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Review

Cell Senescence and the Aging Liver

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Abstract

The liver has an enormous functional reserve, including a regenerative capacity that remains remarkable into old age, helping maintain liver function during physiological aging in the absence of specific disease processes. However, significant morphological and functional changes still occur in the aging liver, including the emergence and accumulation of senescent cells. While cell senescence is sometimes equated with aging at the cellular level, its precise role and significance in shaping the aged phenotype in tissues and the whole organism remain debated. Current evidence suggests that each cell type in the liver may contribute specifically to aging and age-associated morbidities. This review focuses on the "heterogeneity of senescence" and highlights the multifaceted role of cell senescence and its associated secretory patterns in aging. However, a better understanding of the complex interplay among cell types is essential for modulating the positive impact of senescence and delaying the emergence of age-associated changes.

Keywords: cell senescence; liver aging; hepatic regeneration; senescence-associated secretory phenotype (SASP)

Foreword

The term "senescence", from the Latin verb *senescere*, is etymologically linked to aging (the Senate is the council of the elders!), to the point that senescence is sometimes simply equated to aging at the cellular level. It would appear therefore naïve, if not trivial or even useless, to ask the question as to whether cell senescence has anything to do with the process of aging. And yet, the more we delve into the intricacies of either aging or cell senescence, the more it is apparent that both biological processes defy a simplistic and confining definition, making it difficult to establish clear-cut pathogenetic links. In this brief review, major biological changes associated with chronological aging in the liver will first be discussed, followed by a description of the occurrence of cell senescence in different cell types in the liver; finally, the possible role of these multifaceted phenotypes of cell senescence in liver physio-pathological processes associated with aging will be considered.

1. Changes Associated With Chronological Aging

1.1 Replicative/Regenerative Capacity

Albeit other solid organs are able to activate a regenerative response after partial surgical removal, including for example lung [1] and pancreas [2], the liver is exquisitely endowed with this property [3]. It should be emphasized that this is of paramount physiological relevance, in that the liver is by far more exposed than other organs to the risk of toxicity and cell loss due to its anatomical position and functional role as a check point between the myriads of food components absorbed by the intestine, including potential toxicants, and our systemic circulation. It is also noteworthy that such regenerative capacity is well maintained until late in life, although important changes do occur with aging, the most prominent being a lower rate of regeneration documented in both clinical and experimental settings [4,5]. This could be due to either a cell-intrinsic refractoriness to growth stimuli and/or to a decreased availability of one or more factors involved in the regenerative response. For example, using a well characterized model of hepatocyte transplantation, it was shown that aged hepatocytes display a cell-autonomous decrease in proliferative potential compared to younger counterparts [6]. Furthermore, clinical studies indicated that hepatocyte growth factor (HGF) and mesenchymal–epithelial transition factor (HGF receptor) (Met) expression were decreased, while p16 expression was increased, in older vs. younger individual undergoing partial hepatectomy, and this was associated with a significant delay in regeneration at 6 months post-surgery [4]. Consistent with these observations, a most recent study reported that DNA replication initiation dynamics were altered in aged hepatocytes *in vivo* following partial hepatectomy, with inefficient origin firing and activation of a stress/DNA damage response [7]. It was proposed that in cells with a low turnover rate such as hepatocytes, the age-related accumulation of DNA damage may not be phenotypically evident under resting conditions but expresses itself when DNA replication is triggered, resulting in cell cycle block and, possibly, cell senescence [7]. Adding to this complex issue, data obtained using retrospective radiocarbon (^{14}C) birth dating of cells indicated that human hepatocytes do undergo continuous and substantial turnover under physiological conditions, resulting in a liver composed of cells with an average lifespan of <3 years [8].

On the other hand, age-related changes in hepatocyte-extrinsic factors may also contribute to the decreased regenerative rate with age. For example, liver regeneration relies on angiocrine signals derived from sinusoidal endothelium [9] and the latter undergoes structural and functional modifications with aging, including increased thickness and decreased fenestration [10,11], which could translate into altered secretion of hepatotropic cytokines, as it was reported for HGF [4].

