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Review Article

Exploring the roles of non-coding RNAs in liver regeneration

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ABSTRACT

Liver regeneration (LR) is a complex process encompassing three distinct phases: priming, proliferation phase and restoration, all influenced by various regulatory factors. After liver damage or partial resection, the liver tissue demonstrates remarkable restorative capacity, driven by cellular proliferation and repair mechanisms. The essential roles of non-coding RNAs (ncRNAs), predominantly microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNA (circRNA), in regulating LR have been vastly studied. Additionally, the impact of ncRNAs on LR and their abnormal expression profiles during this process have been extensively documented. Mechanistic investigations have revealed that ncRNAs interact with genes involved in proliferation to regulate hepatocyte proliferation, apoptosis and differentiation, along with liver progenitor cell proliferation and migration. Given the significant role of ncRNAs in LR, an in-depth exploration of their involvement in the liver's self-repair capacity can reveal promising therapeutic strategies for LR and liver-related diseases. Moreover, understanding the unique regenerative potential of the adult liver and the mechanisms and regulatory factors of ncRNAs in LR are crucial for improving current treatment strategies and exploring new therapeutic approaches for various liver-related diseases. This review provides a brief overview of the LR process and the ncRNA expression profiles during this process. Furthermore, we also elaborate on the specific molecular mechanisms through which multiple key ncRNAs regulate the LR process. Finally, based on the expression characteristics of ncRNAs and their interactions with proliferation-associated genes, we explore their potential clinical application, such as developing predictive indicators reflecting liver regenerative activity and manipulating LR processes for therapeutic purposes.

1. Introduction

Adult hepatocytes typically exist in a quiescent and highly differentiated state, primarily engaged in various metabolic functions [1–4]. Notably, only a tiny fraction, less than 0.01 %, of liver cells undergo mitosis [5,6]. However, the liver exhibits a remarkable regenerative ability in response to acute or chronic injuries and partial hepatectomy (PH), enabling it to replenish and restore itself [7–10]. The classical model for liver regeneration (LR) was initially established through 2/3 PH in rats [11–13]. When liver cells sustain damage, they undergo 1–2 cell cycles to restore lost liver mass and histologic structure [3,14–16]. LR is a continuous pathophysiological process, generally divided into three stages: initiation (0.5–6 h after PH), proliferation (12–72 h after PH) and termination (72–168 h after PH) [17–19]. During the initiation phase, liver cells are activated and transition from the G0 phase to the G1 phase. Subsequently, activated liver cells enter mitosis and undergo two cell cycles during the proliferation stage. After PH, the liver returns to its original weight within two weeks (Fig. 1) [3,20–22]. LR is a meticulously regulated process involving coordinated interactions among various cytokines, growth factors, transcription factors and signalling pathways [23–27]. Numerous studies have reported the collaboration of various important regulators during the initiation and proliferation stages of LR, including hepatocyte growth factor (HGF), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and epidermal growth factor (EGF) [28,29]. In the termination stage, with the restoration of liver mass and completion of the liver repair process, several negative regulators such as transforming growth factor-beta (TGF-β) and activin A work to suppress liver cell proliferation [30–33]. An in-depth exploration of LR is of significance for the treatment of liver diseases and the success of liver transplantation [34–36].

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Liver transplantation stands as the predominant treatment for end-stage liver disease, albeit its severely constrained application owing to the scarcity of donor livers [37–39]. Additionally, patients with chronic viral hepatitis or long-term alcohol abuse, which leads to chronic liver damage, may exhibit limited LR capacity [40–42]. Therefore, unveiling the mechanisms of LR, particularly strategies to enhance patients' liver regenerative capacity, is pivotal for advancing liver treatment options. Furthermore, currently, there exist only a few effective predictors for the regenerative potential of residual livers or partially transplanted livers. A comprehensive understanding of the molecular mechanisms underlying LR is essential to identify and develop more promising treatment modalities for LR and repair.

Non-coding RNAs (ncRNAs) are considered master regulators of genomic functions and are without protein-coding abilities, predominantly encompassing microRNA (miRNA), small interfering RNA (siRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA). Recent advances in molecular biology and genetics have paved the way for a more precise understanding of the functions of ncRNA in various biological processes [43–46]. Increasing evidence reveals the vital regulatory roles played by ncRNAs in maintaining cell function and gene expression [47–49]. In the context of liver diseases, ncRNAs have attracted widespread attention for their pivotal contributions to multiple aspects of liver physiology and pathology [50–53]. Aberrant ncRNA expression has also been widely reported in liver diseases and is closely associated with the occurrence and progression of liver cancer, liver fibrosis and other liver diseases [54–58]. Moreover, they emerge as crucial players in liver regeneration, with certain miRNAs, lncRNAs and circRNAs being identified as crucial regulators influencing processes such as cell proliferation, differentiation and apoptosis [59–64]. An in-depth study of the functions and regulatory mechanisms of ncRNAs in LR could enrich our understanding of the process of LR and provide novel targets and insights for future treatment strategies and diagnostic methods for liver diseases.

