BME 42-620 Engineering Molecular Cell Biology

Lecture 20:

Control of Gene Expression

Cell Signaling

Chapters 7, & 15

Outline

- Overview of gene expression control
- Noise in gene expression
- Overview of cell signaling
- Classification of related proteins
- G-protein coupled receptors

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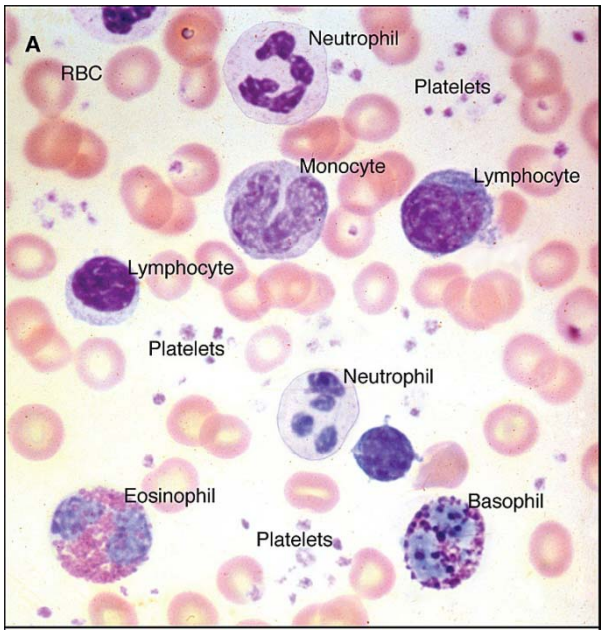
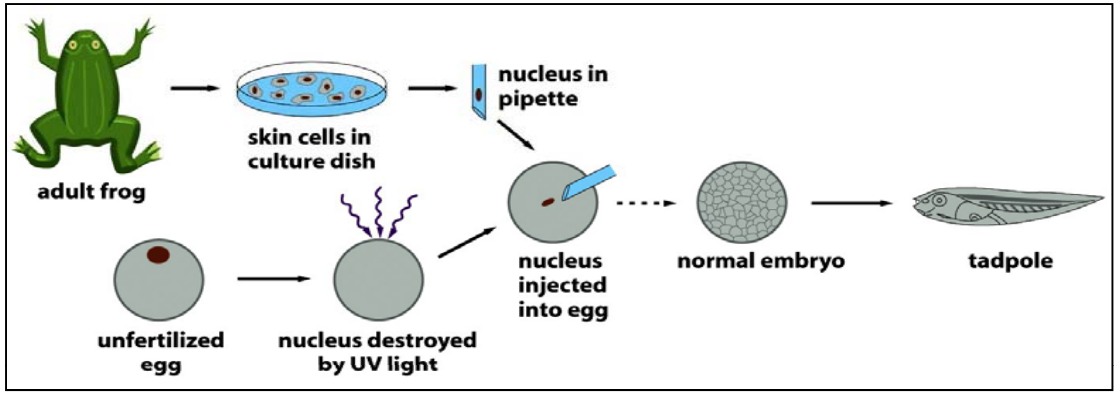
Differential Gene Expression in Different Cells

- The DNA of a cell encodes all the RNA and proteins required for its construction.
- Different cell types of a multicellular organism contain the same DNA.
- The expression of the same DNA differs dramatically in different cell types.

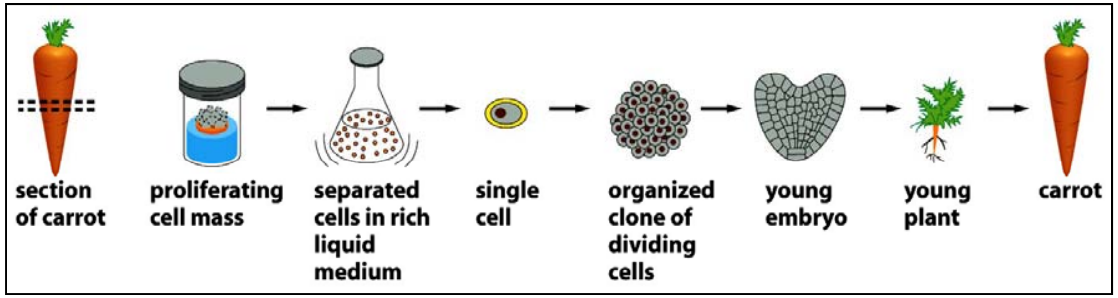


Same DNA in Different Cell of A Multicellular Organism

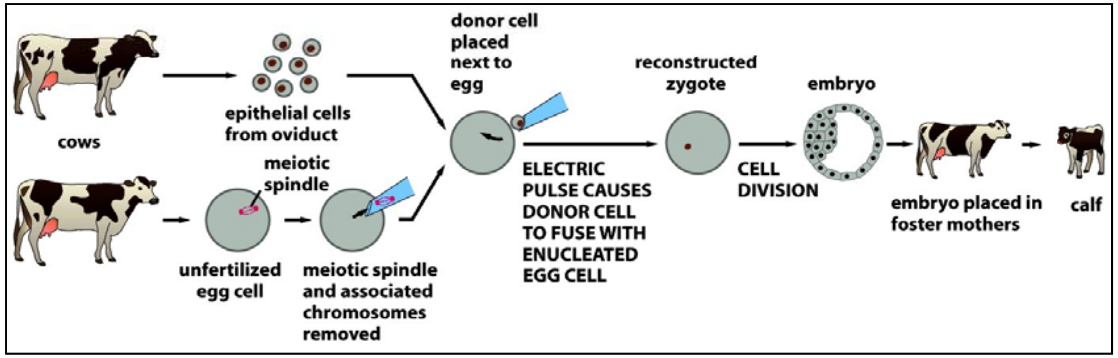
Vertebrates



Plants

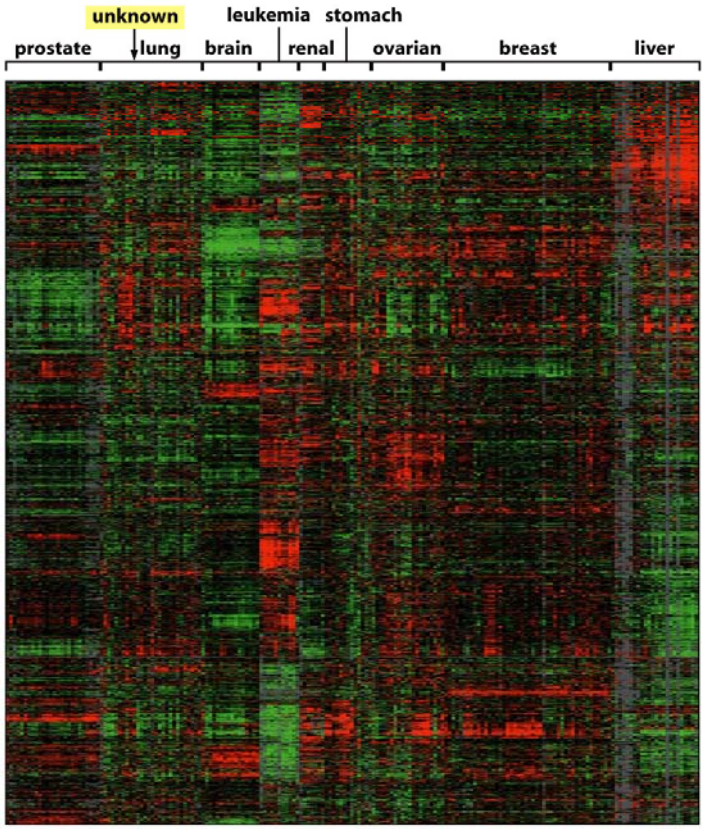


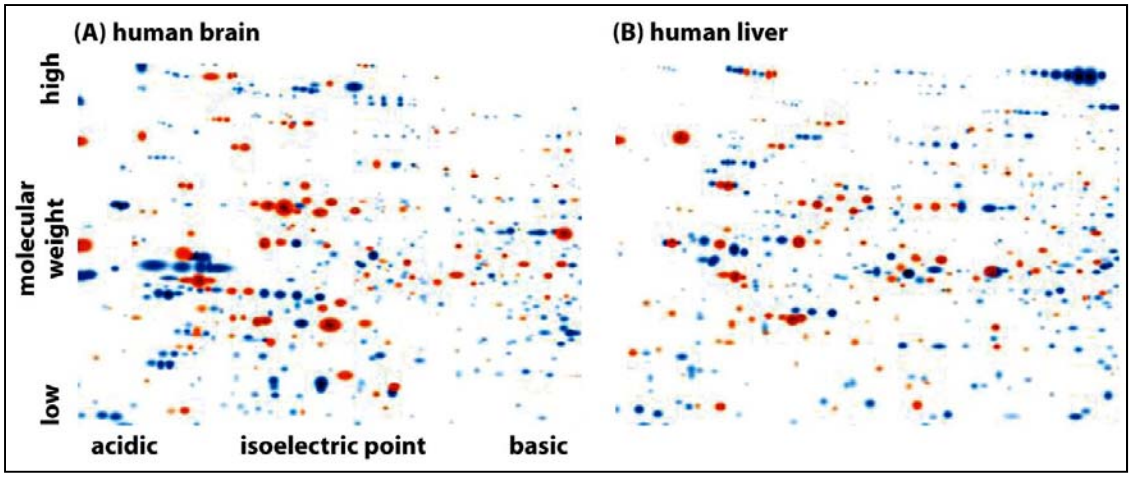
Mammals



Control of Gene Expression

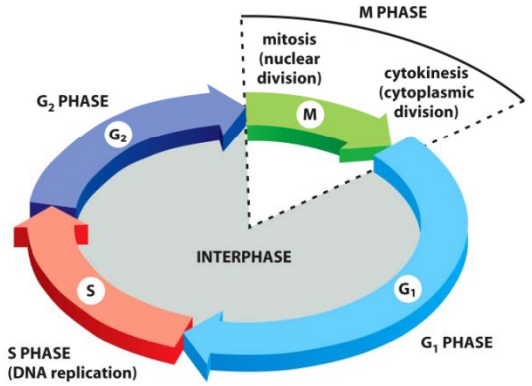
- Different mRNA levels of 1800 genes in 142 different human tumor cell lines.
- Different proteins expressed in human brain and liver.
- Different levels of same proteins in human brain and liver.

