Lesson 1

CYTOLOGY

AIM

Describe and understand the microscopic anatomical features of human cells

Before we investigate the gross anatomical structures of the body, it is important to understand the individual units that make up all tissues; cells. Many vital processes occur in the cell. Different cells have different structures, numbers of organelles and so on, to enable them to perform their specific functions. These cells together form tissues which in turn group to form organs and organ systems that combine different cell types to enable systems to perform coordinated functions.

In order to investigate systemic and regional anatomy later in the course, it is first important that we look at the microscopic anatomy of cells. We will start by discussing common organelles and structures, before examining some of the specialised structures found in some cell types.

COMMON ORGANELLES & STRUCTURES

Plasma Membrane

The plasma membrane encloses a cell, isolating its interior from the external environment. Its structure allows it to be semi-permeable and facilitates the movement of substances across the membrane, as well as the response to external stimuli which never enter the cell. It is not an organelle.

The membrane is a two layer lipid. The molecules making it up are phospholipids, which are themselves made up of fatty tails on a hydrophilic phosphate head group. The fatty tails associate with the fatty tails of other phospholipids, forming a kind of sandwich, with water-loving phosphate groups sandwiching fatty lipid tails.

Embedded in the membrane are a variety of molecules.

Lipids

Aside from the phospholipids which make up the bilayer, several other lipids are also embedded in the plasma membrane. Glycolipids are found on the external face of plasma membranes and make up about 5% of total membrane lipids. Cholesterol lipids have a stiffening effect on plasma membranes and make up about 20% of total membrane proteins. The remainder of the membrane lipids are phospholipids.

Proteins

There are a variety of proteins found in or associated with plasma membranes. Those that span right through the membrane are integral proteins. These include:

- Channels
  Allow movement of molecules into and out of cells.

- Transporters
  Move molecules across the membrane into and out of cells.

- Receptors
  These allow cells to communicate with the external environment. Molecules bind to the external portion of a receptor, and are either internalised, or cause a change in the receptors shape that triggers a cascade of events inside the cell.

- Enzymes
  Perform the same function as enzymes within the cell, but are located in the plasma membrane.

Proteins that are found on one face of the membrane, but do not span right through the membrane are known as peripheral proteins. These have a variety of functions, as antigens, enzymes or anchors for example.

Cytoplasm
The cytoplasm is not solely the gel-like fluid found in the interior of cells. The term encompasses both this semi-fluid component, known as the cytosol, and the organelles and inclusions suspended within it. Inclusions are different in different cells and may include vacuoles, glycogen, lipid droplets and pigments. The cytoplasm is not found in the interior of organelles.

Cytosol
This gel-like substance contains water, suspended proteins, ribosomes, amino acids, saccharides and colloids. Colloids are suspended aggregates of large organic compounds that have an overall electrical charge. The charges force individual colloids away from each other, keeping them distributed throughout the cell. The cytosol is a highly organised matrix that holds organelles and cytoskeletal components and the enzymes and reactants required to perform a variety of processes, including glycolysis and signal transduction from the cell surface to the nucleus. The cytosol is a part of the cytoplasm.

Cytoskeleton
The cytoskeleton is literally the skeleton of the cell. They have a range of functions including maintaining the structure of the cell. (The function of the cytoskeletal elements will be discussed in detail in physiology II). There are three elements that make up the cytoskeleton, micro and intermediate filaments and microtubules.

Microfilaments
Microfilaments are the thinnest of the cytoskeleton at a diameter of 7 nanometres. They are made up of a single, globular protein, actin. The filaments are linear single stranded polymers that coil around each other in a helical fashion. The helical shape occurs because each actin molecule is rotated 166 degrees from its predecessor. Microfilaments are polar proteins, with a minus (also known as pointed) end and a positive (also known as barbed) end.

Intermediate Filaments
As the name suggests, these filaments are larger in diameter than microfilaments, and smaller than microtubules. Though they are diverse, they are all between 9-11nm in diameter in their final conformation. They are made up of a long helical chain with two globular ends. They form dimers (two strands twisted together). They can then assemble into anti-parallel tetramers (two dimers interacting with each other). Unlike the other elements of the cytoskeleton, because of their arrangement, intermediate filaments have no polarity.

Intermediate filaments made by made up of a variety of different proteins, and are categorised as:

- Type I – Acidic Keratins
- Type II – Basic Keratins

These are found in skin cells and cells of external protective structures such as hair and nails.

- Type III

These filaments may be made up of any of four different proteins and are different in different cell types. They are the components of the cytoskeleton that anchor the organelles in place.

- Type IV

A group of filaments found in muscle and nerve cells. Important in protecting cells from mechanical stress, allowing muscle contraction, or axon structure.