1.2 Ploidy

Polyploidy is a known feature of hepatocytes after post-natal development [12], reaching levels of nearly 50% in humans and above 90% in mice [13]. Other mammalian cells, including placental trophoblasts and megakaryocytes, are also polyploid, but in the latter cases this is associated with terminal differentiation. What is unique to hepatocytes is that they can divide, despite being polyploid, implying that multiple copies of the genome must be replicated to complete the cell cycle. It is noteworthy that an increase in polyploidy does not appear to alter the regenerative capacity or liver tissue fitness [14]. While its physiological significance is still debated [15], it was recently shown that polyploid cells are more tolerant to the presence of DNA damage and the induction of cell cycle arrest; in addition, they express lower levels of senescence-associated inflammatory cytokines [16]. Furthermore, polyploid nuclei exhibit more robust transcriptional networks and were more proficient in overcoming age-related genomic perturbations, via non-random allelic segregation to restore a wild-type genome [17]. Possibly related to this finding, old livers were reported to harbor broad heterochromatinization and transcriptional suppression; however, liver regeneration was able to reverse this pattern and rejuvenate multiple molecular and physiological aspects of the aged liver [18]. Additional studies also indicate that polyploidy represents a biological barrier towards the risk of neoplastic disease: increasing polyploidy slows hepatocarcinogenesis [14] while ploidy restriction facilitates chemically-induced neoplastic development [19], in spite of the fact that polyploidy is relatively common in cancer [20]. A slight, but steady increase in ploidy was reported in rat liver with aging, and this change was attenuated by caloric restriction [21]. Taken together, the accruing evidence supports the concept that polyploidy has evolved as an effective strategy to protect functional proficiency of the liver through restoration of a wild-type genome [17] and to reduce the risk of neoplastic disease [14,19], in the face a potentially high (geno)toxic burden related to its anatomical position and the associated metabolic role.

1.3 Liver Structure and Metabolic Activities

In a recent, very elegant study, aging-related changes were investigated in the liver of the primate cynomolgus monkey, as one of the best proxies to the human liver [22]. Young (4–6 years old) and aged (18–21 years old) individuals were compared. Relative size of the liver was decreased in the older cohort, while inflammatory infiltrates were more common and this was paralleled by increased collagen deposition (fibrosis) in the liver lobules; moreover, lipid accumulation was more prominent in old vs. young liver samples. Signs of augmented cellular senescence in aged livers included lipofuscin accumulation, a higher index of p-21 positive cells, increased expression of senescence-associated β-galactosidase (SA-βGal) and concomitant up-regulation of pro-inflammatory cytokines which are part of the senescence-associated secretory phenotype (SASP) [22].

It has been proposed that the liver might be resilient to the aging process, in that it can perform very efficiently until advanced age [23,24]. Nevertheless, distinct changes have been reported in the levels of RNA transcripts, protein translation and protein abundance between young and old livers. While the large majority (>90%) of genes and their products were stably detected until old age, about 5% of cytosolic proteins were differentially expressed in the liver of old (24 months) vs. young (6 months) rats [25]. Transcripts involved in processes such as apoptosis, cell migration, regulation of ion transport, inflammation/immune response were found to be upregulated with age, while those related to lipid biosynthesis and regulation of hormone levels were downregulated; at the protein level, those involved in cell redox homeostasis, tricarboxylic acid cycle and lipid catabolic processes, among others, were more abundant in aged livers, while other activities, including reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase, protein transporter and acetyltransferase, were decreased; these changes were mostly in the range of 2–3 and up to 7 fold between young and old livers [25].

Pomatto and Davies [26] have proposed that a defining metabolic attribute of aging is a decline in what they refer to as “adaptive homeostasis”, i.e., “the transient expansion or contraction of the homeostatic range for any given physiological parameter in response to exposure to sub-toxic, non-damaging, signaling molecules or events, or the removal or cessation of such molecules or events” [27]. Such a relative inability to adapt leads to a constant activation of stress response and this in turn reduces the basal homeostatic range of aged tissues [26]. For example, phase II detoxifying enzymes and the related transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) were upregulated in the liver of aged mice under baseline conditions; however, their ability to respond to environmental toxicants was greatly reduced compared to that observed in young control animals [28]. Such a “latent vulnerability” of the aged liver is in apparent contradiction with its remarkable resiliency, but it is explained, at least in part, by the reduced homeostatic range referred to above [29].

A related concept is that of metabolic flexibility, i.e., “the ability to respond or adapt to conditional changes

in metabolic demand" [30]. An important role in the metabolic flexibility of the liver has been attributed to O-GlcNAcylation processes, consisting in the attachment of a single N-acetylglucosamine (GlcNAc) to serine and threonine residues of target proteins, which is involved in the regulation of carbohydrates, fatty acids, amino acids and nucleotides metabolism [31]. For example, it was shown that O-GlcNAcylation of sirtuin 1 (SIRT1) is essential for liver metabolic flexibility and regulates glucose metabolism according to feeding/fasting cycles [32]. Disruption of this regulatory mechanism results in systemic insulin resistance, hyperglycemia, and hepatic inflammation, and it is also associated with aging [32].

