Liver Regeneration: Changes in Oxidative Stress, Immune System, Cytokines, and Epigenetic Modifications Associated with Aging

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The regenerative capacity of the liver decreases with increase in age. In recent years, studies in mice have found that the regenerative capacity of the liver is associated with changes in the immune system of the liver, cytokines in the body, aging-related epigenetic modifications in the cell, and intracellular signaling pathways. In the immune system of the aging liver, monocytes and macrophages play an important role in tissue repair. During tissue repair, monocytes and macrophages undergo a series of functional and phenotypic changes to initiate and maintain tissue repair. Studies have discovered that knocking out macrophages in the liver during the repair phase results in significant impairment of liver regeneration. Furthermore, as the body ages, the secretion and function of cytokines undergo a series of changes. For example, the levels of interleukin-6, transforming growth factor-alpha, hepatocyte growth factor, and vascular endothelial growth factor undergo changes that alter hepatocyte regulation, thereby affecting its proliferation. In addition, body aging is accompanied by cellular aging, which leads to changes in gene expression and epigenetic modifications. Additionally, this in turn causes alterations in cell function, morphology, and division and affects the regenerative capacity of the liver. As the body ages, the activity of associated functional proteins, such as CCAAT-enhancer-binding proteins, p53, and switch/sucrose nonfermentable complex, changes in the liver, leading to alterations in several signaling pathways, such as the Hippo, PI3K-Akt, mTOR, and STAT3 pathways. Therefore, in recent years, research on aging and liver regeneration has primarily focused on the immune system, signaling pathways, epigenetic changes of senescent cells, and cytokine secretion in the liver. Hence, this review details the roles of these influencing factors in liver regeneration and impact of aging-related factors.
1. Introduction

Liver cells are capable of rapid regeneration and repair. When partial liver resection or liver cell necrosis occurs, the remaining liver cells are regenerated and repaired, restoring not only normal liver function but also normal liver weight and volume. The regeneration of the liver is strictly regulated, with hepatocyte proliferation ceasing once the liver/body weight ratio returns to normal [1, 2]. Adult hepatocytes can reenter the cell cycle quickly after partial liver resection, but they proliferate at a low rate for homeostasis. The replacement rate of hepatocytes is relatively low during homeostasis, with only approximately 20% replaced within a year [3]. The 2/3 heptectomy in a mouse model developed by Higgins and Rogers in 1931 is considered the best model for liver regeneration. When 2/3 of the liver is resected, the remaining hepatocytes transition from the G0 to G1 phase and rapidly reenter the cell cycle, restoring the liver to its normal weight [4]. When this ratio is reached, the associated signaling molecules and pathway activity change to regulate normal liver function. The loss of this regulatory ability leads to abnormal proliferation and cancer development [5]. However, the molecular mechanism of this cell cycle transition is still unknown.

Recently, liver regeneration divided into three basic processes: (a) preparation for liver regeneration that involves the secretion of cytokines and growth factors, which activate the associated signaling pathways and change cell activity; (b) liver recovery, which initiates after signaling pathway activation, the cell cycle of quiescent hepatocytes changes, and hepatocytes initiate proliferation to repopulate the damaged liver; and (c) termination of liver regeneration, which includes the termination of hepatocyte proliferation by regulating signaling pathways after the liver/body weight ratio returns to the original level [6].

As the body ages, changes in several mechanisms of the body occur in varying degrees, which affect the liver’s regeneration capacity. Most recent studies are based on studying such changes to observe their effects on the mechanisms of liver regeneration. The body’s immune system, metabolic system, cell contents, cell microenvironment, and gene expression change as the body ages. However, to date, there is still no clear evidence that fully explains the decline of liver regeneration capacity with aging.

2. The Oxidative Stress and Regeneration of the Aging Liver

ROS are generated in response to tissue injury, and their induction is required for tissue regeneration. Oxidative stress is a complex defense mechanism that involves multiple signaling pathways and related proteins. The intracellular redox state is closely related to the signal transduction pathways involved in cell apoptosis, proliferation, and differentiation [7]. Nuclear factor E2-related factor 2 (NF-E2-related factor 2, Nrf2) is an intracellular transcription factor that is highly sensitive to oxidative stress, mainly in metabolic organs, such as the liver [8]. It was discovered that after partial hepatectomy (PH) in mice, large amounts of ROS were produced in the liver, causing oxidative stress. Compared with the control group, after PH, the liver regeneration of Nrf2 knockout mice was significantly delayed, the rate of hepatocyte apoptosis was doubled, and mitogen-activated protein kinase signaling was transduced in the regenerated liver. The signal transduction of phosphatidylinositol 3-kinase/protein kinase B (PI3K)/protein kinase B (PI3K/Akt) was attenuated, and the number of regenerated hepatocytes was significantly reduced at 60 h after PH [9, 10]. The expression of genes that are closely related to function was downregulated. These results suggest that Nrf2 plays an important role in the regeneration of liver tissue repair.

Nuclear factor κB (NF-κB) is an important transcription factor that helps the body maintain redox balance [11]. Under normal conditions, inactive NF-κB is mainly composed of p50 and p65 subunits, as well as the inhibitor of NF-κB (IκB), which is bound in the cytoplasm. NF-κB can be activated by a variety of stimuli, and the IκB kinases (IκB kinase a and IκB kinase b) promote the phosphorylation and degradation of IκB, resulting in the separation of IκB from NF-κB. The activated NF-κB is then transferred from the cytoplasm to the nucleus, where it participates in cell proliferation and survival, allowing the body to function normally. NF-κB regulates liver regeneration by upregulating the expression of interleukin 6 (IL-6) and hepatocyte growth factors (HGF) [12, 13]. NF-κB activation is one of the earliest responses detected at the onset of liver regeneration after liver injury or PH, suggesting that NF-κB is a key factor capable of preventing apoptosis and regulating hepatic cell cycle progression during liver regeneration (Figure 1).

