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Does IL33/Sst2 Pathway Play a Role in the Pathogenesis of Familial Mediterranean Fever?

Ailevi Akdeniz Ateşi Patogenezinde IL33/sST2 Yolağı Rol Oynamakta mıdır?

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Abstract

Objectives: Interleukin-33 (IL-33) is a novel cytokine which belongs to IL-1 superfamily. It shares structural homology and common signaling pathway with IL-1β whose excessive secretion results in Familial Mediterranean Fever (FMF). In this study, we aimed to evaluate the serum IL-33 and its decoy receptor sST2 levels in patients with FMF and its correlation with disease activity.

Materials and Methods: In this cross-sectional single-centered study, 76 FMF patients and 30 age- and sex-matched healthy individuals were recruited. Disease activity was evaluated according to the autoinflammatory disease activity index, in which ≥9 points were considered as "active disease". Serum IL-33 and sST2 levels were measured using a commercial enzyme-linked immunosorbent assay kit. A p-value <0.05 was considered statistically significant.

Results: Serum IL-33 and sST2 levels were similar in both groups (p=0.899 and p=0.614, respectively). Similarly, there were no statistically significant differences between active (n=24) and inactive (n=52) patients; however, serum C-reactive protein and amyloid-A levels were significantly higher in active FMF patients (p=0.001 and p=0.002, respectively).

Conclusion: This study has revealed that even though IL-33 is similar with IL-1β in terms of structure and signaling, it neither increased in sera of FMF patients nor correlated with disease activity. In contrast to previous studies conducted on autoimmune diseases, the role of IL33/sST2 pathway in autoinflammatory diseases needs to be further evaluated.

Key Words: Familial Mediterranean Fever, Interleukin-1β, Interleukin-33, sST2

Öz

Amaç: İnterlökin-33 (IL-33); IL-1 süper ailesine ait yeni bir sitokindir. Ailevi Akdeniz Ateşi (FMF) patogenezinde yer alan IL-1β ile benzer yapısal ve sinyalizasyon yolağına sahiptir. Bu çalışmada, FMF hastalarının serumlarında IL-33 ve bunun reseptörü olan sST2 reseptör seviyelerinin ve hastalık aktivitesi ile ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Tek merkezli kesitsel olan bu çalışmaya, 18 yaş ve üzeri 76 FMF hastası ile yaş ve cinsiyet uyumlu 30 sağlıklı bireyler dahil edildi. Hastalık aktivitesi oto-enflamatuvar hastalık aktivite indeksi skoru kullanılarak değerlendirilmiş olup ≥9 puan aktif hastalık olarak kabul edildi. Serum IL-33 ve sST2 seviyeleri enzyme-linked immunosrobent assay kullanılarak çalışıldı. P-değeri <0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Serum IL-33 ve sST2 değerleri, FMF hastaları ve sağlıklı kontrol grubunda benzer bulundu [sırasıyla (p=0,899 ve p=0,614)]. Aktif (n=24) ve inaktif (n=52) FMF hastaları arasında da serum IL-33 ve sST2 değerleri arasında fark bulunamadı. Ancak, aktif FMF hastalarında serum C-reaktif protein ve serum amiloid A düzeylerinin inaktif hastalara göre istatistiksel olarak anlamlı bir şekilde daha yüksek olduğu görüldü (sırasıyla, p=0,001 ve p=0,002).

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Sonuç: Bu çalışmada, her ne kadar IL-33, IL-1β ile benzer yapıya ve sinyalizasyon yolağına sahip olsa da FMF hastalarında serum düzeylerinin artmadığı ve hastalık aktivitesi ile de ilişkili olmadığı gösterilmiştir. Otoimmün hastalıklarla yapılan çalışmaların aksine, IL33/sST2 yolağının oto-enflamatuvar hastalıklardaki rolünün ileri çalışmalarla incelenmesi gerekmektedir.

Anahtar Kelimeler: Ailevi Akdeniz Ateşi, İnterlökin-1β, İnterlökin-33, sST2

Introduction

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease characterized with self-limiting recurrent fever, polyserositis and synovitis (1,2). FMF occurs especially among Turkish, Armenians, Jews, Arabs, and its prevalence in Turkey is the highest with a value changing between 1/400-1/1000 (3). The pathogenesis of FMF, which is an autosomal recessive disease, was associated with the mutations of the *MEFV* gene on the short arm of chromosome 16 for the first time in 1997 (4). The *MEFV* gene codes pyrin protein which is a part of the inflammasome complex named NLRP3 (*nod-like receptor pyrin domain-containing 3*) (5). It causes interleukin-1β (IL-1β) cleavage and activation by increasing the caspase-1 activity (3,6,7). Therefore, FMF is considered as an inflammasomeopathy with uncontrolled IL-1 production (7,8). Although the data on the function of pyrin protein have increased in recent years, the pathogenesis of FMF is yet to be understood completely (3).

