# Course Book

## *CELL BIOLOGY*
## *For 4th year of Biology*

**By**


## Assist. Prof. Dr. Treefa F. Ismail

**Department of Biology**

**College of Education**

**University of Salahaddin**


**2023-2024**

# CELL BIOLOGY/ Course Book for 2023-2024

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Lecture Time: Monday 10.30-12.30

REQUIRED TEXTS AND MATERIALS:

Cell biology book

COURSE DESCRIPTION:

This course is designed to explore the appearance, characteristics, development, function, and dysfunction of cells as well as to understand current experimental methodologies for studying cells. This exploration is carried out through lecturing, discussion, and PowerPoint.

COURSE OBJECTIVES:

1. To increase each student's knowledge of basic cell structure and function.
2. To understand more advanced cellular functions, such as regulation of membrane transport, cell signaling, cell death and cellular differentiation.
3. To understand the importance of the cell in biology, and to be able to fit prior knowledge of biology into the context of cell function.
4. To gain experience and understanding of microscopy (light and electron microscopy), basic histological techniques, and other methods of cell visualization.
5. To study some pathological conformational features of the cell.

The lecture textbook is like a reference book-it has more information in it than a student will be required to master. Therefore, attendance at lecture is essential to determine what information to learn. Occasionally, additional material will be given out from other sources and the students will be held responsible for this material as well. In the event of absence from class, a student must assume full responsibility for the material covered in lecture.

# Course Program

**Week 1**
Introduction to Cell Biology, Techniques used for studying the cell, Transmission Electron microscopy (fixation, postfixation, dehydration, clearing and Embedding, Ultrasectioning and different types of sections, mounting, glass knife, staining using heavy metals

**Week 2**
Introduction to Cells: prokaryote and eukaryote cells, general structure of the animal and plant cells.

**Week 3**
Ultrastrucutre of the cell, Cell membrane

**Week 4**
Transport through cell mambrane

**Week 5**
Cell signaling, cell junctions, desmosomes, tight junction, gap junction, microvilli

**Week 6**
Mitochondria**,** ultrastructure, different shapes and size, conformational states, function

**Week 7**
Endoplasmic reticulum, types, SER and RER, location and function, role in detoxification process, and Golgi apparatus, ultrastructure and role in cell trafficking and protein sorting

**Week 8**
Lysosomes, ultrastructure ,enzyme content and functions, peroxisomes and glyoxisomes**,** enzyme content, relationship with each other and role in cell

**Week 9**
Cytoskeleton: types, molecular structure and functions, role and locations

**Week 10**
Cell Cycle and Division

**Week 11**
Cellular change and adaptation

**Week 12**
Cell death: Necrosis and programmed cell death(apoptosis), mechanism, cellular features as revealed by LM and EM and immunofluorescent

**Week 13**
The biology of stem cells, Types of stem cells, application of stem cells in medicine

**Week 14**

The biology of cancer cell, features of cancer cell as revealed by LM and EM, mechanism of metastasis and angiogenesis

**Salahaddin University** **Final Exam** **Cell biology**

**College of Education** **Date: / /**

**Biology Dept.** **4th year** **Time: 3hr**

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**Q1) Fill with suitable answers: ( M)**

1. **Tonoplast is……**
2. **In parietal cells, the mitochondria is …….type, because……..**
3. **The enzyme involved in $H^+$ passage in inner mitochondrial membrane is.....**
4. **Krebs cycle yields……NADH and …….$FADH_2$**
5. ***C. elegans* used as a model for apoptosis has …….mm body length**
6. **Cancer cell digest the components of the basal lamina by secreting metalloproteinase, otherwise it cannot …….**
7. **Osmium tetroxide is considered as stain in EM preparation because……**
8. **The knife used in ultramicrotome is glass and not ……..**
9. **Ultrathin section must not be less than 500A° because……**
10. **The protein in microfilament is……, while in microtubule is ……**
11. **Circular DNA can be found in organism such as ……..and in organelle such as …….**
12. **$P_{53}$ is an inducer of apoptosis, so it is called cell ……**
13. **Primary lysosome is ……**
14. **The main characters of benign tumor are 1).....….2)……3)……. 4)……..…… 5)……**

**Q2) Mention the following: (M)**

1. **Two examples of normal apoptosis in adult human**
2. **Examples of Totipotent and Unipotent stem cells**

**Q3) Draw with labels: (M)**

1) **C.S in centriole as revealed by electron microscopy**
2) **Parietal cells as revealed by electron microscopy**

**Q4) Write about the ultrastructure and molecular structures of cell-cell junctions supporting your explanation by full labeled drawing (M)**

**Assist. Prof. Treefa F. Ismail**

**Salahaddin University** **Final Exam** **Cell biology**

**College of Education/Biology** **4th year/** **Date: /Time:3h Q1)**

**Fill with suitable answers:** **( M)**

**1) Residual body is……**
**2) In liver cells, the mitochondria is …….type, because……..**
**3) Krebs cycle occurs in the ..... of the mitochondria**
**4) Krebs cycle yields……FADH2 and …….ATP**
**5) *C. elegans* used as a model for …….**
**6) Cancer cell digest the components of the basal lamina by secreting ……., otherwise it cannot metastasize.**
**7) Uranyl citrate is considered as stain in EM preparation because……**
**8) The knife used in ultramicrotome is glass and diamond but not ……**
**9) Ultrathin sections thickness is less than ……..µm**
**10) The basic protein in microtubule is……, while in microfilament is ……**
**11) DNA in bacteria is ……..and in liver cell is …….**
**12) $P_{53}$ is an ……..of apoptosis, so it is called cell terminator.**
**13) Primary lysosome is ……**
**14) The main characters of malignant tumor are 1).....….2)…….3)……. 4)……..…… 5)……**

**Q2) Mention the following:** **(M)**

1) **Four examples of normal apoptosis in living organism**
2) **Examples of pluripotent and oligopotent stem cells**

**Q3) Draw with labels:** **(M)**

1) **C.S in flagella as revealed by electron microscopy**
2) **Desmosome**

**Q4) Answer the following:** **(M)**

1) **The most acceptable model of plasma membrane**
2) **Write the name of technique by which scientists become sure about this model.**
3) **Draw the model with full labeling.**

**Assist Prof. Treefa F. Ismail**

# Lecture 1: Introduction into cell biology

## Objectives Introduction to the Course

- Understand Historic Background of Cell Biology
- Understand current role of Cell Biology in scientific research
- Understanding the different methods and techniques used in cell biology
- Brief understanding of Cell Structure and Function

### Early History

**Robert Hooke** (1635-1703): used early microscopes to view cork tree bark , and was the first to use the term CELL (The word *cell* comes from the Latin *cellula*, meaning "a small room". The word *cell* comes from the Latin *cellula*, meaning "a small room".

**Robert Brown** 1825 :identified nuclei in plant cells

**Theodor Schwann** (1810-1882) together with **Matthias Schleiden** (plants) developed the cell theory in 1839

### Cell Theory

1. All organisms consist of one or more cells
2. The cell is the basic unit of structure for all cells
3. All cells arise only from preexisting cells

## The cell

The cell is the functional basic unit of life. It was discovered by Robert Hooke and is the functional unit of all known living organisms. It is the smallest unit of life that is classified as a living thing, and is often called the building block of life. Some organisms, such as most bacteria, are unicellular (consist of a single cell). Other organisms, such as humans, are multicellular. Humans have about 100 trillion or $10^{14}$ cells; a typical cell size is 10 µm and a typical cell mass is 1 nanogram. The longest human cells are about 135 µm in the anterior horn in the spinal cord while granule cells in the cerebellum, the smallest, can be some 4 µm and the longest cell can reach from the toe to the lower brain stem (Pseudounipolar cells). The largest known cells are unfertilized ostrich egg cells, which weigh 3.3 pounds(one pound =0.5kg).

## Cell shape

Cells are in various shape and size. It can have the shapes as oval, spherical, rectangular, polygonal, spindle shaped, star shaped, rod-shaped or totally irregular. The shape of cells sometimes vary according to their function. Cell membrane as well as cell wall

maintain shape of any cell. In case of unicellular organisms mostly cells are oval or spherical. But some cells show an unique property related to shapes of cells.

Pleomorphism is the ability of few cells to change its shape during their life cycle. This property is seen in many bacteria, fungi and in some plant cells.

A specific group of organism have specific shapes of cells. Most bacteria are named according to their shape of cells. In case of unicellular organisms shapes of the cells is an important criteria of identification. Also fungal cells are identified with the help of their shape. In case of plants and animals the shapes of cells vary along with the type of tissues.

## Types of Shapes of Cells in Human Beings

In human, shapes of cells vary from one tissue to another. Following are some example of different types of shapes of cells

1. Cuboidal, columnar shaped cells are found in epithelium.
2. Muscle cells or muscle fibres are elongated in shape.
3. Neuron is thread like in shape with extensions.
4. Red blood cells are flexible biconcave in shape.
5. Leukocytes are mainly oval or irregular in shape.
6. Osteocytes is one type of cells present in bone. These cells are star shaped.
7. Fibroblasts are thread like in shape, but do not have any extension like neuron.
8. Astrocytes are star shaped glial cells found in brain and spinal cord.

## Subcellular structure of the cell:

1) membranes

2) cytoskeleton

3) genetic material

4) organelles

## Microscopes

Cells are too small to see by the naked eye

**Antony van Leeuwenhoek (**1632-1723) - developed some of the earliest microscopes

**Modern Microscopes**

Bright Field, Fluorescence, Phase Contrast, Dark Field, Digital Video Microscopy, Confocal

Electron Microscope (EM): Transmission and scanning EM

Magnetic Resonance Imaging (MRI)

Modern Cell Biology Arose from 3 separate fields becoming interwoven over the last 50 years - Cytology, Biochemistry and Genetics

Microscopy - different types of microscopy

Histology/Immunohistochemistry - fixation and staining of cells

Biochemical - fractionation and analysis

Tissue Culture - growth and modification of cells

There are two types of cells: eukaryotic and prokaryotic. Prokaryotic cells are usually independent, while eukaryotic cells are often found in multicellular organisms.

**Cell types:**

**Table: Comparison of features of prokaryotic and eukaryotic cells**

| | Prokaryotes | Eukaryotes |
|---|---|---|
| **Typical organisms** | bacteria, archaea | protists, fungi, plants, animals |
| **Typical size** | ~ 1–10 µm | ~10–100 µm (sperm cells, apart from the tail, are smaller) |
| **Type of nucleus** | nucleoid region; no real nucleus | real nucleus with double membrane |
| **DNA** | circular (usually) | linear molecules (chromosomes) with histone proteins |
| **RNA-/protein-synthesis** | coupled in cytoplasm | RNA-synthesis inside the nucleus protein synthesis in cytoplasm |
| **Ribosomes** | 50S+30S | 60S+40S |
| **Cytoplasmatic structure** | very few structures | highly structured by endomembranes and a cytoskeleton |
| **Cell movement** | flagella made of flagellin | flagella and cilia containing microtubules; lamellipodia and filopodia containing actin |
| **Mitochondria** | None | one to several thousand (though some lack mitochondria) |
| **Chloroplasts** | None | in algae and plants |
| **Organization** | usually single cells | single cells, colonies, higher multicellular organisms with specialized cells |
| **Cell division** | Binary fission (simple division) | Mitosis (fission or budding)<br>Meiosis |

## Lecture 2&3: Techniques used to study cells

**Cells can be observed under the microscope. This includes:**

- **Optical Microscope**
- **Transmission Electron Microscope**
- **Scanning Electron Microscope**
- **Fluorescence Microscope**
- **Confocal Microscopy**

**Several techniques exist to study cells:**

- **Cell culture is the basic technique of growing cells in a laboratory independent of an organism (in vivo), but in culture (in vitro)**
- **Several molecular biology techniques such as electrophoresis and PCR (polymerase change reaction)**
- **Immunohistochemistry, autoradiography, …etc**
- **Cell fractionation: Purification of cells and their parts after release of cellular organelles by disruption of cells**
- **Electron microscopy techniques**

1. **Transmission EM:**

**A) Routine TEM techniques: for studying the ultrastructure of the sample (mitochondria, lysosomes etc..)**

**Steps:**

**1) Fixation: The tissues are fixed in 2.5%-6% glutaraldehyde prepared in buffer(cacodylate buffer) Ph7.2-7.4,**

**2) Postfixation: postfixed in 1% osmium tetroxide for one hour, $OsO_4$ is a fixative and electron dense stain, but it is dangerous so you must be careful in handling because when it touch the skin it will oxidize and produces a black precipitate in which it will be dangerous to eyes. It has a low penetration rate because it contain osmium with high molecular weight, that is why it is used after primary fixation**

