PHYSIOLOGY

ED.08

HOMEOSTASIS

----- Active space -----

Introduction 00:00:48

Homeostasis is the concept of constancy.

Central theme for bodily function.

Disturbance in homeostasis.

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↓

Disease.

Claude Bernard :

Coined the term milieu interior (Internal environment).

Walter Cannon :

Coined the term homeostasis.

Control systems of homeostasis 00:05:48

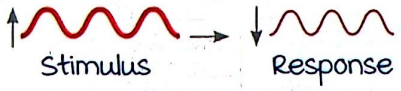
mechanisms of the body to maintain homeostasis.

Control systems

Negative feedback | Positive feedback | Feed forward

Negative feedback :

↑ in stimulus → ↓ parameters



Stimulus Response

Eg :

1. Baroreflex : Change in BP

↓ ↑

↑ during exercise ↓ after exercise.

2. Endocrine hormone regulation (99%).

3. Gastric acid secretion.

Feedback

2 General Physiology

----- Active space -----

Components of -ve Feedback :

Stimulus	↑BP
↓	↓
Acts on receptors	Baroreceptors
↓	↓
Afferents	Afferents
↓	↓
Centre	medulla
↓	↓
Efferents	Efferent → SNS (-), PNS (+) → ↓HR & ↓BP
↓	↓
Response	BP

SNS : Sympathetic nervous system.

PNS : Parasympathetic nervous system.

Assessment of effective of -ve feedback :

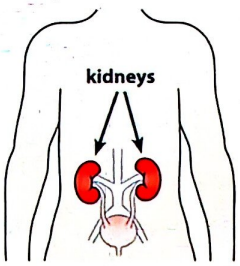
$$\text{Gain} = \frac{\text{Correction by the System (C)}}{\text{Error remaining (E)}}$$

Infinite feedback gain :

When error becomes zero $G = \frac{C}{0} = \infty$

↓

Gain = Infinity



Eg :

Kidneys always correct blood pressure back to normal.

In HTN → Kidneys are affected → BP never comes back to normal.

Positive feedback :

- ↑ in initiating stimulus → Further ↑ in response.

- Amplification/cascade of reactions.
- AKA vicious cycle (Destabilizes our system).

Eg : CLAPS (mnemonic).

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a) Coagulation cascade.

b) LH surge : Only exception for true feedback in endocrine hormone regulation.

c) Action potential.

d) Parturition (Normal delivery) :

AKA Ferguson reflex.

Feedback

----- Active space -----

Fetal head

↓

Pressure on uterine cervix ← (Cycle ↓ Eventually leads to delivery of fetus)

↓

Oxytocin release

↓

Uterine contraction

↓

Pushes fetal head further down

e) Shock

Hemorrhagic shock (Eg : RTA) → Irreversible shock → Death (+ve feedback).

Feedforward control system :

Core theme : Anticipatory control system.

Body responds anticipating a stimulus (No actual stimulus).

Eg :

a) Anticipatory tachycardia & tachypnea : ↑RR and ↑HR before exercise.

b) Anticipatory motor control.

- Centre : Cerebellum
- Person driving on a highway → Applies breaks on seeing a cow (Anticipates danger).

c) Anticipatory regulation of core body temperature :

Skin temperature → Shell temperature.

Body organ temperature → Core temperature.

Cold environment.

↓

↓ shell temperature.

↓

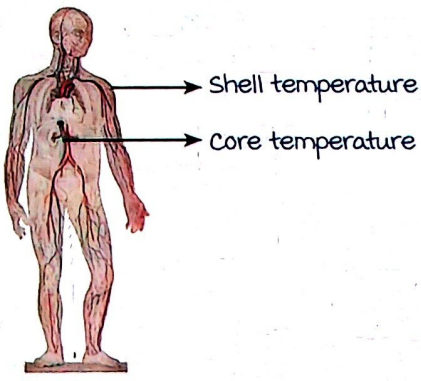
Hypothalamus anticipates ↓ core temperature.

↓

Corrective measures.

↓

Maintanance of core temperature.



Feedback

----- Active space -----

Properties of Homeostasis

00:28:04

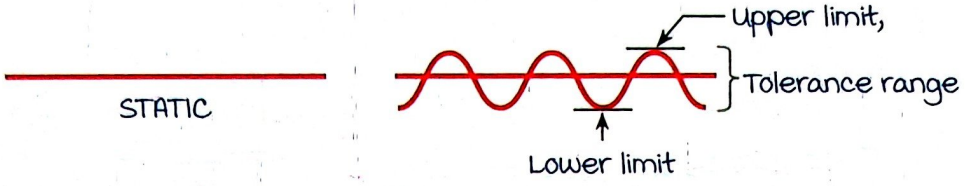
Dynamic constancy :

AKA dynamic equilibrium.

Homeostatic control systems maintain a "range of values"

Eg : Normal HR = 60-100bpm.

Normal RR = 12-18bpm.



