RESEARCH ARTICLE

Interleukin-33 and Familial Mediterranean Fever: A Novel Inflammatory Cytokine and a Common Autoinflammatory Disease

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ABSTRACT

Objective: Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease, including reiterative feverish bouts of joint pain, and abdominal and chest pain as a consequence of serosal inflammation. In the course of acute attacks, multifarious proinflammatory cytokines have been depicted to increase. In previous studies, it has been underlined that IL-33, a recent member of the IL-1 cytokine superfamily, has an essential role in the inflammation. Here, we aimed to evaluate serum IL-33 levels in FMF patients to investigate its presumable importance in the FMF formation mechanism.

Materials and Methods: A total of 58 FMF patients (21 females, 37 males; mean age 27.8 ± 5.2 years, mean disease duration 8.2 ± 3.7 years) and 22 healthy controls (10 females, 12 males, mean age 26.5 ± 5.9 years) were incorporated into this research. ELISA was utilized to measure serum IL-33 concentrations.

Results: The mean concentrations of serum IL-33 were 3.88 ± 2.25 pg/ml and 2.89 ± 0.48 pg/ml in the patient and control groups respectively. The mean serum IL-33 concentrations were 5.48 ± 2.13 pg/ml and 2.27 ± 0.36 pg/ml in the active phase and in the inactive phase respectively. According to these results, serum IL-33 concentrations were prominently higher in FMF patients compared with the control group (p<0.01). Moreover, serum IL-33 concentrations were measured significantly higher in the active phase compared with serum IL-33 levels in the inactive phase and controls respectively (p<0.0001 and p<0.0001). The mean serum IL-33 levels in patients with active FMF was associated with arthritis (p<0.05).

Conclusion: To sum up, the high concentrations of serum IL-33 in the active FMF cases propose that IL-33 may operate a remarkable function in the pathogenesis of FMF.

Keywords: Interleukin-33, Familial Mediterranean Fever, disease activity, inflammation

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most prevalent autoinflammatory disease in the world, predominantly in the Eastern Mediterranean region (1). FMF is classically characterized by repetitive, short-term (1-3 days), feverish episodes of inflammatory attacks of the peritoneum, pleura, joints, and a skin rash mimicking erysipelas (1). An increment in acute phase reactants (Serum Amyloid A (SAA), fibrinogen, leukocyte count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)) is characteristic of acute attacks, and the abovementioned markers decline to their normal ranges in the attack-free periods (1).

MEFV gene mutations which result n the disrupted pyrin protein, which interacts with the components of the inflammasome and in turn is activated in response to

infectious agents under normal conditions, carry out the primary function in the pathogenesis of FMF [2]. Most FMF-associated mutations are autosomal recessive, although autosomal dominant inheritance has also been reported to a lesser extent [1]. As a result of this mutation, an exacerbation in the proteolytic caspase-1 activity and an increment in the proteolytic activation of the inactive precursor Interleukin-1β (IL-1β) occur [2]. IL-1 prompts the translocation of activated NF-kB to the cell nucleus, leading to increased secretion of innate immune response enhancing cytokines such as pro-IL-1β, IL-6, pro-IL-18, which dominate the clinical symptoms of autoinflammatory diseases [2].

Colchicine therapy is the first line of treatment for FMF and is used to both prevent attacks and to avert complications including the emergence of secondary amyloidosis. However, complete unresponsiveness to the maximum tolerated colchicine dose was reported in 5% of patients with FMF, and partial unresponsiveness to colchicine treatment was reported in 20-40% of patients with FMF [2]. The IL-1 inhibitors anakinra, rilonacept, canakinumab, and the IL-6 inhibitor tocilizumab can be utilized as therapy alternatives in instances that do not respond to colchicine [2].

Interleukin-33 (IL-33) is a recently discovered member of the IL-1 cytokine family. IL-33 is expressed in cells that have barrier functions, primarily epithelial cells, as well as innate immune cells such as macrophages and dendritic cells [3]. IL-33 is capable of activating T helper (Th) type 1 immune response in the context of chronic inflammation, aside from its contribution to the emergence of Th type 2 immune response and the pathogenesis of different allergic disorders, including asthma [3,4]. Previous investigations have illustrated that IL-33 has been implicated in a variety of inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease, and Behçet's disease [5]. Evidence from the previously conducted studies illustrates that various cytokines associated with Th17 and Th1 cells, namely IL-6, IL-17, IL-18, IFN-γ, increase in patients with FMF [6]. The purpose of our study was to ascertain whether IL-33 is elevated in the sera of FMF patients, particularly during an attack caused by an aforementioned autoinflammatory disease.

