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Senescence cells in aging - Approaches, Challenges and Opportunities

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Abstract
Cellular senescence is a permanent cell cycle arrest that can be used as a therapeutic approach for many complex diseases. Based on a literature search on PubMed and Google Scholar, this review summarizes information about senescence cells in aging, its approaches, challenges, and opportunities. Recent research suggests that senescent cells could be used as a targeted therapy for many of the diseases discussed in this review. Despite the positive results, much more research in this field is required before such therapy can be implemented.

Keywords: Senescence cells, Targeted therapy, Disease progression prevention

1. Introduction

By definition, cellular senescence represents stable cell cycle arrest that occurs in diploid cells and limits their ability to proliferate [1]. This idea dates from the 1960s, after 2 scientists, Hayflick and Moorhead, saw that human diploid fibroblasts in culture can reach their maximum number of cell divisions before arresting their growth [2]. This mentioned process is actually biological clock, and this phenomenon is known as “Hayflick limit” [3] It is caused by a progressive shortening of telomeres with each cell division and is a physiological response to prevent genomic instability and thus DNA damage accumulation [4] Senescent cells can affect normal tissue physiology, and, in that way, they can influence on progressive functional deterioration [5]. Senescent cells are accumulating with the years, and they can have an effect on the development of osteoarthritis and atherosclerosis [6]. Besides this regular process of telomerase shortening, diploid cells can be involved in processes that accelerate senescence response, and this process is known as premature senescence [7]. Such a response occurs immediately after situations such as genotoxic stress or metabolic shock [8]. Senescence could also be induced in tumor cells by oncogenic stress, which can be experienced due to overexpression of specific oncogenes or, on the other hand, by the loss of tumor suppressor genes (TSGs). Senescence occurs *in vivo* in different tumors with the ability to arrest tumor development and progression, and because of the antiproliferative effect, they could be used as a potential antitumor mechanism. This discovery provides a new opportunity for cancer patients to improve their treatment with the therapy known as prosenescence therapy for cancer [9].

Definitely, we can say that cell senescence is a major cause of aging and all disorders that are related to aging. Senescent cells could not be detected by some universal biomarker; their presence is characterized by many nonexclusive markers such as cell cycle arrest, inability to express genes required for proliferation, etc. [10]. This review will aim on the latest scientific findings about senescent cells in aging, approaches, challenges, and opportunities that have become available in the last decade. Latest findings in this field provide many new

opportunities for the easier and more effective treatment of some diseases in patients who are suffering a lot due to the complexity of their disease.

2. Method

The purpose of this research was to review recently published literature and summarize the key findings. It is based on search results from PubMed and Google Scholar. Articles published in the last decade are considered, as are the most significant clinical trials conducted in this field

3. Discussion

Based on recent studies, many diseases are caused by cell senescence, and one example of that is senescence-associated atherosclerosis, which is the main cause of cardiovascular diseases [11]. Using senolytics and senostatics as a therapeutic strategy, it is expected to mitigate atherogenesis. According to the latest study, cellular senescence is responsible for making organelles dysfunctional. Targeting the subjacent marked dysfunctional organelles is a critical step to counteracting senescence-mediated atherosclerotic events [12]. In addition, statins help reduce DNA damage by accelerating DNA damage repair and reducing replicative senescence [13].
Besides cardiovascular diseases, cellular senescence also plays a crucial role in osteoarthritis, which is characterized by progressive destruction of articular cartilage. Until now, there is no adequate therapy or drugs for this disease. Due to that, inhibition of cell senescence may help in finding potential drugs that are able to treat disease. Those drugs need to be able to reduce or remove senescent cells or to neutralize their harmful effect [14], and they are often referred to as senolytics and senomorphics [15].

Another review paper provides information about the ability of senescent cells to predispose osteoarthritis and their influence on disease progression [16]. Targeting senescent cells in osteoarthritis, a bone related diseases associated with aging, may offer a potential therapeutic strategy to slow down the progression of the disease.
In addition to the therapeutic strategy, one article summarized the results provided by authors from the United States where clearance of the senescence cells could be used as a therapeutic intervention [17]. Several other studies also suggesting that osteoporosis should be treated or stopped by inhibition of cellular senescence [18], [19], [20].

