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IMPACT OF CELL SENESCENCE ON AGE - RELATED NEURODEGENERATIVE DISORDERS: THE MECHANISM TO THERAPY- A REVIEW

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ABSTRACT: Aging is a natural phenomenon; it is a well-known fact that everyone is aging as time passes. A major contributor to this process is cell senescence. Cell senescence can be a result of the exposure to stress such as oxidative stress, epigenomic damage or DNA damage, or it can be due to telomere shortening is also known as end replication problem. It was first observed by Hayflick. Senescent cells show a distinctive feature called Senescent associated secretory phenotypes (SASP) which includes increased expression of p16 and Beta-galactosidase can be used as a marker for senescent cells. Senescent cells are involved in exacerbating various kinds of age-related disorders such as diabetes, obesity, cardiovascular diseases, neurodegenerative diseases, *etc*. This review is focused on the major factors responsible for cell senescence, its related pathways, and the role of cell senescence in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. The paper also throws light on how cell senescence can be used to treat cancer known as therapy-induced senescence and various strategies to treat age-related pathologies by senotherapy in which senescent cells are targeted.

INTRODUCTION: Cellular senescence was first observed by Hayflick and Moorhead about 5 decades ago in 1961. [1] In their studies, they observed that human diploid cells replicate a finite number of times before they undergo irreversible arrest, [1] it was termed as Hayflick limit also known as replicative senescence (RS) [2]. Cells undergo cellular senescence to avoid the formation of cancer or other diseases related to a mutation in the cell due to any kind of stressors such as oxidative stress, telomere damage or epigenomic damage.

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Although, stress plays a major role in the induction of premature senescence, depending upon the damage due to stressor cells react in different ways as it determines if the damage is high, the cell will go under-programmed cell death and if the damage is low senescence will take place [2].

Senescent cells are mitotically inactive but are viable. With the loss of replicative inability changes in metabolism, gene expression and epigenetic regulation also take place. Senescent cells show SASP (senescent associate's secretory phenotype) which includes molecular changes such as morphological changes, expression of pro-inflammatory cytokines and growth factors. Increased expression of p16 and β-galactosidase can be used as markers to identify senescent cells. Senescent cells showing SASP has been associated with various age-related diseases such as obesity,

diabetes, cancer and other cardiovascular diseases. Cellular senescence in neurodegenerative diseases. Due to DNA damage response, senescence-like phenotype has been seen in cortical neurons. Other senescent associated phenotypes like B-gal staining and SASP secretion of pro-inflammatory cytokines has been observed. After exposure to oxidative stress and metabolic stress neurons exhibit CS phenotypes. In this review, we are trying to find the link between cellular senescence and age-related neurological disorders [3].

Cellular Senescence Pathways: Two tumor suppressor proteins p53 and p16 are responsible for cellular senescence [4]. There are two types of tumor suppressor proteins- the caretakers and the gatekeepers. The caretakers protect the genome from mutation; they act as longevity assurance genes as they prevent genome damage, on the other hand, gatekeepers act on intact cells and eliminate potential cancer cells by inducing apoptosis and cellular senescence and prevent the development of cancer [5]. When external stressors such as telomere damage, oxidative stress (RAS activity) or epigenetic stress has been encountered by the cells, it activates ATM/ARF and p19ARF which in turn activates p53 pathway [6]. In the p53 pathway, the gene activates its transcriptional target p21 which is an inhibitor of cyclin / cdk2 as they work for the progression of replication and inactivates RB. The tumor suppressor protein p16 works independent of p53 gene it has been found that silencing of p16 gene is very evident in many cancers, they both can work parallel to the p53-p21 arm. Cells can emerge out of cellular senescence by silencing or by promoter methylation of p16 expression or the deletion of the p16 locus; it will let the cells divide until they reach p53 dependent senescence stage termed M.

