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The role of chemokines and chemokine receptors in mycosis fungoides

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Background: Chemokines are a family of cytokines initially characterized by their capacity to induce chemotaxis, or directed leukocyte migrations. These receptors are activated by chemotactic cytokines called chemokines. Interactions between chemokines and chemokine receptors also are involved in tumorigenesis, migration and invasion of lymphoma cells.

Methods: An English literature search was performed using Medline (Through Pub med; from 1995 to 2011), with limiting factors of "chemokine" and "mycosis fungoides". Peer-reviewed articles were selected for inclusion after excluding identical papers. After reviewing all the articles, a total of 34 papers about the role of chemokines in mycosis fungoides were selected to review.

Results: The potential role of specific chemokine receptors and their chemokines, including CXCR3, CCR4, CCR10, and CCR7 in the pathophysiology of mycosis fungoides, and the role of chemokines in the treatment and outcome of mycosis fungoides were discussed.

Conclusion: Knowing more about the mechanisms of chemokines/chemokine receptors interaction and use of receptor antagonists or anti-receptor antibodies as therapeutic agents could be a new modality for treatment of cutaneous T cell lymphoma.

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INTRODUCTION

Cutaneous Lymphomas (CL) are a distinctive group of lymphomas; they are the second most frequent extra nodal lymphomas. They can be defined as lymphoproliferative skin infiltrates of T-, B- or NK- cell lineage which typically occur in and remain confined to the skin without detectable extracutaneous manifestation [1].

The Cutaneous T-cell Lymphoma (CTCL) spectrum is composed of Mycosis Fungoides (MF), Se´zary Syndrome (SS), and other T-cell lymphomas. Primary cutaneous lymphomas are defined as patients without concurrent extracutaneous disease at the time of diagnosis. Mycosis fungoides (MF) is the most common type of cutaneous T cell lymphoma in which malignant T cell clones are recruited into the skin from the early disease stages. A gradual clonal expansion of atypical CD3+, CD4+, CD8–, skin-homing T lymphocytes occurs in this disease. It has an indolent clinical course with slow progression over years or sometimes decades from patches to more infiltrated plaques and eventually tumors. Epidermotropism may no longer be found in mycosis fungoides after progression to the tumor stage [2,3].

Chemokine and chemokine receptors

Chemokines are a family of cytokines initially characterized by their capacity to induce chemotaxis, or directed leukocyte migrations. Chemoattractants

are postulated to regulate leukocyte trafficking into inflammation sites and into lymphoid and non-lymphoid tissues during recirculation [4,5]. Interactions between chemokines and chemokine receptors are also involved in migration and invasion of lymphoma cells [6,7].

There are approximately 50 human chemokines; they can be classified into four groups depending on the spacing between two N-terminal cysteine residues as either C, CC, CXC, and CX3C chemokines. Chemokines activate their target immune cells through binding to the cell surface receptors. Chemokine receptors are grouped, according to their ligands, into XCR, CCR, CXCR, and CX3CR families. According to functional division of chemokines, inflammatory chemokines are upregulated under conditions of inflammation and are produced by activated leukocytes and tissue cells as well as numerous tumors. They control the recruitment of effector leukocytes and thus, determine the composition of inflammatory infiltrates. Homeostatic chemokines, in contrast, are produced constitutively at non-inflamed sites and are responsible for the trafficking and distribution of immune cells at a steady state. They are responsible for navigating leukocyte precursors during hematopoiesis in the bone marrow and thymus, controlling cellular traffic in the spleen and lymph nodes (LNs), and contribute to immune surveillance of healthy peripheral tissues [5,6,8]. It has been shown that some chemokine receptors are expressed preferentially in the Th1 (CXCR3, CCR5) and Th2 (CCR3, CCR4 and CCR8) subsets of the helper T cells. Expression of CXCR3 and CCR4 is highly specific for Th1 and Th2 cells, respectively. Mig, IP-10 and I-TAC are called Th1 type chemokines because they are the ligands for CXCR3. On the other hand, TARC and MDC are designated Th2 type chemokines since they bind to CCR4 [9-11]. Evidence suggests that chemokines and their receptors have been associated with tumor metastasis, invasion of lymphatic vessels and possibly trafficking of lymphoma cells [12].

