Therapeutic Implication of Senescent Cell Elimination in Neurodegenerative Diseases

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the Bachelor of Pharmacy degree (Hons.)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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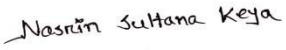

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Approval

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Ethics Statement

Hereby, I, Nasrin Sultana Keya, actively assure that for the project that this review work entitled “Therapeutic implication of senescent cell elimination in neurodegenerative diseases” is submitted for the fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the School of Pharmacy, Brac University, signifies my work under the supervision of Md. Tanvir Kabir, Senior Lecturer, School of Pharmacy, Brac University, and I have been given adequate credit where I have included others’ words, insights, or writings. No animals were used or harmed in this project.

Abstract

Neurodegenerative disease is a condition where the function of the brain gets affected due to neuronal death. Still, there is no proper way to cure this disease, but there are some drugs and treatments that can reduce the side effects caused by this disease. Senescent cell elimination is a treatment used to treat neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), etc. It has been revealed that senescent cell causes impaired learning, memory loss, etc. Excess production of amyloid precursor protein and amyloid-β (Aβ) also cause impaired learning or memory loss problems, so senescent cells contribute to neurodegenerative diseases. So, eliminating senescent cells is an excellent method or treatment for neurodegenerative diseases. Senolytic drugs are one kind of senescent cell elimination treatment that induces apoptosis in senescent cells, and senostatics is another senescent cell elimination treatment that blocks or stops the proliferation of senescence.

Keywords: Neurodegenerative diseases; senescent cell; amyloid-β; senolytic; senostatic.

Dedication

This project is dedicated to the respective Dean of School of Pharmacy Eva Rahman Kabir Ph.D ma'am and my respective supervisor Md. Tanvir Kabir sir.

Acknowledgement

All gratitude is due to Almighty Allah for providing me with the patience and fortitude to finish my endeavor. Md. Tanvir Kabir sir, my respective supervisor, guided me with his extensive knowledge and inspired me to finish my project work. This project would not have been finished without his supervision and direction. I'm also grateful to Eva Rahman Kabir Ph.D. ma'am, my department Dean, for her help and support during my undergraduate career.

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List of Acronyms

UN	United Nation
WHO	World Health Organization
FDA	Food & Drug Administration
NPC	Nasopharyngeal Carcinoma
EB	Embryoid Bodies
ESC	Embryonic Stem Cell
SOD1	Superoxide Dismutase 1 gene
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
NMRS	Nuclear Magnetic Resonance Spectroscopy
CT	Computed Tomography
Aβ	Amyloid-β
HTT	Mouse Huntingtin gene
PRNP	Prion Protein Gene in Human
NBIA	Neurodegeneration with Brain Iron Accumulation
PKAN	Pantothenate Kinase-associate Neurodegeneration
MAO-B	Monoamine Oxidase Type B
ROS	Reactive Oxygen Species

Klf4	Kruppel-like factor 4
TIMPs	Tissue Inhibitors of Metalloproteinases

Chapter 1

Background

The brain is one of the most complex organs, which has a considerable number of pathways responsible for allowing us to do so many amazing things that we can do. Billions of cells are required to construct a brain we rely on for proper functioning every second. There are numerous nerve cells, but the most important are called neurons. These cells are associated with one another for us to think, speak, and walk appropriately and in a sentence to achieve all else we do. One neuron communicates with another neuron to carry out all of the brain's functions, such as moving about, thinking about specific themes, conversing with people, or recalling the list of items we wish to purchase at the supermarket or shopping mall. As the brain has a complex structure and every single brain is connected, the minor miscommunication between cells or miscommunication in one area can create brain disorder by disrupting brain activities. Different brain disorders can affect the brain's normal function, but neurodegenerative disease is the most complicated. Neurodegenerative is a kind of disease of the brain which results in neuronal death or shrinkage of the brain (Berman & Bayati, 2018).

Neurodegenerative disease is highly connected with the age of a person. Age-related neurodegenerative diseases such as Parkinson's Disease (PD) and Alzheimer's Disease (AD) have become more common as populations have grown older. Even for less prevalent neurodegenerative diseases like Amyotrophic Lateral Sclerosis (ALS), this trend seems likely, even if it has not yet been proven (P. Jhonson, 2015). There is significantly less number of treatments that are available for age-related neurodegenerative disorders, which tend to advance irreversibly and are linked with significant economic and personal expenses (Hou et al., 2019).

Proteins that have become misfolded or aggregated are present in a range of chronic neurodegenerative disorders. In rare individuals, protein misfolding is caused by genetic defects, while most patients have sporadic variants that environmental factors may cause. In various neurodegenerative illnesses, misfolded proteins accumulate, impairing brain connections and plasticity while also activating cell death signalling pathways (Nakamura & Lipton, 2009).

Early detection of neurodegeneration is crucial because it enables early intervention, which may help prevent the disease from advancing further. Neuropathology is often considered to be the gold standard of a current diagnosis. Nonetheless, it is frequently predicated on an autopsy performed following the death of a patient. As a result, medical professionals are investigating non-invasive diagnostic techniques that could be used to detect neurodegeneration early on, when pharmaceutical intervention is still possible (Deczkowska et al., 2018).

There are both clinical and pathological diagnosis systems for this disease. The structure of MRI is used to diagnose different neurodegenerative diseases. Some molecular markers are helpful in the neuropathologic diagnosis of neurodegenerative disease, brain-specific biomarkers or proteins in cerebrospinal fluid for the diagnosis of various neurodegenerative disorders, genetic diagnosis of neurodegenerative disease, molecular diagnostics provide such a powerful method for detecting and diagnosing multiple neurodegenerative disorders such as AD and PD, and the confirmation of such a diagnosis allows for early diagnosis and subsequent medical counselling, allowing specific patients to participate in clinically significant drug trials, among other things (Koikkalainen et al., 2016; Lausted et al., 2014).

There is no permanent cure for any neurodegenerative disease, but there is some ways or treatment to improve the patient's condition. Although no solution has yet been discovered,

researchers have developed a few promising theories. The replacement of dead neurons with new ones is one of the most intriguing concepts being explored by researchers. A unique type of cell known as stem cells can replace dying neurons. Stem cells are immature cells that can change into any cell in the body, including neurons, which is why they can be used to replace brain neurons that have died. Most treatments are cell treatments, and various cell treatments help to treat patients with neurodegenerative disease like-mesenchymal stem cell treatment, induced pluripotent stem cell treatment etc. There are also other treatment processes, the endocannabinoid system as a target for neurodegenerative disease treatment, progranulin (a secreted glycoprotein) helps in treating neurodegenerative diseases (Hardy & Gwinn-Hardy, 1998; Feng & Gao, 2011)

Chapter 2

Global impact of neurodegenerative diseases

According to the report of UN (27 February 2007), almost one billion people are suffering from neurodegenerative diseases in the whole world, and this disease affects one in every six people on the planet (UN, 2007).

