MOLECULAR BIOLOGY

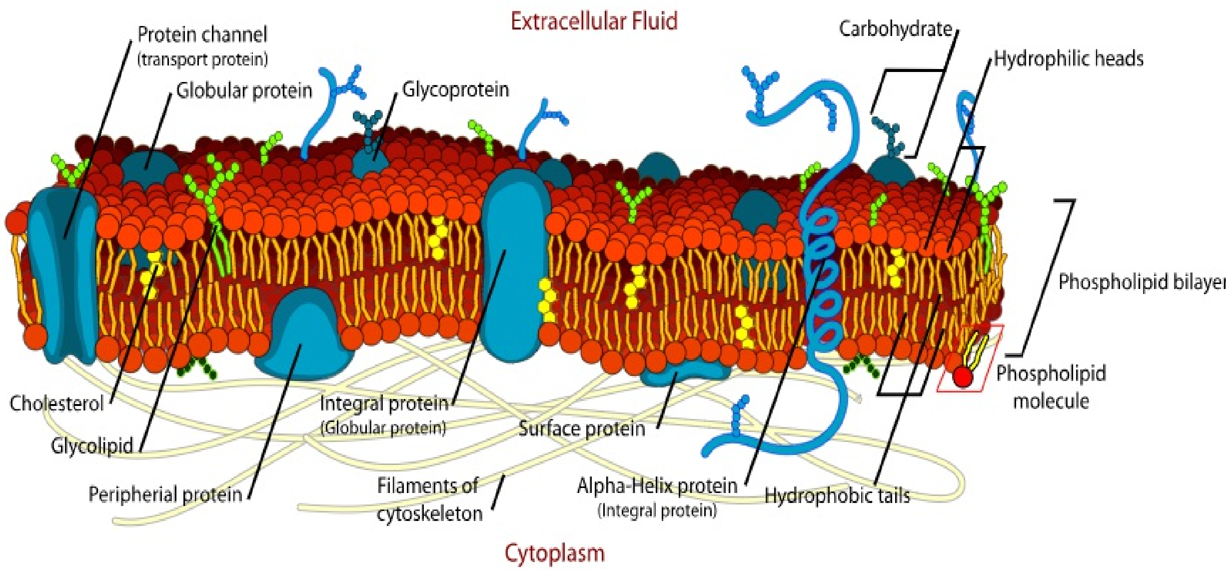

Figure 1 Cell Membrane, with detail examples.
https://commons.wikimedia.org/wiki/File:Cell_membrane_detailed_diagram_en.svg
LadyofHats, Public domain, via Wikimedia Commons

This section, more than the others, is NOT intended as an introduction to molecular biology. I will limit this section to key parts of mammalian cells, and how they are affected by radiation. I intend that what I tell you is brief, informative, and correct; but it is not a complete treatment of the title subject.

Oxidative Damage
Oxidation is the loss of electrons. When iron (Fe) reacts with oxygen (O) to form rust, electrons from iron are more likely to be found near the O than near the Fe. Chemists call that loss of negative charge from iron oxidation. And when ionizing radiation (IR) knocks an electron away from an atom, that is called oxidation with creation of a free radical. Oxidative damage to DNA is routinely repaired. Damaged proteins are destroyed and replaced.

Essentially all of the working machinery of our bodies is made of proteins, so they suffer most of the damage from routine daily oxidation. Fortunately, all of our proteins have been built by our cells, and can therefore be built again, unless we don't survive long enough to rebuild. Damage to proteins is rarely lethal, considering how often they are damaged. This is why you hear and read more about DNA damage than protein damage, which is vastly more common.

Cell Membrane
Mammalian (and all animal) cells have a cell membrane that surrounds them. This membrane is

composed mostly of proteins (60%), and partially by lipids (40%). Lipids are a broad category of water inoluble molecules that includes fatty acids, oils, waxes, phospholipids, and cholesterol. Phospholipids have a phosphorous atom at one end, with long carbon chains (fatty acids) at the other. The phosphorus end has a slightly negative charge which is attracted to the Hydrogen in water (H_2O) both inside and outside the cell. The lipid chains are attracted to each other and are repelled by water. If you shake a mixture of water and lipids, you get water with little spheres full of lipid chains, all trying to minimize their contact with water[1]. If you shake **phospho**lipids in water you get spheres containing water, surrounded by a phospholipid **bi**layer as shown in the cell membrane above, but without the proteins. Such bilayers form cells and are somewhat stable on their own. Living cell membranes are packed with proteins that bind the cell to other cells and strongly hold the cell and cell membrane together. Membrane proteins also have many other functions, e.g., selective pores, transporters, signalers, identifiers, etc. Proteins are inherently redundant; in virtually all cases, if a protein is needed, millions or billions of that protein are needed. This is even more true for phospholipids. So oxidative damage to a single protein or phospholipid, even though it won't be repaired, is so inconsequential that even God wouldn't notice.