**3) Dehydrated in ascending concentrations of ethanol 50%,**

**70%, 90% and 100% ethanol or acetone**

**4) Cleared in propylene oxide because ethanol is immiscible with the plastic embedding medium**

**5) Infiltration by a mixture of plastic medium + propylene oxide**

**6) Embedded in resin (plastic) mixture.**

**7) Sectioning using ultramicrotome (glass or diamond knives) into thick and semithin sections (0.5-1micrometer respectively) or ultrathin sections (600-900A). Figure (1) shows a typical glass knife and steps in knife preparation.**

**8) Mounting: transferring the ultrathin sections to the electron microscope grids which are either copper, nickel or gold, copper is used because it is cheap.**

**8) Staining: The thick and semithin sections on the grids are stained by 1% toluidine blue, while the ultrathin sections are stained by heavy metals such as uranyl acetate and lead citrate.**

**10) Examining by electron microscopy at 60-100Kv**

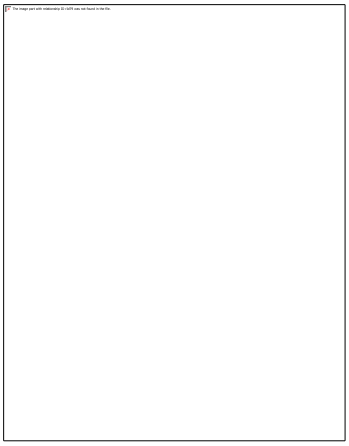
**B) Negative staining: In the case of transmission electron microscopy, opaqueness to electrons is related to the atomic number, i.e., the number of electrons. Some suitable negative stains include uranyl acetate, uranyl formate, phosphotungstic acid and osmium tetroxide. These have been chosen because they scatter electrons well and also adsorb to biological matter well. Here, the method is used to view viruses, bacteria, bacterial flagella, biological membrane structures and proteins or protein aggregates, which all have a low electron-scattering power. Some stains, such as osmium tetroxide are very chemically active. As**

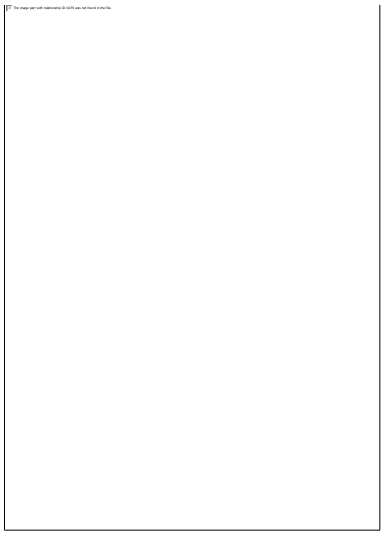
**strong oxidants, they cross-links lipids mainly by reacting with unsaturated carbon-carbon bonds, and thereby both fix biological membranes in place in tissue samples and simultaneously stain them**

**Other special EM techniques involve freeze fracture technique, autoradiography, immunocytochemistry**

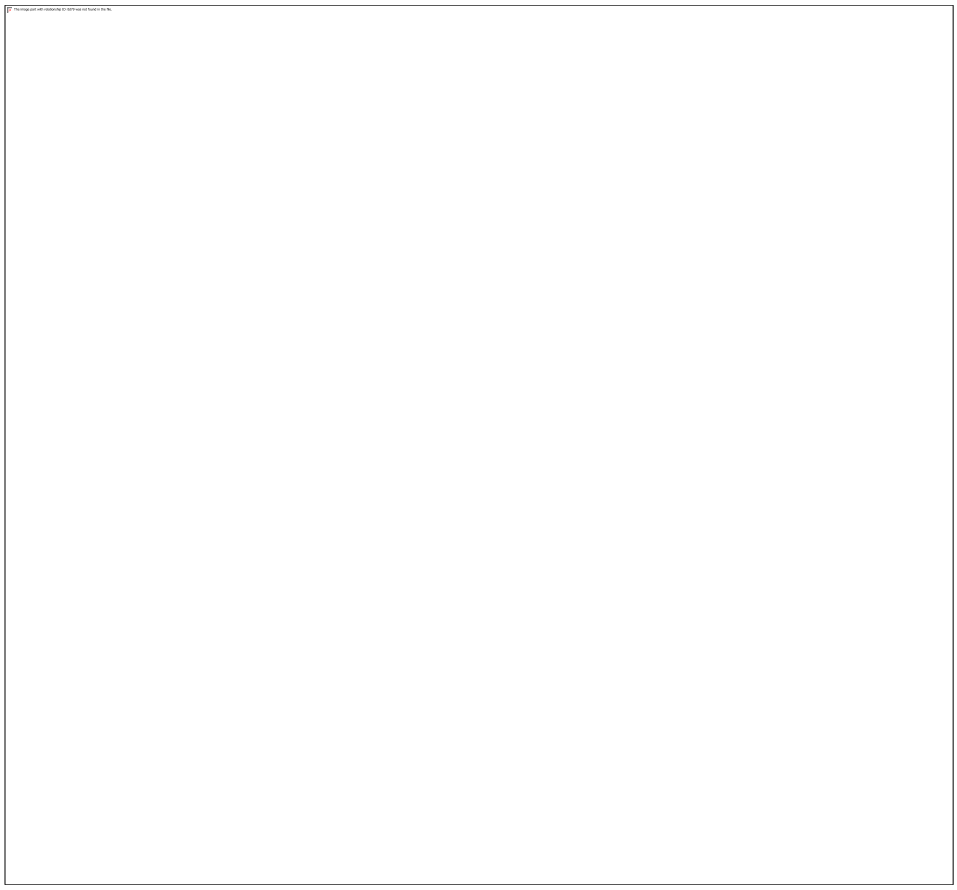
**2. Scanning EM: is a type of electron microscope that images the sample surface after deposition of heavy metal over the surface of the sample vertically.**

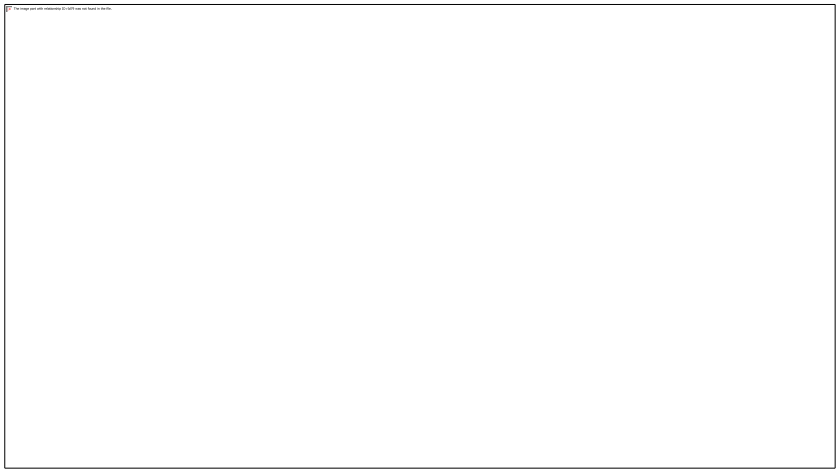
**3. Analytical EM: Characteristic X-rays are used to identify the composition and measure the abundance of elements and.**

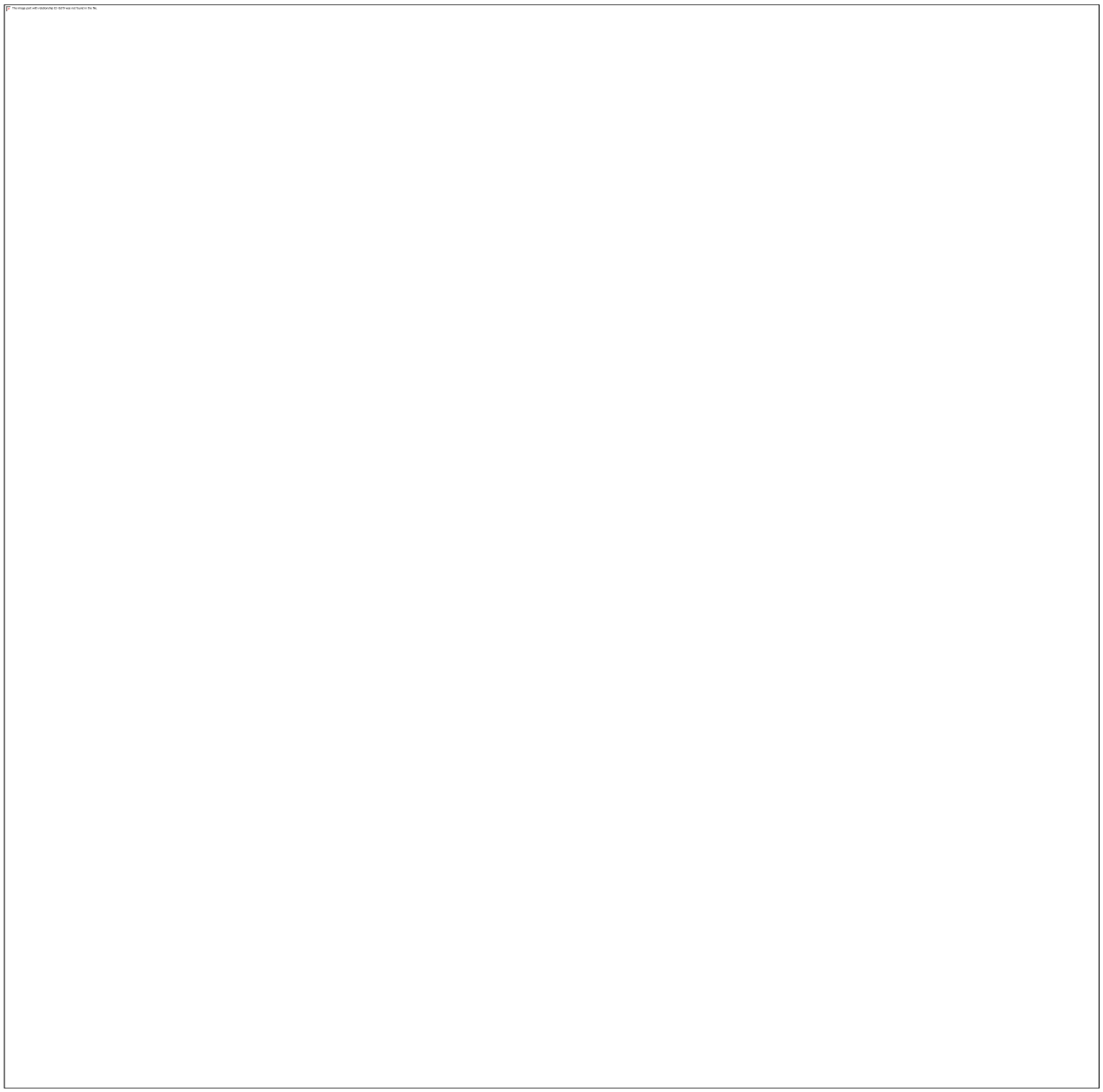


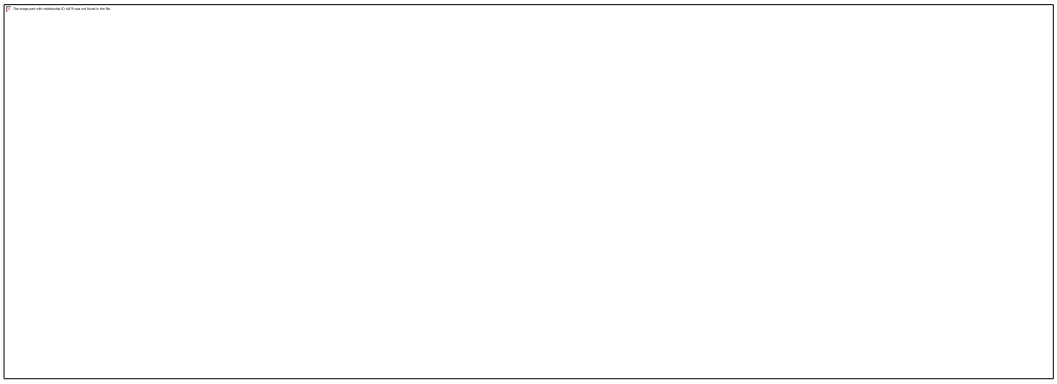


**Fig(1) Glass knife**
**knife preparation**









# Lecture 4: Membranes

## Membrane Structure

The **fluid mosaic model** of membrane structure contends that membranes consist of:

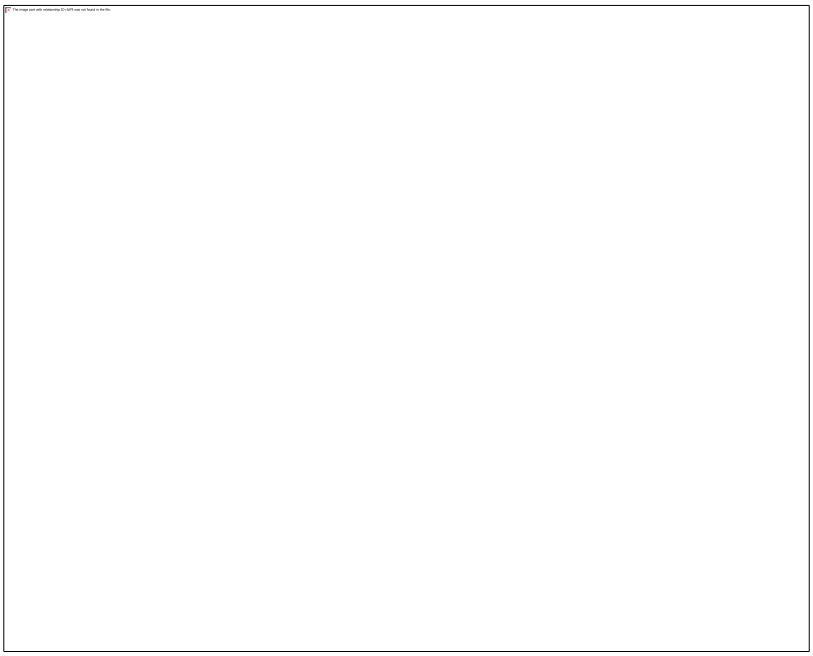
-**phospholipids** arranged in a bilayer

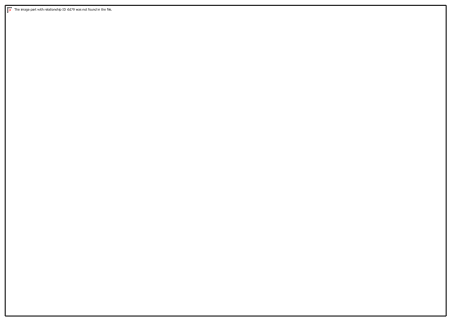
-**globular proteins** inserted in the lipid bilayer

Cellular membranes have 4 components:

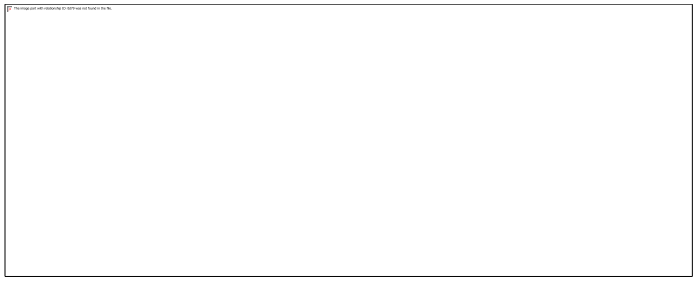
1. phospholipid bilayer
2. transmembrane proteins
3. interior protein network
4. cell surface markers

**The fluid mosaic model of**
**(S. J. Singer and G.Nicolson 1972)**





Membrane is visible under electron microscope as trilaminar structure



# Membrane Functions

Membrane proteins have various functions:

1. transporters
2. enzymes
3. cell surface receptors
4. cell surface identity markers
5. cell-to-cell adhesion proteins
6. attachments to the cytoskeleton

**Types of membrane proteins**

**1) Integral membrane proteins**

The cell membrane contains many integral membrane proteins, which extend through the entire surface. These structures, which can be visualized by electron

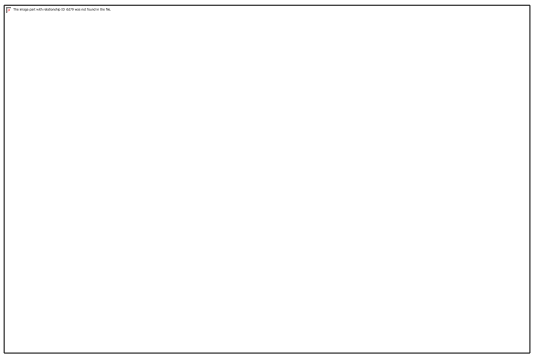
microscopy or fluorescence microscopy, can be found on the inside of the membrane, the outside, or membrane spanning. These may include integrins, cadherins, desmosomes, clathrin-coated pits, caveolaes, and different structures involved in cell adhesion. Integral proteins are the most abundant type of protein to span the lipid bilayer.

**2) Peripheral membrane proteins**

Peripheral proteins are proteins that are bounded to the membrane by electrostatic interactions and hydrogen bonding with the hydrophilic phospholipid heads. Many of these proteins can be found bounded to the surfaces of integral proteins on either the cytoplasmic side of the cell or the extracellular side of the membrane. Some are attached to the bilayer through covalent bond with a fatty acid.

## Types of junctional complexes

- Tight junction
- Desmosome
- Gap junction
- Hemidesmosome
- Interdigitation



Tight Junction **(zonula occludens)**

- Located at the apical pole of the epithelial cells
- Formed by rows of integral proteins that encircle the apical pole
- At the interaction point the 2 membranes appear as fused
- Between the touching point the intercellular space is greatly reduced –2.5nm

### Roles of tight junction

- Mechanical connection
- Barrier

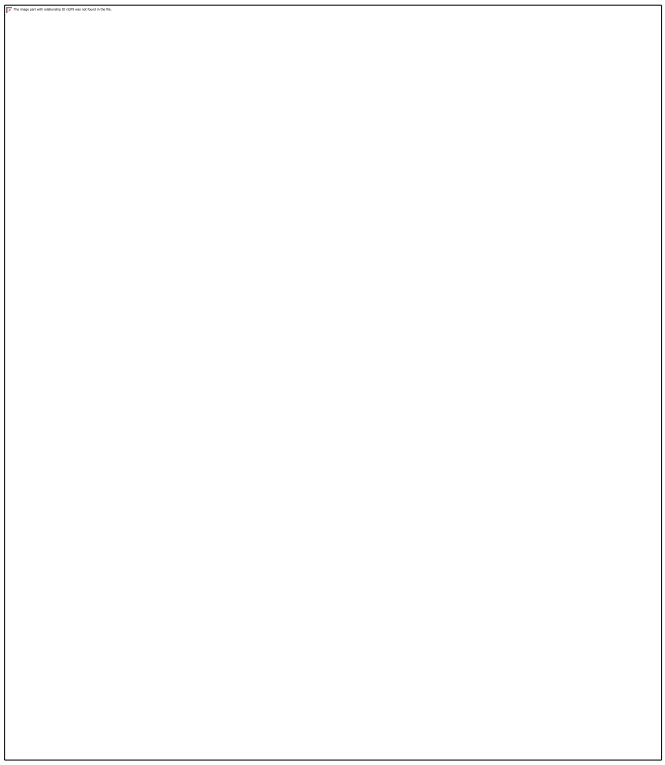
- Inhibits: entry of water-soluble molecules lateral diffusion of membrane-components
- Permeability: inorganic small substances
  -/amino acids

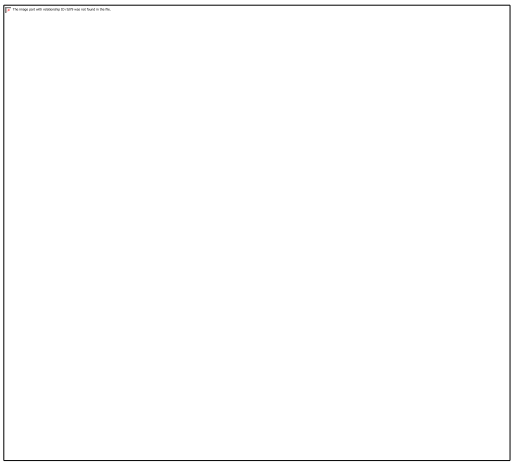
  -/monosaccharides

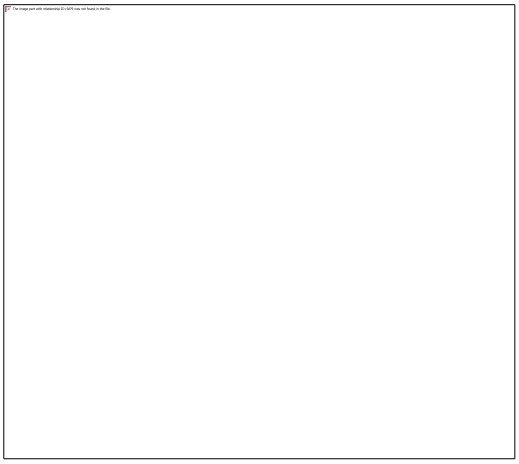
Band=ZONULA Disk =MACULA

## (DESMOSOME) MACULA ADHRENS (Disk shape structure)

- Button like welds joining opposing cell membranes
  FOUND IN: Epithelial tissue, Intercalated disk



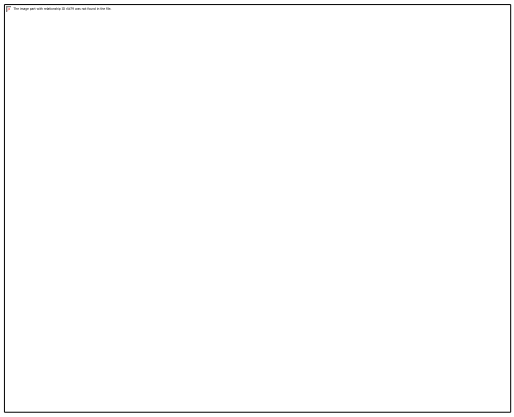




***Different types of cell-cell junctions*** ***Desmosomes***

## **GAP Junction**(MACULA COMUNICANS)

- Found in:
  - Epithelial tissue
  - Intercalated disk
  - Smooth muscle tissue
  - Electrical synapse
  - Glial cells
  - Osteocytes
- Structure :
  - Intercellular space: 2-3nm
    - Selective barrier



A ring of 6 membrane proteins called connexins- connexons

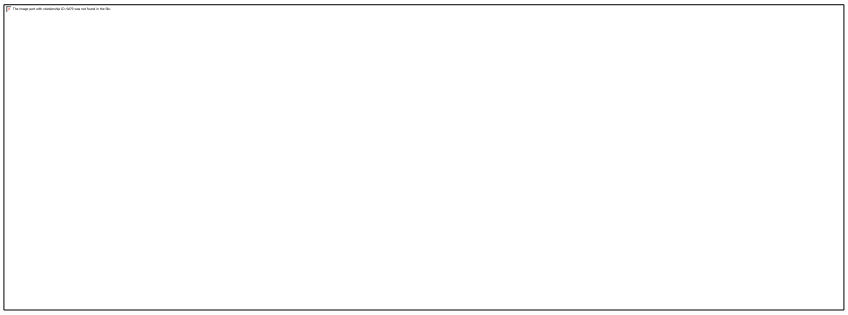
- Two connexons on neighboring membranes form a transmembrane channel that interconnects the cytoplasms of two cells
- Connexons are sizefilters

Function

Allow the passage of: Ions Molecules with a MW<1000 D

## **HEMIDESMOSOMES**

- Attach epithelial cells to the underlying basal lamina.
- STRUCTURE:
  - Transmembrane glycoprotein –**INTEGRIN**
  - Attachment proteins – **adhesion plaque**
  - Cytoskeletal element - **INTERMEDIATE FILAMENTS**
  - the extracellular-matrix protein - **LAMININ**.



## Microvilli

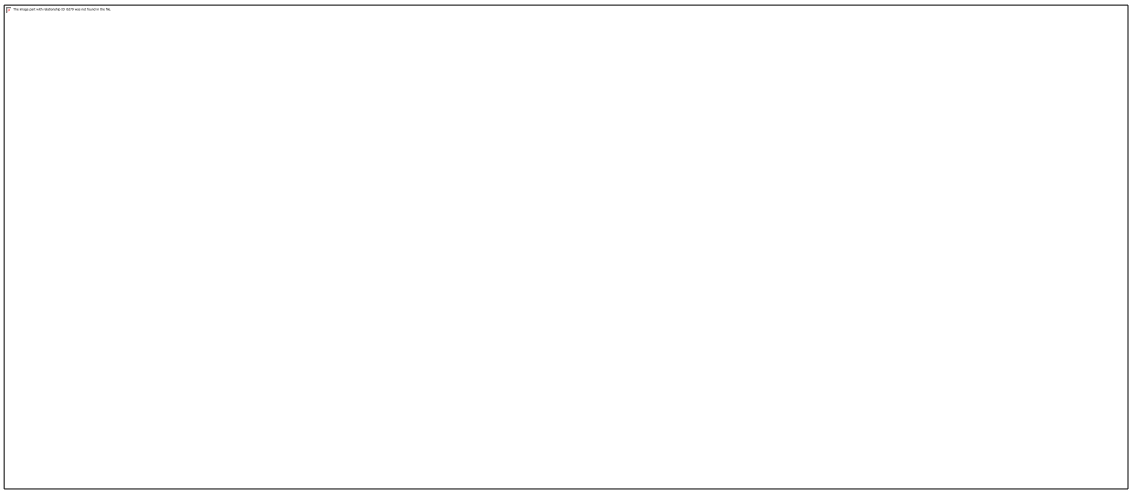
The microvilli are tiny, hairlike structures on the surface of epithelial cells involved in absorption and secretion. The effect they have is to increase the surface area of the cell by a massive amount (in humans, by about 600-fold) and facilitate absorption and secretion. Microvilli are about 0.08µm in diameter.

