

## Is CCR7 a potential target for biologic therapy in psoriasis?: Increased expression of CCR7 in psoriasis vulgaris

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### ABSTRACT

**Background:** Activated T cells present in psoriatic plaques play a key role in the pathogenesis of psoriasis. CCR7 on T cells plays a crucial role in native immune response and formation of secondary lymphoid organ. **Aims:** To determine whether differential expression and functions of the CCR7 occur in psoriasis patients in China, we examined CCR7 on T cells from normal and psoriasis subjects. **Methods:** Skin specimens and T cells from 33 patients and 22 healthy controls were analyzed by immunohistology, flow cytometry, and RT-PCR. **Results:** Patients with psoriasis had a skewed distribution of T lymphocytes, with an increased level of CCR7<sup>+</sup> T lymphocytes compared to healthy controls ( $P < 0.01$ ). By flow cytometry, it was found that CCR7 was selectively, frequently, and functionally expressed on CD4<sup>+</sup> (20.5±6.8%) but not on CD8<sup>+</sup> (9.5±3.4%) T cells from patients with psoriasis, whereas this phenomenon was not seen in normal subjects. Through RT-PCR it was also found that CCR7 was highly expressed on T cells in patients with psoriasis than in healthy controls in the level of gene. **Conclusions:** Patients with psoriasis had a skewed distribution of T lymphocytes, with an increased level of CCR7<sup>+</sup> T lymphocytes compared to healthy controls. CD4<sup>+</sup> CCR7<sup>+</sup> T cells had abnormal expression, which might induce protraction and persistence of psoriasis.

**Key Words:** CC chemokine receptor 7, Psoriasis, Memory lymphocytes

### INTRODUCTION

Psoriasis is estimated to affect 1% to 3% of the world's population.<sup>[1,2]</sup> Cellular alterations in the skin include marked hyperplasia of the epidermis, altered keratinocyte differentiation, angiogenesis, and marked infiltration of the skin by T lymphocytes, dendritic cells (DCs), and neutrophils. The role of T cells in the pathogenesis of psoriasis is widely acknowledged. The pivotal role of T lymphocytes in the pathogenesis of psoriasis has been demonstrated by the presence of activated T cells in psoriatic plaques.<sup>[3,4]</sup>

CCR7 (chemokine [C-C motif] receptor 7) was cloned as the first GTP-binding protein-coupled receptor that has 7

membrane-spanning regions<sup>[5]</sup> specifically expressed on lymphocyte.<sup>[6]</sup> In studies in humans and mice, expression of CCR7 was detected in T and B lymphocytes, natural killer cells, precursors of macrophages, mature DCs, and secondary lymphoid organs such as lymph nodes, spleen, and amygdala. A gene-disruption study in mice implied that CCR7 has a crucial role in native immune response and formation of secondary lymphoid organ.<sup>[7]</sup> Another study in humans reported that CCR7 expressed on a particular subset of memory T lymphocytes, designated central memory T lymphocytes, that express a high level of L-selectin<sup>[8]</sup> and have a tendency to home in on lymphoid organs. Besides the above-mentioned functions, CCR7 and its ligands, CCL19 and CCL21, are involved in lymphocyte recirculation

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through secondary lymphoid organs and they additionally navigate lymphocytes into distinct tissue compartments.<sup>[9]</sup> Homozygous deletion of CCR7 revealed that mice without this receptor were unable to both organize secondary lymphoid organs and mount a normal immune response.<sup>[7]</sup> Other studies have found that effector memory T cells infiltrating inflamed/infected tissues in a normal immune response lacked expression of CCR7.<sup>[10]</sup> Thus it has been hypothesized that CCR7 is essential for appropriate naïve T-cell migration to secondary lymphoid organs for antigen presentation, but that this receptor is not required for effector memory T cells (post-antigen exposure) to migrate toward and respond to the inflammatory stimuli.<sup>[11]</sup> Therefore, CCR7 can be considered a key molecule in lymphocyte trafficking; however, the role of CCR7 in the migration of polarized T effector/memory cell subsets in patients with psoriasis is vastly unknown. In this study, we tested the expression of T-cell CCR7 from normal and psoriasis subjects.

