http://www.bristol.ac.uk/phys-pharm/media/teaching/

Cell and its organelles -1-

The main text for this lecture is:
Vander's Human Physiology
+ some additions from Germann & Stanfield

For advanced readers: Lodish et al "Molecular Cell Biology" and Cooper "The Cell. A Molecular Approach"

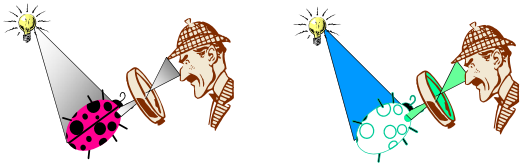
INTRODUCTION

Types of microscopes

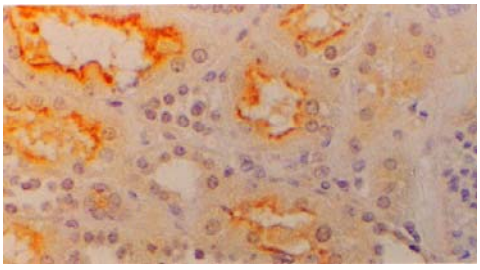
Light microscope

Conventional

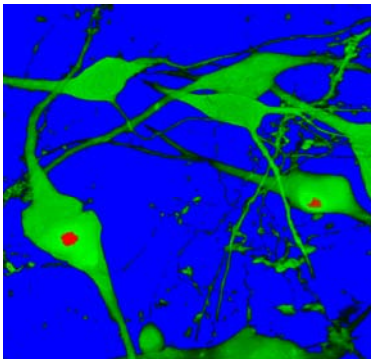
Fluorescent



Normal human kidney – light microscope

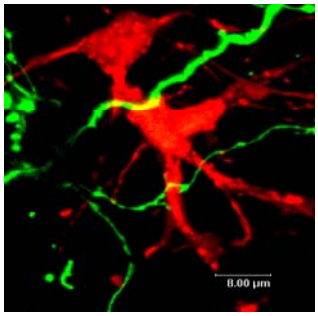


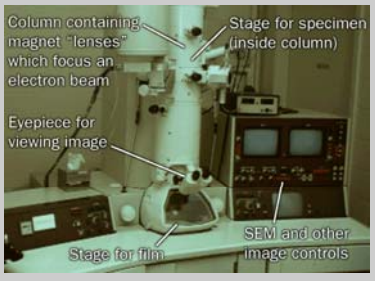
Living nerve cells (neurones) imaged using fluorescence in a slice of brain tissue

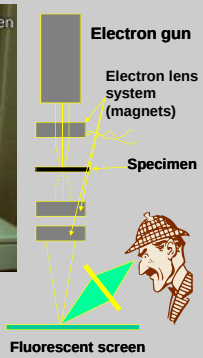


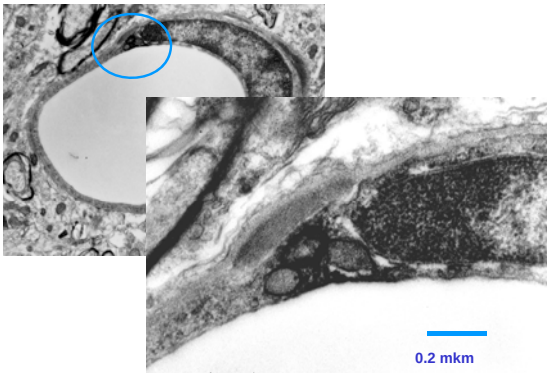
Limit of resolution ~ 0.4 mkm (recently ~ 0.1 mkm!)
(1mkm = 0.000 001 of a meter)

Fluorescent microscopy allows a very good separation of individual colours. 2, 3 and even 4 separate colours may be used to visualise different proteins at the same time



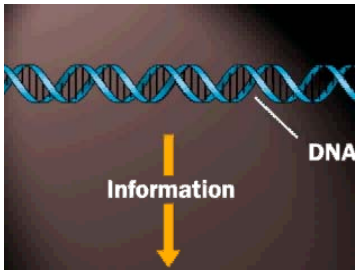






Limit of resolution ~ 0.004 mkm
(1mkm = 0.000 001 of a meter)

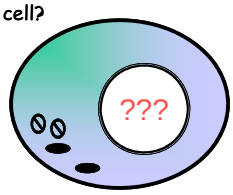
THE CENTRAL DOGMA



Genes (parts of DNA) -
Intermediates (messenger RNA) -
Proteins (cell structure and function)

What is a "eukaryotic" cell?

