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Ageing - Can we live forever?

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Ageing is a multidimensional process of physical, psychological and social change. It is a universal process that can refer to cells that stopped dividing (**cellular senescence**), the process of becoming older (**organismal ageing**) or to the ageing of a population (**population ageing**). Organismal ageing is characterized by a progressive loss of physiological integrity a primary risk factor for major human pathologies, including neurodegenerative diseases cancer, diabetes and cardiovascular disorders. Ageing can be studied by analyzing the two sides of the "ageing coin": supercentenarians and those who age prematurely. This can be done by studying the influence of genetics and the environment on individuals that become 100 years-old and beyond in comparison with those who suffer from progeroid syndromes and age faster. One common denominator of the ageing process is the accumulation of DNA damage throughout life. Most of the progeroid syndromes, such as Werner, Bloom and Cockayne Syndrome, are in fact consequence of failures in DNA repair. The integrity and stability of DNA are continuously challenged by both endogenous and exogenous threats. These include DNA replication errors, reactive oxygen species (ROS), UV-light and pollution.

Besides studying human ageing, the whole ageing process and its genetics can be analysed using model organisms. 35 years ago, the first genetic screen, using *C.elegans* worms, was designed to select for long-lived mutants. This was followed by many others, using other model organisms that helped discover a plethora of "ageing-genes". Many of these are related to the maintenance and integrity of DNA, while others were identified as part of nutrient sensing pathways. Currently, ageing is being studied through several fronts, the different hallmarks of ageing. From genomic instability and epigenetics and stem cells, through telomeres, protein folding, mitochondrial function and intercellular communication.

Students were asked to write an assay on the following:

DNA repair failure is intrinsically connected with premature ageing and cellular senescence. Patients belonging to xeroderma pigmentosum group A (XPA) and Cockayne Syndrome groups A and B (CSA and CSB) display defects in nucleotide excision repair (NER) and early-onset neurodegeneration associated with premature ageing. Discuss a possible hypothesis for the link between the involvement of these DNA repair proteins and neurodegeneration and ageing.

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1. The curious case of Cockayne Syndrome

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Average life span has augmented drastically in the last century but, why has healthspan not increased proportionally? Ageing remains an enigma because it cannot be given a single explanation: both environmental and genetic factors are involved. Scientists speculate DNA damage accumulation in non-dividing cells and, thus, DNA repair failure is partly responsible for ageing. Supercentenarians and progeroid syndromes could help elucidate this topic.

Cockayne Syndrome (CS) is one of these progeroid syndromes. Like many other premature ageing diseases, CS is caused by mutations in DNA repair proteins. In addition, CS patients experience neurodegeneration. How does defective DNA repair link to ageing and neurodegeneration? Finding this connection might enable us to comprehend two of science's biggest conundrums: how we age and why our neurons slowly deteriorate.

Nervous tissue has a specific trait: whereas other tissues can replace cells more easily, neurogenesis appears to be very limited as we age. Thus, the organism cannot afford to get rid of neurons at the first sign of trouble and they are kept, even though damaged. Consequently, DNA damage accumulates overtime.

Mutations responsible for CS affect CSA and CSB proteins, which are involved in nucleotide excision repair (NER). There are two pathways in NER: global excision repair (GGR) and transcription-coupled repair (TCR), which only repairs DNA that is being transcribed. CSA and CSB take part in the latter. Any transcriptionally active neuron, such as the hippocampal neurons, is probably highly dependent on TCR. Therefore, if it is lacking, they might suffer more consequences than other cells types.

Intrinsic neuronal activity relies on transcription. Hence, all the DNA damage accumulated overtime and increased because TCR is missing will make neurons more prone to deterioration.

However, the rest of the tissues are also susceptible to DNA repair malfunction. Not repairing DNA will lead to a higher rate of DNA damage accumulation. This will end up causing early cellular senescence, in which systemic functionality is reduced. Altogether provokes premature ageing.

Nevertheless, there are diseases provoked by DNA repair mutations (i.e. Lynch Syndrome) that do not cause neither neurodegeneration nor premature ageing. In conclusion, this puzzle still has many missing pieces.

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2. Role of the DNA repair pathway NER and inflammation in neurodegeneration and aging

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Aging is the multidimensional process of physical, psychological and social change at a cellular, organismal and population scale. It is a very complex process, which involves both genetic and environmental factors, with a 20-30% and 80-70% influence, respectively. Massive genetic studies in supercentenarians and progeroid syndrome patients have revealed candidate aging-related genes, an important amount of them involved in DNA repair processes.

