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Review Article

Molecular Targets of microRNAs during Liver Regeneration after Acute Injury: Recent Advances

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Abstract

Experimental models using 2/3 partial hepatectomy or chemical injury have helped identify the pathways associated with liver regeneration (LR). Several microRNAs (miRNAs) have been identified as modulators of LR, but the molecular mechanisms underlying their activity are still unclear. Given the development of new therapies targeting miRNAs, this is an important question to address. This review discusses recent studies exploring the molecular mechanisms of miRNA-dependent regulation of LR. In particular, the finding that circ-RBM23 promotes LR by sequestering cytoplasmic miRNA139-5p has furthered the understanding of the molecular mechanisms underlying circRNA activity. Interestingly, although miRNAs are generally considered negative regulators of their target mRNAs, miRNAs182-5p promotes LR by upregulating *Cyp7a*. Furthermore, mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) were shown to enhance LR after 2/3 partial hepatectomy by releasing miRNAs that inhibit gene expression to promote an anti-inflammatory response or miRNA-regulatory factors. Since the administration of MSCs-EVs has no hepatotoxic side effects, this may represent a therapeutic strategy to promote LR. miRNAs also mediate LR after chemical injury. This is the case for miR194 and miR21, whose downregulation activates pro-regeneration pathways to ameliorate acetaminophen-induced liver injury. In addition, the downregulation of miR21 has been shown to improve autophagy and haemostasis after acetaminophen overdose. Although further studies are needed to improve their efficacy as therapeutics, the evidence gathered in this review has led to a better understanding of the molecular mechanisms associated with the control of LR by miRNAs.

Introduction

The liver is involved in many fundamental physiological processes, such as bile production, plasma protein synthesis, nutrient absorption and detoxification, vitamin storage, macronutrient metabolism, and support of the immune system.[1] The liver parenchyma consists of two cell types: hepatocytes and cholangiocytes. In contrast, the non-parenchymal counterpart comprises hepatic stellate cells (HSCs), liver sinusoidal endothelial cells, and resident macrophages known as Kupffer cells (KCs).[1] Liver function is primarily carried out by hepatocytes, which account for approximately 80% of liver mass.[1]

Adult hepatocytes are normally in a quiescent state; however, they can rapidly re-enter the cell cycle following various types of acute injuries, including drug-induced injury or hepatic resection. Hepatocyte regeneration is central to the restoration of normal liver size and function, and impaired liver regeneration (LR) can lead to liver failure and patient death.[2–5]

Several studies have shown that microRNAs (miRNAs) are critical regulators of LR.[5] However, most of these studies do not analyze the molecular mechanisms involved. Consequently, the scientific community is currently making significant efforts to characterize the molecular mechanisms. This seems extremely urgent given the potential therapeutic applications of miRNAs for the treatment of diseases characterized by impaired LR. In this brief review, we summarized the most recent studies (from January 2022 to December 2023) focusing on the molecular mechanisms involved in the regulation of LR after acute injury by miRNAs. The studies reported here have led to a better understanding of how miRNAs regulate LR after acute liver injury by 2/3 partial hepatectomy (PH) or acetaminophen (APAP) overdose. Based on the data obtained, several miRNAs have been proposed as novel molecular targets for tissue repair and functional recovery of LR. Although further research is needed to determine the therapeutic efficacy and safety of miRNA-based therapies, the findings presented here may enable the development of new treatments for liver diseases.

Keywords: miRNA; Liver regeneration; 2/3 partial hepatectomy; Acetaminophen; Mesenchymal stem cells; Extracellular vesicles.

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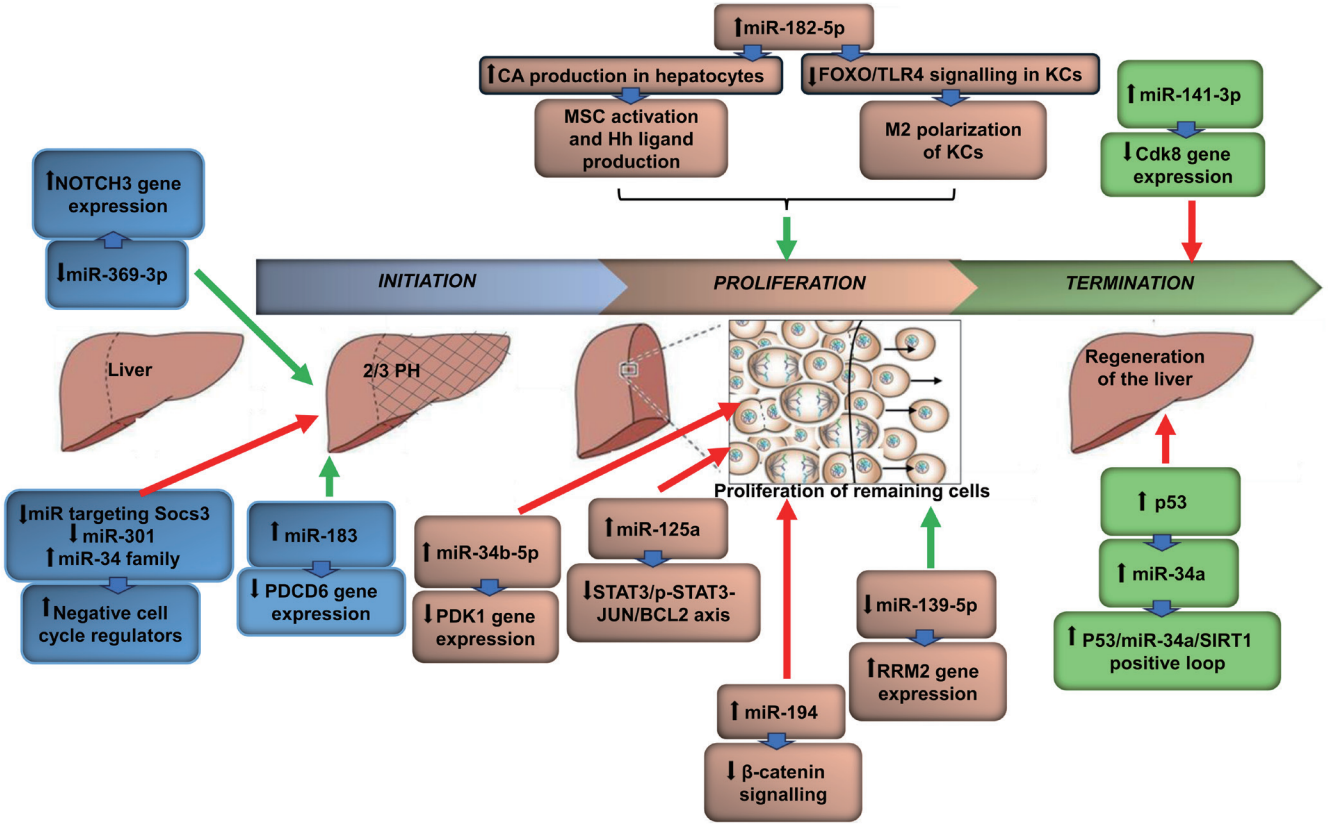