MATERIAL and METHODS

This cross-sectional study comprised 58 unrelated FMF patients who had visited our institution's Allergy and Immunology Department for medical evaluation and management between 01.08.2014 and 01.08.2015. We also included patients attending the emergency department who had been under our team's follow-up. All participants were informed in detail about the research. Written informed consent was obtained from all of the subjects. All participants in this study were given an individual number. The inclusion criteria for patients in this study were being aged 18 or older, being diagnosed with FMF; not having concomitant chronic inflammatory disease, concomitant acute or chronic infection, concomitant allergic or atopic disease; and giving informed consent for participating in this study. The exclusion criteria for patients in this study were being younger than 18 years, not being diagnosed with FMF, having concomitant chronic inflammatory disease, concomitant acute or chronic infection, concomitant allergic or atopic disease, and refusing to give informed consent for participating in this study. All of the participants who were diagnosed with FMF met the Tel-HaShomer criteria [7]. Serositis was documented by radiologic imaging studies such as abdominal ultrasound, chest X-ray, thorax computerized tomography and/or abdominal computerized tomography. In our study, FMF cases with no symptoms related to FMF activation for at least 7 days were considered to be in the attack-free period. Controls included blood donors and relatives of medical professionals who did not have any FMF-compatible symptoms, had no FMF-diagnosed first-degree relatives, no concomitant chronic inflammatory disease, concomitant acute or chronic infection, concomitant allergic or atopic disease, no history of any acute illness at the time of the research, and gave their informed consent for participating in this study. It was noted that all patients were receiving daily colchicine medication. The ordinary daily colchicine dosage was between 0.5 and 2 grams. Examination of the organs and systems, routine laboratory tests, and imaging tests performed so far were evaluated in the patients. In addition, age, gender, educational status, accompanying disease and demographic characteristics were recorded in the patients and the control group participants.

This study was approved by the institutional ethics committee (Approval Number: 12-541-14) and was conducted in accordance with the Helsinki declaration [8].

Laboratory Tests

According to the instructions of the manufacturer (e-Bioscience, San Diego, CA, USA), laboratory tests were carried out using commercially available human enzyme-linked immunosorbent assay (ELISA) kits. Fasting (for at least 10 hours) blood samples were obtained for all laboratory analyses, including IL-33. The plasma fractions were separated and preserved at -80 °C until evaluated for IL-33 levels. Serum levels of highly sensitive C-reactive protein, erythrocyte sedimentation rate, and fibrinogen were also obtained on the same day.

Statistical Analysis

IL-33 concentrations and other laboratory values were described using the median, percentiles, and ranges. The SPSS 17.0 statistical software was used to perform all statistical calculations. The Kolmogorov-Smirnov test was used to examine the distribution of numerical data. Mean ± standard deviation (SD) was used for normally distributed data, while the median (range) values were specified for non-normally distributed data. IL-33 serum concentrations were assessed between normal controls, and inactive and active FMF patients using One-Way ANOVA, Bonferroni, and T-Tests. Statistical significance was set at $p < 0.05$.

RESULTS

The present research incorporated 58 patients who had previously been diagnosed with FMF. Males made up 37 (63.8%) of the 58 patients whereas 21 (36.2%) were female. The mean age was 27.8 ± 5.2 years, and the mean disease duration was 8.2 ± 3.7 years in the patient group. There were 22 control subjects (10 females, 12 males, mean age 26.5 ± 5.9 years). The patient and control groups had similar age and gender distribution with a statistically insignificant variation (p>0.05). In the FMF group, 30 patients (51.7%) were in the active period of the disease, whereas 28 (48.3%) were in remission. FMF attacks were diagnosed with the presence of at least two of the following findings and symptoms such as fever, abdominal pain or demonstrated evidence of serositis or arthritis, and increased acute phase reactants (C-reactive protein, sedimentation rate, fibrinogen).

