Cell and its organelles

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”

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

http://www.sinauer.com/cooper5e/
http://www.whfreeman.com/Catalog/static/loeb6bridgepage/

INTRODUCTION
Types of microscopes

Light microscope
Conventional
Fluorescent

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.

Normal human kidney – light microscope

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

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

Excite with blue colour light
Monitor green light which comes back

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.

Electron gun
Electron lens system (magnets)
Specimen
Fluorescent screen
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?
Kapio = 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)

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 membrane is a continuation of the
"endomembrane".

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

Endoplasmatic reticulum

Nucleolius
Nuclear envelope
Nucleus
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

Outside of the nucleus: the endoplasmatic reticulum

The ability to enter and exit is determined by specific sequences (domains) which are present on proteins involved in this exchange and act as “passwords”.

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.
Organelle which makes the ER "rough": the ribosome

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

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!)

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

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Streptomycin</td>
<td>Inhibits initiation and causes misreading</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Inhibits binding of tRNA</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Inhibits peptidyl transferase activity</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Inhibits translocation</td>
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You are not asked to remember these names yet!
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

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

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)

Rough ER (granular) Smooth ER (agranular)
The key points:

1. Mitochondria are numerous small organelles < 1 μM in size. They are the major site of cell energy production from ingested nutrients.
2. This process involves oxygen consumption and CO₂ 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 (so-called symbiosis), rather than harmful.

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. Mitochondria are important stores of Ca²⁺ in the cell and remove excess of Ca²⁺ from cytoplasm. Breakdown of this process is lethal for cells.
6. We inherit our mitochondria from mothers because sperms only release their DNA during fertilisation
 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

**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).

**Rubbish:** ingested bacteria, broken down proteins

**Treasures:** The membrane itself, receptors, ion channels, specialised proteins involved in vesicle traffic

**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.

Peroxisomes small vesicular organelles similar to lysosomes but contain chemical machinery which uses oxygen to oxidise various potentially toxic substances. This leads to formation of hydrogen peroxide (H₂O₂) which in high concentrations is itself toxic to cells. In order to degrade H₂O₂ peroxysomes contain large amounts of an enzyme called catalase.

Peroxisomes play an important role in oxidation 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)

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

Other important elements of actin-based elements of mechanical stability:
- filamin - cross-links actin fibres
- cadherins - extracellular connectors of cells
- catenins - membrane-spanning anchors

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.
Deuchenne's muscular dystrophy: poor anchoring of muscle bundles

Dystrophin mutations – Duchenne's and Becker's dystrophy

Actin is a component of molecular motors

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

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

Microtubules may form a network in the cytoplasm of a cell
**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: microvilli on the intestine epithelium

- **Supported by microtubules**
  - "Tail"- like long beating protrusion - flagella
  - Example: sperma tail

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

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

**Cytoskeleton component**

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<thead>
<tr>
<th>Diameter</th>
<th>Building blocks (protein monomers)</th>
<th>Examples of function</th>
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<tbody>
<tr>
<td>Microfilament</td>
<td>7 nm</td>
<td>G-Actin</td>
</tr>
<tr>
<td>Intermediate filament</td>
<td>10 nm</td>
<td>Various</td>
</tr>
<tr>
<td>Microtubule (also form centrioles)</td>
<td>25 nm</td>
<td>Tubulin</td>
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**Movement of cilia is due to traction generated by cross-linking dynein-like proteins attached to microtubules**

**Medical Importance:**

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