This review systematically outlines the expression characteristics and regulatory functions of various common ncRNAs in LR based on high-quality articles in the current literature (Table 1). This review also delves into the regulatory mechanisms of ncRNAs in LR and elucidates their potential application in LR (Table 2). Exploring ncRNA expression patterns may contribute to evaluating the activity of LR and the extent of liver cell proliferation. Furthermore, the targeted regulation of ncRNA expression in specific disease states could serve to promote or inhibit LR processes, offering therapeutic avenues to explore.

2. Roles and mechanisms of miRNAs during LR

As crucial components of epigenetic modification, miRNAs negatively regulate the expression of target genes involved in multiple physiological processes such as cell proliferation and apoptosis [65–69]. The role of miRNAs extends across virtually all facets of cellular activity pertinent to liver development and maturation, underscoring their ubiquity and importance in hepatic biology [70–72]. Increasing evidence underscored the prominent role of miRNA-mediated regulation in the proliferation of liver cells during LR becomes increasingly apparent, marking miRNAs as pivotal players in this critical biological process [59, 73,74]. Following partial hepatectomy (PH), a common experimental model for studying liver regeneration, miRNAs exhibit distinctly dysregulated expression profiles. This dysregulation is characterized by dynamic changes and a time-dependent expression pattern, crucial for adapting to the varying demands of different LR stages. Typically, the levels of specific miRNAs surge shortly after PH, reaching their zenith

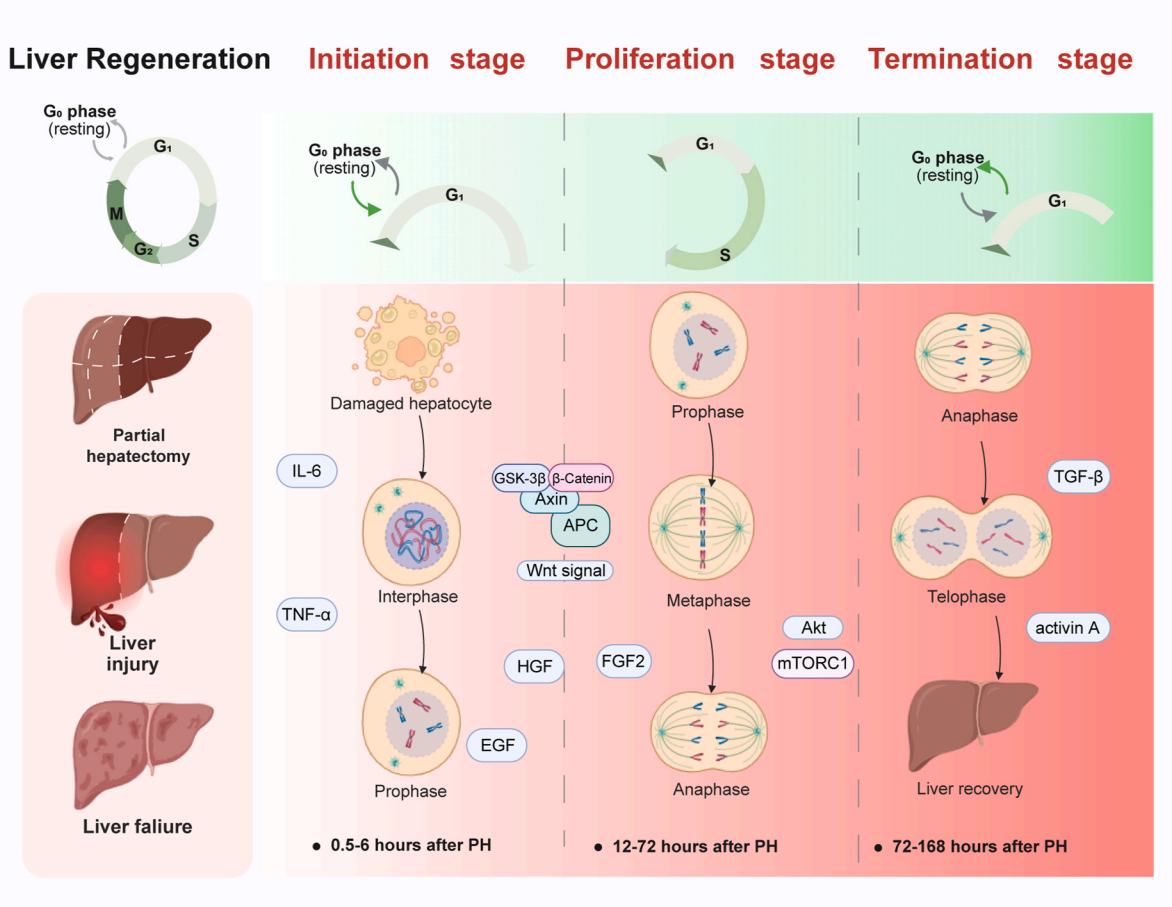

Fig. 1. The overview of liver regeneration. The regeneration process is divided into three main stages: initiation, proliferation and termination.

