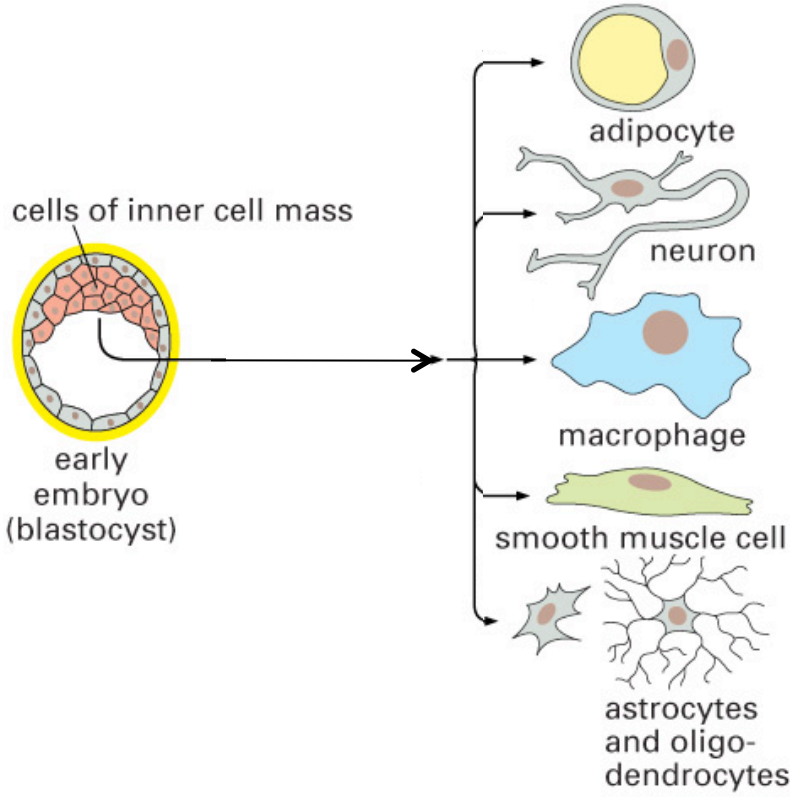
Chemical Biology 03

Oct 28, 2009

Gene Regulation and Cell Differentiation (and stem cells and cancer)

Cell Differentiation



terminally differentiated cells

some need to be replenished often

- blood cells
- surface epidermal cells
- intestinal lining cells

Differentiated cells are continuously Supplied by a **stem cell** population

- No limit to number of cell divisions
- One daughter is always a stem cell
- Other daughter begins process of differentiation into precursor cell

Precursor cells can divide a limited number of times

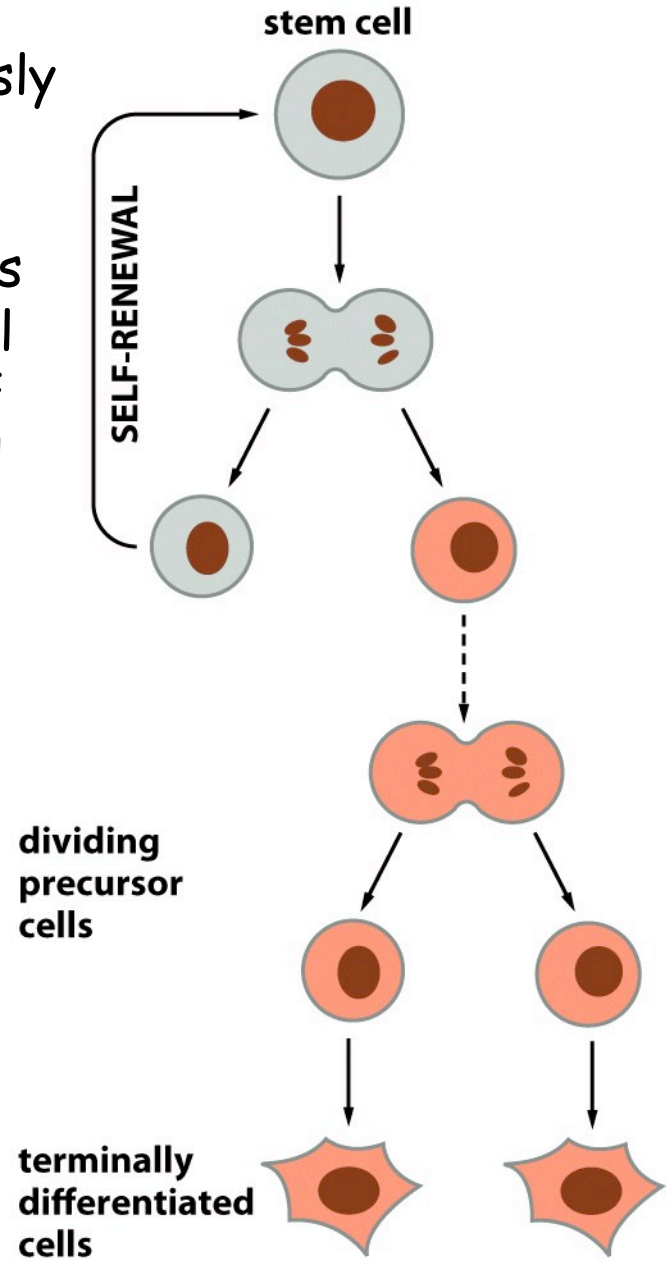


Figure 20-35 Essential Cell Biology 3/e (© Garland Science 2010)