IL-33 is a novel cytokine which was discovered for the first time in 2005 and is a member of IL-1 cytokine superfamily (9). The IL-1 cytokine family includes IL-1α, IL-1β, IL-18, and IL-1Ra (9). IL-33 is expressed in many cells including epithelial cells, endothelial cells, smooth muscle cells, macrophages, and fibroblasts (10). IL-33 functions by binding to its specific receptor ST2L. *ST2* gene (suppression of tumorigenicity 2) is expressed in T helper 2 (Th2), mast cells, basophils, eosinophils, and natural killer T-cells. Recently, it has been shown that it is also expressed in regulatory T cells (Treg), macrophages, B cells, and neutrophils but it is not expressed in Th1 cells (11,12). It has also been shown that the *ST2* gene codes at least two isoforms other than ST2L formed with alternative splicing (13). Soluble ST2 (sST2), one of these isoforms, is the antagonistic decoy receptor of IL-33 and prevents the ligand from binding to membrane-bound ST2L (13). In recent years, there has been an increasing interest in the role of IL33/sST2 pathway in various autoimmune rheumatic diseases and in fact it was found to be increased and related with disease activity in diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, and Behçet's syndrome (14-18). However, to our best knowledge, its role in autoinflammatory diseases such as FMF has not been studied before. In this study, we hypothesized that due to its similarities with IL-1β, IL33/sST2 pathway may also have a role in the pathogenesis of FMF. Thus, we aimed to examine the serum levels of IL-33 and sST2 in patients with FMF, and their associations with disease activity.

Materials and Methods

Patients and Study Design

Eighteen years old and older seventy-six FMF and 30 age and sex matched healthy controls (HC) followed in the Rheumatology Department of Ankara University Faculty of Medicine between December 2017 and June 2018 were recruited for this cross-sectional study. FMF patients included in the study were diagnosed based on the Tel-Hashomer Criteria (19). Patients with concomitant other autoimmune or autoinflammatory diseases other than FMF were excluded from the study. The data collection at baseline included demographic characteristics, disease duration, *MEFV* gene mutation, comorbidities and treatment features. At the time of study recruitment, routine laboratory tests such as complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA), serum creatinine were studied.

Assessment of Disease Activity

Disease activity assessment for FMF patient were performed by autoinflammatory disease activity index (AIDAI) which is a valid and simple tool to assess diease activity in hereditary recurrent fever syndromes including FMF (20). AIDAI is a 31-day dichotomized patient reported symptom diary that consists of following symptoms: fever, overall symptoms, abdominal pain, nausea/vomiting, diarrhea, headache, chest pain, painful nodes, athralgia or myalgia, joint swelling, eye manifestations, skin rash and pain relief taken. It is scored as yes (1) or no (0) daily and the cumulative score ranges from 0 to 372. An AIDAI score of ≥9 points identifies active patients (20). In this study, patients were asked to complete AIDAI one month prior to recruitment. Patients with a score of ≥9 points were classified as "active".

IL-33 and sST2 Measurements

Peripheral blood samples were drawn at the time of study recruitment and centrifuged at 4 °C at 3000 RPM for 15 min and stored at -80 °C for later analysis. The serum IL-33 (pg/mL) and sST2 (pg/mL) levels were measured by the enzym-linked immunosorbent assay method according to manifacturer's instructions (R&D Systems, Minneapolis, MN, USA).

Ethical Considerations

The study was approved by Ankara University Faculty of Medicine Ethics Board (approval number: 07-358-17). Written consent was received from all participants.

Statistical Analysis

Data analysis was conducted using the SPSS software version 22 (SPSS, Chicago, I11). The conformity to normal distribution of the data was examined using visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were presented as the mean and standard deviation for variables with normal distribution, as the median and interquartile range for variables without normal distribution, and as frequency tables for ordinal and categorical variables. The study used the Student's t-test for normally distributed data in inter-group comparisons, the Mann-Whitney U test for data without normal distribution, and the chi-square test for categorical variables. A p-value $p<0.05$ was accepted as statistically significant.

