Oncology for Scientists
RPN 530
Fall 2016

Growth Factors/Signal Transduction

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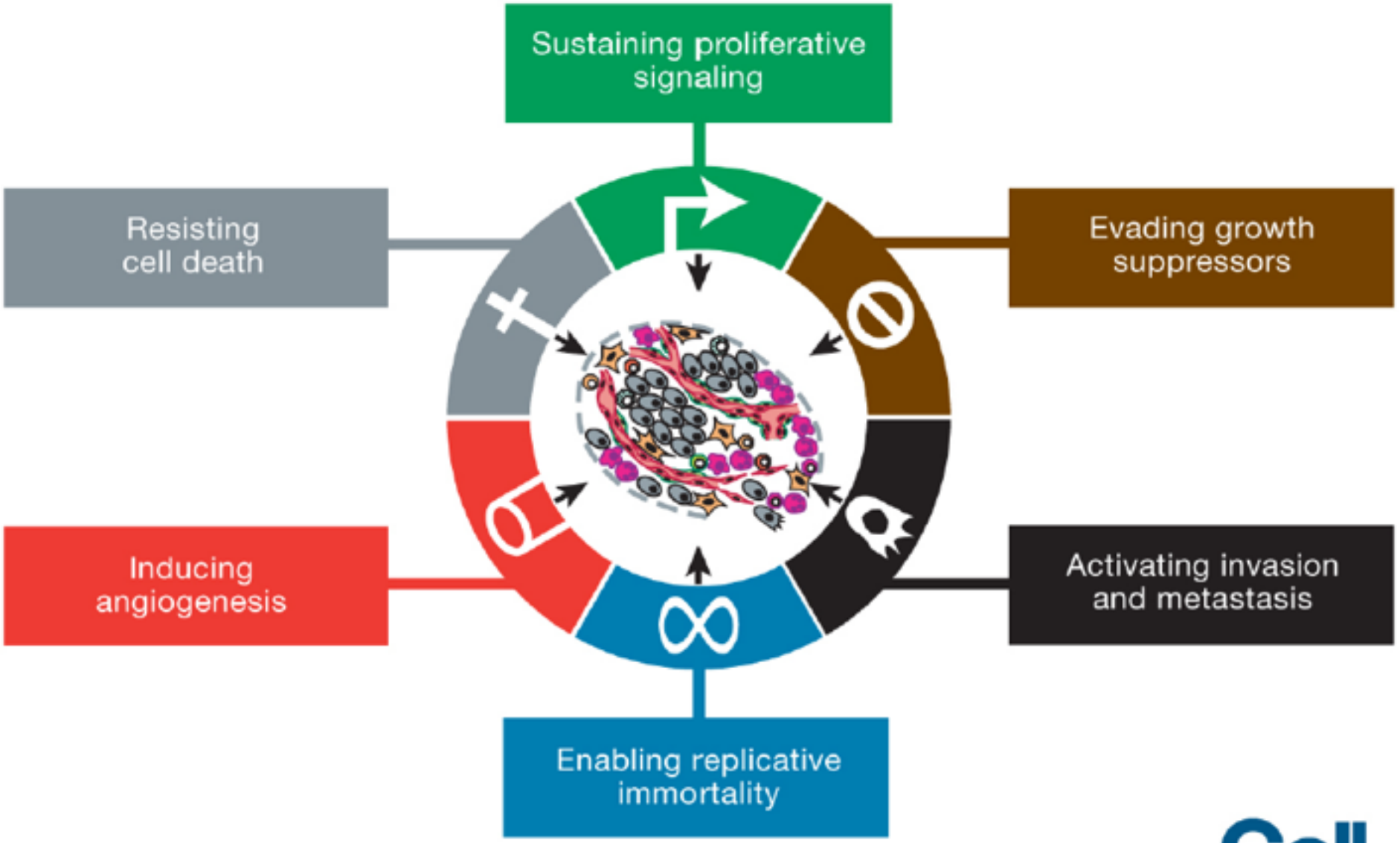
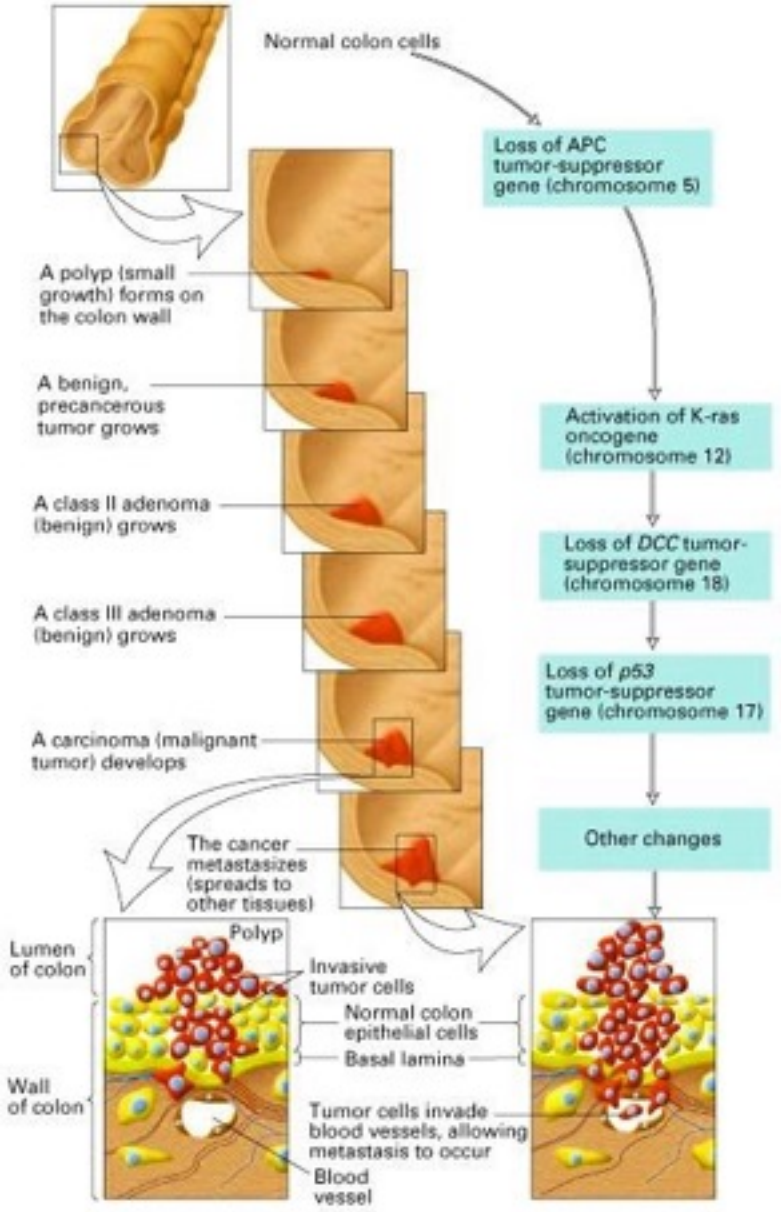


Hanahan and Weinberg, 2011

Cell PRESS

Cell, 144:646

The Development and Metastasis of Human Colorectal Cancer and its Genetic Basis



Lodish et al., Molecular Cell Biology

Signal transduction is the process of converting extracellular signals into cellular responses

Signal Transduction

- Signal transduction was initially viewed as a collection of linear information transporting pipelines.

- Now we know that pathway crosstalk enables signals to propagate through a tangled network of interconnecting networks and cascades.

- Recent findings from genome research reveal a new problem:
there are fewer genes than biological processes.

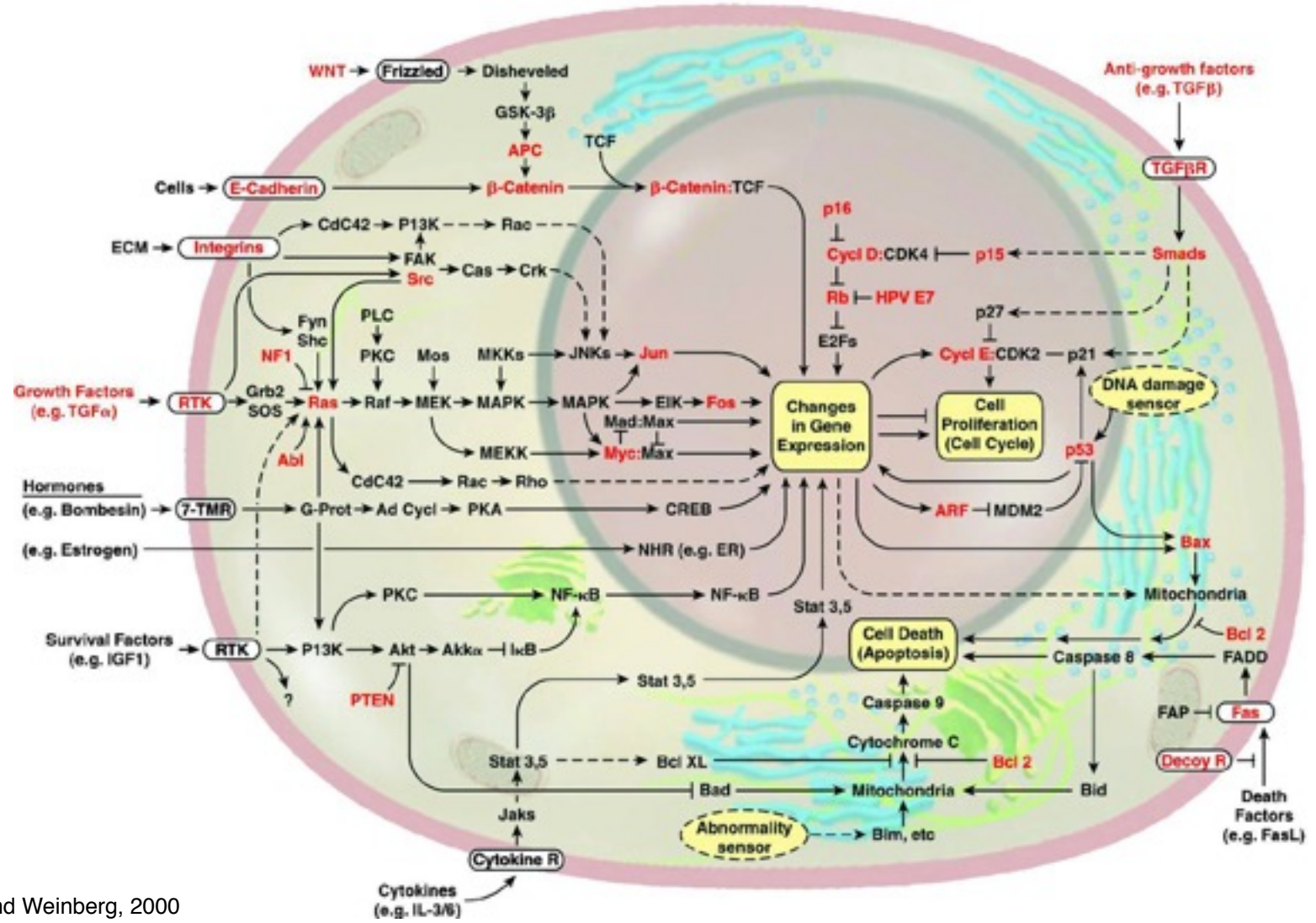
- Spatiotemporal control is an important means by which Signal transduction is regulated. Our understanding in this area is lagging behind.

Genes in the Human Genome

- About 10 years ago we thought there would be about 100,000 because there were so many different proteins known. Now after we have analyzed the human genome sequence, we know that there are about 21,000 genes. Many of these 21,000 genes can make multiple proteins each. Now we are discovering "non-coding" RNA genes. There are thousands of these and it looks like these non coding RNAs help regulate the protein coding genes. The real answer will be more than 21,000 depending on how you define a gene, in other words do you count the non-coding regulatory "genes"

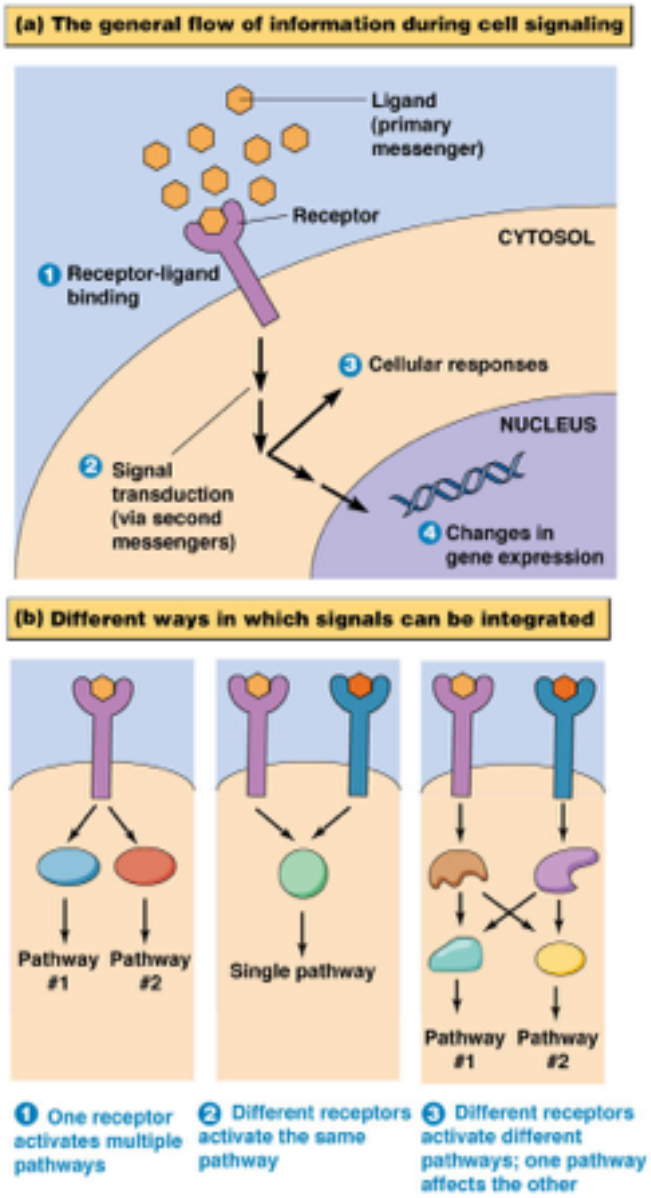
David Bodine, Ph.D., Chief & Senior Investigator of NHGRI's Genetics and Molecular Biology Branch

Integrated Circuit of the Cell



Hanahan and Weinberg, 2000

Signal Transduction



How Cells Communicate with their Surroundings

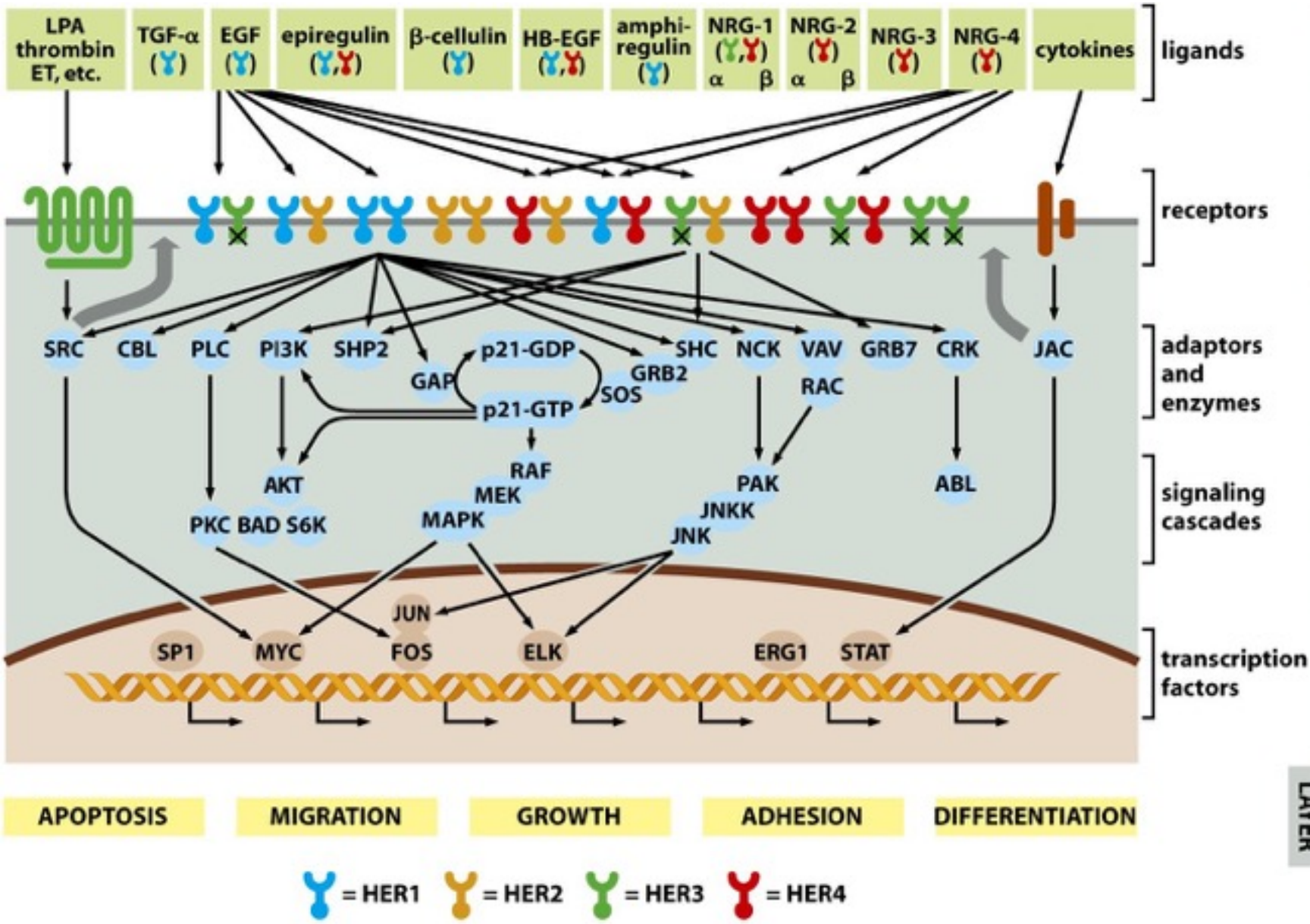
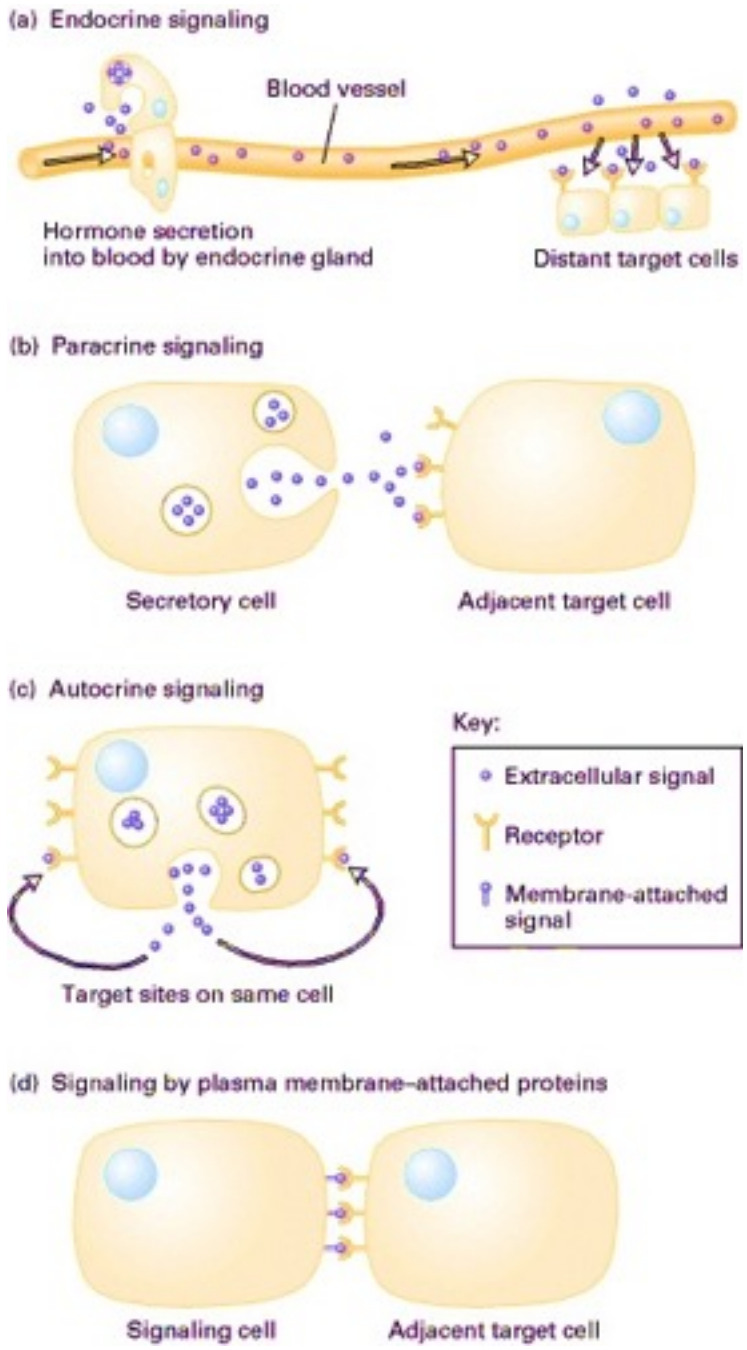


Figure 5.1 *The Biology of Cancer* (© Garland Science 2007)



General schemes of intercellular signaling in animals
(a – c) Cell-to-cell signaling by extracellular chemicals occurs over distances from a few micrometers in autocrine and paracrine signaling to several meters in endocrine signaling.
(d) Proteins attached to the plasma membrane of one cell can interact directly with receptors on an adjacent cell.

