Role of cellular senescence in hepatic diseases (Review)

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Abstract. Cellular senescence, a hallmark of aging, is characterized by irreversible, permanent cell cycle arrest accompanied by halted proliferation triggered by endogenous or exogenous stimuli. The accumulation of senescent cells in tissues or organs elicits detrimental effects on adjacent normal cells through their pathogenic senescence-associated secretory phenotype (SASP), driving secondary senescence, disrupting tissue homeostasis and ultimately exacerbating age-related pathologies such as types of cancer and neurodegenerative disorders. Hepatic disorders constitute a leading cause of global mortality, imposing considerable healthcare burdens. Robust clinical evidence has now demonstrated a strong correlation between cellular senescence and poor clinical outcomes in various hepatopathies. This intricate yet critical signaling network is dynamically regulated in both physiological homeostasis and chronic hepatic inflammatory conditions. Notably, recent years have witnessed extensive research into pharmacological strategies to deplete senescent cells, inhibit SASP, and target other senescence markers across diverse contexts, thereby establishing the field of senotherapeutics. The present review systematically summarized key molecular pathways and biomarkers of hepatic senescence, while outlining the emerging role of cellular senescence in inflammatory liver disorders. It also discussed the therapeutic potential of senescence-regulating drugs for liver disease, which could alleviate hepatic inflammation and enhance clinical outcomes.

Contents

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1. Introduction

Aging, a natural yet complex process, is marked by gradual deterioration of physiological function at both the organ and organismal levels over the lifespan. Notably, disease-induced pathological alterations in aged tissues often act as accelerants, amplifying this degenerative cascade (1,2). Among the numerous hallmarks of aging, senescent cell accumulation, an essentially irreversible proliferative arrest, serves as a key driver of aging and diverse age-related illnesses (3). Cellular senescence is regarded as a fundamental stress-responsive mechanism triggered by diverse intrinsic and extrinsic cues, including viral infections, hypoxia, oxidative stress, telomere attrition, genomic instability and oncogene activation (4). Recent progress has clearly established links between cellular senescence and cardiac diseases, chronic lung diseases, types of cancer, metabolic disorders and neurodegenerative conditions (5,6). In hepatology, nevertheless, the pathobiological significance of senescence has only recently become the focus of intensive research. Untreated hepatic inflammation frequently progresses to chronic liver diseases, including liver cirrhosis and hepatocellular carcinoma (HCC), posing a significant global health burden, particularly among middle-aged and geriatric populations (7). Mechanistically, cellular senescence induces multifaceted hepatic dysfunction via senescence-associated secretory phenotype (SASP)-mediated effects. These secretory factors disrupt lobular architecture, impair multiple biochemical processes (particularly hepatic lipid homeostasis) and propagate inflammatory cascades (8). Of interest, it is reported that a category of compounds, namely senotherapeutics, are able to ameliorate the natural history of chronic liver disease by targeting senescent cells using molecular pathways associated with senescence phenotypes (9).

Importantly, cellular senescence is a fundamental biological hallmark of aging and a major risk factor for hepatic pathologies. The present review systematically analyzed the most cutting-edge advances in the pathophysiology of cellular senescence, key features of associated cellular stress responses and the susceptibility of liver-resident cells to senescence.

Subsequently, due to space limitations, recent findings on cellular senescence in specific hepatic pathological contexts are summarized. Finally, the present review critically evaluated the potential of 'senolytic therapies', defined as strategies targeting cellular senescence through selective inhibition of senescence pathways (senomorphics) or elimination of senescent cells (senolytics), for treating liver diseases and highlighted both the advantages and limitations of these approaches.

2. Fundamental aspects of cellular senescence

One of the earliest reports on the phenomenon of cellular senescence was described in 1961 by Leonard Hayflick and Paul Moorhead (10), as the limited proliferative capacity of normal human diploid fibroblasts *in vitro*, which manifests as growth arrest after ~40-60 population doublings (10). Since then, cellular senescence has been increasingly recognized as a multifactorial determinant of cell fate. Extensive studies have documented that this permanent cell cycle arrest negatively affects tissue regenerative capacity and promotes conditions conducive to the onset and development of various diseases (11-13).

Cellular senescence is mainly divided into two principal mechanistic paradigms. Replicative senescence, an intrinsically regulated process, irreversibly arrests cells at the G_1/S or S phase. It is initiated by telomere erosion and persistent DNA damage during repeated replication cycles, which in turn activates the ataxia-telangiectasia mutated (ATM)/ataxia-telangiectasia and RAD3-related (ATR) protein kinases (14). These kinases stabilize p53 via phosphorylation and block mouse double minute 2 (MDM2)-mediated ubiquitin degradation, enabling nuclear p53 accumulation and the subsequent p21 induction (6). As a core cell cycle inhibitor, p21 both suppresses key G1/S-phase kinases and directly binds to proliferating cell nuclear antigen, thereby inhibiting DNA synthesis and enforcing synergistic cell cycle arrest (11). Besides, ATM and ATR block the p62-dependent autophagic degradation of GATA binding protein 4, contributing to NF-κB activation (14). Various stressors, including but not limited to oxidative stress, therapy-induced damage (such as ionizing radiation and chemotherapeutic agents), genomic instability and epigenetic changes can trigger premature senescence. This process is predominantly mediated by the activation of the cyclin-dependent kinase (CDK) inhibitor 2A (also called $p16^{INK4a}$) (15). Excessive p16 accumulation inhibits CDK4/6-cyclin D complex formation, inducing irreversible arrest. Mechanistically, p16 inhibits CDK4/6 kinase activity, preventing full retinoblastoma protein (pRB) phosphorylation and maintaining its hypophosphorylated state. Hypophosphorylated pRB binds and inhibits E2 promoter-binding factor, blocking the G_1-to-S phase transition (16). Compared with other pathways, $p16^{INK4a}$/retinoblastoma protein (Rb)-driven senescence exhibits enhanced stability. The DNA damage response (DDR) pathway functions as an upstream regulatory hub that activates p53 while indirectly modulating p16. Markedly, persistent DDR signaling also directly triggers pro-inflammatory pathways such as NF-κB and mitogen-activated protein kinase (MAPK) (17). Additionally, other senescence-associated pathways, such as the mTOR pathway and mitochondrial dysfunction-reactive oxygen species (ROS)-mediated signaling pathway, also frequently play roles in the process of organismal aging. Crucially, these pathways do not operate in isolation but synergistically drive the cellular senescence transition through extensive crosstalk.

Upon entering senescence, cells rewire their metabolic activity and exhibit distinct cytomorphological transformations (such as flattened and enlarged appearance) despite being in a state of growth arrest (18). More importantly, the secretion of a wide range of bioactive factors, including inflammatory chemokines, cytokines, growth factors, receptors/ligands, oxidative factors and extracellular matrix (ECM) remodeling proteases, constitutes a defining pathophysiological feature of cellular senescence, collectively termed as SASP (19). This pro-inflammatory and pro-apoptotic phenotype encompasses IL-1α, IL-1β, IL-6, IL-8, TGF-β, matrix metalloproteinases (MMPs), ROS, and exosomes. Critically, the SASP operates via multimodal signaling cascades. A unique 'bystander effect' occurs wherein senescence extends beyond intracellular impacts as primary senescent cells secrete bioactive signals that alter the microenvironment, thereby inducing secondary senescence in neighboring or distant non-senescent cells through distinct mechanisms (such as autocrine, paracrine and juxtacrine) (20). This transmissible state might also explain why senescent cells exert far-reaching effects even though they constitute an actual low proportion in any particular tissue. In addition, exogenous triggers (such as lipopolysaccharide) and endogenous danger signals lead to the intensification of SASP amplification (21). Notably, these senescence risk factors often interact cumulatively over time, triggering aberrant pathological cascades that ultimately induce chronic low-grade systemic inflammation, even without pathogenic processes.

Mechanistically, senescent cells present a paradoxical duality in their ability to recruit immune cells and activate immunosurveillance. For example, during acute or incipient tissue injury, senescent cells attract, anchor, and activate immune cells via the secretion of specific SASP factors and immunomodulators, facilitating transient immune activation that reinforces tissue plasticity and regeneration, thereby facilitating wound healing and tissue repair (22). However, not all senescent cells produce a pro-inflammatory SASP phenotype. For instance, in bone marrow adipose tissue, the abundance of senescent cells does not exhibit a positive correlation with the expression of proinflammatory factors (23). Furthermore, the concept of the 'Threshold Theory of Senescent Cell Burden' posits that surpassing a critical threshold in the number or percentage of senescent cells can lead to organismal or tissue dysfunction (24). It is also noteworthy that this threshold varies with individual characteristics such as age and health status. Consequently, the failure to effectively and promptly eliminate senescent cells under chronic pathogenic conditions leads to an increase in their burden beyond the tolerance limit of the tissue. This subsequently promotes the SASP to amplify aseptic inflammation and abnormal fibrotic hyperplasia, ultimately exacerbating the disease. Multiple studies have demonstrated that the SASP plays a significant role in the progression of liver disease, with its diverse cytokines exerting distinct effects (Fig. 1; Table I).

3. Cellular senescence in specific liver-resident cells

Liver tissue harbors diverse cell populations, including hepatocytes (constituting 70-85% of the total) and non-parenchymal

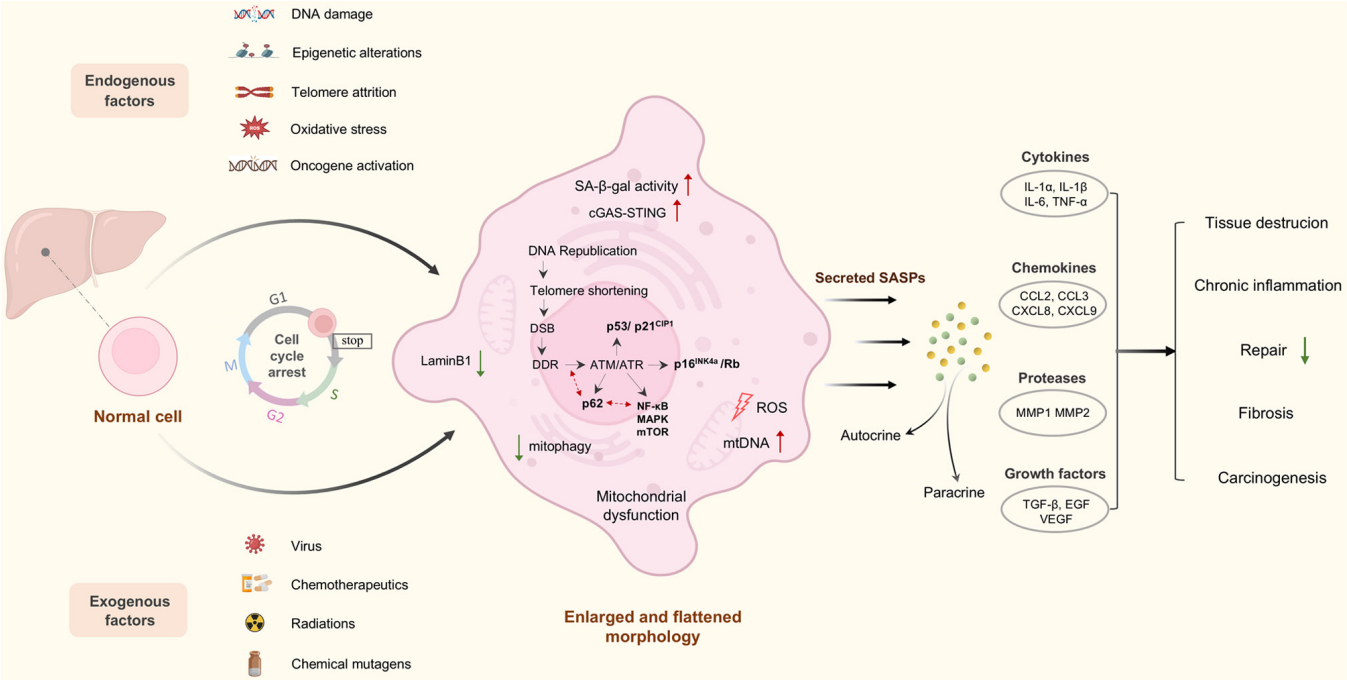

Figure 1. Schematic diagram of the molecular mechanism of cellular senescence. Diverse endogenous and exogenous stimuli induce irreversible G_1 arrest, triggering premature senescence. Repeated DNA replication and telomere shortening initiate DSB/DDR signaling, activating ATM/ATR kinases. This dysregulates the p53/ $p21^{CIP1}$ and $p16^{INK4a}$/Rb pathways and aberrantly activates p62, NF-κB, MAPK and mTOR signaling. Notably, p62 and ATR kinase exhibit bidirectional regulation: p62 recruits ATR to sites of DNA replication stress, enhancing its kinase activity, while ATR-mediated phosphorylation of p62 promotes its transcriptional expression and facilitates interaction between phosphorylated p62 and NF-κB. These pathways synergize via crosstalk to drive senescence, manifesting as enlarged and flattened morphology, Lamin B1 downregulation, SA-β-Gal activity, cGAS-STING induction and mitochondrial dysfunction. Senescence is reinforced autocrinely and propagated paracrinely via SASP factors (inflammatory cytokines, chemokines, proteases and growth factors), ultimately promoting tissue destruction, chronic inflammation, fibrosis and carcinogenesis. ATM, ataxia-telangiectasia mutated; ATR, ATM and Rad3-related; CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; DDR, DNA damage response; DSB, DNA double-strand break; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; mtDNA, mitochondrial DNA; NF-κB, nuclear factor κ-B; ROS, reactive oxygen species; SA-β-Gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

cells such as endothelial cells, epithelial cells, hepatic stellate cells (HSCs), and Kupffer cells (KCs) (38). Cumulative evidence from *in vivo* and *in vitro* models confirms cell-type-specific senescence susceptibility across hepatic lineages. Thus, senescence of these liver-resident cells can profoundly impact the pathogenesis of inflammatory hepatic disorders (Fig. 2).