PD, ALS, AD, and other neurodegenerative diseases are firmly related to age, so this situation is expected to take off as the population ages due to the improvement of medical science. Only AD affects approximately one-third to one-half of those over the age of 85, and this data can give the idea of the gravity of other neurodegnerative diseases (Academies, 2017)

Chapter 3

The situation of neurodegenerative diseases in Bangladesh

In Bangladesh, the importance of neurology is introduced during the 1960s. Although the number of neurologists in Bangladesh has increased, this is insufficient, and the lack of facilities for the treatment of this disease makes things more complicated. For this, many patients seek help from the internet or from different specialists to prevent this disease (Alam, 2017). According to a study, the number of practitioners and experts are highest in neurology department and lowest in neurophysiology department. However, the highest number is not enough if the population of Bangladesh is considered. In the developed countries, caregivers are available for neurodegenerative patients, but according to the study of WHO Global Dementia Observatory Provisional Country Profile 2017, the density of caregiver professionals in Bangladesh is 3.067% per 10000 population; this report also mentioned that the accessible number of neurologists is 0.9 which is for every 100,000 population. There are some special training and nursing courses in Bangladesh for the caregiver, but in the end, it is proved that this training and nursing course are not enough for handling neurodegenerative patients (Roberts & Connell, 2000)

Chapter 4

Types of neurodegenerative diseases

Neurodegenerative diseases affect the central nervous system and is characterized by the gradual deterioration of neural tissues or the death of neural cells. There are different neurodegenerative diseases, but the most common diseases are- Parkinson's disease, Alzheimer's disease, Huntington's disease, and Amyotrophic lateral sclerosis. In AD, the neuron of the brain is attacked and caused by loss of memory which is also known as dementia; PD mainly attacks the dopaminergic neurons, which are situated between the substantianigra and the striatum; ALS primarily affects the neurons that regulate voluntary muscles, and HD is a genetic disorder which can affect the motor and cognitive ability (Agrawal, 2015)

4.1 Alzheimer's disease

Alzheimer's disease is a common term for memory loss that primarily affects the patient's memory, thinking, and behaviour and is the most prevalent cause of dementia. Dementia or memory loss is a condition where the loss of cognitive functioning like- remembering, thinking, behavioural abilities etc., occurs to some extent that it becomes impossible for a patient to continue a normal lifestyle by themselves. It slowly destroys the ability of thinking and memory, and gradually, it destroys the ability to do simple tasks. It is titled after Dr Alois Alzheimer, who observed the first alterations in brain tissue in a woman who died of an atypical mental disease; after the death of that woman, he tested the brain of that patient and found many unusual plaques and twisted bundles of fibres (G, 2020)

In the brain of AD patients, an irregular clump or cluster of beta-amyloid protein is found, and several fragments of beta-amyloid protein clumps are formed, and later they bind together to form plaque. These plaques interrupt the signal between the synapses and interfere

with the information passing from one cell to another, which initiates neuronal cell death. There are three stages of AD and they are- mild, moderate and severe AD (Colbert, 2017).

4.1.1 Mild Alzheimer's disease

The problems in this stage- patient face trouble handling money and face difficulty paying the bill; tendency to repeat questions; take a long time to accomplish the everyday task; started changing patient's behaviour and personality (Colbert, 2017).

4.1.2 Moderate Alzheimer's disease

This stage targets the areas of the brain that regulate language, logical reasoning, and sensory systems, such as the ability to recognize appropriate smells and sounds. Patients start facing trouble recognizing their family members and close ones in this stage as memory loss and confusion become worse day by day. Hallucinations, delusions, impulsive behaviour may also start in this stage (Colbert, 2017).

4.1.3 Severe Alzheimer's disease

Plaques and tangles began to colonize the brain, causing remarkable brain tissue atrophy. With severe stage AD, a person cannot communicate with other and have to be entirely dependent on other people (Colbert, 2017).

4.2 Parkinson's disease

Parkinson's disease is a neurological system ailment that impairs the body's movement, resulting in tremors or stiffness in various body parts and slow movement. People with PD face difficulty with balance and coordination, symptoms of PD getting worse over time, and difficulty walking and talking (slurred speech). Men are highly affected than women in this disease (Davie, 2008).

PD attacks the part of the brain that controls the body's movement and also the part that produces dopamine. Dopamine is a vital brain chemical that plays an essential role in the movement. So, when the neurons which are attacked by PD die or become impaired, it causes less or stop the production of dopamine which results in difficulty in movement, though the scientists are still confused about the actual cell death of the cells which produce dopamine (Parkinson's Disease, 2017).

4.3 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a disorder that affects the motor neurons and causes different indications in the upper and lower motor neurons, resulting in muscular control impairment. Only upper motor neurons are affected in the early stage, followed by lower motor neurons. However, in most cases, both upper and lower motor neurons are affected simultaneously, and individuals with ALS have an average life expectancy of three to five years (Rowland & Shneider, 2001).

ALS is also known as Lou Gehrig's illness. Lou Gehrig was a baseball star and was the first person to be diagnosed with the condition. With the progression of this disease, some complications start to arise in the patient's body, like – speaking problems, breathing problems, dementia, and eating problems (ALS - Symptoms and Causes, 2021).

People who are diagnosed with ALS tend to lose weight because they have difficulty swallowing and chewing. For that, they cannot eat properly, and also they burn calorie faster than ordinary people, which result in losing weight. There are two onsets of ALS; one is 'limb onset' ALS, when ALS symptoms are first noticed in the leg or hand, and another one is 'bulbar onset' ALS when a person first notice speech or swallowing problems (NINDS, 2021).

4.4 Huntington’s disease

Huntington's disease is a genetic disorder that causes brain damage and eventually deteriorates a portion of the brain. The condition of the patient becomes worse over time (NHS website, 2021).

HD is a genetic disorder inherited from parents, and a person can survive 10-30 years from the day of the emergence of the disease. However, death happens within ten years of the onset of juvenile HD symptoms. With the progression of this disease, the risk of suicide also increases as the person starts facing difficulties with their regular task. In the end, they start losing their independence because of the complexity of the disease. Some people with HD have the ability to understand the language and also can recognize their friends and family members, but some cannot recognize their family members and friends (Huntington’s Disease - Symptoms and Causes, 2020).

According to a study, HD affects 1-10 of 100,000 people, and it varies according to the location of the world, but it affects both males and females equally. HD mainly affects the caudate nucleus and putamen, which are located in the basal ganglia, a part of the brain and gradually degenerate this part which is responsible for coordinating movement (Gonzalez-Usigli, 2022)

Chapter 5

Causes of neurodegenerative diseases

The word neurodegenerative can be divided into two parts; the first part is neuro which means brain, and the second part is degenerative, which means breaking down or dying, so neurodegenerative means breaking down brain cells. Neurodegenerative disease is a complex process for that the actual cause or reasons for this disease is still unclear to the scientist. Though the exact causes are still unknown, some causes are proven by scientists are related to neurodegenerative diseases (Armstrong, 2013)

5.1 Alzheimer's disease

Several theories cause AD- a) ageing theory; b) theories which are based on the degeneration of anatomical pathways; c) environmental factors, such as exposure to aluminium, any type of head injury, malnutrition etc. d) theories based on genetic factors like mutations of amyloid precursor protein and presenilin; e) theory based on mitochondrial dysfunction; f) theories based on blood-brain barrier dysfunction; g) theories based on immunology; h) theories based on infectious disease (Armstrong, 2013).