Prioritization of parameters :

- Priority of order of correction of parameters :

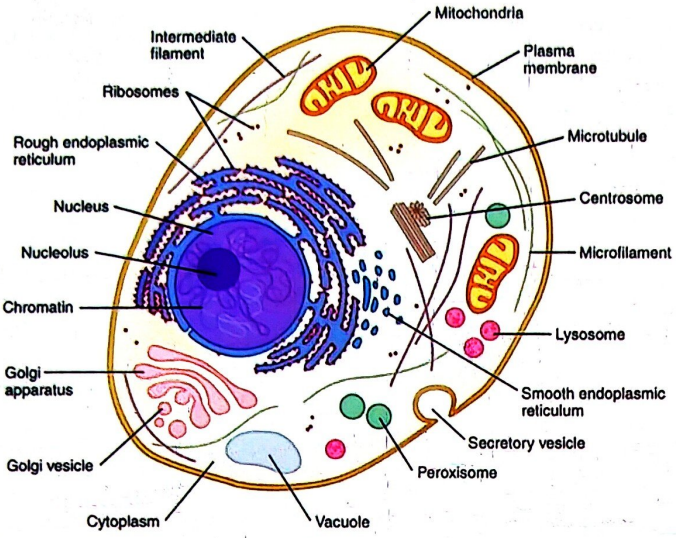
  pH > BP > Temperature.

- pH changes are given more priority : As they affect the activity of enzymes → Death.

CELLULAR PHYSIOLOGY

----- Active space -----

Cell is the fundamental unit of all living organisms.



Eukaryotic Human Cell

Cell Membrane

00:01:13

AKA plasma membrane.

FUNCTION :

It is a outer barrier with selective permeability in cell.

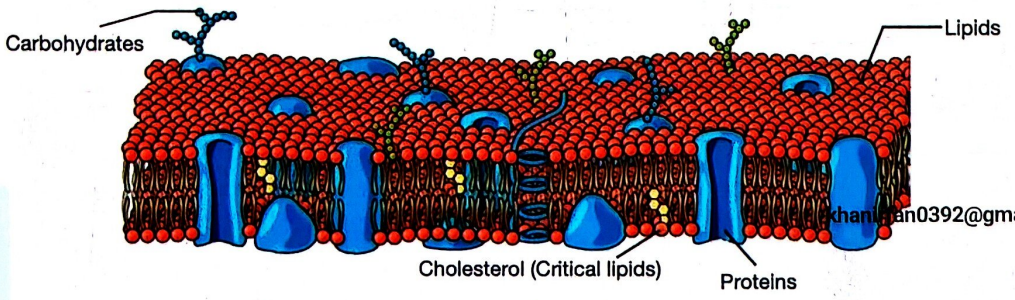
STRUCTURE :

Fluid mosaic model of cell membrane. Proposed by Singer and Nicolson.

COMPOSITION :

Macromolecules.

1. Proteins (55%) : Arranged in mosaic pattern in cell membrane.
2. Lipids (40%) : Responsible for fluidity of cell membrane.
3. Carbohydrates (5%).



Cell membrane

----- Active space -----

Lipids

00:04:40

INTRODUCTION :

Structure :

- Bilayer : Outer and Inner lipids.
- Asymmetry : Arranged specifically either on inner or outer side.

Types :

- Phospholipids (PO_4^{3-} group).
- Glycolipids (Carbohydrate side chain).
- Cholesterol (Critical lipid).

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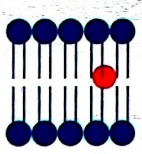
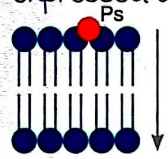
PHOSPHOLIPIDS :

major lipid.

Types	Site	Significance
Phosphatidyl choline (Pc) AKA lecithin	Lungs : Surfactant	• Prevent alveolar collapse. • major lipid in surfactant.
Sphingomyelin	• Nerve cell membrane. • Surfactant.	Minor lipid in surfactant
Phosphatidylinositol (IP3)	Endocrine cells	• Part of second messenger system ($IP3 \rightarrow DAG \rightarrow Ca^{2+}$)
Phosphatidylserine (Ps)	Inner surface of cell membrane in all cells 	If expressed on outer surface.  Eat me Signal • Apoptosis (Programmed cell death). • Detected by Annexin V : Binds & forms complex with Ps. (Annexin V staining).
Cardiolipin (CL)	Heart : Mitochondria	In syphilis : Serum anti-CL antibody + (Detected by VDRL test)

Note :

$\frac{L\ (Lecithin)}{S\ (Sphingomyelin)}$ ratio :

- To assess fetal lung maturity.
- Mature lung : ≥ 2.

GLYCOLIPIDS :

Types	Site	Significance
Cerebrosides	CNS	-
Gangliosides	GIT	GM-1 gangliosides : Receptors for cholera toxin-Fragment B.

Feedback

----- Active space -----

CHOLESTEROL :

Site : Cell membrane of skin.

