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REVIEW

Aging and metabolic dysfunction-associated steatotic liver disease: a bidirectional relationship

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Abstract **In recent years, aging and cellular senescence have triggered an increased interest in corresponding research fields. Evidence shows that the complex aging process is involved in the development of many chronic liver diseases, such as metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). In fact, aging has a tremendous effect on the liver, leading to a gradual decline in the metabolism, detoxification and immune functions of the liver, which in turn increases the risk of liver disease. These changes can be based on the aging of liver cells (hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells). Similarly, patients with liver diseases exhibit increases in the aging phenotype and aging cells, often manifesting as faster physical functional decline, which is closely related to the promoting effect of liver disease on aging. This review summarizes the interplay between MASLD/MASH development and aging, aiming to reveal the complex relationships that exacerbate one another. Moreover, the corresponding schemes for delaying aging or treating diseases are discussed to provide a basis for the development of effective prevention and treatment strategies in the future.**

Keywords cell senescence; aging; metabolic dysfunction-associated steatotic liver disease; metabolic dysfunction-associated steatohepatitis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is estimated to affect up to 38% of the global adult population, making it the most common cause of chronic liver disease worldwide as its incidence continues to rise [1]. In 2023, NAFLD was renamed metabolic dysfunction-associated steatotic liver disease (MASLD). According to the current epidemiological evidence, NAFLD data are still reasonable and highly consistent under the new MASLD definition. With the progression of MASLD, hepatocyte injury and inflammation occur, resulting in more severe metabolic dysfunction-associated steatohepatitis (MASH) [2]. MASH is present in approximately 20% of patients with MASLD and gradually progresses to liver fibrosis, and cirrhosis. At the same time, MASH is expected to become a leading cause of cirrhosis worldwide in the near future due to improvements in the prevention and treatment of viral hepatitis [3].

Multiple recent studies have highlighted the role of aging in the onset and progression of hepatic steatosis. The liver is the largest organ of substance metabolism in the human body and is responsible for the synthesis, decomposition and transformation of substances to maintain the balance and homeostasis of the body [4]. Therefore, age-related decline in liver function can lead to the disruption of metabolic balance and induce disease [5]. Aging is a universal phenomenon in all living organisms and refers to the progressive loss of the body's physiologic integrity, leading to impaired functioning and an increased risk of death. Aging can induce inflammation and changes in microenvironment homeostasis resulting in a progressive decline in the function of cells, tissues, and organs [6,7].

In this review, we summarize the pathological and physiologic changes in the liver after aging and discuss the impact of senescence on MASLD/MASH, as well as strategies to improve MASLD by targeting aging or senescent cells. Finally, we identify the lingering skepticism and future problems that need to be solved.

Pathological and physiological manifestations of the liver after aging

It is reported that the volume and blood flow of the liver

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are reduced by approximately one-third in elderly individuals, which has a great impact on the function of the liver [8]. The liver is the most important cause of lipid and glucose metabolism disorders during aging. Aging increases lipid accumulation in the liver and decreases cholesterol metabolism, leading to increases in blood cholesterol and fat contents [9–11]. The possible underlying mechanisms include decreased β-oxidation, an increased density of β-adrenergic receptors, and leptin resistance after aging, which eventually lead to increased fat production and uptake [9,12,13].

Furthermore, aging-related phenomena are also associated with disorders of glucose metabolism. First, there is a distinct biological connection between diabetes and MASLD: a staggering 75% of individuals with type 2 diabetes also suffer from MASLD, and those diagnosed with MASLD face an increased risk of developing diabetes [14,15]. Glycerophosphocholine phosphodiesterase 1 (GPCPD1) is an abundant muscle enzyme that hydrolyzes glycerophosphocholine (GPC) [16]. The GPCPD1-GPC pathway, which plays an important role in the regulation of glucose homeostasis, is severely compromised with aging, leading to systemic disturbances in glucose metabolism [17]. Moreover, as reactive oxygen species (ROS) increase during aging, they can increase glucose and cholesterol uptake by cells, thereby also increasing cholesterol accumulation [18]. In addition, a major cause of glucose metabolism disorders is insulin resistance, which is also considered to be the main reason for the progression of MASLD [19,20]. Studies have shown that the degree of insulin resistance in MASLD/MASH patients is highly consistent with and correlated with liver aging [21]. Depletion of p53 in mice has also been found to improve insulin resistance in animal models of obesity [22]. Insulin resistance is followed by dysregulation of lipolysis and excessive delivery of fatty acids to the liver, leading to MASLD [23]. Furthermore, leptin deficiency affects the action of insulin, resulting in insulin resistance, which may affect lipid metabolism in the liver again [24,25].