## METHODS

Written informed consent was obtained and protocols were approved by the affiliated Xi-Jing Hospital of the Fourth Military Medical University. Thirty-three patients with moderate-to-severe psoriasis (19 males, 14 females; age range, 29-68 years; median, 49 years) were enrolled in this study, which was approved by The Fourth Military Medical University-affiliated Xi-Jing Hospital Institutional Review Board. Disease duration ranged from 2 months to 10 years, with a mean of 4.1 years. None of the patients had taken systemic steroids or received therapies such as PUVA in the 6 months prior to blood sampling or biopsy. All patients gave informed written consent. During 1 month prior to biopsy, they had received no therapy for psoriasis. Six-millimeter punch biopsies were taken under local anesthetic (2% lignocaine with no added adrenaline) from chronic plaques, which had been present for 14 weeks. Twenty-two normal subjects served as controls.

### Preparation of human lymphocytes

Human peripheral blood was collected in heparinized tubes from patients and normal subjects. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized samples by using standard Ficoll-Hypaque (Pharmacia Biotech) density gradient sedimentation. Granulocytes were removed as described.<sup>[12,13]</sup> Monocytes were removed by two 30-minute rounds of adherence to a culture flask (model T-175; Nunc, Roskilde, Denmark) at 37°C and 5% CO<sub>2</sub> in RPMI 1642 medium supplemented with 10% calf serum. These cells are referred to as 'T lymphocytes'. Parts of PBMCs

were frozen in 10% DMSO (American type culture collection) in RPMI medium 1640 (GIBCO/BRL) with 1 mM Hepes buffer (Sigma Aldrich), 0.1% gentamicin (GIBCO/BRL), and 5% normal human serum (C-Six Diagnostics, Germantown, WI) and stored at -80°C until required.

### Reagents and antibodies

Phycoerythrin (PE)-, fluorescein isothiocyanate (FITC)-anti-CD3, anti-CD4, and anti-CD8 monoclonal antibodies (mAbs) were purchased from Sigma (USA). Mice monoclonal antibodies (MAbs) against human CCR7 were purchased from RandD Systems (Minneapolis, MN). Appropriate secondary biotinylated antibodies were purchased from BD Pharmingen (San Diego, CA). Human-adsorbed PE-conjugated goat anti-mouse IgG was procured from Southern Biotechnology Associates, Inc.

### Immunohistochemistry

Immunohistology of paraffin-embedded specimens was performed, essentially as we previously described<sup>[14]</sup> but with the exception that the strep-avidin peroxidase reaction was performed directly on the primary antibodies for those antibodies that were biotinylated. Briefly, skin models were fixed in 10% (v/v) buffered formalin prior to processing in paraffin wax for immunohistochemistry. Paraffin sections were cut onto aminopropyltriethoxysilane-silane coated slides and dried overnight at 37°C. Immunohistochemical staining to characterize the skin models was carried out using antibodies at the stated dilutions using the streptavidinbiotin complex (ABC) method. Positive cells were counted manually by using computer-assisted image analysis. All samples showed results identical to those shown in the photomicrographs here.

### Flow cytometry

For detection of CCR7, lymphocytes either isolated from patients with psoriasis or from healthy controls were re-suspended in PBS containing 2% FCS and 0.1% NaN<sub>3</sub> at a concentration of 10<sup>6</sup> to 10<sup>7</sup> cells/mL, followed by incubation at 4°C for 20 minutes with 100 μL of mAbs at the working dilution and were washed twice in PBS. Cells were washed twice and stained with PE-conjugated goat anti-mouse antibodies for 15 minutes at room temperature. Cells were washed twice and stained with FITC-labeled anti-human CD4 or CD8 MAbs for 15 minutes at 4°C. Cells were washed and re-suspended in PBS containing 0.5% formaldehyde for FACS analysis. Cells were analyzed on a FACSort flow cytometer (BD Biosciences, Mountain View, CA) using CellQuest (BD Biosciences) software. Cellular debris was eliminated from the analysis using a gate on forward and side scatter. For

each sample,  $10^4$  cells were analyzed.

