# Cell Cycle II: Extracellular Control

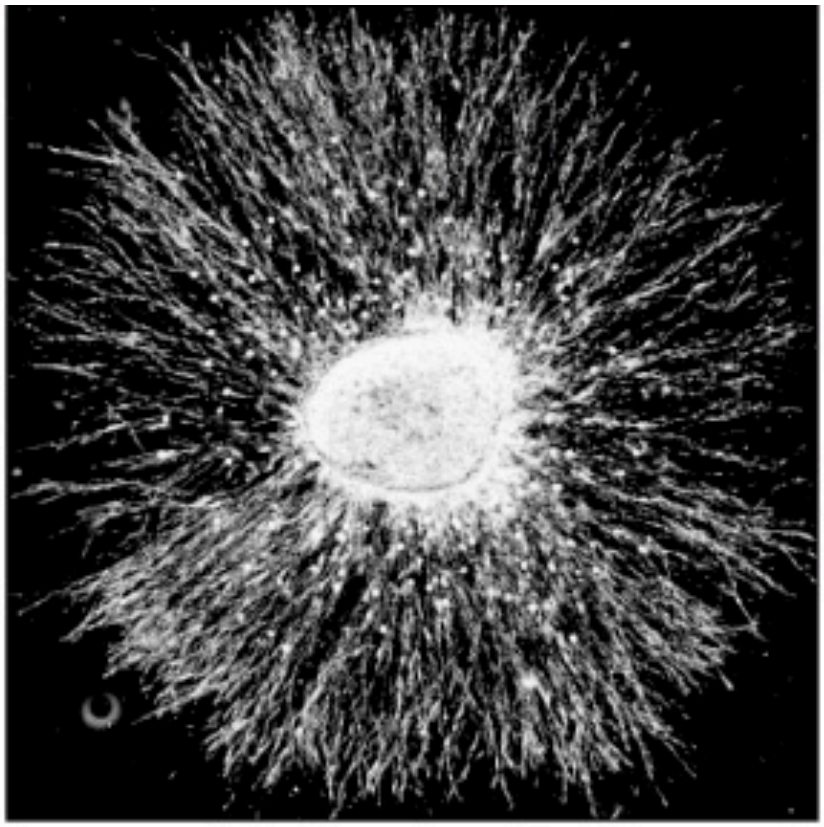


Fig. 22-103. Alberts et al.

# Total Cell Mass

***Total cell mass (size of organ / organism)***

*Total cell number*

*Cell Growth*

*Cell division* – *Cell death*

# Total Cell Mass

Dependent on Extracellular Factors:

1. *Growth Factors*: ↑ synthesis and ↓ degradation of proteins

2. *Mitogens*: ↑ cell division

3. *Survival Factors*: ↓ apoptosis (next lecture)

*Note: It's confusing, but some "growth factors" also have mitogenic and survival effects. Therefore, please remember* **processes** *and not specific factors.*

# Growth Factors

- Needed for growth of animal cells.
- ↑ synthesis, ↓ degradation.
- e.g. platelet-derived growth factor (PDGF), epidermal growth factor (EGF), nerve growth factor (NGF).

Extracellular signalling proteins (GFs)

Cell surface receptors

Intracellular pathways

# Growth Factors

- Act through *receptor tyrosine kinase* (“enzyme-linked receptors”).
- Extracellular binding, transmembrane domain, and intrinsic enzyme acitivity (“autophosphorylation”).
- Ligand (dimer) binding → receptor dimerization and transfer of $P_i$ from ATP by tyrosine kinase (TK domain).
- “*Autophosphorylation*” initiates intracellular pathways.