Table 1
Aberrantly expressed ncRNAs during liver regeneration.

ncRNAs	Method	Model/Tissue/Cell Type (Sample source)	Expression of ncRNAs	Detailed expression changes	Ref.
miR-21	2/3 PH	2/3 PH mouse models, and mouse Hepa1,6 cells	increased	increased at 6 h, peaked between 18 and 24 h, and returned to almost normal levels by 36 h after PH	89
miR-21	2/3 PH	2/3 PH mouse models, and mouse Hepa1,6 cells	increased	peaked at 18 h after PH	90
miR-182	2/3 PH	2/3 PH mouse models, hepatocytes, and hepatic stellate cells	increased	peaked at 3 days after PH	100
miR-182	70 % PH	70 % PH mouse models, and mouse BM-derived MSCs	increased	/	105
miR-199a-5p	70 % PH	70 % PH rat models, and rat liver cell line BRL-3A	increased	increased at 12–30 h after PH	110
miR-199a-5p	70 % PH	Thy1+ cells (Thy1-MCs)	increased	/	118
miR-26a/b	2/3 PH	2/3 PH mouse models, and primary fibroblasts	decreased	decreased at 24 h, and began to elevate around 48 h after PH	129
miR-26a	70 % PH	70 % PH mouse models, and mouse liver cell line NCTC-1469	decreased	/	128
miR-26a	50 % PH	50 % PH rat models, and HepG2 cells	decreased	decreased at 2 days, and gradually recovered to nearly normal levels at 3 days after PH	127
miR-125a-5p	2/3 PH	2/3 PH mouse models, 2/3 PH rat models, and rat BRL-3A cells	decreased	decreased at 24 and 30 h after PH	130
miR-378	2/3 PH	2/3 PH mouse models, and mouse Hepa1,6 cells	decreased	/	90
lncHand2	70 % PH	2/3 PH mouse models, and mouse primary hepatocytes	increased	peaked at 1.5 days after PH	134
lncRNA-LALR1	2/3 PH	2/3 PH mouse models, normal mouse liver cell line CCL-9.1, and mouse embryo liver cell line BNL CL.2	increased	increased at 6 h, peaked between 18 and 24 h, and returned to almost normal levels at 72 h after PH	139
lncRNA MALAT1	2/3 PH	2/3 PH mouse models, mouse embryo liver cell line BNL CL.2, and mouse liver cell line NCTC-1469	increased	increased at 2 h, peaked at 15 h, and returned to almost normal levels at 120 h after PH	140
lncPHx2	2/3 PH	2/3 PH mouse models, mouse embryo liver cell line BNL CL.2, mouse liver cell lines MHT, and Hepa1-6	decreased	increased between 24 and 72 h, peaked at 60 h after PH	131
circ-RBM23	70 % PH	70 % PH mouse models, and L02 cells	increased	/	142
circ-LRBA	2/3 PH	2/3 PH mouse models, non-tumorous human liver tissues, mouse live cell lines AML12, and Hepa1-6	increased	increased at 24 h, peaked at 36 h, and gradually decreased at 48 h after PH	143
circRNA-14723	2/3 PH	2/3 PH rat models, and rat liver cell line BRL-3A	increased	/	13

during the intermediary phases, and subsequently taper off as the regeneration process progresses towards completion [72,75,76]. Intriguingly, genome-wide miRNA microarray analyses have elucidated that approximately 40 % of miRNAs are selectively upregulated in the early to mid-phases post-PH, whereas a significant majority, around 70 %, show a downregulation at the 24-h mark post-PH [77,78]. This nuanced orchestration of miRNA expression is instrumental in maintaining the delicate balance essential for the liver's regenerative process, ensuring that regeneration proceeds efficiently and effectively [14,79,80]. Further illuminating the role of miRNAs in LR, a plethora of functional experimental studies have delved into the intricate mechanisms by which miRNAs and their target genes influence liver regeneration. These studies have not only expanded our understanding of miRNA functionality but have also highlighted the complexity of their regulatory roles [81–83]. Notably, miRNAs that are prominently expressed during LR tend to exhibit biphasic effects, either promoting or suppressing cell proliferation, cell cycle regulation, apoptosis and differentiation (Fig. 2) [84–87]. This duality underscores the versatility of miRNAs as both promoters and inhibitors of liver regeneration, depending on the specific context and the stage of the regenerative process.

