



Systematic review on nine hallmarks of neurodegenerative disease

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Alzheimer's disease (AD) and Parkinson's disease (PD) are the primary diseases in neurodegenerative diseases. Nowadays, AD is common in one of the ten individuals whose age is more than 65, and its prevalence is kept on increasing with aging. Very few treatments and no effective treatments are available for curing neurodegenerative diseases. Pathogenesis of neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, and their association with the nine hallmarks of aging were clearly described in this review. Instability in genomic, attrition in telomere, alterations in epigenetics, proteostasis loss, dysfunction in mitochondria, senescence in cells, sensing of deregulated nutrition, exhaustion of stem cells, and alterations in intercellular communication are the nine biological hallmarks of Aging. Improving the medical facilities for neurodegenerative diseases is very much essential. Doctors and researchers are doing surplus research to overcome the unavailability of proper treatments for such neurodegenerative diseases. Reason and the causes behind the diseases and their effects are explained in this review to enhance the further research to help the society.

Keywords: Alzheimer's disease, Amyloid-beta, dysfunction in mitochondria, Parkinson's disease

Introduction

The risk of disease and death increases with aging-associated with physical deterioration. Aging of different species occurs at different rates, inter-individual variations exist within the individuals, and they also live in various tissues of the same individual¹. Nine critical hallmarks of the aging processes are identified. The primary mechanism of Aging and its role in neurodegenerative disease is essential to develop successful interventions. The aged population in the US is estimated to increase to 8.8 crores by 2050². Due to the increase in the population of older adults, health disorders related to Aging and financial burden will increase. So, therapeutic approaches are urgently needed. Neurodegenerative disease is common in older adults, and the brain free of infection is rare. The progression of neurodegenerative

disease is determined by the genes of humans and environmental factors. The most commonly occurring neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD)

Alzheimer's disease was first described in 1907 by Alois Alzheimer while studying the histopathology of his patient's brain and found anomalies in the sections of the brain with dementia. Deposits of insoluble peptides (Abeta or amyloid-beta) are called Plaques. Sequential cleaving of gamma and beta-secretase on Amyloid Precursor Protein enzyme leads to the formation of Abeta. The main culprit is Abeta, among the other molecules generated by this cleavage³. Abeta is dysregulated and becomes sticky. By and by, they are combining and forming soluble oligomers. Several of them are aggregated and turn into large insoluble fibrils, which deposit in the brain as plaques—retrieving or making them stop memories. Not only the neurons, microglia, and astrocytes are also affected by Alzheimer's disease. Waste and prune

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synapses are cleared out during the development by the immune cells called microglia. Abeta's are also taken up by the microglia, but the Abeta triggers microglia to release the inflammatory cytokines that can damage neurons⁴.

The other most occurring neurodegenerative disease next to Alzheimer's disease is Parkinson's disease (PD). Muscle rigidity, slowness of movement, and tremors at rest are the impacts of this disease. Several areas of the nervous system and various types of neurons are affected by PD¹. Notably, a region named substantia nigra pars compacta in the midbrain. In Parkinson's disease, dopaminergic neurons in the substantia nigra have gradually died which leads to malfunction in the pathway and some characteristic issues. These deficits can often be treated by drugs that replace or impersonate dopamine, but they grow less effective over time⁵. A bunch of dysregulated proteins within neurons is the distinctive pathology in most cases of Parkinson's disease. Figure 1 depicts the prevalence of Parkinson's disease globally. Alpha-synuclein is a characteristic component of this dysregulated protein. Small repeated units called oligomers or longer fibrils have formed these molecules. Evidence in the mounting indicates that they are toxic to neurons, and it has a significant role in driving PD⁶. Among the 30-69 aged women in India, 17 percent of death caused by cancers is from cervix cancer. It is the second leading cause of mortality in India. On accounting for the worldwide extinction of cervical cancer, one-third of it is from India. Nearly 6.8 lakhs of Indian women have died per annum by this disease. This disease is major civic-related trouble for women in India. Almost 75% of Indian women have cervical cancer and are diagnosed at advanced stages⁷.

