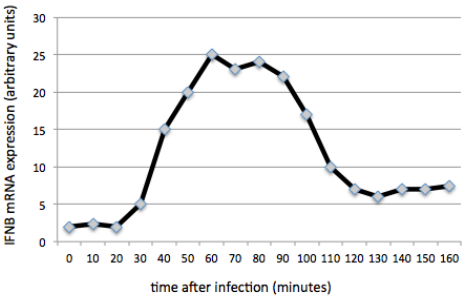
Questions Cell signaling Part 3

1) During viral infection of a cell, the cytoplasmic receptor RIG-I recognizes and binds to viral nucleic acids. This leads to activation of an adaptor protein, CARDIF, which binds to RIG-I. In turn, CARDIF recruits a kinase that phosphorylates a transcription factor, IRF3. This allows the transcription factor to enter the nucleus of the infected cell, and to trigger the transcription of antiviral genes.

1A) You perform an experiment in the lab, where you infect cells with a virus, and then measure the induction of one such response gene, *IFNB*. You notice the following pattern of expression:



Propose two different mechanisms that can help to explain why there is a decrease in *IFNB* mRNA levels starting 90 minutes after the infection.

1B) Draw a model whereby interferon-beta will trigger an intracellular response, implicating:

a transcription factor,
a kinase,
a tyrosine kinase-associated receptor

2) A virus infection triggers a cell to secrete TNFa, a secreted ligand. This will activate NF-KB in surrounding cells.

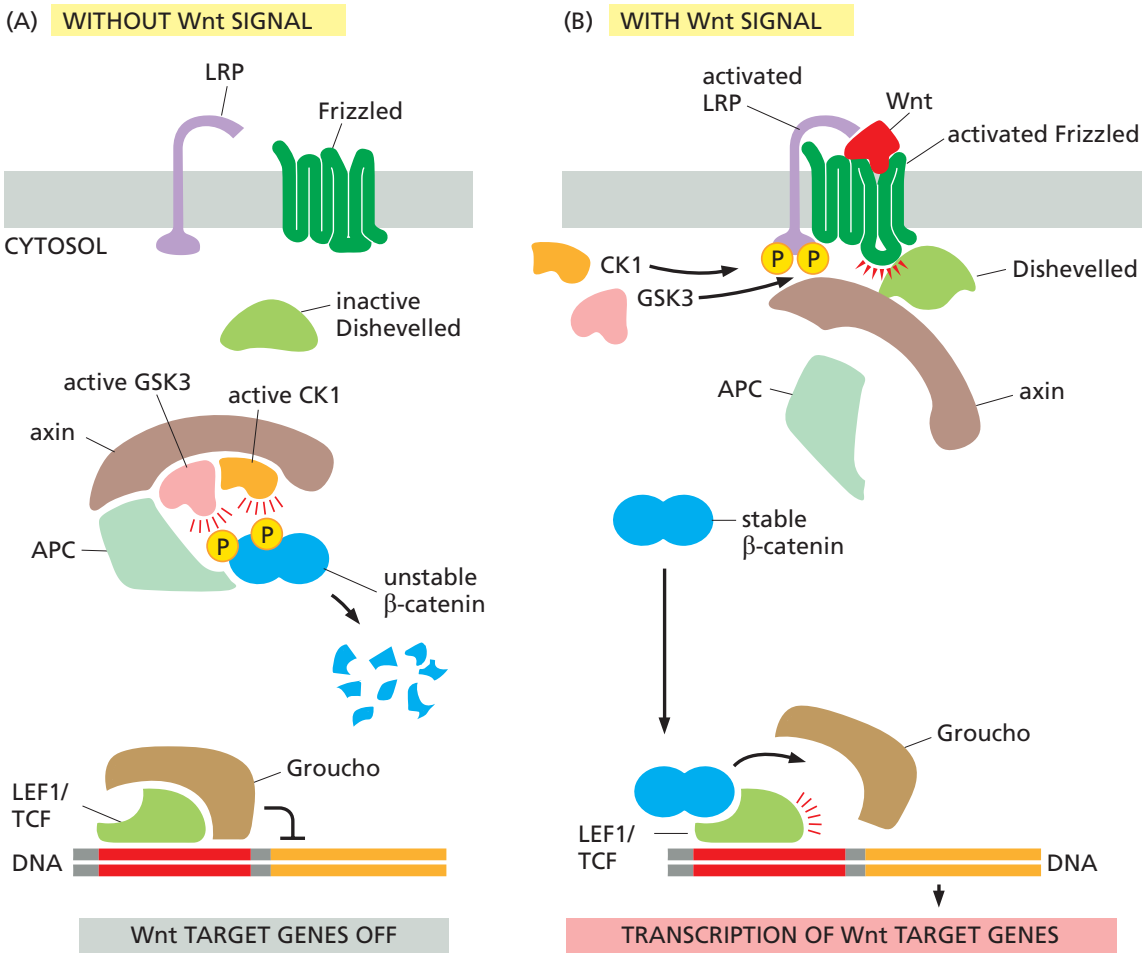
2A) Which kind of signaling is this?