Abdominal pain was the most frequent finding, and all of the patients with active disease had complained of it. Fever equal or higher than 38°C was measured in 11 of active patients (36.7%) and none of the inactive patients. Serositis was documented in 22 of 30 active patients (73.3%) using radiologic imaging methods. Arthritis was present in 5 (16.7%) patients as a physical examination finding. Arthralgia without swelling, tenderness or erythema was not considered to be arthritis. Only 4 of the FMF patients had previously documented amyloidosis, and 75% of them had been diagnosed with an acute attack (Table I).

The mean serum IL-33 concentrations were measured as 3.88 ± 2.25 pg/ml (minimum-maximum 1.86-10.50 pg/ml) in the FMF group (active and inactive) and 2.89 ± 0.48 pg/ml (minimum-maximum 1.91-3.99 pg/ml) in the control group. The mean concentrations of serum IL-33 were 5.48 ± 2.13 pg/ml (minimum-maximum 3.29-10.50 pg/ml) in the active phase and 2.27 ± 0.36 pg/ml (minimum-maximum 1.86-3.02 pg/ml) in the inactive phase (Figure 1). Multiple comparisons were made using Bonferroni tests. Based on these findings, levels of serum IL-33 were considerably greater in FMF patients than those in healthy controls (p<0.01, 95% CI). Beyond that, serum IL-33 concentrations were substantially higher in the active phase compared with the inactive phase and control group

Table I: Demographic and clinical features of the study group.

Demographic and Clinical Features	FMF Patients (n=58)	Healthy Controls (n=22)	p
Age (years, mean ± SD), (range)	27.8 ± 5.2 (19-38)	26.5 ± 5.9 (18-37)	>0.05
Gender (M/F)	37/21	12/10	>0.05
Disease Duration (years, mean ± SD)	8.2 ± 3.7	N/A	
Amyloidosis	4	N/A	
Fever	11	N/A	
Serositis	22	N/A	
Abdominal Pain	30	N/A	
Arthritis	5	N/A	

respectively (p<0.0001 and p<0.0001, 95% CI). When compared with healthy controls, serum IL-33 concentrations in the inactive FMF patients were determined to be lower, albeit not statistically significant (p>0.05, 95% CI) (Table II).

Serum IL-33 levels were positively correlated with arthritis (p<0.05, r = 0,483), but they were not correlated with other findings such as abdominal pain, serositis, disease duration, or levels of C-reactive protein and the sedimentation rate. Because of the small number of individuals who had amyloidosis, statistical comparisons could not be made for that complication.

DISCUSSION

We hypothesized that serum levels of the IL-1 family, including IL-33 as a member of the IL-1 superfamily,
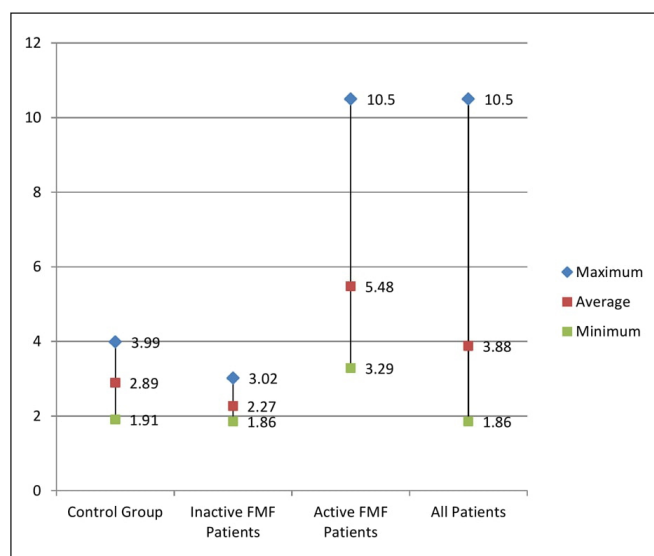

Figure 1: Schematic representation of serum IL-33 levels in all patients and the healthy control groups.

could be altered during the course of autoinflammation led by FMF. In the present research, serum IL-33 levels in a group of FMF patients from Türkiye were assessed. We demonstrated that IL-33 concentrations in FMF patients were considerably higher than those in healthy controls (p<0.01). Moreover, we revealed that patients in the active phase of the disorder had notably higher serum IL-33 levels than those in the attack-free phase and healthy controls, respectively (p<0.0001 and p<0.0001). Our findings support our hypothesis, during an acute FMF attack in particular.

