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Role of MicroRNA in Chronic Alcoholic and Non-alcoholic Liver Disease and Pathology

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Abstract

MicroRNAs (miRNA) are highly conserve non-coding RNAs which regulate gene expression, different aspect of cell signaling, cellular activity, cell differentiation and development, metabolism, proliferation, programmed cell death, viral and bacterial infection and oncogenesis etc. Current findings suggest that miRNAs are plentiful in liver and regulate large number of liver function. Perturbation of miRNA expression is a key genetic factor in many liver diseases including Alcoholic Liver Disease (ALD), Alcoholic Steatohepatitis (ASH), Non-alcoholic Steatohepatitis (NASH), viral hepatitis, hepatocellular cancer and polycystic liver diseases. The mechanisms involved in miRNA deregulation will offer new diagnostic and therapeutic strategies for the treatment of liver diseases. In addition, better understanding of miRNA regulation and identification of tissue-specific miRNA expression will improve our knowledge of liver physiology and diseases.

1. Introduction

MicroRNAs (miRNAs) are a 19-25 nucleotide (nt) non-coding RNA and are processed from 70-to 100-nt double-stranded hairpin precursors by RNaseIII Dicer and endogenously expressed in the RNA-induced silencing complex in cytoplasm (Liu et al., 2007) and participate in cellular activity. The miRNAs recognize the 3′-untranslated region of target mRNAs to cause translational repression or mRNA cleavage (Ambros, 2004). From its first discovered in *c.elegans* in 1993 (Lee et al., 1993), miRNAs have been found in all multicellular organisms with strain and tissue specificity and regulate important biological functions (Pasquinelli et al., 2000). It has been reported aberrant expressions of tissue miRNAs have been widely reported in human cancer (Calin and Croce, 2006), ALD, non-alcoholic fatty liver disease (NAFLD) (Jin et al., 2009) and other diseases (Marcucci et al., 2009), helping as a potential diagnostic tool. In addition, miRNA downstream target pairs are actively involved in various cell signaling, pathological and cellular pathways (Bartel, 2004).

Current studies have confirmed that many portions of the human genome do not encode conventional protein coding genes but encode biologically active non-coding RNA species (Kiss, 2002). One important class of such small non-coding RNAs is microRNAs (miRNAs), a group of regulatory RNAs of 19-22 nucleotides involved in control of gene expression at the post-transcriptional level (Bartel, 2004). The latest findings suggest that miRNAs are involved in regulating cell death and proliferation, initiation and progression of human cancer, developmental timing, and inflammatory responses (Ambros, 2004, Voinnet, 2005, Taganov, 2007). We collected the recent key findings on miRNAs in alcoholic non-alcoholic liver diseases and carcinogenesis. We have summarized the potential use of miRNA inhibition to target miRNAs in vivo, which may interpret into novel therapeutic strategies for liver disease in the future.

2. miRNAS are Plentiful and Regulated in the Liver

It is hypothetical that expression of 30% of human genes may be synchronized by miRNAs (Lewis et al., 2005). The existence of miRNAs in mammals came from studies on genetic alterations in liver tumors. A transcript, named hcr, was characterized as liver-specific, non-coding, specifically nuclear, and processed by endonucleases in one of woodchuck liver tumors investigated in 1989 (Moroy et al., 1989). In later date, the hcr transcript was found to encompass the so-called

pri-miRNA for miR-122 (Chang et al., 2003, Chang et al., 2004). Besides miR-122, many other miRNAs, such as miR-1, miR-16, miR-27b, miR-30d, miR-126, miR-133, miR-143, and the let-7 family, are also plentifully expressed in human primary hepatocytes and in adult liver tissue. While miR-122 appears as the most highly expressed miRNA in adult liver, miR-92a and miR-483 seem to be more specifically expressed in the fetal liver (Girard et al., 2008).

3. miRNA and Transcription Factor Regulation

Manipulation of HNF-1α function through RNA interference causes reciprocal changes in miR-107 expression and thus, may be involved in the regulation of miR-107 transcription in the liver (Ladeiro et al., 2008). The myocyte enhancer factor-2 can amplify the expression of miR-1-2 and miR-133a-1(Liu et al., 2007). The transcription factor Myc can up-regulate the expression of miR17-92 cluster and down-regulate several other miRNAs in tumorigenesis (Aguda et al., 2008). It is showed that decrease of let-7 family expression in human cholangiocytes in response to microbial stimulation appears to be nuclear factor (NF)-kB-dependent (Chen et al., 2007). Promoter enrichment analysis predicted a role for NFκB in the immediate-early miRNA response to PHx. NFκB binding at target miRNA promoters in the chronic EtOH-fed group was significantly altered and these changes directly correlated with the observed expression dynamics of the target miRNA (Dippold et al., 2013). The functional expression of transcription factors can also be regulated by miRNAs, has been shown for signal transducer and activator of transcription 3 (STAT-3) (Meng et al., 2007b).

4. miRNA Host Defense Mechanism against HCV

Pedersen et al., 2007 confirmed IFN-mediated modulation of the expression of numerous cellular miRNAs in the treatment of hepatocytes infected with HCV. The expression of a total of 30 cellular miRNAs in hepatocytes was influenced by IFN-α/β or IFN-γ. Specifically, eight of the miRNAs (miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431 and miR-448), having nearly perfect complementarity in their seed sequences with HCV RNA genomes, were up regulated. Significantly, these miRNAs are capable of inhibiting HCV replication and infection. This has focused our understanding of novel host–defense mechanisms that exist in mammalian cells as well as the antiviral mechanisms employed by interferon (Chen, 2009).