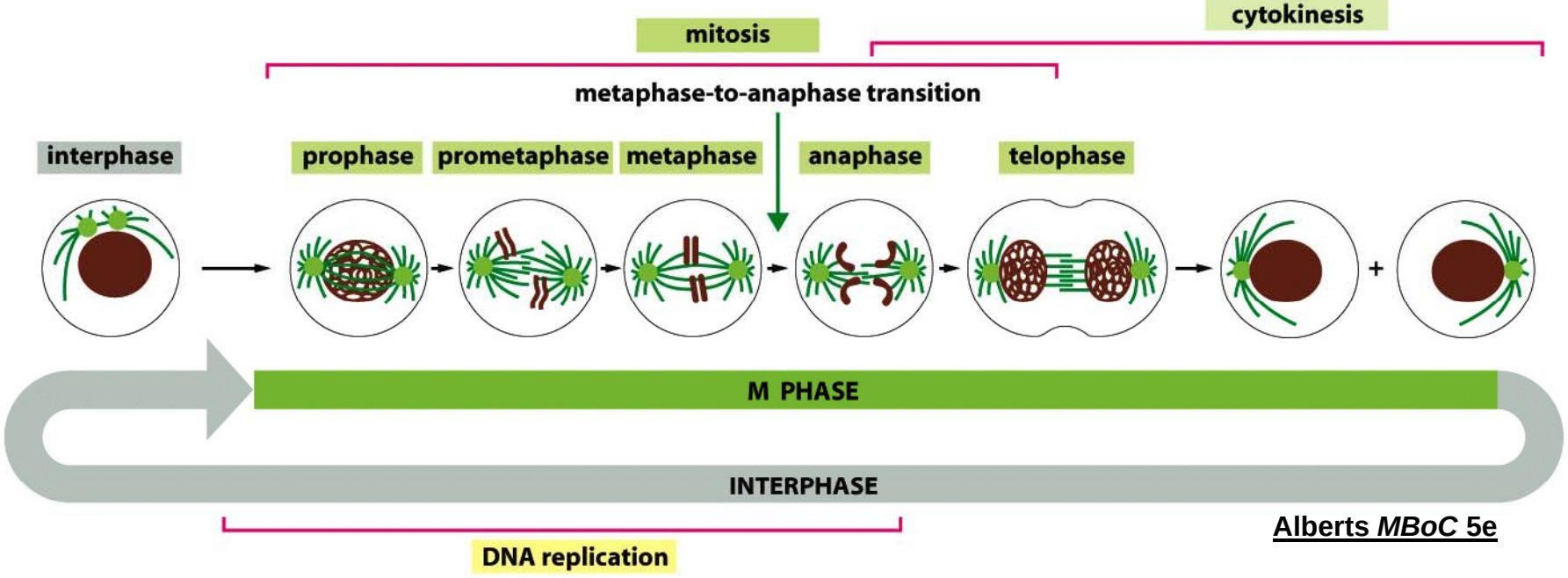




Internal Signals Change Gene Expression

- Different expression profiles in different phases of the cell cycle.





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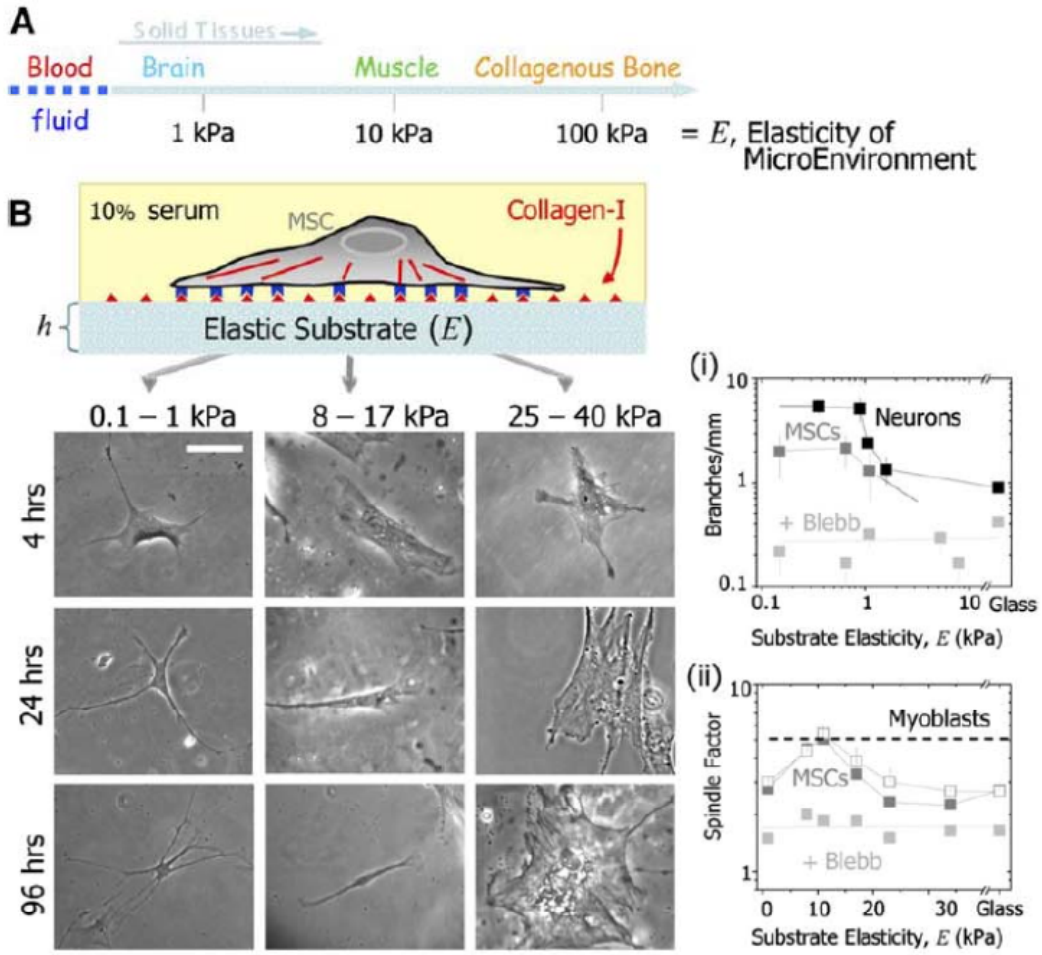
External Signals Can Change Gene Expression

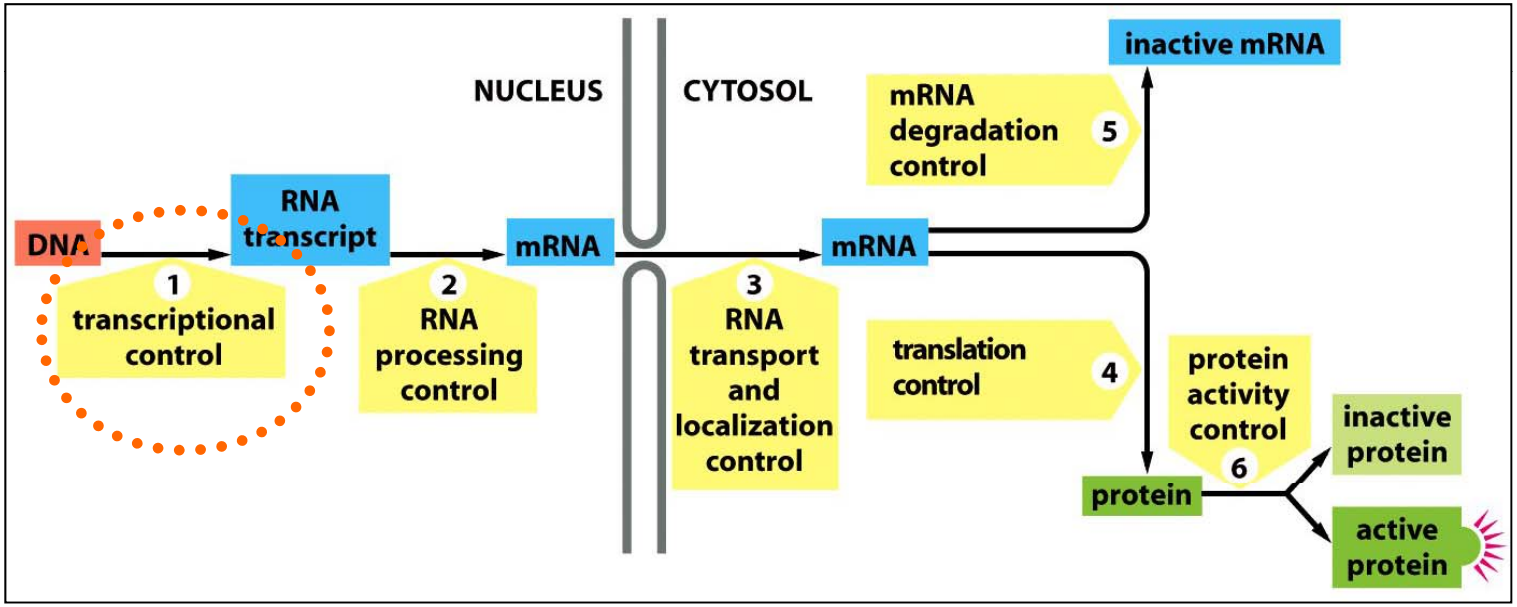
- Mesenchymal stem cells differentiate into different cell types under different substrate stiffness.



Engler et al, *Cell*, 126:677, 2006.

