Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Musterlösung Übung 9

Vorlesung Bio-Engineering

Frühlingssemester 2021

Part 1. Cell Signaling

Signaling Some Questions:

Q1. 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?

A1. In both cases the signaling pathways themselves are rapid. If the pathway modifies a protein that is already present in the cell, its activity is changed immediately, leading to a rapid response. If the pathway modifies gene expression, there will be a delay corresponding to the time it takes for the mRNA and protein to be made and for the cellular levels of the protein to be altered sufficiently to invoke a response, which would usually take an hour or more.

Q2. How is it that different cells can respond in different ways to exactly the same signaling molecule even when they have identical receptors?

A2. Cells with identical receptors can respond differently to the same signal molecule because of differences in the internal machinery to which the receptors are coupled. Even when the entire signaling pathway is the same, cells can respond differently if they express different effector proteins at the ends of the pathways.

Q3. Choose if the following statement are right or wrong:

	Right	Wrong
Signal molecules have to be hydrophobic to be able to cross the plasma membrane	X	
Hydrophilic molecules can bind to cell surface receptors as well as intracellular receptors located in the cytosol or nucleus.		X
Paracrine signaling acts over far distances		X

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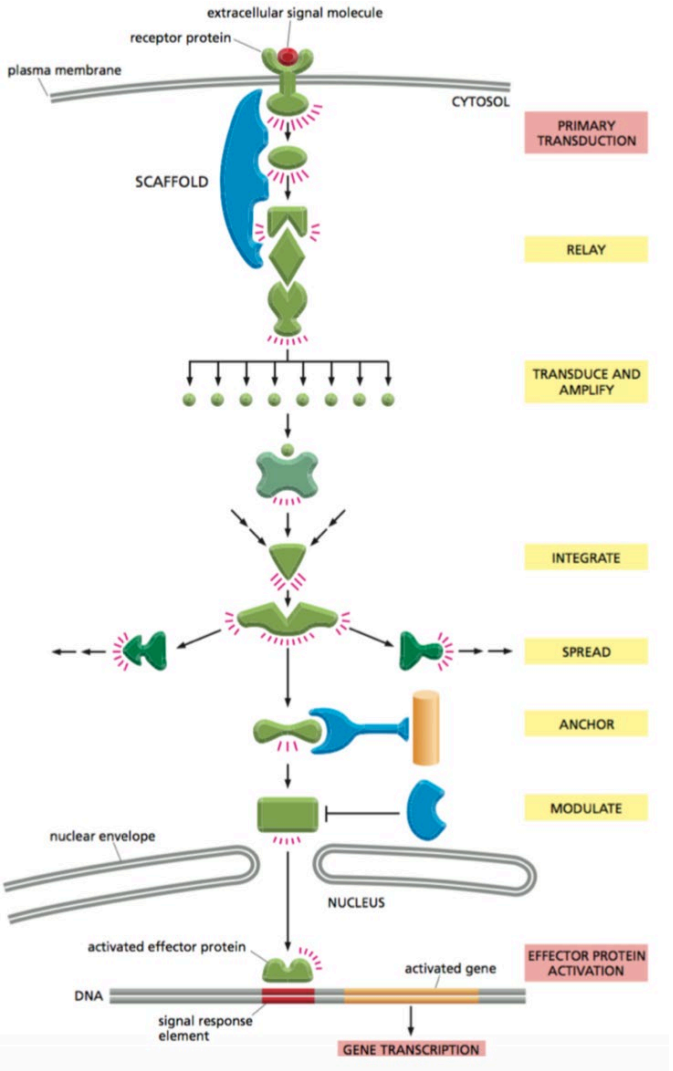
Most signaling molecules are used in paracrine, endocrine and synaptic signaling. The crucial difference is the speed and the selectivity of the signals	X	
Endocrine cells mostly use the same molecule for signaling, while nerve cells have to uses different neurotransmitters		X

Q4. Label the steps of the hypothetical intracellular pathway using the following terms:

- spread
- anchor
- effector protein activation
- relay
- primary transduction
- integrate
- gene transcription
- transduce and amplify
- modulate



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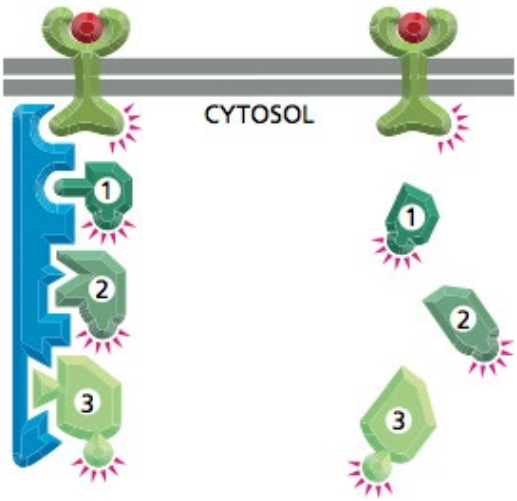
Q5. Consider a signaling pathway that proceeds through three protein kinases that are sequentially activated by phosphorylation. In one case, the kinases are held in a signaling complex by a scaffolding protein; in the other, the kinases are freely diffusible (see fig). Discuss the properties of these two types of organization in terms of signal amplification, speed, and potential for cross-talk between signaling pathways.



A5. The use of a scaffolding protein to hold the three kinases into a signaling complex increases the speed of signal transmission and eliminates crosstalk between pathways; however, there is relatively little opportunity for amplification of the signal from the receptor to the third kinase. Freely diffusing kinases offer the possibility for greater signal amplification since the first kinase can phosphorylate many molecules of the second kinase, which in turn can phosphorylate many molecules of the third kinase. The speed of signal transmission is likely to be slower, unless the concentration of kinases (and the potential for amplification) is high enough to compensate for their separateness. Finally, free kinases offer the potential for spreading the signal to other signaling pathways and to other parts of the cell. The organization that a cell uses for a particular signaling pathway depends on what the pathway is intended to accomplish.

