New Advances in Micrornas in Diagnosing Chronic Diffuse Liver Disease in Rheumatoid Arthritis

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Abstract:
At present, multidisciplinary and multifactorial problems that have arisen and are developing at the intersection of several medical specialties are becoming particularly complex. One of these tasks is to study the features of diagnosis and treatment of rheumatic diseases in patients with chronic diffuse liver disease (CDD), especially chronic viral hepatitis (CHD), HAI and fatty liver (hepatic steatosis - SP). More precisely, liver damage in rheumatoid arthritis (RA) can be associated with toxic lesions caused by various drugs, primary (in autoimmune hepatitis - AIH) or secondary (against the background of diffuse connective tissue diseases), immunological and viral damage. This, in turn, requires the exclusion of secondary conditions before assessing pathological conditions in the liver. For early diagnosis of liver damage in RA patients, it is necessary to conduct regular examinations to assess the functional and organic state of the liver. In addition, it is very important to correctly and fully collect anamnestic data, to choose the right methods of clinical and laboratory examination. According to the literature, the use of determination of microRNA expression as a molecular diagnostic marker in this category of patients may prove to be highly effective in addressing these complications. Despite a lot of research, there is still no clear opinion on the use of treatments for patients with RA and liver disease. If it is possible to clarify the etiology and pathogenesis of liver damage in RA depending on the expression of microRNAs or to stratify risk groups for liver damage in RA by these biomarkers, it will be possible to achieve some progress in the treatment of these comorbid pathologies. The following literature review comprehensively discusses these problems and their modern solutions.

Keywords: chronic diffuse liver diseases, rheumatoid arthritis, microRNA 122, microRNA 221.

Introduction

Although the liver is often not considered a target organ in primary diseases, abnormal conditions in the liver sometimes occur as secondary diseases in the setting of primary diseases, sometimes as a result of treatment toxicity of the primary disease and complications of extrahepatic diseases. In each of the cases mentioned above, it is very important for a rheumatologist to know the procedure for timely detection and diagnosis of liver damage. RA is often associated with secondary liver pathologies due to

autoimmune liver disease (especially AIH), direct damage to the liver parenchyma, or the presence of drugs (especially methotrexate and steroids) on the liver. In addition, the effect of immunosuppressive drugs on major viral infections, especially viral hepatitis, should be noted. The overlap in disease patterns is largely due to genetic determinants, and both diseases share common susceptibility loci. Early detection of RA-like aspects in CDP is important, since such comorbidity affects the course and prognosis of the disease. RA, one of the most common rheumatic diseases, should be distinguished from the extra-articular systemic lesions associated with RA. Therefore, in these two cases, the complications of the disease and the methods of treatment are different. If the above recommendations are followed, it is possible to personalize the immune status of the liver and control rheumatic manifestations in CDS and RA. Such collaboration between hepatologists and rheumatologists can lead to breakthroughs in solving complex multidisciplinary problems.

Hepatic manifestations of rheumatoid arthritis
It is known that RA is manifested mainly by joint involvement. However, it is important to remember that there are a number of extra-articular clinical manifestations of RA. Extra-articular clinical manifestations of RA are observed in approximately 40% of RA patients [1]. Extra-articular clinical manifestations of RA can manifest as diseases of various organs, such as the eyes, lungs, skin, heart, and nervous system [2]. Liver involvement is often not considered an extra-articular clinical manifestation of RA. It should be noted here that that liver involvement is not an extra-articular clinical manifestation of RA, but rather conflicting opinions that RA is a manifestation of RA in the liver. Rigby et al. state that liver damage is usually not a hepatic manifestation of RA [3], another group of scientists suggested that hepatic manifestations of RA occur in 6–74% of patients with RA [4, 5, 6, 7]. A slight increase in aminotransferases or an increase in alkaline phosphatase and gamma-glutamylpeptidase for unknown reasons is sometimes considered a hepatic manifestation of RA. That is, pathological conditions occurring in the liver due to an unknown etiology, sometimes referred to as the hepatic manifestation of RA. The pathogenesis of this liver disease, defined as the hepatic manifestation of RA, is still unclear. Currently, there is a body of evidence supporting the important role of the liver in modulating the immune response in autoimmune and chronic inflammatory diseases [8]. However, the pathogenesis of liver damage in RA is still not fully understood. Histopathological analysis of the affected liver often reveals general, i.e. non-specific changes, such as Kupffer cell hyperplasia, increased lipofuscin in the central lobes, and infiltration by inflammatory cells in the portal tracts [9]. However, with a limited increase in alkaline phosphatase, it is not always possible to distinguish whether alkaline phosphatase is caused by liver or joint damage.

