Alternative Signaling Routes in Genes Regulation

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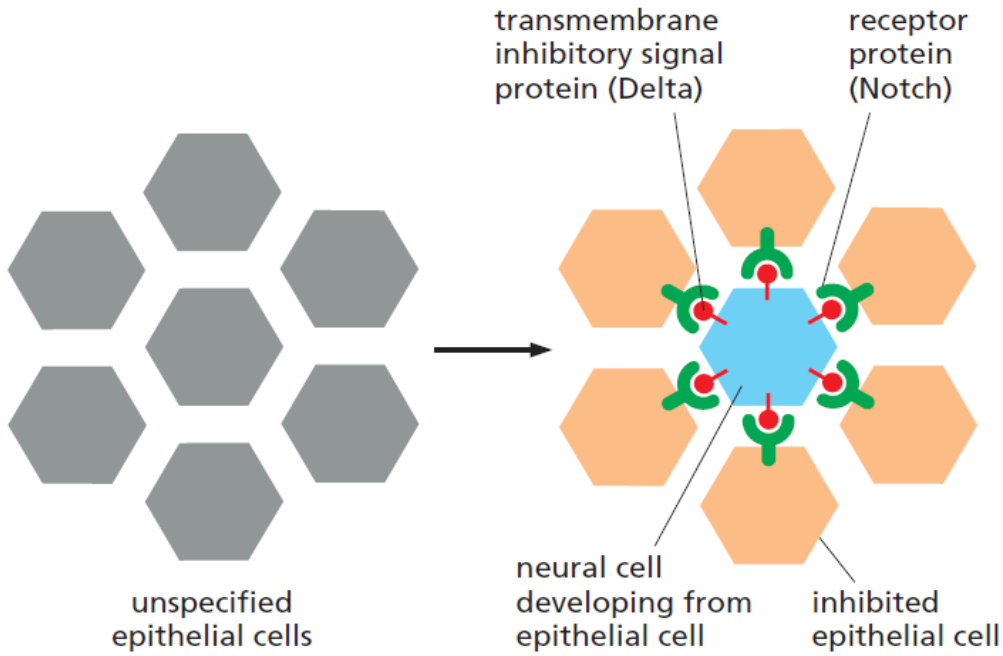
- Major changes in the behavior of a cell tend to depend on changes in the expression of numerous genes.
- Thus, many extracellular signaling molecules carry out their effects, in whole or in part, by initiating signaling pathways that change the activities of transcription regulators.
- There are numerous examples of gene regulation in both GPCR and enzyme-coupled receptor pathways.
- In this section, we describe some of the less common signaling mechanisms by which gene expression can be controlled.
- We begin with several pathways that depend on **regulated proteolysis** to control the activity and location of latent transcription regulators.
- We then turn to a class of extracellular signal molecules that do not employ cell-surface receptors but enter the cell and interact directly with transcription regulators to perform their functions.
- Finally, we briefly discuss some of the mechanisms by which gene expression is controlled by the circadian rhythm: the daily cycle of light and dark.

The Receptor Notch Is a Latent Transcription Regulatory Protein

- Signaling through the **Notch receptor protein** is used widely in animal development.
- It has a general role in **controlling cell fate choices** and **regulating pattern formation** during the development of most tissues, as well as in the **continual renewal of tissues** such as the lining of the gut.
- It is best known, however, for its role in the production of Drosophila neural cells, which usually arise as isolated single cells within an epithelial sheet of precursor cells.
- During this process, when a precursor cell commits to becoming a neural cell, it signals to its immediate neighbors not to do the same; the inhibited cells develop into epidermal cells instead.
- This process, called **lateral inhibition**, depends on a **contact-dependent** signaling mechanism that is activated by a single-pass transmembrane signal protein called Delta, displayed on the surface of the future neural cell.
- By binding to the Notch receptor protein on a neighboring cell, Delta signals to the neighbor not to become neural.
- In many tissues, all the cells in a cluster initially express both Delta and Notch, and a competition occurs, with one cell emerging as **winner,** expressing Delta strongly and inhibiting its neighbors from doing likewise.
- In other cases, **additional factors** interact with Delta or Notch to make some cells susceptible to the lateral inhibition signal and others unresponsive to it.



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- When this signaling process is defective, **a huge excess of neural cells** is produced at the expense of epidermal cells, which is **lethal**.