AD is a type of dementia that develops gradually and leads to the complete loss of cognitive ability and memory. Some studies show that β-amyloid is one of the main reasons for this disease or of this cytotoxic process which interferes with the intracellular calcium and results production of free radicals by storing intracellular calcium, which occurs by activating the calcium channel (Holscher, 1998).

Another revised article mention the causes for AD, Aβ deposition, pathologic tau. It damages the brain structure and stops the function of the brain (D. James and A. Bennett, 2019). β-amyloid proteins bind together and form several plaques, which interfere with the connection

of synapses that are responsible for transferring information from one cell to another. This process results in the early onset of AD. Due to this impairment in synapses, the connection is lost, which affects the ability to learn, remember and communicate in the patient's body. Protein strands which are essential for the brain got tangled in a patient's brain with AD, and subsequently, brain cells die; brain inflammation and brain shrinks are also the consequences of AD (Colbert, 2017).

5.2 Parkinson's disease

Parkinson's disease is one type of movement disorder that affects the movement of the body. There are several symptoms that are mostly related to the movement of distinct body parts due to the death of neurons which produce dopamine and results in impaired movement (CM & C, 2017).

Like other neurodegenerative disorders, the exact or specific cause of PD is still unknown, but some factors are responsible for this disease; a) genes: some genetic mutations are responsible for PD, b) environmental factors: subjection to definite toxins or environmental factors may increase the risk of PD, c) presence of Lewy bodies: a cluster of some specific substance which is known as Lewy bodies in brain is the clue for the scientist to identify that the patient is suffering from PD, d) Alpha-synuclein found in Lewy bodies: there are several chemical substances in Lewy bodies, but Alpha-synuclein is an important one among them which also form a clump, and that clump is unbreakable (CM & C, 2017).

Along with the nerves that produce dopamine, patients with PD also lose nerves that produce norepinephrine. It is another essential chemical substance in the brain and the primary chemical messenger of the synaptic nervous system, which controls several critical body functions such as heart rate, blood pressure etc. Thus, a deficiency of norepinephrine results

in fluctuating blood pressure, tiredness, and slower food transport through the digestive tract (*Parkinson's Disease*, 2017).

5.3 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis damages the neurological system of upper and lower motor neurons, which control voluntary muscular movement. Motor neurons are situated in the brain and spinal cord, which are mainly responsible for conducting movement, swallowing, speaking, and breathing by sending messages or commands from the brain to the voluntary muscle to accomplish the functions (C. Zayia & Tadi, 2021). So, in ALS, motor neuron gets affected. Eventually, they are damaged, which result in the stop of sending messages to the voluntary muscle, and for this, lacking muscle cannot work (Orrell, 2007).

Genetic and environmental factors both contribute significantly to the development of ALS. Different genetic mutations are responsible for ALS, and some specific genetic mutations alter the processing of RNA molecules, leading to motor neuron degeneration related to ALS. Other genetic mutations occur due to unusual protein recycling. Several environmental factors are responsible for ALS, like exposure to a toxic substance, virus, any type of physical trauma, food habit etc. e.g. strenuous physical activity may increase the risk of developing ALS (NINDS, 2021).

5.4 Huntington's disease

Huntington's disease is a genetic disorder mostly related to the gene. If one of the parents has HD, then there is a 50% chance of their children getting affected by HD later, and affected children can also pass the gene to their children; on the other hand, there is a 50% chance of not getting affected by HD (NHS website, 2021)

HD is also referred to as autosomal dominant disorder; an autosomal dominant disorder, just one copy of a gene is required for the development of the disease in a person's body (Novak, 2010).

Chapter 6

Symptoms of neurodegenerative diseases

Symptoms of neurodegenerative disease increase with time as the degeneration of brain cells increases. There are several symptoms like memory loss, difficulty in talking, difficulty in movement etc. (Patterson et al., 1990).

6.1 Alzheimer's disease

Alzheimer's disease or dementia is a brain disease where brain cells or neurons die for different factors. At that time, some specific signs and symptoms are visible in the patient's body, which helps the physician get an idea of the disease. Delusion, hallucination, anxiety, activity disturbances, depression but not at a severe level, paranoid feature etc. are the symptoms of this disease (Patterson et al., 1990).

The first sign of AD is a memory problem then it gradually worsens the movement, and sometimes it interferes with the smell ability of a person (Bruen et al., 2008).

6.2 Parkinson's disease

Parkinson's disorder is also known as a movement disorder because it gradually slows down the movement and stiffens the movements. There are both movements and non-movement symptoms for PD. Movement symptoms occur when the brain stops producing dopamine. Bradykinesia, tremor, rigidity help a doctor to diagnose the disease, but there are more movement symptoms, such as- cramping, which is also known as dystonia; drooling, another name sialorrhea; micrographia (cramped handwriting); dyskinesia; shuffling gait; festination; freezing; masked face also called hypomimia (combination of bradykinesia and rigidity); soft speech another name hypophonia (Sveinbjornsdottir, 2016).

Non-movement symptoms include- cognitive changes, constipation, excess sweating, fatigue, seborrheic dermatitis, hallucination, lightheadedness (orthostatic hypotension), mood disorders (depression, anxiety), pain, sexual dysfunction, sleep disorder (insomnia), weight loss etc. (Poewe, 2008).

6.3 Amyotrophic lateral sclerosis

Symptoms of ALS are divided into two types based on the location of the first sign of ALS in the body, one is limb onset ALS (when symptoms start in arms or legs), and another one is bulbar onset ALS (when speech or swallowing problem type symptom appear first). Without these two types of primary symptoms, other symptoms appear in a patient's body gradually and lead the doctors to identify the disease (Mitchell & Borasio, 2007)

Signs or symptoms of ALS vary from person to person based on different brain cell parts affected by ALS, so ALS does not affect the same part of the brain in every patient. It varies from person to person, so signs or symptoms also vary. Weakness in legs or feet as the muscle of this part got pretentious by ALS, difficulty in walking (tripping or falling), hand weakness, therefore, trouble writing, bulbar onset ALS causes difficulty in swallowing and slurred speech, muscle cramp, sudden crying or laughing without any reason, changes in behaviour etc. are some symptoms of ALS (ALS - Symptoms and Causes, 2021)

Chapter 7

Diagnosis and Test

Neurodegenerative disease is a condition in which the central nervous system gets affected, and eventually, loss of neural tissue or neuron death occurs. After the deterioration of neurons, they cannot regenerate by themselves, for that the change in neurons causes function abnormally, which later affect the other parts of the body. With time, the patient's condition becomes worse, so early detection of the disease help to prevent further progression of the disease. Molecular diagnosis, a powerful technique that helps in the early detection of neurodegenerative disease and among all molecular diagnostics, the application of biomarkers is the powerful one. The measurement of biomarkers can be done by several imaging techniques such as PET, MRI, NMRS etc. (Agrawal & Biswas, 2015)

Disease	**Genetic Diagnostic markers**	**Biochemical diagnostic markers**
Alzheimer's disease (AD)	Amyloid precursor protein(APP) mutation Presinilin-1 gene mutation Presinilin-2 gene mutation ApoE isoforms ApoE polymorphism	Plasma/CSF $A\beta_{1-42}$ peptide CSF tau protein Phospho-tau
Parkinson's disease (PD)	α-synuclein gene mutation Parkin gene mutation	Loss of dopamine transporter(DAT)