Fig. 1. miRNA changes modulating initiation, proliferation, or termination phases of liver regeneration. *Initiation phase*. Early after PH, the downregulation of miRs targeting *Socs3* and miR301 targeting *Cdk1* induces genes that inhibit cell proliferation. The same effect is also achieved by upregulating the miR34 family through the downregulation of their target genes. Conversely, the upregulation of miR183 positively mediates cell proliferation by inhibiting the gene *Pdcd6*, while the downregulation of miR369-3p promotes the G0-G1 transition by upregulating *Notch3*. *Proliferation phase.* Upregulation of miR182-5p promotes LR by inducing hepatocyte-HSC crosstalk, leading to hepatocyte proliferation, and by promoting M2 polarization in KCs through the downregulation of the FOXO1/TLR4 pathway. The downregulation of miR139-5p also promotes the proliferative phase of LR by upregulating its target *Rrm2*, which activates hepatocyte proliferation via the AKT/mTOR signaling pathway. Inhibitory signals also regulate the proliferation phase of LR. Upregulation of miR34b-5p negatively modulates hepatocyte proliferation by downregulating *Pdk1* gene expression, while the upregulation of miR194 and miR125a has the same effect by downregulating β-catenin signaling and the STAT3/P-STAT3/JUN/BCL2 axis, respectively. *Termination phase.* At later time points after 2/3 PH, upregulation of miR141-3p possibly mediates LR termination by inhibiting the *Cdk8* gene, while p53-induced upregulation of miR34a exerts the same effect through the activation of the pro-apoptotic p53/miR34a/SIRT1 positive loop. Green arrow: ACTIVATION; red arrow: INHIBITION. Akt, protein kinase B; BCL-2, B-cell lymphoma 2; HSC, hepatic stellate cells; KCs, Kupffer cells; LR, liver regeneration; miRNA, microRNA; mTOR, mammalian target of rapamycin; P-STAT3, phospho-Signal transducer and activator of transcription 3; SIRT1 , sirtuin 1; STAT3, signal transducer and activator of transcription 3.

The most common *in vivo* experimental model for studying LR is 2/3 PH in rodents.[6] After 2/3 PH, hypertrophy occurs, followed by cell proliferation, with hyperplasia being the major contributor to liver mass recovery.[7] In response to surgery, the remaining hepatocytes proliferate until the original organ size is restored without activation of progenitor cells.[8] LR undergoes three main phases: i) priming or initiation, which is associated with growth factor (GF) activation and cytokine release; ii) proliferation, which is promoted by immediate early gene or transcription factor activation; and iii) termination, which is likely driven by signaling pathways leading to inhibition of the regenerative response. Initiation of the LR response is partly related to an early increase in portal vein flow and pressure that produces shear stress on liver sinusoidal endothelial cells.[9]

Briefly, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are two key regulators of the initiation phase. Their production is mediated by the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in KCs.[2,10] Interaction with KCs makes hepatocytes more susceptible to proliferative stimuli and contributes to the progression of LR.[11] The increase in IL-6 triggers hepatocyte entry into the G1 phase by acting on Janus kinase and inducing phosphorylation of signal transducer and activator of transcription 3 (STAT3).[2,12,13]

Another cytokine that plays an important role in LR is IL-17.[14] IL-17 regulates the expression of key molecules such as IL-6, C/EBPβ, and the recently identified A20, which, in turn, reduces inflammation and promotes cell proliferation through IL-6/STAT3 and NF-κB signaling.[15–18] In addition, high levels of IL-17 interfere with the activation of natural killer T cells, which stimulate LR through IL-4 production.[16]

Hepatocyte progression into the cell cycle is ensured by GF-mediated signaling, leading to the transcription of delayed early genes encoding cell cycle regulatory proteins, namely cyclins.[19–21] The most important factors in this scenario are hepatocyte growth factor (HGF) and specific ligands of epidermal growth factor receptor (EGFR).[9] Proliferating hepatocytes release many GFs that

Table 1. miRNAs involved in liver regeneration after acute liver injury

miRNA	Sample source	Effect	Reference
miRs targeting Socs3 miR301, miR34 family	Mouse liver tissues at early time points after 2/3 PH	Inhibition of mitogenic signals early after PH.	Pal *et al*.[41]
miR182-5p	Mouse liver tissues isolated three days after 2/3 PH; Primary mouse hepatocyte cultures; Primary mouse hepatocytes/primary HCS co-cultures	Promotes Cyp7a1/colic acid (CA) signaling-dependent HSCs activation and their Hh ligand production which promote hepatocyte proliferation during LR.	Xiao *et al*.[52]
	Liver tissues from hepatectomized mice treated with Hp-MSC-derived Exo	miR182-5p contained in Hp-Exo promotes LR via inducing M2 macrophage polarization through the FOXO1/TLR4 signaling pathway.	Xu *et al*.[57]
miR183	Liver tissues from hepatectomized rats isolated from 0 to 168 h; BRL3A cell line	Promotes the initiation of liver proliferation and accelerates the cell cycle of hepatocytes by reducing the expression of its target gene *Pdcd6.*	Hou *et al*.[51]
miR369-3p	Liver tissues from hepatectomized rats isolated at 0, 6, and 24 h after surgery	Regulates *Notch3* expression in the initial phase of LR to promote G0-G1 transition.	Zhang *et al*.[44]
miR34b-5p	Liver tissues from hepatectomized mice isolated at 48 h after surgery; NCTC 1469 cell line	Negatively modulates hepatocyte proliferation by downregulating *Pdk1* expression during the progression stage of LR.	Lei *et al*.[53]
miR34a	Liver tissues from hepatectomized mice	Regulates the termination phase of liver regeneration as a part of the pro-apoptotic p53/miR34a/SIRT1 positive loop.	Gong *et al*.[55]
miR141-3p	Perfused rat livers and rat primary hepatocytes in response to hypoosmolarity-induced cell swelling; Liver tissues from hepatectomized rats (0–14 days); Rat primary hepatocytes; Huh7 cell line	Exerts a central role in the osmo- and mechanical sensing of hepatocytes. Increases after 2/3 PH, possibly mediating LR termination through *Cdk8* inhibition.	Bardeck *et al*.[56]
miR125a	Liver tissue of hepatectomized rats at 24 h after PH; BRL3A cell line	Represses hepatocyte proliferation and the proliferation stage of LR by affecting the axis of STAT3/P-STAT3/JUN/BCL2.	Zhang *et al*.[54]
miR194	Liver tissue from miR192/194 KO/WT mice treated with APAP; Liver tissues from hepatectomized miR192/194 KO/WT mice (0–7 days); AML-12 cell line	Increases liver injury after APAP overdose and negatively regulated LR by downregulating the β-catenin signaling.	Chang *et al*.[59]
miR21	Liver tissues from miR21 KO/WT mice treated with APAP	Inhibits LR by downregulating the β-catenin signaling. Retards the autophagic breakdown of damaged organelles and misfolded protein response. Directly modulates the increased expression of the hypofibrinolytic molecule PAI1	Huffman *et al*.[60]
miR139-5p	Liver tissues from hepatectomized mice treated with hPMSCs-EVs 24 h before 2/3 PH; LO2 cell line	Promotion of LR mediated by circ-RBM23 contained in hPMSCs-EVs which sponges miR139-5p in hepatocytes to inhibit the suppression of its target gene *Rrm2*.	Li *et al*.[58]

