CXCR4 Expression on Peripheral Blood T-Lymphocytes in Patients with Systemic Lupus Erythematosus and its Relation to Disease Activity

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Abstract: Aim: In this study, we evaluated the expression of CXCR4 on peripheral blood T cells from SLE patients and studied the association between these levels and various clinical and laboratory parameters in order to find out whether SLE patients demonstrated expression abnormalities of CXCR4 to establish if there is a relation between its expression and disease activity in SLE. **Patients and Methods**: This study was conducted on thirty two patients with SLE. All patients were diagnosed according to the 1997 updated American College of Rheumatology (ACR) revised Criteria for diagnosis of SLE. The study also included ten ages and sex matched apparently healthy controls. All patients were subjected to full history taking, thorough clinical examination, assessment of the disease activity according to the modified SLE disease activity index (SLEDAI), SLE cumulative organ damage was scored using the Systemic Lupus International Collaborating Clinics (SLICC) damage index. Routine laboratory investigations were done as well as estimation of CXCR4 expression by flowcytometry on Total Lymphocytes and T-Lymphocytes. **Results:** There was a significant increase in CXCR4 expression on Lymphocytes in general and specifically on T- lymphocytes among SLE patients compared to healthy controls. SLE patients with joint manifestations had significantly lower frequency of expression of CXCR4 on their T cells. On the other hand, patients with serositis had significantly higher levels of expression of CXCR4 on their lymphocytes. Patients with nephritis did not show a significant difference in their chemokine receptor expression as compared to patients without nephritis. Also, no such difference was found regarding the any other clinical or lab characteristic of the patients. A positive significant correlation between T lymphocytes expressing CXCR4 and disease activity measured by the SLEDAI was found. The test validity characters of CXCR4 expression on T lymphocytes for discrimination of SLE at the best cutoff value of 34.6% showed 100% specificity, 87.5% sensitivity and 90.5% efficacy. **Conclusion:** CXCR4 expression levels are elevated on total lymphocytes as well as T cells from SLE patients. This increase in cell expression of CXCR4 correlates positively with disease activity. These findings suggest that CXCR4 hyperexpression may play a vital role in the pathogenesis of SLE, and may after further studies be used as an indicator of disease activity. This also suggests CXCR4 antagonists may halt the role of these cells in the pathogenesis of the disease and improve prognosis for SLE patients.
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Key words: Systemic lupus erythematosus, Lymphocytes, T lymphocytes, CXCR4

1. Introduction:

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that is characterized by the loss of immune tolerance and the production of autoantibodies to nucleic acids and nucleoproteins (Rahman and Isenberg, 2008). Immunopathogenesis of SLE is a complex process that involves the interaction and synergistic effect of various cytokines, chemokines, and signaling molecules which cause the disease activity in SLE (Yu *et al.,* 2012).

T cells have a role in assisting in B cell hyperactivity in lupus by inducing B cell differentiation and facilitating autoantibody production. They also display abnormalities that do not affect B cells directly such as resistance to apoptosis and enhanced signal transduction through the T cell receptor (TCR) (Chong and Mohan, 2009). Furthermore, there has been growing evidence suggesting that infiltration of T lymphocytes and other leucocytes into the sites of inflammation plays a critical role in organ involvement in SLE (Yu *et al.,* 2012).

The chemokine receptor type 4 (CXCR-4), also known as fusin or CD184 and its ligand CXCL12 belong to a large family of chemoattractant cytokines. These chemokines are also implicated in various biological functions other than chemotaxis, including immunomodulation, angiogenesis, angiostasis, embryogenesis, hematopoiesis, lymphopoiesis, wound healing, cancer, inflammatory disease and HIV-1 pathogenesis (Busihho and Benovic, 2007 and Peled *et al.,* 2012). CXCR4 is expressed in a broad

range of tissues, including immune and the central nervous systems and can mediate migration of resting leukocytes and hematopoietic progenitors in response to CXCL12 functioning in a number of physiological processes. In the immune system, CXCR4 is highly expressed by monocytes, B cells, and naïve T cells in peripheral blood as well as early hematopoietic progenitor cells in bone marrow. Differential expression of CXCR4 in CD34+ progenitor cells may be involved in maintaining hematopoietic progenitor cells in the marrow and regulating stem cell trafficking (Sun *et al.,* 2010).This diverse and crucial role explains why knockout mice of CXCR4 die of hematopoietic, cardiac, vascular and cerebellar defects during embryogenesis (Choi and An, 2011).