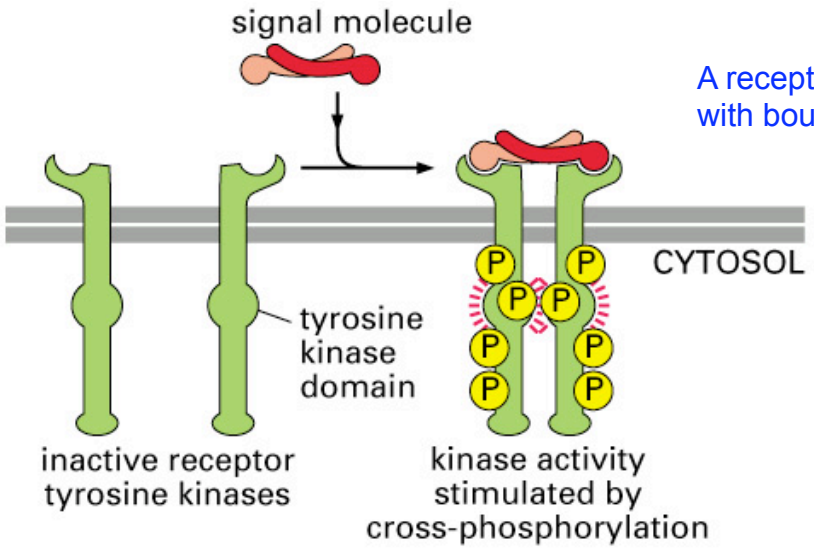



Fig. 15-51a. Alberts 4th ed.

A receptor tyrosine kinase with bound ligand (dimer)

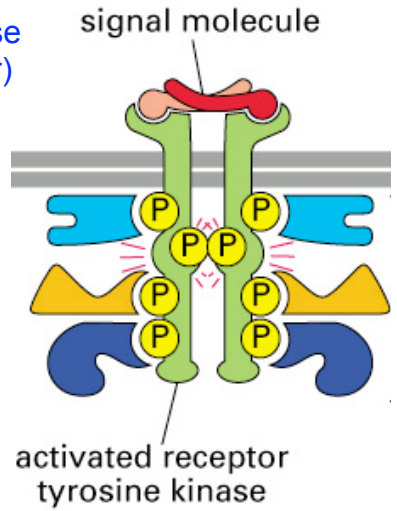
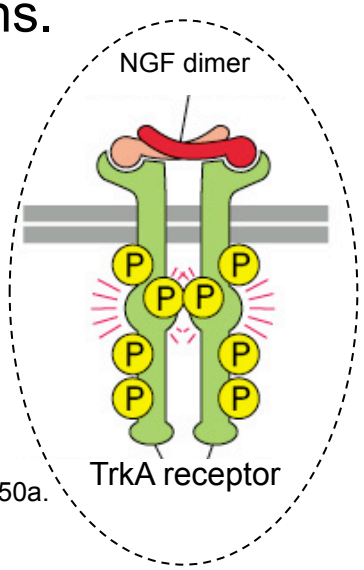


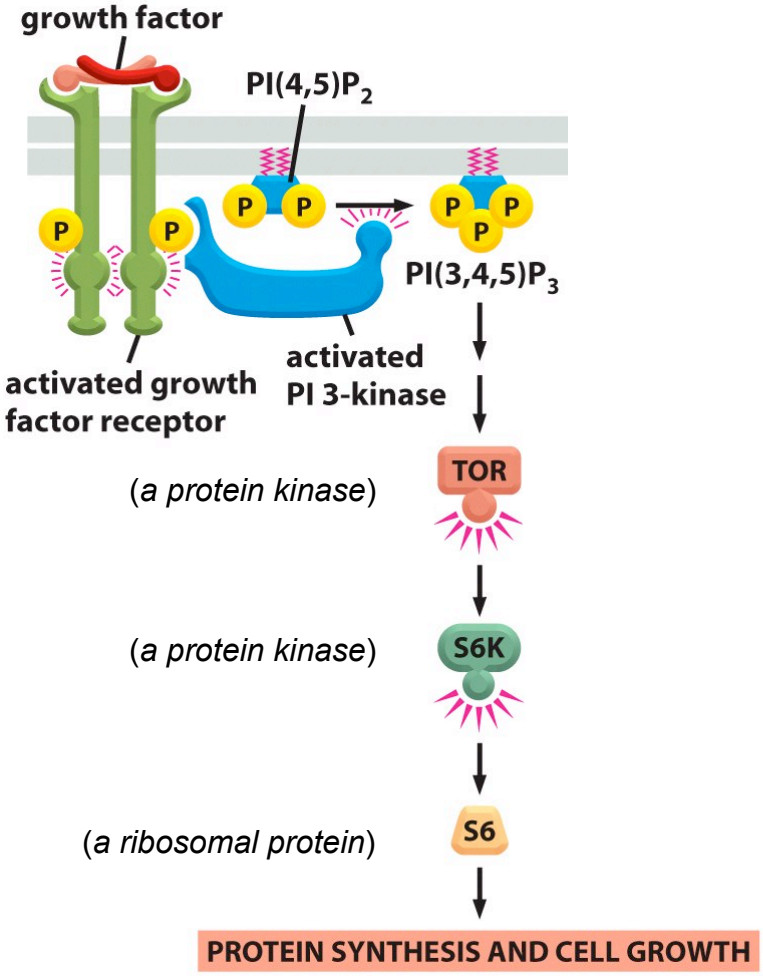

Fig. 15-52. Alberts 4th ed.