IL-33, a recently discovered member of the IL-1 cytokine family, functions as a proinflammatory cytokine, as well as a nuclear factor, and it is produced by various cells including endothelial cells, epithelial cells, macrophages, and dendritic cells as an alarm response (alarmin) to various pathological stimuli such as cell necrosis, viral infections, stress, and trauma (9). ST2, the receptor of IL-33, pertains to the Toll-like Receptor (TLR) superfamily and is prominently expressed in Th2, CD8+ T cells, basophils, eosinophils, type 2 innate lymphoid cells (ILC2), Natural Killer T (NKT) cells, macrophages, and dendritic cells (9). IL-33 is involved in the development of a variety of allergic disorders including asthma, allergic rhinitis, and atopic dermatitis by controlling the expression of Th2 cytokines, particularly IL-5 and IL-13 (4,9). Several studies have indicated that IL-33/ST2 signaling may have an impact in the pathogenesis of autoimmune disease by modifying the equilibrium between inflammatory Th1/Th17 cells and Treg cells; in addition, IL-33/ST2 signaling may have an anti-inflammatory function in autoimmune diseases through its effect on the Th type 2 immune response (9). To date, evidence is scarce on how IL-33 status changes with the autoinflammatory disease course, particularly in FMF.

Table II: Laboratory parameters in the study group.

Laboratory Parameters	FMF Patients with Acute Attack (n=30)	FMF Patients in Remission (n=28)	Healthy Controls (n=22)	p¹	p²	p³
C-Reactive Protein (mg/L)	34.23±6.44	4.11±1.42	N/A			<0.05
Sedimentation Rate (mm/h)	47.40±7.80	23.21±6.56	N/A			<0.05
Fibrinogen (mg/dL)	559.8±85.3	225.3±59.9	N/A			<0.05
IL-33 (pg/ml) (mean ± SD), (range)	5.48±2.13 (3.29-10.50)	2.27±0.36 (1.86-3.02)	2.89±0.48 (1.91-3.99)	<0.0001	>0.05	<0.0001

p¹: values for comparison between FMF patients with acute attack and healthy controls.

p²: values for comparison between FMF patients in remission and healthy controls.

p³: values for comparison between FMF patients with an acute attack and FMF patients in remission.

There are numerous data indicating that patients with FMF have a higher incidence of certain inflammatory and autoimmune disorders in comparison with the rest of the population, including those with Behçet's disease, SLE, inflammatory bowel diseases, psoriasis, and AS (10,11). Many of these disorders have been linked to an increase in the blood level of IL-33, as demonstrated by numerous studies (5,9). Various studies tracking the connection between Behçet's disease and IL-33 have generated contrasting findings; there are data indicating that blood IL-33 levels tend to rise in individuals suffering from active Behçet's disease, but there are also some contentious studies that assert serum IL-33 levels are reduced in those with active Behçet's disease when compared with inactive cases and a healthy control group (12,13). Considering that IL-33 is a cytokine with a dual function in the immune system, both pro-inflammatory and anti-inflammatory, the movement of IL-33 serum levels in different directions in active Behçet's disease patients can be at least partially explained (9,12).

TLR2 expression has been demonstrated to be enhanced in neutrophils and monocytes of FMF patients in comparison with a healthy control group (14,15). Furthermore, TLR2 expression in monocytes was observed to reduce considerably after colchicine treatment in FMF patients (15). Besides, in a current study, serum IL-33 levels of the cases with the TLR2 rs111200466 variant genotype in early childhood were found to be significantly lower compared to cases with the wild TLR2 genotype (16).

The abovementioned findings may serve as an explanation of our data that revealed attack-free FMF patients had even lower levels of serum IL-33 than healthy controls, as they were on regular colchicine treatment. We suggest that regular use of colchicine might have interacted with TLR2 expression in the absence of an acute attack, leading to lower levels of IL-33 in FMF patients. Analyzing the serum levels of IL-33 in a population with FMF refusing to use colchicine would add more value to this study, which is very hard to apply in real life.

