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Review

Cellular senescence and liver disease: Mechanisms and therapeutic strategies

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ABSTRACT

Cellular senescence is a fundamental cell fate caused by several cellular injuries which results in irreversible cell cycle arrest yet remaining metabolically active across all species. Cellular senescence not only can prevent tumor occurrence by inhibiting the proliferation of injured cells, but also can affect the surrounding cells through the senescence-associated secretory phenotype (SASP). Attractively, accumulating evidence shows that cellular senescence is closely related to various liver diseases. Therapeutic opportunities based on targeting senescent cells and the SASP are considered to be potential strategy for liver diseases. However, although research on cell senescence has attracted widespread attention, the overview on detailed mechanism and biological function of cell senescence in liver disease is still largely unknown. The present review summarizes the specific role of cell senescence in various liver diseases, and updates the molecular mechanisms underlying cell senescence. Moreover, the review also explores new strategies for prevention and treatment of liver disease through promoting senescence or counteracting excessive pathological senescence.

1. Introduction

Cellular senescence is considered a terminal arrest of cell cycle triggered by many types of intrinsic and extrinsic stresses [1–4]. Senescent cell production occurs throughout life and plays beneficial roles in many physiological and pathological conditions including embryogenesis, wound healing, host immunity, and tumor suppression [5–7]. However, abnormal or pathological cell senescence is conducive to the development of age-related diseases [8,9]. Interestingly, accumulating evidence indicates that cellular senescence is not just a cellular arrest but rather an active mechanism providing regulation of cellular homeostasis [10], fibrosis [11], and microenvironment [12], by blocking proliferation of aberrant cells. During senescence, DNA-damaged or senescent cells are kept irreversibly during cell division and being inhibited from returning to their active stages [13,14]. Therefore, tissue integrity can be guaranteed and the risk of malignancy reduced. Moreover, senescent cells also have the potential to influence neighboring cells through secreted senescence-associated secretory phenotype (SASP) [15,16]. Numerous studies have confirmed that the SASP can contribute to senescence-related inflammation, metabolic dysregulation, stem cell dysfunction, aging phenotypes, chronic diseases, geriatric syndromes, and loss of resilience [17–19]. Attractively, regulation of senescent cells and SASP can be considered as novel therapeutic methods.

The liver plays a significant role in the regulation of lipid metabolism, glycolysis, oxidative phosphorylation, and amino acid synthesis, and hence determines the material and energy cycle of the entire body [20]. In the initial stages of various chronic liver diseases, cellular senescence serves as a protective mechanism to block the proliferation of damaged cells, and hence reduce the risk of carcinogenesis [21]. However, with the development of the disease, abnormal senescent cells affect nearby cells by releasing large amounts of proinflammatory cytokines [21]. The dual role of cellular senescence in liver diseases adds to the difficulty of intervention therapy. Interestingly, Park et al. showed that senescence marker protein-30 (SMP30) was related to the occurrence and development of nonalcoholic fatty liver disease (NAFLD), suggesting the close relations between cellular senescence and NAFLD [22]. Furthermore, Lim et al. reported that hepatitis C virus Core protein improves premature senescence via inhibiting p16 expression [23]. Oxidative stresses-induced cell senescence is considered to be an important protective mechanism for hepatitis C virus infection [23]. Besides, Krizhanovsky et al. found that senescent activated stellate cells limit the process of liver fibrosis [24]. Natural killer cells preferentially removal senescent cells, and hence promotes the reversal of liver fibrosis [24]. Moreover, Wiemann et al. showed that hepatocyte senescence is a general marker of liver cirrhosis [25]. Formation of fibrotic scars at the cirrhosis stage may be the result of hepatocyte senescence [25]. In addition, Yoshimoto et al. reported that the SASP contributes to the occurrence and development of hepatocellular carcinoma (HCC) [26]. The SASP phenotype in hepatocytes and stellate cells promotes HCC development by secreting various tumor-promoting factors [26]. Overall, these studies suggest that cellular senescence

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attracts more and more attention in the prevention and treatment of various liver diseases.