The PI3K/Akt pathway is associated with physiological processes, such as cell antiapoptosis, antioxidation, and protein synthesis. The PI3K/Akt pathway plays an important role in the regenerative activity of the liver, and Akt inactivation can lead to the inhibition of hepatocyte proliferation after PH [14]. Jackson et al. found that PI3K was activated as soon as PH was performed [15]. The use of PI3K inhibitors or selective inhibition of P3K subunits using siRNA technology was found to significantly reduce liver regeneration. The inhibition of PI3K resulted not only in a reduction of Kupffer cells and macrophages in the regenerating liver but also in secretory dysfunction of Kupffer cells and macrophages, resulting in decreased cytokine production and a decreased hepatocyte proliferation rate. This result suggests that activation of the PI3K/Akt pathway plays a critical role in the early stages of liver regeneration after PH.

3. The Immune System and Regeneration of the Aging Liver

In recent years, increasing evidences have shown that the liver is a metabolic organ and an “immune system organ” [16]. Most of the cells in the liver are hepatocytes, accounting for about 78%–80% of the total liver tissue, whereas the nonparenchymal cells only account for 5%–6% of the total liver tissue [17–21]; and the remaining 14%–17% of the liver tissue comprise the cellular components in the extracellular space [17]. The nonparenchymal cells are of various types, such as Kupffer cells, lymphocytes,
cholangiocytes, endothelial cells, and stellate cells [22]. Endig et al. reported that lymphocytes have significant effects on liver injury and cancer but can also protect mice from acute injury caused by chronic liver failure and support proliferation of hepatic progenitor cells during chronic liver injury. These findings highlight the body’s immune system to be tightly and specifically regulated to balance its immune surveillance and reduce the risk of cancer. More importantly, the inhibition of lymphotoxin-β receptor signaling may be an interesting approach to prevent tumor development in patients with chronic liver disease with high levels of lymphotoxin-beta [23]. Various lymphocytes in the liver play different roles in liver regeneration. In 2006, Castellana et al. found that interstitial Langerhans-type dendritic cells are essential in regulating local immunity during liver regeneration, proposing that this phenomenon may be associated with the regulation of estrogen-mediated immunity and hepatocyte proliferation. Recent studies have demonstrated the existence of a large number of natural killer (NK) cells in the liver and found that liver-resident NK (LrNK) cells inhibit T cell function in the liver during viral infection through the programmed cell death protein 1–programmed death-ligand 1 interaction. The results also revealed that LrNK cells play a significant regulatory role in liver injury [24]. As aging progresses, the immune system of the liver further changes, exhibiting distinct inflammation. Simultaneously, immune cell infiltration is increased [25], which increases the number of lymphocytes, resulting in an increased expression of the proinflammatory cytokines, including interferon-gamma (IFN-γ), interleukin-beta (IL-β), IL-6, tumor necrosis factor-alpha (TNF-α), and IL-2, and the anti-inflammatory cytokines, which include transforming growth factor-beta (TGF-β) and IL-10 [26–29] (Figure 2). Singh et al. found that the elevated levels of IFN-γ in the aging liver lead to phosphorylation of STAT1 (an H3 deacetylase that upregulates the postoperative levels of glucose (Glu) and triglycerides (TG), which play an essential role in liver regeneration), which activates p21 protein that inhibits cyclin-dependent kinases (CDKs), thereby inhibiting cell cycle progression [30]. In addition, it was found that liver inflammation became more severe as aging progressed. These results indicate that cytokines play an essential role in regulating liver aging via regulatory proteins. In recent years, it has been reported that IL-6 and TGF-β have positive regulatory effects on the in vitro growth and regeneration of hepatocytes [31–33], although attributed to the excessive inflammatory response in vivo, resulting in a decreased liver regeneration capacity [34].

4. Metabolism and Regeneration in the Aging Liver

Liver regeneration largely depends on the energy required to regenerate the hepatic lobules [6]. However, aging is often accompanied by changes in metabolism. Cholesterol accumulation, glycogen storage disorders, and disruption of ketone body synthesis, accompanied by the downregulation of adenosine triphosphate (ATP) and upregulation of adenosine diphosphate and reactive oxygen species, occur in the aging liver [35]. Kachaylo et al. demonstrated transient

![Diagram](Figure 1: The diagram of ROS and its related pathway in liver regeneration.)
regeneration-associated steatosis (TRAS) during liver regeneration and found this to be indispensable for liver repair [3, 36]. Lipid synthesis is a critical process in the early stages of liver regeneration. Kachaylo et al. demonstrated that the downregulation of phosphatase and tensin homolog promotes the degradation of TRAS-derived lipids, thereby enhancing the regenerative capacity of the liver [37]. If the production of these lipids is disturbed, the regenerative ability of the liver becomes significantly impaired [3, 36]. Mastrodonato et al. and Fernandez-Rojo et al. showed that the specific knockout of caveolin-1 protein expression (which affects lipid accumulation and is important for maintenance of glucose homeostasis) results in a significantly impaired liver regeneration and repair in mice [38, 39]. Furthermore, SIRT1 is critical for controlling cellular metabolism since it facilitates catalytic processes that restore cellular energy homeostasis in conditions with low energy availability (low ATP) [40, 41]. However, SIRT1 overexpression has adverse effects on liver regeneration, manifesting as poor survival and impaired proliferation after hepatectomy. Interestingly, a recent study by Jin et al. showed that decreased expression of SIRT1 in aging mice was associated with impaired liver regeneration (Figure 3). Additional SIRT1 protein injections to normalize their in vivo levels significantly upregulated the regenerative capacity of aging mice, indicating that restoring normal metabolic processes in aging mice could improve their regenerative capacity [42]. Although liver metabolism still changes with aging, restoring this disordered metabolic phenomenon to normal can significantly improve the poor regeneration of the aging liver [35, 42].