Cytosol

There is a water solution of proteins containing organelles surrounded by even more membranes inside the cell membrane. There is a different water solution outside the cell membrane. The proteins in the cytosol are busy keeping the cell fed, eliminating damaged proteins, and replacing damaged copies of each other. There are various organelles within the cytosol, composed

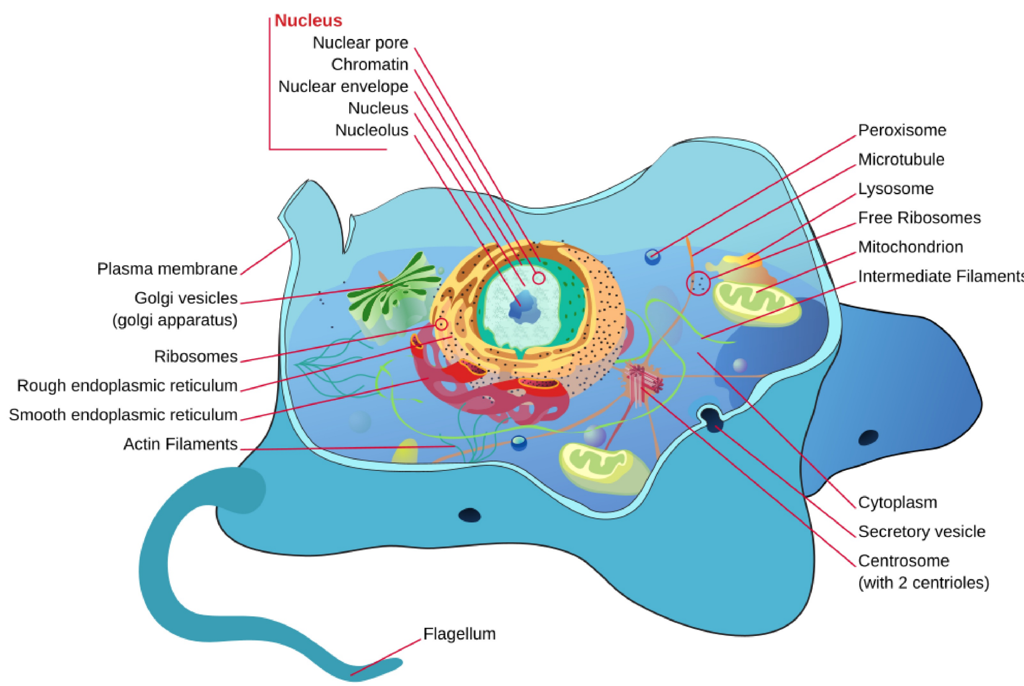

Figure 2 Animal cell with internal components. https://commons.wikimedia.org/wiki/File:Animal_cell_structure_en.svg LadyofHats, Public domain, via Wikimedia Commons

[1] Molecules with partial or full electric charges are called polar. Molecules or portions of molecules without charges are called nonpolar. Polar molecules dissolve in water and are called hydrophilic. Non-polar molecules are repelled by water and are called hydrophobic.

mostly of protein and phospholipids, but the only organelle that can suffer permanent oxidative damage is the mitochondrion, because it carries the maternal mitochondrial DNA[2]. I'll address repairing damage to DNA later.

Nucleus

The nucleus contains most of the cell's DNA. Because it is susceptible to oxidative damage, this DNA gets its own barrier to all of the oxidative events going on in the cytosol: the nuclear membrane. DNA is stored in coils wrapped tightly around histones (special proteins) to form a mass of DNA & protein called chromatin. The DNA in chromatin is believed to be protected against oxidative damage from chemicals and radiation. It is only uncoiled for translation and replication.

DNA is normally repaired when damaged. There are hundreds of repair mechanisms (proteins again) for different kinds of DNA damage. There are proteins to repair single strand breaks (SSBs), double strand breaks (DSBs), and damaged, missing, or replaced nucleotides. SSBs in one strand of DNA are easier to repair because the other strand provides a template. DSBs are most often caused by high energy ionizing radiation like heavy charged particles. DSB repair is often imperfect because the templates are broken and the ends are often damaged. DNA repair takes place mostly at night.

The process of replacing damaged proteins is continuous, daily, minute by minute. Proteins are made in the cytosol. The equipment for making proteins is made in the nucleolus[3]. The equipment is a mass of protein called a ribosome. Ribosomes are transported from the nucleolus, through the nuclear membrane, to the cytosol, where the ribosome waits for instructions from mRNA (messenger RNA[4]).