Results

Clinical Characteristics of Patients

The mean age of FMF patients were 33.8±11.8 years of whom 73.7% were women. There was no statistical significant difference in age and gender between patients and healthy individuals (p=0.12 and p=0.167, respectively). The clinical characteristics of FMF patients were shown at Table 1. The most common clinical findings during FMF attacks were peritonitis, fever and athralgia. Pleuritis was seen in 11 patients (14.5%), arthritis was present in ten patients (13.2%) and erysipelas-like erythema was only seen in four patients (5.3%). In 41 patient the family history of FMF was known in which 28 of them (68.3%) reported a positive family history. Seventy-four

Table 1: The demographic, clinical and laboratory characteristics of FMF patients and healthy control group

	FMF (n=76)	HC (n=30)	p-value
Age (years), mean±SD	33.8±11.8	37.0±8.4	0.123
Female, n (%)	56 (73.7)	18 (60)	0.167
Disease duration (months), median (IQR)	96 (117)		
FMF attacks per year, median (IQR)	2 (3)		
Clinical features n (%)			
Fever	52 (68.4)		
Peritonitis	64 (84.2)		
Pleuritis	11 (14.5)		
Arthritis	10 (13.2)		
Athralgia	15 (19.7)		
Erysipelas-like erythema	4 (5.3)		
Positive family history of FMF, n (%)	28 (68.3)		
Treatment features n (%)			
Colchicine	74 (97.4)		
Anakinra	11 (14.5)		
Canakinumab	2 (2.6)		
Laboratory features			
Serum IL-33 level (pg/mL), median (IQR)	3.37 (1.15)	3.50 (1.35)	0.899
Serum sST2 level (pg/mL), median (IQR)	2836.3 (322.6)	2864.6 (189.4)	0.614
ESR (mm/h) median (IQR)	12 (13)		
CRP (mg/L), median (IQR)	2.35 (7.27)		
Hb (g/L), median (IQR)	13.6 (2.2)		
WBC (x10^9/L), median (IQR)	7040 (2180)		
PLT (x10^9/L), median (IQR)	284 (85)		
ALT (U/L) median (IQR)	19 (13)		
AST (U/L), median (IQR)	21 (7)		
Creatinine (mg/dL), median (IQR)	0.69 (0.21)		
Fibrinojen (g/L), median (IQR)	3.07 (1.52)		
Serum-amyloid A (mg/L), median (IQR)	3.3 (9)		

ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, HC: Healthy controls, PLT: Platelet count, SD: Standard deviation, WBC: White blood cell count, FMF: Familial Mediterranean Fever, IQR: Interquartile range

of patients were on colchicine treatment while in two patients colchicine was stopped due to side effects. Thirteen patients (17.1%) were on anti-IL-1 treatment. The FMF patients were subgroupped according to their AIDAI score in which an AIDAI score ≥9 showed active disease. Twenty-four (31.6%) of FMF patients had an AIDAI score of ≥9 with a median of 16 points out of 372. The number of attacks per year was statistically significantly higher in active group (p<0.001) (Table 2)

Laboratory findings: There was no statistically significant difference in serum IL-33 level between FMF group [3.37 (pg/mL) (1.15)] and HC [3.50 (pg/mL) (1.35)] (p=0.899). There was also no significant difference in serum sST2 level between groups. (p=0.614) (Table 1).

When the serum IL-33 and sST2 levels were compared between active and inactive patients, we did not find statistically significant difference (p=0.793 and p=0.675, respectively) (Table 2).

The serum CRP levels [6.3 (31.55);1.35 (4.57)] and SAA levels [8.3 (40.5); 2.2 (5.5)] were significantly higher in acive FMF patients compared to inactive patients according to AIDAI score (p=0.001, p=0.002, respectively) (Table 2).

Mutations of *MEFV* gene were analyzed in 43 (56.6%) of patients. We detected M694V variants in 58.1%, M680I in 25.6%, R202Q in 9.3%, E148Q in 9.3% and V726A in 7% of patients. Of 25 patients with M694V mutation, twelve of them had homozygote mutations. Five patients had M680I, two patients had D102D, and two patients had R202Q homozygote variants.

Discussion

It has been shown that cytokines of the IL-1 family are involved in many inflammatory, infectious and autoimmune diseases (21). IL-33 is a novel cytokine considered as a member of the IL-1 superfamily due to its resemblance to IL-1β and IL-18 in terms of gene sequence and structure (22). IL-33 mediates the release of proinflammatory cytokines and chemokines through IL-1 receptor-related protein ST2 (9). Besides, IL-33 signaling requires IL-1 receptor accessory protein which indicates that IL-33 shares common signalling pathways with IL-1.