The most prevalent diseases such as AD and PD are focused on in this review. Amyotrophic lateral

sclerosis, Dementia with Lewy bodies, Huntington disease, Cockayne syndrome, Ataxia telangiectasia are the Other important neurodegenerative diseases that have significant links with Aging are discussed in (Table 1).

Aging phenomena

Some effects of Abeta seem to be conciliated by another protein seen in the patient's brain called Tau. But Tau is modified in Alzheimer's disease and it causes to dissociate from the microtubules. Drugs are being developed for targeting Tau or Amyloid Beta. Current knowledge about the biological processes in neurodegeneration and the average brain is synthesized in this review. The ubiquitous neurodegenerative diseases AD, PD, and the hallmarks in Aging are the main focus here. Aging is a relentless and irremediable process that corresponds to sudden identification, physical appearance changes, and functionality of individual organisms. Nine hallmarks of Aging were identified and arranged by López-Otin *et al.* and it was categorized into primary, antagonistic, and integrative. Pictorial representation for all the nine hallmarks is shown in (Fig. 2). Instability in Genomic, attrition in telomere, alterations in epigenetics, and loss of proteostasis are the primary hallmarks of Aging. The dominating force driving Aging is Genomic instability, and it is one of the dominant theories of aging. Senescence in cells, sensing of deregulated nutrition, and mitochondrial dysfunction are the antagonistic hallmarks. that are compensatory responses to the direct damage. At first, the damage was lessened by these responses, but at last, they became deleterious. Exhaustion of stem cells and the Alterations in intercellular communication are the integrative hallmarks that arise from joint damage initiated by the antagonistic and primary hallmarks¹⁸.

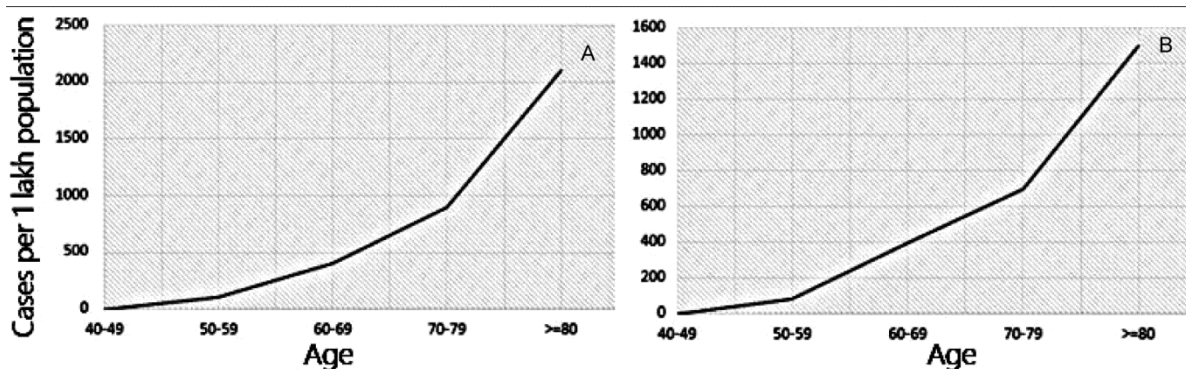


Fig. 1 — (A) The global prevalence of Parkinson' disease in women; and (B) the global prevalence of Parkinson's disease in Men

