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Review Article

The Role of Circulating MicroRNAs as Biomarkers in NAFLD

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a frequent chronic disease, diagnosed in patients who do not abuse alcohol, which includes hepatic damage conditions with different degree of severity. It is known that a percentage of NAFLD patients can develop non-alcoholic steato-hepatitis, fibrosis, cirrhosis and, lastly, hepatocarcinoma. The reference standard for NAFLD diagnosis is liver histological analysis, an invasive procedure usually performed when damage has progressed to advanced stages. MicroRNAs (miRNAs) are short non-coding RNA molecules directly involved in numerous physiological and pathophysiological processes, playing a role in the regulation of cell proliferation, metabolism, apoptosis. MicroRNA scan be also foundin an adequately stable structure in serum/plasma. For these reasons, miRNA are emerging as very promising putative non-invasive biomarkers to define diagnosis and prognosis. Several studies have analyzed the diagnostic and/or prognostic potential of circulating miRNAs in characterizing liver injury. In this review we describe circulating microRNAs identified as putative biomarkers in NAFLD.

ABBREVIATIONS

NAFLD: Non Alcoholic Fatty Liver Disease; NASH: Non Alcoholic steato-Hepatitis; HCC: Hepatocarcinoma; BMI: Body Mass Index; FGF: Fibroblast Growth Factor; PEDF: Pigment Epithelium-Derived Factor; OPG: Osteoprogerinil-1: Interleukin 1; AST: Aspartate Transaminase; ALT: Alanine Transaminase; HIF: Hypoxia Inducible Factor

INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) identifies a frequent form of chronic liver damage, especially in American and European populations [1]. NAFLD can be considered as the hepatic manifestation of the metabolic syndrome: obesity, both in terms of BMI and visceral fat, dyslipidemia and diabetes mellitus are classified major risk factors. Currently, there is no pharmacological therapy for NAFLD, and lifestyle measures finalized to weight loss are strongly suggested. NAFLD is an insidious disease: indeed, simple steatosis can progress to more severe liver damage revealed by presence of inflammation (non alcoholic steato-hepatitis NASH), which represents a predisposing factor for fibrosis and cirrhotic stage [2]. As a consequence of those chronic liver injuries, it is known that a variable percentage of patients can also develop liver tumors. In general, it has been reported that patients affected by NAFLD/NASH have increased mortality, principally due to cardiovascular or liver-related diseases [3].

Diagnosis of NAFLD/NASH

The diagnosis of NAFLD is based on the presence of hepatic steatosis, not associated with any evident cause of fat accumulation, such as high alcohol consumption, hereditary disorders or use of steatogenic drugs. Steatosis is revealed by imaging or, if necessary, by histological analysis. When unsuspected steatosis is detected, mainly by imaging, some actions, focused to assess metabolic risk factors, hepatic biochemistry values, and liver's histological analysis, are recommended. However, non-invasive diagnostic procedures, such as ultrasound, magnetic resonance, computerized tomography, and serum aminotransferase increased levels, with AST/ALT ratio less than 1, are not sufficient to accurately diagnose more severe hepatic damage, as in the case of steato-hepatitis or fibrosis [4]. Liver biopsy is actually considered as the "gold standard" to define histology and characterize without doubts NAFLD/NASH patients, although it should be performed on selected cases, being an expensive and invasive procedure, which entails possible complications and, infrequently, mortality risk. Infrared (IR) spectroscopy, a non-invasive method, has been described as a promising technology for analysis of different parameters and analytes in several clinical samples. In particular, mid-IR (MIR) methods have been developed to analyze blood, serum and plasma [5]. These methods are based on the property of organic molecular chemical bonds to acquire vibrational transitions in the mid-IR region, providing absorption bands in this range of frequencies [6]. Very recently, a study [7] on an *in vivo* NAFLD/NASH mouse model demonstrated that one of the above-mentioned technologies, the mid-infrared fibre evanescent wave spectroscopy (MIR-FEWS), applied to the analysis of serum samples, and combined to clinical chemistry data, is able to provide important biological information about the presence of liver steatosis. In this scenario, in order to support and improve the diagnosis of NAFLD, the identification of new non-invasive serum biomarkers is in the same way

desirable. Recently, increased serum level of citokeratin 18 (CK18) fragments, principally due to caspases cleavage during liver apoptosis, has been described as a method to diagnose steato-hepatitis in NAFLD patients, although this method is not yet diffusely used in clinical practice [4]. A recent study has also analyzed the combination of different serum biomarkers, including the CK-18-M30 fragment, FGF-21, IL-1Ra, PEDF and OPG, which could improve the non-invasive diagnosis of NASH [8].