During aging, liver regeneration is reduced and proliferation is weakened, which may also be one of the causes of liver volume reduction [26,27]. In a rat model of partial hepatectomy, the liver recovery rate of old animals was slower than that of young animals [28]. Moreover, the incidence and mortality of acute liver failure secondary to viral hepatitis are higher in elderly individuals [29]. The reduced regenerative capacity of the aged liver may be related to the following factors: telomere dysfunction, reduced expression of regeneration-specific proteins, and oxidative stress. Rudolph *et al*. reported that telomere dysfunction is associated with defects in liver regeneration and that telomerase deficiency accelerates the development of cirrhosis caused by chronic liver injury [30]. However, the restoration of telomerase activity and telomere function improved hepatocyte regeneration in cirrhotic livers. It also reduced transforming growth factor-β (TGF-β) signaling and hepatic stellate cell (HSC) activation [30]. Bird *et al*. reported that in human and mouse models, the spread of senescence was dependent on the delivery of macrophage-derived TGF-β receptor-1 (TGF-βR1) ligands to locally uninjured hepatocytes, and that this phenomenon was reversed upon TGF-βR1 inhibition [31]. The roles of HSCs and liver sinusoidal endothelial cells (LSECs) in liver regeneration are described in detail below. Moreover, the expression of proteins involved in cell cycle division such as DNA polymerase I, Cell Division Cycle protein 2 （CDC2） and Forkhead Box M1B (FoxM1B）, is reduced or delayed in aged mice [32,33]. The CCAAT/enhancer-binding protein alpha (C/EBPα)-Brm complex has been found to play an inhibitory role in liver regeneration in aged mice by occupying and silencing E2F-dependent promoters, blocking the activation of these genes, and thereby reducing the regenerative capacity of the liver in aged mice [34,35].

In conclusion, structural changes in the liver after aging lead to a decline in various physiologic functions (Fig. 1).

Relationship between aging and MASLD/MASH

Role of senescence in liver diseases

MASLD is mainly observed in middle-aged and elderly people, and its prevalence increases with age [10,27]. Elderly patients have more risk factors for MASLD, including obesity, diabetes, and hyperlipidemia. Moreover, aging itself enhances the progression of MASLD to MASH and the associated mortality [36]. A cross-sectional analysis of prospectively enrolled patients showed a higher prevalence of MASH in elderly patients than in nonelderly with MASLD [37]. The higher incidence of advanced fibrosis in elderly MASH patients than in nonelderly MASH patients suggests that increasing age can serve as an independent factor related to cirrhosis in MASLD patients [37–39]. One possible explanation is that aging causes M1 macrophage polarization, increases inflammation, and causes liver damage.

Ogrodnik *et al*. demonstrated that the accumulation of liver fat was reduced by eliminating senescent cells, indicating that hepatocyte-specific senescence induces fatty liver disease [5]. Meanwhile, an analysis of human liver biopsies from MASLD patients revealed that hepatocyte senescence was associated with the severity of MASLD [5]. Similarly, Wan *et al*. examined liver triglyceride (TG) content and gene expression profiles at different ages and reported that TG significantly