Table 1 — Neurodegenerative diseases related to Aging

Disease	Neuropathological hallmarks	Major symptoms	Risk factors	Prevalence
Amyotrophic lateral sclerosis	TAR DNA-binding protein 43 aggregations	Motor defect progress, weakness in muscles, spasms, and atrophy	Familial aggregation Physical activity, occupational and environmental exposure (for example, to pesticides, solvents, or heavy metals), genetics, head injury, and smoking ⁸	0.6 cases per million globally in 2016 ⁹
Dementia with Lewy bodies	Lewy bodies and Lewy neurites	Cognitive problems, movement disorders, Visual hallucinations, difficulties in sleeping, depression	Age >50 years, family history, male gender ¹⁰	1.3 million in the USA in 2014 ⁹
Huntington disease	neuronal loss, psychiatric symptoms, Striatal atrophy. ¹⁰	Dystonia, chorea, loss of coordination, behavioral difficulties, cognitive decline	Genetic mutation in HTT, inheritance	5–7 per 100,000 white people in 2007 ¹¹
Cockayne syndrome	Growth retardation and neurodegeneration	Neurological disorders, Growth failure, eye disorders, premature aging, photosensitivity.	Genetics (mutations in CSA or CSB gene)	2–3 per million globally in 2008 ¹²
Ataxia telangiectasia	Ataxia and telangiectasias	Immunodeficiency, Cerebellar degeneration, diabetes, cancer predisposition, radiation sensitivity	Genetics (mutations in ATM gene)	From 1 in 40,000 to 1 in 100,000 live births worldwide in 2016 ¹³
Alzheimer's disease	neuroinflammation, neuronal loss, neurofibrillary tangles, A β plaques	Impairment of memory and learning, speech difficulties	family history, Age, history of head trauma, genetics, environmental factors, female gender, vascular risk factors ¹⁴	5.7 million in the USA in 2018 ²
Parkinson's disease	grey matter atrophy, α -Synuclein-containing Lewy bodies, and loss of dopaminergic neurons ¹⁶	Rigidity in muscles, alterations in speech and gait, tremors	Factor in the environment, male gender genetics, psychiatric symptoms ethnicity, age ¹⁷	2–3% of the global population aged >65 years in 2017 ¹⁵

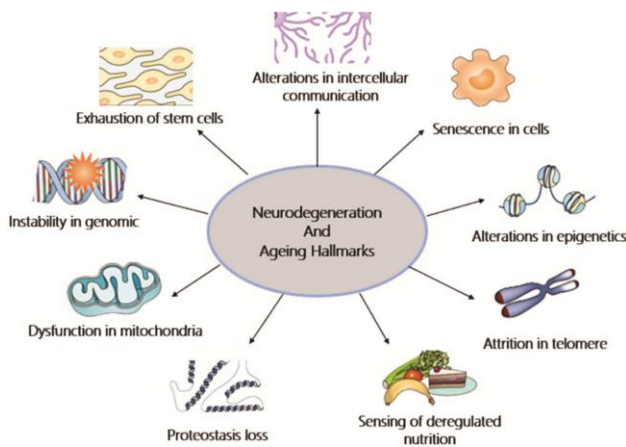


Fig. 2 — The nine hallmarks of aging

Primary hallmarks of aging

Instability in genomic

Some types of damages in DNA include a primary site, bulky adducts, DNA single, double-strand breaks, insertions, deletions, and base mismatches are accompanied by neurodegeneration. Oxidative damages can increase inflammation from endogenous reactive oxygen species (ROS). It even can accelerate

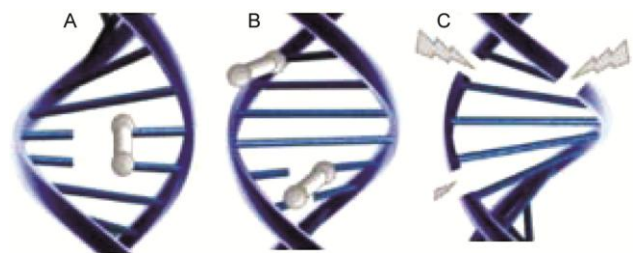


Fig. 3 — (A) Maintained genome stability; (B) cell death occurs; and (C) Unstabilized genome