MicroRNAs: biosynthesis and function

Non-coding RNAs play an important role in the regulation of the main cell processes, being involved in different biological functions. On the other hand, their dysregulation is frequently described in the pathogenesis of many diseases, including those of the liver. MicroRNAs are small (18-22 nucleotides in length) non-coding RNA molecules able to control gene expression at the post-transcriptional level [9,10], and to mediate fundamental cell functions, such as proliferation, apoptosis, differentiation, metabolism, cell signaling [11-13]. MiRNAs regulate the translation of specific mRNAs by their imperfect or perfect pairing at the level of the 3'UTR [14]. In the human genome it is estimated that approximately 30% of genes are targeted by miRNAs [15], and that a single miRNA can potentially regulate hundreds, or even thousands, of transcripts. Approximately 1,900 and 2,600 sequences of Homo sapiens precursor and mature miRNAs are listed in the miRbase database (www.mirbase.org). MiRNAs biosynthesis is tightly regulated by a process, which begins within the cell nucleus and moves to the cytoplasm, where the mature form of the molecule exerts its functions. Long primary transcripts (pri-miR) are transcribed by RNA polymerase II to be subsequently processed in the nucleus by the ribonuclease microprocessor complex containing Drosha-DGCR8 to generate the 60-70 nucleotides precursor pre-miRNAs. They are transported into cytoplasm by exportin-5: here, pre-miRs are further cleaved by Dicer into mature miRNA/miRNA* duplexes. The miR/miR* is loaded onto the multicomponent RISC complex. Mature miRNAs guide strands are incorporated within the RNA-induced silencing complex (RISC) and bind to the target mRNA at the level of the 6-8 mer seed region, whereas the miRNA* passenger strand is usually cleaved. Every single microRNA can suppress activity of multiple mRNAs by interacting with them at the level of the 3'-UTR, driving to reduced translation, or deadenylation and degradation of the transcript.

MicroRNAs as circulating biomarkers

Tissue microRNAcan be releasedinto the bloodstream by active (i.e. secretion) or passive (i.e. cell death) mechanisms. Several studies have demonstrated that endogenous miRNAs in plasma are very stable andRNase-protected, even in difficult conditions and extended storage (e.g. low/high pH environment, freeze-thaw cycles). The retention of this exceptional stability can be due to the association between miRNA and RNA-binding proteins (Argonaute 2) or complexes of lipoproteins (HDL), and, as an alternative, to miRin clusion within micro/nanoparticles released by cells (e.g. microvesicles, exosomes, apoptotic bodies) [16]. Extracellular vesicles derive from dying or activated cells and are involved in the process of communication among cells through interaction with surface receptor or internalization. They are able to work both in the tissue whose they originate and in the blood stream by transporting several types of molecules, such as proteins and RNAs, including mRNA and microRNA. MiRNAs detection in plasma or serum is feasible by using specific and dedicated methods [17,18], although standardization of internal controls and normalization process should be improved [19]. Overall, the above-mentioned characteristics made miRs extremely interesting in terms of relevance as biomarkers. MiRNAs have been described as regulators of liver homeostasis, by controlling the expression of molecules involved in pathways related to lipid and glucose metabolism, inflammatory processes, apoptosis, necrosis, cell proliferation [20]; furthermore, hepatic microRNAs dysregulated expression and activity was described

Table 1: Circulating microRNA identified as putative NAFLD biomarkers.

