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Cellular Senescence and SENEX Gene on the Peripheral CD4+CD25+ Treg Cells Enhancement in Elderly

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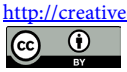

Abstract

Cellular senescence is a signal transduction process which maintained genomic stability and stopped mammalian cell growth. Furthermore, cellular senescence induces a protective response to a variety of DNA damage. However, this process is also associated with apoptosis, upregulated secretion of inflammatory cytokine, and promoted surrounding tissue damage. When cellular senescence accumulates to a certain extent, it triggers geriatric diseases, such as chronic inflammation, immune senescence-associated tumors and incontrollable infections. Cellular senescence gene SENEX, which was cloned in 2004, has been demonstrated to play a unique gatekeeper function in human endothelial cells when stress-induced pre-mature senescence and apoptosis occurr. The phenomenon that CD4+CD25+ Treg cells accumulated in the aged population has been well studied in recent years. Now Treg accumulation related to immune-pathology has attracted more interest. CD4+CD25+ Treg did not decline and age, but accumulated and suppressed immunoreaction. The enhanced Treg number and function may be associated with stress-induced premature senescence-mediated unique cellular senescence protection mechanisms, and SENEX may play a critical role in this process. In this article, we summarize the cellular senescence and SENEX gene in the accumulation and functional activity of CD4+CD25+ Treg in the elderly.

Keywords

Cellular Senescence, Gene, SENEX, CD4, CD25, Treg, Elder

1. Introduction

The balance between the number and the function of various immune cells and their sub-types is one of the most basic conditions for the body to obtain and maintain normal immune function. Studies have shown that the proportion and function of CD4+CD25+Regulatory T Cells in the elderly over 60 years old are increased, and the balance between CD4+CD25+ Treg and CD4+effector T cells has changed. CD4+CD25+ Treg does not age and decay with age, but rather tends to accumulate and increase relatively. This change promotes the occurrence of immunosenescence, and increases the risk of elderly people suffering from malignant tumors, infections and other immune deficiency-related diseases [1]. However, the mechanism of CD4+CD25+ Treg enhancement in the elderly is still unclear. Some scholars believe that the accumulation of CD4+CD25+Treg is related to individual health status and the apoptosis intensity of CD4+CD25+ Treg [2] [3]. Cell senescence is the key mechanism to regulate the cell growth cycle, maintain cell homeostasis and affect apoptosis. SENEX gene is a recently discovered gatekeeper gene that plays an important role in the process of "stress aging" and apoptosis of vascular endothelial cells [4]. Cell senescence and the SENEX gene may play a key role in the accumulation and functional activity of CD4+CD25+ Treg in the elderly.

2. Cell Senescence

Cell senescence refers to the accumulation of internal and progressive harmful changes that commonly occur in the cells of the human body with age. It is a gradual degradation process of organisms under the long-term joint action of multiple factors. At present, it has been recognized that the essence of cell senescence is a signal transduction process leading to the irreversible stop of cell proliferation, which is accompanied by specific changes in genetic material, molecular phenotype and other aspects of the impact on the body [5]. According to its mechanism, cell senescence can be divided into two categories: replicative senescence and stress premature senescence. Replicative senility depends on wear or functional defects of "telomeres". A telomere is a special structure composed of multiple repetitive non transcriptional sequences (TTAGGG) with short ends of linear chromosomes and some binding proteins. Its basic function is not only to provide a buffer for non transcriptional DNA, but also to protect the ends of chromosomes from fusion and degradation. It plays an important role in maintaining genome stability and controlling cell growth and life span. Every time the cell divides, the telomere of the chromosome will become shorter. The telomere length of various tissues except brain and heart muscle decreases by 20 - 60 bp every year. When cells lose too much telomere due to multiple divisions, cells will stop dividing and go to senescence or apoptosis [5] [6] [7]. Therefore, severely shortened telomeres are a signal of cell senescence. However, this does not mean that human aging is simply caused by telomere shortening. In fact, other senescence inducing factors in the body start to function long before telomere

loss. This is another major form of cell senescence—stress induced premature senility (SIPS). SIPS is telomere independent, including oncogene induced senility (OIS). In addition to tumor genes, oxidative, genotoxic, infectious and other factors can induce cell senescence [8]-[13]. Therefore, cell senescence can occur in advance due to the depletion of replication power, as well as changes in the surrounding environment and stress.