Aging and increase susceptibility to neurodegenerative disease and cancer. Base excision repair, mismatch repair, nucleotide excision repair, direct reversal, and DNA double-strand break repair are the five main DNA repair pathways. The difference between the proper cell and the damaged cell is shown in (Fig. 3). The primary mechanism for repairing minor base modifications in DNA, such as single-strand breaks and oxidative base damage, is Base excision repair (BER). Mutator phenotype caused by mutations in BER pathway genes increases the risk of Aging and neurodegeneration¹⁹. In BER, damaged DNA bases are recognized and removed by the DNA glycosylase

is the first step. BER progress through one of the two BER sub-pathways, which is known as long and short-patch BER. Four proteins are used to reconstitute BER, such as AP endonuclease 1 (APE1), a DNA glycosylase, DNA ligase III (Lig III), and DNA polymerase β (Pol β). Damage in DNA generates genomic instability and starts off the cascade of signaling that permeates throughout the cell. BER, NER, and DSBR are promoted efficiently by sirtuin 1, sirtuin3, and sirtuins 1 and 6, respectively²⁰. Damage in DNA promotes inflammation and cellular senescence, which aggravates aging-related neurodegeneration

Attrition in telomere

The composition of protein and DNA in the linear chromosome's ends are called Telomeres. As the cell divides, telomeres become shorter unless either telomerase or other mechanisms are expressed by the parental cells to prevent the telomere's attrition. Shortening in the telomere will lead to senescence in cells, and organismal Aging is most probably involved. The Aging of humans and mice is accelerated due to the defects in telomere maintenance. Pathogenesis related to telomere in neurodegenerative diseases has to be clarified further²¹. Reduction in the telomere over years is pictorially explained in (Fig. 4). Studies in the topic of associated telomere length with hypertensive cases are only two from India, which were done by Balasubramanyam²² and Das²³, and Bhupatiraju *et al.* are also attempted to resolute the telomere size among hypertensive and normotensive Hyderabad individuals²⁴. Finding the telomere length associated with the hypertensive cases from the population of India would be interesting as the population in India is

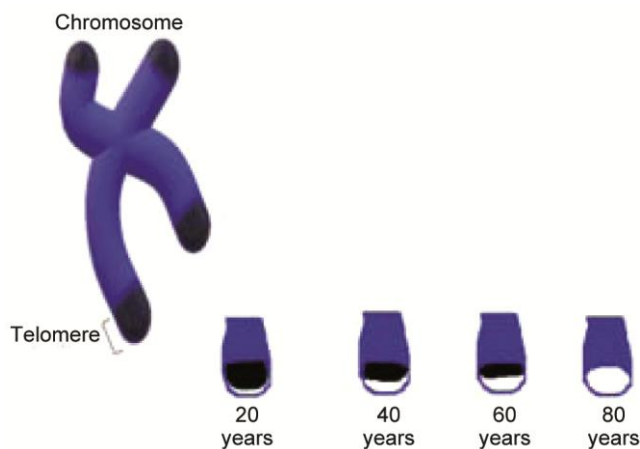


Fig. 4 — Telomere shortening over the years

highly diverse. In 2012, diagnosis of essential hypertension was confirmed in 98 people in the age groups of 30-70 years, and the results depict that the relative telomere length was determined in a total of 98 normal (66 males and 32 females) and 96 hypertensive individuals (50 males and 46 females)²².

Alterations in epigenetics

Epigenetic alterations are the changes in the chemical structure of DNA without changing the DNA coding sequence. When chemical groups named methyl groups are added or eliminated from DNA, Epigenetic alterations occur in the body or when changes are made in histones that bind in chromosomes with DNA. The modifications collectively influence chromatin tertiary epigenetic structures, including PARylation, acetylation, and methylation of histones and DNA²⁵. The function and activity of chromatin are strongly influenced by the Epigenetic markers, including replication and transcription. Mechanisms related to epigenetic ages possess roles in neurodegenerative diseases. Epigenetic control of Abeta productions is revealed in several studies in the progression of AD, and it is reported that chromatin remodeling will assist the Abeta production.

Proteostasis loss

Proteostasis is created by the balance between protein synthesis and degradation. The proteostasis maintenance in eukaryotic cells relies on Autophagy and the proper regulation of the proteasome, the lysosomal system, and ubiquitination machinery. The degradation system of intracellular that aided lysosomal degradation of damaged organelles and unfolded or misfolded proteins is known as Autophagy²⁶. It reduces the secretion of inflammatory cytokines. In many neurodegenerative disorders, increased misfolded, aggregated protein and depositions are observed. Studies suggest that the functional decline of the proteostasis network may occur before the anticipated lifespan of an organism. Studies from *Elegans* have challenged the idea that the gradual accumulation of cellular anomalies fails proteostasis. Instead, programmed events in the early ages are responsible for the collapse in proteostasis later in life. Such observations are limited to invertebrates at present. If the findings in the *Elegans* studies hold in mammals, it will be essential to recognize the early time frame and to determine whether it will be standard for all organisms or not. Correct interventions are tailored when these factors are understood clearly.