Although research on cell senescence has attracted widespread attention, the detailed mechanisms and biological functions of cellular senescence in various liver diseases are still not summarized. In the present study, we will update functions and roles of cellular senescence in five common and high-risk liver diseases, including NAFLD, viral hepatitis, liver fibrosis, liver cirrhosis, and liver cancer. Moreover, we will also explore novel therapeutic strategies to reverse various liver diseases via cellular senescence regulation mechanism.

2. Cellular senescence plays an important role in non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of abnormal lipid metabolism and has become one of the most typical chronic liver diseases in clinical practice [27]. Excessive accumulation of lipid droplets (LDs) in hepatocytes is a striking feature of NAFLD, which may be attributed to both hypernomic intake of fatty acids and increased de novo hepatic lipogenesis [28]. Large amounts of epidemiological evidence shows that the approximately one-third of the adults suffer from NAFLD in developed countries, while in the light of the considerably growing population and the prevalence of unhealthy lifestyles, its incidence is expected to rise in developing countries, especially in advanced cities and younger groups [29]. Mechanistic investigations indicate that insulin resistance has a crucial role in inducing hepatic LD accumulation, lipotoxicity, lipoapoptosis, and oxidative stress [30,31]. Insulin resistance increases the ability of white adipose tissue to release free fatty acids, and in turn leads to abnormally elevated levels of free fatty acids, eventually resulting in excessive hepatic uptake [32]. Besides, insulin resistance can also promote the activity of catalyzing enzymes, thereby enhancing lipid de novo synthesis pathway in the liver [32]. In addition to insulin resistance, accumulating evidence suggest that cellular senescence plays a pivotal role in NAFLD [33–36].

In clinical research, Park et al. reported that SMP30 was related to the occurrence and development of NAFLD [22]. They performed immunohistochemical analysis (IHC) and Enzyme-linked immunosorbent assay (ELISA) to determine the expression of SMP30 in liver biopsies from patients with NAFLD. They found that the expression level of SMP30 in liver was markedly down-regulated in a NAFLD stage-dependent manner [22]. Furthermore, Aravinthan et al. showed that cell senescence in hepatocytes can forecast the condition and development of non-alcohol-related fatty liver disease [33]. 105 liver biopsies from 70 patients with NAFLD and 60 normal liver tissues were collected to monitor telomerase activity, cell cycle arrest, and the severity of DNA damage [33]. They showed that the telomerase activity in hepatocytes was lower in NAFLD than that in controls. Hepatocytes in liver biopsies from patients with NAFLD exhibited cell cycle arrest at stage G1/S phase and high-level expression of senescence marker p21 [33]. Moreover, the expression level of cell senescence marker p21 was positively correlated with the pathological stage of NAFLD [33]. Further follow-up studies revealed that higher p21 expression in hepatocytes, but not telomerase activity, was strongly related to poor treatment results [33]. Similarly, Nakajima et al. is also committed to exploring the potential mechanisms underlying telomere length changes in human liver biopsies from patients with NAFLD [34]. It is well known that telomere shortening is a typical feature of cellular senescence. They revealed that increased insulin resistance contributed to liver steatosis, and hence induced excessive accumulation of reactive oxygen species (ROS), and eventually accelerated telomere shortening [34]. Additionally, Laish et al. further studied the average length of telomere in peripheral lymphocytes from 20 patients with cryptogenic cirrhosis, 22 patients with NAFLD, and 20 normal controls [35]. They demonstrated that telomere average length was shorter in NAFLD in comparison with the cryptogenic cirrhosis and normal controls [35]. Attractively, Aravinthan et al. revealed the effects of CDKN1A (it encodes cellular senescence marker p21) on the occurrence and development of NAFLD [36]. 323 NAFLD patients from UK and 123 NAFLD patients from Finland were naturally divided into two cohorts in their studies. They found that CDKN1A variant rs762623 can bind to the promoter region of cellular senescence marker p21, and in turn regulate the expression level of p21 by modifying the promoter activity [36]. Overall, these results suggest that therapies aimed to block hepatic senescence might attenuate or prevent the progression of NAFLD.