	UCH-L1 gene mutation PINK1 gene mutation DJ-1 gene mutation NR4A2 gene mutation	Lewy bodies
Amyotrophic lateral sclerosis (ALS)	ALS2 gene mutation NEFH gene mutation SOD1 gene mutation C9orf72 gene mutation FUS gene mutation TARDBP gene mutation	mGLUR2 SOD1 Glutathione 8OH2'dG Cytokines
Huntington's disease (HD)	HTT gene mutation	Growth hormones Cytokines mGLUR2 SOD1

Table 1 : *Genetic & biochemical diagnostic markers of different neurodegenerative disease*

Source: (Agrawal & Biswas, 2015)

There are also other tests for neurodegenerative disease. For AD, several tests like memory testing, problem-solving, testing attention and counting ability etc. blood and urine tests are also done to identify causes of the problem (Alzheimer's Disease Fact Sheet, 2021). For

Parkinson’s disease, diagnosis processes are different. At present, there is no blood or urine test for PD, but by checking previous medical history and by doing the neurological examination, PD can be diagnosed (Parkinson’s Disease, 2017). As with other neurodegenerative diseases, ALS lacks a particular diagnostic test, making it often difficult to distinguish ALS from other motor neuron diseases. The abnormality of the lower motor neurons can be confirmed electromyographically by demonstrating denervation in at least three limbs. Additionally, the drug's efficacy can be determined by electromyography by determining the number of surviving motor neurons; also, magnetic resonance spectroscopy can be used to determine the number of surviving neurons in the motor cortex (Rowland, & Shneider, 2001). For Huntington’s disease, blood tests, genetic testing, magnetic resonance imaging, CT scan etc., are done to diagnose HD. In the genetic testing of HD, the test tries to find out if there is any mutation in the HTT gene. On the other hand, CT scans and MRIs monitor basal ganglia degeneration (Martino et al., 2012).

Chapter 8

Pathophysiology of neurodegenerative diseases

8.1 Glutamate excito-toxicity

Glutamate is a major excitatory amino acid and a neurotransmitter in the human nervous system. It has an effect named excitotoxicity effect on neurons, which occurs due to glutamate over-reactivity caused by exogenous or endogenous factors and gradually cause neuronal cell death. Without exogenous and endogenous neurotoxins, glutamate activity can be enhanced by genetic, metabolic, or other environmental factors. Also, this glutamate excitotoxicity affects intracellular calcium homeostasis and cause excessive free radical production. This glutamate-mediated toxicity contributes to motor neuron diseases like ALS (Relja, 2004a).

8.2 Protein disorder

The misprocessing of protein cause neurodegenerative disorder, which leads to the accumulation of one or more proteins in the central nervous system. Some proteins are named infectious Prion proteins. In humans, prion proteins are encoded by the PRNP gene, located on the short arm of chromosome 20. This prion causes central nervous system degeneration (Relja, 2004b).

8.3 Brain iron accumulation

NBIA, or neurodegeneration with brain iron accumulation, is a disorder in which iron accumulates in the brain's basal ganglia. The most common cause of NBIA is a mutation in the pantothenate kinase 2 gene. In children, this pantothenate kinase-associate neurodegeneration (PKAN) cause dystonia and pigmentary retinopathy. In an adult, PKAN causes neuropsychiatric disorders. NBIA is also related to neuroferritinopathy, resulting from

the mutation in the ferritin light chain. PKAN is generally divided into two categories based on the age of onset, signs and symptoms and the rate of progression; one is classic PKAN, and another is atypical PKAN. Classical PKAN is early-onset (before age 6), homogeneous and rapid progression; the main clinical feature of classical PKAN are dystonia, dysarthria, rigidity, hyperreflexia, extensor toe signs etc. After 10-15 years of onset, the affected children lose the ability to walk. Atypical PKAN is a heterogeneous group; later onset (avg onset is 13-14 years), slow progression rate, psychiatric symptoms, speech difficulty, dysarthria etc., are the main features of this disease (Gregory & Hayflick, 2005)

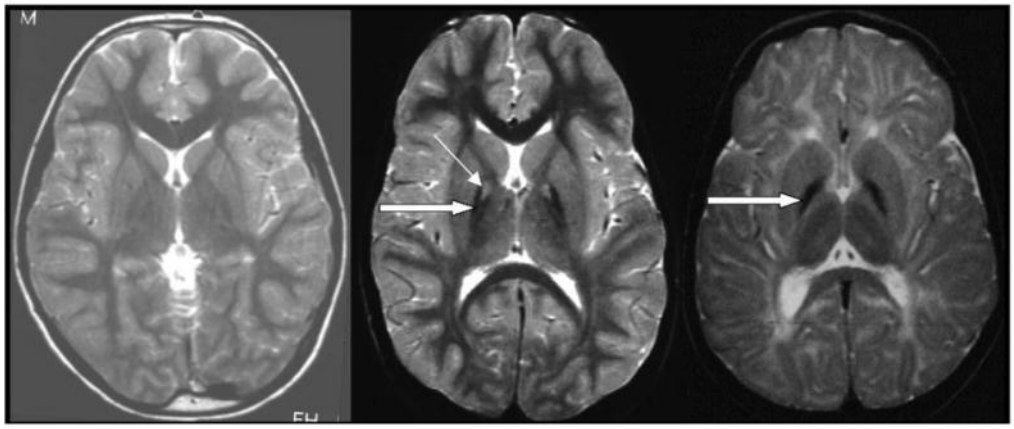

Figure 1 : Magnetic resonance imaging of normal brain (left), PANK2 mutation-positive patient's brain (middle), PANK2-negative patient's brain (right)

Source: (Gregory & J. Hayflick, 2005)

8.4 Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases and their natural tissue inhibitors are involved in cell signalling processes and the release of extracellular matrix (ECM) and non-ECM molecules. If the MMP activity is disturbed, it leads to the imbalance between metalloproteinases and results in various disorders like neurodegenerative disorder by their inhibitors. It causes AD, and AD

has a complex relationship with MMP and TIMPs. MMPs and TIMPs are identified in neuritic senile plaques and neurofibrillary tangles in the postmortem brains of people with AD. In the in-vitro experiment, it is found that MMPs induce tau aggregation and neurofibrillary tangles. Moreover, MMPs initiates AD pathogenesis by disrupting the blood-brain barrier (Barbaraa et al., 2013).

8.5 Oxidative stress

Oxidative stress results when a considerable amount of derivatives of reactive oxygen species are generated during the pathological condition. This oxidative stress causes the degradation of protein, lipid, and nucleic acids, which results in neuronal cell death by necrosis or apoptosis. When the level of ROS exceeds the standard level, then it causes the impairment of structure and function of the cell and leads to the modification of cellular DNA, protein and lipid and cause different neurodegenerative disorder by affecting the brain cells (Freire et al., 2012).