AML-12, alpha mouse liver 12 cells; APAP, acetaminophen; BCL-2, B-cell lymphoma 2; BRL3A, rat fibroblast-like cell line; FOXO1/TLR4, forkhead box protein O1/toll-like receptor4; HCS, hepatic stellate cells; Hh, Hedgehog; hPMCSCs-EVs, exosomes isolated from human placenta-derived mesenchymal cells; Hp-MSC-derived Exo, exosomes derived from bone marrow-derived hypoxic mesenchymal stem cells; Huh7, human hepatic cell line; KO, knock-out; LO2, human fetal hepatocyte cell line; LR, liver regeneration; miRNA, microRNA; NCTC 1469 cells, mouse epithelial-like cell line; PAI-1, plasminogen activator inhibitor-1; PH, partial hepatectomy; P-STAT3, phospho-Signal transducer and activator of transcription 3; SIRT1, sirtuin 1; STAT3, signal transducer and activator of transcription 3; WT, wild type.

stimulate the proliferation of non-parenchymal cells, thus orchestrating the regeneration response.[9]

Hepatocyte proliferation stops immediately when the original liver mass is restored, during the termination phase. This event is likely promoted by the activation of signal transduction pathways associated with cell growth inhibition, such as those mediated by transforming growth factor beta (TGF-β)/TGF-β receptor (TGFβR),[22] mammalian target of rapamycin (mTOR), and cell-extracellular matrix interaction.[23–25]

In clinical settings, LR occurs after chemical injuries. Among the hepatotoxic agents used to study LR, APAP overdose is particularly significant, as it represents the leading cause of acute liver failure (ALF) in the Western world.[9,26] APAP hepatotoxicity develops mainly in three phases.[26] In the initiation phase, APAP

overdose leads to the accumulation of its reactive metabolite, N-acetyl-p-benzoquinoneimine. Subsequently, the formation of radicals and cytokines, along with macrophage activation, results in centrilobular hepatocellular necrosis. In the progression phase, the initial acute liver injury (ALI) worsens. Proteolytic enzymes released from dying hepatocytes damage neighboring hepatocytes, exacerbating the injury. Finally, the injury phases of APAP hepatotoxicity are followed by a recovery phase, during which compensatory hepatocellular proliferation occurs, restoring liver size. If the regenerative response is ineffective, ALI progresses to ALF, which is associated with multi-organ failure and death.[26] Similar to the 2/3 PH model, early dose-dependent activation of EGFR and HGF receptor (MET) also occurs in mice after APAP overdose.[27,28] However, in this case, LR is more dependent on EGFR signaling, suggesting that alternative proliferation pathways cannot compensate in a toxic and inflammatory environment where timely LR is critical.[9] The expression of TNF-α and IL-6 and their downstream signaling pathways, as well as the concentrations of vascular endothelial growth factor (VEGF) and its receptors, also increase after APAP overdose in mice.[27] LR after APAP hepatotoxicity is dose-dependent and positively correlated with injury but is significantly impaired beyond a threshold. This impairment is likely due to the persistent activation of cell cycle arrest signaling pathways and DNA damage, without activation of DNA repair mechanisms in perinecrotic hepatocytes.[26,27,29,30] A key role for TGF-β1 in promoting cell cycle arrest in uninjured perinecrotic hepatocytes has also been demonstrated in mice.[29] Despite these findings, the processes involved in LR during APAP hepatotoxicity are still poorly understood; further studies are crucial for developing regenerative therapies for the treatment of drug-induced ALF.[9]

miRNAs are endogenous, single-chain, non-coding RNAs that are 18–25 nucleotides long. They bind to complementary sequences on protein-coding mRNAs, causing their degradation or translational repression.[31] miRNAs control various cellular and developmental processes, and dysregulation of their expression is associated with many human diseases.[32–34] Therefore, circulating miRNAs are considered potential biomarkers for a wide range of diseases.[34]

Several studies have shown the involvement of miRNAs in the regeneration response. During LR, miRNAs provide the necessary dynamics for liver cells to promptly adapt to an altered environment or signaling messages.[35] These changes in miRNA expression drive hepatocyte proliferation, innate immunity, and angiogenesis. Conversely, impaired LR is associated with specific miRNAs that enhance cell cycle arrest and promote DNA methylation.[5] After 2/3 PH in rodents, the priming phase of LR is associated with several miRNAs targeting genes involved in cell apoptosis, survival, cell cycle, inflammation, metabolism, etc.[5] Previous studies have shown the most significant change in miRNA profiles occurs during the peak of DNA replication, which is 24 h after surgery in the rat liver.[36] Genome-wide microarray studies have revealed a biphasic miRNA expression pattern in hepatectomized rats, showing upregulation of approximately 40% of miRNAs early after surgery, while up to 70% were downregulated 24 h post-PH.[37] Subsequent analyses suggested that the early upregulation of specific miRNAs might mediate the downregulation of miRNA processing genes, leading to a global decrease in miRNAs observed 24 h after surgery.[37] It is hypothesized that the early phase after 2/3 PH is associated with the upregulation of specific miRNAs that promote the priming phase of LR, where hepatocytes are refractory to growth signals. Their downregulation 24 h after surgery is ultimately required for efficient liver tissue recovery.[37]

Overall, after 2/3 PH, some miRNAs are overexpressed while others are under expressed. These dynamic variations contribute to the modulation of the complex and articulated process of LR.[38] As discussed in detail elsewhere, the best-studied miRNA in LR is miR21, which regulates LR either positively or negatively by targeting multiple genes.[5] However, the exact mechanisms by which individual miRNAs regulate LR are still largely unknown.

Following APAP overdose, several miRNAs are readily detectable in the blood of mice and humans even before liver enzyme levels increase, and their levels correlate with the histopathology of liver degeneration. Therefore, miR122 and miR192, among others, are considered reliable biomarkers for APAP-induced hepatotoxicity.[35,39,40] However, their involvement in LR cannot be excluded.

miRNAs as modulators of LR after 2/3 PH

Initiation phase

Recently, Pal *et al*.[41] performed a transcriptomic and miRNomic analysis of livers from mice sacrificed at early time points after 2/3 PH (LR). Although a large number of genes are deregulated after 2/3 PH, most are thought to be related to both the reconstitution of liver mass and the stress response. In addition, miRNAs controlling negative regulators of the cell cycle, such as miR106a-5p, miR340-5p, miR196b-3p, and miR455-5p targeting Socs3, and miR301 targeting *Cyclin-dependent kinase inhibitor 1a*, were downregulated at early time points after surgery, accompanied by the increased expression of their target genes. Additionally, there was a strong upregulation of the oncosuppressor miR34 family, a known mediator of the termination phase of LR, after 2/3 PH.[42] The activation of inhibitory signals after surgery is consistent with the fact that the initiation phase of LR is a preparatory event characterized by refractoriness to DNA synthesis.