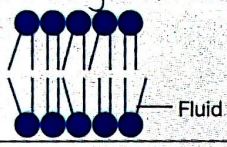
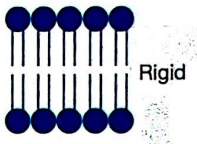
Significance :

- Precursor of Vit.D.
- 7-dehydrocholesterol $\xrightarrow[(Skin)]{Sunlight}$ Vit.D
- Fluidity buffer : maintains membrane fluidity in optimal range.

MEMBRANE FLUIDITY :

Lubricative property of lipid → Maintain fluidity of membrane → Allows mobility.

Characteristics of Fluidity :

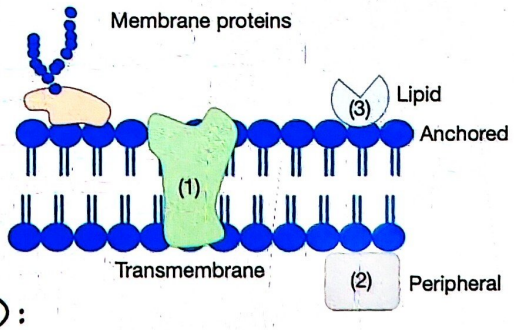
	Increased Fluidity	Decreased Fluidity
Effect on health	Good	Bad
Type of fatty acids	Unsaturated (Essential)	Saturated (Trans)
Examples	• Linoleic acid. • Linolenic acid. • Arachidonic acid. • Omega-3 fatty acids : Abundant in fish. 	• Stearic acid. • Palmitic acid. (Abundant in junk food) 

Proteins

00:24:00

Classification based on location in cell membrane :

1. Transmembrane proteins/integral membrane protein : Present throughout.
2. Peripheral proteins : Present peripherally.
3. Lipid-anchored proteins : Requires lipid for attachment.



TRANSMEMBRANE PROTEINS (INTEGRAL MEMBRANE PROTEIN) :

Most important.

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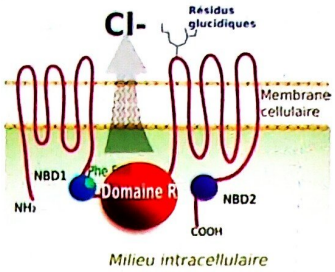
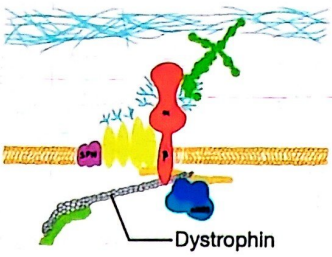
Functions	Examples
Hormone receptors (m/c)	GPCR (G-protein coupled receptors).
Pump channels.	Na^+-K^+ ATPase
Ion channels	• Cl^- channel (CFTR). (Cystic fibrosis transmembrane conductance regulator.) • In cystic fibrosis → CFTR mutation (+).

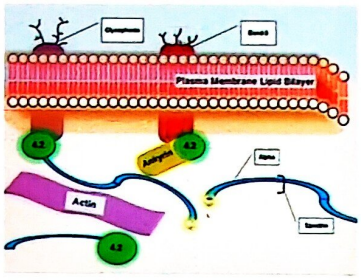
Feedback

----- Active space -----



Transmembrane protein : Cl^- channel (CFTR)





Peripheral protein

PERIPHERAL PROTEINS :

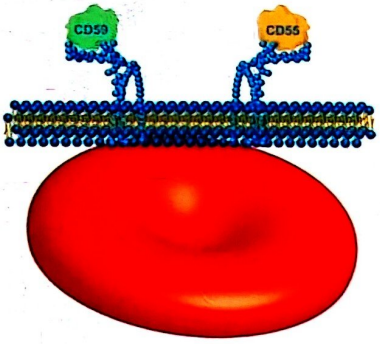
Functions :

1. Support shape of cell :

Cell	Protein	Diseases due to mutations
RBC (Biconcave disc)	Spectrin	Elliptocytosis
	Ankyrin	Spherocytosis
Skeletal muscle	Dystrophin	• Duchenne Muscular Dystrophy (DMD). • Muscular weakness. Typical presentation. • Gower's sign : Climb on own body to stand up (Knee → Hip → Stand). • Respiratory paralysis (Weakness of diaphragm) → Death.

2. Cell surface receptors.

LIPID ANCHORED PROTEINS :



Lipid anchored proteins in RBC.

In RBC :

- PIGA (Phosphatidylinositol Glycan-A) gene synthesises proteins :
  - CD55 (Decay accelerating factor).
  - CD59 (membrane inhibitor of reactive lysis).
  - C8 binding protein.
- Proteins bind to lipid : Phosphatidylinositol.
- Significance :
  - Normal gene : Prevent hemolysis.
  - Mutated gene : Paroxysmal Nocturnal Hemoglobinuria.

Paroxysmal Nocturnal Hemoglobinuria

Pathology : Mutated or absent PIGA gene.