In addition, in a recent study on the results of experimentally-induced TLR2 activation in the murine model, it was observed that IL-33 release from keratinocytes and satellite glial cells placed in the dorsal root ganglion increased through innate immune hyperactivity, inflammation development, and macrophage activation in the skin and neural tissue, while acute pain formation was triggered via the IL-33/ST2 pathway, and pain reduction was observed with IL-33 inhibition (17). This study is intriguing in terms of investigating the relationship between pain sensation and serum IL-33 levels in FMF patients, particularly during painful attacks. Besides, prospectively determining the pain level and analyzing IL-33 levels to test for a correlation between the two would add more value to our work. Further studies are a must in order to elucidate the interaction between IL-33 and painful inflammatory diseases.

In various studies previously conducted, it was determined that some cytokines that are related to T helper 17 (Th17) and Th1 such as IL-6, IL-17, IL-12p40, IL-18, IFN-γ, increase in FMF cases (6). IL-1 and IL-6 are pronounced as potent promoters of Th17 polarization (18). With the presence of IL-12, IL-18 serves as a cytokine that drives activated Th1 cells to release IFN-γ (19). Growing scientific evidence shows that IL-33 can stimulate the Th17 response through IL-1β and IL-6 by providing maturation of dendritic cells; moreover, it has been determined that dendritic cells matured by IL-33 can enable Treg cells to differentiate into Th17 cells (20,21). In the near future, we believe that studies delving into IL-33 during the course of autoinflammatory disease, particularly FMF, will increase both in number and quality.

Additionally, we observed in FMF patients with active disease that the mean serum IL-33 level was positively correlated with arthritis ($p < 0.05$, $r = 0.483$). Serum IL-33 levels were found to be significantly higher in AS patients compared with healthy participants in a study that questioned the association between AS and IL-33; besides, serum IL-33 levels in AS patients were also correlated with vascular endothelial growth factor levels and the Bath Ankylosing Spondylitis Disease Activity Index (22). Koga et al, in their study in which they evaluated the cytokine characteristics in FMF and RA patients, concluded that the cytokine network engaged in the disease processes of FMF and RA is noticeably comparable (23). It was determined that IL-33 levels were elevated in the serum and synovial tissue of RA patients, and that these levels were correlated with RA disease activity (24). It has been revealed that IL-33 increases the expression of inflammatory cytokines such as TNF-α, IL-6, and expression of NF-κB, an important transcriptional factor for inflammatory cytokines, in patients with RA (25). Considering the increased frequency of MEFV mutations in patients with RA and AS compared with the rest of the population, the possible common pathogenetic pathways in FMF, AS, and RA patients may explain the

increase in the IL-33 serum level and the correlation of the IL-33 serum level with arthritis in these diseases, albeit partially (26,27).

Our findings have demonstrated that, relative to healthy controls, inactive FMF patients have decreased serum IL-33 concentrations; however, this result was not of statistical significance (p>0.05). This situation may be explained at least partially by the self-limiting nature of FMF disease in which the immune system may prompt a sort of negative feedback mechanism to limit the effect of various inflammatory cytokines that are excessively secreted during the FMF attack period. For instance, in the first 24 hours of an acute FMF attack, it has been demonstrated that mature IL-1β-bearing NETs, which constitute one sort of important effector mechanism in the process of neutrophil-mediated inflammatory diseases, including FMF, are generated and released; additionally, NETs have the ability to reduce their own production through a negative feedback mechanism (28). A pore-forming protein known as gasdermin D (GSDMD) can release inflammatory cytokines such as IL-1β and IL-18 in the process of inflammatory cell death (pyroptosis) and has a significant part in the pathophysiology of several infectious and inflammatory illnesses, including FMF, that are mediated by the inflammasome (29). It has been revealed that GSDMD can induce release of IL-33 via generating pores in the cell membrane (30). In a recent study, it also has been established that the N-terminal fragment of GSDMD, which draws attention with its central role in the inflammasome cascade, could unexpectedly inhibit caspase-1/11 directly, and this has been evaluated as a negative feedback mechanism followed by inflammasome activation (31). Last but not the least, there is mounting evidence showing that routine colchicine treatment could limit the expression of E-selectin on endothelial cells, as well as regular colchicine therapy during the dormant disease phase could drastically diminish the biomarkers of inflammation (32,33). These findings imply that reduced IL-33 concentrations in our inactive FMF group may be led by a negative feedback mechanism in the pyrin inflammasome or by the regular usage of colchicine treatment, as discussed in detail earlier. To comprehend this issue better, further investigations are necessary.

