Cell signaling

Cell ← signal ← surroundings

Cell → Cell → cell response.

signal molecule

by signal molecules, secreted / expressed on the surface of cells.

Signal molecule + b receptors (expressed by other cells.

↓

integrating and coordinating functions of many individual cells that make up organisms.

Each cell is programmed to respond to specific extracellular signal molecules.

Steps of extracellular Signalling :-

1. Synthesis and release of the signalling molecule by the signalling cell.
2. Transport of the signal to the target cell.
3. Binding of the signal by a specific receptor leading to its activation.
4. Initiation of signal-transduction pathways.

Extracellular signaling

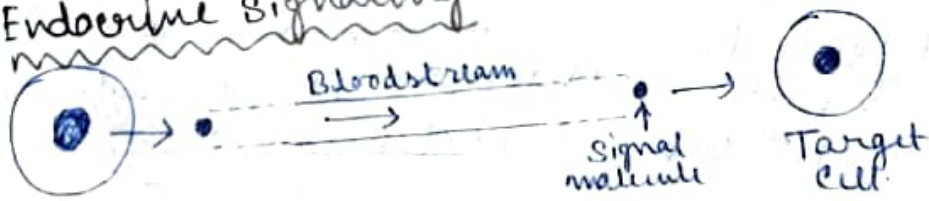
endocrine → distantly located

paracrine → closely located

autocrine → same cell

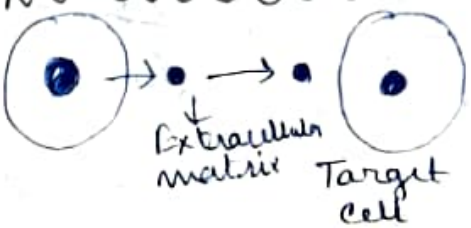
juxtacrine → requires physical contact

a) Endocrine Signaling



long-range signalling.
Signal molecule is transported by blood stream.
e.g., hormones

b) Paracrine signaling → target cells in close proximity.
across the extracellular matrix
e.g., neurotransmitters (between nerve cells at a synapse)
tissue hormones or local mediators



c) Autocrine signaling

Signalling molecules produce an effect on same cell that produces it.

e.g., vertebrate immune system to foreign antigens.

Certain types of T-lymphocytes respond to antigenic stimulation by synthesizing a growth factor that drives their own proliferation, increasing the number of responsive T-lymphocytes and amplifying the immune response.

d) Juxtracrine signaling

Signal molecules do not diffuse from the cell producing it.

Cell bearing signal molecules interact with receptor proteins of adjacent responding cells.

This requires physical contact between the cells involved.

e.g., Notch signalling and classical cadherin signalling.

A) Signal molecules

Chemically heterogenous compounds.

Signal molecules

- Membrane-bound
  - contact dependent, remain bound to the surface of the cells.
- Secretory
  - endocrine
  - paracrine
  - autocrine
  - (extracellular signal molecules).

Extracellular signal molecules are synthesized and released by signalling cells and produce a specific response only in target cells that have either (cell surface receptors) or (intracellular receptors) for the signalling molecules.

Extracellular signal molecules

- Small lipophilic molecules
- hydrophilic molecules

small lipophilic molecules → Diffuses across the plasma membrane and interact with intracellular receptors.

hydrophilic molecules → binds to cell-surface receptors.

Few lipophilic signal molecules bind to cell-surface receptors also.

Most of these molecules are members of eicosanoids — prostaglandins, prostacyclin, thromboxanes, leukotrienes. } Synthesized from arachidonic acid ← formed from phospholipids.

Most of the extracellular signal molecules are hydrophilic and bind to the cell-surface receptors of the target cell.

See examples from book (P=342)

Binding of extracellular signal molecules + cell surface receptor

⇓

increase/decrease in conc. of low MW intracellular signaling molecules (secondary messengers)

e.g., cAMP, cGMP, diacylglycerol (DAG), inositol 1,4,5-triphosphate (IP3), phosphoinositides, calcium.

B) Receptors — Intracellular (nucleus or cytosol)
Cell-surface

Receptors are chemically protein/glycoprotein molecules which bind to signalling molecules (ligand)

(ligand + Receptor) ⇒ a conformational change in receptor

⇓

initiates a sequence of reactions leading to a specific cellular response.

i) Intracellular receptor

Located in cytosol / Nucleus.

Extracellular lipophilic signaling molecules like steroids and retinoids spontaneously diffuse through the plasma membrane and bind to intracellular receptors present in the cytoplasm / nucleus.

Within the cell, the intracellular receptor - ligand complex controls the activities of responsive genes.

↓

gene transcription occurs

e.g.:

Steroid hormone + cytosolic receptor proteins

⇓

conformational change

↓

bind to regulatory DNA sequences (Hormone Response Element, HRE)

↓

activate transcription of responsive genes

In many cases, the response takes place in two steps:

Primary response ⇒ direct induction of the transcription of a small number of specific genes within about 30 minutes.

Secondary response ⇒ products of these genes activate other genes and produce a delayed secondary response.

See Fig (P=343).

Intracellular receptor

| (Class)

- type I receptors
  - ↓
  - steroid hormone receptor
- type II receptors
  - ↓
  - (Cholecalciferol) ← Vitamin D_3 and thyroxine receptor

type I receptors → All steroid hormone receptors have similar structures.

Hormone binding domain is less conserved among steroid hormone receptors and present at the C-terminal.

Glucocorticoid receptor is representative of this class. It is present in the cytoplasm complexed with a hsp90 (heat shock protein 90) * see detail (P-32)

(Glucocorticoid receptor + hsp90)
[normal condition]
(before ligand binding)

+

glucocorticoid ligand

⇩

conformational change, dissociates from hsp90

↓

move into nucleus, activate genes after binding with Glucocorticoid Response Elements (GREs)

It is a HRE

Type II receptors → Present in nucleus. receptors for vitamin D_3 and thyroxine

example - thyroid hormone receptors

Type II receptor + Response elements (in both the presence and absence of ligands)

In the absence of ligand, receptor can repress transcription.

In the ~~absence~~ presence of ligand, receptor can stimulate transcription.

Thus, the same protein can act as either an activator or a repressor.

The intracellular receptors for steroid hormone, thyroid hormone, retinoid and vitamin D_3 are all structurally related and belong to the nuclear receptor superfamily.

All nuclear receptors are dimers.

homodimer heterodimer