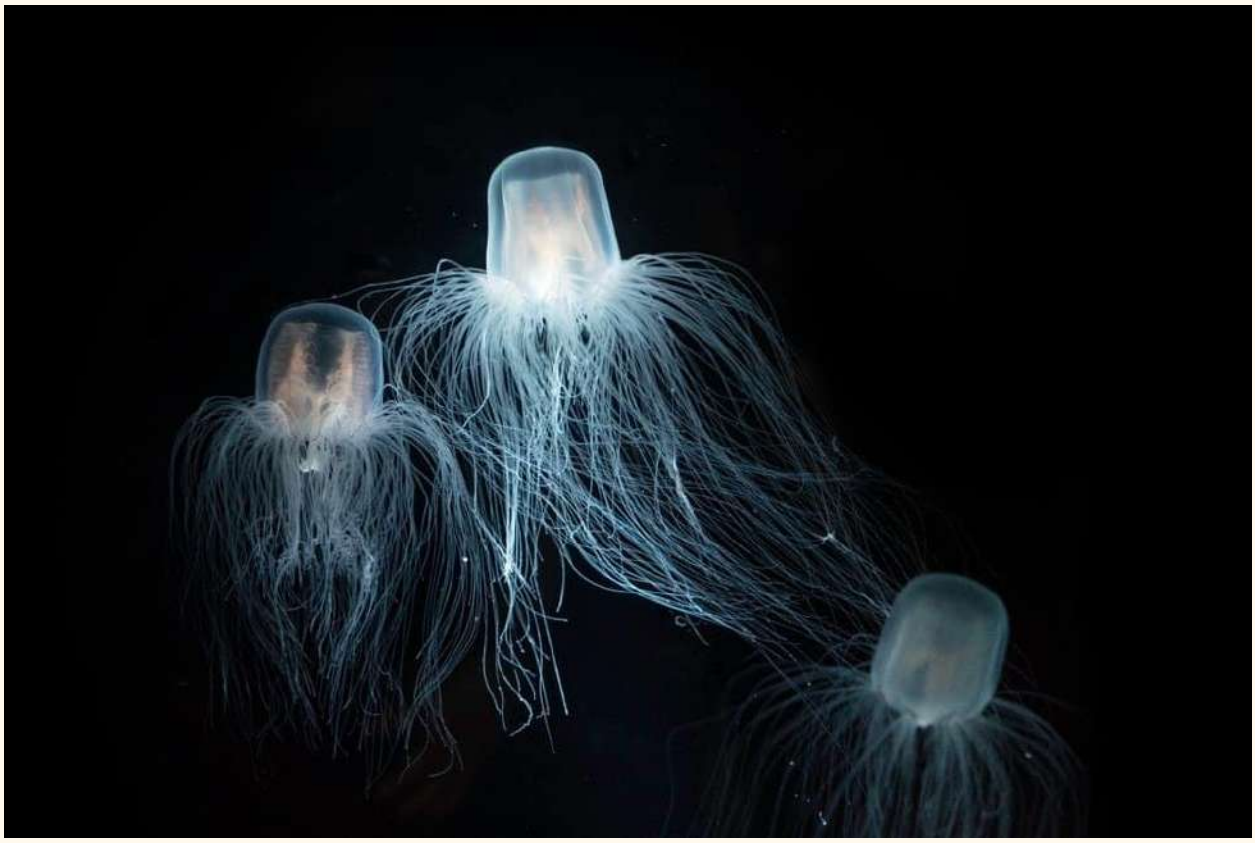
June 2022

BIOLOGY NEWSLETTER



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Welcome back, welcome back! As I'm sure we're all feeling at least 10 years older from all those exams, I thought you might enjoy a little something on the theme of ageing! As always, if you have any questions, or would like to contribute an article, don't hesitate to drop me an email!