Overall, these results support the concept that mitogenic signaling is actively inhibited early after surgery.[37,43]

In a recent study by Zang *et al*.,[44] Large-scale quantitative detecting and analyzing was used to determine the regulation of hepatocyte proliferation by competing endogenous RNAs during the initiation phase of LR in rats. Competing endogenous RNAs include noncoding RNAs, mRNAs, and transcribed pseudogenes that regulate each other by competing for shared miRNAs.[45] Noncoding RNAs include circular noncoding RNAs (circRNAs), which increase the complexity of RNA regulatory networks by acting as miRNA sponges, thereby repressing the functional activity of miRNAs.[46] In the study by Zang *et al*.,[44] miR369-3 and the circRNA rno-Rmdn 2_0006, which interacts with miR369-3 and inhibits its activity, were found to affect the expression of G0 and G1 phase genes during LR by regulating the expression of *Notch3*. Notch3, a member of the Notch family, promotes cell proliferation.[47–49] Overall, the results indicated that *Notch3* mRNA is affected by miR369-3p at 0 h. Inhibition of *Notch3* by miR369-3p at 0 h leads to inhibition of *Notch3*-mediated activities, such as the upregulation of G1 phase genes and the inhibition of G0 phase genes, resulting in hepatocytes remaining in the G0 phase. However, the decreased expression of miR369-3p 6 h after surgery, possibly due to inhibition mediated by rno-Rmdn 2_0006, leads to an increase in Notch3 protein, which promotes the expression of G1 phase genes and inhibits the expression of G0 phase genes. Consequently, the hepatocytes enter the G1 phase. As reported in detail elsewhere, activation of Notch signaling during LR plays a key role in regulating other important events besides hepatocyte proliferation, such as biliary regeneration and neovascularization

of the newly formed liver tissue.[50]

These results have shown that miR369-3p-mediated Notch3 regulation is crucial in triggering the initial phase of LR (Fig. 1, Table 1).[41,44,51–60] This finding represents progress in characterizing the molecular mechanisms underlying LR initiation following 2/3 PH.

Another miRNA that has recently attracted attention for its role in LR is miR183. Based on previous studies showing strong miR183 upregulation early after 2/3 PH, Hou *et al*. recently attempted to characterize the molecular mechanisms underlying miR183 upregulation during LR in hepatectomized rats.[51,61] The results showed that the expression levels of miR183 peaked at 2 h and 120 h after surgery. Consistently, upregulation of miR183 induced the transition to the G0/G1 phase and subsequent entry into the S phase in a rat fibroblast cell line (BRL-3A), suggesting that miR183 may promote LR by stimulating cell proliferation. Interestingly, the expression of the miR183 target *Programmed cell death protein 6 (Pdcd6)* was inversely correlated during LR. The *Pdcd6* gene encodes a calcium-binding protein that plays an important role in promoting apoptosis.[62] In addition, the Pdcd6 protein has been shown to bind to VEGFR2, possibly inhibiting VEGFR2-mediated angiogenesis.[63] Therefore, the inhibition of *Pdcd6* by miR183 upregulation in the initiation phase of LR might be related to the promotion of angiogenesis as well as the facilitation of liver proliferation. Overexpression of miR183 was able to positively regulate LR in hepatectomized rats. *In vitro* experiments showed that miR183 directly regulated the expression of the *Pdcd6* gene, which was inversely correlated with miR183 expression. Accordingly, inhibition of miR183 or overexpression of *Pdcd6* resulted in cell cycle arrest, while upregulation of miR183 or silencing of *Pdcd6* had the opposite effect.

Overall, the study by Hou *et al*.[51] showed that overexpression of miR183 can promote cell cycle initiation and acceleration in hepatocytes by reducing Pdcd6 expression (Fig. 1, Table 1). Although the role of Pdcd6 in mediating the effects of miR183 on LR requires further characterization, this finding has helped clarify the role that overexpression of miR183 plays during LR.

Proliferation phase

The LR is strongly influenced by the dynamic interaction between different resident cell types. In particular, HSCs contribute to regulating LR after 2/3 PH by releasing various GFs and cytokines. However, the molecular mechanisms that stimulate the secretory activity of HSCs after surgery still need elucidation.[64,65] Recently, Xiao *et al*.[52] have shown that miR182-5p plays a key role in regulating LR in mice by promoting hepatocyte-HSC crosstalk. Their results demonstrated that in mouse models where miR182-5p was either downregulated or upregulated, hepatocyte proliferation after 2/3 PH correlated positively with miR182-5p expression.[52] However, overexpression or inhibition of miR182-5p had no significant effect on cell proliferation in primary hepatocytes, while it stimulated proliferation when hepatocytes were cultured with non-parenchymal cells. Previous *in vitro* experiments revealed that hepatocyte-derived miR182-5p promotes hepatocyte proliferation via HSC-dependent activation of the Hedgehog (Hh) signaling pathway in hepatocytes.[66,67] Accordingly, Xiao *et al*. found that overexpression of miR182-5p in hepatocytes during LR resulted in *Cyp7a1*-mediated production of colic acid (CA) from hepatocytes.[52] Once released in the liver, CA promoted the production of Hh ligands from HSCs, which activated the Hh signaling pathway in hepatocytes, triggering their proliferation. Interestingly, the expression of *Cyp7a1* was strongly suppressed 24 h after surgery but gradually increased in the proliferation phase, associated with the upregulation of miR182-5p. However, the mechanisms underlying the positive role of miRNA182-5p in the translation of the *Cyp7a1* gene have not been characterized in this study and require further analysis.

Notably, conflicting results have been reported regarding the temporal activation of miRNA182-5p in rats and mice, placed in the initiation phase of rat LR by Geng *et al*.[61] and in the proliferation phase of mouse LR by Xiao *et al*.[52] However, while in rat liver miR182-5p, whose expression was analyzed from 2 h to 168 h, seems to effectively regulate the initiation phase, its involvement in both the initiation and proliferation phases cannot be excluded in mice, as the earliest time point analyzed in mouse livers was 24 h. Further studies could help better clarify the role of miRNA182-5p in LR.

Overall, the study by Xiao *et al*.[52] helped clarify the molecular mechanisms that stimulate HSC secretory activity after 2/3 PH by revealing a novel molecular mechanism based on the crosstalk between hepatocytes and HSCs, which is promoted by the activation of miR182-5p (Fig. 1, Table 1). Moreover, upregulation of miR182-5p has been shown to mediate the proliferation phase of LR in mice by positively regulating *Cyp7a1* expression in hepatocytes. Therefore, this study provides new evidence for the positive regulation of mRNA expression by miRNAs.