# Growth Factors

- Phosphorylated receptor activates PI-3 kinase…
- Phosphorylation of ribosomal protein S6 and ↑translation of many important proteins.
- e.g. NGF and TrkA receptors in neurons.




Modified from Fig. 15-50a. Alberts et al., 4th ed.




Modified from Fig. 17-65, Alberts, 5th ed.

***p**hosphatidyl**i**nositol **3**-kinase; **p**hospho**i**nositol di/tri**p**hosphate*

# Nerve Growth Factor (NGF)

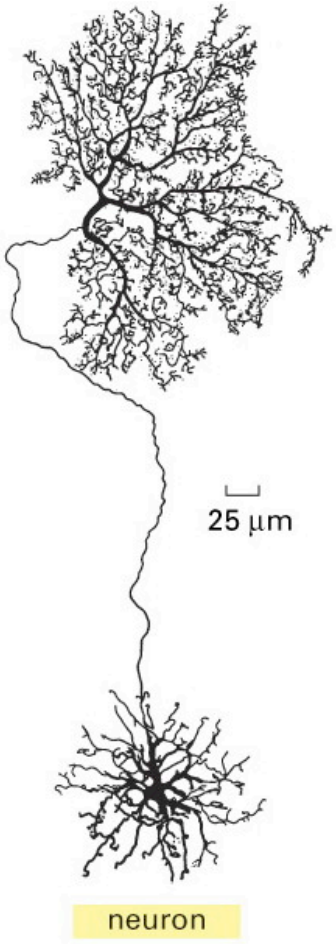



Fig.17-45. Alberts et al.

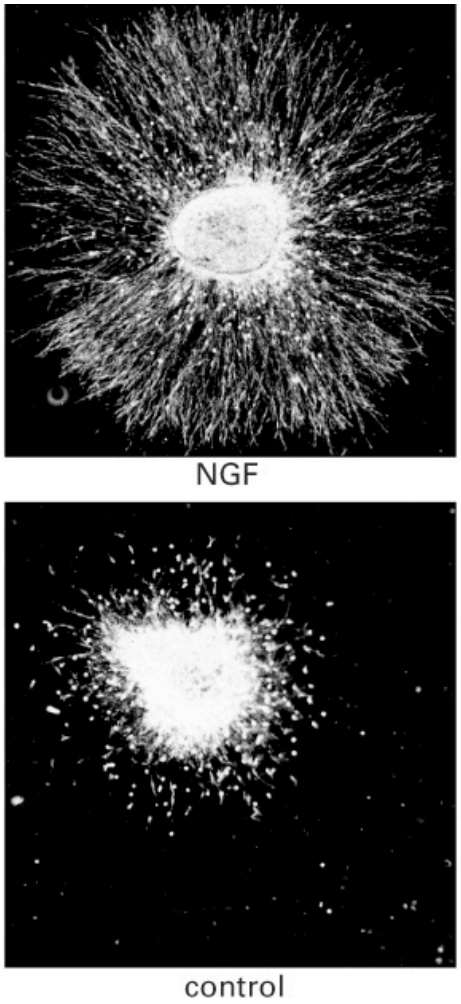



Figure 21–99. Molecular Biology of the Cell, 4th Edition.

Nobel Prize, 1986

Rita Levi-Montalcini

The Nobel Foundation

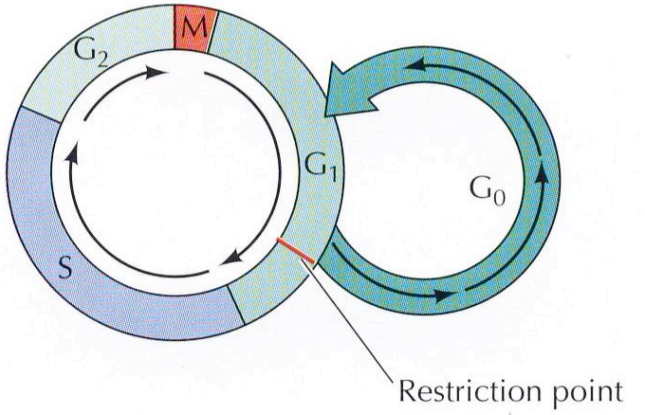
Mouse sarcoma tissue released “neurotrophins”.