Hemopoiesis

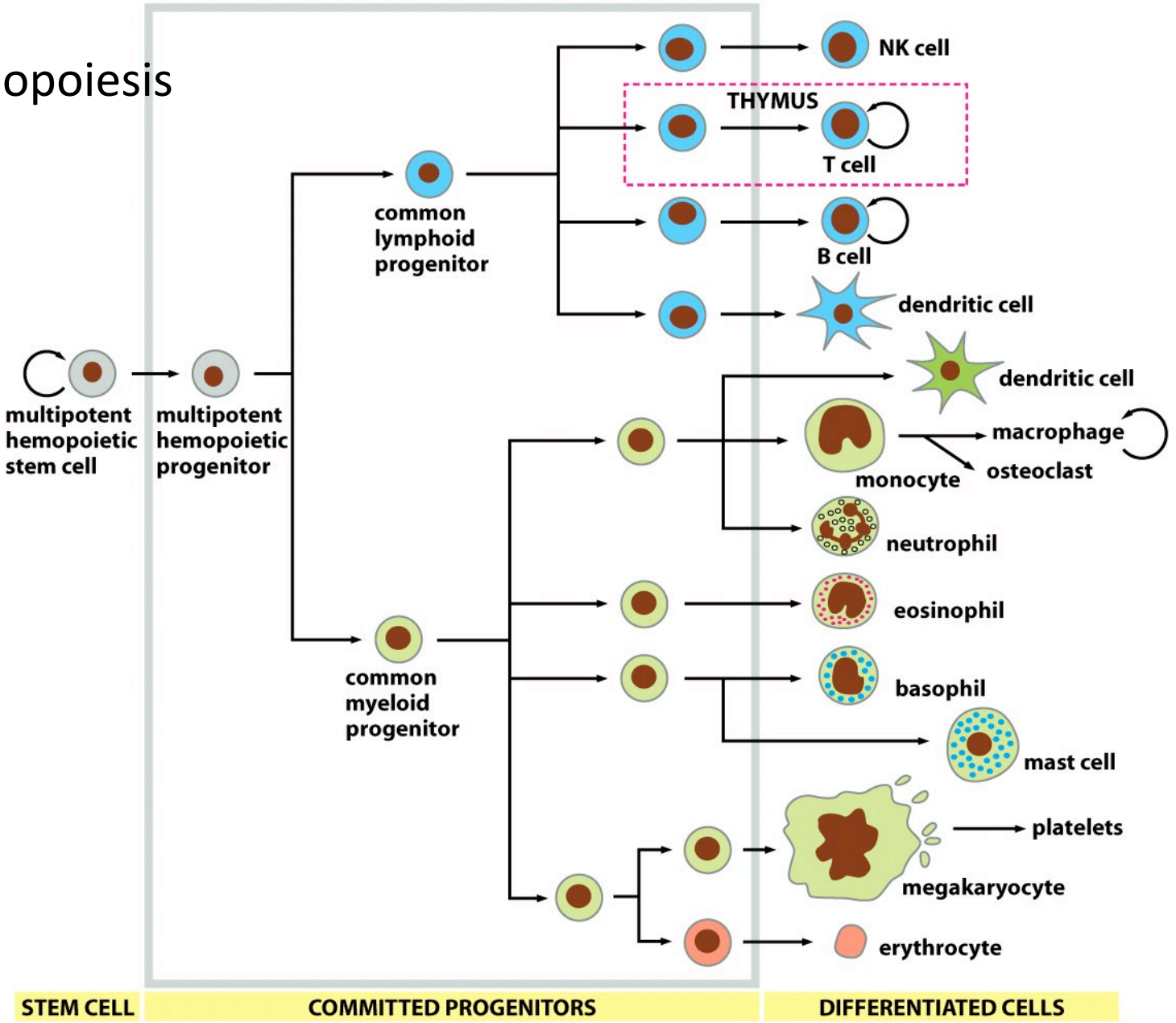


Figure 23-42 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Hematopoietic cell lineage