5. Gene Expression and Regeneration in the Aging Liver

Along with the growth and development of the liver, gene expression in hepatocytes is constantly changing [43]. Elias et al. analyzed the RNA transcriptomes of livers from 5-, 24-, and 36-month-old mice and found 56 miRNAs whose expression profiles changed with age. These included a cluster of 18 miRNAs that were upregulated 50 and 1,000 folds at 24 and 36 months of age, respectively [44]. In addition, senescent cells express p16Ink4a, a CDK inhibitor and tumor suppressor. This pathway leads to impaired cellular regeneration in senescent organisms and may be a hallmark of senescence [45]. Aging is associated with replicative senescence, and p16 levels increase with the aging of most mammalian tissues. However, p16 expression is increased after hepatectomy in mouse models, and the expression of downstream molecular target cyclin D1 decreased, suggesting that the mechanism of hepatocyte cell cycle declines gradually with age, followed by cell cycle arrest [46]. Both hepatocyte growth factor and receptor tyrosine-protein kinase MET (cMET) are essential for liver regeneration [47]. In a mouse model of partial liver resection, HGF and cMET expression were downregulated in aging mice [48], suggesting that a decreased expression of HGF and cMET is one of the mechanisms of impaired liver regeneration in aging mice. Cell aging is often accompanied by changes in the chromosomal structure, increased complexity of cellular contents, DNA damage, inhibition of CDK activity, and increased autophagy [49]. Some genes originally located in the heterochromatin regions expressed and regulated the progression of cell cycle after contact with the inhibited state during aging. For example, the members of the miR-465 family are present in a low expression state in young mice but begin transitioning to a high expression state with age. Elias et al. transfected the hepatocyte cell line AML12 with the miR-465 family members, showing a 40% reduction in the mRNA levels of growth hormone receptors and a 25% reduction in Kit1 and PPP2R3C [44]. The result confirms that the miR-465 family members are continuously upregulated with aging and attenuate the expression of related...
genes in the glucocorticoid signaling pathway, thereby affecting the corresponding signaling pathways and further affecting the liver regeneration capacity. Recent studies showed that miRNAs are closely associated with liver regeneration. Most miRNAs play a regulatory role, and Kren et al. revealed the role of miRNAs in the regulation of c-Myc and p53, which leads to changes in gene expression during liver regeneration [50]; an increasing number of miRNAs have been found that regulate liver regeneration, including miR-21 and miR-34 [51, 52]. Raschzok et al. studied the expression of 323 miRNAs after hepatectomy and found that the expression levels of 29 miRNAs were significantly changed [53]. Among these, seven miRNAs (miR-33, miR-153, miR-298, miR-301b, miR-489, miR-743b, and miR-883) were upregulated but did not attain a peak until 24 h after resection, which is consistent with DNA replication. The result showed that these seven miRNAs play an essential role primarily during the G1/S phase in the early stage of liver regeneration (Table 1). Further studies by Raschzok et al. found that the target genes of these miRNAs are CDK6, RAP2A, TNF, CCND1, and MAP3K1. Some genes are also involved in regulating the signaling pathways that affect liver regeneration. For example, Castro et al. found that miR-19a, miR-21, and miR-214 regulate the phosphatase and tensin homolog (a negative regulator of the phosphatidylinositol 3-kinase (PI3K)–protein kinase B (Akt) survival pathway) [54] (Figure 4). Due to changes in chromatin structure caused by cellular aging, the expression of intracellular genes becomes more complex. Hence, several studies have found that miRNAs expressed during aging play major roles in regulating the regenerative capacity of the aging liver. Pibiri et al. studied the RNA levels of mice at different time intervals after liver resection. They reported that the gene expression levels of aging mice were significantly different from those of young mice. Furthermore, the time of expression of some growth factors and cytokines was delayed in aging mice than in young mice [55]. In addition, recent studies revealed that the changes in epigenetic modifications in senescent cells could regulate hepatocyte proliferation as aging progressed, which may explain the decreased regenerative capacity of the aging liver. Sen et al. found through high-throughput screening that the histone acetyltransferase p300 is a key protein that regulates aging, induces the formation of new super-enhancers, and promotes the expression of aging-related genes [56]. By knocking out the p300 gene, they found that cell aging was delayed and replicative senescence was alleviated, suggesting the use of p300 as a potential target for treating aging-related lesions. DNA methylation plays an extremely important role in gene expression and silencing, including the degree of DNA methylation, which
changes with age. Age-induced changes in methylation can lead to several aging-related diseases [57]. Kaji et al. found that knocking out the expression of DNA methyltransferase results in severe DNA damage, cell cycle arrest, senescence, and cell death. They also found that such defective or down-regulated DNA methyltransferase expression impaired liver regeneration capacity [58]. Varela-Rey et al. showed that glycine-N-methyltransferase (GNMT) knockout impaired

**Table 1:** Significantly regulated miRNAs during HSC activation. References upregulated.

| References          | Up-regulated               | Down-regulated               |
|---------------------|----------------------------|------------------------------|
| Guo et al. 2009b [93] | miR–29c, –138, –140, –143, –193, –207, –325–5p, –328, –349, –501, –872, –874 | miR–15, –16, –20b–3p, –92b, –122, –126, –146a, –341, –375 |
| Ji et al. 2009 [94]  | miR-27a, –27b, –30a, –30c, –30d, –130a, –130b, –450, –455 | miR-9, –19b, –301, –520b, –520c, –721 |
| Maubach et al. 2011 [95] | Let-7b, –7c, –7e, miR-125b, –21, –22, –31, –132, –143, –145, –152, –199a, –210, –214, –221, –222 | Let-7i, miR–10a, –16, –26b, –29a, –30a–5p, –30b, –30c, –30d, –99a, –122a, –125a, –126, –146a, –150, –151, –181a, –192, –194, –195, –207, –296, –335, –422b, –483 |
| Chen et al. 2011 [96] | miR-31, –34b, –34c, –125b–5p, –143, –145, –152, –199a, –5p, –349, –350, –365, –378, –450a, –497, –877 | miR-10a–5p, –101a, –126, –139–5p, –150, –192, –195, –335, –338, –378, –450a, –497, –877 |
| Lakner et al. 2012 [97] | miR–34c, –184, –221 | miR–16, –19a, –29a, –29b, –29c, –92a, –150, –194 |
| Raschzok et al. 2011 [53] | miR33, –153, –298, –301b, –489, –743b, –883 |
| Castro et al. 2010 [54] | miR19A, –21, –214 |

Summary of published data regarding microRNA microarray profiling of activating primary rat HSCs. miRNAs which display an overlap in different published data sets are displayed in bold.

