May 2022

BIOLOGY NEWSLETTER

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Hey everyone!! I hope you've been keeping well and have (slightly) relaxed over Easter. Summer Term is short and sweet so here's an issue of the bio newsletter to keep you energised throughout! This month, we have two articles adapted from lectures, as well as a write up of a practical. As always, if you'd like to give us some feedback, or even better write an article for an issue yourself, just drop us an email!

Enjoy,

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Protecting your most precious molecule - the repair of damaged DNA

Adapted from a lecture by Peter J McHugh, Professor of Molecular Oncology

The causes are vast and the list of diseases it gives rise to are even greater: DNA damage is ubiquitous in eukaryotes and prokaryotes, and so poses a fundamental challenge to the existence of life. On average, every one of your 3.7×10^{13} cells obtains more than 10,000 individual bits of damage per day - in your whole body that would be 3,700,000,000,000,000,000 bits of damage (basically a lot of 0s so I hope I got all of them…) By this point you're probably wondering how we're even alive, much less reading this right now, so in order to enlighten you I'm going to cover some of the mechanisms of DNA repair. Bear with me - it's a lot of jargon…

So, let's kick off with a whistle-stop tour of DNA. Deoxyribose Nucleic Acid is the repository of our hereditary information, and is the only molecule in our body that is intentionally repaired (all others are broken down and then replaced). It consists of 4 bases , where A only fits with T, and G only fits with C, kind of like 2 jigsaw pieces. There are over 6 billion of these bases, and scientists at the University of Leicester actually printed out a genome - 130 volumes in total of the "Encyclopaedia Genomica".

So now onto the fun stuff.

Sources of damage can be categorised into endogenous and exogenous damage. Endo, in a biological context, just means within, so endogenous damage arises within the cells of an organism. This includes things like replication stress, which is a rather general term to encompass anything that compromises the success of replication, and the production of **oxygen radicals**. Exogenous damage consists of the standard DNA damage exam answer of radiation, as well as viral infection and chemotherapy. Of course, age is also a major factor, purely due to the fact that mutations can accumulate over the years, and so drive diseases such as cancer.

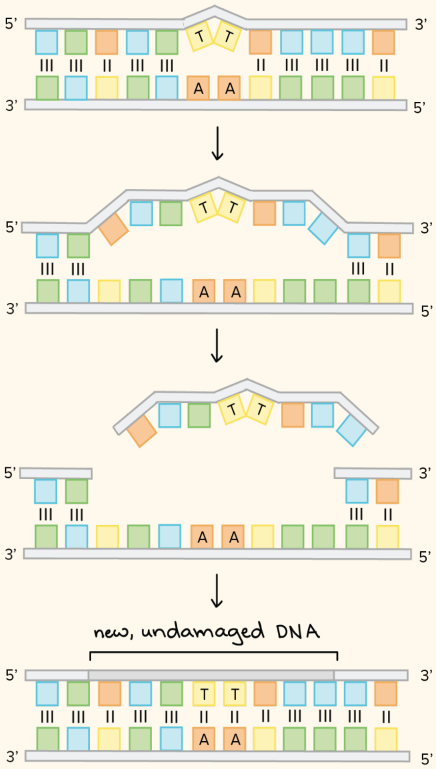
Cancer is a polygenic disease, so much of it arises from changes in several classes of genes. Some of the ways in which mutations can lead to major issues in cells, thus causing disease are as follows:

- Loss of genome stability → DNA is no longer able to repair itself
- Loss of tumour suppressors (genes that regulate cell division)
- Oncogene expression
- Escape from apoptosis (cell death)

Now let's zoom right into the double helix and have a look at what's going on there. The most common, and most easily repaired damages are single-strand breaks (SSBs) and base damage, which arises through oxidation or **methylation**. Although not as common as SSBs, double-strand breaks can snap the chromosomes as the phosphate backbones break simultaneously. And the last type is the formation of crosslinks between strands. These can be intra (covalent linkage within 1 strand) or inter (covalent linkage of 2 strands), and as the helix can henceforth no longer be opened, is highly cytotoxic.