The instructions for making proteins come from DNA, most of which is kept in the nucleus. The DNA code for a protein is first **transcribed** from DNA to mRNA, in the nucleus. The mRNA is transported through the nuclear membrane to the cytosol and a waiting ribosome where it will be **translated** into amino acids of a protein.

---

[2] Remember that the oxygen we breath causes more oxidative damage than does environmental doses of ionizing radiation. Most of that damage is easy to repair like SSBs or damage to a single nucleotide.

[3] The nucleolus is a region of protein, DNA, and RNA that is not bound by a membrane. It makes up about 25% of the volume of the nucleus.

[4] RNA is chemically very similar to DNA, but it occurs mostly in single strands.

But while we're still in the nucleus, note that tRNA as well as mRNA is made in the nucleus. tRNA is modified as it crosses the nuclear membrane, and it acquires a specific 3D spatial configuration. In the cytosol, each tRNA then binds to the particular amino acid for which it is genetically and spatially designed. Then the tRNA finds its way to a ribosome that needs its specific amino acid.

Back in the Cytosol
Messenger RNA carries triplets of bases in one long string almost the same as the original DNA gene from which it was transcribed. Each triplet of C, G, U, and A codes for one specific amino acid out of 20 possible amino acids. (In RNA, U replaces T). Each triplet is called a codon.

Each tRNA has one coding triplet. The rest of the tRNA is non-coding but has a geometry that holds a specific amino acid in place. The tRNA coding triplet is called an anti-codon. The anticodon of a tRNA pairs with the codon from the mRNA. The tRNA brings with it a specific amino acid that matches its anticodon and the codon from the mRNA. Then it happens again: a second tRNA snuggles into the groove right next to the first, and the ribosome links the two amino acids together into a growing protein molecule.

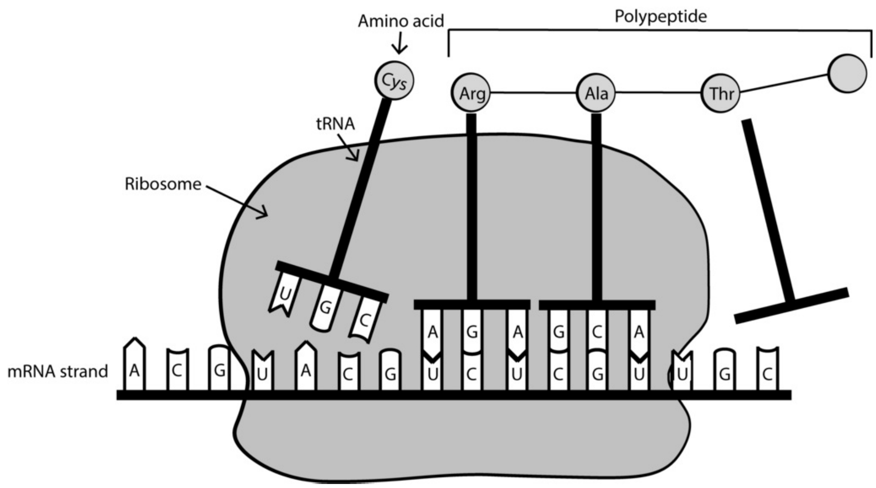

Figure 3 A ribosome translates codons from mRNA nucleotides into amino acid components of a protein.
https://commons.wikimedia.org/wiki/File:Protein_Synthesis-Translation.png
Sarah Greenwood, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

To translate DNA into proteins, you need a code that can specify at least 20 amino acids (AAs).
* 4 different DNA (or RNA) molecules can only code for 4 AAs.
* 4 different molecules can code for 16 unique AAs if taken in pairs.
* 4 different molecules can code for 64 unique AAs if taken in triplets. A codon is a sequence of three RNA molecules that codes for a unique amino acid.

Cell Cycle

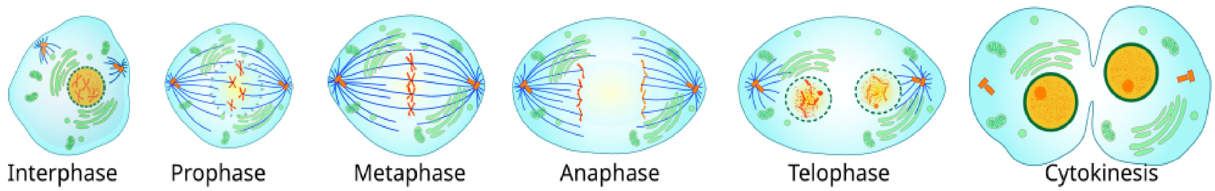

Figure 4 Mitosis sequence
https://commons.wikimedia.org/wiki/File:Mitosis_cells_sequence_English.svg
LadyofHats, CC0, via Wikimedia Commons

Growing cells go through a cycle that leads to cell division. The protein in the cell must be nearly doubled, then the DNA must be exactly doubled and separated into two daughter cells. DNA is most vulnerable to oxidative damage when it is un-wound and separated into single strands. This occurs during replication and transcription.