MiRNAs	Serum level	Ref.
miR-122, miR-34a	Higher in chronic HCV infection and NAFLD	[36]
miR-122, miR-21, miR-34a, miR-451	Higher in NAFLD	[37]
miR-122, miR-192, miR-19a/b, mir-125b, miR-375	Higher in simple steatosis and NASH (biopsy proven)	[38]
miR-181d, miR-99a, miR-197, miR-146b	Lower in NAFLD (biopsy proven)	[39]
miR-122, miR-192, miR-21 (in association to ALT and CK18)	Higher in NAFL and NASH	[40]
miR-122	Decrease before the progression to fibrotic stage	[41]
miR-122	Decrease from mild to severe fibrosis	[42]
miR-122, miR-34a	Higher in NAFLD patients (biopsy proven)	[43]
miR-122, miR-181a, miR-192, miR-200b, miR-34a	Higher in NAFLD liver injury (choline and folate-deficient diet fed mouse model)	[44]
miR-122 (combined to ALT/AST)	Higher in NAFLD liver injury (methionine-choline deficient diet fed mouse model)	[45]
miR-122	Higher in NAFLD liver injury (methionine-choline deficient diet fed mouse model)	[46]
miR-122, miR-192	Higher in NAFLD extracellular vesicles (choline deficient diet induced NAFLD mouse model)	[47]
miR-122	Higher in high-fat diet induced NAFLD rat model	[48]

in several liver diseases (e.g. viral hepatitis, autoimmune liver diseases, alcoholic and nonalchololic steatohepatitis, drug-induced hepatic damage) and cancer [20-23]. MicroRNAs are highly expressed in liver tissue, and can enter into the bloodstream after apoptosis or necrosis due to hepatic damage, or through secretion of exosomes and microvescicles [24-27]. It has been demonstrated that, depending on liver conditions, miRNA levels in hepatic tissue and/or serum can change, being influenced by the stage of the disease, diet, and genetic manipulations in animal models [21,28]. Levels of stable endogenous miRNAs, released from liver in plasma or serum, can promptly and accurately reflect cellular changes, providing new potential biomarkers for the diagnosis, with consequent reduction of risks associated to invasive diagnostic procedures, and/or prognosis of liver disease. In this context, some efforts are being made in order to assess the levels of specific miRNAs in serum, which could be representative of a specific hepatic pathological condition, such as NAFLD. Several available, sensitive technologies, in particular qRT-PCR and next generation sequencing (NGS), provide precious tools to identify and characterize these molecules.