**Figure 4:** The molecular mechanisms of certain miRNAs to regulate liver regeneration.
multiple signaling pathways involved in liver regeneration in mice, suggesting GNMT participation in liver regeneration and the survival and normal proliferation of hepatocytes [59]. Although there is currently abundant evidence that epigenetic changes can directly lead to impaired liver regeneration, there is still no clear evidence that epigenetic changes due to aging are the principal cause of liver damage. In summary, the changes in gene expression caused by aging are directly involved in regulating liver function, regeneration, and energy balance. These changes in gene expressions are mainly reflected as changes at the transcriptional level. The primary proteins and stably expressed genes are regulated by miRNA, thereby changing numerous liver functions. There remain several influencing factors and processes at the gene level that are yet to be discovered.

6. The Effect of Signaling Pathways on the Regeneration of the Aging Liver

Cell aging increases the complexity of the cellular microenvironment. Senescent cells produce cytokines, chemokines, and protein enzymes, possessing both positive and negative effects in several physiological processes, such as tissue repair, tumor development, and other processes [60–62], causing changes in cellular signaling pathways that play an indispensable role in cell development, differentiation, and proliferation [63]. During the progression of cell aging, changes occur in the interaction between some primary proteins, which alter the original function of the associated signaling pathways [64]. In the liver, TNF-α, IL-6, NF-κB, and STAT3 were first detected in young mice after partial liver resection [65–67]. This further activated tyrosine kinase receptors, cMET, and EGF ligands, thereby activating the expression of transcription factors involved in liver regeneration [68]. The transcription factors activated after resection primarily include c-jun, C/EBPb, and cAMP response element modulator [69–72]. The liver subsequently initiates the expression of certain proteins required for the S-phase transition, including DNA polymerase A, c-myc, cdc2, and FoxM1B [73–79]. In addition to gene activation, the liver must abrogate the inhibition of the C/EBPa and E2F–Rb complexes, which inhibit E2F-dependent promoters. In the young liver, the elimination of these inhibitory effects is mediated by the PI3K–Akt signaling pathway [80]. Stocker and Heine found that 99% of hepatocytes in young mouse livers proliferated after PH, whereas only 30% proliferated in aging mouse livers after PH [81]. Fry et al. found that DNA polymerase A activity, a key enzyme in DNA replication, was significantly inhibited in the liver of aging mice after PH [73]. The expression of several cell cycle proteins (e.g., c-myc, c-fos, cdc2, and FoxM1B) is also inhibited in the liver of aging mice after PH [81]. Wilkinson et al. demonstrated that diploid hepatocytes proliferate faster than polyploid hepatocytes, with polyploidy inhibiting the proliferation of most hepatocytes [85]. These studies suggested that the molecular basis of the reduced proliferative response in the aging liver may be associated with the alterations of signaling pathways at the translational and/or posttranslational modification levels. Notably, the first evidence of epigenetic effects on liver proliferation in aged mice was obtained by studying...
the expression of C/EBPα in the livers of aging mice. The high levels of C/EBPα expression in the liver prevent the proliferation of the young liver by CDK2 inhibition [86, 87]. The detection of C/EBPα complexes in the liver of aging mice showed that aging could convert C/EBPα from CDK2 complexes to macromolecular complexes containing Rb, E2F4, and the chromatin-remodeling protein BRM (i.e., the C/EBPα–Brm complex) [75, 88]. The C/EBPα–Brm complex occupies E2F-dependent promoters, such as b-myb, cdc2, dihydrofolate reductase, and c-myc, and represses the expression of these genes after resection [75] (Figure 5). Studies have further revealed that the C/EBPα–Brm complex inhibits the expression of FoxM1B, which is necessary for normal liver regeneration [82, 83]. Therefore, changes in the signaling pathways in aging hepatocytes can lead to changes in the expression of several genes, consequently leading to decreased cellular regeneration capacity. In recent years, increased changes in signaling pathways have been discovered in the aging liver. For example, Loforese et al. found that the Hippo signaling pathway is damaged in aging mice and that inhibiting the expression of the key enzyme MST1/2 enhanced the regenerative capacity of aging hepatocytes in mice [89]. These studies showed that with the progression of aging, liver regeneration capacity decreases due to the changes in the associated cellular signaling pathways. If these changes caused by aging are reversed, the regeneration capacity of the aging liver may also be restored. It is therefore important to identify the signaling pathways by which cells proliferate and maintain their differentiated functions and to determine the impact of aging on these pathways.

7. Conclusion

The decreased liver regeneration capacity due to aging results from many factors, such as the intracellular and extracellular changes caused by cell aging. Although no clear evidence exists to explain the mechanism of this occurrence, the notion that hepatocytes lose their ability to increase with age is challenged by some experimental evidence based on the successful in vitro expansion of hepatocytes [90]. Recent studies have proposed that decreased liver regeneration capacity in aging organisms is not due to replicative senescence of hepatocytes in the liver. The addition of cytokines to the culture medium in vitro allows isolated primary hepatocytes to enter the cell cycle, maintaining growth in vitro for a long time [91]. Therefore, the reduced regenerative capacity of the aging liver can likely be summarized as follows: (1) the decreased expression of cell adhesion proteins leads to weakened microstructural adaptation and p21-dependent cell cycle arrest after tissue injury [92]. (2) Changes in the secretion of cytokines, such as TGF, IL-6, and IL-1β, in the aging liver lead to an imbalance of the liver’s internal environment, resulting in the increased complexity of cellular components in the liver and its continuous effects on hepatocyte function and proliferation. (3) Changes in the metabolic capacity of the aging liver lead to the accumulation of associated substances that affect the microenvironment of hepatocytes and compromise their proliferation. (4) Ineffective clearance of aging hepatocytes results in continuous changes in the immune system of the liver and differential secretion of cytokines and chemokine. Therefore, this regulates the accumulation of lymphocytes, such as macrophages, in the liver, further increasing the internal environment complexity of the aging liver to regulate the native cells in the liver. (5) With age, the expression of genes constantly changes and the genes that were primarily not expressed in the heterochromatin are gradually be upregulated, leading to numerous phenotypic and morphological changes in hepatocytes, which in turn leads to hepatocyte damage and decreased liver regeneration capacity (Figure 6).
Currently, the mechanisms of decreased liver regeneration capacity caused by aging have not been fully examined, but with the increase in the aging population, such studies have become increasingly urgent.

Data Availability
No data were used to support this study.

Conflicts of Interest
No conflicts of interest are declared by the authors.

