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RESEARCH

Epigenetic regulators and inflammation antagonists in familial Mediterranean fever: the role of hsa-miR-335-5p, hsa-miR-26b-5p, hsa-miR-16-5p miRNAs and IL-36Ra levels in pathogenesis

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Abstract

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease characterized by mutations in the *MEFV* and an over-activation of the pyrin inflammatory cascade. In this study, the roles of three specific microRNAs (miRNAs) and the inflammatory cytokine antagonist IL-36Ra in the pathogenesis of FMF were investigated due to their potential roles in chronic inflammation. 40 FMF patients and 45 healthy control individuals who applied to the Balikesir University Genetic Disorders Evaluation Center between February 2021 and June 2024 were included in the study. miRNA expression levels were determined by Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR), and IL-36Ra protein levels were determined using the ELISA method. Gene expression levels were analyzed by the 2–ΔΔCt method. A significant decrease ($p < 0.005$) in hsa-miR-335-5p and hsa-miR-26b-5p expression levels and a significant increase ($p < 0.005$) in hsa-miR-16-5p and IL-36Ra protein levels were observed in FMF patients. These findings point to the existence of a two-way molecular mechanism in FMF pathogenesis: on one hand, there is a deficit in epigenetic regulators with anti-inflammatory properties, such as hsa-miR-335-5p and hsa-miR-26b-5p, while on the other hand, molecules like hsa-miR-16-5p and IL-36Ra increase as a compensatory response to balance the inflammatory load. These molecules show promise as potential biomarkers for the diagnosis and follow-up of FMF.

Keywords Familial Mediterranean fever · FMF · miRNA · IL-36Ra · hsa-miR-335-5p · hsa-miR-26b-5p · hsa-miR-16-5p

Abbreviations

cDNA	Complementary DNA
ELISA	Enzyme-Linked Immunosorbent Assay
FMF	Familial Mediterranean Fever
hsa-miR-16-5p	*Homo sapiens* microRNA 16-5p
hsa-miR-26b-5p	*Homo sapiens* microRNA 26b-5p
hsa-miR-335-5p	*Homo sapiens* microRNA 335-5p
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-18	Interleukin-18
IL-36	Interleukin-36
IL-36α	Interleukin-36 alpha
IL-36β	Interleukin-36 beta
IL-36γ	Interleukin-36 gamma
IL-36Ra	Interleukin-36 receptor antagonist
MEFV	*MEditerranean FeVer* (gene)
miRNA	microRNA
mRNA	Messenger RNA
n (%)	Number (percentage)
NF-κB	Nuclear factor-kappa B
ng/L	Nanograms per liter
P / LP	Pathogenic / Likely Pathogenic
qRT-PCR	Quantitative Real-Time Polymerase Chain Reaction

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SPSS	Statistical Package for the Social Sciences
TNF-α	Tumor Necrosis Factor-alpha

Introduction

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent episodes of fever and inflammatory symptoms such as serositis, synovitis, or erysipelas-like erythema [1]. Although it is more prevalent in communities of Mediterranean and Middle Eastern origin, it has become a global condition affecting over 100,000 people worldwide [2–4]. In Turkey, its prevalence is 1/1000, with a high carrier rate of 1/5 [5, 6]. The genetic basis of the disease lies in pathogenic and likely pathogenic variants in the *MEFV* (*MEditerranean FeVer*), located on chromosome 16p13.3. This gene encodes the pyrin protein, which plays a critical role in regulating inflammatory responses [7].

Variants in the *MEFV* disrupt the function of the pyrin protein, leading to hyperactivation of inflammasomes and the subsequent uncontrolled release of pro-inflammatory cytokines, particularly IL-1β [8]. This process triggers the characteristic inflammatory attacks of the disease [9].

Recent research indicates that the autosomal recessive inheritance pattern of the disease cannot solely account for all clinical phenotypes. Notably, the observation of mild inflammatory responses in approximately 30% of heterozygous individuals carrying only one variant in the *MEFV* suggests that epigenetic mechanisms may also play a significant role in the disease's pathogenesis [10]. In this context, microRNAs (miRNAs), which are key regulators of gene expression at the post-transcriptional level, have become an important area of research. These small, non-coding RNAs, approximately 22 nucleotides in length, undertake critical roles in regulating various cellular processes such as the cell cycle, apoptosis, and inflammation by suppressing the translation of or degrading their target messenger RNAs (mRNAs) [11]. The dysregulation of miRNAs is implicated in the pathogenesis of numerous inflammatory and autoimmune diseases [12].