Rheumatoid Arthritis and Primary Liver Disease

Exclusion or confirmation of primary liver disease with increased liver enzyme activity in patients with RA or clinical manifestations of advanced liver disease in RA requires additional and thorough investigations [4]. Examples of primary liver diseases associated with RA include autoimmune liver disease.

It is known that patients with some autoimmune diseases have a higher predisposition to other autoimmune diseases, which has also been confirmed for RA patients [10]. The most common autoimmune liver pathologies in RA patients are primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis. According to R. Pupon, K.D. Lindor et al., PBC is detected in 1-10% of patients diagnosed with RA. PBC is an autoimmune chronic cholestatic liver disease [11, 12]. The diagnosis of PBC is based on the positivity of two of the three criteria: increased levels of alkaline phosphatase and gamma-glutamyl peptidase, the presence of antimitochondrial antibodies (AMAs), and histological features of PBC [12]. In PBC, there is only a small group of AMA-positive patients with normal liver enzyme values. Alternatively, AMA is not detected in about 5-10% of patients according to the diagnosis of PBC based on cholestasis and histology (AMA-negative PBCs) [13,14]. The presence of AMA in patients diagnosed with RA indicates the presence of PBC or development during RA [15].

The importance of these antibodies has also been confirmed in patients with very mild clinical symptoms without biochemical signs of cholestasis [16]. Based on the results of the study by Siegel et al., they emphasized that AMA should be added to the list of laboratory tests that should be performed in all RA patients with impaired liver function, especially cholestasis enzymes [17]. In a study by K. Whaley et al., AMA was detected in 0.9% of 997 patients diagnosed with RA [18]. The specificity of AMA in RA patients is not well understood. Genetic studies are aimed at finding the pathogenetic relationship between RA and the development of PBC, in other words, at finding factors that increase susceptibility to PBC in RA patients or contribute to the development of RA in patients with autoimmune liver disease. Studies have shown that RA patients share genes with patients diagnosed with PBC, such as HLA-DQB1, STAT4, IRF5, MMEL1, and CTLA4. Patients with RA may be more likely to develop PBC according to gene regulation [19]. Although the role of genes in the pathogenesis of RA has been widely studied, there is insufficient data on the role of epigenetic changes in autoimmune liver diseases, including the induction of GBT [20,21]. To determine the factors that contribute to the development of RA and PBC in some people, it is assumed that a specific infectious agent is responsible for the occurrence of these diseases. Molecular mimicry and cross-reactivity between own and bacterial antigens are thought to play a role in PBC induction [22].

Guan Wee Wong and Michael A. Heneghan stated that there is often a comorbid course of RA and CDP, including AIH, that is, several types of autoimmune diseases are combined in 20-50% of patients with AIH in adults and children. In 10-60% of these

patients, non-specific, sometimes transient joint pain is detected. Sometimes, along with pain, swelling of the joints occurs. Alternatively, the authors noted RA in 2-4% of patients diagnosed with AIH. In most patients, the symptoms of these joint lesions disappear within a few days of starting immunosuppressive therapy. However, in some cases, patients with AIH experienced joint pain and stiffness, which persisted even after exclusion from treatment and discontinuation of anti-inflammatory steroids (NSAIDs) [23].

CDSP, in particular hepatotropic viruses, may be one of the triggers involved in the formation of RA. Some researchers claim that in patients with systemic connective tissue diseases, reduced protection against viruses (due to both the underlying disease and immunosuppressive therapy) is the reason for the detection of coinfections in most cases [24].