Multiple murine lupus strains have demonstrated elevated expression of CXCR4 in peripheral blood leukocyte subsets, and in various immune and non-immune organs. Human studies have yielded conflicting results on CXCR4 levels in peripheral blood leukocytes, particularly on B and T cells, but differences may be due to SLE patient population characteristics and disease activity (Chong and Mohan, 2009).

Given its ability to attract multiple leukocyte subsets and stimulate B cell production and myelopoeisis, recent attention has been directed to CXCR4 and a role of its inhibitors in the treatment of autoimmune diseases, such as systemic lupus erythematosus (SLE) has been proposed (Chong and Mohan, 2009). This was encouraged by the findings of several studies that reported CXCR4 antagonists were able to impede trafficking of leukocytes to peripheral organs in autoimmune diseases. Restricting the leukocytes' ability to enter peripheral organs has significantly hampered disease progression in murine models with various autoimmune diseases (De Klerck *et al.,* 2005 and Kohler *et al.,* 2008). Advances in the understanding of CXCR4 regulation and function and the development of CXCR4 antagonists with different biochemical and pharmacokinetic properties will allow us to safely and fully explore the potential therapeutic benefit of this important axis (Peled *et al.,* 2012)

In order to exploit such an axis and the benefit of development of novel CXCR4-based therapeutics for SLE we must first better understand the role of CXCR4 in this autoimmune disease.

Aim:

In this study, we evaluated the expression of CXCR4 on peripheral blood T cells from SLE patients and studied the association between these levels and various clinical and laboratory parameters in order to find out whether SLE patients demonstrated expression abnormalities of CXCR4 to establish if there is a relation between its expression and disease activity in SLE or specific organ damage.

2. Patients and Methods

This study was conducted on thirty two patients with SLE (30 females and 2 males). All patients were diagnosed according to the Updated American Collage of Rheumatology (ACR) revised Criteria for diagnosis of SLE (Hochberg, 1997). Patients attended the outpatient clinic of the Physical medicine, Rheumatology and Rehabilitation departments, Ain Shams and Cairo University hospitals. The study also included ten age and sex matched apparently healthy controls.

Patients with other rheumatic diseases and nephritis due to other causes were excluded from the study.

All patients were subjected to the following:

I- Full history taking.

II- Thorough clinical examination was performed on each patient with special emphasis on symptoms and signs of renal affection and clinical parameters of disease activity.

III- Assessment of the disease activity of SLE patients according to the modified SLE disease activity index (SLEDAI) (Bombardier *et al.,* 1992).

IV- The SLE cumulative organ damage was scored using the Systemic Lupus International Collaborating Clinics (SLICC) damage index (Gladman *et al.,* 1996).

V- Routine laboratory investigations including:

- Complete blood picture by Coulter counter (Coulter Microdiff 18, Fullerton, CA, USA).
- Erythrocyte sedimentation rate by Westergren method.
- Serum Anti nuclear antibody (ANA) assessment by indirect immunoflourescence by the Kallestad kit.
- Serum anti double stranded DNA (dsDNA) and anti single stranded DNA (ssDNA) antibodies were measured using ELISA technique (ORGENTEC).
- Complement level assessment: C3 immunoglobulin by the Synchron apparatus.
- Renal function tests including serum creatinine, blood urea, creatinine clearance and routine microscopic urine analysis for presence of pyurea, hematurea and casts. Twenty four hours urine was collected to assay protein.

VI- Estimation of CXCR4 expression by flowcytometry:

Two mL of venous blood were collected in EDTA- vacutainers for complete blood count and flowcytometric analysis of CXCR4 on CD3+lymphocytes.