- http://www.genome.jp/dbget-bin/show_pathway?hsa04640+2056

Hemopoiesis

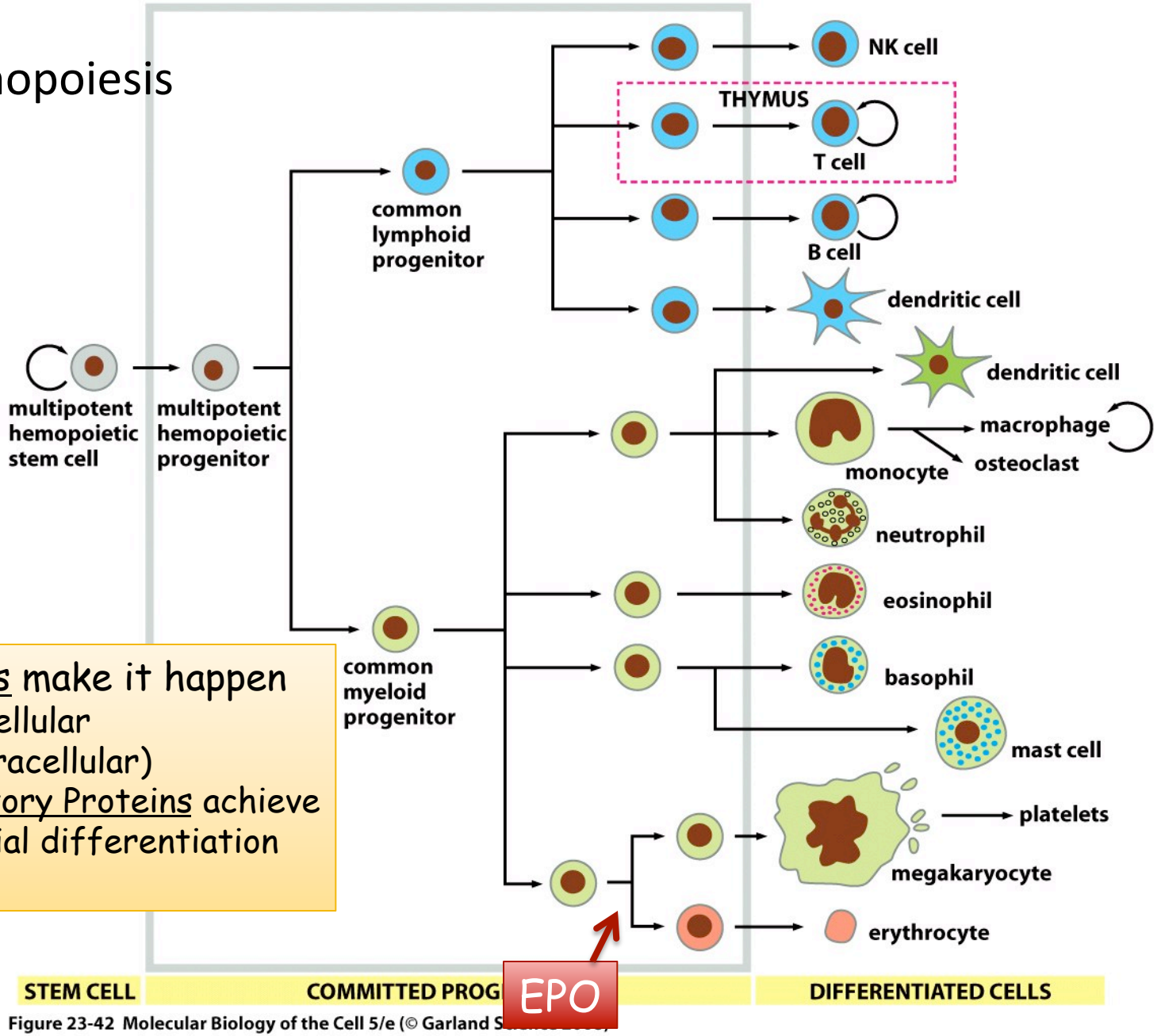
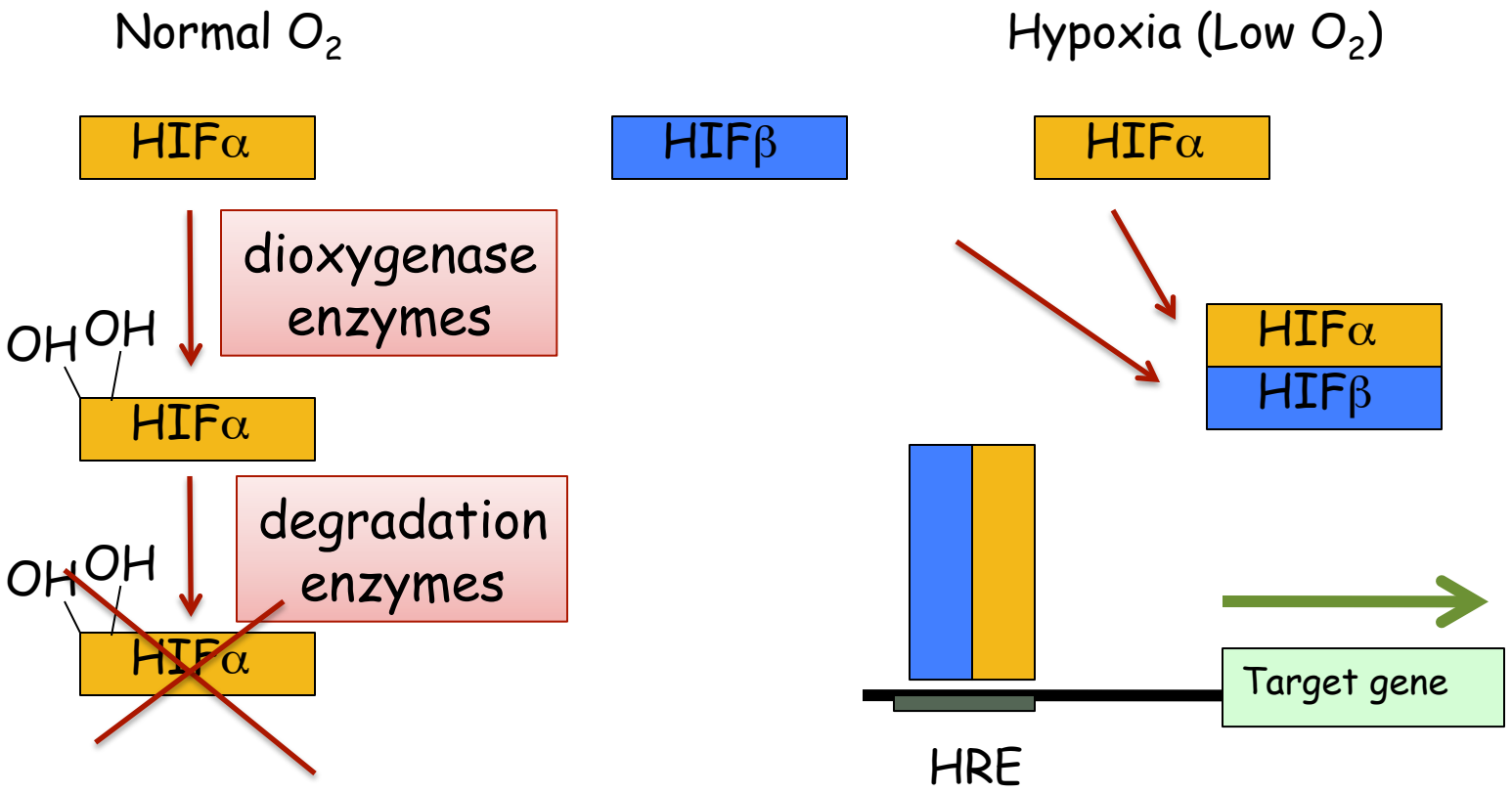