↓

During sleep (Night)

↓↓ pH

Activates complement proteins : C5-C9 (membrane attack complex),

↓

Attacks RBC membrane

↓

Hemolysis (Hemoglobinuria).

Treatment :

----- Active space -----

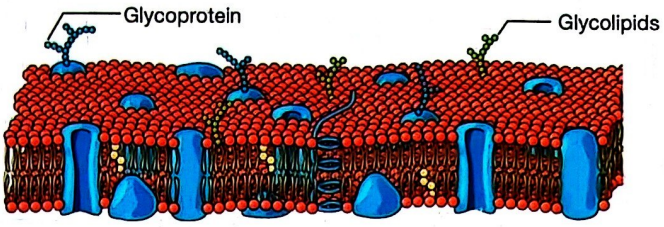
- Anti C5 monoclonal antibody : Supportive.
  - Eculizumab.
  - Ravulizumab (Long acting).
- Hematopoietic stem cell transplant : Definitive.

Carbohydrates

00:41:30

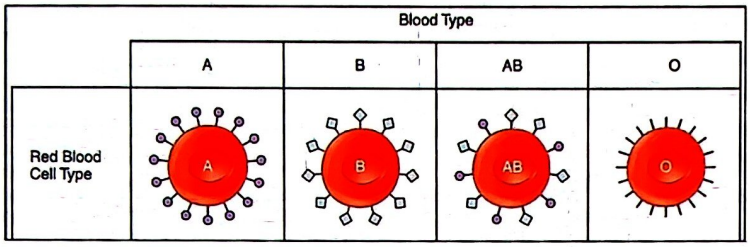
CLASSIFICATIONS :

1. Glycoprotein : Attached to proteins.
2. Glycolipids : Attached to lipids.



SIGNIFICANCE :

Glycolipids on RBC membrane : Determine blood groups.



Note :

- membrane with highest protein : Inner mitochondrial membrane.
- In nerve cell membrane (myelin) : Lipid (80%) : Protein (20%).
- Repair of damaged cell membrane is by resealing of lipid bilayer.
- Deficiency of lecithin in pre-term baby : Hyaline membrane Disease.

Feedback

----- Active space -----

CELL ORGANELLES

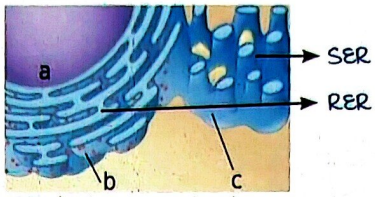
Endoplasmic Reticulum

00:00:30

Types

Rough endoplasmic reticulum (RER)

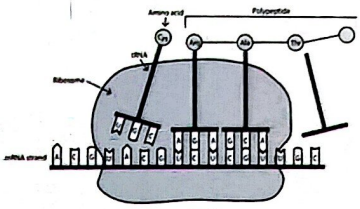
- Granular surface d/t presence of ribosomes.
- AKA granular ER.



Endoplasmic reticulum

Smooth endoplasmic reticulum (SER)

- Smooth surface d/t absence of ribosomes.
- AKA agranular ER.


Translation

ROUGH ENDOPLASMIC RETICULUM :

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Functions :

1. Protein synthesis/translation.
2. Folding of proteins : using chaperones/heat shock proteins (HSP).
3. Degradation of mis folded proteins & quality control of proteins by unfolded protein response or ER stress response.
   ↑↑misfolded proteins → ER → 1. Halts protein synthesis.
   2. Endoplasmic reticulum associated degradation (ERAD).

ERAD :

Misfolded proteins are tagged to ubiquitin (kiss of death)

↓

Protein-ubiquitin complex

↓

moves to proteasome (Graveyard of the cell)

↓

Degradation

Applied aspect : misfolded protein diseases.

1. Alzheimer's disease : more common.
   - Due to accumulation of misfolded Aβ amyloid protein.
2. Prion disease :
   - PrPc (Normal protein in CNS) → PrPsc (Prion protein : misfolded).
   - Eg : Creutzfeldt Jakob disease (very fatal).

SMOOTH ENDOPLASMIC RETICULUM :

----- Active space -----

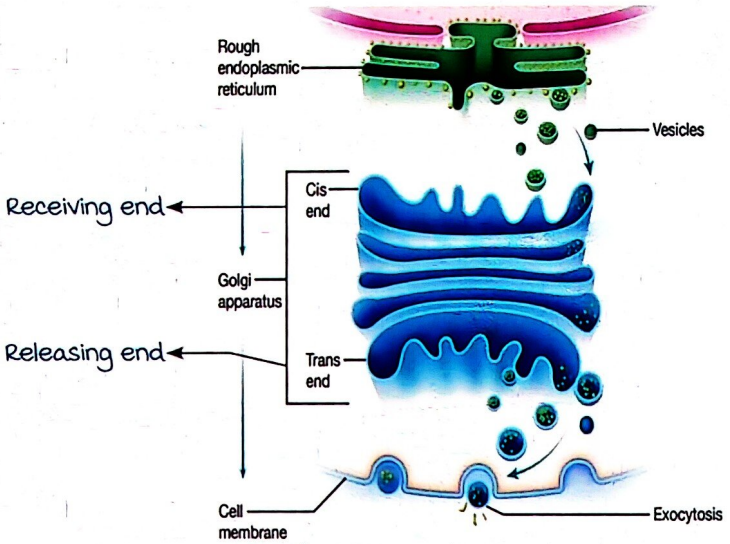
Functions :