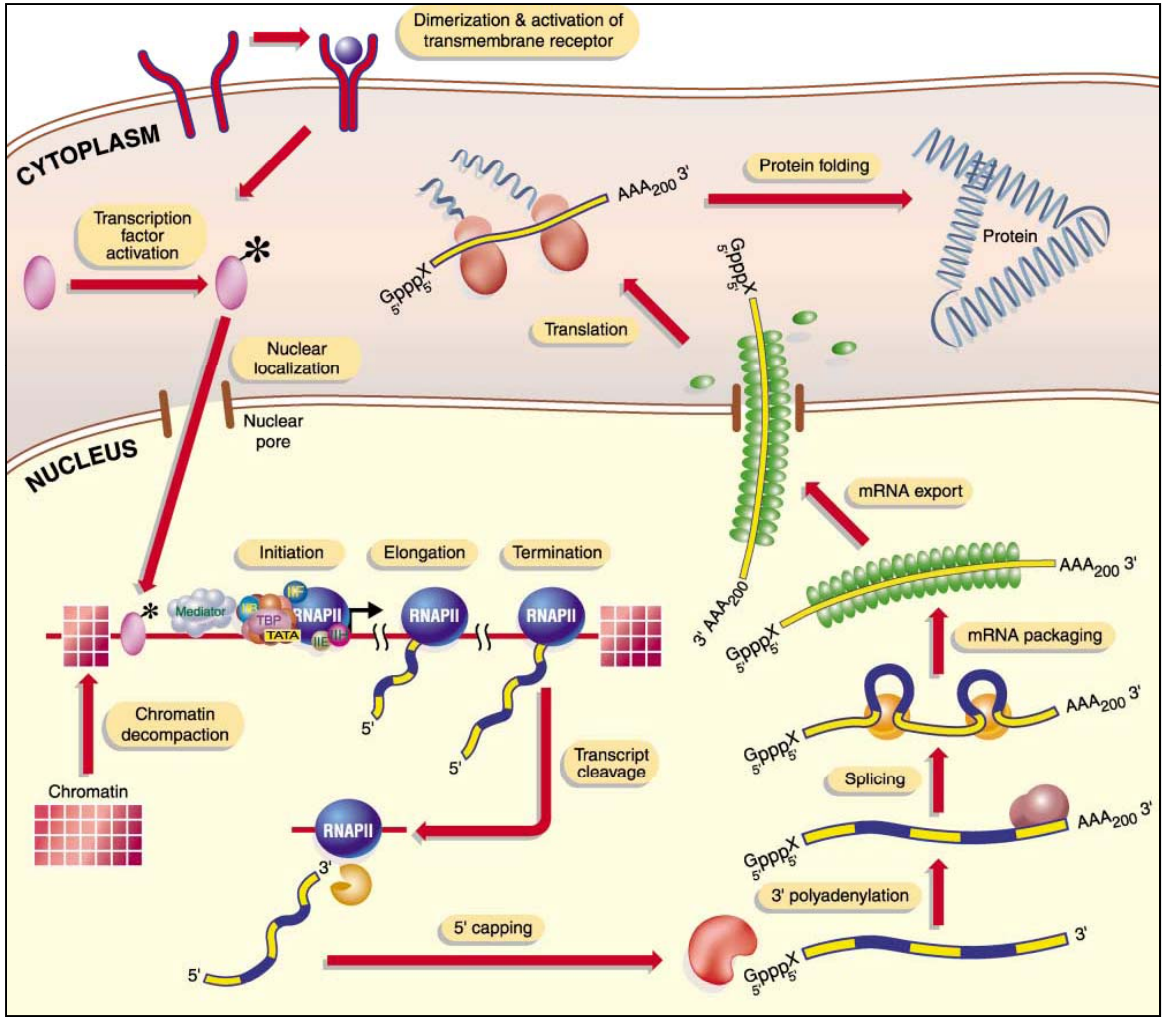
Regulation of Gene Expression at Different Levels

- Gene expression is regulated at different levels.
- For most genes, transcriptional control is the most important.



Traditional View of Eukaryotic Gene Expression

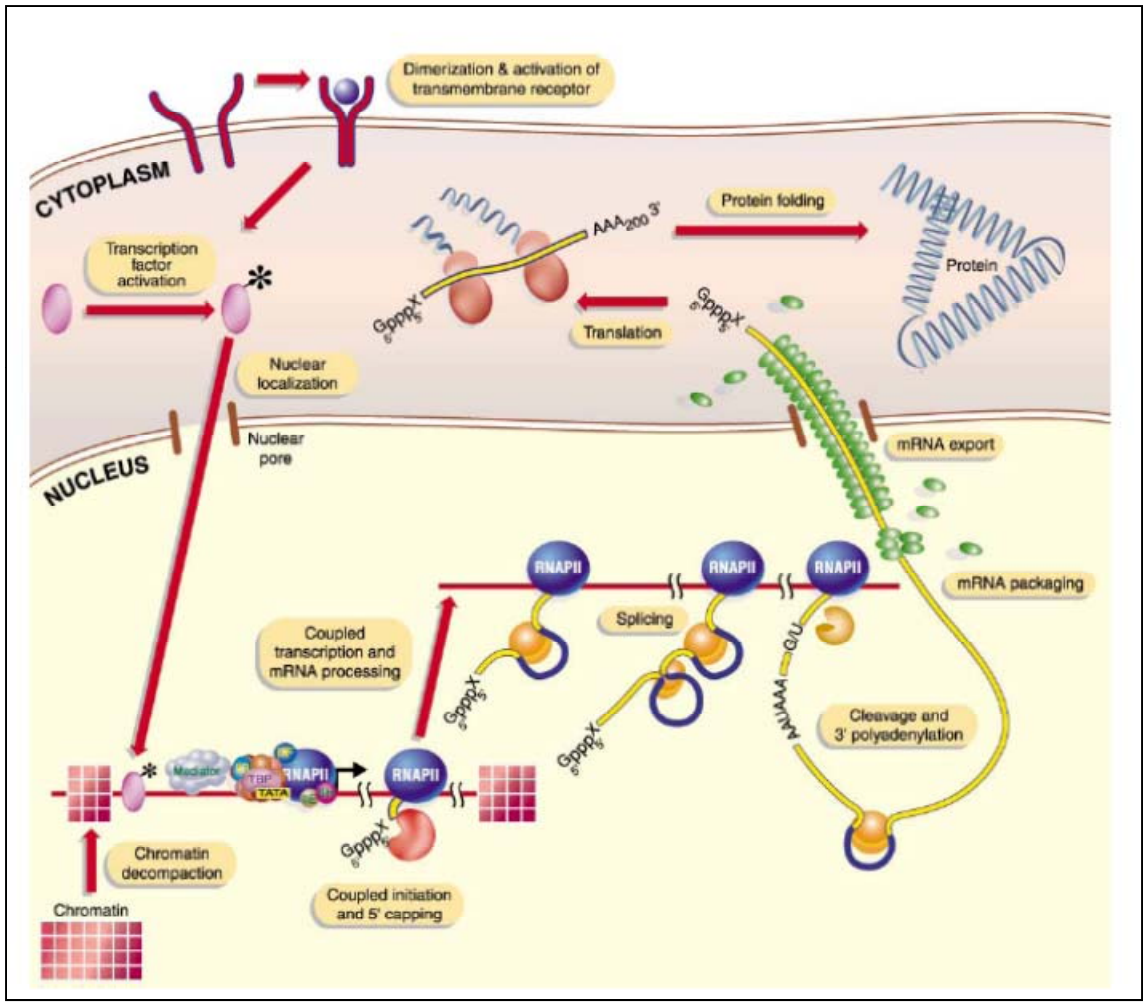
- Gene expression consists of multiple steps.
- Different steps are relatively independent of each other.



Orphanides & Reinberg, *Cell*, 108:439, 2002.

A Contemporary View of Gene Expression

- Gene expression is a continuous process that can be divided into different stages.
- Different stages are physically and functionally connected.

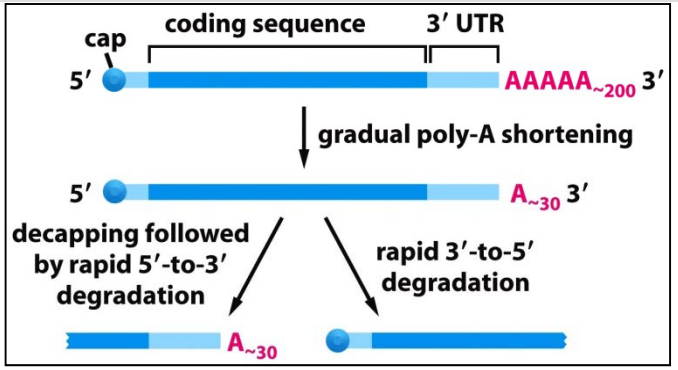


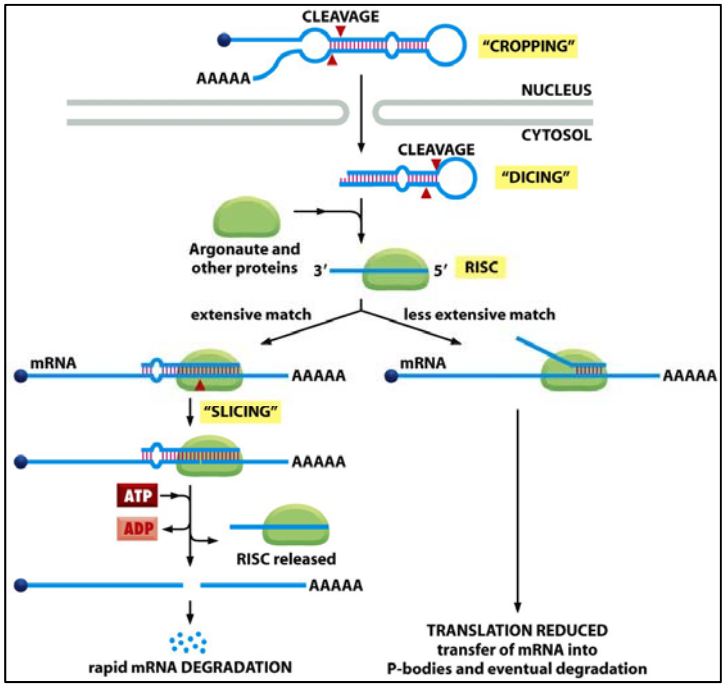
Orphanides & Reinberg, *Cell*, 108:439, 2002.

Example I : Gene Expression Regulation by microRNA

- One type of short noncoding RNA
  → microRNA
    → 22 nucleotides on average

- It is estimated that humans may express 1000 microRNA.
    → Regulates 1/3 of human protein-encoding genes