Chapter 9

Drugs and Treatment

9.1 Drugs

Neurodegeneration occurs when the brain and spinal cord neurons are affected and result in problems in motor or cognitive functions. Neurodegeneration is a complex process, so it is difficult to identify specific drugs to cure this disease, but some limited drugs are used to delay the deterioration caused by this disease or used to cure the symptoms, not to cure or prevent the disease (Aldewachi et al., 2021).

Galantamine, rivastigmine, and donepezil are cholinesterase inhibitors prescribed to patients with mild to moderate AD. Researchers find out that cholinesterase inhibitors prevent the breakdown of acetylcholine. Acetylcholine is an essential chemical of the brain vital for memory and thinking, so these drugs help minimize cognitive and behavioural symptoms. Aducanumab is the first drug which FDA approves to treat the underlying AD process, it contributes to the reduction of amyloid plaques in the brain and may decrease the progression of AD, but it will be prescribed when the amyloid plaque is seen in the brain by PET scan (Durães et al., 2018).

The primary treatment for PD is levodopa, which stimulates nerve cells to create dopamine, as dopamine production is impaired in Parkinson's disease. Carbidopa is frequently used with L-dopa to mitigate some of the adverse effects of levodopa therapy. Other drug classes prescribed for PD include those that help manage non-motor symptoms and those that boost the brain's dopamine level. MAO-B inhibitors are used to suppress a specific enzyme that decreases the amount of dopamine in the brain; amantadine is an antiviral medication used to treat uncontrollable movements. Additionally, cholinesterase inhibitors are utilized to

alleviate tremor and muscle stiffness. When persons with PD do not respond well to medication, deep brain stimulation (DBS) is used (Lees, 2002).

Riluzole (Rilutek) and Edaravone (Radicava) are the two drugs approved by Food and Drug Administration for treating ALS. Riluzole is a glutamate antagonist taken orally, and it increases the life span from 3-6 months. This drug has some side effects like dizziness, gastrointestinal disorder, liver problem etc. Edaravone is another drug administered intravenously, and this drug also has some side effects like bruising, headache, breathing problem etc. (Lu et al., 2016).

Currently, there is no medication available to slow or stop the progression of HD. Nevertheless, there are some medicines that the physician prescribes to reduce the symptoms of HD. To control the hallucination, angry outbursts, agitation, antipsychotic drugs like-chlorpromazine, haloperidol, risperidone, olanzapine etc., are prescribed to the patient. Depression is another side effect of HD. Fluoxetine and sertraline are prescribed as an antidepressant. Mood stabilizing drugs such as lithium suppresses anxiety and severe mood swings. The amount of dopamine needs to be reduced for stopping the abnormal movement. Tetrabenazine, deutetrabenazine etc., drugs are prescribed to reduce the level of dopamine (Roos, 2010).

9.2 Cell treatment

Neurodegenerative disease cause progressive cell death, the actual process of cell death is complex, and it is difficult to identify specific treatment for this disease. No treatment can cure neurodegenerative disease, but some treatment processes are introduced by which the patient's condition, like a patient's life span, can improve; stem cell treatment is such a kind of treatment. Stem cell therapy or treatment offers potentiality for all forms of neurodegenerative disease. There are several types of stem cell treatment: human induced

pluripotent stem cell treatment, mesenchymal stem cell treatment, embryonic stem treatment, senescent cell elimination, neural stem cell treatment etc. (Sakthiswary & Raymond, 2012).

9.2.1 Mesenchymal stem cell treatment

Mesenchymal stem cell, also known as Marrow stromal cells (MSC), is a therapeutic tool for neurodegenerative diseases such as AD, PD, HD, ALS, MS. MSCs mainly work by transplantation process; they are transplanted into the brain, which helps to regenerate of damaged tissue by producing neurotrophic and growth factor and MSCs also work as gene delivery vehicle (Tanmay & Vatsal, 2014).

There are some advantages of MSCs transplantation over other stem cells for treating neurodegenerative disease; compared to other stem cells, they are easy to isolate from patient's bone marrow, and they do not cause any further CNS(central nervous system) problems during the isolation process. According to some studies, MSCs can transdifferentiate into functional neuronal cells, which can open up the possibility of cell replacement in neurodegenerative disease, but it is pretty challenging for the cell fusion event (Torrente & Polli, 2008).

Targets diseases	**Pre-clinical advantages**
Parkinson's disease (PD) 6-OHDA rat MPTP primate	Neuroprotection of degenerating neurons Differentiation in neuron-like cells expressing TH
Huntington's disease (HD) HD mouse	Long-term functional improvement

Alzheimer's disease (AD) AD mouse	Migration into different areas of the CNS but does not reach sufficient concentrations in relation to the extent of the AD-induced lesions
Amyotrophic lateral sclerosis (ALS) SOD 1 mice	Neuroprotection of degenerating neurons and increased survival of transplanted mice
Multiple sclerosis (MS) EAE mouse model	Decrease inflammation and reduce tissue injury

Table 2: *Advantages of MSC transplantation in neurodegenerative disease*

Source: (Torrente & Polli, 2008)

9.2.2 Human induced pluripotent stem cell treatment (iPSC)

Pluripotent cells are formed from blastocysts' inner cell mass and can proliferate and differentiate into three germ layers of cells. Additionally, pluripotent cells aid in the internal repair mechanism by regenerating indefinitely into differentiated cell progeny of new stem cells. In 2006, the Yamanaka group at Kyoto University published a study demonstrating that by inducing only four pluripotency-associated transcription factors (Sox2, Oct3/4, Klf4 and c-Myc) in mouse fibroblast cells, they were able to generate induced pluripotent stem cells, which play an essential role in the treatment of neurodegenerative disorders (Bahmad et al., 2017).

Reprogramming can be affected by several conditions, if the delivery is inefficient, improper culture condition, time etc. While direct reprogramming is a straightforward procedure, it is a slow and vulnerable one that can be harmed by various circumstances, impairing the efficiency, reproducibility, and quality of iPSCs. For the iPSCs regeneration technique, fibroblasts are the most used cell, but that does not mean fibroblasts have the most efficacy (Bahmad et al., 2017).