Hepatocytes. Hepatocytes, comprising a substantial proportion of the liver and orchestrating critical metabolic, synthetic and detoxification processes, exhibit age-associated genomic instability, as supported by current evidence (39). Notably, senescent hepatocytes are prevalent across diverse hepatic pathologies, suggesting their relevance as a mechanism underlying liver disease. Data from murine aging models show that, alongside reduced hepatocyte volume, polyploid and/or aneuploid senescent hepatocytes accumulate extensively in the liver (40). A study identified a hepatocyte subset with high telomerase expression; comparative RNA sequencing analysis of hepatocyte subtypes further revealed that this subpopulation enhances liver regeneration during homeostasis and injury (41). Hence, hepatocytes are relatively resistant to telomere attrition, with the causal link between telomere loss and hepatocyte senescence remaining controversial; a plausible hypothesis thus posits that hepatocyte senescence arises via telomere shortening-independent pathways. Enhanced oxidative stress caused by the imbalance of ROS induces cumulative DNA damage in senescent hepatocytes, a feature prevalent in chronic liver disease among the elderly (42). A recent work using a hepatocyte-specific MDM2 knockout mouse model showed that MDM2 inactivation resulted in p53 accumulation in the hepatocytes, followed by elevated its target gene, the cell cycle inhibitor p21, which is a key sign of senescence (43). A comprehensive study analyzing human clinical samples and *in vitro* models characterized senescent hepatocyte gene signatures in chronic liver disease. It revealed upregulated expression of key senescence markers, including SASP components, p53, and cell cycle regulators (such as cyclin D), in both cirrhotic liver tissues and experimentally induced senescent HepG2 cells (44).

HSCs. HSCs, normally quiescent under physiological conditions, are primarily recognized for activating in response to liver injury. Single-cell sequencing has revealed that activated HSCs display marked cellular heterogeneity, with distinct subpopulations exhibiting proliferative, inflammatory, or fibrogenic phenotypes tailored to specific functions (45). Notably, a subset of activated HSCs is considered an important source of the pro-fibrotic and inflammatory effects of the SASP. TGF-β, a core SASP factor, is a master regulator of HSC activation, driving their transdifferentiation into myofibroblasts (46). These transformed cells proliferate and secrete ECM components, excessive collagen deposition (such

Table I. Major components of SASPs and their function in liver diseases.

Authors, year	Category	SASPs	Effects on liver diseases	(Refs.)
Naseem *et al*, 2018	Cytokines	IL-1/6/8/13/15/33	Persistent production of IL-6 seems to cause tissue damage, which can even lead to the development of HCC.	(25)
Widjaja *et al*, 2020			Expression of IL-11 in stromal and parenchymal cells is associated with inflammation, steatosis, fibrosis and liver failure.	(26)
Yamagishi *et al*, 2022			IL-33 is strongly related to fibrosis in chronic liver injury and promotes HCC development through immune cell activation in the liver tumor microenvironment.	(27)
Luciano-Mateo *et al*, 2020	Chemokines	CCL1/2/3/11/26, CXCL5/8/9/13, MCP-1/2/4, MIP-1α/3α	CCL2 overexpression induces hepatic steatosis and disrupts mitochondrial dynamics.	(28)
Xu *et al*, 2021			CCL3 facilitates macrophage infiltration into the liver during progression of steatohepatitis.	(29)
Yu *et al*, 2022			CXCL8, CXCL9, and CXCL11 can be used as predictive markers for HBV-induced liver injury.	(30)
Queck *et al*, 2020			MCP-1 reflects monocyte recruitment and inflammation in liver disease and correlates with cirrhosis complications.	(31)
Yan *et al*, 2021	Growth factors	Amphiregulin, heregulin, epiregulin, EGF, bFGF, HGF, VEGF, PDGF, TGF-β	TGF-β signaling drives progression from liver fibrosis to cancer.	(32)
Borkham-Kamphorst *et al*, 2016			PDGF leads to HSC proliferation and hepatic fibrogenesis.	(33)
Campana *et al*, 2021	Oxidative factors	NO, ROS, COX2	ROS induces lipid peroxidation, triggers inflammatory cascades and exacerbates hepatocellular injury, driving persistent liver fibrosis and chronic disease progression.	(34)
Wójcik *et al*, 2012			COX2-driven prostaglandin synthesis promotes liver inflammation and facilitates carcinogenesis.	(35)
Lichtinghagen *et al*, 2001	Extracellular matrix contents	MMP1/2/7/10/12/13, collagen, fibronectin, laminin,	MMP2 and MMP7 synergistically drive the fibroproliferative process in HCV-related chronic liver injury.	(36)
Thiele *et al*, 2021			An accumulation of fibrillar collagens drives fibrosis progression.	(37)

IL, interleukin; SASPs, senescence-associated secretory phenotypes; HCC, hepatocellular carcinoma; CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; HSC, hepatic stellate cell; HBV, hepatitis B virus; NO, nitric oxide; ROS, reactive oxygen species; COX2, cyclooxygenase-2; MMP, matrix metalloproteinase; HCV, hepatitis C virus.

as Col1a1) and dysregulated MMPs, at the site of injury, which alter the structure of the liver and continue to impair its cellular function (47). Importantly, persistent HSC proliferation, combined with impaired senescence mechanisms creates a permissive microenvironment that drives fibrotic progression and even hepatocellular carcinogenesis. Additional

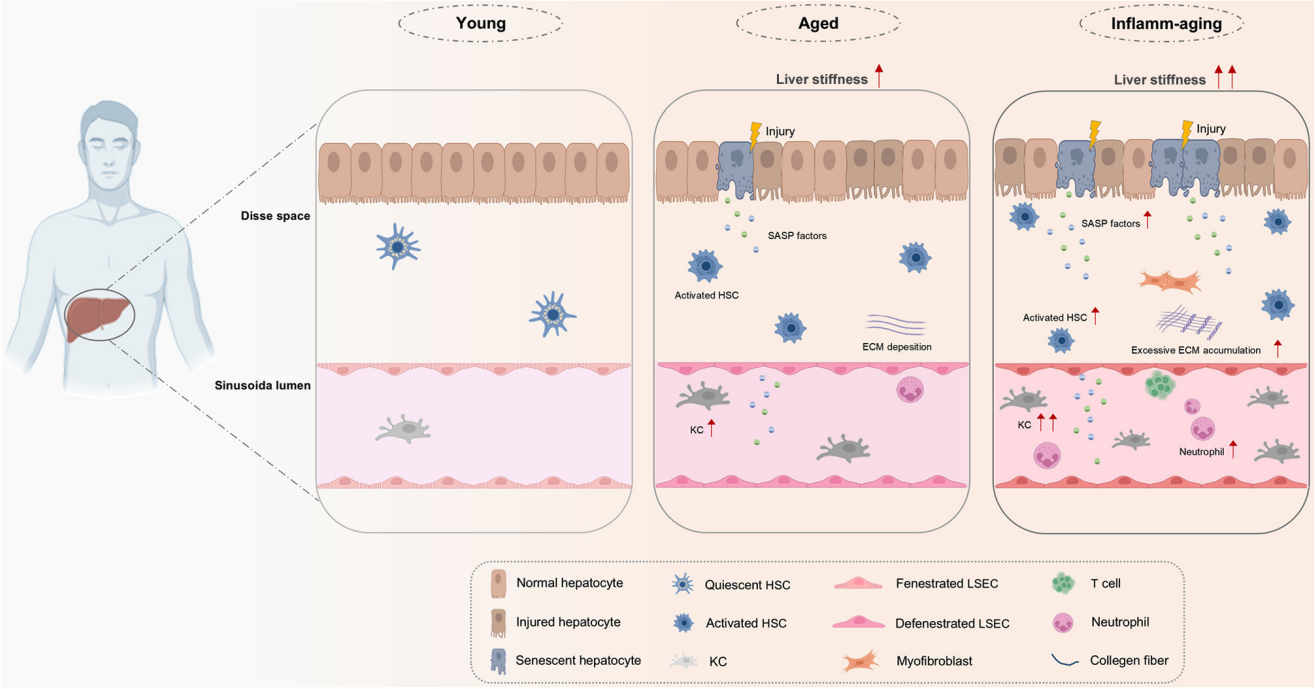

Figure 2. Cellular and functional alterations in liver under aging conditions. Schematic depicts livers in young (left), aged (middle), and inflamm-aging (right) states, showing region-specific changes in cellular composition and architecture. In youth, hepatocytes with microvilli, KCs, quiescent HSCs and fenestrated LSECs maintain structural integrity. Aging involves progressive anatomical changes: Fenestrated LSECs disappear in the space of Disse, capillarization occurs, and SASP factors from senescent cells activate HSCs, triggering ECM deposition. Concurrently, activated KCs release inflammatory mediators that recruit immune cells. Multidirectional interactions among activated HSCs, KCs, and innate immune cells drive pathological ECM accumulation and myofibroblast formation. These changes collectively cause tissue stiffening and immune dysregulation, establishing a pro-inflammatory microenvironment. Emerging evidence indicates interdependence of senescence across liver cell types. ECM, extracellular matrix; HSC, hepatic stellate cell; KC, Kupffer cell; LSEC, liver sinusoidal endothelial cell; SASP, senescence-associated secretory phenotype.

inducers of senescence in activated HSCs have been identified, including increased susceptibility to DNA damage. Moreover, IL-22 upregulation induces HSC senescence while inhibiting α-smooth muscle actin expression. Transcriptomic analyses have comprehensively characterized HSCs senescence in human and rodent models, with findings showing that senescent HSCs originate from activated HSCs (48). HSC senescence is largely absent in healthy livers, but increases with disease progression, these senescent cells interact closely with recruited immune cells, possibly in response to SASP mediators.

Liver sinusoidal endothelial cells (LSECs). LSECs, a distinctive endothelial population in the liver, are regarded as key regulators of hepatic homeostasis (49). With aging, these cells exhibit marked phenotypic dysregulation, characterized by ultrastructural and functional changes. LSECs exhibit pseudocapillarization, an ultrastructural alteration involving reduced fenestration number and size, thereby disrupting the physiological filtration barrier, a phenomenon validated across species including humans, murine models and non-human primates (50,51). This, combined with hepatic aging, contributes to increased mitochondrial oxidative stress, reduced intrahepatic nitric oxide availability, upregulated p16 expression and a moderate pro-inflammatory state, such as enhanced expression of IL-1, IL-6 and TNF-α at the mRNA level, as shown in aged rats and human samples (52). In addition, senescent LSECs exhibit increased expression of cell adhesion markers [such as intercellular adhesion molecule-1 (ICAM-1)], leading to an accumulation of substantial leukocyte and reduced hepatic blood flow. This impairs the liver's ability to balance fibrosis and regeneration, indicating an age-related hepatic inflammatory response (49). Research on LSECs of rats has furthermore shown that aged rats exhibit more pronounced reductions in LSEC fenestrations and impaired injury recovery capacity compared with young counterparts, according to the model of CCl4- and phenobarbital-induced cirrhosis (53).

