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Assessment of Association between Duffy Blood Group Phenotypes and Susceptibility to Systemic Lupus Erythematosus and its Severity

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ABSTRACT

Background: Considering the role of Duffy antigenic system expression on RBCs as chemokines for inflammatory cytokines, expression of Duffy antigens as different phenotypes was studied in a group of patients with SLE. The association between different phenotypes of Duffy antigens and occurrence of SLE and its severity was assessed.
Methods: This cross-sectional study was carried out on 100 patients diagnosed as SLE using the "Systemic Lupus International Collaborating Clinics 2012 (SLICC) classification" criteria and 100 age-matched healthy subjects as control from April to June 2017. Duffy blood group status was determined in both groups. The patients were categorized into three groups of mild, moderate and severe according to "Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)" scores.
Results: The results of this study showed no significant association between the three different phenotypes of Duffy antigen system and increased risk of SLE or its severity.
Conclusion: The results of the current study did not approve of any association between three different Duffy phenotypes and increased risk of SLE or its severity.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease characterized by multi organ involvement mediated by tissue-binding autoantibodies and immune complexes (1, 2). This autoimmune disease is associated with various clinical manifestations could result in a complex of complications that may vary significantly among patients (3, 4). It has been documented that both genetic and environmental factors play pivotal roles in the pathogenesis and progression of this disease (5). Various mechanisms have been proposed about the pathogenesis of SLE, but the underlying pathophysiological mechanism is not well understood and several gaps remain to be filled in this area (6). Indeed, all of these proposed mechanisms share some key processes and features; one of them is the reduction in the clearance of immune complexes and apoptotic cells and inflammatory cytokines observed in almost all cases of SLE (7-9). Recent studies have shown that there is a significant relationship between the disease severity and the main signs and symptoms of the disease and serum levels of the cytokines such as interleukin (IL)-1, IL-2, IL-6, IL-8, IFNγ (10-13).

Duffy antigen receptor chemokine (DARC); also known as Fy glycoprotein (Fy), is a glycosylated membrane protein which is located on the outer surface of erythroid precursors and red blood cells (RBCs) and the lining surface of the post-capillary venules of several organs such as the spleen, liver and kidney (14-18). DARK antigen system also serves as a nonspecific receptor for most proinflammatory chemokines with high affinity

for the CXC class of pro-inflammatory chemokines such as IL-8 and CC chemokines (10, 19, 20). As a result, Duffy antigen system can influence plasma levels of the cytokines and take part in the process of leukocyte recruitment and thus can modulate inflammation (21, 22). In other words, DARK receptors are scavengers for chemokines which acts as a "chemokine sink" (23).

The probable association between SLE and Duffy antigen system has not yet been evaluated. We aimed to assess any possible association between SLE and the presence of different Duffy phenotypes.

Materials and Methods

In this cross-sectional study which was supported by Shiraz University of Medical Sciences, 100 patients suffering from SLE and equal number of healthy individuals who were among volunteer blood donors referring to the blood transfusion center regularly were enrolled. Due to a relatively large number of this population, the process of age- and sex-matching was conducted precisely. Individuals with positive history of SLE in their first-degree relatives and those who were exposed actively or passively to tobacco were excluded from the control group. The process of participation was completely arbitrary. Patients were employed from those who referred to Hafez Medical Clinic of Shiraz and were diagnosed with SLE during April to June 2017.

Diagnosis of SLE was based upon the "Systemic Lupus International Collaborating Clinics 2012 (SLICC) classification criteria" (24, 25). Then the disease activity was measured using "Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)" and the patient groups were categorized into three groups of mild, moderate and severe depending on the SLEDAI-2K score (26). Then, the patient and control groups were analysed for the assessment of the Duffy blood group status.

Statistical Package for Social Sciences (SPSS) version 11.5 was used for data analysis. Chi-square and Fisher's exact tests were used to compare the phenotype frequencies between case and control group and to assess if there was any association between individual phenotype and severity of SLE in the patients. $P<0.05$ was considered statistically significant.