Several studies have revealed that many miRNAs are highly expressed during the early stages of LR, contributing to enhanced cell proliferation and differentiation [88]. For instance, miR-21, one of the most extensively studied miRNAs, is rapidly upregulated in hepatocytes following 2/3 PH surgery. Elevated miR-21 expression becomes detectable at 6 h post 2/3 PH, peaks at 18–24 h and gradually restores to nearly baseline levels by 36 h [89,90]. During the early stages of LR, miR-21 primarily facilitates hepatocyte proliferation by promoting the transition from cell cycle G1 to S phase. It achieves this by suppressing B-cell translocation gene 2 (BTG2), a family of antiproliferation genes, which strongly inactivate forkhead box transcription factor M1 (FoxM1), thus inhibiting DNA repair, cell cycle progression, cellular growth and cell apoptosis [91–95]. Mechanistic investigations have revealed that the absence of miR-21 results in increased expression of BTG2, impairing the activation of FoxM1 phosphorylation [89]. Additionally, miR-21 exerts its effects by inhibiting the Ras homolog gene family member B (Rhob), enhancing AKT1-induced mTORC1 activation and thereby initiating cyclin D1 expression [90]. Another example is the liver-specific overexpression of miR-182, which was observed to peak at 3 days post-PH. Cholesterol 7α-hydroxylase (CYP7A1), a key rate-limiting enzyme in cholesterol metabolism, is involved in the biosynthesis of bile acids in the liver [96–99]. Research demonstrates that miR-182 stimulates the expression of CYP7A1, which facilitates the production of bile acids for the subsequent generation of hedgehog (Hh) ligands in hepatic stellate cells. This process leads to the activation of Hh signalling and consequent cell proliferation in hepatocytes [100]. Mesenchymal stromal cells (MSCs) possess a compatible regeneration potential in the aspects of the proliferative capacity, differentiation potential and paracrine effects, which are reported to ameliorate hepatic function, stimulate LR and alleviate hepatic fibrosis [101–104]. Microarray analysis revealed that miR-182 is also significantly enriched in hypoxia-preconditioned MSCs (Hp-MSCs). Furthermore, miR-182-5p in Hp-MSC-derived exosomes is mainly taken up by macrophages and contributes to M2 macrophage polarization and anti-inflammatory response during LR. Additionally, it has been suggested that miR-182-5p represses the expression of FoxO1 to further downregulate toll-like receptor 4 (TLR4) expression in macrophages, thereby enhancing hepatic regeneration [105]. The aberrant miR-199a expression has also been frequently reported in various types of malignancies [106–109]. Notably, it has been observed to be significantly increased in the rat liver 12–30 h post PH, which consequently triggers hepatocyte proliferation, G1-to-S phase transition and reduced hepatocyte apoptosis, thereby playing a vital role during LR [110]. By negatively

Table 2
Effects and mechanisms of differently expressed ncRNAs in liver regeneration.

ncRNAs	Roles	Specific effects	Direct Targets	Mechanisms	Ref.
miR-21	promoting regeneration	promote hepatocyte proliferation, and cell cycle progression in the early phase of liver regeneration	Rhob	miR-21, Rhob, AKT1, mTORC1, and cyclin D1	1
miR-21	promoting regeneration	promote cell cycle progression	Btg2	miR-21, Btg2, and FoxM1	2
miR-182	promoting regeneration	promote hepatocyte proliferation	CYP7A1, and Hh signaling	miR-182, CYP7A1, and Hh signaling	3
miR-182	promoting regeneration	promote M2 macrophage polarization, and induce anti-inflammatory responses	FOXO1	miR-182, FOXO1, and TLR4	4
miR-199a-5p	promoting regeneration	promote hepatocyte proliferation, and inhibit hepatocyte apoptosis	TNF-α	miR-199a-5p, TNF-α, TNFR1, TRADD, CASPASE8, and CASPASE3	5
miR-199a-5p	promoting regeneration	promote proliferation of SHPCs and the expansion of SHPC clusters	/	miR-199a-5p, CINC-2, and IL17RB	6
miR-26a/b	suppressing regeneration	inhibit cell cycle progression	CDK6, and cyclin E1	miR-26a/b, CTDSP1/2/L, CDK6, multiple G1-phase cyclins, and pRb protein	7
miR-26a	suppressing regeneration	inhibit hepatocyte proliferation and promote hepatocyte apoptosis	mdm2	miR-26a, mdm2, and p53	8
miR-26a	suppressing regeneration	inhibit hepatocyte proliferation	cyclin E2	miR-26a, and cyclin E2	9
miR-125a-5p	suppressing regeneration	inhibit cell cycle progression, hepatocyte proliferation, and promote hepatocyte apoptosis	STAT3	miR-125a, STAT3, p-STAT3, JUN, and BCL2	10
miR-378	suppressing regeneration	inhibit hepatocyte proliferation	Odc1	miR-378, and Odc1	2
lncHand2	promoting regeneration	promote hepatocyte proliferation	Ino80 remodeling complex	lncHand2, Ino80 complex, Nkx1-2, and c-Met signaling	11
lncRNA-LALR1	promoting regeneration	promote hepatocyte proliferation, and cell cycle progression	Axin1	HGF, lncRNA-LALR1, Axin1, Wnt/β-catenin signaling, and cyclin D1	12
lncRNA MALAT1	promoting regeneration	promote cell cycle progression, hepatocyte proliferation, and inhibit hepatocyte apoptosis	Axin1	lncRNA MALAT1, Axin1, APC,Wnt/β-catenin pathway, and cyclin D1	13
lncPHx2	suppressing regeneration	inhibit cell cycle progression, and hepatocyte proliferation	MCM2, MCM3, and MCMC7	lncPHx2, MCM2, MCM3, and MCMC7	14
circ-RBM23	promoting regeneration	promote liver mitosis, and hepatocyte proliferation	miR-139-5p	circ-RBM23, miR-139-5p, RRM2, AKT, and mTOR signaling	15
circ-LRBA	promoting regeneration	promote liver parenchymal cell proliferation	RNF123, and P27	circLRBA, RNF123, and p27	16
circRNA-14723	promoting regeneration	promote hepatocyte proliferation, cell cycle progression, and inhibit hepatocyte apoptosis	miR-16-5p	circ-14723, rno-miR-16-5p, CCND1, and CCNE1	17