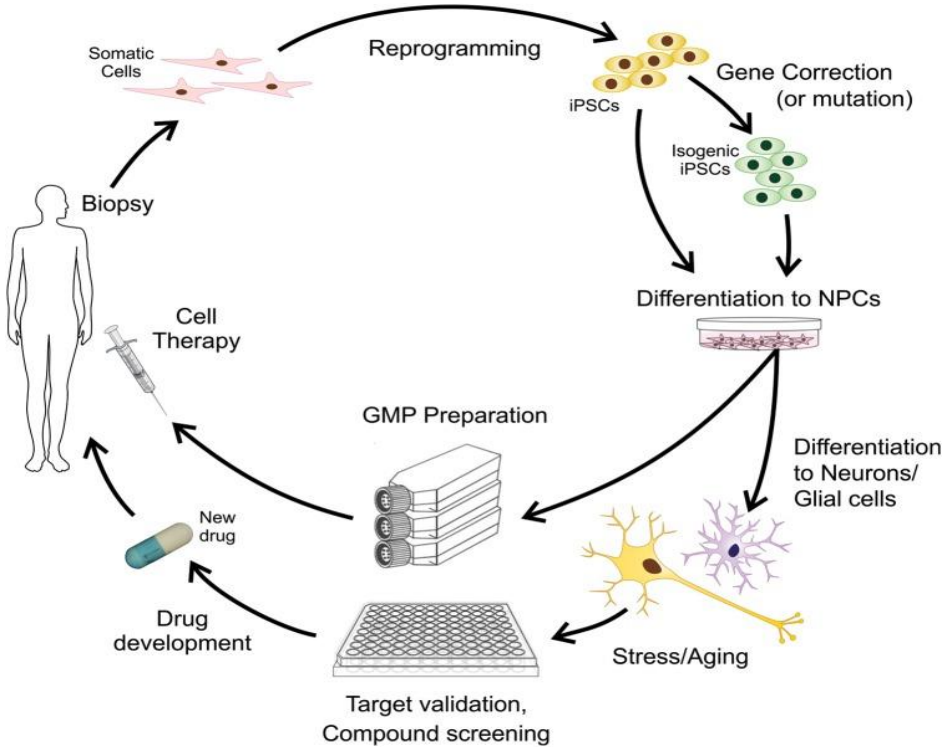

Figure 2 : Human somatic cells, such as mature skin fibroblasts transformed into pluripotent stem cells, are used in this illustration

Source: (A. Ross & S. Akimov, 2014)

In a model of HD cell culture, the combination of HD iPSCs with an inhibitor of mitochondrial fission related protein termed Drp1 improves mitochondrial measurements and increases cell viability. This study demonstrates the utility of HD iPSCs for studying disease aetiology and evaluating experimental treatments. Cell transplantation is another option for

treating HD iPSCs. In one study, neuronal precursors produced from HD iPSCs were transplanted into an HD rat model with excitotoxic striatal lesions, and behavioural recovery was observed (Ross & Akimov, 2014). For PD, it is demonstrated that some behavioural improvement was observed when iPSCs were differentiated into dopamine neurons and implanted into a PD rat model. Another study has shown that adult mouse striatum can be transplanted with differentiated PD iPSCs and that some of these cells can form axons projecting into the striatum (Ross & Akimov, 2014). Although motor neurons can be successfully differentiated from ALS-iPSCs, there is no information on the effect of the SOD1 mutation on this differentiation. In 2015, Li et al. used retroviruses to generate ALS-iPSCs from fibroblasts. The ALS-iPSCs were generated by differentiation into NPCs via an EB formation experiment while blocking the SMAD pathway (Bahmad et al., 2017).

9.2.3 Neural cell treatment

The primary cause of the neurodegenerative disease is the death of neurons or glial cells in the brain and spinal cord. Different types of stem cell treatments are there to regenerate the glial cells and neurons like ESCs, MSCs, iPSCs, and NSCs. Transplantation of neural stem cells which are generated from stem cells in in-vitro models Neurodegenerative diseases, like- AD, PD, ALS, HD etc., shows clinical improvement and also this treatment helps to extend the lifespan of a patient and lower the side effects (Kim et al., 2013).

NSCs have an endless development capacity and the ability to differentiate into three distinct cell types that comprise the central nervous system's essential cells: astrocytes, oligodendrocytes, and neurons. The generation of immortalized cell lines of NSCs that can divide indefinitely is accomplished by introducing oncogenes. These cells are used to study essential neuronal development, cell replacement therapy, and gene therapy due to their advantageous characteristics. Stable immortalized NSCs are homogeneous because they

originate from a single cell, NSCs can expand rapidly to large numbers, and stable expression of therapeutic genes is easily obtained. After being genetically modified in vitro, immortalized NSCs survive and integrate into host tissues. They develop into neurons and glial cells following in vivo transfer to the intact or injured brain. However, numerous challenges must be overcome before NSCs may be used clinically to treat patients with neurodegenerative illnesses (Kim et al., 2013).

Chapter 10

Senescent cell

A senescent cell is a condition where permanent cell cycle arrests occur due to intrinsic and extrinsic stimuli and developmental signals. It is a multi-step process, and in each process, it changes its characteristics continuously. Cellular senescence has an impact on tissue repair and regeneration, so it is related to the ageing process (Álvarez & Collado, 2016).

Like cellular senescence, there is another type of growth arrest known as quiescence, but they are different from each other. Cellular senescence occurs in G1 and sometimes in the G2 phase of the cell cycle, whether quiescence occurs in the G0 phase of the cell cycle (Ruchi & Parmjit, 2021).

Various factors contribute to the initiation of cell senescence, one of which is an activation of one or both of the p53/p21WAF1/CIP1 and p16INK4A/pRB tumour suppressor pathways. However, these two pathways are complex. p21WAF1/CIP1 and p16INK4A are cyclin-dependent kinase inhibitors and negative regulators of cell cycle progression, respectively. Therefore, if one of these two components is overexpressed, there is a substantial probability of senescent cell generation. When DNA is damaged due to telomere attrition, oxidative or carcinogenic stress, p53/p21WAF1/CIP1 is activated. Constitutive DNA damage results in chronic p53 activation, eventually ending in cell senescence. When RB1 or pRB is dephosphorylated, it interacts with E2Fs, forming a repressive RB-E2F complex. The restrictive RB-E2F complexes then bind to the promoter regions of E2F target genes, inhibiting transcription of genes necessary for cell cycle advancement and ultimately causing cellular senescence (Ruchi & Parmjit, 2021).

10.1 Senescent cell elimination

One of the leading causes of neurodegenerative disease is an increase in age or ageing, and the amount of senescent cells is increased with the ageing of a person. Senescent cell condition is also known as sustained cell cycle arrest, which actively promotes tissue deterioration. Knowing that senescent cells have been identified in the context of brain ageing and neurodegenerative disease, it is logical to think that they could contribute to dysfunction. Senescence accelerated mouse, or SAMP8 mouse may exhibit various early ageing-related symptoms, including decreased learning and memory. These issues are related to an excess of amyloid precursor protein and amyloid- (A). Both of them have been linked to neurological illness in humans (J. Baker & C. Petersen, 2018).

AD is defined by the neuropathological deposition of amyloid-peptides, including amyloid plaques and neurofibrillary tangles. Amyloid plaques and neurofibrillary tangles are formed when hyperphosphorylated, or misfolded tau protein aggregates. These occurrences have an adverse effect on neurons, resulting in cognitive impairment and neurodegenerative disorders. These cells are predisposed to form senescent cells during normal ageing and exhibit AD changes. However, the true association between the accumulation of senescent cells and AD has not been demonstrated, and thus additional work in this subject is required (J. Baker & C. Petersen, 2018).

PD is a condition in which individuals lose control of their motor neurons due to dopamine-producing neurons in the substantia nigra being destroyed. It occurs due to ageing, although the underlying pathophysiology is yet unknown. A typical hallmark of patients with PD is the increase of activated microglia and astrocytes, contributing to neurodegeneration. These active microglia and astrocytes demonstrate that senescent cells are about to be created (Baker & Petersen, 2018).

10.2 Senescent cell elimination treatment

Senolytic drugs kill the senescent cells, and senolytic drugs are considered second-line adjuvant tumour therapy. The senescent cells induce multiple anti-apoptotic pathways, and the senolytic drugs help to inhibit those pathways, and that results in the induction of apoptosis in senescent cells (Short et al., 2019).

