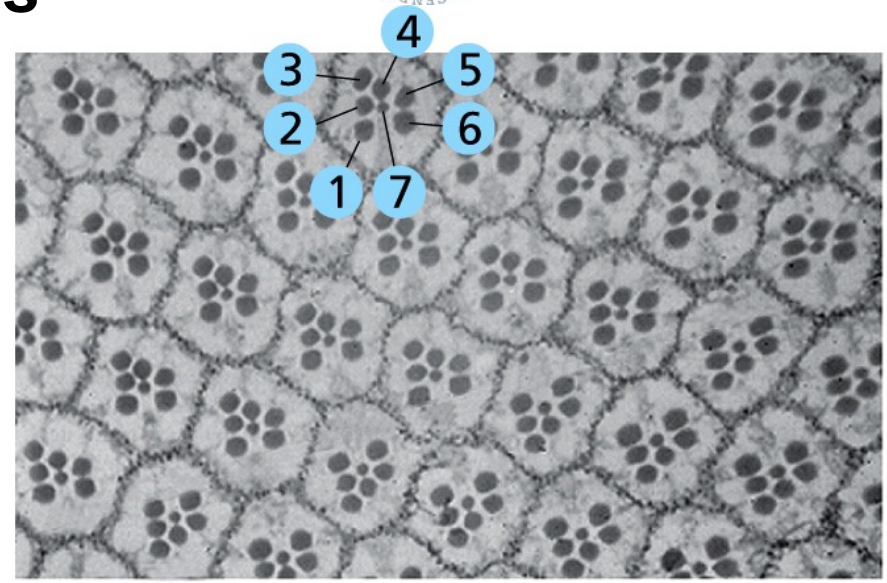


Figure 5.11a The Biology of Cancer (© Garland Science 2014)

Genetics and oncology helped to unravel signaling pathways

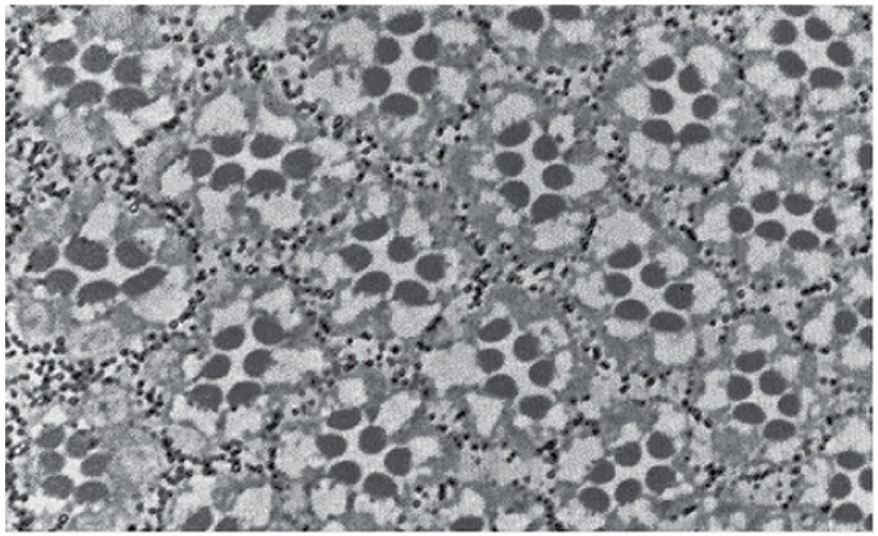
Drosophila eye (ommatidium) with seven photoreceptor cells



wild type

Drosophila sevenless mutant (FGF-receptor homolog)

Similar phenotype in mutant called son of sevenless (SOS)



sevenless mutant

Figure 6.5 The Biology of Cancer (© Garland Science 2014)

RTKs signal to Ras proteins

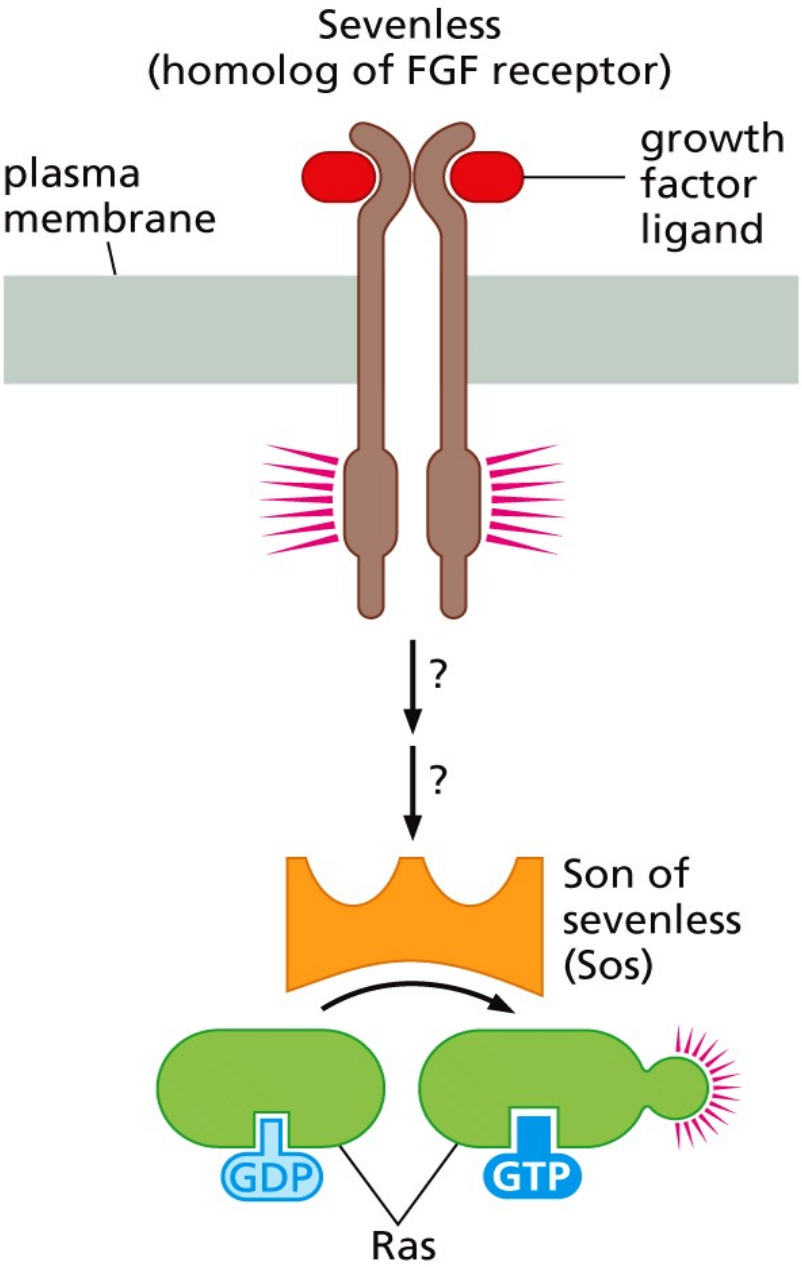


Figure 6.6 The Biology of Cancer (© Garland Science 2014)

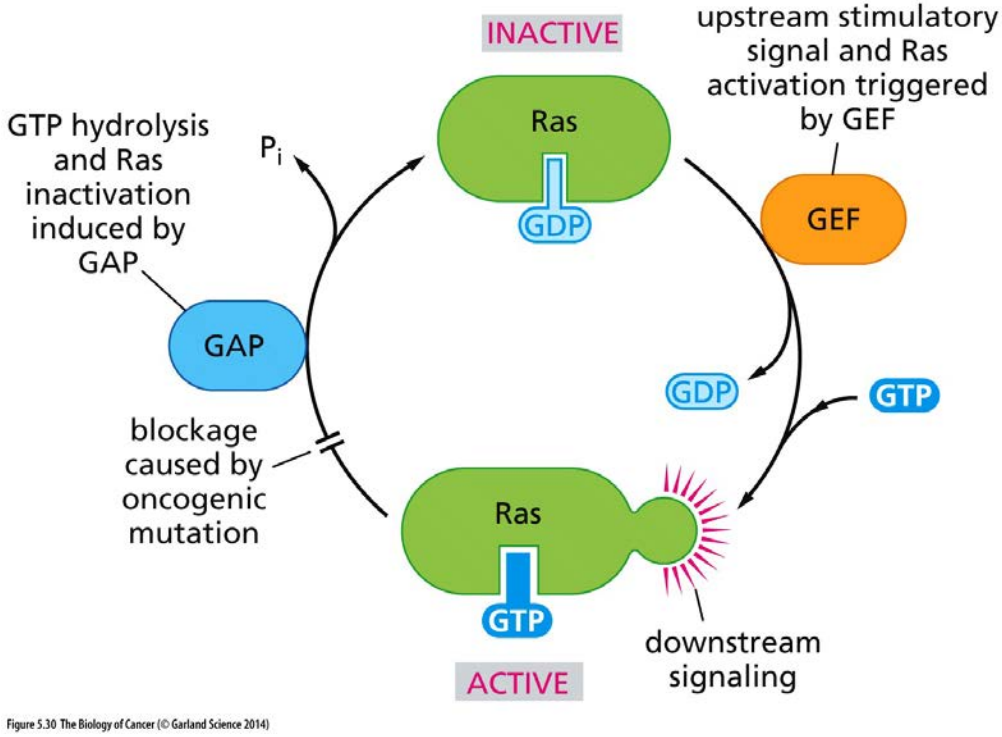


Figure 5.30 The Biology of Cancer (© Garland Science 2014)

GAP: GTPase activating protein
GEF: Guanine-nucleotide exchange factor

Structure of the src protein

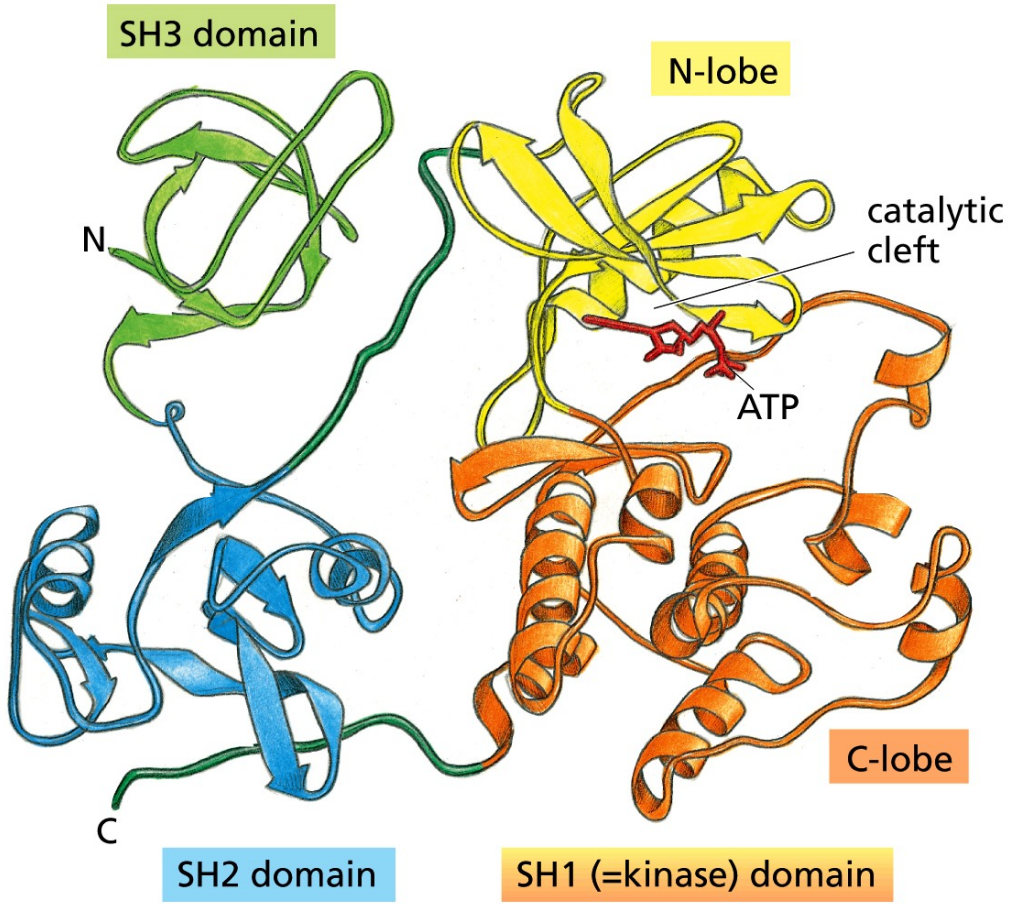


Figure 6.7a The Biology of Cancer (© Garland Science 2014)

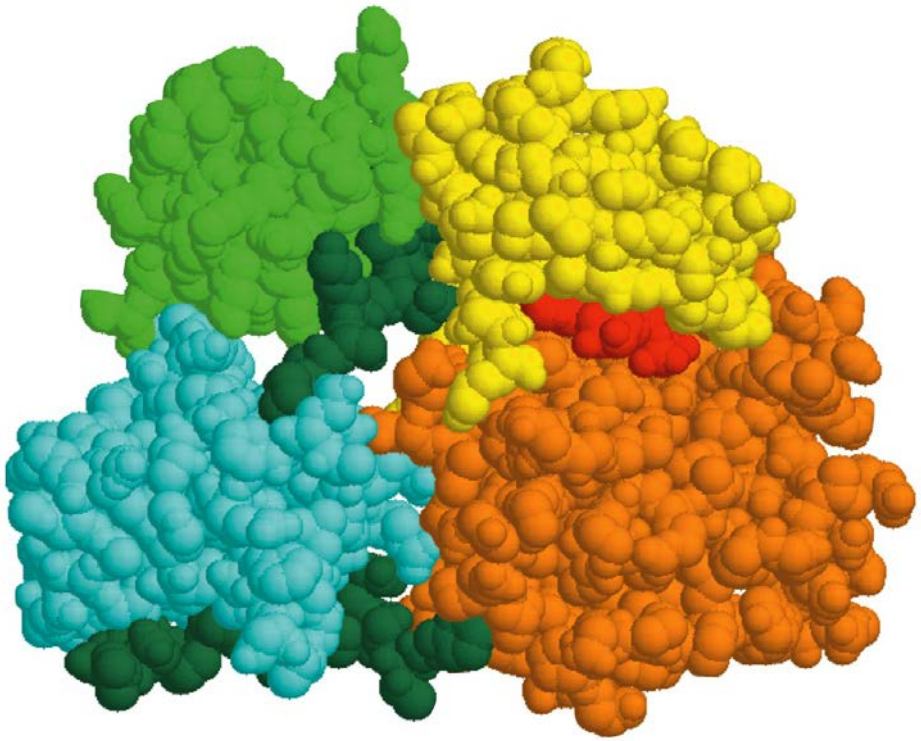


Figure 6.7b The Biology of Cancer (© Garland Science 2014)

The oncogenic src protein (cytoplasmic tyrosine kinase) is made of three distinct domains:
SH1 (src-homology domain 1): kinase domain
SH2: phyosphotyrosine binding domain
SH3: domain that interacts with proline-rich sequence motifs

SH2 domain proteins have distinct functions

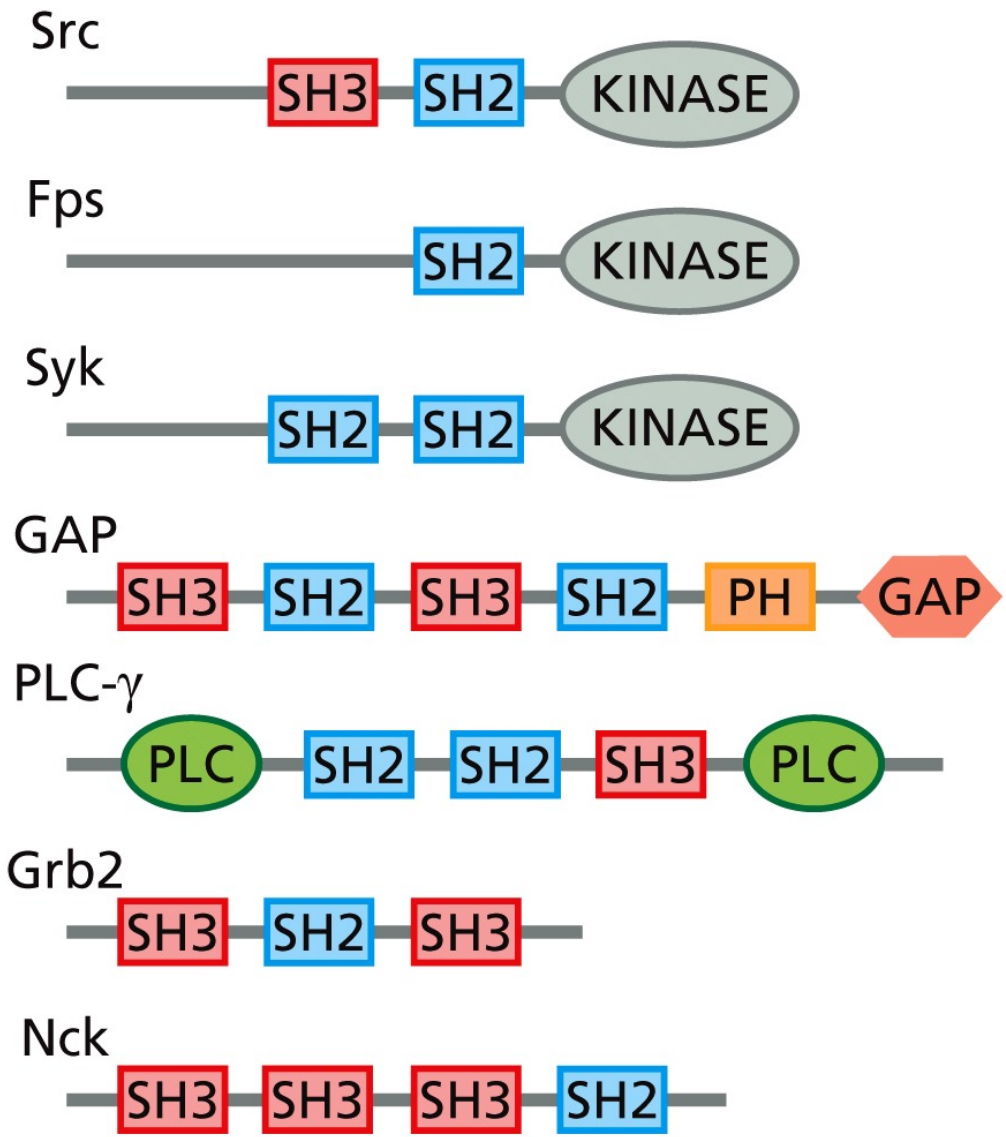


Figure 6.10a The Biology of Cancer (© Garland Science 2014)