1. Synthesis of steroid hormones :
   - Eg : Adrenal cortex : Aldosterone, cortisol.
   - Testis : Testosterone.
   - Ovary : Estrogen.
2. Storage of Ca^{2+} :
   - SER of skeletal muscle stores Ca^{2+} (Sarcoplasmic reticulum).
3. Drug detoxification (Xenobiosis) :
   - Major site : Liver SER.
   - Enzyme : Cytochrome P450 (CYP450).

Golgi Apparatus

00:14:20

Location : Close to RER.



Golgi apparatus

Functions :

1. Post translational modifications:

Proteins synthesised by RER
↓
Cis end of Golgi apparatus (GA)
↓
Glycosylation (Carbohydrate side side chain is added to the protein)
↓
Glycoprotein (↑stability of protein)
↓
Stored in vesicles
↓ Stimulus
Released from trans end

GA are abundant in secretory cells.
Eg : Antibody secreting plasma cells.
Goblet cells of GI tract.

2. Sorting of proteins :
   - GA determines where a protein is delivered.
   - Eg : Protein —Phosphotransferase→ Protein + mannose-6-phosphate
     ↓
     moves to lysosome
     ↓
     Degraded

Feedback

----- Active space -----

Applied aspect :

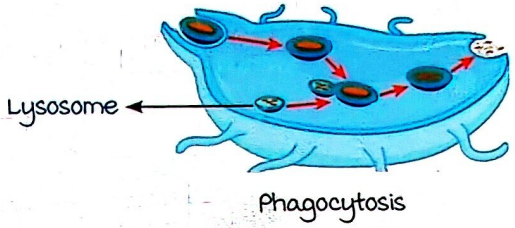
I cell disease :

Absence of phosphotransferase
↓
mannose-6-phosphate not added
↓
Lysosomal function affected
↓
Proteins not degraded
↓
Inclusion bodies accumulate in cell

Lysosomes

00:23:30

Recycle bin of the cell.



Phagocytosis

Functions :

Acid mediated destruction.

- H^+ATPase acid hydrolase.
- Acid hydrosylase enzyme.

Note : Acid in the lysosome can destroy itself : Suicidal bags/residual bodies.

Autophagy :

Destruction of cell's own part.

Late stages of starvation
↓
Lysosomes engulf mitochondria
↓
Proteins released from mitochondria
↓
Undergo metabolism
↓
Energy for survival

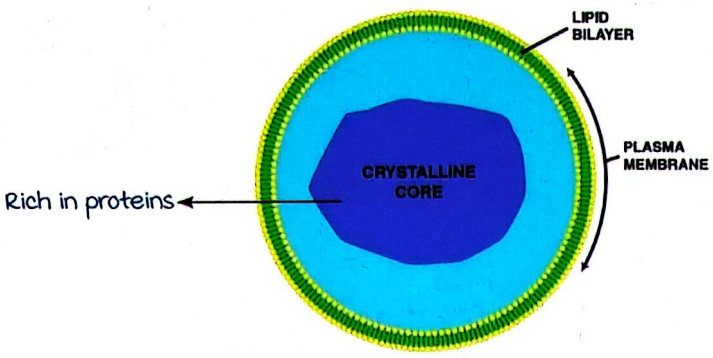
Clinical application :

Neutrophil : High content of lysosomes.

CHSI gene —Normal→ LYST (Lysosomal transport protein)
↓ mutation
Chediak Higashi syndrome
↓
Patient is more prone to bacterial infections

Peroxisomes

00:31:55 ----- Active space -----



Peroxisomes/microbodies

Function :

1. Oxidation of very long chain fatty acids (VLCFA's).
   - Generate H_2O_2 (Free radical).
2. Degradation of H_2O_2 : By catalase.
   - Pseudocatalase : Commercial/drug form of catalase.
   - Used to treat free radical mediated disorders. Eg : Vitiligo.

Enzymes produced by peroxisomes :

1. Plasminogens : Abundant in myelin sheath of nerve fibres.
2. Luciferase : Responsible for glow in fireflies.

Peroxisomal storage disorders :

Zellweger syndrome :

- PEX gene mutation.
- PEX codes for peroxins (Proteins for peroxisome synthesis).
- Features :
  - Accumulation of VLCFA's.
  - ↓ plasmologens.

} Neurological impairment

Refsum's disease :

- PAHX gene mutation.
- Defect in phytanyl CoA α hydroxylase.
- Defective oxidation of phytanic acid.