Lodish et al., Molecular Cell Biology

Structure of the Epidermal Growth Factor (EGF) Receptor

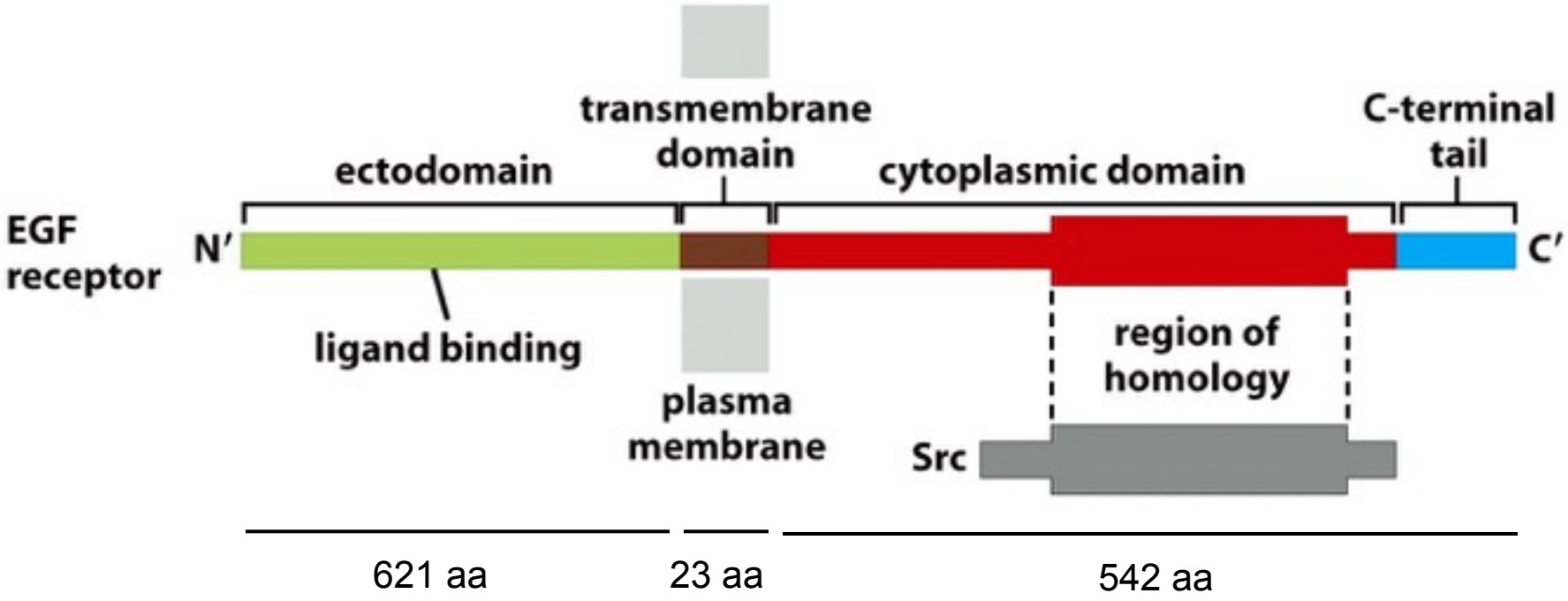


Figure 5.9a *The Biology of Cancer* (© Garland Science 2007)

The EGF Receptor and v-ErbB (Oncoprotein Specified by *erbB* Oncogene of Avian Erythroblastosis Virus)

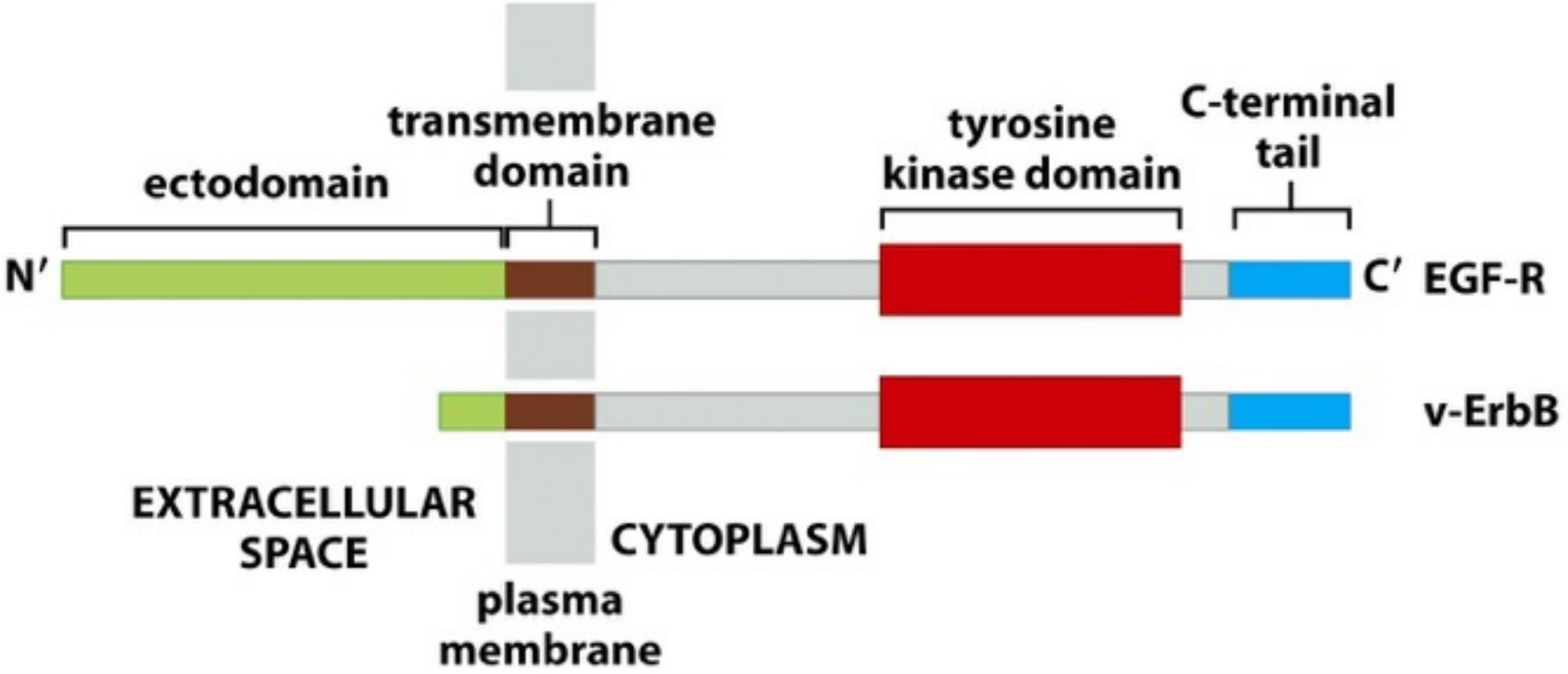


Figure 5.11 *The Biology of Cancer* (© Garland Science 2007)

erb-B Receptor family

- Derives its name from its sequence homology with the avian erytroblastosis retroviral oncogene v-*erb*-B
- The receptors of the family are also frequently referred to as HERs: ***H***uman ***E***GF ***R***eceptor
- Members of this family include EGFR/HER1, HER2, HER3, and HER4

EGFR: Epidermal Growth Factor Receptor

Structure of Membrane Tyrosine Kinase Receptors

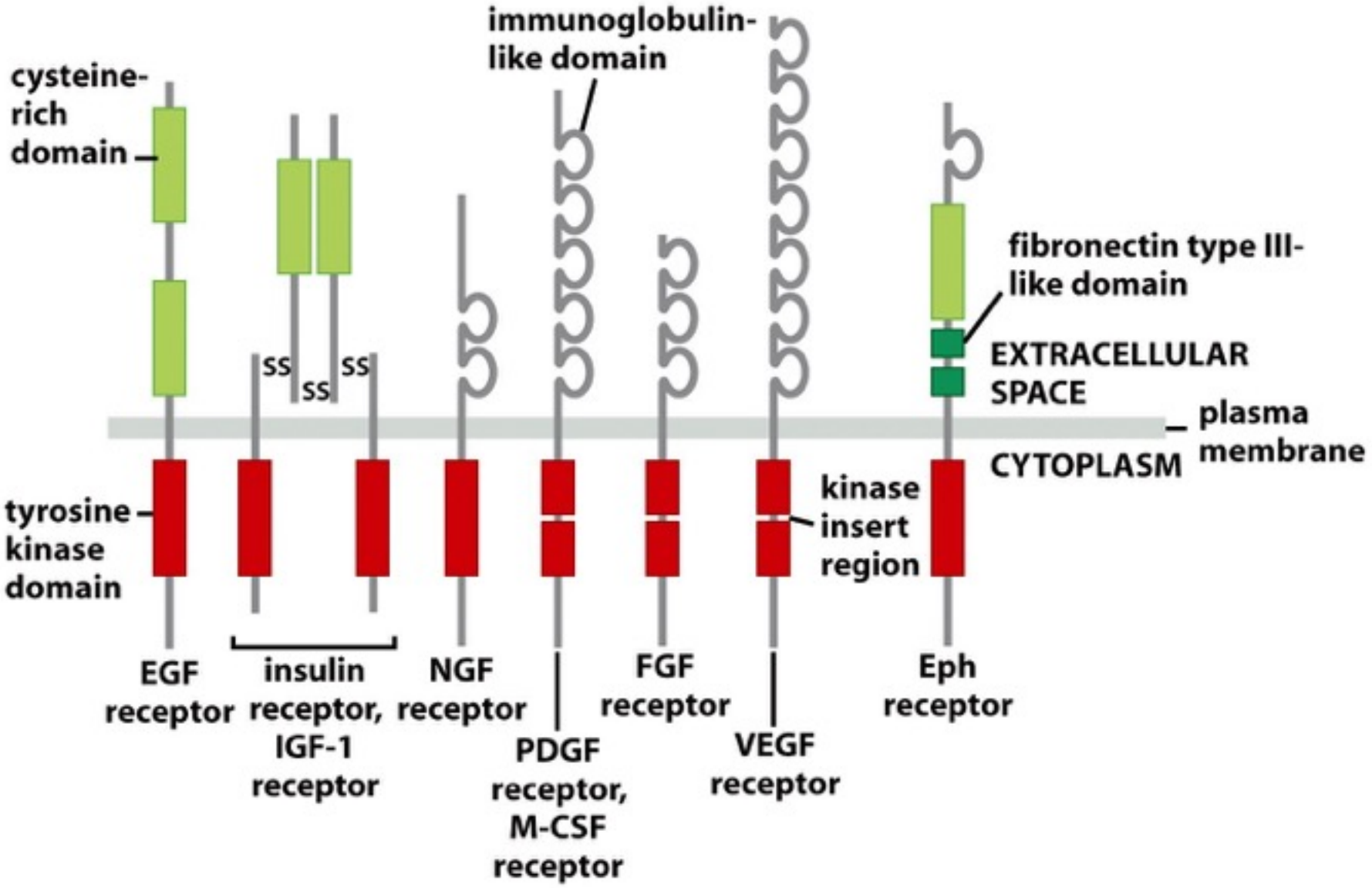


Figure 5.10 *The Biology of Cancer* (© Garland Science 2007)

PDGF was found to be closely related in sequence to the v-*sis* oncogene of simian sarcoma virus.

Simian sarcoma virus transform fibroblasts,
but not epithelial cells.
-because PDGF receptor is expressed on the surfaces of mesenchymal cells, and not on epithelial cell surface.

Effect of Platelet-Derived Growth Factor (PDGF) on Cells

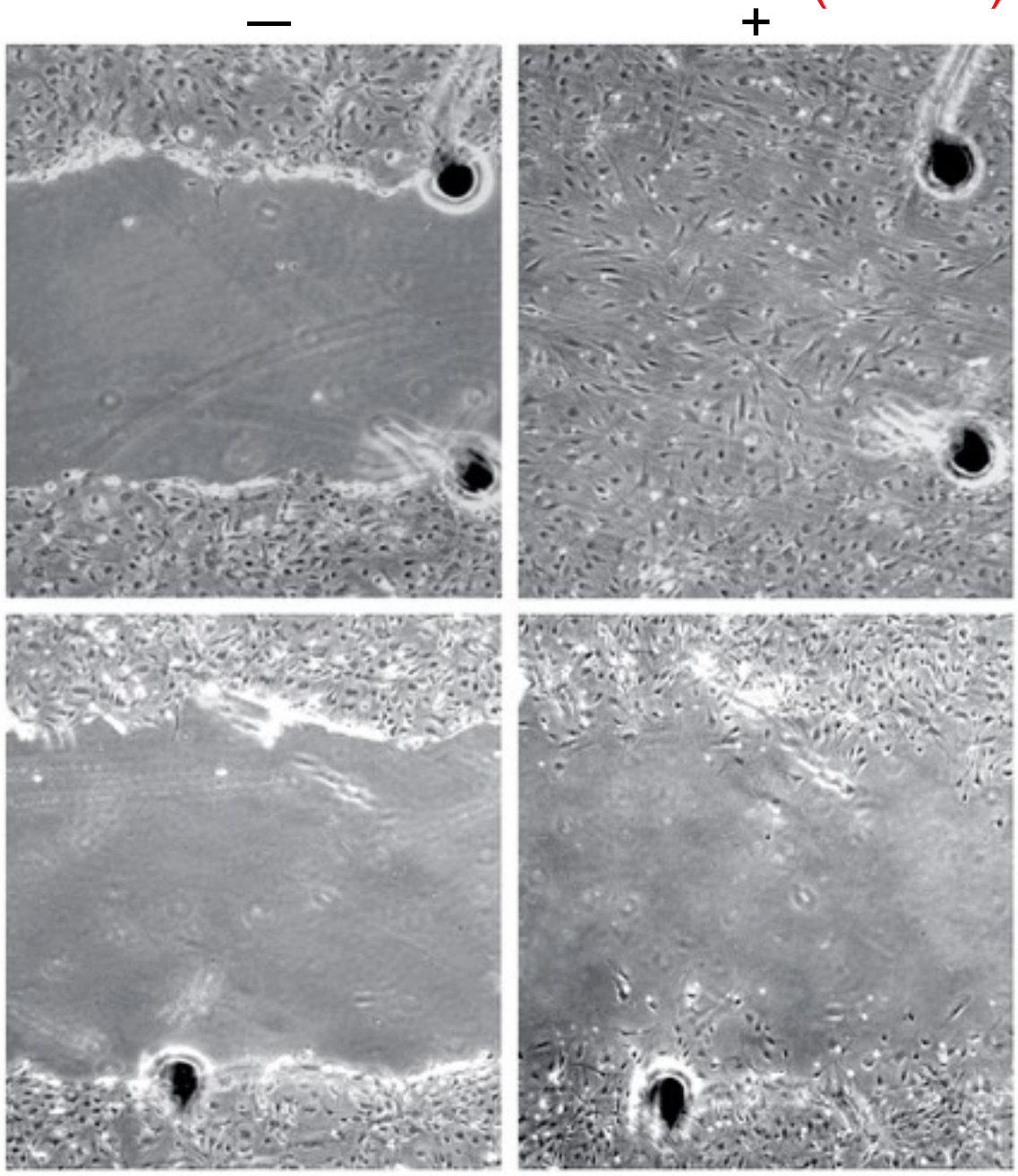


Figure 5.4a *The Biology of Cancer* (© Garland Science 2007)

Table 5.2 Tyrosine kinase GF receptors altered in human tumors[a]

Name of receptor	Main ligand	Type of alteration	Types of tumor
EGF-R/ErbB1	EGF, TGF-α	overexpression	non-small cell lung cancer; breast, head and neck, stomach, colorectal, esophageal, prostate, bladder, renal, pancreatic, and ovarian carcinomas; glioblastoma
EGF-R/ErbB1		truncation of ectodomain	glioblastoma, lung and breast carcinomas
ErbB2/HER2/Neu	NRG, EGF	overexpression	30% of breast adenocarcinomas
ErbB3, 4	various	overexpression	oral squamous cell carcinoma
Flt-3	FL	tandem duplication	acute myelogenous leukemia
Kit	SCF	amino acid substitutions	gastrointestinal stromal tumor
Ret		fusion with other proteins, point mutations	papillary thyroid carcinomas, multiple endocrine neoplasias 2A and 2B
FGF-R3	FGF	overexpression; amino acid substitutions	multiple myeloma, bladder and cervical carcinomas

[a]See also Figure 5.17.

How do Receptor Tyrosine Kinases (RTKs) Transduce Signals from the Extracellular Space into the Cytoplasm of Cells?

Receptor Dimerization Following Ligand Binding

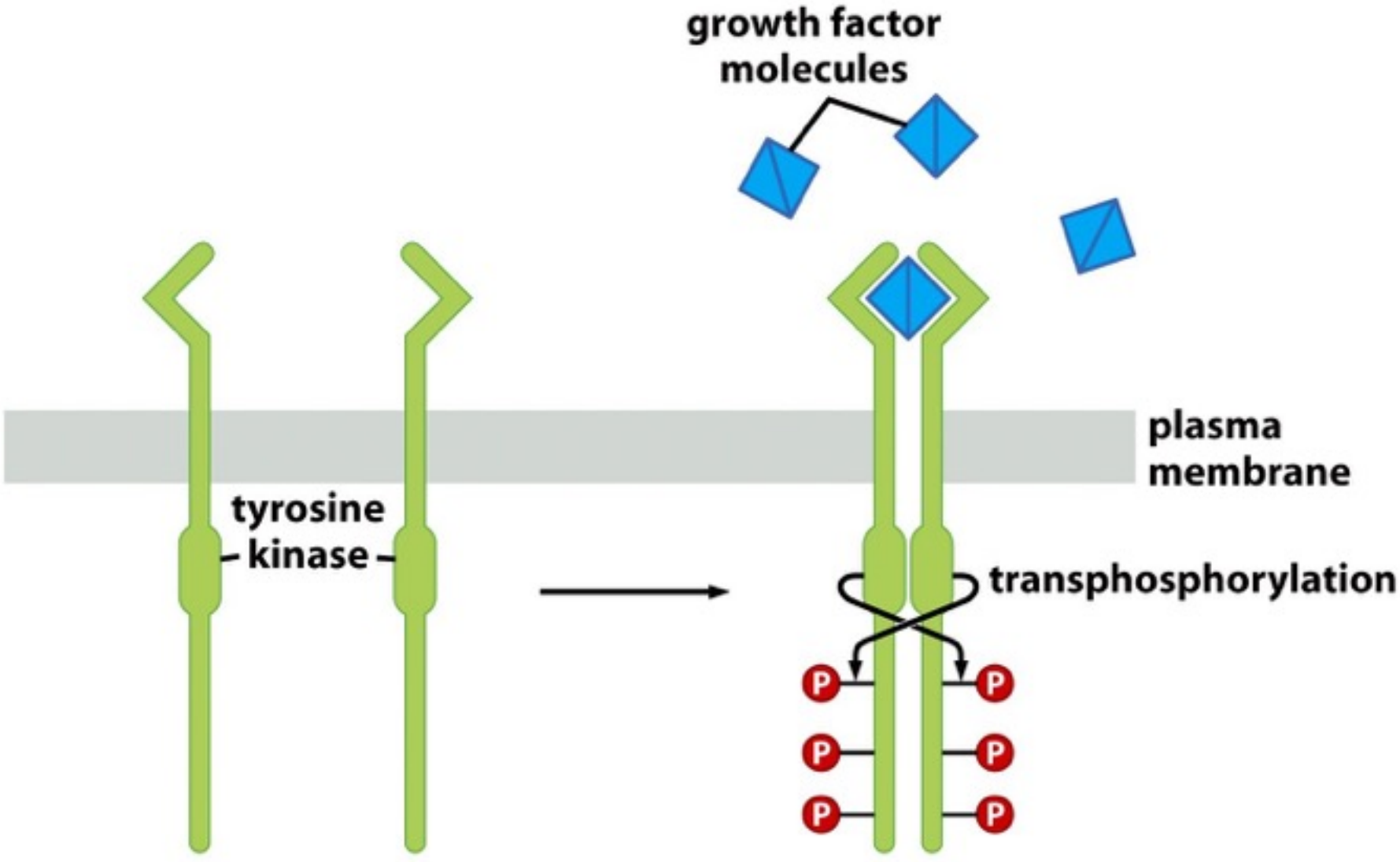


Figure 5.15 *The Biology of Cancer* (© Garland Science 2007)

Deregulation of Receptor Activation

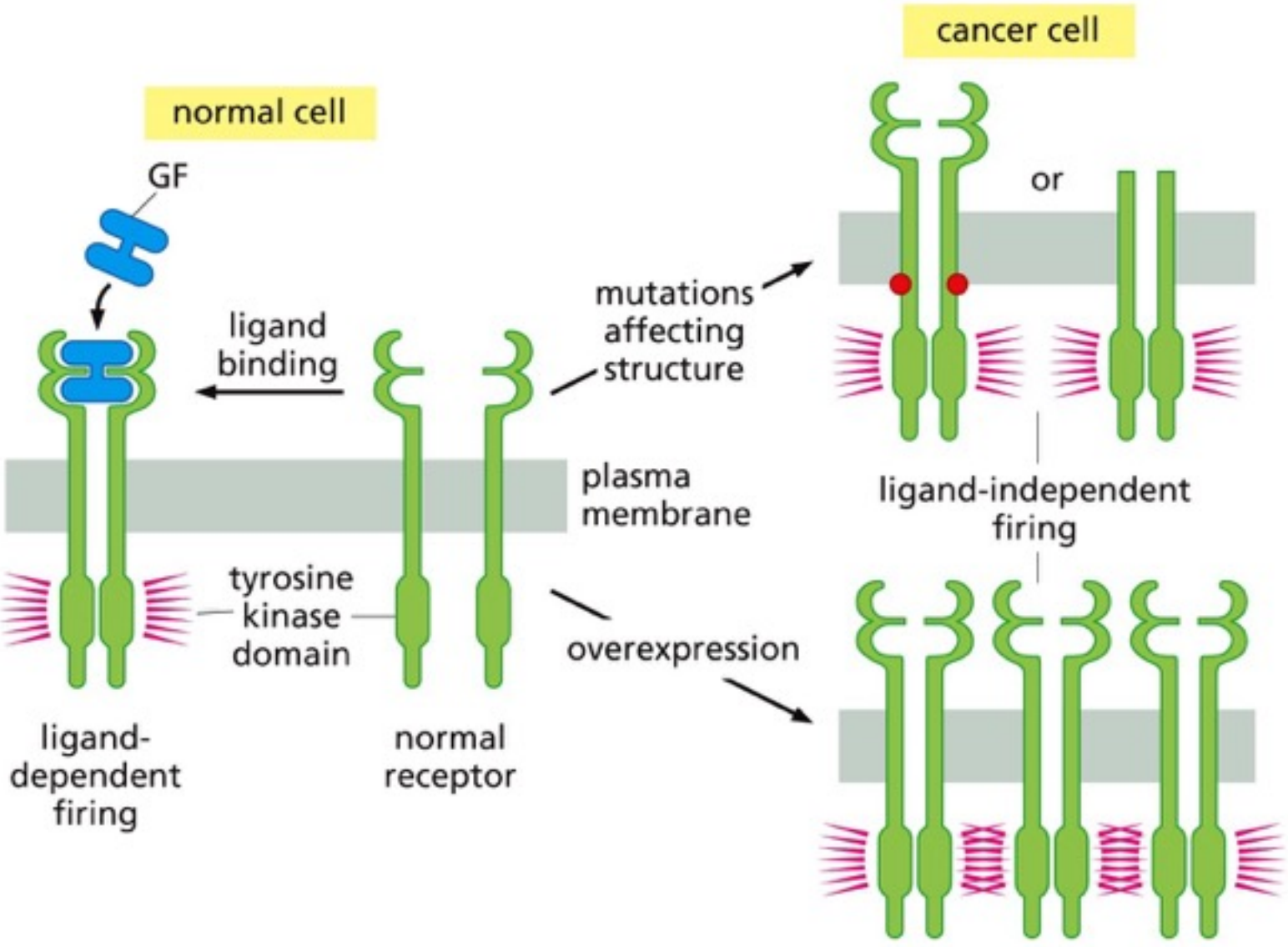


Figure 5.11a The Biology of Cancer (© Garland Science 2014)

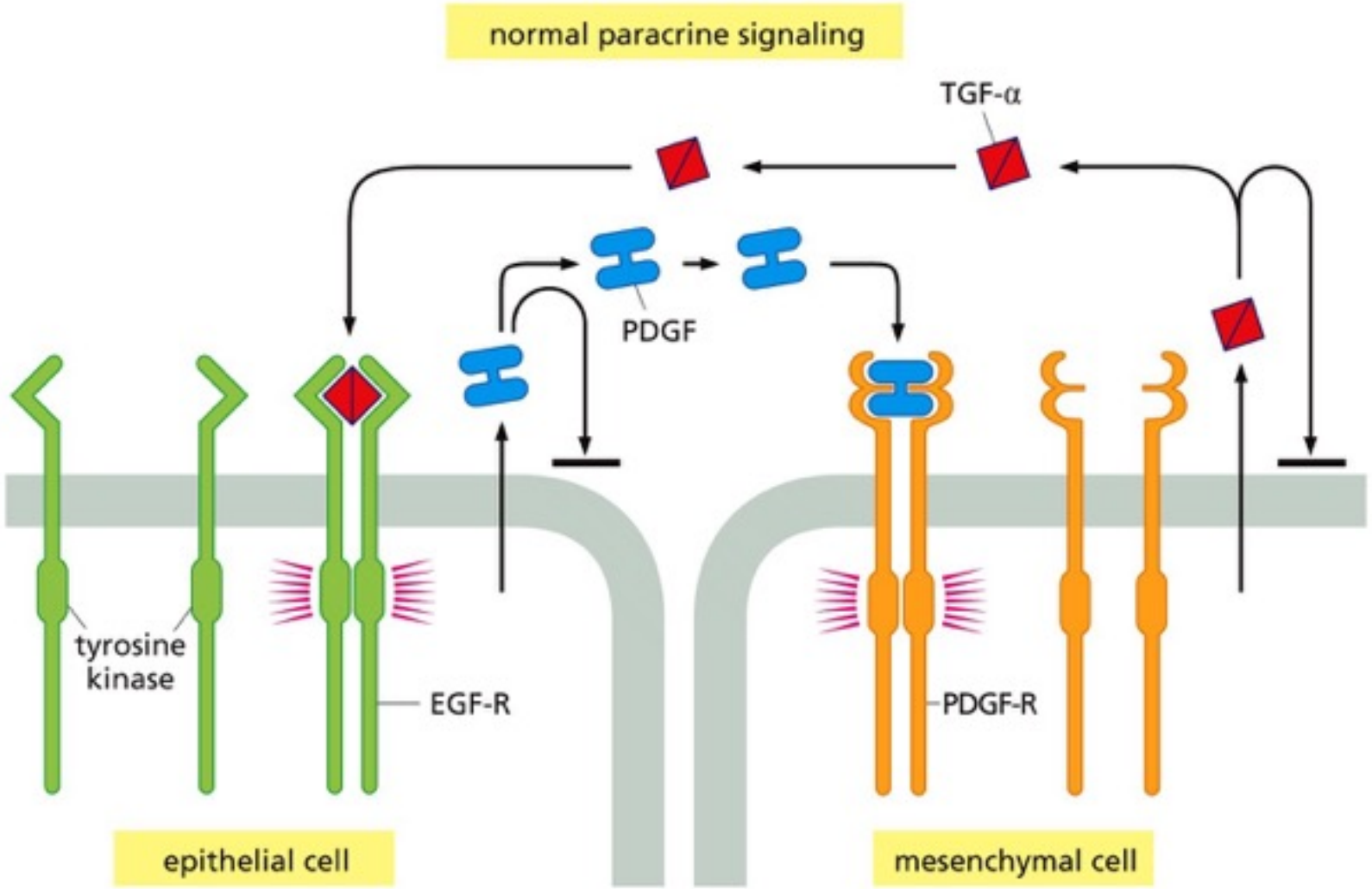


Figure 5.11b The Biology of Cancer (© Garland Science 2014)