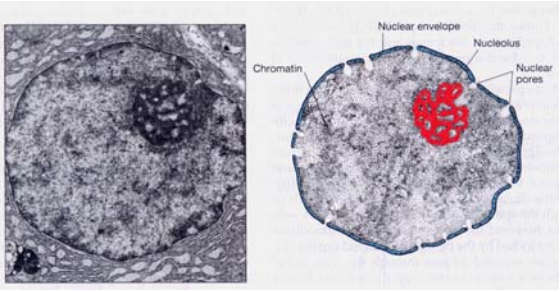
Καριοη - nucleus.



Cell = nucleus + cytoplasm.
Cytoplasm = cytosol + organelles.

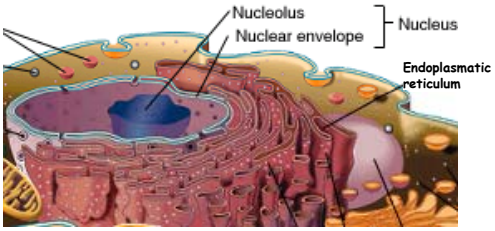
Nucleus contains the ultimate value of the cell:
its genetic code.

Consider: Why the first primitive cells could do without a nucleus? (In fact, bacteria still do not have one!)

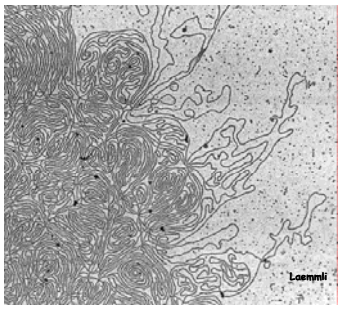


1. Nuclear envelope (2 layers of membrane)
2. Nuclear pores (tightly controlled gates!)
3. Chromatin (loose strings of DNA, the genetic material)
4. Nucleolus

Nuclear membrane is a continuation of the "endomembrane".

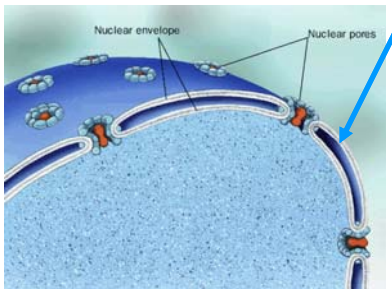


What is chromatin?



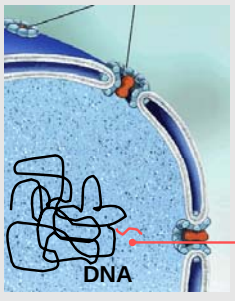
DNA – the molecule which contains the genetic code. Between the divisions it needs to be loosely spread to allow access to its various parts.

Nuclear pores are not just "holes"



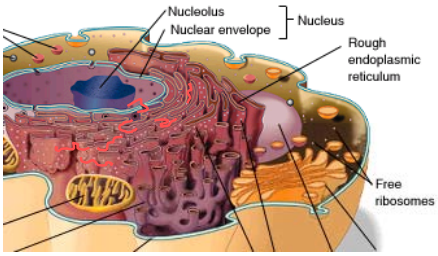
These are specialised micro-channels which are highly selective and allow traffic of specific molecules from the nucleus and into the nucleus.

Nuclear pores visualised by freeze-fracture technique

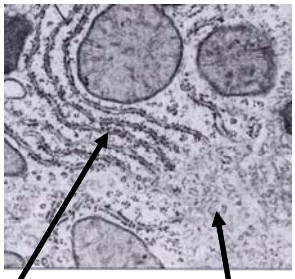


1. There is a continuous exchange of information between the nucleus and cytoplasm.
2. Specialised proteins come into nucleus, they bind to DNA to regulate production of specific messenger RNAs (mRNAs).
3. Messenger RNAs pass from nucleus into the cytoplasm. They encode proteins which determine i) cell structure ii) cell function.