- Type V – Nuclear Lamins

As the name suggests, these fibres are found in nuclei. They provide structure and then in mitotic cells, are important for the break down and re-building of the nucleus.

- Type VI – Nestin

Found in the axon of nerve cells and also in muscle cells. Forms tetramers with other filament proteins. Important in proliferating cells.

Microtubules
These are the largest components of the cytoskeleton, ranging from several hundred nanometres to a relatively enormous 25 micrometers. Microtubules have a variety of functions, in intracellular transport and during cell division. They form a sort of cellular highway along which vesicles and organelles can be shuttled.

Microtubules are all made up of the protein tubulin, which comes in two isoforms, alpha and beta. Tubulin is a globular protein. Alpha and beta tubulin molecules bind together forming small dimers. These link to other dimers to form linear structures known as protofilaments. Protofilaments take a helical conformation, forming hollow cylindrical structures, the microtubules.

Microtubules are polar. Atone end polymerisation is occurring and at the other depolymerisation occurs. This makes the microtubules dynamic (changing) instable. They can form singlets (single cylinder) or associations of cylinders, doublets and triplets. Triplets make up the centrioles.

Nucleus
This is a roughly spherical membrane bound organelle that houses the genetic material of the cell. The nuclear membrane (or envelope) is made up of two parallel phospholipid bilayers. There is a microscopic gap between the two membranes, known as the perinuclear cisterna. Molecules move in and out of the nucleus via large nuclear pores. Ribosomes stud the outer face of the outermost membrane and this membrane is continuous with the rough endoplasmic reticulum. The nucleus can be position anywhere in a cell; it does not have to be central. Some cells have more than one nucleus.

Inside the nucleus DNA is present in the form of chromatin. DNA can also exist in a condensed structure known as chromosomes. This is the structure seen in cells that are preparing to divide. To form these structures the DNA double helix winds around proteins known as histones (which associate to form an 8 histone ball), forming a complex known as a nucleosome. Between nucleosomes the strands of DNA are known as linker DNA. The nucleosomes fold together to form a cord like structure known as a chromatin fibre – the prevalent DNA structure in cells that are not dividing. IN dividing cells the chromatin fibres fold into large loops. During the cell division process, the DNA is copied, and the loops coil further to form chromatids. Two chromatids for a chromosome. The end of a chromatid is the telomere, the central point where two chromatids join to form a chromosome is the centromere. The arms of the chromosome can be different lengths, the shorter two are the p arms, and the longer two are the q arms.

Nucleolus
This is a small, spherical body found in the nucleus. It is not bound by its own membrane and there may be more than one in a nucleus. The nucleolus is composed of DNA, ribosomes and proteins. The nucleolus is the major site of translation in a cell. That is, the conversion of the mRNA formed by copying the DNA code of a gene, into a protein.

Centrosome & Centrioles
Centrosomes are important for organising elements of the cytoskeleton (microtubules) for cell division. They are formed by pairs of centrioles that are orientated at right angles to each other. Between the centrioles is pericentriolar material (also known as the microtubule organising centre). The centrioles themselves are cylindrical structures of nine triplets of microtubules.

Endoplasmic Reticulum (ER)
There are two types of ER in cells, rough and smooth. They are distinguished by the presence or absence of ribosomes on their outer face. They are continuous with one another and form a folded, membranous organelle, with enclosed regions known as cisternae.

The Rough ER
The rough ER, because of its bound ribosomes, is a region of protein synthesis. Newly synthesised proteins may be transferred into cisternae for storage, or modification. The folding of the membrane maximises the surface area available for protein synthesis

The Smooth ER
With no ribosomes, the surface of this membranous organelle is smooth. The organelle is involved in the synthesis of a range of molecules and also for detoxification.

Ribosomes
Ribosomes may be found in the cytoplasm (free ribosomes) or on the rough ER (bound ribosomes). Structurally, they are composed of proteins and ribonucleic acids. These form a large and a small subunit that lock together to form the functional ribosome. The small subunit binds mRNA and the large subunit has an A site and a P site, where tRNAs bind. The tRNAs bring amino acids to the ribosome to make the new protein. In some cases, a single mRNA may be translated by a cluster of ribosomes. These clusters are known as polyribosomes. Free ribosomes have a characteristic rosette shape. Those bound in the ER insert newly forming proteins into the lumen of the cisterna.

Golgi Apparatus
This is another membranous organelle that is located near to the nucleus. Unlike the ER it has a slightly more regular structure, forming individual flattened sacs (cisternae) that stack against each other. Transport of molecules between the discontinuous cisternae occurs via small sacs that bud from cisternae, known as the Golgi vesicles. The Golgi apparatus receives molecules from the rough ER via transport vesicles which fuse with the cis cisternae (the face closest to the rough ER). Golgi vesicles bud from the lateral ends of the cisternae. From the trans cisternae vesicles may bud off to become lysosomes, or secretory vesicles which fuse with the plasma membrane to expel molecules from the cell.