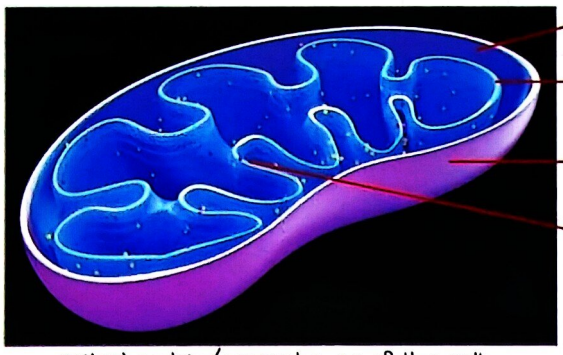
Adrenoleukodystrophy :
Defect in transport proteins.
↑↑ VLCFA's → Neurological impairment.

Feedback

----- Active space -----

Mitochondria

00:40:06



Mitochondria/power house of the cell

Mitochondrial DNA :

- Mitochondria has its own DNA (Endosymbiotic theory).
- Source : Ovum → Inheritance is always maternal.
- ds DNA with 16500 base pairs.
- 10 times more prone for mutation than nuclear DNA.
  - Repair of mutations in mitochondrial DNA is ineffective.
- Cannot function without nuclear DNA (To produce enzymes for ATP synthesis).

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Mitochondrial disorders :

Affects organs with high metabolic requirements : Mitochondria.

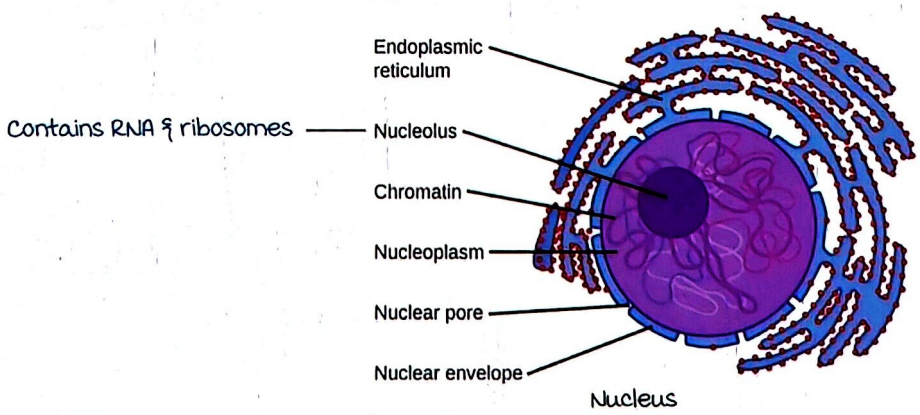
Features : Encephalopathy.

- Skeletal muscles : Contraction & relaxation is affected. Lactic Acidosis.
- CNS : Stroke like symptoms. Stroke.
- GI tract is affected.
- ↑ susceptibility to infection.
- Lactic acidosis is common.

Mnemonic : MELAS.

Nucleus

00:48:13



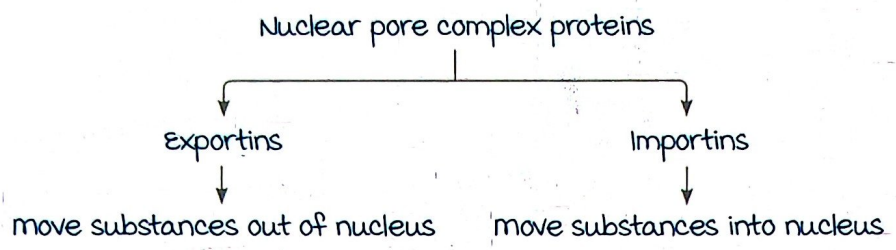
Nucleus

Feedback

Features :

----- Active space -----

- Controls all cellular functions.
- Contain DNA (Chromosomes).
  - DNA + histones → Chromatin.
  - Structural repeating unit of chromatin : Nucleosome.
- Entry/exit of substances into the nucleus is regulated by Nuclear pore complex (NPC).
  - Substances expressing nuclear localization sequence (NLS) can move across NPC.



Marker Enzymes

00:52:30

Helps identify cell organelles.

Cell organelle	Marker enzyme
Cell membrane	Na^+ -K^+-ATPase Adenylyl cyclase
Endoplasmic reticulum	Glucose-6-phosphatase
Golgi apparatus	Galactosyl transferase
Lysosomes	Acid phosphatase
Peroxisomes	Catalase Urate oxidase
Mitochondria	ATP synthase Creatine Kinase
Nucleus	RNA polymerase Histone deacetylase

Feedback

----- Active space -----

CYTOSKELETAL FILAMENTS AND CELLULAR JUNCTIONS

Cytoskeletal Filaments

00:00:19

INTRODUCTION :

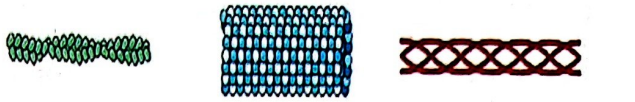
Cyto : Cell, Skeleton : Bone.