## Glycocalyx

**The term was initially applied to the polysaccharide matrix excreted by epithelial cells forming a coating on the surface of epithelial tissue. External to the plasma membrane, all animal cells have a fuzzy coat called the glycocalyx. This coat consists of the carbohydrate moieties of membrane glycolipids and glycoproteins. Only identical twins have chemically identical glycocalyx, everyone else is unique. The glycocalyx is a type** of **identification that the body uses to distinguish between its own healthy cells and transplanted tissues, diseased cells, and invading organisms. The glycocalyx also includes the cell-adhesion molecules that enable cells to adhere to each other and guide the movement of cells during embryonic development.**

# Functions

- **Protection**: Cushions the plasma membrane and protects it from chemical injury
- **Immunity to infection**: Enables the immune system to recognize and selectively attack foreign organisms
- **Defense against cancer**: Changes in the glycocalyx of cancerous cells enable the immune system to recognize and destroy them
- **Transplant compatibility**: Forms the basis for compatibility of blood transfusions, tissue grafts, and organ transplants
- **Cell adhesion**: Binds cells together so that tissues do not fall apart
- **Inflammation regulation**: Glycocalyx coating on endothelial walls in blood vessels prevents leukocytes from rolling/binding in healthy states
- **Fertilization**: Enables sperm to recognize and bind to eggs
- **Embryonic development**: Guides embryonic cells to their destinations in the body



## Plasmodesmata

- **Plasmodesmata** are narrow membrane-lined channels that pass through cell walls of neighboring cells and connect their cytoplasm, allowing direct exchange of molecules and ions between neighboring plant cells.

# Cell surface receptors

Cell surface **receptors** are responsible for the binding of an extracellular signalling molecule and **transduction** of its messages into one or more intracellular signalling molecules, which changes the cell's behaviour.

A cell surface receptor exists intrinsically embedded in the plasma membrane. It has two domains of significance – the signal molecule**binding domain**, which is exposed to the exterior of the cell and the **intra-cellular domain** in contact with the cytoplasm.

Cell surface receptors fall into three main classes;

- Ligand-gated ion channel receptors
- Enzyme-coupled receptors
- G-protein-coupled receptors

**Ligand-gated ion channel receptors:** also known as **ionotropic** receptors, are responsible for the rapid transmission of signals across **synapses** in the nervous system by allowing a flow of ions across the plasma membrane, which changes the **membrane potential**, causing an electrical current. Ionotropic receptors transduce a chemical signal, in the form of a pulse of neurotransmitters delivered to the outside of the target cell, directly into an electrical signal in the form of change in voltage across the target cell's membrane. The opening and closing of

ion channels in the membrane allows the flow of specific types of ions such as $Na^+$, $K^+$, $Ca^+$ or $Cl^-$ (Figure).

Although the ligand-gated ion channel receptors are found mainly in the nervous system and other electrically excitable cells such as muscle cells, the other two types of cell surface receptors are found practically in every cell type of the body.

Figure : Ligand-gated ion channel receptors and their activation by ligands.

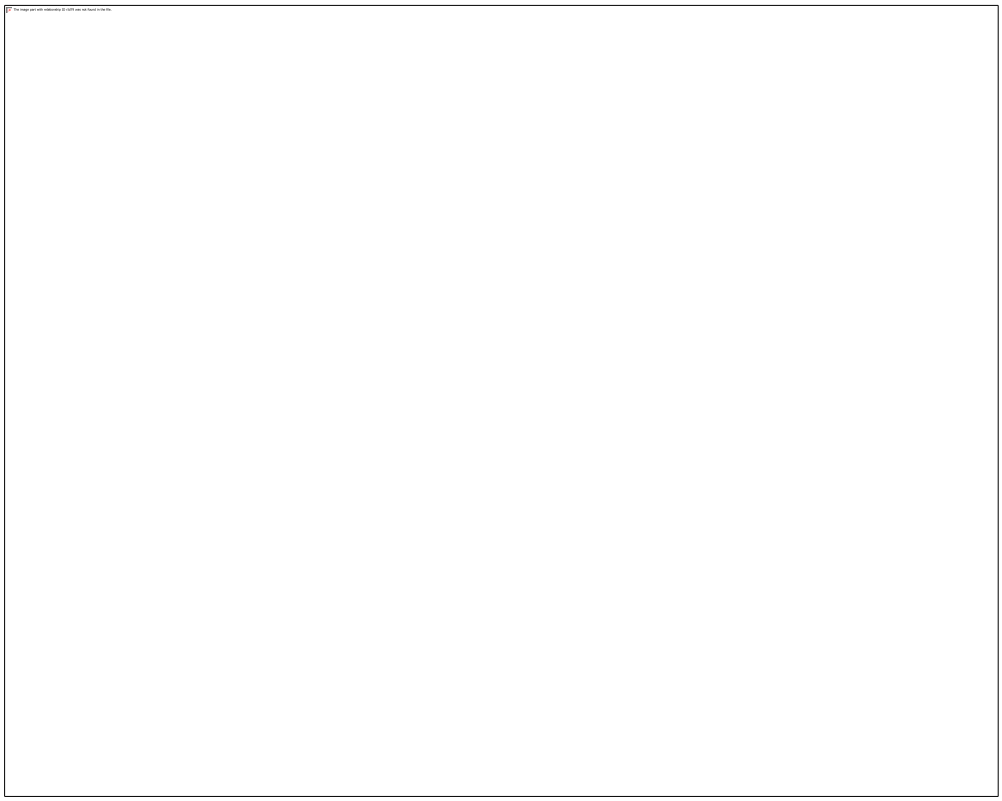
**Enzyme-coupled receptors:** these are transmembrane proteins which as of 2009, only six types were known. They are;

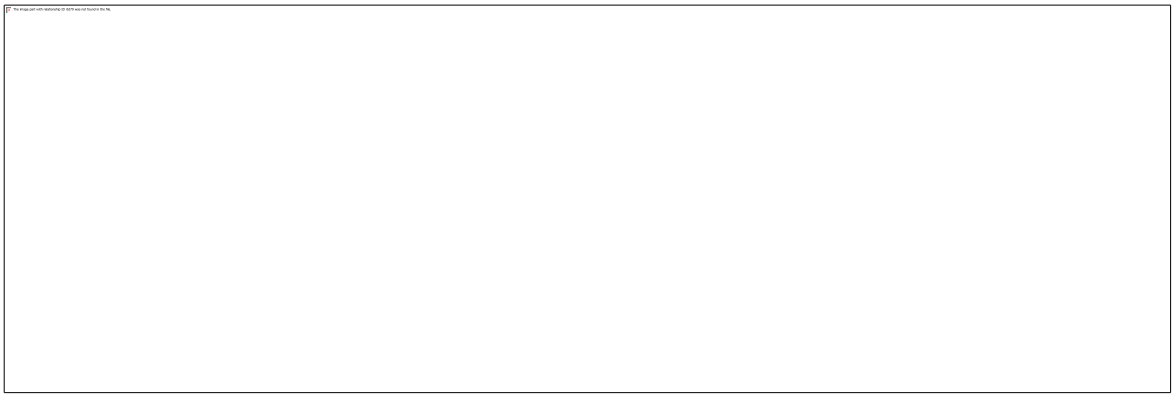
- Receptor tyrosine kinases
- Tyrosine kinase associated receptors
- Receptor-like tyrosine phosphatases
- Receptor serine/ threonine kinases
- Receptor Guanylyl cyclases
- Histidine kinase associated receptors

These receptors acts as enzymes or associate with enzymes inside the cell. When stimulated, the enzyme activate a variety of intracellular signalling pathways. They were discovered through their role in responses to extracellular signal proteins that regulates the growth, proliferation, differentiation and survival of cells in animal tissues. Disorders of cell growth, proliferation, differentiation, survival and migration are fundamental to cancer, and abnormalities in signalling via enzyme-coupled receptors have a major role in the development of this class of diseases.

**G-protein-coupled receptors (GPCR's):** these are the largest of all the cell surface receptors. They activate membrane-bound, trimeric GTP binding proteins

(G-proteins) which then activate either an enzyme or an ion channel (effector) in the plasma membrane, initiating a sequence of other effects. These receptors mediate responses involving hormones, local mediators and neurotransmitters. Due to the large variety of cellular processes that GPCR's are involved in, they are usually an attractive target for the development of drugs to treat a variety of disorders. About half of all known drugs work through GPCR's. All GPCR's have been analysed and are believed to have similar structures. A signalling molecule binds to a GPCR which causes a conformational change in the receptor. The GPCR now binds to an inactive G-protein, causing a GTP to displace the GDP (nucleotide exchange) on the alpha subunit of the G-protein. The GTP-bound G- alpha dissociates from the G-beta/gamma complex and the GPCR and binds to a specific effector and activates it, triggering a cascade of responses





# Lecture 5: Mitochondria

**Mitochondria: Mitochondria are membranous cytoplasmic organelles (0.5-1.0 microns wide,up to 10 microns long) capable of trapping chemical energy released by oxidation of compounds derived from food. They then fix that energy in a form, adenosine triphosphate (ATP), that is readily utilizable by the cell. They are present as punctate or linear structures just within the resolving power of the light microscope. By electron microscopy, mitochondria are tubular or spherical structures bounded by one membrane called the outer membrane and containing a second internal folded membrane termed the inner membrane.**

**The unit membrane is modified in the cristae. The surface exposed to the inner chamber possesses knoblike repeating units attached to a basal membrane by slender stalks. These units, called elementary particles, are best revealed at high magnification with negative staining after osmotic shock. Elementary particles contain a mitochondrial ATPase complex that appears to provide a channel for proton translocation. Normally the particles may be embedded in the membrane rather than project from it.**

**Types of mitochondria according to activity:**

**1) The orthodox form (inactive form) is typical of mitochondria in tissue section, mitochondria inactive in oxidative phosphorylation**

**2) Condensed mitochondrial conformation (active form) . In this form the volume of the outer chamber is increased to approximately 50% of the organelle, and the inner chamber is reduced in volume.**

**Isolation of mitochondria: Mitochondria may be isolated relatively easily by a technique that requires disruption of cells and centrifugation of the fragments. In density-gradient centrifugation, the mitochondria form a tan colored stratum lying above nuclei and below lysosomes and ribosomes.**

**The number and size of mitochondria are, in general, correlated with the level of oxidative phosphorylation. Hepatocytes may each contain about 1,000 to 1,500 mitochondria. Mature erythrocytes, totally dependent for energy on glycolysis, contain none.**

**In striated muscle cells, which contain myofilaments that slide on one another to effect contraction, mitochondria are present close to the myofilaments. In the development of fat cells, the minute fat droplets that form and then coalesce are intimately associated with mitochondria.**

**The primary function of mitochondria is respiratory. They may display other activities as well, notably the concentration of cations. The dense granules of the mitochondrial matrix in the inner chamber may represent concentrations of Ca++.**

**Mitochondria contain circular DNA typical of prokaryotes, and mitochondrial ribosomes are similar to bacterial ribosomes. Mitochondria may divide, moreover, to produce new mitochondria.**

