Chapter 11

Overview: Cellular Messaging

- Cell-to-cell communication is essential for both multicellular and unicellular organisms
- Biologists have discovered some universal mechanisms of cellular regulation
- Cells most often communicate with each other via chemical signals
- For example, the fight-or-flight response is triggered by a signaling molecule called epinephrine

Concept 11.1: External signals are converted to responses within the cell

- Microbes provide a glimpse of the role of cell signaling in the evolution of life

Evolution of Cell Signaling

- The yeast, *Saccharomyces cerevisiae*, has two mating types, **a** and α
- Cells of different mating types locate each other via secreted factors specific to each type
- A **signal transduction pathway** is a series of steps by which a signal on a cell's surface is converted into a specific cellular response
- Signal transduction pathways convert signals on a cell's surface into cellular responses
- Pathway similarities suggest that ancestral signaling molecules evolved in prokaryotes and were modified later in eukaryotes
- The concentration of signaling molecules allows bacteria to sense local population density

Local and Long-Distance Signaling

- Cells in a multicellular organism communicate by chemical messengers
- Animal and plant cells have cell junctions that directly connect the cytoplasm of adjacent cells
- In local signaling, animal cells may communicate by direct contact, or cell-cell recognition
- In many other cases, animal cells communicate using **local regulators**, messenger molecules that travel only short distances
- In long-distance signaling, plants and animals use chemicals called **hormones**
- The ability of a cell to respond to a signal depends on whether or not it has a receptor specific to that signal

The Three Stages of Cell Signaling: *A Preview*

- Earl W. Sutherland discovered how the hormone epinephrine acts on cells
- Sutherland suggested that cells receiving signals went through three processes
    - **Reception**
    - **Transduction**
    - **Response**

Concept 11.2: Reception: A signaling molecule binds to a receptor protein, causing it to change shape

- The binding between a signal molecule (**ligand**) and receptor is highly specific
- A shape change in a receptor is often the initial transduction of the signal
- Most signal receptors are plasma membrane proteins

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Receptors in the Plasma Membrane

- Most water-soluble signal molecules bind to specific sites on receptor proteins that span the plasma membrane
- There are three main types of membrane receptors
  - G protein-coupled receptors
  - Receptor tyrosine kinases
  - Ion channel receptors
- **G protein-coupled receptors (GPCRs)** are the largest family of cell-surface receptors
- A GPCR is a plasma membrane receptor that works with the help of a **G protein**
- The G protein acts as an on/off switch: If GDP is bound to the G protein, the G protein is inactive
- **Receptor tyrosine kinases (RTKs)** are membrane receptors that attach phosphates to tyrosines
- A receptor tyrosine kinase can trigger multiple signal transduction pathways at once
- Abnormal functioning of RTKs is associated with many types of cancers
- A **ligand-gated ion channel** receptor acts as a gate when the receptor changes shape
- When a signal molecule binds as a ligand to the receptor, the gate allows specific ions, such as Na^+ or Ca^{2+}, through a channel in the receptor

Intracellular Receptors

- Intracellular receptor proteins are found in the cytosol or nucleus of target cells
- Small or hydrophobic chemical messengers can readily cross the membrane and activate receptors
- Examples of hydrophobic messengers are the steroid and thyroid hormones of animals
- An activated hormone-receptor complex can act as a transcription factor, turning on specific genes

Concept 11.3: Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

- Signal transduction usually involves multiple steps
- Multistep pathways can amplify a signal: A few molecules can produce a large cellular response
- Multistep pathways provide more opportunities for coordination and regulation of the cellular response

Signal Transduction Pathways

- The molecules that relay a signal from receptor to response are mostly proteins
- Like falling dominoes, the receptor activates another protein, which activates another, and so on, until the protein producing the response is activated

•At each step, the signal is transduced into a different form, usually a shape change **Protein Phosphorylation and Dephosphorylation**