1.4 Circadian Clocks

Another important facet of hepatic metabolic regulation relates to circadian clocks [33]. A large fraction (~40%) of the hepatic transcriptome exhibits 24-h rhythms, and this is paralleled by circadian changes in protein levels, posttranslational modification, and metabolic products [34]. While the circadian activity of the central clock (located in the suprachiasmatic nucleus of the hypothalamus) is dictated by the light/darkness cycle, the daily oscillations in liver metabolic activity are exquisitely sensitive to other, additional inputs, including, above all, those related to the quality, the quantity and the rhythms of food intake [35]. It has been reported that an intact hepatocyte insulin receptor is required to program the liver clock and the associated rhythmic gene expression [36]. A chronic misalignment between metabolic oscillations originating from the central clock and those generated from peripheral inputs (e.g., diet) is detrimental for overall health and increases the risk of age-associated diseases [37,38]. Of note, the number of genes displaying diurnal rhythmicity in their expression decreases with age and the amplitude of the oscillation also decreases [39].

It is apparent that adaptive homeostasis, metabolic flexibility and circadian modulation of gene expression are interrelated phenomena converging towards ensuring functional proficiency of the liver. Unsurprisingly, they are all negatively affected by age.

1.5 Clones of Aging in the Liver

About two decades ago we reported that normal isolated hepatocytes injected into the liver of either young or aged syngeneic rats formed larger clusters in older compared to younger hosts [40]. We concluded that the microenvironment of the aged liver is clonogenic and suggested that this could be related to the relative loss of proliferative potential of resident parenchymal cells associated with aging [40]. In more recent years, the emergence of clonal proliferations of altered cells has been described in several aged tissues, including liver (see: [41] for refs). Their functional significance is still being debated. It has been argued that they result from somatic mutations conferring increased proliferative fitness in a context of decreased functional proficiency [42]. Aging is associated with the accumulation of somatic mutations and other genetic alterations, and this is particularly evident in hepatocytes, where up to 3.3 times more mutations in aged vs. young individuals were reported. Moreover, these genetic alterations were more common in gene regulatory sequences [42]. It was suggested that such stochastic gene expression changes could account, at least in part, for the in age-related loss of organ function through an increase in transcriptional noise, a molecular phenotype which is common in cells from aged individuals [42]. Thus, a high burden of genetic changes could result in both a parenchymal microenvironment with a generalized decreased fitness (including proliferative fitness) and the emergence of rare hepatocytes endowed with specific alterations conferring a competitive clonal advantage [40,41].

1.6 Sexual Dimorphism and Liver Aging

Given the relevance of DNA methylation pattern as a marker of biological aging, a recent study explored how this pattern changes in aging male and female mice [43]. Although the epigenetic clock did not show any intersexual difference, 12 CpG sites across six genes displayed significant differences in methylation between male and female animals. Importantly, these differences were not apparent in young animals.

2. Cell Senescence in the Liver

The term cell senescence was initially introduced by Hayflick and Moorhead [44] to describe the irreversible cell cycle arrest experienced by primary fibroblasts cultured *in vitro*, after a discrete number of passages; in their words, "there does exist a finite limit to the cultivation period of diploid cell strains". Although the possible relevance of this finding to organismal aging was considered, the authors deemed it more appropriate to interpret the phenomenon at the cellular level [44].

Following the discovery of telomere shortening with age and the role of telomerase in countering this effect in the early 90's [45,46,47], the phenomenon of cell senescence found, after almost 3 decades, a satisfactory molecular explanation. However, the issue regained complexity as new research indicated that the phenotype of cell senescence was also associated with a diverse array of inciting stimuli or physio-pathological conditions, including DNA damage, oncogene activation, metabolic alterations, chronic disease processes or even early developmental phases [48]. Given this scenario, it also became apparent that the role and biological significance of cell senescence might well be different according to the tissue type and context in which it occurs (Fig. 1) [49].