Similarly, glaucoma is a disease associated with cell senescence, and it is classified as a disease of early cellular senescence [21]. Another publication presents information about the removal of senescent cells in order to protect against the loss of retinal ganglion cells. The drug used for that purpose was dasatinib [22].
The main risk factor for Alzheimer's disease is aging, but the mechanism that is responsible for developing Alzheimer's disease due to aging is still unknown.

Similarly, to other age-related diseases previously mentioned, cellular senescence appears to be a major causative factor, and by its removal, it can serve as a potential treatment for Alzheimer's [23]. Many other publications confirm the potential of senescence cells being a part of treatments for Alzheimer's disease [24], [25], [26]. Another neurodegenerative disease for which senescent cells may provide therapeutic effect is Parkinson's disease. Many studies have been done until now, and they provide outstanding results when it comes to the involvement of these cells in the treatment of a variety of diseases [27], [28], [29], [30].

However, their application goes beyond neurodegenerative disease, as represented in Table 1, as their impact is seen on pancreatic β-cell function that is critical in the development of type 2 diabetes. Nowadays, studies show how potential usage of senescence cells provides an opportunity for prevention of disease progression that can be better than already available drugs [31], [32], [33], [34].

Table 1. Senescence cells in aging - approaches and opportunities – summary.

Disease	Approaches/Opportunities	Reference
Atherosclerosis	Using senolytics and senostatics as a therapeutic strategy, it is expected to mitigate atherogenesis.	[12]
Osteoarthritis	Drugs that can remove senescent cells and stop the progression of the disease are senolytics and senomorphics	[15]
Osteoporosis	Osteoporosis should be treated or stopped by the inhibition of cellular senescence.	[18], [19], [20]
Glaucoma	Usage of dasatinib to clear senescence cells.	[22]
Neurodegenerative (Alzheimer's and Parkinson's disease)	Senescence cells are a possible treatment for Alzheimer's disease as well as for Parkinson's disease	[24] - [30]
Type 2 diabetes	Targeted therapies associated with senescence cells are better than available drugs.	[31] - [34]

Besides the above-mentioned senescence cells, senescence plays an important role in cancer as well. Senescence can promote cancer development in a way that alters the cellular microenvironment through a senescence-associated secretory phenotype [35]. Cell senescence can be induced in the following ways: loss of tumor suppressor genes, activation of oncogenes, and chemotherapy or radiotherapy. It is known that early-stage senescence plays an important role in protecting cells from transformation, while cancer development is usually associated with prolonged senescence [36]. Activation of the host immune system could provide an interesting way for the clearance of senescent cancer cells [37].

When addressing the hurdles within this field, mapping senescent cells in tissue poses several challenges, including the lack of distinct markers, their relatively scarce presence, and extensive heterogeneity. This senescence cell theory is almost 60 years old, and there has been huge progress in this field, especially in understanding senescence *in vivo* [38]. So far, scientists have focused their attention on biomedical research and its association with senescence. All their efforts thus far have been geared towards enhancing the clinical success of senescence-based therapy. Despite numerous challenges persisting, the ongoing research in this field is bound to intensify, and success is deemed inevitable [39], [40].

4. Conclusions

Senescent cells can influence normal tissue physiology and, as a result, progressive functional deterioration. Interestingly, senescent cells accumulate over time and can influence the development of osteoarthritis and

atherosclerosis. Apart from the regular process of telomerase shortening, diploid cells can be involved in processes that accelerate the senescence response, which is known as premature senescence. The use of these cells is diverse and is used in many biomedical fields for the treatment of many complex diseases, such as atherosclerosis, osteoarthritis, osteoporosis, glaucoma, neurodegenerative diseases, type 2 diabetes, and many cancer types. Still, there are many challenges as well as opportunities in this field, and a lot of research is needed to be ready to use them as therapeutic agents. It is critical to recognize their significance to make life easier for many patients who are subjected to extremely complex and difficult therapies. This review work is just one in a series of similar ones that attempted to summarize all of the important items in this field's achievements thus far.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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