KCs. KCs, the resident liver macrophages of the hepatic sinusoids, constitute 80-90% of the body's total macrophage population. These cells serve as sentinels of hepatic innate and adaptive immunity, and their distribution altering during aging (54). Single-cell transcriptomic profiling has revealed that compared with younger counterparts, hepatic macrophages in aged mice exhibit a heightened pro-inflammatory (M1) phenotype, with markedly upregulated expression of pro-inflammatory cytokine genes such as IL-6, TNF-α and IL-1β (55). Therefore, KCs play a pivotal role in hepatic inflammatory aging, where the M1/M2 polarization ratio reflects age-related functional alterations in macrophages. Aging also attenuates macrophage functions, including the phagocytic clearance of extracellular pathogens and antigen-presenting capacity, which impairs bacterial killing and inflammation resolution (56). This phenomenon explains why, despite similar inflammatory responses in young and aged individuals, the capacity for inflammation resolution is markedly impaired in the elderly, resulting in persistent chronic inflammation.

Mechanistically, liver macrophages promote bystander cell senescence through TGF-β1 signaling, thereby accelerating aging-related pathologies (such as fibrosis) during hepatic injury (57). Fontana *et al* (58) revealed that under identical high-fat diet (HFD) conditions, aged mice exhibit exacerbated hepatocellular injury and inflammatory responses compared with young controls. This age-dependent susceptibility is associated with heightened M1-polarized macrophage infiltration both in hepatic and adipose tissues. Macrophage-targeted therapies may effectively reduce susceptibility to age-associated liver diseases.

4. Typical responses in liver cellular senescence

The human liver, owing to its unique anatomical location, is constantly exposed to numerous xenobiotic and metabolic stressors, including dietary metabolites, bacterial products, pathogens, carcinogens and other substances involved in detoxification and metabolic processes (59). To combat these challenges, specialized hepatic cell populations initiate elaborate stress-responsive pathways, and the liver, renowned for robust regenerative capacity, achieves full recovery even after partial resection or severe acute injury. Nevertheless, cumulative anatomical and functional hepatic alterations driven by aging, disease, or chronic injury lead to an age-related decline in the diverse mechanisms critical for preserving cellular homeostasis (Fig. 3).

Metabolic reprogramming. Biochemical studies have consistently established the liver as a master metabolic regulator, orchestrating systemic energy balance through hepatic lipid and glucose homeostasis, steroid biosynthesis/degradation and insulin signaling (60). Under homeostatic conditions, cellular ATP is primarily generated from energy substrates (glucose, fatty acids and amino acids) via core biochemical pathways including glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation and amino acid catabolism (61). It is now recognized that dysregulation of these metabolic pathways critically drives chronic liver disease pathogenesis. Single-cell RNA sequencing and proteomic studies have revealed remarkable heterogeneity and plasticity in liver-resident cells. Metabolic reprogramming and bioenergetic shifts within distinct hepatic cell populations drive complex physiological and pathological processes, initiating and sustaining tissue damage while promoting fibrogenesis (62,63). Critically, it remains uncertain whether metabolic dysregulation is a cause or consequence of age-related hepatic pathologies.

It is well established that during liver disease progression, hepatocellular damage and chronic low-grade inflammation induce metabolic reprogramming, which is characterized by dysregulated hepatic metabolism and ectopic lipid deposition (64,65). Growing evidence highlights the pivotal role of aerobic glycolysis in this pathological process. First, aerobic glycolysis promotes a pro-inflammatory state in immune cells, perpetuating hepatic inflammation and injury (66). Second, enhanced aerobic glycolysis sustains HCC progression by facilitating proliferation, metastasis and chemoresistance (67). The pivotal regulatory enzyme pyruvate kinase M2 (PKM2) functions as a central metabolic switch, mechanistically reflecting the Warburg effect observed in hepatocarcinogenesis (65). Experimental and clinical evidence demonstrates that while PKM2 expression is scarcely detectable in healthy livers, its levels are upregulated in HSCs during fibrosis, as well as in KCs and Th17 cells in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (68,69). Notably, PKM2 expression increases in precancerous cirrhotic livers and is strongly associated with elevated HCC risk. These findings collectively indicate that glycolytic reprogramming acts as a critical driver of HCC precursor lesions and tumor microenvironment remodeling. Intriguingly, glycolysis is augmented during both replicative and oncogene-induced senescence (70). Mechanistically, disturbances in lipid metabolism, amino acid dysregulation, and impaired mitochondrial energy production synergistically promote inflammation and oxidative stress; pathological features that have been validated in the progression of fibrogenesis (71).

Mitochondrial dysfunction. Mitochondria function not only as cellular energy hubs but also as potential triggers of chronic inflammation and cell necrosis (72). With aging, mitochondrial function in senescent cells undergoes complex changes due to intertwined mechanisms, including structural damage (such as swelling, loss of cristae definition and inner membrane disruption), accumulation of mitochondrial DNA (mtDNA) deletions and mutations, and electron transport chain (ETC) impairment (73,74). These alterations also increase ROS production, which can damage cellular components through oxidative stress. Importantly, mitochondria are the most abundant organelles in liver tissue and their dysfunction is a common feature of both hepatic metabolic impairment and disease progression (75). Consistent with this, accumulating evidence confirms that mitochondrial dysregulation contributes to the pathogenesis of age-related hepatic disorders and their progression (76,77). These contain metabolic associated fatty liver disease (MAFLD), hepatic fibrosis, cirrhosis and HCC, among others.

Consistent with the microprotein humanin, plasma levels of another mtDNA-encoded microprotein, MOTS-c, also declined with age. Notably, exercise promotes the production of its metabolite 5-aminoimidazole-4-carboxamide-1-β-4-ribofuranoside, which acts as an endogenous AMPK agonist and protects against age-dependent and HFD-induced insulin resistance, including in MAFLD (78,79). Mitochondrial dysregulation also drives lipofuscin accumulation and increased lipid deposits. Furthermore, lipid-derived aldehydes are also altered in senescent cells. Given these observations, while a strong link between cellular aging and lipid accumulation has been hypothesized, lipid metabolism within senescent microenvironments remains poorly understood. A recent study demonstrated that both HFD and aging induce mitochondrial dysfunction, reduce lipid oxidation, and cause liver damage (80). Specifically, rats with HFD intake or aging show reduced mitochondrial uncoupling, and decreased superoxide dismutase (SOD) activity is accompanied by increased ROS production, which impairs energy substrate utilization. In this scenario, hepatic lipid accumulation is substantial, and increased pro-inflammatory cytokine release from adipose tissue exacerbates liver damage, worsening with age and occurring earlier in HFD-fed models. Aldehyde dehydrogenase2 (ALDH2) is a mitochondrial enzyme that reduces cellular

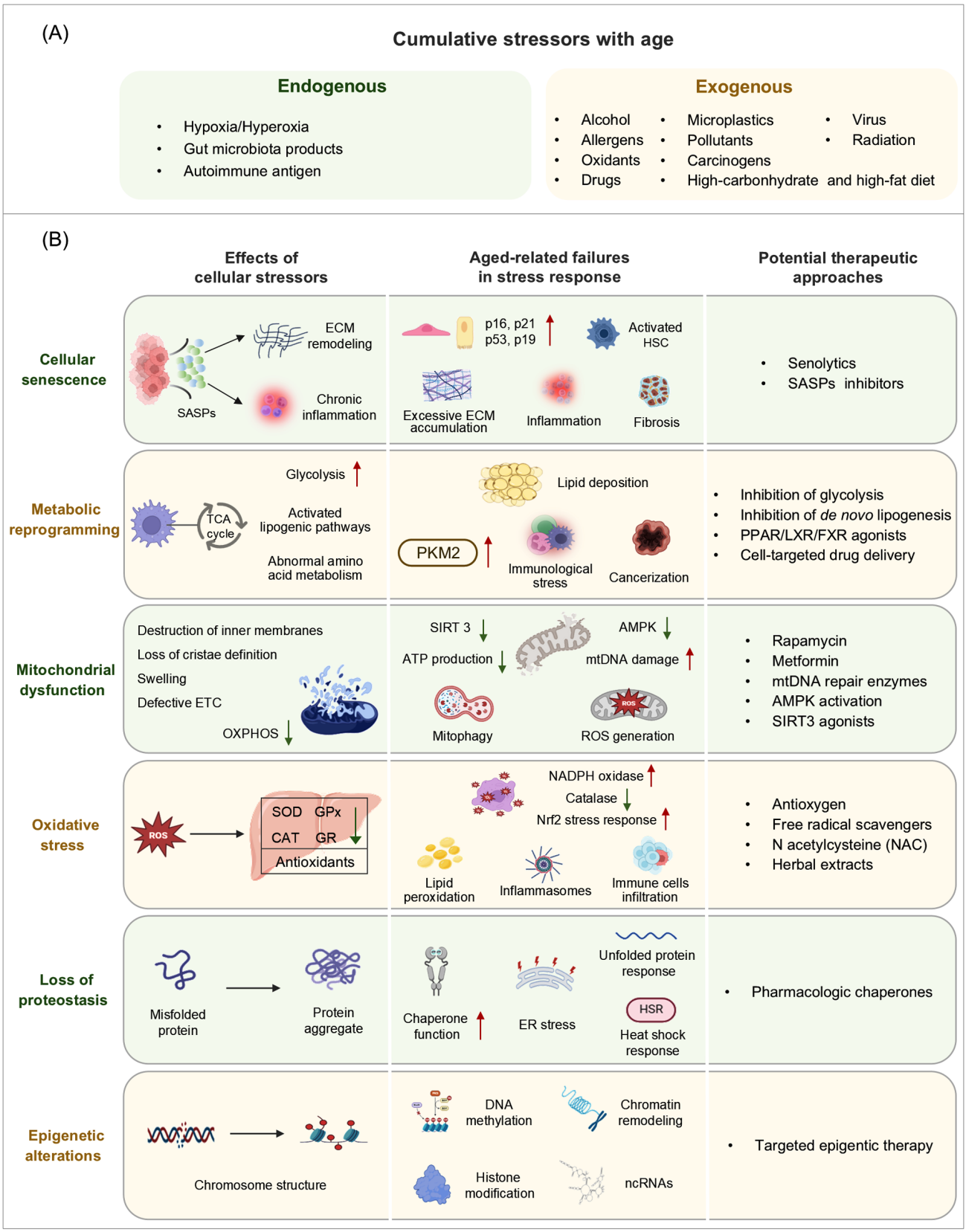

Figure 3. Stress responses in liver cellular senescence and therapeutic pathway approaches. (A) Endogenous and exogenous insults accumulate in liver tissue throughout aging. (B) Progressive anatomical and functional changes caused by disease or persistent injury impair mechanisms maintaining cellular homeostasis during aging. Concurrently, the liver develops stress responses including cellular senescence, metabolic reprogramming, mitochondrial dysfunction, oxidative stress, disrupted protein homeostasis and epigenetic alterations. Targeting these pathways may ameliorate age-related pathology. AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; CAT, catalase; ECM, extracellular matrix; ER, endoplasmic reticulum; ETC, electron transport chain; FXR, farnesoid X receptor; GPx, glutathione peroxidase; GR, glutathione reductase; HSC, hepatic stellate cell; LXR, liver X receptor; mtDNA, mitochondrial DNA; NADPH, nicotinamide adenine dinucleotide phosphate; ncRNA, non-coding RNA; OXPHOS, oxidative phosphorylation; PKM2, pyruvate kinase M2; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT3, sirtuin 3; SOD, superoxide dismutase; TCA, tricarboxylic acid cycle.

oxidative stress and prevents associated damage. ALDH2 gene mutation or knockout reduces mitochondrial enzyme activity and mitophagy, increases ROS production, and promotes the development of liver fibrosis-related diseases (81).

Adding to its significance, generally, diminished mitophagy is assumed to be a hallmark of liver diseases. Impaired mitophagy has been observed in most cases of chronic alcohol consumption (82). Indeed, the influence of alcohol on mitophagy depends on exposure duration and dose, with acute high-dose intake inducing excessive mitophagy activating PINK1/Parkin or BNIP3-mediated pathways to drive alcoholic hepatitis progression (83). Another study found that autophagy machinery defects in LSECs from NASH patients upregulate inflammatory pathways (including CCL2, CCL5, TNFα, IL-6 and Tgfb1 expression), confirmed *in vitro*, and inadequate endothelial autophagy exacerbates liver inflammation to drive disease progression (84). Paradoxically, existing reports are conflicting: For example, autophagy acts as a tumor suppressor, as Beclin 1 disruption accelerates hepatitis B virus-induced premalignant lesions and increases malignancy risk, whereas it can promote established tumors by driving metastasis and drug resistance in later stages (85).