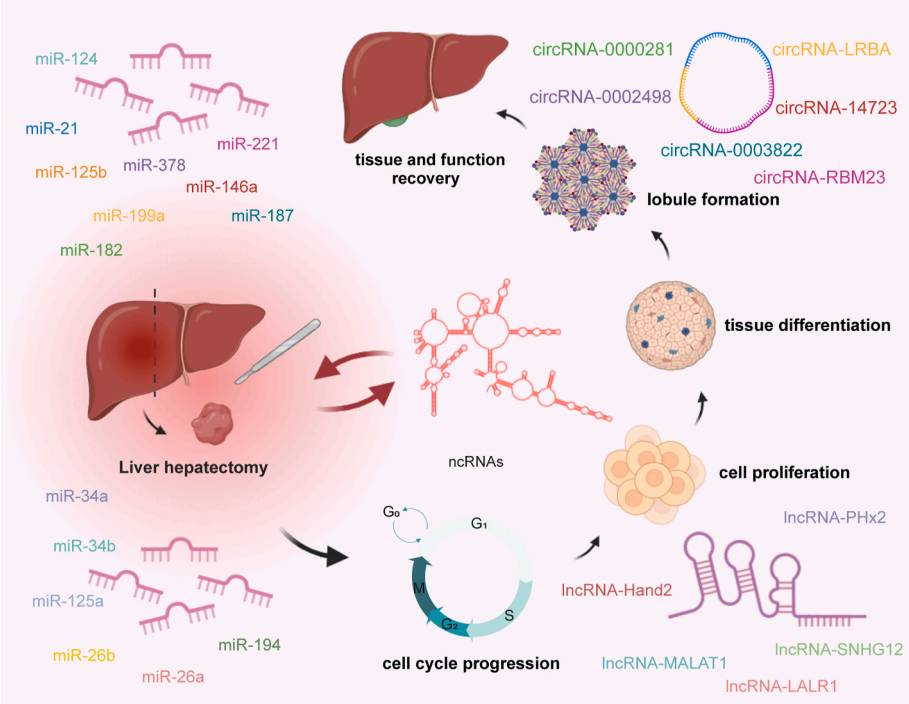

Fig. 2. The role of major ncRNAs in the process of liver regeneration. ncRNAs are important regulators of liver regeneration. Multiple ncRNAs, particularly miRNAs, lncRNAs and cirRNAs, exhibit aberrant expression patterns during liver regeneration, indicating their crucial involvement in regulating cell proliferation, cell cycle progression and apoptosis throughout this process. ncRNAs: non-coding RNAs, miRNAs: microRNAs, lncRNAs: long non-coding RNAs and circRNA: circular RNA.

regulating TNF-α levels, miR-199a inhibits the binding of TNF-α to TNFR, as well as the subsequent cascade activation of the TRADD/-CASPASE8/CASPASE3 signalling pathway. CD90/Thy1, a characteristic membrane marker of MSCs, is significantly expressed during periods of rapid growth [111–114]. Previous studies have validated that Thy1-positive mesenchymal cells (Thy1+ MC) facilitate the differentiation of CD49f-positive primitive hepatic endodermal cells to mature progenitor cells through mutual contact between the two cell populations [115–117]. Recently, the transplantation of Thy1-MCs into Retrorsine (Ret)/PH-treated rat livers, along with elevated miR-199a levels, in extracellular vesicles (EVs) has been observed to facilitate small hepatocyte-like progenitor cell (SHPC) proliferation. Thy1-MCs stimulate sinusoidal endothelial cells and Kupffer cells through cytokine-induced neutrophil chemoattractant-2 (CINC-2)/IL17RB signalling activation and miR-199a, promoting LR [118]. Additionally, human umbilical cord blood MSC (hUCB-MSC) derived exosomal miR-124 has been demonstrated to efficiently initiate LR and alleviate liver injury after PH in rats by interfering with Foxg1 expression to enhance rat LR [119].