SH2 domains recognize phosphotyrosine plus C-terminal amino acids

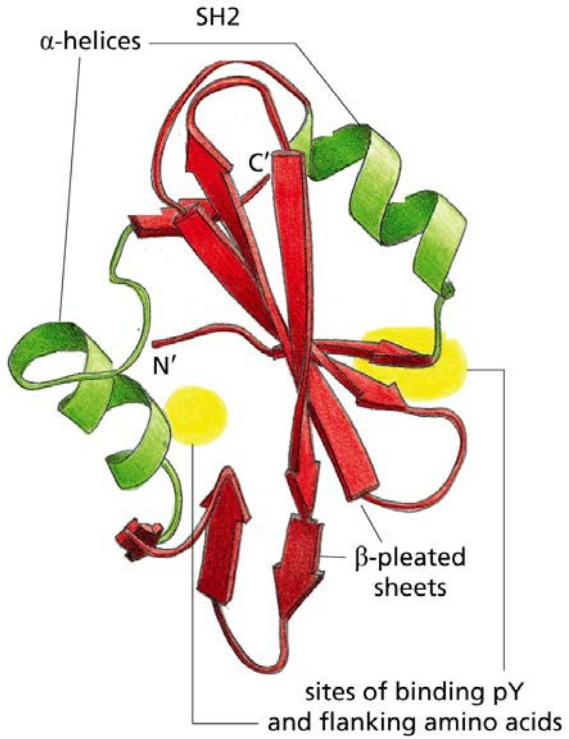


Figure 6.8a The Biology of Cancer (© Garland Science 2014)

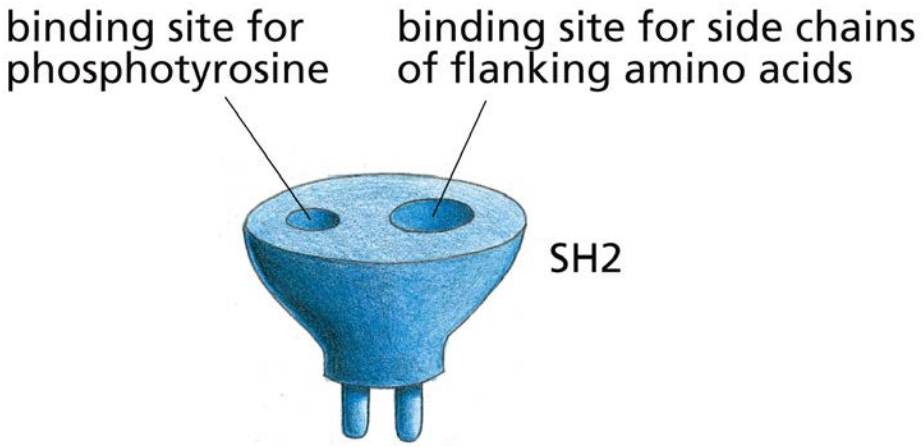


Figure 6.8b The Biology of Cancer (© Garland Science 2014)

SH2 domain: about 100 amino acids in length
there are 110 SH2 domain protein encoded in the human genome
they recognize the phosphotyrosine residue plus the next three amino acids C-terminal to the phosphotyrosine residue
PTB (phosphotyrosine binding) domains. Recognize the phosphotyrosine residue plus amino acids N-terminal to the phosphotyrosine residue

Table 6.2 Binding domains that are carried by various proteins[a]

Name of domain	Ligand	Examples of proteins carrying this domain
SH2	phosphotyrosine	Src (tyrosine kinase), Grb2 (adaptor protein), Shc (scaffolding protein), SHP2 (phosphatase), Cbl (ubiquitylation)
PTB	phosphotyrosine	Shc (adaptor protein), IRS-1 (adaptor for insulin RTK signaling), X11 (neuronal protein)
SH3	proline-rich	Src (tyrosine kinase), Crk (adaptor protein), Grb2 (adaptor protein)
14-3-3	phosphoserine	Cdc25 (CDK phosphatase), Bad (apoptosis regulator), Raf (Ser/Thr kinase), PKC (protein kinase C Ser/Thr kinase)
Bromo	acetylated lysine	P/CAF (transcription co-factor), chromatin proteins
PH[b]	phosphorylated inositides	PLC-δ (phospholipase C-δ), Akt/PKB (Ser/Thr kinase), BTK

[a]At least 32 distinct types of binding domains have been identified (see Figure 6.10B). This table presents six of these that are often associated with transduction of mitogenic signals.

[b]The phosphoinositide-binding groups include, in addition to the PH domain, the Fab1, YOTB, Vac1, EEA1 (FYVE), PX, ENTH, and FERM domains.

Table 6.2 The Biology of Cancer (© Garland Science 2014)

Different signaling pathways can emanate from one RTK

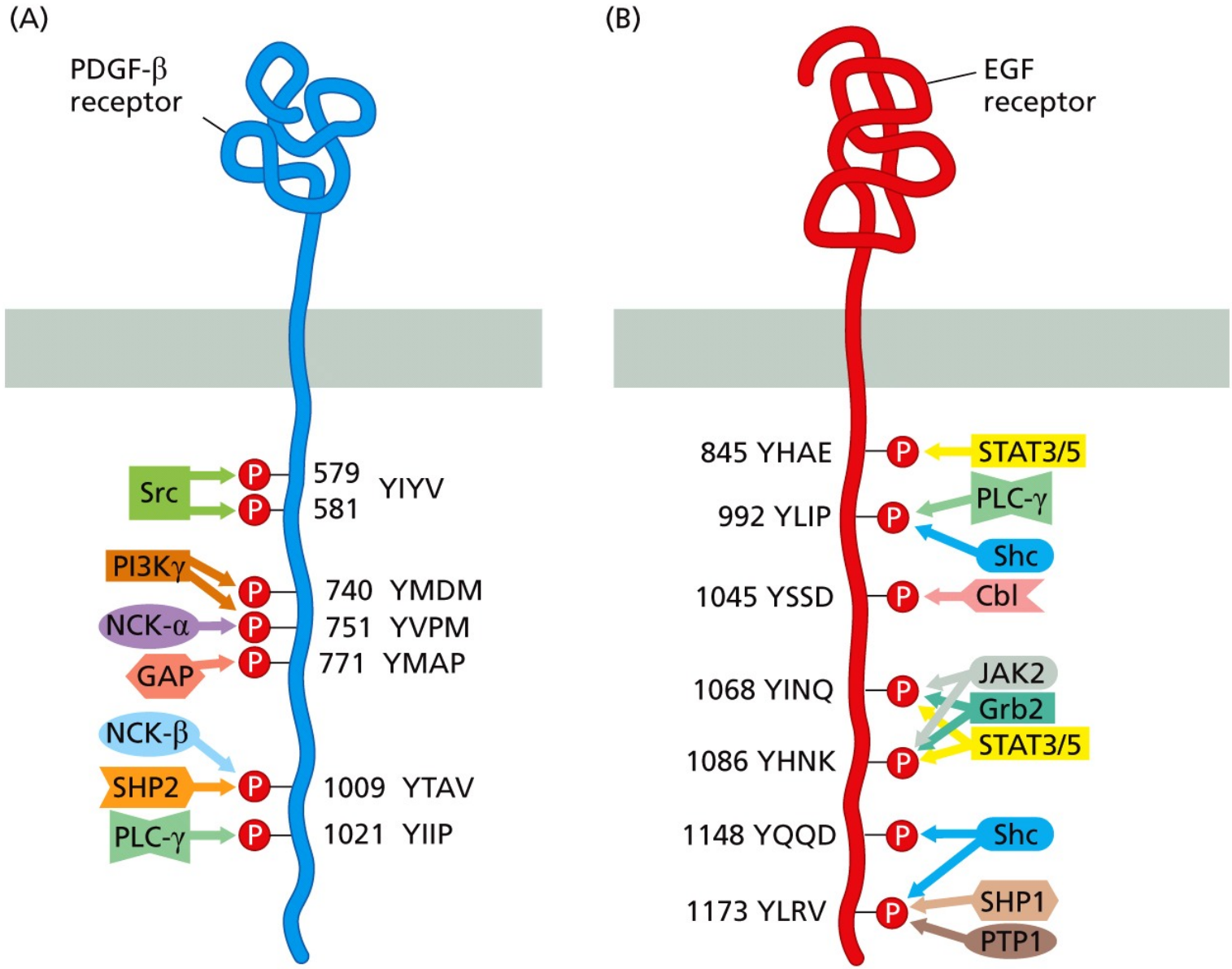


Figure 6.9 The Biology of Cancer (© Garland Science 2014)

SH2 and SH3 domain adaptor proteins link Ras to RTKs

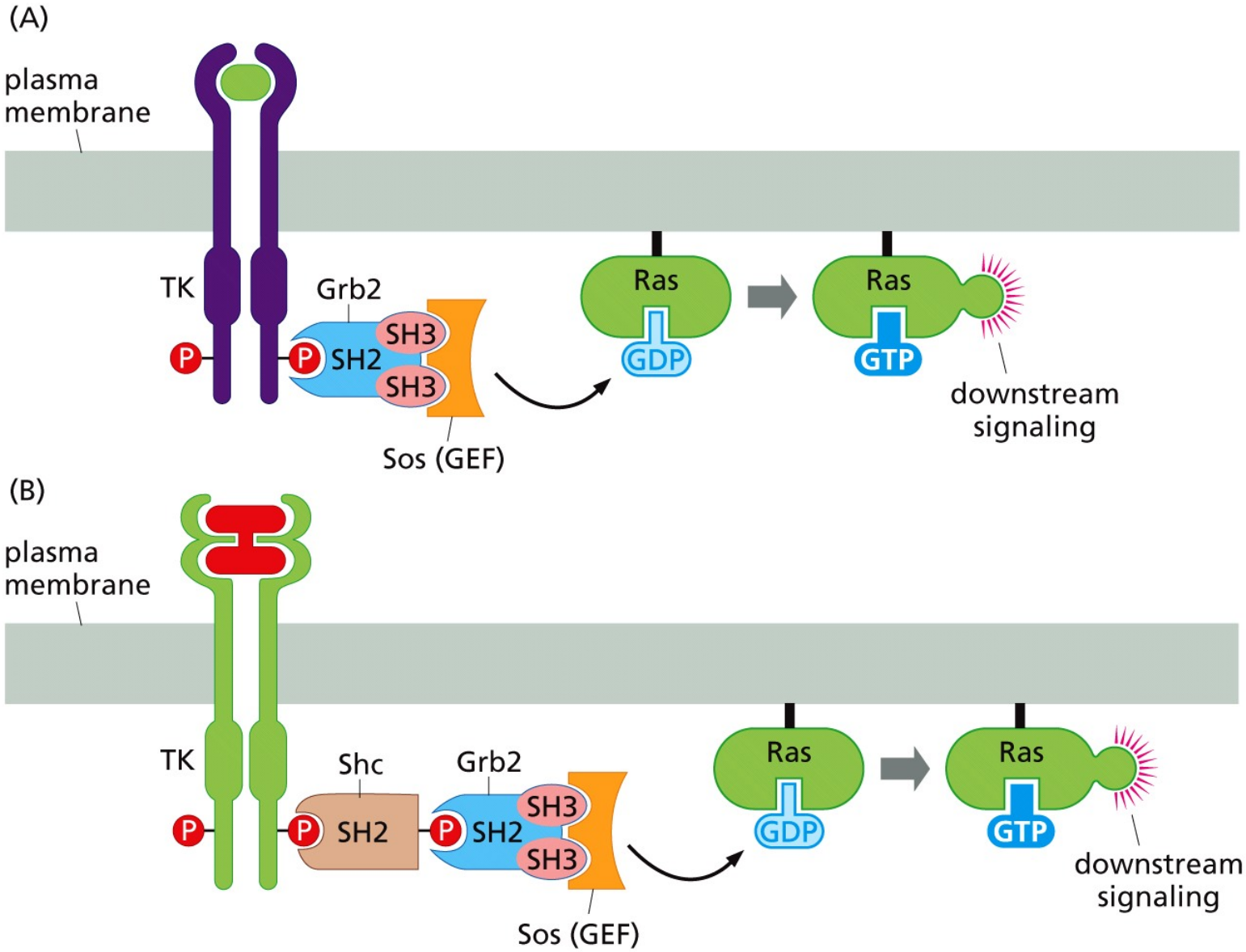


Figure 6.12 The Biology of Cancer (© Garland Science 2014)

Ras/GTP can interact with distinct downstream effectors

Exchange of GDP towards GTP results in an altered conformation of the effector loop.
Affinity for interacting proteins changes by 1000 fold!

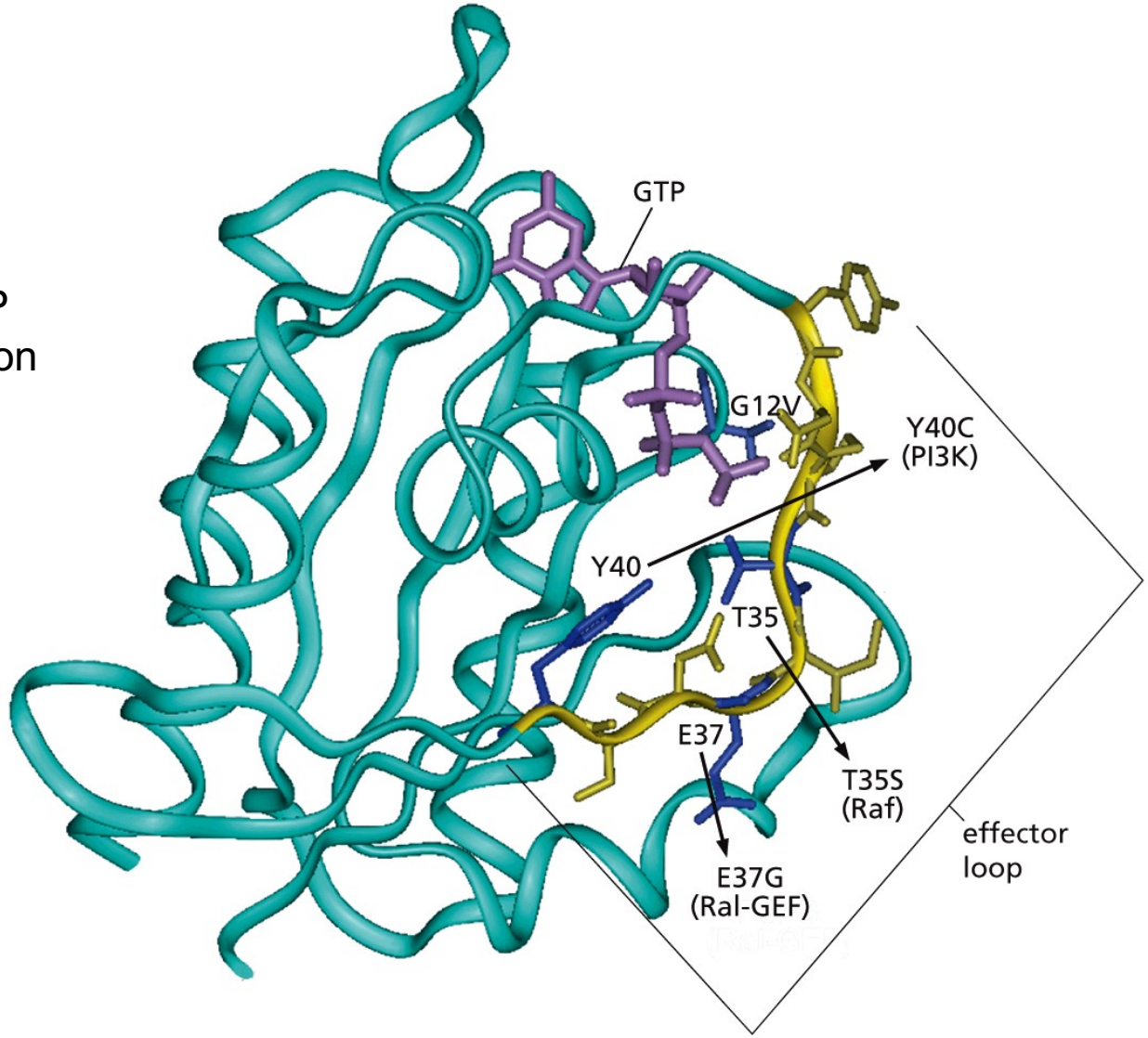


Figure 6.13 The Biology of Cancer (© Garland Science 2014)