Authors’ Contributions
Chaoliang Tang and Lai Jiang were involved in the manuscript conception, design, and drafting. Hao Chen was involved in the manuscript conception. Lianxin Liu was involved in the manuscript conception and design. All authors provided final approval of the version to be submitted. Chaoliang Tang, Hao Chen, and Lai Jiang contributed equally to this work.

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References
[1] G. K. Michalopoulos, “Hepatostat: liver regeneration and normal liver tissue maintenance,” Hepatology, vol. 65, no. 4, pp. 1384–1392, 2017.
[2] D. H. Van Thiel, J. S. Gavaler, I. Kam et al., “Rapid growth of an intact human liver transplanted into a pdf,” Gastroenterology, vol. 93, no. 6, pp. 1414–1419, 1987.
[3] D. A. Rudnick and N. O. Davidson, “Functional relationships between lipid metabolism and liver regeneration,” International Journal of Hepatology, vol. 2012, article 549241, 8 pages, 2012.
[4] G. M. Higgins and J. C. Rogers, “Effect of radium emanation on the histocyte in the liver of the white rat,” The American Journal of Pathology, vol. 8, no. 3, pp. 355–365, 1932.
[5] F. X. Yu, B. Zhao, and K. L. Guan, “Hippocampus pathway in organ size control, tissue homeostasis, and cancer,” Cell, vol. 163, no. 4, pp. 811–828, 2015.
[6] G. K. Michalopoulos, “Liver regeneration,” Journal of Cellular Physiology, vol. 213, no. 2, pp. 286–300, 2007.
[7] F. Dai, C. Hu, Z. Zhang, F. Tang, and C. Tang, “Mechanisms and status of research on the protective effects of traditional Chinese medicine against ischemic brain injury,” Traditional Medicine Research, vol. 7, no. 1, 2022.
[8] Y. Xu, Q. Zeng, B. Sun, S. Wei, Q. Wang, and A. Zhang, “Assessing the role of Nrf2/GPX4-mediated oxidative stress in arsenic-induced liver damage and the potential application value of Rosa roxburghii Tratt [Rosaceae],” Oxidative Medicine and Cellular Longevity, vol. 2022, Article ID 9865606, 15 pages, 2022.
[9] D. J. Cook, B. Patra, L. Kuttipurathu, J. B. Hoek, and R. Vadigepalli, “A novel, dynamic pattern-based analysis of NF-kB binding during the priming phase of liver regeneration reveals switch-like functional regulation of target genes,” Frontiers in Physiology, vol. 6, p. 189, 2015.
[10] S. Hiemstra, M. Fehling-Kaschek, I. A. Kuijper et al., “Dynamic modeling of Nrf2 pathway activation in liver cells after toxicant exposure,” Scientific Reports, vol. 12, no. 1, article 7336, 2022.
[11] C. Tang, J. Hong, C. Hu et al., “Palmitate protects against cerebral ischemia/reperfusion injury by activation of the AMPK/Nrf2 pathway,” Oxidative Medicine and Cellular Longevity, vol. 2021, Article ID 6660193, 12 pages, 2021.
[12] W. M. Zhao, Y. L. Qin, Z. P. Niu et al., “Branches of the NF-kappaB signaling pathway regulate proliferation of oval cells in rat liver regeneration,” Genetics and Molecular Research, vol. 15, no. 1, 2016.
[13] C. F. Chang, W. M. Zhao, J. X. Mei et al., “Branches of NF-kB signaling pathway regulate hepatocyte proliferation in rat liver regeneration,” Genetics and Molecular Research, vol. 14, no. 3, pp. 7643–7654, 2015.
[14] S. Haga, W. Ogawa, H. Inoue et al., “Compensatory recovery of liver mass by Akt-mediated hepatocellular hypertrophy in liver-specific STAT3-deficient mice,” Journal of Hepatology, vol. 43, no. 5, pp. 799–807, 2005.
[15] L. N. Jackson, S. D. Larson, S. R. Silva et al., “PI3K/Akt activation is critical for early hepatic regeneration after partial hepatectomy,” American Journal of Physiology. Gastrointestinal and Liver Physiology, vol. 294, no. 6, pp. G1401–G1410, 2008.
[16] B. Gao, “Basic liver immunology,” Cellular & Molecular Immunology, vol. 13, no. 3, pp. 265–266, 2016.
[17] A. Blouin, R. P. Bolender, and E. R. Weibel, “Distribution of organelles and membranes between hepatocytes and nonhepatocytes in the rat liver parenchyma,” The Journal of Cell Biology, vol. 72, pp. 441–455, 1977.
[18] R. P. Bolender and E. R. Weibel, “A morphometric study of the removal of phenobarbitol-induced membranes from hepatocytes after cessation of treatment,” The Journal of Cell Biology, vol. 56, pp. 746–761, 1973.
[19] A. V. Loud, “A quantitative stereological description of the ultrastructure of normal rat liver parenchymal cells,” The Journal of Cell Biology, vol. 37, pp. 27–46, 1968.
[20] E. R. Weibel, W. Staubli, H. R. Gnagi, and F. A. Hess, “Correlated morphometric and biochemical study on the liver cell,” The Journal of Cell Biology, vol. 42, pp. 68–91, 1969.
[21] W. Staubli, R. Hess, and E. R. Weibel, “Correlated morphometric and biochemical studies on the liver cell,” The Journal of Cell Biology, vol. 42, pp. 92–112, 1969.
[22] V. Racanelli and B. Rehermann, “The liver as an immunological organ,” Hepatology, vol. 43, no. S1, pp. S54–S62, 2006.
[23] J. Endig, L. E. Buitrago-Molina, S. Marhenke et al., “Dual role of the adaptive immune system in liver injury and hepatocellular carcinoma development,” Cancer Cell, vol. 30, no. 2, pp. 308–323, 2016.
[24] J. Zhou, H. Peng, K. Li et al., “Liver-resident NK cells control antiviral activity of hepatic T cells via the PD-1-PD-L1 axis,” Immunity, vol. 50, no. 2, pp. 403–417, 2019.
[25] G. Baggio, S. Donazzan, D. Monti et al., “Lipoprotein(a) and lipoprotein profile in healthy centenarians: a reappraisal of vascular risk factors,” *The FASEB Journal*, vol. 12, no. 6, pp. 433–437, 1998.