Recently, Lei *et al*.[53] investigated the regulatory networks of long noncoding RNA-miRNA-mRNA involved in LR in hepatectomized mice 48 h after surgery. Analysis of genes differentially expressed during LR revealed associations with biological processes closely related to hepatocyte proliferation, involving important signaling pathways, such as Wnt, mitogen activated protein kinase (MAPK), Ras, and mTOR, which are highly interconnected.[53] Regarding miRNAs, Lei *et al*.[53] found that the upregulation of miR34b-5p negatively modulated the expression of *3-Phosphoinositide-dependent kinase 1 (Pdk1)* mRNA and protein during the progression of hepatocyte proliferation. The *Pdk1* gene encodes a component of the PI3K/PDK1/Akt signaling pathway, which plays a central, albeit controversial, role in LR after PH.[68–70] In Lei's study, *in vitro* experiments showed that the interaction between miR34b-5p and *Pdk1* mRNA led to the inhibition of hepatocyte proliferation.[53]

This study, for the first time, characterized the role of the miR34b-5p/PDK1 axis in hepatocyte proliferation and demonstrated its negative modulation of this process. Based on this finding, the miR34b-5p/PDK1 axis may represent a novel molecular target for regulating LR in clinical settings.

miR125a-5p has been shown to negatively modulate the proliferation and metastasis of hepatocarcinoma (HCC) and viral replication in the liver.[71,72] In addition, its downregulation was recently found to protect against chemical liver injury by modulating hepatocyte proliferation and apoptosis.[73] Despite reports of miR125a upregulation 2 h after 2/3 PH, its role in LR has not been fully characterized. Therefore, Zhang *et al*.[54] recently investigated the role of miR125a-5p in LR in rats sacrificed 24 h and 30 h after surgery. Their results indicated that miR125a was strongly downregulated in rat livers after 2/3 PH. Moreover, cell transfection experiments showed that the upregulation of miR125a suppressed the G1/S transition as well as the proliferation phase in BRL-3A cells. Proliferation signaling pathway screening revealed an inverse correlation between miR125a and *Stat3* in regenerating rat livers and BRL-3A cells. STAT3 is a complex transcription factor that can regulate numerous processes such as apoptosis, proliferation, differentiation, and survival.[74] Recent studies have reported

that STAT3 can either promote or suppress tumorigenesis depending on the oncogenic environment, alternative mRNA splicing, and integration of different signals.[74] Previous studies in human cancer samples demonstrated the synergistic activity of STAT3 and c-JUN proteins, leading to the identification of the pro-survival *C-JUN* or the anti-apoptotic *BCL-2* genes as downstream targets of STAT3 in tumorigenesis.[74] Accordingly, Zhang *et al*.[54] found that the upregulation of miR125a was correlated with the inhibition of the expression of STAT3, p-STAT3, JUN, and BCL2 in cultured hepatocytes and livers from hepatectomized mice.

Overall, this study characterized the role of miR125a in LR and demonstrated that it acts as a negative regulator of the proliferation phase of LR by affecting the STAT3/P-STAT3/JUN/BCL2 axis (Fig. 1, Table 1). Since this axis is also involved in promoting human carcinogenesis, miR125a has been proposed as a potentially promising new molecular target for both modulating LR and treating liver carcinomas.[54]

Termination phase

Previous studies have demonstrated that miR34a inhibits LR after 2/3 PH in rats.[42] Specifically, it acts as a direct target of p53 and is part of a positive feedback loop with p53 and the *Silent Information Regulator 1 (SIRT1)* gene. In this loop, p53 activates miR34a, which in turn induces acetylation and transcription of *p53* by repressing the nicotinamide adenine dinucleotide-dependent deacetylase SIRT1, ultimately promoting cell apoptosis.[75] Building on this understanding, Gong *et al*.[55] recently aimed to further characterize the involvement of the p53/miR34a/SIRT1 positive feedback loop in LR termination in hepatectomized mice. The results showed that this loop was strongly activated in the late stage of LR. Furthermore, the overexpression of p53 increased hepatocyte apoptosis during LR and anticipated its termination. Conversely, knock-down of miR34a abolished the p53/miR34a/SIRT1 positive feedback loop and suppressed LR termination. Interestingly, increased p53 expression during the initiation phase failed to stimulate the p53/miR34a/SIRT1 positive feedback loop.

Previous studies have shown that the activation of miR34a by p53 can be inhibited by the farnesoid X receptor/small heterodimer partner (FXR/SHP) signaling pathway. Since the ligands of FXR also include bile acids (BAs),[76] Gong *et al*.[55] investigated the involvement of BAs in LR as activators of this signaling pathway. The data obtained showed that the total amount of BAs was higher in the early phase of LR and lower in the termination phase, with a gradual increase in the proportion of T-β-muricholic acid (MCA) in the total amount of BAs. Consistent with the identification of T-β-MCA as an FXR antagonist,[77] subsequent analyses showed that T-β-MCA suppressed the FXR/SHP signaling pathway and enhanced the proapoptotic effects of the p53-activated positive feedback loop p53/miR34a/SIRT1, both *in vitro* and *in vivo*. Since impairment of LR termination may lead to hepatocarcinogenesis, the relationship between the p53/miR34a/SIRT1 positive feedback loop and tumorigenesis in human HCCs was next investigated. The results showed that this positive feedback loop was deficient in p53-mutated and p53-deficient tumors.[55]

Overall, this study has shed light on the molecular mechanisms associated with the termination phase of LR by better characterizing the involvement of the p53/miR34a/SIRT1 positive feedback loop in mediating the process and identifying the factors involved in its regulation (Fig. 1, Table 1). Furthermore, a link between deficiency in the p53/miR34a/SIRT1 positive feedback loop and the promotion of hepatocarcinogenesis was discovered, providing new insights for the treatment of malignant liver diseases.