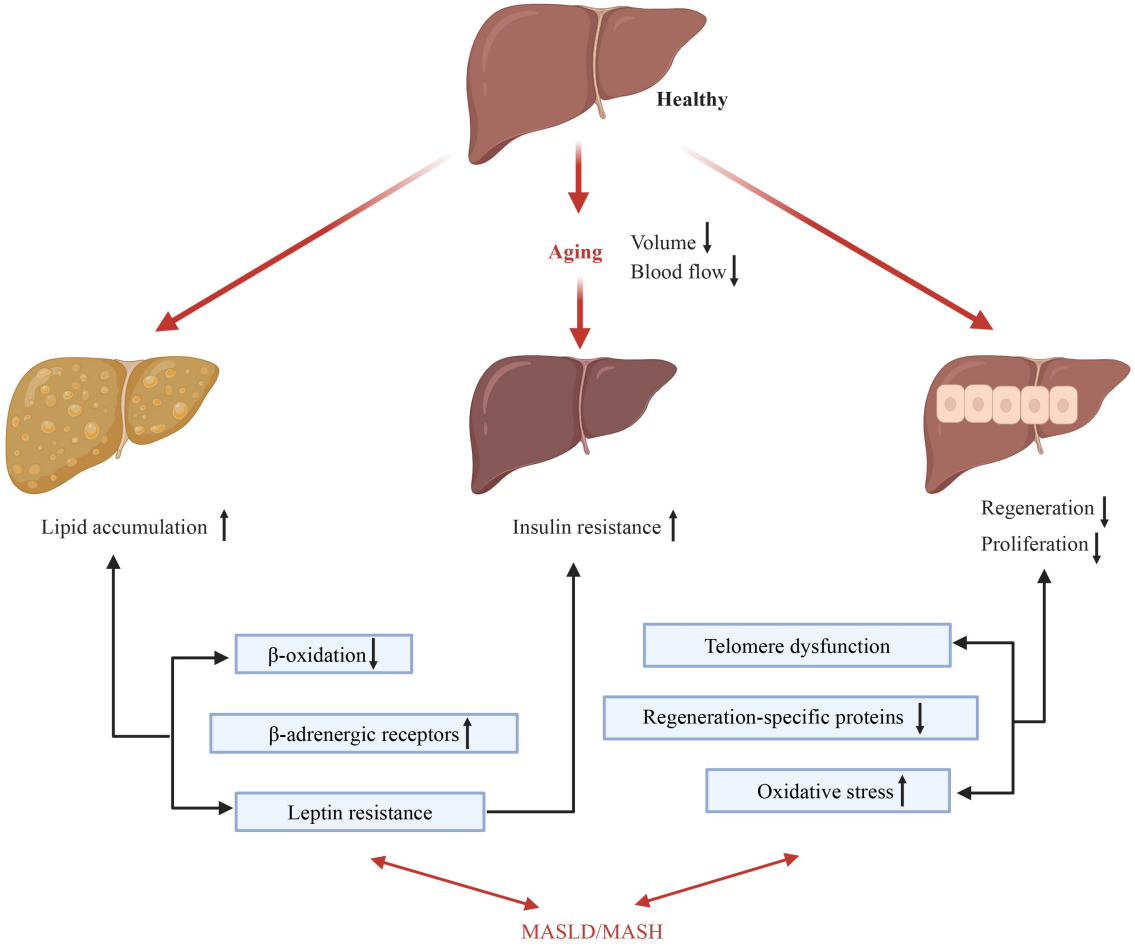

Fig. 1 Pathological and physiologic manifestations of the liver after aging. The main changes after aging are lipid accumulation, insulin resistance and decreased regenerative capacity.

accumulated in the livers of aged mice, leading to hepatic steatosis [40]. At the same time, expression of the mitochondrial β-oxidation-related gene PPARα was downregulated, and expression of the receptor for advanced glycation end products (RAGE) was upregulated [40]. They found that RAGE inhibition upregulated PPARα and its downstream target genes, resulting in reduced TG retention, whereas PPARα inhibition had the opposite effect, indicating that RAGE upregulation might play a key role in aging-related hepatic steatosis [40]. Similarly, our group reported that fat deposition, fibrosis and inflammation were increased in aged mice compared with control mice. The relevant data has revealed that pathways associated with fibrosis and inflammation are activated in LSECs of aged mice [41]. Furthermore, clinical samples from the aged group also presented increased liver oil red O staining and TG and total cholesterol (TC) levels [41]. In conclusion, the results of the present study suggest that aging leads to fat deposition and aggravation of the associated damage.

Effects of senescence on liver cells

It was found that the levels of p16, p21, p53 and senescence-associated β-galactosidase (SA-β-Gal) were significantly increased in obese rats and humans [21,42,43], and activation of the p21 and p16 pathways is increased in fatty liver indicating that aging-related changes also occur after steatosis. Based on human liver biopsy and analysis, Baboota *et al*. also concluded that the visceral fat area increases with the severity of liver disease and is significantly positively correlated with all aging markers [21]. Moreover, inflammatory and fibrosis-related markers, including interleukin-1 β (IL-1β), IL-6, TGF-β1, collagen type I (COL1A1), and α-smooth muscle actin (α-SMA), are also associated with the degree of aging [21]. Researchers have also reported an increase in cellular senescence in the liver of patients with MASLD/MASH [5,44]. Therefore, it can be assumed that the development and pathogenesis of MASLD/MASH are closely related to aging and cellular senescence.