Antagonistic hallmarks of aging

Dysfunction in mitochondria

To perform neuronal activities, neurons have high energy demands and are purposely conscious of the changes in function in mitochondria. Reactive Oxygen Species (ROS) production in injured mitochondria is amplified and involved in the process of normal Aging. Besides the formulation of ATP, mitochondria possess specific significant roles in the various inter cell pathways. Mitochondrial functions in the brain become impaired with age, and it is adhering to be an early and critical benefactor in the process of aging²⁷. For maintaining the optimal mitochondrial function, several quality control measures are involved, including the export of damaged mitochondrial-derived proteins vesicles, proteasome degradation, fission, and fusion in mitochondria, deportation of flawed proteins by mitophagy and proteases. A comparison between mitochondria's physiological and pathological conditions is explained in (Fig. 5). In recent years, mitophagy has received particular attention among these mechanisms. Dysfunctional mitochondria are selectively degraded by mitophagy and have a prominent role in preventing age-related diseases²⁸. Studies indicate that mitochondrial dysfunction can be caused due to damage in the nuclear DNA. A transduction pathway from mitochondria to the nucleus is mitochondrial unfolded protein response (UPR) and it dysregulates when the stress is developed in mitochondria which will lead to neurodegeneration. Neurodegeneration and Aging will be understood better while researching the mechanisms facilitating communication between mitochondrial compartments and nuclear.

Senescence in cells

Cellular senescence in fibroblasts for the first time in 1965 was identified by Hayflick. Senescence-associated secretory phenotype (SASP) and a stress-induced stable cell cycle arrest occur with Age^{69,70}. When the pro-inflammatory properties are acquired by the dying or damaged cells, SASP emerges, which may advertise the tumor's advancement through the expansion of cytokines, chemokines, proteases, and growth factors. Reduced NAD⁺: NADH ratios are observed in the cells that undergo dysfunction in mitochondria-associated senescence, which improves the growth arrest, and SASP formation associated with IL-1 is prevented²⁹. Phenotypic change associated with senescence is shown in (Fig. 6). The NAD⁺ mechanism is also presented in the SASP regulation through the high mobility group A (HMGA)–nicotinamide phosphoribosyl transferase (NAMPT)–NAD⁺ signalling axis and the pro-inflammatory SASP is governed by the NAD⁺ metabolism. An essential process linked with cellular senescence is Autophagy³⁰. Whether Autophagy is promoting or inhibiting senescence is still under confusion. Senescence might be enhanced by the inhibition of Autophagy under certain circumstances, but on the other hand, macro-autophagy might assist SASP by expediting the synthesis of secretory protein. GATA4 is to be activated in response to the damage of DNA in a method that relies on the kinases ATR and ATM, and it has a keen role in triggering the SASP. The brain was observed with an age-related decline in Autophagy. Even so, the mechanism connecting senescence and the reduced Autophagy in the brain needs to be established.

