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Review Article

Senescence and its Effect on Aging and Dementia

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Abstract

The term senescence was first proposed by Hayflick and Moorhead in 1960. They defined it as an interchangeable term with aging, which is an additional response by proliferating cells that adopt permanent arrest of cell cycles. Cellular senescence is considered a hallmark of aging termed 'antagonistic pleiotropy' that describes the deterioration causing tissue dysfunction in brain cells. Mainly senescent cell inhibits the growth of DNA in the G1 phase. Since aging is the main risk factor for causing neurodegenerative diseases, senescence plays a crucial role in causing Alzheimer's disease leading to dementia. Besides, senolytic therapies are in development to prevent neuronal loss and restrict disease progression.

Keywords: Hyperbaric oxygen therapy; Cartilage repair; Sports injury; Regenerative medicine; Diabetes.

Introduction

The concept of senescence was coined by Hayflick and Moorhead in 1960. Cellular senescence is defined as an additional response initiated by proliferating cells by adopting a state of the permanent arrest of cell cycles [1]. Senescence is an interchangeable term with aging that describes the process of deterioration followed by maturation and development [1,2,3]. Senescent cells usually inhibit the growth of DNA content particularly in the G1 phase however, they remain functional metabolically [2]. Aging and age-related diseases are primarily associated with cellular senescence. Consequently, it plays a crucial role in several biological processes such as embryogenesis, pregnancy, and wound healing [4]. Tissue dysfunction is caused due to accumulation of senescent cells whereas SASP factors cause detrimental effects in senescent cells [5,6]. These SASP factors can be pro-inflammatory cytokines such as Tumour Necrosis Factor-α (TNF-α), viral FK506-Binding Protein (vFKBP), and interleukin (IL) 6, chemokines, and extracellular matrix proteases, as well as bioactive lipids (bradykines, ceramides,

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prostenoids), microRNAs (miRNAs), other non-coding nucleotides, and extracellular vesicles [3,4]. These factors induce senescence in non-senescent cells, tissue destruction, aggregation of the protein, and neurotic and apoptotic cell death in distant and local tissues [4]. This review explains senescence and its effect on aging and dementia.

Senescence and its effect on aging

The effect of senescence on aging is explained by the combination of inefficient clearance, excessive SASP, and ineffective regeneration [5]. Senescent cells are accumulated in some but not in all tissues in aged humans, monkeys, and mice [6,7,8]. In mice, it is observed that elimination of senescent cells with an increased level of fundamental damage due to a hypomorphic mutation in Bub1b some of the damaged tissue cells can be rejuvenated such that muscles and fat, and protected from cataracts [9,10]. It is a prolific strategy to decrease chronic inflammation and rejuvenate tissues [11,12]. It is a response that is primarily designed to eradicate damaged tissues or cells [9]. Significantly, with rising age, it is not entirely accomplished besides becoming a problem and as result, it is termed as 'antagonistic pleiotropy' that is considered a hallmark of aging [11].

However, they accumulate with age at age-related pathologies such as osteoarthritis and atherosclerosis [13]. The most conspicuous increase is perceived in areas likely skin, liver, lung, and spleen [14]. Age-associated senescence is primarily triggered due to DNA damage, loss of telomere protective functions, and derepression of the CDKN2A locus encoding p16 and ARF3 [14,15,16]. The predominant function of senescence is to start a sequence of the process that eradicates damaged cells and terminates tissue regeneration [15]. Consequently, this valuable process is degraded in aged tissues due to several factors likewise immune system clearing senescent cells may cause the impairment which could result in leading to the net accumulation of senescent cells that could further initiate tissue dysfunction via senescence-associated secretory phenotype (SASP) [16]. Additionally, senescence not only affects the differentiation of cells but also the stem and progenitor cells along with restricting the regenerative ability of tissues [17].

Senescence and its effect on dementia

Alzheimer's disease is the most common cause of dementia, characterized by the accumulation of amyloid β (Aβ), phosphorylated tau, and neuroinflammation [18]. It is equitable to contend that cellular senescence plays a crucial role in AD, as age is of the main risk factors for neurodegenerative diseases [19,20,21]. However, no research is published that confirms a clear and direct relationship between brain senescence and AD pathology [22]. It is reasonable to hypothesize that age-related accumulation of senescent cells in the brain could result from a pro-inflammatory environment for the development of AD [23,24,25]. According to observed pathology of AD due to an increase in the burden of senescent cells and inflammation in the aged brain a positive feedback loop is developed which as a result exacerbates the disease [26,27,28]. Thus, it is essential to understand the mechanism which transforms healthy brain aging into pathological aging and neurodegeneration [29].

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Cellular changes observed in AD are like those observed during senescence in other brain cell types [30]. For instance, it is reported from AD subjects that p16INK4a is upregulated in pyramidal neurons in the hippocampus [31,32,33]. Furthermore, from post-mortem AD brain's transcriptomic analysis of micro-dissected NFT-containing neurons, it is revealed that the expression profiles contain cellular senescence [34]. The presence of senescent astrocytes has been also found in cultures obtained from the post-mortem AD brain tissues. Intriguingly, upregulated p16INK4a expression and β-galactosidase activity, and SASP are identified in these senescent astrocytes [35,36,37,38]. Likewise, in human brain slices, a relationship between senescent microglia with AD is seen that includes the identification of senescent disease-associated microglia phenotype (DAM) along with intracellular/phagocytic Aβ particles [39,40,41]. Some researchers also demonstrate that Aβ oligomers induce senescence in aged-microglia cultures from AD brains [42]. Moreover, increased level of SASP-associated proteins such as IL-6, IGFBP, TGF-β, and matrix metalloproteinases (MMPs) found in both CSF and plasma samples from AD patients provides a high contribution to senescence in AD [43,44,45]. Whereas individuals with AD carry a high burden of genetic risk variants in genes known to be convoluted with senescence likewise metalloproteinase domain 10 (ADAM10), ADAM metallopeptidase with thrombospondin type 1 motif 4 (ADAMTS4) and bridging integrator 1 (BIN1) according to genome-wide association studies (GWAS) [46,47,48].

Conclusion

To conclude, for the process related to aging neuroinflammation is considered a key driver whereas it is induced by brain senescence. Though several researchers explain a dominant role of senescence in the pathogenic processes leading to dementia nonetheless no clear definition of "cellular senescence" in the brain is proposed yet that impedes the advances of specific targets related to senescence for drug development. Moreover, understanding how a healthy aging brain differentiates from pathological aging brain diseases remains a major area of research, especially because not all senescent cell populations have adverse effects. Whereas current hypothesis in this field is to develop senolytic therapies to prevent neuronal loss and tissue damage leading to the decline in risk of disease progression.

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