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REVIEW

Potential of miRNAs to predict and treat inflammation from the perspective of Familial Mediterranean Fever

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Abstract

Aim microRNAs (miRNAs) are small noncoding RNAs that play critical roles in physiological networks by regulating host genome expression at the post-transcriptional level. miRNAs are known to be key regulators of various biological processes in different types of immune cells, and they are known to regulate immunological functions. Differential expression of miRNAs has been documented in several diseases, including autoinflammatory and autoimmune diseases. This review aimed to focus on miRNAs and their association with autoimmune and autoinflammatory diseases.

Methods All related literature was screened from PubMed, and we discussed the possible role of miRNAs in disease prediction and usage as therapeutic agents from the perspective of Familial Mediterranean Fever (FMF).

Conclusions FMF is an inherited autosomal recessive autoinflammatory disease caused by mutations in the MEditerranean FeVer (MEFV) gene, which encodes the protein pyrin. Recent studies have demonstrated that miRNAs may be effective in the pathogenesis of FMF and offer a potential explanation for phenotypic heterogeneity. Further understanding of the role of miRNAs in the pathogenesis of these diseases may help to identify molecular diagnostic markers, which may be important for the differential diagnosis of autoinflammatory diseases. Studies have shown that in the near future, traditional therapies in autoinflammatory diseases may be replaced with novel effective, miRNA-based therapies, such as the delivery of miRNA mimics or antagonists. These approaches may be important for predictive, preventive, and personalized medicine.

Keywords microRNAs · Autoinflammatory diseases · Familial Mediterranean Fever

Introduction

The discovery of miRNAs is one of the most interesting scientific developments in the last 25 years. miRNAs are small RNA molecules that do not encode proteins, and they function in the regulation of gene expression. Approximately 2654 mature miRNAs (miRBase, http://www.mirbase.org, 2018) have been identified in humans and are thought to regulate 60% of protein-encoding gene expression [1]. A single miRNA is known to regulate the expression of multiple genes [2].

miRNAs have a regulatory role in a variety of biological processes, including cell cycle control, metabolism, viral replication, stem cell differentiation, and immune response. Many miRNAs are conserved between species, which supports the idea that miRNAs may be regulators of critical biological pathways. miRNA expression is altered in many diseases with different characteristics, including heart failure, cancer, and viral infections [3]. Targeting miRNAs using antisense oligonucleotide inhibitors or miR-mimics constitutes a unique approach for the treatment of the diseases by regulating biological pathways.

In this review, we aimed to focus on miRNAs and their association with autoimmune and autoinflammatory diseases from the perspective of Familial Mediterranean Fever (FMF). FMF is the most prevalent autoinflammatory disease resulting from mutations in the MEditerranean FeVer (MEFV) gene. The disease is marked with a dysregulated innate immune system response associated with excess IL1 production. FMF tends to be common in individuals with an eastern Mediterranean origin, predominantly in Armenians, Arabs, Jews, and Turks [4, 5].

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Although FMF has an autosomal recessive mode of inheritance, several studies examining phenotypic heterogeneity seen in patients showed that FMF may not be a typical monogenic disease [6, 7]. Recent studies have demonstrated that miRNAs, as an epigenetic mechanism, may be associated with the pathogenesis of FMF.

Thus, in this review, we summarized the importance of miRNAs and experimental approaches for miRNA detection, and mainly focused on potential diagnostic biomarkers and therapeutic approaches of miRNAs in autoimmune and autoinflammatory diseases that may be relevant for PPPM [8, 9].

Overview of miRNAs

miRNAs are a large family of genes that act as post-transcriptional regulators of genes. miRNAs are ~21 nucleotides in length and are involved in many cellular development and control mechanisms in eukaryotes. In recent years, the study of miRNAs has become one of the most important areas of research given their treatment potential for many diseases.

Over the past 2 decades, many of the components involved in miRNA biogenesis have been identified, and the basic principles of miRNA function have been understood [3]. Studies in recent years have shown that miRNA biogenesis is regulated by multiple proteins. To fully understand the role of miRNAs in development, physiology, and diseases, it is necessary to clarify the synthesis, processing, and control mechanisms of miRNAs [10].