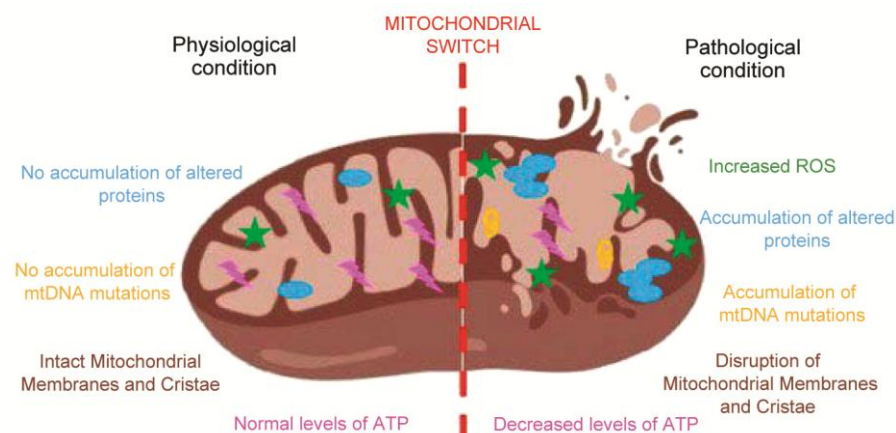


Fig. 5 — Features and appearance of mitochondrion before and after the accumulation of damage responsible for its impairment²⁸

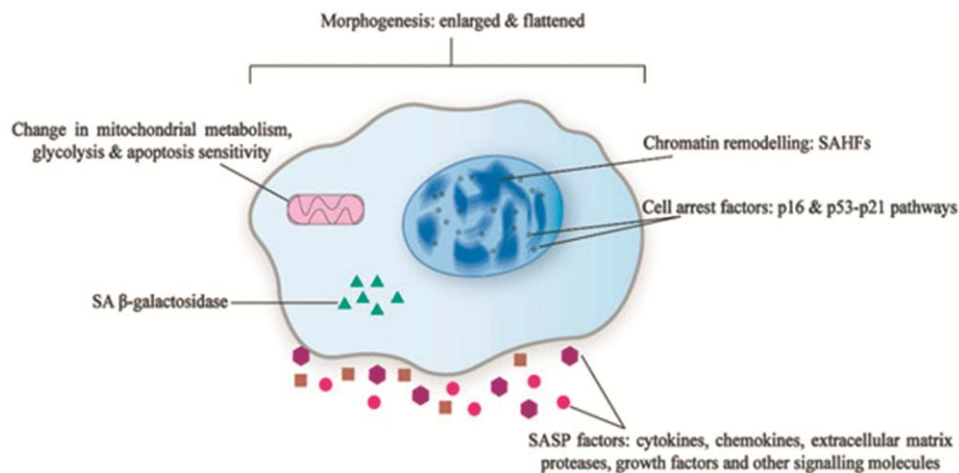


Fig. 6 — Phenotypic changes that are associated with senescence³¹

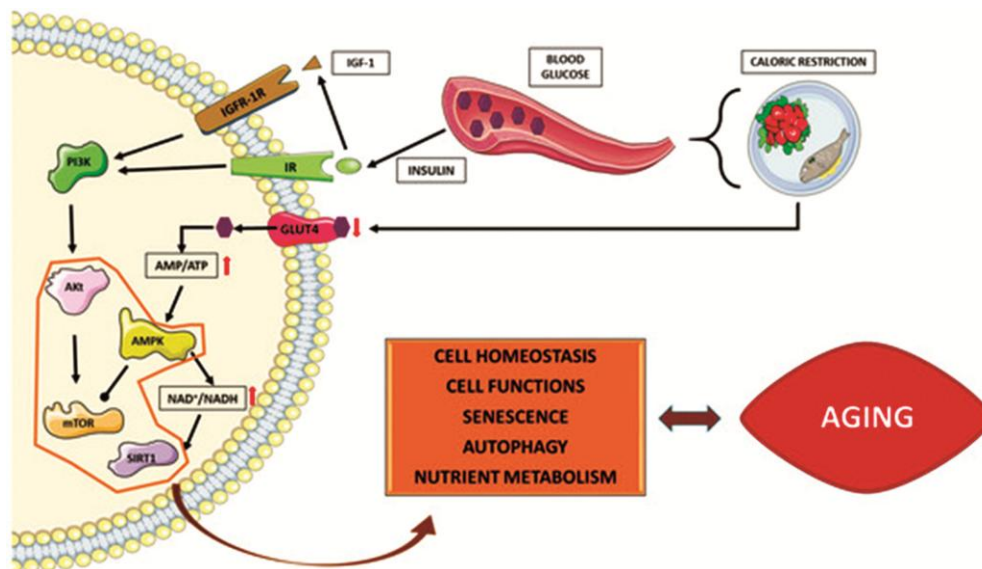


Fig. 7 — (CR) Caloric restriction-mediated modulation of nutrient-sensing pathways³⁴