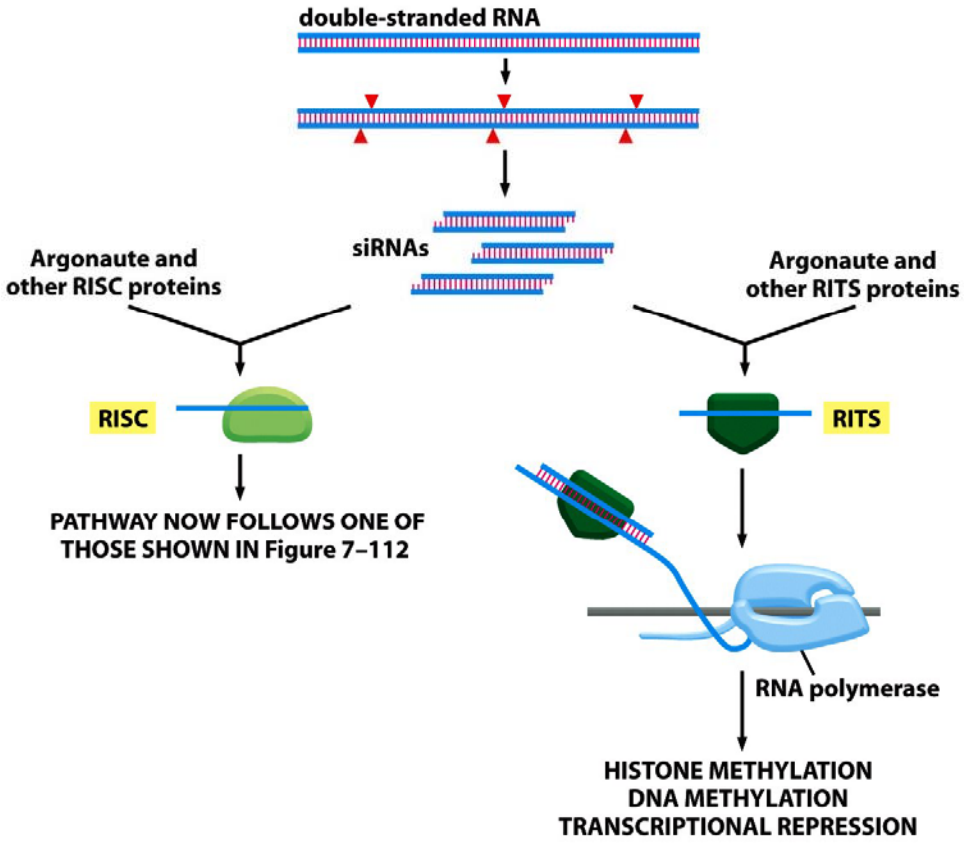




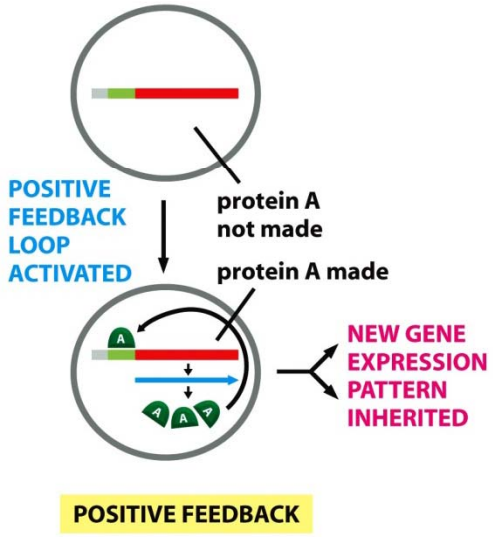
RISC: RNA-induced silencing complex

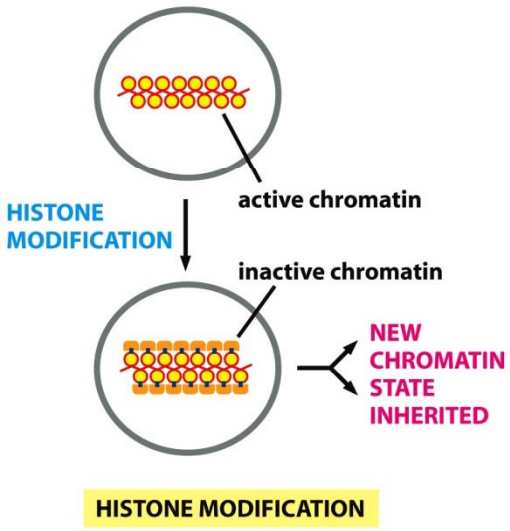
Example II : RNA Interference

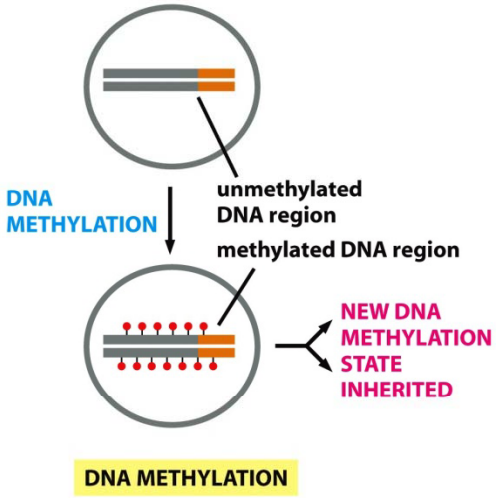
- Often used as a defense mechanism again foreign RNA
- Have been developed into a powerful approach to silence genes.

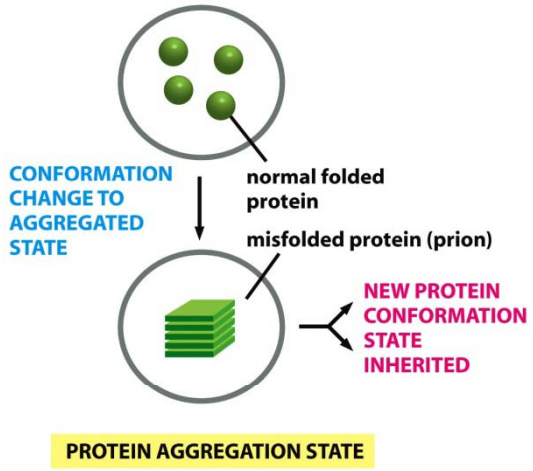


Maintaining Differentiation through Epigenetic Inheritance









- Overview of gene expression control
- Noise in gene expression
- Overview of cell signaling
- Classification of related proteins
- G-protein coupled receptors

Regulation of Gene Expression at Different Levels

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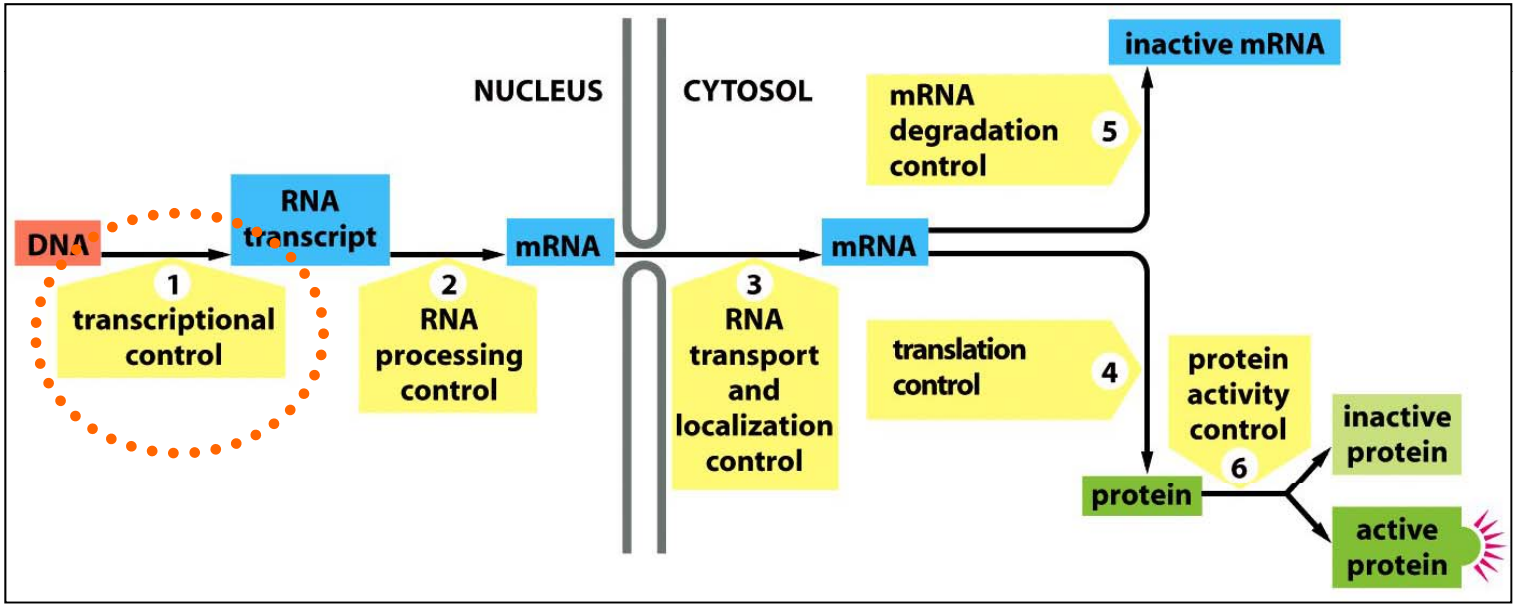


Quantitative Analysis and Modeling of Gene Expression

- Different classes of genes are regulated at different stages by different regulation mechanisms.

- Strategy I: Using simplified models:
  - bacterial cells provide convenience of manipulation but lacks advanced regulatory mechanisms of higher eukaryotic cells.

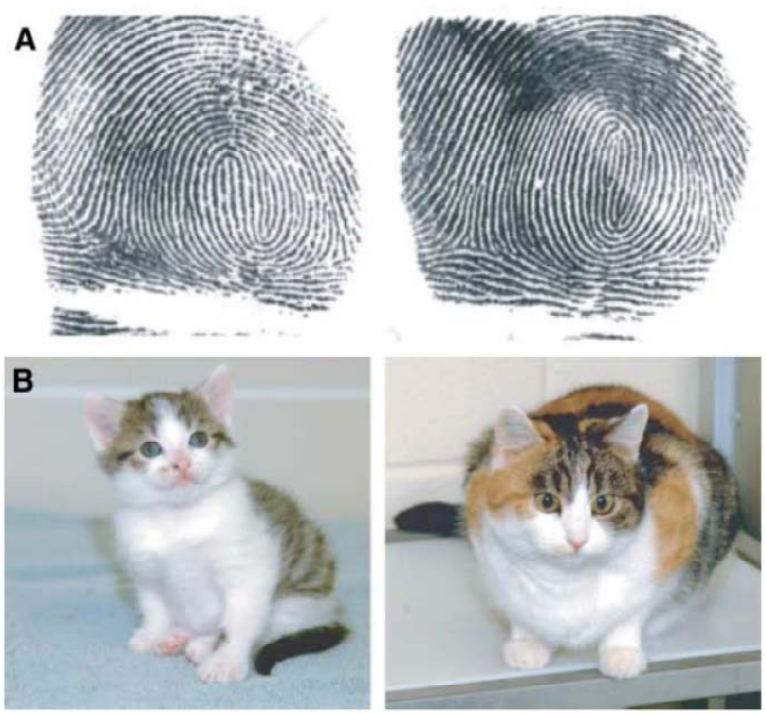
- Strategy II: Identification and analysis of modules.

- Strategy III: Synthetic approach.

Noise in Gene Expression

- Identical twin humans and animal clones differ in appearance and behavior.

- Cells with the same genes, the same environment display variations in form and behavior due to the stochastic nature of biochemical reactions.



Raser & O'Shea, *Science*, 309:2010, 2005.