It was performed by direct immunofluorescence using Coulter EPICS XL flow cytometer system equipped with 488nm air-cooled Argon Laser. Dual staining was done using fluorescien isothiocyanate (FITC) conjugated CD3 and Phycoerythrin(PE) conjugated CXCR4 (Immunotech, Coulter, CA, France). Ten µl of each of conjugated monoclonal antibody was added to 100 µl of EDTA- treated blood. Incubation with monoclonal antibodies was done for 30 minutes at RT in the dark. Two ml of ammonium chloride lysing solution (Al-Gomhoreya CA, Egypt) were then added and mixed thoroughly to lyse peripheral blood erythrocytes. The tubes were further incubated for 5–10 minutes at room temperature in the dark, followed by centrifugation at 3000 rpm for 5 minutes. The supernatants were removed and cells were washed with phosphate buffered saline (PBS). After two washes, the cells were resuspended in 500 µl PBS and analyzed by flow cytometry. Lymphocytes were selected in the forward scatter vs side scatter dot plot and additionally gated as CD3 positive cells. Data were represented as the percentage of cells double-positive for CD3 (pan T-lymphocytes marker) and the chemokine receptor CXCR4. Isotypic matched monoclonal antibodies were used as negative control. A minimum of 1000 cells were collected. MFI of CXCR4 was collected and recorded.

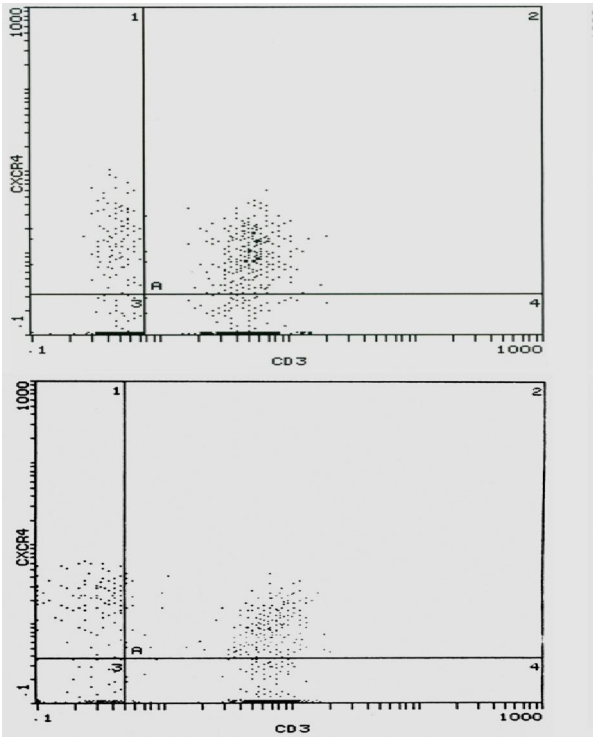

Figure 1: Dot plots histograms of samples of a SLE patient (top) and a control subject (bottom).

VII- Radiological studies including plain X-ray of the chest, affected joints and echocardiography when needed.

VIII- Statistical analysis was done using statistical software package "SPSS" version 10. The descriptive data for quantitative data were expressed as ranges, mean, standard deviation (SD) and numbers and percentages for qualitative data. Student's t test was used to compare between two independent means, and Pearson's correlation coefficient, for relationship between different variables in the same group. Diagnostic validity test including sensitivity, specificity, negative and positive predictive values were calculated. P value <0.05 was considered significant and p<0.01 was considered highly significant.

3. Results

Demographic, clinical and laboratory characteristics of patients:

Thirty two SLE patients (30 females and 2 males) were included in this study in addition to 10 healthy subjects as a control group matched to both age and sex. The age of the patient group ranged from 18 - 52 years with a mean of 28.94 ± 9.6 years. The disease duration ranged from 2 to 96 months with a mean of 40.9 ± 29.9 months. The mean age of onset was 24.8 ± 7.9 years. The clinical findings in SLE patients are shown in table (1).