Sensing of deregulated nutrition

The sensing ability and response to the environmental nutrient level fluctuations are needed for life. The evolution of most cellular processes has been shaped by a selective pressure called nutrient scarcity. Intracellular and extracellular levels of sugar, lipids, surrogate metabolites, and amino acids are detected by different pathways and are coordinated and integrated at the organismal level through hormonal signals³². Caloric restriction-mediated modulation of nutrient-sensing pathways is modulated in (Fig. 7). Nutrient signaling pathways are downregulated by restricting the calorie. Insulin-like growth factor 1 (IGF1), Insulin, AMP-activated protein kinase (AMPK), sirtuins, and mechanistic target of rapamycin (mTOR) are the molecules and major nutrient-sensing pathways.

AMPK, sirtuins, and mTOR are being discovered to target neurodegenerative diseases³³. Patients with the neurological disease are observed with metabolic dysfunction frequently and might correlate with NAD⁺ abundance, oxidative stress, and dysfunction in mitochondria.

Integrative hallmarks of aging

Exhaustion of stem cells

High precision in the mechanisms is required for high-turnover tissues in stem cells for maintaining the genome to ensure their maintenance in the long term. DNA repair machinery and cell cycle checkpoints are effectively included in the invertebrate stem cell production mechanisms³⁵. Exhaustion in stem cells has resulted when a deficiency occurs in these

mechanisms. Especially during the time of high proliferative pressure, increasing the potential for cancers, stem cell exhaustion, and genome integrity become quickly compromised. A crucial role was played by the DNA repair pathways in the fatigue during replicative pressure and limiting the stem-cell failure. This loss contributes to the growth of age-associated phenotypes. For acquiring optimal health in later life, functional cells are needed. Even so, the function of stem cells and proliferative capacity decline over an organism's lifespan. Low capacity in repairing DNA, deregulation in epigenetics, proteostasis defects, dysfunction in mitochondria, high levels of DNA damage related to aging, inactivation in telomerase, and cell senescence are the causes for this functional loss³⁶. The function of stem cells is improved by increasing the expression of forkhead transcription factor (FOXO4) or heat shock protein (HSP70) and by the rapamycin58 treatment. Exposure to young blood in aged animals improves the function of stem cells in the liver, muscle, brain, and spinal cord rejuvenates cognitive processes, and counteracts aging through heterochronic parabiosis. Therefore, age-associated neurodegenerative diseases are targeting the regeneration of aged stem cells. Identifications of the stem cell actions through preclinical studies are shown in (Fig. 8).

Alterations in intercellular communication

Hormones like insulin, leptin, adiponectin, IGF1 and ghrelin are altered to regulate neurodegeneration

and damage in neurons. Understanding the role of innate and adaptive immunes in neurodegenerative diseases and such enlightenment will be vital for developing productive immune-based inventions. Interactions of support cells such as oligodendrocytes and astrocytes with microglia might be involved in the pathological mechanisms of neurodegenerative diseases³⁸. Regulatory T cells are also crucial for the immune privilege and tolerance of the CNS itself, and it is not only vital for maintaining the peripheral immune system alone. Crosstalk between the microglia, T cells, mast cells, and oligodendrocytes is also necessary for the function of the immune system and prevents neurodegenerative diseases. Changes in the link between immune responses with Aging and the raised incidence of neurodegenerative diseases in the aging population might be given the necessitous insights into this interaction. Autophagy degradation systems, sex steroid hormone deficiency related to Aging, cellular senescence, defects in the proteasome, increased oxidative DNA damage, decreased innate and adaptive responses of the immune system, environmental stressors, and impaired DNA repair are the other various factors reported contributing to the pathogenesis of neurodegenerative disorders and inflammatory response. Neuroinflammatory processes are targeted to attain beneficial outcomes in neurodegenerative diseases related to aging. Even though neurodegenerative diseases related to Aging-related diseases are treated by Anti-inflammatory drugs, developing drugs that could cross the barrier in the

