CELL SIGNALLING

INTRODUCTION

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INTRODUCTION TO CELL SIGNALLING & SIGNAL TRANSDUCTION

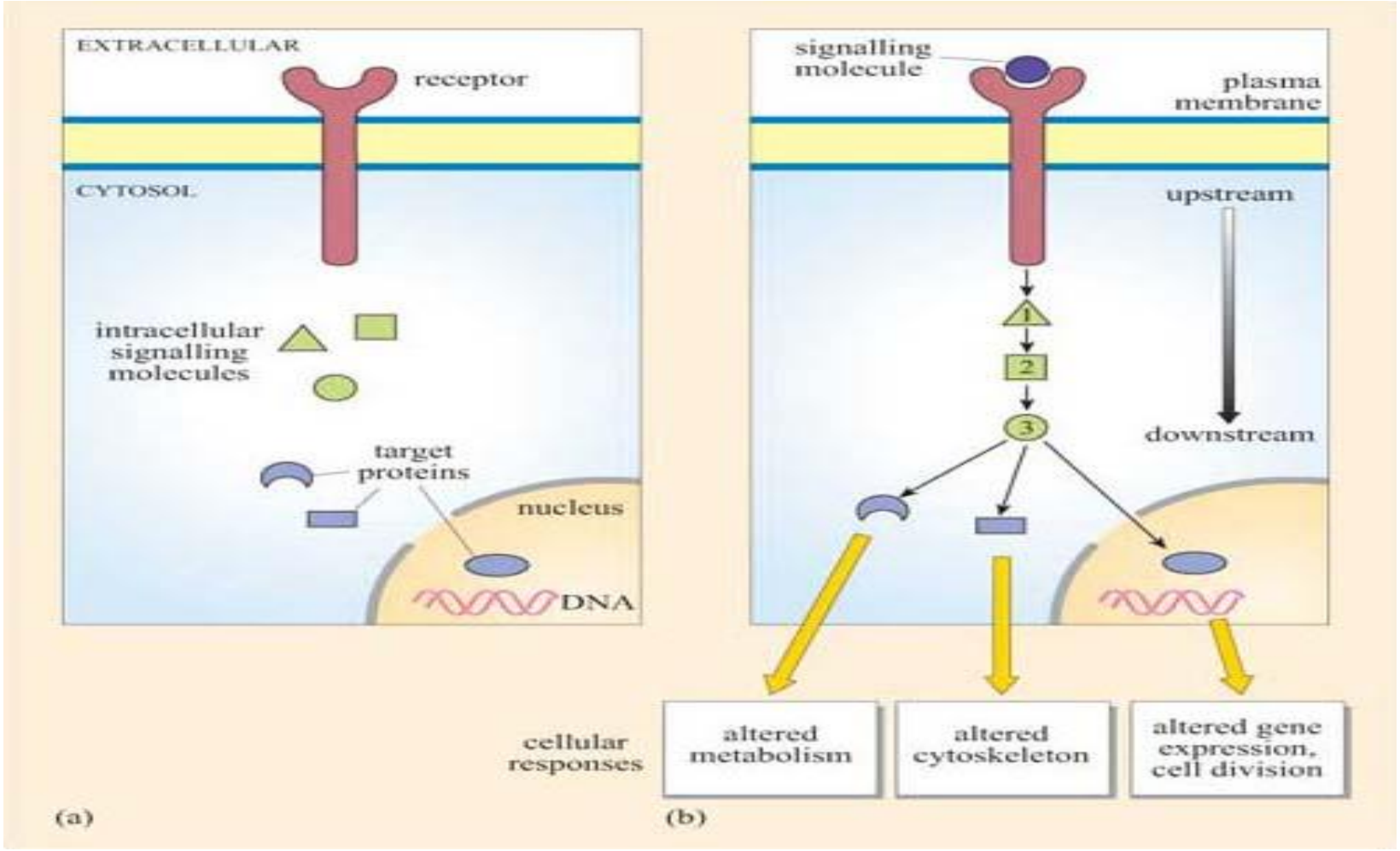
- Can be illustrated by simple example of mating in yeast S. cerevesiae
- To sexually reproduce a yeast cell needs to make physical contact with another yeast cell ----- So first it has to “ call “ to other yeast cells of the opposite mating type ---- It does so by secreting a “ mating factor “ peptide an extracellular signal which can also be called inter-cellular signal.
- Yeast mating factor binds to specific cell surface receptors on cells of the opposite mating type and the signal is relayed into the target cell in a series of interacting intracellular signalling molecules which switch from an inactive state to an active state.
- Yeast is a simple single celled eukaryote with both a diploid and haploid mode of existence and mating occurs between haploids which can be “ a “ or ‘ alpha ‘ mating type. Both haploid and diploid cells reproduce by mitosis with daughter cells budding of mother cells.
- Haploid cells are capable of mating with other haploid cells of opposite mating type eg an a cell can mate only with alpha cells and vice versa to produce a diploid cell. During stressful conditions such as nutrient depletion they undergo meiosis to produce 4 haploids 2 a spores and 2 alpha spores.