Table (1): Frequency of various clinical presentations in SLE patients

Clinical manifestations	Number of patients (frequency)	Percentage (%)
Constitutional symptoms	25	78.1%
Arthritis/ arthralgia	18	56.3%
Photosensitivity	8	25%
Malar rash	24	75%
Alopecia	14	43.8%
Oral ulcers	6	18.8%
Raynaud's phenomenon	5	15.6%
Serositis	6	18.8%
Renal affection	12	37.5%
Neuropsychiatric affection	4	12.5%
Thrombotic events	3	9.4%

All of our patients were positive for ANA, and 29 patients were positive for anti-DNA antibodies at the time of the study. One patient was positive for anti-RO antibodies. The mean ESR of the patients was 72.6 ± 38.8 mm/hr and ranged from 25 to 160 mm/hr. The complete blood picture of our patients revealed thrombocytopenia in 7 patients (21.9%),

lymphopenia in 5 patients (15.6%) and anemia in 21 patients (65.6%) with mean Hemoglobin of 10.04 ± 2.1 gm/dl and ranging from 5.7 to 14.2 gm/dl. Liver function tests were normal in all patients while creatinine was high in 7 patients (21.9%).

Disease Activity by the SLEDAI of our patients revealed a range from 0-28 with a mean of 9.7 ± 7.2. The organ damage as assessed by the SLICC score and revealed a mean of 1.38 ± 1.43 and a range of 0-4.

Expression of CXCR4 on lymphocytes

The mean percent of patients' lymphocytes expressing CXCR4 was 53.6 ± 17.4% with a range of 5-82%, while their T lymphocytes showed positivity for CXCR4 in 43.4% ± 8.97% with a range of 24.3 - 57%. As for the control group the mean percent of lymphocytes expressing CXCR4 was 40.1 ± 9.7% with a range of 29-56%, while the T lymphocytes showed a mean percent of expression of 26.3 ± 6.8% and a range of 16.9% to 34.6%. There was a significant increase in CXCR4 expression on Lymphocytes in general and T- lymphocytes among SLE patients compared to healthy controls as shown in table (2).

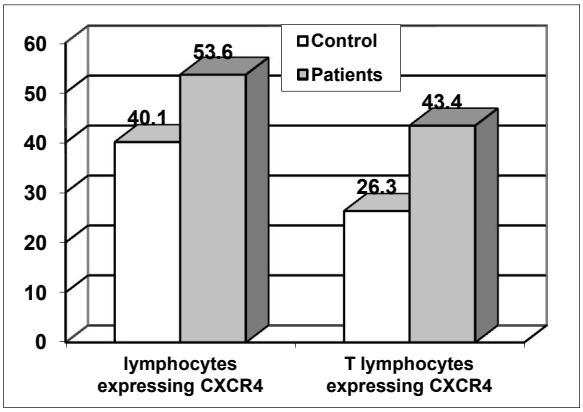

Fig. (2): Mean percentage of Total lymphocytes and T lymphocytes expressing CXCR4 among the control group and patients.

Table (2): Comparison between the percentage of Total lymphocytes and T lymphocytes expressing CXCR4 among the control group and patients using student t test.

	Group	Mean	SD	t	P value	Sig.
Percentage of lymphocytes expressing CXCR4	Control	40.08	9.67	3.1	<0.01	HS
	Patients	53.58	17.43			
Percentage of T-lymphocytes expressing CXCR4	Control	26.3	6.79	6.4	<0.001	HS
	Patients	43.37	8.97			

The relation between CXCR4 expression and different clinical and lab parameters:

SLE patients with joint manifestations had significantly lower frequency of expression of CXCR4 on their T cells than patients without joint manifestations (40.1% and 47.6% respectively, t=2.69, $p<0.05$). On the other hand, patients with serositis had significantly higher levels of expression of CXCR4 on their lymphocytes (58.7%) when compared to patients free from serositis (38.2%) (t= -2.5, $p<0.05$). Patients with nephritis did not show a significant difference in their chemokine receptor expression as compared to patients without nephritis. Also, no such difference was found regarding the any other clinical or lab characteristic of the patients.

Correlation between percentage of T-lymphocytes expressing CXCR4 receptors and different clinical and laboratory data of the patients revealed a positive significant correlation between T lymphocytes expressing CXCR4 and disease activity measured by the SLEDAI as well as with the ESR (r= 0.38, $p<0.05$ and r= 0.41,$p<0.05$). There was also a significant negative correlation between the percent of lymphocytes expressing CXCR4 and the organ damage measured by the SLICC score (r=-0.36, $p<0.05$). Correlation studies between CXCR4 expression and all the other clinical or lab characteristic of the patients did not reach statistical significance.