Although numerous monoclonal antibody treatments that inhibit the IL-33/ST2 axis remain to be developed, these investigations are mostly concerned with the treatment of asthma and atopic diseases (34,35). There are also various murine model studies indicating that anti IL-33 treatment could reduce proinflammatory cytokine levels and disease severity in lupus and collagen-induced arthritis (36,37). In the future, it is possible that new treatment strategies on IL-33 inhibition for different autoimmune and inflammatory diseases, including FMF, will be developed.

These current literature data we shared enlightened us in terms of the formation of our hypothesis that serum levels of IL-33, which regulates innate and acquired immune responses and which has an active function in the formation of inflammatory responses, may be altered in FMF patients. Although there was only one previous study reported as a congress abstract examining the relationship between FMF and the IL-33 serum level, no significant relationship could be demonstrated (38). To our best knowledge, the research we have conducted is the initial one to demonstrate a substantial correlation between serum IL-33 levels and FMF patients, particularly during disease activation. Additional studies are required to clarify the connection between FMF and IL-33.

We acknowledge that there are certain limitations in the current introductory investigation. The small size of our population and our cross-sectional study design are our primary limiting factors. Furthermore, the fact that all of our FMF patients were receiving ordinary colchicine treatment may have changed the cytokine status of our patients, as some studies concluded that continuous colchicine therapy during the dormant illness state may notably reduce levels of the markers linked to vascular damage (32). We also could not demonstrate the variability of genes encoding IL-33; however, it is unclear if IL-33 gene variations affect susceptibility, whether by raising or lowering IL-33 activity and level (13). Last but not least, in our study, the Auto-Inflammatory Diseases Activity Index (AIDAI) was not used to determine the active and inactive FMF cases; instead, the FMF cases' symptom-free period, which was at least seven days, was considered (39). However, at the time our study was planned and conducted, AIDAI had not yet been described in the literature as a validated scale and had not yet been routinely used in our clinics (39). Furthermore, due to the fact that our study was designed as a cross-sectional study, we reasoned that the evaluation of FMF cases without keeping a diary for the last 1-week period, rather than the last 1-month period evaluation recommended by AIDAI, would be easier to remember and more reliable in determining disease activ-

ity, similar to previously conducted studies on FMF taking the last week into consideration as an attack-free period (32,40).

CONCLUSION

It is explicit that the IL-33 pathway has an essential function in autoimmune and inflammatory disorders. Here, we present an investigation outlining that FMF, an inherited autoinflammatory condition, may also be associated with the IL-33 pathway. Additional research on this novel cytokine is necessary to examine its functional significance in order to thoroughly investigate its clinical application, including the utilization of anti-IL-33 biological treatment modalities, for FMF.

Conflict of Interest

The authors declare no conflicts of interest.

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Authorship Contributions

Concept: **Seda Altiner,** Design: **Pamir Cerci,** Data collection or processing: **Seda Altiner, Pamir Cerci,** Analysis or Interpretation: **Seda Altiner, Pamir Cerci, Alper Ekinci, Ali Inal, Goksal Keskin,** Literature search: **Seda Altiner, Pamir Cerci, Alper Ekinci,** Writing: **Seda Altiner, Pamir Cerci, Alper Ekinci,** Approval: **Seda Altiner, Pamir Cerci, Alper Ekinci, Ali Inal, Goksal Keskin.**

Consent for Publication

We obtained informed consent from all the patients who are still under our clinic's follow-up.

Ethical Approval

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethics committee approval of the Ankara University Faculty of Medicine was obtained for this study (Approval Number: 12-541-14).

REFERENCES

1. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci 2020;50(7):1591-610.

2. Lancieri M, Bustaffa M, Palmeri S, Prigione I, Penco F, Papa R, et al. An update on Familial Mediterranean Fever. Int J Mol Sci 2023;24(11):9584.

3. Vasanthakumar A, Kallies A. Interleukin (IL)-33 and the IL-1 family of cytokines—regulators of inflammation and tissue homeostasis. Cold Spring Harb Perspect Biol 2019;11:a028506.