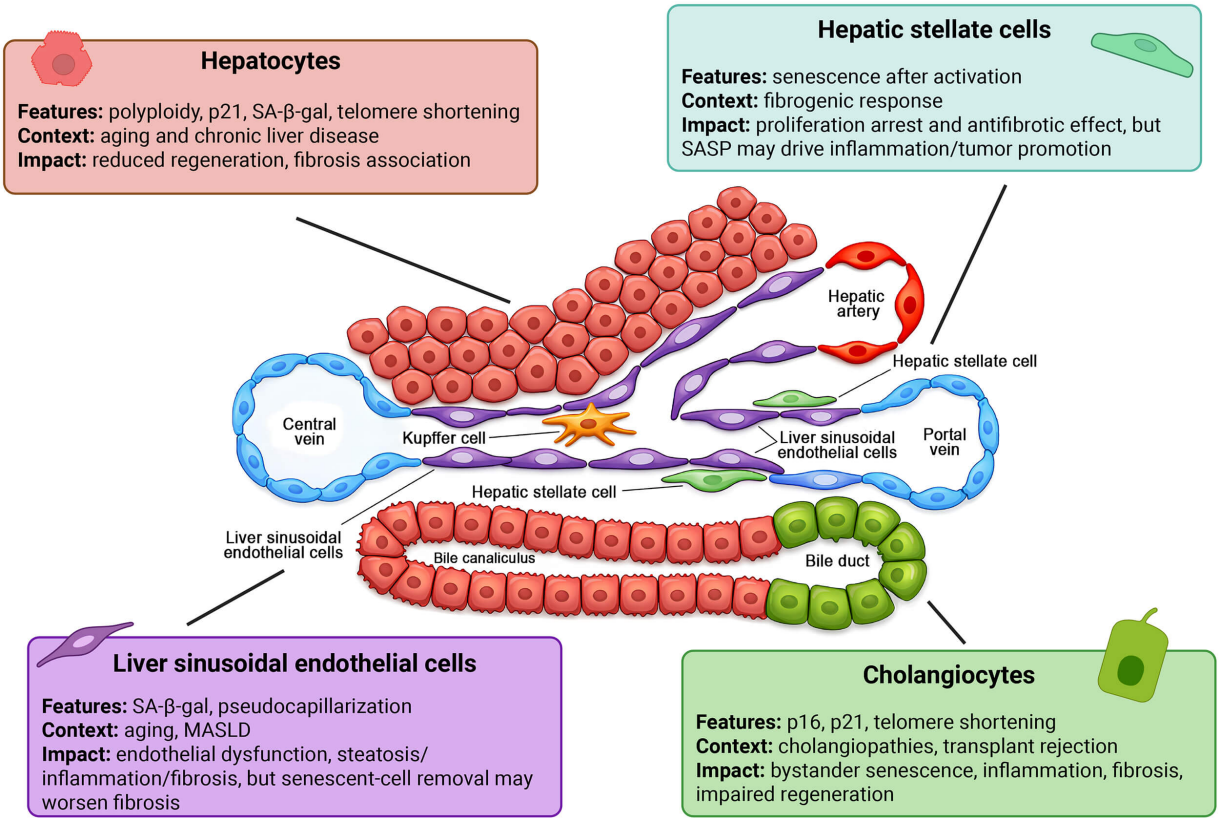

Fig. 1. Cell-type-specific features of senescence in the liver. Schematic overview of the main liver cell types (hepatocytes, cholangiocytes, hepatic stellate cells, and liver sinusoidal endothelial cells), highlighting their principal senescence-associated features, the contexts in which they arise, and their main functional consequences. SASP, senescence-associated secretory phenotype; MASLD, metabolic dysfunction–associated steatotic liver disease. Created in BioRender. Marongiu, F. (2026). https://BioRender.com/qb1re01.

2.1 Hepatocyte Senescence

A case in point in this regard is hepatocyte senescence. One of the first accounts of parenchymal cell senescence in the liver is that of Sigal et al. [50], who observed the accumulation of polyploid hepatocytes expressing the makers beta-galactosidase and p21 in normal rat liver following partial surgical hepatectomy. Interestingly, these changes were paralleled by a reduced proliferative capacity of hepatocytes, both *in vivo* and *in vitro* [50]. A few years later Wiemann et al. [51] described the presence of hepatocyte senescence as a general marker of human liver cirrhosis. Telomere shortening and increased expression of beta-galactosidase were specifically detected in hepatocytes and correlated with the degree of liver fibrosis, suggesting a direct pathogenetic link between the former and the latter [51]. Subsequent studies have supported this association. Thus, hepatocyte senescence was reported to correlate with progression of fibrosis both in alcohol-related [52] and in non-alcohol-related fatty liver disease [53] as well as in hereditary hemochromatosis [54]. In fact, it has been observed that accumulation of senescent hepatocytes appears to be a common characteristic of chronic liver disease irrespective of etiology [55].

Hepatocyte senescence also occurs during aging in the absence of evident signs of liver pathology. For example, the liver of untreated, 22-month-old mice exhibited up to 20% of hepatocytes expressing markers of cell senescence, while negligible levels were observed in young control animals [56]. In humans, senescence-related genes were overexpressed in the liver of elderly (age >65 years) compared to younger (<65 years) subjects undergoing hepatic resection for primary or metastatic cancer [4]. Whether this phenotype is attributable to aging per se or to any differential effects of the underlying pathologies on the older vs. younger livers was not clarified in those studies. Interestingly, repeated rounds of cell division, such as observed in serial transplantation studies involving rodent or human isolated hepatocytes, were shown to result in activation of telomerase, reversal of telomere shortening and attenuation of cell senescence [57]. This is in apparent contrast with the findings of Sigal et al. [50] referred to above, describing the increase in senescence markers in hepatocytes following cell proliferation elicited by partial hepatectomy. It is possible that the type of growth (e.g., compensatory vs. hyperplastic) or the rate of cell division might be important; however, the relevance of these observations to liver aging remains to be established.