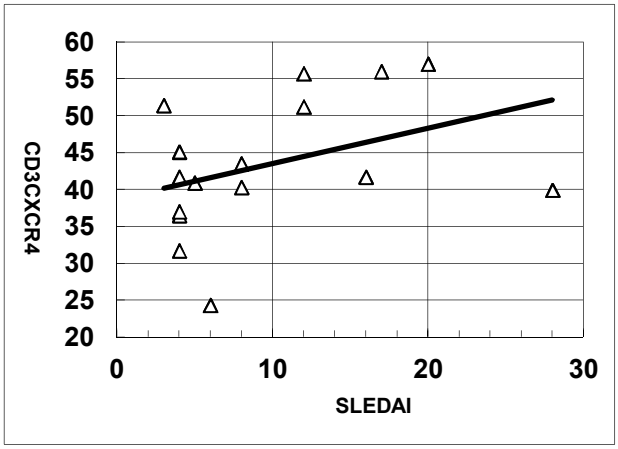

Fig. (3): Regression analysis showing the correlation between CXCR4 expression on T lymphocytes and SLEDAI among SLE patients

ROC curve analysis:

The test validity characters of CXCR4 expression on T lymphocytes for discrimination of SLE at the best cutoff value of 34.6% showed 100% specificity, 87.5% sensitivity and 90.5% efficacy.

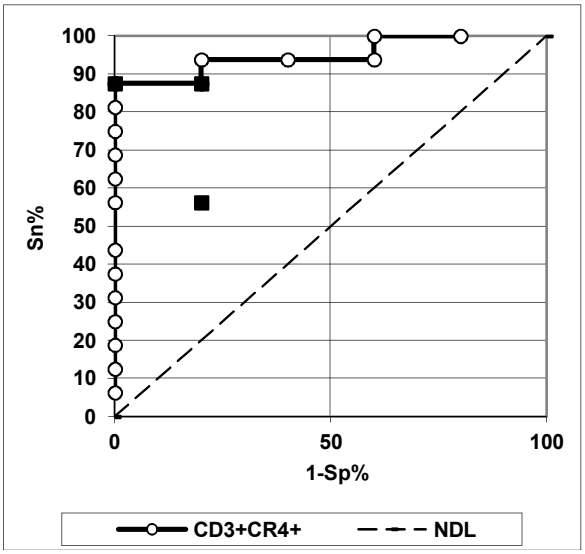

Fig. (4): ROC curve analysis showing the diagnostic performance of percentage of T lymphocytes expressing CXCR4 in discriminating patients with SLE from healthy controls

4. Discussion:

In systemic lupus erythematosus (SLE), the combination between specific environmental factors and a predisposing genetic background contributes to the development of impaired immune tolerance the uncontrolled production of autoantibodies. This multistep process involves many immune cell populations. Among the cells that participate in the initiation, progression and perpetration of the disease, T lymphocytes play a key role in all stages. T-cell abnormalities and aberrant T helper cytokine profiles have been implicated in the loss of immune tolerance to nuclear and cytoplasmic antigens and linked to a variety of clinical manifestations in SLE (La Cava, 2009).

The interaction of CXCL12 and CXCR4 results in migration, integrin activation, and chemotaxis of lymphocytes, monocytes, and neutrophils and hematopoietic progenitor cells. These processes assist in the recruitment of these cells to affected peripheral tissues in lupus, such as the kidney and skin. In addition, this binding enhances survival, proliferation, and transcription in the CXCR4-expressing cells (Nanki and Lipsky, 2000, & Wong and Korz, 2008).

Involvement of CXCR4 in the pathogenesis of SLE was suggested by several findings in murine models of lupus. One of these findings was the significant up-regulation of CXCR4 on monocytes, neutrophils, B cell subsets, and plasma cells in multiple murine models of lupus. Tissue samples from the kidneys of these mice showed CXCL 12 upregulation in the glomeruli and tubules. Furthermore upon administration of a CXCR4 peptide antagonist the mice kidney disease improved (Wang *et al.,* 2009). Several researches confirmed a role of the CXCR4/CXCL12 axis in human SLE. Among these is the finding of strong CXCR4 staining in perivascular inflammatory cells upon immunohistochemical staining of cutaneous lupus skin biopsies and increased CXCL12 reactivity in dendritic and endothelial cells in the skin (Meller *et al.,* 2005). Another report has documented that SLE patients exhibited significantly higher CXCL12 serum levels compared with healthy controls (Robak *et al.*, 2007).