According to the analysis of research results, hepatitis C virus (HCV) is observed in 0.7-8% of patients with rheumatoid arthritis, and RA in 5-15% of patients with viral hepatitis C. This indicator is explained by the following situation: a high level of rheumatoid factor (RF) plays a stimulating role in relation to immune complexes circulating in the blood and prevents the spread of HCV infection [25]. However, this information on the comorbid course of RA and HCV infection in a sufficient number of patients has not been studied [26]. Antibodies to HCV are found in serum, synovial fluid, and saliva. The difficulty of interpreting the involvement of HCV infection in the general joint syndrome is associated with the same involvement of the small proximal joints of the hands in both diseases, but in patients with a confirmed diagnosis of RA and the detection of antibodies to HCV. Palm tenosynovitis, carpal tunnel syndrome and small joint tenosynovitis predominate. The addition of Still's syndrome has also been observed in adult patients with HCV infection [27,28, 29]. Some authors substantiated this situation with the following clinical example: a patient with hepatitis was diagnosed with seropositive RA after a blood transfusion. This patient developed RA three years after testing positive for HCV antigen. The patient's genetic material contained the genes HLA-DR4 and HLA-BW54, which are closely related to RA [30].

Possibilities of Molecular Diagnostics and Instrumental Methods for the Study of Chronic Diffuse Liver Diseases in RA

Increasing the speed and efficiency of early diagnosis of complex comorbidities, such as RA and CDSP, requires the introduction of highly sensitive and specific biomarkers. The assessment of the development, clinical course, and complications of these diseases also largely depends on the study of CDP and RA biomarkers. Biomarkers are also important in the development of individualized treatment plans. In the last two decades, which we can call a new era of molecular diagnostics, great progress has been made in studying the interactions between genes, their products, and environmental factors. The peculiarity of epigenetic regulation is that with its help, changes in gene expression occur without damaging the structure of DNA, and this change can be stably transmitted

for several generations. An important area of epigenetics is the study of the properties of the epigenome in various tissues of the body in normal and pathological conditions. The activity of many genes is specific in time and space: such genes are expressed only at certain stages of cell differentiation and/or in certain tissues of the body. In general, more than 20% of all genes work at the same time in adults. The required level of activity of each gene at the right time and place is mainly provided by epigenetic mechanisms [31]. There are three levels of epigenetic regulation and, accordingly, its three main mechanisms: genomic (DNA methylation), proteomic (protein modification), and transcriptomic (regulation by RNA, primarily microRNA) [32].

Structure, Functions and Methods of Studying MicroRNA as an Epigenetic Agent in the Development and Course of Diseases

Chronic liver inflammation can progress to severe liver fibrosis and cirrhosis in conditions such as HBV, HCV infections, non-alcoholic fatty liver disease (NAFLD), and a number of metabolic diseases. It is known that up to 90% of cases of hepatocellular carcinoma (HCC) occur against the background of cirrhosis or fibrosis of the liver [33]. According to the results of recent studies, microRNAs can serve as new biomarkers in the diagnosis of diseases and provide a new gene therapy strategy using microRNA technologies [34].

The emergence and evolution of the microRNA system has led to a significant increase in the plasticity of DNA-RNA protein interactions. It was possible to form several connections between different genes, as well as between genes and their products mediated by RNA signals, which led to the emergence of multifunctional integrated protein complexes. Information on all microRNAs known to date has been collected in the international electronic database miRBase, which currently contains information on about 3,000 mature human microRNAs. They regulate the expression of more than 30% of genes that control information about the structure of proteins, making them one of the most important gene regulators [34].

The regulatory nature of microRNAs is characterized by an increase or decrease in the expression of cellular microRNAs, which is observed in almost all pathological conditions. That is, this explains their different expression in biological fluids in different pathological processes, and the expression of circulating microRNAs is of interest as non-invasive biomarkers of pathological conditions.

If the pathways of biological appearance of microRNAs in the body are aberrant (deviate from the norm), they can become the main participants in many pathological processes. A biological process can be controlled at several levels and lead to a decrease or increase in the number of microRNAs in a cell. Thus, the control of biological processes in the body may be impaired or the aberrant manifestation may be genetic. Therefore, it can be said that aberrant expression of microRNAs can occur due to chromosomal deletion, amplification, translocation, or very small gene mutations. Internal factors can also

influence microRNA expression. In addition, protein abnormalities that occur at different stages of microRNA maturation also disrupt their expression [35].

