Chin Med Sci J
June 2016

Vol. 31, No. 2
P. 121-126

CHINESE
MEDICAL SCIENCES
JOURNAL

REVIEW

Relation Between Cellular Senescence and Liver Diseases

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Key words: cellular senescence; mechanism; liver diseases; liver fibrosis; liver cancer

Abstract Cellular senescence refers to a process that cellular proliferation and differentiation modulated by the multiple stimulating factors gradually decline. Aging cells present the irreversible stop of proliferation and differentiation and change in secretory function because the cell cycle of aging cells is steadily blocked at some point. It has have been shown that cellular senescence plays an important role in the occurrence and development of liver diseases. In this paper, we review the advances in relations between cellular senescence and liver diseases.

Chin Med Sci J 2016; 31(2):121-126

CELLULAR senescence is a biological phenomenon in normal life activities. If the senescent cells in tissues and organs are not cleared away in time, the accumulated cells will onset the pathological conditions.[1] Cellular senescence may be one of contributors of liver diseases, such as chronic hepatitis, fatty liver, liver cirrhosis, liver cancer, etc. Environmental factors, for example virus, overexposure to alcohol and toxin cause liver cell injury. The cumulative damage accelerates liver cell senescence. When the process cannot be halted or reversed, pathological pathway in the damaged liver cells will be activated. Therefore, cellular senescence plays an important role in the process of occurrence and development of liver diseases. Here, we review the mechanisms that induce cellular senescence and relationships of cellular senescence with liver diseases to provide potential therapeutic targets for delaying and preventing liver diseases.

Received for publication September 18, 2015.

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CHARACTERISTICS OF CELLULAR SENESCENCE

In aging cells, cell proliferation and differentiation stop irreversibly, which may contribute to changes in cell shape and secretory function. Aging cells are in a relatively stable state and still maintain their metabolic activity.[2] The common characteristics of senescent cells are cell cycle arrest at G1 or G2/M phase; increased cell and nucleus size and decreased cell permeability; not sensitive to pro-apoptosis factors; changes in secretory functions. Senescent cells secrete growth factors, inflammatory cytokines, chemokines, and protease that can trigger the surrounding normal cells to senesce *via* inflammation.[3]

MECHANISMS OF CELLULAR SENESCENCE

Cells can be induced to senesce, a state of irreversible cell cycle, by oxidative stress, telomere shortening, DNA damage response, and activation of oncogenes through cyclin-dependent kinase inhibitor (CKI) pathway.

Oxidative stress

Oxidative stress refers to a state where intracellular reactive oxygen species (ROS) is at a high level and an imbalance between biological system's ability to antioxidant defenses and oxidative damage. ROS can trigger a DNA damage response, thus inducing cellular senescence.[4] Oxidative stress can activate nuclear factor-κB (NF-κB) signaling pathway and p38 mitogen activated protein kinases (MAPK) signaling pathway to increase expressions of p53 and p16, causing cellular senescence.[5, 6]

Telomere shortening

Telomere that is located at the end of eukaryotic chromosome, will periodically and progressively shorten as cell division. Telomerase is a reverse transcriptase enzyme that can reverse telomere shortening. There is strong evidence that telomere shortening is a potent mechanism of programmed cellular aging,[7, 8] at least in yeast,[9, 10] and human glomerular mesangial cells.[11] Moreover, the decrease of telomerase activity can provoke cellular aging in vascular intimal smooth muscle cells from mice.[12] Interleukin-8 (IL-8) and resveratrol can delay cell aging, which may be associated with activation of telomerase.[13, 14] This findings suggest that telomere shortening and telomerase activity changes are the important drivers of cell aging.

DNA damage response

DNA damage response is a DNA injury caused by multiple factors. Ataxia-telangiectasia-mutated (ATM) and ATM and Rad3-related (ATR) protein kinases are acvtivated by DNA damage response, subsequently activating p53. The activated p53 can induce p21 to activate, which leads to cell cycle arrest, thus resulting in cell aging.[15-17] Raf kinase inhibitory protein (RKIP) has been considered as a target gene of p53 taking part in the process. DNA damage response induces cell aging as well as it can inhibit activity of extracellular-signal regulated protein kinase (ERK).[18] These results suggest that cell aging caused by DNA damage response is closely related to p53 signalling pathways.

Oncogene activation

Oncogene-induced senescence (OIS) is, in fact, a tumor-inhibitory mechanism and can inhibit cell proliferation induced by oncogenes. OIS triggers the senescent effector p21 and p16 to block cell cycle and induce cell aging *via* activating Ras GTP enzyme or Raf protein kinase.[19]

Simultaneously, these mechanisms likely interact on each other in the process of cell aging. Rossiello *et al*[20] reported telomeric DNA damage occurs in the process of DNA damage response and OIS. That is to say, telomere shortening may be a decisive factor in cellular senescence.

SIGNALING PATHWAYS RELATED TO CELLULAR SENESCENCE

Many signaling pathways have been identified to be associated with cellular senescence, such as p16-retinoblastoma protein (pRb), p53-p21-pRb, Sirtuin 1 (SIRT1), mechanistic target of rapamycin (mTOR), p38 MAPK, and NF-κB signaling pathway.

p16-pRb and p53-p21-pRb signaling pathways

p53 and pRb genes are the main components of these two signaling pathways that contribute to inducing and maintaining cell aging.[21-23] p53 and p16 genes can activate downstream gene expression through hindering the formation of cyclin-dependent kinase (CDK) complex, which can cause retinoblastoma (RB) protein accumulation and block cell cycle, ultimately leading to senescence. Both p16-pRb and p53-p21-pRb signaling pathways are two classic pathways of cellular senescence. p16, p21, and p53 expressions have been found to be increased in senescent cells.[24-26] However, the expression level of p53 is decreased in the replicatively senescent and OIS human keratinocytes. The decrease of p53 expression may be related to histone 3 that can induce acetylation of promoter of p53.[27]

SIRT1 signaling pathway

SIRT1 can delay cellular senescence *via* up-regulating p53.[28] microRNAs (miRs), a class of small, non-coding RNAs that modulate SIRT1 expression, can promote cellular aging by inhibiting SIRT1 expression.[29] A study has shown that inhibiting SIRT1 expression can induce cellular aging mediated by promoting p53 acetylation as well as p21 expression.[30] Hsa-miR-22 can phosphorylate pRb *via* inhibiting SIRT1 expression, thus resulting in cellular senescence.[31] A report has shown that resveratrol can induce SIRT1-dependent cellular aging in the gastric cancer cells.[32]

mTOR signaling pathway

mTOR signaling pathway appears to be regulated by