MATING IN YEAST

- “A” cells produce ‘a’ factor a mating pheromone which signals the presence of ‘a’ cell to neighbouring ‘alpha’ cells. ‘a’ cells respond to alpha cell mating pheromone by growing a projection known as ‘shmoo’ due to its shape towards the source of the alpha factor. Likewise alpha cells produce alpha factor and respond to a-factor by growing a similar projection towards the source of the hormone.
- Phenotype difference between a and alpha cells are due to a set of genes being actively transcribed and repressed in cells of the two mating types. Thus ‘a’ cells activate genes which produce ‘a’ factor and also produce a cell surface receptor **STE2** which binds to alpha factor and and triggers signalling within the cell – ‘a’ cells also repress genes associated being an alpha cell.
- Similarly alpha cells activate genes that produce alpha factor and produce a cell surface receptor **STE3** which binds and responds to ‘a’ factor and alpha cells repress genes associated with an a cell. All these transcriptional activation and repression reactions are caused by the presence of one of 2 alleles of a locus called **MAT** – Mat a or Mat alpha on chr. III. Mat a allele encodes a gene called a1 while Mat alpha encodes two genes alpha1 and 2 which ensure ‘a’ specific transcription program or alpha specific.

Signalling molecules are either upstream or downstream

- Signalling molecules are either upstream or downstream of other components of pathway (not to be mixed up with structure of genes in relation to transcription) in a sequential manner.
- Ultimately signalling molecules activate target effector protein (an effector is a molecule that carries out cellular response of the signalling pathway).
- Thus in yeast, signal transduction to mating factor ultimately stops the target cell from proliferating and induces morphological changes which results in the form of protrusions towards the cell that release the mating factor.
- Signalling in multicellular organisms is complex process – thus many millions of highly specialized cells may act in a coordinated fashion. Cells may need to respond to several signals at once and different cells may need to respond to same signal in different ways. All this is made possible **because the mechanism of detection of signal is not directly coupled to response but is separated by a chain of signalling events** as shown in picture.


EXTRACELLULAR
receptor
CYTOSOL
intracellular signalling molecules
target proteins
nucleus
DNA
(a)
signalling molecule
plasma membrane
upstream
1
2
3
downstream
cellular responses
altered metabolism
altered cytoskeleton
altered gene expression, cell division
(b)

- Examples of how the signalling system is flexible can be shown as follows :
- 1. Same type of receptor can be coupled to different signalling pathways in different cell types. 2. Signal can be amplified (or clamped down) as it travels along the pathway 3. It can switch on multiple pathways leading to several cellular responses in diverse regions of the cell. 4. Information can be processed from several differen receptors at once to produce an integrated response.
- Most of this is made possible by protein-protein interactions and protein regulatory mechanisms.
- Despite the complexity **basic model of signalling as shown in the figure holds true for most species and often the signalling moleules are highly conserved.** For eg. A high degree of homology between major proteins in the yeast mating factor signalling pathway and human mitogen activated (MAP) kinase growth signalling pathway. A mitogen is an extracellular molecule that induces mitosis in cells.

Extracellular Signals can Act Locally or at a Distance

- General types of intercellular signalling mechanisms – Cells may interact directly requiring cell-cell contact, or indirectly via molecules secreted by one cell, which are then targeted to target cells.

1. Cell – Cell Contact Dependent Signalling --- Done through Gap-Junctions

- Communication via gap junctions bypasses the signalling model proposed earlier whereby molecule is accepted via a receptor.
- Gap Junctions connect the cytoplasam of neighbouring cells via protein channels which allow passage of ions and small molecules (such as amino acids) between them (as an example gap junctions allow the coordinated contraction of cardiac muscle cells --- Gap junctions are made up of 2 Connexin proteins and are of huge significance in intercellular trafikking.
- Alternatively, cells can interact in a ‘classic’ signalling manner, through cell surface molecules in a so called contact-dependent way – Here signalling molecule is not secreted but is bound to the plasma membrane of signalling cell (or may form part of extracellular matrix) and interacts directly with receptor exposed on the surface of target cell. Usually seen and important between immune cells as in APC and intitiation of immune response.