MicroRNA is a potential non-invasive biomarker for early diagnosis of the development and progression of CDS in RA

Deepening research in molecular biology has led to the emergence of new approaches, such as the study of microRNAs. Compared to mRNA or proteins, microRNAs as biomarkers have been found to be directly and more closely related to cellular genomic activity. This made it necessary to consider biomarkers as an effective additional method to the generally accepted methods (histological analysis) for clarifying and verifying the clinical diagnosis. They are less profoundly affected than mRNA, especially through some post-transcriptional modifications. In addition, when comparing microRNAs and proteins, the sensitivity achieved for microRNAs by qRT-PCR is now quantitatively higher than for proteins. In addition, microRNAs are more stable in body fluids than mRNAs. The reason is that most microRNAs are transported in microvesicular, exosomal, liposomal forms, in which lipid envelopes or lipoprotein complexes protect them from the action of RNases of biological fluids. Depending on these modes of transport (vesicular or non-vesicular), the value of microRNAs as biomarkers also varies. Non-vesicular forms may reflect cell damage and death due to tissue-specific apoptosis or necrosis in microRNA studies that are more detectable in these tissues. Indeed, some microRNAs have very strong cellular specificity (e.g., miR-122 for hepatocytes). MicroRNAs in microvesicular form reflect other processes. The profile of microRNAs contained in exosomes is partially specific to the cell that secretes it and is modified depending on physiological or pathological conditions. Thus, tumor cells do not develop a normal microRNA profile in the body. Therefore, the analysis of microRNAs in body fluids can reflect molecular changes in cells and provide information to aid diagnostic and therapeutic decisions [36].

At present, the diverse interest in biomarkers is expressed not only by the progress in the diagnosis or monitoring of the treatment of diseases, but also by the fact that when we detect them before the clinical manifestations of diseases, they make it possible to predict the occurrence of an important course of the disease even before the onset of its symptoms or complications (risk stratification – stratification approach).

If we consider microRNAs and the hepatobiliary system, it is not difficult to understand that these molecules are necessary for the development of the liver during embryogenesis and childhood, as well as for cellular metabolism throughout the life of the organism. In recent years, an important role of some microRNAs in the pathogenesis of various diseases, including autoimmune liver diseases, viral hepatitis, NAFLD, and severe pathologies such as hepatocellular carcinoma, has been identified, but due to some contradictions in these data, it shows the need for further study of these processes. The effect of microRNAs is associated with their incomplete hybridization with a 3′-untranslated mRNA region with complementary sites [37]. MicroRNAs reflect various

biological functions associated with the pathogenesis of NAFLD, including regulation of lipid and glucose metabolism, oxidation, endoplasmic reticulum effects, cell differentiation, inflammation, apoptosis, etc. [38]. Overexpression of miP-34a has been shown to increase the acetylation of r53 and activate r53-induced apoptosis of hepatocytes due to increased expression of sirtuin 1 (SIRT1) in experimental rat models [39]. A decrease in the expression of miP-34a leads to the activation of transcription factors involved in the body's homeostasis: the NAFLD α receptor activated by peroxisome proliferators (PPARα) and 5'AMF protein kinases has been reported to cause a decrease in lipid levels and a decrease in steatosis in cell culture [40]. In an experimental animal model of NASH, a decrease in the expression of miR-21 leads to the activation of genes responsible for tissue regeneration and the development of liver fibrosis: hypoxia-induced factor 1-alpha (HIF-1α) and the protein kinase family [41]. miR-21 has a profibrotic effect, stimulating the expression of transforming growth factor (TGFβ), the main mediator of fibrogenesis, the SMAD signaling cascade, as well as the degradation of intercellular matrix molecules and fibroblast infiltration [42].

SiRNA-122 is the most abundant microRNA in liver tissue, accounting for 70% of the microRNAs expressed in this organ, and the liver is virtually the only organ in which MiR-122 is expressed [43]. This microRNA is involved in many physiological and pathological functions, such as the regulation of lipid metabolism and the suppression of the tumor process. Esav S. and co-authors' experiments on mice showed that inhibition of miR-122 stimulates oxidation processes, reduces the level of fatty acids, and reduces the severity of hepatic steatosis [44].

Although there are currently standard diagnostic criteria for diagnosing RA, the most important challenge remains the search for biomarkers for early diagnosis, especially in cases where it is not possible to make an accurate diagnosis during initial examinations. That is, clinical and/or radiological methods are insufficient for RA patients, sometimes with extra-articular clinical manifestations associated with involvement of organs such as the lungs, heart, kidneys, and liver. Antibody detection also has high diagnostic accuracy for diagnosing RA at an early stage. In particular, anti-CCP antibodies are highly specific for the early detection of severe erosive RA and allow for early diagnosis and treatment of RA patients with favorable outcomes [45]. Recent studies point to an important role for microRNAs in RA, and it has been suggested that dysregulation of microRNA expression contributes to the molecular mechanisms of the disease. In this direction, according to the data accumulated in recent years, microRNAs can be abnormally expressed both in inflamed synovial membranes and in the circulating blood of RA patients [46], and the role of microRNAs in RA may meet the criteria for their use. as novel molecular diagnostic markers [47].