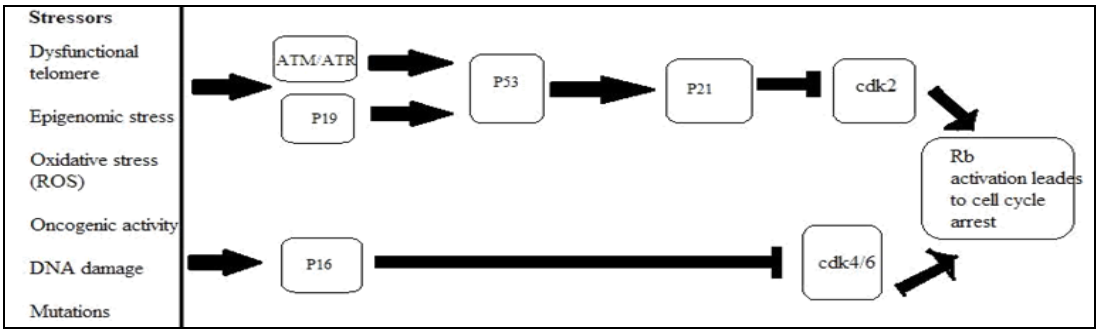

FIG. 1: CELLULAR SENESCENCE PATHWAY

Causes of Cell Senescence:

Telomere Shortening: The telomere consists of a tract of tandemly repeated short DNA repeats and associated protective protein [7], they consist of six base pair repeats TTAGGG [8] and shows end replication problem. This is due to the intrinsic inability of DNA polymerases to replicate the telomere C-rich lagging-strand. During the process of lagging-strand synthesis, RNA primers allow DNA polymerases to initiate DNA replication; however, upon removal of the last primer from the 3′ end, the newly synthesized strand will inevitably be a few nucleotides shorter.

Functional telomeres play a major role in preventing the recognition of chromosomal ends as DNA DSBs by DNA repair machinery; if the telomere is repaired and is followed by cell division, it can cause genomic instability due to cycles of chromosomal fusion and breakage of DNA. When the telomere is dysfunction, it activates DDR response but suppresses DNA repair mechanism [9]. After the activation of DDR response, several pathways of tumor suppressor proteins like p53, p16, p19 are activated which leads to cell cycle arrest or apoptosis.

Epigenetics of Aging: Aged cells show various features on their chromatin. In aged cells, it has been observed that CDKN2A locus [10] (which codes for cyclin-dependent kinase inhibitor p16) is progressively expressed which results in cell cycle arrest. The polycomb group protein which is a gene silencing complex epigenetically controls the CDKN2A locus. With the combined efforts of polycomb repressive complex PRC2 and EZH2 trimethylation of lysine 27 of histone H3 takes place which then hires PRC1 to modify the chromatin to impose gene silencing [11]. In young cells, CDKN2A locus has been occupied by PRC2

which in turn prevents p16 expression and delays cell senescence. Whereas in old pancreatic beta cells the levels of EZH2 mRNA and proteins declines and the level of CDKN2A locus and H3K27me3 shrinks or decreases, these changes permit p16 expression resulting in senescence [12].

Disturbance with the epigenome can induce the response of cell senescence. The epigenomic perturbations can induce DDR response even without actual DNA damage. *e.g.*, HDAC inhibitors activate DDR protein ATM (ataxia telangiectasia mutated).

Oxidative Stress: Denham Herman proposed the first theory of aging in 1955 known as the free radical theory of aging (FRTA) [13]. This theory suggests that free radicals that are produced due to aerobic respiration are responsible for causing cumulative oxidative damage and aging [18] and later reformed by Herman stating that most of the ROS production **Fig. 2** takes place inside mitochondria as a result of ETC (electron transport chain) in which electron leakage takes place, and it was termed as mitochondrial theory of aging [14].