The initiation of cell proliferation can be controlled by changes in cell volume.[78] In particular, it has been reported that hepatocyte swelling induced by hypoosmolarity or insulin triggers hepatocyte proliferation mediated by integrin and c-Src kinase-dependent EGFR activation.[79,80] Nevertheless, the role of miRNAs in hepatocyte swelling-associated osmosignaling is largely unknown. Therefore, Bardeck *et al*.[56] recently analyzed the role of miRNAs in rat livers perfused with a hypoosmotic medium to induce cell swelling. It was found that the expression of miR141-3p was upregulated in perfused rat livers, which was accompanied by the downregulation of its target genes. The same results were obtained in primary hepatocytes under hypoosmotic conditions. The upregulation of miR141-3p required Src-mediated activation of Erk and p38 MAPK, known downstream effectors of hypoosmotically induced signaling pathways.[56,80] Furthermore, the addition of colchicine to the perfusion buffer prevented the upregulation of miR141-3p under hypoosmotic conditions. Since colchicine triggers depolymerization of the microtubule network, this suggests a possible involvement of miR141-3p in microtubule formation and inhibition of proteolysis associated with hepatocellular swelling.[81] Overall, these data suggest the involvement of miR141-3p in hypoosmolarity-induced osmotic signaling pathways.

miR141 is frequently dysregulated in malignant tumors, where it controls epithelial-to-mesenchymal transition, apoptosis, proliferation, and metastasis, strongly influencing tumor development and progression.[82] Among the genes that were downregulated at hypoosmolarity in association with upregulation of miR141-3p, Bardeck *et al*. identified *Cyclin-dependent kinase 8 (Cdk8)* as a direct target of miR141-3p. Since Cdk8, as part of the mediator complex, regulates the transcription of almost all RNA polymerase II-dependent genes, and miR141-3p plays a role in cell proliferation, their expressions were also analyzed in hepatectomized rats.[56,82,83]

Interestingly, miR141-3p upregulation and *Cdk8* mRNA downregulation were simultaneously detected three days after surgery, indicating their possible involvement in the termination phase of LR. Moreover, overexpression of miR141-3p inhibited both the expression of its target genes in primary hepatocytes and the proliferation of human hepatoma cells.[56] In the latter case, upregulation of miR141-3p inhibited tumor cell proliferation without affecting their viability, suggesting the triggering of a counterregulatory antiproliferative response.

During hypoosmotically induced cell swelling, compression and stretching of liver cells occur.[84] Similarly, mechanical stretching of hepatocytes can be observed after a 2/3 PH, due to the flow of blood volume from the portal vein through a liver reduced to 1/3 of its normal mass. Consistent with this, Bardeck *et al*.[56] found miR141-3p upregulation and decreased *Cdk8* expression, albeit not significantly, in primary rat hepatocytes seeded in a stretch chamber.

Although the importance of miR141-3p and Cdk8 as regulators of LR needs further characterization, these data suggest a central role of MAPK-mediated miR141-3p activation in hepatocyte osmo- and mechanosensing. MAPK-mediated proliferation signaling may increase miR141-3p to create a negative feedback loop, preventing excessive hepatocyte growth during liver repair (Fig. 1, Table 1).

Regulation of LR after 2/3 PH by miRNAs contained in mesenchymal stem cell (MSC)-derived extracellular vesicles

Infusion of MSCs after 2/3 PH has been shown to improve the LR response.[85] MSCs are a heterogeneous group of multipotent

stromal cells present in many tissues and endowed with therapeutic properties in acute and chronic liver diseases due to their self-renewal potential, differentiation capacity, and immunomodulatory role.[86] Recently, accumulating evidence has shown that the secretion of extracellular vesicles (EVs) by MSCs strongly influences their biological functions.[87] Among EVs, exosomes (Exo) form a group characterized by a diameter of 30 to 160 nm, which may mediate intercellular transitions by transferring various biologically active substances such as proteins, mRNA, and miRNAs.[87] These miRNA-containing EVs can be taken up by neighboring cells or enter the circulation, allowing miRNA-dependent modification of gene expression in recipient cells both locally and distally. MSC-Exo have previously been shown to replace MSCs in improving recovery in animal models of LR.[88] Based on this, Xu *et al*.[57] recently investigated the ability of MSCs to improve LR after 2/3 PH in mice and the potential involvement of Exo in this event. Since hypoxia treatment stimulates the proliferation of MSCs, this study was performed using bone marrow-derived (BM) hypoxic MSCs (Hp-MSCs).[57,89] The results showed that BM-Hp-MSCs improve LR in hepatectomized mice mainly through the secretion of exosomes. Accordingly, treatment with exosomes from BM-Hp-MSCs (Hp-Exo) promoted LR after 2/3 PH and reduced liver injury in hepatectomized animals compared to controls. Remarkably, Hp-Exo were found to be taken up by liver macrophages, which subsequently underwent M2 polarization, resulting in anti-inflammatory and tissue repair responses.[57] miRNA array analysis showed the enrichment of miR182-5p in Hp-Exo, suggesting its contribution to the enhancement of their anti-inflammatory effects. Accordingly, miR182-5p inhibition partially abrogated the beneficial effects of Hp-Exo on macrophage M2 polarization both *in vitro* and *in vivo*.[57] The *Foxo1* gene, a known regulator of macrophage polarization through toll-like receptor (TLR)-mediated signaling, was identified as the target of miR182-5p in inducing M2 polarization of KCs.

Taken together, these results suggest that miR182-5p promotes LR after 2/3 PH by inducing Hp-Exo-mediated M2 macrophage polarization, targeting the FOXO1/TLR4 pathway (Fig. 1, Table 1). These results, similar to those of Xiao *et al*., highlight the role of miRNA182-5p in promoting LR.[52,57]

The effects of MSC-derived EVs on LR were also investigated by Li *et al*.[58] In this study, mice were intravenously administered EVs isolated from human placenta-derived MSCs (hPMSCs-EVs) 24 h before 2/3 PH. The data obtained showed that pretreatment with hPMSCs-EVs promoted LR and exerted a hepatoprotective effect. Molecular analysis showed that hPMSCs-EVs contained circRNAs. Among these, circ-RBM23 showed the highest expression, and its silencing significantly reduced hepatocyte proliferation *in vitro*, suggesting that its upregulation could stimulate hepatocyte growth. Bioinformatic analysis led to the identification of miR139-5p as the most important potential miRNA target of circ-RBM23, and molecular analyses confirmed their interaction. Furthermore, upregulation of circ-RBM23 was associated with a decrease in miR139-5p in 2/3 PH animals. Taken together, these results suggest that circ-RBM23 may sponge miR139-5p to inhibit its function in hepatocytes during LR. Inhibition of miR139-5p by circ-RBM23 resulted in the upregulation of the miR139-5p target gene *Ribonucleotide reductase regulatory subunit M2 (Rrm2)*, which encodes an enzyme that catalyzes deoxyribonucleotide synthesis.[90] Upregulation of *Rrm2* in hepatocytes treated with hPMSCs-EVs and in mice in which circ-RBM23 was silenced 24 h before surgery promoted hepatocyte proliferation via the protein kinase B (AKT)/mTOR signaling pathway, a known mediator of RRM2 action.[91,92] The study by Li *et al*. is the first to report a link between circ-RBM23 and LR.[90] Overall, these results show that circ-RBM23 delivered by hPMSCs-EVs promotes hepatocyte proliferation by sponging miR139-5p via the RRM2/AKT/mTOR signaling pathway (Fig. 1, Table 1). Remarkably, the proliferative effect of hPMSCs-EVs in hepatectomized mice was devoid of hepatotoxic effects, indicating the potential usefulness of these vesicles as therapeutic agents for tissue repair and functional recovery in LR.