Aberrant expression of several microRNAs in different cell types has already been identified in RA, and these microRNAs can regulate specific pathways leading to the inflammatory environment that occurs in RA [48].

The decrease in the expression of miR-221 is inversely proportional to the level of circulating pro-inflammatory cytokines [49]. Increased expression of miR-221 in RA leads to increased expression of VEO'O (VEGF-vascular endothelial growth factor), MMP-1 and MMP-3 (matrix metalloproteinases), which are mediators of angiogenesis and inflammation [49]. In addition, overexpression of miR-221 in RA may enhance the activation of synovial fibroblasts and increase their resistance to apoptosis [49].

MicroRNA-222 has the same regions of origin as microRNA-221, targets the same genes as microRNA-221 [50], and also affects angiogenesis and inflammation [51,52]. Its expression increases with the activity of RA disease [52]. High levels of expression of microRNA-221/222 indicate high RA activity.

Conclusion

In the presence of liver damage in RA patients, determining whether it is an extra-articular systemic manifestation of RA, primary liver disease, or hepatotoxic liver disease developed during RA treatment is one of the sometimes difficult problems. Liver damage in RA often presents with asymptomatic changes in liver function. In some cases, liver damage can be diagnosed even after cirrhosis develops. It has also been studied that patients with RA are more prone to autoimmune liver disease. Drugs used in rheumatology are often hepatotoxic, and the clinical symptoms of primary underlying liver disease are difficult to distinguish from the consequences of severe hepatotoxicity of drugs taken in RA, which reflects the urgency of this problem, which is often encountered in clinical practice today. Timely diagnosis and treatment of concomitant liver diseases in patients with RA can have a significant impact on the course, treatment plan, and prognosis of both types of pathology. For early diagnosis of liver damage in RA patients, it is necessary to conduct regular examinations to assess the functional and organic state of the liver. In addition, it is very important to correctly and fully collect anamnestic data, to choose the right methods of clinical and laboratory examination. The use of microRNA expression detection as a molecular diagnostic marker in this group of patients may improve the efficiency of early diagnosis and treatment of the disease. Despite a lot of research, there is still no clear opinion on the use of treatments for patients with RA and liver disease. If it is possible to clarify the etiology and pathogenesis of liver damage in RA depending on the expression of microRNAs or stratify risk groups for liver damage in RA according to these biomarkers, it will be possible to achieve some progress in the treatment of these pathologies.

The risk of developing RA and liver pathologies and their severe complications is currently an important medical and social issue. It is not uncommon for the working-age population to have a high morbidity and long-term organic and functional disorders of the musculoskeletal system and chronic, fibrotic, oncological processes in the hepatobiliary system that lead to early disability of patients.

The use of epigenetic methods, in particular the level of microRNA expression, as biomarkers of early non-invasive diagnosis and prognosis of CDP in RA, makes it

possible to diagnose severe clinical manifestations and complications occurring in patients with these comorbid pathological conditions at an early stage. This, in turn, reduces the level of disability and mortality from complications in this category of patients, and also saves costs for the treatment of symptoms and complications, and maintains the ability to work.

1. Based on the literature review, it can be said that the indicators of complex clinical and laboratory studies reflecting the development and course of CDP in RA help to analyze the features of its development and course, and also play an important role in prognosing, as well as play an important role in predicting the risk of exacerbation of clinical symptoms of RA due to viral infection in patients with chronic viral hepatitis.

2. It can be said that epigenetic analysis of the level of expression of microRNA-122/221 in patients with RA and CRD, due to its high sensitivity to diagnostic accuracy, can be useful for diagnosing the features of CRP (predominance of RA or CDP symptoms) and disease progression in RA patients.

3. Based on the analysis, it is possible to recommend the use of epigenetic methods of molecular biology, data on the level of expression of microRNA 122/221 for the differential diagnosis of RA and primary liver damage.

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