4. Cayrol C. IL-33, an Alarmin of the IL-1 Family Involved in Allergic and Non Allergic Inflammation: Focus on the Mechanisms of Regulation of Its Activity. Cells 2021;11(1):107.

5. Yuan C. IL-33 in autoimmunity; possible therapeutic target. Int Immunopharmacol 2022;108:108887.

6. Koga T, Migita K, Sato S, Umeda M, Nonaka F, Kawashiri SY, et al. Multiple serum cytokine profiling to identify combinational diagnostic biomarkers in attacks of Familial Mediterranean Fever. Medicine (Baltimore) 2016;95(16):e3449.

7. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40(10):1879-85.

8. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA 2013;310(20):2191-4.

9. Ramezani F, Babaie F, Aslani S, Hemmatzadeh M, Mohammadi FS, Gowhari-Shabgah A, et al. The Role of the IL-33/ST2 Immune Pathway in Autoimmunity: New Insights and Perspectives. Immunol Invest 2022;51(4):1060-86.

10. Klein TL, Tiosano S, Gilboa Y, Shoenfeld Y, Cohen A, Amital H. The coexistence of familial Mediterranean fever (FMF) in systemic lupus erythematosus (SLE) patients – A cross sectional study. Lupus 2021;30(7):1094-9.

11. Watad A, Bragazzi NL, Adawi M, Shoenfeld Y, Comaneshter D, Cohen AD, et al. FMF Is Associated With a Wide Spectrum of MHC Class I- and Allied SpA Disorders but Not With Classical MHC Class II-Associated Autoimmune Disease: Insights From a Large Cohort Study. Front Immunol 2019;10:2733.

12. Çerçi P, Altıner S, İnal A, Köse K, Keskin G, Ölmez Ü. Investigating the role of IL-33 in the pathogenesis of Behçet's Disease. Acta Clin Belg 2017;72(6):434-8.

13. Koca SS, Kara M, Deniz F, Ozgen M, Demir CF, Ilhan N, et al. Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease. Rheumatol Int 2015;35(3):471-7.

14. Manukyan G, Petrek M, Kriegova E, Ghazaryan K, Fillerova R, Boyajyan A. Activated phenotype of circulating neutrophils in familial Mediterranean fever. Immunobiology 2013;218(6):892-8.

15. Ben-David H, Livneh A, Lidar M, Feld O, Haj Yahia S, Grossman C, et al. Toll-like receptor 2 is overexpressed in Familial Mediterranean fever patients and is inhibited by colchicine treatment. Best Pract Res Clin Rheumatol 2018;32(5):651-61.

16. Teräsjärvi JT, Toivonen L, Mertsola J, Peltola V, He Q. Association of Toll-like receptor 2 rs111200466 polymorphism with low serum levels of IL-33 in early childhood. APMIS 2023;131(6):303-9.

17. Huang J, Gandini MA, Chen L, M'Dahoma S, Stemkowski PL, Chung H, et al. Hyperactivity of Innate Immunity Triggers Pain via TLR2-IL-33-Mediated Neuroimmune Crosstalk. Cell Rep 2020;33(1):108233.

18. Ovadia A, Livneh A, Feld O, Ben-Zvi I, Kukuy E, Kivity S, et al. T helper 17 polarization in familial Mediterranean fever. Genes Immun 2013;14(4):212-6.

19. Nakanishi K. Unique Action of Interleukin-18 on T Cells and Other Immune Cells. Front Immunol. 2018;9. Accessed August 26, 2023. https://www.frontiersin.org/articles/10.3389/fimmu.2018.00763

20. Park SH, Kim MS, Lim HX, Cho D, Kim TS. IL-33-matured dendritic cells promote Th17 cell responses via IL-1β and IL-6. Cytokine 2017;99:106-13.

21. Park SH, Jung HJ, Kim TS. IL-33 changes CD25hi Tregs to Th17 cells through a dendritic cell-mediated pathway. Immunol Lett 2020;218:5-10.

22. Li XL, Lin TT, Qi CY, Yuan L, Xia LP, Shen H, et al. Elevated Serum Level of IL-33 and sST2 in Patients with Ankylosing Spondylitis: Associated with Disease Activity and Vascular Endothelial Growth Factor. J Investig Med 2013;61(5):848-51.

