Review Article

Role of microRNA in liver regeneration

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BACKGROUND: Liver regeneration is a complex process. microRNAs (miRNAs) are short, single-stranded RNAs that modify gene expression at the post-transcriptional level. Recent investigations have revealed that miRNAs are closely linked to liver regeneration.

DATA SOURCES: All included studies were obtained from PubMed, Embase, the ScienceDirect databases and Web of Science, with no limitation on publication year. Only studies published in English were considered.

RESULTS: We grouped studies that involved miRNA and liver regeneration into two groups: miRNAs as promoters and as inhibitors of liver regeneration. We summarized the relevant miRNAs separately from the related pathways.

CONCLUSIONS: Blocking or stimulating the pathways of miRNAs in liver regeneration may be novel therapeutic strategies in future regeneration-related liver managements. We may discover additional chemotherapy targets of miRNA.

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KEY WORDS: microRNAs; liver regeneration; gene expression; target; pathway

Introduction

MicroRNAs (miRNAs) are a group of small regulatory RNAs, most of which are 22-nucleotides long. These miRNAs participate in a variety of pathological and physiological processes. Lee et al[1] identified the first miRNA (lin-4) in 1993. However, miRNAs were not recognized as a distinct class of biological regulators until the early 2000s when Pasquinelli and coworkers found the regulatory function of let-7 in invertebrates and vertebrates.[2] The biosynthesis of miRNA was firstly described by Bartel.[3] Generally, RNA polymerase II transcribes miRNA genes into hair-pin stem-loop structures, which is known as primary miRNA. Primary miRNA is transformed to precursor miRNAs within the nucleus by the Drosha-DGCR8, further processed by the Dicer1-TARBP2 complex and generated the mature miRNA duplexes. miRNAs function is via the inhibition of expression of protein-encoding genes and through binding to complementary sequences in the 3'-untranslated regions (UTRs) of their target mRNAs. Studies[4, 5] demonstrated that miRNAs are correlated with cell proliferation, apoptosis, differentiation, and tumor progression. It was reported that differential expression of miRNAs might be involved in liver development or carcinogenesis. Commonly, in both cases, miRNAs modulate the expression of genes that function in proliferation and replication.[6]

The liver is a typical organ with a unique ability to regenerate after injury, which is the theoretical basis of liver transplantation.[7] The demand for high quality donor graft far outweighs the graft we can supply, one of the limitations is the gap between insufficient liver volume for the safety of donors and the adequate liver volume for survival of recipients. The capability of liver regeneration after partial hepatectomy or trauma is a critical prognostic factor for patients with living donor liver transplantation or acute liver injury. Liver regeneration is a complex process that consists of three main phases: initiation, proliferation, and metabolic adaption. In the past several decades, investigators have identified a large number of molecules that associated with liver regeneration, such as hepatocyte growth factor, cytokines, and matrix remodeling factors, etc. Additionally, the processes of initiation and termination of liver regeneration have already been partially clarified. However, the mechanism of liver regeneration is not completely understood.

Recently, emerging evidence has shown a close association between miRNAs and liver regeneration. Kren et al[8] revealed the role of miRNA in the regulation of c-Myc

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and p53, which caused an expression alteration in liver regeneration. Afterward, a variety of miRNAs including micro-21 and micro-34 were found to participate in liver regeneration.[9, 10] Generally, the study protocols on miRNAs in liver regeneration are similar. In general, liver samples were processed for RNA extraction with the TRIZOL reagent. Briefly, the frozen tissue was placed in TRIZOL reagent and immediately homogenized by using a prechilled mortar and pestle. The samples were then processed for isolation of total RNA. miRNA was isolated from frozen liver specimens by different techniques following the manufacturer's recommendations. Finally, miRNA was detected by qRT-PCR miRNA assays, which is the standardized equipment for this detection. However, few reviews have summarized the function of specific miRNAs in liver regeneration. The latest review by Finch et al[4] presented an overview of miRNAs in liver development, regeneration, and disease. The present review is to summarize our knowledge of miRNAs in the modulation of liver regeneration.