### RT-PCR

Total RNA was extracted after lysis of cells in TRIzol reagent (Invitrogen) by the guanidium thiocyanate method as mentioned by the manufacturer. RNA was quantified by spectrophotometry. First strand cDNA was synthesized from total RNA extracted in RNase-free conditions. The reaction was performed on 2  $\mu$ g of total RNA with an oligo dT primer and 100 U of SuperScript III RT (No. 18080, Invitrogen, CA). PCR reaction was performed using 5 U of Taq polymerase (No. DR100AM, Takara, Dalian) and 30 cycles (94°C for 1 minute, 56°C for 2 minutes and 72°C for 3 minutes). Specific CCR7 primers were previously described.<sup>[15]</sup> 5'-GATTACATCGGAGACAACACC-3' forward primer and 5'-TAGTCCAGGCAGAAG-AGTCCG-3' reverse primer were used in PCR reaction mixture. PCR products were visualized at 1067 bp on 1% agarose gel containing ethidium bromide.  $\beta$ -actin was used to control and calibrate cDNA synthesis.  $\beta$ -actin primers 5'-CAACGATGGAGGGCCGGACTCATC-3' for the forward primer and 5'-TAAAGACCTCTATGCCAACACAGT-3' for the reverse primer were used in PCR reaction mixture (23 cycles; 95°C, 30 seconds; 55°C, 1 minute; and 72°C, 1 minute). The folds indicated the ratio CCR7/ $\beta$ -actin of treated cells compared with control cells at the same time of stimulation. To the negative RT reactions, an equal volume of DEPC-treated water was added. The PCR products were loaded on a 2% agarose gel containing 15 g/mL ethidium bromide, and gels were run at 150 V for 2 hours. The resulting bands were visualized on a UV transilluminator and images captured using a gel documentation system. The results were examined for models derived from 10 cases of psoriasis and 10 controls.

### Statistical analysis

Data were analyzed using Stat View SE program and expressed as means  $\pm$  SD and an alpha value of 0.05, unless stated otherwise. Student *t* test was used to determine the significance of difference between groups or between patients and healthy controls. Statistical significance was assumed for values of  $P < 0.05$ .

## RESULTS

1. Expression of CCR7 in psoriasis vs. that in healthy controls

Immunohistologic analysis revealed that healthy skin did not express CCR7 protein in any cell type [Figure 1A]. However, as seen in Figure 1B, some lymphocytes in psoriasis express CCR7. Interestingly,

there are also a few dendritic cells that express CCR7 and that are present in the psoriasis lesions.

2. Expression of CCR7 in the peripheral blood of patients with psoriasis vs. that in the peripheral blood of healthy controls; Figure 2 demonstrates expression of CCR7 on T cells in the peripheral blood of normal subjects and patients with psoriasis. This was significantly higher in patients with psoriasis than in normal subjects ( $56.8\% \pm 13.5\%$  vs.  $32.5\% \pm 10.5\%$ ) ( $P < 0.01$ ) [Figure 2A]. The percentages of surface molecules on CD4<sup>+</sup> T cells vs. CD8<sup>+</sup> T cells were  $20.5\% \pm 6.8\%$  vs.  $9.5\% \pm 3.4\%$  in patients with psoriasis and were  $8.1\% \pm 2.6\%$  vs.  $9.3\% \pm 2.8\%$  in healthy controls [Figures 2B, 2C]. The percentage of CD4<sup>+</sup> T cells expressing CCR7 in patients with psoriasis was significantly higher than that in healthy controls ( $P=0.0021$ , Student's *t*-test), whereas there was no statistically significant difference in the percentage of CD8<sup>+</sup> T cells