Mitochondria
A cell can have a number of mitochondria in its cytoplasm. The more energy a cell requires the more mitochondria it will have.   A mitochondrion has a jellybean like shape, being encased by two phospholipid bilayers. Like the plasma membrane these are semi-permeable membrane studded with a variety of proteins. The outer bilayer has special porins that allow molecules up to a certain molecular weight (about 5000 Daltons) to move freely across the outer membrane. The space between the bilayers is the intermembrane space. This is roughly the same composition as the cytoplasm because of the porins. However, the inner membrane does not have these porins, so not all molecules crossing the outer bilayer can move through the inner bilayer.

The inner bilayer is convoluted, and forms cristae. The convolutions serve to increase the surface area of the membrane. The membrane has specific proteins that allow for the transport of specific molecules across it. It is here also that enzymes are embedded, functioning to catalyse many of the reactions of glucose metabolism and ATP production.

The cristae house a massive array of proteins, enzymes for ATP production, RNA and even unique DNA, known as mitochondrial DNA. This allows mitochondria to independently produce their own proteins and divide to form new mitochondria.

Lysosome
These are membrane enclosed organelles that are filled with powerful digestive enzymes known as acid hydrolases. They are formed by budding of the trans face of the Golgi and so, they are enclosed by the same lipid bilayer. Lysosomes are roughly spherical in shape and merge with endosomes containing molecules for digestion. They are particularly abundant in immune cells.

Peroxisome
These are small self-replicating organelles that detoxify harmful substances (a poorly understood process, but peroxisomes do not have their own DNA, unlike the self-replicating mitochondria). They are surrounded by a lipid bilayer with embedded protein receptors that are used to gather proteins required for replication. Internally, they have a variety of oxidases and other enzymes with a crystalline core made of urate oxidase.

SPECIALISED ORGANELLES & STRUCTURES

Sarcolemma

This is the term given for the plasma membrane of muscle cells (smooth and skeletal). Like other cells, the membrane is a lipid bilayer. Characteristically however, the sarcolemma invaginates into the cell itself. This forms a special structure known as the t-tubule, which we will discuss later. Overlying the lipid bilayer is a polysaccharide coat and many collagen fibrils. The sarcolemmas of adjacent muscle cells are all continuous with the muscle's tendon. Importantly the sarcolemma regulates entry of ions, potassium, sodium and calcium, all crucial for muscle contraction.

Sarcoplasmic Reticulum

This is a modified smooth endoplasmic reticulum found in muscle cells (smooth and skeletal). Calcium channels in the membrane allow the storage of calcium ions and the pumping of them out into the cytosol, to allow for muscle contraction.

T-Tubules

T-Tubules are formed by invaginations of the sarcolemma. They run at right angles to the long axis of the muscle cell (cardiac and skeletal) and are studded with calcium channels. They sit adjacent to the terminal cisternae of the sarcoplasmic reticulum, allowing rapid movement of calcium ions into the cell. The standard arrangement of a t-tubule intermediate to two terminal cisternae is known as a triad.

Undulipodia

Flagella and cilia are together known as undulipodia, cellular structures (not organelles) that provide locomotion, or the movement of molecules over the surface of stationary cells. They are not present on most human cells. They are both similar in structure, being long, thin, tail or whip-like structures. The structure is supported by microtubules in a characteristic nine doublet arrangement, with a core of two single microtubules. This is known as the axoneme and is the skeleton of the undulipodia. The microtubule doublets are linked by the intermediate filament nexin. Each doublet also has two bound dynein proteins. Dynein uses ATP to provide the energy and force required for movement of the flagellum or cilium. From each doublet a radial spoke extends towards the core of the axoneme. The axoneme is flexible allowing the undulipodia to move. Cilia and flagella move very differently.

There are two types of cilia. Motile and non-motile.

- Motile

Many per cell, beat in a single direction, move molecules across cell surface.

- Non-motile

Typically found singularly on a cell, serve a sensory function. Do not have the central pair of microtubules, and have only one dynein protein per doublet.

Microvilli

These are fine hair-like extensions of the plasma membrane that serve to increase a cell's surface area. They are found on the apical surface of many epithelial cells. The external face of the microvilli, outside of the plasma membrane is a fine coating of a glycoprotein known as glycocalyx. Internally they have a skeleton of microfilaments. The filaments are arranged in bundles of 20-30 filaments. Microvilli contain cytoplasm in which a high concentration of enzymes are suspended. In the intestinal villi, the cellular microvilli are packed with digestive enzymes, to begin metabolism of absorbed nutrients.