- This type of response is also seen during development, where tissues are forming and communication between cells and neighbours is important in deciding between cell fates such as proliferation, migration, death or differentiation.
- 2. Cell – Cell Signalling via Secreted Molecules
- A. Extracellular signalling molecules are fairly small and easily transported to site of action ; they are structurally very diverse.
- B. They are water – soluble mediators and the classification and individual names reflect their first discovered actions rather than structure. For ex Growth Factors direct cell survival, growth and proliferation while Interleukins stimulate immune cells like IL-1, IL-2 etc. Thus signalling via secreted molecules can be **PARACRINE** (acting on neighbouring cells), **AUTOCRINE** (acting on cell that secretes signalling molecules), **ENDOCRINE** (acting on cells that are remote from secreting cells via bloodstream), **ELECTRICAL** (acting between 2 neurons or between neurons and target cells via a chemical (neurotransmitter) or via gap junctions)

PARACRINE SIGNALLING

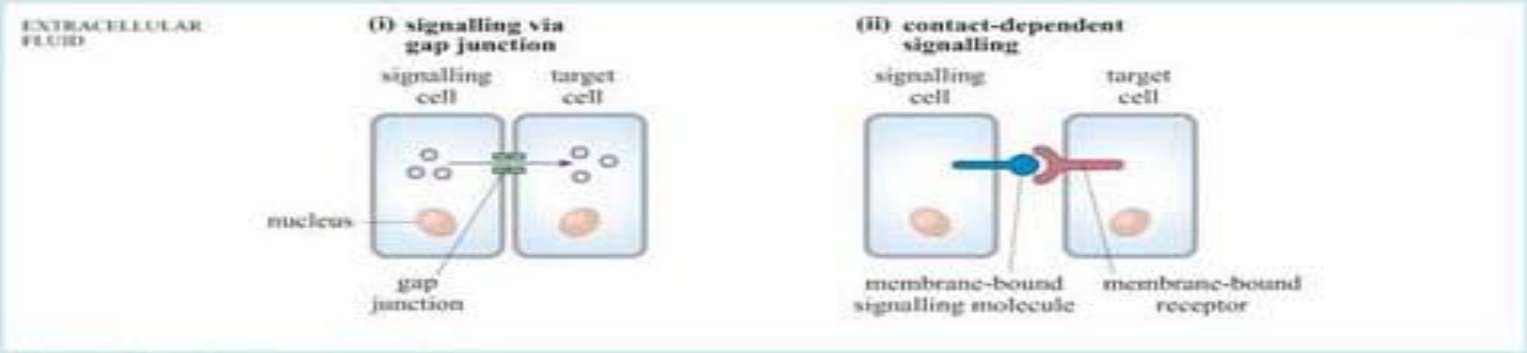
- In Paracrine Signalling water-soluble signal molecules called cytokines diffuse through the extracellular fluid and act locally on nearby cells.
- Results in a signal concentration gradient with the cells in the area responding differentially to the signalling molecule according to the concentration they are exposed to and is an important strategy in development.
- To keep a check on the effect of the molecule it exerts, signalling molecules involved in paracrine signalling are usually rapidly taken up by cells or degraded by extracellular enzymes. Eg. NO (gaseous molecules nitric oxide) acts by relaxing smooth muscle around blood vessels resulting in increased blood flow. Since the NO molecules is small and degradable (short lived) having only little time to produce local effects, it fulfils requirements for a paracrine signalling molecule.