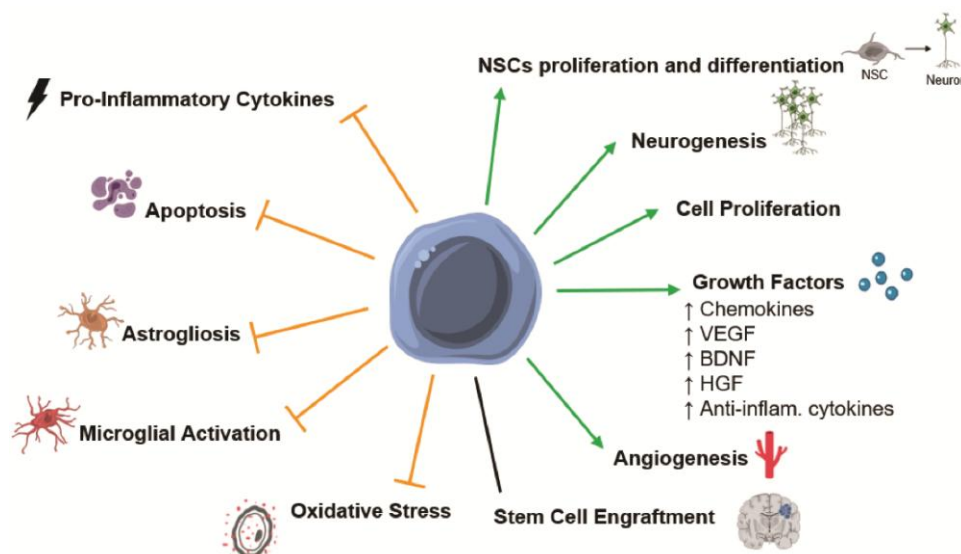


Fig. 8 — The action of stem cells identified by preclinical studies³⁷

blood-brain and possess fewer unfavorable effects than the prevailing strategies³⁹. The relationship between age-related neurodegenerative diseases and the inflammatory process has to be understood clearly for further interventions

Futuristic treatments

Memory loss symptoms, thinking and reasoning problems can only be temporarily improved by the current treatment of Alzheimer's. Chemical performance in the brain is boosted by these treatments, which carry data from one cell in the brain to another cell⁴⁰. These treatments can't stop the underlying decline and death of brain cells. Combined medications might be included in the future treatment of Alzheimer's, like the current treatment for HIV/AIDS or many cancers. The strategy currently being studied for treating Alzheimer's is a strategy that includes beta-amyloid for the treatment of Alzheimer's. The characteristic sign of Alzheimer's disease is plaques (beta-amyloids). Monoclonal antibodies are the drugs that may prevent the clumping of beta-amyloid into plaques or remove the pre-formed plaques so that it helps in clearing the beta-amyloid in brains. Monoclonal antibodies resemble the antibodies produced by the body naturally as a part of the response of an immune system to vaccines or strange invaders.

Conclusion

Alzheimer's and its dementia in India are not effective in India when compared to other countries. India occupies 133rd position in the world health ranking of Alzheimer's and its dementia with a death rate of 16.97%. All the nine hallmarks which are responsible for the neurodegenerative diseases were described understandably in this review along with the two main neurodegenerative diseases namely Alzheimer's disease and Parkinson's disease were also explained. Efforts are being taken to develop treatment strategies based on evidence of neurodegenerative diseases. The proper method for treating such neurodegenerative diseases hasn't been founded. The existing treatment improves certain symptoms temporarily such as thinking, reasoning, and losing memory. For overcoming this, current researchers and doctors are concentrating on the combined medications as in the case of the treatments like HIV/AIDS. Understanding all the nine hallmarks is very important and needs to be concentrated on. The reason and causes for those nine hallmarks were

explicated clearly for improving the medications in neurodegenerative diseases.

Conflict of interest

All authors declare no conflict of interest.

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