Outside of the nucleus: the endoplasmatic reticulum

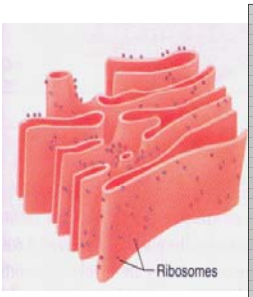


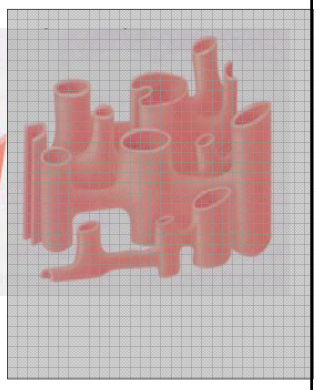
Endoplasmatic reticulum



Rough ER (granular)

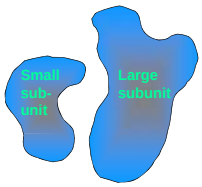
Smooth ER (agranular)



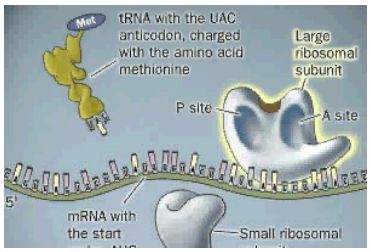


Rough (or granular) endoplasmatic reticulum

Organelle which makes the ER "rough": the ribosome



1. Ribosomes consist of 2 parts (subunits) of different sizes.
2. They synthesise proteins according to the instructions provided by the messenger molecules (mRNA) which arrive from nucleus
3. Synthesis of proteins involves formation of long chains of aminoacids
4. Catalytic activity of ribosomes is provided by RNA (!!!), in contrast to almost all other catalytic reactions in the cell



Translation.avi

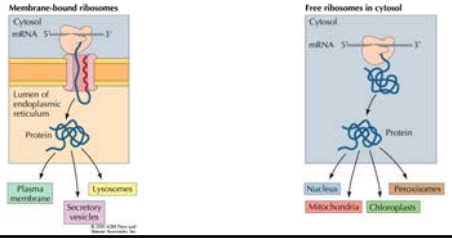
Key points:
1. The messenger molecule (mRNA) arrives from the nucleus and acts as a template.
2. Subunits of the ribosome "embrace" this template and act as a docking station for the arriving building blocks of the protein
3. Protein is being assembled from the smaller "building blocks" (aminoacids). The sequence of these blocks is encoded by the messenger molecule (mRNA).
4. After the protein chain has been completed the ribosome releases the messenger molecule and the newly made protein. Cycle may repeat.

(ALL THIS IS PRESENT IN YOUR HANDOUTS!)

Do all ribosomes associate with ER and why do they do it?

ER-bound ribosomes insert the new polypeptide chain into the lumen of ER via special micro-channels. Some of these proteins remain inserted into the membrane where they belong (e.g. integral membrane proteins) or because some proteins have to be then locked into the vesicular organelles and targeted for secretion out of the cell

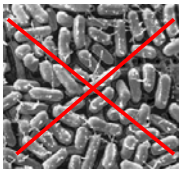
Proteins which need to remain in the cytoplasm or move to the nucleus or mitochondria are synthesised by the free ribosomes.



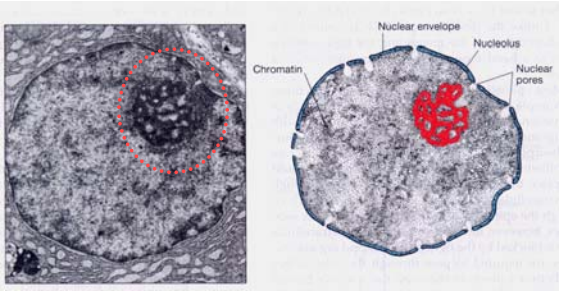
Many antibiotics block protein synthesis in prokaryotic (bacterial) cells, but not in eukaryotic (mammalian) cells

Streptomycin	Inhibits initiation and causes misreading
Tetracycline	Inhibits binding of tRNA
Chloramphenicol	Inhibits peptidyl transferase activity
Erythromycin	Inhibits translocation

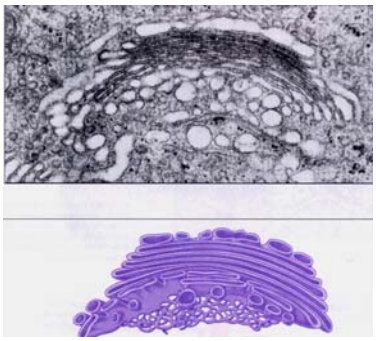
You are not asked to remember these names yet!