Now of course, with all that damage, our cells are constantly in overdrive, slaving away to patch up the leaks and ensure we all stay alive and kicking. One of these DNA repair pathways is called Nucleotide Excision Repair, and is used to remove lesions in DNA that distort the helix. It's quite a generalised repair pathway, as it can recognise a variety of mishaps, including UV-induced pyrimidine **dimers** and large bulky groups that have been cobbled on to the end of a base. How it works is as follows:

1. Detection of a dimer
2. Surrounding DNA opened to form a bubble
3. Enzymes cut damaged region out of bubble
4. DNA polymerase replace bases



(image courtesy of Khan Academy)

Xeroderma Pigmentosum is the prime example of where this mechanism isn't quite pulling its weight. The NER pathway isn't able to fully repair damage caused by UV light. Severe photosensitivity, skin cancers by the age of 10 unless kept out of the sun and neurological abnormalities are all consequences of this.

There are of course many other, more specialised mechanisms of DNA repair, one of which being a little something called Translesion Synthesis. Most DNA lesions block the action of DNA polymerase, the enzyme which joins up all the little DUPLO® blocks that make up the DNA, which is obviously a bit of a problem. In this case, a specialised polymerase just bulldozes forward and copies straight over the lesion. This is quite error-prone so results in a higher mutation potential and decreased accuracy

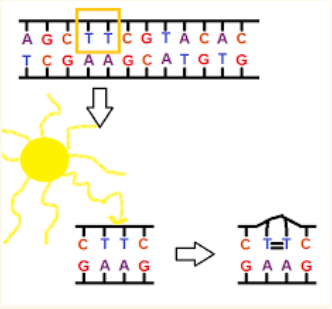
And so, I think I'll stop here, before I start rambling on about how 13 of the 16 DNA polymerases in our bodies are involved in tolerating DNA damage, and how some of the pathways that repair UV damage are actually decreasing the efficacy of cancer drugs… but I'll spare you the headache ;)

Glossary

Oxygen radicals: A radical is essentially an atom or group of atoms that have one or more unpaired electrons. They are formed as necessary intermediates in a variety of biochemical processes, but like most things in life, too many radicals can really mess up cells and their reactions. Some examples of when they are produced is during an immune response, where white blood cells produce free radicals as a mechanism to kill pathogens.

Methylation: The process of adding a methyl group to a molecule, which, when not sufficiently regulated, can silence a gene.

Dimer: two identical molecules linked together. In the case of a thymine dimer, two thymine molecules become covalently linked, due to UV light. Have a look at this stunning piece of art to get a better idea:



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By Lucia

The Pleural Membrane

Adapted from a lecture from Professor Rahman, a respiratory consultant.

The pleura is a thin, double-layered membrane that completely surrounds the heart, lungs and the diaphragm. Previously, scientists have not deemed the pleura to have a significant purpose in the body, then again, it seems we were of one mind with Dr Rahman when he commented on the tendency of scientists to label anything they don't understand as unnecessary and useless, a prime example being that of “junk” DNA .

There is one pleura for each lung, making sure that any damage on one side does not impact the other. This also helps contain any infection to one lung, allowing the other to function and provide the body with oxygen.

The pleurae are sometimes referred to as “potential space”, which is because they do allow expansion of the lungs. However, they can also act as a site for fluid build up. Pleural fluid (along with mesothelial cells) help to avoid friction between the two layers of the pleura. Usually, the rate of drainage of this fluid in the pleurae is equal to or more than the rate of formation. However when this balance is interrupted (usually by decrease of drainage), this can lead to a build-up of fluid in the pleural cavity known as a pleural effusion. This causes a restriction in the volume of air being breathed in, as well as being an indicator to other medical issues such as tumours, which can block the lymphatic drainage systems and cause an effusion.

Dr Rahman then used a case study to explain why those with tumours in their lungs feel breathless. You may think that it was due to lack of oxygen as the tumour pushed aside the alveoli, but a pulse oximeter showed healthy levels of oxygen saturation level. This was because there was no V/Q (ventilation/perfusion) mismatch.

To have the wrong oxygen saturation level, there must be a mismatch between the amount of air available for gas exchange (ventilation) and blood flow (perfusion). Reduced blood flow to the lungs (which can be caused by clots blocking blood vessels) causes dead space - ventilation without perfusion, so there is less blood to be oxygenated and oxygen saturation would decrease. Reduced oxygenation of blood (can be caused by pneumonia filling alveoli with infected fluid) causes shunt - perfusion without ventilation, so there is less oxygenation of blood in the lungs and oxygen saturation would decrease.