2.2 Biliary Epithelial Cell Senescence

Expression of cell senescence markers in bile epithelium has been mostly associated with chronic disease processes involving the biliary tree and to liver allograft rejection. Sasaki et al. [58] proposed a possible link between the frequent occurrence of cell senescence and the ultimate loss of bile ductular epithelium during the evolution of primary biliary cirrhosis (PBC). The senescence phenotype of biliary cells included telomere shortening and increased expression of cell cycle negative regulators p16(INK4a) and p21(WAF1/Cip1) [59]. Mechanistic studies using a mouse model of biliary senescence, with conditional deletion of Mdm2 in bile ducts under the control of the Krt19 promoter, revealed a bystander effect on surrounding cholangiocytes and hepatocytes, which were also induced to express the senescence phenotype; furthermore, this caused recruitment of myofibroblasts and macrophages leading to transforming growth factor beta (TGF-β) production, fibrosis and impairment of liver regeneration [60]. In another report, induced pluripotent stem cells generated from individuals with primary sclerosing cholangitis (PSC) were shown to undergo cell senescence upon differentiation *in vitro* towards the biliary phenotype, and this was associated with secretion of proinflammatory cytokines and chemokines [61]. In fact, biliary senescence is also a phenotypic feature and has a role in the pathogenesis of liver fibrosis in Mdr2-/- mice, a model of human PSC [62].

Senescence of biliary epithelium is also an early event during chronic rejection of liver allografts, preceding loss of ductular cells [63]. In acute allograft rejection, expression of the senescence marker p21(WAF1/Cip) in biliary cells correlated with the intensity of T lymphocyte infiltration [64]. It was further observed that the frequency of biliary cell senescence increased with time post liver transplantation in subjects with signs of rejection, suggesting that the presence of this phenotype is a marker of poor prognosis for the survival of the transplant [65]. Most recent results have pointed to an important role of primary cilia in biliary cell proliferation: damage to these structures during the ischemic period before organ transplantation leads to cell senescence and impaired regeneration, thereby affecting the outcome of the transplant [66].

2.3 Stellate Cell Senescence

What is referred to as “activation” of hepatic stellate cells has long been associated with the pathogenesis of liver fibrosis [67]. The term “activation” includes increased proliferation, acquisition of a myofibroblast phenotype and deposition of extracellular matrix components [68]. Inhibition of stellate cell proliferation limits liver fibrosis [69] and spontaneous resolution of fibrosis in experimental models has been related to apoptosis of the same cells [70]. Based on these findings, it might not surprise that stellate cell senescence has also been linked to antifibrotic effects in the liver [71]. However, the senescence phenotype in these cells is a classic example of a two-edged sword. On one hand it halts cell division, thereby limiting accumulation of stellate cells; on the other, it promotes secretion of an array of cytokines (including pro-inflammatory interleukins) and growth factors that can profoundly affect cell behaviour along different paths in the surrounding tissue. For example, the secretory phenotype of senescent stellate cells, induced by an increase in the enterohepatic circulation of deoxycholic acid, comprises inflammatory and tumour-promoting factors that were suggested to contribute to the development of hepatocellular carcinoma in both experimental animals and in humans [72]. Given the pleiotropic effects of such senescence-associated secretory phenotype, the exact role of stellate cell senescence in liver fibrosis needs further consideration [73].

2.4 Liver Sinusoidal Endothelial Cell Senescence

Liver sinusoidal endothelial cells (LSECs) play a central role in clearing microbial-derived particles (including lipopolysaccharide [LPS]) and macromolecular debris from portal blood and in the uptake of oxidized lipoproteins [11]. With age, sinusoids undergo profound alterations referred to as pseudo-capillarization, with a decrease in fenestration, establishment of a basement membrane and a space of Disse, which in turn affects hepatocyte function [74,75]. The end stage of this process is the emergence of sinusoidal cell senescence: it was reported that greater than 50% of LSECs express the SA-β-gal senescence marker in 2-years old mice, compared to <1% in young controls [76]. However, removal of senescent LSECs resulted in accelerated liver fibrosis and an overall worsening of health conditions in rodents [76]. Importantly, age-associated dysfunction of the sinusoidal endothelium has been attributed a pathogenetic role during progression of metabolic dysfunction–associated steatotic liver disease (MASLD): specifically, it was found that LSEC senescence hampered the protective effect of endothelial cells against hepatocyte steatosis and the ensuing inflammation and fibrosis [77]. *In vitro* studies revealed that the senescence phenotype of LSECs is critically dependent of the presence of the protein p19ARF: while liver endothelial cells from WT mice rapidly undergo stress-induced senescence within a few days post-isolation, those derived from p19ARF-/- mice survive for at least 50 population doublings [78]. More recently, expression levels of the senescence marker P16Ink4a were suggested to regulate LSEC function: low levels of P16Ink4a were associated with generation of reactive oxygen species (ROS) and an increase endothelial permeability, while P16Ink4a overexpression was related to DNA damage and led to decreased proliferation and cell senescence [79].