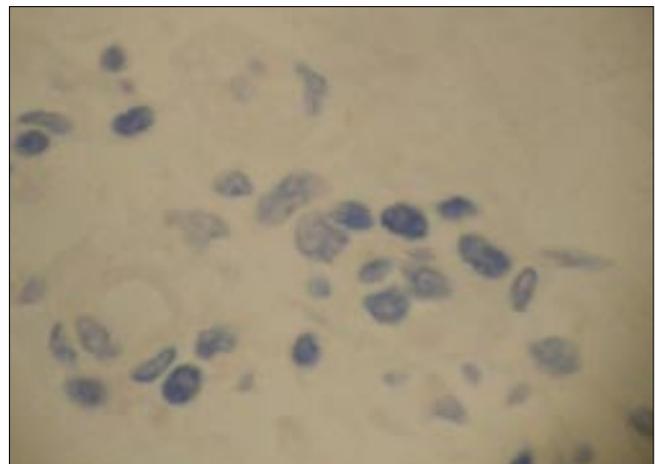


Figure 1A: Immunohistologic analysis of the expression of CCR7 in healthy controls ( $\times 400$ )

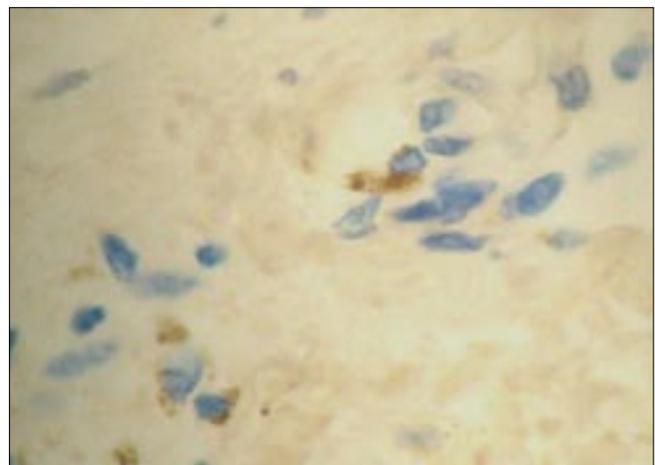


Figure 1B: Immunohistologic analysis of the expression of CCR7 in patients with psoriasis ( $\times 400$ )

expressing CCR7 between patients with psoriasis and normal subjects ( $P=0.3719$ , Student's t-test).

Figure 3 demonstrates expression of CCR7 gene on the peripheral blood of healthy controls and patients with psoriasis. This was significantly higher in patients with psoriasis than in normal subjects ( $P < 0.01$ ).

## DISCUSSION

Motility is a hallmark of leukocytes, and breakdown in the control of migration contributes to many inflammatory diseases. Tissue-targeted recruitment and localization are thought to be achieved by regulated expression of particular homing receptors on lymphocytes including adhesion and chemokine receptors.<sup>[16,17]</sup> In humans, CCR7 has been described as a defining factor for two different types of memory T cells, termed central (T<sub>cm</sub>) and effector (T<sub>em</sub>) memory T cells.<sup>[8,18]</sup> This novel classification of memory T cells has attracted much attention and is widely cited in the current literature.

Psoriasis is a chronic inflammatory skin disease of multifactorial etiology. The role of T cells in the pathogenesis of psoriasis is well known. But the effect of CCR7 on T cells subsets *in vivo* in psoriasis is still poorly understood. We find that lymphocytes in the skin of the patients increased the expression of CCR7, and no CCR7 expression was observed in the skin of healthy individuals. And these data strongly support classical *in vivo* animal work<sup>[19]</sup> indicating that memory cell subsets can traffic to any soft tissue in the body. In addition, some find that CCR7<sup>+</sup> cells can indeed migrate to skin but need CCR7 to emigrate from skin to lymph nodes, at least in the mouse.<sup>[20,21]</sup> Others have found CCR7<sup>+</sup> T cells in psoriatic epidermis and CCR7<sup>+</sup> neoplastic cells in the skin of patients with mycosis fungoides.<sup>[22]</sup> These demonstrate that inflammatory cells in skin can express chemokines receptor-like CCR7. But how inflammatory conditions influence CCR7 expression by T cells in the skin and in lymphoid tissues during an activated status is poorly defined. We have known that the CCR7<sup>+</sup> T lymphocytes circulate between the blood and secondary