Support system : movement of cells (Gives strength).

Types :

Based on size (Diameter).

- Microtubules : Big.
- Microfilaments : Small.
- Intermediate filaments : most abundant.



Microfilaments Microtubules Intermediate filaments

Cytoskeletal filaments

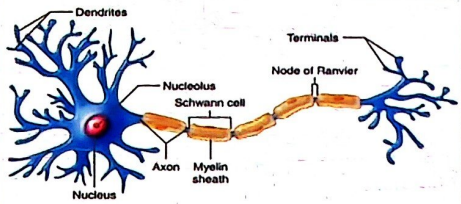
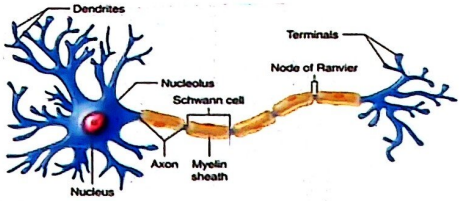
I. MICROTUBULES :

Proteins :

1. Kinesin.
2. Dynein.
3. Tubulin.

Functions :

1. Axonal transport (AT) :

	Forward AT	Reverse AT
Transport direction	 Cell body to synapse (Anterograde/ antegrade)	 Syapse to cell body
Protein	Kinesin	Dynein
Speed of transport	Fast : 400 mm/day Slow : 0.5-10 mm/day	Fast : 200 mm/day
Clinical significance	-	Invasion of microorganism : • Rabies virus. • Tetanus toxin : Tetanospasmin.

2. Ciliary motility :

- Physiological cilia motility :
  - In lung : Clearing sputum (Protective).
  - During embryological development : Rotation of internal organs.

----- Active space -----

- Cilia structure :
  - 9+2 microtubule arrangement.
  - Dynein (Arm-like structure) : Cilia, sperm, fallopian tube motility.
- Clinical significance :

  Immotile cilia syndrome (Kartagener syndrome) : Absent dynein.
  - Bronchiectasis : Absent cilia motility → Sputum accumulated → Infections.
  - Infertility : Absent sperm & fallopian tube motility.
  - Situs inversus : Absent rotation of organs.

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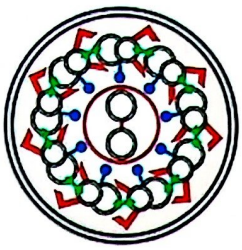
3. Chromosomal movement during cell division :
- Protein : Tubulin (In micriotubule organising centre : MTOC).
- Significance : Movement of chromosomes into daughter cells during mitosis (For cell survival).
- Applied aspect : Microtubule inhibitor drugs.
  - Anti cancer drugs : Vinca alkaloids (Vincristine, Vinblastine), Taxanes (Paclitaxel).
  - Anti gout drugs : Colchicine.

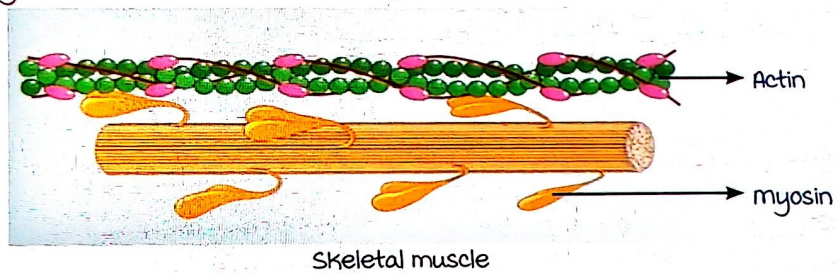


motile cilium

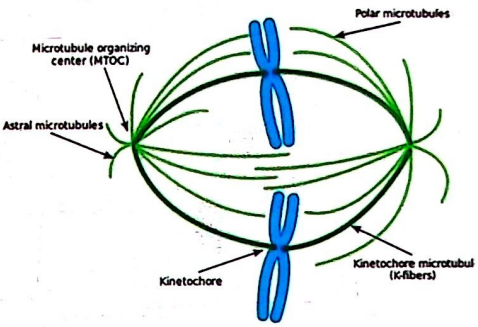
2. MICROFILAMENTS :

Proteins :

1. Actin.
2. Myosin.



Skeletal muscle

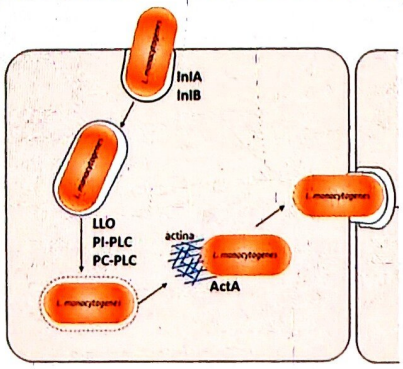


microtubules during mitosis

Functions :

1. Skeletal muscle contraction & relaxation : Sliding filament theory.
2. Cell motility : Actin polymerization → Enhances motility.