In addition to the majority of miRNAs that promote LR, a subset of miRNAs exerts inhibitory effects during liver regeneration [120–123]. These inhibitory miRNAs fine-tune and balance the regenerative process, ensuring proper tissue repair without excessive cellular proliferation or aberrant growth. Therefore, understanding the precise roles of these inhibitory miRNAs in LR can provide valuable insights into developing novel therapeutic strategies for liver-related diseases [124–126]. For example, miR-26a/b expression decreases during cell proliferation, with miR-26a significantly decreasing two days after 50 % PH in rats, returning to near-normal levels by the third day [127]. Multiple studies have indicated that miR-26a plays a critical role in regulating liver cell proliferation and apoptosis. Overexpression of miR-26a is found to reduce the levels of E3 ubiquitin-protein ligase Mdm2 (mdm2), leading to elevated expression of p53 and thereby inhibiting cell proliferation and increasing apoptosis [128]. Furthermore, miR-26a/b and their host genes, such as carboxy-terminal domain RNA polymerase II polypeptide A small phosphatase ½/L (CTDSP1/2/L), cooperate to induce cell cycle arrest and accumulate G1-phase liver cancer cell lines (MHCC-97L, HepG2 and Huh7) [129]. Moreover, miR-26a/b and their host genes have been reported to synergistically activate the retinoblastoma protein (pRb) by directly downregulating CDK6 and multiple G1-phase cyclins. The repression of miR-378 was also detected in a 2/3 PH mouse model, where it suppressed ornithine decarboxylase (Odc1), interfering with DNA synthesis and contributing to LR impairment [90]. Similarly, miR-125a was observed to exhibit a significant reduction at 24- and 30-h following PH. Moreover, increased miR-125a expression suppressed the proliferation and transition from the G1-to-S phase in rat hepatocytes (BRL-3A cells), augmenting hepatocyte apoptosis. Through direct targeting of STAT3, miR-125a decreases p-STAT3, JUN and BCL2 expression while increasing CASPASE3 levels to inhibit proliferation [130].

3. Roles and mechanisms of lncRNAs and cirRNAs during LR

In addition to the foundational influence of miRNAs in LR, lncRNAs and cirRNAs have emerged as pivotal contributors, orchestrating a wide array of cellular mechanisms that facilitate the progression of LR through diverse and complex pathways (Fig. 3). Genome-wide analyses have not only mapped the landscape of lncRNA expression but have also highlighted the dynamic changes these molecules undergo in response to partial hepatectomy (PH). The discovery of 465 differentially expressed lncRNAs in mouse liver tissue post-PH underscores the depth of regulatory diversity these entities possess. Among them, lncRNA induced by PHx 2 (lncRNA-PHx2) stands out for its pronounced expression peak at 60 h post-PH, signifying a critical phase of liver cell proliferation [131]. Experimental studies demonstrate that lncPHx2 depletion significantly enhanced liver cell proliferation and regeneration, acting as a negative regulator during the process. By interacting with mRNAs of proliferation-promoting proteins such as mini-chromosome maintenance proteins 2, 3, and 7 (MCM2/3/7), lncRNA-PHx2 effectively downregulates cell cycle genes, providing a