Ras itself can activate different downstream effector pathways

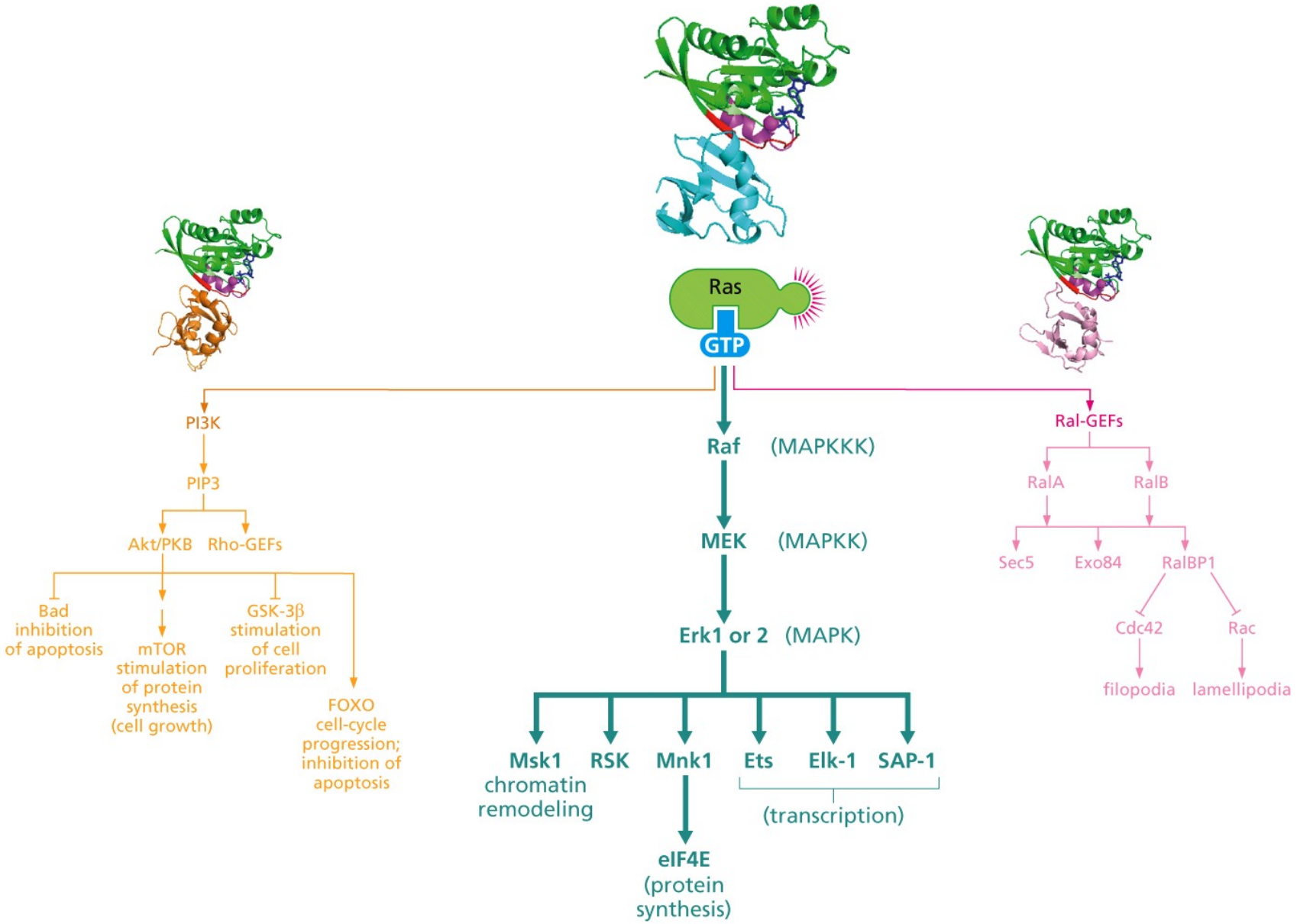


Figure 6.14 The Biology of Cancer (© Garland Science 2014)

B-Raf is mutated in 50% of melanoma patients

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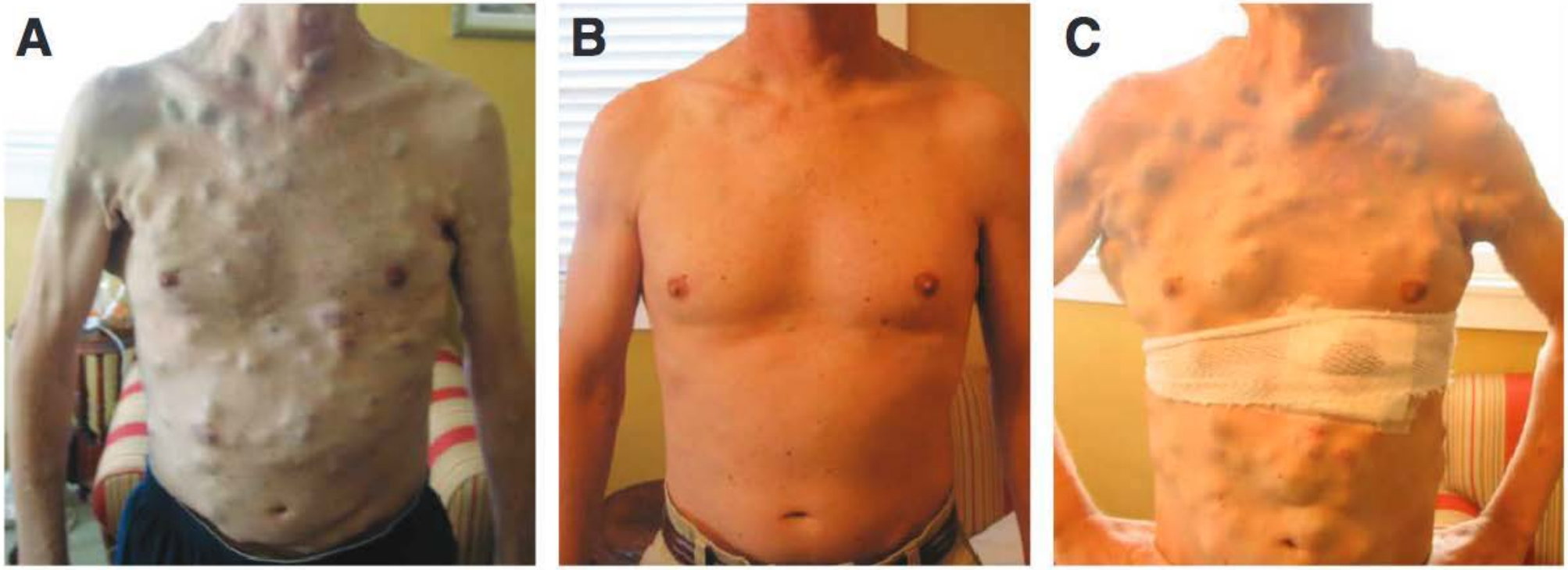
Typical mutation is V600E – this mutation renders B-Raf constitutively active
There is an inhibitor of V600E B-Raf: **Vemurafenib**
This substance has a high initial response rate, however in virtually all cases tumors develop resistencies after weeks or months



Ras itself can activate different downstream effector pathways

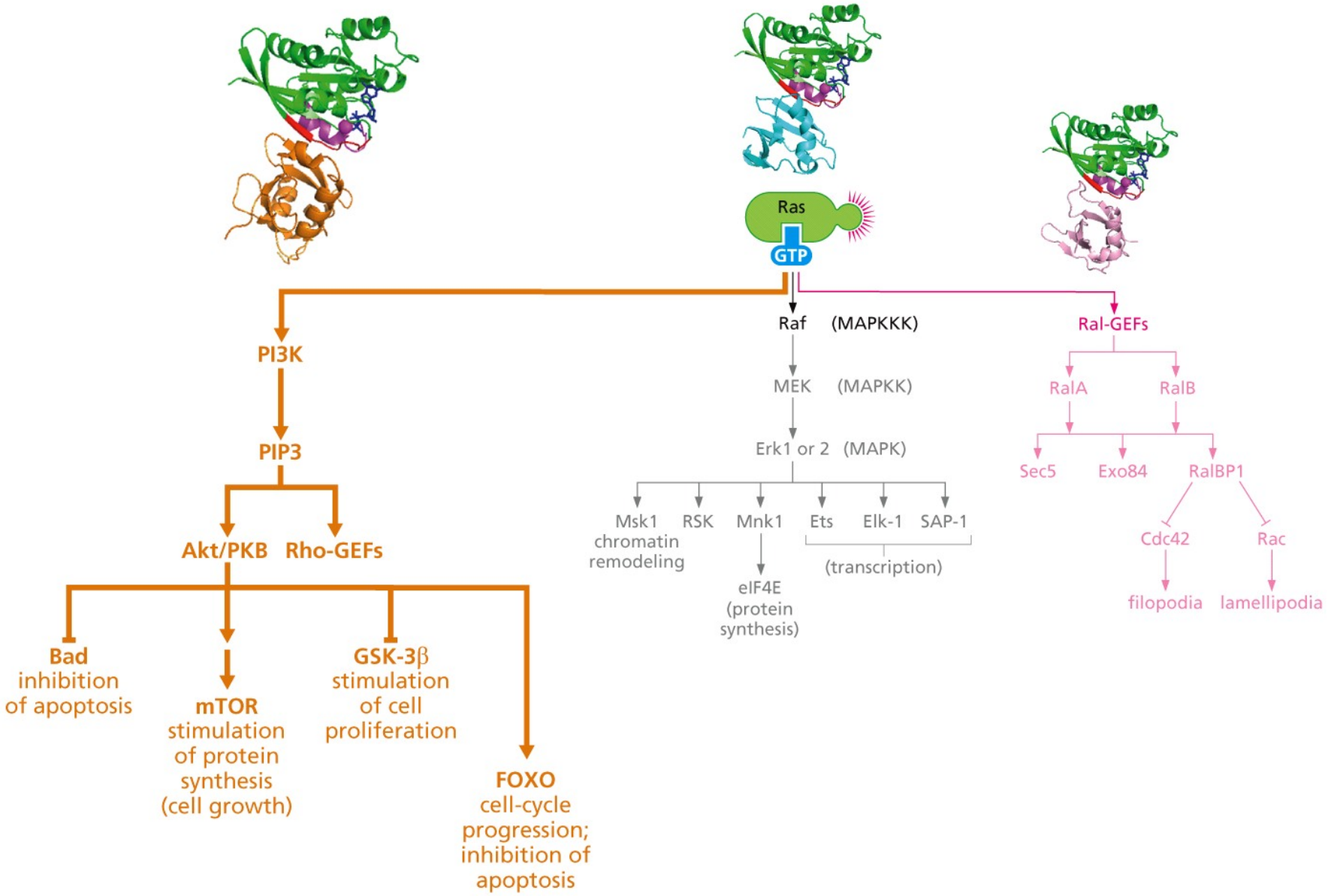


Figure 6.15 The Biology of Cancer (© Garland Science 2014)

Asymmetric distribution of phospholipids in cell membrane

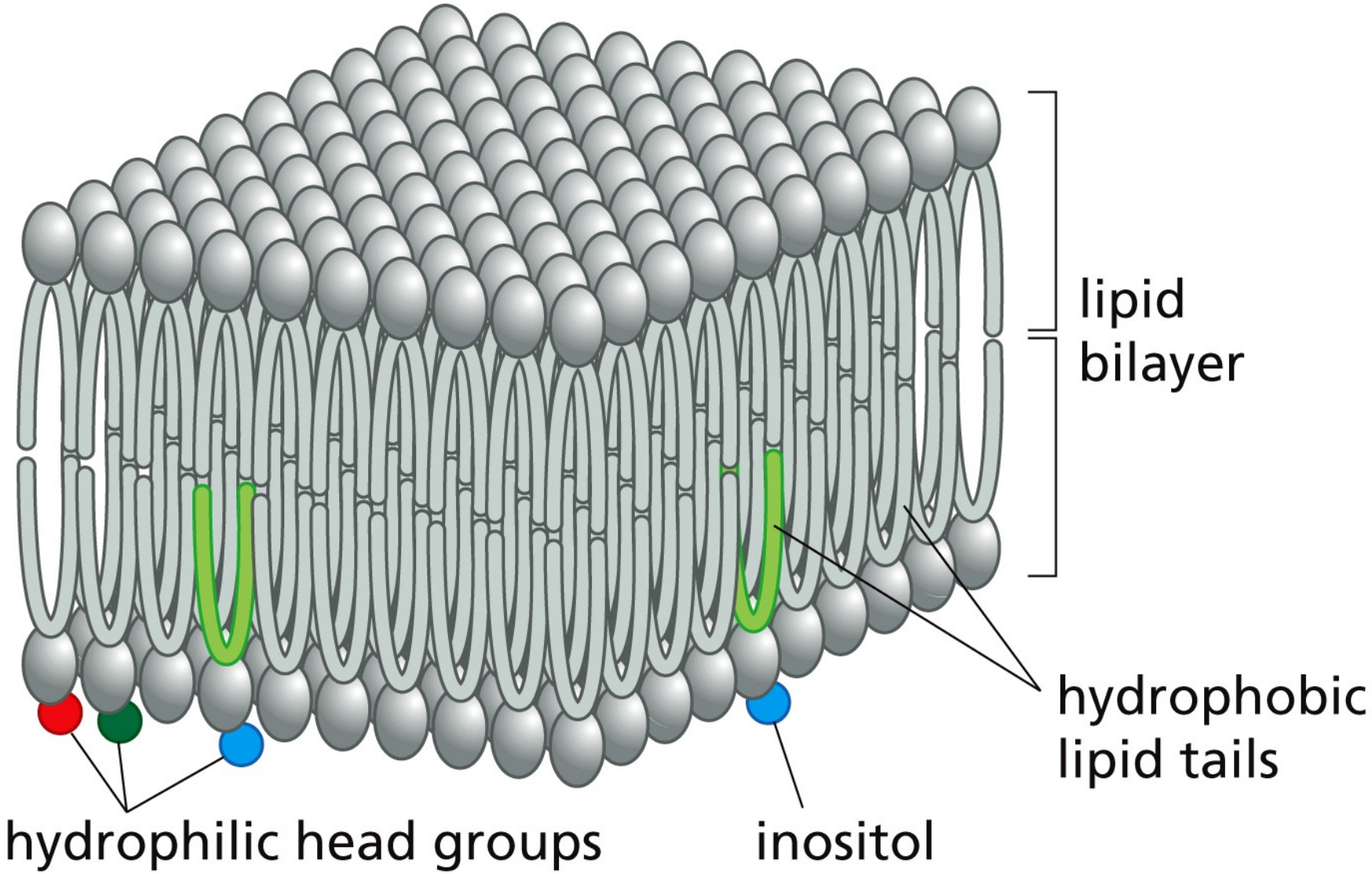


Figure 6.16a The Biology of Cancer (© Garland Science 2014)

PI3K generates a novel anchoring platform at the membrane

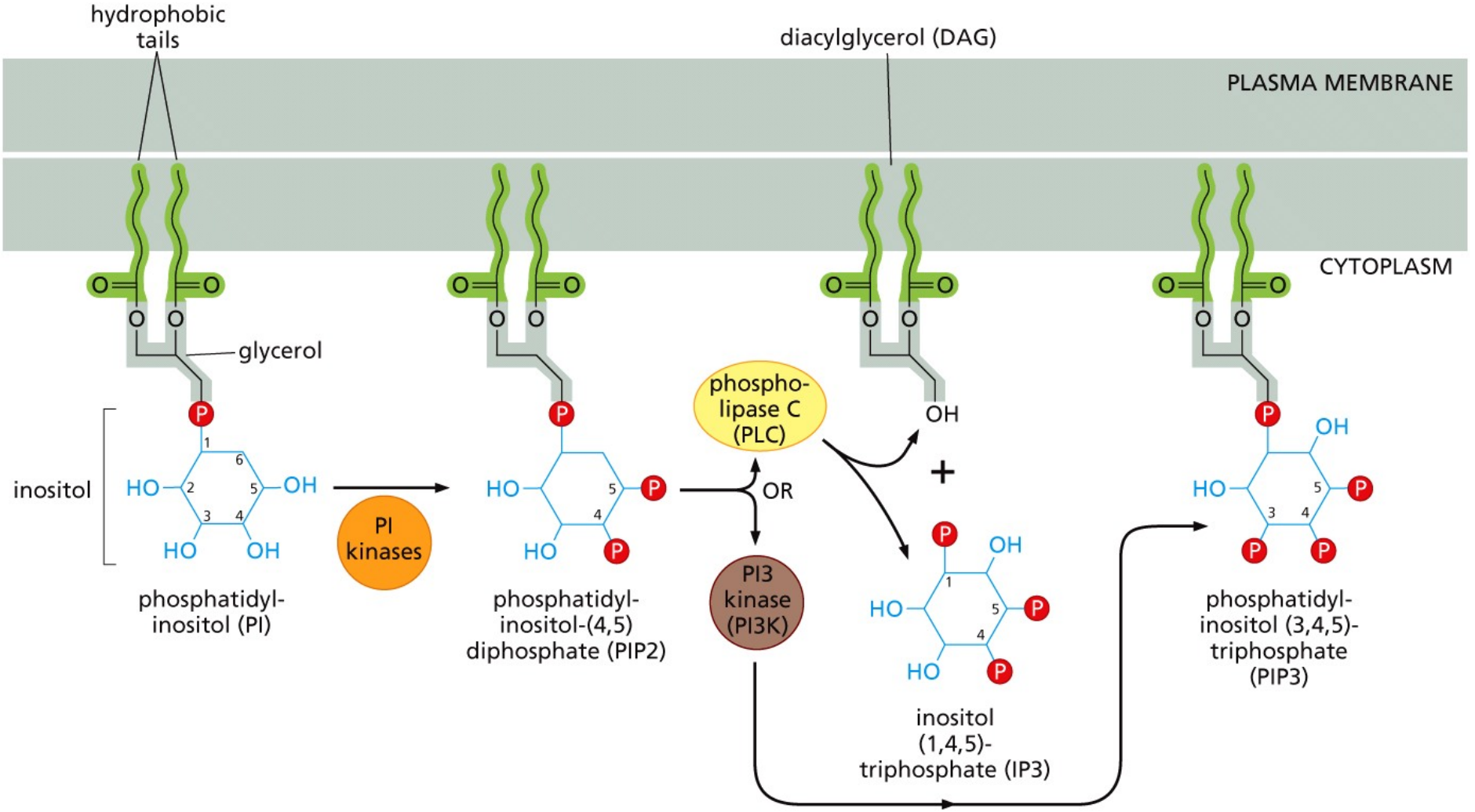


Figure 6.16b The Biology of Cancer (© Garland Science 2014)

There is a phospholipid-phosphatase counteracting PI3K PTEN – often mutated (see below)

PI3K can be directly activated by Ras

PI3K is made up of a catalytic subunit (p110) and a regulatory subunit (p85) – prototypic

Several classes, several genes

The p85 subunit has SH2 domain and can also directly get activated at RTKs
however, direct activation via RAS/GTP interaction is also possible

Phosphatidylinositoltriphosphate is recognized by proteins that contain a pleckstrin homology domain (PH domain)