# Mitogens

- Extracellular signals necessary for cell proliferation.
- e.g. PDGF, EGF, erythropoietin (EPO).
- Increases cyclin synthesis, and thus Cdk activation.
- Promotes entry into S-phase from $G_1$ (e.g. Slide 11).

# $G_1$ Restriction Point

- Also a “checkpoint”, but requires an *extracellular signal* (mitogen).
- Most vertebrate cells are in $G_0$.




Cooper and Hausman, 2008

| No mitogens | Mitogens |
|---|---|
| ↓ | ↓ |
| Cell enters $G_0$ | Cell re-enters $G_1$ and continues |
| e.g. neurons, muscle | e.g. fibroblasts, PDGF, wound healing |

# Mitogens Stimulate Cell Division

- Mitogen binding.
- Ras (G-protein "switch").
- MAP kinase activation.
- ↑*myc* gene expression.
- e.g. PDGF, EGF.

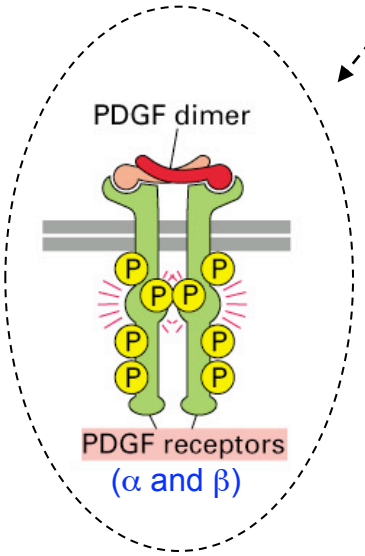



Fig. 15-50a. Alberts et al.

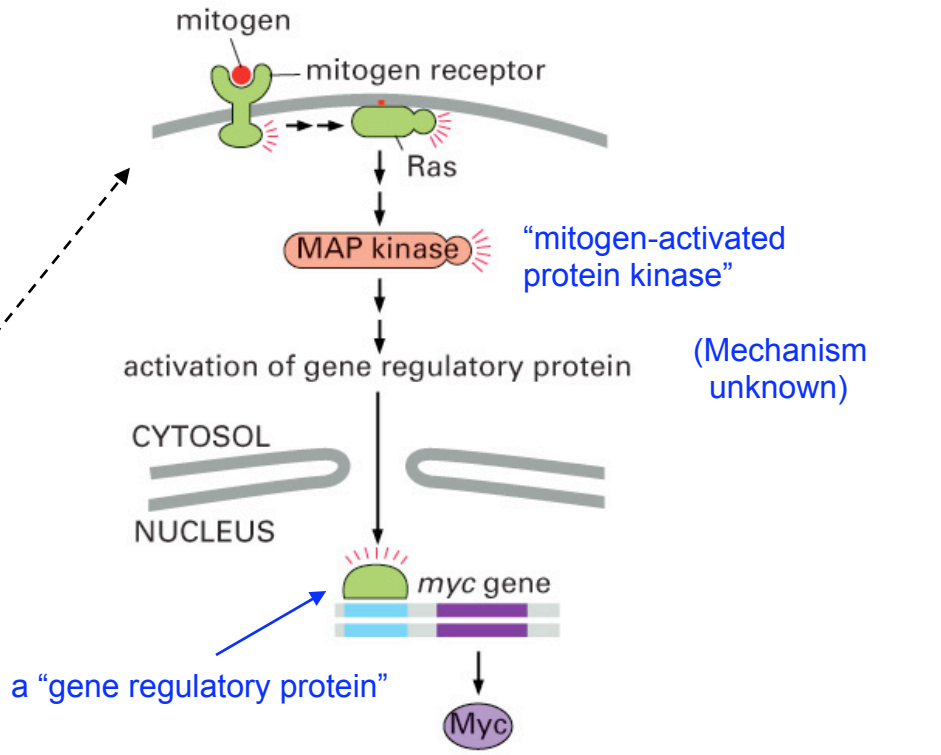



Figure 17–41 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

"mitogen-activated protein kinase"; "*rat sarcoma*"

# Mitogens Stimulate Cell Division

- Myc is a gene-regulatory protein.
- ↑$G_1$-Cdk and S-Cdk activity via transcription of cyclin or SCF.
- Rb proteins (which inh. cell cycle) are inactivated.
- Production of S-cyclin and S-Cdk activation.
- Progression to S-phase.