MicroRNAs as putative serum biomarkers in NAFLD

Many studies, focused on characterizing circulating miRNAs as putative biomarkers in NAFLD/NASH, have been published. Among the miRs identified, some of the most interesting and (Table 1) frequently described are miR-122, miR-21, miR-34a. MiR-122 is one of the most abundant microRNA in hepatocytes [29], where it regulates different targets acting in controlling liver homeostasis [30]. MiR-122 expression is reduced in liver tissues from NASH patients compared to those affected by simple steatosis, and, contextually is increased in serum [31]. MiR-21 has been described as a regulator of lipid metabolism [32] and a potential molecular link between NAFLD and HCC, by modulation of HBP1-p53-Srebp1c pathway [33]. MiR-34a is known to regulate several target involved in oxidative stress and metabolism. Recently, it has been described that induction of miR-34a is associated with HNF4α (hepatocyte nuclear factor α) inhibition in NAFLD patients, and that miR-34a-HNF4α pathway plays a role in regulating lipid and lipoprotein metabolism [34]. SIRT1, a NAD-dependent deacetylase acting as a modulator of metabolism, and PPARα, an essential factor regulating lipid transport and metabolism, have been identified as miR-34a targets in NAFLD [35] (Table 1). Several studies, reviewed below, have described miR-122, -21, and -34a as putative circulating biomarkers in humans, individually or in association with other microRNAs (Table 1). Serum levels of miR-122, -34a, -16, and -21, known as microRNAs frequently dysregulated in fibrosis and HCC,were analyzed in chronic hepatitis C as well as NAFLD patients with respect to healthy individuals without any evidence of liver disease. MiR-122 and -34awere described as potential non-invasive biomarkers and correlated with the severity of the disease in patients affected by chronic hepatitis C and NAFLD [36]. Yamada et al. [37] analyzed serum levels of 5 miRNAs (122, 34a, 21, 451, 145) involved in cholesterol and fatty acid homeostasis in human and mouse hepatic tissues. Higher levels of serum miR-122, -34a as well as miR-21 and -451 were detectedin patients affected by NAFLD. In particular, serum level of miR-122 was correlated with the severity of hepatic steatosis. In a cohort of patients with histological NAFLD diagnosis, a panel of 84 miRNAs was analyzed, and circulating miR-122, -192, -19a/b, -125b and -375 were shown to be up-regulated more than 2-fold in steatosis and NASH, with the most relevant increase shown by miR-122 and -192 [38]. Celikbilek and colleagues [39] analyzed by qRT-PCR a panel of microRNAs whose altered expression was already described in NAFLD human and animal liver samples. Among the analyzed miRs (miR-197, -146b, -10b, -181d, -34a, -122, -99a, -29a), miR-181d, miR-99a, miR-197, miR-146b were found hypo-expressed in biopsy-proven NAFLD patients with respect to healthy controls. In addition, miR-197/miR-10b and miR-181d/miR-99a serum levels resulted inversely correlated with inflammation and serum gamma glutamyl transferase, respectively, in NASH patients. Becker et al. [40] conducted a study in order to assess the real significance of circulating miRNAs in NAFLD diagnosis by evaluating serum profiles of four miRNAs (122,192, 21, 223), previously described as involved in chronic inflammatory liver disease and NAFLD, in association to ALT and CK18-Asp396 levels in 137 patients and 61 healthy controls. They demonstrated that miR-122, -21, -192 expression profiles combined to CK18-Asp396 serum levels were able to predict NASH with 91% sensitivity and 83% specificity. Akuta et al. [41] analyzed circulating miR-122 in patients with different degree of liver damage, from NAFLD to HCC, and found expression decrease before the progression to fibrosis. Correlation between hepatic/serum miR-122 levels and steatosis or fibrosis was also described. MiR-122 hepatic and serum levels were higher in patients affected by mild fibrosis with respect to those with more severe disease, indicating that miR-122 could be a suitable marker of liver fibrosis in NAFLD patients [42] Salvoza et al. [43] analyzed serum levels of miR-21, -34a, -122, -125b, -375 in 28 biopsy-diagnosed NAFLD patients compared to healthy controls, identifying significant higher levels of miR-122 and 34a, positively correlated with very low density lipoprotein cholesterol (VLDL-C) and triglycerides amount. Several studies, highlighting results in general similar to those found in humans, were also performed on *in vivo* models. Plasma levels of miR-122, -181a, -192, -200b, and, in particular, miR-34a were associated to hepatic pathomorphological changes and NAFLD injury in mice fed a choline and folate-deficient diet for 12 weeks [44]. Significant increase of serum miR-122, combined to ALT/AST levels, was also detected in a methionine-choline deficient diet-induced NAFLD mouse model, indicating its potential use as biomarker for evaluating hepatotoxicity and NAFLD liver damage [45]. Increased level of circulating miR-122, in exosome-rich and protein-rich serum fractions, was associated to miR-122 expression decrease in livers from methionine-choline-deficient fed mice. In this study, the authors described HIF-1α, MAP3K3, and vimentin as miR-122 targets [46]. In a NAFLD mouse model described by Povero et al. [47], miR-122 and -192 were found to increase in circulating extracellular vesicles and to decrease in hepatic tissues. Yamada et al. [48] used a high-fat fed rat model to investigate the levels of circulating miR-122 during the NAFLD development. They assessed that, despite not significant changes observed in serum alanine aminotransferase, indicating an initial stage of the disease, miR-122 was highly up-regulated, providing information about early diagnosis of the disease.

DISCUSSION & CONCLUSION

Liver biopsy is considered the “gold standard” for NAFLD/

NASH diagnosis, although it is an invasive procedure with potentially serious complications. MicroRNAs have emerged as crucial regulators of hepatic homeostasis, being involved in the control of cell death and proliferation, inflammation, metabolism. Several dysregulated miRNAs were described in liver tissues during NAFLD progression, and many studies have been focused on exploring the level of those hepatic miRNAs released in plasma/serum, reflecting the pathological liver condition, in order to start to identify molecules to be putatively used as diagnostic and/or prognostic markers of the disease progression.Differences in circulating miRNAs' levels, by considering panels containing multiple miRNAs, even associated with other molecules' level in serum (e.g. classical serum biomarkers, CK18 fragments analysis) could be used to stratify patients and support decisions about diagnosis and treatment. The results collected are encouraging, and sensitive technologies to detect differences in circulating microRNA and then identify new biomarkers are now available. However, due to the complexity of serum/plasma specimens, standardization of sample preparation and methods as well as rigorous validation of results, by using well-defined cohorts of patients, is needed to identify specific molecules to be used for non-invasive NAFLD diagnosis.

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