Results

As stated earlier, the current study was established to assess the association between three different Duffy positive phenotypes and increased risk of developing SLE or its severity. Distribution of different phenotypes of DARC among both groups is shown in Table 1.

The association between the presence of different Duffy phenotypes and SLE was investigated using the Chi-Square test and no significant association ($P=0.426$) (Table 2). Then, the patient group was classified into three groups in terms of the severity according to SLEDAI-2K score. The association between the severity of the disease among the patients and the presence of the three different Duffy positive phenotypes was evaluated. The results did not support any significant association ($P=0.929$).

Discussion

Duffy antigen/chemokine receptor (DARC) is a glycosylated membrane protein, serving as a non-specific receptor for a variety of chemokines including angiogenic CXC chemokines (27). There are several known antigens in "Duffy blood group system" including Fy^a, Fy^b, Fy3, Fy4, Fy5, and Fy6 (28). The four most commonly used phenotypes for Duffy blood group system are $Fy^{(a+/b+)}$, $Fy^{(a-/b+)}$, $Fy^{(a+/b-)}$, and $Fy^{(a-/b-)}$. The Duffy null phenotype is uncommon in white people (29).

DARC plays an important role in inflammatory diseases and malignancies. In a study, DARC expression was showed to be boosted in the early phase of rheumatoid arthritis due to its function of neutrophil recruitment (30). In another study, DARC was found to be upregulated in microvascular endothelial cells of the CNS during active phase of diseases such as immune encephalomyelitis and multiple sclerosis (31). Furthermore, another study showed that rs2814778 polymorphism in the gene encoding DARK has an association with high IgE levels; increasing susceptibility to develop asthma and atopy among certain populations of African descent (32). Besides, in another study, this polymorphism was associated with benign neutropenia among people of African ancestry and specific Middle Eastern ethnic groups (33). To support any role of Duffy antigens in disease processes, enhanced expression of DARK by breast cancer cells was proposed

Table 1: Frequency of different phenotypes of Duffy antigen among patients with SLE and healthy subjects

	Duffy antigen Phenotypes		
	Fy^a	Fy^b	Double positive $Fy^{(a+/b+)}$
Control group	24	32	44
Patients with SLE	31	33	36
Total	55	65	80

Table 2: Distribution of different phenotypes of Duffy antigens between different groups of patients with SLE according to disease severity

Severity of the disease	Phenotypes			Total
	Fy^a	Fy^b	$Fy^{(a+/b+)}$	
Mild	11	11	11	33
Moderate	9	8	12	29
Severe	11	14	13	38
Total	31	33	36	100

as a protection against breast cancer (34). The lack of Duffy antigen expression in patients with sickle cell anemia has been suggested as a poor prognostic factor for end-organ damage in these patients (35).

Moreover, the presence of different Duffy phenotypes (a+/b+, a+/b-, and a-/b+) could determine the severity of various diseases; however, our study did not support this hypothesis. In 2018, Fong and colleagues documented that Plasmodium knowlesi has more affinity for binding to $Fy^{a+/b+}$ erythrocytes than to $Fy^{a+/b-}$ erythrocytes (36). In another study, double positive Duffy phenotype was more common in patients with multiple myeloma rather than healthy subjects. The authors assumed that some cytokine cascades involved in the pathogenesis of multiple myeloma, act through the DARC pathway (37).

The limitations of our study were small sample size and short period of the study which might influence the results of the study. Meanwhile, to find such associations, conducting epidemiological studies across different geographical regions sound necessary.

Conclusion

The results of the current study did not approve of any association between three different Duffy phenotypes and increased risk of SLE or its severity. Such studies are recommended to elucidate various pathologic cascades involved in inflammatory diseases, giving us an opportunity to interfere in these pathways.

Conflict of Interest: None declared.

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