The most important downstream effector is the Akt/PKB serine/threonine kinase

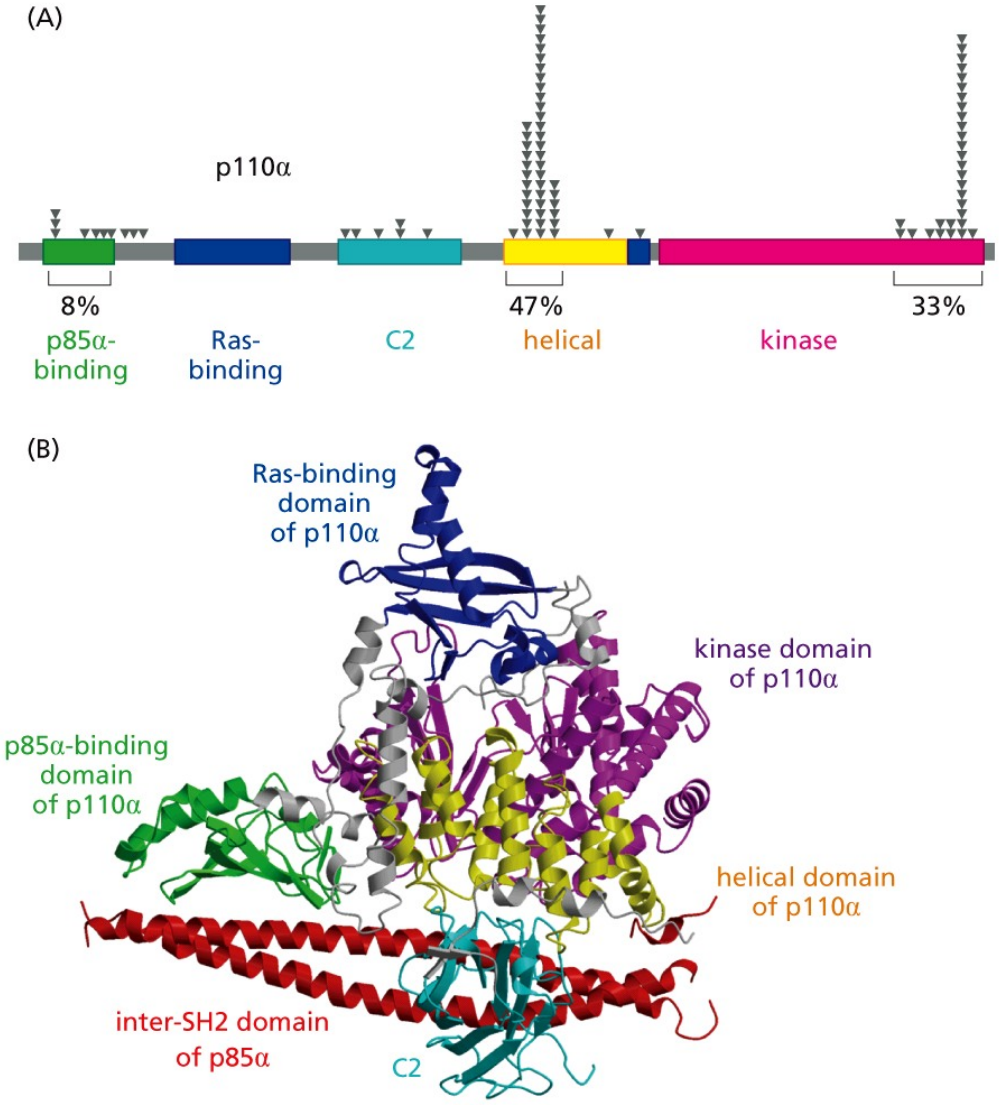


Figure 6.17 The Biology of Cancer (© Garland Science 2014)

Relocalization of PH-domain proteins to PIP3 upon RTK stimulation

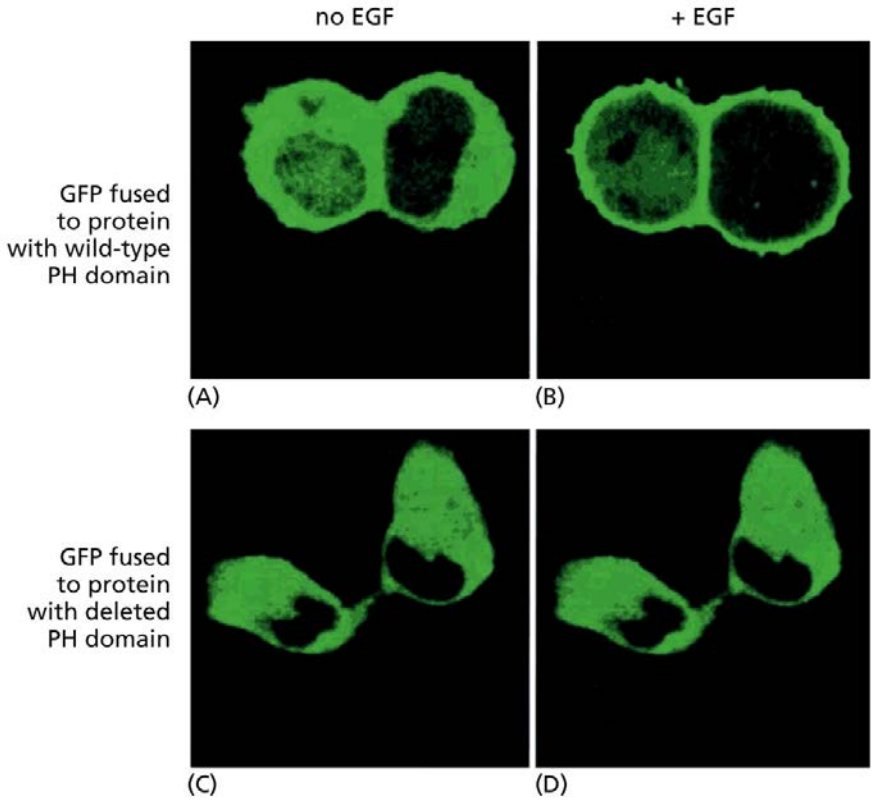


Figure 6.18 The Biology of Cancer (© Garland Science 2014)

PH domain: about 120 amino acids
About 100 PH domain proteins

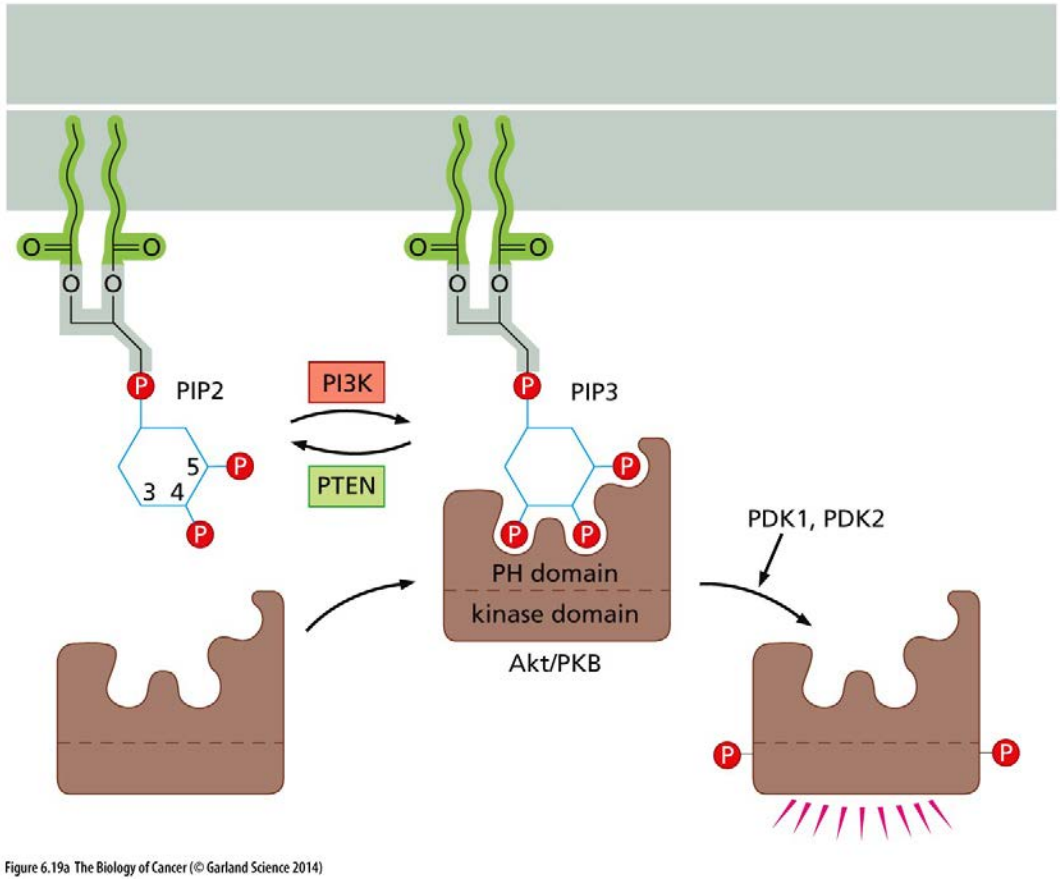


Figure 6.19a The Biology of Cancer (© Garland Science 2014)

Akt/PKB is activated by two phosphorylation events. Threonine 308 is phosphorylated by PDK1 (Phosphatidylinositol-dependent kinase), serine 473 by mTORC2 (see below)

PTEN antagonizes PI3K

PTEN is repressed/mutated in about 30 – 40% of all human tumors

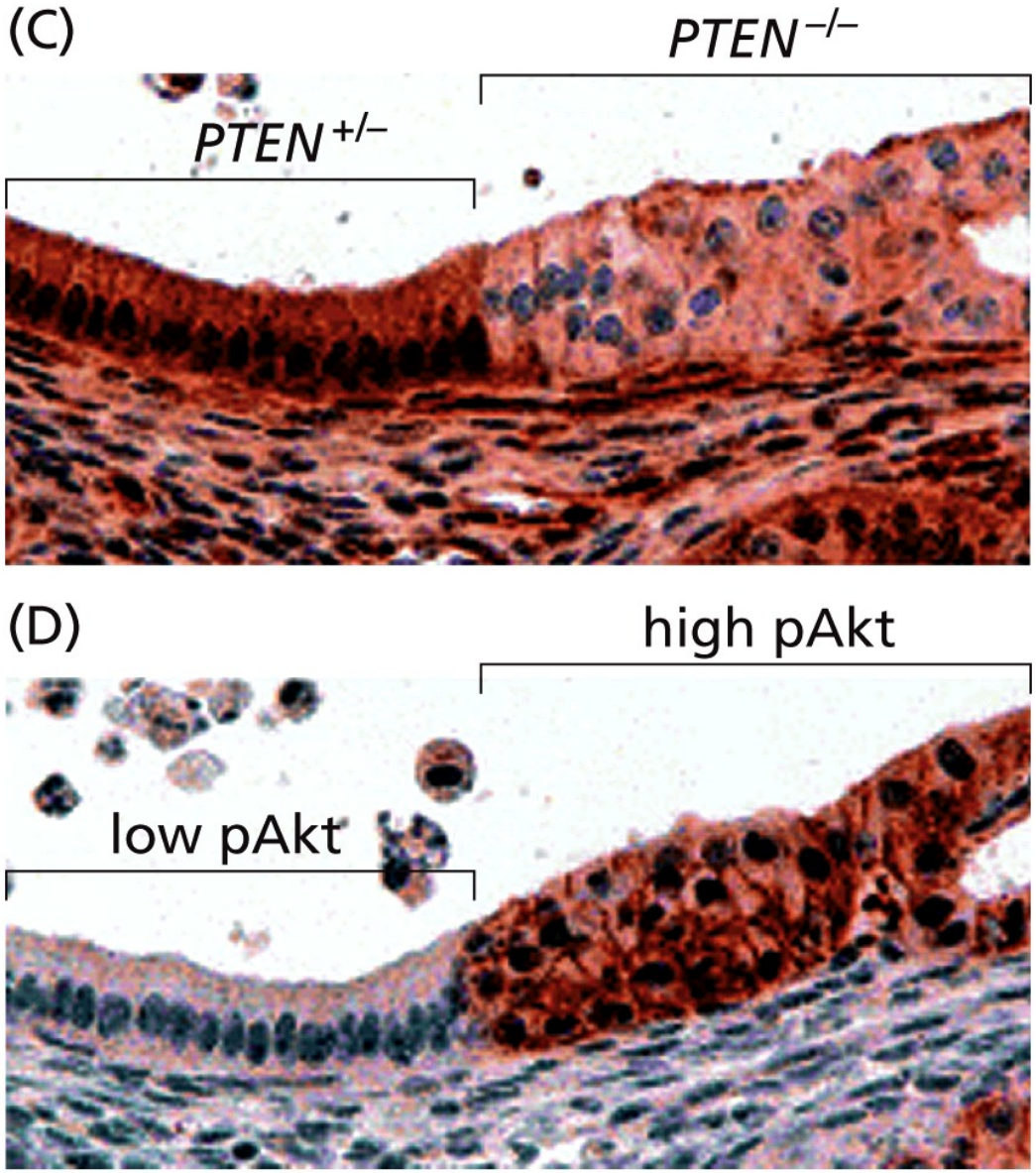


Figure 6.19cd The Biology of Cancer (© Garland Science 2014)

Physiological consequences of Akt activation

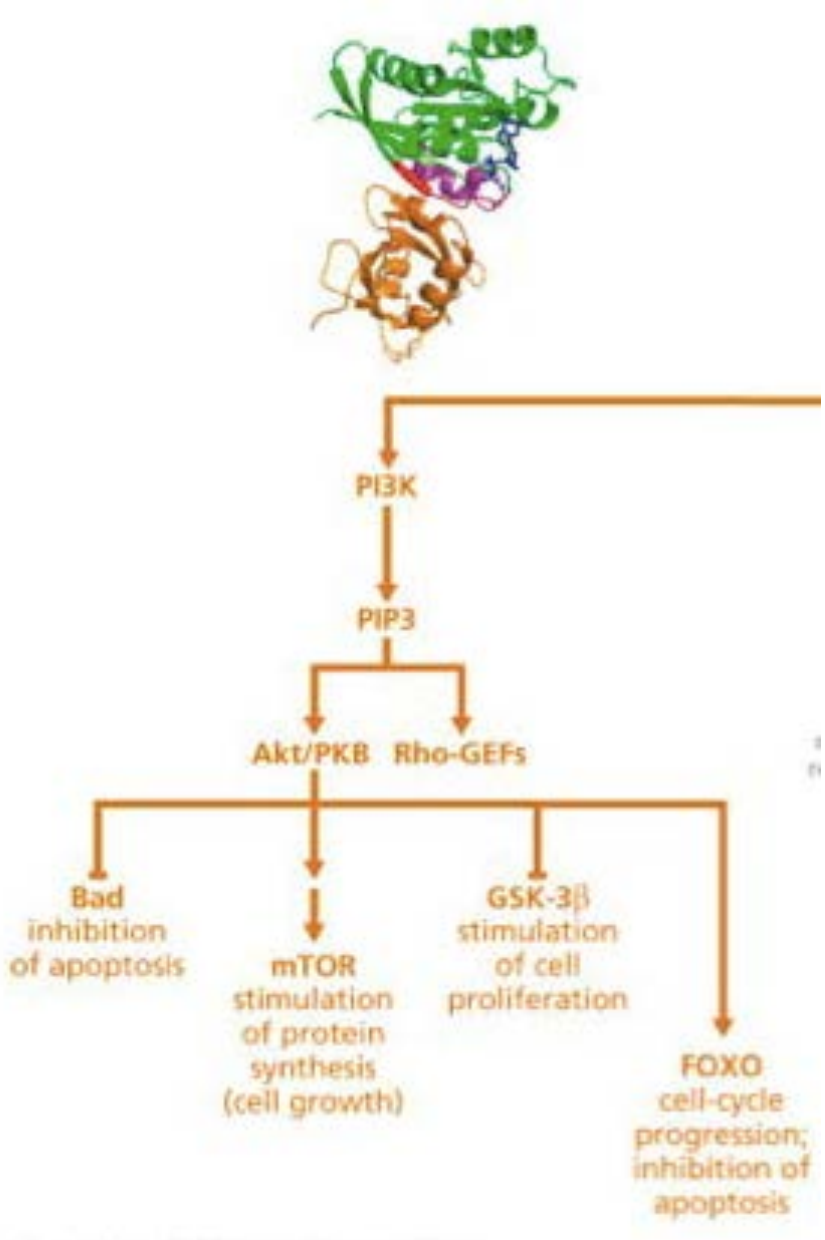


Figure 6.15 The Biology of Cancer (© Garland Science 2014)

Physiological consequences of Akt activation

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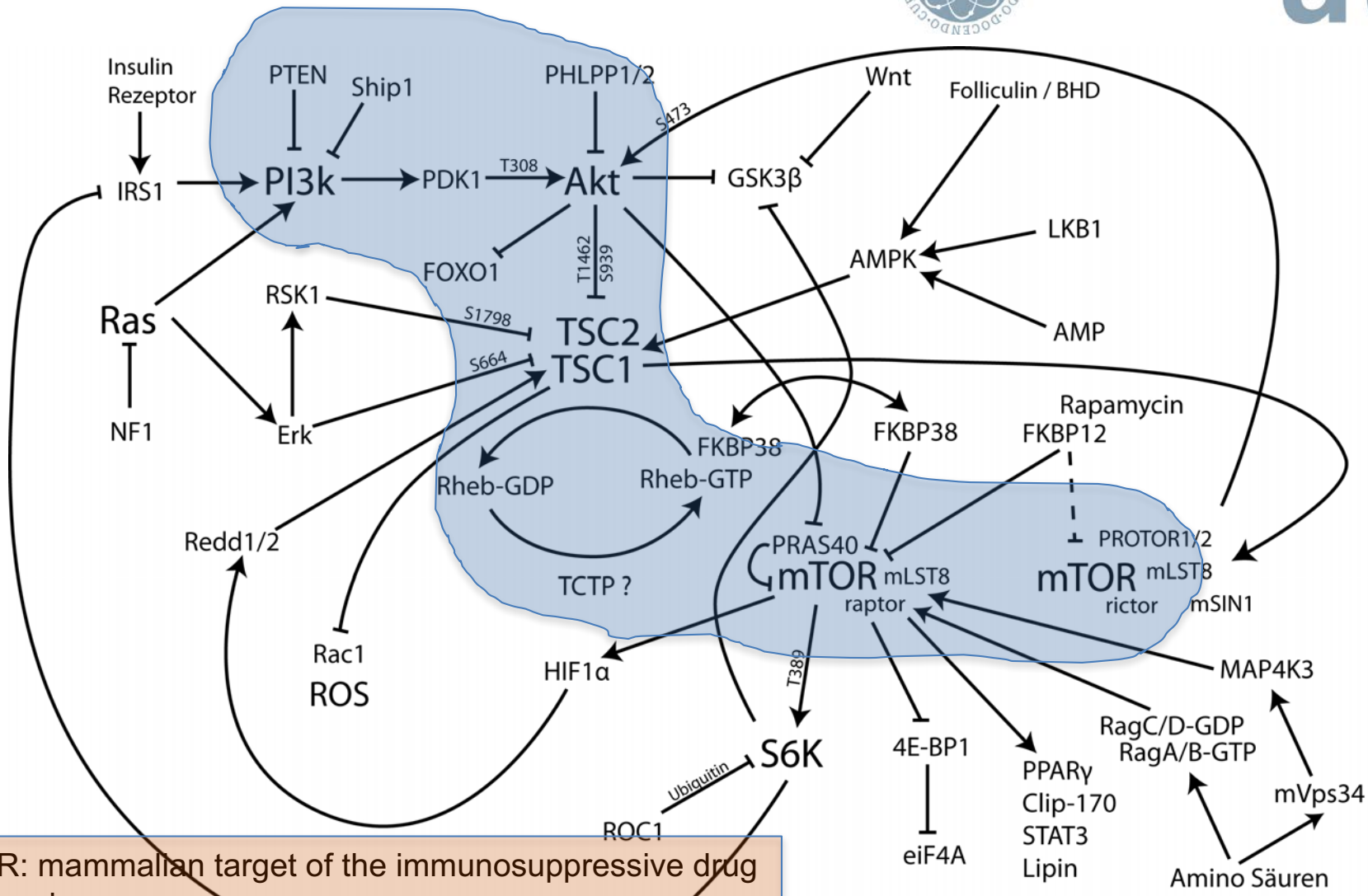
Table 6.3 Effects of Akt/PKB on survival, proliferation, and cell growth