**Why 2 membranes?**

**increase surface area for membrane-bound enzymes that synthesize ATP**

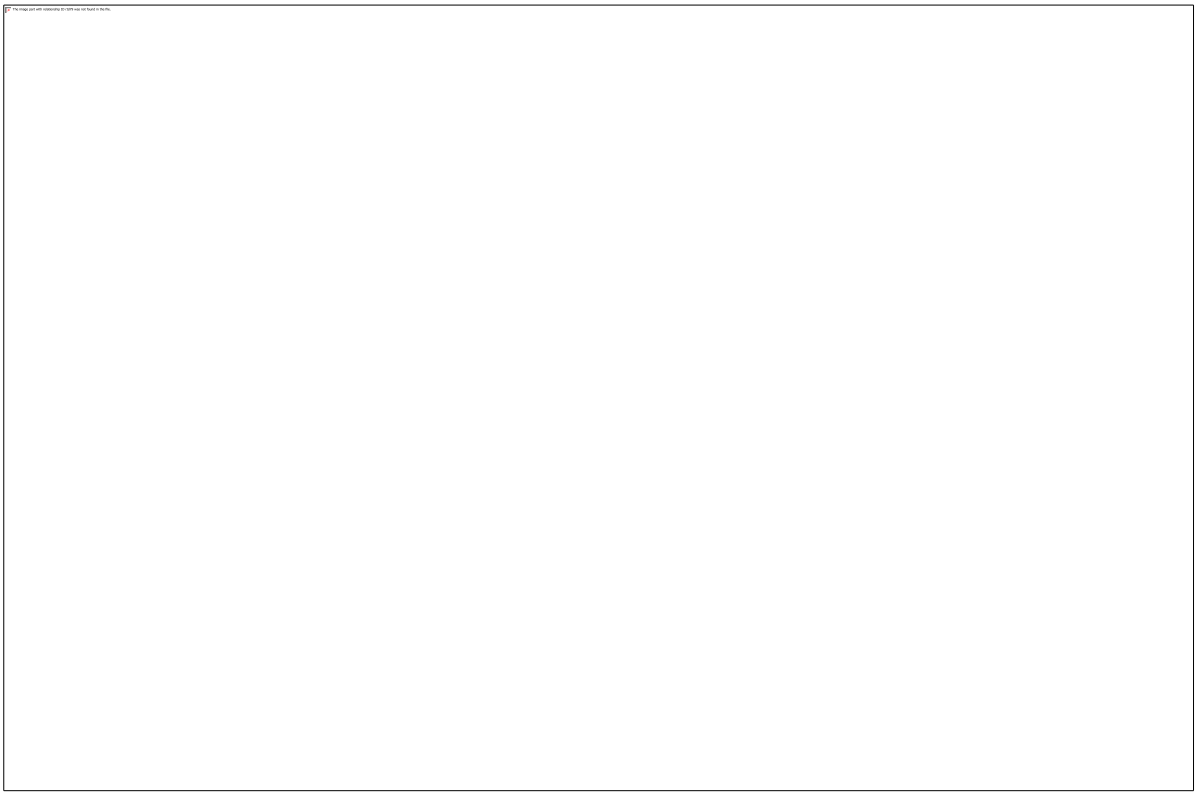
Despite having their own genome, most mitochondrial proteins are encoded in the nucleus, made in the cytosol and imported into the mitochondria

**Mitochondrial function**

- **Oxidative phosphorylation**

– the process by which the enzymatic oxidation of cellmetabolites is converted into ATP
– Uses electrons from biochemical reactions
– Occurs in a membrane bound **electron transport system**
– Needs **ATP-synthetase**
    - Uses H+ gradient to generate ATP

- essential for cell death: unprogrammed death: necrosis (eg, due to loss of energy status), programmed cell death: (apoptosis - controlled cell destruction)



## Types of mitochondria according to cristae:

1) **lamellar mitochondria: arranged in shelves e.g. parietal gastric cell**
2) **Tubular m. the cristae appear as finger like, e.g.: steroid secreting cells**

**Matrix Granules**

- **Are accumulations of calcium phosphate**
- **Helps maintain low levels of calcium ions in the cytosol**

## More mitochondria are found in cells that:

- **have motile machinery**
- **sequester low pH substances**
- **pump large amounts of ions**

**Small lymphocytes have a few while hepatocytes have about 1000**

**Cells contain low number of mitochondria**

- **Type II skeletal muscle fiber**
- **Skin epithelia (stratified squamous keratinizing epithelia)**
- **Neutrophil**

**Cells known to have high number of mitochondria**

- **Hepatocyte**
- **Cardiac muscles**
- **Skeletal Muscle**
- **Parietal cell of the stomach**
- **Ciliated cells:ATP is needed to move the microtubules in the cilia, Cilia helps move mucus along in the lumen of the trachea and the ovum in the oviduct**
- **Presynaptic terminal of neuron**
- **Tail of sperm**
- **Cells of proximal convoluted tubule**

## Lecture 6: Lysosomes, Peroxisome, and glyoxisomes

It is a membrane-bounded organelle, found in the cytoplasm of eukaryotic cells, which contains digestive enzymes. It acts as the "garbage disposal" of the cell by breaking down cell components that are no longer needed as well as molecules or even bacteria that are ingested by the cell. Lysosomes are organelles containing digestive enzymes (acid hydrolases). They are found in animal cells, while in plant cells the same roles are performed by the vacuole. The name *lysosome* derives from the Greek words *lysis*, which means dissolution or destruction, and *soma*, which means body. They are frequently nicknamed "suicide-bags" or "suicide-sacs" by cell biologists due to their role in autolysis. Lysosomes were discovered by the Belgian cytologist Christian de Duve in 1955.

**Occurrence:**

Lysosomes occur in most animal cells and in a few plant cells as vacuoles. They are most abundant in cells which are related with enzymatic reactions such as liver cells, pancreatic cells, kidney cells, spleen cells, leucocytes, macrophages etc.,

**Shape:**

Lysosomes are usually spherical in shape; but they are irregular in certain meristematic cells of roots.

**Size:**

The size of the lysosomes usually ranges from 0.2micron to 0.8micron in diameter, but it might present as large as 8 microns in mammalian kidney cells and macrophages.

**Structure:**

Lysosomes are single membrane bound organelle. They are round dense bodies filled with large number of hydrolytic enzymes and lytic components. Lysosomes are so called because they contain lytic enzymes. **The enzymes are kept inside by the lysosomal membrane. These enzymes remain inactive inside the lysosomes. When the pH of the interior lysosomes changed to acidic pH 4.8, enzymes become active. At pH 4.8, the interior of the lysosomes is acidic compared to the slightly alkaline cytosol (pH 7.2). The lysosome maintains this pH differential by pumping protons ($H^+$ ions) from the cytosol across the membrane via proton pumps and chloride ion channels. The lysosomal membrane protects the cytosol, and therefore the rest of the cell, from the degradative enzymes within the lysosome. The cell is additionally protected from any lysosomal acid hydrolases that leak into the cytosol as these enzymes are pH-sensitive and function less well in the alkaline environment of the cytosol.**

The lysosomal enzymes are collectively called as hydrolases. The hydrolases bring about the cleavage of substrates by the addition of a water molecules. Most of the lysosomal enzymes function in the acid medium. Hence they are called as acid hydrolases. The lysosomes may contain about 40 varieties of enzymes. The lysosomal

enzymes are classified into six main types namely Nucleases, Proteases, glycosidases, lipases, phosphatases and sulphatases.

**Types of lysosomes**

1) **Primary lysosomes: these are the lysosomes that are not involved in digestion yet, they are also called virgin lysosomes**
2) **Secondary lysosomes: when primary lysosomes fuse with a phagosome, the whole vacuole is called secondary lysosome, the enzymes of the primary lysosome will release into the lumen of phagosome and start digest its components**
3) **Autolysosomes: or internal digestion of aged or unwanted cellular organelles such as mitochondria and endoplasmic reticulum**
4) **Residual bodies: the remaining vacuole after digestion of their content by lysosomal enzymes are called residual bodies, it takes many shapes, the most common are the whorls shape.**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# Peroxisomes

Peroxisomes are about the size of lysosomes (0.5–1.5 μm) and like them are enclosed by a single membrane. They also resemble lysosomes in being filled with enzymes.

However, peroxisomes bud off from the endoplasmic reticulum, not the Golgi apparatus (that is the source of lysosomes).

The enzymes and other proteins destined for peroxisomes are synthesized in the cytosol. Each contains a **p**eroxisomal **t**argeting **s**ignal (**PTS**) that binds to a receptor molecule that takes the protein into the peroxisome and then returns for another load.

Each has its own receptor to take it to the peroxisome.

Some of the functions of the peroxisomes in the human liver:

- Breakdown (by oxidation) of excess fatty acids.
- Breakdown of hydrogen peroxide ($H_2O_2$), a potentially dangerous product of fatty-acid oxidation. It is catalyzed by the enzyme **catalase**.
- Participates in the synthesis of cholesterol. One of the enzymes involved, HMG-CoA reductase
- Participates in the synthesis of bile acids.
- Participates in the synthesis of the lipids used to make myelin.
- Breakdown of excess purines (AMP, GMP) to uric acid.

Peroxisomes are also present in **plant** cells where they participate is such functions as

- symbiotic nitrogen fixation
- photorespiration

## Glyoxisomes

**Glyoxysomes** are specialized peroxisomes found in plants (particularly in the fat storage tissues of germinating seeds) and also in filamentous fungi. As in all peroxisomes, in glyoxysomes the fatty acids are hydrolyzed to acetyl-CoA by peroxisomal β-oxidation enzymes. Besides peroxisomal functions, glyoxysomes possess additionally the key enzymes of glyoxylate cycle (isocitrate lyase and malate synthase) which accomplish the glyoxylate cycle bypass. Thus, glyoxysomes (as all peroxisomes) contain enzymes that initiate the breakdown of fatty acids and additionally possess the enzymes to produce intermediate products for the synthesis of sugars by gluconeogenesis. The seedling uses these sugars synthesized from fats until it is mature enough to produce them by photosynthesis.

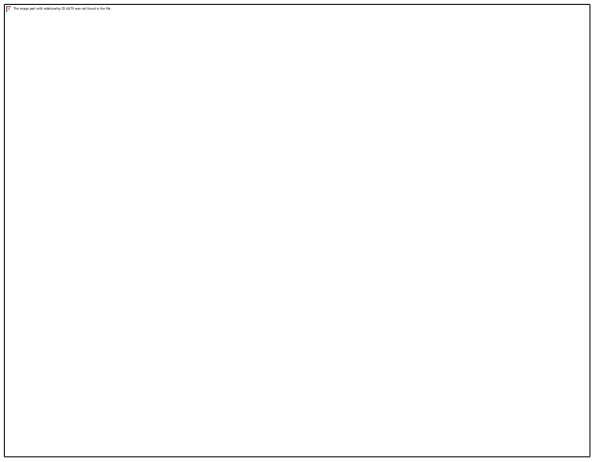
Glyoxysomes also participate in photorespiration and nitrogen metabolism in root nodules.

# Lecture 7: Ribosomes

- small semi-spherical, black dots
- some are free in cytoplasm (cytoplasmic ribosomes), others are attached to the ER (ER ribosomes)

**FUNCTION:**

With the help of tRNA, ribosomes use information in mRNA to assemble proteins



- **Smooth ER** (no ribosomes): The smooth endoplasmic reticulum packages proteins for transport, synthesizes membrane phosolipids, and releases calcium. Other functions of the smooth endoplasmic reticulum include transformation of bile pigments, glycogenolysis (the breakdown of glycogen), and detoxification of many drugs and chemical agents.

**Rough ER** (has ribosomes on it) responsible for the synthesis of other proteins). Part of the rough ER is continuous with the nuclear envelope. The Golgi apparatus is also closely associated with the ER and recent observations suggest that parts of the two organelles, i.e. the ER and the Golgi complex, are so close that some chemical products probably pass directly between them instead of being packaged into vesicles (droplets enclosed within a membrane) and transported to them through the cytoplasm. These are called membrane bound ribosomes and are firmly attached to the outer cytosolic side of the ER About 13 million ribosomes are present on the RER in the average liver cell. Rough ER is found throughout the cell but the density is higher near the nucleus and the Golgi apparatus.

Ribosomes on the rough endoplasmic reticulum are called ‘membrane bound’ and are responsible for the assembly of many proteins. This process is called translation. Certain cells of the pancreas and digestive tract produce a high volume of protein as enzymes. Many of the proteins are produced in quantity in the cells of the pancreas and the digestive tract and function as digestive enzymes. The rough ER working with membrane bound ribosomes takes polypeptides and amino acids from the cytosol and continues protein assembly including, at an early stage, recognising a ‘destination label’ attached to each of them. Proteins are produced for the plasma membrane, Golgi apparatus, secretory vesicles, plant vacuoles, lysosomes, endosomes and the endoplasmic reticulum itself. Some of the proteins are delivered into the lumen or space inside the ER whilst others are processed within the ER membrane itself. In the lumen some proteins have sugar groups added to them to form glycoproteins. Some have metal groups added to them. It is in the rough ER for example that four polypeptide chains are brought together to form haemoglobin. In most cases proteins are transferred to the Golgi apparatus for ‘finishing’. They are conveyed in vesicles or possibly directly between the ER and Golgi surfaces. After ‘finishing’ they are delivered to specific locations.

## Golgi Apparatus

Golgi apparatus was discovered in the year 1898 by an Italian biologist Camillo Golgi. It was on of the first cellular organelles to be discovered and observed in detail due to its large size. The term Golgi apparatus was used in 1910 and in 1913 it first appeared in the scientific literature.