The cell cycle is divided into 4 phases based on what is happening in the cell at that time.
* G1 phase is a period during which the cell grows more proteins and membranes, performs maintenance, or just functions.
* S phase is the period during which DNA is replicated (and exposed).
* G2 is a damage check and repair phase.
* M phase is when the cell divides into two daughters

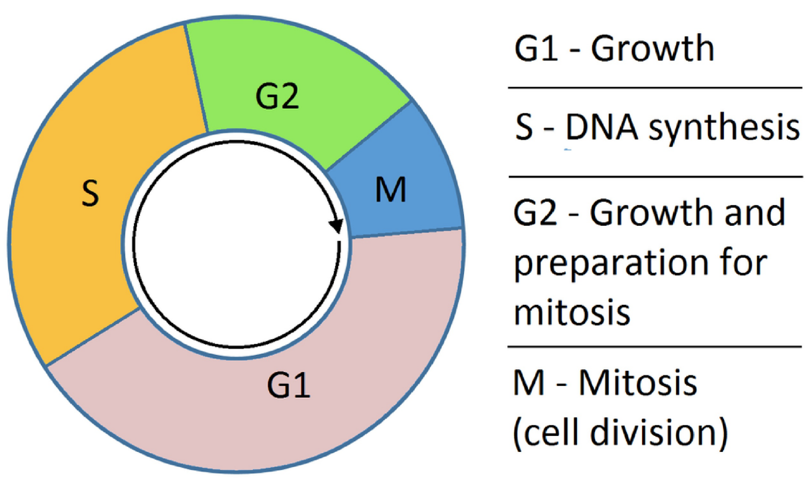

Figure 5 Cell cycle simplification.
https://commons.wikimedia.org/wiki/File:Cell_cycle_simple.png
Simon Caulton, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Commons

Fast growing cells like those in the intestinal lining, bone marrow, testicles, or an embryo are often in S phase and most susceptible to DNA oxidation from ionizing radiation or mutagenic chemicals.

Some experts think that it takes at least 4 mutations and usually 20 years to create an immortal cell. Less time if one of the early mutations is to a DNA repair enzyme.

HOMEWORK Test your understanding and memory. Open book, open internet.

Draw a short length of membrane with a single protein in it.
Draw a cell membrane surrounding a cell with a nucleus, a ribosome, mRNA, and TRNA.
Sketch a nucleotide pair.
What is a histone?
What is chromatin?
Is sunlight UVC strong enough to oxidize DNA?
Assume the energies shown to the right are correct.
Is sunlight UVB strong enough to oxidize DNA?
Do our cells have repair enzymes for single strand defects?
How many mutations does it take to make an immortal cancer cell?
How long does it take for a single cell to accumulate that many **specific** and permanent mutations?

Ultraviolet B	UV B	3.94–4.43 eV
Ultraviolet C	UV C	4.43–12.4 eV

No score, just your opinion on the following:
Do nuclear weapons in Russia scare you?
Do nuclear power plants in USA scare you?
Do dental X rays scare you?
What should we do with depleted nuclear fuel rods?
Should we send people to Mars?

1) Cells and their membranes are composed mostly of ________________________.
2) A cell membrane is a nonpolar sandwich of lipids and nonpolar proteins with external layers of phosphorous and polar __________________, which are soluble in ___________ .
3) _____________________ in water just naturally form cell membrane bilayers.________ have evolved to stabilize the bilayer membranes of living cells, allow specific ___________ through membranes, actively transport other _____________ through membranes, bind _________ on one side of a membrane and interact with a __________________ on the other side, etc.
4) Living cells have organelles surrounded by ____________________ . Name two such organelles:
5) The water solution inside a cell is called the:
6) DNA is stored in coils wrapped tightly around _____________________.
7) Why are SSBs easier to repair?
8) DSBs are usually caused by:
9) Why is oxidative damage to DNA more important than protein damage or phospholipid damage?
10) Ribosomes manufacture ___________________ based on instructions provided by ______.

11) A codon is how many nucleotides?
12) A codon identifies the ___________________________ that the ribosome must next add to the growing _____________________.
13) How many different amino acids must our codons be able to specify?
14) Oxidation is the loss of ________________________.
15) DNA is most vulnerable to oxidative damage when it is unwound from around its _______ ______, and separated into single _____________ during _______________ phase.
16) Why are rapidly cycling cells like sperm cells, bone marrow cells, and intestinal lining cells more susceptible to DNA oxidation?