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- Vilar JM, Guet CC, Leibler S, Modeling network dynamics: the lac operon, as case study, *J. Cell Biology*, 2003. 161:471-476.
- Uri Alon, Network motifs: theory and experimental approaches, *Nature Reviews Genetics*. 2007, 8, 450-461.
- http://www.elowitz.caltech.edu/index.html
- http://www.weizmann.ac.il/mcb/UriAlon/

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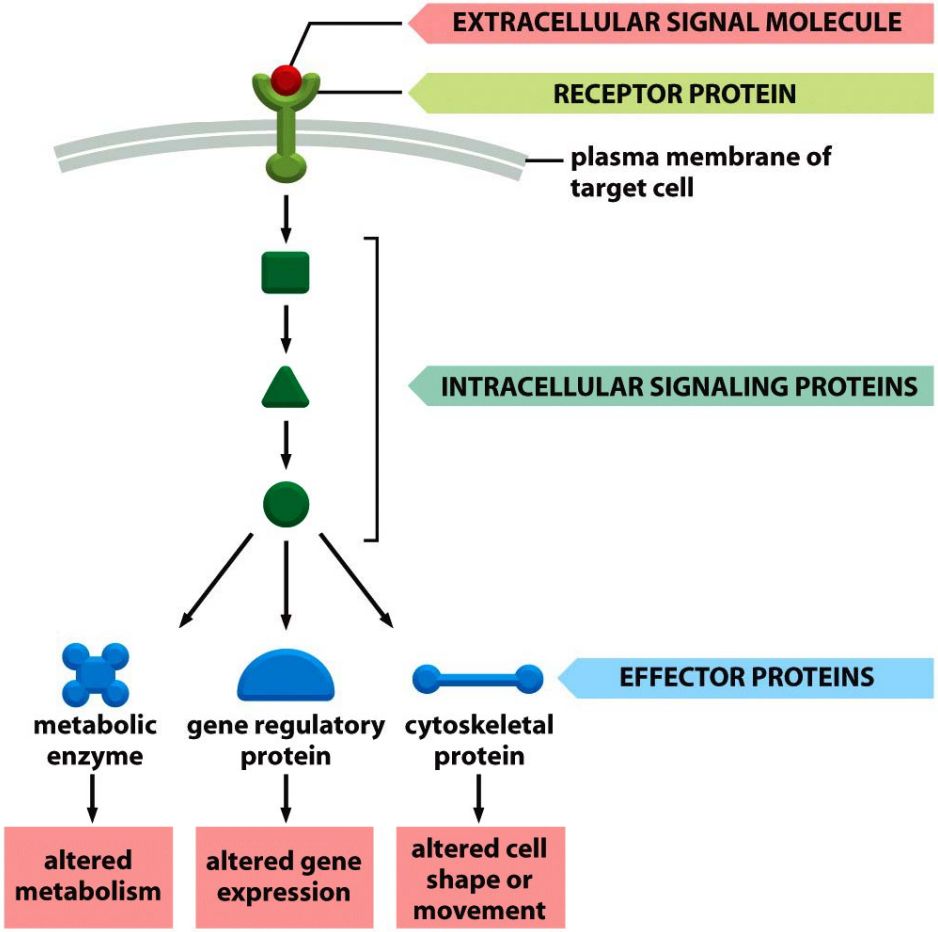
Overview of Cell Signaling

- Sources of extracellular signal
  - Non-cellular environment
  - Cellular environment (cell-cell communication)
  - Hundreds of types of signals

- Cells signaling
  - Stimulus sensing; communication
  - Information processing; decision making

- ↓Receptors
  ↓Signaling proteins
  ↓Effector proteins

- Signaling pathways regulate nearly all cellular functions.



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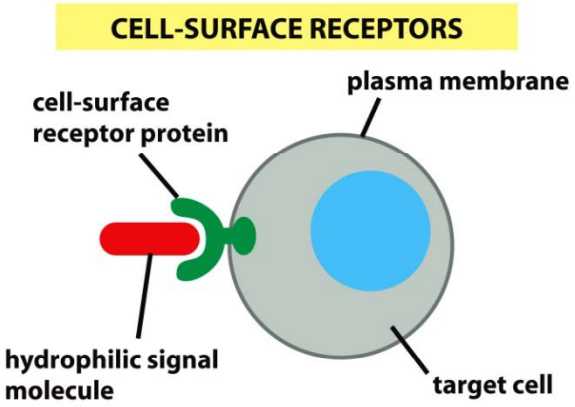
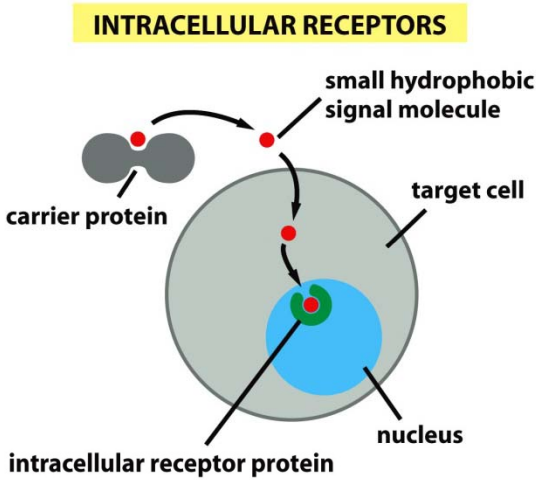
Membrane & Intracellular Receptors

- Receptors bind signaling molecules (ligands)
- Receptors are highly sensitive and specific.
  - Typical signal molecule concentration $<10^{-8}$ M
  - More than 1500 human genes encode receptors
- Most receptors are at the cell surface.
- Some receptors are intracellular (e.g. light, gas receptors).





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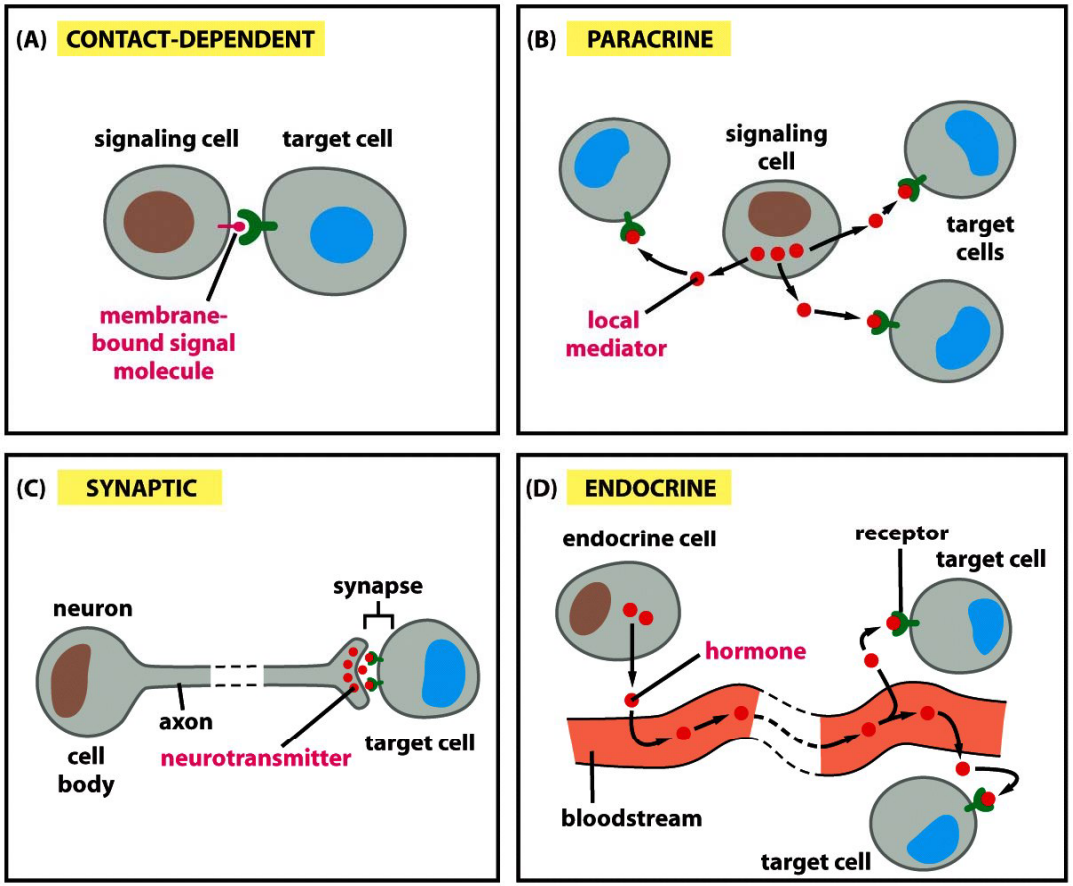
General Principles of Signaling (I)

- Four forms of intercellular signaling
- Paracrine signaling acts locally over different types of cells.
- Autocrine signaling acts locally over the same types of cells including themselves.
- Endocrine signaling acts over long distance.



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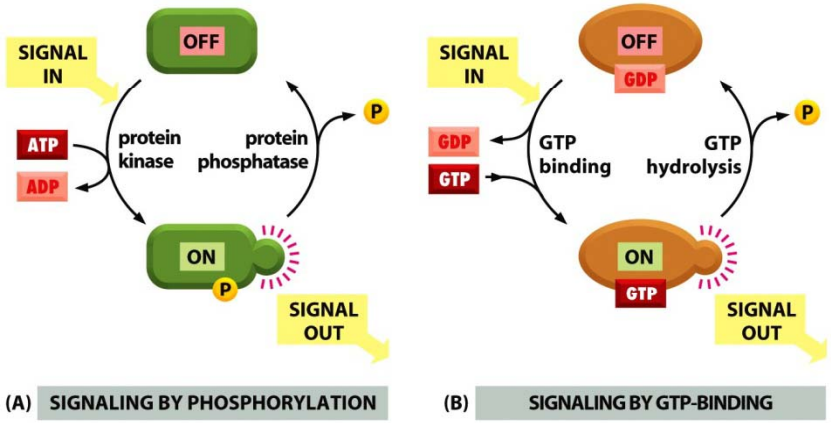
General Principles of Signaling (II)

- Many signaling proteins act as molecular switches
- Two ways to activate/deactivate signaling proteins
- Human genomes encodes ~520 kinases and ~150 phosphatases
- Two main types of kinases
  - tyrosine kinase
  - serine/threonine kinase
- Two types of GTP-binding proteins
  - Trimeric G proteins
  - Monomeric GTPases



