An aging population in need of better treatments for dementia

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Dementia diseases like Parkinson's and Alzheimer's include continuous dysfunction and death of nerve cells in the brain, and are therefore known as neurodegenerative disorders. They lead to disabled movement, loss of sensation, decline of memory as well as the mind, and eventually death[1]. These diseases cause a lot of suffering worldwide, not only for patients, but also for relatives and loved ones compelled to observe the mental changes[2]. It's very common for older people to develop neurodegenerative diseases. One person in nine above the age of 65 has some kind of dementia[3], exponentially increasing to one in three when passing 85 years[4]. On top of that, Alzheimer's alone is the sixth leading cause of death in the U.S[3]. Since the risk of getting diagnosed with neurodegenerative disorders increase drastically with age[5], a larger part of the population will be affected every day as a consequence of our expanding lifespan[3, 6]. This will lead to an escalating economic burden on the healthcare system, which already is estimated to over $400 billion per year in the U.S[3]. Eventually we will reach a point where the affected part of the population becomes so abundant that it won't be possible to provide care for everyone without access to new therapeutic methods, considering the only option today is symptom relief[1]. Our work is aimed towards better understanding the mechanisms that causes nerve cells to become dysfunctional and die with advancing age and in dementia diseases, with the hope to help develop new treatments.

The human body is made up by many different kinds of specialized cells. Skin cells obtain properties to shield us from external violence, while nerve cells become experts in communicating information, etc. Cells that still haven't been assigned their final task are known as stem cells. Stem cells can be sculptured into any kind of specialized cell, and assist in building up and maintaining the body. They also have the ability for limitless duplication while retaining the capacity to mature into organ specific tissue[7]. There are different kinds of stem cells. Neural stem cells contain stem cell properties, but are restricted to a destiny within the nervous system. They remain active throughout adult life in two compartments of the brain, with the option to commit to a future as nerve cells in order to replace dying cells[8]. The birth of new nerve cells is known as neurogenesis, a process that declines with age due to lower amount of stem cells and slower turnover[9]. It is also heavily reduced in neurodegenerative diseases through extensive degradation of the environment where neural stem cells reside[10]. In this study we examined how small fragments of our genome could have a negative impact on neurogenesis and nerve cells during aging. These fragments, often described as mobile elements, were originally inherited from external organisms during evolution, and some have the ability to copy and paste themselves into new locations of the DNA. Insertion in the wrong position can disrupt the normal genetic code, and lead to impairment of the cell. To avoid major damage, these fragments are substantially hindered to duplicate by several different mechanisms[11].

In this study we show that mobile elements are more active in aged mice compared to adult, and actually are able to copy and paste themselves into new positions of the genome in mouse neural stem cells. However, at the same time we saw that a protein known to inhibit the insertion mechanism simultaneously was increased in aged mice, which probably were the reason that we did not detect any buildup of inserted fragments. Putting the results together, a possible chain of events could be that even though mobile elements are copied more frequently with age, they are blocked by a parallel increase of the inhibitor before being able to land at the intended position, denying insertion, and thus defending the genome from damage. But we don't rule out that insertions happen, or that the higher activity can lead to other kinds of damage. The next step of our studies will be to validate the result by a more detailed method; looking at a specific type of fragment to get a clearer readout. We also want to investigate a signaling particle that has been suggested to increase with age[12], are triggered by activity of mobile elements[13], and boost the amount of the inhibitor[14]. This particle is interesting since it agrees with our findings, and could possibly activate other mechanisms that are unfavorable for neurogenesis. Finally we want to see how cells react if we block or induce the activity of the element that we found to be more mobile in aged cells.

Our findings suggest that there is a connection between mobile elements and the age dependent decline in neurogenesis, although not directly through insertion. A more probable case is that the inhibitor that increase together with element activity could be involved in hindrance of other mechanisms that are important for the cell, and thereby lead to impairment and reduced neurogenesis. With further investigation we could determine how to use this mechanism in order to propose new treatments for dementia.

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