The dysregulated inflammatory response underlying FMF is closely associated with the activity of cytokines like the IL-1 superfamily [13]. Within this family, the IL-36 cytokines (IL-36α, IL-36β, IL-36γ) exhibit potent pro-inflammatory effects, while the IL-36 receptor antagonist (IL-36Ra) acts as a brake against these effects, suppressing inflammation [14, 15]. Since FMF involves the dysregulated production of IL-1 family cytokines, investigating the levels of an antagonistic molecule such as IL-36Ra is of great importance for understanding the inflammatory homeostasis of the disease. The potential roles of these molecules in FMF pathogenesis help to elucidate the complex nature of the disease.

The selection of hsa-miR-335-5p, hsa-miR-26b-5p, and hsa-miR-16-5p for this study was based on their established roles in regulating inflammatory and autoimmune processes. Specifically, hsa-miR-335-5p has been documented to inhibit the production of pro-inflammatory cytokines, acting as a critical regulator in conditions like rheumatoid arthritis and obesity-related inflammation [16]. Similarly, hsa-miR-26b-5p was chosen for its ability to suppress the NF-κB signaling pathway and reduce TNF-α, IL-1β, and IL-6 production, while hsa-miR-16-5p was included due to its role in modulating cellular stress and apoptosis during chronic inflammatory states [17, 18].

The aim of this study is to determine the role of three different miRNAs (hsa-miR-335-5p, hsa-miR-26b-5p, and hsa-miR-16-5p), known for their association with inflammatory processes, and the protein levels of IL-36Ra in FMF patients by comparing them with healthy controls. This multi-marker approach aims to provide a more holistic view of the molecular landscape of FMF, contributing to the discovery of potential biomarkers and offering new insights into the mechanistic foundations of the disease. This study is the first to investigate the association of hsa-miR-335-5p with FMF and may contribute to evaluating the utility of these molecules in the diagnosis or monitoring of the disease.

Materials and methods

Study design and sample selection

This study was designed as a retrospective case-control study involving individuals diagnosed with FMF who presented to the Balikesir University Genetic Diseases Evaluation Center between February 2021 and June 2024. A total of 40 patients and 45 healthy control individuals without FMF symptoms were included in the study. FMF diagnosis was supported by clinical findings and genetic tests. Demographic and clinical data of the patient and control groups were evaluated retrospectively. Total RNA was isolated from plasma samples obtained from fresh anti-coagulated blood. The study cohort consisted of individuals referred to our center for the diagnostic support of FMF, and none of the participants had initiated colchicine therapy at the time of enrollment. Therefore, the biochemical and molecular analyses reflect the patients' status prior to the commencement of standard treatment.

MEFV pathogenic and likely pathogenic variant analyses were performed for the 12 most frequently reported

variants in exons 2, 3, 5, and 10 in the *INFEVERS* database using the qRT-PCR method. The study protocol was approved by the Balıkesir University Health Sciences Non-Interventional Research Ethics Committee with decision number 2024/99, and all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

RNA isolation, cDNA synthesis, and miRNA expression analysis

Total RNA was isolated from plasma samples obtained from fresh anti-coagulated blood, as plasma is preferred over serum to avoid potential microRNA contamination released from platelets during the coagulation process [19]. Total RNA was isolated by using the Thermo Fisher PureLink® RNA Extraction Mini Kit according to the manufacturer's instructions. RNA concentration and purity were determined using a Thermo Scientific Nanodrop device. cDNA was synthesized from the isolated RNA samples using the Applied Biological Materials Inc. miRNA All-In-One cDNA Synthesis Kit. The synthesized cDNA was used in a qRT-PCR application to quantitatively determine the expression levels of hsa-miR-335-5p, hsa-miR-26b-5p, and hsa-miR-16-5p miRNAs. This analysis was performed using the BlasTaq™ 2X qPCR MasterMix kit and a Bio-rad CFX96 C1000 Touch instrument. Gene expression levels were normalized to the internal reference gene U6-2 and calculated using the 2–ΔΔCt method.

Measurement of IL-36Ra protein levels

IL-36Ra protein levels in FMF patients and the healthy control group were determined using the SunRed Biotechnology Company Human IL1F5 ELISA kit, based on the double-antibody sandwich principle. In accordance with the kit's procedures, standard dilutions, samples, and reagents were added to the microtiter plate. After incubation and washing steps, color development was achieved, and the reaction was stopped. Measurements were performed on a plate reader at a wavelength of 450 nm. IL-36Ra concentrations in the samples were calculated using a standard curve.