Enjoy,

Lucia

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The biology of senescence (an overly fancy word for ageing) is riddled with mysteries. With there being a ridiculous number of causes and factors, and with each organism/ environment feeling the need to do things a little differently, this phenomenon is a pain to thoroughly understand.

Essentially, bio gerontologists agree only on the most superficial processes behind ageing. In terms of what it looks like, it's the progressive decline in physical function that we tend to experience as the years pass by (Claire Ainsworth). Some of the cellular changes include damaged DNA and the degradation of chromosome ends. Various theories have been created to explain this - the action of free radicals that prevent various mechanisms of DNA repair for example. This would explain why limiting the amount of food in rodents can increase life span - less food means slower metabolism inorder to conserve energy, so less free radicals are produced through cellular processes.

But of course, things generally aren't that straightforward. Researchers are starting to reconsider a theory from the 1950s, where it is not the random damage of life that causes ageing, but rather the excessive expression of genes that control your growth and development in the early stages of life.

A classic example of this are your eyes. As you get older, the **lenses** in your eyes continue to grow. Another example is the continual pruning of neurons in the brain. During childhood, a large amount of excess synapse connections are removed, whereas the "useful" ones are reinforced. (If you want to read more about this, have a look at white and grey matter!) As this process does not stop, by removing more and more connections, it could lead to cognitive decline - another side effect of ageing. One last example, as all good things come in threes, is about the loss of bone density in women after menopause, which can be attributed to the continuation of the processes that remove calcium, which is used in breast milk formation.

In this way, instead of cells completely giving up and going into early retirement, it seems that they just become increasingly unable to fully complete their functions.

Moving on to something slightly less depressing, let's talk about *reversing* ageing. In a sense, every single one of you reading this newsletter has been on a similar level to the so-called immortal jellyfish. *Turritopsis dohrnii* can continually revert from their medusae state (tentacles with a bell shaped body) to a polyp (think anemone), from which new jellyfish can bud off. For us, a perhaps slightly less flashy process happened in the womb. The cells from our parents are able to reverse their cellular ageing and essentially re-start as a freshly made embryo. Certain proteins active only during this early embryonic period, called Yamanaka factors, can make fully developed adult cells "forget" their functions and revert into a state similar to that of when they were "born". From here, similarly to the immortal jellyfish, they can re-differentiate into a totally different cell.

Now while we will probably never be able to completely turn back the clock for our own bodies (not that I'd want to return to being a snotty 3 year old!), increasing our understanding about such hidden mechanisms opens gives us an opportunity to develop brand new sparkly therapies to lessen the weight on our arthritic shoulders. Yamanaka factor transfusion, anyone?

Glossary

Lens growth - most of the cells that make up a lens are characterised by their long, fibrous appearance, so they are aptly named - well you guessed it - fiber cells (Augusteyn). These cells are synthesised, and laid down on top of existing cells. Due to the compression of these cells because of limiting space, some of the water of the cells is lost, therefore increasing the concentration of the proteins within the cells, thus increasing the refractive index (how much it bends light) leading to longsightedness in later life.

References

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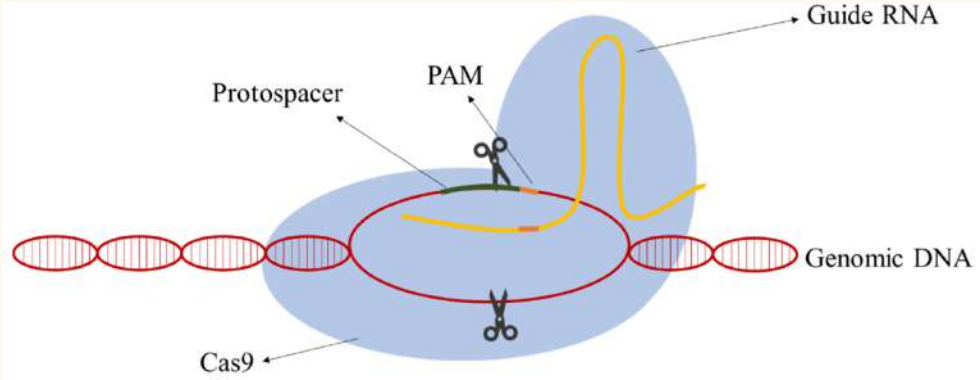
Lucia