Recent research has shown that miRNAs can be packaged in exosomes or microparticles and then released from cells into surrounding tissue or circulation [11–13]. Unlike other extracellular RNA molecules, membrane-bound or lipid-bound extracellular miRNAs are highly stable and can be detected in almost all body fluids, including blood, saliva, bronchial secretions, urine, and breast milk. Given these unique features (disease specificity, high stability, and accessibility), miRNAs are potential clinical biomarkers for the diagnosis and prognosis of specific diseases and monitoring treatment responses. miRNAs also exhibit high potential for treatment given their broad regulatory properties [14].

Successful results have been achieved with miRNA studies related to therapeutic approaches in many diseases, including immuno-inflammatory diseases, oncology, cardiovascular and metabolic diseases, hepatitis C infection, and fibrosis [10, 15–20].

Experimental approaches for miRNA detection

miRNA analysis can be performed using different strategies as indicated in Fig. 1. The starting biological material can vary from whole blood to plasma/serum. In addition, cell lines or primary cells can be used for detection of miRNAs related with disease pathogenesis. For rapid screening of known miRNAs, miRNA microarrays (targeted) can be selected, whereas RNA sequencing platforms (untargeted) can be selected for the analysis of both known and unknown miRNAs. Then, bioinformatics analyses should be performed to identify significantly differentially expressed miRNAs and their related pathways. miRWalk is the most

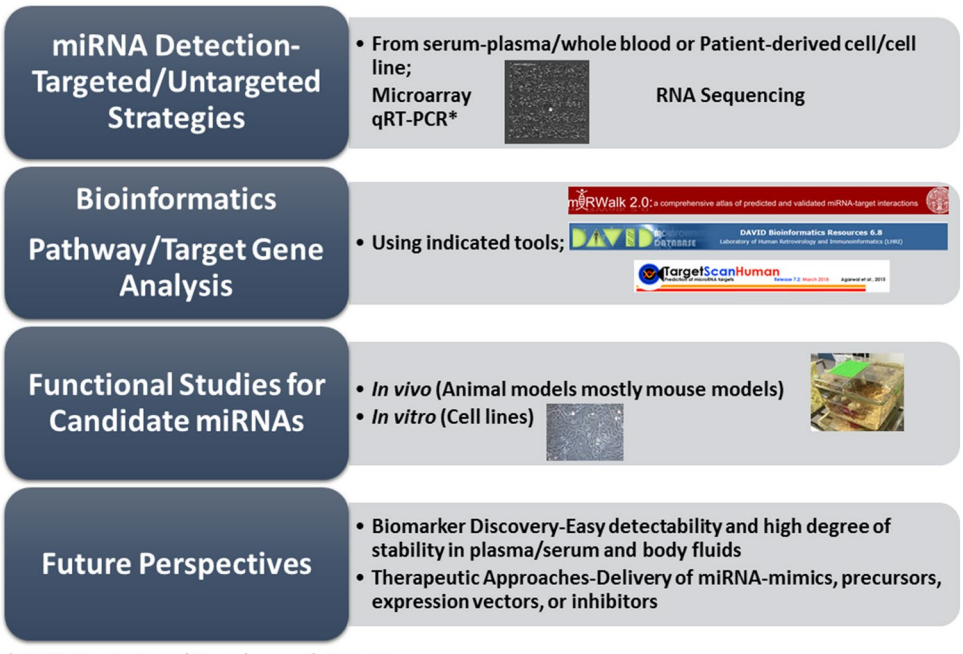

Fig. 1 Schematic workflow of miRNA studies. For screening miRNAs, miRNA micro arrays (targeted) and RNA sequencing platforms (untargeted) can be used. After bioinformatics analyses, functional studies should be performed to determining the target genes and related pathways. Functionally identified miRNAs may be suggested as potential biomarkers for disease diagnosis and/or therapeutic approach for treatment

common target prediction database that combines the results of 12 databases for target gene identification. Databases, such as DAVID and PANTHER, are then used for the pathway analysis of these possible target genes. In recent years, databases used in this field have improved significantly. Therefore, more reliable results can be obtained with these types of bioinformatics tools. After identifying candidate miRNAs, functional analyses can be made using either cell lines/primary cells or animal models. miRNA-related pathways and target gene expression levels should be examined. Mostly, for animal models, miRNA research studies relied on two genetic approaches: (i) an overexpression approach in which a chosen miRNA-related pathway is affected upon overexpression of an miRNA target in wild-type (WT) animals; (ii) a knockdown/knockout approach in which a chosen miRNA-related pathway or phenotype is recovered by knocking down the proposed miRNA target in genetically modified animals. According to the results, miRNAs may be suggested as a potential biomarker for disease diagnosis and/or therapeutic approaches for treatment in the future (Fig. 1).