Figure 23-42 Molecular Biology of the Cell 5/e (© Garland S

- Signals make it happen (inter-cellular and extracellular)
- Regulatory Proteins achieve sequential differentiation

- drop in O_2 levels in any tissue (ex. high altitude) = hypoxia
- →activation of HIF1 Transcription Regulator
  - (hypoxia-inducible factor 1)
  - HIF1 = α and β subunits, both transcribed and translated "constitutively"
  - HIFβ is constitutively active but HIFα is regulated by O_2 levels in tissues



HIF1 Target Genes (only those that are known)

Function	Gene (abbreviation)	Reference
Erythropoiesis/ iron metabolism	Erythropoietin (EPO)	Semenza et al., 1991
	Transferrin (Tf)	Rolfs et al., 1997
	Transferrin receptor (Tfr)	Bianchi et al., 1999
	Ceruloplasmin	Lok and Ponka, 1999
Angiogenesis	Vascular endothelial growth factor (VEGF)	Levy et al., 1995
	Endocrine-gland-derived VEGF (EG-VEGF)	LeCouter et al., 2001
	Leptin (LEP)	Grosfeld et al., 2002
	Transforming growth factor-β3 (TGF-β3)	Scheid et al., 2002
Vascular tone	Nitric oxide synthase (NOS2)	Melillo et al., 1995
	Heme oxygenase 1	Lee et al., 1997
	Endothelin 1 (ET1)	Hu et al., 1998
	Adrenomedulin (ADM)	Nguyen and Claycomb, 1999
	α_{1B}-Adrenergic receptor	Eckhart et al., 1997
Matrix metabolism	Matrix metalloproteinases (MMPs)	Ben-Yosef et al., 2002
	Plasminogen activator receptors and inhibitors (PAIs)	Kietzmann et al., 1999
	Collagen prolyl hydroxylase	Takahashi et al., 2000
Glucose metabolism	Adenylate kinase-3	O'Rourke et al., 1996
	Aldolase-A,C (ALDA,C)	Semenza et al., 1996
	Carbonic anhydrase-9	Wykoff et al., 2000
	Enolase-1 (ENO1)	Semenza et al., 1996
	Glucose transporter-1,3 (GLU1,3)	Chen et al., 2001
	Glyceraldehyde phosphate dehydrogenase (GAPDH)	Graven et al., 1999
	Hexokinase 1,2 (HK1,2)	Mathupala et al., 2001

RBC production

Increase glycolysis (O_2-independent energy production

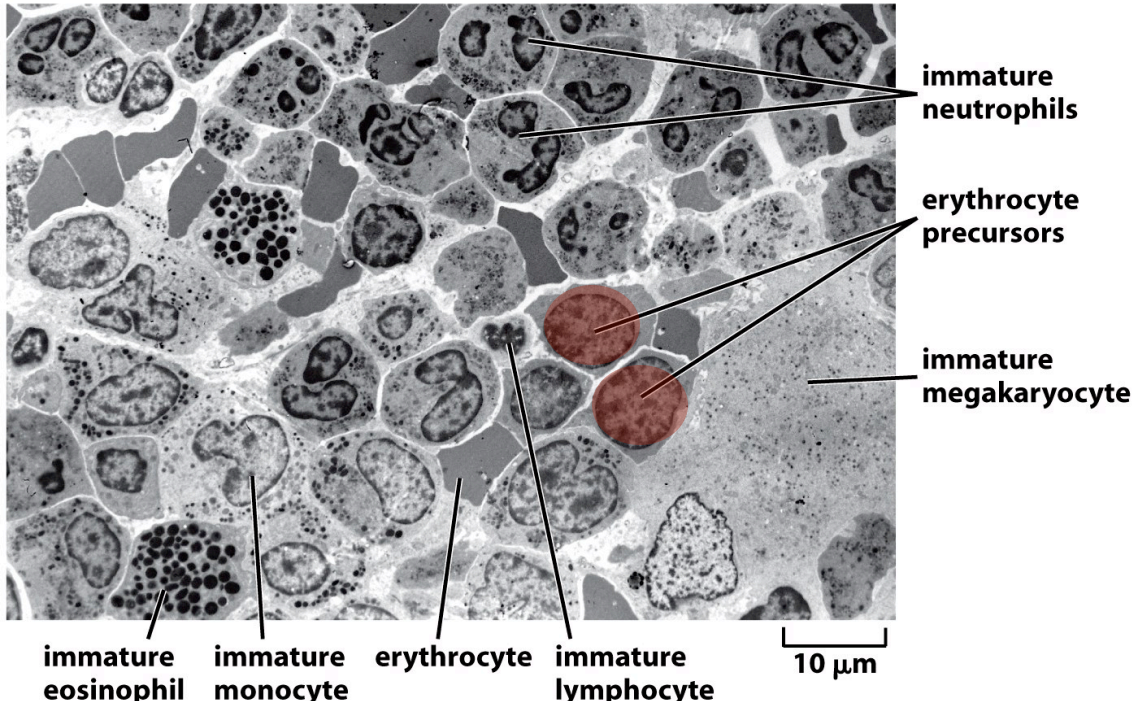
Mol Pharm -- Ke and Costa 70 (5): 1469 Table BL2