miRNAs promote liver regeneration and related pathway

A variety of miRNAs have been reported to promote liver regeneration. Castro et al[11] harvested RNA at 3-72 hours after partial hepatectomy in rats and found that the feeding of ursodeoxycholic acid induced a sustained increase of proliferative miRNAs at early phase after partial hepatectomy. In all, 26 miRNAs were found to be differentially expressed by 1.5-fold or more following partial hepatectomy, especially micro-21. They elucidated that micro-19a, micro-21, and micro-214 target the phosphatase and tensin homolog deleted on chromosome ten (PTEN), which is a negative regulator of the PI3K/Akt survival pathway. Additional studies demonstrated that PI3K/Akt is key mediator in the modulation of regeneration by IL-6. Chou et al[12] described the anti-apoptotic role of Mcl-1L during liver regeneration and found that Mcl-1L was stimulated by IL-6 through the JAK/PI3K/Akt/CREB signaling pathway. Therefore, PI3K/Akt might be a common pathway in liver regeneration.

Several other miRNAs, such as micro-106a, micro-20a, micro-20b, and micro-93, are modulators of vascular endothelial growth factor (VEGF).[11] VEGF has been widely accepted as a key mediator in carcinogenesis due to its angiogenic effects. Scartozzi and colleagues[13] recommended VEGF and VEGFR genotyping as the predictor factors of patients with hepatocellular carcinoma who receiving treatment with sorafenib. Liver regeneration is a process that consists of proliferation and angiogenesis, and VEGF is a potent angiogenic factor. It has been demonstrated that tissue resection increases this cytokine which plays an important role during liver regeneration.[14] In addition, VEGF acts through the mediation of liver endothelial cells to communicate with neighboring parenchymal cells. This communication promotes the expression of VEGF and its receptors, and induces the proliferation of endothelial cells.

Raschzok et al[15] investigated the expression of 323 miRNAs after hepatectomy, and the expression level of 29 miRNAs was significantly altered. Among the 29 miRNAs, 7 miRNAs (micro-33, micro-153, micro-298, micro-301b, micro-489, micro-743b and micro-883) were up-regulated. Interestingly, none of these changes reached statistical significance in the early phase of regeneration, but rather, the significant upregulation peaked at 24 hours after hepatectomy, which is consistent with DNA replication. This result revealed that these 7 miRNAs play key roles in the early phase of liver regeneration, primarily during G1/S. Putative targets of these miRNAs are CDK6, RAP2A, TNF, CCND1, and MAP3K1.[15] Salehi et al[16] reported that the expression of micro-126, micro-130a, micro-20a and micro-520e was significantly upregulated after liver transplantation. They also discovered that angiogenesis was induced by micro-126 through the VEGF signaling pathway, which is similar to the pathway through which micro-106a, micro-20a, micro-20b, and micro-93 modulate regeneration. Increasing expression of micro-520e attenuated the expression of the membrane-bound complement regulator CD46 and thereby increased the expression of the complement components C4b and C3b, which are mediators of early liver regeneration. As well-known, the liver is the primary source of complement proteins, and emerging evidences indicate that the complement cascade (especially C3 and C5) might regulate liver regeneration. Rutkowski et al[17] found that C3 and C5 double knockout mice showed significant hepatocyte apoptosis following partial hepatectomy, in addition, reconstitution of C3 or C5 attenuated this injury, reconstitution of both almost completely prevented apoptotic injury.

A study[18] on the role of specific miRNAs in liver regeneration showed that micro-21 promotes liver regeneration directly via the inhibition of Btg2. Btg2 is a cell cycle inhibitor that prevents the activation of forkhead box M1, which is essential for DNA synthesis in hepatocytes after 2/3 partial hepatectomy. The PI3K/Akt survival pathway is known to be related to micro-21 in liver regeneration,[11] and it is likely that micro-21 may participate in the regulation of liver regeneration by other pathways. On the basis of the above findings, Ng et al[19] knocked out micro-21 in rodent hepatocytes during liver regeneration after 2/3 partial hepatectomy. Their