With the aids of special staining techniques the Golgi bodies were seen as densely stained region of the cytoplasm under the optical microscope. Under the electron microscope the Golgi apparatus is seen to be composed of stacks of flattened structures which contains numerous vesicles containing secretory granules. The newly synthesized proteins, found in the channels of the rough endoplasmic reticulum are moved to the Golgi body where the carbohydrates are added to them and these molecules are enveloped in a part of the Golgi membrane and then the enveloped molecules leave the cell. The Golgi

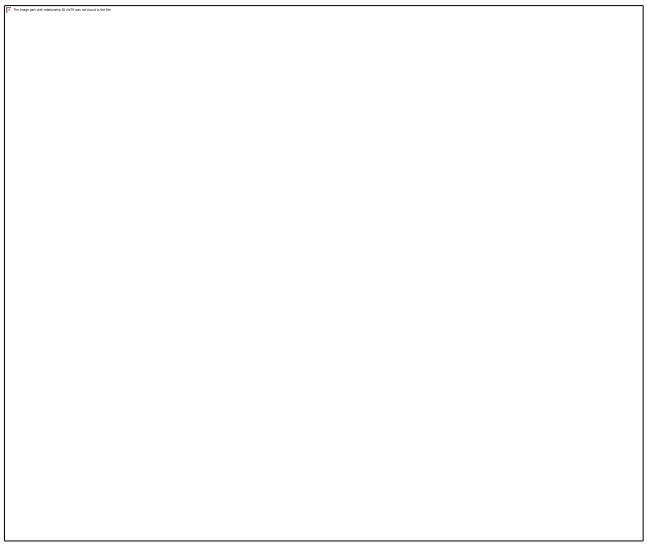
apparatus hence acts as the assembly factory of the cell where the raw materials are directed to the Golgi apparatus before being passed out from the cell.

## Golgi Apparatus Definition

**The Golgi complex is referred to as the manufacturing and the shipping center of the eukaryoric cell. The Golgi apparatus or the Golgi body or Golgi complex or Golgi is a cellular organelle present in most of the cells of the eukaryotic organisms. The Golgi bodies were identified by an Italian biologist Camillo Golgi in the year 1897 and was maned after him in the year 1898. The Golgi complex is responsible inside the cell for packaging of the protein molecules before they are sent to their destination. This organelles helps in processing and packaging the macromolecules like proteins and lipids that are synthesized by the cell, It is known as the 'post office' of the cell. The major function of the Golgi body is to modify , sort and package the macromolecules. It also helps in transportation of lipids around the cell and the creation of lysosomes.**

## Golgi Apparatus Structure

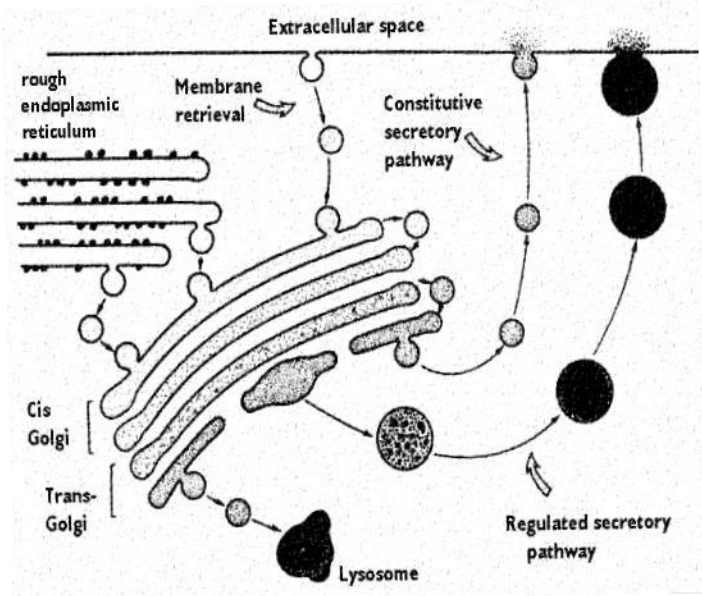
**The Golgi apparatus is a major organelle in most of the eukarytoic cells. They are membrane bound organelles, which are sac-like. They are found in the cytoplasm of plant and animal cells. The Golgi complex is composed of stacks of membrane-bound structures, these structures are known as the cisternae. An individual stack of the cisternae is sometimes referred as dictyosome. In a typical animal cell, there are about 40 to 100 stacks. In a stack there are about four to eight cisternae. Each cisternae is a disc enclosed in a membrane, it possess special enzymes of the Golgi which help to modify and transport of the modified proteins to their destination. The flat sacs of the cisternae are stacked and is bent and semicircular in shape. Each group of stacks is membrane bound and its insides are separated from the cytoplasm of the cell. The interaction in the Golgi membrane in responsible for the unique shape of the apparatus. The Golgi complex is polar in nature. The membranes of one end of the stack is different in composition and thickness to the membranes at the other end. One end of the stack is known as the cis face, it is the 'receiving department" while the other end is the trans face and is the "shipping department". The cis face of the Golgi apparatus is closely associated with the endoplasmic reticulum.**

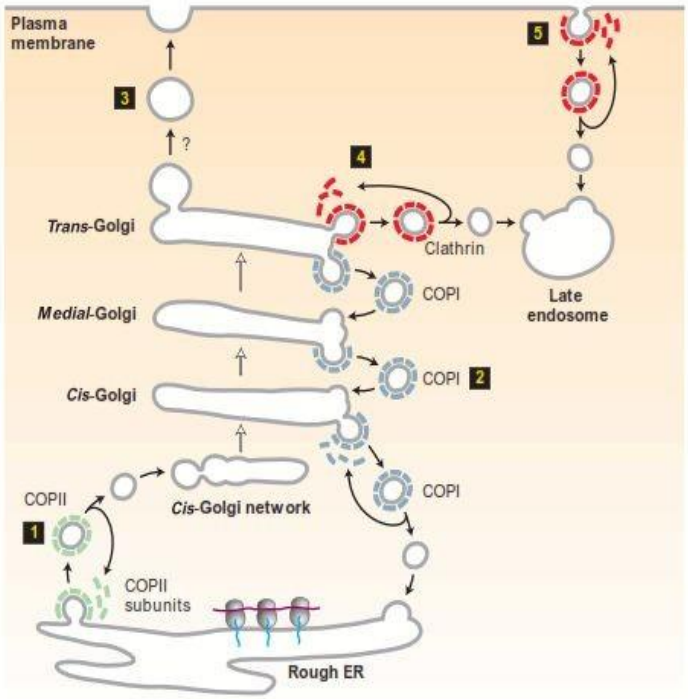


## Golgi Apparatus Function

1. **The cell synthesize a huge amount of variety of macromolecules. The main function of the Golgi apparatus is to modify, sort and package the macromolecules that are synthesized by the cells for secretion purposes or for use within the cell.**
2. **It mainly modifies the proteins that are prepared by the rough endoplasmic reticulum.**
3. **They are also involved in the transport of lipid molecules around the cell.**
4. **They also create lysosomes.**
5. **The Golgi complex is thus referred as post office where the molecules are packaged, labelled and sent to different parts of the cell.**
6. **The enzymes in the cisternae have the ability to modify proteins by the addition of carbohydrates and phosphate by the process of glycosylation and phoshphorylation respectively.**
7. **In order to modify the proteins the golgi complex imports substances like nucleotides from the cytosol of the cell. The modifications brought about by the golgi body might form a signal sequence. This determines the final destination of the protein.**
8. **The Golgi complex also plays an important role in the production of proteoglycans. The proteoglycans are molecules that are present in the extracellular matrix of the animal cells.**

9. **It is also a major site of synthesis of carbohydrates. These carbohydratres includes the synthesis of glycoasaminoglycans, Golgi attaches to these polysaccharides which then attaches to a protein produced in the endeoplasmic reticulum to form proteoglycans.**
10. **The Golgi involves in the sulfation process of certain molecules.**
11. **The process of phosphorylation of molecules by the Golgi requires the import of ATP into the lumen of the Golgi.**

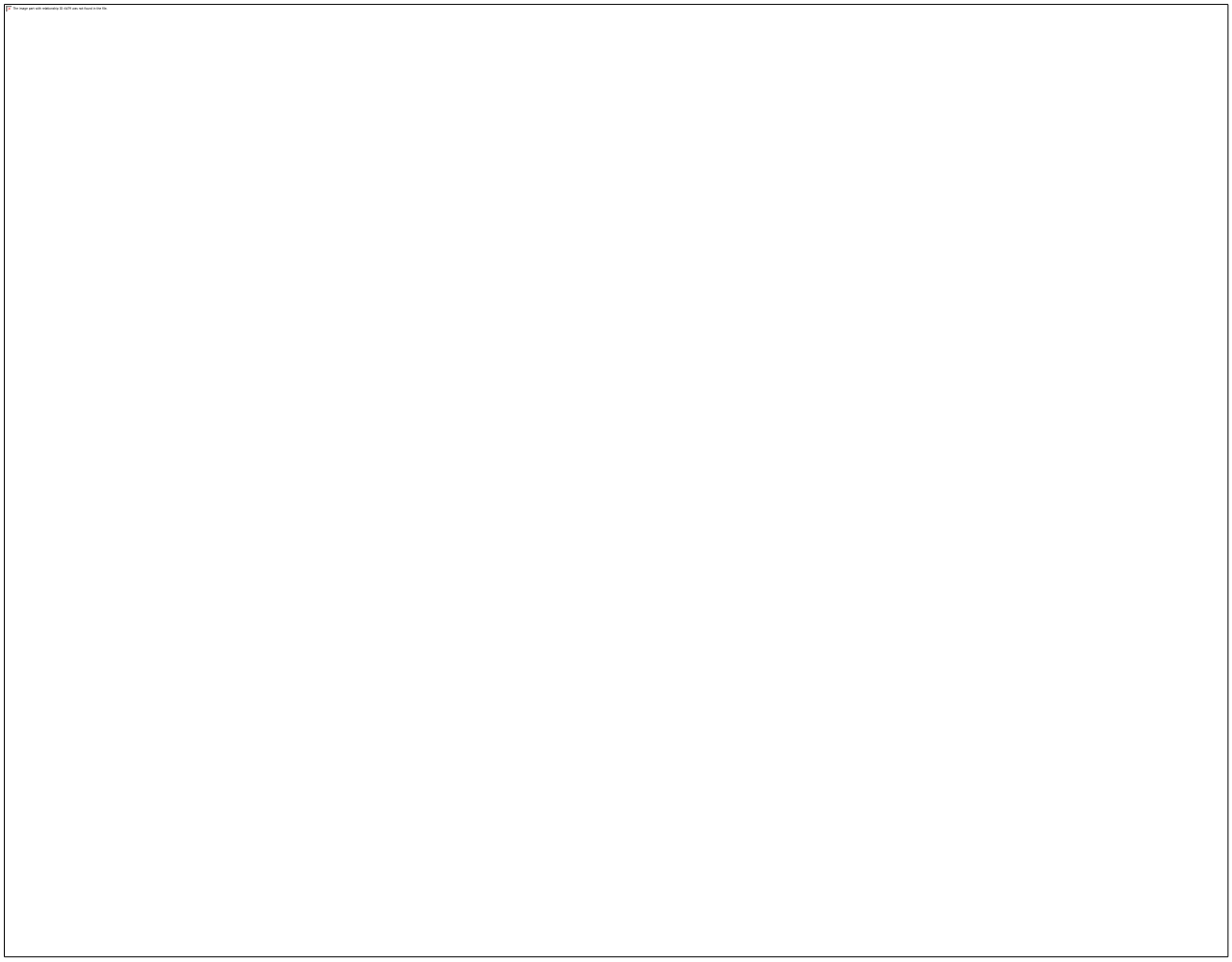


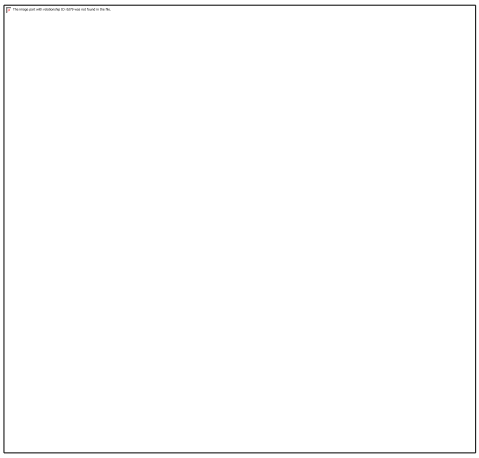

◀ **FIGURE 17-18 Involvement of the three major types of coat proteins in vesicular traffic in the secretory and endocytic pathways.** After formation of vesicles by budding from a donor membrane, the coats depolymerize into their subunits, which are re-used to form additional transport vesicles. COPII vesicles (1) mediate anterograde transport from the rough ER to the *cis*-Golgi/*cis*-Golgi network. COPI vesicles (2) mediate retrograde transport within the Golgi and from the *cis*-Golgi/*cis*-Golgi network to the rough ER. The coat proteins surrounding secretory vesicles (3) are not yet characterized; these vesicles carry secreted proteins and plasma-membrane proteins from the *trans*-Golgi network to the cell surface. Vesicles coated with clathrin (red) bud from the *trans*-Golgi network (4) and from the plasma membrane (5); after uncoating, these vesicles fuse with late endosomes. The coat on most clathrin vesicles contains additional proteins not indicated here. Note that secretory proteins move from the *cis*- to *trans*-Golgi by cisternal progression, which is not mediated by vesicles. [See H. Pelham, 1997, *Nature* **389**:17, and J. F. Presley et al., 1997, *Nature* **389**:81.]