Oxidative stress response. Owing to its central role in metabolism and detoxification, the liver exhibits greater susceptibility to oxidative stress than other organs (86). To counteract such insults, hepatic antioxidant defense systems, comprising enzymatic and non-enzymatic components including SOD, glutathione peroxidase (GPx), catalase (CAT) and glutathione reductase (GR), protect the liver microenvironment from oxidative damage while maintaining physiological function (87). However, chronic exposure to physiological and pathological stressors elevates ROS beyond homeostatic thresholds, triggering oxidative damage to DNA, lipids and proteins. This cascade subsequently activates senescence-associated signaling pathways, culminating in irreversible cell cycle arrest (88). Consequently, oxidative stress represents a critical driver of age-related hepatic injury progression.

Proteomic profiling analysis revealed that in the liver of aged Wistar rats, the defense capacity against oxidative stress, microsomal fatty acid oxidation and peroxisomal function are impaired, accompanied by marked downregulation of antioxidant genes (Cyp2C11, Sod2 and Fmo3) (89). Similarly, long-term alcohol consumption markedly upregulated CYP2E1 gene expression via the CB1R-ERγ-FGF23 axis, inducing hepatic oxidative stress and accelerating the progression of alcoholic liver disease (ALD) (90). During aging, excess ROS markedly disrupt the ECM, primarily by impairing MMP activity. This interaction accelerates ECM breakdown and stiffening, dysregulates MMP activity, and enhances collagen cross-linking and deposition in the liver. Collectively, these alterations remodel the hepatic architecture and drive a pro-fibrotic microenvironment conducive to liver fibrosis. Furthermore, reduced levels of the critical anti-aging factor sirtuin (SIRT)1, potentially due to repression by CCAAT/enhancer-binding-protein/histone deacetylase 1 (C/EBPβ-HDAC1) complexes, may contribute to accelerated liver aging (91). Additionally, the age-related decline in the hepatic NAD^+/NADH ratio further impairs SIRT1 function.

Loss of proteostasis. Proteostasis, a delicate dynamic equilibrium among protein synthesis, folding, trafficking and degradation, involves quality control mechanisms whose disruption triggers systemic network failure (92). For instance, cellular stress or tissue damage often leads to misfolded and dysfunctional proteins, which gradually form aggregates. Misfolded proteins are degraded by endoplasmic reticulum (ER)-dependent mechanisms, most prominently the unfolded protein response (UPR) and the heat shock response. Impaired proteostasis is considered hallmark of aging, with research showing that proteostatic capacity declines with age, independent of underlying disease (93,94). The mRNA and protein levels of molecular chaperones, which are essential for protein folding, are markedly reduced with aging. Meanwhile, more and more evidence indicates that UPR-regulated protein degradation critically affects chronic liver disease. For instance, ethanol or HFD could induce hepatic ER stress and activate the UPR, causing severe hepatic oxidative damage, inflammation and apoptosis (95). In addition, heat shock proteins (HSPs) facilitate ER signaling in response to stress stimuli. Analyses showed that the induction levels of HSP70, HSP27 and HSP90 in hepatocytes of aged rats exhibit a marked downward trend (51). Heat shock factor 1 (HSF1), a molecular trigger and transcription factor, controls the heat shock response, which is activated during abnormal cellular events. A recent study shows that HSF1 may increase the accumulation of collagen and promote liver fibrosis, whereas inhibition of this factor delays or attenuates fibrotic progression by suppressing the expression of profibrotic markers and cell proliferation (96). Young individuals counteract protein misfolding caused by diverse stressors through intact chaperone responses and proteolytic systems. By contrast, elderly individuals exhibit depleted proteostatic capacity, leading to impaired adaptive defense and repair under oxidative, inflammatory, or other pathological conditions, thereby accelerating disease progression (97,98).

Epigenetic alterations. Epigenetics, a reversible heritable mechanism that regulates gene expression without altering the DNA sequence, represents a key mediator of the complex aging process in response to environmental cues (99). Epigenetic events include DNA methylation, histone modification, chromatin remodeling and non-coding RNA regulation. The human DNA methylation landscape changes with chronological aging: Cytosine-phosphate-guanine (CpG) sites in promoter regions typically undergo hypermethylation, while other genomic CpG sites exhibit hypomethylation (100). This signature is linked to the age-associated progression of fibrosis, cirrhosis and even HCC, as validated across diverse cohorts of liver disease patients (101). RNA-seq and DNA methylation array analyses of liver tissues and peripheral blood leukocytes from HCC patients identified DNA methylation as a regulator of chronic liver disease, mediating tumorigenesis, shaping HCC transcriptional landscapes and influencing disease outcomes (102).

The activation or silencing of gene expression by post-translational modifications of histones is bound up with the aging process, with histone acetylation being the most well-documented. Accumulating evidence indicates that alterations in histone acetyltransferase and histone

deacetylases affect cellular transformation and hepatic metabolism, thereby disrupting hepatic function and causing liver injury (103,104). For instance, acetylation of histone 3 and histone 4 is a well-recognized alteration in MAFLD (105). Acetylation of H3K9 and H3K18 activates the transcription of key pro-inflammatory genes (such as TNFα, CCL2 and components of the NF-κB pathway), further triggering or exacerbating the inflammatory response in MAFLD (106). SIRTs, nicotinamide adenine dinucleotide (NAD)-dependent class III HDACs that adapt to metabolic stress, are inactivated, thereby driving the induction of a senescent phenotype. These observations confirm that SIRT1 and SIRT3 are essential for redox homeostasis and hepatic lipid metabolism. Notably, MAFLD patients and individuals with alcohol consumption exhibit reduced hepatic SIRT1 and natural SIRT1 activator supplementation protects against these liver diseases (107). MacroH2A1, one of the molecular targets of SIRT1, exists in two isoforms: MacroH2A1.1 and macroH2A1.2 and is involved in cellular senescence and tumorigenic processes. The enhanced expression of the SIRT1-binding isoform macroH2A1.1 protects hepatocytes from lipid accumulation (108). Forkhead box O (FOXO) is a key transcription factor implicated in aging and is regulated by NAD^+/SIRT1, promoting the hypothesis that the SIRT1/FOXO axis is a potential target for countering premature cellular senescence and hepatic pathology. In addition, perturbed SIRT3 function in mice is associated with MASLD-like abnormalities and SIRT3 knockout mice are prone to metabolic dysfunction-associated steatohepatitis (MASH) development. Beyond these mechanisms, *in vivo* metabolic tracing has demonstrated that histone methylation and phosphorylation in intrahepatic cells also contribute to the development of ALD (109).

Non-coding RNAs (ncRNAs) constitute a diverse class of regulatory molecules that have emerged as epigenetic factors affecting aging, including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs) (110). Their ubiquitous presence in the tissues and biological fluids of different species under diverse pathological conditions underscores their significant role in liver biology. Among the mechanisms regulating fibrogenesis, miRNA-mediated pathways, which operate through senescence-associated regulatory protein control, have been the most extensively studied. In MAFLD and HCC, for instance, miR-21 overexpression increased p53 activity (a protein that normally suppresses cell cycle proteins and lipogenesis) (111). Notably, alongside increased miR-221 expression in hepatitis C virus (HCV) infection, miR-221 is elevated in MASH-associated fibrosis (112). Besides, expression levels of miR-19a, miR-19b, miR-122, miR-125b, miR-192 and miR-375 are increased in MAFLD individuals (113). Fortunately, unlike DNA mutations, these regulatory and often reversible changes enable the design of new anti-aging therapies.

5. Hepatic diseases and cellular senescence

The past decade has seen a surge in rigorously designed clinical and mechanistic studies exploring the involvement of cellular senescence in the pathogenesis of diverse hepatic diseases. This surge is driven by the recognition that cellular senescence is a stress adaptation. At the macroscopic level, the prevalence of numerous liver diseases, such as MAFLD, increases with age and advanced liver diseases, such as HCC, are more common in older compared with younger individuals (114). In addition, cellular senescence drives progressive decline in cell viability, liver function and tissue regeneration, accelerating the progression of diverse diseases. Although the detailed mechanisms and biological functions, such as determining whether cellular senescence is a causative factor or an epiphenomenon of pathological phenotypes, remain incompletely elucidated, substantial progress has been made in this field. Subsequent sections open with a concise overview of clinical entities underpinning disease pathophysiology, proceeding to discuss experimental evidence that links cellular senescence to liver cell subtypes impacted by chronic hepatic inflammation (Fig. 4).

Chronic viral hepatitis B. Hepatitis B virus (HBV), a member of the *Hepadnaviridae* family, causes liver damage through acute and chronic infections. The latter accounts for the vast majority of severe disease burden (115). While HBV infection rates are highest in infancy and childhood, chronic progression occurs in only ~5% of adults infected later in life due to reduced exposure risk. By contrast, elderly patients exhibit markedly higher rates of progression to chronic hepatitis B (CHB) following disease onset, compared with <5% in younger individuals (116). An outbreak investigation of acute HBV in a Japanese nursing home revealed nearly 60% chronicity among patients aged >65 years (117). Moreover, advanced age is a risk factor not only for cirrhosis progression but also for HCC development. This phenomenon may be attributed to an age-related decline in pathogen-specific immune responses, warranting further research to elucidate the underlying pathophysiology and immunological mechanisms in this population.

Age-dependent telomere attrition serves as a robust indicator of the cumulative effect of cellular aging on inflammation in HBV infection. Available evidence indicates that peripheral blood mononuclear cells lose ~50 bp of telomeric DNA per year on average, however, this loss is likely to increase during chronic viral infections (118). Notably, in CHB, hepatocytes exhibit elevated p21 expression and G_1 phase arrest, indicating the presence of p21-mediated G_1 arrest and all indicative of a strong senescent response. For example, telomere length measurements in HBV, performed in hepatocytes, showed shorter telomeres in both liver biopsy tissue and peripheral blood lymphocytes of HBV-infected patients (119). Consistent with this, another study identified fewer and shorter telomeres in CHB patients compared with matched controls (120), whereas both symptomatic and asymptomatic HBV-positive individuals exhibited elevated serum telomerase activity, probably countering telomere shortening-induced cellular senescence (121). Extensive hepatocyte telomere shortening aligns with accelerated aging, telomere length is comparable to that of individuals with normal aging of 10 years and can be extended to 15 years in the case of more severe fibrosis in this pathological context, which helps to explain, at least in part, the pathological features of accelerated aging (122).