2.5 Liver Immunosenescence

The immunological landscape of the aged liver undergoes a process of “adaptive homeostasis” such as that proposed by Davies [27], characterized by upregulation of

inflammatory immune pathways and pro-inflammatory cytokines on one hand, while on the other hand T and B lymphocytes and natural killer cells progressively accumulate exhausted or senescent phenotypes [80]. This results in the inability to remove various types of senescent cells, igniting a vicious circle whereby SASP products further increase age-associated sterile inflammation, which in turn exacerbates exhaustion and senescence of immune cells [81]. Increased generation of reactive oxygen species by dysfunctional mitochondria can also contribute to this cycle, by both inducing cell senescence and fueling cell damage and inflammation [81].

3. Cell Senescence in Liver Pathophysiology

3.1 Chronic Liver Disease

As already mentioned, the available evidence has led to the conclusion that cell senescence represents a constant feature of chronic disease states in the liver, irrespective of etiology [82]. This conclusion carries the obvious implication that the senescence phenotype may play a role in the onset and/or long-term evolution of liver pathologies.

However, dissecting this putative role has revealed very complex in that different cell types appear to exert different and even contrasting effects on chronic disease processes, as mentioned above. Overall, senescence in hepatocytes and/or biliary epithelium is positively associated with steatosis and progression of fibrosis, while the opposite is generally true when the senescence phenotype is expressed by stellate cells and LSEC (Fig. 2) [83]. This dichotomy is exemplified by the results of a study conducted in a mouse model of cholestatic liver injury, in which a decrease in liver fibrosis coincided with differential changes in cell senescence between cholangiocytes and stellate cells: lower levels were observed in the former cell type while higher levels of senescence were present in the latter [84].

Hepatocyte senescence was in fact proposed as a direct driver of aging- and obesity-related liver steatosis [85]. In fact, targeted elimination of p16-expressing cells decreased the level of steatosis in aging mice while administration of senolytics dasatinib+quercetin reduced fatty liver in genetically obese animals; furthermore, hepatocyte-specific inactivation of the DNA repair gene Xpg induced both cell senescence markers and fat accumulation in the liver [86].

On the other hand, several reports have described a positive association between levels of cell senescence in hepatocytes and rate of progression in chronic liver disease, as already mentioned [52,53,54,55]. More to the point, factors secreted by senescent HepG2 human hepatocytes were able to induce the expression of inflammatory and fibrogenic genes in cultured hepatic stellate cells [87], suggesting the conclusion that such factors are directly involved in the pathogenesis of liver fibrosis. Recently, the senescence-associated secretome of Hedgehog-deficient mouse hepatocytes was found to drive MASLD [88]; moreover, a specific senescent hepatocyte gene signature, originating from p21-expessing cells, was identified in both mouse and human liver with MASLD, which correlated with disease progression [89]. These results would further suggest that hepatocyte senescence could inevitably lead to liver fibrosis. However, caution should be used in reaching this conclusion given the heterogeneity of the senescence phenotype [89]. For example, no prominent fibrosis was observed in rat liver exposed to retrorsine, a pyrrolizidine alkaloid, despite the extensive presence of senescent hepatocytes [90].

By contrast, the overwhelming evidence indicates that senescence of liver stellate cells counters fibrosis and its evolution towards cirrhosis [91]. Considering the key role of these cells, in their activated phenotype, in secreting major components of the extracellular matrix, the above findings make plain biological sense: in a state of senescence, they are unable to divide and no longer contribute to matrix deposition [92]. On the other hand, the issue has been raised on the possible role of their senescence-associated secretory pattern in fuelling inflammation and other disease processes, including cancer development [92,93,94]. Thus, it was reported that the obesity-induced increase in the enterohepatic circulation of deoxycholic acid leads to hepatic stellate cells senescence and the release of tumour-promoting factors [72]. Similar findings were obtained in mice with hepatocyte-specific loss of the gluconeogenic enzyme fructose 1,6-bisphosphatase 1: the ensuing alteration in liver metabolic homeostasis and lead to senescence of hepatic stellate cells, which in turn fuelled cancer development through secretory factors [95].

3.2 Cell Senescence and Liver Repopulation

Liver repopulation by transplanted hepatocytes is achieved when normal isolated cells are infused into a host animal whose endogenous parenchymal cells have an intrinsic proliferative hindrance and/or increased susceptibility to cell loss [96]. Interestingly, it was found that experimental conditions sustaining liver repopulation are often associated with the presence of extensive hepatocyte senescence [90,97,98]. Based on these findings, it was suggested that the secretory pattern of senescent hepatocytes, including IL-6, a known cytokine involved in liver regeneration and repair, plays a direct role in driving proliferation of transplanted cells [90,97]. A quantitative dimension in the relationship between cell senescence and liver repopulation was recently introduced by Gadd et al. [99]. While it is true that inhibition of host hepatocyte proliferation is a requirement for donor hepatocyte engraftment, as reported above, their results suggested that excessive senescence of resident cells limits repopulation by transplanted hepatocytes, possibly due to paracrine transmission of the senescence phenotype from the former to the latter cells [99]. These new findings add further complexity to the fascinating phenomenon of liver repopulation through cell transplantation.