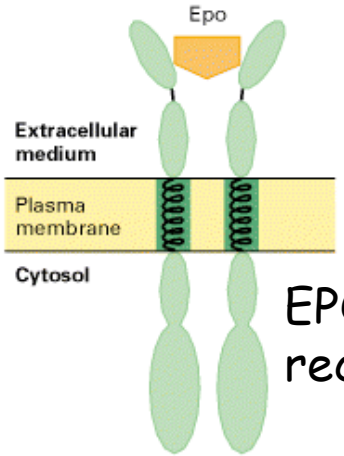
	Lactate dehydrogenase-A (LDHA)	Semenza
	Pyruvate kinase M (PKM)	Semenza
	Phosphofructokinase L (PFKL)	Semenza
	Phosphoglycerate kinase 1 (PGK1)	Semenza
	6-phosphofructo-2-kinase/gructose-2,6-bisphosphate-3 (PFKFB3)	Minchen
Cell proliferation/survival	Insulin-like growth factor-2 (IGF2)	Feldser e
	Transforming growth factor-α (TGF- α)	Krishnan 2003
	Adrenomedullin (ADM)	Cormier- 1998
Apoptosis	Bcl-2/adenovirus EIB 19kD-interacting protein 3 (BNip3)	Carrero e
	Nip3-like protein X (NIX)	Bruick, 2

- EPO (erythropoietin) gene is now transcribed under influence of HIF1
  - 165 a.a. protein hormone that travels through blood stream

in bone marrow some cells have
EPO Receptor Protein
on their cell surface
allowing them to be stimulated
by EPO...
erythropoiesis yields new RBCs
within ~ 4 days

(what genes are ativated?)





EPO receptor

Hemopoiesis

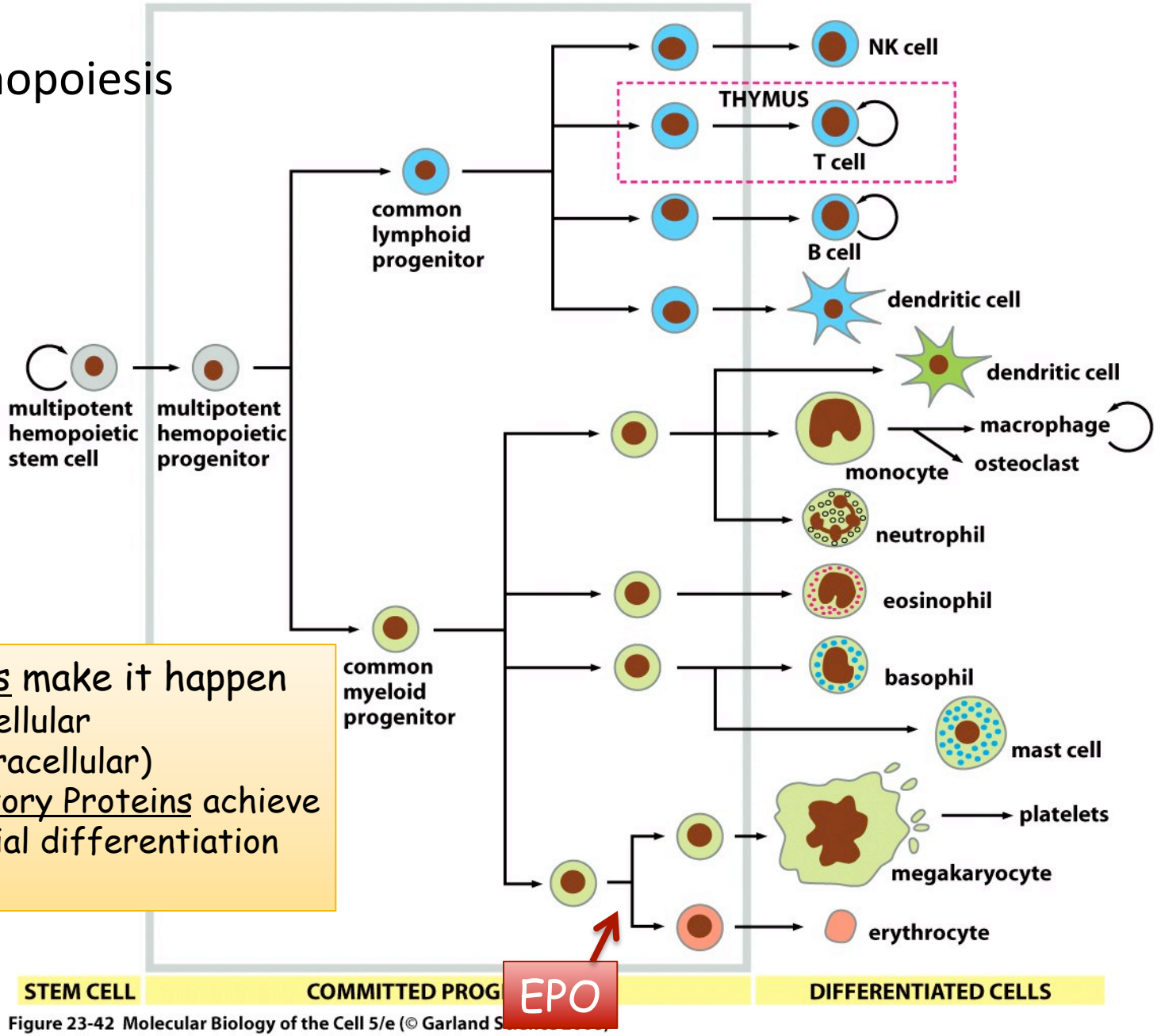
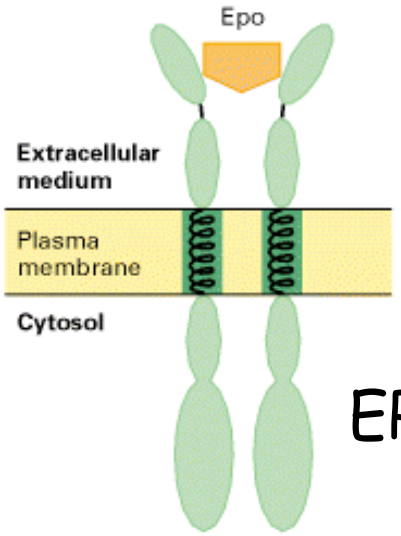