Statistical evaluation

Statistical analyses of the data obtained in the study were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 26.0 (IBM SPSS Inc. Chicago, USA). Student's t-test and Levene's test for homogeneity of variances were used to compare continuous and categorical variables between groups. A p-value below 0.05 was considered statistically significant.

Results

Of the 40 FMF patients included in the study, 23 were female (57.5%) and 17 were male (42.5%), with a mean age of 24.25 ± 18.64 years. The control group consisted of 45 healthy individuals, of whom 24 were female (53.33%) and 21 were male (46.67%), with a mean age of 31.38 ± 13.94 years. The demographic and clinical characteristics of the patients are summarized in Table 1.

The most common clinical findings in the patient group were fever, abdominal pain, arthritis/arthralgia, and multiple symptoms. Among the genotypes of the analyzed patients were R761H and M694V homozygous variants; M694V, V726A, R761H, E148Q, M680I/C, L110P, R202Q heterozygous variants; and (M694V, V726A), (E148Q, P369S), (R761H, M694V), (E148Q, V726A), (V726A, M680I/C), (E148Q, M680I/C), (M694V, M680I/A) compound genotypes were identified. The *MEFV* variant analysis results of the patients, according to their genotypes, are shown in Table 2.

The main findings of our study revealed significant differences in the levels of the selected miRNAs and IL-36Ra protein in FMF patients. The levels of hsa-miR-335-5p miRNA, as measured by qRT-PCR, were observed to be

Table 1 Demographic and characteristic features of FMF patients

	Male, *n* (%)	Female, *n* (%)
Gender	17 (42.5%)	23 (57.5%)
Mean Age	24.25 ± 18.64	
Symptoms, n (%)		
Abdominal pain	7 (17.95%)	
Fever	4 (10.25%)	
Arthritis/arthralgia	2 (5.13%)	
Multiple symptoms	26 (66.67%)	

Table 2 Percentages of *MEFV* variants detected in the patient group

P / LP Varyant	Genotip	*n* (%)
Homozygous genotype	R761H/R761H	2 (5%)
	M694V/M694V	2 (5%)
Heterozygous genotype	M694V	10 (25%)
	V726A	6 (15%)
	R761H	2 (5%)
	E148Q	2 (5%)
	M680I/C	2 (5%)
	L110P	2 (5%)
	R202Q	1 (2.5%)
Compound genotype	M694V, V726A	3 (7.5%)
	E148Q, P369S	2 (5%)
	R761H, M694V	2 (5%)
	E148Q, V726A	1 (2.5%)
	V726A, M680I/C	1 (2.5%)
	E148Q, M680I/C	1 (2.5%)
	M694V, M680I/A	1 (2.5%)

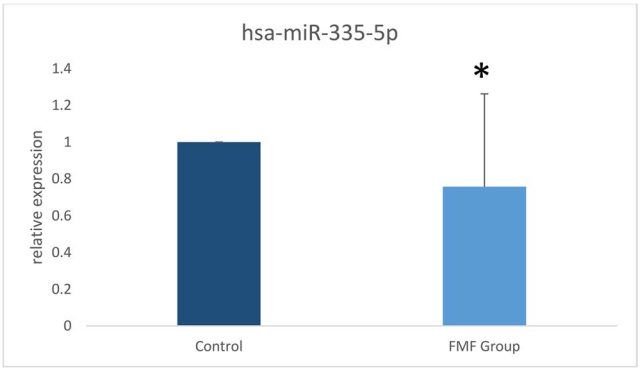

Fig. 1 Comparison of hsa-miR-335-5p miRNA levels normalized to U6-2 levels. Data are presented as mean ± SEM. *$p < 0.05$ indicates a significant difference compared to the Control Group

significantly lower in FMF patients compared to the healthy control group. This finding is visualized in Fig. 1.

Similarly, hsa-miR-26b-5p expression levels were also significantly lower in FMF patients than in healthy controls. This decrease is clearly shown in Fig. 2.