The mechanistic crosstalk between telomere attrition and DDR is well-established and underpinned by persistent DDR activation that, when surpassing cellular repair capacity ultimately triggers premature senescence. Existing data

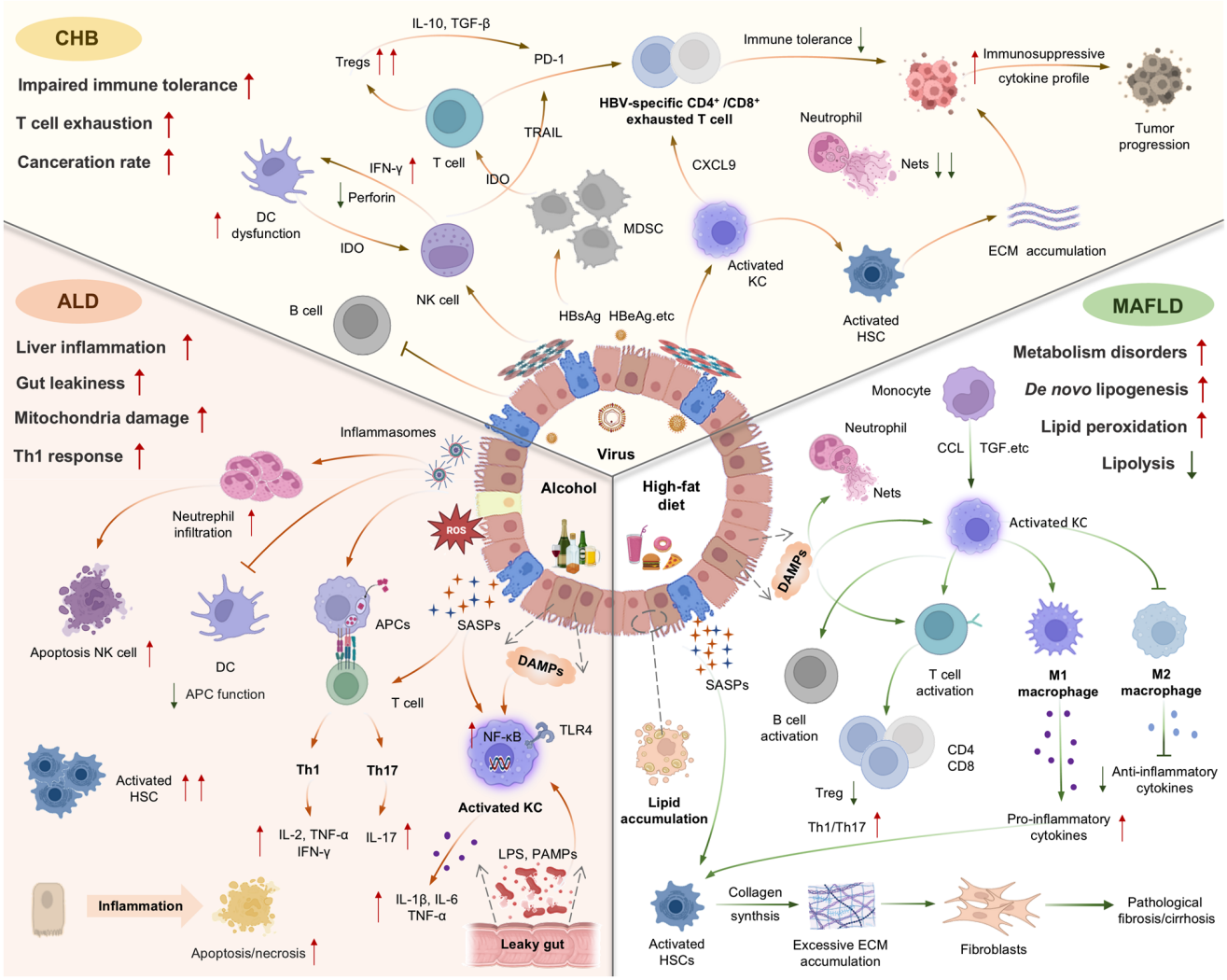

Figure 4. Immune mechanisms in the pathogenesis of CHB, ALD and MAFLD. Chronic liver diseases consistently exhibit disease-related immune dysregulation affecting innate and adaptive systems. However, each disease displays a distinct inflammatory signature, characterized by unique recruited cell populations and expressed bioactive molecules. ALD, alcoholic liver disease; APC, antigen-presenting cell; CCL, CC-chemokine ligand; CHB, chronic hepatitis B; CXCL, CXC-chemokine ligand; DAMPs, damage-associated molecular patterns; DC, dendritic cell; ECM, extracellular matrix; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HSC, hepatic stellate cell; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-gamma; IL, interleukin; KC, Kupffer cell; LPS, lipopolysaccharide; M1, classically activated macrophage; M2, alternatively activated macrophage; MAFLD, metabolic dysfunction-associated fatty liver disease; MDSC, myeloid-derived suppressor cell; NETs, neutrophil extracellular traps; NF-κB, nuclear factor kappa-B; NK, natural killer cell; PAMPs, pathogen-associated molecular patterns; PD-1, programmed cell death protein 1; SASP, senescence-associated secretory phenotype; TGF, transforming growth factor; TGF-β, transforming growth factor-beta; Th, T helper cell; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell.

demonstrate that aged liver samples exhibit aberrant DNA methylation at multiple loci, this pattern of epigenetic alteration is further exacerbated in CHB. An earlier study revealed more pronounced DNA damage in peripheral lymphocytes from HBV patients (123). As aforementioned, the pathology of cellular senescence is involved in the phenotypic alterations of infected cells, a notion that at least partially justifies some conflicting findings. For instance, although most HBV-encoded proteins drive aging or enhance hepatocarcinogenesis risk, HBx represents an exception: Methylated HBx downregulates $p16^{INK4a}$ and $p21^{Waf1/Cip1}$, inactivates Rb phosphorylation and thereby enables escape from cellular senescence (124). Notably, another study on the interaction between HBV and cellular senescence in patients with CHB, in which HBx is not involved as a key player (125).

Beyond this, early-life HBV exposure induces premature immunosenescence. Specifically, viral-mediated inhibition of topoisomerase I induces topological DNA damage and telomere attrition in $CD4^+$ and $CD8^+$ T cells. Epidemiological studies on HBV-endemic individuals carrying the HBV-specific T-cell marker TCR Vβ12, revealed lower $CD3^+$ and $CD4^+$ T-cell counts, indicating impaired immune function from CHB (126). Mechanistic studies demonstrated that in a mouse model of HBV persistence-induced systemic tolerance, hepatic $CD4^+$ T cells continuously produce IFN-γ, which stimulate CXCL9 secretion by KCs to facilitate CXCR3-dependent retention of antiviral $CD4^+$ T cells, ultimately driving their apoptotic clearance (127).

Age-related immunosenescence and immune checkpoint dysfunction profoundly influence HBV pathogenesis. Under physiological conditions, harmful senescent cells are cleared by recruited immune cells, such as monocytes and macrophages. During aging, nevertheless, immune surveillance and host defense mechanisms become widely suppressed and

rendered ineffective in HBV, resulting in insufficient clearance of senescent and precancerous cells, a process that appears to play an important role in carcinogenesis (126,128). *In viv*o and *in vitro* findings indicate elevated SASP levels in chronic HBV infection, with excessive secretion of its components (growth factors, interleukins and MMPs) promoting HBV-associated HCC development, an effect exacerbated by aging (129). Compared with HBV-negative HCC cells, HBV-positive cell lines showed increased MMP-9 expression, reduced tissue inhibitor of metalloproteinase expression and higher invasive potential (130). Similarly, HBsAg-positive patients have higher peripheral blood TNF-α and IL-6 levels (131). Of note, consistent with these findings, a clinical study conducted by Rosenberg *et al* (132) found that donor-derived T cells from older donors exhibit reduced hepatitis B surface antigen-specific proliferative response, while younger donors show stronger responses.

Metabolic associated fatty liver disease. MAFLD, previously termed as NAFLD, is characterized by hepatic steatosis and affects up to one-third of the global population. While the age of MAFLD onset has decreased in recent years, its prevalence, risk of hepatic/extrahepatic complications and rates of all-cause and disease-specific mortality increase with advancing age (133). Moreover, geriatric patients harbor more MAFLD risk factors, including hyperlipidemia, obesity, diabetes and hypertension and exhibit more severe biochemical, hematological and histological alterations than younger cohorts. A cross-sectional analysis of adult participants found that elderly patients with MAFLD had a higher likelihood of MASH and advanced fibrosis compared with younger adults (134). The detrimental effect of aging on hepatic homeostasis manifests through cellular-level structural damage, progressive decline in liver function and metabolic dysregulation. Extensive research indicates that MAFLD-associated pathological changes, including abnormal hepatocyte morphology, lipofuscin accumulation and ECM deposition, are associated with accelerated liver aging, potentially driving age-related hepatic steatosis. Notably, Gao *et al* (135) demonstrated that lipid accumulation directly exacerbates hepatic aging. These findings suggest that the pathogenesis of MAFLD may be intrinsically linked to biological aging. However, whether cellular senescence initiates or results from hepatic metabolic dysfunction and inflammation remains unresolved.

Clinical and preclinical evidence supports a link between cellular senescence and MAFLD. Senescent hepatocytes are more abundant in patients with MAFLD and, as observed in other chronic liver diseases, their senescence levels correlate with the severity of MAFLD, as confirmed by liver biopsies in these patients (136). Several markers of senescence, such as SA-β-Gal, p16, p21 and p53, are elevated in individuals with MAFLD/MASH (137). Similarly, rodent studies demonstrate that HFD reduces the phosphorylation of Rb by upregulating p16 and p21, inducing hepatocyte cell cycle arrest, activating senescence pathways, and ultimately promoting MAFLD (138). Analogously, in p53-null mice, inhibition of p66Shc signaling reduces hepatic lipid peroxidation and hepatocyte apoptosis, delaying nutritional steatohepatitis development (139). Meanwhile, a similar effect occurs after the systemic clearance of p16-expressing cells. DNA methylation additionally serves as a key mechanism: In high-fructose/high-cholesterol-fed mice, its patterns alter liver lipid gene expression (upregulating lipid genes and downregulating proliferation/transcription genes) and specific histone modifications induce proliferation arrest (140). Other markers of senescence (genomic instability and DNA damage), are also directly associated with the progression of MAFLD.

Of great importance, immune system aging is closely linked to MAFLD/MASH via proinflammatory factor secretion. The local microenvironment and the aging immune cell population engage in a vicious cycle, the resultant inflammatory milieu triggers and amplifies microenvironmental responses, thereby exacerbating hepatic dysfunction. A recent pivotal study identified that marked hepatic T-cell senescence and exhaustion drive metabolic liver disease progression in humans (141). Specifically, in contrast to normal individuals, patients with MASH show upregulated expression of senescence- and exhaustion-related genes in hepatic $CD4^+$ and $CD8^+$ T cells, along with increased expression of IL-2, IL-15 and IL-18 in these cells. Hepatic macrophage accumulation relies on CCL2-CCR2-mediated chemotaxis: M1 activation (marker CD86) is associated with MAFLD severity in humans, and older mice show more pronounced M1 infiltration in both liver and adipose tissue (142).

ALD. ALD is a globally prevalent condition driven by chronic excessive alcohol consumption, posing a serious health threat to ~75 million individuals (143). Alcohol metabolites generated during hepatic processing produce toxic substances that trigger hepatocyte inflammation and severe liver damage via inflammatory cascades involving cytokines, chemokines and ROS (144). Evidence indicates higher rates of binge drinking among middle-aged and older adults, with the risk of alcohol abuse being further elevated by age-related metabolic changes, smoking, or illicit drug use. Chronic low-grade inflammation in older adults, characterized by elevated circulating pro-inflammatory cytokines and tissue inflammatory cell infiltration, exacerbates ALD progression (145). Concurrently, emerging evidence demonstrates that ALD accelerates cellular senescence. Murine ALD models show increased senescence-associated biomarkers, such as miR-34, p16, p21 and p53, along with elevated SASP factors (TGF-β1, PAI-1 and CCL2) (146). Additionally, ALD patients exhibit significant hepatic telomere shortening, accompanied by upregulation of telomere-binding protein genes, which suggests a compensatory response to DNA damage (147).

Notably, immunosenescence plays a central role in ALD pathogenesis through senescence-associated regulatory mechanisms. Following chronic ethanol exposure, activated immune cells trigger cytokine and chemokine production, initiating a pro-inflammatory cascade (148). Current evidence indicates that most KCs polarize predominantly toward pro-inflammatory M1 phenotypes, releasing abundant cytokines including IL-1β, IL-18, TNF-α, IL-12 and IL-23. These mediators induce potent innate immune responses and critically contribute to alcohol-induced liver injury. By contrast, activated M2 macrophages increase in number and secrete abundant anti-inflammatory factors during tissue repair following injury (149). Nevertheless, macrophage polarization remains vaguely defined and controversial due to the inherent

plasticity of these cells and their context-dependent responses to pathological signals. Notably, Wan *et al* (150) demonstrated that M2-polarized macrophages induce hepatocyte senescence via IL-6 secretion, accelerating alcohol-induced senescence both *in vivo* and *in vitro* Extensive evidence indicates that chronic ethanol exposure alters T-cell immunophenotypes in mice and humans. Liver biopsy specimens from patients with moderate-to-severe ALD reveal significant $CD3^+$ T cell infiltration and activation (including $CD4^+$ and $CD8^+$ subsets) (151) Compared with controls, T cells from alcohol-fed mice produce elevated levels of IFN-γ and IL-4. A pronounced Th1-dominant response promotes ALD progression through IL-2, TNF-α, and IFN-γ production, while Th17 cells exacerbate liver damage via IL-17 secretion. Notably, Th17 cell populations expand with aging, and Th17-derived IL-17 enhances SASP production, thereby amplifying the inflammatory cascade (152).