miRNAs as modulators of LR after chemical injury

Several studies have shown that miR192/194 are suitable biomarkers for ALI due to their rapid serum increase after liver injury.[93] To characterize the role of miR192/194 in ALI, Chang *et al*.[59] generated miR192/194 knock-out mice and established an animal model of ALF by APAP administration. Remarkably, the livers of the mutant mice appeared physiologically normal, with no spontaneous damage associated with the loss of miR192/194. The data obtained showed that depletion of miR192/194 protected the liver from APAP-induced damage. Accordingly, loss of miR192/194 promoted liver cell proliferation and reduced cell death after APAP treatment. In addition, a strong upregulation of molecules that protect the liver from APAP damage, such as FXR and hepatic glutathione (GSH), was also observed.[94,95] Overall, these data suggest that the loss of miR192/194 may protect the liver from APAP by activating genes that promote liver proliferation, reduce cell death, and increase GSH synthesis. The same study also examined LR in both mutant and control mice one to seven days after 2/3 PH, which is a better-synchronized proliferation model compared to APAP treatment. The results confirmed that the mutant livers proliferated more than the control livers during LR. Moreover, the expression of β-catenin target genes (e.g., *glutathione synthase*) and of the Wnt/Fzd receptors CTNNB1 and FZD6 were higher in the APAP-treated mutant mice than in the treated controls 6 and 12 h after treatment. Similar results were obtained in the hepatectomized groups with or without APAP administration (Fig. 1, Table 1). In addition, immunohistochemical analysis showed that after 2/3 PH, glutathione synthase staining was higher in the mutant livers than in the control livers. It was also shown that β-catenin was responsible for protection against APAP toxicity, as its inhibition reduced both the expression of β-catenin target genes and liver injury in APAP-treated mutant mice. Finally, *in vitro* transfection studies revealed that only miR194, and not miR192, regulates β-catenin signaling.[59]

Overall, this study has characterized the biological role of miR194 during drug-induced ALI. miR194 depletion can either promote LR after APAP overdose and 2/3 PH or protect from APAP-induced liver injury by upregulating β-catenin signaling. These data suggest that downregulation of miR194 can promote hepatocyte proliferation after acute injury by inducing the β-catenin signaling pathway (Fig. 1, Table 1). Remarkably, liver proliferation was not spontaneously activated in the mutant mice, suggesting that miR194 depletion was not associated with changes in normal liver physiology or oncogene promotion. Therefore, downregulation of miR194 may serve as a valuable therapeutic option in acute liver injury.[59]

miR21 has been shown to regulate gene expression in various liver diseases. Specifically, higher serum concentrations of miR21 have been found in AFL patients during the spontaneous recovery phase, while its inhibition has been shown to exacerbate acute liver injury.[96,97] Nevertheless, the role of miR21 in APAP-induced

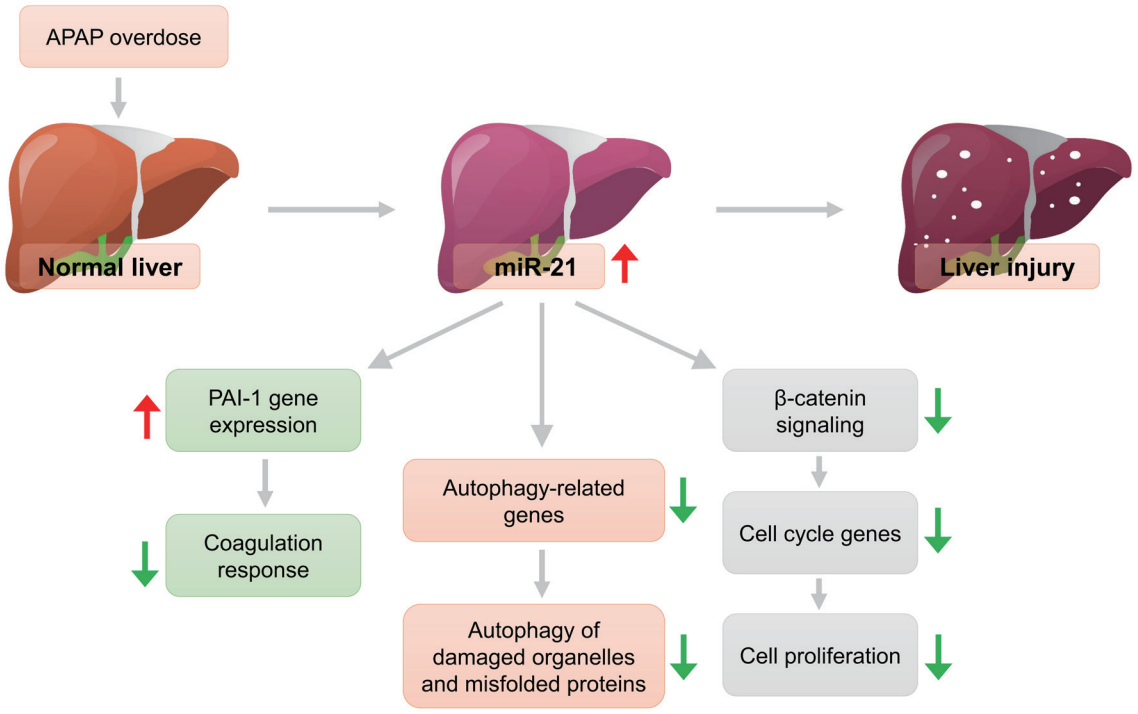

Fig. 2. Role of miRNA21 in APAP-induced liver injury. Upregulation of miR21 during APAP hepatotoxicity inhibits hepatocyte proliferation by downregulating the β-catenin signaling pathway. Additionally, miR21 overexpression affects liver repair by inducing changes in gene expression, leading to the downregulation of autophagy and haemostasis. APAP, acetaminophen.

liver injury is largely unknown. Therefore, recently Huffman *et al*.[60] investigated the role of miR21 in APAP-induced liver injury using miR21 knock-out (miR21KO) mice. Their results showed that the mutant mice were protected from APAP-induced toxicity and exhibited increased LR compared to wild type (WT) mice. Although liver injury was similar in both groups 6 h after treatment, enhanced recovery, arrest of necrosis progression, and sustained liver repair were observed 24 h after treatment only in the mutant mice. Additionally, activation of the Wnt/β-catenin signaling pathway was observed at 24 h only in the APAP-treated mutant mice, which was associated with the increased expression of the β-catenin target *cyclin D1*.[27,60] Furthermore, miR21 KO mice exhibited increased PCNA (proliferating cell nuclear antigen) protein levels at the same time point, whereas these were unchanged in APAP-treated WT mice. Overall, these results suggest that miR21 may delay LR by affecting the proliferation phase of recovery. Notably, increased proliferation due to miR21 overexpression has been demonstrated in several human cancers.[98] Nevertheless, several studies are consistent with the results obtained by Huffman *et al*. in WT mice 24 h after APAP treatment, where increased expression of miR21 was associated with impaired hepatocyte proliferation.[60,99,100] Therefore, it was hypothesized that the proliferative role of miR21 may be tissue-specific and absent in noncancerous cells. Moreover, since *Tgfb1* expression was found to be upregulated at 24 h only in APAP-treated WT mice, which showed decreased expression of proliferation markers compared to mutant mice, it was hypothesized that miR21 inhibited LR rather than promoted proliferation.[60]

Selective autophagy has been shown to favor the repair process after APAP intoxication by removing damaged mitochondria.[101] Consistent with this, Huffman *et al*.[60] found that mutant mice showed stronger activation of autophagy-related genes 24 h after APAP treatment than WT mice. This suggests that miR21 delays the autophagic degradation of damaged organelles and the response to misfolded proteins, thereby impairing LR after APAP overdose.[60] Finally, this study is the first to report that miR21 directly modulates the increased expression of the gene encoding the hypofibrinolytic molecule PAI1 after APAP overdose, as its depletion significantly restricted this increase and thus improved the hypofibrinolytic state in miR21KO mice.