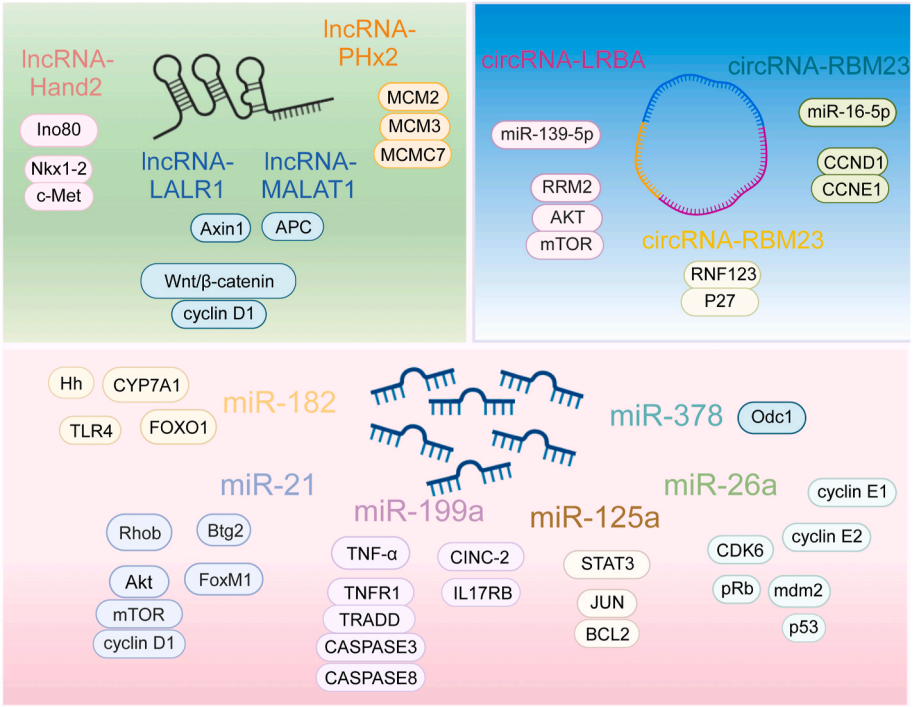

Fig. 3. Underlying molecular mechanisms of diverse ncRNAs during liver regeneration. ncRNAs target and regulate the expression and activity of multiple different genes and signalling pathways related to cell proliferation. The complex and intertwined mechanisms of ncRNAs also actively participate in cell proliferation, differentiation and apoptosis during liver regeneration. ncRNAs: non-coding RNAs.

fine-tuning mechanism for cell proliferation during LR [131]. Furthermore, several other lncRNAs exhibit upregulation in LR, indicating their promoting role in this process [132,133]. The case of lncRNA-Hand2, a branching lncRNA relative to its neighbouring coding gene Hand2, illustrates the intricate interplay between lncRNAs and liver regeneration. Highly upregulated in mouse liver cells post-hepatectomy, lncRNA--Hand2 acts as a key regulatory mediator by influencing NK homeobox 1–2 (Nkx1-2) levels through the recruitment of the Ino80 remodeling complex, thus activating c-Met signaling pathways critical for LR [134]. The significant involvement of the Wnt/β-catenin pathway, known for its critical role in cell proliferation and differentiation, further illuminates the multifaceted roles of lncRNAs in LR [135–138]. Genome-wide lncRNA microarray analysis at 2/3 PH reveals a significant increase in the levels of the LR-associated lncRNA, lncRNA-LALR1 [139]. Notably, lncRNA-LALR1 enhances mouse liver cell proliferation by promoting the cell cycle process and activating the Wnt/β-catenin signalling pathway through the suppression of Axin1, subsequently increasing cyclin D1 expression. Additionally, increased lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression in 2/3 PH mice was also observed to activate Wnt/β-catenin signalling and elevate cyclin D1 levels through the suppression of Axin1 and adenomatous polyposis coli (APC) expressions [140]. After 2/3 PH, the expression of MALAT1 in liver tissue exhibits a sharp increase, which, in turn, accelerates the progression of the liver cell cycle from the G1 to S phase and inhibits cell apoptosis, thereby promoting cell proliferation [140].

High-throughput RNA sequencing analysis detected 100 differentially expressed circRNAs in the liver tissues of three pairs of mice during LR, with 66 upregulated and 34 downregulated circRNAs [141]. Certain circRNAs exhibit distinct expression patterns during LR. For example, circRNA-0008115 and circRNA-0002498 display significant increases throughout the entire proliferative stage from 6 to 72 h, while circRNA-0004992 and circRNA-0000173 peak after 24 h of PH. Cell viability experiments validated the roles of these critical circRNAs in LR, aligning with their expression patterns, thus indicating their ability to modulate liver cell proliferation and DNA synthesis. Additionally, circRNA-RBM23, highly expressed in extracellular vesicles derived from human placenta-derived mesenchymal stem cells (hPMSCs), has been reported to play a proliferative role in L02 cells [142]. Overexpressed hPMSCs-EVs circRNA-RBM23 sponges miR-139-5p to upregulate RRM2 expression, which elevates eIF4G expression and activates the AKT/mTOR pathway. Interestingly, circRNAs derived from lipopolysaccharide-responsive beige-like anchor protein (LRBA) also exert proliferative functions during LR. Moreover, significantly upregulated circRNA-LRBA in the liver tissues after 2/3 PH strengthens liver parenchymal cell growth. Mechanistically, circRNA-LRBA reinforces the interaction between E3 ubiquitin-protein ligase ring finger protein 123 (RNF123) and p27, facilitating p27 degradation in a ubiquitination-dependent manner [143]. Another high-throughput sequencing analysis indicates differential overexpression of circRNA-14723 during the proliferation phase of rat LR. Increased circRNA-14723 levels in rat BRL-3A cells exert a critical role in accelerating G1/S transition and cell proliferation by sponging rno-miR-16-5p to upregulate CCND1 and CCNE1 levels [13]. As the field of genomic and epigenetic studies advances, the identification and functional characterization of lncRNAs and circRNAs in liver regeneration continue to provide valuable insights into their regulatory roles and mechanisms [144]. The intricate regulatory networks involving lncRNAs, circRNAs, and their interplay with miRNAs offer a rich tapestry of molecular interactions that underlie the liver's remarkable regenerative capacity. Understanding these networks in greater depth not only enhances our comprehension of liver biology but also opens new avenues for developing targeted therapies aimed at improving liver regeneration outcomes. The integration of these findings into a cohesive framework emphasizes the complexity and dynamism of epigenetic regulation in liver regeneration, setting the stage for future research aimed at unveiling the molecular intricacies of this vital process.