Deregulation of Receptor Activation

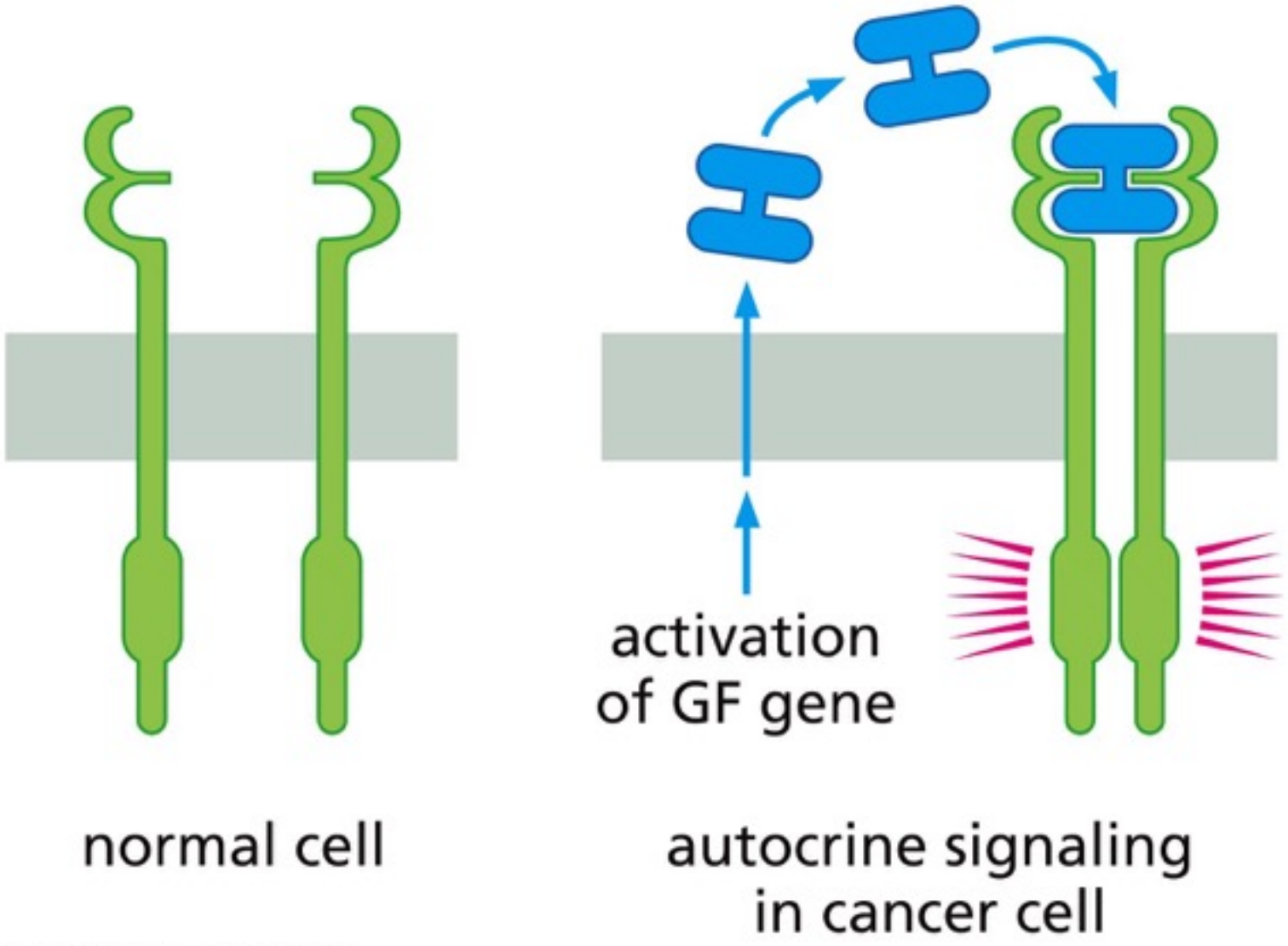


Figure 5.11c The Biology of Cancer (© Garland Science 2014)

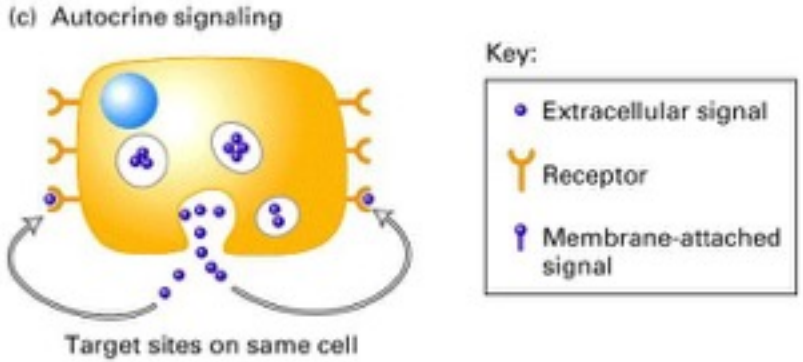
Autocrine Signaling in Cancer

Certain lung cancers produce:
Growth factors such as tumor growth factor α (TGFα),
stem cell factor (SCF),
Insulin-like growth factor (IGF).

These cancers also express the **receptors**
for these **ligands**:
EGF receptor, Kit, and IGF-1 receptor.

Autocrine Signaling in Kaposi's Sarcoma

- In Kaposi's sarcoma (discovered by Moritz Kaposi, 1872; caused by human herpes virus 8 (HHV-8); a tumor of cells closely related to the endothelial cells that form lymph ducts), the tumor cells produce PDGF, TGF-β, IGF-1, Ang2, CC18/14, CXCL11, and endothelin (ligands of cellular origin) as well as receptors for these ligands.
- Also, the HHV-8 genome produces two additional ligands-vIL6 (viral IL6) and vMIP (viral macrohage inflammatory protein), and their receptors



Lodish et al., Molecular Cell Biology

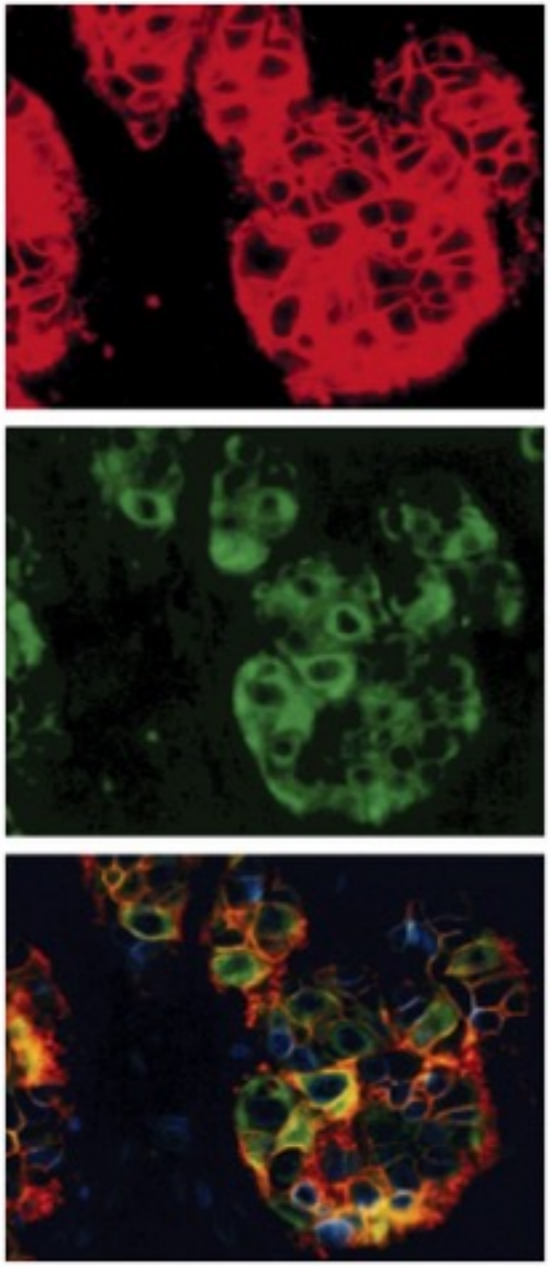
Table 5.3 Examples of human tumors making autocrine growth factors

Ligand	Receptor	Tumor type(s)
HGF	Met	miscellaneous endocrinal tumors, invasive breast and lung cancers, osteosarcoma
IGF-2	IGF-1R	colorectal
IL-6	IL-6R	myeloma, HNSCC
IL-8	IL-8R A	bladder cancer
NRG	ErbB2[a]/ErbB3	ovarian carcinoma
PDGF-BB	PDGF-Rα/β	osteosarcoma, glioma
PDGF-C	PDGF-α/β	Ewing's sarcoma
PRL	PRL-R	breast carcinoma
SCF	Kit	Ewing's sarcoma, SCLC
VEGF-A	VEGF-R (Flt-1)	neuroblastoma, prostate cancer, Kaposi's sarcoma
TGF-α	EGF-R	squamous cell lung, breast and prostate adenocarcinoma, pancreatic, mesothelioma
GRP	GRP-R	small-cell lung cancer

[a]Also known as HER2 or Neu receptor.

Table 5.3 *The Biology of Cancer* (© Garland Science 2007)

Deregulation of Receptor Firing: Autocrine Signaling in Human Breast Carcinoma



Over-expression of
EFG **receptor** (EGFR)

Over-expression of
TGF-α(**ligand** of EGFR)

Superimposed
image

Figure 5.11D *The Biology of Cancer* (© Garland Science 2007)

Important Features of Membrane Receptor Tyrosine Kinases (RTKs)

- Lateral mobility in the membrane
- Dimerization
- Autophosphorylation

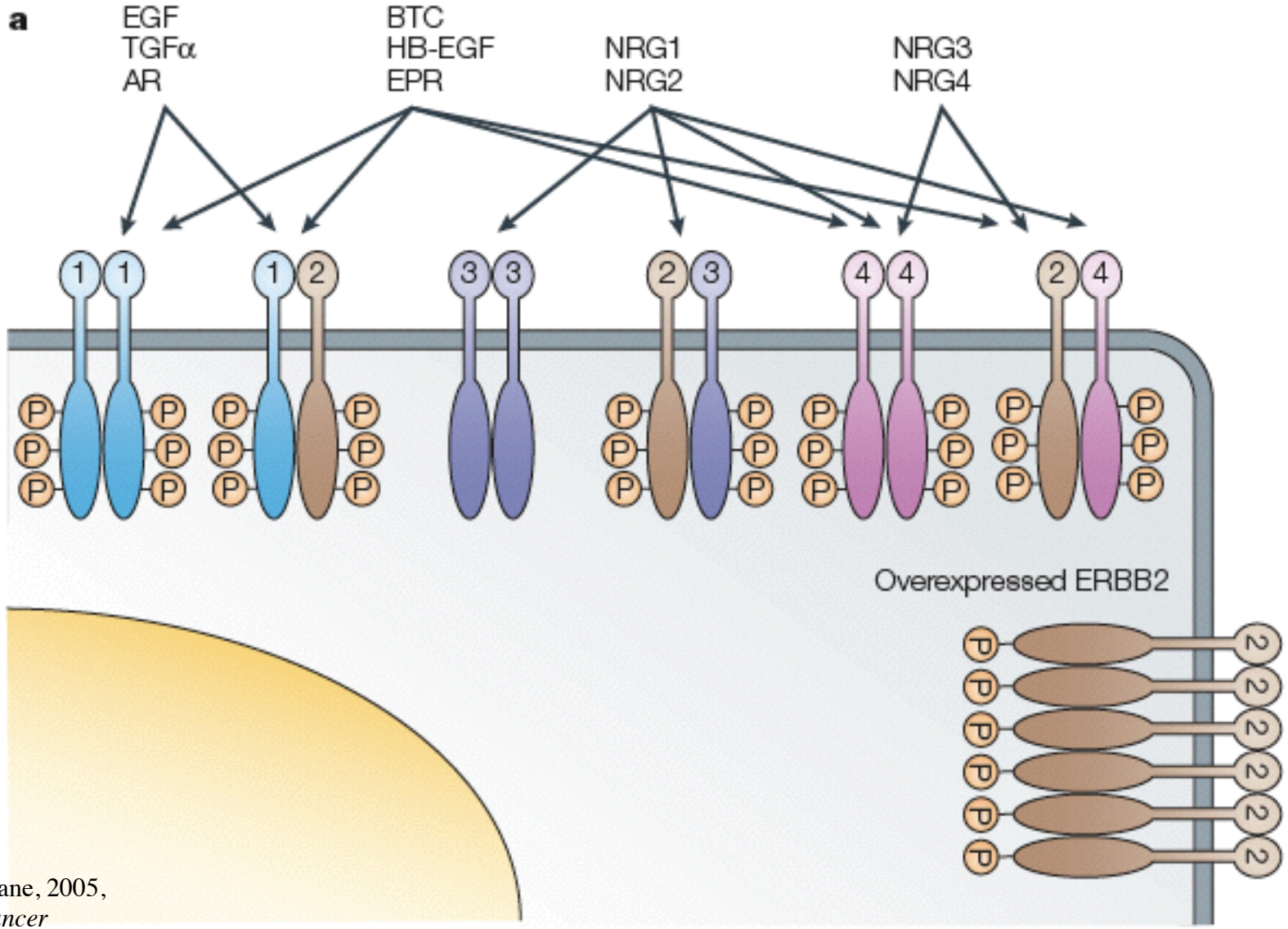
erb-B Receptor family

- Derives its name from its sequence homology with the avian erytroblastosis retroviral oncogene v-*erb*-B
- The receptors of the family are also frequently referred to as HERs, based on their homology to the ***H***uman ***E***GF ***R***eceptor
- Members of this family include EGFR/HER1, HER2, HER3, and HER4
- **HER2 is the preferred dimerization partner for all *erb*-B receptors**

EGFR: Epidermal Growth Factor Receptor

Erb-B Receptor Family, Ligands and Dimers

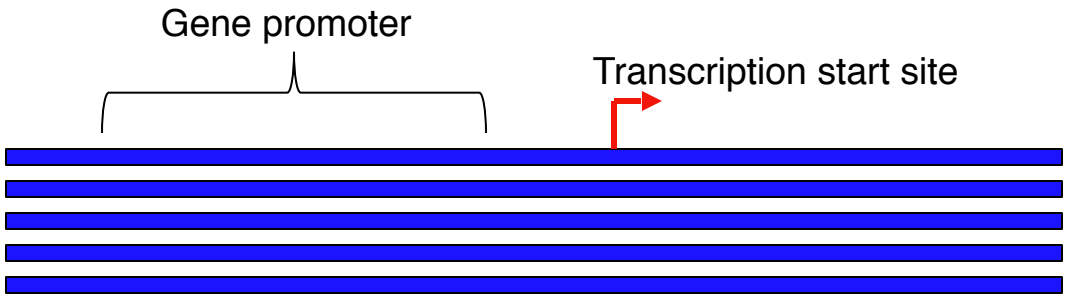
AR, amphiregulin; BTC, betacellulin; EPR, epiregulin; HB-EGF, heparin-binding EGF; NRGs, neuregulins; TGF, transforming growth factor-α.



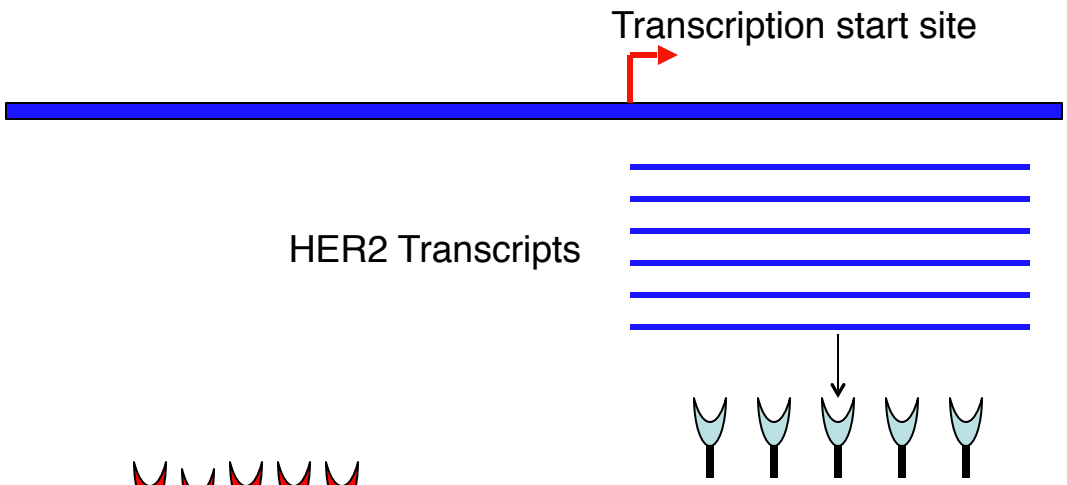
Hynes & Lane, 2005,
Nat Rev Cancer

Factors Contributing to Abnormal HER2 Signaling

1. Receptor gene amplification

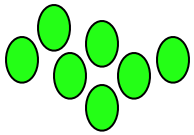


2. Increased receptor gene transcription



3. Mutations in the **receptor**

4. Increased production of growth factor (**ligand**)



5. Increased *life-time* of receptor at the cell surface

Overexpression of HER2 can Result from Increased DNA, RNA, or Protein

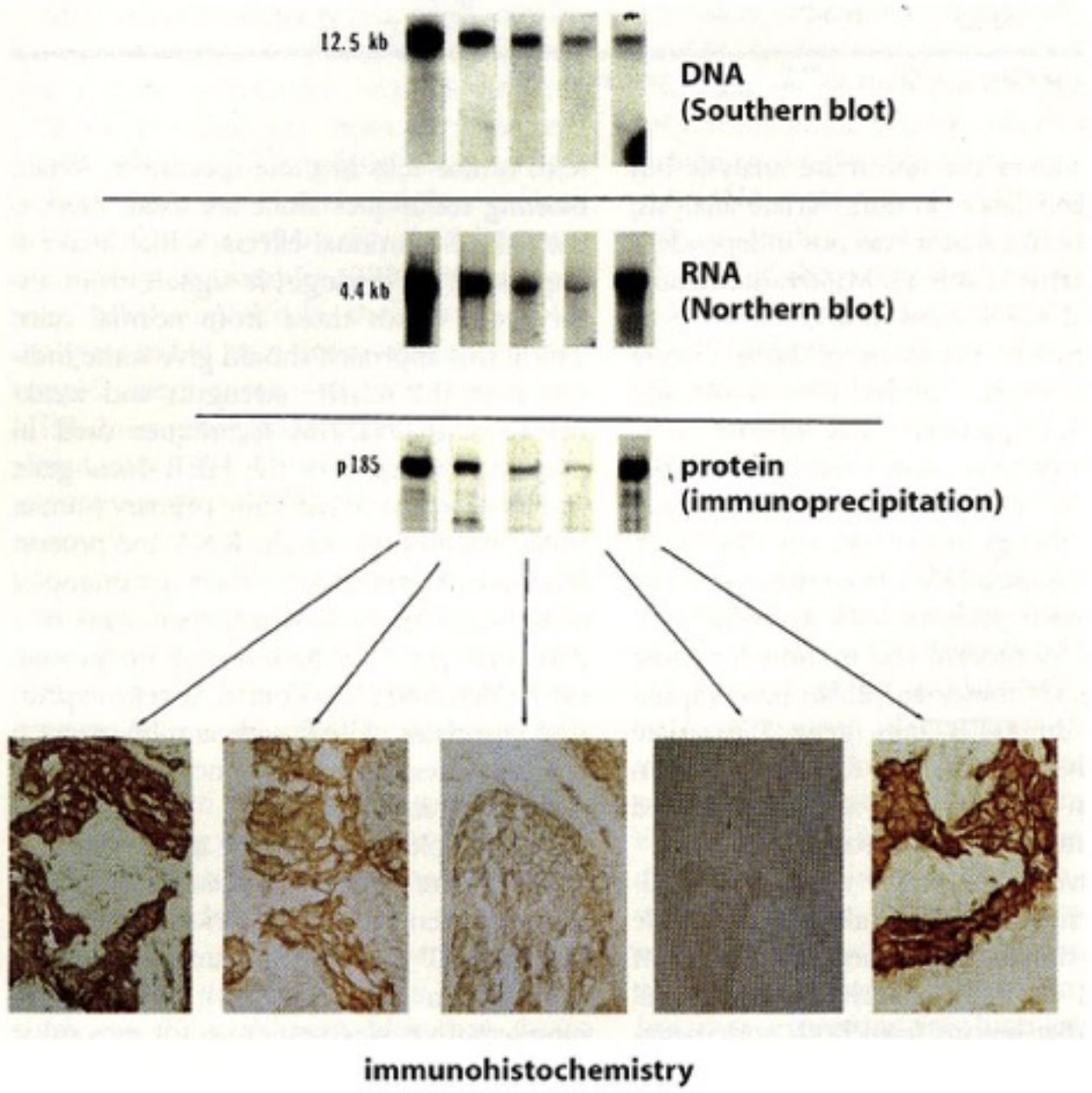
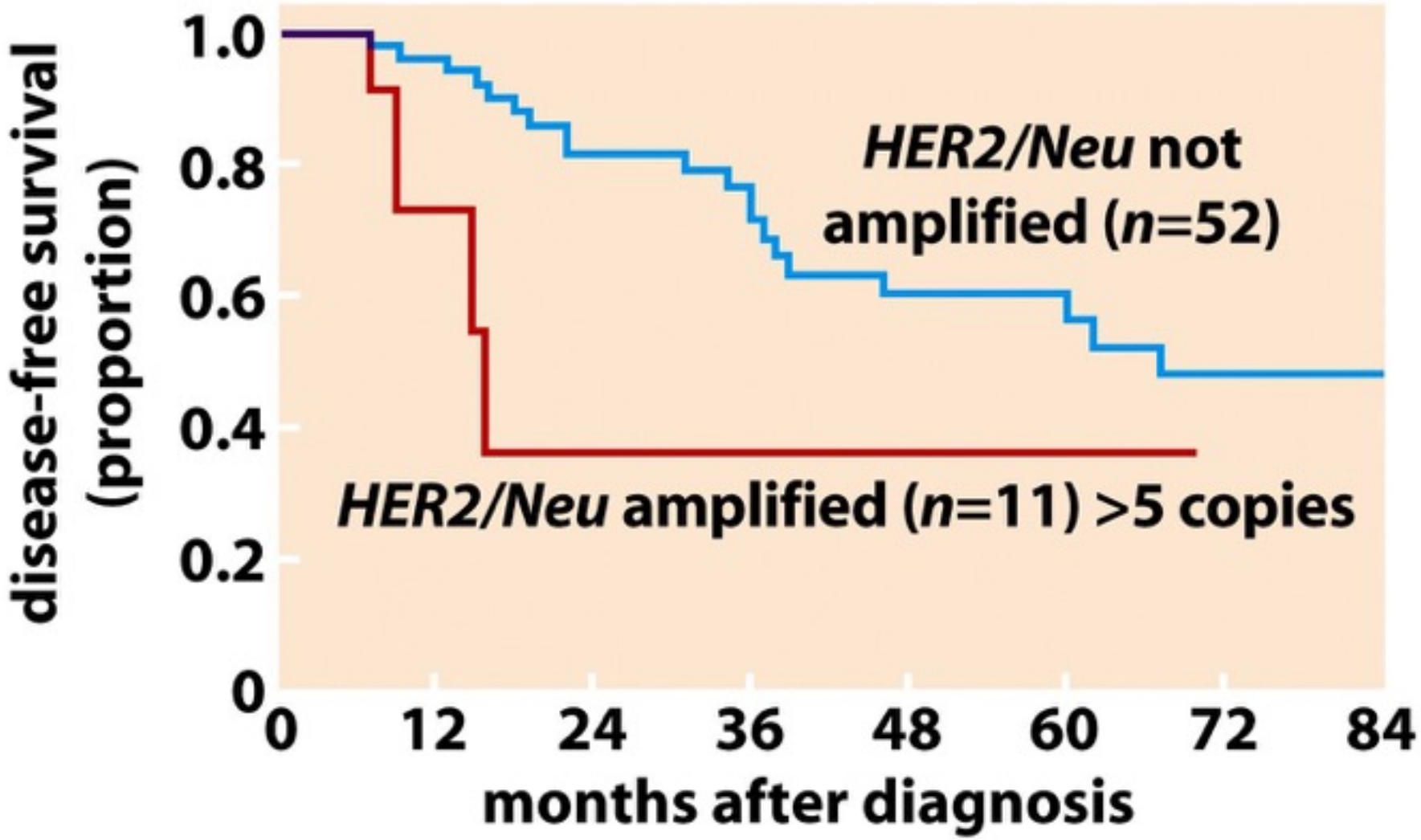


Figure 4.4. *The Biology of Cancer* (© Garland Science 2014)

HER2 Amplification is Associated with Poor Patient Prognosis (Kaplan-Meir Plot)



D. J. Slamon et al., *Science* 235:177-182

Figure 4.4 B *The Biology of Cancer* (© Garland Science 2014)