Biological effect	Substrate of Akt/PKB	Description	Functional consequence
Anti-apoptotic			
	Bad (pro-apoptotic)	Bcl-X antagonist; like Bad, belongs to Bcl-2 protein family controlling mitochondrial membrane pores (Section 9.13).	inhibition
	caspase-9 (pro-apoptotic)	Component of the protease cascade that affects the apoptotic program (Section 9.13).	inhibition
	IκB kinase, abbreviated IKK (anti-apoptotic)	Activated by Akt/PKB phosphorylation (Section 6.12).	activation
	FOXO1 TF, formerly called FKHR TF (pro-apoptotic)	Phosphorylation prevents its nuclear translocation and activation of pro-apoptotic genes.	inhibition
	Mdm2 (anti-apoptotic)	Activated via phosphorylation by Akt/PKB; it triggers destruction of p53 (Section 9.7).	activation
Proliferative			
	GSK-3β (anti-proliferative)	Phosphorylates β-catenin, cyclin D1, and Myc (Sections 7.11, 8.3, 8.9), causing their degradation; inactivated via phosphorylation by Akt/PKB.	inhibition
	FOXO4, formerly called AFX (anti-proliferative)	Induces expression of the CDK inhibitor $p27^{Kip1}$ (Section 8.4) gene and some pro-apoptotic genes; exported from the nucleus when phosphorylated by Akt/PKB.	inhibition
	$p21^{Cip1}$ (anti-proliferative)	CDK inhibitor, like $p27^{Kip1}$ (Section 8.4). Exits the nucleus upon phosphorylation by Akt/PKB; in the cytoplasm, phosphorylated $p21^{Cip1}$ inhibits caspases, thereby acquiring anti-apoptotic functions (Section 9.13).	inhibition
Growth			
	Tsc2 (anti-growth)	Phosphorylation by Akt/PKB causes Tsc1/Tsc2 complex to dissociate, allowing activation of mTOR, which then up-regulates protein synthesis (Section 16.15).	inhibition

Table 6.3 The Biology of Cancer (© Garland Science 2014)

Akt/PKB activates mTOR complexes



Transkription
Metabolismus
Autophagie
Ribosom Biogenese

Wikipedia

mTOR: mammalian target of the immunosuppressive drug rapamycin
two complxes in the cell that contain the mTOR protein
mTORC1: contains Raptor (regulatory associated protein of mTOR) – the main effector
mTORC2: contains Rictor (rapamycin-insensitive companion of mTOR) – phosphorylates Ser473 of Akt/PKB

Physiological consequences of Akt activation

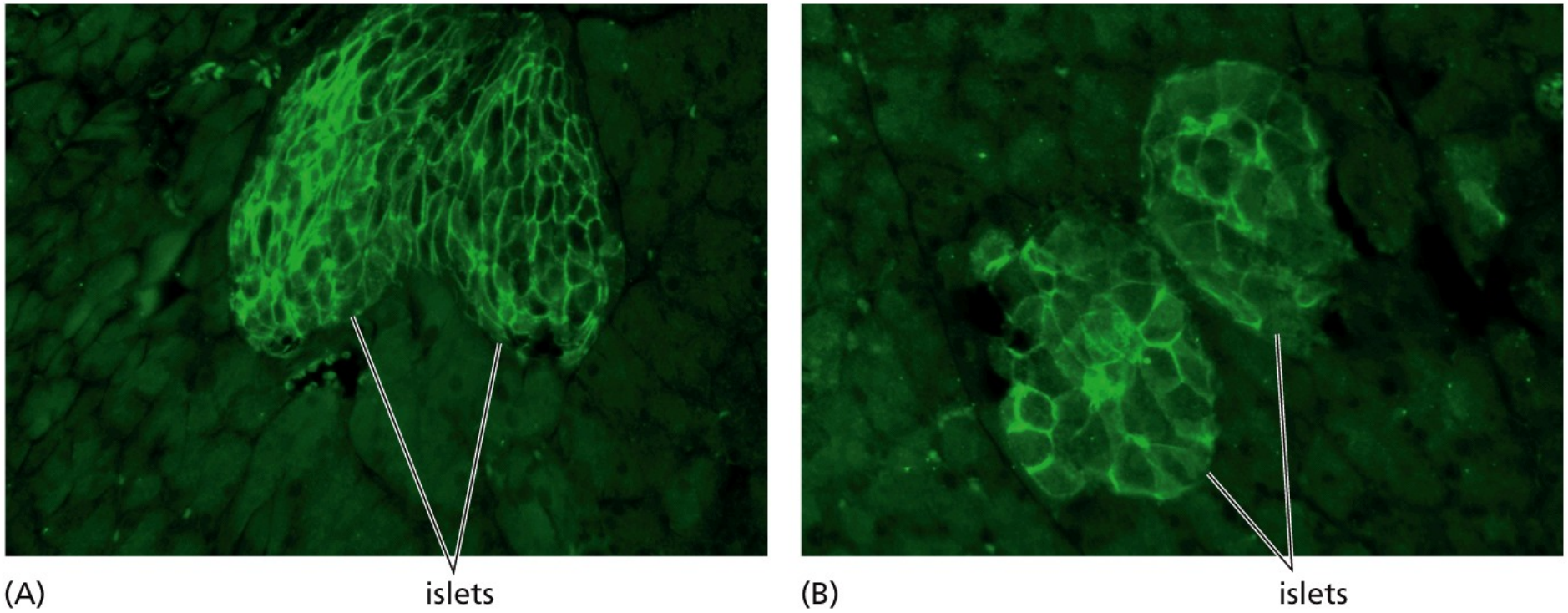


Figure 6.20 The Biology of Cancer (© Garland Science 2014)

Increased cell size (beta cells in endocrine pancreas) as a consequence of expression of active Akt/PKB

PI3K activation in human tumors

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Table 6.4 Alteration of the PI3K pathway in human tumors[a]

Cancer type	*Akt/PKB hyperactive*	*PIKC3A hyperactive*[b]	*p85α*[c]	*PTEN*-mutant or repressed[d]
Glioblastoma		6–27%	8%	20%
Ovarian carcinoma	~2%	4–12%	4%	8%
Endometrial carcinoma		22%		42–54%
Hepatocellular carcinoma		6–36%		5%
Melanoma	~80%	~9%		40–50%
Lung carcinoma		3–4%		9%
Renal cell carcinoma		3%		4%
Thyroid carcinoma		5%		5%
Lymphoid		3%		8%
Prostate carcinoma		2%		10%
Colon carcinoma	~6%	14–32%	2–8%	13–54%
Breast carcinoma	~8%	18–40%	2%	20–33%
Bladder		23%		8%
Pancreatic		25%	17%	
Gastric		8%		

[a]The percentages in this table are approximate, since the proportion of tumors bearing the indicated alteration increases progressively as tumor progression proceeds, often dramatically, and because many reports do not distinguish between inactivation by mutation and inactivation by promoter methylation.
[b]*PIKC3A* appears to be the only gene of the 16 members of the PI3K-encoding gene family to undergo somatic mutation during tumor development. These mutations affect the p110 catalytic subunit of PI3 kinase; frequently occurring amplifications of this gene are not registered in this table.
[c]*PI3KR1* mutations affect the regulatory subunit of PI3K kinase and are most commonly observed in human cancers; alterations of the four other members of this family of PI3K regulatory subunits are not registered here. Alterations of the encoded p85α subunit cited here were few in number and the indicated percentages are likely to change dramatically as more data are collected.
[d]*PTEN* nonsense mutations and deletions are registered here and, in many cases, the even more frequent shutdown of expression through promoter methylation or the actions of microRNAs . (Promoter methylation often results in shutdown of transcription of a gene; see Section 7.8.)

From www.sanger.ac.uk/perl/genetics/CGP/cosmic; T.L. Yuan and L.C. Cantley, *Oncogene* 27:5497–5510; B.S. Jaiswal et al., *Cancer Cell* 16:463–474, 2009; D.W. Parsons et al., *Science* 321:1807–1812, 2008; and Y. Samuels and K. Ericson, *Curr. Opin. Oncol.* 18:77–82, 2006.

Table 6.4 The Biology of Cancer (© Garland Science 2014)

Ras/GTP can also activate Ral-GEFs

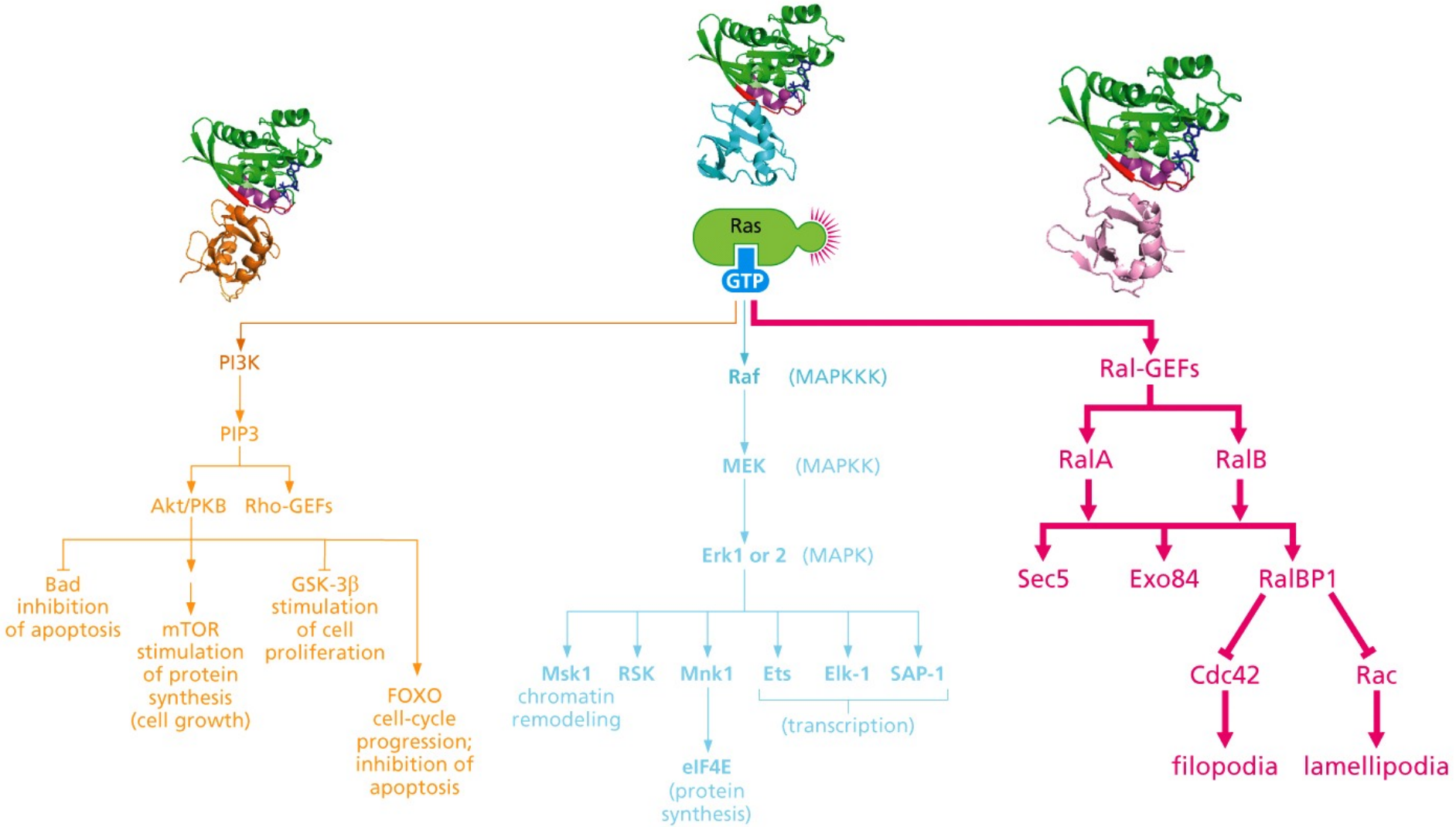
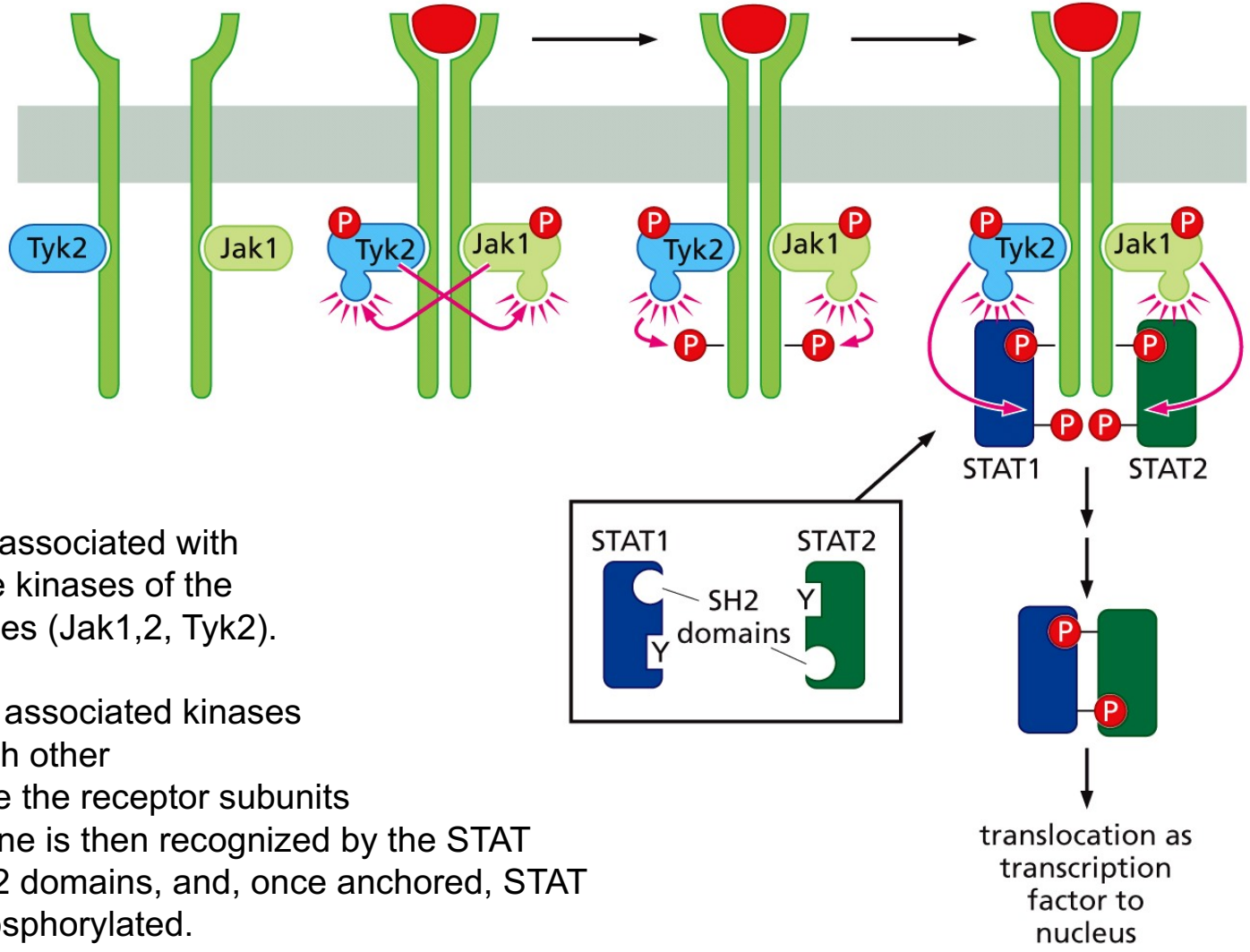


Figure 6.21 The Biology of Cancer (© Garland Science 2014)

This pathway is not completely understood, seems to play a role in exocytosis, autophagy, migration and metastasis

Signal transduction of cytokine receptors



These receptors are associated with non-receptor tyrosine kinases of the family of Janus kinases (Jak1,2, Tyk2).

