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REVIEW

Relation Between Cellular Senescence and Liver Diseases

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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 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.

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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.

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 SENESENCE

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- κ B (NF- κ B) 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 activated 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 SENESENCE

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- κ B 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

insulin/insulin like growth factor-1 (IGF-1) signaling pathways.³³ The signal triggered by insulin, IGF, and other growth factors can activate protein kinase B (PKB/AKT), thereby inhibiting function of tuberous sclerosis complex (TSC)1/TSC2. It can activate mTOR signal. mTOR mainly regulates cellular aging and cell cycle through phosphorylation of its downstream target proteins S6 kinase 1 (S6K1) and 4E-binding protein (4EBP-1).³⁴ A report has shown coenzyme Q10 can inhibit the senescence of mesenchymal stem cells through Akt/mTOR signaling pathways.³⁵

p38 MAPK signaling pathways

p38 MAPK is a member of MAPK family and can spread signals from the cell surface to the nucleus through three levels of signal amplification cascade, which is able to regulate the expression of target gene. A study has suggested that high-temperature requirement serine protease A1 (HtrA1) induced by oxidative stress can activate p38 MAPK, thus causing cellular senescence immediately, which resulted in activation of p16, p21, and beta-galactose glucoside enzyme. HtrA1-induced senescence was abrogated by inhibition of p38 MAPK.³⁶ A research has shown that radiation can selectively activate p38 in bone marrow hematopoietic cells *in vitro*, resulting in up-regulation of p16 and beta-galactose glucoside enzyme expressions, while inducing cellular senescence. Inhibition of p38 MAPK can reduce radiation-induced senescence.³⁷

NF- κ B signaling pathway

NF- κ B is a nuclear transcription factor and might be involved in cellular senescence. Chien *et al*³⁸ identified a NF- κ B subunit p65, known as a major transcription factor, which accumulates in the chromatin of senescent cells. Moreover, they found NF- κ B suppression can cause the cultured fibroblasts to escape immune recognition by natural killer cells as well as inactivate p53, which can delay senescence. Continuous activation of NF- κ B signal can promote cellular senescence.³⁹

These signaling pathways are related to cellular senescence and their mechanisms are not clearly understood. Further researches should aim to explore the relationship among these pathways.

CELLULAR SENESCENCE AND LIVER DISEASES

Cellular senescence might involve in the occurrence and development of liver diseases, such as viral hepatitis, fatty liver, liver fibrosis and liver cancer. Several signaling pathways have been identified to participate in cellular

senescence in the liver that suffers from insults. Sequentially the senescent liver cells are removed by immune system. The senescence of damaged hepatocytes can limit proliferation of other cells that experience some insults and reduce the risk of malignant tumor formation. When the capacity of the immune system to remove senescent cells is overwhelmed, cellular senescence will promote liver dysfunction.

Chronic viral hepatitis

Viral hepatitis refers to hepatitis virus infection that causes inflammatory reaction of the liver tissues. The most common causes of chronic viral hepatitis are hepatitis B virus and hepatitis C virus. Telomere length is related to transformation and development of chronic hepatitis C. The telomere length in patients with hepatitis C was shorter than that in the healthy people. It means that hepatitis C virus (HCV) is an inducer that pushes hepatocytes into senescence.⁴⁰ Chronic hepatitis B virus (HBV) infection can arrest cell cycle of liver cells in G1 phase, resulting in hepatocyte senescence.⁴¹ In addition, HBV and HCV can inhibit liver cell aging. HCV core protein has anti-aging effect on hepatocytes exposed to H₂O₂ through down-regulating expression of p16, eventually reinforcing DNA methylation.⁴² Hepatitis B virus x (HBx) protein can carry out its anti-senescence effect on hepatocytes through down-regulating expressions of p53, p16, as well as p21, thus associated with DNA methylation.^{43, 44} When uncontrolled growth cells accumulate over time, liver cancer will eventually occur.⁴⁵ Therefore, cellular senescence is a potent anticancer mechanism.

Fatty liver disease

Fatty liver disease is caused by lipid deposit in the liver cells. There are two main types of fatty liver disease: alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD). M2 macrophages can induce liver cellular senescence *via* producing interleukin-6 (IL-6), thus inhibiting liver cell apoptosis and fatty degeneration caused by alcohol.⁴⁶ Liver cellular senescence is closely related to diabetes and liver fibrosis in patients with NAFLD. Liver cellular senescence is involved in prognosis of fatty liver disease. The higher the proportion of aging liver cell, the higher the degree of liver tissue fibrosis; the prognosis is worse.⁴⁷ Similar results have been found in patients with AFLD.⁴⁸ Liver cellular senescence can inhibit fatty degeneration to a certain extent and it also can activate hepatic stellate cells (HSCs), which lead to liver fibrosis.

Liver fibrosis

Liver fibrosis is a self-repairing and self-healing process

after liver damage. The activation and proliferation of HSCs is the key in the process of liver fibrosis.⁴⁹ The formation of liver fibrosis mainly is associated with activation of HSCs and deposition of extracellular matrix. Related studies have found that liver cells, hepatic sinus endothelial cells, and Kupffer cells can induce HSCs activation *via* paracrine mechanisms.⁵⁰⁻⁵² Meanwhile, these cells are involved in the secretion and accumulation of extracellular matrix.

Liver cells aging can promote liver fibrosis formation. However, it has been confirmed that promoting the activated HSC to senesce can inhibit liver fibrosis and promote liver fibrosis recovery.^{53, 54} Kim *et al*⁵⁵ found cysteine-rich 61 (CYR61/CCN1) induced the activated HSCs to senesce and inhibit liver fibrosis through $\alpha 6\beta 1$ binding sites. Injecting CCN1 protein *via* tail vein can promote the recovery of liver fibrosis in mice. In addition, CCN1 can induce liver myofibroblasts senescence, thus limiting liver fibrosis.⁵⁵ IL-22 can improve liver fibrosis through promoting senescence of activated HSCs. IL-22 also up-regulates expressions of p-p53ser15, p53, p21, and suppressor of cytokine signaling 3 (SOCS3), which are the senescence-associated protein, thus inducing senescence of activated HSCs.⁵⁶

Liver cancer

As mentioned earlier, cellular senescence can inhibit formation and growth of tumor. Aging cells can be quickly recognized and removed by immune cells. It is an important mechanism to prevent cancer.⁵⁷ Transforming growth factor- $\beta 1$ (TGF- $\beta 1$) can induce cell aging of liver tumor and inhibit tumor growth through sustained response of p21cip1 and p15ink4b.⁵⁸ Anti-tumor drugs, such as oxaliplatin can induce liver cancer cellular senescence by up-regulating the expressions of both p53 and p21. The regulation of p53 is related with forkhead box M1 (FoxM1). Over-expressing FoxM1 can inhibit the cellular senescence induced by oxaliplatin in liver cancer cells. FoxM1 can down-regulate p53 to inhibit liver cancer cell aging and has no effect on p21, an aging-related gene.⁵⁹ Studies have found that N-myc downstream regulated gene 1 (NDRG1)-knockout, results in inhibition of tumor growth in mice, increase of p53, p21 and p16 expressions and increase of cellular senescence.⁶⁰ These results suggest that cellular senescence can inhibit growth of liver cancer cells.

To sum up, cellular senescence is a defensive mechanism after liver damage to avoid further harm. How cellular senescence causes or prevents liver diseases remains to be elucidated. In the near future, selective inducing senescence of damaged cells and promoting to eliminate senescent

cells might be used in the prevention and treatment of liver diseases.

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