Chimeric Receptors Leading to Aberrant Signaling

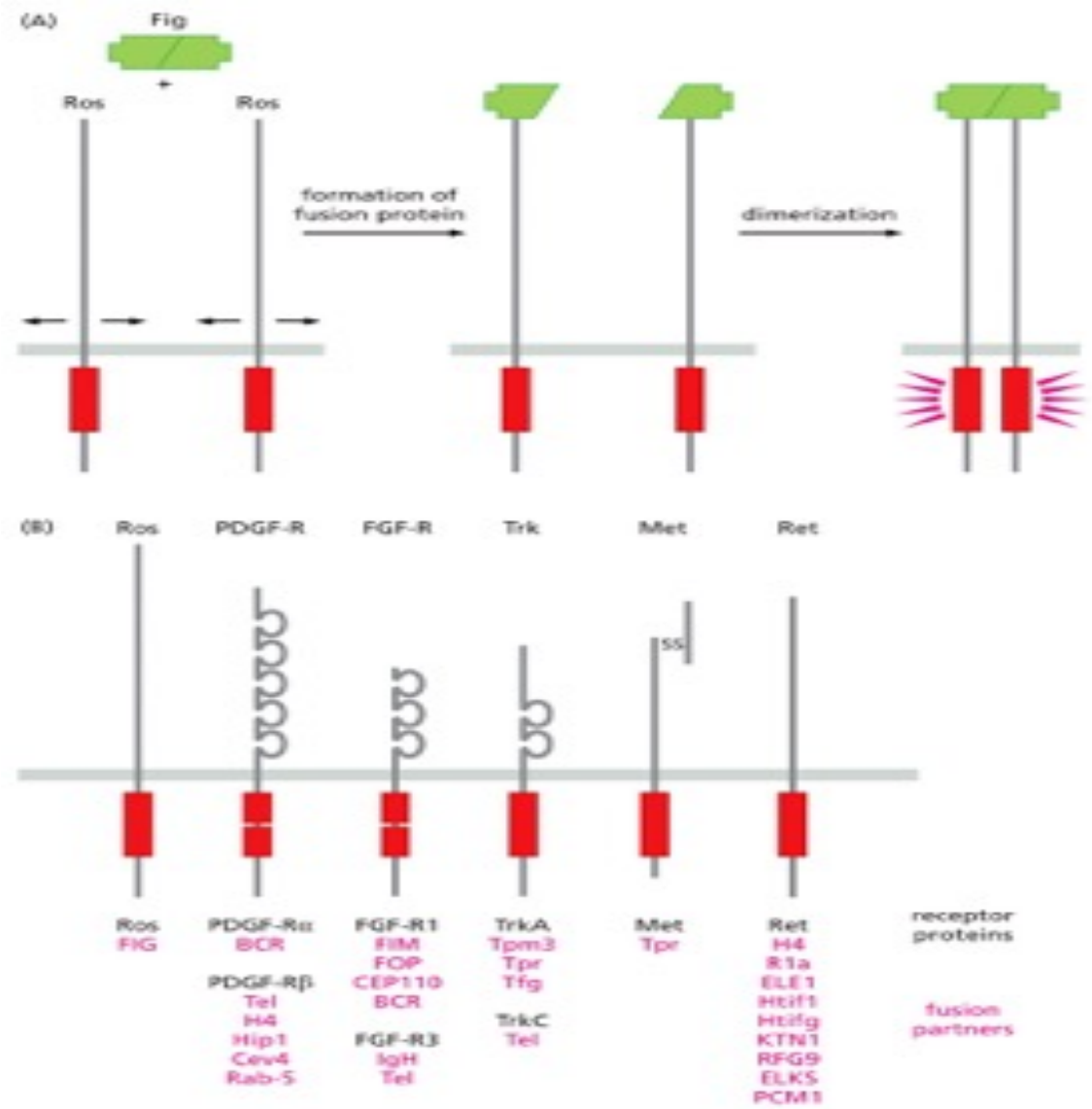


Figure 5.16 The Biology of Cancer (© Garland Science 2014)

Complexity of Signaling Circuitry

- **Of the Approximately 21,000 genes in the human genome, 518 genes encode various types of protein kinases; 40% of these genes generate alternatively spliced mRNAs encoding slightly different variant structures of kinase proteins, leading to more than 1,000 distinct kinase proteins.**
- **Of the 518 kinase genes, 90 encode tyrosine kinases, the remainder being serine/threonine kniases.**
- **Among the 90 tyrosine kinases, 58 encode proteins with general structures of the EGF and PDGF receptors (ligand-binding ectodomain,a transmembrane domain, and a cytoplasmic tyrosine kinase domain).**

Each protein component of a signaling circuit must solve two problems:

(1)Specificity: how can it exchange signals only with the small subset of cellular proteins that are its intended signaling partners in the circuit?

(2) How can this protein acquire rapid, almost Instantaneous access to these signaling partners, doing so while operating in the viscous soup in the cytoplasm and nucleus?

Domain Structure of the Src Protein

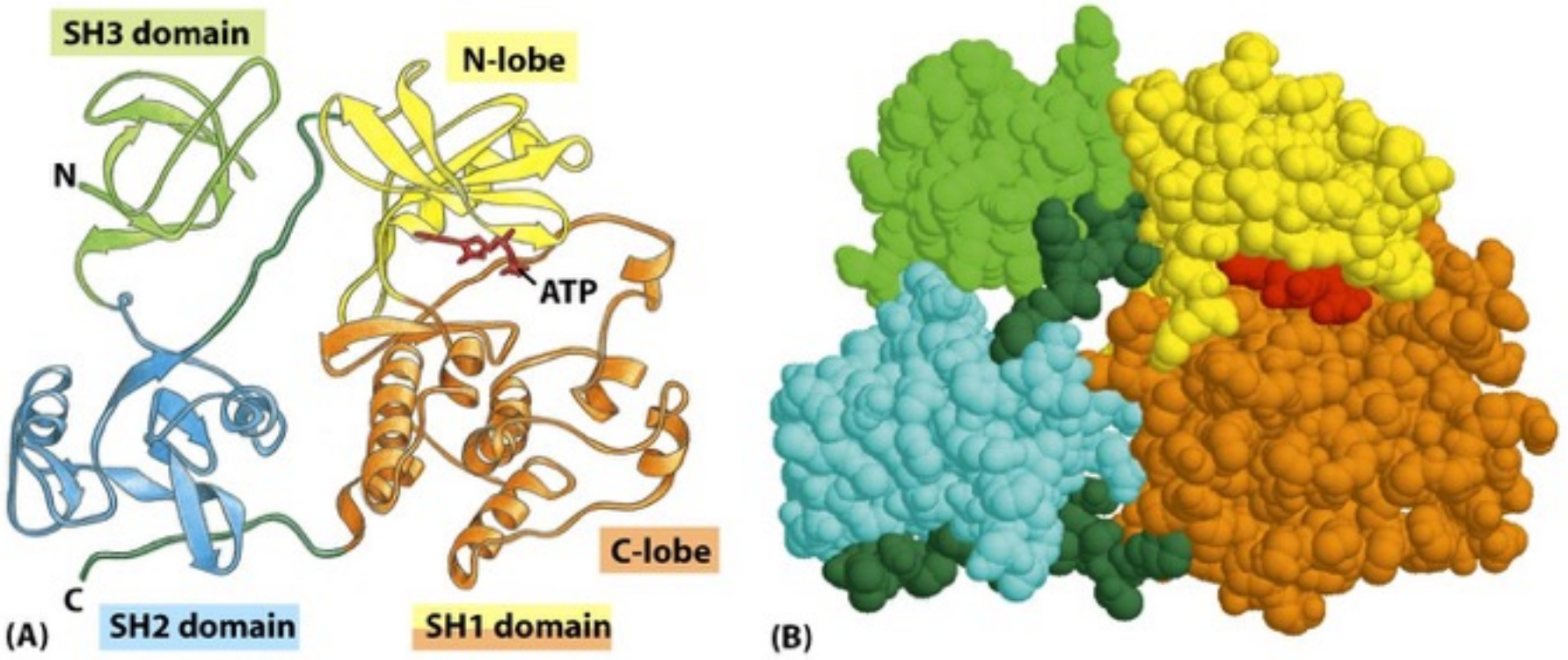
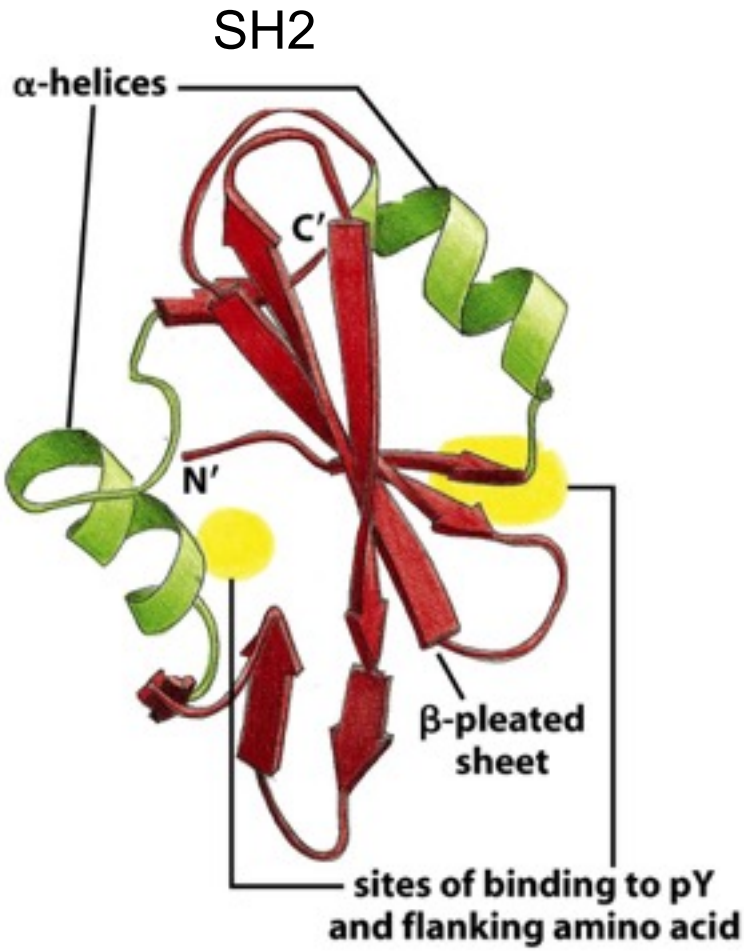
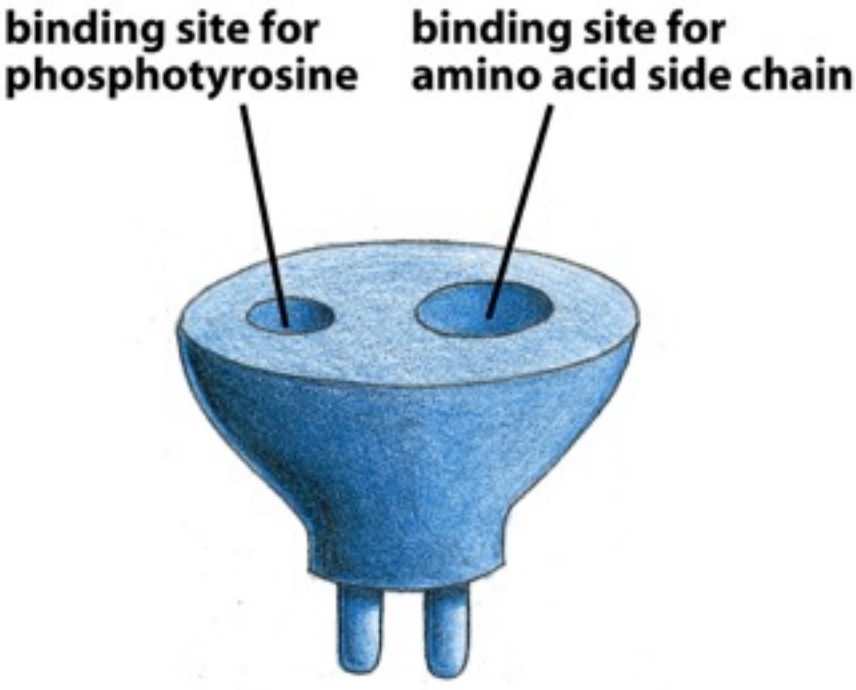


Figure 6.7 *The Biology of Cancer* (© Garland Science 2007)

Structure and Function of SH2 Groups





The human genome encodes at least 117 distinct SH2 groups each constituting a domain of a larger protein and each apparently having an affinity for binding a particular phosphotyrosine with a flanking peptide sequence.

Figure 6.8a *The Biology of Cancer* (© Garland Science 2007)

Structure and Function of SH3 Groups

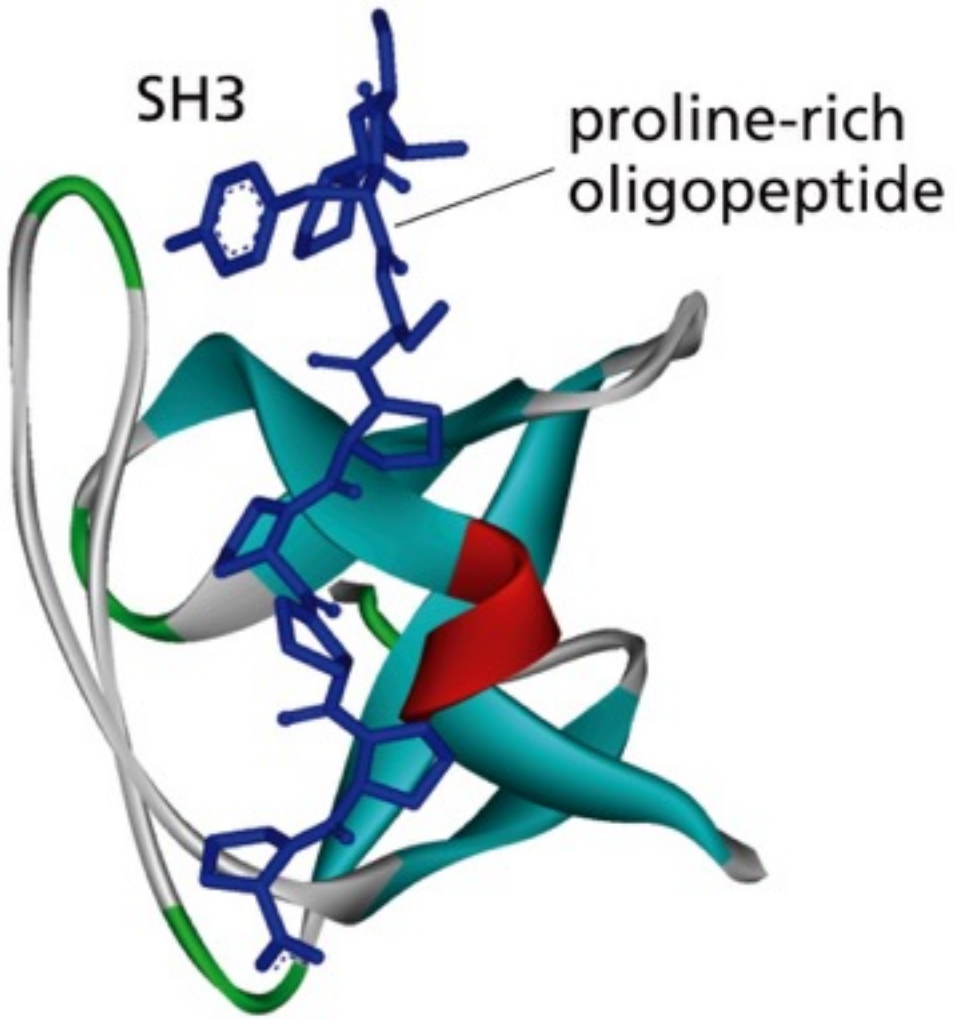
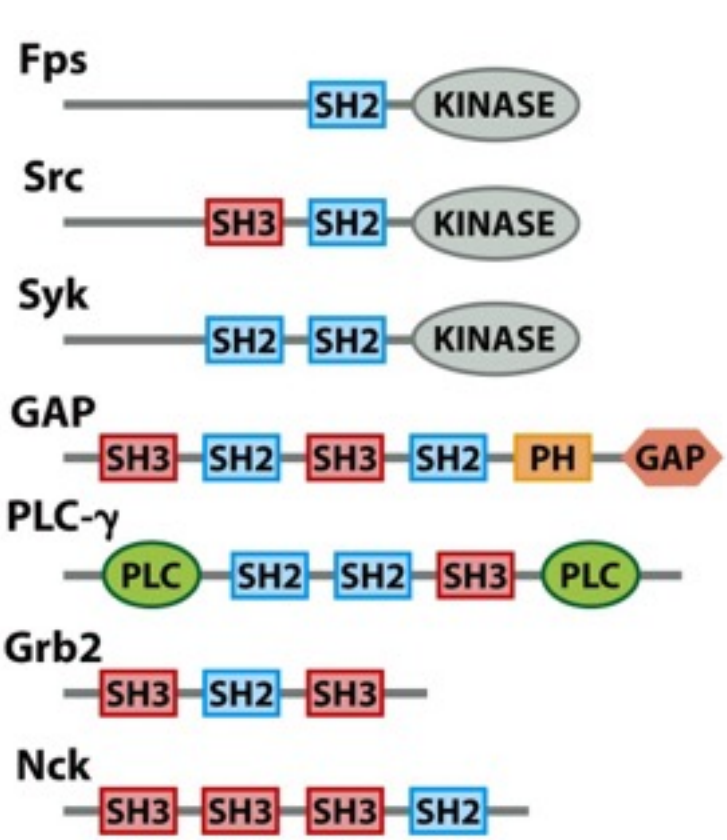


Figure 6.8c The Biology of Cancer (© Garland Science 2014)

Protein Interaction Domains as Modular Units of Protein Structure



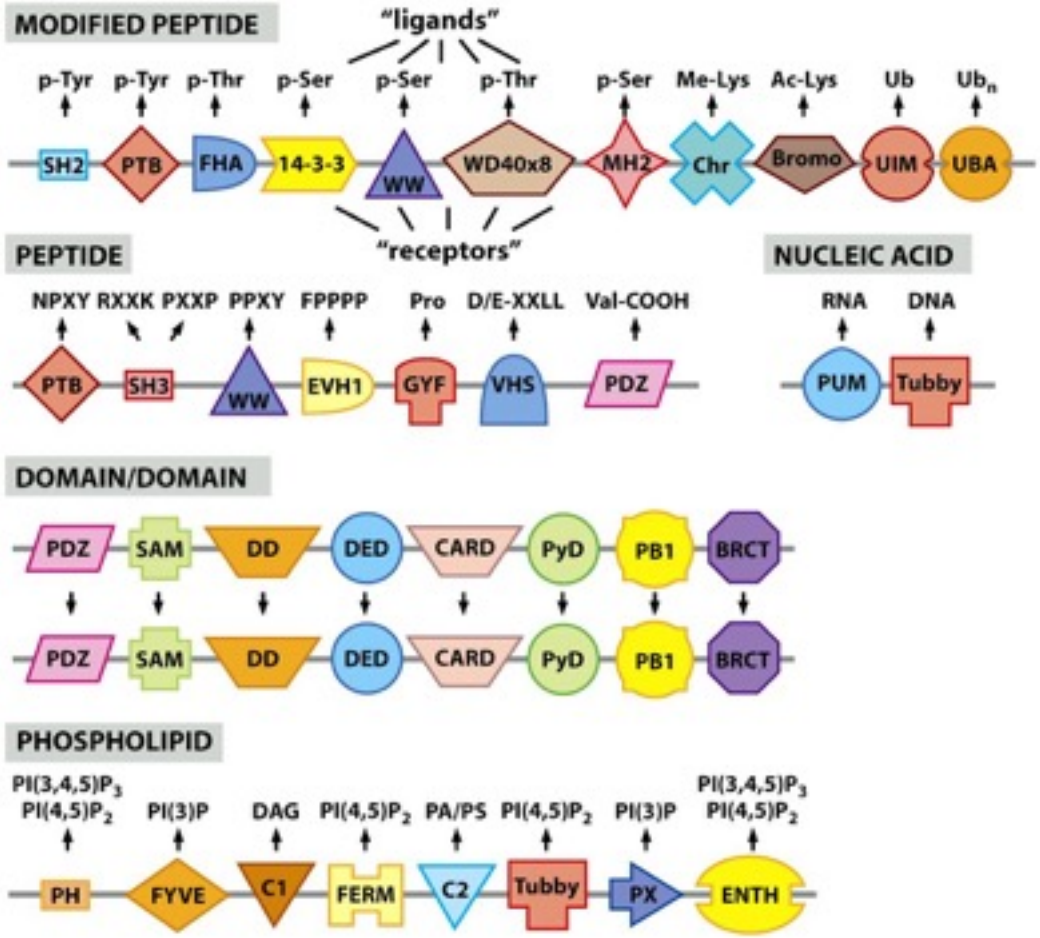
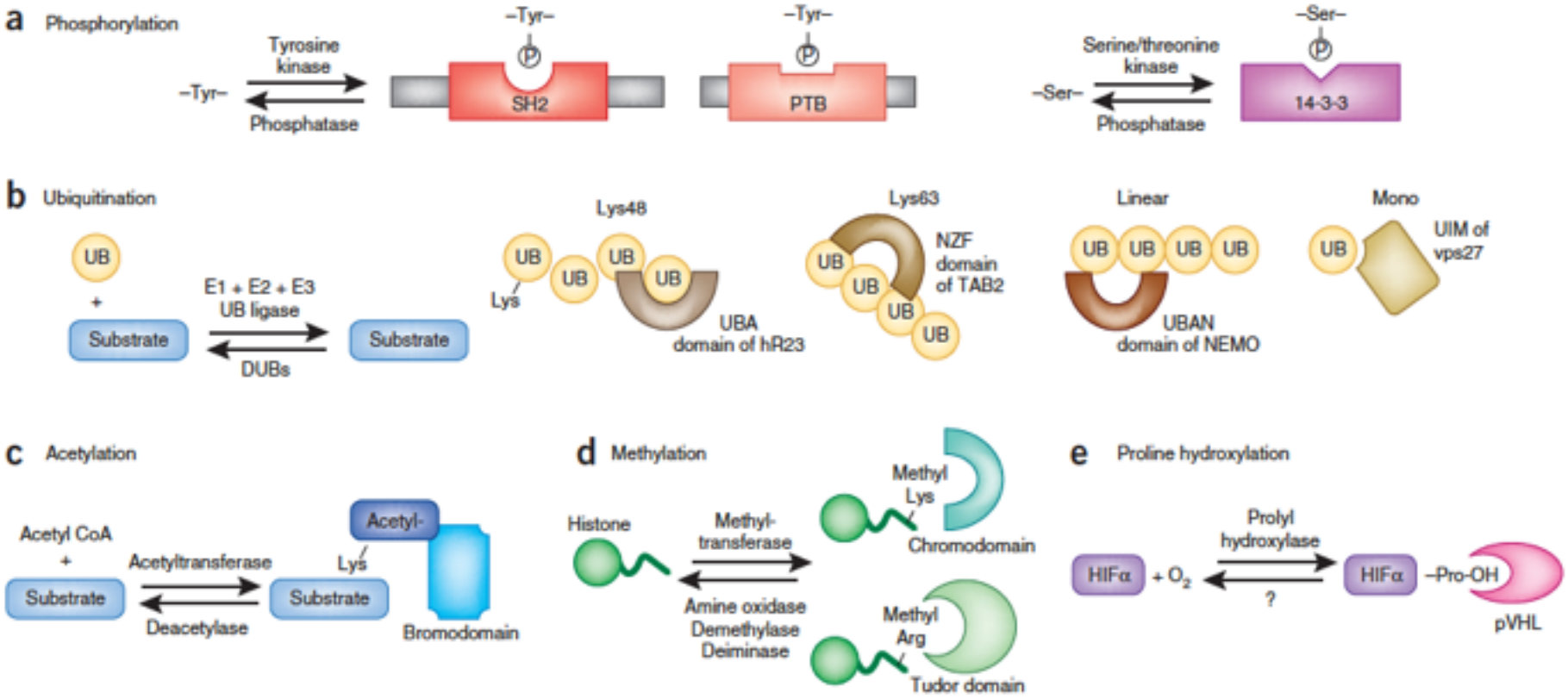


Figure 6.10a *The Biology of Cancer* (© Garland Science 2014)

Post-ranslational Modifications (PTMs) in Signal Transduction



Representative PTMs, the enzymes that catalyze the reactions and PTM-specific binding domains. Phosphorylation (**a**), ubiquitination (**b**), acetylation (**c**), methylation (**d**) and proline hydroxylation (**e**). Left, simplified depictions of the reactions that add or remove the PTM. Right, typical domains that bind the protein substrates only when decorated with the specific PTMs. UB, ubiquitin; DUB, deubiquitinating enzyme; UBA, ubiquitin associated; NZF, novel zinc finger; Pro-OH, hydroxylated proline.

Deribe et al., 2010. *Nature Structural & Molecular Biology*, 17: 667- 672

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

Name of domain	Ligand	Example 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), Akt/PKB (ser/thr kinase), BTK

[a]At least 32 distinct types of binding domains have been identified. 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.