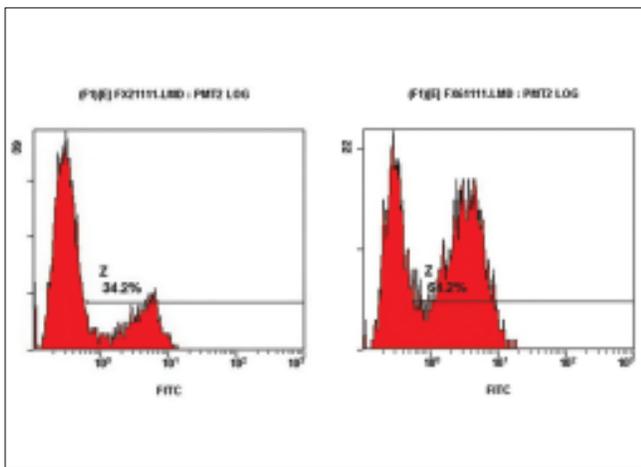


Figure 2A: Expression of CCR7 on T cells in the peripheral blood of normal subjects (left) and patients with psoriasis (right)

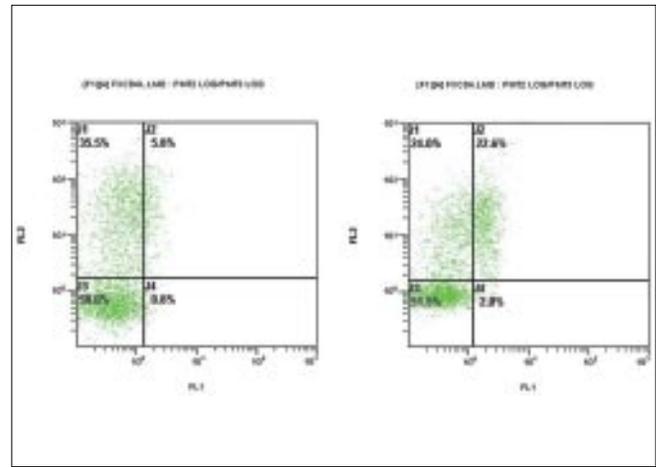


Figure 2B: Expression of CCR7 on CD4+ T cells in the peripheral blood of normal subjects (left) and patients with psoriasis (right)

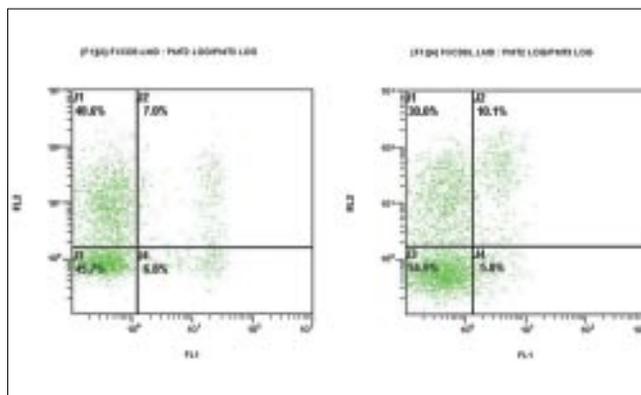


Figure 2C: Expression of CCR7 on CD8+ T cells in the peripheral blood of normal subjects (left) and patients with psoriasis (right)

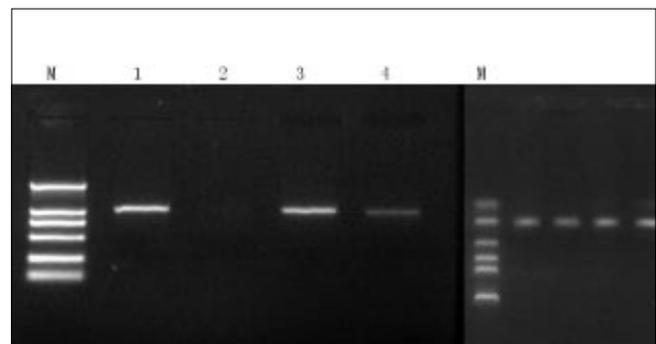


Figure 3: Expression of CCR7 gene on T cells in the peripheral blood of normal subjects and patients with psoriasis (left) and in patients with  $\beta$ -actin(right) M: DNA marker; 1, 3: patients with psoriasis; 2: negative control double distilled water; 4: healthy control.