Components of ribosomes are produced in the nucleus by the structure known as nucleolus



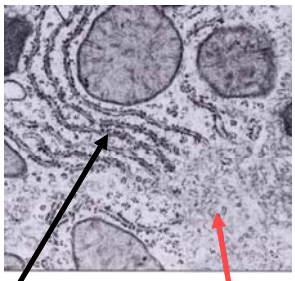
Rough ER is involved in protein traffic. Proteins which need to be secreted out of the cell are directed into the Golgi apparatus (Golgi complex)



Traffic of the new proteins from the ER to the Golgi complex for further processing and secretion from the cell

Golgi-exocytosis-2

THE SECRETORY PATHWAY:
Ribosomes – ER – Golgi – vesicles – outer membrane - secretion



Rough ER (granular)

Smooth ER (agranular)

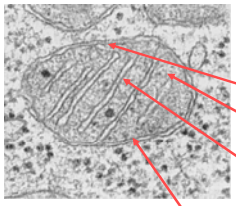
Smooth (or agranular) endoplasmatic reticulum

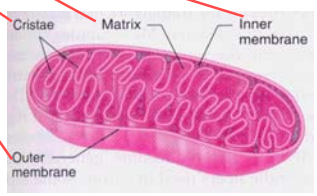
Smooth (agranular) ER:

1. Tubular network that does not have ribosomes attached to it.
2. Functions:

- A. Contains machinery for production of certain molecules (i.e. lipids)
- B. Stores and releases calcium ions, which control various cell activities, for example contraction of cardiac muscle cells

Mitochondria (singular: mitochondrion)



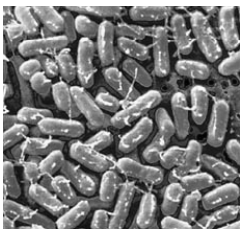


The key points:

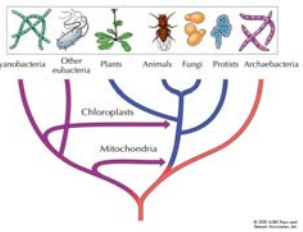
1. Mitochondria are numerous small organelles < 1μM in size. They are the major site of cell energy production from ingested nutrients.
2. This process involves oxygen consumption and CO_2 formation. It leads to formation of ATP (adenosine triphosphate).
3. Cells which utilize large amounts of energy contain as many as 1000 of them.
4. Have two layers of membrane. The inner layer forms "cristae" –membrane folds to increase the inner surface area.

Mitochondria may replicate independently of the host cell

The origin of mitochondria:
It is thought that mitochondria have originated from bacteria which have "learned" to permanently live inside of their host cells and be useful, rather than harmful.

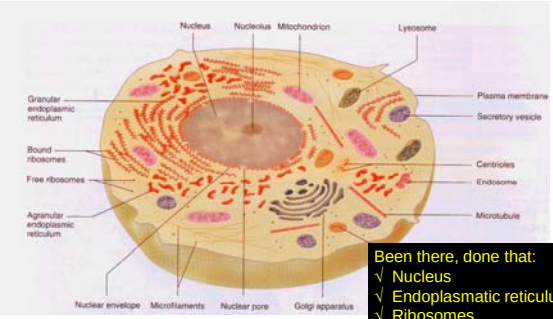


Bacteria from human intestine



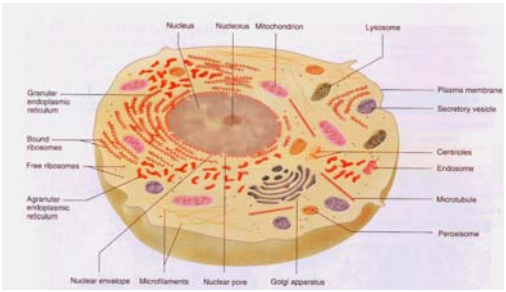
Additional interesting facts:

1. Mitochondria have their own DNA, which replicates independent of the nuclear DNA
2. Genetic code of the mitochondria is different from the main code of the cell
3. Mitochondria have their own ribosomes on which some of the mitochondrial proteins are produced. Others are imported from the outside
4. There are genetic disorders which are due to mutations in mitochondrial genes
5. We inherit our mitochondria from mothers because sperms only release their DNA during fertilisation



Been there, done that:
√ Nucleus
√ Endoplasmatic reticulum
√ Ribosomes
√ Golgi complex
√ Nucleolus
√ Mitochondria

Cell and its organelles-2



Been there, done that:
√ Nucleus √ Endoplasmatic reticulum √ Ribosomes √ Golgi complex
√ Nucleolus √ Mitochondria

Vesicular organelles involved in transport in and out of the cell: Endosomes, lysosomes, peroxysomes.

Endocytosis:

The membrane folds into the cell and forms a vesicle.

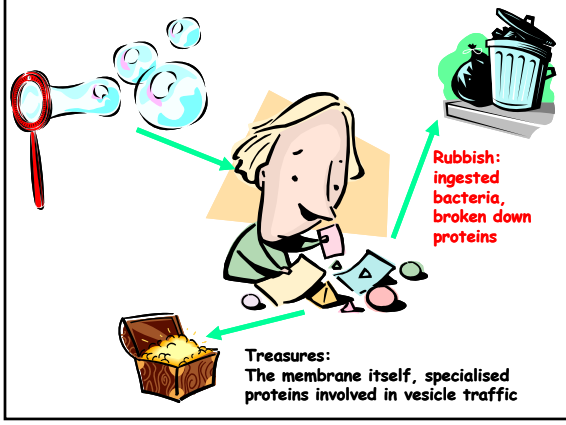
1. Pinocytosis ("cell drinking"): Vesicle contains mainly fluid with soluble materials

2. Phagocytosis ("cell eating"): Vesicle contains large particles, such as bacteria or debris from damaged tissue

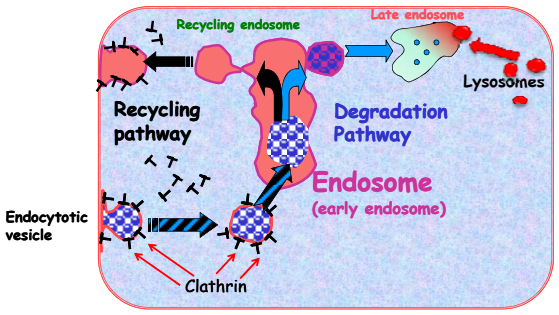
Cell Endocytosis Movie
cell_memendocytosis.mov

Phagocytosis Movie
phagocytosis.MOV

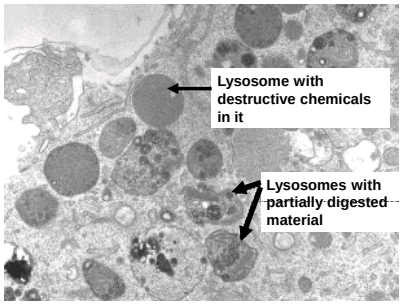
Pinocytosis Movie
pinocytosis.MOV



Endosomes are the intracellular sorting machines



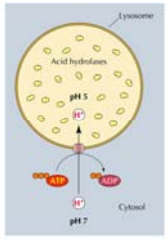
Membrane fragments and useful membrane proteins may be re-cycled. Materials intended for digestion are passed to the late endosomes which fuse with lysosomes (for example bacteria in immune cells).



N.B.

1. Broken cell organelles may be also destroyed by lysosomes.
2. Release of the contents of the lysosmes into the cytoplasm is fatal for cells

Lysosomes – small vesicular organelle s which contain a battery of digestive enzymes (~50 types)



Lysosomal enzymes are all "acid hydrolases" – this means they are active in acid conditions but not at normal pH. A clever way of making them more aggressive to pathogens and at the same time protecting the cell!