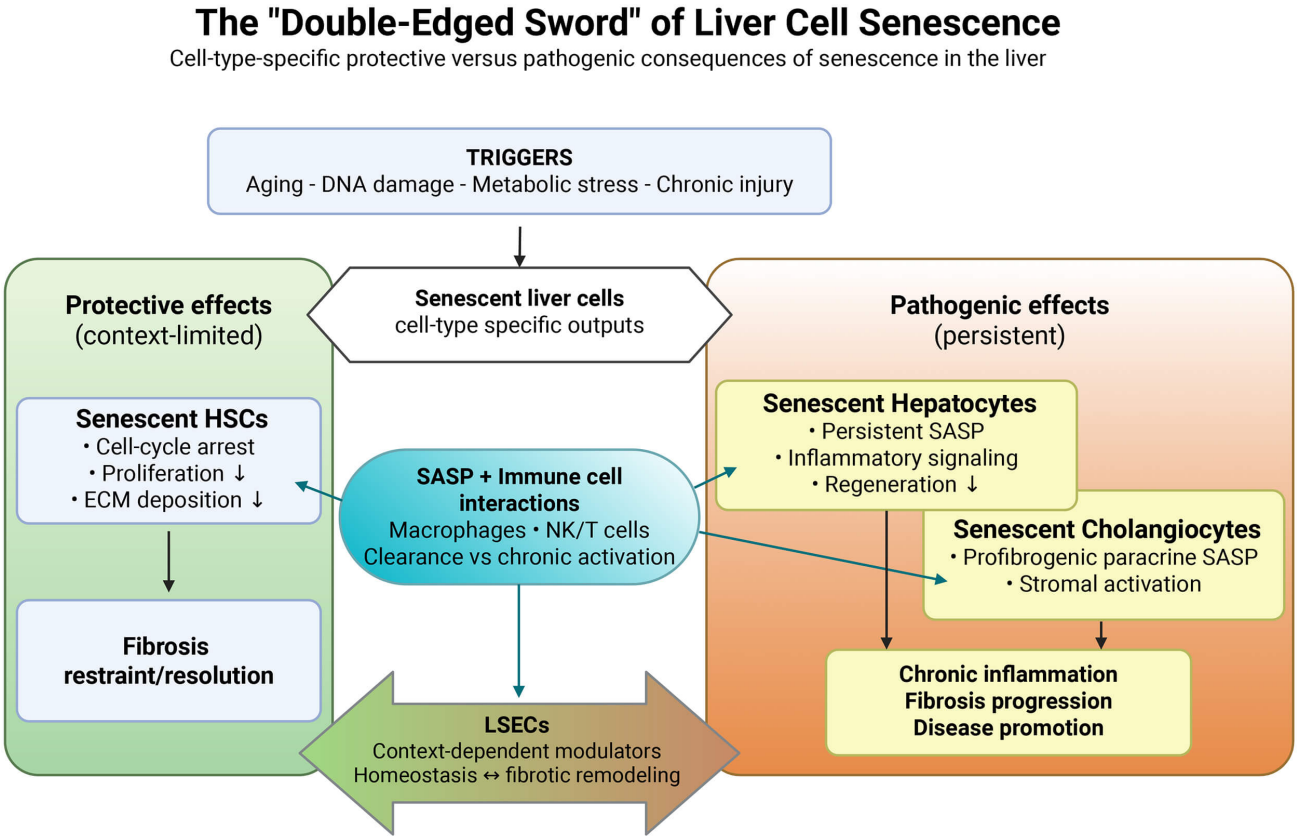

Fig. 2. The double-edged sword of liver cell senescence in pathophysiology. Senescence can exert beneficial or deleterious effects depending on the cell type involved and the surrounding context, including fibrosis restraint on one hand and chronic inflammation, fibrogenesis, and disease progression on the other. HSCs, hepatic stellate cells; ECM, extracellular matrix; LSEC, liver sinusoidal endothelial cell. Created in BioRender. Marongiu, F. (2026) https://BioRender.com/orilxd6.

3.3 Cell Senescence in Liver Neoplasia

Almost 2 decades ago, we called attention to intriguing similarities existing between the clonal expansion of normal transplanted hepatocytes in the setting of liver repopulation and the clonal/focal growth of preneoplastic hepatocytes during early phases of carcinogenesis [100]. Specifically, it emerged that experimental conditions that favour liver repopulation by transplanted normal cells were also associated with an increased risk of neoplastic disease in the liver [96]. Moreover, we observed that pre-neoplastic hepatocytes could also proliferate and form hepatic nodules upon transplantation into a host tissue environment pre-conditioned for liver repopulation [101]. Given these analogies, it was proposed that biological driving forces fuelling liver repopulation by normal transplanted hepatocytes could also be exploited by endogenous altered/pre-neoplastic cells to grow and progress towards overt neoplastic disease [100]. Cell senescence is a likely contributing factor in this regard.