Somatic cells maintain the ability to enter the aging process. No matter what form of cell senescence is, it is currently believed that the process of cell senescence is mainly regulated by two tumor suppressor proteins, p53 and Rb, and sometimes they can be independently regulated. P53 and Rb genes are necessary to stop the cell proliferation cycle. If abnormal loss or mutation occurs, cells often lose control and enter unlimited proliferation, thus promoting tumor occurrence. In response to stress induced cell senescence, phosphorylated and stable p53 activates its target genes, including cyclin dependent protein kinase inhibitor p21, which encodes proteins that activate Rb by inhibiting a cyclin dependent protein kinase complex (E/Cdk2). Dephosphorylated Rb inhibits the transcription factor of the E2F target gene, and E2F stops cells in the G1 phase. Rb is also activated by another Cdk inhibitor p16, which acts through cyclin D/Cdk4,6 complex, eventually stopping the permanent growth of cells and changing their morphology and function [10] [14] [15] [16].

In the process of cell senescence entering the "reprogramming of gene programs", for most senescence programs, the final path to irreversible growth stop is generally similar. Both telomere dependent and non telomere dependent cell senescence trigger DNA damage and induce persistent DNA damage response (DDR). In cells with tumor suppressor genes such as p53, p16 mutations and nonfunctional telomeres, proliferation continues and enters a slow growth period characterized by genomic instability, known as the "crisis". In a crisis period, unprotected telomere ends can fuse abnormally through the chromosome repair mechanism, leading to non exchangeable translocation. Most cells tend to apoptosis due to fatal chromosomal abnormalities, while a few cells escape from the crisis by activating the telomere stabilization mechanism (that is, part of the aging mechanism) that has the potential to cause malignant tumors [7] [11] [12] [15] [17].

In conclusion, it is currently believed that cell senescence is a protective reaction mechanism of mammalian cells to maintain genomic stability, i.e., cell homeostasis, prevent the unlimited proliferation of affected cells after the activation of carcinogenic genes, or damage or stress. Its process and ultimate goal is to control cell proliferation and tumors, but it can also trigger apoptosis and obtain the secretion function of a variety of inflammatory factors. Too much and too strong aging reaction will produce harmful effects around the local area, causing age-related diseases, such as chronic inflammation, decreased immunity, tumors, infections, etc.

3. SENEX Gene and SIPS

SENEX noun is derived from Latin and means "old people". It can be seen that it

is closely related to aging. The SENEX gene is located in the long arm of chromosome 4 (4q31.23). It was identified and cloned successfully in 2004. It was named ARHGAP18 in the RefSeq system. The SENEX gene has a total length of 2901 bp, encoding 663 amino acid residues and a protein with a molecular weight of about 75 KD. The protein has a RhoGAP determinant and belongs to the Rho/RAC/Cdc42 like GTPase activating protein (GAP) family. It makes Rho (a member of the small G protein family) protein accelerate the dissociation of GTP, and plays the role of closing the signal pathway. In addition, it does not contain any other known protein determinants. The panel expression profile analysis showed that the gene was expressed in the heart, lung, skeletal muscle, kidney, pancreas, spleen, brain, testicular tissue and peripheral blood leukocytes. One of the basic functions of the Rho family is to regulate actin polarity and affect the remodeling of the cytoskeleton. Early research mainly focused on the role of the Rho protein in regulating cell morphology, migration, adhesion, phagocytosis and cell growth and development. Later, it was found that Rho protein was up-regulated in many tumors, but low or no expression in normal tissues. This suggests that the Rho protein is closely related to tumors. It is now known that Rho protein can regulate gene transcription and control cell growth cycle, aging and apoptosis [4] [18] [19] [20] [21]. A recent research report by Coleman *et al*. shows that whether the adenovirus carrying human SENEX gene recombination is used as gene delivery, or the human vascular endothelial cells are continuously cultured under normal conditions after obtaining SENEX gene overexpression by plasmid introduction, various manifestations of inhibitory proliferation of aging cells appear, and these indicators are significantly related to SENEX overexpression. In addition, after repeated passage of human umbilical vein endothelial cells to obtain replicative senescence, compared with them, it was found that the telomere length of senescent endothelial cells induced by SENEX overexpression did not shorten, while the three genes that should be expressed to increase as markers of replicative senescence, PAI-1 (plasminogen activator inhibitor-1), IL-1 α (interleukin-1 α) And COX2 (cycloxygenase 2) did not increase when the expression of SENEX increased, that is, SENEX induced cell senescence did not have a replicative senescence genotype. In addition, in the stress premature aging model induced by hydrogen peroxide (H_2O_2) as an inducer, when endothelial cells were exposed to a sub toxic dose of H_2O_2 (concentration 10~100 uM) for 2 hours, they were cultured on ordinary fresh medium for 24 - 48 hours. The results showed that the cells showed morphological changes, SA-β-Increased GAL activity and other aging performance, but no telomere shortening, and these cells SENEX protein increased. These results indicate that the SENEX gene can mediate SIPS, but does not involve the process of replicative senescence. Their research also showed that the expression of p53 or p21 protein did not change when SENEX was overexpressed, but the mRNA and protein levels of p16 were increased, and the expression of highly phosphorylated Rb protein was decreased, which further suggested that SENEX induced aging by activating the p16/Rb pathway. Senex induced senescence of endothelial cells is