Contrary to maximum lifespan, average lifespan has been greatly increased in the last centuries, thus making health span improvements a social need. Elucidating the pathways involved in DNA repair (such as Nucleotide Excision Repair, NER) and their alterations could potentially give us new targets for increasing both health and lifespan, while ameliorating progeroid rare diseases. Moreover, those pathways are also closely related to cancer and neurodegeneration processes, thus findings could also shed some light on those fields.

In the light of this, we decided to hypothesize the relationship between mutations in proteins of the DNA repair system and neurodegeneration and aging, focusing in syndromes derived from NER pathway alterations. NER is a multistep pathway capable of repairing DNA damage by removing short oligonucleotide containing the lesion and copying the opposite undamaged strand. Its alteration leads to DNA damage accumulation, specifically those repaired only via this pathway (for instance 8,5'-cyclo purines). NER can be divided into two sub-pathways, GG-NER and TC-NER, that differ in DNA lesion recognition. Our study is focused on Cockayne syndrome (CS) and Xeroderma Pigmentosum (XP) which present an alteration in the TC-NER pathway resulting in transcription blockage when error happens.

Our hypothesis is that the reported accumulation of DNA alterations and its consequences are sensed by the cell triggering a signalling route which results in an aging-related impairment in insulin and IGF-1 pathways. Furthermore, this alteration could activate the immune system via NF-κβ, in order to promote the elimination of the DNA damaged cell by the immunologic system, among other processes. Consequently, a chronic systemic inflammation state would be induced, accelerating aging processes, especially neurodegeneration.

We would like to emphasise the complexity of the process, as a wide range of completely different pathways work together, therefore many other non-mentioned alterations would be also taking part in the whole acceleration of the aging in those individuals. In this regard, mitochondrial alterations or neural apoptosis have also been reported.

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3. Ageing - Can we live forever?

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Background: Ageing is a complex multifactorial process that involves physical, mental and social changes over time. In recent years there has been a significant increase in life expectancy, but the maximum life span in humans has remained constant around 120 years. The study of supercentenarians and progeroid syndromes allows us to deepen the knowledge of genetic and molecular aspects of ageing, considering events such as DNA damage, caloric restriction and oxidative stress.
Relevance: Progeroid syndromes, such as Xeroderma Pigmentosum and Cockayne Syndrome, are caused by the accumulation of unrepaired DNA damage. Therefore, the malfunction of DNA repair mechanisms can be associated with aging. It has been shown that certain genes have a major influence on this phenomenon: aging genes, so we hypothesize which of these genes could cause the neurodegeneration and premature aging observed in these patients.
Response: Xeroderma Pigmentosum group A (XPA) and Cockayne Syndrome groups A and B (CSA and CSB) are progeroid syndromes caused by mutations in DNA repair proteins. Specifically, they affect the nucleotide excision repair mechanism (NER) and are characterized by an extreme sensitivity to ultraviolet light.
Regarding Xeroderma Pigmentosum group A, XPA is a protein involved in the NER repair mechanism, acting as a scaffold protein. Affected patients present mutations in this gene. We hypothesize that these alterations could lead to mitochondrial dysfunction and, consequently, to an increase in the production of reactive oxygen species (ROS). These would cause toxicity and an inflammatory state. Due to these alterations in the XPA protein of NER repair mechanism, the accumulation of DNA damage could result in a hyperactivation of the enzyme PARP1 and a decrease in SIRT1 activity, leading to deficiencies in mitophagy. All in all, this mitochondrial dysfunction in the central nervous system (CNS) would cause a severe neurodegenerative state, as mitochondria play a key role in the maintenance of neurons and their functionality. Consequently, these phenomena would cause a loss of neurons in the CNS, which would be directly associated with the premature aging observed in the affected patients.

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4. El paper de les proteïnes de reparació del DNA i del mitocondri en la neurodegeneració i envelliment

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Tots els organismes envelleixen i acaben morint. Malgrat això, hi ha diferències en la longevitat ja que aquesta depèn tant de factors genètics com ambientals. Històricament, s'han utilitzat diversos organismes model per estudiar aquestes diferències: *C. elegans* per estudiar els efectes genètics de les mutacions i *Drosophila* per estudiar efectes ambientals com la temperatura. Per altra banda, estudis genètics en supercentenaris i en persones amb síndromes progeroides van permetre trobar alguns gens implicats en l'envelliment.