Receptor Dimerization and Autophosphorylation Following Ligand Binding

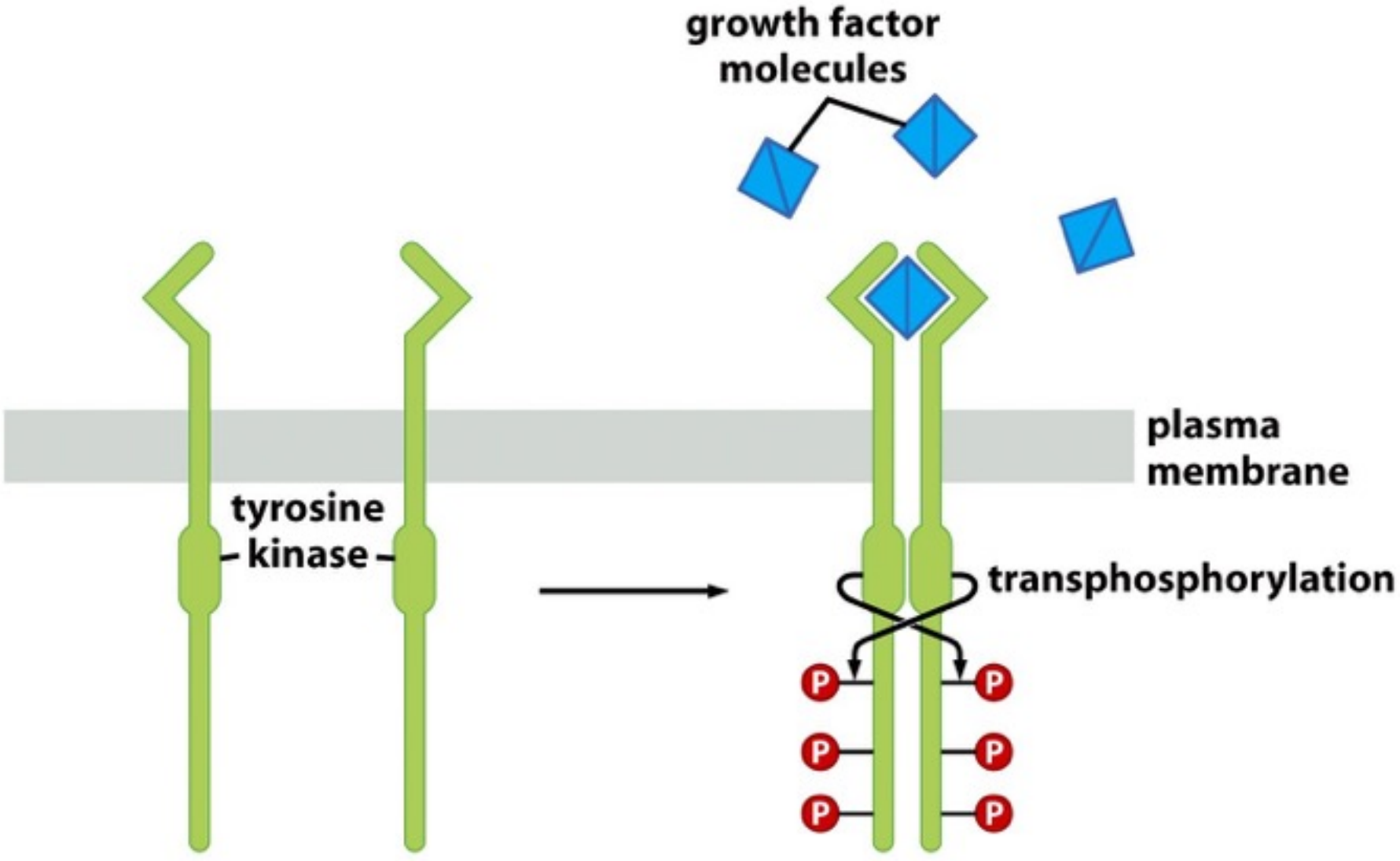
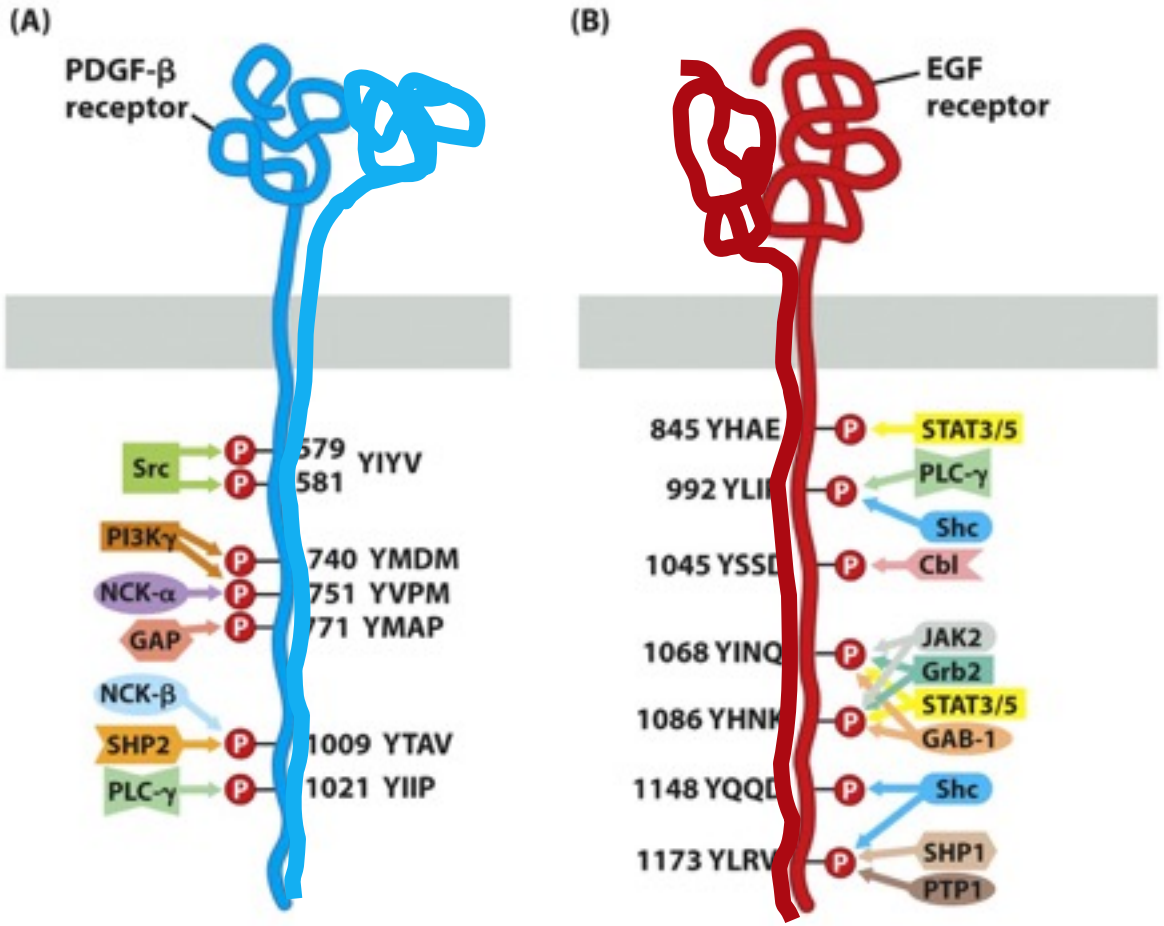


Figure 5.15 *The Biology of Cancer* (© Garland Science 2007)

Attraction of Signal Transducing Proteins by Phosphorylated Receptors



Adapted from: Figure 6.9 *The Biology of Cancer* (© Garland Science 2007)

Which proteins are affected thereafter by the receptor phosphorylation events?

How does this phosphorylation lead further to a mitogenic response by the cell −its entrance into a phase of active growth and division?

Ras Activation by GEF

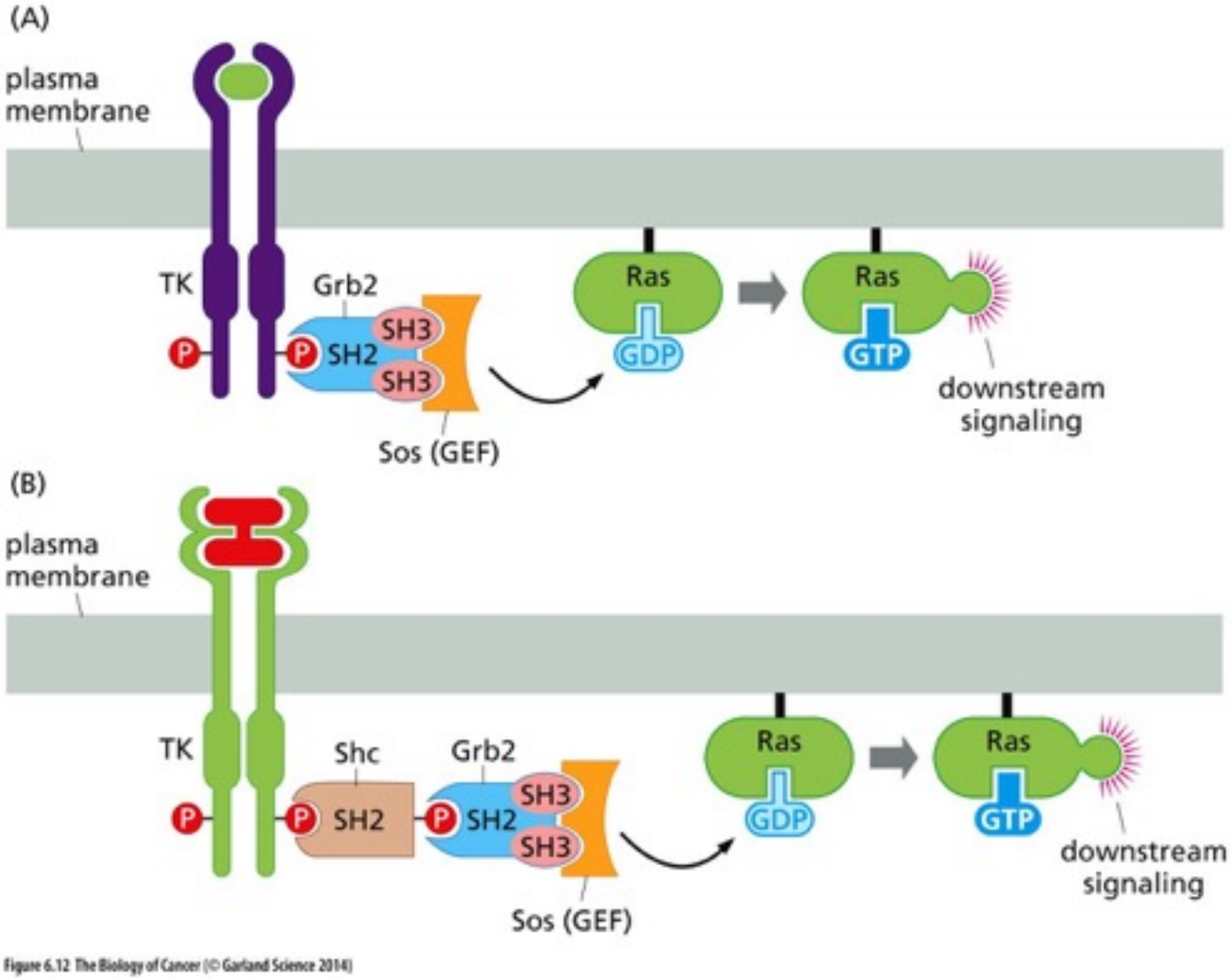


Figure 6.12 The Biology of Cancer (© Garland Science 2014)

Receptor → Grb2 → Sos → Ras or Receptor → Shc → Grb2 → Sos → Ras

The Ras Signaling Cycle

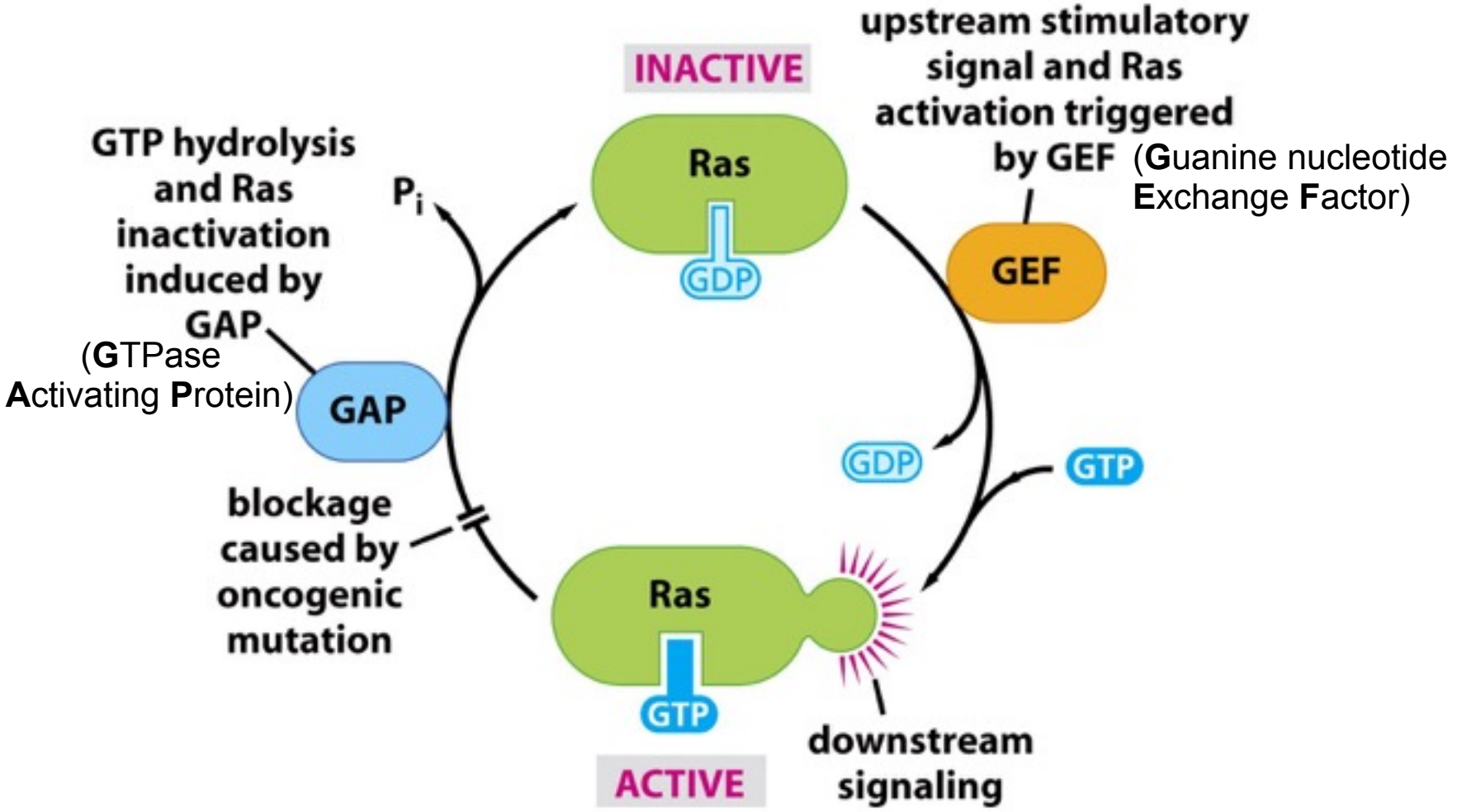


Figure 5.30 *The Biology of Cancer* (© Garland Science 2007)

The Structure of The Ras Protein

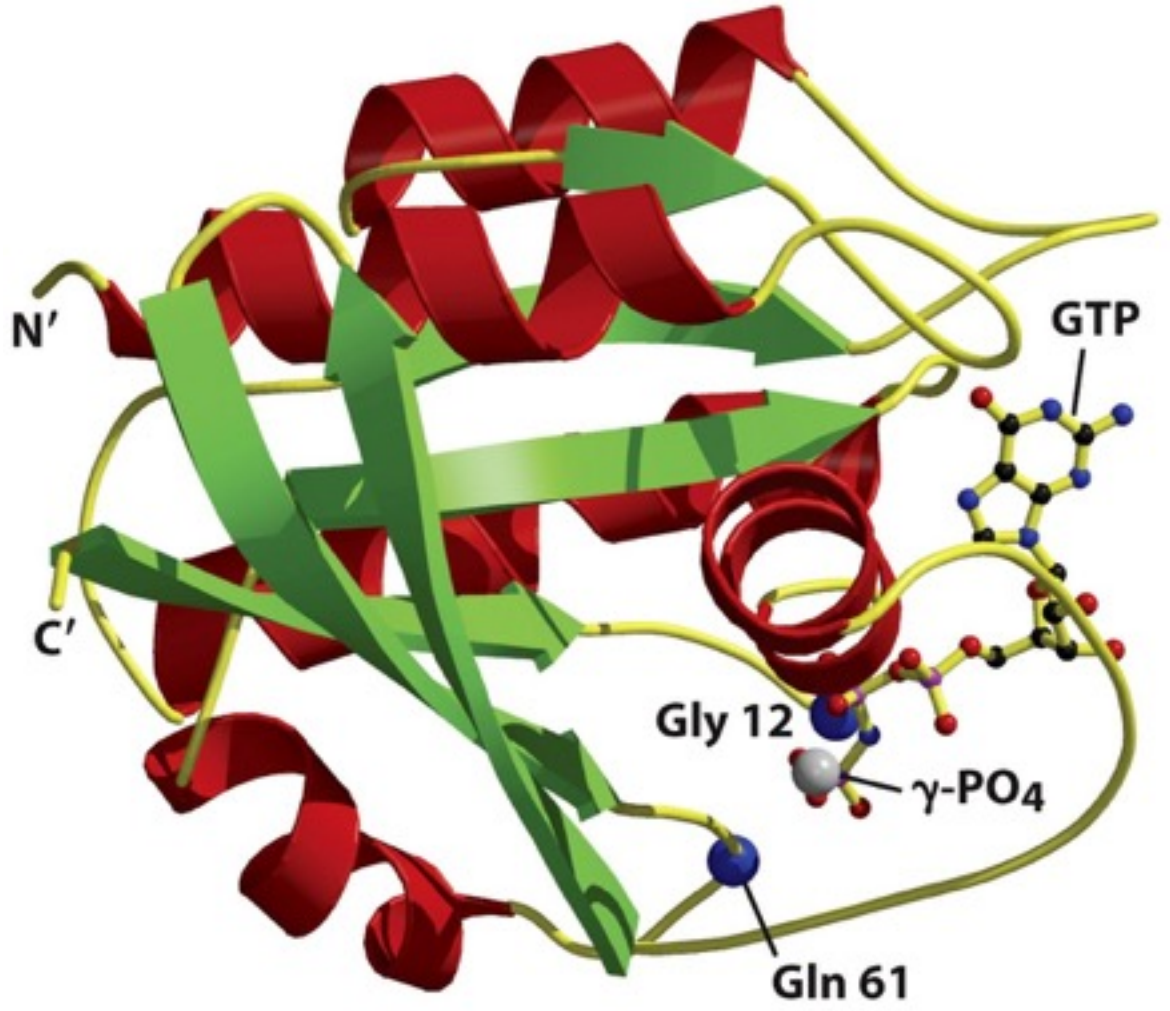


Figure 5.31 *The Biology of Cancer* (© Garland Science 2007)

The Ras Effector Loop

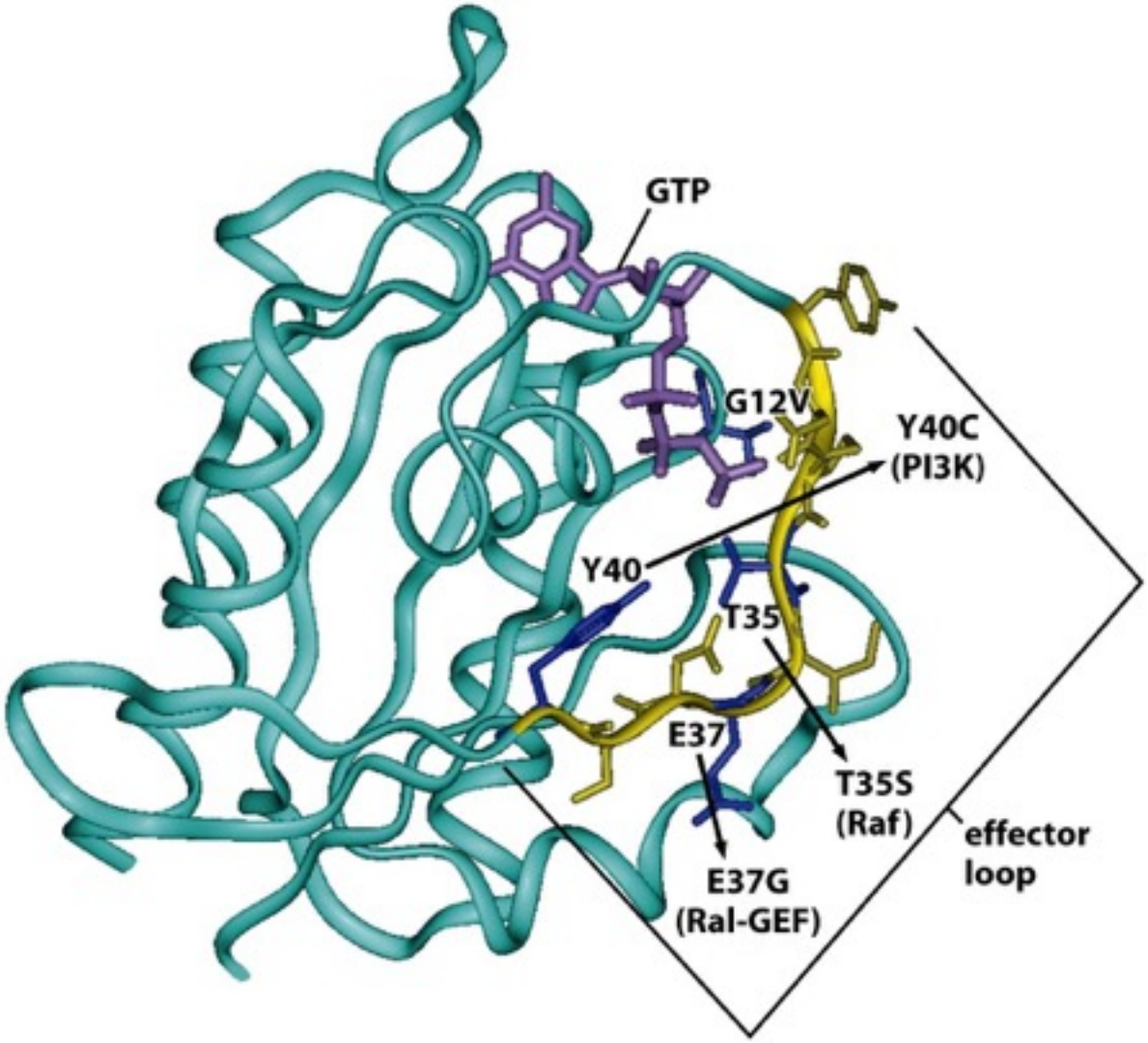


Figure 6.13 *The Biology of Cancer* (© Garland Science 2007)