Azithromycin and Roxithromycin are considered senolytic drugs which can selectively target and eliminate the senescent cells by creating the anti-inflammatory effect. After that, two more drugs were proposed as senolytic drugs - quercetin and dasatinib, which were approved by FDA (Food and Drug Administration) (Qiu et al., 2021).

The bystander effect is one of the main reasons for the increasing number of senescent cells. It causes the proliferation of senescence. There is a method that can inhibit this proliferation, known as senostatics. These senostatics do not kill the senescent cell like senolytics, but it inhibits paracrine signalling that helps to block or stop the proliferation of senescence which is caused by the bystander effect (Short et al., 2019).

Another treatment for senescent cell elimination is direct inhibition of BCL-W and BCL-XL; mutual inhibition of these two proteins induces apoptosis in senescent cells (Yosef et al., 2016).

Chapter 11

Methodology

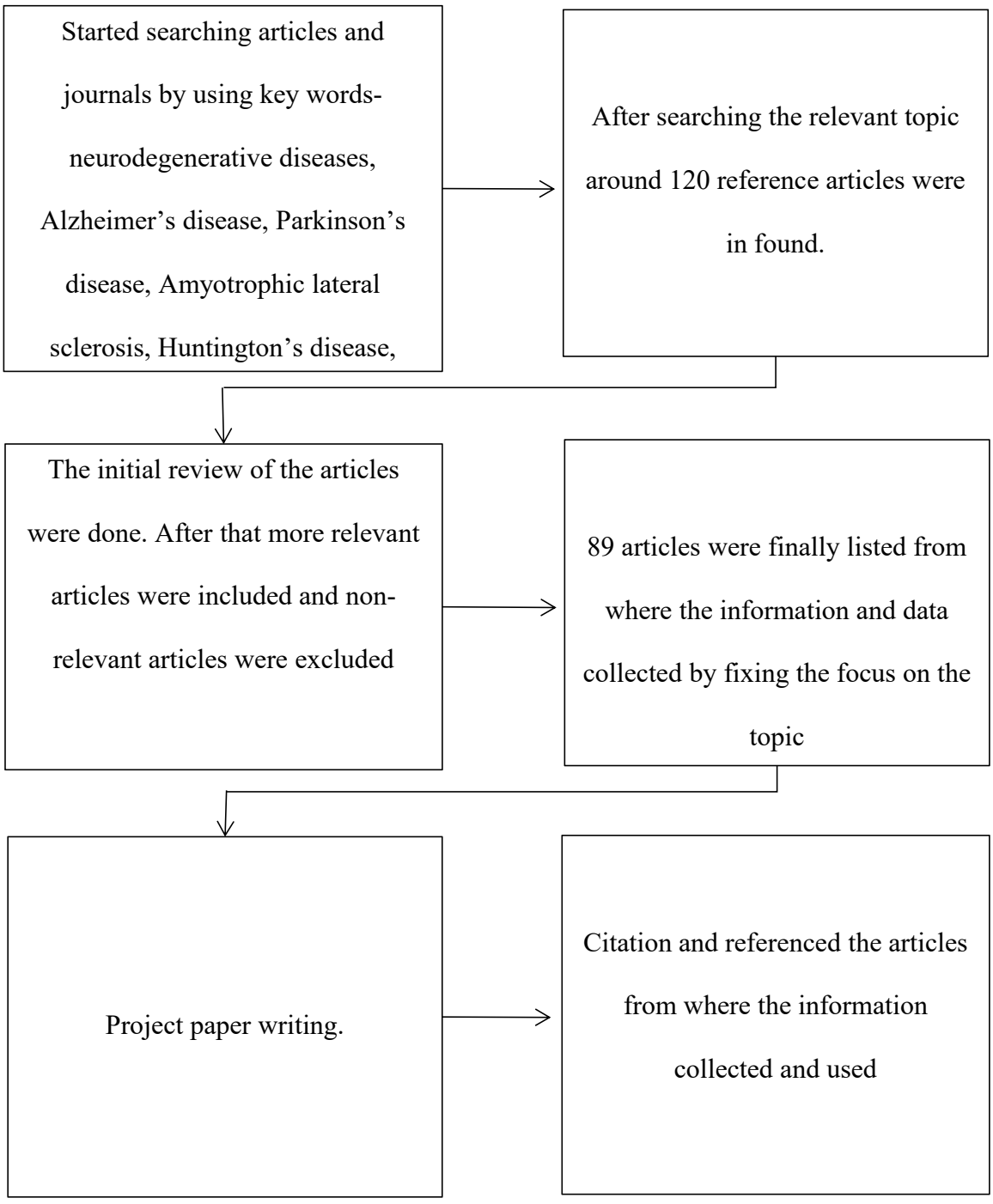

Figure-3: Schematic Representation of the Project Methodology

Chapter 12

Discussion

Senescent cell elimination treatment are used in other diseases as well as neurodegenerative diseases. Cancer is caused mostly by ageing (DePinho, 2000), and the presence of senescent cells in old tissues or xenograft models is linked to cancer incidence (Magalhães, 2013). Removing senescent cells caused tumour formation to be delayed and metastasis to be minimized (Baker et al., 2016). Both senolytics and senomorphics are now being tested in clinical trials to treat a variety of cancers, including leukaemia, lung cancer, melanoma, and glioblastoma, among others (Sun et al., 2018).

Senescent cells play a critical part in atherosclerosis, and the specific removal of senescent cells slowed the disease's progression (Childs et al., 2016). Furthermore, senescent macrophages appear to have a role in coronary heart disease, and aortic cell senescence enhances arterial stiffness (Myrianthopoulos et al., 2019).

Osteoarthritis generates painful and stiff joints, and the formation of senescent cells is linked to the disease's progression (Price et al., 2002). Local injections of these cells cause osteoarthritis-like symptoms in mice (Xu et al., 2016), whilst their removal improves health by slowing the progression of post-traumatic osteoarthritis (Jeon et al., 2017).

Type 2 diabetes is caused primarily by ageing. There is a link between disease progression and the identification of senescent markers. Senescent β-cells affect glucose homeostasis; however, further research is needed to determine the exact impact of senescence (Helman et al., 2016; Aguayo-Mazzucato et al., 2017).

Increased senescent cells are linked to diseases including glomerulosclerosis and nephropathies (McHugh & Gil, 2017). Surprisingly, kidney function increased when these cells were eradicated via genetic approaches (Baker et al., 2016b).

Scarring is a symptom of idiopathic pulmonary fibrosis, mainly affecting older people. Senescent cells were found in IPF patients' tissues, and when these cells were eliminated with senolytics, pulmonary function improved (Schafer et al., 2017).

The emergence of liver fibrosis, cirrhosis, and non-alcoholic fatty liver disease is linked to the existence of senescent cells. The removal of these cells lowered the formation of fat in the liver (Ogrodnik et al., 2017).