Figure 23-42 Molecular Biology of the Cell 5/e (© Garland S

- Signals make it happen (inter-cellular and extracellular)
- Regulatory Proteins achieve sequential differentiation

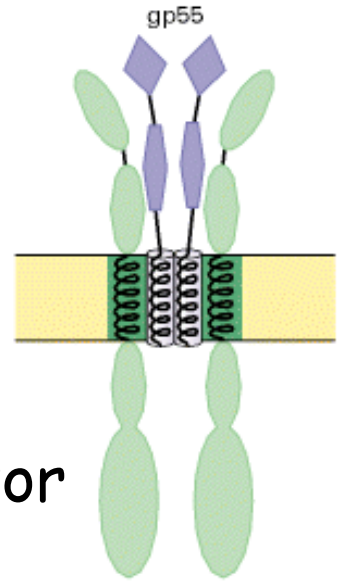
EPO hormone is recognized and bound by a cell-surface receptor protein (EPO receptor)



EPO receptor

erythrocyte progenitor cells are induced to proliferate

SFFV (spleen focus-forming virus)
hijacks the system:
viral gp55 envelope protein tricks EPO receptor



EPO receptor

erythrocyte progenitor cells
are induced to proliferate
even though there is no EPO

Misbehaving cells: cancer
(when normal controls are
absent or ignored)

misbehaving cells: cancer

1) uncontrolled proliferation
2) invasion of other territories

benign tumor = (1) alone
malignant tumor = (1) + (2)