As for other chronic disease states, the relationship between cell senescence and liver cancer development is indeed complex. The initial interpretation of cell senescence as a protective barrier on the path to neoplasia in cells harbouring DNA lesions is clearly an oversimplification [102]. In fact, several reports have documented the enhancing effect of cell senescence on promotion/progression of hepatocellular carcinoma, via secretion of SASP factors [103]. Furthermore, the phenotype of senescent cells associated with metabolic dysfunction–associated steatohepatitis (MASH) could be reversed by activation of protein kinase B (AKT) and NRF2, which in turn accelerated the degradation of p53 and the enzyme fructose-1,6-bisphosphatase 1 (FBP1) [104]. Such NRF2-FBP1-AKT-p53 metabolic switch sustained proliferation of previously senescent hepatocytes and favoured accumulation of additional DNA damage in these cells, thereby fostering their progression to hepatocellular carcinoma (HCC) [104]. Along these lines, a recent study has attempted to relate the extent of oncogene expression in single hepatocytes to their resulting phenotype. It was reported that cells expressing high levels of rat sarcoma (RAS) became senescent (via oncogene-induced senescence) and were cleared by the immune system, while lower levels of RAS expression rendered cells immune resistant and were associated with increased risk of neoplastic development [105]. These findings shed light on quantitative aspects regulating the

phenotype of senescent cells, illustrating both its plasticity and its potentially reversible nature.

3.4 Cell Senescence and the Phenotype of the Aging Liver

Does cell senescence contribute to phenotypic changes occurring in the aging liver in the absence of obvious concomitant pathological processes? Answering this question is complicated by at least two issues: "pure" aging is not easy to define and/or identify and, secondly, any direct role of cell senescence in such a slowly evolving process has revealed difficult to assess [106].

The best evidence implying a direct role for cell senescence in aging has been obtained from investigations involving transplantation of senescent cells and/or their selective removal through senolytic approaches. In a landmark study, it was observed that transplantation of a relatively low number of *in vitro*-generated senescent preadipocytes resulted in persistent physical dysfunction, accelerated aging and reduced health-span and lifespan in mice; furthermore, administration of senolytics dasatinib+quercetin to either senescent cell-transplanted young mice or mice undergoing natural aging was able to reduce the risk of mortality by 35% [107]. More recently, transplantation of senescent fibroblasts into dermal skin were reported to induce both local and systemic detrimental effects, including impaired musculoskeletal function and cognitive decline [108]. However, no liver specific effects were mentioned in either study. Using a different approach, involving specific targeting of glutaminase, whose enzyme activity revealed critical to stabilize the senescent phenotype, Johmura et al. [109] reported both elimination of senescent cells and functional improvement in different tissues of aged mice, including liver. A general strategy for selective deletion of senescent cells was subsequently proposed by Shi et al. [110], who described the use of a photosensitive senolytic prodrug (KSL0608-Se), which is a specific substrate for SA-β-gal and can generate oxidative species in the target cell expressing the enzyme. Studies on cell culture mixtures comprising normal and senescent cells confirmed the ability of the drug to selectively kill the latter cell type, following exposure to light [110]. Moreover, when this strategy was extended to a whole animal system, it resulted in a decreased expression of senescence cell markers and improved functional proficiency in both kidney and liver of aged mice, suggesting a generalized beneficial effect on the evolution of the aging phenotype *in vivo* [111]. Additional approaches based on the use of senolytics have recently been developed (see [82] for refs). However, a word of caution should be used on the possible translational relevance of these findings, given the complex interplay of different senescent cell types in shaping the microenvironmental landscape of the aging and/or diseased liver.

4. Conclusions

The accruing evidence indicates that both aging and cell senescence are complex and distinct biological processes which result from several different inciting stimuli. However, it is also clear that changes occurring at single cell level, corresponding to features associated with the senescence phenotype, can impact tissue physiology and function and ultimately the rate of aging at organismal level. A better understanding of these effects may help develop effective approaches to positively modulate the cross talk between cell senescence and the aging process.

Abbreviations

HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; LPS, lipopolysaccharide; LSEC, liver sinusoidal endothelial cell; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; Met, mesenchymal–epithelial transition factor (HGF receptor); PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; ROS, reactive oxygen species; SA-βGal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype.

Author Contributions

RP, EL and FM contributed to the conception and design of the review, literature search and selection, and interpretation and synthesis of the relevant literature. All authors contributed to drafting and critically revising the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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