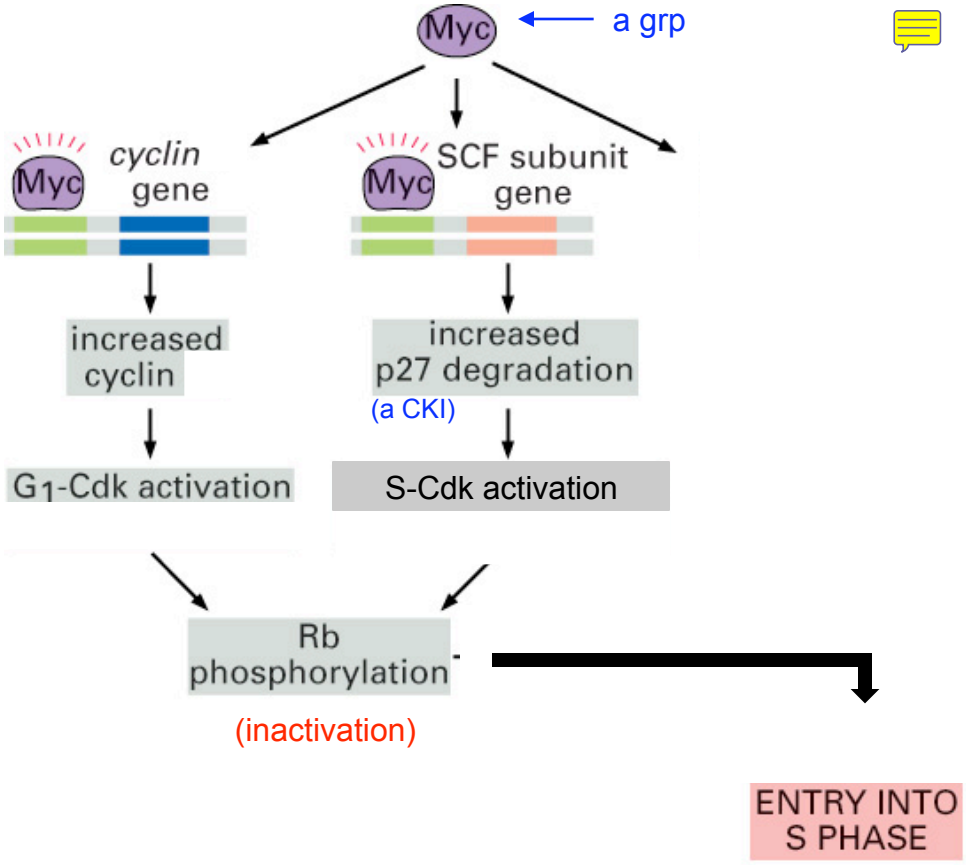



Figure 17–41 part 2 of 2. Molecular Biology of the Cell, 4th Edition.



Rb: retinoblastoma protein, an inhibitor of cell cycle progression

# Abnormal Mitogenic Stimulation

- Mutations can sometimes lead to abnormal mitogenic stimulation.
- Excessive ↑ Ras or Myc mimics stimulation.
- e.g. cancer, inappropriate entry into S-phase.
- Normal cells detect these changes and prevent further division.

# Prevention of Abnormal Mitogenic Stimulation

(in normal cells)

- Recall, p53 is normally degraded, and cell cycle normal.
- But if excessive Myc production, $p19^{ARF}$ will bind Mdm2 and stabilize (release) p53.
- Arrest or apoptosis.
- In cancer, this mechanism may not work because of p19 and p53 mutation.