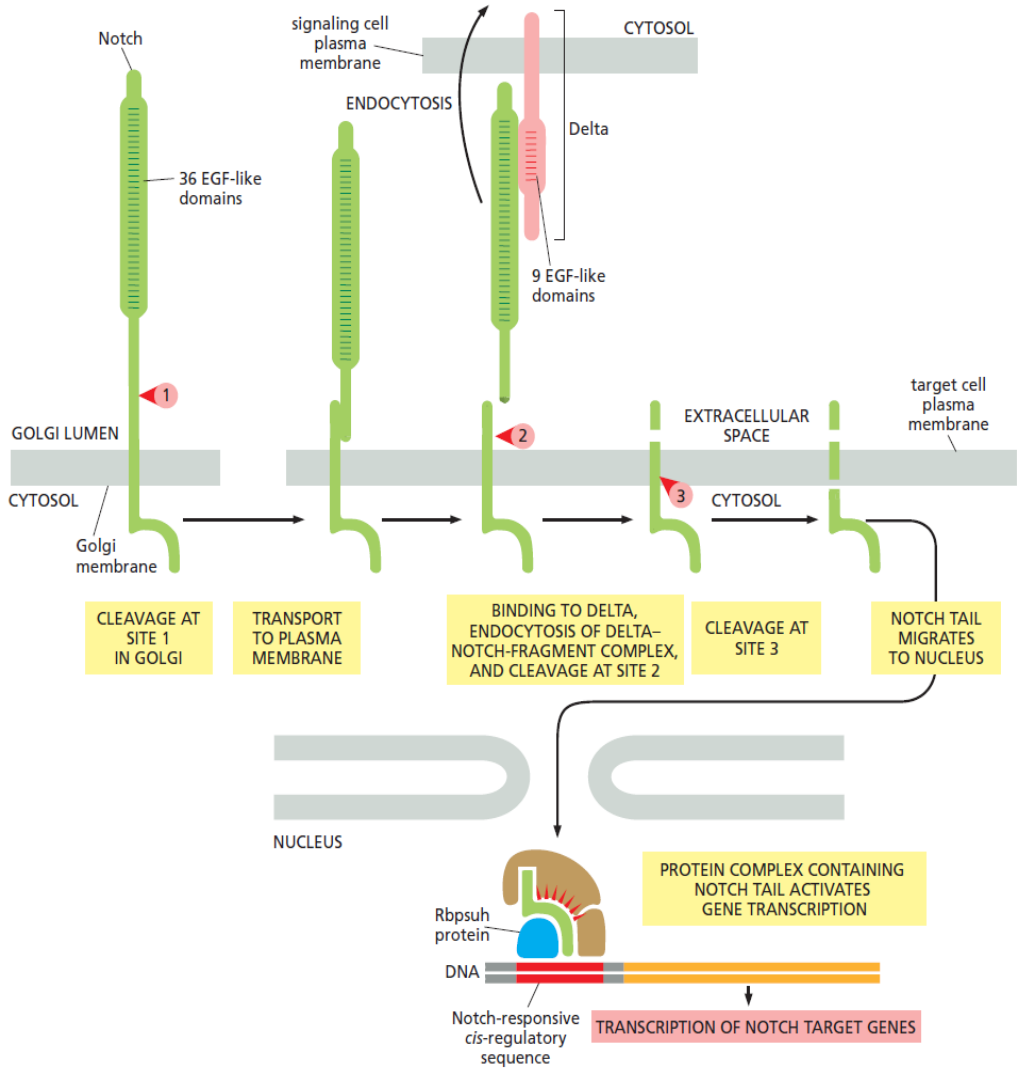
- Notch is a single-pass transmembrane protein that requires **proteolytic processing** to function.

- It acts as a **latent transcription regulator** and provides the **simplest** and most direct signaling pathway known from a cell-surface receptor to the nucleus.
- When activated by the binding of Delta on another cell, a plasma-membrane-bound protease cleaves off the cytoplasmic tail of Notch, and the released tail translocates into the nucleus to activate the transcription of a set of Notch response genes.

- The Notch tail fragment acts by binding to a **DNA-binding protein**, converting it from a transcriptional repressor into a transcriptional activator.

- The Notch receptor undergoes three successive proteolytic cleavage steps, but only the last two depend on Delta binding:
  - -As part of its normal biosynthesis, it is cleaved in the **Golgi apparatus** to form a heterodimer, which is then transported to the cell surface as the mature receptor.
  - -The binding of Delta to Notch induces a second cleavage in the extracellular domain, mediated by an extracellular protease.
  - -A final cleavage quickly follows, cutting free the cytoplasmic tail of the activated receptor.

- Note that, unlike most receptors, the activation of Notch is **irreversible**; once activated by ligand binding, the protein cannot be used again.