Q6. Cells communicate in ways that resemble human communication. Decide which of the following forms of human communication are analogous to autocrine, paracrine, endocrine, and synaptic signaling by cells.

A. A telephone conversation
B. Talking to people at a cocktail party
C. A radio announcement
D. Talking to yourself

A6.

A. A telephone conversation is analogous to synaptic signaling in the sense that it is a private communication from one person to another, usually some distance away and sometimes very far away. It differs from synaptic signaling because it is (usually) a two-way exchange, whereas synaptic signaling is a one-way communication.
B. Talking to people at a cocktail party is analogous to paracrine signaling, which occurs between different cells (individuals) and is locally confined.

C. A radio announcement is analogous to an endocrine signal, which is sent out to the whole body (the audience) with only target cells (individuals tuned to the specific radio station) affected by it.
D. Talking to yourself is analogous to an autocrine signal, which is a signal that is sent and received by the same cell.

Q7. Proteins play a variety of roles in signaling pathways. Match the following list of signaling proteins with the best description of their functions. Each description should be matched with only one protein.

A. Amplifier proteins	1. Bind multiple signaling proteins together in a functional complex
B. Anchoring proteins	2. Combine signals from two or more pathways before passing it onward
C. Integrator proteins	3. Convert the signal to a different form
D. Modulator proteins	4. Greatly increase the signal they receive
E. Relay proteins	5. Maintain specific signaling proteins at a precise location in the cell
F. Scaffold proteins	6. Modify the activity of signaling proteins to regulate signal strength
G. Transducer proteins	7. Pass the message to the next signaling component in the pathway

A7: A. 4; B. 5; C. 2; D. 6; E. 7; F. 1; G. 3

Q8. Extracellular Matrix - TRUE/FALSE (Decide whether each of these statements is true or false, and then explain why.)

a) The extracellular matrix is a relatively inert scaffolding that stabilizes the structure of tissues.
b) One of the main chemical differences between proteoglycans and other glycoproteins lies in the structure of their carbohydrate side chains: proteoglycans mostly contain long, unbranched polysaccharide side chains, whereas other glycoproteins contain much shorter, highly branched oligosaccharides.
c) Integrins can convert mechanical signals into molecular signals.
d) Various types of integrins connect extracellular binding sites to all the different kinds of cytoskeletal elements, including actin, microtubules, and intermediate filaments.
e) Integrins are thought to be rigid rods that span the membrane and link binding sites outside the cell to those inside the cell.

A8.

A. False. The extracellular matrix plays an active role influencing the development, migration, proliferation, shape, and metabolism of cells that contact it.

B. True. In addition to these differences, proteoglycans can contain as much as 95% carbohydrate by weight, whereas other glycoproteins generally contain a lower fraction of carbohydrate (1–60%).
C. True. Tension—a mechanical signal—applied to an integrin can cause it to tighten its grip on intracellular and extracellular structures, including not only cytoskeletal and matrix components, but also molecular signaling complexes. Similarly, loss of tension can loosen its hold, so that molecular signaling complexes fall apart on either side of the membrane. Thus, the tension on the integrin can trigger or inhibit molecular signaling.
D. False. Of the 24 or so different kinds of integrins in humans, all but one are linked to actin filaments. The remaining variety connects to the intermediate filament network formed by keratin.
E. False. Integrins are dynamic molecules that fold to hide their binding sites in the absence of strong intracellular or extracellular ligands.

Q9. Extracellular Matrix - General - It is not an easy matter to assign particular functions to specific components of the extracellular matrix, since the overall structure is a complicated composite material with both mechanical and signaling properties. Nidogen, for example. cross-links two central components of the basal lamina by binding to the laminin-γl chain and to type IV collagen. Given such a key role, it was surprising that mice with a homozygous knockout of the gene for nidogen-l were entirely healthy, with no abnormal phenotype. Similarly, mice homozygous for a knockout of the gene for nidogen-2 also appeared completely normal.

By contrast. mice that were homozygous for a defined mutation in the gene for laminin-γl, which eliminated just the binding site for nidogen, died at birth with severe defects in lung and kidney formation. The mutant portion of the laminin-γl chain is thought to have no other function than to bind nidogen, and does not affect laminin structure or its ability to assemble into basal lamina.

How would you explain these genetic observations, which are summarized in Table Q9? What would you predict would be the phenotype of a mouse that was homozygous for knockouts of both nidogen genes?

Table Q9: Phenotypes of mice with genetic defects in components of the basal lamina

PROTEIN	GENETIC DEFECT	PHENOTYPE
nidogen-1	gene knockout (–/–)	none
nidogen-2	gene knockout (–/–)	none
laminin-γ1	nidogen binding-site deletion (+/–)	none
laminin-γ1	nidogen binding-site deletion (–/–)	dead at birth

+/– stands for heterozygous, –/– stands for homozygous.

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A9. Mice that are homozygous for knockout of the gene for either nidogen-1 or nidogen-2 presumably have no phenotype because the two forms of nidogen can substitute for one another. Mice that are homozygous for the mutant form of laminin-γ1, which does not bind nidogen, have a much more severe phenotype than either of the individual nidogen gene knockouts because they eliminate the ability of both nidogens to bind to laminin. As a result, these mice do not form proper basal lamina and die at birth with severe defects in kidney and lung. If this is the correct explanation for the genetic observations, then you would predict that mice that are homozygous for knockouts of both nidogen genes would have a very severe phenotype, comparable to that of the laminin-γ1 mutant. Such mice have been made and they do have a severe phenotype.