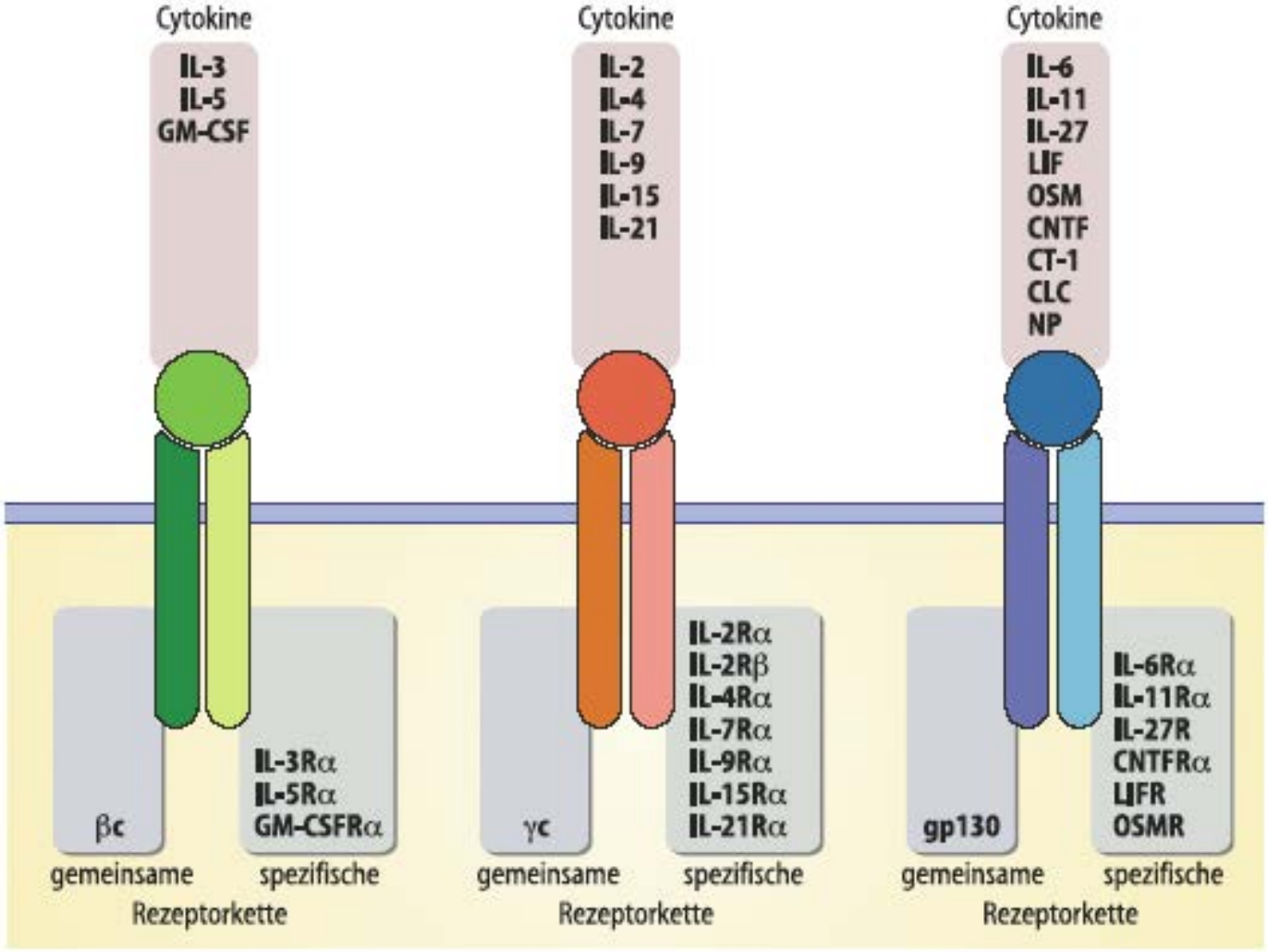
Upon ligand binding, associated kinases
1. phosphorylate each other
2. then phosphorylate the receptor subunits
3. this phosphotyrosine is then recognized by the STAT proteins via their SH2 domains, and, once anchored, STAT proteins are also phosphorylated.

Figure 6.22 The Biology of Cancer (© Garland Science 2014)

This induces dimerization (SH2) and nuclear translocation

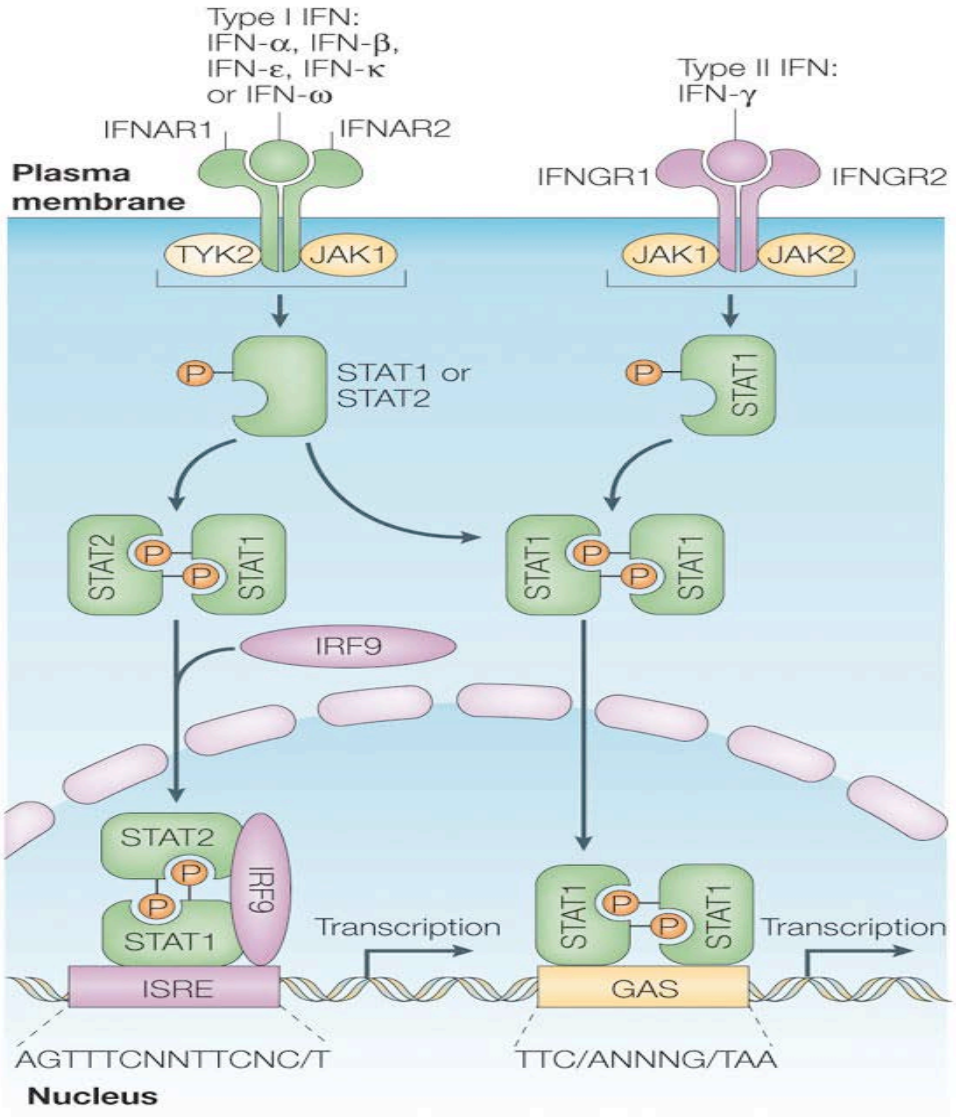
STAT: signal transducer and activator of transcription
7 STAT family members (STAT1-STAT7), STAT3 and STAT5 most relevant to cancer

Signal transduction of cytokine receptors



Cytokine receptors often share common receptor chains critical for signaling

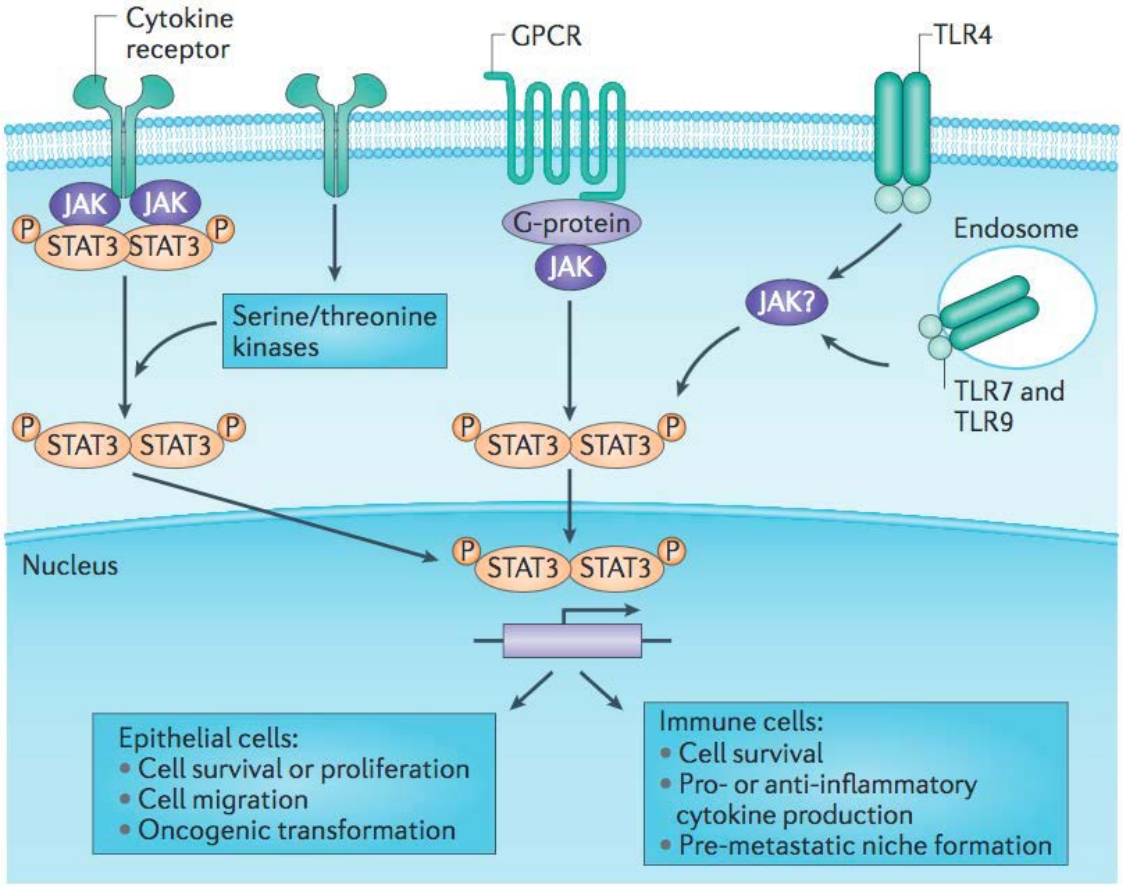
Signal transduction of cytokine receptors



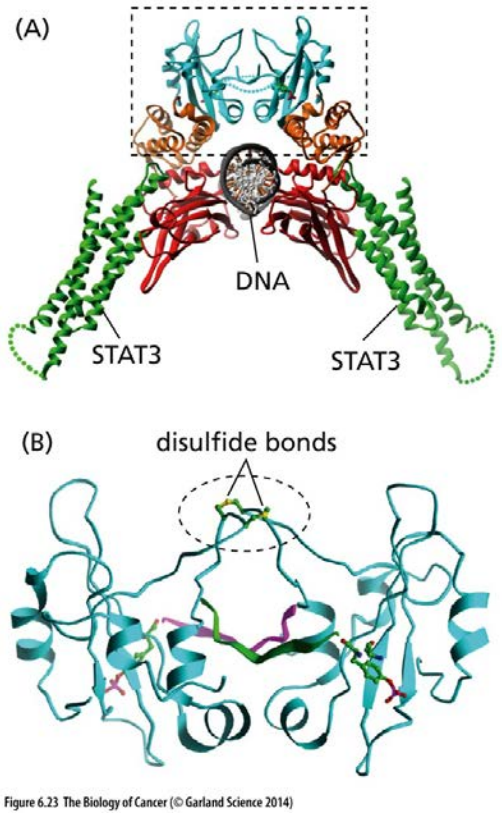
Type I Interferons: IFNα (hematopoietic cells) and IFNβ (most cell types)
Heterodimeric receptor (IFNAR1 and IFNAR2).
Activate STAT1 and STAT2 via JAK1/TYK2.
Typ II Interferons (IFNγ e.g. T-lymphocytes).
Heterodimeric/Heterotetrameric (IFNGR1/2 bzw. a/b).
Activates STAT1-dimer via JAK1/JAK2

STAT: signal transducer and activator of transcription
7 STAT family members (STAT1-STAT7), STAT3 and STAT5 most relevant to cancer

Active STAT3 is oncogenic



Yu et al., Nat.Rev.Cancer 2014



Activated STAT3 has been found in a variety of cancer entities
Deleting/repressing STAT3 was shown to interfere with tumorigenesis in various mouse models (including pancreatic adenocarcinoma)
Specifically in inflammation associated tumorigenesis, STAT3 plays an important role (activated by IL6 secreted from tumor infiltrating macrophages)
A constitutively active STAT3 (dimerization via disulfide bond) is oncogenic in immortilized cells
STAT3 target genes include: Myc, Bcl2, $BclX_l$, Survivin, Mcl1, ZEB1, Twist, SOX2, Nanog, Hif1α, VEGF

G-protein coupled receptor (GPCR) signaling in cancer

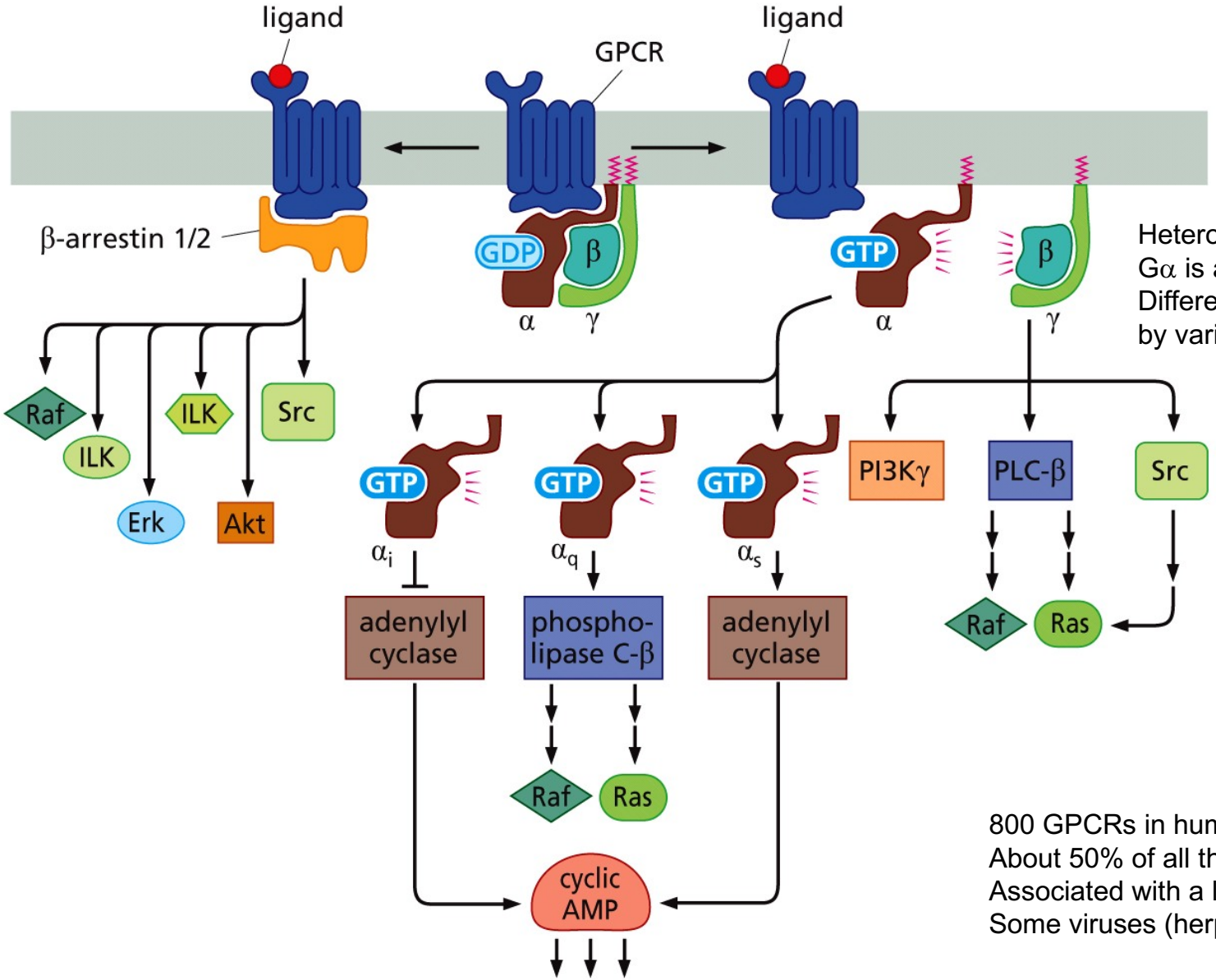
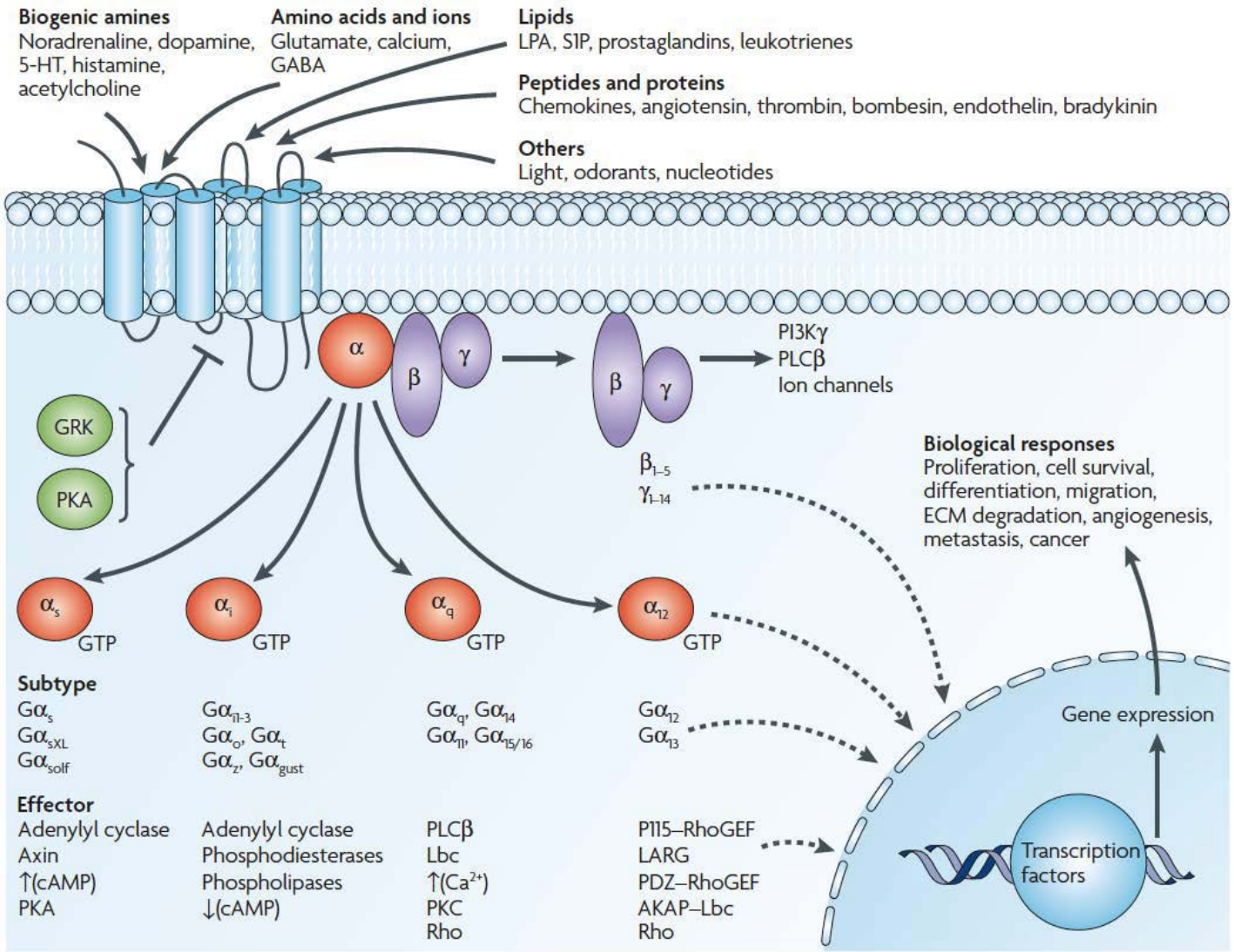