[26] N. Ahmed, R. Abbas, M. A. Khan, H. Bashir, S. Tahir, and A. U. Zafar, “Enhancing recombinant interleukin-6 production yield by fermentation optimization, two-step denaturing, and one-step purification,” *Biotechnology and Applied Chemistry*, vol. 65, no. 3, pp. 490–496, 2018.

[27] K. Thompson, J. Maltby, J. Fallowfield, M. McAulay, H. Millward-Sadler, and N. Sheron, "Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis," *Hepatology*, vol. 28, no. 6, pp. 1597–1606, 1998.

[28] A. O. Williams, A. D. Knapton, A. Geiser, J. J. Letterio, and A. B. Roberts, "The liver in transforming growth factor-beta 1 (TGF-β1) null mutant mice," *Ultrastructural Pathology*, vol. 20, no. 5, pp. 477–490, 1996.

[29] W. B. Ershler, “Interleukin-6: a cytokine for gerontologists,” *Journal of the American Geriatrics Society*, vol. 41, no. 2, pp. 176–181, 1993.

[30] P. Singh, Z. Z. Coskun, C. Goode, A. Dean, L. Thompson-Snipes, and G. Darlington, “Lymphoid neogenesis and immune infiltration in aged liver,” *Hepatology*, vol. 47, no. 5, pp. 1680–1690, 2008.

[31] W. C. Peng, C. Y. Logan, M. Fish et al., “Inflammatory cytokine Tnfalpha promotes the long-term expansion of primary hepatocytes in 3D culture,” *Cell*, vol. 175, no. 6, pp. 1607–1619, 2018.

[32] P. A. Clavien, “IL-6, a key cytokine in liver regeneration,” *Hepatology*, vol. 25, no. 5, pp. 1294–1296, 1997.

[33] J. Liao, J. Luo, Y. Wang et al., “Advances in traditional Chinese medicine for liver disease therapy in 2021,” *Traditional Medicine Research*, vol. 7, no. 6, article 58, 2022.

[34] S. A. Mao, J. M. Gliorioso, and S. L. Nyberg, “Liver regeneration,” *Translational Research*, vol. 163, no. 4, pp. 352–362, 2014.

[35] E. Seo, H. Kang, H. Choi, W. Choi, and H. S. Jun, “Reactive oxygen species-induced changes in glucose and lipid metabolism contribute to the accumulation of cholesterol in the liver during aging,” *Aging Cell*, vol. 18, no. 2, article e12895, 2019.

[36] E. Shieyer, Y. Liao, L. J. Muglia, P. W. Hruz, and D. A. Radnich, “Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice,” *Hepatology*, vol. 40, no. 6, pp. 1322–1332, 2004.

[37] E. Kachayo, C. Tschuur, N. Calo et al., “PTEN downregulation promotes β-oxidation to fuel hypertrophic liver growth after hepatectomy in mice,” *Hepatology*, vol. 66, no. 3, pp. 908–921, 2017.

[38] M. Mastrodonato, P. Portincasa, D. Mentino et al., “Caveolin-1 and mitochondrial alterations in regenerating rat liver,” *Microscopy Research and Technique*, vol. 75, no. 8, pp. 1026–1032, 2012.

[39] M. A. Fernandez-Rojo, C. Restall, C. Ferguson et al., “Caveolin-1 orchestrates the balance between glucose and lipid-dependent energy metabolism: implications for liver regeneration,” *Hepatology*, vol. 55, no. 5, pp. 1574–1584, 2012.

[40] N. B. Ruderman, X. J. Xu, L. Nelson et al., “AMPK and SIRT1: a long-standing partnership?,” *American Journal of Physiology. Endocrinology and Metabolism*, vol. 298, no. 4, pp. E751–E760, 2010.

[41] T. T. Schug and X. Li, “Sirtuin 1 in lipid metabolism and obesity,” *Annals of Medicine*, vol. 43, no. 3, pp. 198–211, 2011.

[42] J. Jin, P. Iakova, Y. Jiang, E. E. Medrano, and N. A. Timchenko, “The reduction of SIRT1 in livers of old mice leads to impaired body homeostasis and to inhibition of liver proliferation,” *Hepatology*, vol. 54, no. 3, pp. 989–998, 2011.

[43] M. Bybsani, A. Perifilev, V. D. de Mello et al., “Epigenetic alterations in blood mirror age-associated DNA methylation and gene expression changes in human liver,” *Epigenomics*, vol. 9, no. 2, pp. 105–122, 2017.

[44] A. E. Elias, B. Kun, I. M. C. Sabula, G. Golomb-Mello, A. Cespedes Zablah, and J. A. Kreiling, “The mir-465 family is upregulated with age and attenuates growth hormone signaling in mouse liver,” *Aging Cell*, vol. 18, no. 2, article e12892, 2019.

[45] N. E. Sharpless, “Ink4a/Arf links senescence and aging,” *Experimental Gerontology*, vol. 39, no. 11-12, pp. 1751–1759, 2004.

[46] C. Enkhbold, Y. Morine, T. Utsunomiya et al., “Dysfunction of liver regeneration in aged liver after partial hepatectomy,” *Journal of Gastroenterology and Hepatology*, vol. 30, no. 7, pp. 1217–1224, 2015.

[47] K. Nejak-Bowen, A. Orr, W. C. Bowen Jr., and G. K. Michalopoulos, “Conditional genetic elimination of hepatocyte growth factor in mice compromises liver regeneration after partial hepatectomy,” *PloS One*, vol. 8, no. 3, article e59836, 2013.

[48] J. H. Chen, C. N. Hales, and S. E. Ozanne, “DNA damage, cellular senescence and organisinal ageing: causal or correlative?,” *Nucleic Acids Research*, vol. 35, no. 22, pp. 7417–7428, 2007.

[49] A. Hernandez-Segura, J. Nehme, and M. Demaria, “Hallmarks of cellular senescence,” *Trends in Cell Biology*, vol. 28, no. 6, pp. 436–453, 2018.

[50] B. T. Kren, P. Y. Wong, A. Shiota, X. Zhang, Y. Zeng, and C. J. Steer, “Polysome trafficking of transcripts and microRNAs in regenerating liver after partial hepatectomy,” *American Journal of Physiology. Gastrointestinal and Liver Physiology*, vol. 297, no. 6, pp. G1181–G1192, 2009.