The Ras—Raf—Map kinase Pathway

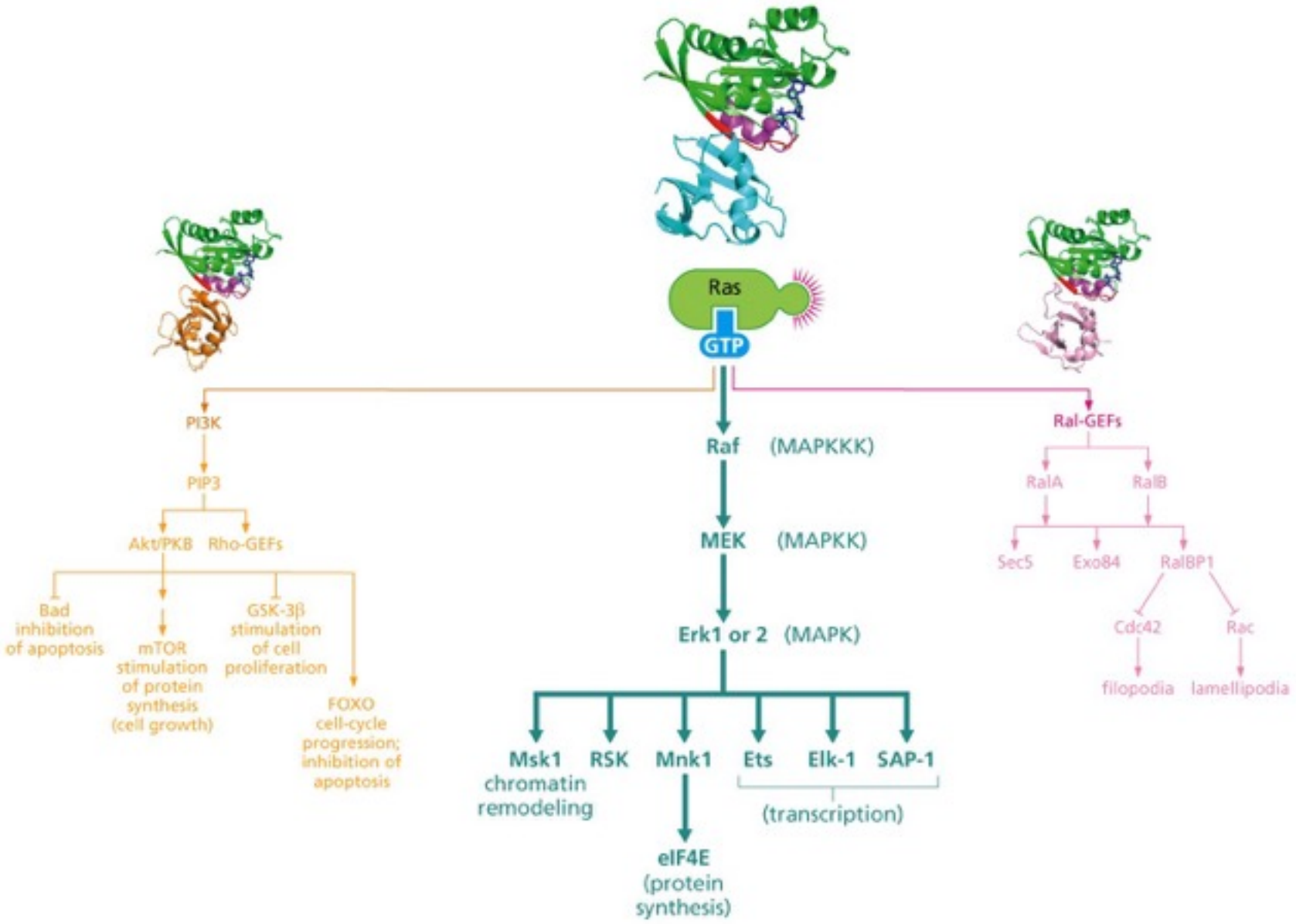
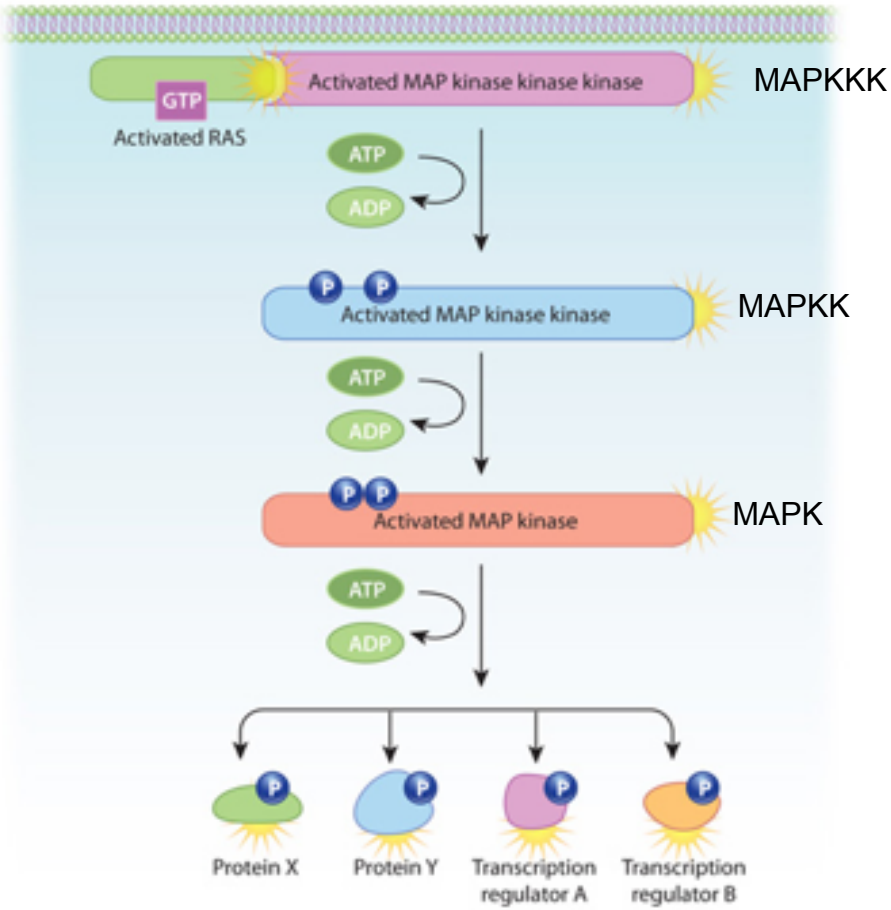


Figure 6.14 The Biology of Cancer (© Garland Science 2014)



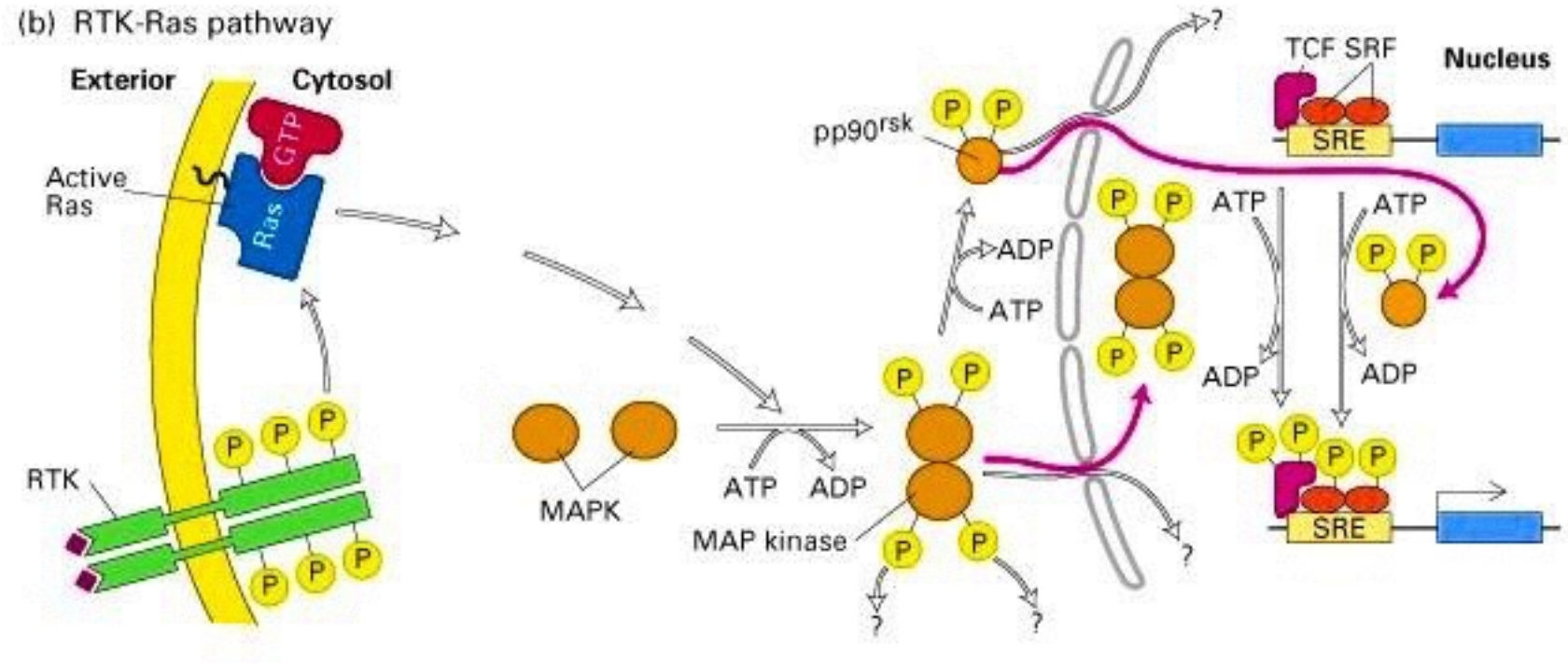
Ras MAP kinase activation: A common pathway activated by growth factors

RTKs can activate Ras, a protein that is tethered to the plasma membrane, by causing it to bind GTP. Once activated, Ras can do a variety of things. In this example, it activates an enzymatic cascade of MAP kinases. This results in potent changes in the cell, such as the alteration of key proteins and changes in gene transcription.

http://www.nature.com/scitable

Activation of Ras Pathway Following Binding of A Hormone (e.g., EGF) to An RTK

(From Cell Membrane to the Nucleus)



Lodish et al., Molecular Cell Biology

Expression of Immediate Early Genes -Analyzed by Gene Expression Array

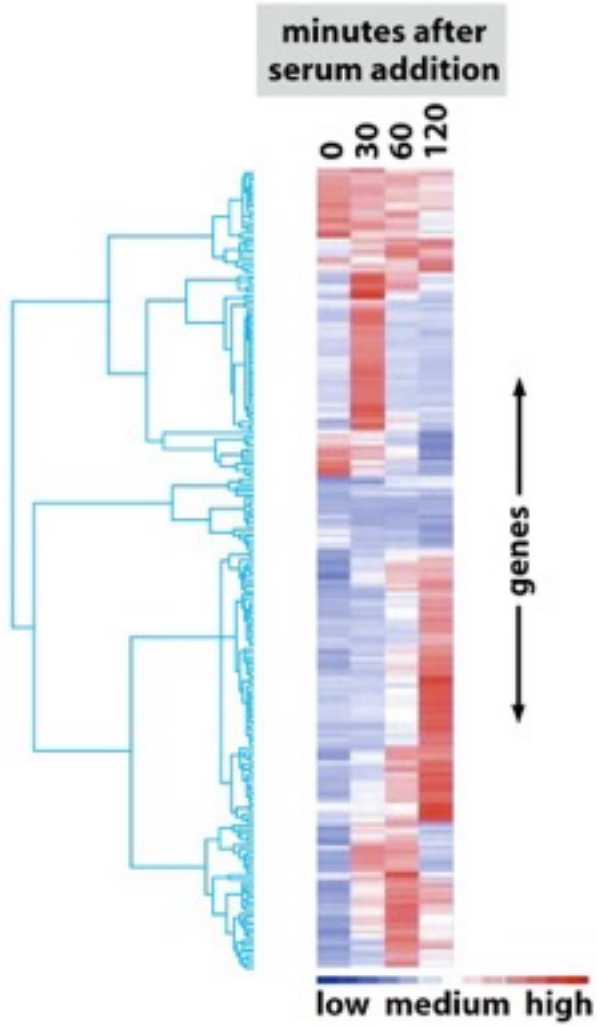
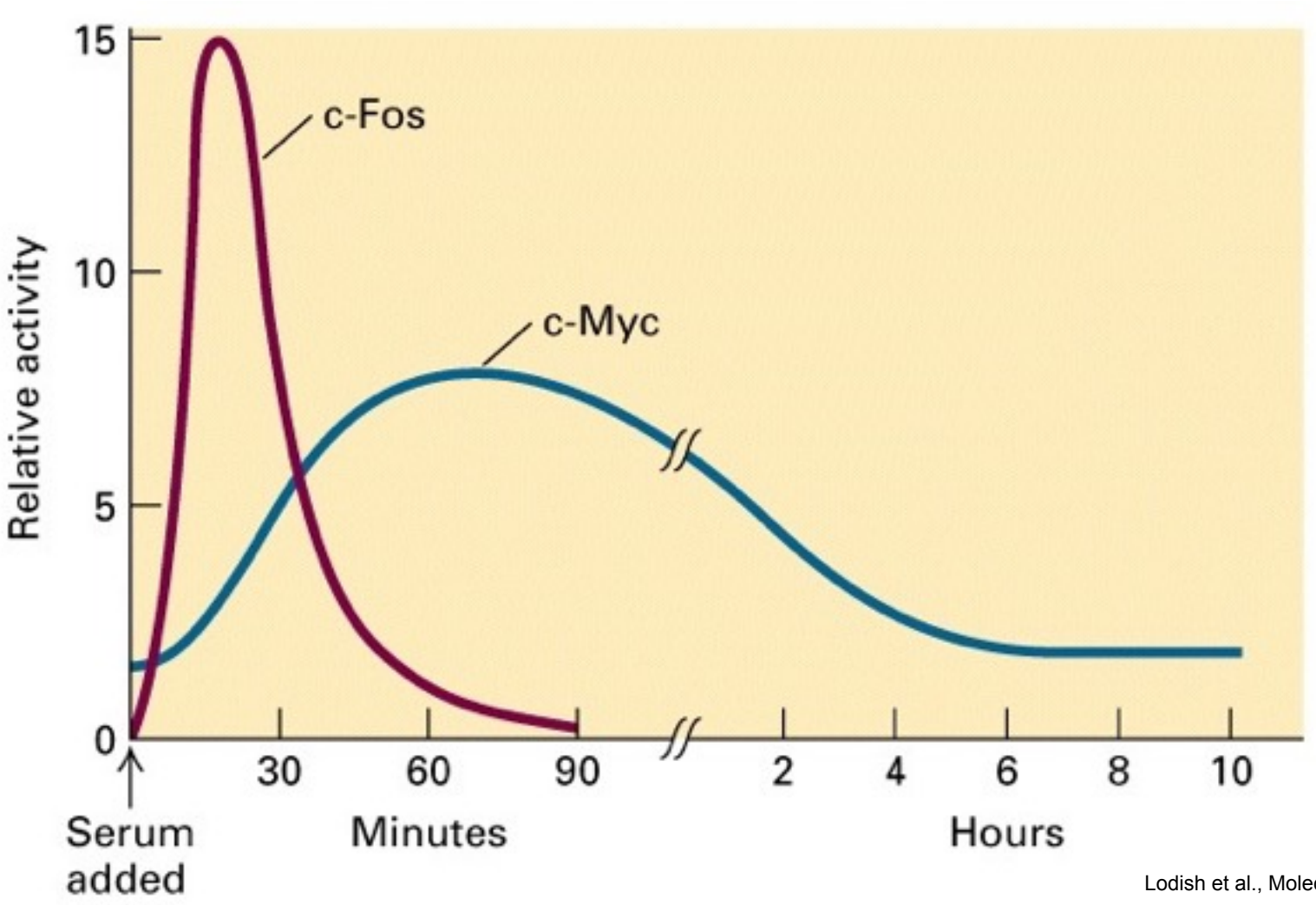


Figure 6.2 *The Biology of Cancer* (© Garland Science 2007)

Activity of Two Proto-Oncogene Products Following Serum Stimulation of Quiescent Cells



Lodish et al., Molecular Cell Biology

The PI3 Kinase Pathway

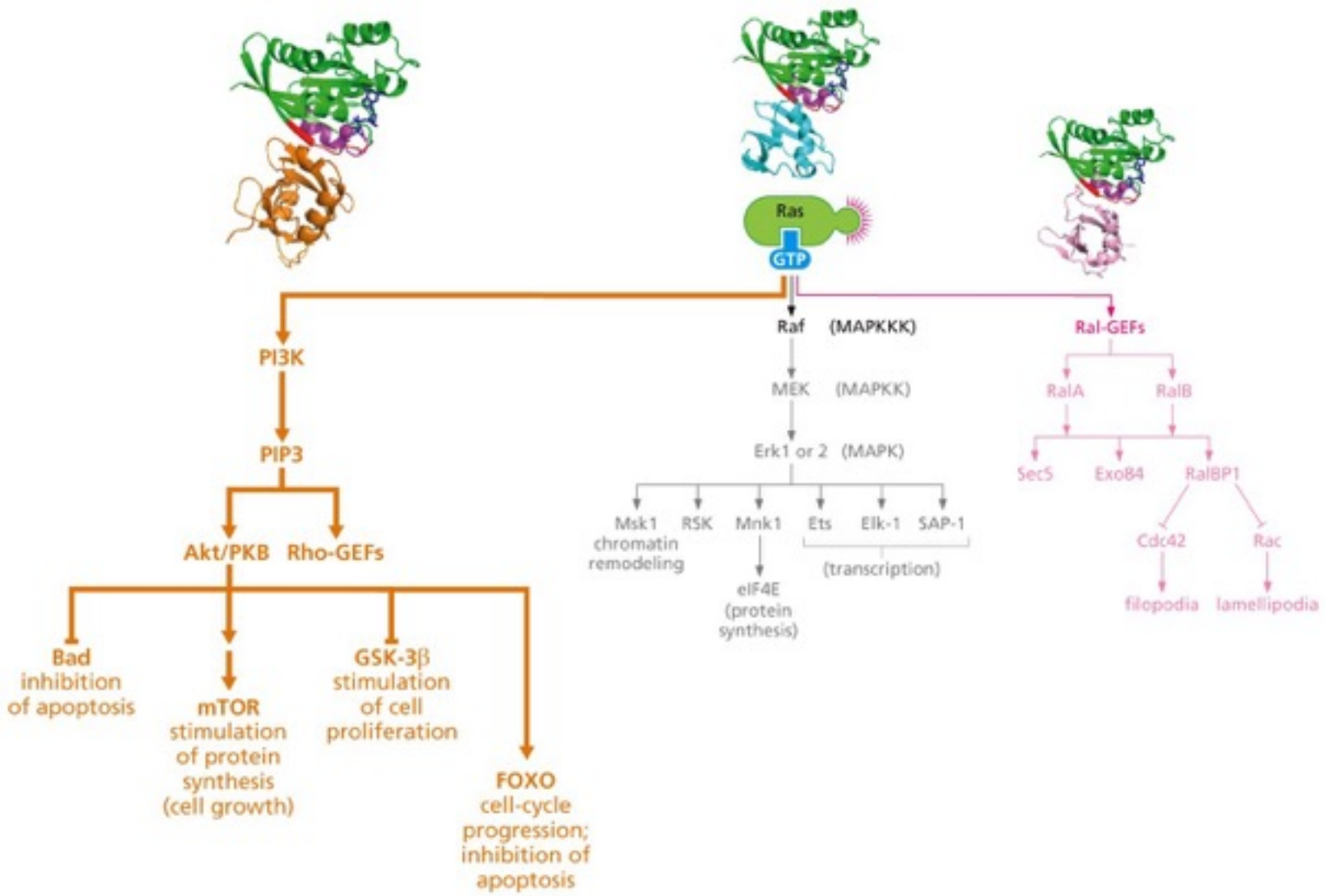


Figure 6.15 The Biology of Cancer (© Garland Science 2014)

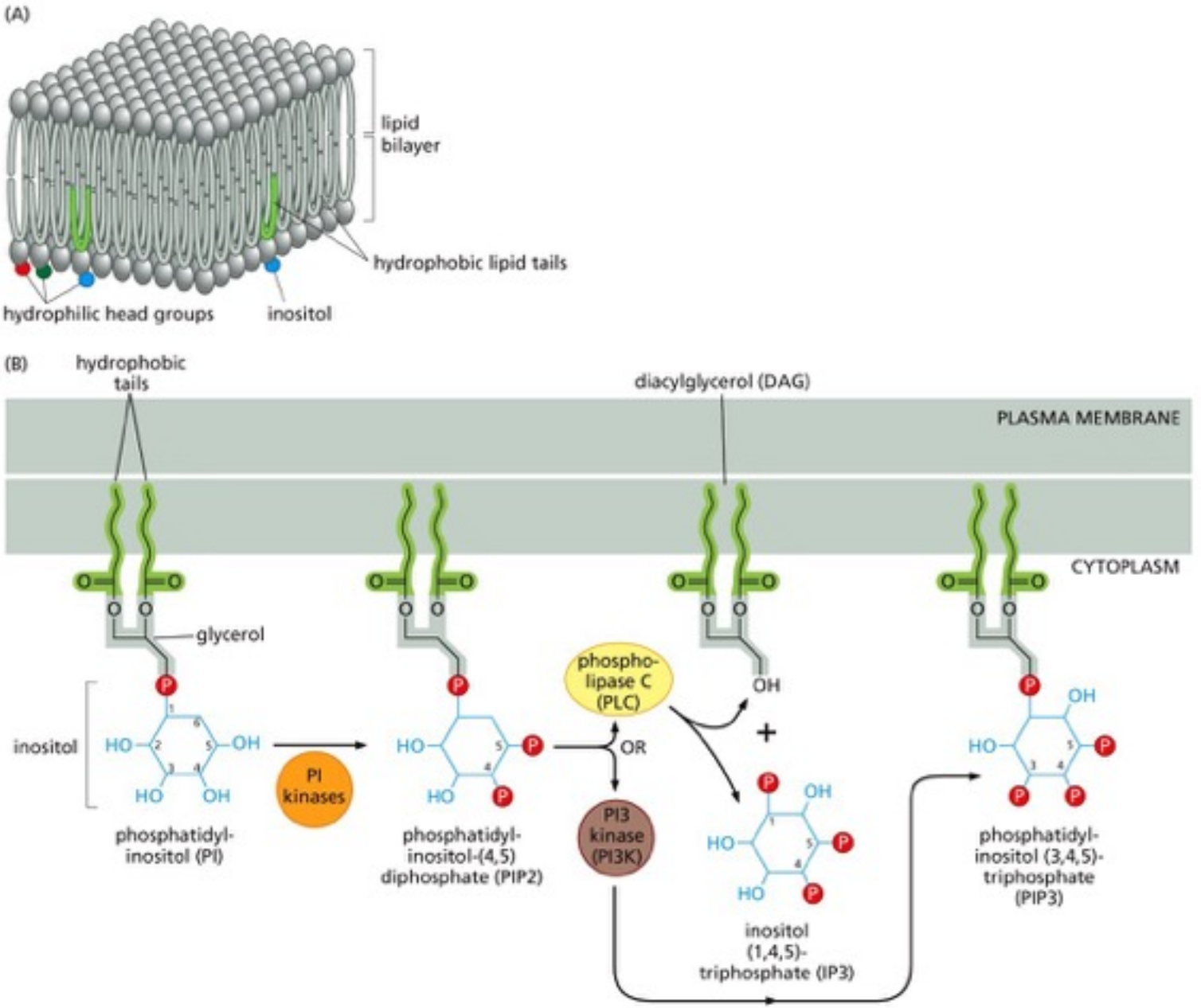


Figure 6.16 The Biology of Cancer (© Garland Science 2014)