characterized by their anti-inflammatory effects compared with other cell senescence induced by SIPS. Senescent cells induced by SENEX were not activated by TNF-a to promote the adhesion of neutrophils and monocytes, the synthesis of IL-8 was also reduced, and this cell barrier function was enhanced, which could protect cells from TNF-a induced apoptosis. Secondly, when endothelial cells were costimulated with low and medium concentrations of H_2O_2, the SENEX protein of senescent cells increased, but when high doses of H_2O_2 induced apoptosis of endothelial cells, SENEX expression was inhibited and SENEX protein was downregulated. This suggests that SENEX induced senescence phenotype has a protective effect on the cells themselves. The decreased level of SENEX can induce apoptosis in essence, while the enhanced expression can inhibit TNF-a induced endothelial cell apoptosis. SENEX gene provides a unique gatekeeper function in SIPS and the apoptosis pathway of vascular endothelial cells.

4. Enhancement of CD4+CD25+ Treg and Immunosenescence in the Elderly

CD4+CD25+Treg refers to a special CD4+T cell subtype that constitutively and stably expresses CD25 on its surface, with non reactive and immunosuppressive functions. Under the same environment, it can inhibit the proliferation and function of CD4+, CD8+and other effector immune cells, but it is in a non response or low response state [22] [23] [24].

CD25 is an interleukin-2 (IL-2) receptor *α*. In the beginning, people only thought that CD25 was the expression product of T lymphocytes and other immune cells when they were activated. CD4+T cells were just one of the most important immune cells that could play a one-way immune effect or promote other immune cells to play a role. However, since Sakaguchi *et al*. [25] first reported that mouse CD4+CD25+T cells have "organ specific autoimmune diseases" caused by anti effector T cells in 1995, people's understanding of CD4+T cells has gradually changed. CD4+T cells not only have the important functions of anti infection and anti-tumor to promote and maintain the immunity of the body, but also play an important role in maintaining autoimmune tolerance and regulating the stability of the immune internal environment of the body. Since then, according to the functional and phenotypic characteristics of CD4+T cells, they have been divided into two categories: one is the traditional CD4+Teff, which does not express, or only expresses, the weak to moderate intensity of CD25 (CD4+CD25 -~mid); the other is the regulatory CD4+CD25+ Treg, which mostly expresses stronger CD25 (CD4+CD25 high), followed by the expression of transcription factors FoxP3, CD62L (Leukocyte endogenetic adhesion molecule-1) CD152 (CTLA-4, cytotoxic-T-lymphocyte-associated antigen), GITR (glucocorticoid-induced T cell receptor), TGF-*β* (transforming growth factor), etc. The balance and stability of the number and function of these two types of cells is one of the key factors to ensure the health of the body. When the number

of CD4+CD25+ Treg decreases or the function is defective, it is easy to induce autoimmune related diseases such as rheumatoid arthritis, inflammatory bowel disease or transplant rejection. On the contrary, when CD4+CD25+ Treg is too much or the function is enhanced, it may also promote the escape, proliferation and transfer of tumor cells. Pathogens continue to exist in the body, and infection cannot be controlled, or recurrence of tumor and infection [26]-[31].