FMF is the prototype of autoinflammatory diseases, and is related to the *MEFV* gene mutations. The pyrin protein coded by *MEFV* gene is expressed in innate immune system cells such as granulocyte, monocyte, eosinophil, and dendritic cells (23). Pyrin belongs to the cytosolic pattern recognition receptors that have a role in the control of the innate immune response and once activated by pathogen/danger-associated molecular patterns, it enables the assembly of multiprotein signalization complexes namely inflammasomes (24,25). Thus, caspase-1 becomes activated which increases the proteolytic maturation and secretion of cytokines like IL-1β and IL-18. Pyrin gene mutations cause excessive caspase-1 activation and IL-1β secretion (25).

In this study, due to its homology with IL-1β which is implicated in the pathogenesis of FMF, the role of IL-33 was evaluated in FMF; however, serum IL-33 and sST2 levels were

Table 2: The demographic and laboratory features of FMF patients according to their disease activity scores with AIDAI >9 defining active disease

	Active (n=24)	Inactive (n=52)	p-value
Age (years), mean±SD	31.8±10.8	34.8±12.2	0.310
Female, n (%)	17 (70.8)	39 (75)	0.701
Disease duration (months), median (IQR)	108 (126)	96 (132)	0.494
Number of FMF attacks per year, median (IQR)	4 (5)	2 (4)	**<0.001**
AIDAI score, median (IQR)	16 (16)	0 (3)	**<0.001**
Laboratory features			
Serum IL-33 level (pg/mL), median (IQR)	3.37 (2)	3.43 (1.14)	0.793
Serum sST2 level (pg/mL), median (IQR)	2820.3 (352.4)	2836.3 (328.8)	0.675
ESR (mm/h), median (IQR)	13 (22.5)	11.5 (9.3)	0.093
CRP (mg/L), median (IQR)	6.3 (31.55)	1.35 (4.57)	**0.001**
Hb (g/dL), median (IQR)	13.8 (3.2)	13.6 (1.9)	0.869
WBC (x10^9/L), median (IQR)	7185 (2355)	7040 (2180)	0.923
PLT (x10^9/L), median (IQR)	304.5 (128.8)	280 (91)	0.108
Creatinine (mg/dL), median (IQR)	0.7 (0.21)	0.67 (0.21)	0.437
Fibrinogen (g/L), median (IQR)	3.08 (1.38)	2.95 (1.17)	0.265
Serum-amyloid A (mg/L), median (IQR)	8.3 (40.5)	2.2 (5.5)	**0.002**

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, PLT: Platelet count, SD: Standard deviation, WBC: White blood cell count, FMF: Familial Mediterranean Fever, IQR: Interquartile range, AIDAI: Autoinflammatory disease activity index

found to be similar in both groups. Additionally, serum levels did not differ between active and inactive FMF patients according to AIDAI score. These results may be due to a couple of reasons. Firstly, even though IL-33 is a member of the IL-1 family, it does not need to be cleaved by caspase-1 for activation unlike other cytokines such as IL-1β and IL-18, and the full-length IL-33 is biologically active (21). Cayrol and Girard (21) showed that IL-33 cleaved by caspase-1 becomes inactive instead of becoming active contrary to what was believed. Therefore, it has been concluded that IL-33 is the only member of the IL-1 family becoming inactive with caspase-1 cleavage and it is unique with this characteristic. IL-33 causes MyD88 adaptor protein recruitment and NF-κβ activation by forming a complex with IL-1R accessory protein after binding to ST2 receptor and induces the secretion of proinflammatory mediators like IL-1β, IL-3, IL-6, and TNF-α (26,27). Nevertheless, the proteolitic processing by caspases decreases the activity of IL-33 through destabilizing the protein and/or promoting the seperation of IL-33 into fragments that are not capable of efficient promotion of ST2 stimulation which then results in the supression of proinflammatory properties of IL-33 (28). Therefore, the excessive caspase-1 activity present in the pathogenesis of FMF, in contrary to IL-1β, may cause the cleavage and thereby the inactivation of full-length IL-33 which may result in the suppression of the proinflammatory feature of this cytokine.

Secondly, despite the structural resemblance to cytokines from the IL-1 family, another distinguishing feature of IL-33 is that, it primarily induces Th2 response (26). The specific receptor ST2L, which is necessary for the activation of IL-33, exists in Th2, mast cells, eosinophil, and basophil while Th1 cells do not contain ST2L (29). Studies have shown that IL-33 polarizes T cells towards Th2 phenotype, acts as a chemoattractant for Th2 cells, and increases the secretion of Th2 cytokines like IL-5 and IL-13 (30-32).