Figure 6.28 The Biology of Cancer (© Garland Science 2014)

Heterotrimeric G-protein,
Gα is active when GTP-bound
Different pathways activated
by various Gα subunits and Gβγ

800 GPCRs in human genome
About 50% of all therpeutics today target GPCRs
Associated with a large number of tumor entities
Some viruses (herpesviruses) encode viral GPCRs

G-protein coupled receptor (GPCR) signaling in cancer



800 GPCRs in human genome
About 50% of all therapeutics today target GPCRs
Associated with a large number of tumor entities

Dorsam and Gutkind, Nat.Rev.Cancer 2007

Canonical Wnt signaling also results in activation of a cytoplasmic transcriptional regulator (β-catenin)

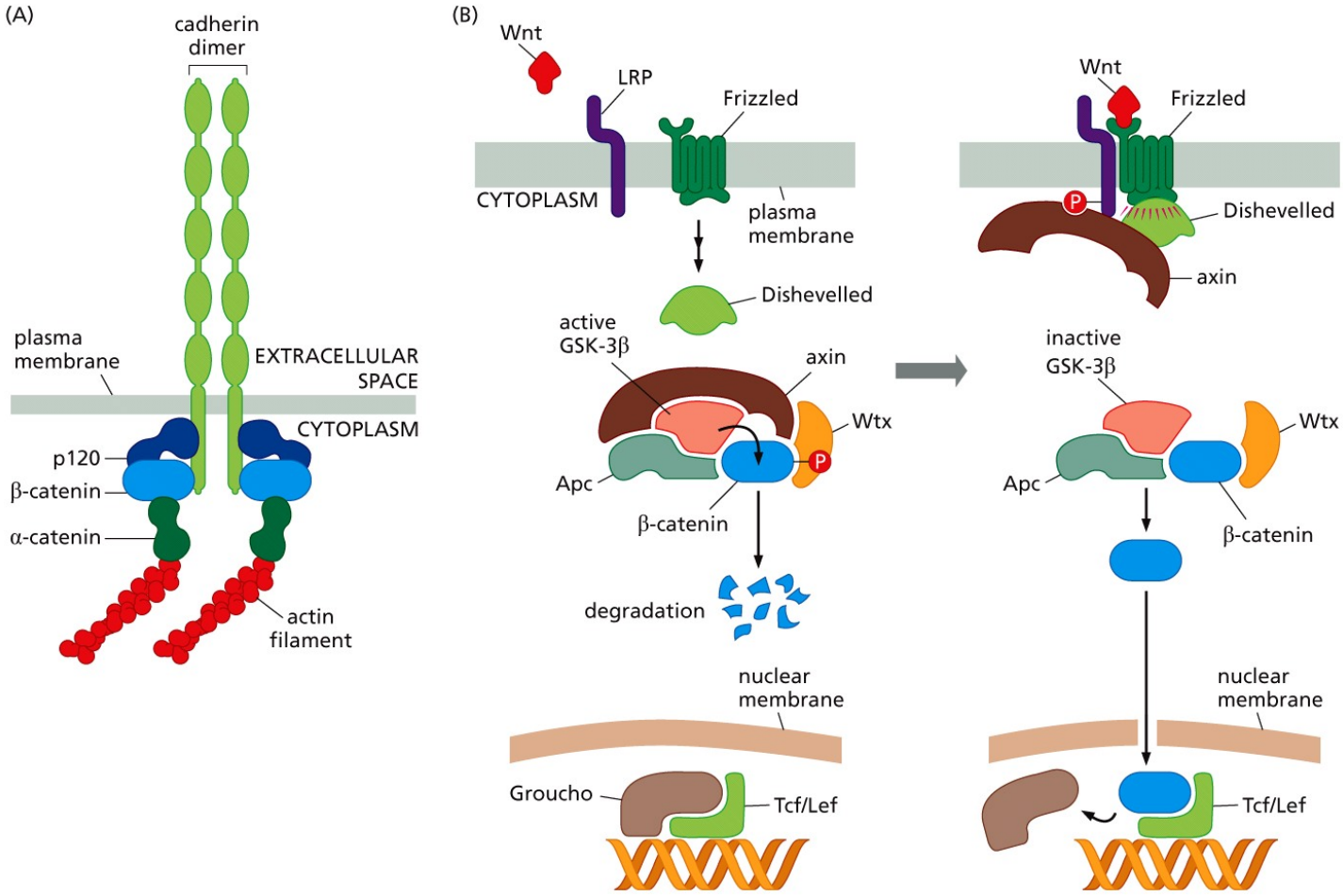
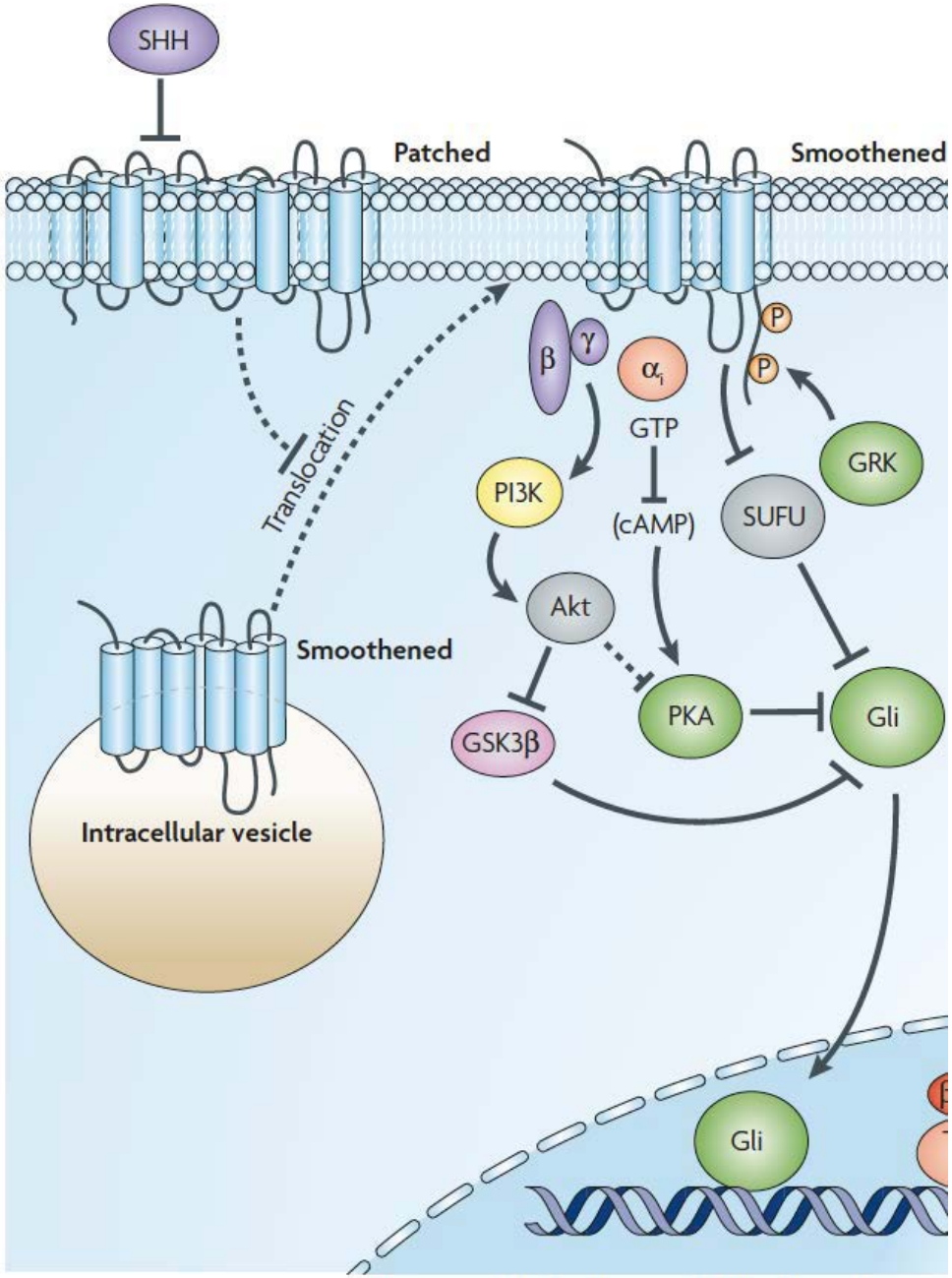


Figure 6.26 The Biology of Cancer (© Garland Science 2014)

19 Wnt proteins (especially Wnt1, Wnt2, Wnt5a and Wnt7a associated with cancer)
10 Frizzled receptors
Non-canonical Wnt-signaling involves heterotrimeric G-protein

Hedgehog signaling



3 members of the hedgehog ligand family **sonic hedgehog (SHH)**, indian hedgehog (IHH), and dessert hedgehog (DHH)

In unstimulated cells, the membrane protein **Patched** represses accumulation of **Smoothened**, a member of the GPCR family.
Upon binding of **Hedgehog** to **Patched**, the inhibitory effect is released and **Smoothened** can relieve the transcription factor **Gli** (Gli1) from continuous degradation, resulting in **Gli** accumulation, nuclear transport and activation of transcription.

Target genes have pro-proliferative, anti-apoptotic etc effects

This signaling cascade plays a role in a number of tumor entities including basal cell carcinoma of the skin,medulloblastomas, meningiomas .....

The NF-κB system

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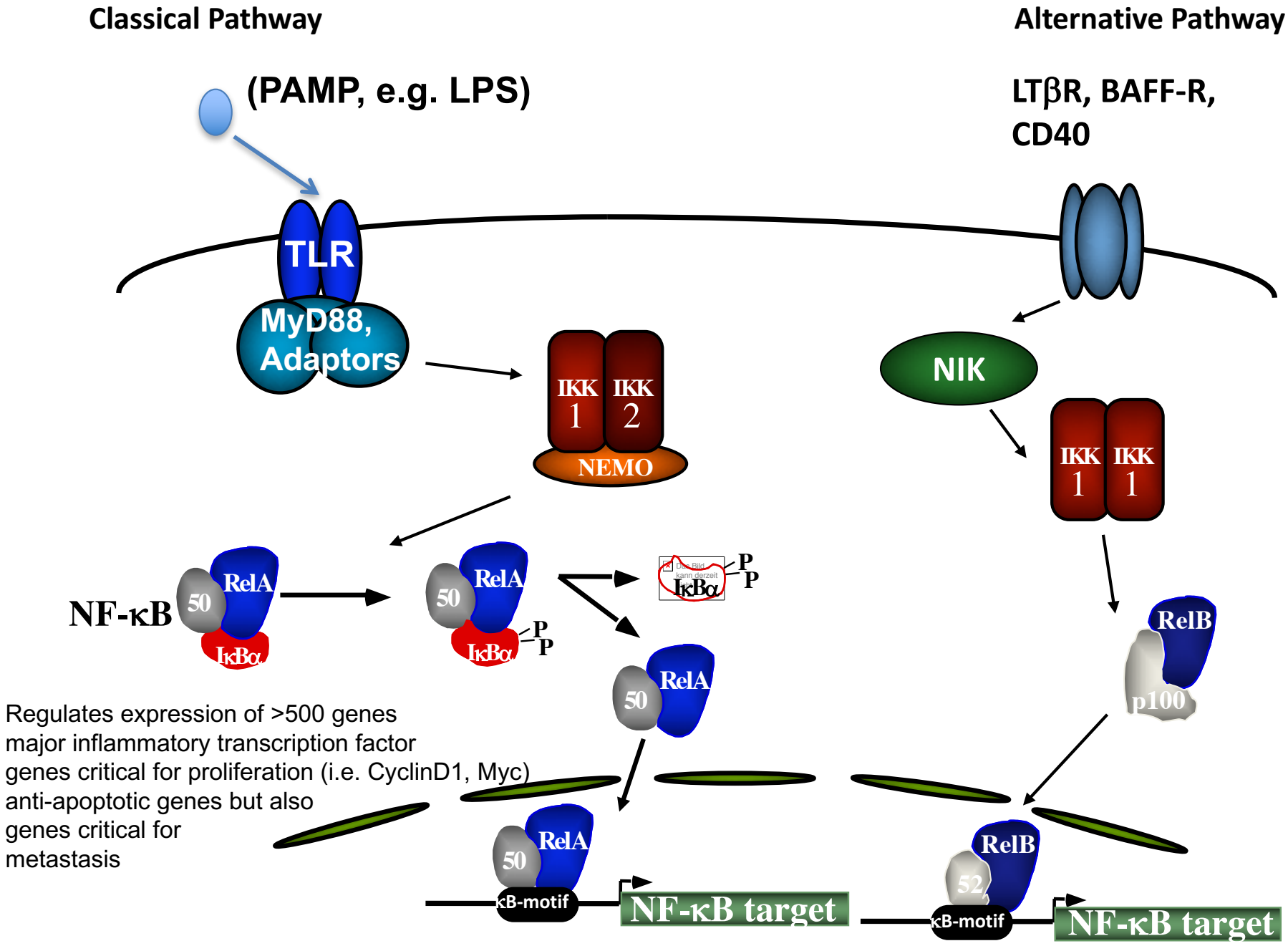
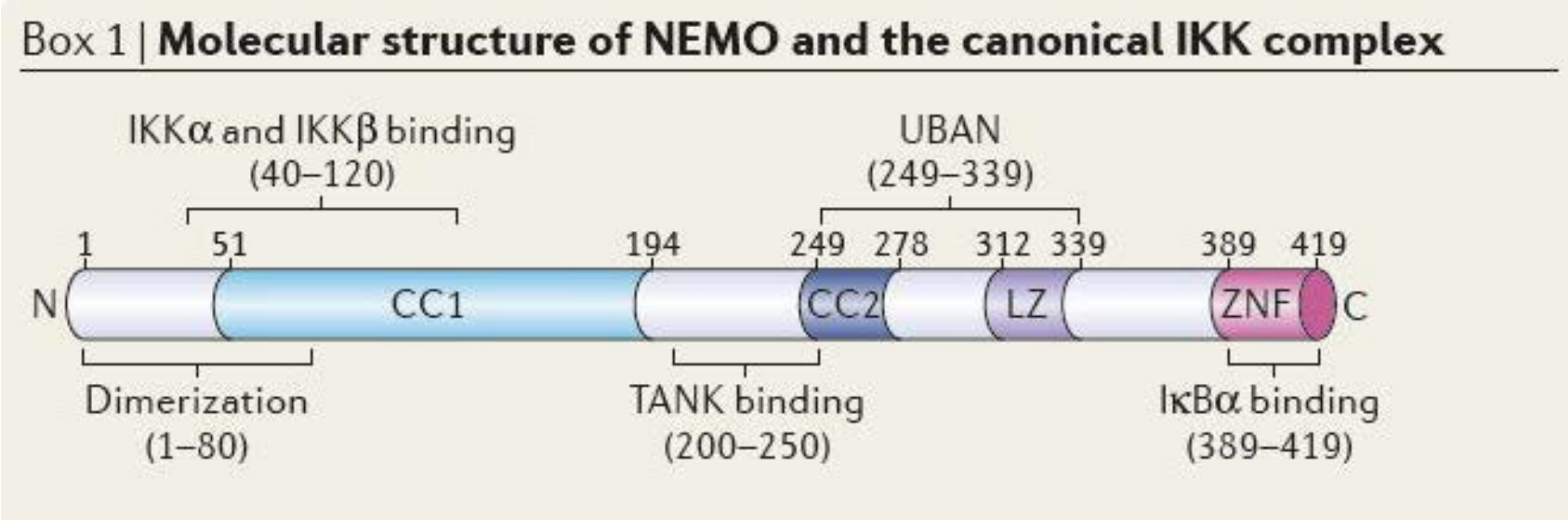


The protein NF-κB essential modulator (NEMO/IKKγ) is critical for NF-κB activation