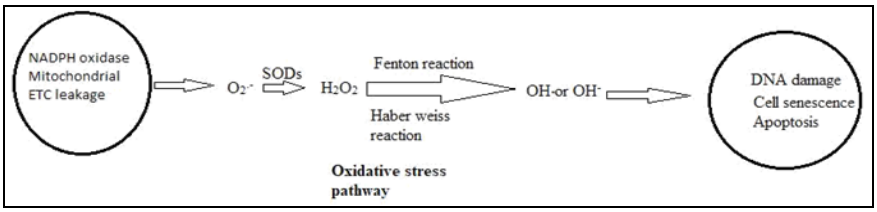

FIG. 2: OXIDATIVE STRESS PATHWAY OF CELLULAR SENESCENCE

Senescent Cells Phenotype: While discussing senescent cell the main questions that arise are what can they possibly do? How they cause diseases? Are beneficial for the body or not? Or what kind of characteristics they have? Senescent cells change their gene expression and end up showing a change in morphology like they become enlarge, double in volume and if adherent adapts flattened morphology. In a culture, senescent cells can be detected by histochemical staining for beta-galactosidase (SA-Bgal) the senescent cells stain blue in the culture, various dyes can be used for this purpose like zombie UV dye or lipofusion staining using GL13. Senescent cells are also marked by the overexpression of p16INK4A or insulin growth factors [1]. Proliferation markers such as p53, PCNA are absent in senescent cells. All these factors serve as a marker for senescent cells.

The senescence-associated secretory phenotype is an important factor of senescent cells. SASP has the potential of explaining the various pathologies related to aging such as age-related disorders or cancer development because of aging. SASP is itself is not a defined expression it varies from cell to cell and upon the pathways that lead to senescence. SASP components include a huge number of cytokines and growth factors which is related to age-related pathologies and inflammation. SASP is not developed just after the cell has become senescent it develops when a cell shows constant DDR signals.

SASP promote inflammation it regulates transcriptional factors such as NF-kB which controls the function of the cytokines such as IL6, IL-alpha which can cause inflammation. Senescent cells can also initiate cancer formation as SASP downregulate the expression of p53 which is a tumor suppressor pathway so if a cell has the deletion of locus p16 and p53 is down-regulated by SASP that cell will develop a tumor. Apart from the bad effects senescent cells also have some good factors such as it prevents fibrosis in liver injury, it was observed in mouse models that when any liver injury has occurred senescent cells cause inflammation over there which was later cleared by the immune response which prevents the formation of fibrosis.

Senescence in Brain Cells and Age-Related Neurodegenerative Diseases: Age-related declined the function of tissues and cell function is the major cause of age-associated neurological disorders like Alzheimer's and Parkinson's disease. The senescent cells losses their regenerative potential and that leads to age-associated diseases, in that case not only the tissues which are related to the disease are affected, but the other tissues also go under function decline [15].

According to the studies of researchers from the data of Netherlands study of depression and anxiety (NESOA) showed that people who have depression and anxiety disorder show shorter leukocyte telomere length (LTL which serves as the mitotic clock) which is a sign of senescent cells. LTL can serve as a biomarker for these types of mental disorder also depression leaves a telomere scar even after the episode is over, that is an imprint of past exposure to the disease [8].

The aging brain shows the characteristics of chronic inflammation, it is known as neuro-inflammation in the brain. It causes major pathologies related to aging. Changes that a brain undergoes due to chronic inflammation are decreased in neuronal populations, postsynaptic densities, cortical volume, pre-synaptic marker, *etc*. senescent cells in the brain secrete pro-inflammatory SASP factors and disrupting cell-cell contact which is necessary for the structural and functional neuron-glial interaction by all these functions they contribute to neurodegenerative diseases [16]. As compared to other organs the brain consumes more oxygen hence high activity with high levels of oxygen creates more oxidative species (ROS) which can damage the neurons.