2B) Because you were interested in looking at the signaling dynamics you built in a red fluorescent reporter in your cells that turns on when NF-KB is active. You find that even in absence of TNFa there are a few cells red. What happened in these cells?

3 In the development of tumors, two categories of genes are particularly important: 1) proto-oncogenes, whose alteration (often mutation) changes the encoded protein products, such that they gain in activity. Such gain-of-function mutations are usually present in one allele only, not the other because the effect is dominant; 2) tumor suppressor genes, whose alteration (often mutation) changes the encoded protein

products, such that they lose activity. Such loss-of-function mutations are usually present in both alleles, because the effect is recessive (one wild-type copy can still exert tumor suppressive function).

3A) Mutations in the *APC* gene are very frequent (80% of the cases) in human colorectal cancer. Wnt/b-catenin target genes are very important for tumor cell proliferation. Given this information, and the picture from the course pasted below, which category – proto-oncogene or tumor suppressor gene – would you expect *APC* to belong to, and why?



3B) In some colorectal cancers, *APC* is not mutated but *CTNNB1*, the gene coding for b- catenin, is mutated. Propose how such mutations affect b-catenin and the Wnt pathway. Is *CTNNB1* a proto-oncogene or a tumor suppressor gene?

4) You want to create a truncated protein that is constitutively present in the nucleus starting from the nuclear hormone receptor AR. What part of the protein would you remove and why? Which feature you absolutely cannot remove?

5) In the intestine enterocytes and mucus goblet cells are defined by having active notch signaling (enterocytes) or inactive notch signaling (goblet cells).

5A) You are looking at the intestine of a mutant mouse and see a lot of goblet cells. What has happened?

5B) You find that goblet cells are always surrounded by several enterocytes. What do you think is causing this pattern? What do you think is the receptor ligand distribution?

6) Match each deinition below with its term from the list above.

β-catenin
circadian clock
Cubitus interruptus (Ci)
Delta
Dishevelled
Frizzled
Hedgehog protein
iHog
IκB
LDL-receptor-related protein (LRP)
NFκB proteins
Notch
nuclear receptor superfamily
Patched
Smoothened
steroid hormone
Wnt/β-catenin pathway
Wnt proteins

A: Receptor protein involved in what may be the most widely used signaling pathway in animal development; its ligands are cell surface proteins such as Delta.

B: A family of secreted signal molecules that act as local mediators and morphogens during development; they were initially discovered as the products of the Wingless gene in lies and the Int1 gene in mice.

C: A signaling pathway activated by Wnt binding to both the Frizzled receptor and the LRP co-receptor.

D: A group of secreted signal molecules that act as local mediators and morphogens during development and whose effects are mediated through the cell-surface receptor Patched and its binding partner Smoothened.

E: A target of Hedgehog signaling, this gene regulatory molecule is a full length gene activator in the presence of Hedgehog and a partially proteolyzed gene repressor in its absence.

F: Latent gene regulatory proteins that are present in most cells in both animals and plants and are central to many stress, inflammatory, and innate immune responses.

G: Hydrophobic signaling molecule with a characteristic four-ringed structure derived from cholesterol.

7) The steroid hormones cortisol, estradiol, and testosterone are all derived from cholesterol by modifications that introduce polar groups such as – OH and =O (Figure 15–22). If cholesterol itself was not normally found in cell membranes, do you suppose it could be used effectively as a hormone, provided that an appropriate intracellular receptor was available?

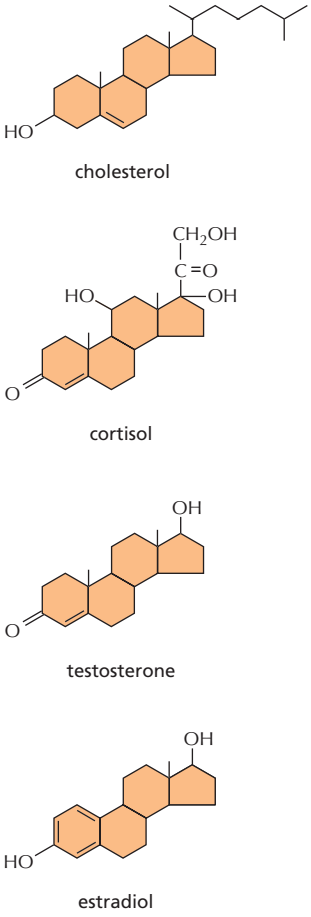


Figure 15–22 Steroid hormones and their parent molecule, cholesterol

8) Why do signaling responses that involve changes in proteins already present in the cell occur in milliseconds to seconds, whereas responses that require changes in gene expression require minutes to hours?

9) Decide whether each of these statements is true or false, and then explain why.
A: Signaling pathways that activate latent gene regulatory proteins depend on regulated proteolysis to control activity and location.
B: Notch is both a cell-surface receptor and a latent gene regulatory protein.
C: Because one of the targets of NFκB activation is the gene for IκBα, the cytoplasmic inhibitor of NFκB, a negative feedback loop is established that limits the duration of the NFκB response.

10) What do you think will happen to a WNT ligand if the lipid modifications were no longer made?