Hi ha una teoria de l'envelliment que es basa en acumulacions de dany en el DNA. A mesura que les non-dividing cells van envellint, els mecanismes de reparació del DNA es redueixen, fet que possibilita la acumulació de dany al DNA. Aleshores, les cèl·lules velles acaben entrant en senescència i morint.

L'envelliment prematur en els síndromes progeroides s'explica per mutacions en proteïnes implicades en la reparació: XPA en el cas del xeroderma pigmentosum i CSA i CSB en el cas de Cockayne Syndrome.

En els síndromes progeroides s'han observat uns patrons de neurodegeneració propis de persones d'edat avançada. Tenint en compte la naturalesa genètica d'aquests síndromes, se'ns ha demanat hipotetitzar sobre la relació entre mutacions en proteïnes del sistema de reparació del DNA i la neurodegeneració i l'envelliment.

Per una banda, les mutacions disminueixen la efectivitat del *DNA repair* i, per l'altra, comporten alteracions en la senyalització nuclear-mitocondrial. Els mitocondris disfuncionals actuen com a font principal productora de radicals lliures i a més a més, no cobreixen els requeriments energètics necessaris per les neurones. Així doncs, tots aquests factors poden contribuir a la mort neuronal que resulta en neurodegeneració.

Basem la nostra hipòtesi en la via de senyalització de SIRT1 explicada al seminari. SIRT1 és una acetilasa implicada en augmentar la longevitat neuronal. Aquesta, utilitza com a cofactor el NAD i actua inhibint a p53, promovent la supervivència cel·lular i activant al factor de transcripció FOXO per promoure la resposta contra les ROS.

En el cas dels síndromes progeroides, hipotetitzem que la baixa activitat de SIRT1 pot ser explicada per una baixada en els nivells de NAD disponibles, ja que pot ser segrestat per algun enzim implicat en la via del *DNA repair*. Com que el dany no pot ser reparat correctament degut a les mutacions en les proteïnes, l'enzim es troba constantment actiu i d'aquesta manera disminueixen els nivells de NAD disponibles per a SIRT1.

Per tant, el dany al DNA inicia una senyalització mediada per p53, la qual no es troba inhibida per SIRT1. Com que no hi ha una resposta efectiva contra els radicals lliures, es produeix dany irreversible a les macromolècules. A més a més, la baixa disponibilitat de NAD comporta alteracions greus en el metabolisme energètic. En conseqüència a aquestes situacions cel·lulars desfavorables, s'inicien vies que resulten en la mort neuronal.

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5. Ageing: can we live forever?

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Ageing is the process of becoming older and is regulated by multifactorial factors like environmental and genetic mechanisms. This concept includes organismal and population ageing and cellular senescence. The factors under research involved in ageing are: oxidative stress, telomeres, ageing genes (calorie sensing) and dietary restrictions. One way to study ageing is focussing on supercentenarians and patients with premature ageing.

Studying the connection between patients with xeroderma pigmentosum group A or Cockayne Syndrome groups A and B (CSA and CSB) and their result in neurodegeneration and ageing may help us to understand the normal process of ageing in healthy people. Furthermore, it may be useful to improve the treatments and alleviate the symptoms of these patients and increase the health and life span, both of affected and unaffected people.

Patients belonging to xeroderma pigmentosum group A (XP-A) and Cockayne Syndrome groups A and B (CS-A and CS-B) present symptoms such as early-onset neurodegeneration and premature ageing. These diseases belong to the group of progeroid syndromes. They are caused by mutations in genes involved in nucleotide excision repair (NER). The impaired NER mechanism affects both dividing and non-dividing cells.

In XP-A the most common damage is produced because the UV light causes the formation of thymine dimers in the DNA of skin cells that cannot be repaired. As they are dividing cells, this leads to mutations giving rise to skin cancer. What happens in non-dividing cells, as neurons, is that damage accumulates over time. Our hypothesis is that the neurons accumulate DNA damage, which also affects mitochondria, leading to mitochondrial dysfunction so that a lot of Reactive Oxygen Species (ROS) accumulate in the neurons causing oxidative stress. These ROS damage the DNA, which cannot be repaired due to the mutation in the gene involved in the NER. Moreover, the impaired mitochondria affect neurons, as they need a lot of energy. Neurons stop working and die, leading to neurodegeneration and premature ageing, since there are no stem cells to replace them. This premature ageing is a consequence of the failure of DNA damage repair in all cells, not only neurons. Besides, this failure in DNA repair also affects stem cells that regenerate tissues, who will transmit these errors to their daughter cells, so that the failures accumulate and contribute more and more to ageing.