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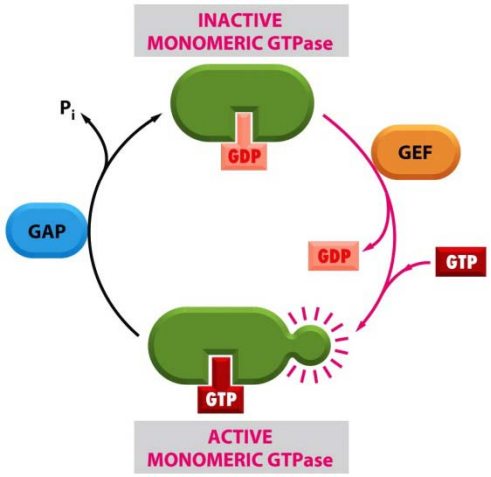
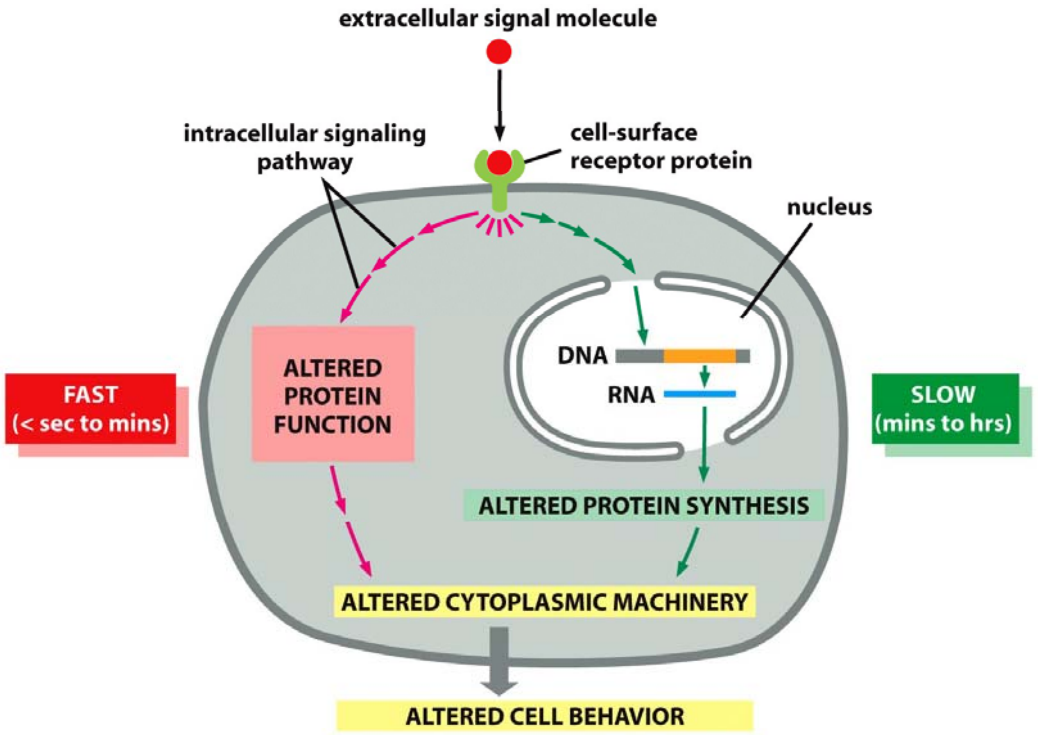


General Principles of Signaling (III)

- Different pathways have different rates of response.
- Pathways involve gene expression regulation are usually slow.



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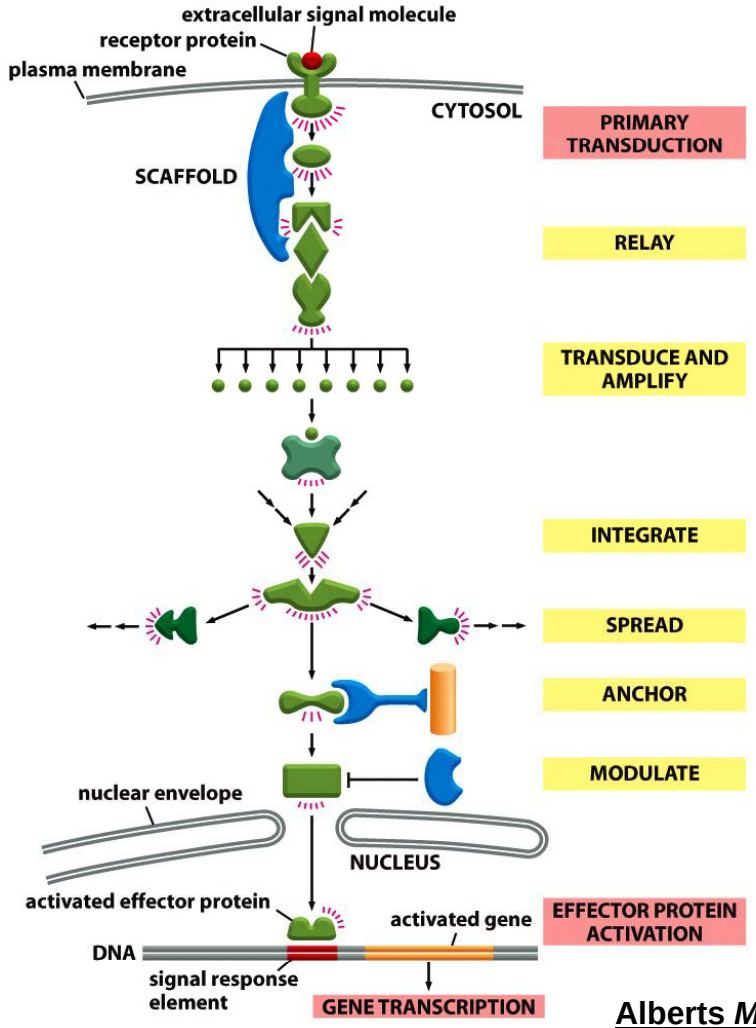
General Principles of Signaling (IV)

- A scaffold brings multiple signaling proteins together for faster and more efficient interactions.
- Signaling proteins may be anchored to a specific cellular structure.
- Activities of signaling proteins may be modulated by other signaling proteins.



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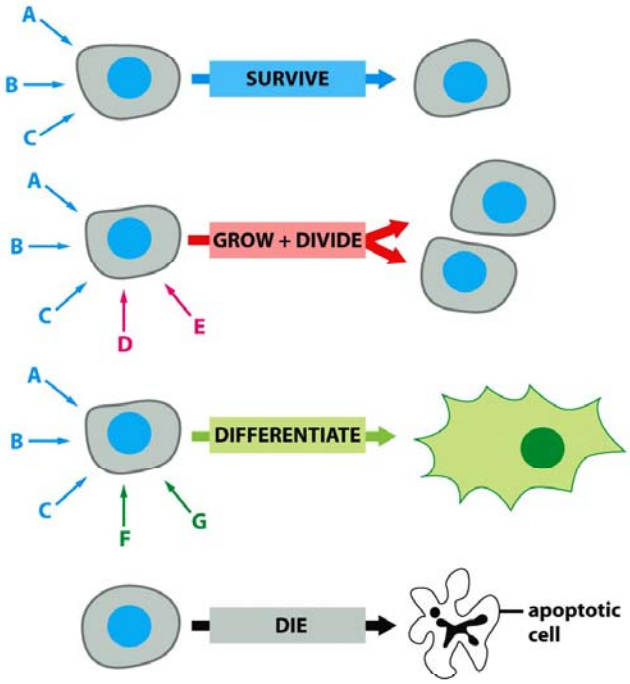
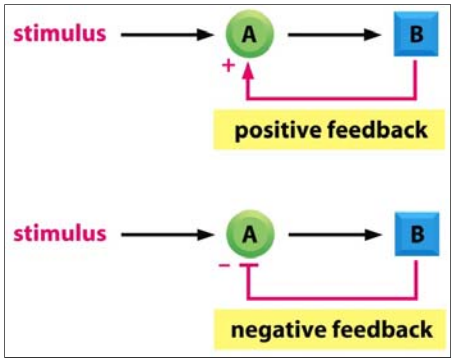
Specific Reponses of Cells to Signaling

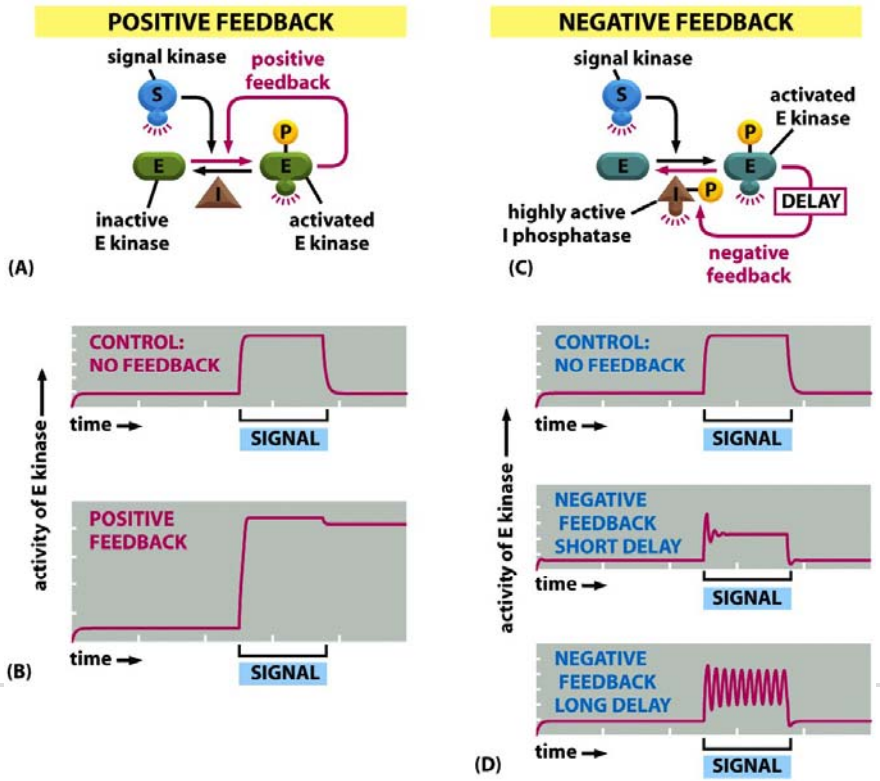
- A cell in a multicellular organism may be exposed to hundreds of signals.
- Different types of cells respond differently to the same type of signals.
- A major challenge is to understand how the cells process such information and make decisions.