The important issue is to evaluate miRNA studies according to biological sample type and experimental approach. Several groups have identified different miRNAs from serum/plasma or total blood samples of patients afflicted by the same group of diseases. The identification of numerous differentially expressed miRNAs in different studies indicates that more than one miRNA may be involved in the same pathway. In addition, the biological materials and the method selected for analysis are very important. The most commonly used screening method is microarray analysis. In addition, miRNA panels generated in the literature have also been analyzed by qRT-PCR. The biological material mainly used in analyses was blood samples, whereas serum samples were also being used in different studies. Consequently, the type and expression level of miRNAs may vary between different analysis methods. Therefore, the number of common miRNAs identified in the same disease groups may be quite low. Since the expression of miRNAs also varies by age and gender [21], the difference in the demographic characteristics of sample groups may be another reason for the identification of different miRNAs.

The role of miRNAs in immune system-related pathologies

Autoinflammatory and autoimmune disorders are both systemic diseases characterized by abnormal alterations that result in the activation of immunity [22].

miRNA expression patterns in different tissues are highly specific and contribute to the formation of tissue characteristics and functions. Some miRNAs are expressed continuously, even in specific tissues or cell types. Therefore, it is not surprising that a specific miRNA expression pattern can be defined for a wide range of human diseases, ranging from cancer, hematological, cardiovascular, and neurological diseases to pathological conditions caused by dysfunction of the immune system [23–26]. miRNAs affect not only gene expression of their target genes but also act as signaling molecules that support intercellular communication. In recent years, studies demonstrate that immune cell development and homeostasis are regulated by miRNAs, which is critical for the normal function of immune responses.

Many studies on miRNAs have shown that miRNAs may also be involved in the regulation of inflammatory processes [27]. A large number of miRNAs have been identified in pathways involved in the development and differentiation of B and T cells, proliferation of monocytes and neutrophils, activation of the antibody, and release of inflammatory regulators [28]. Many common miRNAs, such as miR-155 and miR-146a, have been identified in rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), and bacterial infections [27]. In recent years, miR-21 has been found to be effective in the pathogenesis of autoimmune diseases, and has an important role in the regulation of autoimmune responses [29–32].

Many of the autoinflammatory syndromes are also known to be regulated by miRNAs. Lucherini et al. analyzed miRNAs in patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and correlated their levels with parameters of disease activity and/or disease severity. They showed that miR-92a-3p and miR-150-3p expressions were significantly reduced in untreated TRAPS patients [33].

In another study based on primary mouse macrophages, dendritic cells, and HEK293T cell line, Bauernfeind et al. showed that miR-223 is a critical regulator of NLRP3 inflammasome. Researchers determined that miR-223 reduced NLRP3 inflammasome activity by suppressing NLRP3 expression through a conserved binding site within the 3′ UTR of NLRP3. This result may allow an understanding of epigenetic regulation in cryopyrin-associated autoinflammatory syndromes (CAPS) patients in which NLRP3 is over-active [34].

Puccetti et al. aimed to identify differential expression of miRNAs associated with Behçet's disease (BD) which is a rare and chronic inflammatory multisystem disease. They performed miRNA microarray analysis (GeneChip miRNA 4.0 arrays) in peripheral blood mononuclear cells (PBMC) from BD patients. miRNAs; miR-4505, miR-149-3p were increased and let-7d-5p, miR-181a-5p, miR-146a-5p, miR-361-5p, miR-532-3p, miR-423-5p, miR-200c-3p, miR-30e-5p, miR-28-5p, miR-30c-5p, miR-330-3p, miR-194-5p miR-423-3p, miR-28-3p, miR-15b-5p, miR-30d-5p, miR-193a-5p, miR-192-5p, miR-152-3p, miR-25-3p, miR-181d-5p, let-7f-5p, miR-92b-3p, miR-30a-5p, miR-223-3p, miR-505-3p, miR-128-3p, miR-148b-3p, miR-328-3p,