Therefore, IL-33/ST2 pathway is considered to play role especially in the pathogenesis of allergic diseases, atopy, and mucosal immune responses (22). Additionally, IgG2-ST2 fusion proteins or antibodies blocking ST2 were shown to increase Th1 response by activating Th1 cells and suppress the allergic airway inflammation induced by Th2 cells (33). Recent studieshave demonstrated that Th1 polarization is the key feature in the pathogenesis of FMF (34,35). Th1 cells secrete IL-2, interferon-γ (IFN-γ), and tumor necrosis factor (TNF) (34). Serum IFN-γ level was found to be high in patients with FMF even in the attack-free period and this condition was related to ongoing subclinical inflammation (34). Centola et al. (36) reported that *MEFV* acts as negative feedback for Th1; however, this feedback cannot be provided with the defective pyrin due to the *MEFV* gene mutation and this results in increasing Th1 activity and IFN-γ secretion. Musabak et al. (37) demonstrated that the increased sIL-2R levels, an *in vivo* marker of T cell activation, in patients with FMF during an attack compared to patients in attack-free period, supporting the emerge of Th1 response in attack periods (37). Again, in this study, the low serum IL-10 levels in patients with FMF in the attack-free period indicated that the attack-free period was associated with the overactivation of Th1 subsets in peripheral blood as well as the decreased function of Th2 cells (37). In addition, the lower prevalence of atopic diseases which are caused by Th2 immune response, in patients with FMF is an indirect evidence of the predominant presence of Th1 polarization in FMF (38). To sum up, reduced Th2 but increased Th1 responses in the pathogenesis of FMF may be another explanation for the lack of increase in serum IL-33 levels in FMF patients.

Even though there is inconsistent data, some studies showed that serum IL-33 level increases in autoimmune diseases and it is related with disease activity Talabot-Ayer et al. (39) found that despite being statistically insignificant, serum IL-33 level was higher in patients with RA compared to patients with osteoarthritis; however, IL-33 levels in serum and synovial fluid did not increase in patients with psoriatic arthritis. On the contrary to autoimmune diseases, IL-33 was shown to have a beneficial role in autoimmune uveitis, which is an autoinflammatory disease like FMF, and treatment with IL-33 decreases the severity of uveitis by reducing IFN-γ and IL-17 levels and increasing IL-4 and IL-5 levels leading to M2 macrophage polarization (40). Given these results, the difference in the pathogenesis of autoimmune and autoinflammatory diseases might be another reason why IL-33 does not increase in autoinflammatory diseases, and in fact it helps to reduce the severity of the autoinflammatory disease in animal studies.

To our best knowledge, this is the first study that investigated the role of IL-33/sST2 pathway in the pathogenesis of FMF. Even though we did not find any significant increase or correlation with disease activity in patients with FMF, this study showed that IL-33 is an unique cytokine belonging to IL-1.

Study Limitations

This study has some limitations. The fact that it is a cross-sectional study and the low number of patients with an acute attack during the inclusion period are the main limitations of this study. On the other hand, AIDAI is a reliable method for the assessment of disease activity and in this study, there were significant differences between active and inactive patients in inflammatory markers such as CRP and SAA which are commonly used in the follow-up of FMF patients. The different results obtained in rheumatic diseases may suggest that investigating only serum cytokine levels may not be a reliable method but also evaluating IL-33 mRNA levels and protein expressions may be necessary to make a definite conclusion.

Conclusion

In conclusion, this study revealed that serum IL-33 and sST2 levels did not increase in patients with FMF. Even though, there is structural homology and common signalling pathway between IL-33 and IL-1β, IL-33 has some unique characteristics which may explain why it does not involve in FMF pathogenesis. The role of IL-33 in inflammatory immune responses is complex and many questions remain unanswered. Further studies are required to evaluate the regulation, function and role of IL-33 in autoinflammatory rheumatic diseases.

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Ethics

Ethics Committee Approval: The study was approved by Ankara University Faculty of Medicine Ethics Board (approval number: 07-358-17).

Informed Consent: Written consent was received from all participants.

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Authorship Contributions

Surgical and Medical Practices: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Concept: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Design: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Data Collection or Processing: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Analysis or Interpretation: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Literature Search: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A., Writing: A.B.K.D., S.S., E.G.A.G., M.E.Y., M.T., E.U.Y., İ.E.O., E.U., T.M.T., G.K., A.A.

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