[51] W. Q. Li, C. Chen, M. D. Xu et al., “The rno-miR-34 family is upregulated and targets ACSL1 in dimethylsulfoximine-induced hepatic fibrosis in rats,” *The FEBBS Journal*, vol. 278, no. 9, pp. 1522–1532, 2011.

[52] S. Balas, M. Marcos, and G. Szabo, “Emerging role of microRNAs in liver diseases,” *World Journal of Gastroenterology*, vol. 15, no. 45, article 5633, 2009.

[53] N. Raschzok, W. Werner, H. Sallmon et al., “Temporal expression profiles indicate a primary function for microRNA during the peak of DNA replication after rat partial hepatectomy,” *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, vol. 300, no. 6, pp. R1363–R1372, 2011.

[54] R. E. Castro, D. M. Ferreira, X. Zhang et al., “Identification of microRNAs during rat liver regeneration after partial hepatectomy and modulation by ursodeoxycholic acid,” *American Journal of Physiology. Gastrointestinal and Liver Physiology*, vol. 299, no. 4, pp. G887–G897, 2010.

[55] M. Pibiri, P. Sulas, V. P. Leoni et al., “Global gene expression profile of normal and regenerating liver in young and old mice,” *Age*, vol. 37, no. 3, article 9796, 2015.

[56] P. Sen, Y. Lan, C. Y. Li et al., “Histone acetyltransferase p300 induces de novo super-enhancers to drive cellular senescence,” *Molecular Cell*, vol. 73, no. 4, pp. 684–698, 2019.

[57] A. E. Field, N. A. Robertson, T. Wang, A. Havas, T. Ideker, and P. D. Adams, “DNA methylation clocks in aging: categories, causes, and consequences,” *Molecular Cell*, vol. 71, no. 6, pp. 882–895, 2018.
[58] K. Kaji, V. M. Factor, J. B. Andersen et al., “DNMT1 is a required genomic regulator for murine liver histogenesis and regeneration,” *Hepatology*, vol. 64, no. 2, pp. 582–598, 2016.

[59] M. Varela-Rey, D. Fernandez-Ramos, N. Martinez-Lopez et al., “Impaired liver regeneration in mice lacking glycine N-methyltransferase,” *Hepatology*, vol. 50, no. 2, pp. 443–452, 2009.

[60] M. Demaria, N. Ohtani, S. A. Youssef et al., “An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA,” *Developmental Cell*, vol. 31, no. 6, pp. 722–733, 2014.

[61] J. P. Coppe, C. K. Patil, F. Rodier et al., “Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor,” *PLoS Biology*, vol. 6, no. 12, pp. 2853–2868, 2008.

[62] J. P. Coppe, P. Y. Desprez, A. Krtolica, and J. Campisi, “The senescence-associated secretory phenotype: the dark side of tumor suppression,” *Annual Review of Pathology*, vol. 5, no. 1, pp. 99–118, 2010.

[63] M. A. Lemmon, D. M. Freed, J. Schlessinger, and A. Kiyatkin, “The dark side of cell signaling: positive roles for negative regulators,” *Cell*, vol. 164, no. 6, pp. 1172–1184, 2016.

[64] N. A. Timchenko, “Aging and liver regeneration,” *Trends in Endocrinology and Metabolism*, vol. 20, no. 4, pp. 171–176, 2009.

[65] C. Trautwein, T. Rakemann, M. Niehof, S. Rose-John, and M. P. Manns, “Acute-phase response factor, increased binding, and target gene transcription during liver regeneration,” *Gastroenterology*, vol. 110, no. 6, pp. 1854–1862, 1996.

[66] M. Iwai, T. X. Cui, H. Kitamura, M. Saito, and T. Shimazu, “Increased secretion of tumour necrosis factor and interleukin 6 from isolated, perfused liver of rats after partial hepatectomy,” *Cytokine*, vol. 13, no. 1, pp. 60–64, 2001.

[67] M. J. FitzGerald, E. M. Webber, J. R. Donovon, and N. Fausto, “Rapid DNA binding by nuclear factor kappa B in hepatocytes at the start of liver regeneration,” *Cell Growth & Differentiation*, vol. 6, no. 4, pp. 417–427, 1995.

[68] N. Fausto, J. S. Campbell, and K. J. Riehle, “Liver regeneration,” *Hepatology*, vol. 43, no. S1, pp. S45–S53, 2006.

[69] J. L. Rodriguez, J. Sandoval, G. Serviddio et al., “Id2 leaves the chromatin of the E2F4-p130-controlled c-myc promoter during hepatectomy priming for liver regeneration,” *The Biochemical Journal*, vol. 398, no. 3, pp. 431–437, 2006.

[70] N. Gagliano, F. Grizzi, and G. Annioni, “Mechanisms of aging and liver functions,” *Digestive Diseases*, vol. 25, no. 2, pp. 118–123, 2007.

[71] L. E. Greenbaum, W. Li, D. E. Cressman et al., “CCAAT enhancer-binding protein beta is required for normal hepatocyte proliferation in mice after partial hepatectomy,” *The Journal of Clinical Investigation*, vol. 102, no. 5, pp. 996–1007, 1998.

[72] D. E. Cressman, R. H. Diamond, and R. Taub, “Rapid activation of the Stat3 transcription complex in liver regeneration,” *Hepatology*, vol. 21, no. 5, pp. 1433–1449, 1995.

[73] M. Fry, J. Silber, L. A. Loeb, and G. M. Martin, “Delayed and reduced cell replication and diminishing levels of DNA polymerase-alpha in regenerating liver of aging mice,” *Journal of Cellular Physiology*, vol. 118, no. 3, pp. 225–232, 1984.

[74] N. A. Timchenko, M. Wilde, K. I. Kosiak et al., “Regenerating livers of old rats contain high levels of C/EBPalpha that correlate with altered expression of cell cycle associated proteins,” *Nucleic Acids Research*, vol. 26, no. 13, pp. 3293–3299, 1998.

[75] P. Iakova, S. S. Awad, and N. A. Timchenko, “Aging reduces proliferative capacities of liver by switching pathways of C/EBPalpha growth arrest,” *Cell*, vol. 113, no. 4, pp. 495–506, 2003.