Feedback Loops in Signaling Networks

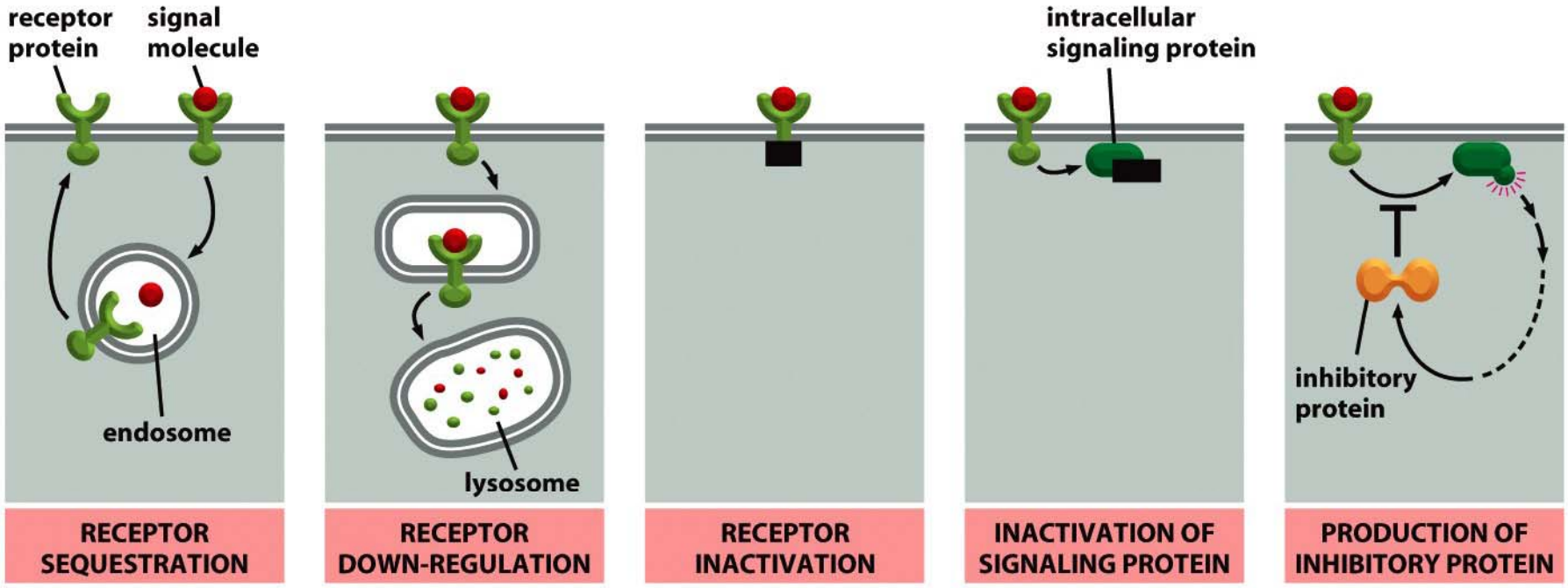
- Two types of feedback loops
  - Positive feedback
  - Negative feedback
- Positive feedback loop
  - Bistability
- Negative feedback loop
  - Robustness to noise





Adaptation of Sensitivity to Signaling

- Cells can adapt to external stimuli through sensitivity adjustment.



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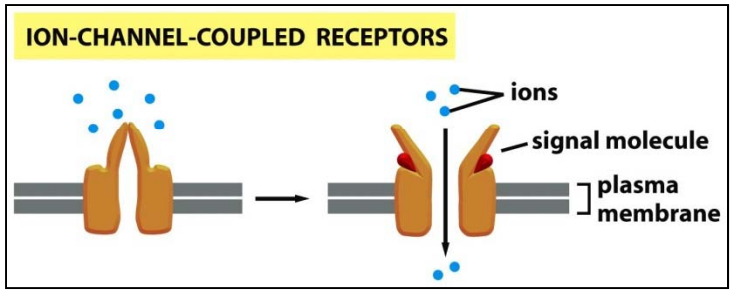
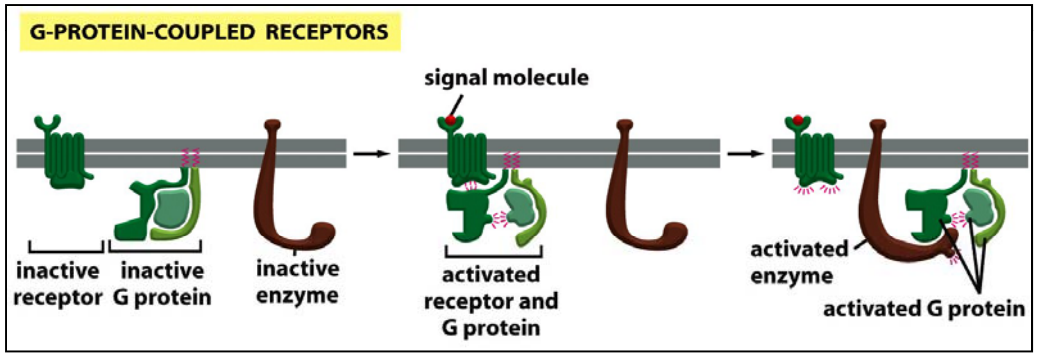
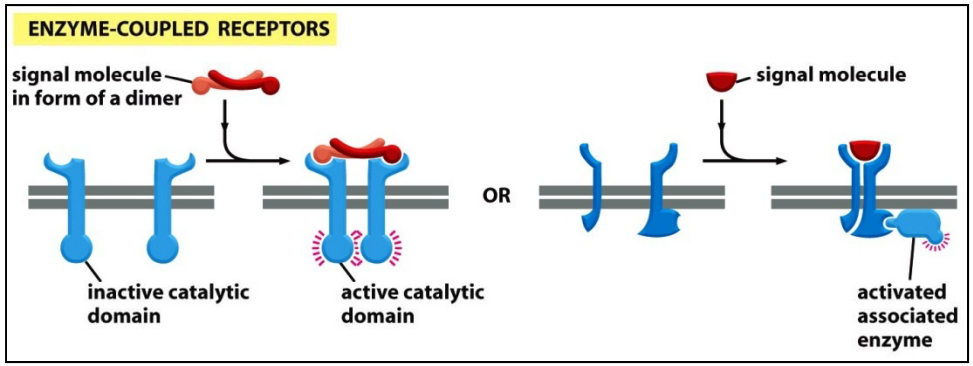
Membrane Receptors

- Most extracellular signal molecules bind to specific membrane receptors.
- Three largest classes of receptors, defining three transduction mechanisms.
- Two common strategies used to transfer signals
  - conformation changes
  - clustering







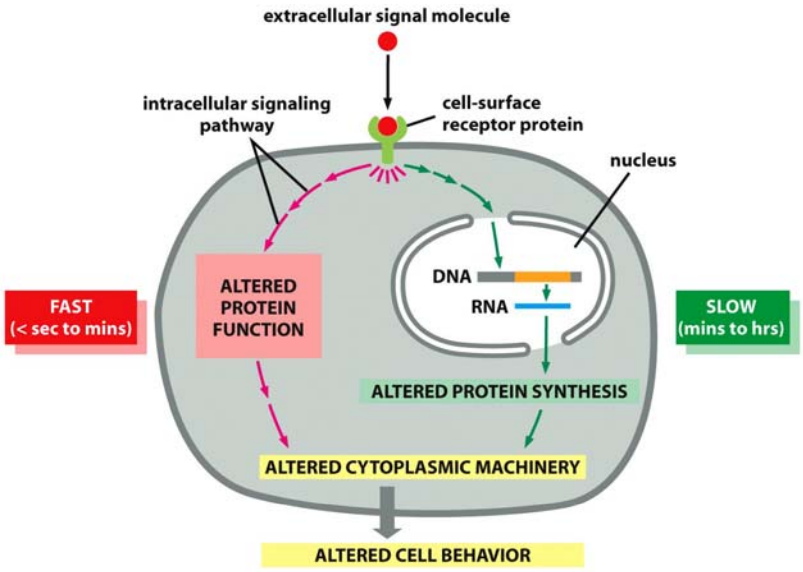
Intracellular Signaling Proteins & Second Messengers

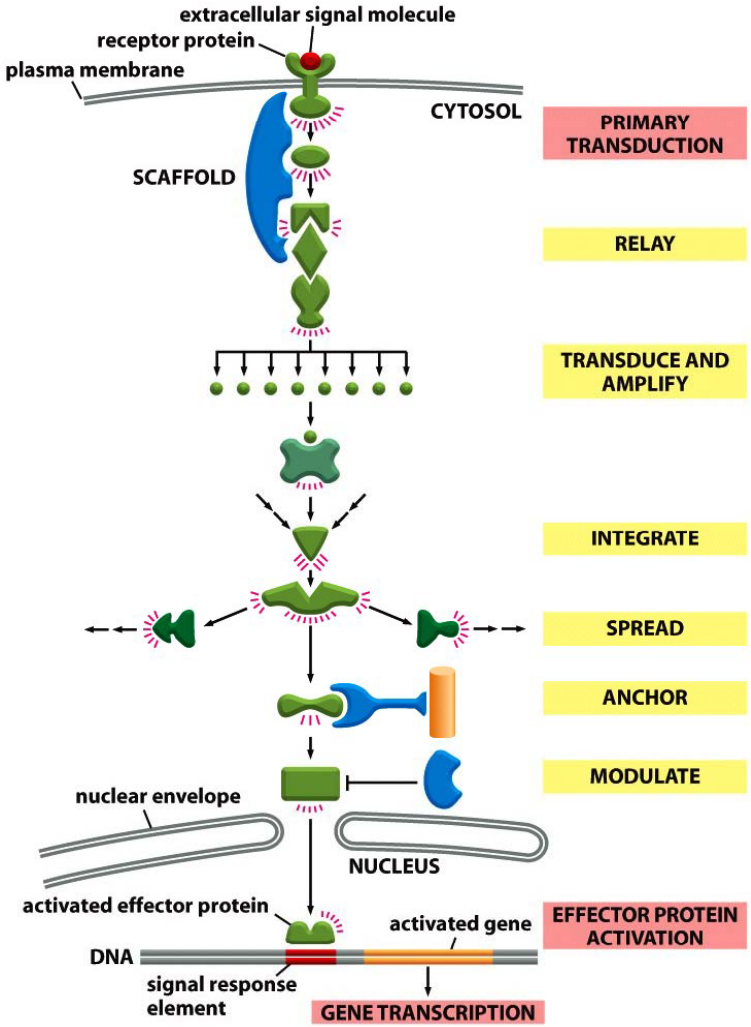
- Signaling proteins

  → Serving a broad range of signal processing functions

- Second messengers

  → cAMP, Ca^{2+}





Signaling Proteins

- Many signaling proteins act as molecular switches
- Two ways to activate/deactivate signaling proteins
- Human genomes encodes ~520 kinases and ~150 phosphatases
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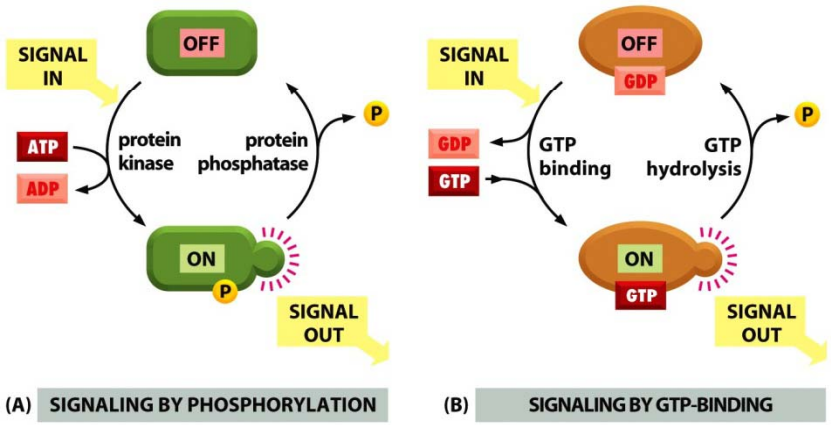