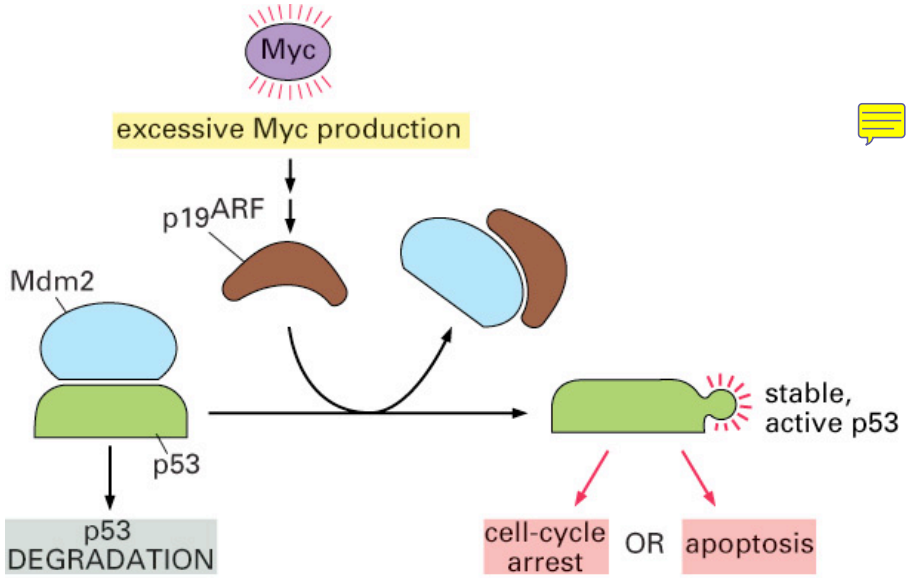



Figure 17–42. Molecular Biology of the Cell, 4th Edition.

# Survival Factors

- Extracellular signals required for cells to survive.
- Secreted by cells in surrounding tissue.
- Without it, cells undergo apoptosis (next lecture).
- Some growth factors are survival factors.
- e.g. nervous system development.

# Survival Factors

- Extracellular signal.
- Protein kinase B (PKB) activation.
- Phosphorylation of BAD and GRP inhibit apoptosis.

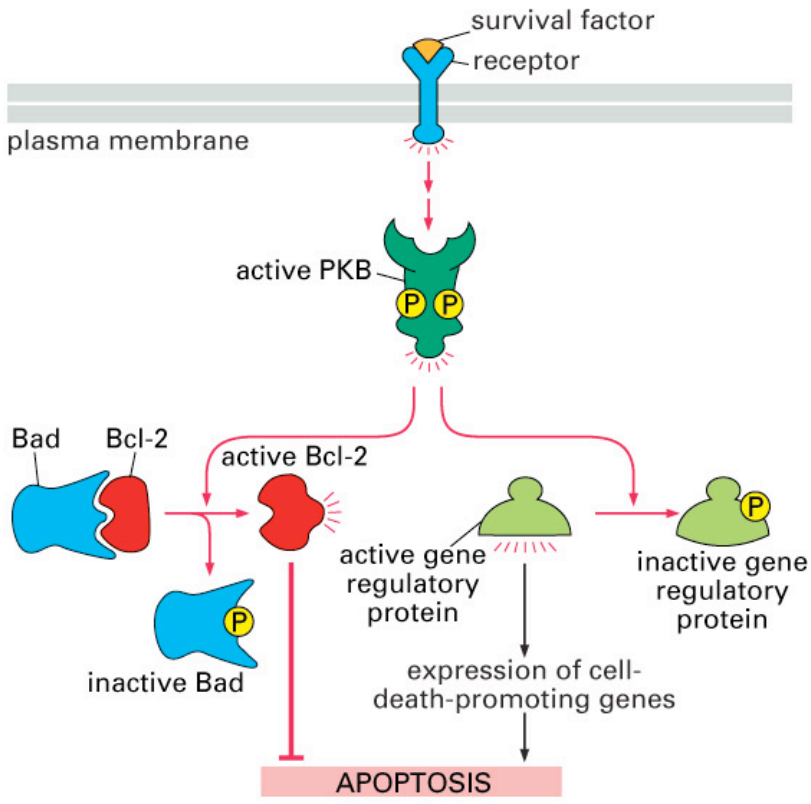



Figure 17–47 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

*Bcl2 family of proteins promote or inhibit apoptosis by regulating cytochrome c release from the mitochondrion (next lecture).*

# Things to Consider...

1. There are many details that you've learned in these two lectures. Try to piece everything together and think about where in the cell cycle everything fits, i.e. in 'chronological' order.
2. What roles do feedback mechanisms play in cell cycle control?
3. Remember the differences between extracellular and intracellular mechanisms of cell cycle control.