However, we should accurately distinguish between

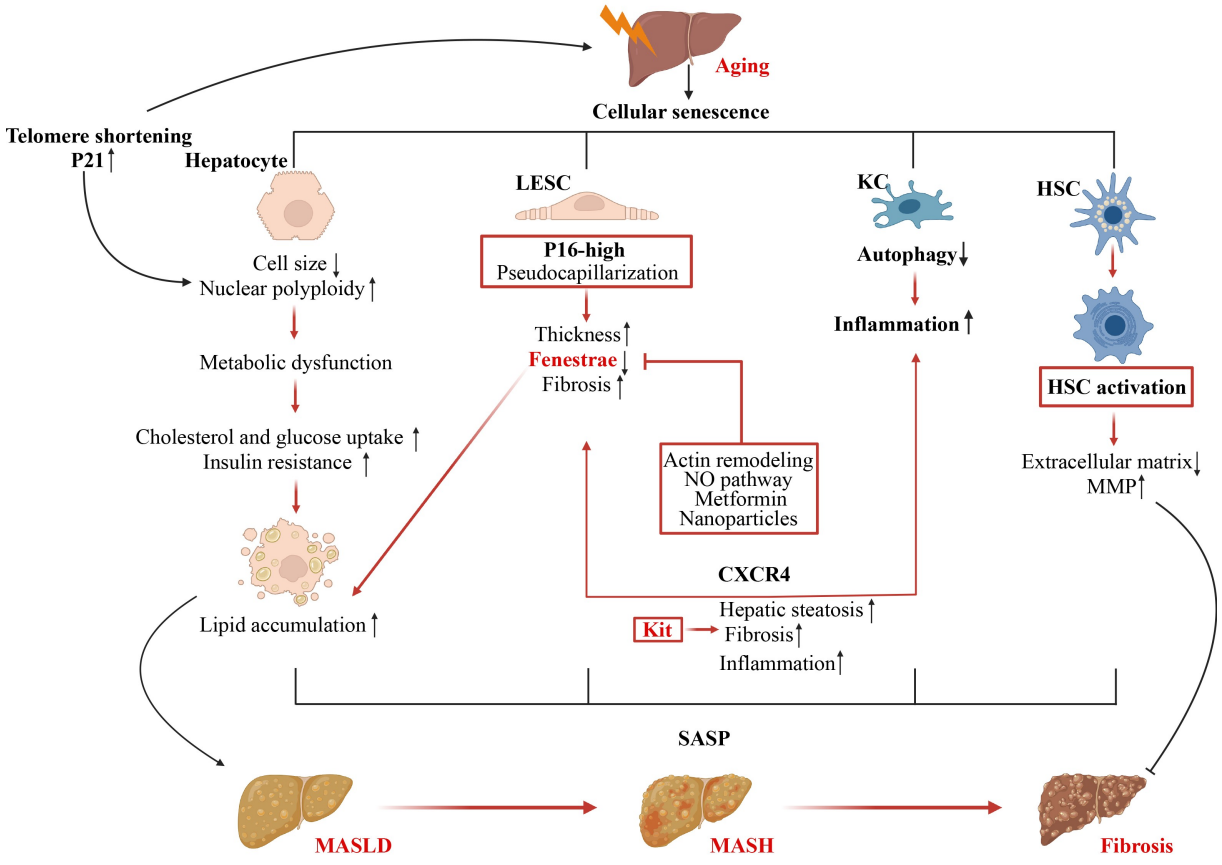

Fig. 2 The aging can be based on the aging of liver cells. Hepatocyte senescence mainly causes lipid deposition and aggravates MASLD. LSECs exhibit pseudocapillarization, which reduces the number of fenestrae. The autophagy level of KCs is reduced after senescence, which is likely to cause more severe inflammatory responses. After HSC senescence, the ECM decreases and MMP increases, which can alleviate liver fibrosis. The SASP is a complex mixture composed of cytokines, chemokines, growth factors, proteases, and other components and plays an important role in the senescence process of various cells.

aging and cellular senescence. Cellular senescence is a stable state of cell cycle arrest, and the continuous accumulation of senescent cells in the liver leads to disease progression, which occurs throughout life. The characteristics of the main cell types in the liver after aging are described (Fig. 2).