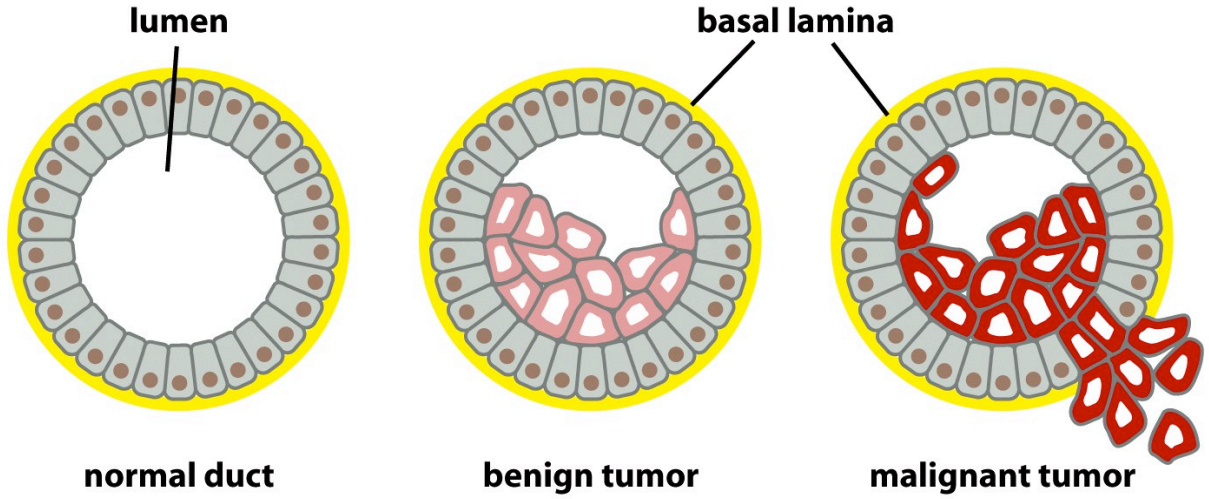


Figure 20-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

cancer = genetic disease

1) consequence of mutations
2) somatic cells

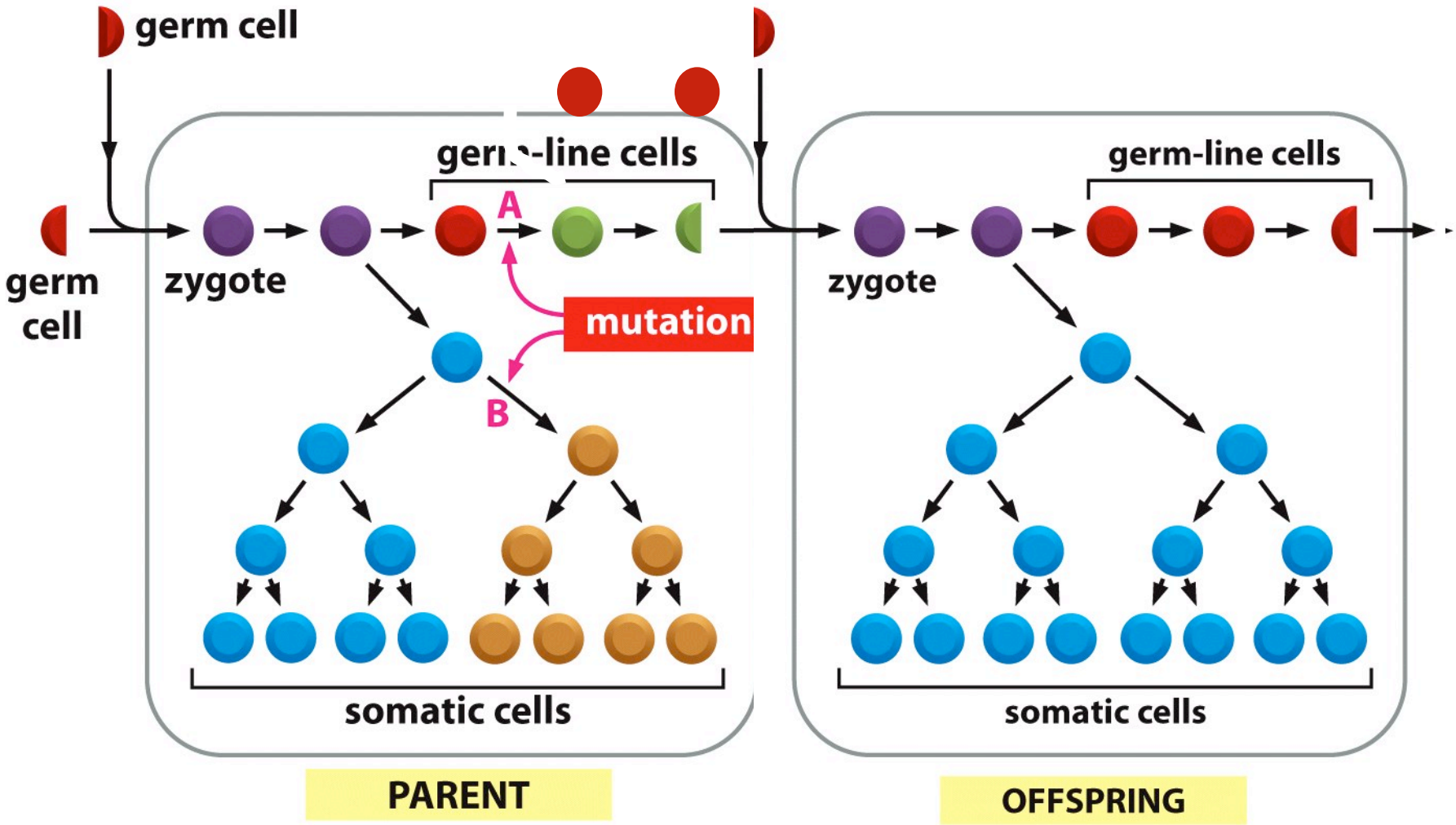
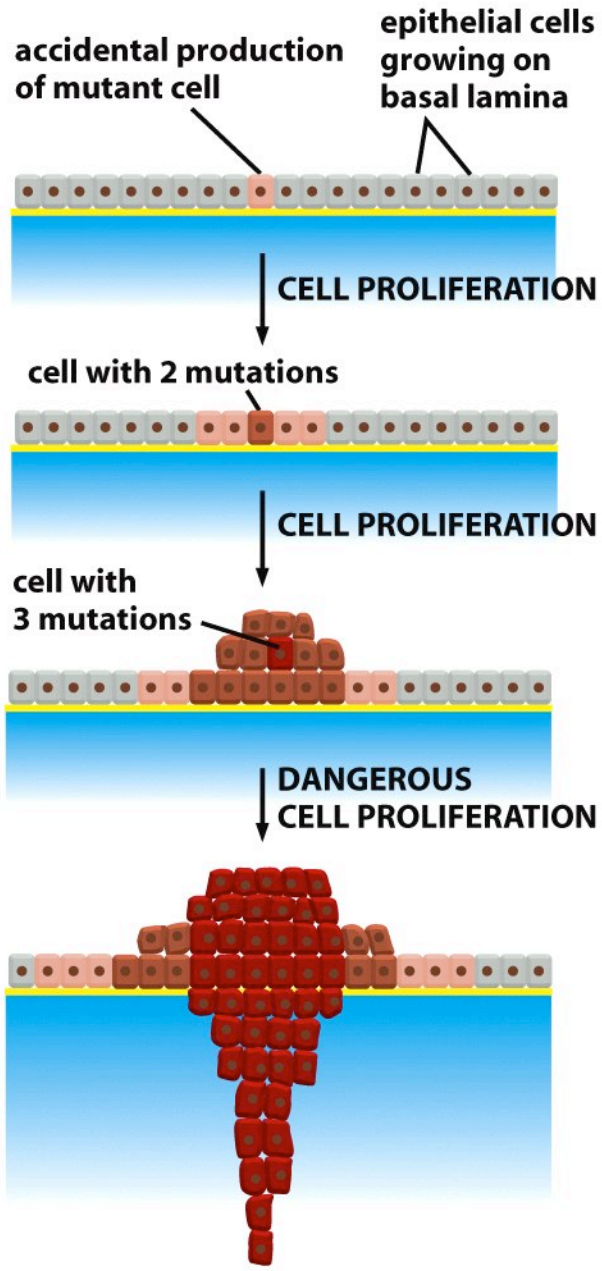


Figure 9-4 Essential Cell Biology 3/e (© Garland Science 2010)

cancer = genetic disease

1) consequence of mutations
2) somatic cells
3) cumulative mutations (~5-7)



human lifetime
= 10^{16} cell divisions

spontaneous mutation rate
= between 10^{-6} and 10^{-7}
mutations per gene per cell

in one lifetime: a given gene
could mutate 10^{9} times!!

why will most of these not matter?