Clinical significance:

"Lysosomal storage diseases": genetic disorders whereby lysosomes cannot destroy certain components they normally digest. The reason for that are mutations in the genes which code for the lysosomal enzymes. As a result certain cells start dying.
(i.e. Gaucher's disease, Tay-Sachs disease and ~ 20 others are known)

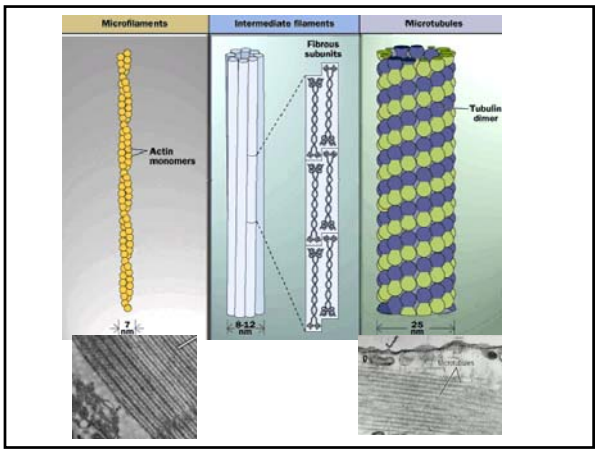
Gaucher's disease:
Found primarily in Jewish population at frequency 1:2500. Caused by mutations in lysosomal enzyme glucocerebrosidase. In most cases the only cells affected are macrophages leading to liver and spleen abnormalities. In severe cases leads to neuro-degeneration.

Peroxysomes small vesicular organneles similar to lysosomes but contain chemical machinery which uses oxygen to oxidise various potentially toxic substances. This leads to formation of hydrogen peroxide (H_2O_2) which in high concentrations is itself toxic to cells. In order to degrade H_2O_2 peroxysomes contain large amounts of an enzyme called catalase.

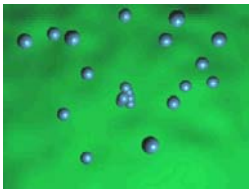
Peroxysomes play an important role in oxydation of fatty acids but this does not lead to ATP (energy) production as in mitochondria. Instead heat is produced and acetyl groups which are then used for synthesis of cholesterol.

There also are genetic disorders due to malfunction of peroxysomal enzymes (i.e. Zellweger syndrome and others)

Cytoskeleton

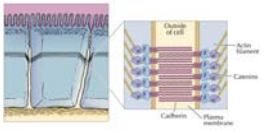


Growth of an actin microfilament

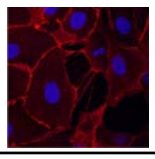


Actin filaments grow by polymerisation of actin monomers. One end always grows faster than the other. Hence the fibres are "polar". The fast growing end is the "plus" end.

Examples of actin's functions: actin meshwork is a key element of the cell's stability



From Cooper's "The Cell A Molecular Approach"

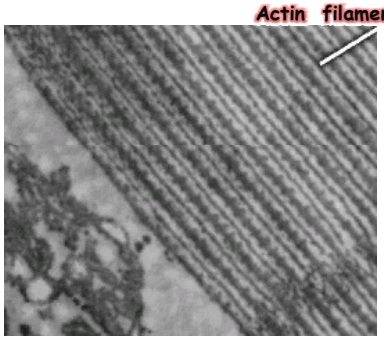


Deuchenne's muscular dystrophy: poor anchoring of muscle bundles

Dystrophin mutations –
Deuchenne's and Becker's dystrophy

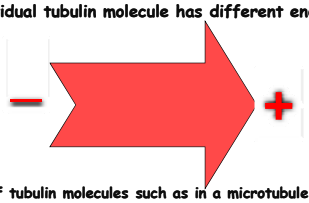
Actin is a component of molecular motors

Actin filaments (thin)



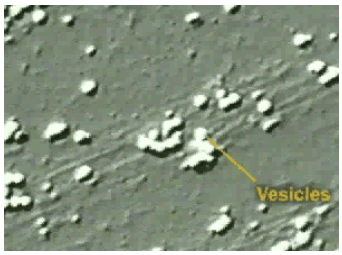
Microtubules have plus (+) and minus (-) ends. They therefore may act as "rails" for long-distance traffic in the cell.

