Biosignaling

Cells - receive and act on signals
Signal brings about response

Types of signals:
**Autocrine** - acting on same cell that produces them
**Paracrine** - acting on nearby cell
**Endocrine** - carried in bloodstream from producer cell to a distant target cell

Lots of signals but just a few evolutionarily conserved mechanisms to detect signals and transduce them into change in cell

(a) **Specificity**
Signal molecule fits binding site on its complementary receptor; other signals do not fit.

Weak interactions
Receptor cell-specific
High affinity of receptors for signal
Cooperativity
(b) Amplification
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.

(c) Desensitization/Adaptation
Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.

(d) Integration
When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential $V_m$, the regulatory outcome results from the integrated input from both receptors.
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Types of signal transducers

- **Gated ion channel**: Opens or closes in response to concentration of signal ligand (S) or membrane potential.

- **Serpentine receptor**: External ligand binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger, X.

- **Receptor with no intrinsic enzyme activity**: Interacts with cytosolic protein kinase, which activates a gene-regulating protein (directly or through a cascade of protein kinases), changing gene expression.

- **Receptor enzyme**: Ligand binding to extracellular domain stimulates enzyme activity in intracellular domain.

- **Steroid receptor**: Steroid binding to a nuclear receptor protein allows the receptor to regulate the expression of specific genes.

- **Adhesion receptor**: Binds molecules in extracellular matrix, changes conformation, thus altering its interaction with cytoskeleton.
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I. Ligand-gated Ion Channel

Nicotinic Acetylcholine receptor
opens in response to neurotransmitter acetylcholine and to nicotine
Found in neurons and muscle fibers

Receptor = Allosteric protein
Cooperative binding of Ach

Desensitization
Specificity
**Biosignaling**

II. Receptor Enzymes

**Insulin Receptor**
Ligand-binding domain on extracellular surface of plasma membrane
Enzyme active site on cytosolic side

![Diagram of Insulin Receptor](image)

- **Specificity Amplification** (Phosphorylation)
- nucleus
II. Receptor Enzymes

Insulin Receptor

1. Insulin receptor binds insulin and undergoes autophosphorylation on its carboxyl-terminal Tyr residues.

2. Insulin receptor phosphorylates IRS-1 on its Tyr residues.

3. SH2 domain of Grb2 binds to P-Tyr of IRS-1. Sos binds to Grb2, then to Ras, causing GDP release and GTP binding to Ras.


5. Raf-1 phosphorylates MEK on two Ser residues, activating it. MEK phosphorylates ERK on a Thr and a Tyr residue, activating it.

6. ERK moves into the nucleus and phosphorylates nuclear transcription factors such as Elk1, activating them.

7. Phosphorylated Elk1 joins SRF to stimulate the transcription and translation of a set of genes needed for cell division.
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III. G protein-coupled Receptors and Second Messengers

β-Adrenergic Receptor

\[ \text{Epinephrine} \]

- a.k.a. Adrenaline
- Regulates metabolism in muscle, liver and fat
- Breakdown of glycogen and fat

Specificity

Amplification

*(Phosphorylation)*
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III. G protein-coupled Receptors and Second Messengers

Epinephrine

Epinephrine $\xrightarrow{x \text{ molecules}}$ Epinephrine-receptor complex $\xrightarrow{x \text{ molecules}}$

Hepatocyte

ATP $\xrightarrow{\text{adenylyl cyclase}}$ Cyclic AMP $\xrightarrow{20 \times \text{ molecules}}$

Inactive PKA $\xrightarrow{\text{Active PKA}}$ $\xrightarrow{10 \times \text{ molecules}}$

Inactive phosphorylase $b$ kinase $\xrightarrow{\text{Active phosphorylase } b \text{ kinase}}$ $\xrightarrow{100 \times \text{ molecules}}$

Inactive glycogen phosphorylase $b$ $\xrightarrow{\text{Active glycogen phosphorylase } a}$ $\xrightarrow{1,000 \times \text{ molecules}}$

Glycogen $\xrightarrow{\text{Glucose 1-phosphate}}$ $\xrightarrow{10,000 \times \text{ molecules}}$

many steps $\xrightarrow{\text{Glucose}}$ Blood glucose $\xrightarrow{10,000 \times \text{ molecules}}$

Specificity Amplification
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IV. Steroid receptors

Act in nucleus to alter gene expression

Steroid hormones (estrogen, progesterone, cortisol, etc.) hydrophobic

Receptors (proteins) and HREs (hormone response elements in DNA)

1. Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.

2. Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

3. Binding regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

4. Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.
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IV. Steroid receptors
Receptor for estrogen
Breast cancer - some types need estrogen present for tumor growth
Tamoxifen = antagonist of estrogen
Tamoxifen competes with estrogen for binding to receptor
Tamoxifen has no effect on gene expression like estrogen does

RU486 = antagonist of progesterone
Competes with prog for binding to receptor
Prog needed for proper implantation of fertilized ovum in uterus
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Oncogenes, Tumor Suppressor Genes, Programmed Cell Death

Tumors --> result of uncontrolled cell division - biosignaling gone BAD!
Oncogenes --> a cancer-causing gene, any of several mutant genes that cause cells to exhibit rapid, uncontrolled proliferation
Discovered in tumor-causing viruses
Very similar to normal genes in the body called proto-oncogenes (growth regulating genes)
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Oncogenes, Tumor Suppressor Genes, Programmed Cell Death

Truncated version of EGF receptor
Oncogenic form
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Oncogenes, Tumor Suppressor Genes, Programmed Cell Death

**Tumor Suppressor Genes -->** encode proteins that normally restrain cell division, mutation in one or more can lead to tumor growth

p53 - mutated in 90% skin cancers, 50% all other cancers
Rb - mutated in retinoblastoma

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**Diagram:**

- **Normal colorectal epithelium**
  - **APC**
  - Tumor suppressor gene
  - Oncogene
  - Unknown status

- **Early adenoma**
  - **ras**
  - Adenomaous polyposis coli (TS gene)

- **Intermediate adenoma**
  - **DCC?**
  - **Ras** (oncogene)

- **Advanced adenoma**
  - **p53**
  - Deleted colon carcinoma (TS gene)

- **Colorectal carcinoma**
  - ?
  - p53 (TS gene)

- **Invasive carcinoma**
  - ?

- **Metastatic carcinoma**
  - ?
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Oncogenes, Tumor Suppressor Genes, Programmed Cell Death

Programmed Cell Death (Apoptosis) --> cell brings about its own death and lysis, signaled from outside or programmed in its genes, by systematically degrading its own macromolecules
When?
Development of embryo (fingers)
Anti-self antibodies present
Menstruation
Stressed cells (virus-infected to prevent infection, heat, UV light)

Mutation to any of these proteins can lead to cancers