Hepatocytes

Hepatocyte senescence appears to be a common phenomenon in liver disease and has gradually become a consensus. Up to 80% of hepatocytes exhibit senescence phenotypes in advanced liver disease [44,45], and the number of senescent hepatocytes with inflammatory activity and fibrosis increase [44,46]. Hepatocyte senescence has also been demonstrated in animal models of liver disease [47]. The metabolic capacity of hepatocytes decreases after aging, resulting in a decrease in liver function and a compensatory imbalance, leading to disease progression [44]. Therefore, hepatocyte senescence can be used to predict disease progression and poor prognosis [44,48]. First, the detoxification function of the liver is reduced so that harmful substances accumulate [49]. Second, during aging, the expression of ROS and cholesterol synthesis genes increases, which enhances the ability of senescent hepatocytes to take up cholesterol and glucose, and leads to fat accumulation [18]. In addition, aged hepatocytes have altered expression of the glucose transporters GLUT2 and GLUT4 and exhibit selective insulin resistance [45].

In addition to significant changes in metabolic function, hepatocytes undergo significant morphological changes during aging [26,50]. It has been shown that vacuolar hepatocyte nuclei are more abundant in senescent hepatocytes expressing p21, suggesting that they can be used as markers of hepatocyte senescence [51]. Moreover, in MASLD, the size of the hepatocyte nucleus is correlated with telomere shortening and p21 upregulation, indicating that nuclear size is also associated with hepatocyte senescence and demonstrating the relationship between the two factors [52]. In addition, researchers have recently reported that hepatocyte polyploidy leads to diverse cellular states, which may open new avenues for the treatment of aging-associated

fatty liver disease. Yin *et al*. reported that early hepatocyte polyploidy is a common response to stress, which may be a potential mechanism by which the liver can cope with functional decline during aging. Interestingly, they consider that hepatocyte size is primarily determined by ploidy and may not be a marker of aging [53]. There are also changes in the relative volume of hepatic organelles during cell senescence, such as a continuous decrease in the surface area of the smooth endoplasmic reticulum [54]. The volume of individual mitochondria increases, but the number of mitochondria decreases.

Senescent hepatocytes also secrete the senescence-associated secretory phenotype (SASP), which is an important marker of cellular senescence [55]. The SASP includes cytokines, chemokines (C-C motif chemokine ligands), growth factors and matrix metalloproteinases (MMP-1, MMP-3) that trigger senescence in neighboring cells in a paracrine manner [56–58]. For example, IL-6, tumor necrosis factor-α (TNF-α), and IL-8 can recruit proinflammatory macrophages to cause local or systemic inflammation and tissue damage, thereby aggravating liver disease [55,59]. In addition, IL-6, IL-8 and other cytokines and chemokines have been shown to be involved in MASLD/MASH development processes with related functions [60–62].

Senescent hepatocytes have also been reported to influence hepatocellular carcinoma (HCC) development through SASP. On the one hand, SASP may prevent HCC by limiting cell growth and immune surveillance. On the other hand, SASP can also promote cell proliferation leading to HCC development and invasion in the late stage [63,64]. In conclusion, SASP plays an important role in the development of liver diseases and opens new possibilities for the control of liver diseases.

Liver sinusoidal endothelial cells

Multiple studies have shown that senescent LSECs are the main p16-positive cells in aging mice [65,66]. Omori *et al*. established a p16-CreERT2-tdTomato mouse model and discovered p16-high-expressing cells with great heterogeneity, which became enriched as age increased. Similar to hepatocytes, LSECs undergo significant structural and functional changes during aging [66]. Under an electron microscope, the thickness of LSECs increases, the number of fenestrae decreases, and the formation of the perisinusoidal basement membrane and increases in fibrosis were observed [67,68]. These changes, known as pseudocapillarization, have been identified in several species, including mice, rats, and humans [68–71]. These morphological changes in LSECs are also accompanied by functional changes. First, owing to the reduction in the number of fenestrae, the scavenger receptors and endocytosis capacity in LSECs decrease, which can remove macromolecules from the circulation [72,73]. After impaired endocytosis, hyperlipidemia may occur, increasing the incidence of heart-related diseases such as atherosclerosis [67,74]. It may also disrupt the exchange of lipids between hepatocytes and blood, leading to lipid accumulation in the liver [75]. Moreover, the fenestrae are the windows of insulin uptake, and a certain degree of insulin resistance occurs after the reduction of the function of fenestrae [76,77]. In addition, the expression of vascular secretory receptors (stabilin-2, VEGFR2 and CD32b) and the nitric oxide (NO) pathway decreases, and liver blood flow is reduced [69,78]. These changes in aged LSECs may increase the susceptibility to liver and cardiovascular diseases. Therefore, from the perspective of treatment, some scholars have proposed methods to reverse or prevent the age-related reduction in fenestrations and pseudocapillarization. For example, the induction of actin remodeling and the targeting of the NO pathway may increase fenestration after LSEC senescence [79]. Similarly, the use of metformin can improve the typical changes caused by age through the upregulation of AMPK and endothelial NO, increasing insulin sensitivity [77,80]. LSEC fenestration can also be modulated by targeted drug delivery methods such as nanoparticles and quantum dots [77].