Activation of PI3K by Ras

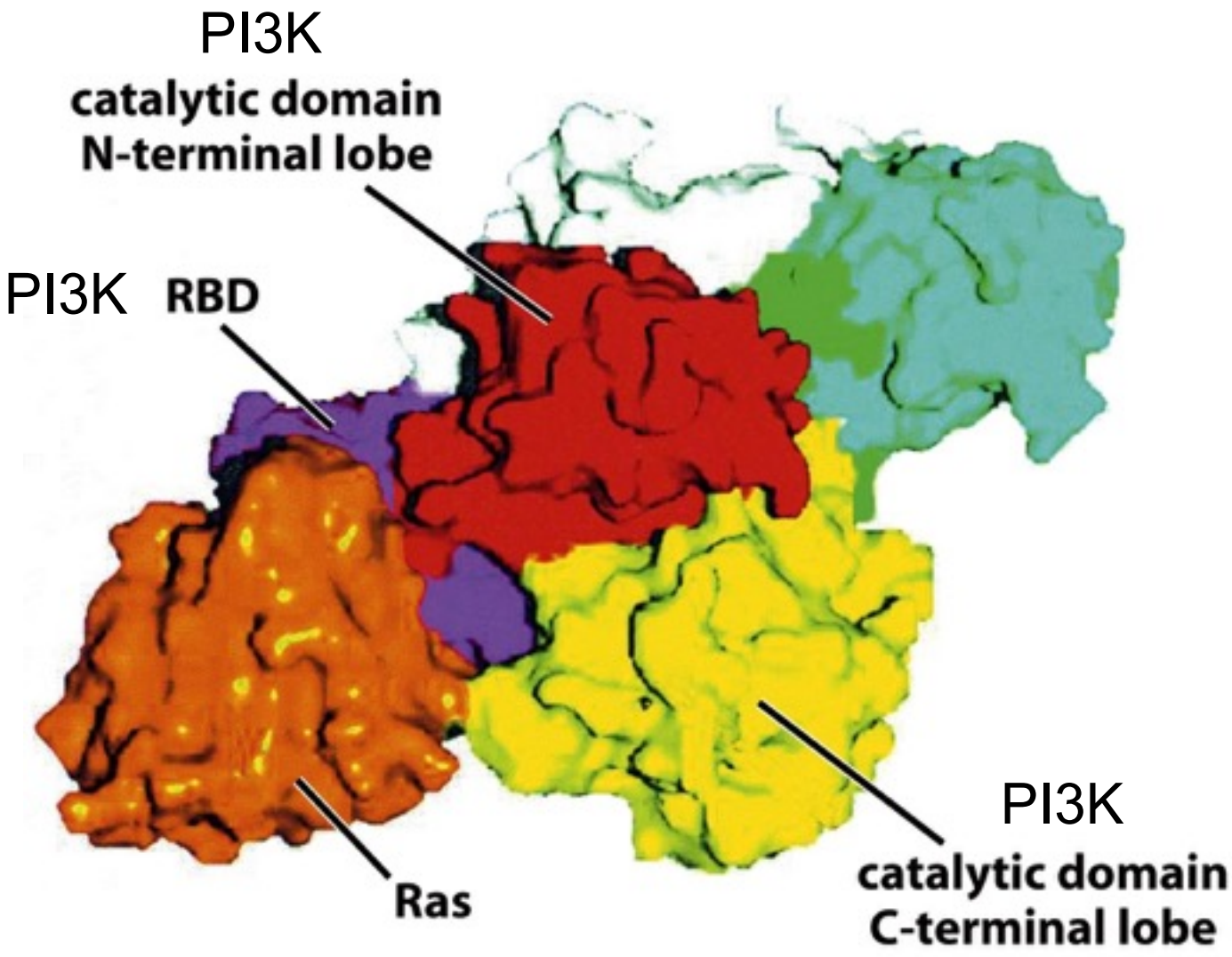
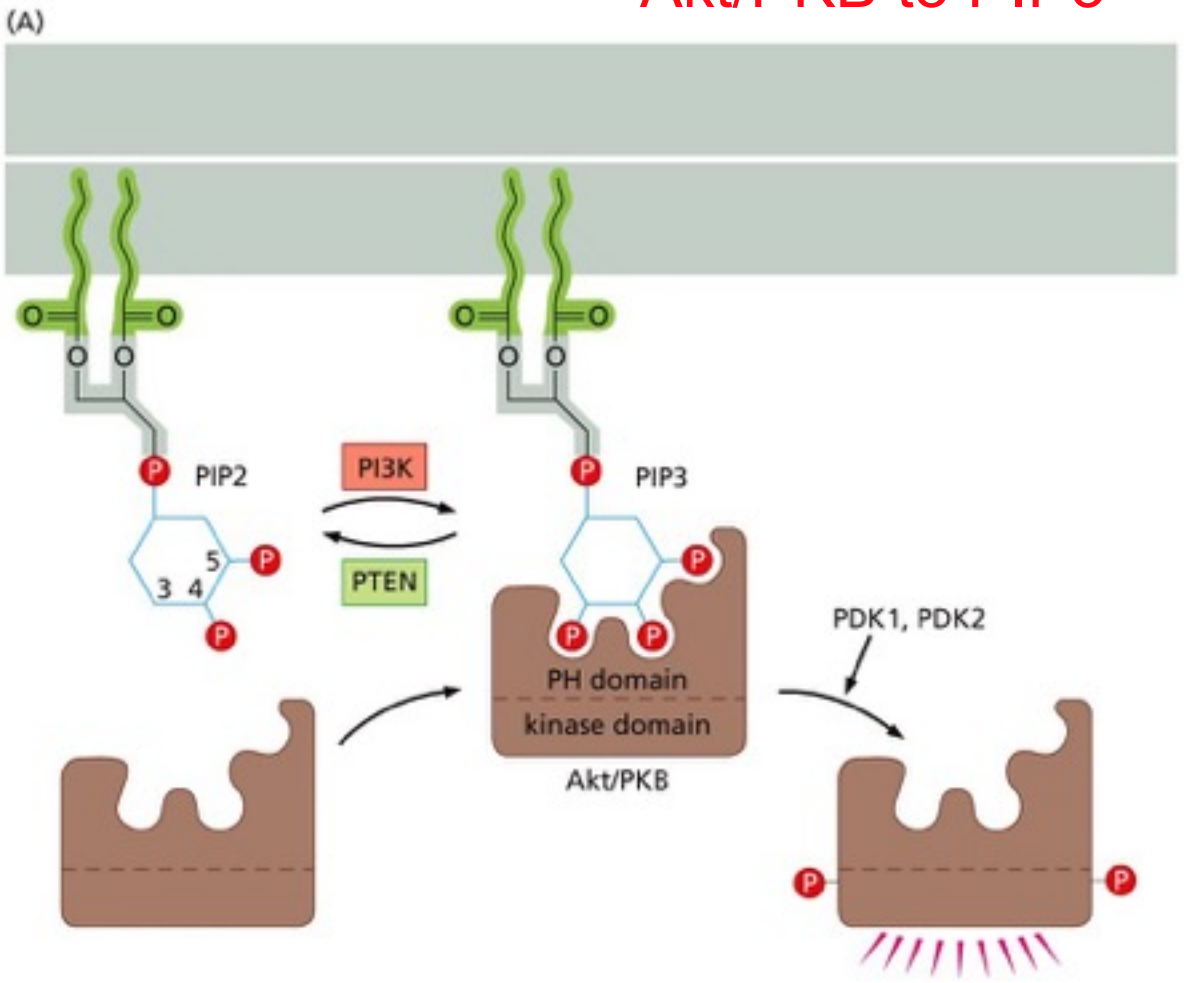
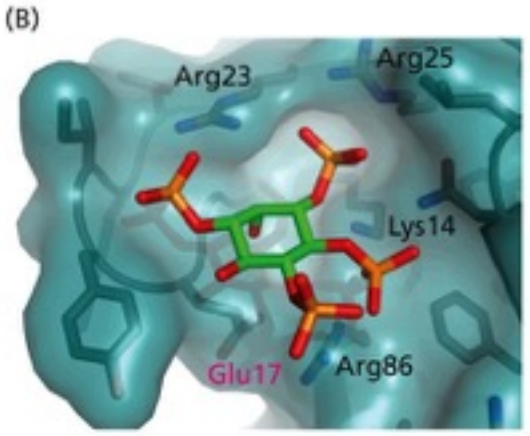
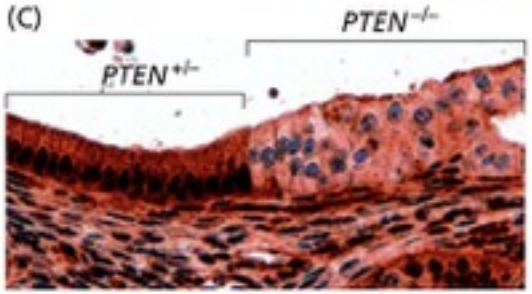


Figure 6.17 *The Biology of Cancer* (© Garland Science 2007)

Docking of PH (Peckstrin Homology) Domains of Akt/PKB to PIP3







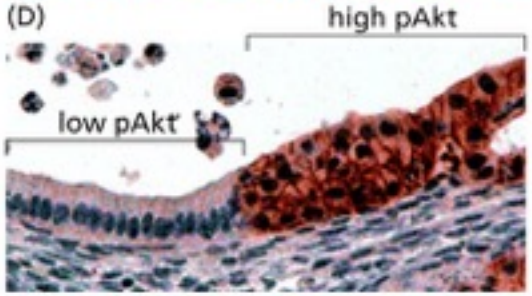


Figure 6.19 The Biology of Cancer (© Garland Science 2014)

New Somatic Mutation in AKT Identified

A somatic mutation in human breast, colorectal, and ovarian cancers that results in **glutamic acid to lysine** substitution at aminoacid 17 (E17K) in the lipid-binding pocket (that includes the PH domain) of AKT1 has been identified. This results in activation of AKT by pathological localization to the plasma membrane stimulating downstream signaling, transforms cells and induces leukemia in mice.

This mutation decreases the sensitivity to an allosteric kinase inhibitor.

Nature, 2007 July 26, 448:439-444.

Phosphorylation by Serine/Threonine Kinase Akt/PKB

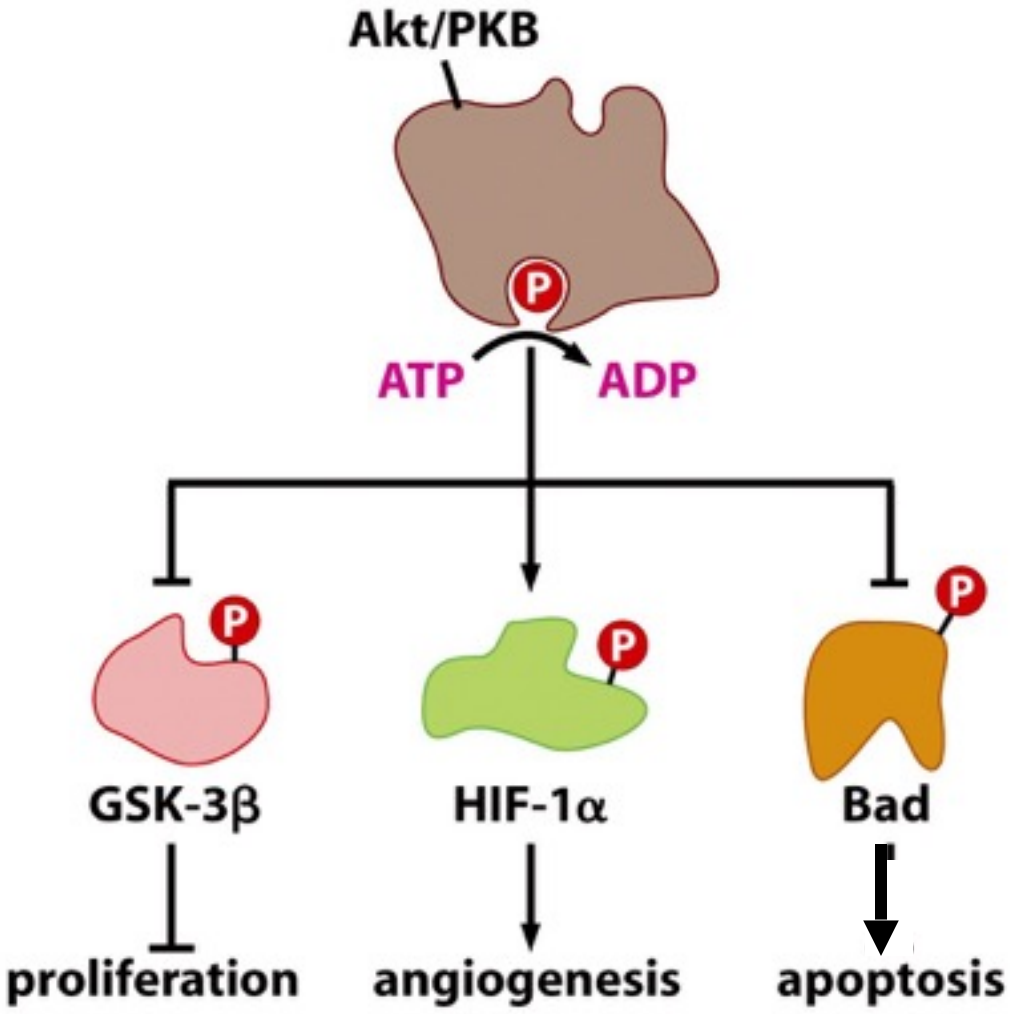
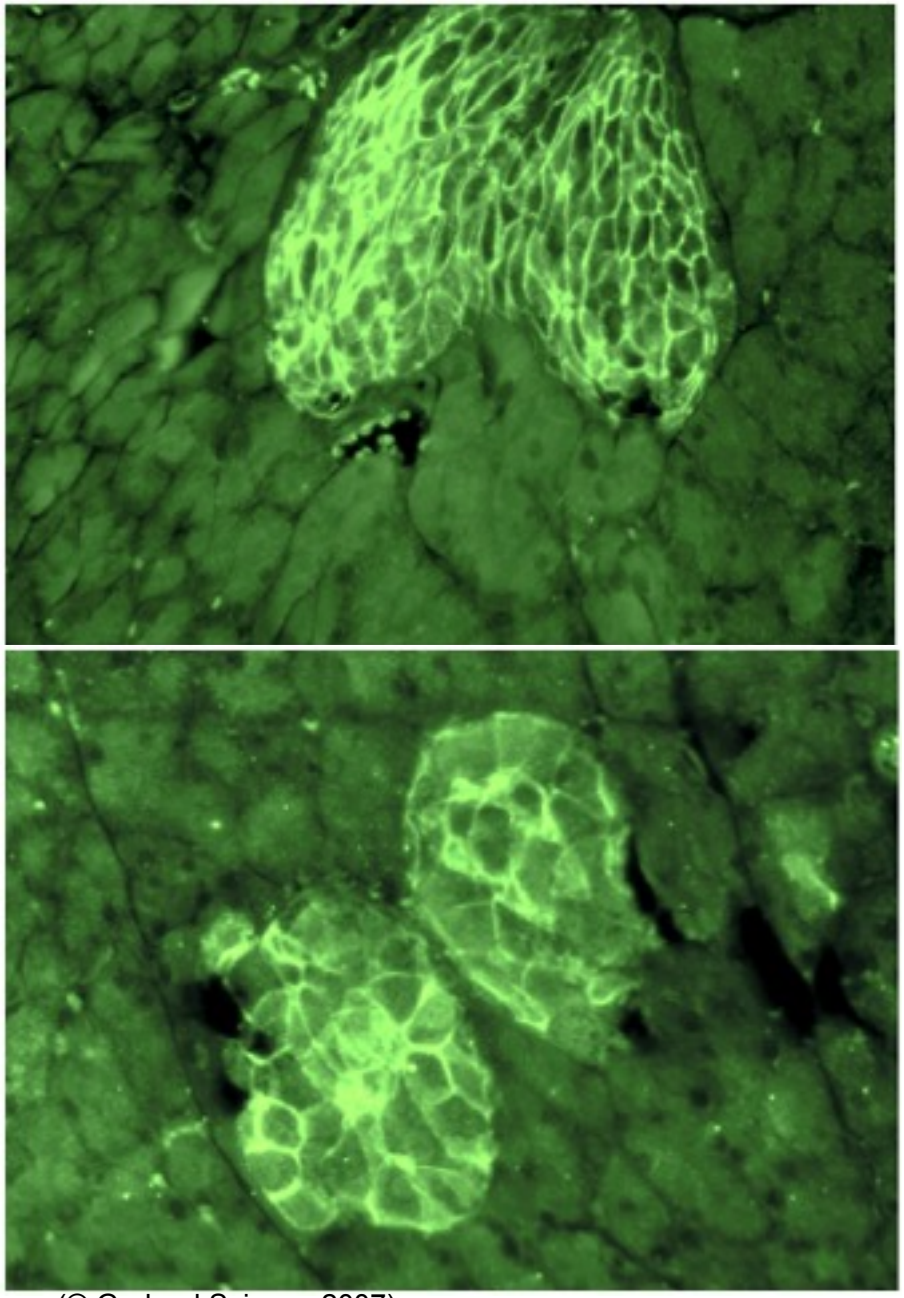


Figure 5.7b *The Biology of Cancer* (© Garland Science 2007)

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

Akt/PKB and the Control of Cell Growth



A. Normal Pancreatic Islet

B. Pancreatic Islet with Constitutively Active Akt/PKB kinase

Figure 6.20 A&B *The Biology of Cancer* (© Garland Science 2007)

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.

Viral Strategy
to Subvert Cellular Signaling

Autocrine Signaling in Kaposi's Sarcoma

- In Kaposi's sarcoma (discovered by Moritz Kaposi, 1872; caused by human herpes virus 8 (HHV-8); a tumor of cells closely related to the endothelial cells that form lymph ducts), the tumor cells produce PDGF, TGF-β, IGF-1, Ang2, CC18/14, CXCL11, and endothelin (ligands of cellular origin) as well as receptors for these ligands.
- Also, the HHV-8 genome produces two additional ligands-vIL6 (viral IL6) and vMIP (viral macrohage inflammatory protein), and their receptors

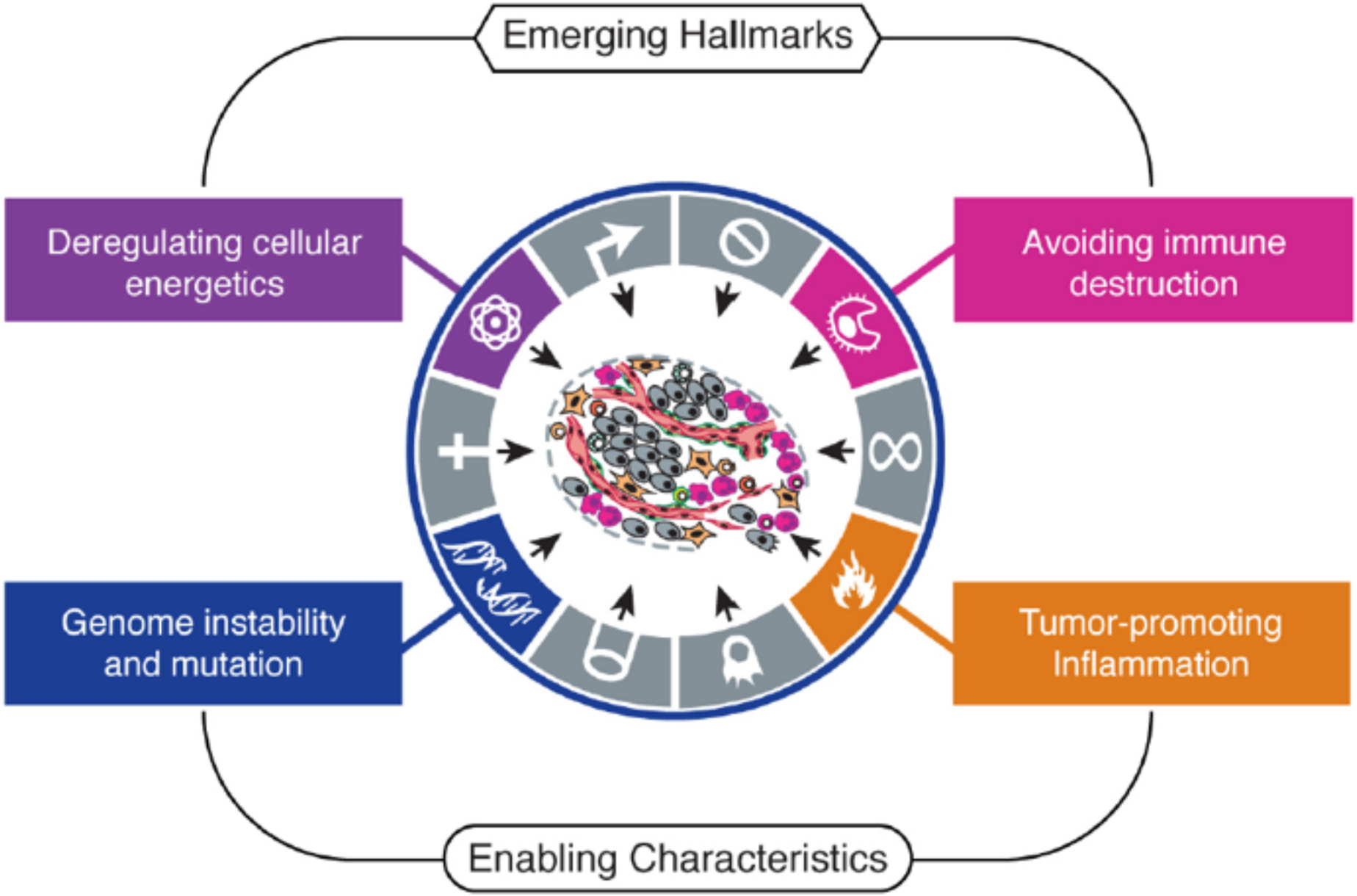
HPV Strategy to Cause Human Cervical Cancer by Defeating Cellular Regulatory Signaling

E6 protein inhibits p53

E7 protein inhibits Rb

E5 protein causes sustained activation of PDGF receptor

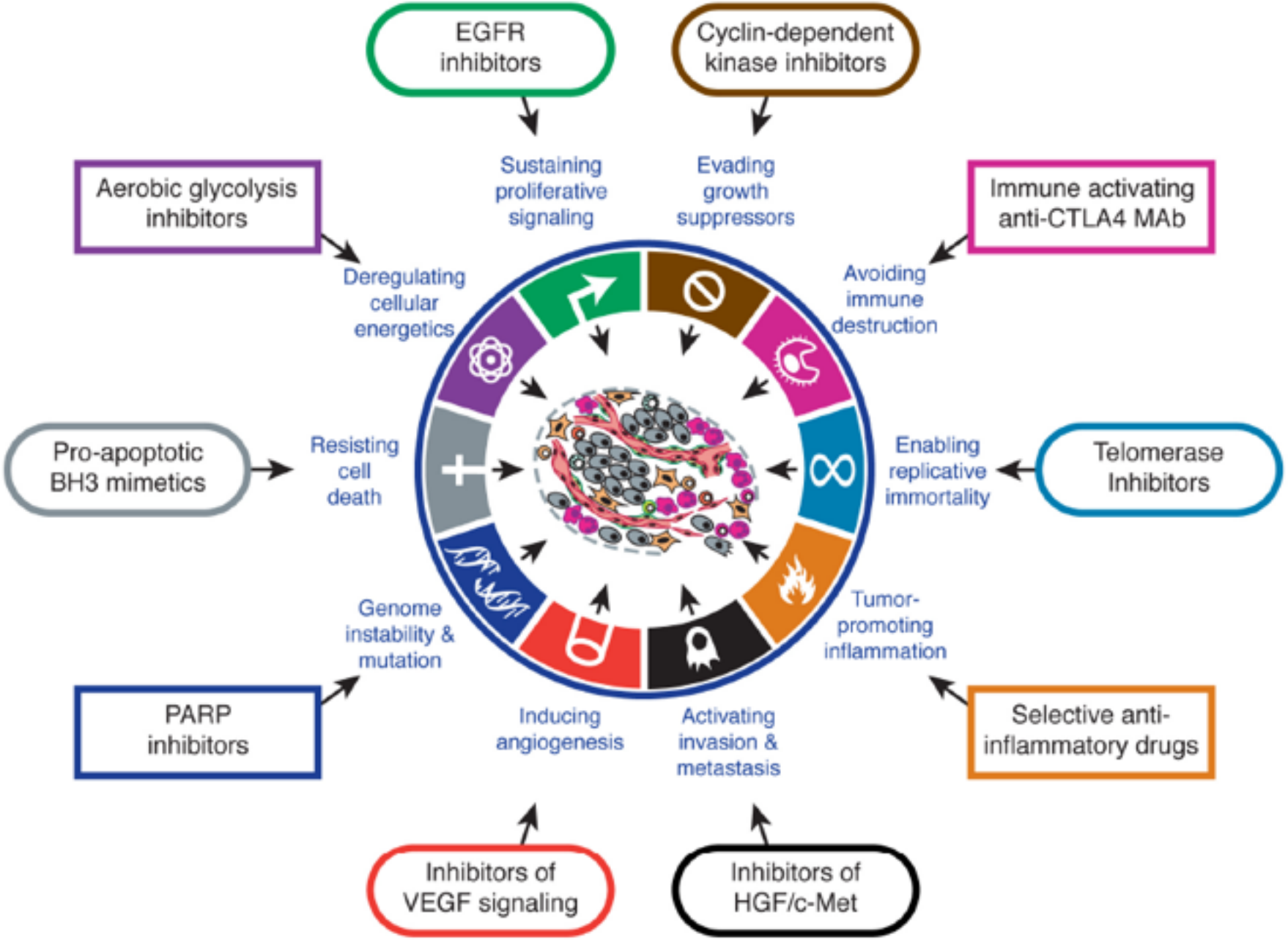
Estrogen increases E5's ability to cause cervical cancer



Hanahan and Weinberg, 2011

Cell PRESS

Signal Transduction and Cancer Therapy



Hanahan and Weinberg, 2011

Cell PRESS

Inhibition of Tumor Growth by Targeting Signaling Proteins

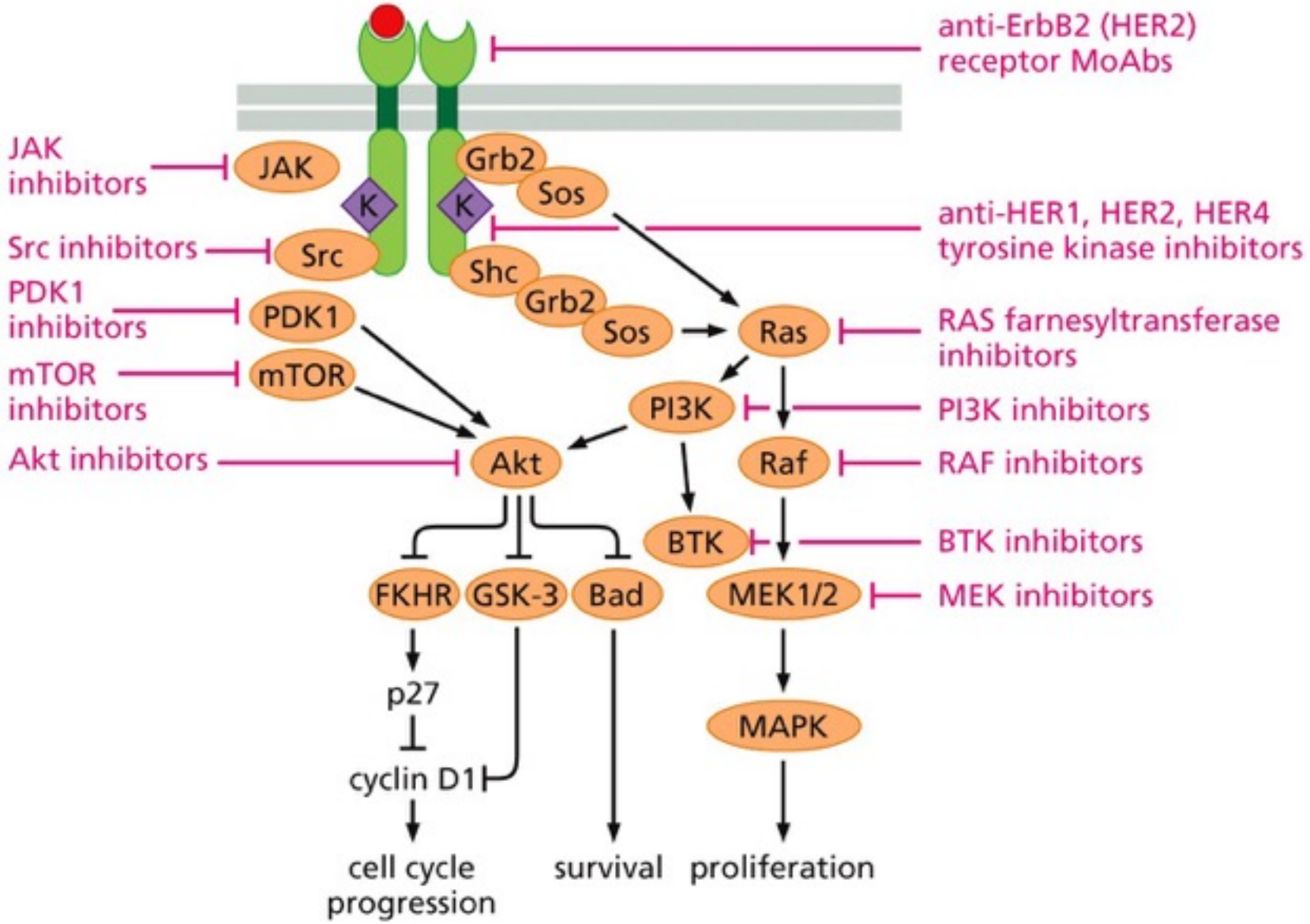


Figure 16.9 The Biology of Cancer (© Garland Science 2014)