THE ANATOMY OF CELLULAR DIVISION

Review

The cell cycle is broken up into two stages – interphase and mitosis. Interphase is further divided into the following phases (we will list them in order following mitosis):

- G1

Gap 1. This is a period where the new daughter cell increases its metabolic activity after cell division has finished. The cell is producing proteins that are needed to allow it to perform its function.

- S phase

Synthesis (DNA) phase. This is the period when the cell's genome is replicated.

- G2

Gap 2. Another period of high metabolic activity. However, compared to G1, the cell is now producing the proteins it will need for the upcoming mitosis.

Mitosis can be broken down into 6 phases which we will discuss further later in the lesson.

Characteristic Interphase Structures

DNA structure varies throughout the cell cycle. In interphase, many genes are being transcribed. This requires them to be in a loose, open structure, so regulatory proteins can bind to them. This structure is known as euchromatin, the DNA is loosely wound around the histones. Genes that are not being transcribed are found in regions of heterochromatin. Heterochromatin is a closed, tight DNA structure, where the DNA is wrapped tightly around histones.

During S phase, the entire genome is copied, resulting in chromosomes made up of two identical 'sister' chromatids. During replication of DNA, a replication fork forms. An enzyme known as helicase (the suffix –ase indicates something is being broken or broken down) breaks the bonds that hold the two strands of DNA together in the double helix conformation. The point where the separation is the replication fork, where the original double helix has branched into two single strands that are then replicated to form their own new double helices.

Characteristic Mitosis Structures

As cells enter M phase, or mitosis they have gone from having single chromatids to chromosomes made up of two chromatids bound together. We will look at each phase of mitosis individually, in the order they occur in the cell:

Prophase

Chromatin is condensed into chromosomes. These are clearly visible under a microscope. The point where the chromatids are joined is the centromere. The distal ends of each chromatid are the telomeres. The centrosome is replicated during S phase and so two are present in prophase, adjacent to the nucleus and in relatively close proximity to each other. These each start to build microtubules and each centriole begins to be pushed away from the other.

Prometaphase

The centrosomes are on opposite sides of the nucleus with the microtubules they have produced spanning between them and creating the mitotic spindle. The centrosomes are said to be at opposite 'poles' of the cell. In this phase, the nuclear envelope breaks down, so the microtubules run through what used to be the nucleus. Protein ring structures known as kinetochores are formed at the centrosome of each chromosome. One attached to each chromatid. The microtubules attach to the chromatids via these kinetochores.

(Note: You will sometimes see Prophase and Prometaphase combined and referred to as Prophase, they are not always viewed as separate/distinct phases)

Metaphase

The chromosomes line up vertically along the central axis of the cell, intermediate to the poles of the cell. This is known as the metaphase plate. The lining up of the chromosomes is a feature that allows scientists to distinguish cells that are in metaphase from those in other stages of the cell cycle, using a microscope.

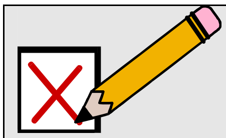
Anaphase

In this phase the bonds between sister chromatids are broken. The sister chromatids are then pulled by to the opposite poles of the cell as its attached microtubule shortens. The centrioles are pushed further apart, right to the poles of the cell, dragging the chromatids, which are attached via the microtubules, with them. This results in two identical sets of DNA/centrosomes separated from each other on opposite sides of the cell.

Telophase
The cell becomes elongated as the centrosomes continue to be pulled to the poles of the cell. This gives the cell a slightly oval shape. In this phase the nuclear envelope begins to reassemble, one around each set of DNA. Chromatids decondense so that the cell now has two nuclei, full of chromatin.

Cytokinesis
Cytokinesis occurs with telophase. As the nuclear envelopes are forming and the DNA decondensing the cell begins to pinch in along the short axis of the cell. This pinching forms a depression, known as the cleavage furrow. This furrow continues to deepen; pinching the cell until it completely separates into two identical daughter cells, with one nucleus each.

Using the anatomical features of cells, it is possible to distinguish cells in different phases, by microscopy at high magnification. This is important in scientific research investigating events occurring at very specific times during the cell cycle.



SELF ASSESSMENT
Perform the self assessment test titled ‘Self Assessment Test 1.1.’
If you answer incorrectly, review the notes and try the test again.

SET TASK
The process of producing, processing and exporting a protein from a cell involves many different organelles. Sketch a diagram of a cell, with all the organelles that would be involved in this process. Label each and note the events that would occur in them. Include the structures that permit their movement between organelles.

ASSIGNMENT
Download and do the assignment called ‘Lesson 1 Assignment’.