Animal models have also been used to investigate the role of cell senescence in NAFLD. Recently, Ogrodnik et al. reported that hepatocyte senescence was closely related to hepatic fat accumulation in NAFLD [37]. The accumulation of senescent hepatocytes promoted hepatic fat accumulation and steatosis [37]. Furthermore, the clearance of senescent hepatocytes through siRNA-meditated knockdown of p16 or treatment with inhibitors of cell senescence in INK-ATTAC mice can significantly alleviate liver steatosis [37]. In contrast, induction of hepatocyte senescence by p16 overexpression plasmid or DNA damage reagents aggravated liver steatosis [37]. Moreover, Ballestri et al. showed that ovarian senescence promoted the pathological process of liver steatosis, and hence facilitated the occurrence and development of NAFLD in an experimental overfed zebrafish model [38]. Besides, Yilmaz et al. demonstrated that the induction of cell senescence in steatotic hepatocytes may be a key factor in the transformation of NAFLD to HCC [39]. In addition, Kondo et al. found that hepatic senescence marker protein SMP30 knockout mice present more severe liver steatosis, inflammatory infiltration, and stress damage compared with normal mice [40]. Interestingly, Yang et al. revealed that the functional impairment induced by mature hepatocyte senescence can be relieved by oval cells in mice with fatty liver disease [41]. Targeted induction of damaged hepatocyte senescence and Targeted activation of oval cells can be a potential strategy for NAFLD [41]. Importantly, Kim et al. reported that differential expression of microRNA (miRNA) between NAFLD and healthy controls trigger several hypotheses about the function of miRNA [42]. Through systematic analysis, 6 of the 27 miRNAs showed correlations with cell senescence in NAFLD, including miR-130a-3p, miR-16-5p, miR-21a-5p, miR-103-3p, miR-17-5p, and miR-30c-5p [42]. Further exploration of the functional properties of these miRNAs is beneficial to understand the critical role of cell senescence in NAFLD [42]. Altogether, these data indicate that cellular senescence promotes the occurrence and development of NAFLD.

The increased recent studies in vitro also showed that cell senescence plays a pivotal role in NAFLD. Peverill et al. showed that oxidative stress may be the major cause of hepatocyte senescence, which is a common phenomenon in the occurrence and development of NAFLD [43]. Enhanced oxidative stress contributed to telomere shortening, and hence induced cell senescence [43]. Furthermore, Skoien et al. demonstrated that senescent cells may promote the progression of NAFLD through the secretion of cytokines and proinflammatory factors [44]. Utilizing a new cell model of senescence in vitro, senescence associated secretory phenotypes SASP has been identified [44]. Moreover, Sarkar et al. found that SASP may promote NAFLD disease progression via excessive secretion of proinflammatory factors and up-regulation of molecules that induce ROS accumulation and NF-κB activation [45].

Besides, Campisi et al. indicated that senescent cells released a great deal of senescence-associated chemokines including IL-12, IL-8, IL-6, and matrix-degrading enzymes (MMPs), which was closely related to the occurrence and development of NAFLD [46]. In addition, Gong et al. found that novel mitochondrial peptides (such as SHLPs, HN analogs and MOTS-C) and recombinant FGF21 analogs may provide new Therapeutic strategies for age-related NAFLD [47].

NAFLD as a series of substantially undervalued clinical pathologic syndromes, besides its destructive effects on liver itself, intensive investigations have reported NAFLD also accounts significantly for diabetes and cardiovascular diseases [27–32]. Like other earlier stage liver diseases, it's a potential reversible lesion. Summarizing the above