The tumour in this case study had caused lung deflation, so it had blocked the blood vessels leading to the lungs as well as drastically reducing the alveoli area for gas exchange. As both the perfusion and ventilation of this lung was 0, there was no mismatch, so the other lung functioned as normal, and the oxygen saturation remained at a healthy value.

The real reason the patient was breathless was due to the tumour being so large, it impacted the movement of the diaphragm. When breathing in, the diaphragm muscle flattens to allow the lungs to inflate. When breathing out, the diaphragm muscle contracts into a dome shape to push out air from the lungs outside. The size of the tumour impacted the contraction of the diaphragm so that the patient could not exhale properly, leading to the feeling of not being able to catch their breath.

By Sahana Jain

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Daphnia Practical

In the first BioSoc practical for Year 12s, a dozen keen biologists arrived to investigate the effects of certain stimulants on the microorganism 'Daphnia'. With all of the equipment displayed before us, we started off the lunch session with a quick recap of the theory that was covered a week before. Whilst a couple of people made the various concentration of our two stimulants - **caffeine and ethanol** - I ran through the preparation of the slide as well as the 'pencil technique' to count the heartbeat of the transparent Daphnia to provide a quantitative result to measure the effect of the various stimulants and their multiple concentrations

Method

1. Create stimulant solutions (e.g ethanol 1% and 10%)
2. Place a small piece of cotton wool in the cavity of the slide - stops Daphnia moving around
3. Using a (modified) pipette, transfer one Daphnia organism onto the slide in the cavity
4. Count the number of heart beats using the pencil technique (under the microscope), taking 3 sets of readings
5. Use a tissue to draw away as much water from the Daphnia as possible
6. Add a drop of the first (more dilute) solution of stimulant to the well and leave it for one minute
7. Measure the heart rate again

As our biologists prepared the slides and measured the effect of one concentration of a stimulant against a control of just water, these are the results of the practical:

	Caffeine Concentration ($mgcm^3$)	Beats/min
Control	0	268
Stimulant	0.1	320

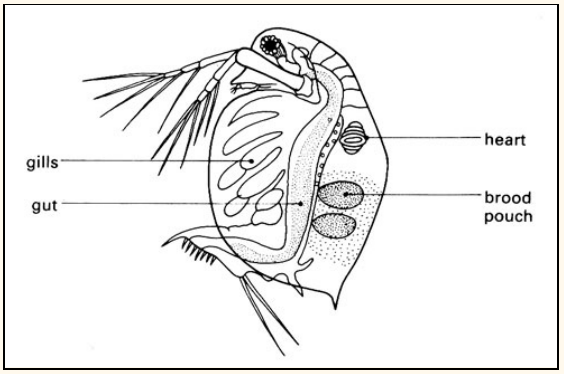
	Caffeine Concentration ($mgcm^3$)	Beats/min
Control	0	297
Stimulant	1	403

	Ethanol Concentration (%)	Beats/min

Control	0	241
Stimulant	1	196

Under our microscope

Diagram



Glossary

Caffeine: Caffeine mimics some of the effects of adrenaline and noradrenaline in the heart. By a different mechanism not involving beta-1 adrenoceptors, caffeine also increases the amount of cAMP in the sinoatrial node. Then cAMP levels increase and this increases the electrical activity of the sinoatrial node, making it depolarize and 'beat' faster. Caffeine has additional effects on the heart. Like adrenaline and noradrenaline, it can affect the main pumping chambers (ventricles), leading to an increase in the rate of contraction and relaxation of each heart beat. This means that, as well as beating faster, the heart's individual beats are associated with an increased volume of blood ejected into the circulation per unit time. This is called increasing cardiac output. Two or three cups of strong coffee or tea contain enough caffeine (and a similar acting compound called theobromine) to cause an increase in human heart rate of 5-20 beats/min.

Ethanol: Ethanol slows heart rate. At the concentrations used in this experiment, ethanol depresses the nervous system by acting as what is known as a non-selective neurodepressant. The amounts of ethanol necessary to achieve this effect in humans would also be sufficient to depress the respiratory centres of the brain, rather like the effect of an overdose of general anaesthetic, resulting in death.

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