Monomer is called tubulin.
An individual tubulin molecule has different ends:

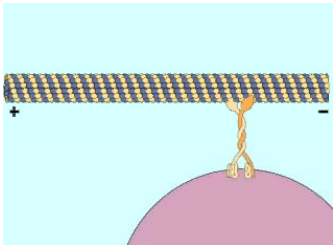


A chain of tubulin molecules such as in a microtubule also has "poles"

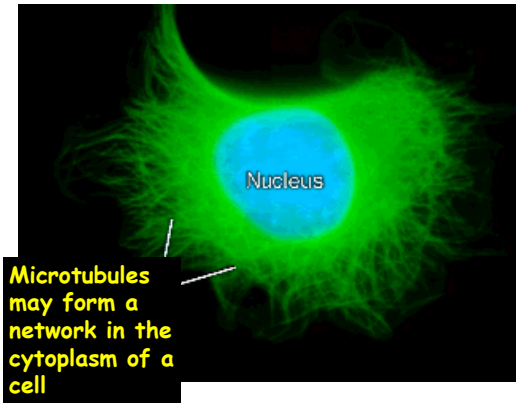
Specialised molecular motors carry intracellular cargoes towards plus or minus ends of microtubules



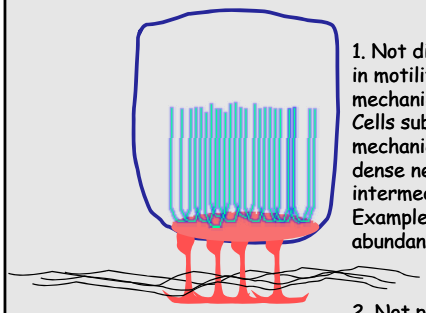
Kinesin – a motor which moves towards (+) end
Dynein – a motor which moves towards (-) end



Kinesisn.avi



Intermediate filaments act as ropes attached to anchors in extracellular matrix



1. Not directly involved in motility, but provide mechanical support. Cells subject to high mechanical strain have dense networks of intermediate filaments. Example: keratin is abundant in skin.

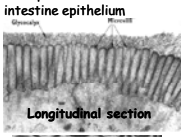
2. Not polarised.

Protrusions of cell membrane

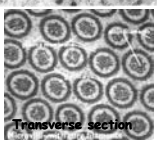
Supported by actin bundles

"Brush"- like short protrusions with slow or no active movement

Example: microvillli on the intestine epithelium



Longitudinal section



Transverse section

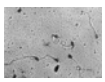
Supported by microtubules

"Brush"- like short protrusions with active movement

Example: cilia on the respiratory epithelium

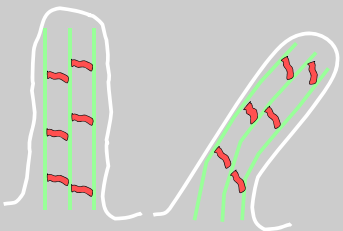
"Tail"- like long beating protrusions - flagella

Example: sperms tails



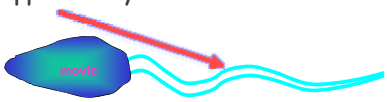
But note: "stereocilia" in auditory cells are supported by actin bundles!

Movement of cilia is due to traction generated by cross-linking dynein-like proteins attached to microtubules



Flagella-cilia movie

Flagella – long "tails" capable of "beating" action, such as in a sperm. They are also supported my microtubules.



Cytoskeleton component	Dia-meter	Building blocks (protein monomers)	Examples of function
Microfilament	7 nm	G-Actin	Ubiquitous component of cytoskeleton. Contractile protein of skeletal muscles. Support permanent membrane protrusions (e.g. microvilli in intestine epithelium) and slow cellular protrusions during phagocytosis. Together with myosin form the contractile ring which separates dividing cells.
Interm filame			Strengthen cell regions subject to mechanical stress and areas of cell-to-cell contact. Keratins are intermediate filament proteins abundant in skin, nails, hair.
Microtubule (also form centrioles)	25		Support beating membrane protrusions, such as cilia in airway epithelium or flagella (sperm tails). Act as cell's "railways". Separate chromosomes during cell division.

Medical importance: Some anti-cancer drugs (vincristine, taxol) interfere with microtubules.

THE END