In summary, this study identified three signaling pathways that could be beneficially modulated by miR21 downregulation during the recovery phase after APAP hepatotoxicity, namely cell regeneration, autophagy, and coagulation homeostasis (Fig. 2, Table 1). Although longer follow-up studies are required, these results suggest that downregulation of miR21 may represent a therapeutic means to improve LR after APAP-induced injury.

Future perspectives

miRNA deregulation is associated with liver damage, fibrosis, and HCC development; therefore, miRNAs represent a promising therapeutic strategy for treating liver diseases.[102] Due to their high stability and easy detection in the bloodstream, miRNAs are considered superior biomarkers for early diagnosis, prognosis, and liver disease evaluation compared to conventional biomarkers.[103] As comorbidities can alter miRNA profiles, particularly in liver disease patients, high-throughput detection methods have been developed to obtain a global profile of circulating miRNAs, aiding in identifying a panel of miRNAs as biomarkers with improved diagnostic sensitivity and/or specificity.[103] However, extreme caution is required when developing miRNA-based therapeutic options, as

miRNAs can affect multiple downstream mRNA targets, and their functions are largely cell-type-specific. Therefore, altering a particular miRNA may have unexpected off-target effects that should be considered and avoided.[104] On this basis, characterizing the molecular mechanisms underlying miRNA actions is fundamental to improving their therapeutic efficacy. In this context, the studies summarized in this brief review shed light on the molecular strategies employed by miRNAs to regulate LR caused by 2/3 PH or APAP overdose, aiding in the development of new therapeutic approaches for liver diseases associated with impaired LR. For example, the studies reported here have advanced the understanding of the molecular mechanism underlying the activity of circRNAs.[44,58] This is particularly important because, although circRNAs play an active role in various liver diseases,[105] their therapeutic application is currently limited by the few reports on their mechanism of action and upstream regulatory targets.[105] In addition, it has been shown how MSC-derived EVs could improve LR by releasing miRNAs inhibiting gene expression to promote an anti-inflammatory response or by releasing miRNA-regulatory factors, such as circRNAs.[57,58] Remarkably, administration of MSCs-EVs was found to improve LR without inducing hepatotoxic effects, suggesting their potential utility as therapeutic agents for tissue repair and functional recovery in LR. Recently, there has been increasing evidence for the importance of MSC-derived EVs in mediating the biological functions of MSCs.[87,88] EVs have low toxicity and high stability and are preferentially taken up by the liver, making them attractive delivery vehicles for miRNA-based therapies.[103] Moreover, it has been shown that exosomal miRNAs promote the progression of liver disease.[106] Therefore, interrupting specific miRNA transport mediated by EVs has been proposed as a novel therapeutic strategy for the treatment of liver disease.[103] However, some unanswered questions limit the therapeutic use of EVs, such as their kinetics, toxicity, off-target effects, and uptake.[35] In this context, the recent availability of genetic tools, such as reporter mice and novel reporters for exosome secretion and uptake in living cells, as well as the identification of highly sensitive exosome isolation and purification protocols, could enable the development of new therapies for liver diseases.[107] Finally, protection against APAP-induced ALI is associated with the downregulation of miR194 and miR21 expression.[59,60] Interestingly, antisense oligonucleotide (ASO)-based therapies targeting miR21 are currently in clinical trials to treat pathologic conditions such as cardiovascular disease.[108] ASOs are used to regulate the expression of mRNAs and noncoding RNAs. However, many aspects of the clinical application of ASO-based therapies still need clarification. The major hurdles to overcome in ASO-based therapeutic strategies are reducing potential off-target and unwanted on-target effects, improving potential immunostimulatory effects, reducing liver and kidney toxicity, and improving delivery to disease-specific sites. Therefore, further studies are needed to improve their efficacy as therapeutic agents.[108]

Overall, although many challenges remain, these studies have provided a deeper understanding of molecular targets of miRNAs that contribute to developing new liver disease therapies.

Conclusions

The studies reported here demonstrate that miRNAs are deeply involved in controlling LR by directly and indirectly regulating the expression of genes associated with cell proliferation and liver repair. As for the 2/3 PH model, miRNA-mediated regulation of gene expression was observed in each phase of LR. Overall, modifications in miRNAs during the initiation and proliferation phases result in both inhibition and activation of proliferation signaling. Since the initiation phase is characterized by refractoriness to proliferative stimuli, the activation of inhibitory signals is consistent, while the activation of proliferative signals is less clear. In this context, it is important to note that changes during this phase should be considered beneficial for both cell cycle entry and preparation for entry. In particular, the activation of proliferation genes by miRNAs in the initiation phase might mediate processes involved in LR beyond hepatic cell proliferation, such as metabolic remodeling associated with liver resection.

On the contrary, the integration of positive and negative proliferation signals during the proliferation phase is crucial for ensuring a safe and stable LR. Indeed, activating inhibitors during this phase may prevent an overshooting of the regeneration response that could lead to adverse effects such as HCC development. Therefore, although their effect on LR needs further characterization, these miRNAs might be considered potential novel targets for regulating LR and HCC development.

Compared to the other two phases, molecular mechanisms associated with the termination phase of LR have been less studied. Given the risks associated with sustaining the regeneration response, characterizing these mechanisms is urgently needed. The reviewed studies indicate that the upregulation of miRNAs promotes LR termination by triggering pro-apoptotic signaling while inhibiting proliferation signaling.

Lastly, two recent studies discussed here demonstrate that miRNAs may serve as therapeutic tools for treating APAP-mediated liver injury.

Although a deeper understanding of miRNA-dependent molecular strategies to regulate LR is necessary, these studies have helped identify new potential molecular targets for the diagnosis and therapy of liver disease.

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Conflict of interest

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Author contributions

Review concept and design, illustration preparation, and data collection (MP), data interpretation (MP, RL), and drafting and revision of the manuscript (MP, RL, GS). All authors have made significant contributions to this paper and have approved the final text.

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