# Cytoskeleton

- There are three main types of fibers in the cytoskeleton: **microtubules**, **microfilaments**, and **intermediate filaments**.



# Centriol

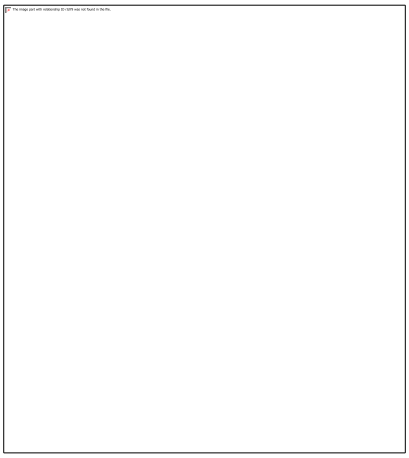


**Centrioles are built from a cylindrical array of only 9 microtubules, each of which has 3 subunits**

**As seen by EM**

**Sperm cells contain a pair of centrioles; eggs have none.**

**C.S. in cilium and flagellum (9+2)**



# Cell Cycle

In Prokaryotic cell

Cells, whether prokaryotic or eukaryotic, eventually reproduce or die. For prokaryotes, the mechanism of reproduction is relatively simple, since there are no internal organelles. The process consists of three distinct but short phases: first, a growth phase in which the mass of the cell is increased, then the chromosomal replication phase, and finally the chromosomes are separated and the cells are physically split into two independent new cells. In bacteria, these are referred to as the B, C, and D periods, respectively. Generation times for bacteria can vary from under half an hour to several days, although most bacterial cultures in laboratory settings and nutrient-rich media have generation times under a day.

In eukaryotic cell

The Eukaryotic Cell Cycle Most eukaryotic cells undergo a reproductive cycle to generate either another copy of themselves or to generate gametes (sex cells), and in doing so require a complex mechanism to govern the safe and accurate replication of their much larger (than prokaryote) genomes. Immediately following mitosis, the newly created cells are in the G1 phase. This is largely a growth phase, during which there is a lot of biosynthesis of proteins, lipids, and carbohydrates. However, there is no synthesis of new DNA at this time. G1 is the longest of the cell cycle phases in many cell types, and most of the physiological activity of a cell happens during G1. Following G1, the next phase of the cell cycle is the S phase, during which synthesis of new DNA occurs. In other words, the genome is being replicated during this phase; thus at the end of S phase, the cell has twice the normal amount of DNA. After S phase, the cell proceeds into G2, which provides an opportunity for the cell to perform a self-assessment and make final preparations (such as more cell growth, repairs of DNA) as necessary before it finally heads into mitosis. Mitosis, or M phase, is primarily (1) the breakdown of the nucleus, (2) re-distribution of the DNA to opposite sides of the cell, and (3) formation of two new nuclei around that DNA, and cytokinesis, the final splitting of the cell itself.

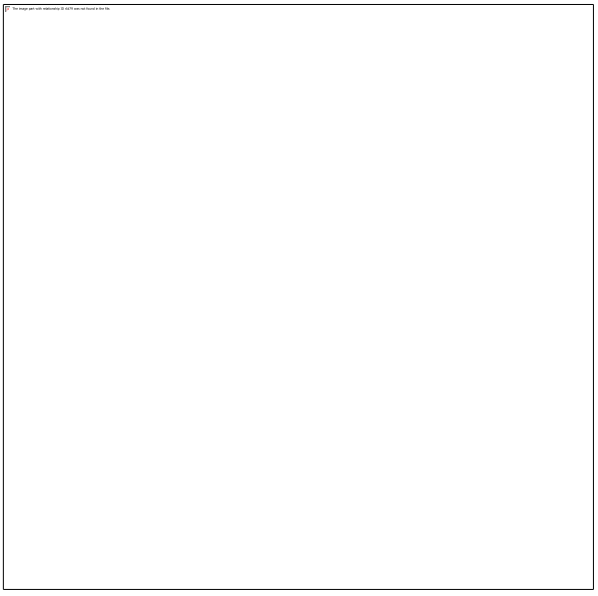


Fig: Cell Cycle

# Lecture 8; Cell death

## Cell death

## Types of cell death: انواع الموت الخلوي \ □□□□ □□□□□ □□□□□□□□□

1. **Necrosis: caused by:**

    - Mechanical damage
    - Exposure to toxic chemicals

2. **Programmed cell death (PCD) or apoptosis: Cell suicide: caused by:**
    i. -Internal signals
    ii. -External signals

- Apoptosis or programmed cell death, is carefully coordinated collapse of cell, protein degradation , DNA fragmentation followed by rapid engulfment of corpses by neighbouring cells.

**Why should a cell commit suicide?**

**لماذا تموت الخلية بطريقة الموت الخلوي المبرمج** \ □□□□□□ □□□□□□□ □□□□□ □□ □□□□ □□ □□□□

1. **Apoptosis is needed for proper development**

    Examples:

    a. **The resorption of the tadpole tail**
    b. **The formation of the fingers and toes of the fetus**
    c. **The sloughing off of the inner lining of the uterus**
    d. **The formation of the proper connections between neurons in the brain**
2. **Apoptosis is needed for destroying injured cells,** Examples:
    a. **Cells infected with viruses**
    b. **Cells of the immune system**
    c. **Cells with DNA damage**
    d. **Cancer cells**

**What makes a cell decide to commit suicide?**

1. **Withdrawal of positive signals**
    a. **growth factors for neurons**
    b. **Interleukin-2 (IL-2)**
2. **Receipt of negative signals**
    a. **increased levels of oxidants within the cell**

b. **damage to DNA by oxidants**
c. **death activators which include:**

i. **Tumor necrosis factor alpha (TNF-□)**
ii. **Lymphotoxin (TNF-β)**
iii. **Fas ligand (FasL)**

**History of cell death / apoptosis research**

- **1800s** **Numerous observation of cell death**
- **1908** **Mechnikov wins Nobel prize (phagocytosis)**
- **1930-40** **Studies of metamorphosis**
- **1948-49** **Cell death in chick limb & exploration of NGF**
- **1955** **Beginning of studies of lysosomes**
- **1964-66** **Necrosis & PCD described**
- **1971** **Term apoptosis coined**
- **1977** **Cell death genes in *C. elegans***
- **1980-82** **DNA ladder observed & ced-3 identified**
- **1989-91** **Apoptosis genes identified, including bcl-2, fas/apo1 & p53, ced-3 sequenced**

## APOPTOSIS: Morphological steps

1. cell shrinkage
2. organelle reduction
3. mitochondrial leakage
4. chromatin condensation
5. nuclear fragmentation
6. membrane blebbing & changes
7. phagocytosed by a macrophage

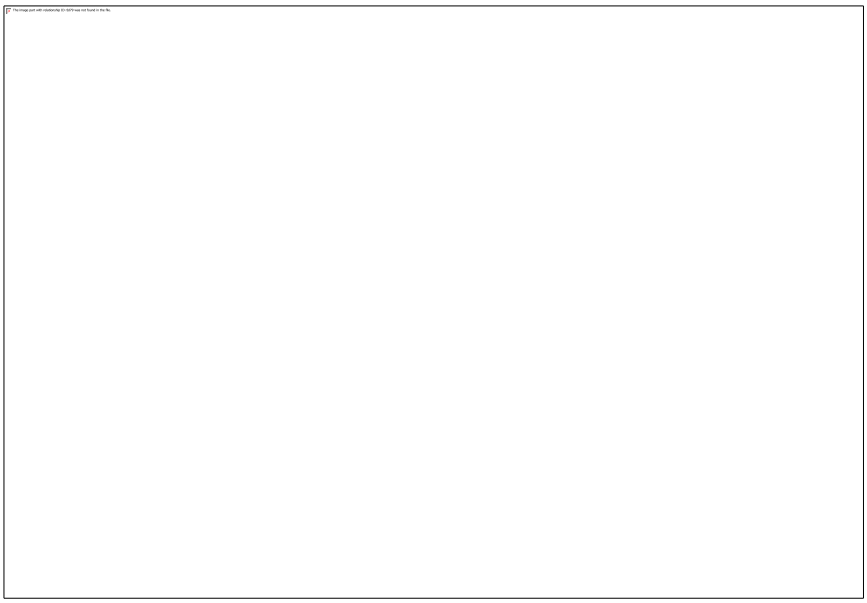
## *Caenorhabditis elegans*: Is a nematode which became a model for the genetic study of apoptosis

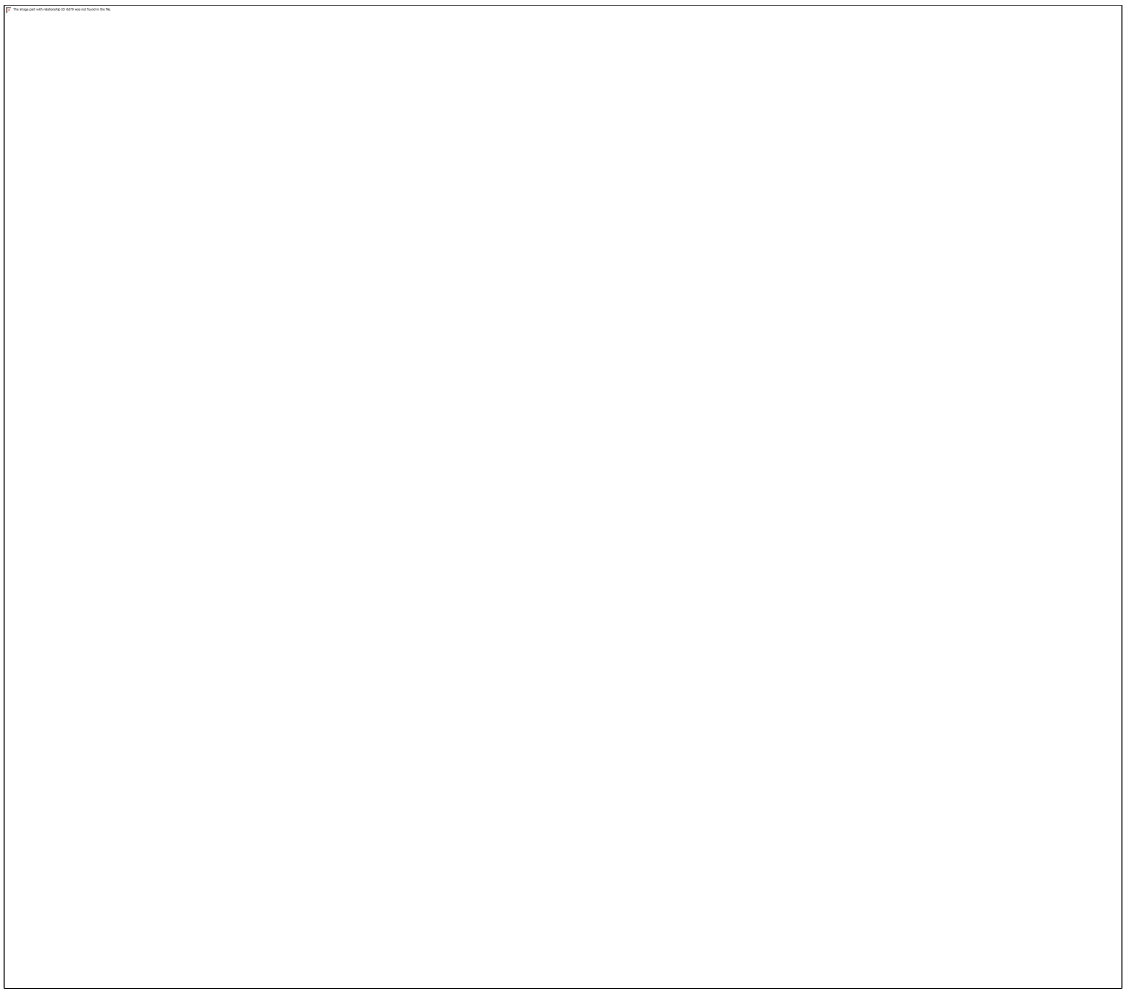
**MAJOR PLAYERS IN APOPTOSIS**

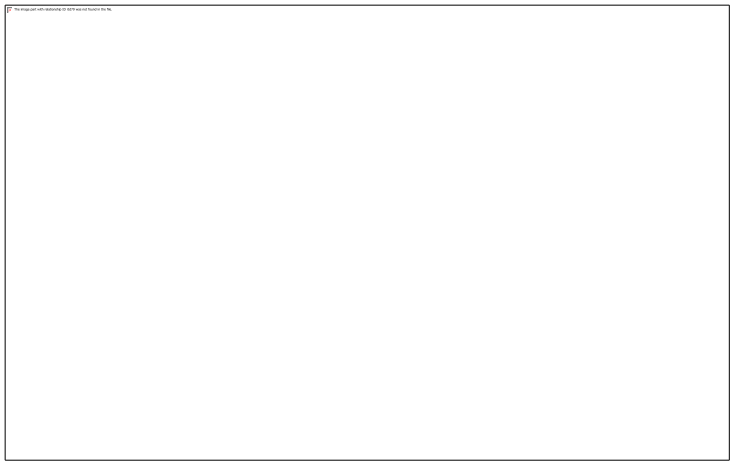
1. **<u>Caspases</u> (proteases)**
2. **Adaptor proteins**
3. **TNF & TNFR family**
4. **Bcl-2 family**