23. Koga T, Kawashiri SY, Migita K, Sato S, Umeda M, Fukui S, et al. Comparison of serum inflammatory cytokine concentrations in familial Mediterranean fever and rheumatoid arthritis patients. Scand J Rheumatol 2018;47(4):331-3.

24. Tang S, Huang H, Hu F, Zhou W, Guo J, Jiang H, et al. Increased IL-33 in Synovial Fluid and Paired Serum Is Associated with Disease Activity and Autoantibodies in Rheumatoid Arthritis. J Immunol Res 2013;2013:e985301.

25. Wu S, Jiang Y, Teng Y, Liu X, Zhou L, Li W. Interleukin-33 promotes proliferation and inhibits apoptosis of fibroblast-like synoviocytes in rheumatoid arthritis. Clin Exp Rheumatol 2021;39(4):844-51.

26. Merashli M, Noureldine MHA, Tfayli Y, Jawad A, Uthman I. Ankylosing Spondylitis Among Familial Mediterranean Fever Patients. Endocr Metab Immune Disord Drug Targets 2018;18(2):148-54.

27. Missoum H, Adadi N, Alami M, Toufik H, Bouyahya A, Laarabi FZ, et al. Correlation genotype-phenotype: MEFV gene mutations and Moroccan patients with rheumatoid arthritis. Pan Afr Med J 2022;41:121.

28. Apostolidou E, Skendros P, Kambas K, Mitroulis I, Konstantinidis T, Chrysanthopoulou A, et al. Neutrophil extracellular traps regulate IL-1β-mediated inflammation in familial Mediterranean fever. Ann Rheum Dis 2016;75(1):269-77.

29. Burdette BE, Esparza AN, Zhu H, Wang S. Gasdermin D in pyroptosis. Acta Pharm Sin B 2021;11(9):2768-82.

30. Chen W, Chen S, Yan C, Zhang Y, Zhang R, Chen M, et al. Allergen protease-activated stress granule assembly and gasdermin D fragmentation control interleukin-33 secretion. Nat Immuno. 2022;23(7):1021-30.

31. Hu Y, Jiang Y, Li S, Ma X, Chen M, Yang R, et al. The Gasdermin D N-terminal fragment acts as a negative feedback system to inhibit inflammasome-mediated activation of Caspase-1/11. Proc Natl Acad Sci U S A 2022;119(45):e2210809119.

32. Pamuk BO, Sari I, Selcuk S, Gokce G, Kozaci DL. Evaluation of circulating endothelial biomarkers in familial Mediterranean fever. Rheumatol Int 2013;33(8):1967-72.

33. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96(2):994-1002.

34. Kosloski MP, Kalliolias GD, Xu CR, Harel S, Lai CH, Zheng W, et al. Pharmacokinetics and pharmacodynamics of itepekimab in healthy adults and patients with asthma: Phase I first-in-human and first-in-patient trials. Clin Transl Sci 2022;15(2):384-95.

35. England E, Rees DG, Scott IC, Carmen S, Chan DTY, Chaillan Huntington CE, et al. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. Sci Rep 2023;13(1):9825.

36. Li Y, Fu Y, Chen H, Liu X, Li M. Blocking Interleukin-33 Alleviates the Joint Inflammation and Inhibits the Development of Collagen-Induced Arthritis in Mice. J Immunol Res 2020;2020:4297354.

37. Li P, Lin W, Zheng X. IL-33 neutralization suppresses lupus disease in lupus-prone mice. Inflammation 2014;37(3):824-32.

38. Dincer ABK, Gülöksüz EGA, Torgutalp M, Yayla ME, Yurteri EU, Sezer S, et al. IL-33, a novel cytokine for FMF? How is it related with disease pathogenesis?. Ann Rheum Dis 2018;77 (Suppl. 2):1671.

39. Piram M, Koné-Paut I, Lachmann HJ, Frenkel J, Ozen S, Kuemmerle-Deschner J, et al. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis 2014;73(12):2168-73.

40. Sari I, Yuksel A, Kozaci D, Selcuk S, Gokce G, Yildiz Y, et al. The effect of regular colchicine treatment on biomarkers related with vascular injury in newly diagnosed patients with familial Mediterranean fever. Inflammation 2012;35(3):1191-7.