miR-195-5p, let-7e-5p, miR-29b-1-5p, miR-628-3p, miR-92a-1-5p, miR-27b-3p, miR-671-3p, miR-151a-3p, miR-486-5p, miR-199a-3p, miR-199b-3p, miR-126-3p, miR-584-5p, miR-199a-5p, miR-139-5p, and miR-143-3p were decreased in the patient group when compared to controls. They also performed pathway analysis by Network Construction and Network Clustering for the possible target genes of these miRNAs, and showed that miRNAs target pathways such as TNF, IFN gamma, and VEGF-VEGFR signaling cascades relevant in BD [35]. In another study, miR-155 was up-regulated in PBMCs and monocyte-derived dendritic cells of BD patients compared to healthy controls. This miRNA was found to target TGF-Beta Activated Kinase 1 (MAP3K7) Binding Protein 2 (TAB2) gene and have a role in TLR/IL-1 signaling pathway [36].

Aubert et al. [37] compared the skin biopsies from Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease (NOMID) patients compared with skin samples with both nonlesional skin and normal skin. miR-29c and miR-103-2 were significantly down-regulated in lesions, whereas miR-9-1, miR-199a-2, miR-203, and miR-320a were up-regulated. These studies mainly focus on identifying additional disease biomarkers in autoinflammatory diseases.

Recent studies on autoinflammatory diseases with miRNAs are provided in Table 1. All of these studies demonstrate an association between miRNA expression levels and immune system-related diseases.

miRNAs in Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) is an autoinflammatory disease with autosomal recessive inheritance resulting from mutations in the MEFV gene located on chromosome 16 [38, 39]. The MEFV gene encodes the protein pyrin [39].

Three different phenotypes are described in FMF. Type 1, which is characterized by two MEFV mutations, is typically associated with recurrent short duration episodes. Type 2 involves a "silence homozygous or compound heterozygous status" in which the first clinical symptom of the disease is amyloidosis, and type 3 is characterized by asymptomatic patients [40].

Although FMF is a monogenic autoinflammatory disease with an autosomal recessive mode of inheritance, a significant number of patients had only one mutation in the MEFV gene. In addition, many FMF patients with similar genotypes can express different disease phenotypes. These differences in disease phenotype can be explained by modifying genes, epigenetic factors, or environmental effects. Patients in the Eastern Mediterranean region express a less severe disease phenotype if they migrate to Europe [6]. Previously, Ozen et al. demonstrated that Turkish children with FMF who live in Germany express a less severe FMF phenotype compared with people who live in Turkey [7]. All of these findings highlight the effect of environmental factors on the FMF disease phenotype.

Several studies have demonstrated that miRNAs, as an epigenetic mechanism, may be associated with the pathogenesis of FMF, as summarized in Table 2. Wada et al. [41] showed that the levels of circulating miRNAs changed during FMF attacks in patients in three FMF subgroups. The study group including 24 FMF patients classified into the following subgroups was analyzed: (i) patients with exon 10 mutation, (ii) patients with exon 3 mutation, and (iii) patients with neither exon 3 nor 10 mutation (with exon 1, 2 or 5 mutations). Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) patients were used as disease controls. Human microRNA microarray release 14.0 and Agilent analysis were performed. As a result, they observed specific miRNA patterns in different subgroups dependent on MEFV mutations. The difference in expression pattern of miRNAs between the groups with and without an exon 10 mutation was more significant.

In another study based on cell culture techniques, Latsoudis et al. [42] analyzed the miRNAs expression levels in the MEFV gene-silenced human pre-monocytic (THP-1) cell line. A significant increase in miR-4520a expression was observed. Functional analyses were then performed for this miRNA, revealing that the target gene for miR-4520a is Ras homolog enriched in brain (RHEB), which is the target of the main activator in the mammalian target of rapamycin (mTOR) signal pathway. Researchers then analyzed the expression of miR-4520a in patients with FMF who have exon 2 or 10 mutations, and concluded that gain of function mutations in MEFV, especially M694V variant, may be associated with the differential expression pattern of miR-4520a seen in patients.

In a study by Amarilyo et al. [43], the expression levels of 798 mature miRNAs were investigated by multiplexed NanoString nCounter miRNA expression microarray in peripheral blood mononuclear cells (PBMCs) obtained from ten M694V homozygous FMF patients. Expression levels of miR-144-3p, miR-21-5p, miR-4454, and miR-451a were increased in FMF patients compared with healthy controls. On the other hand, the expression levels of miR-107, let-7d-5p, and miR-148b-3p were decreased.