## Ligand-induced cell death

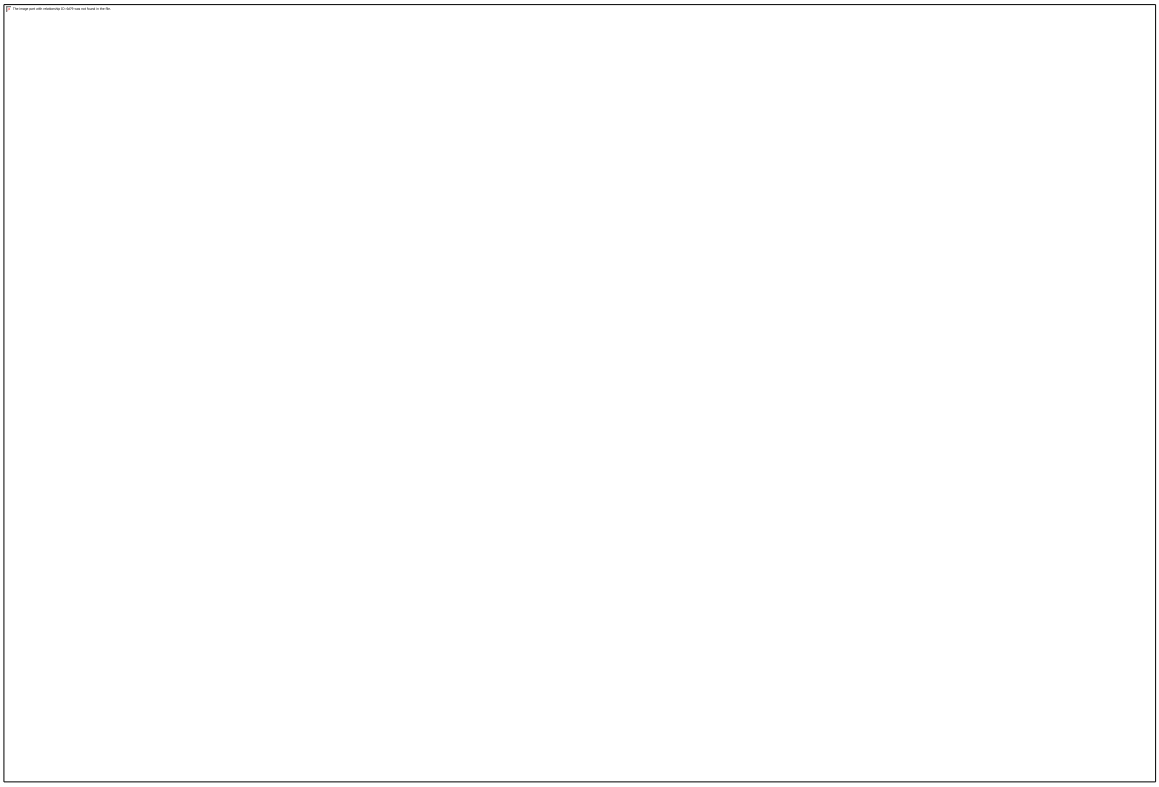
| Ligand | Receptor |
|---|---|
| **FasL** | **Fas (CD95)** |
| **TNF** | **TNF-R** |
| **TRAIL** | **DR4 (Trail-R)** |

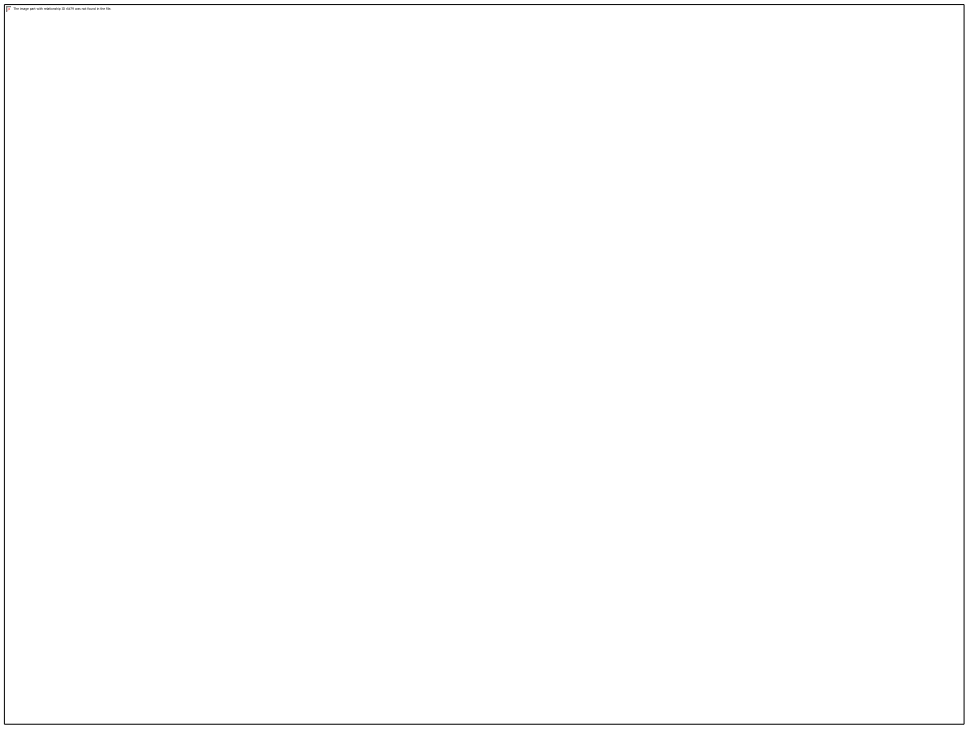






Apoptotic bodies containing chromatin marginated nuclei





# Lecture 9: Stem cells

**Stem cells are cells found in all multi cellular organisms. They are characterized by the ability to renew themselves through mitotic cell division and differentiate into a diverse range of specialized cell types.Stem cells are cells that divide by mitosis to form either**

- **two stem cells, thus increasing the size of the stem cell "pool",**
- **or**
  - **one daughter that goes on to differentiate, and**
  - **one daughter that retains its stem-cell properties.**

**The two general types of mammalian stem cells are: embryonic stem cells that are isolated from the inner cell mass of blastocysts, and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.**

**Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies**

**Types of stem cell according to the capacity of differentiation:**

- **Totipotent : stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable, organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.**
- **Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells,i.e. cells derived from any of the three germ layers.**
- **Multipotent stem cells can differentiate into a number of cells, but only those of a closely related family of cells**
- **Oligopotent stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.**
- **Unipotent cells can produce only one cell type, their own, but have the property of self-renewal which distinguishes them from non-stem cells (e.g. muscle stem cells).**

# Lecture 10: Biology of Cancer cell

**Cancer cell**

**a cell that divides and reproduces abnormally with uncontrolled growth. This cell can break away and travel to other parts of the body and set up another site, referred to as metastasis**

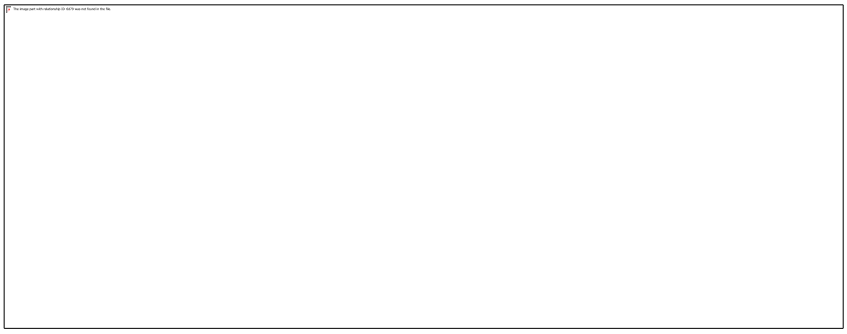
**Tumor**

**An abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function**

**Two types of tumor:**

**Benign Growths and Malignant Tumors**

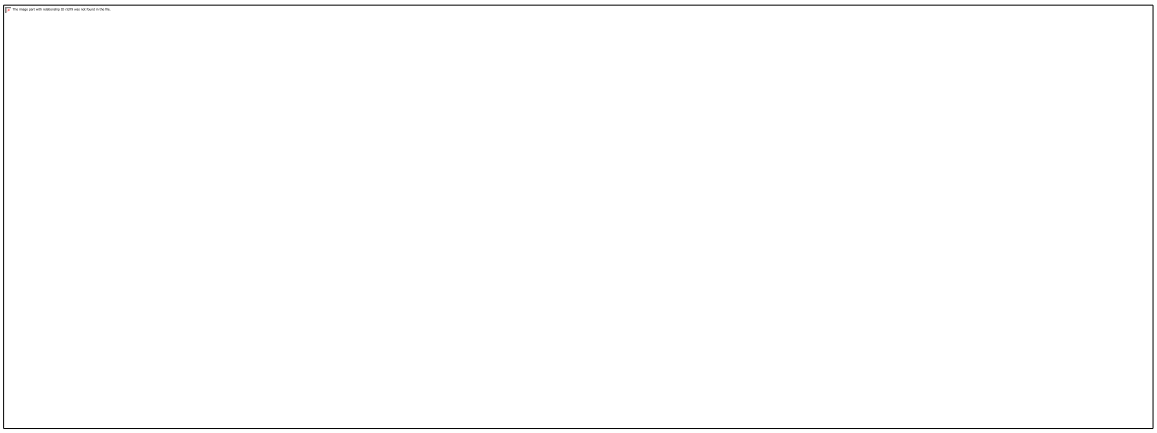
**Benign growths and cancers (malignant tumors) are not the same thing. As the points below indicate, benign tumors are generally not life threatening while malignant tumors typically are**.



| Benign Growths | Malignant Tumors |
|---|---|
| 1. Encapsulated | 1. Not-encapsulated |
| 2. Non-invasive | 2. Invasive |
| 3. Limited growth | 3. Uncontrolled growth |
| 4. Doesn't metastasize | 4. May metastasize |
| 5. Rarely lethal | 5. Often lethal |

**Tissue Culture: Normal vs. Malignant Cells**

The growth of normal and transformed cells in culture reflects the differences between them.



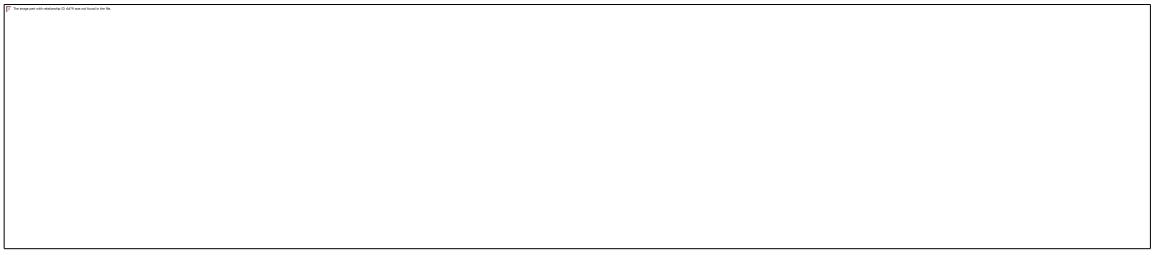
**Normal cells**

**• Normal cells show "Contact Inhibition" of growth & of cell division**

**• When they make contact, they stop moving and then move off in the opposite direction; until they contact another cell; once they are surrounded on all sides, they stop moving completely**

**• Contact also inhibits cell division, so once a cell is surrounded by other cells, it stops dividing**

**• These behaviors result in the formation of a monolayer or pavement of cells**



**Metastasis: The Formation of Secondary Tumor**

**Cells in an invasive tumor can separate off, digest a pathway through the extracellular matrix and enter the bloodstream. When they reach a permissible site, they can exit (extravasation) the blood stream and set up shop as secondary tumor (metastases).**

**Matrix Metalloproteinases (MMPs) & ECM Digestion**

**Recently a lot of research has focused on matrix metalloproteinases (MMPs) as targets for the development of anti-cancer drugs. For metastasis to occur, the cancer cell must be able to leave the original tumor. This requires that it penetrate through various types of extracellular matrices. The basal lamina are dense, highly organized extracellular matrix structures. Some cancer cells secrete MMPs but in most cases the cancer cells induce local normal cells to secrete MMPs. Either way, the MMPs digest the protein and proteoglycan components of the basal lamina making a hole through which the cancer cell can move. Drugs that inhibit MMPs, prevent this digestion and the ability of the cancer cell to migrate out of the tumor.**