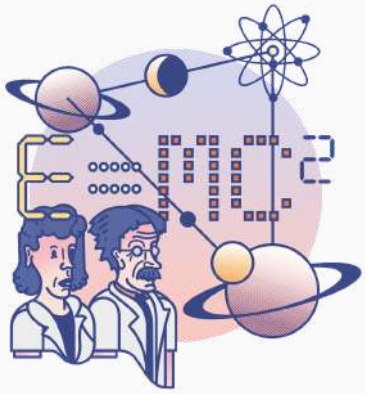

Neurodegeneration Project

Ani Poghosyan

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Minds Underground Project: Neurodegeneration
Host: Research Associate for the Nuffield Department of Clinical Neurosciences at the Oxford University Hospital Trust (NHS)
Student Name: Ani Poghosyan
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Is ageing a disease?

Ageing is an inevitable process that affects not only every living organism, but also buildings, stars and anything else that exists in the Universe. Everything has its own lifespan, whether it be billions of years, like the Sun's, or just a day, like a butterfly's - everything gradually tends towards a state of higher entropy. With age comes reduced memory, physical function and vitality. Ageing is commonly seen as unwanted, and many remedies have been devised by scientists to mask ageing and lessen its effects on the body, although a successful cure is yet to be found. Take anti-wrinkle creams - the skin may look 'younger' after treatment, but existing damage to cells is not reversed. If we are looking to cure ageing, does that mean we think of it as a disease? A disease is defined as the disorder of structure or function in an organism, especially one with specific symptoms that target a certain location in the body. The main question I am looking to answer is whether ageing can be classified as such based on the processes that ageing impacts in our brains, looking at the changes on both a cellular level and from an overall perspective. Although the main effects of ageing are observed in the individual's physical features and abilities, many of the processes that are affected by ageing take place in the brain's neural networks. Aged bones shrink in size and density, and so do some areas of the brain, which is often accompanied by diseases such as Parkinson's (PD) and Alzheimer's disease (AD). It is important to understand how ageing affects the brain because each and every living being will eventually experience its consequences.

What is ageing?

The main warning flag that ageing is beginning to affect the cells of the brain is macromolecule aggregation. This is when, over time, cells become clogged up with molecules such as proteins, carbohydrates and lipids - much like an old drainpipe. The reason behind macromolecule aggregation is mainly the misfolding of proteins, which can be caused by an excess of reactive substances in cells, such as mono-atomic oxygen free radicals (referred to as reactive oxygen species or ROS) wanting to fill up their outer electron shells. This normally happens when the antioxidants in our bodies fail to sufficiently take care of them. Aggregation of lipofuscin, for example, is a reliable marker of how old cells are. The only way lipofuscin can be ejected is through cell division and growth. Other factors can also contribute to protein misfolding, such as genetic mutations or toxins in the environment. But why do these processes become dangerous with advanced age? We can think of chaperones - proteins that assist other proteins in folding properly - as machines that need fuel. In this case the fuel is adenosine triphosphate (ATP), and the gas stations that produce it are the mitochondria. When the organism grows older, some gas stations start breaking down and rusting, meaning that they cannot produce sufficient amounts of fuel for the chaperones, and proteins don't have their machines to help them fold into their original configuration. The vital molecule ATP will be in shortage if mitochondria deteriorate to the extent of not being able to produce ATP when needed, and protein complexes in electron transport chains break down over time. This is closely linked to increased macromolecule aggregation, since healthy proteins are not available to replace toxic proteins during

autophagy, and so misfolded proteins build up in cells. Therefore, aged organisms have trouble generating the energy needed for their cellular mechanisms to run smoothly, which is why macromolecule aggregation does not cause problems for younger organisms most of the time.

What is autophagy?

In reality, proteins misfold throughout an individual's lifetime, but young people rarely suffer from diseases caused by misfolded proteins. Autophagy is constantly at work - it is the name given to the cleaning out of damaged cells by removing toxic proteins, mitochondria and other cell components from cells that are attributed to neurodegenerative diseases - but as the body ages, autophagy is slowed. Its role as the body's recycling centre and cleanser is impeded, since not enough energy is being supplied by respiration to power the process. When autophagy is delayed, there is an increase in buildup of macromolecule aggregates and slower removal of deteriorated mitochondria. When the latter process does not take place quickly enough, toxic waste from the mitochondria can leak out and damage surrounding organelles. These toxic chemicals are reactive mono-atomic oxygen atoms with a single unpaired electron (known as free radicals), which cause oxidative stress. Since oxidative stress can happen anywhere in the body, it is important to note why it is a matter of concern in the brain specifically. The reason lies in the brain's overwhelming oxygen consumption. 20% of the oxygen we breathe in is used up by the brain, despite the organ making up only 2% of our body weight. Oxygen consumption is indicative of high metabolic rate by brain tissue, and therefore the presence of many mitochondria. If these mitochondria begin to feel the effects of oxidative stress, the brain will sense it acutely. This is why something as seemingly insignificant as single oxygen atoms on the loose in our brains has the potential to negatively impact normal functions of our Central Nervous System (CNS).

Can we think of ageing as a disease like AD and PD?

The likelihood of our bodies developing both neurodegenerative and other types of diseases climbs as we age. Interestingly, genetically inherited neurodegenerative diseases are relatively rare. If age is a catalyst for these diseases, does that make it a disease in its own right? Autophagy has a role in preventing diseases such as cancer since it cleans out the body's cells and destroys mutated cells. Moreover, AD is commonly caused by atrophy of certain areas of the brain and production of unstable molecules called free radicals, both of which take place during ageing. Interestingly, the problem molecule of oxygen is the most well-known free radical in our bodies, and as we have discovered, it plays an important role in ageing our brains. All these similarities can only lead to the conclusion that ageing is just as much of a disease as AD and PD.

Conclusion

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Overall, once the aging of the body begins to cause protein misfolding and the resultant macromolecule aggregation ages the brain and body further, the organism is stuck in a constant loop that eventually leads to deterioration of the body's function beyond repair. I find that this is very similar to the way diseases like AD can impact an individual's life, corrupting the most fundamental mechanisms in their brain and steadily deteriorating vital processes. This observation naturally leads to the conclusion that ageing is a disease. On the other hand, diseases and illnesses theoretically all have some kind of cure, so does this mean that ageing has a remedy that would prevent everything that exists in the universe from having a finite lifespan? Of course, finding a cure for ageing initially sounds ideal - but taking a step back and realising the long-term consequences of virtual immortality leads to questions such as how our planet would cope with an ever-increasing population of living beings. Furthermore, even if cells can continue living and functioning forever without completely dying out, processes like autophagy simply cannot continue infinitely since they require energy. How can ageing be completely cured and removed from our lives if the second law of thermodynamics states that everything must trend towards higher disorder? Finally, death is the scrapyard of evolution. From the perspective of ensuring the survival of a species, outdated organisms wandering the earth would impede the rhythm of natural experimentation and development. In my opinion, ageing should be classified as a disease, but looking to completely cure it would create far more problems than it solves, and defies the fundamental nature of the universe.

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