Liver fibrosis and cirrhosis. Liver fibrogenesis constitutes a highly integrated, dynamic process involving molecular, cellular and tissue-level changes. This process is primarily characterized by excessive ECM deposition, driving extensive disruption of hepatic architecture and functional integrity (153). Organ fibrosis represents a hallmark manifestation of chronic inflammatory disease progression, accounting for ~45% of global all-cause mortality. Accordingly, hepatic fibrosis development critically determines both disease prognosis and patient quality of life (154). The aging global population and the rising prevalence of fibrosis-predisposing conditions (including viral hepatitis, MAFLD, ALD, primary sclerosing cholangitis and autoimmune hepatitis) are driving the growing burden of liver fibrosis. Regardless of etiology, clinical severity escalates substantially with fibrotic septa formation and progression toward cirrhosis, leading to increased mortality and HCC incidence. Globally, liver diseases account for 1.5-4% of annual deaths (155,156). Experimental and clinical studies have demonstrated that matrix remodeling and partial architectural restoration can occur even in advanced fibrosis/cirrhosis, suggesting this stage represents a potential therapeutic window in chronic liver disease progression (157). Thus, targeted investigations of the underlying pathophysiological mechanisms are needed.

Fundamentally, fibrosis is not a unidirectional process but rather a dynamic interplay of factors including persistent inflammation, dysregulated ECM remodeling, and myofibroblast formation and proliferation during tissue wound healing and fibrogenesis (158). Aging populations exhibit increased susceptibility to irreversible fibrotic damage due to a diminished wound-healing capacity and impaired fibrosis resolution. Substantial emerging evidence indicates that established biomarkers of cellular senescence in liver tissue (such as miR-378, miR-18b-3p and the lncRNA-ATB/miR-200a/β-catenin axis) are elevated in patients with liver fibrosis and cirrhosis, underscoring the role of senescence in the pathogenesis of these disorders (159). The SASP drives fibrosis by establishing a pro-inflammatory and pro-fibrotic microenvironment. Wijayasiri *et al* (160) found that HSCs exposed to conditioned media from senescent HepG2 cells exhibited activation and secreted abundant inflammatory and fibrotic mediators. HSC activation represents a key pro-fibrotic consequence of the SASP. Furthermore, during fibrotic progression, activated HSCs can undergo spontaneous senescence. TGF-β key component acts as a potent activator of HSCs, driving their transformation into myofibroblast-like cells and promoting excessive ECM protein production. Notably, immune defenses are compromised in aging patients with fibrosis, increasing susceptibility to inflammation and infection-related complications (161). The recruitment of abundant immune cells (neutrophils and macrophages) to the liver via elevated pro-inflammatory SASP factors, including IL-6, IL-8 and TNF-α, perpetuates cycles of oxidative stress, inflammation and fibrosis, a phenomenon that intensifies with aging. Single-cell transcriptome analyses have revealed expanded populations of $CD4^+$ T cells, $CD8^+$ T cells and γδ T cells in fibrotic liver tissue, with further increases observed in cirrhosis (162). Typically, Th1 and Th17 cells accelerate fibrotic progression by acting on hepatocytes, KCs and HSCs through pro-inflammatory mediators. By contrast, substantial evidence indicates that Treg cells exert antifibrotic effects, partly mediated by IL-10-dependent immunosuppression (163). In brief, the convergence of inflammation, immune cells mobilization, and activation of HSCs and hepatocytes drives both liver fibrosis and aging-related pathology.

Additional links between cellular senescence and fibrosis include telomere attrition and mitochondrial dysfunction. Dysregulation of the mitochondrial ETC drives oxidative stress, damaging cellular components and promoting fibrogenesis. Besides, the age-related decline in mitochondrial function predisposes the liver to heightened stress sensitivity and fibrosis susceptibility. In accordance with this, substantial release of mtDNA and mitochondria-derived damage-associated molecular patterns has been observed in both human patients and CCl4-induced mouse models with significant liver fibrosis, directly implicating mitochondrial dysfunction in fibrotic pathogenesis (164,165). Given the age-dependent prevalence of hepatic fibrosis/cirrhosis and the established role of telomere attrition as a biomarker of biological aging, replicative senescence is likely to contribute to fibrosis/cirrhosis pathogenesis. Calado *et al* (166) demonstrated that telomerase abnormalities are associated with hematological disorders and severe liver diseases characterized by fibrosis and inflammation. In line with this, a cross-sectional study revealed an inverse correlation between telomere length and cirrhosis severity, while mutations in telomerase-related genes were identified as cirrhosis risk factors (167,168). Of great importance, emerging evidence positions telomere attrition as a genetic determinant of cirrhosis susceptibility (169).

HCC. HCC, as the predominant form of primary liver cancer, accounts for ~90% of hepatic malignancies. Its development is associated with multiple risk factors, including chronic alcohol consumption, persistent viral infections (such as HBV/HCV), chemical exposures, and metabolic disorders (170). Regardless of etiology, hepatocarcinogenesis typically involves recurrent cycles of hepatocellular injury, inflammation and necrosis, processes exhibiting marked molecular and cellular heterogeneity and irreversibility (171). According to GLOBOCAN data, the global incidence of liver cancer reached 906,000 new cases with 830,000 mortalities annually, reflecting rapidly rising rates that impose a substantial global health burden (172).

Epidemiological studies consistently demonstrate an age-dependent increase in HCC incidence, with markedly higher rates in individuals over 75 years (173). Notably, older adults may develop HCC even in the absence of fibrosis or cirrhosis, probably due to age-related physiological and metabolic alterations, underscoring the direct role of aging in hepatocarcinogenesis (174).

HCC predominantly arises from persistent viral infections or sterile inflammation These pathological states impair telomerase activity, accelerate telomere shortening, induce hepatocyte malignant transformation and foster a pro-tumorigenic microenvironment. Crucially, senescent cells act as key initiators of this process, serving as chronic inflammatory foci throughout the natural course of the disease (175). Senescent hepatocytes disrupt the local microenvironment through sustained secretion of proinflammatory mediators. These cell populations engage in a self-perpetuating cycle with their microenvironment: Inflammatory signaling induces senescence, which further amplifies microenvironmental inflammation and exacerbates hepatic dysfunction. For example, Li *et al* (176) revealed that the activation and senescence of HSCs were observed in both human and murine liver tumors, concomitant with SASP secretion. Similarly, in diethylnitrosamine (DEN)/CCl4 -induced HCC models, senescent hepatocytes upregulate SASP secretion (especially IL-8) during hepatocarcinogenesis and a similar phenomenon is observed in human HCC tissues (177). Furthermore, cellular senescence in this context can be prematurely induced by diverse stressors or naturally by replicative exhaustion. Research from Ho *et al* (178) found that aged mice with senescent β-catenin-deficient hepatocytes developed an inflammatory microenvironment that promoted HCC progression. Intriguingly, as aforementioned, the pathological role of cellular senescence is also environment-dependent, which partly explains some conflicting findings. Senescence is proposed to function as a physiological tumor-suppressive mechanism by recruiting immune cells and inhibiting the progression from benign to malignant lesions in early disease. Therefore, its complex role in cancer needs to be studied under specific conditions.

Indeed, age-related immune dysregulation and immunosenescence profoundly affect the long-term HCC prognosis. As HCC progresses to advanced stages, multiple hepatic cell types, such as immune cells, hepatocytes and endothelial cells, acquire senescence-associated phenotypes, driving systemic failure of antitumor defenses in HCC patients. This process is age-exacerbated, driven by inflammatory cascade signaling and amplified SASP production. RNA sequencing of treatment-naïve HCC tumor has revealed increased Tregs and exhausted $CD8^+$ T cell accumulation (179). Comparative analyses further showed elevated levels of Tregs and $CD25^+$ $CD4^+$ T cells in the peripheral blood of HCC patients compared to healthy individuals, with higher serum immunosuppressive cytokines (TGF-β1 and IL-10) (180). Paradoxically, a meta-analysis showed that higher infiltration of neutrophils and Tregs were correlated with improved overall and disease-free survival, suggesting context-dependent immune roles (181). Notably, tumor-associated macrophages within the tumor microenvironment display aberrant activation. Another study found that M2 macrophages, along with Tregs, Th2, and Th17 cells, increase with HCC progression, and produce elevated levels of IL-6, VEGF, Arg1 and IDO, thereby promoting immune evasion and tumor progression (182).

6. Senescence-targeted interventions

Fundamentally, transient cellular senescence is a physiological process that supports tissue homeostasis and embryonic development by promoting acute tissue repair and limiting its further deterioration. By contrast, the chronic persistence of senescent cells has the opposite effect, their progressive accumulation in the organism impairs tissue and organ function, ultimately driving aging and age-related diseases. In the hepatic system, growing evidence highlights the central role of cellular senescence in the initiation, progression, and exacerbation of liver disease (183). Consequently, senescence-targeted interventions (senescence therapies), can serve as potential treatments to improve liver status and extend healthy lifespan during aging. Surprisingly, the effectiveness of using senolytics to eliminate senescent cells from tissues to delay illness has been elucidated. Up to now, senotherapeutic strategies primarily include senolytics (drugs that selectively clear senescent cells) and senomorphics (agents that inhibit SASP), as discussed below (Tables II and III; Fig. 5).

Senolytic interventions. Senolytics, which encompass small molecules, peptides and antibodies, selectively eliminate senescent cells while sparing normal proliferating cells. These agents induce apoptosis in senescent cells by targeting key survival pathways known as senescent cell anti-apoptotic pathways, including p53, p21 and PI3K/Akt signaling, BCL-2 family members, HSP-90 and other targets (21). Recent systematic screening approaches have identified numerous senolytic compounds with therapeutic potential.

Dasatinib and quercetin. The first-generation senolytic combination of dasatinib and quercetin (D+Q) induces more potent apoptosis and ameliorates age-related pathologies compared with either compound administered alone. Preclinical studies demonstrate that D+Q alleviates multiple age-related conditions in mice, including insulin resistance, hepatic steatosis, pulmonary fibrosis and chronic kidney disease (184,185). Mechanistic studies in aged mice have revealed that D+Q triggers apoptosis in senescent hepatic progenitor cells, effectively reducing senescence-associated phenotypes including reduced SA-β-gal activity and clearance of $p16^{INK4a}$-positive cells in the liver (186). Additional evidence confirms that this senolytic combination attenuates hepatic steatosis and ameliorates MAFLD pathology in HFD-induced models (187). Conditional knockout of fructose-1,6-bisphosphatase 1 (FBP1), a key tumor-suppressive metabolic enzyme, induces hepatic metabolic dysregulation in mice. This promotes HSC senescence, which accelerates hepatocarcinogenesis via SASP mechanisms. Li *et al* (176) demonstrated that intermittent D+Q treatment selectively eliminated senescent HSCs in hepatocyte-specific FBP1-deficient mice, thereby halting HCC progression. Moreover, D+Q reduced HCC-associated gene expression in $Sod1^{-/-}$ mice and markedly lowered HCC incidence (188). While this senolytic regimen shows therapeutic potential, its precise mechanisms require further exploration. Paradoxically, another preclinical

Table II. Potential senotherapeutic strategies in liver diseases (Senolytics).

Authors, year	Pathway	Compound	Model	Disease	Outcome characteristics	(Refs.)
Yakubo *et al*, 2024	Tyrosine kinase inhibitors; targeting PI3K/AKT	Dasatinib + quercetin	HFD induced medaka	MAFLD	Eliminates senescent cells, reduces hepatic lipid accumulation and inhibits fibrotic genes expression.	(213)
Ogrodnik *et al*, 2017			HFD induced mice	MAFLD	Induces selective apoptosis of senescent cells and attenuated hepatocyte senescence and hepatic steatosis.	(187)
Song *et al*, 2023			CCl4 induced mice	Fibrosis	Decreases the abundance of senescent macrophages.	(214)
Thadathil *et al*, 2022			$Sod1^{-/-}$ mice	HCC	Reduces the expression of inflammatory, cancer-related genes and the incidence of HCC.	(188)
-	Targeting p53	FOXO4-DRI	-	-	No studies in liver disease reported.	-
Gold *et al*, 2025	BCL-2 family inhibitors	Navitoclax (ABT-263)	Lieber-DeCarli alcohol liquid diet induced mice; AML12 and LX2 cells	ALD	Downregulates genes involved in adipogenesis while activating the complement pathway.	(193)
Zhao *et al*, 2011			Huh7 cells	HCC	Induces apoptosis.	(191)
Wang *et al*, 2012			HepG2, Huh7, FHCC98 and BEL-7402 cells	HCC	Reverses TRAIL resistance without affecting normal hepatocytes.	(215)
Hikita *et al*, 2010		ABT-737	$Bcl\text{-}X_L^{-/-}$ and $Mcl\text{-}1^{-/-}$mice; primary human hepatocytes	HCC	Inhibits xenograft tumor growth	(194)
Cucarull *et al*, 2020		A-1331852	HepG2 sorafenib-resistant cells or BCLC9 cells injected into mice; Hep3B, PLC/PRF/5, HepG2 and LX2 cells	HCC	Enhances regorafenib efficacy.	(197)
Ambade *et al*, 2014	HSP90 inhibitors	17-DMAG (alvespimycin)	Acute and chronic alcoholic liver injury mice	ALD	Decreases oxidative stress, inhibits NFκB and pro-inflammatory cytokine production.	(205)
Leng *et al*, 2012			HepG2 cells	HCC	Decreases survivin, and NF-κB protein levels and increases p53 level.	(201)
Ma *et al*, 2023		17-AAG (tanespimycin)	HFD-induced mice; HepG2 cells	MAFLD	Promotes hepatic albumosomal accumulation.	(216)
Abu-Elsaad *et al*, 2016			Thioacetamide induced mice	Fibrosis	Rebalances oxidative stress, reduces stellate cells activity and induces apoptosis.	(217)

Table II. Continued.