The brain consists of two types of cells glial cells and neurons. The glial cells are further divided into two part astrocytes and microglia. Out of all these cells, glial cells can show senescence because they undergo mitosis while neurons are post-mitotic cells. Astrocytes are the cells which maintain synaptic transmission and plasticity [17]. They appear starlike hence named astrocytes, these cells are derived from neural stem cells, and they are highly branched have a special characteristic of endfeet and perform most functions than any of the other cells in the brain like maintaining homeostasis, blood-brain barrier, clear out synapsis between neurons and serves as a glial scar. Astrocytes are the chief responders to neurodegeneration, when they detect degeneration they initiate tissue defense mechanisms. When astrocytes are found to be dysfunctional, it can lead to neurodegenerative diseases [16].

Microglia cells can be determined as resident macrophage [16]. They normally stay under resting state only activated in response to injury or inflammation. Activated microglia appears larger than the inactivated one with enlarged soma. It secretes ROS and apoptotic factors to kill the pathogen or bacterial cell and after that the cell phagocyte the remaining debris of pathogen. Chronic activation of microglia has been seen in neural death related to age-associated neurological disorders like Parkinsons and Alzheimer's [16]. Neurodegenerative diseases deregulate the activity of specific circuits affecting the cell number, cell function and cell interactions with different neurons. Parkinson's disease is the most common type of neurodegenerative disorder [24] which is caused due to loss of substantiamigra pars compacta of the brain. Most of the patients with this disorder experience symptoms such as postural rigidity and instability, dopaminergic cell loss, tremor in the body. According to studies by Eilam *et al*., ATM deficiency is related to dopaminergic cell loss [18]. Cell senescence pathways that are linked with this disease are increased in ROC concentration in the brain which can damage nigrostriatal neurons, activation of mitochondrial BER and DNA damage in neurons [16].

In Alzheimer's disease, the part of the brain that is affected is cerebral cortex. Patients with this disease experience symptoms such as dementia, memory loss, and cognitive decline. This can be caused due to the accumulation of ROS, reduced NHEJ (non- homologous end joining), accumulated DSBs, reduction in MRN complex components (Mre II Rad 50 Nbs I, which plays a great role in the detection and signaling of DSBs) because of all these factors the neurons losses their function and go under degeneration process [17].

Ataxia- Telangiectasia (A-T) is the best studied neurodegenerative disorder caused by mutation at single gene encoding ATM (ataxia telangiectasia mutated) which plays a great role in cell senescence pathway therefore due to mutation the DSBs pathway is elucidated. Patients with A-T are highly sensitive to ionization radiation and are wheelchair bound by their teenage and show immunodeficiency and loss of cerebellar Purkinje cells and granule neurons. Cerebral dysfunction in this disease results in muscle hypotonia, abnormal eye moment and truncal swaying while sitting or standing [19].

Senescence as Therapy: Therapy-induced senescence is a well-known method to limit the proliferation of cancer cell without inducing apoptosis. It is much better than the conventional therapies such as a high dose of radiation or chemotherapy as these treatments are highly aggressive, cytotoxic and have a lot of side effects as they can also target normal proliferating cells, *e.g*., hair follicles, bone marrow cells. Even after such aggressive treatment cancer often grows back and develop resistance to the treatment [20]. Senescence induced by treatment was first observed in cancer cells after genotoxic chemotherapy or radiation [21].

As the morphology of cancer cells changes, it makes them susceptible to injury. In TIS the major goal is to restore the tumor suppressor-like p16, p53 or RB or signaling pathway [20], it can also be achieved by inactivating oncogenes like MYC [21]. If in cancer cells all these pathways are intact they can respond to stressors such as DNA damage, telomere shortening or any mutation.

In normal proliferating cells, growth arrest is maintained by certain mechanisms like G1 or G2/M checkpoint, senescence can be gained by increasing CDKIs inhibitors such as p21, P16, p27 by using palbociclib [21]. Tumor cells that lack p53 or RB can be transformed into a new form by using p53 stabilizer nutlin-3a [21], therefore, they can respond to stress. In SAOS-2 osteosarcoma and DUI45 prostate cancer cells, they lack p53 and RB proteins, doxorubicin drugs induced senescence in more than 50% of cells.