In addition, pseudocapillarization is accompanied by aging-related changes: increased expression of p16 and proinflammatory factors (TNF-α, IL-1, and IL-6) [69,78]. This phenomenon is considered to be related to SASP secretion, which regulates endothelium-dependent immune cell recruitment by inducing NF-κB activity [81]. Our group also reported that aging and diet-induced MASH could be treated by modulating C-kit (CD 117). The expression of hepatic C-kit, a receptor tyrosine kinase used to label the pericentral region of the liver, decreases with age [82,83]. At the same time, C-kit depletion can promote LSEC senescence and aggravate hepatic steatosis, leading to MASH-related fibrosis and inflammation [41]. We hypothesize that the inhibition of endothelially derived C-kit aggravates hepatic steatosis and fibrosis by promoting the transcription of CXCR4 signaling in macrophages and neutrophils [41]. We subsequently infused C-kit$^+$ LSECs and found that it alleviated liver senescence and steatosis, thus greatly aiding the future treatment of aging-related MASH.

LSEC senescence is also associated with liver regeneration. We found that senescent LSECs accumulate in the late stage of liver regeneration after partial hepatectomy (PHx), mainly due to shear stress [84]. Shear stress is regulated by Notch signaling to trigger cell senescence promoting SASP in liver endothelial cells and interfering with liver regeneration [84]. Sirtuin 1 (Sirt1), which serves as a target gene in the Notch-Hes1 signal transduction pathway, plays a pivotal role in improving aging and enhancing liver regeneration, through its

overexpression and activation [84].

Hepatic stellate cells

HSCs are the main precursors of myofibroblasts, and their activation has been recognized as the main driver of liver fibrosis [85,86]. Studies have shown that expression of the HSC activation markers αSMA and desmin increases during aging [69]. Meanwhile, the expression of collagen deposition markers and platelet-derived growth factor (PDGF) receptor-β increases, indicating the activation and proliferation of HSCs [69]. An increased number of HSCs and intracellular lipid droplets have also been found in animal models of aging [69,70,87]. Interestingly, previous studies have reported that the loss of lipid droplets is a feature of HSC activation [86].

During the process of aging, HSCs exhibit a less fibrotic phenotype, which specifically manifests as less extracellular matrix (ECM) deposition and more MMPs [88–90]. The MMP is the main participating enzyme responsible for the degradation of the ECM, which facilitates the regression of liver fibrosis. At the same time, p53 activity is critical for regulating aging, and mice lacking p53 exhibit increased fibrosis [88]. Multiple studies have shown that insulin-like growth factor 1 (IGF-1) may induce HSC senescence by ameliorating oxidative stress and mitochondrial function in the liver, thereby reducing steatosis, inflammation, and fibrosis in MASH or cirrhotic mice [91–93]. However, a similar phenomenon was not observed in p53-deficient mice, indicating that IGF-1 induces HSC senescence in a p53-dependent manner [91,93]. Senescent HSCs express cell surface ligands of receptors on NK cells, which can target and recruit NK cells [94]. NK cells are key components of the innate immune system and can effectively eliminate aged HSCs [95]. In addition, HSCs express relatively high levels of IL-10R2 and IL-22R1 [96]. Several studies have shown that IL-22 induces HSC senescence by activating the signal transducer and activator of transcription (STAT)-3, suppressor of cytokine signaling (SOCS)-3 and p53 pathways, and inactivates HSCs by downregulating the TGF-β1/Notch signaling pathway, thereby inhibiting liver fibrosis [96,97]. Some researchers also believe that senescent HSCs transform macrophages into the M1 proinflammatory type, promoting immune surveillance and facilitating the clearance of senescent cells [98].