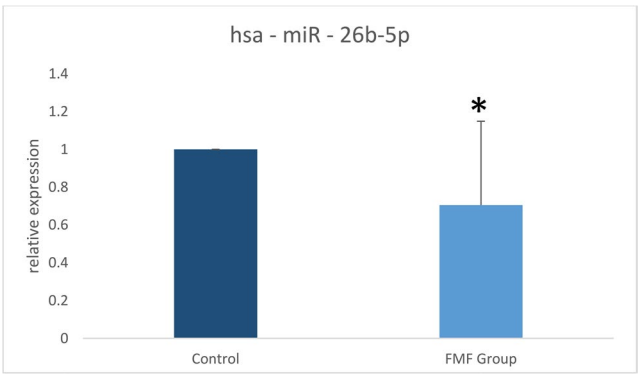

Fig. 2 Comparison of hsa-miR-26b-5p miRNA levels normalized to U6-2 levels. Data are presented as mean ± SEM. *$p < 0.05$ indicates a significant difference compared to the Control Group

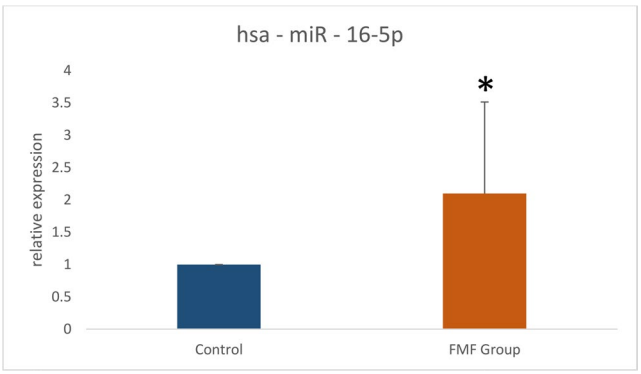

Fig. 3 Comparison of hsa-miR-16-5p miRNA levels normalized to U6-2 levels. Data are presented as mean ± SEM. *$p < 0.05$ indicates a significant difference compared to the Control Group

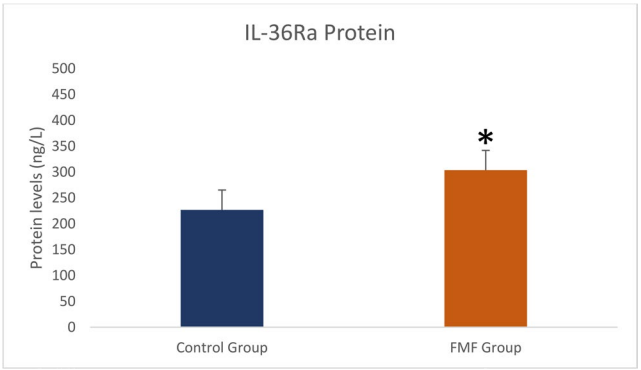

Fig. 4 Comparison of IL-36Ra protein levels. Data are presented as mean ± SEM. *$p < 0.05$ indicates a significant difference compared to the Control Group

In contrast to these two miRNAs, a significant increase in the expression level of hsa-miR-16-5p was detected in FMF patients compared to the healthy control group. This increase is presented in Fig. 3.

Finally, the IL-36Ra protein levels, measured by the ELISA method, were found to be 303.73 ng/L on average in FMF patients, whereas this value was 227.03 ng/L in the healthy control group. This increase (76.7 ng/L) is statistically significant. This finding is visualized in Fig. 4.

Discussion

This study has revealed significant changes in the expression levels of three specific miRNAs (hsa-miR-335-5p, hsa-miR-26b-5p, hsa-miR-16-5p) and the IL-36Ra protein in patients with Familial Mediterranean Fever. The findings suggest that complex epigenetic and inflammatory regulatory mechanisms, in addition to genetic variations, play a role in the pathogenesis of FMF.

For the first time, our study has determined that hsa-miR-335-5p levels are significantly decreased in FMF patients compared to healthy individuals. The literature has shown that hsa-miR-335-5p suppresses inflammation by inhibiting the production of pro-inflammatory cytokines [20]. In this context, the decrease in its levels may be an indicator of the excessive inflammatory response in FMF and could contribute to the exacerbation of the disease. This result provides new data on the molecular pathophysiology of FMF and can be considered an epigenetic dysregulation reflecting the chronic inflammatory nature of the disease.