Apart from that cell cycle arrest can also be induced by growth factors such as insulin growth factor binding protein-related protein 1 (IGFBP-rp1). Growth factors of the same family like IGFBP3, IGFBP5, and IGFBP7 are found to be overexpressed in senescent cells, and the down-regulation of IGF-1 is associated with the longevity of cells, this can serve as a link between proliferation and senescence for novel therapies [20].

Drugs that can induce senescence to generate DNA damage and produce single and double strand breaks inside the cells which can trigger pathways like ATM/ATR, checkpoint, *etc*. Drugs that are capable of doing so are aphidicolin, Doxorubicin and cisplatin [22].

Therapy for Aging Cells:

Senotherapies: Evacuation of senescent cells can give security to life as senescent cells can cause age-related disorders as well as can skip senescence and turn into a cancer cell, to avoid all these problems and to find new therapies for age-related disorders senotherapies came into limelight. The concept of senotherapies is that it directly target senescent cells without damaging the normal cells, it promises to overcome age-related disorders and promote healthy aging. There are various ways through which senescent cells can be removed either by directly killing them by apoptotic or non-apoptotic means like immune-system mediated therapies which includes antibody mediated drug delivery, cytotoxic T cell targeting and through Natural killer cells. It can also be done by SASP inhibition by using drugs [21] such as metformin [23], rapamycin or dasatinib, or by targeting IL1- alpha blockers, p38 or NFKB inhibitors metformin drug inhibits IKKa/b kinases but not the p38MAPK[23].

Genoprotectors are the factors or drugs that can increase lifespan hence can be linked with anti-aging properties. It has been reported that anti-diabetic drugs have life-prolonging and anti-cancerous effects. IGF-1 (insulin growth factors) signals have been linked to longevity including daf-2 and InR, inactivation of corresponding genes leads to increase in longevity, therefore if IGF-1 is down-regulated the lifespan is more [24] drugs that can be used to kill senescent cells or as anti-aging therapy are metformin, rapamycin, and dasatinib. NF-kB, ROS, and inflammatory cytokines have been found in the physiology of aging. Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kB activation [24].

Another example is a cancer drug that can target senescent cells is dasatinib, it is a broad spectrum kinase inhibitor has senolytic effect on cultured cells. The only concern related to the field of senotherapy is it does not have a proposed target, increasing the risk of off-target on cells. To minimize the effects of off-target on cells antibody that are specific to senescent cell surface antigen can also be used *e.g*. CD44 in the senescent endothelium can be used to direct T cells for killing senescent cells [21]. Moreover, having a healthy lifestyle can promote healthy aging like exercising

daily, having food rich in anti-oxidants that can scavenge free radicles in the body naturally, or reduce drinking and smoking can prevent age-related disorders.

CONCLUSION: It is a well-known fact that senescent cells accumulate with age but the reason behind this is still unclear, the fact that can be exploited for this issue is the decline in the function of the immune system that scavenges senescent cells in young adults is not very prominent in old ones. Neurodegenerative diseases that are found in aged people are due to the inflammation of the brain [21] caused by the pro-inflammatory SASP from senescent cells [9]. It can be avoided if we can target inflammation causing microglia cells, but the side effects of these kinds of therapies can be catastrophic as well as we cannot target senescent neurons because they play a vital role in the functioning of the brain. Novel drugs that can cross blood-brain barrier can be made with the help of nanotechnology that can either target senescent glial cells or can hinder senescent related pathways in cells can be introduced but keeping in account the limitation or side effects of these kinds of therapies as tumor formation can take place if we target senescent pathway. The fact that senolytics have its problems and some issues should be taken into account before introducing this therapy as senescent cells also help in tissue repair and prevent fibrosis. Senolytic therapy should be taken at a particular interval when the patient is in good health by this the patient can be prevented from chronic inflammation as well as prevention fibrosis function of senescent cells can be retained, with continuous senotherapy the functions of senescent cell that are important can be lost [20].

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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