In contrast to the previous cells, HSC senescence has a positive effect on liver regeneration. Cheng *et al*. reported that senescent HSCs secrete IL-6 and CXCR2 ligands as part of the SASP promoting liver cell proliferation and liver regeneration [99]. Although IL-6 is derived primarily from Kupffer cells (KCs) in the early stage, after PHx, senescent cells drive IL-6 production to regenerate the liver. In addition, the depletion of senescent astrocytes results in decreased liver proliferation and impaired liver regeneration [99], which differs from the views of previous researchers and merits further exploration.

Kupffer cells

KCs are resident hepatic macrophages located in the liver sinusoidal lumen and account for approximately 80% to 90% of all hepatic macrophages. Animal experiments and clinical trials have revealed that during the process of aging, the number and activity of macrophages in the liver increase, accompanied by a redistribution in lymphatic aggregates [100–102]. The main effect of aging on macrophages is that the level of macrophage autophagy is reduced, which leads to a greater degree of inflammatory response after liver injury [103,104]. However, whether the phagocytic activity of macrophages is increased or decreased at the present stage of research is not uniform [100,105]. Moreover, the body produces more cytokines to promote the recruitment of inflammatory cells, thereby promoting hepatocyte senescence. KCs in aged rats secrete more IL-6, a known inducer of senescence [69,106]. At the same time, studies have revealed that older mice fed a high-fat diet (HFD) present more severe liver cell damage and inflammation, which can be attributed to the increased polarization of M1 macrophages in the liver and white adipose tissue [107].

As an important part of the pathogenesis of MASLD, KCs accumulate in the liver with the progression of the disease. Macrophage accumulation and the release of cytokines can stimulate the proinflammatory cascade reaction, inducing lipid metabolism-related gene expression [108]. Animal experiments have shown that their depletion slows the progression of MASLD to MASH [109,110]. Other clinical studies have also shown that liver macrophages are involved in the progression of MASH in humans [111–113]. These cells exhibit a proinflammatory phenotype during disease progression and recruit monocytes mainly through the CCR2-CCL2 and CXCR3-CXCL10 axes [111,114]. Alzaid *et al*. suggested that the emergence of the M1 proinflammatory phenotype during fibrosis may be modulated by interferon regulatory factor 5 (IRF5), which has been validated in both mice and humans [115]. IRF5 is an important proinflammatory transcription factor that is involved in the activation of macrophages under acute and chronic inflammatory conditions and can be used as a new target for therapeutic intervention [115]. To date, studies on the relationship between aging and KCs are superficial, and further analyses are needed to identify new therapeutic strategies. In summary, KCs play a significant role in the progression of disease. However, the connection between KCs and aging remains relatively

cursory, necessitating additional research to uncover novel therapeutic approaches.

Potential for the treatment of MASLD in the context of aging

As described above, aging is an important driver of MASLD/MASH in humans, so MASLD can be improved in terms of improving aging. First, the accumulation of senescent cells has been shown to exacerbate the progression of aging-related diseases. Therefore, the specific removal of senescent cells may delay age-related organ dysfunction and improve the progression of MASLD/MASH. In recent years, the emergence of a new class of drugs known as "senolytics" has infused hope in this idea [116,117]. The first described anti-aging drug was a combination of dasatinib (D) and quercetin (Q), which was investigated in a hypothesis-driven investigation [118]. D and Q are highly effective and synergistic in the targeted reduction of senescent cells [118,119]. In a mouse model of diet-induced MASLD, the combination of D and Q ameliorated the disease process by reducing the number of senescent hepatocytes and liver fat content [5]. Similarly, the ABT-737 inhibitor, a member of the Bcl-2 family, can induce cell apoptosis and the removal of senescent cells [120]. Ritschka *et al.* used ABT-737 to eliminate senescent hepatocytes, resulting in increased liver regeneration and decreased SASP and p21 expression [121]. Because ABT-737 is poorly absorbed in humans, researchers have modified it to create navitoclax (ABT-263). ABT-263 has high affinity for Bcl-2 and Bcl-xl and has been shown to improve metabolic function while reducing the number of senescent cells and alleviating the effects of SASP [122]. Recently, Suda *et al.* suggested that senolytic vaccination could be a potential strategy for improving age-related phenotypes [123]. They targeted glycoprotein non-metastatic melanoma protein B (GPNMB) as a molecular target for anti-aging therapy, and vaccination improved the normal and pathological phenotypes associated with aging, accompanied by improved survival [123].