AUTOCRINE AND ENDOCRINE SIGNALLING

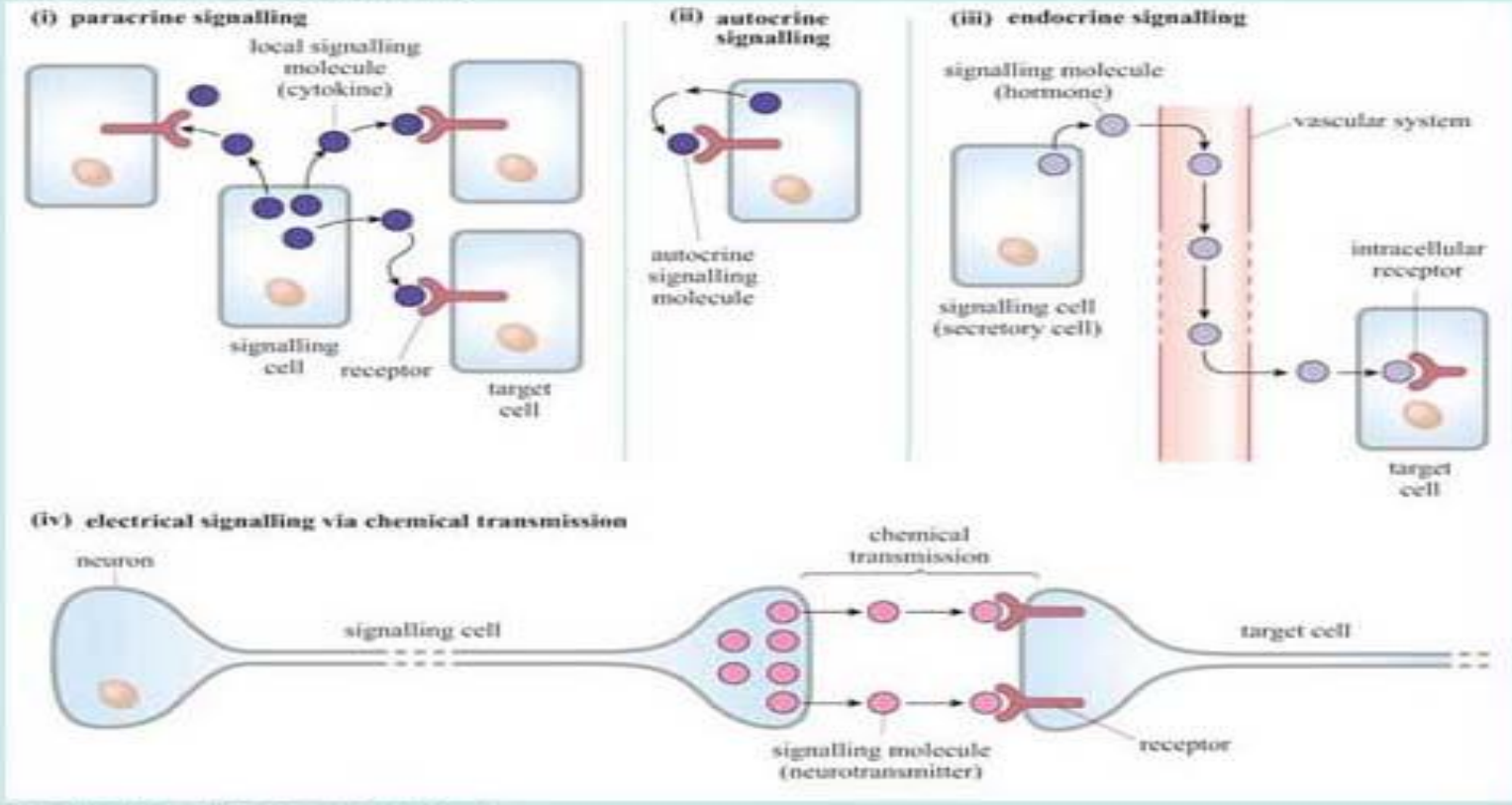
- AUTOCRINE SIGNALLING - Is a variant of Paracrine signalling – In this scenario signal acts back on the same cell or group of cells it was secreted from. In development autocrine signalling reinforces a particular development commitment of a cell type. It can also promote inappropriate proliferation, as may be the case in tumour cells.
- ENDOCRINE SIGNALLING - Signals are transmitted over long distances for ex from one organ such as brain to another such as adrenal gland. For long distance signalling diffusion through the extracellular fluid is obviously inadequate.
- In such cases signalling molecules may be **transported in blood**. Secretory cells that produce signalling molecules are called **endocrine cells** and often found in specialized organs called **endocrine organs**. Blood borne signalling molecules were the first to be discovered and collectively known as hormones, and chemically are quite diverse.

- Steroid hormones (Sex hormones & Cortisol)
- Peptide hormones (Insulin and modified amines that can act as neurotransmitters such as noradrenalin)
- Steroid hormones are synthesized by cholesterol which are water-insoluble and hence transported by specific carrier proteins and quite stable in terms of half-lives can be measured in hours or days. When compared to water-soluble molecules which are prone to quick degradation by enzymes and involved in short term paracrine signalling.
- ELECTRICAL SIGNALLING – Via Chemical transmission (also called synaptic transmission) is a faster and more specific form of cell – cell signalling. Nerve cells or neurons can convey signals across considerable distances to the next neuron in the neuronal network within milliseconds in contrast to blood borne messages can only operate fast as blood circulates but reach more targets in different tissues.

- Transfer of information from one neuron to next is mediated by complex structures called **synapses**, which are essentially formed by a pre-synaptic terminal (neuron 1), a synaptic cleft (tiny gap between 2 neurons) and a post synaptic membrane (neuron 2). When electrical signals reach the end of neuronal axon (the thin tube like part of neurons) molecules released from the axon can cross the physical gap between cells and bind to receptors in target cells.
- These signalling molecules are called **neurotransmitters** and can be diverse group of molecules such as glutamate, nucleotides such as ATP, CoA derivatives such as acetylcholine.



(a) cell–cell contact-dependent signalling



(b) cell–cell signalling via secreted molecules