4. Clinical prospects of non-coding RNA for LR

Increasing evidence suggests that investigating the mechanisms of LR through the lens of ncRNA holds promise for clinical diagnosis and treatment of liver diseases related to regeneration [119,145]. Particularly, ncRNAs hold potential as diagnostic markers to evaluate LR status and function. Given the distinct changes in ncRNA expression during LR, they can serve as potential biomarkers to evaluate the activity and effectiveness of LR [50,146,147]. By measuring specific ncRNA expression levels, physicians can gauge the extent of liver function recovery based on the reflected liver cell proliferation. However, it is important to note that the majority of research on ncRNA in LR is currently based on animal models and cell experiments. Further research is necessary to validate the reliability and effectiveness of these ncRNAs in clinical applications. Additionally, ncRNA can function as therapeutic targets to regulate LR by interfering with or enhancing their expression [88,123,125,148]. This modulation can influence signalling pathways and gene expression related to LR, such as the Wnt/β-catenin pathway [126,132]. Additionally, cutting-edge approaches such as stem cell therapy and gene therapy harness the liver's regenerative ability to replace damaged tissues or address liver dysfunction caused by genetic diseases.

Overall, significant progress has been made in studying the mechanisms by which ncRNA function in LR. ncRNAs such as miRNAs, lncRNAs, and circRNAs have been found to play key roles in regulating liver cell proliferation, differentiation, and apoptosis. These findings not only deepen our understanding of the complex regulatory mechanisms of LR but also reveal the tremendous potential of ncRNAs as therapeutic targets and diagnostic markers. In terms of clinical applications, modulating the expression of ncRNAs associated with LR holds promise for developing new therapeutic strategies to promote liver cell proliferation and for using ncRNAs as biomarkers to assess the activity and effectiveness of LR, providing physicians with more accurate disease evaluation and treatment guidance. However, the prerequisite for realizing these potential applications is to validate their feasibility and efficacy through further empirical studies. Nonetheless, the application research of ncRNA in LR still faces many challenges, including the complexity of their functions, the difficulty of specific regulation under certain physiological or disease conditions, and the feasibility of clinical application. Future research needs to explore the interaction mechanisms between ncRNAs and other biomolecules more deeply and develop more precise and effective ncRNA targeting therapies and diagnostic technologies.

5. Conclusions

LR represents a profoundly intricate biological process, governed by a myriad of regulatory factors. The liver's exceptional ability to regenerate itself holds substantial promise for advancing treatments for a variety of liver diseases, including but not limited to liver cancer and liver failure. Numerous studies have shed light on the significant role of ncRNAs in the regulation of LR, encompassing miRNAs, lncRNAs and circRNAs. These diverse ncRNAs are known to undergo distinctive expression changes during the LR process, thereby influencing cell proliferation, differentiation and apoptosis, either upregulating or inhibiting these processes. The intricate impacts of ncRNA activity during liver regeneration are a testament to their potential as both biomarkers for liver disease states and targets for therapeutic intervention. For instance, specific miRNAs have been identified to play dual roles, acting as oncogenes in certain contexts while exhibiting tumor suppressor functions in others, thus influencing liver cancer progression and the liver's regenerative response post-surgery. Similarly, lncRNAs and circRNAs have been implicated in modulating the liver's response to injury and its subsequent recovery, highlighting their importance in both pathological and regenerative contexts. Given this backdrop, an in-depth examination of ncRNA expression profiles, their functional roles,

and the overarching regulatory mechanisms by which they influence LR is not just beneficial but essential. Such exploration could unveil novel ncRNA targets, whose modulation could significantly enhance liver regeneration efficiency, offering a beacon of hope for patients with severe liver diseases. Moreover, understanding the nuanced regulatory roles of ncRNAs could lead to the development of innovative, precision medicine approaches for liver disease treatment, tailored to individual patient's genetic makeup and disease pathology. As we continue to unravel the complex roles of ncRNAs in liver biology, we edge closer to a future where liver diseases can be treated more effectively and with greater precision, ultimately improving patient outcomes and quality of life.

Declaration of competing interest

All authors declare that there are no competing interests.

CRediT authorship contribution statement

Penghui Li: Writing – review & editing, Writing – original draft. **Xiao Ma:** Writing – review & editing, Writing – original draft. **Di Huang:** Writing – review & editing, Writing – original draft. **Xinyu Gu:** Writing – review & editing, Conceptualization.

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