Authors, year	Pathway	Compound	Model	Disease	Outcome characteristics	(Refs.)
Abdelhamid *et al*, 2024		Ganetespib (STA-9090)	DENA, TAA and HFD induced rats; HepG2 cells	Fibrosis	Affects hedgehog signaling.	(218)
Saber *et al*, 2023			N-Nitrosodiethylamine induced mice; HepG2 cells	HCC	Enhances the effectiveness of sorafenib monotherapy.	(207)
Goyal *et al*, 2015			Advanced HCC patients	HCC	Demonstrates acceptable safety and tolerability.	(206)
Augello *et al*, 2019		AUY92 (luminespib)	HepG2, Hep3B and SNU475 cells	HCC	Reduces the proliferation and viability of HCC cells and inhibits the tumor growth.	(219)
Zhang *et al*, 2022		7-aminocephalosporanic acid	HFD induced mice	MAFLD	Decreases TC and TG and protects the liver and the adipose tissue from lipid accumulation.	(220)

HFD, high-fat diet; MAFLD, metabolic associated fatty liver disease; HCC, hepatocellular carcinoma; MASH, metabolic steatohepatitis; MSG, monosodium glutamate, CLD, chronic liver disease; ACH, acetaldehyde; TG, triglyceride; TC, total cholesterol; HSP, heat shock protein; SASP, senescence related secretion phenotype; ALD, alcoholic liver disease; VEGF, vascular endothelial growth factor; HMGB1, high mobility group box 1 protein; FOXO4-DRI, FOXO4-D-retro-inverso; CCl4, carbontetrachloride; TRAIL, TNF-related apoptosis-inducing ligand; SOD, superoxide dismutase.

study reported that D+Q exacerbated liver histopathology and tumorigenesis, accelerating disease progression without effectively clearing senescent cells (189). Given the exclusively preclinical evidence regarding D+Q and liver interactions, rigorous studies are warranted to evaluate therapeutic efficacy, while human safety profiles require thorough assessment.

BCL-2 family member inhibitors. The BCL-2 family proteins, including BCL-2, BCL-X_L, and BCL-W, serve as key regulators of cellular survival and death. These proteins are upregulated during senescence across diverse cell types, establishing them as prime targets for senolytic therapies (190). ABT-263 (navitoclax), a pan-inhibitor of BCL-2 family proteins, suppresses tumor metastasis and recurrence by eliminating chemotherapy-induced senescent cancer cells and hepatocytes within the tumor microenvironment. Preclinically, its demonstrated dose-dependent pro-apoptotic effects against HCC *in vitro* have now been validated in a phase I clinical trial (NCT01364051) involving HCC patients (191,192). Gold *et al* (193) recently established that ABT-263 clears senescent stellate cells and hepatocytes in ALD mice, concomitantly attenuating hepatic triglyceride deposition. *Ex vivo* analyses confirmed caspase-3-mediated apoptosis in acetaldehyde-induced senescent hepatocytes following ABT-263 treatment. ABT-737, a precursor to ABT-263, exhibits senolytic activity in experimental models. In murine models, ABT-737 synergistically enhances sorafenib-induced apoptosis in hepatoma cells, with the combination therapy demonstrating superior suppression of xenograft tumor growth compared with sorafenib monotherapy (194). However, ABT-737 lacks oral bioavailability and exhibits low aqueous solubility. Structural optimization subsequently yielded its derivative ABT-263, which was developed as an orally bioavailable BCL-2 inhibitor (195). Targeted inhibition of BCL-X_L may mitigate side effects (such as thrombocytopenia and neutropenia) associated with pan-BCL-2 inhibition while preserving therapeutic efficacy (196). Indeed, BCL-X_L inhibitors A-1331852 and A-1155463 demonstrate senolytic effects in senescent HUVECs and human lung fibroblasts (196). Although Cucarull *et al* (197) reported that A-1331852 restored regorafenib efficacy (a second-line HCC therapeutic) in both xenograft models and *in vitro* systems, BCL-X_L inhibitors remain underexplored for liver pathologies. Further studies are needed to evaluate their safety and efficacy profiles. Overall, BCL-2 family inhibition represents a mechanism-based strategy for senolytic discovery, however, their associated side effects hinder clinical translation.

p53 pathway targeting compounds. Research has revealed that forkhead box protein O4 (FOXO4) regulates senescent cell viability by binding and sequestering nuclear p53, thereby inhibiting apoptosis. Based on this mechanism, a retro-inverso peptide, FOXO4-D-retro-inverso (FOXO4-DRI), was developed to disrupt FOXO4-p53 interaction and selectively induces apoptosis in senescent cells (198). Furthermore, FOXO4-DRI conferred protection against doxorubicin-induced accelerated senescence and hepatic damage in mice, suggesting its potential as a therapeutic strategy against senescence-driven liver pathologies (199). However, the short *in vivo* half-life of FOXO4-DRI necessitates development of stabilization approaches or alternative p53-activating strategies for effective senescent cell clearance.

Table III. Potential senotherapeutic strategies in liver diseases (Senomorphics).

Authors, year	Pathway	Compound	Model	Disease	Outcome characteristics	(Refs.)
Ge *et al*, 2023	mTOR inhibition	Rapamycin	HFD induced mice	MAFLD	Suppresses inflammation and increase the interaction between p65 and IκBα.	(229)
Kang *et al*, 2024			TA induced mice	Fibrosis	Reduces the expression of IL-10, IL-1, TNF-α.	(227)
Lee *et al*, 2022			Transgenic mice with HCC	HCC	Low-dose rapamycin may be effective to prevent HCC growth.	(226)
Rastegar *et al*, 2018			HepG2 cells	HCC	Has an anti-angiogenesis effect via inhibition of VEGF expression.	(248)
Smith *et al*, 2020	AMPK activation	Metformin	Patients with CLD	CLD	Well-tolerated in CLD cohort.	(249)
Gkiourtzis *et al*, 2023			Pediatric patients with MAFLD	MAFLD	Reduces steatosis on ultrasound and improve liver histology and insulin resistance.	(234)
Sato *et al*, 2021			Polycystic kidney rats	Fibrosis	Attenuates excessive hepatic cell proliferation via mTOR/ERK pathway inactivation and reduce expression of liver fibrosis-related proteins.	(250)
de Oliveira *et al*, 2019			HFD induced transgenic zebrafish HCC model	MAFLD/ MASH-HCC:	Affects macrophage polarization and T cell infiltration and regulates the immune response.	(251)
He *et al*, 2023	Sirtuin activation	Resveratrol	HFD induced rats	MAFLD	Reduces blood lipids and attenuates hepatic steatosis.	(252)
Li *et al*, 2024			Inorganic mercury induced mice	Fibrosis	Activates the Sirt1/PGC-1α signaling pathway	(240)
Chai *et al*, 2017			HepG2, Bel-7402 and SMMC-7721 cells	HCC	Inhibits proliferation and migration through SIRT1 mediated post-translational modification of PI3K/AKT pathway in HCC cells.	(241)
Zhang *et al*, 2018			MHCC97-H cells	HCC	Induces autophagy via activating p53 and inhibiting PI3K-Akt	(242)
Yamazaki *et al*, 2009		SRT1720	MSG mice	MAFLD	Reduces the expression of lipogenic genes and decreases hepatic lipid accumulation.	(246)
Elmorsy *et al*, 2025			HFD induced rats	MAFLD/ MASH	Improves liver function and histology.	(253)
Fu *et al*, 2023			Ethanol induced HepG2 cells and mice	ALD	Reverses the upregulation of HMGB1 acetylation, nuclear translocation, and release.	(245)

Table III. Continued.

Authors, year	Pathway	Compound	Model	Disease	Outcome characteristics	(Refs.)
Gold *et al*, 2025		Nicotinamide	ACH induced AML12 and LX2 cells; Lieber-DeCarli alcohol liquid diet induced mice	ALD	Reduces senescence and SASP, decreases liver injury markers and improves metabolic function.	(193)
Al-Gayyar *et al*, 2019			HepG2 cells; TA induced rats	HCC	Produces cytotoxic effects against HCC.	(254)

HFD, high-fat diet; MAFLD, metabolic associated fatty liver disease; HCC, hepatocellular carcinoma; MASH, metabolic steatohepatitis; MSG, monosodium glutamate, CLD, chronic liver disease; ACH, acetaldehyde; ALD, alcoholic liver disease; VEGF, vascular endothelial growth factor; TRAIL, TNF-related apoptosis-inducing ligand; SOD, superoxide dismutase; TA, thioacetamide; IL, interleukin.

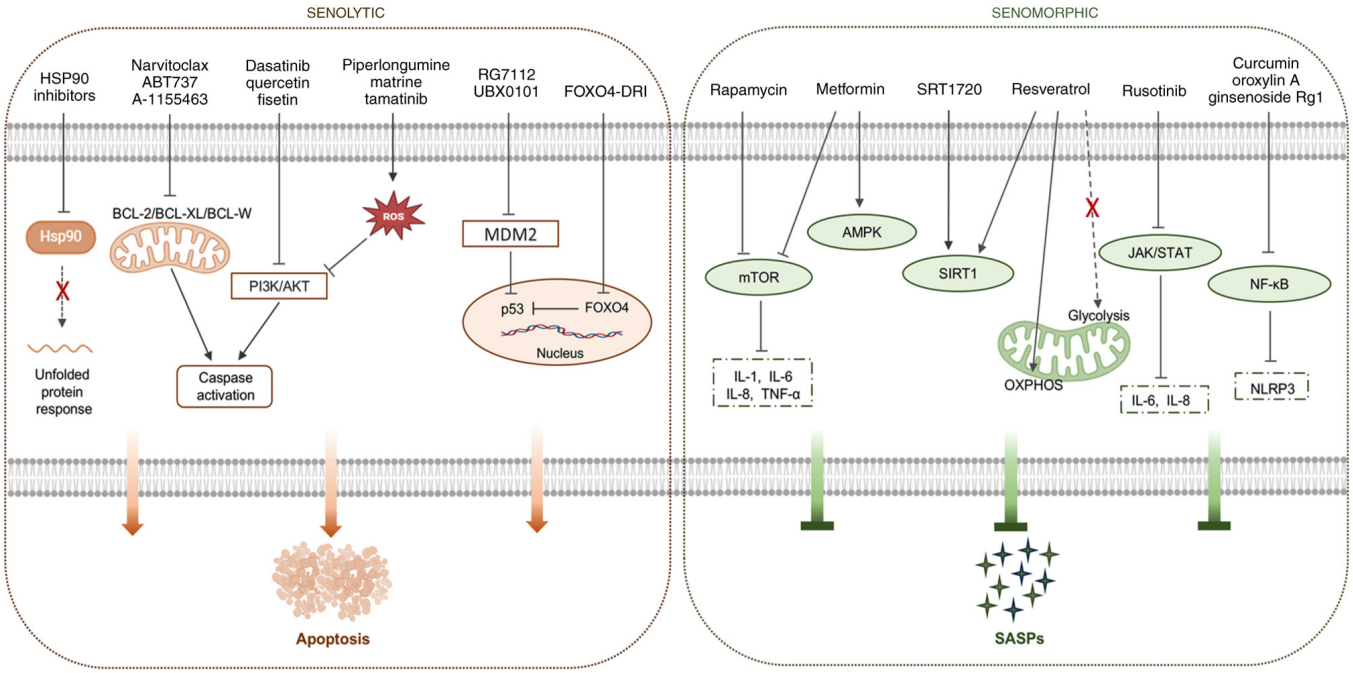

Figure 5. Molecular mechanisms underlying senescence-targeted interventions. Senotherapeutic approaches involve selectively eliminating senescent cells through apoptosis induction and suppressing SASP. Several of these interventions and drugs have shown promising therapeutic efficacy for chronic liver diseases by targeting cellular senescence. Akt, protein kinase B; AMPK, adenosine 5'-monophosphate-activated protein kinase; BCL, B-cell lymphoma; DRI, D-retro-inverso isoform; FOXO4, forkhead box protein O4; HSP, heat shock protein; IL, interleukin; JAK/STAT, Janus kinase/signal transducers and activators of transcription; MDM2, mouse double minute 2; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; OXPHOS, oxidative phosphorylation; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SIRT1, sirtuin 1; SASP, senescence-associated secretory phenotype; TNF-α, tumor necrosis factor-α.