Clinical significance :



Action of Listeria

----- Active space -----

Listeria —Internalins (A/B)→ Enters into cell
↓
Engulfed into vacuole (To contain its spread)
Listeriolysin-O (LLO)↓
Breakdown vacuole
↓ Act-A
Actin polymerization
↓
Comet tail pattern (Polymerized actin)
↓
Tumbling motility
↓
Infect nearby cells

3. INTERMEDIATE FILAMENTS :

Cell specific : Used as tumor markers.

Protein	Location	Clinical significance
Keratin (Cytokeratin)	Epithelial cells	• Tumor marker in squamous cell carcinoma. • Mallory Denk bodies : Pathological deposition in liver in alcoholic liver disease.
Desmin	muscle	Tumor markers in sarcoma (Rhabdomyosarcoma)
Vimentin	Connective tissues : Fibroblast	markers for tumors of mesenchymal origin
Glial Fibrillary Acidic Protein (GFAP)	Astrocytes (Star shaped glial cells)	Tumor markers in glioma (Astrocytoma, Glioblastoma multiforme)
Lamin	Nucleus of cells	Progeria : Disorder of premature ageing (Werner syndrome)

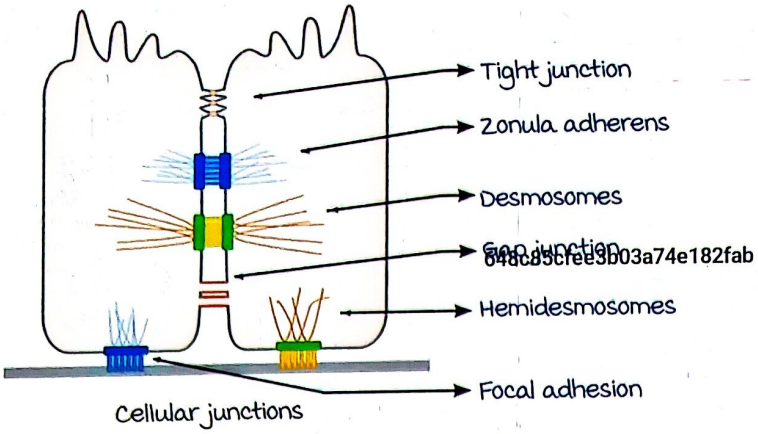
Cellular Junctions

00:27:34

Types
↓
Cell-cell junction
↓
Tight junction
Cell adhesive junctions (Zonula adherens, Desmosomes)
Gap junctions

Cell-basal lamina junction
↓
Hemidesmosomes
Focal adhesions

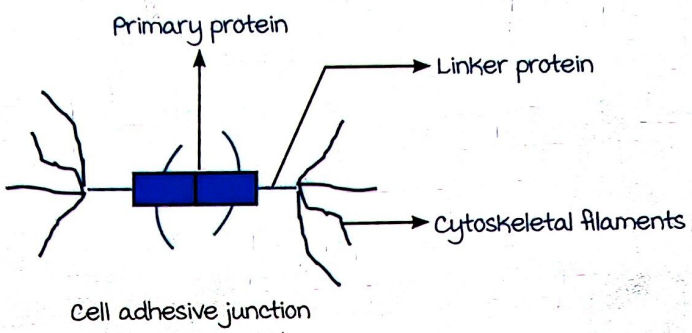
----- Active space -----



CELL ADHESIVE JUNCTIONS :

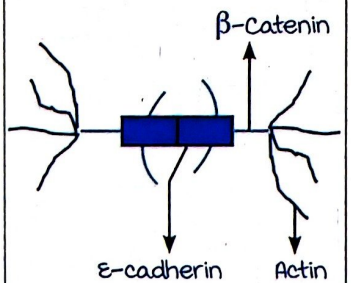
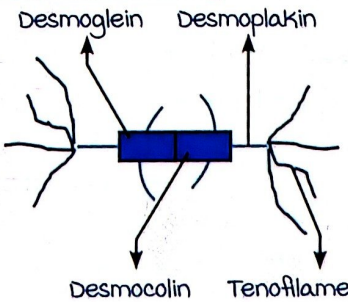
Uses cell adhesive molecules (CAMs) :

- Cadherins.
- Integrin.
- Selectin.



Structure :

- Primary protein.
- Linker protein.
- Cytoskeletal filaments.

	Zonula adherens	Desmosomes
Primary protein	E-cadherin	• Desmoglein. • Desmocolin.
Linker protein	β-Catenin	Desmoplakin
Cytoskeletal filament	Actin	Tonofilaments (Intermediate filament)
Clinical significance	Molecular hijacking : Internalins (In Listeria) ↓ Recognizes E-cadherin ↓ Invade cells.	• Abundant in structures with mechanical stress (Heart, skin & uterine cervix). • Pemphigus disorders (Skin blistering disorder). • Autoantibodies against desmoglein.
		

Feedback