5. miRNAs and Human Hepatocellular Cancer (HCC)

It is interesting to found that miRNAs such as miR-21, miR-224, miR-34a, miR-221/222, miR-106a, and miR-203 are up regulated in HCC compared to benign hepatocellular tumors such as adenomas or focal nodular hyperplasia. It is found that miRNAs decreased in HCC compared to non-tumoral tissue, such as miR-122a, miR-422b, miR-145, and miR-199a. Murakami et al., 2006 found a correlation between miR-222, miR-106a, miR-92, miR-17-5p, miR-20, and miR-18 and involvement of specific miRNAs in the progression of the disease. Interestingly, the altered expression of some miRNAs such as miR-96 with hepatitis B virus infection, miR-126* with alcohol use, miR-223 and miR-222 could unambiguously distinguish HCC from adjacent non-tumoral liver, irrespective of viral association (Wong et al., 2008). In HCC with hepatitis C and liver cirrhosis, miR-122, miR-100, and miR-10a were over expressed, whereas miR-198 and miR-145 were up to five-fold down-regulated in hepatic tumors (Chen, 2009).

6. miRNAs and Alcoholic Liver Diseases

A number of miRNAs that were significantly altered by chronic EtOH feeding, including miR-34a, miR-103, miR-107, and miR-122 have been reported to play a role in regulating hepatic metabolism. Chronic EtOH feeding also altered the dynamic miRNA profile during liver regeneration. Promoter analysis predicted a role for NFκB in the immediate-early miRNA response to PHx. NFκB binding at target miRNA promoters in the chronic EtOH-fed group was significantly altered and these changes directly correlated with the observed expression dynamics of the target miRNA (Dippold et al., 2013). Dippold et al., 2012 also reported that miR-21 may play a greater role in regulating gene expression during regeneration in the ethanol-fed rat than in the control rat. There analysis of potential targets of miR-21 suggests that miR-21 affects a broad range of target processes and may have a widespread regulatory role under conditions of suppressed liver regeneration in ethanol-treated animals.

7. miRNAs and Non-alcoholic Steatohepatitis (NASH)

It is found that 113 miRNA differentially expressed between NASH patients and non-NASH patients (p<0.05). They showed that seven remained significant after multiple test correction (hsa-miR-132, hsa-miR-150, hsa-miR-433, hsa-miR-28-3p, hsa-miR-511, hsa-miR-517a, hsa-miR-671). They also predicted target genes for these miRNAs include insulin receptor pathway components (IGF1, IGFR13), cytokines (CCL3, IL6), ghrelin/obestatin gene, and inflammation-related genes (NFKB1, RELB, FAS). Two miRNAspecies, hsa-miR-197 and hsa-miR-99, were significantly associated with pericellular fibrosis in NASH patients (p<0.05). The serum IL-6 level negatively correlated with the expression levels of all seven miRNAs capable of down regulating IL-6 encoding gene. The miRNA expression from visceral adipose tissue may contribute to the pathogenesis of NAFLD, a finding

which may distinguish relatively simple steatosis from NASH (Estep et al., 2010).

Pogribny et al., 2010, discovered expression of fibrosis-related genes in the livers of methyl-deficient DBA/2J mice. The development of NASH was as a consequence by prominent changes in the expression of miRNAs, including miR-29c, miR-34a, miR-155, and miR-200b. The changes in the expression of these miRNAs and protein levels of their targets, including C/EBPβ, Socs 1, Zeb-1, and E-cadherin, in the livers of DBA/2J mice fed a methyl-deficient diet were more pronounced as compared with those in C57BL/6J mice. It is proved that alterations in the expression of miRNAs are a prominent event during development of NASH induced by methyl deficiency and strongly suggest that severity of NASH and susceptibility to NASH may be determined by variations in miRNA expression response.

8. miRNA as Therapeutic Targets

Chemically engineered oligonucleotides, termed 'antagomirs', have recently been developed and proven to be efficient and specific silencers of endogenous miRNAs in mice and rat. The effect of miR-122 antagomir in high-fat fed mice may be of therapeutic potential to reduce hepatic steatosis (Krutzfeldt et al., 2005). MicroRNA-141, which showed strong overexpression in malignant cholangiocytes, was specifically localized in 12p, a region of known chromosomal aberration in biliary tract cancers can be inhibited for cancer therapy. Inhibition of miR-21 sensitized the response of cholangiocarcinoma cell lines to chemotherapy (Meng et al., 2007a). Dippold et al., 2012 discovered potential targets of miR-21 suggests that miR-21 affects a broad range of target processes and may have a widespread regulatory role under conditions of suppressed liver regeneration in ethanol-treated animals. They also showed inhibition of miR-21 induced proliferation of hepatocytes in rats and reduced alcoholic liver damage to a significant level.

9. Conclusion

Knowledge and application of non-coding RNA or miRNAs grows enormously during the decade after their discovery. It is now obvious that miRNAs can potentially regulate all aspect of cellular activity, from differentiation and proliferation to apoptosis, organogenesis and carcinogenesis etc. miRNAs also alter a diverse scale of liver functions with developmental, physiological, and clinical implications. In future, the distinctive signature patterns of miRNA expression associated with liver cancer should allow classification of different stages in tumor progression. Further, creating artificial miRNAs environment with beneficial effects by promoting the expression of favorable gene products (e.g. tumor-suppressor or anti-inflammatory proteins) or targeting viral genomes may become future therapeutic approaches. Largely, discovering the regulatory circuits of miRNAs in the liver is a great challenge, but may provide clue for mechanism-based treatment of liver diseases.

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