[76] O. A. Kalinina, S. A. Kalinin, E. W. Polack et al., “Sustained hepatic expression of FoxM1B in transgenic mice has minimal effects on hepatocellular carcinoma development but increases cell proliferation rates in preneoplastic and early neoplastic lesions,” *Oncogene*, vol. 22, no. 40, pp. 6266–6276, 2003.

[77] X. Wang, K. Krupczak-Hollis, Y. Tan, M. B. Dennewitz, G. R. Adami, and R. H. Costa, “Increased hepatic forkhead box M1B (FoxM1B) levels in old-aged mice stimulated liver regeneration through diminished p27Kip1 protein levels and increased Cdk25B expression,” *The Journal of Biological Chemistry*, vol. 277, no. 46, pp. 44310–44316, 2002.

[78] X. Wang, E. Quail, N. J. Hung, Y. Tan, H. Ye, and R. H. Costa, “Increased levels of forkhead box M1B transcription factor in transgenic mouse hepatocytes prevent age-related proliferation defects in regenerating liver,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 20, pp. 11468–11473, 2001.

[79] K. Krupczak-Hollis, X. Wang, M. B. Dennewitz, and R. H. Costa, “Growth hormone stimulates proliferation of old-aged regenerating liver through forkhead box m1b,” *Hepatology*, vol. 38, no. 6, pp. 1552–1562, 2003.

[80] T. Doerks, R. R. Copley, J. Schultz, C. P. Ponting, and P. Bork, “Systematic identification of novel protein domain families associated with nuclear functions,” *Genome Research*, vol. 12, no. 1, pp. 47–56, 2002.

[81] E. Stocker and W. D. Heine, “Regeneration of liver parenchyma under normal and pathological conditions,” *Beiträge zur Pathologie*, vol. 144, no. 4, pp. 400–408, 1971.

[82] G. L. Wang, E. Salisbury, X. Shi, L. Timchenko, E. E. Medrano, and N. A. Timchenko, “HDAC1 cooperates with C/EBPa in the inhibition of liver proliferation in old mice,” *The Journal of Biological Chemistry*, vol. 283, no. 38, pp. 26169–26178, 2008.

[83] G. L. Wang, X. Shi, E. Salisbury et al., “Growth hormone corrects proliferation and transcription of phosphoenolpyruvate carboxykinase in livers of old mice via elimination of CCAAT/enhancer-binding protein α-Brn complex,” *The Journal of Biological Chemistry*, vol. 282, no. 2, pp. 1468–1478, 2007.

[84] M. D. Chipchase, M. O'Neill, and D. W. Melton, “Characterization of premature liver polyploidy in DNA repair (Ercc1)-deficient mice,” *Hepatology*, vol. 38, no. 4, pp. 958–966, 2003.

[85] P. D. Wilkinson, E. R. Delgado, F. Alencastro et al., “The polyploid state restricts hepatocyte proliferation and liver regeneration in mice,” *Hepatology*, vol. 69, no. 3, pp. 1242–1258, 2019.

[86] E. H. Tan, S. C. Hooi, M. Laban et al., “CCAAT/enhancer binding protein alpha knock-in mice exhibit early liver glyco- gen storage and reduced susceptibility to hepatocellular carni- noma,” *Cancer Research*, vol. 65, no. 22, pp. 10330–10337, 2005.

[87] H. Wang, P. Iakova, M. Wilde et al., “C/EBPα arrests cell proliferation through direct inhibition of Cdk2 and Cdk4,” *Molecular Cell*, vol. 8, no. 4, pp. 817–828, 2001.

[88] I. M. Conboy, M. J. Conboy, A. J. Wagers, E. R. Girma, I. L. Weissman, and T. A. Rando, “Rejuvenation of aged progenitor cells by exposure to a young systemic environment,” *Nature*, vol. 433, no. 7027, pp. 760–764, 2005.
[89] G. Loforese, T. Malinka, A. Keogh et al., “Impaired liver regeneration in aged mice can be rescued by silencing Hippo core kinases MST1 and MST2,” EMBO Molecular Medicine, vol. 9, no. 1, pp. 46–60, 2017.

[90] M. J. Wang, F. Chen, J. X. Li et al., “Reversal of hepatocyte senescence after continuous in vivo cell proliferation,” Hepatology, vol. 60, no. 1, pp. 349–361, 2014.

[91] H. Hu, H. Gehart, B. Artegiani et al., “Long-term expansion of functional mouse and human hepatocytes as 3d organoids,” Cell, vol. 175, no. 6, pp. 1591–1606.e19, 2018.

[92] Y. T. Lin, S. M. Liang, Y. J. Wu et al., “Cordycepin suppresses endothelial cell proliferation, migration, angiogenesis, and tumor growth by regulating focal adhesion kinase and p53,” Cancers, vol. 11, no. 2, 2019.

[93] C. J. Guo, Q. Pan, D. G. Li, H. Sun, and B. W. Liu, "miR-15b and miR-16 are implicated in activation of the rat hepatic stellate cell: an essential role for apoptosis," Journal of Hepatology, vol. 50, no. 4, pp. 766–778, 2009.

[94] J. Ji, J. Zhang, G. Huang, J. Qian, X. Wang, and S. Mei, "Over-expressed microRNA-27a and 27b influence fat accumulation and cell proliferation during rat hepatic stellate cell activation," FEBS Letters, vol. 583, no. 4, pp. 759–766, 2009.

[95] G. Maubach, M. C. Lim, J. Chen, H. Yang, and L. Zhuo, "miRNA studies in in vitro and in vivo activated hepatic stellate cells," World Journal of Gastroenterology, vol. 17, no. 22, pp. 2748–2773, 2011.

[96] C. Chen, C. Q. Wu, Z. Q. Zhang, D. K. Yao, and L. Zhu, "Loss of expression of miR-335 is implicated in hepatic stellate cell migration and activation," Experimental Cell Research, vol. 317, no. 12, pp. 1714–1725, 2011.

[97] A. M. Lakner, N. M. Steuerwald, T. L. Walling et al., "Inhibitory effects of microRNA 19b in hepatic stellate cell-mediated fibrogenesis," Hepatology, vol. 56, no. 1, pp. 300–310, 2012.