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This final cleavage of the Notch tail occurs just within the **transmembrane segment**, and it is mediated by a protease complex called **γ-secretase**, which is also responsible for the intramembrane cleavage of various other proteins.

One of its essential subunits is **Presenilin**, so called because mutations in the gene encoding it are a frequent cause of early-onset, familial Alzheimer's disease, a form of presenile dementia.

The protease complex is thought to contribute to this and other forms of Alzheimer's disease by generating **extracellular peptide fragments from a transmembrane neuronal protein**; the fragments accumulate in excessive amounts and form aggregates of misfolded protein called **amyloid plaques**, which may injure nerve cells and contribute to their degeneration and loss.

Both Notch and Delta are glycoproteins, and their interaction is regulated by the **glycosylation of Notch**.

The Fringe family of glycosyl transferases, in particular, adds extra sugars to the O-linked oligosaccharide on Notch, which alters the specificity of Notch for its ligands.

This has provided the first example of the modulation of ligand–receptor signaling by differential receptor glycosylation.

Wnt Proteins Bind to Frizzled Receptors and Inhibit the Degradation of β-Catenin

- **Wnt proteins** are secreted signal molecules that act as local mediators and morphogens to control many aspects of development in all animals that have been studied.

- They were discovered independently in flies and in mice: in Drosophila, the ***Wingless (Wg)*** gene originally came to light because of its role as a morphogen in wing development, while in mice, the ***Int1*** gene was found because it promoted the development of breast tumors when activated by the integration of a virus next to it.
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- Both of these genes encode **Wnt proteins**.

- Wnts are unusual as secreted proteins in that they have a fatty acid chain covalently attached to their N-terminus, which increases their binding to cell surfaces.

- There are 19 Wnts in humans, each having distinct, but often overlapping, functions.

- Wnts can activate at least two types of intracellular signaling pathways.

- Our primary focus here is the **Wnt/β-catenin pathway** (also known as the canonical Wnt pathway), which is centered on **the latent transcription regulator β-catenin**.

- A second pathway, called the planar polarity pathway, coordinates the polarization of cells in the plane of a developing epithelium and depends on Rho family GTPases.

- Both of these pathways begin with the binding of Wnts to Frizzled family cell-surface receptors, which are seven-pass transmembrane proteins that resemble GPCRs in structure but do not generally work through the activation of G proteins.

- Instead, when activated by Wnt binding, Frizzled proteins recruit the scaffold protein **Dishevelled**, which helps relay the signal to other signaling molecules.

Wnt Proteins Bind to Frizzled Receptors and Inhibit the Degradation of β-Catenin

The Wnt/β-catenin pathway acts by regulating the proteolysis of the multifunctional protein β-catenin.

A portion of the cell's β-catenin is located at cell–cell junctions and thereby contributes to the control of cell– cell adhesion, while the remaining β-catenin is rapidly degraded in the cytoplasm.

Degradation depends on **a large protein degradation complex**, which binds β-catenin and keeps it out of the nucleus while promoting its degradation.

The complex contains at least four other proteins: a protein kinase called **casein kinase 1 (CK1)** phosphorylates the β-catenin on a serine, priming it for further phosphorylation by another protein kinase called **glycogen synthase kinase 3 (GSK3);** this final phosphorylation marks the protein for **ubiquitylation** and rapid degradation in proteasomes.