lymphoid organs, providing routine immune surveillance and maximizing chances of immune priming, or triggering memory responses upon secondary antigen encounter.<sup>[23,24]</sup> During inflammatory responses, effector T-cell generation is often accompanied by down-regulation of CCR7 and up-regulation of receptors that bind pro-inflammatory chemokines.<sup>[25]</sup>

Alefacept is the first therapeutic agent targeted towards T lymphocytes<sup>[26]</sup> that is effective in improving psoriasis symptoms in oriental patients<sup>[27]</sup> and has been shown to have a selective effect on Tem versus Tcm in humans and causes a selective reduction in circulating Tem and relative preservation of Tcm in psoriasis. Thus alefacept selectively targets CD45RO<sup>+</sup> memory effector T lymphocytes because CD45RO<sup>+</sup> memory effector T cells express more CD2 than do CD45RA<sup>+</sup> naïve T cells.<sup>[28]</sup> Although it is not yet clear which cells are actually most important for maintaining immunological memory, it is logical that maintenance of the naïve and central memory populations should leave primary and recall responses intact.

Our results reveal substantial differences in CCR7 expression between psoriasis patients and healthy controls. Furthermore through flow cytometry and RT-PCR, we find that there is higher expression of CCR7 on CD4<sup>+</sup> T cells of patients than those of normal subjects. CD4<sup>+</sup> T cells have an important role in pathogenesis of psoriasis, and expression of CCR7 on these cells may increase capability of emigration into epidermis, which may lead to development and persistence of local inflammation. We have not detected precise role of CCR7<sup>+</sup> CD4<sup>+</sup> T cells in psoriasis but CCR7<sup>+</sup> CD8<sup>+</sup> T cells infiltrate endomysium in polymyositis,<sup>[29]</sup> which suggests that CCR7<sup>+</sup> CD4<sup>+</sup> T cells may have some effect in psoriasis.

Is CCR7 expressed as a result of the disease, or does its expression produce the disease? Our studies here clearly indicate that CCR7 is overexpressed in patients with psoriasis; it is not clear whether such overexpression is important in initiating or rather maintaining the skin pathology. Indeed, as mentioned earlier, an increased number of CCR7<sup>+</sup> T cells in psoriasis may not only be explained by increased influx from blood but also by deficient migration to lymph nodes, as speculated by others regarding dendritic cells.<sup>[30]</sup> Although mechanisms for regulation of expression of CCR7 are poorly understood, yet our findings are very important clinically in considering strategies for immune reconstitution. Thus a better understanding of the mechanisms of lymphoid CCR7<sup>+</sup> T cell trafficking to non-lymphoid tissues could facilitate the development of new therapeutic strategy for human

disease. Blocking T-cell transmigration from the blood to the target tissues may at least decrease the pathologic damage of these tissues by cytotoxic T cells.

Efalizumab has important role in leukocyte trafficking across the endothelium, antigen presentation to T cells, and immune synapse formation. It is focused on alternative trafficking during CD11a blockade; however, the other interaction is also important for antigen presentation to T cells. Our findings showed that CD4<sup>+</sup>CCR7<sup>+</sup>T cells have higher expression in psoriasis patients. Therefore, this study also implies that CCR7 may be an important new pharmacologic target in T-cell autoimmune diseases such as psoriasis. However, psoriasis exhibits a high IFN- $\gamma$ /IL-4 ratio; and in the skin, IL-4 therapy skewed the IFN- $\gamma$ -dominated Th1 response toward a characteristic anti-inflammatory Th2 response. IL-4 does not modify the cytokine phenotype of either naïve or memory T cells in the resting state.<sup>[31]</sup>

As mentioned above, it indicates that a modification of the effector memory hypothesis of T-cell trafficking and function needs to be made for psoriasis. Finally, these data imply that CCR7 may be a novel and beneficial target of therapy in these diseases.

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