- In many pathways, the signal is transmitted by a cascade of protein phosphorylations
- **Protein kinases** transfer phosphates from ATP to protein, a process called phosphorylation
- **Protein phosphatases** remove the phosphates from proteins, a process called dephosphorylation
- This phosphorylation and dephosphorylation system acts as a molecular switch, turning

activities on and off or up or down, as required

Small Molecules and Ions as Second Messengers

- The extracellular signal molecule (ligand) that binds to the receptor is a pathway's "first messenger"
- **Second messengers** are small, nonprotein, water-soluble molecules or ions that spread throughout a cell by diffusion
- Second messengers participate in pathways initiated by GPCRs and RTKs
- Cyclic AMP and calcium ions are common second messengers

Cyclic AMP

- **Cyclic AMP (cAMP)** is one of the most widely used second messengers
- **Adenylyl cyclase**, an enzyme in the plasma membrane, converts ATP to cAMP in response to an extracellular signal
- Many signal molecules trigger formation of cAMP
- Other components of cAMP pathways are G proteins, G protein-coupled receptors, and protein kinases
- cAMP usually activates protein kinase A, which phosphorylates various other proteins
- Further regulation of cell metabolism is provided by G-protein systems that inhibit adenylyl cyclase

Calcium Ions and Inositol Triphosphate (IP_3)

- Calcium ions (Ca^{2+}) act as a second messenger in many pathways
- Calcium is an important second messenger because cells can regulate its concentration
- A signal relayed by a signal transduction pathway may trigger an increase in calcium in the cytosol
- Pathways leading to the release of calcium involve **inositol triphosphate (IP_3)** and **diacylglycerol (DAG)** as additional second messengers

Concept 11.4: Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

- The cell's response to an extracellular signal is sometimes called the "output response"

Nuclear and Cytoplasmic Responses

- Ultimately, a signal transduction pathway leads to regulation of one or more cellular activities
- The response may occur in the cytoplasm or in the nucleus
- Many signaling pathways regulate the synthesis of enzymes or other proteins, usually by turning genes on or off in the nucleus
- The final activated molecule in the signaling pathway may function as a transcription factor
- Other pathways regulate the activity of enzymes rather than their synthesis
- Signaling pathways can also affect the overall behavior of a cell, for example, changes in cell shape

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Fine-Tuning of the Response

- There are four aspects of fine-tuning to consider
  - Amplification of the signal (and thus the response)
  - Specificity of the response
  - Overall efficiency of response, enhanced by scaffolding proteins
  - Termination of the signal

Signal Amplification

- Enzyme cascades amplify the cell's response
- At each step, the number of activated products is much greater than in the preceding step

The Specificity of Cell Signaling and Coordination of the Response

- Different kinds of cells have different collections of proteins
- These different proteins allow cells to detect and respond to different signals
- Even the same signal can have different effects in cells with different proteins and pathways
- Pathway branching and "cross-talk" further help the cell coordinate incoming signals

Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- **Scaffolding proteins** are large relay proteins to which other relay proteins are attached
- Scaffolding proteins can increase the signal transduction efficiency by grouping together different proteins involved in the same pathway
- In some cases, scaffolding proteins may also help activate some of the relay proteins

Termination of the Signal

- Inactivation mechanisms are an essential aspect of cell signaling
- If ligand concentration falls, fewer receptors will be bound
- Unbound receptors revert to an inactive state

Concept 11.5: Apoptosis integrates multiple cell-signaling pathways

- **Apoptosis** is programmed or controlled cell suicide
- Components of the cell are chopped up and packaged into vesicles that are digested by scavenger cells
- Apoptosis prevents enzymes from leaking out of a dying cell and damaging neighboring cells

Apoptosis in the Soil Worm *Caenorhabditis elegans*

- Apoptosis is important in shaping an organism during embryonic development
- The role of apoptosis in embryonic development was studied in *Caenorhabditis elegans*
- In *C. elegans*, apoptosis results when proteins that "accelerate" apoptosis override those that "put the brakes" on apoptosis

Apoptotic Pathways and the Signals That Trigger Them

- Caspases are the main proteases (enzymes that cut up proteins) that carry out apoptosis
- Apoptosis can be triggered by
  - An extracellular death-signaling ligand

  - DNA damage in the nucleus
  - Protein misfolding in the endoplasmic reticulum
- Apoptosis evolved early in animal evolution and is essential for the development and maintenance of all animals
- Apoptosis may be involved in some diseases (for example, Parkinson's and Alzheimer's); interference with apoptosis may contribute to some cancers