In a recent study, miRNA analyses in a large cohort of FMF patients with exon 2, 3, or 10 mutations and healthy controls were performed to investigate the effect of miRNAs on disease pathogenesis. Many different miRNAs were determined in different comparison groups [44]. Expression analysis was performed with quantitative real-time polymerase chain reaction (qRT-PCR) on 15 miRNAs selected from the literature. miR-125a, miR-132, miR-146a, miR-155, miR-15a, miR-16, miR-181a, miR-21, miR-223, miR-26a,

Table 1 miRNAs in autoinflammatory diseases

Disease type	Up/down-regulation		Tissue or cell line	Target gene	Affected signaling pathway	References
	Up-regulated	Down-regulated				
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)		miR-134, miR-17-5p, miR-498, miR-451a, miR-572, miR-92a-3p	TRAPS patients' and controls' blood samples	Target genes are not identified		[33]
Cryopyrin-associated autoinflammatory syndromes (CAPS)		miR-223	Primary mouse macrophages, dendritic cells and HEK293T cell line	NLRP3		[34]
Behçet's disease (BD)	miR-4505, miR-149-3p	let-7d-5p, miR-181a-5p, miR-146a-5p, miR-361-5p, miR-532-3p, miR-423-5p, miR-200c-3p, miR-30e-5p, miR-28-5p, miR-30c-5p, miR-330-3p, miR-194-5p miR-423-3p, miR-28-3p, miR-15b-5p, miR-30d-5p, miR-193a-5p, miR-192-5p, miR-152-3p, miR-25-3p, miR-181d-5p, let-7f-5p, miR-92b-3p, miR-30a-5p, miR-223-3p, miR-505-3p, miR-128-3p, miR-148b-3p, miR-328-3p, miR-195-5p, let-7e-5p, miR-29b-1-5p, miR-628-3p, miR-92a-1-5p, miR-27b-3p, miR-671-3p, miR-151a-3p, miR-486-5p, miR-199a-3p, miR-199b-3p, miR-126-3p, miR-584-5p, miR-199a-5p, miR-139-5p, miR-143-3p	Peripheral blood mononuclear cells (PBMCs) from BD patients and healthy controls	Target genes are not identified	TNF, IFN gamma, and VEGF-VEGFR signaling cascades	[35]
		miR-155	PBMCs and monocyte-derived dendritic cells (mo-DCs) of BD patients and healthy controls	TAB2	TLR/IL-1 signaling cascade	[36]
Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease (NOMID)	miR-9-1, miR-199a-2, miR-203, miR-320	miR-29c, miR-103-2	Muckle–Wells syndrome and NOMID patients compared with skin samples with both nonlesional skin and normal skin	Target genes are not identified	Affected signaling pathway is not identified	[37]