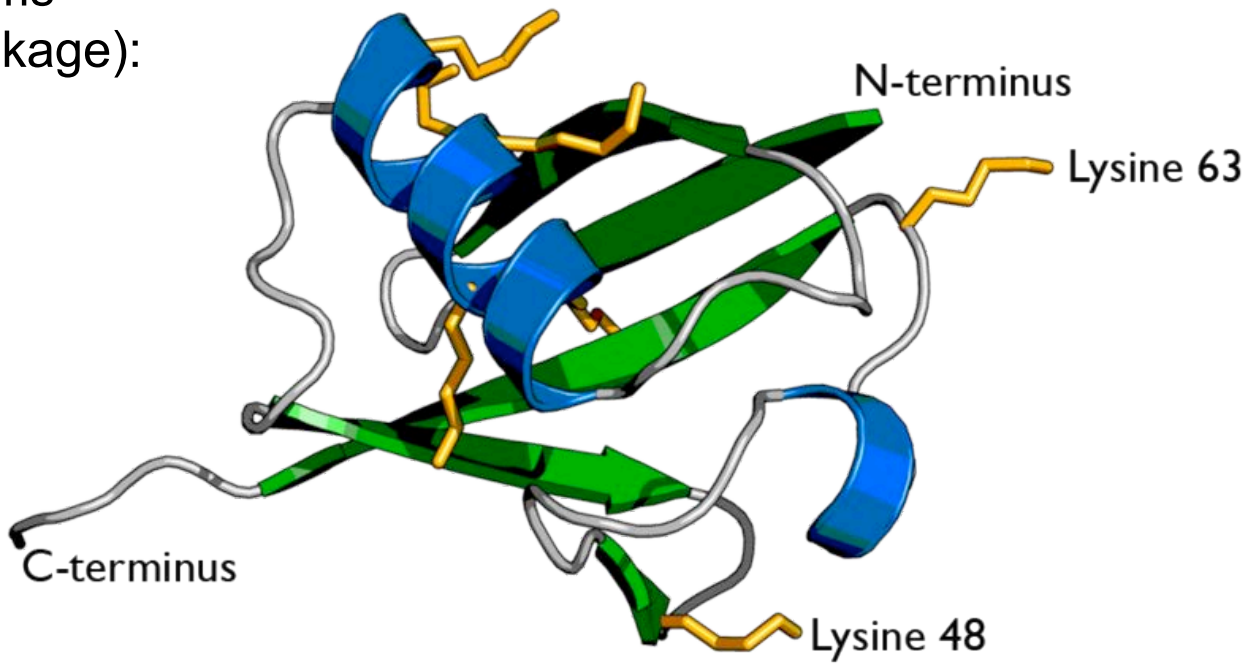
The N-terminal domain is needed for dimerization and binding to the IKKα/β proteins

A Zinc-finger domain in the C-terminus mediates substrate interaction (IκBα)

UBAN represents a ubiquitin binding domain with preference for binding of linear ubiquitin chains

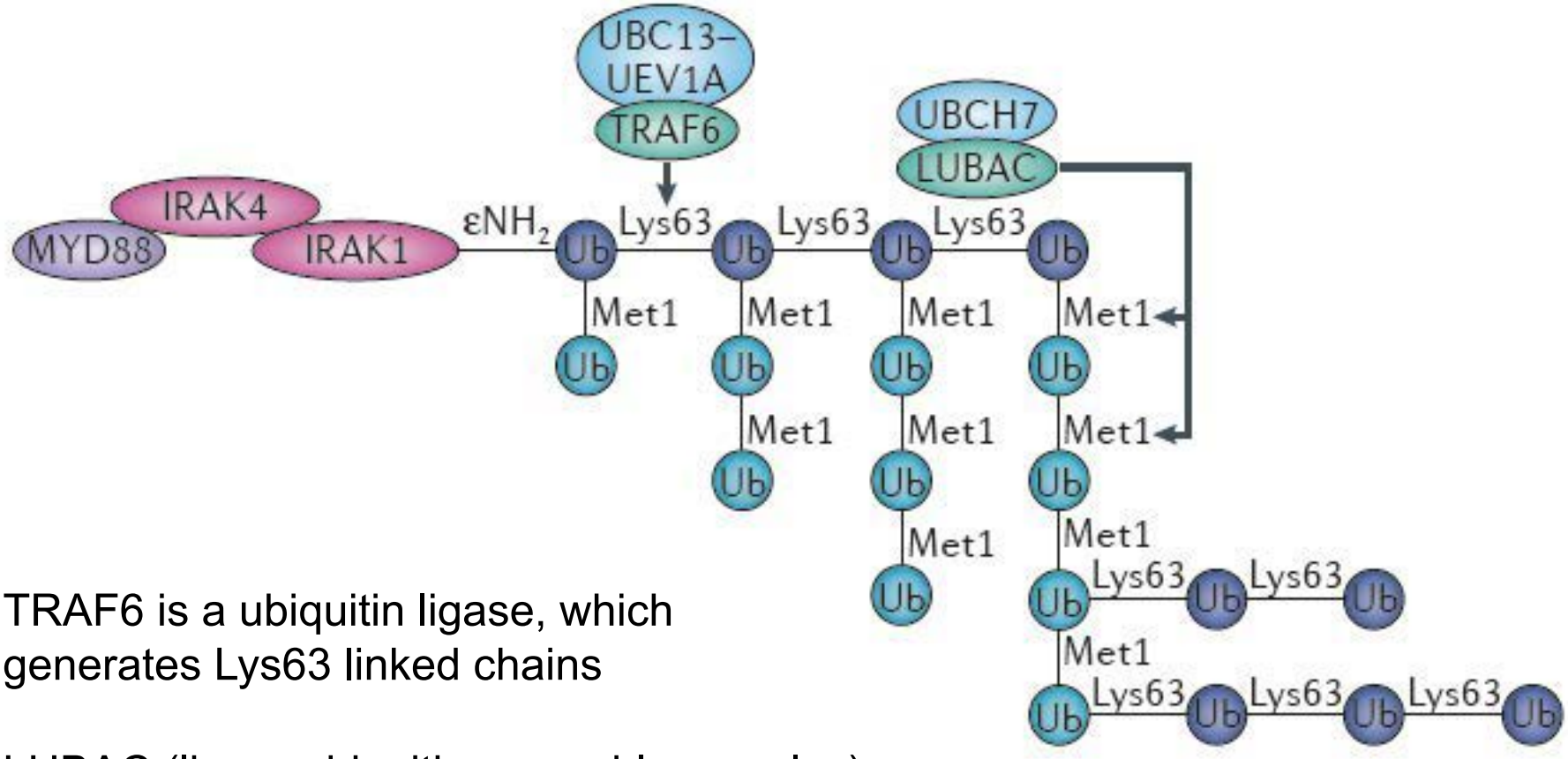
Ubiquitin

- ubiquitously present in virtually all tissues of eucaryotes, 76 aa/8.5 kD
- can be linked to lysine residues of target proteins by ubiquitin ligases „ubiquitinases“
- removal of ubiquitin by „deubiquitinases“ (DUBs)
- polyubiquitination by adding more ubiquitin moieties using lysine residues in ubiquitin
- K48 linkage: degradation
- K63 linkage: signaling platforms
- linear ubiquitination (Met-1 linkage): signaling platforms



Wikipedia

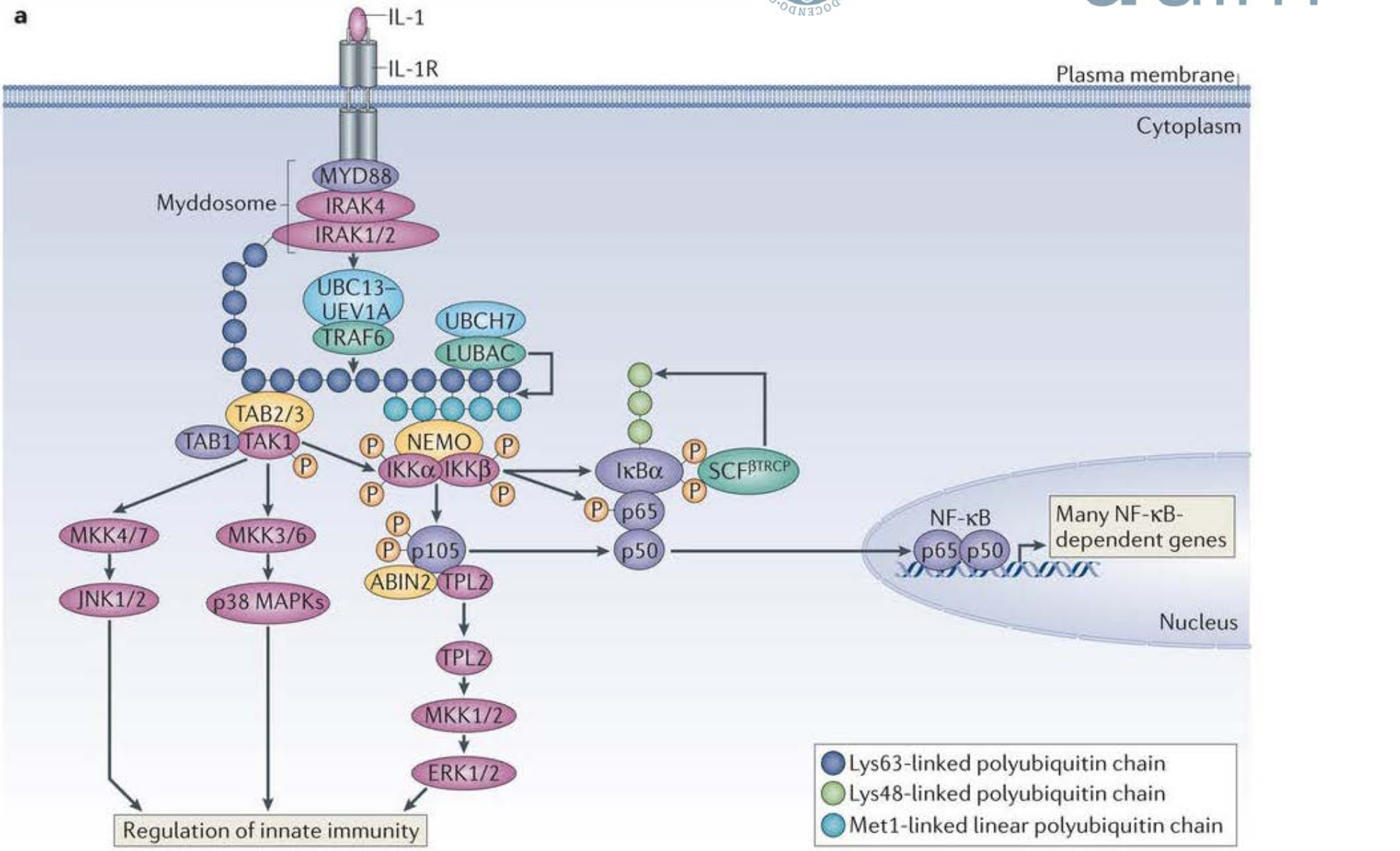
A ubiquitin platform is generated at the TLR



TRAF6 is a ubiquitin ligase, which generates Lys63 linked chains

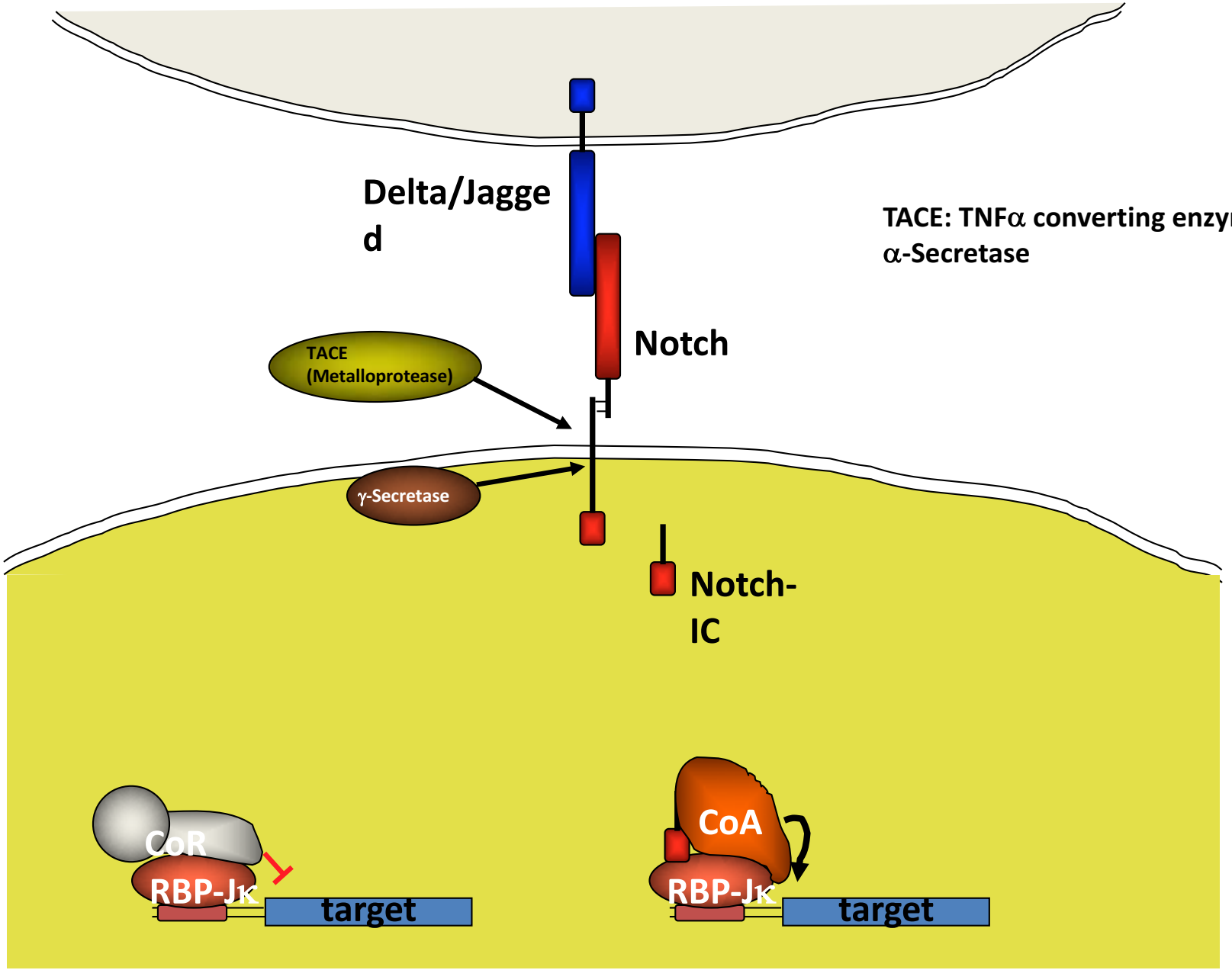
LUBAC (linear ubiquitin assembly complex)
consists of three proteins (HOIL1, HOIP, SHARPIN) that generate linear ubiquitin chains
- Met1 of new ubiquitin is linked to the C-terminal end of a ubiquitin protein

NF-κB activation



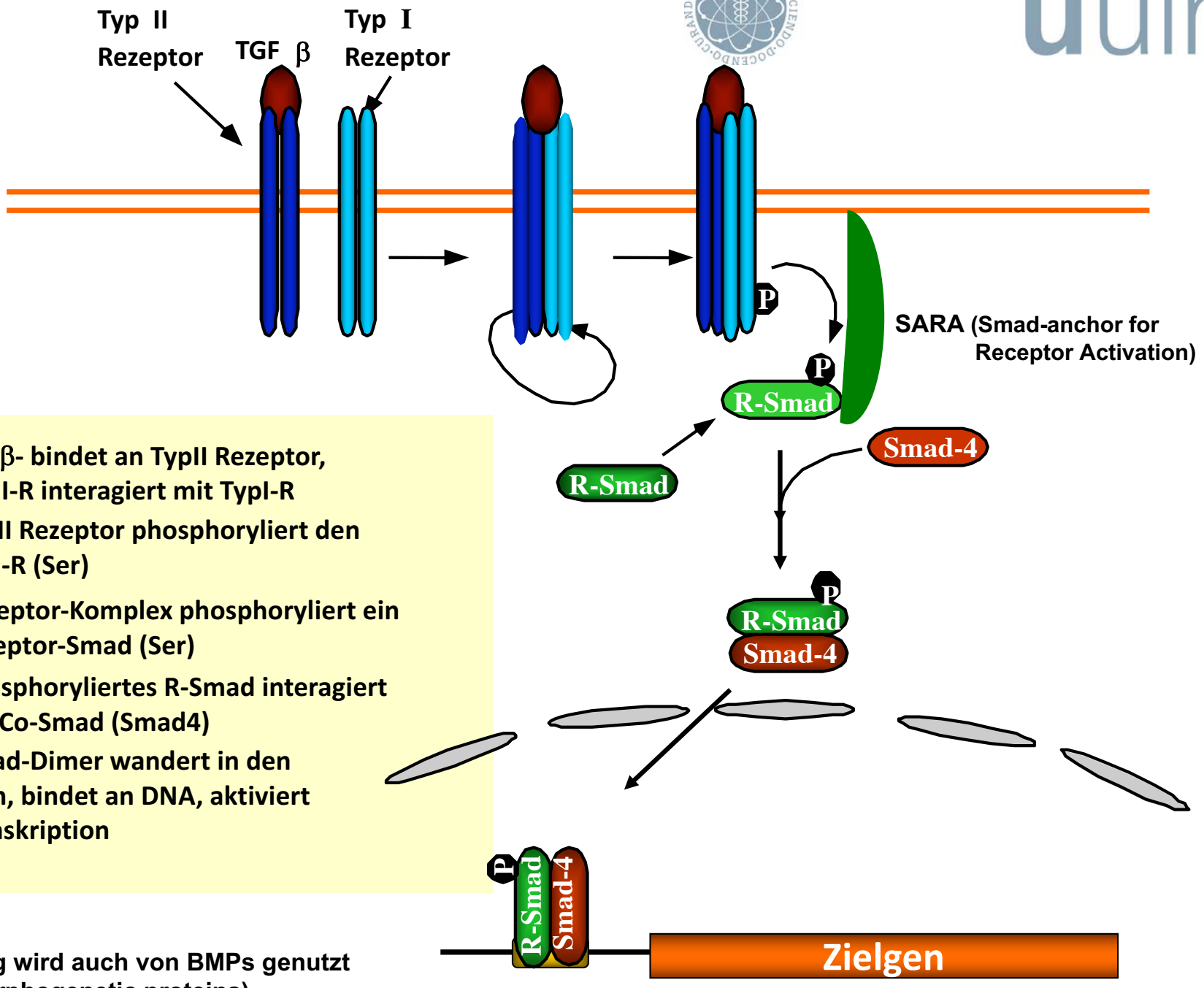
Clark et al. (2013), Nature Rev. Mol Cell Biol

Activation of Notch pathway



TACE: TNFα converting enzyme.
α-Secretase

Activation of TGFβ pathway



1. TGFβ- bindet an TypII Rezeptor, TypII-R interagiert mit TypI-R
2. TypII Rezeptor phosphoryliert den TypI-R (Ser)
3. Rezeptor-Komplex phosphoryliert ein Rezeptor-Smad (Ser)
4. Phosphoryliertes R-Smad interagiert mit Co-Smad (Smad4)
5. Smad-Dimer wandert in den Kern, bindet an DNA, aktiviert Transkription

Signalweg wird auch von BMPs genutzt (bone morphogenetic proteins)