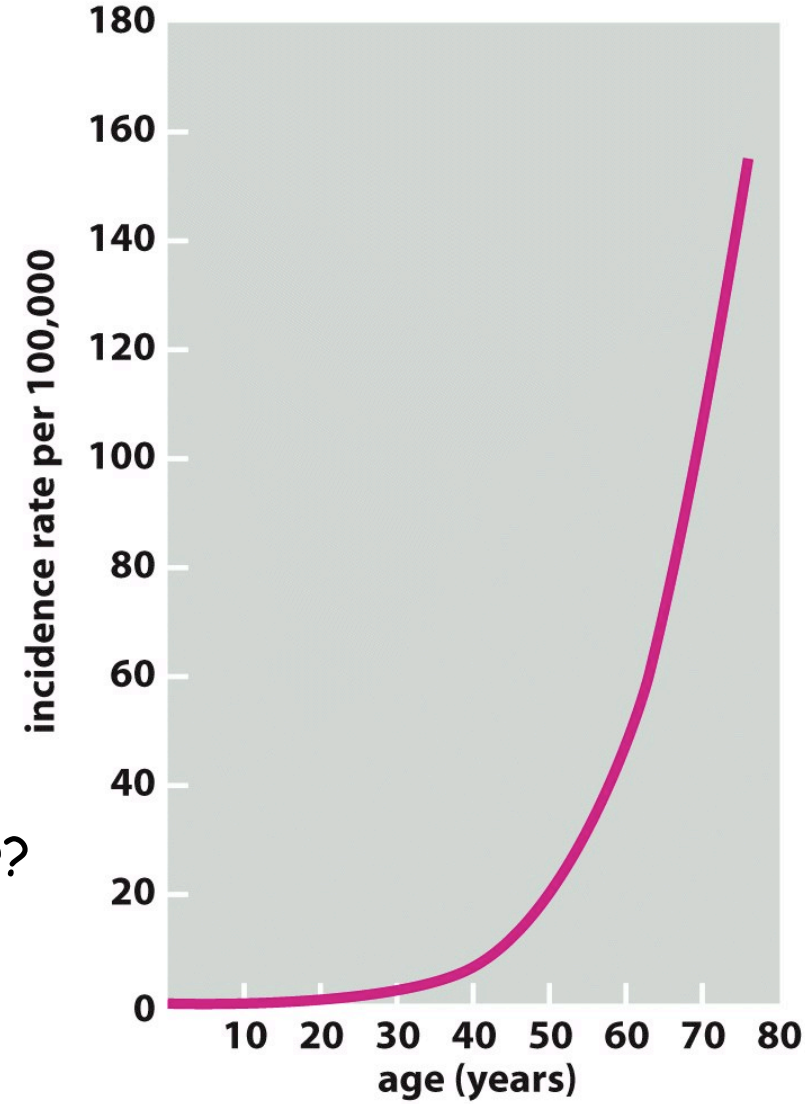


Figure 20-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Two classes of mutations can cause cancer:

1)Those that inactivate gene function of a protein that *halts* cell proliferation (or other cancerous bad behavior)
= Tumor Suppressor Genes
ex. p53, APC ($\frac{1}{2}$ of all cancers have mutant p53)

2) Those that hyperactivate gene function of a protein that *promotes* cell proliferation (or other cancerous bad behavior)
= Oncogene
ex. Ras

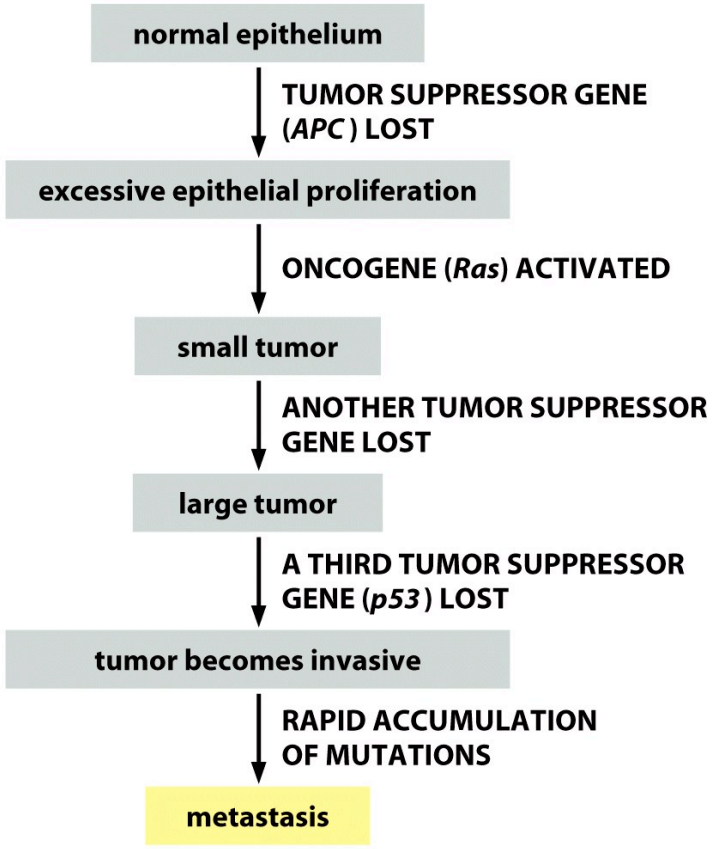


Figure 20-52 Essential Cell Biology 3/e (© Garland Science 2010)