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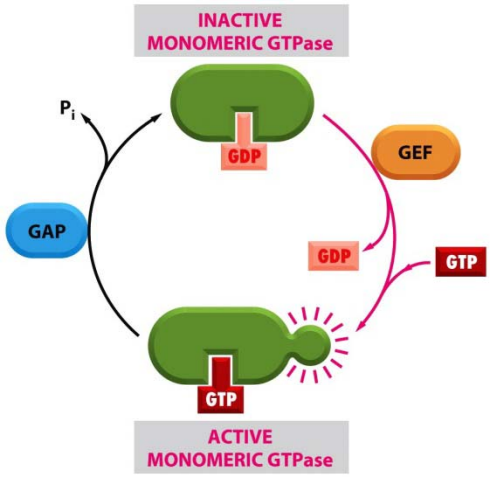

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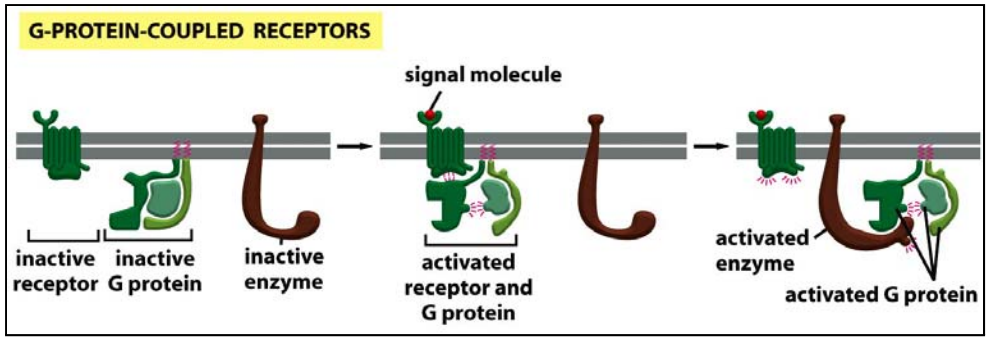
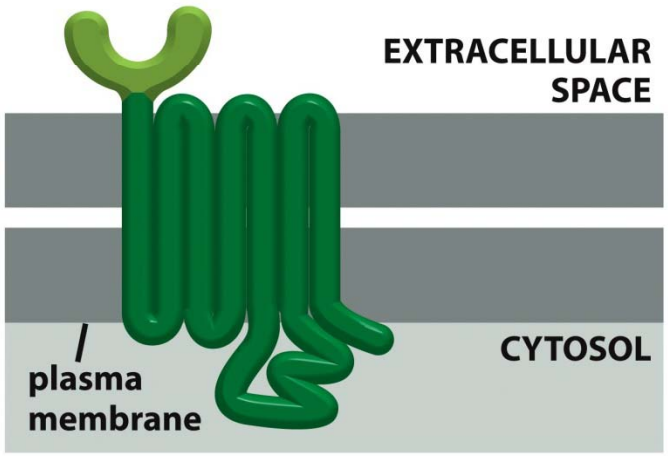
G-Protein Coupled Receptors (I)

- Signal molecules of GPCR include
  - photons
  - molecules of taste and smell
  - hormones, neurotransmitters, …
  - proteins, small peptides, etc…



- Function
  - Nearly all human senses: sight, smell, taste
  - Behavior and mood regulation
  - Regulation of immune system and inflammation
  - Nervous system regulation



- Half of known drugs work through GPCR directly or indirectly

Different Trimeric G-Protein Families

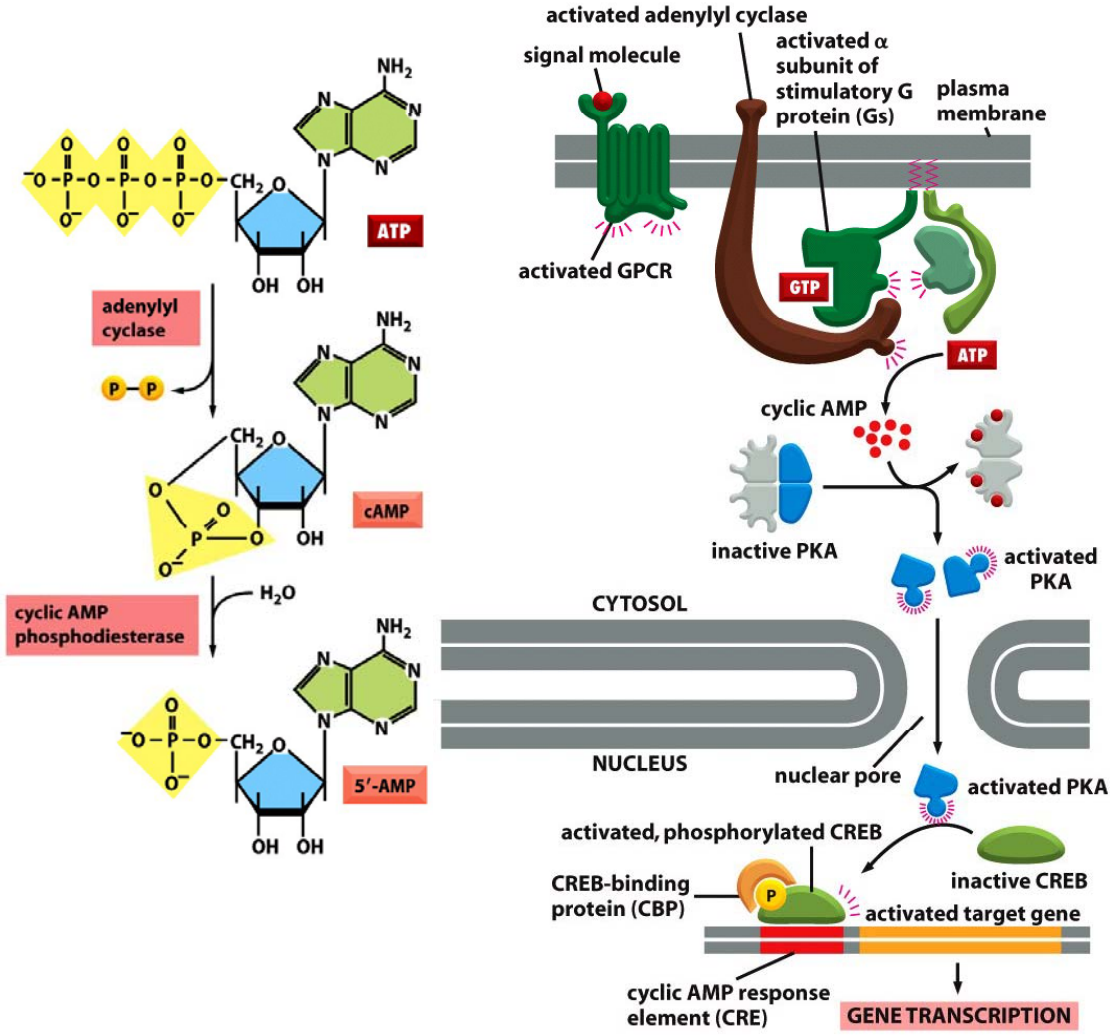
Table 15–3 Four Major Families of Trimeric G Proteins*

FAMILY	SOME FAMILY MEMBERS	SUBUNITS THAT MEDIATE ACTION	SOME FUNCTIONS
I	G_s	α	activates adenylyl cyclase; activates Ca^{2+} channels
	G_{olf}	α	activates adenylyl cyclase in olfactory sensory neurons
II	G_i	α	inhibits adenylyl cyclase
		βγ	activates K^+ channels
	G_o	βγ	activates K^+ channels; inactivates Ca^{2+} channels
		α and βγ	activates phospholipase C-β
	G_t (transducin)	α	activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors
III	G_q	α	activates phospholipase C-β
IV	$G_{12/13}$	α	activates Rho family monomeric GTPases (via Rho-GEF) to regulate the actin cytoskeleton

*Families are determined by amino acid sequence relatedness of the α subunits. Only selected examples are included. About 20 α subunits and at least 6 β subunits and 11 γ subunits have been described in humans.

Example: Regulation of cAMP by G Proteins

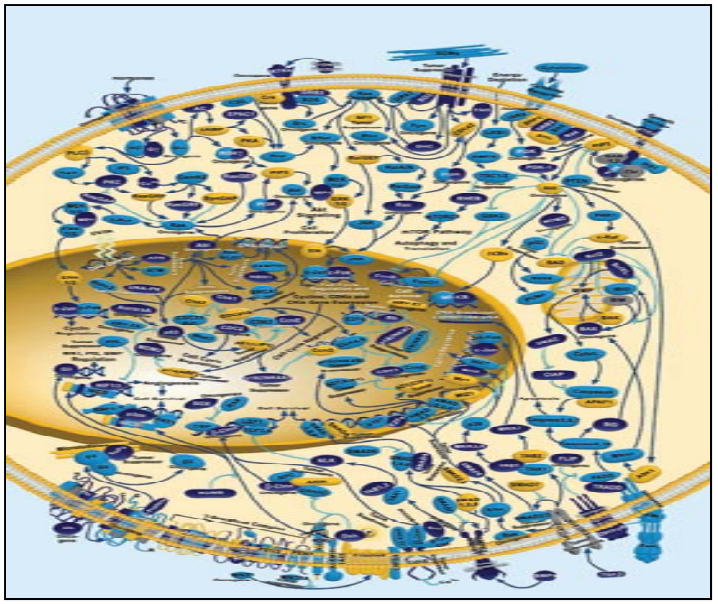
- Cyclic AMP is synthesized from ATP by adenylyl cyclase.
- Cyclic AMP is degraded by cAMP phosphodiesterases through hydrolysis.



Challenges in Analyzing Signaling Pathways

- Hundreds of signaling pathways.
- Pathways frequently branch and converge.
- Positive and negative feedback loops are common.
- Outcomes of signaling pathways can be spatial and temporal dependent.
- Analysis typically uses graph models.

Human cancer pathways



References

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- F. Marks et al, Cell Signal Processing, Garland Science, 2008.

Questions ?