In agreement with the hypothesis that CXCR4 has an important role in SLE, our study revealed a significant increase in CXCR4 expression on Lymphocytes in general and T- lymphocytes among SLE patients compared to healthy controls. These findings support the findings of Wang et al who documented increased expression of CXCR4 on CD4 T cells (Wang *et al.,* 2010)

Amoura and colleagues have reported that SLE patients did not differ significantly in CXCR4 expression on CD4+ and CD8+ T cells compared with controls (Amoura *et al.,* 2003). Discrepancies in the findings of this study and the current one may be due to varying characteristics of the SLE patients studied especially that the report did not delineate clinical characteristics of the SLE patients investigated.

Another group found that three subclasses of memory CD4+ T cells, CCR7+/CD27+, CCR7-/CD27+, and CCR7-/CD27-, isolated from eight SLE patients showed lower percentages expressing CXCR4 compared with controls (Fritsch *et al.,* 2006). This discrepancy in findings may be due to the fact that this study only assessed memory CD4+ T cells which are only a subclass of T cells and though expression on them may be lower than controls yet the total T cell expression may yet be high. Also this finding was reported from a sample of 8 SLE patients which is too small a number to draw conclusions from.

We found a positive significant correlation between T lymphocytes expressing CXCR4 and disease activity measured by the SLEDAI. This is in accordance with the results of Wang *et al.,* 2010 whose results showed 1.18-fold increase in CXCR4 on CD4 T cells in the group of patients with higher SLEDAI scores though the values did not reach statistical significance. These results imply a possible role of CXCR4 in driving active disease in SLE.

Our results demonstrate that patients with nephritis did not show a significant difference in CXCR4 expression as compared to patients without

nephritis. SLE patients with joint manifestations had significantly lower frequency of expression of CXCR4 on their T cells than patients without joint manifestations. Such a difference was not found regarding the any other clinical or lab characteristic of the patients. Also, we report a significant negative correlation between the percent of circulating lymphocytes expressing CXCR4 and the organ damage measured by the SLICC score. These findings are similar to the results of Wang *et al.,* 2010 who reported that correlations between CXCR4 surface expression and various laboratory parameters, including anti–double-stranded DNA titer, 24-hour proteinuria, serum creatinine, C3, or C4, were not found to be significant. This could be explained by the possibility that CXCR4 positive cells are attracted to the damaged organs and the homing of these cells to peripheral tissue, since they are more likely than naive cells to position themselves in these areas. This is reinforced by results of research that demonstrated enhanced levels of CXCL12 in tubules and glomeruli of kidneys (Wang *et al.,* 2010). Balabanian et al. also found higher CXCL12 expression in the kidneys in murine studies and reported prevention of nephritis and antibody production by mABs against CXCL12 (the ligand for CXCR4) (Balabanian *et al.*, 2003). This peripheralization may result in the varying levels of circulating CXCR4 expressing lymphocytes in relation to the different organs affected especially given the multiple organ affection found in SLE resulting in the wide dispersion of these cells.

The test validity characters of CXCR4 expression on T lymphocytes for discrimination of SLE at the best cutoff value of 34.6% showed 100% specificity, 87.5% sensitivity and 90.5% efficacy which further reinforces its importance in the pathogenesis of SLE and directs our attention to it as a possible marker of SLE and an indicator of disease activity.

Conclusion:

CXCR4 expression levels are elevated on total lymphocytes as well as T cells from SLE patients. This increase in cell expression of CXCR4 correlates positively with disease activity. These findings suggest that CXCR4 hyperexpression may play a vital role in the pathogenesis of SLE, and may after further studies be used as an indicator of disease activity. This also suggests CXCR4 antagonists may halt the role that these cells in the pathogenesis of the disease and improve prognosis for SLE patients.

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