Table 1 | **Agents that target ERBB2 and ERBB3 for the treatment of human cancers**

Agent	Molecular target	Mechanism of action	Highest development status (protocol number or NCT ID number)	Licensed indications
Antibody-based agents				
Trastuzumab (Herceptin; Genentech)	ERBB2	Suppression of ERBB2 signalling, ERBB2 stabilization, marks cells for immunological attack	• Launched for breast cancer • ERBB2-positive gastric cancer — Phase III (BO18255)	ERBB2-positive metastatic breast cancer, ERBB2-positive early breast cancer
Pertuzumab (Genentech/ Hoffmann-La Roche)	ERBB2	Dimerization inhibitor, marks cells for immunological attack	• Breast cancer — Phase III (NCT00567190) • Ovarian cancer — Phase II (NCT00096993, NCT00058552)	None
Trastuzumab–DM1 (Genentech)	ERBB2	Targeted delivery of a potent anti-microtubule cytotoxic agent	Breast cancer — Phase III (NCT00829166)	None
Ertumaxomab (Fresenius Biotech GmbH)	ERBB2	Bispecific affinity allows recruitment of T cells	Breast cancer — Phase II (NCT00351858, NCT00522457, NCT00452140)	None
AMG 888 or U3-1287 (Amgen)	ERBB3	Not yet defined	Phase I (NCT00730470)	None
TKIs				
Lapatinib (Tykerb; GlaxoSmithKline)	ERBB2	TKI	• Launched for breast cancer • ERBB2-positive gastric cancer — Phase III (NCT00486954, NCT00650901) • NSCLC — Phase II (NCT00528281) • Head and neck cancer — Phase II (NCT00490061, NCT00387127, NCT00424255) • Colorectal adenocarcinoma — Phase II (NCT00574171)	In combination with capecitabine for advanced ERBB2-positive breast cancer previously treated with an anthracycline, a taxane or trastuzumab
HKI-272 (Wyeth)	EGFR, ERBB2	Irreversible TKI	Breast cancer — Phase III (NCT00777101)	None
ARRY-334543 (Array BioPharma)	EGFR, ERBB2, ERBB4	Reversible TKI	Breast cancer — Phase II (NCT00710736)	None
BIBW-2992 (Boehringer Ingelheim)	EGFR, ERBB2	Irreversible TKI	• Breast cancer — Phase II (NCT00425854, NCT00826267, NCT00708214) • NSCLC — Phase III (NCT00425854, NCT00826267, NCT00708214) • Head and neck cancer — Phase II (NCT00514943)	None
Heat-shock protein inhibitors				
17-AAG (Bristol-Myers Squibb)	HSP90	Inhibitory activity reduces the stability of ERBB2, causes abrogation of ERBB2 signalling	• Multiple myeloma — Phase III (NCT00514371) • Breast cancer — Phase II (NCT00817362)	None
IPI-504 (Infinity Pharmaceuticals)	HSP90	Inhibitory activity reduces the stability of ERBB2, causes abrogation of ERBB2 signalling	• Multiple myeloma — Phase II and III (NCT00514371) • Breast cancer— Phase II (NCT00817362) • NSCLC — Phase II (NCT00431015) • Melanoma — Phase II (NCT00087386) • Ovarian cancer — Phase II (NCT00093496)	None

EGFR, epidermal growth factor receptor; HSP90, heat shock protein 90; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Baselga & Swain, *Nature Reviews Cancer*, 2009, 9: 463-475

Cancer drugs that act against tyrosine kinases

Drug	Cancer	Target
Small-molecule drugs		
Imatinib (Gleevec)	Leukemia (CML)	BCR-ABL tyrosine kinase
Gefitinib (Iressa)	Lung cancer	EGFR tyrosine kinase
Erlotinib (Tarceva)	Lung cancer	EGFR tyrosine kinase
Sunitinib (Sutent)	GIST/renal carcinoma	KIT receptor tyrosine kinase
Dasatinib (Sprycel)	Leukemia (CML)	BCR-ABL tyrosine kinase
Lapatinib (Tykerb)	Breast cancer	ERBB2 receptor tyrosine kinase
Many in clinical trials	Several types/AML	Angiogenesis/FLT3 receptor tyrosine kinases
Monoclonal antibody drugs		
Trastuzumab (Herceptin)	Breast cancer	ERBB2 receptor tyrosine kinase
Cetuximab (Erbitux)	Breast/renal cancer	EGFR tyrosine kinase
Cevacizumab (Avastin)	Colon cancer	VEGF

More than 70 protein kinase inhibitors are in cancer clinical trials, including several directed against serine/threonine kinases implicated in cancer. The RAF inhibitor sorafenib (Nexavar) has recently been approved for treatment of renal cell carcinoma. Rapamycin, an mTOR kinase inhibitor, and rapamycin analogues are also in clinical trials for several cancers.

Hunter, *J. Clinical Investigations*, 2007, 117: 2036.

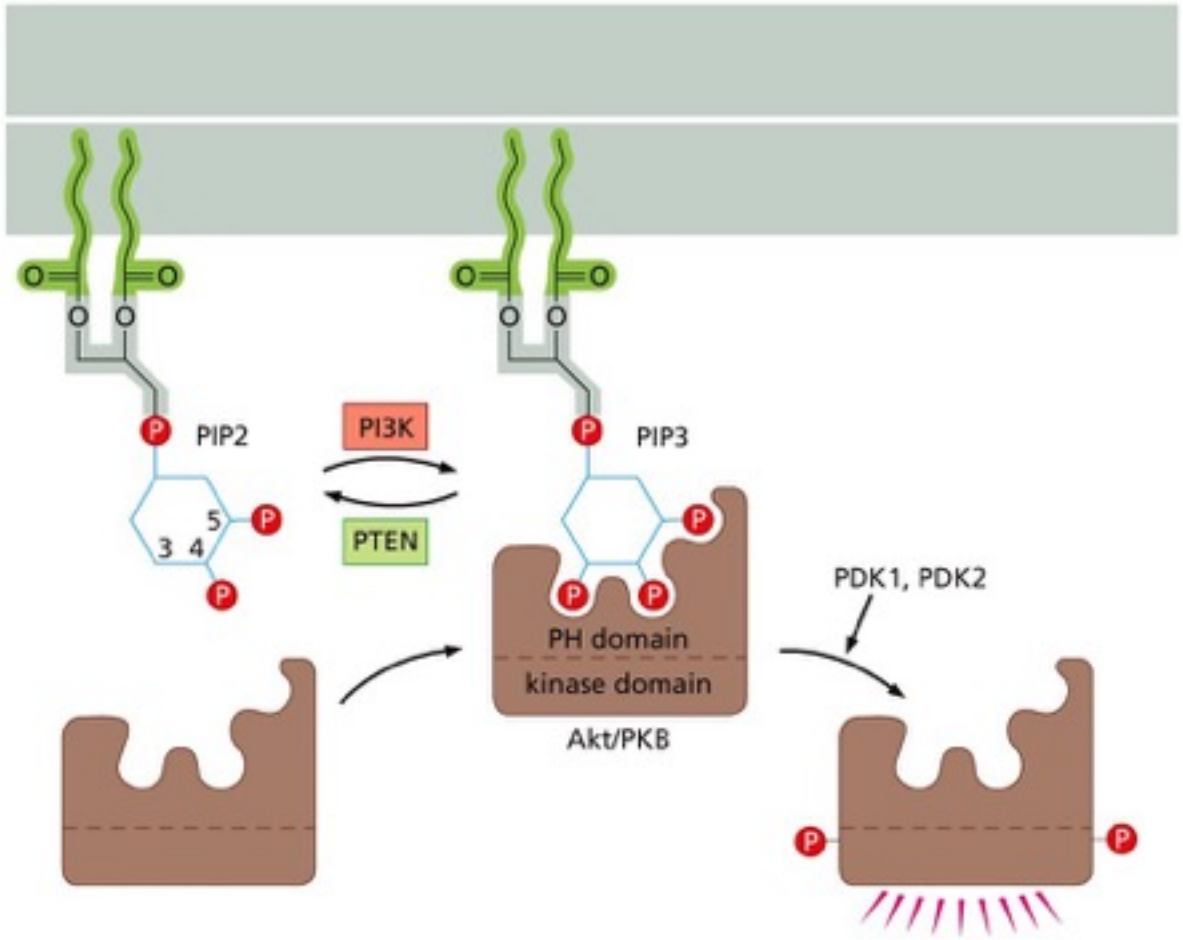
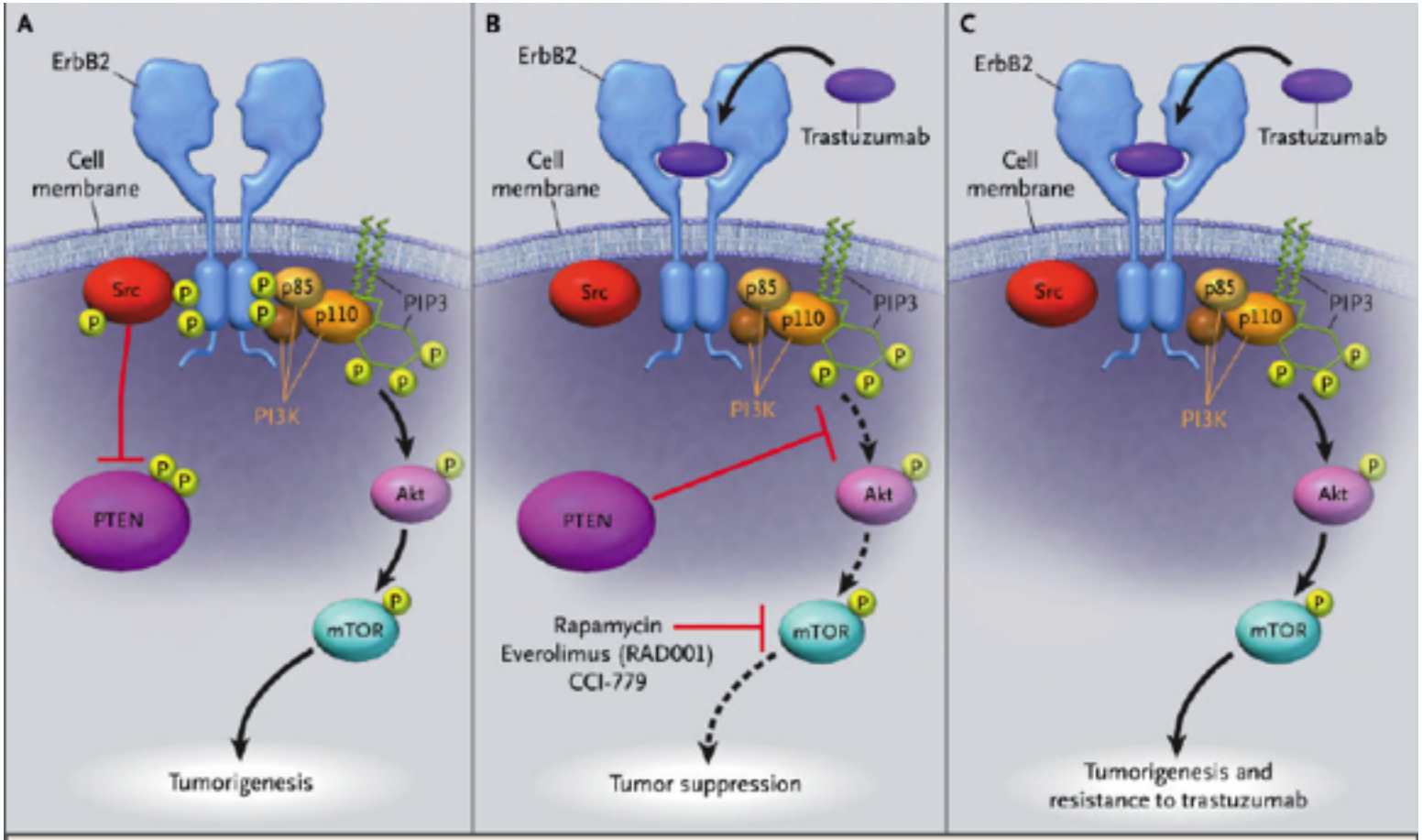


Figure 6.19 The Biology of Cancer (© Garland Science 2014)



Resistance to Trastuzumab Due to PTEN Deficiency.

In Panel A, the overexpression of ErbB2 leads to its activation through autophosphorylation (P). As a result, Src kinase and phosphatidylinositol 3' kinase (PI3K), with its regulatory subunits p85 and p110, are recruited to the receptor and kept in their active state. The activation of PI3K leads in turn to the activation of the proto-oncogenic signaling pathway consisting of Akt and the mammalian target of rapamycin (mTOR). Nagata and colleagues[2] show that when active, Src can inactivate PTEN through the phosphorylation of its C-terminal end. This triggers the production of elevated levels of phosphatidylinositol 3,4,5-triphosphate (PIP3), further potentiating the activation of PI3K. On binding to the ErbB2 receptor, trastuzumab causes the dissociation of the receptor from Src and its inactivation through unknown mechanisms (Panel B). PTEN thus becomes free to antagonize the activation of the PI3K–AKT–mTOR signaling pathway through the dephosphorylation of PIP3. Trastuzumab could be combined with drugs such as sirolimus (rapamycin) and its analogues, everolimus (RAD001) and CCI-779, which inhibit mTOR, to block this critical signaling pathway at two different points. Nagata et al. show that a partial or total deficiency of PTEN (Panel C) may account for resistance to trastuzumab.[2]

(1) Pandolfi, (2004) *N England J Med*, 351, 2327; (2) Nagata et al., (2004) *Cancer Cell*, 6, 117

Underlying Major Themes

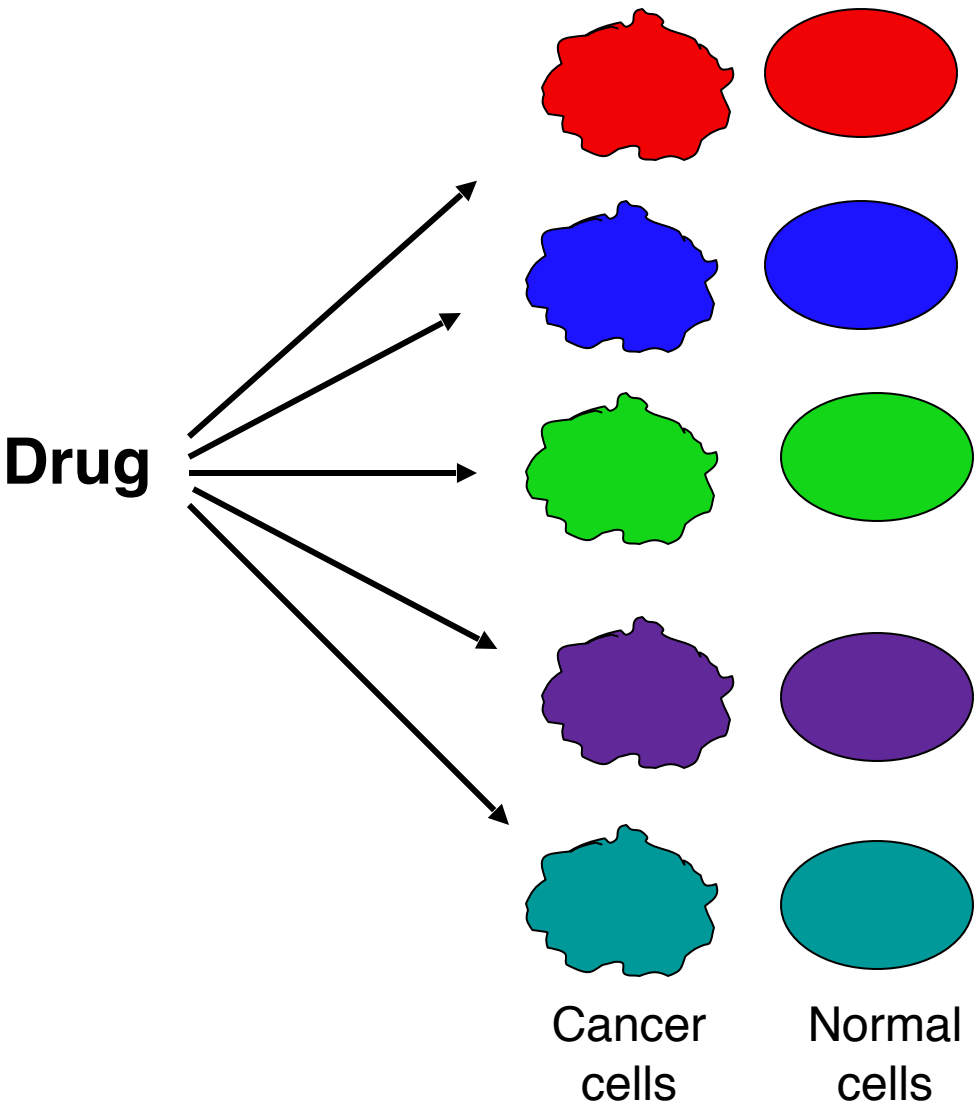
Modulation of:

- **Intrinsic activity** of signaling molecules
- **Concentration** of signaling molecules
- **Intracellular localization** of signaling molecules
- **Post translational modifications** (PMT)

Complexity of Cancer

- In each type of cell, the signaling pathways work in a combinatorial fashion to ensure that proliferation occurs in the right place at the right time during development and repair. Moreover, different cell types use different combinations of pathways to regulate their growth and division. This explains why the biochemistry of cancer is so complex.

Challenges in Cancer Drug Discovery



There can be differences in signaling pathways that are altered among various cancer cells. In other words, defects that caused conversion of a normal cell to a cancer cells need not be the same in all cancers. Moreover, signaling pathways can change during progression of cancer.

Further, variation in **drug delivery**, **drug metabolism**, **drug resistance** and **drug specificity** on cancer cells with minimal effect on normal cells are also major concerns to be confronted in developing effective drugs.

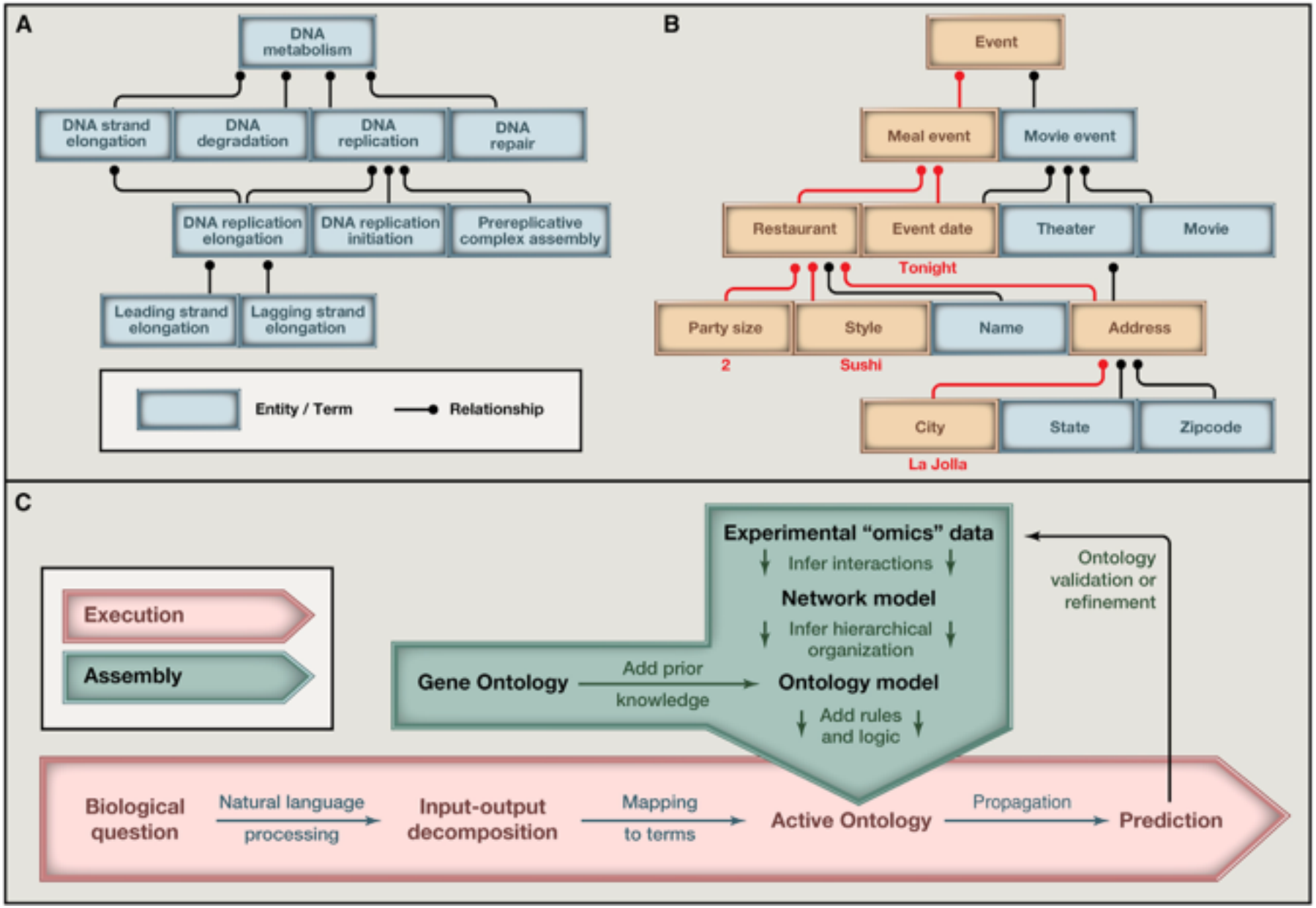
Prevention is better than Cure

The challenge is how to develop an effective prevention strategy with minimal side effects.

Safety
Timing

Better understanding of signaling abnormalities in cancer cells should help develop effective prevention strategies.

Cell ~~Phone~~ Siri?



Carvunis and Ideker, 2014. *Cell*,157: 534-538

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for
Growth Factors/Signal Transduction Lecture

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Robert Weinberg
Garland Science, 2014

(2) Molecular Cell Biology, **Chapters 13, 14, and 23**
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or
Molecular Cell Biology, **Chapters 20 & 24**
H. Lodish, . Berk, S. Zipursky, P. Matsudaria,
D. Baltimore, J. Darnell.
W. H. Freeman and Company (4th Edition), 2000.

Other Recommended reading:
1. D. Hanahan & R.A. Weinberg, *Cell* (2011), 144:646-674.
2. S. Mukherjee, "The Emperor of All Maladies: A Biography of Cancer"

- **Winner of the 2011 Pulitzer prize for general nonfiction.**
- *"The Emperor of All Maladies* is a magnificent, profoundly humane "biography" of cancer—from its first documented appearances thousands of years ago through the epic battles in the twentieth century to cure, control, and conquer it to a radical new understanding of its essence. Physician, researcher, and award- winning science writer, Siddhartha Mukherjee examines cancer with a cellular biologist's precision, a historian's perspective, and a biographer's passion. The result is an astonishingly lucid and eloquent chronicle of a disease humans have lived with—and perished from—for more than five thousand years". –Extracted from the book description.