Second, we can consider individual genes that regulate aging. Baboota *et al*. proposed bone morphogenetic protein 4 (BMP4) and anti-Gremlin 1 (GREM1) treatment as new ways to prevent MASLD/MASH and delay aging by affecting the important YAP/TAZ signaling pathway. The results revealed that BMP4 had anti-aging, anti-steatosis, anti-inflammatory and antifibrotic effects [21]. BMP4 significantly reduced the increase in IL-8, SA-β-Gal, p16 and p53 levels in the DOX-induced aging model. In contrast, Gremlin 1 has a pro-senescent effect and antagonizes BMP4 [21]. Maeso-Díaz *et al*. proposed that vorapaxar, an inhibitor of thrombomodulin–protease-activated receptor-1 (THBD-PAR1), could be targeted to senescent hepatocytes to ameliorate the progression of MASLD [124]. They reported that THBD-PAR1 expression was increased and that liver regeneration was inhibited after the induction of hepatocyte senescence. Meanwhile, THBD-PAR1 is positively correlated with the severity of MASH in humans. The results showed that vorapaxar reduced the burden of aging hepatocytes, inflammation and fibrosis in MASH mice [124]. Massemin *et al*. proposed that the pro-senescent phospholipase A2 receptor 1 (PLA2R1) plays an important role in regulating age-related liver changes and glucose homeostasis. They reduced liver steatosis, fibrosis and cell senescence in mice by knocking out PLA2R1 [125].

In addition to the use of drugs to improve aging and aging-related MASLD/MASH, exercise and dietary intervention can also be considered to regulate the disease process. Gao *et al*. reported that exercise and dietary intervention reduced the formation of lipid droplets in the liver induced by a HFD and improved nonalcoholic fatty liver disease in rats [126]. Exercise and dietary intervention enhance fat phagocytosis by activating the AMPK/ULK1 pathway and inhibiting the Akt/mTOR/ULK1 pathway, respectively [126]. Moreover, both can improve liver senescence induced by a HFD in rats [126]. Furthermore, a number of clinical studies have shown that regular physical exercise can reduce the liver fat content and improve insulin sensitivity, as well as other age-related metabolic abnormalities [127–129]. In addition, the combination of the two treatments is more effective in improving MASLD.

Conclusions and future perspectives

In conclusion, there is a close bidirectional relationship between MASLD/MASH and aging. After aging, the prevalence, severity, and mortality of MASLD/MASH all increase. At the same time, MASLD/MASH can exacerbate liver aging, leading to the senescence of liver cells and affecting the normal functions of the liver. However, the detailed mechanisms by which aging contributes to the development of MASLD/MASH and why aging is exacerbated by this disease remain unclear. Moreover, the causal relationship between the two is not explained in detail, which one comes first and which one comes next. Future studies should further explore the specific mechanisms of this relationship and develop targeted preventive and therapeutic strategies to mitigate the impact of liver disease on the aging process and delay the progression of liver disease in the elderly population. At the same time, we mentioned the elimination of senescent cells to delay the disease process in the treatment section. Many studies have reported that this method can indeed improve aging-related diseases. However, recent research has also suggested that removing senescent cells from the body may be harmful

to health. Accumulating evidence shows that senescent cells also have important physiologic functions, such as tumor inhibition, wound healing, embryonic development, and tissue remodeling [130,131]. As described above, the removal of aged HSCs of aging has delayed the regeneration of liver cells and their proliferation. It may be beneficial to remove some senescent cells, but we should identify precisely which ones to remove and attempt to preserve their beneficial effects. Therefore, the potential effects of eliminating senescent cells in the context of the beneficial effects of senescent cells are still worth reconsidering. Moreover, a strict distinction should be made between aging and cellular senescence. Cellular senescence, which refers to the morphological changes in cells and the gradual loss of their proliferation ability and biological function over time, is the basis of aging. Aging refers to a physiologic process that is the result of the accumulation of cellular senescence. In conclusion, researchers should focus on exploring the aging-related pathological mechanisms in MASLD and MASH in the future to identify effective treatment options that may prevent the progression of the disease and aging.

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Compliance with ethics guidelines

Conflicts of interest Chen Chen and Lin Wang declare that they have no competing interests.

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