HSP90 inhibitors. As HSP90 is a cancer-promoting protein that regulates apoptosis, proliferation and angiogenesis, its inhibition has emerged as a validated strategy for cancer chemotherapy (200). Several HSP90 inhibitors, including 17-DMAG (alvespimycin), 17-AAG (tanespimycin), ganetespib and geldanamycin, exhibit senolytic effects across multiple senescent cell types through distinct, cell-type-specific mechanisms. For example, 17-DMAG suppresses HCC cell proliferation in a time- and concentration-dependent manner, probably by modulating cyclin D1, p53 and NF-κB protein levels (201). Mechanistically, studies indicate that 17-DMAG induces apoptosis in senescent cells, partially through disruption of the HSP90-AKT interaction and impairment of AKT activation (202-204). In both chronic and acute models of alcoholic liver injury, 17-DMAG attenuated oxidative stress and modulated inflammatory responses (205). Another HSP90 inhibitor, ganetespib (STA-9090), was well-tolerated in a phase I dose-escalation trial involving patients with advanced HCC who had progressed after at least one line of systemic therapy, though it did not confer significant clinical benefit (206).

However, subsequent preclinical studies revealed that the ganetespib-sorafenib combination synergistically enhanced cytotoxicity by disrupting HIF-1α stability, increasing p62 accumulation, and inhibiting autophagy, thereby augmenting sorafenib monotherapy efficacy (207). Collectively, these findings indicate that sustained research is essential to maximize the clinical translation potential of this therapeutic combination. Critically, precise identification of the dominant senolytic mechanisms in each disease context is essential, as these mechanisms vary markedly across cell types.

Natural products. Several natural products and their derivatives, including fisetin, piperlongumine and matrine, also possess senolytic properties. For example, fisetin acts through multimodal mechanisms by targeting key regulators such as the PI3K/AKT, BCL-2, p53 and NF-κB signaling pathways (208). In a Lieber-DeCarli ethanol diet-induced ALD mouse model, fisetin alleviated age-related pathologies and improved the local tissue microenvironment *in vivo* via anti-inflammatory and anti-fibrotic mechanisms (209). Sundarraj *et al* (210) discovered that fisetin dose-dependently reduced autophagic flux by activating the PI3K/AKT/mTOR signaling and modulating the AMPK pathway, thereby showing therapeutic efficacy against HCC. Piperlongumine, a natural amide alkaloid from long pepper, selectively induces senescent cell death by increasing ROS production and inhibiting PI3K/AKT and NF-κB pathways. It also exerts hepatoprotective and anti-fibrotic effects in bile duct ligation (BDL)-induced liver fibrosis model (211). Due to its biological characteristics, the precise senolytic mechanism of piperlongumine remains unclear. Researchers have developed several piperlongumine analogues (compounds 47-49) through a series of structural modifications. These analogs exhibit enhanced senolytic activity and modulate multiple antioxidant enzyme expressions (212). Nonetheless, most natural compounds exert multi-target, multi-pathway effects, making it challenging to attribute their therapeutic benefits exclusively to senescent cell clearance. Moreover, since senescent cells exert context-dependent beneficial effects, selectively targeting the SASP may represent a safer and more effective anti-aging strategy.

Senomorphic interventions. While completely halting physiological aging remains unrealistic, modulating pathways associated with premature senescence represents a promising therapeutic strategy to counteract accelerated aging in liver disease. Senomorphics inhibit detrimental effects of SASP without inducing senescent cell death. In general, these agents suppress SASP expression by targeting key signaling pathways, including mTOR, NF-κB, SIRT1/SIRT3 and JAK. thereby inhibiting cellular senescence (221). While less targeted than senolytics, this approach represents viable intervention strategy.

Rapamycin. Originally developed as an anti-fungal agent, rapamycin (sirolimus) ranks among the best-established senomorphic compounds for modulating aging and suppressing the SASP. In multiple animal models, rapamycin has been found to extend lifespan not only in worms and drosophila, but also to increase both median and maximum lifespan in mice when administered later in life (222,223). Evidence confirms that rapamycin effectively suppresses SASP markers, reduces cellular senescence and thereby ameliorates age-related functional decline or delays tumorigenesis in rodent models (224). Mechanistically, rapamycin primarily inhibits mammalian target of rapamycin complex 1 (mTORC1), although chronic administration also attenuates mTORC2 signaling, while potently blocking the translation of membrane-bound IL-1α. This reduction in IL-1α suppresses NF-κB transcriptional activity, consequently inhibiting secretion of most SASP components (225). Notably, the mTOR signaling pathway has expanded markedly beyond coordinating cellular growth and metabolism in response to nutrient availability, and now includes the regulation of aging processes, particularly cellular senescence. Additional mechanisms by which rapamycin may modulate aging, such as nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activation, are under investigation. Lee *et al* (226) investigated the therapeutic effects of rapamycin in transgenic mice with HCC induced by activated HrasG12V and p53 suppression. A low-dose of rapamycin effectively prevented HCC initiation but failed to inhibit established tumor growth. This stage-specific efficacy was mechanistically linked to the expansion of $CD4^+$ Tregs and suppression of mTOR downstream targets (including 4E-BP1 and S6K1). Similarly, oral administration of rapamycin effectively inhibits activated hepatic mTOR in ALD mice and inhibits thioacetamide-induced liver fibrosis (227,228). In HFD-induced mice, rapamycin suppresses pro-inflammatory NFκB signaling by increasing p65 and IκBα interaction (229). Regrettably, chronic mTORC1 inhibition via long-term rapamycin administration increased hepatic inflammation and liver tumor incidence (230). Besides, rapamycin and its analogs exhibit various side effects (including pneumonitis, immunosuppression, kidney toxicity and thrombocytopenia and impaired wound healing) complicating long-term therapeutic use (231) Developing next-generation rapamycin analogs may overcome these adverse effects while improving potency and pharmacokinetic profiles.

Metformin. Metformin, the first drug evaluated in the Targeting Aging with Metformin trial, modulates multiple aging pathways including inflammatory regulation, oxidative stress defense and proteostasis. For example, metformin reduces SA-β-gal activity and downregulates senescence markers across diverse senescent cell types (232). It protects against liver injury in acute viral hepatitis by regulating mTORC1 signaling and mitochondrial function to control effector T-cell activation. Metformin is also well-tolerated in NAFLD patients, though its effects on senescence phenotypes remain unassessed in these contexts (233,234). Metformin activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, demonstrably preventing age-related loss of hepatic sinusoidal fenestration through chronic treatment in young mice and reversing this via acute treatment in aged mice, as shown in LSECs (235). It could be hypothesized that the effect of metformin on LSECs may contribute to the beneficial outcomes of AMPK agonists for liver fibrosis treatment. *In vitro* studies reveal that metformin suppresses HepG2 cell proliferation by inducing cell cycle arrest at the G_0/G_1 phase, as evidenced by elevated KLF6/p21 protein levels and enhanced AMPK activation (236). This provides a basis for metformin's therapeutic potential in HCC. Corresponding clinical data reveal that prediagnostic metformin use markedly prolonged overall survival in older patients with HCC

and type 2 diabetes (237). However, while metformin regulates senescence, its broader effects against age-related pathologies likely involve both senescence-dependent and -independent mechanisms.

Sirtuin (SIRT) activators. SIRT1 expression declines with age, yet its increased expression attenuates cellular senescence and prolongs longevity across species. Resveratrol, a natural SIRT1 activator, exerts therapeutic effects against obesity, tumorigenesis and age-related organ dysfunction (238). As a senomorphic and antioxidant agent, resveratrol prevents cellular senescence by activating telomerase via the PI3K-Akt pathway (239). Additionally, it suppresses SASP factors by inhibiting NF-κB signaling while upregulating the anti-oxidant Nrf2 pathway. In inorganic mercury-induced liver fibrosis, resveratrol activates the SIRT1/PGC-1α pathway, alleviating oxidative stress and suppressing hepatic stellate cell activation (240). Across multiple human HCC cell lines, resveratrol inhibits viability, proliferation, invasion and migration in a time- and dose-dependent manner by activating p53 and suppressing the PI3K-Akt signaling (241,242). At high concentrations, however, resveratrol exerts pro-oxidant effects inducing growth arrest, senescence, or apoptosis (243). While resveratrol extends organismal lifespan, its murine effects are context-dependent, markedly prolonging survival in HFD models but not in standard-diet controls (244). Besides, the poor bioavailability and instability of resveratrol necessitate developing structurally distinct SIRT-activating compounds. SRT1720, which is 1,000-fold more potent than resveratrol, extends lifespan in HFD mice (22). It demonstrates therapeutic efficacy against both MAFLD and ALD, though its mechanisms remain incompletely characterized (245,246).

NAD^+, an upstream regulator of SIRT1, modulates both the SIRT1 and NF-κB pathways. These pathways antagonize each other in inflammatory and metabolic processes and critically regulate pathogenic mechanisms in MAFLD progression (247). The senomorphic NAD^+ precursor NAM improves metabolic function in ALD mice by inhibiting cellular senescence and suppressing SASP production, while reducing liver injury markers (193). Although NAM shows promising therapeutic potential, its adverse effect profile and optimal dosage require careful evaluation. Further trials are needed to establish safe regimens and assess long-term patient outcomes.

7. Conclusion and perspectives

The past decades have witnessed considerable advances in the fundamental role of cellular senescence in health and various illnesses (255). Accumulating evidence identifies cellular senescence as a primary driver of inflammatory liver diseases. Global laboratories and clinical translational investigators are exploring whether senescence-targeted interventions can delay or reverse cellular senescence to restore hepatic physiological homeostasis. As detailed in the present study, aging and SASP-mediated intrinsic hepatic cellular senescence are vital risk factor in the pathogenesis of chronic inflammatory liver diseases. Current understanding holds that inflammation-related triggers, including viral infection, alcohol and HFD, induce metabolic reprogramming, mitochondrial dysfunction, oxidative stress, loss of proteostasis and epigenetic changes, driving cellular senescence in endothelial and immune cells (256). Subsequently, senescence in these cells will promote senescence in adjacent normal cells via SASP secretion, disrupting the hepatic microenvironment, and inducing liver inflammation and tissue remodeling (257). This self-perpetuating pathological cycle accelerates progression to severe liver diseases (such as cirrhosis and HCC). Hence, anti-senescence strategies to curb this complex process may help prevent the onset and progression of chronic liver diseases.

At present, despite exponential growth in efforts to target senescent cells and SASP in normal physiological and disease-specific models, limitations remain, particularly regarding disease-specific effects and differential aging susceptibility among individual hepatic cell types. For instance, while the detrimental effects of hepatic senescence are well established, questions remain about how individual induced senescent cells drive distinct clinical outcomes and whether senescent cell clearance is feasible across all liver disease contexts. Thus, further research is warranted in linking the pathogenesis of different types of liver disease to specific senescence pathways, which could provide theoretical guidance for the precise design of antisenescence drugs. Additionally, senescence intervention data in liver disease remain largely preclinical (animal/*in vitro*), leaving a critical clinical trial gap; urgent trials are needed to assess targeted therapy efficacy and safety in patients and translate findings to practice. Notably, a number of senotherapeutics have only been tested at a single concentration in preclinical settings. Future preclinical and clinical investigations should focus on optimizing dose, administration route, and potential combination therapies to minimize adverse effects and improve treatment outcomes. Overall, advances in novel technologies are poised to drive progress in developing clinically viable therapies to prevent or mitigate cellular senescence.

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Authors' contributions

JZ provided supervision and guidance for this manuscript. YX performed literature collection, drafted the manuscript and prepared figures and tables. JZ supervised the project and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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