In situations where senescent cells accumulate, anti-senescence therapy could be applied. On one side, numerous pharmacological treatments may work by preventing senescence (Muñoz-Espín & Serrano, 2014). Such as, reducing senescence through pharmacological suppression of NOX4 or the anti-inflammatory drug rupatadine can help with lung fibrosis (Lv et al., 2013). On the other side, targeting senescent cells could help people live longer because genetic removal of senescent cells can slow down and reverse aging in a mouse model of accelerated aging (Finn et al., 2015). Dasatinib (a Bcr-Abl tyrosine kinase inhibitor) and quercetin (a flavonol) were found to kill senescent cells selectively in a recent study (Zhu et al., 2015). In chronologically aged mice, radiation-exposed mice, and progeroid mice, this combination reduced senescent cell load in vivo. In addition, progeroid mice who were given drugs regularly lived longer. These findings show that senolytic medicines are viable and could improve health and even lengthen lifespan (Lujambio, 2016).

Senolytics are the compound which target activated pathways in senescent cells and eliminates the negative effect of senescent cells by killing them specifically. Senolytics are supposed to be specific for senescent cells. Still, there is always undesired damage/side

effects because the administration is not directed. In this context, nanocapsules carrying toxins were recently described as a new method for precisely targeting senescent cells in mice (or senolytics). The outer layer of these nanocapsules comprises enzyme substrates that are overexpressed in senescent cells. Only senescent cells will be exposed to the toxin (senolytic), which will kill them. As a result, these nanocapsules can be used to deliver any sort of senolytic to senescent cells in mice. In non-targeted senolytics such as quercetin and fisetin, the specificity of the administration is essential (von Kobbe, 2019).

The fate of the dead senescent cells is a legitimate concern, significantly when the patient's immune system is compromised. The buildup of these apoptotic bodies could have unfavourable consequences (McHugh & Gil, 2017b). Patients have had thrombocytopenia and neutropenia due to systemic administration of BCL family inhibitors (Rudin et al., 2012). It would be ideal if senolytic therapies were as infrequent as possible without compromising efficacy (von Kobbe, 2019b).

Senescence-associated secretory phenotype (SASP) is the complex mixture of several factors like growth factors, cytokines, proteases, chemokines and angiogenic factors that regulates the paracrine and autocrine activities of senescent cells. Senomorphics or SASP inhibitors inhibit the function of senescent cells by targeting pathways such as mTOR, NF-κB, p38 mitogen-activated protein kinase (MAPK), PI3K/AKT, and IL-1α (von Kobbe, 2019c).

One concern with this method is how SASP-silenced/attenuated senescent cells would be removed. In a study, it is mentioned that some SASP components are involved in immune cell recruitment. SASP inhibition could effectively make senescent cells "invisible" to the immune system, allowing them to persist in the tissue for a long time. The lack of specificity for senescent cells is a key drawback of these classes of SASP inhibitors. Individual SASP

components might be inhibited by neutralizing antibodies, reducing the risk of adverse effects (Lim et al., 2015).

Immunosurveillance is another strategy that targets senescent cells by strengthing the ability of the immune system to identify the senescent cells and then eliminate them. The immune system plays a vital role in removing senescent cells, and a decline in immune function is linked to an increase in the number of senescent cells and, ultimately, illness (van Deursen, 2014).

Macrophages, NK cells, and CD4+ T cells have been shown to have anti-senescent activities. Because these tasks are carried out by membrane receptors, one possibility is to improve the binding affinity of the receptors involved. In this regard, targeting specific senescent-related molecules with chimeric antigen receptor (CAR) T cells would be a promising strategy. As an anti-cancer therapeutic, this technique is currently demonstrating exceptional outcomes. It might also be possible to try enhancing the surface expression of these receptors in senescent cells. Another option is to "rejuvenate" the immune system by reducing the amount of senescent immune cells, maybe by depletion using particular antibodies that recognize surface markers of senescence (Yu et al., 2017).

In situations like immunosenescence or immunosuppression, improving immune system activities to target senescent cells could be problematic (Chou et al., 2013). CAR-based methods and immune system "rejuvenation" would be highly individualized treatments, taking a long time and costing a lot of money. These solutions would rely on specialized senescence receptors, and the lack of universal indicators is a limiting issue in identifying cell senescence (Myrianthopoulos et al., 2019b). Although new methods improve the accuracy of detecting senescent cells in tissues, confirmation is still required for using a combination of different biomarkers (Galbiati et al., 2017).

Senolytic drugs are one way of senescent cell elimination treatment. Some drugs are used as senolytic drugs for senolysis like quercetin, dasatinib etc. One study showed that quercetin effectively against senescent human endothelial cells and dasatinib eliminated senescent human fat cells progenitors. The combination of these two drugs was adequate for eliminating senescent mouse embryonic fibroblasts. However, these two drugs have adverse effects, like they can cause non-senescent human endothelial cell death. Also, it can cause a pro-tumorigenic effect in mouse (Qiu et al., 2021).

Senolytics provide cytotoxic activity for senescent cells, but the therapies of senolytics in the human body are hampered due to the lack of specificity for senescent cells and the toxicities that narrow down their therapeutic window. Navitoclax is a senolytic drug that has high potency in destroying senescent cells. However, it causes haematological toxicity, which narrows its therapeutic window (González-Gualda et al., 2020).

Cellular senescence is detrimental, which results in ageing and different ageing-related side effects. Nevertheless, at the same time, cellular senescence is beneficial, which works as a tumour suppressor. Senescence can prevent the proliferation of potentially cancerous cells by the anti-tumour mechanism (Ruchi & Parmjit, 2021).

Clinical trials to assess the efficacy of medicines that target senescent cells are challenging to design (Kirkland & Peterson, 2009). Examining the effects on the human life span or health span is impossible in a reasonable amount of time. Drugs that must be given early in life to have a good effect in later life would likewise be difficult to convert into clinical practice. Over the years to decades, such treatments would have to have essentially minimal adverse effects. Clinical studies would take an excessive amount of time. Senolytic medications would need to be created for people who already have symptoms or will develop them soon.

Regulatory authorities would have to establish and approve easily measurable outcome parameters (Tchkonia et al., 2013).

Chapter 13

Future work

Effects of senescent cell elimination treatment in neurodegenerative diseases are still lacking in studies and evidence. A very few clinical trials have been conducted in humans. However, more clinical trials are needed to understand the precise effectiveness of senescent cell elimination treatment for neurodegenerative diseases. As many people are suffering from different types of neurodegenerative diseases throughout the world and it is not curable, it will be better to speed up the research work of this treatment, and it can decline the progression of neurodegenerative diseases. More studies are required to identify the actual mechanism of neuronal death or the specific cause of neuronal death for clear evidence. Then more studies can develop the effectiveness of senescent cell elimination treatment and reduce the side effects in neurodegenerative patients.

Chapter 14

Conclusion

Senescent cell elimination is a significant discovery for neurodegenerative diseases like AD, PD etc. Since this treatment can eliminate the senescence cell, there is a substantial potential for further development. The possibility emerges because this treatment can block the proliferation of senescence and induce apoptosis in senescent cells by inhibiting multiple anti-apoptotic pathways. Scientists are regularly working to find out a proper way of treatment to cure or stop the progression of neurodegenerative diseases. There are several stem cell treatments for which scientists are still working, expecting to get a good result to start clinical trials.

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