Immunosenescence is a phenomenon in the immune function of the body gradually decreases with age, and it is one of the most obvious manifestations of human aging. Walford was the first to put forward the theory of immune senility, which believed that the immune system was fundamentally involved in the aging process of mammals and was also one of the main regulatory systems in the aging process [32]. Later, some scholars also proposed that the decline of immune system function is one of the earliest and most obvious changes in aging after the human body enters old age. When immune senescence develops to a certain extent, the immune system cannot monitor and recognize the subtle changes of cells or molecules in the body, or even if it can recognize, it cannot mobilize the immune response to effectively remove abnormal cells or pathogens, resulting in the elderly being prone to the tumor, infection and other immune deficiency related diseases. At this time, the immune state is called "immune crisis" or "pathological immune senescence" [33] [34] [35]. At present, although the phenomenon of immunosenescence and its impact on the health of the elderly has been widely recognized, the causes and mechanisms of its occurrence have not been clarified. The traditional view is that the thymus shrinks with age, which affects the development of T cells, thus causing abnormalities in the quality and quantity of T cells in peripheral lymphoid tissues [36] [37]. Secondly, studies have shown that when lymphocytes repeatedly respond to infection, chronic inflammation and other stimuli, they will be damaged or protect themselves by activating the aging mechanism. However, if the stimulus is too strong, the DNA repair ability will be reduced, the number and frequency of cell apoptosis will be increased, and the number and function of lymphoid cells will be reduced [38] [39] [40] [41]. However, because the changes in the elderly immune system are a very complex system, there should be other factors affecting immunosenescence besides thymus atrophy and weakening of effector immune cells.

In recent years, with the in-depth promotion of the research on CD4+CD25+ Treg, more and more studies have shown that the proportion of CD4+CD25+ Treg in the elderly is significantly increased and maintains the original functional characteristics, that is, "the balance between CD4+Teff and CD4+CD25+ Treg in the elderly has changed, significantly shifting to CD4+CD25+ Treg". CD4+CD25+ Treg, as a group of T cell subtypes with obvious inhibitory function, has a dominant accumulation in the elderly, and naturally plays a key role in the occurrence and development of immunosenescence and "pathological immunosenescence" in the elderly [38] [39].

5. Effects of Cell Senescence and SENEX Gene on CD4+CD25+ Treg in the Elderly

Due to the particularity of the structure and function of the immune system, it is necessary to identify, eliminate the "alien" invading the body and the "non self" material components generated in the body (including bacteria, viruses, mutant cells generated in the body, tumor cells, etc.) at any time. Therefore, in order to maintain the stability of the internal environment, immune cells are in frequent stress state for a long time, and will start the cell senescence mechanism to protect themselves. However, the initiated cell senescence program is limited. Excessive cell division and stress will damage chromosomes and reduce their repair function, leading to increased apoptosis, decreased number and decreased function of immune cells. In a few cases, it even induces proliferation, uncontrolled differentiation and tumor development. By analogy, in the process of immunosenescence, the number of immune cells should generally be reduced and the function should be reduced, but why does the elderly CD4+CD25+ Treg increase on the contrary and the function is not weakened? Does CD4+CD25+ Treg have a special self-protection mechanism different from other effector cells? Our research team carefully analyzed the biological characteristics of CD4+CD25+ Treg and the process and functional effects of cell senescence mechanism, and found that under the same culture environment and antigen stimulation conditions, CD4+Teff and other effector cells proliferated actively, while CD4+CD25+ Treg almost did not respond. This suggests that CD4+CD25+ Treg has a more sensitive and powerful "aging" protection system, especially the "stress premature aging" regulated by the SENEX gene has the effect of allowing cell survival, inhibiting proliferation and reducing apoptosis, during which it may play a more important role. Secondly, as the body grows older, various forms of aging cells will continuously accumulate and produce the senility associated secretary phenotype (SASP) [4] [5] [8] [40]. The inflammatory factors secreted from it, such as IL-1, IL-6, and IL-8, may interfere with the homeostasis of CD4+CD25+ Treg, promote CD4+CD25+ Treg to enter the cell cycle again, and maintain its differentiation and proliferation [28] [41] [42].

In conclusion, common diseases of the elderly, such as malignant tumors and infections, have seriously endangered the health and quality of life of the elderly. A thorough study of the relationship between cell senescence and SENEX gene, CD4+CD25+Treg, and immunosenescence can help explain the reason and mechanism of the increase of CD4+CD25+ Treg in the elderly, further reveal and comprehensively understand the mechanism of immunosenescence, and provide the experimental basis and new ideas for the future development of new methods that can effectively improve the immune status of the elderly, as well as prevent and control tumor, infection, and other immune related diseases in the elderly.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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