Table 2 miRNAs in FMF

miRNA	Sample group	Sample type	Up/down-regulation	References
miR-4520a	MEFV gene-silenced human pre-monocytic (THP-1) cell line FMF patients-E148Q/M694I (Exon 2/Exon 10), E148Q/− (Exon 2/−), M694V/M694V (Exon 10/Exon 10), M694V/E148Q (Exon 10/Exon 2), M694V/V726A (Exon 10/Exon 10), M694V/− (Exon 10/−), K695R/− (Exon 10/−) compared to healthy controls	THP-1 cell line	Up	[42]
miR-204*	FMF patients in attack-M694I/M694I (Exon 10/Exon 10), M694I/− (Exon 10/−), E148Q/M694I (Exon 2/Exon 10) compared to healthy controls	Serum	Down	[45]
miR-125a, miR-132, miR146a, miR-155, miR-15a, miR-16, miR-181a, miR-21, miR223, miR-34a, miR-26a	FMF patients-M694V/M694V (Exon 10/Exon 10), E148Q/E148Q (Exon 2/Exon 2), R202Q/R202Q (Exon 2/Exon 2), M694I/M694I (Exon 10/Exon 10), V726A/V726A (Exon 10/Exon 10), M680I/M680I (Exon 10/Exon 10), M680I + M694V (Exon 10 + Exon 10), E148Q + M694V (Exon 2 + Exon 10), R202Q/M694V (Exon 2/Exon 10) M680I + V726A(Exon 10 + Exon 10), E251 K/V726A (Exon 2/Exon 10), E148Q + K695R(Exon 2 + Exon 10), M694 V/R202Q/E148Q (Exon 10/Exon 2/Exon 2), M694V/R202Q/V726A (Exon 10/Exon 2/Exon 10), E148Q/E230 K/P369S (Exon 2/Exon 2/Exon 3), E148Q + R202Q + R761I (Exon 2 + Exon 2 + Exon 10) compared to healthy controls	Venous blood samples	Down	[44]
miR-1225*, miR-2861*, miR-320b*, miR-320c*, miR-320d*, miR-320e*, miR-3960*, miR-4281*, miR-4485*, miR-4516*, miR-451a*, miR-6087*, miR-6088*, miR-6089*, miR-6090*, miR-6125*, miR-638*,miR-6510*, miR-6800*, miR-6869*, miR-6891*, miR-7107*, miR-7150*, miR-7704*, miR-7975*, miR-8069*	FMF patients with exon 3, exon 10 or without exon 3 or 10 mutations between attacks M694I/E148Q (Exon 10/Exon2) M694I/L110P/E148Q (Exon 10/Exon 2/Exon 2) M680I/V726A (Exon 10/Exon10) P369S/R408Q (Exon 3/Exon 3) P369S/R408Q/E148Q (Exon 3/Exon 3/Exon 2) P369S/R408Q/E148Q/R202Q (Exon 3/Exon 3/Exon 2/Exon 2) P369S/R408Q/E148Q/G304R (Exon 3/Exon 3/Exon 2/Exon 2) E84K/− (Exon 1/−) L110P/E148Q (Exon 2/Exon 2) E148Q/− (Exon 2/−) R202Q/− (Exon 2/−) S503C/− (Exon 5/−) and PFAPA patients as disease control	Serum	Up	[41]
miR-20a, miR-5743p, let-7d	M694V/M694V (Exon 10/Exon 10) FMF patients (the most severe phenotype) compared to healthy controls	Peripheral Blood	Up	[46]
miR-197	M694V/M694V (Exon 10/Exon 10) FMF patients (the most severe phenotype) compared to healthy controls	Peripheral blood	Down	
let-7d, miR-107, miR-148b	M694V/M694V (Exon 10/Exon 10) FMF patients (the most severe phenotype) compared to healthy controls	PBMCs	Down	[43]
miR-144, miR-21, miR-4454, miR-451a	M694V/M694V (Exon 10/Exon 10) FMF patients (the most severe phenotype) compared to healthy controls	PBMCs	Up	

*Circulating miRNAs

and miR-34a were significantly decreased in the patient group when compared to controls. miR-132, miR-15a, miR-181a, miR-23b, and miR-26a were increased in the patient group receiving colchicine compared to controls; in contrast to miR-146a, miR-15a, miR-16, miR-26a, and miR-34a were reduced. In relapsed patients, miR-132, miR-15a, miR-21, and miR-34a expression was significantly decreased. miR-132, miR-146a, miR-15a, miR-16, miR-181a, miR-21, miR-223, miR-26a, and miR-34a expression was significantly decreased in patients without an attack compared to those that did have an attack.

Koga et al. [45] performed miRNA microarray analysis (3D-Gene miRNA labeling kit, human_miRNA_V20, Toray) in serum samples from FMF patients [M694I/M694I (Exon 10/Exon 10), M694I/− (Exon 10/−), E148Q/M694I (Exon 2/Exon 10)] experiencing an attack or remission. miR-204-3p expression was decreased in the serum from FMF patients experiencing an attack. Bioinformatics analysis and reporter assay showed that miR-204-3p inhibits inflammatory cytokine release via the phosphoinositide 3-kinase gamma (PI3Kγ) pathway and can, therefore, be considered as a potential biomarker in FMF patients. The miRNA-target gene identification and functional results of this study are promising, since the inhibition of phosphoinositide 3-kinase γ may be considered as a therapeutic target for FMF therapy in the future.

Akkaya-Ulum et al. aimed to explore the potential involvement of miRNAs in the pathogenesis of FMF and whether they could explain the phenotypic heterogeneity observed in the disease. For this purpose, miRNAs were analyzed by miRNA microarray analysis (GeneChip miRNA 2.0 Array, Affymetrix) and by qRT-PCR for validation, in total blood samples obtained from homozygous patients with M694V mutation with a severe disease phenotype and healthy controls. miR-20a-5p was significantly up-regulated, whereas miR-197-3p was down-regulated in homozygous patients [46]. Then, functional analyses were performed with two different cell lines that were transfected with anti- or pre-miRNAs of these miRNAs. miR-197 and miR-20a affect inflammation-related pathways, including cell migration, caspase 1 activation, and cytokine secretion. Both miRNAs were found to have anti-inflammatory effects (unpublished data).