Similarly, the levels of hsa-miR-26b-5p were also found to be significantly decreased in FMF patients. This finding is consistent with the results of a previous study conducted on pediatric FMF patients [21]. This miRNA is known to play a central role in the regulation of mechanisms related to apoptosis and inflammation [22]. Hsa-miR-26b-5p has

been shown to suppress inflammation by regulating the NF-κB signaling pathway and reducing the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) [23]. Therefore, a decrease in the expression of this microRNA could lead to the uncontrolled progression of the inflammatory cascade, thereby exacerbating the disease's symptoms.

On the other hand, a significant increase in hsa-miR-16-5p levels was observed in FMF patients. This contrasts with the decrease reported in some pediatric patient studies [24]. This discrepancy could be explained by factors such as the stage of the disease, patient age, and treatment. hsa-miR-16-5p is known to suppress the inflammatory response by promoting cellular apoptosis and inhibiting pro-inflammatory signaling pathways such as NF-κB [25]. Therefore, this increase in adult FMF patients can be interpreted as a compensatory mechanism developed against the chronic inflammatory load. As the disease progresses, the organism may activate such adaptive molecular mechanisms to limit inflammation and reduce cellular stress. This positions hsa-miR-16-5p not merely as a simple biomarker, but as an indicator of the body's dynamic response to an inflammatory state.

One of the most significant findings of our study is that IL-36Ra protein levels were substantially elevated in FMF patients compared to healthy individuals. There are no specific studies in the literature that directly measure the levels of this cytokine antagonist in FMF patients. FMF is a disease characterized by the over-activation of the pyrin inflammasome, resulting in an increase of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-18. IL-36Ra inhibits the action of IL-36 agonists (IL-36α, β, γ), which trigger inflammation, by binding to the IL-36 receptor, and it is known to play a critical role in regulating inflammatory responses [26]. Consequently, the elevation of IL-36Ra levels as a result of the chronic inflammatory load in FMF represents a physiological and endogenous defense mechanism activated by the body to counterbalance the excessive inflammatory response.

An overall assessment of these findings demonstrates that the pathogenesis of FMF is too complex to be explained by a single gene variation alone. Epigenetic regulators like miRNAs can significantly influence the course of the disease by controlling inflammatory processes at the post-transcriptional level. The decrease in anti-inflammatory miRNAs and the increase in compensatory mechanisms (miR-16-5p and IL-36Ra) reveals the dynamic molecular landscape of the disease. These molecules could be considered potential biomarkers for the diagnosis of FMF, the determination of its subtypes, and the monitoring of treatment response. The use of these molecules as a panel may yield more accurate results than a single marker.

Our study has some limitations. Although we analyzed miRNA expression profiles across various *MEFV* genotype subgroups, the distribution of cases within specific mutation categories was not sufficient to identify statistically significant correlations. Consequently, a Principal Component Analysis (PCA) could not be robustly performed due to the limited number of subjects available for such complex subclustering. Future research with larger cohorts is necessary to provide a more comprehensive understanding of these molecular associations.

Conclusion

This study sheds light on the molecular pathogenesis of Familial Mediterranean Fever, demonstrating significant changes in the expression levels of miRNAs such as hsa-miR-335-5p, hsa-miR-26b-5p, and hsa-miR-16-5p, and in the protein level of IL-36Ra. The findings reveal that FMF possesses a complex and dynamic molecular pathology, characterized by a deficit in certain epigenetic regulators with anti-inflammatory effects (hsa-miR-335-5p and hsa-miR-26b-5p), while simultaneously activating compensatory mechanisms (hsa-miR-16-5p and IL-36Ra) to balance the inflammatory load.

Our study suggests that these molecules could be used as potential biomarkers in the diagnosis of FMF, for monitoring disease activity, and even in the development of new, targeted therapeutic strategies. In particular, the hypothesis that the increase in IL-36Ra is an endogenous defense mechanism against the hyperactivation of the pyrin inflammasome offers valuable insights into the molecular underpinnings of the disease. This work is an important step towards a better understanding of FMF and paving the way for more effective and individualized approaches to its management. Future functional studies will more clearly define the precise role of these molecules in inflammatory pathways and their therapeutic potential.

Author contributions Concept – S.E., A.S.A.; Design – S.E., A.S.A.; Supervision – A.S.A.; Data collection –S.E., A.S.A., HB.; Analysis and Interpretation – S.E., A.S.A.; Literature search – S.E., A.S.A.; Writing manuscript – S.E., A.S.A.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study was approved by the Balikesir University Health Sciences Non-Interventional Research Ethics Committee (Decision No: 2024/99, dated June 25, 2024). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Competing interests The authors declare no competing interests.

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