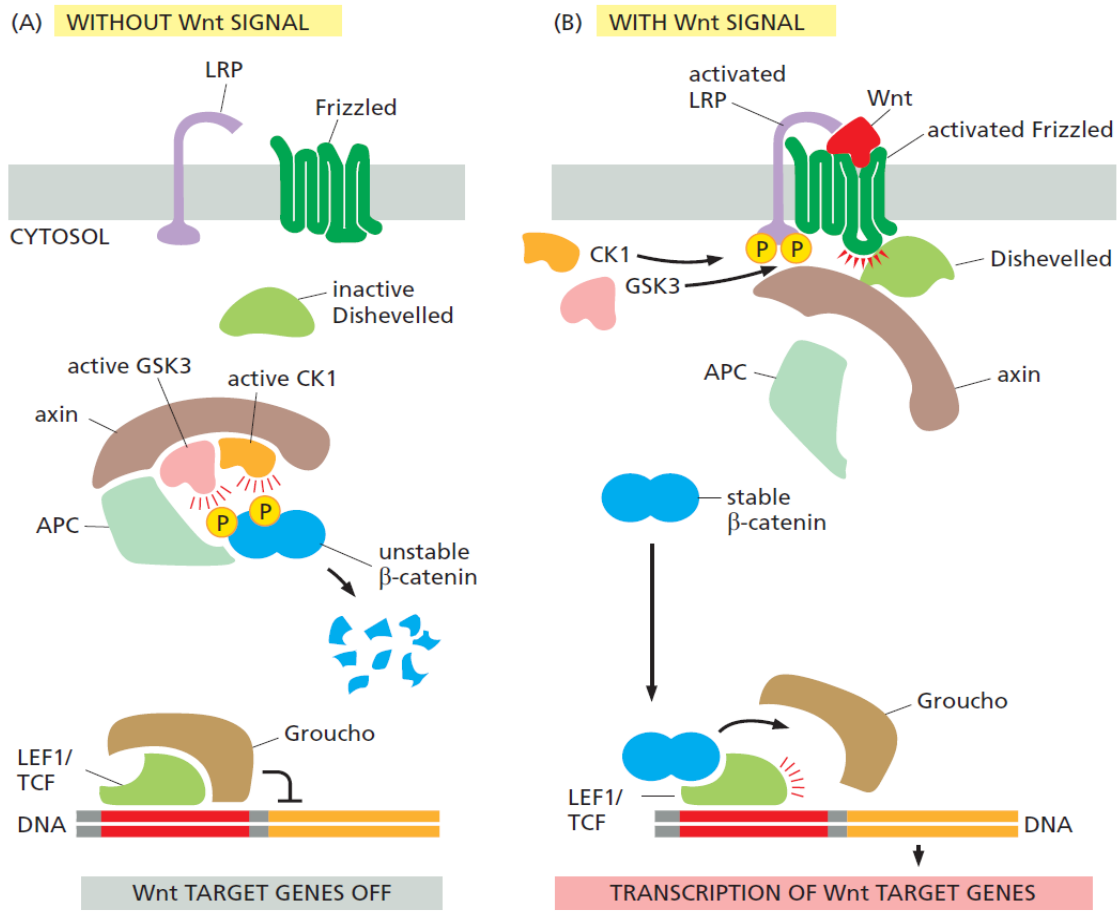
Two scaffold proteins called **axin** and **Adenomatous polyposis coli (APC)** hold the protein complex together.

APC gets its name from the finding that the gene encoding it is often mutated in a type of benign tumor (adenoma) of the colon; the tumor projects into the lumen as a **polyp** and can eventually become malignant.

Wnt proteins regulate β-catenin proteolysis by binding to both a Frizzled protein and a co-receptor that is related to the low-density lipoprotein (LDL) receptor and is therefore called an LDL-receptor-related protein (LRP).
In a poorly understood process, the activated receptor complex recruits the Dishevelled scaffold and promotes the phosphorylation of the LRP receptor by the two protein kinases, GSK3 and CK1.

Axin is brought to the receptor complex and inactivated, thereby disrupting the β-catenin degradation complex in the cytoplasm.

In this way, the phosphorylation and degradation of β-catenin are prevented, enabling unphosphorylated β-catenin to accumulate and translocate to the nucleus, where it alters the pattern of gene transcription.



Wnt Proteins Bind to Frizzled Receptors and Inhibit the Degradation of β-Catenin

In the absence of Wnt signaling, Wnt-responsive genes are kept silent by an inhibitory complex of transcription regulatory proteins.

The complex includes proteins of the **LEF1/TCF family** bound to a co-repressor protein of the **Groucho family**.

In response to a Wnt signal, β-catenin enters the nucleus and binds to the LEF1/TCF proteins, displacing Groucho.

The β-catenin now functions as a **coactivator**, inducing the transcription of the Wnt target genes.

Thus, as in the case of Notch signaling, Wnt/β-catenin signaling triggers **a switch from transcriptional repression to transcriptional activation.**

Among the genes activated by β-catenin is ***Myc***, which encodes a protein (Myc) that is an important regulator of cell growth and proliferation.

Mutations of the ***Apc* gene** occur in 80% of human colon cancers.

These mutations inhibit the protein's ability to bind β-catenin, so that β-catenin accumulates in the nucleus and stimulates the transcription of c-Myc and other Wnt target genes, even in the absence of Wnt signaling.
The resulting uncontrolled cell growth and proliferation promote the development of cancer.

Various secreted inhibitory proteins regulate Wnt signaling in development.
Some bind to the LRP receptors and promote their down-regulation, whereas others compete with Frizzled receptors for secreted Wnts.

In Drosophila at least, Wnts activate **negative feedback loops**, in which Wnt target genes encode proteins that help shut the response off; some of these proteins inhibit Dishevelled, and others are secreted inhibitors.