CRISPR - Curing Genetic Disease

The repeated reference to the organisation CRISPR, particularly after Dr Banzhaf's talk on chemical genomics, made me interested in investigating the process used by this institution to edit genes. In this article I am going to dissect the method CRISPR is using in gene modification, explore some biomedical impacts and appreciate the limitations of the current system.

"CRISPR" itself stands for "clusters of regularly interspaced short palindromic repeats", which was derived from a natural defence mechanism of bacterial cells in response to viruses. The bacteria produces a short RNA strand which is complementary to the viral DNA known as guide RNA: when these two strands join, a complex forms with a nuclease known as Cas9, which cuts the viral DNA. As a result of the damage caused to the viral DNA, the invading virus experiences complete deactivation.

Researchers realised that this interaction with viral DNA could be manipulated, making it possible to alter any DNA sequence at a precise location. This could be achieved by changing the guide RNA to match the target: the gene which we want to modify. I have outlined a simplified version of the process below:



1. Scientists identify the section of the human genome responsible for disease before creating a guide RNA complementary to this section of bases. This is made to form a complex with Cas9.
2. The complex is injected into the nucleus of living cells where the RNA guide recognises and binds to a short sequence of DNA known as the PAM. The PAM is a location typically 3 nucleotides downstream from the cut site.
3. The Cas9 protein (commonly referred to as the "molecular scissors") snips this specific section of DNA such that it can be modified by an insertion, deletion or substitution. The substitution (most commonly used when rectifying genes) is achieved through the addition of a template to the complex that carries the desired base sequence, where it is able to join to the cut ends of the DNA strand.

Now we understand how CRISPR works in simple terms, it might be more obvious as to how we can potentially use this mechanism to combat genetically inspired diseases. A point to note, unlike other genetic engineering techniques, the CRISPR method has the potential of editing several genes, which is useful for most diseases which are polygenic.

For example, CRISPR has helped to identify A673T precursor gene which reduces the biomarker beta-amyloid in the brain. This reduces the formation of neurotangling, presenting the possibility of preventing the development of Alzheimer's and Dementia. Although the use of CRISPR therapy in treating such brain diseases is still in the early days of research, the technique has already been used to cure Sickle Cell Anaemia by editing the gene that codes for ß-globin. The edited gene causes cells to produce high levels of fetal haemoglobin (which from our A level studies we know has a higher affinity to oxygen). In 2020, CRISPR was used to treat the first patient with Sickle Cell Disease, Victoria Gray: post-therapy she no longer requires any blood transfusions and has reported that she "ha[sn't] had any problems with sickle cell at all".

There are some current limitations of using CRISPR techniques to fight disease, the two major ones being the off-target effects and concerns with the editing efficiency. For example, as CRISPR methods are moving towards cancer therapy there are concerns that the low efficacy might present difficulties in destroying tumour cells. However, the risk of these is relatively low considering the high specificity of the Cas9 protein complex, and thus far have presented no major issues in practice. Similarly, in recent years, many bioinformatics tools have been developed to help predict and reduce off-target modification further minimising concerns.

Without a doubt, the future of CRISPR in curing complex conditions is extremely exciting and the incredible results that have already been achieved since 2012 are very impressive. I hope you have a better understanding of what CRISPR actually is, and if you are interested to explore other areas that CRISPR has impacted or read a little more into Alzheimer's and Sickle Cell Disease there are some handy links under the references.

References:

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...Photo time!!! (courtesy of NewScientist)

To give you a little serotonin boost, here are some pretty little photos of some plankton!!