A list of miRNAs identified to date in FMF studies are provided in Table 2. Different studies identified various miRNAs that may be related with FMF pathogenesis. This is an expected result of having been analyzed miRNAs by diverse experimental systems in different patient groups and sample types. All of these miRNAs may be considered for a theranostic approach that integrates therapeutics with personalized medicine. There are more miRNA studies in complex diseases given the multifactorial property of these diseases and higher available sample size compared with rare diseases. However, the number of these types of studies is increasing in rare diseases, as the potential of miRNAs is being understood in individualized therapy.

Conclusions and future perspectives

For the last 2 decades, miRNAs have become an important field among epigenetic factors. Epigenetic factors and changes are responsible for a broad range of human diseases, although it was believed that disorders are caused either by genetic and/or environmental factors. Epigenetic modifications, such as DNA methylation and demethylation as well as histone and nonhistone modifications, are altered in many cancers and autoimmune and neurological disorders. There are numerous specific and effective therapeutic agents in clinical use that can modulate epigenetic mechanisms in various disease conditions. Demethylating agents and histone modifiers, including ‘histone deacetylase (HDAC) inhibitors, and their combinations have great efficacy and promise. In particular, different combinations of these agents may help to treat cancer by activating tumor-suppressor genes and sensitizing cells that are resistant to drugs. Many of these drugs have been approved by the US Food and Drug Administration (FDA) [47].

In the near future, miRNAs may have strong potential to become important tools not only for diagnostics but also for therapeutics. Following expression analysis and in vitro functional studies, animal models should be used to evaluate the potential role of miRNAs in therapy. Mouse models are being used for either diagnostic or treatment approaches, especially for cancer. The main issue in these approaches is obtaining efficient delivery of miRNA mimics, precursors, expression vectors, or inhibitors [48]. Two experimental miRNA-based therapies are listed on ClinicalTrials.gov with phase I and II studies. Although there are fewer mouse model studies of miRNA regulation for autoimmune and autoinflammatory diseases, these studies are promising. miRNA studies for multiple sclerosis and psoriasis-like mouse models are available for identifying the function of miRNAs related with these diseases [49, 50]. These preclinical models show that miRNAs may have potential therapeutic applications [51].

A large number of studies have been published, suggesting that miRNAs may serve as prognostic or predictive biomarkers. miRNAs have a unique, signature-like pattern for diseases. Their pathogenic contribution is noted in almost every type of disease. miRNAs represent a promising tool due to their relatively easy detectability and high degree of stability in plasma/serum and body fluids. As shown in Table 2, many different miRNAs have been identified in separate studies in the same type of disease. The limitations of these studies on FMF include the small sample size and

patients treated with colchicine which may have an effect on miRNA expression level, as well. Another limitation was that most of the research conducted to date has focused on expression analysis, and functional analyses in this area remain very limited. It is necessary to use shared workflow for miRNAs for their evaluation and functional analysis to determine their value as biomarkers [52]. In addition, increasing the number of studies and cases may be more promising for therapeutic approaches and identifying the targeted pathway. There are still miRNA-gene pathways that are not identified as related to autoimmune and autoinflammatory diseases. When these are completed, we may have a clearer picture of miRNAs that have more targeted potential for new therapeutic modalities.

The importance of miRNA studies on rare monogenic diseases is that they may be considered as potential tools of gene therapy approaches. In the near future, novel effective miRNA-based gene therapies may be developed to treat immune system-related pathologies. These therapies may help to replace traditional drug regiments, such as immune suppressive therapies, which have life-long undesirable side effects [53]. As further studies in FMF are conducted and functional analyzes increase, common miRNAs will be found and the potential of miRNAs as diagnostic tools or therapeutic agents may be developed in clinical settings not only for FMF but also for other related autoinflammatory disorders.

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Compliance with ethical standards

Conflict of interest The authors have no conflicting financial, personal, or professional interest to disclose.

Statement of informed consent Patients have not been involved in the study.

Statement of human and animal rights No experiments have been performed, including experiments with patients and/or animals.

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