In the remainder of this overview, the roles of chemokine receptors in the biology of mycosis fungoides will be reviewed and the impact of chemokine receptors in migration, survival of malignant cells, and treatment will be discussed in more details.

METHODS

Search criteria

An English literature search was performed using Medline (Through Pub med; from 1995 to 2011). The search was performed with limiting factors of "chemokine" and "mycosis fungoides". Some papers were found by manual methods. Then, additional articles identified from the references that contained relevant supporting information were included.

Inclusion/exclusion criteria

Peer-reviewed articles were selected for inclusion after excluding identical papers. The selected articles had to meet the following criteria:

- The papers that focused on the role of chemokines or chemokine receptors in the MF were selected.
- The articles without a clear description of the role of chemokines or chemokine receptors in the MF were excluded.

Data extraction

After reviewing all the articles, a total of 34 papers on the role of chemokines in mycosis fungoides were selected to review and the full text of each article was carefully read. All the extracted references were imported into ENDnote.

Chemokine and chemokine receptors in CTCL

Chemokine receptor CXCR3

Three CXC chemokines, Mig, IP-10, and IP9/I-TAC, are expressed highly in the epidermis. They are strongly upregulated in MF and various inflammatory skin diseases. Sarris et al, demonstrated that the IP-10 was expressed constitutively in the basal keratinocytes of normal epidermis. In MF, IP-10 appears to overexpress in lesional keratinocytes, and its expression extends to suprabasal cells. The high affinity receptor for these chemokines, CXCR3, is highly expressed in both reactive and MF cells in the patch and plaque stages of the disease. In the more progressed stage of the disease and in the tumor-stage MF, lack of CXCR3 on MF cells is found. This absence of CXCR3 on the neoplastic cells is accompanied by a continuously high expression of

CXCR3 on the reactive T cells [8,13]. Lu et al, suggested that CXC chemokine expression in the epidermis of the patients with MF may be increased differentially, possibly induced by interferon-gamma and tumor necrosis factor alpha produced by lymphoma cells. As the tumor undergoes transformation and loss of CXCR3 expression, cells no longer would be attracted to the epidermis via keratinocyte-produced IP-10/Mig/I-TAC. The absence of infiltrating lymphocytes producing interferon gamma may in turn reduce the cytokine-mediated induction of CXC chemokine expression in the epidermis [13]. Winter et al, described this pattern by down modulation of CXCR3 surface expression and function in CD8+ T cells from advanced cutaneous T cell lymphoma patients. In this immune escape mechanism, cytotoxic effector T cells that have strongly reduced surface CXCR3 expression accumulate in the peripheral blood, but are virtually absent from CTCL tumor lesions. Serum levels of CXCR3 Ligands (CXCR3L) are increased in these patients. Winter showed that CXCR3 transcripts and the total amount of CXCR3 protein were not reduced in the peripheral cytotoxic effector T cells resulting from CXCR3 protein accumulation in endomysial organelles (ligand-induced receptor internalization). Impairment of CXCR3 function prevents the recruitment of circulating effector CD8+ T cells into tumor lesions, independent of the absence of CXCR3L within the lesions; [14] therefore, expression patterns of chemokine receptors in cutaneous lymphoma depend on clinical subtypes, immune characteristics of malignant cells, and stages of the disease. CXCR3 is positively expressed in epidermotropic tumor cells prominent in the patch/plaque stages of MF except for folliculotropic MF, early Sezary syndrome (SS), pagetoid reticulosis, and cytotoxic CD8/NK cell lymphoma. On the other hand, dermis-based tumor cells at late MF and CD30+ cutaneous lymphoproliferative disorders express CCR4 [7]. MF in transformation exhibits a CCR4-dominant expression [15,16]. One case of granulomatous mycosis fungoides with CXCR3 and CCR4 double positive tumor cells has also been reported [17].

Chemokine receptors CCR4 and CCR10

The chemokine receptors CCR4 and CCR10, and the Cutaneous Lymphocyte Antigen (CLA), have each been proposed as critical mediators of skin-specific T helper lymphocyte homing in mice and humans. CCR10 is expressed by only a minority (approximately 30%) of blood borne, skin-homing (CLA+/CCR4+) T helper cells. However, essentially all members of the relatively small "effector" skin-homing T helper cells population show CCR10. Soler suggested that, in contrast to CCR4, CCR10 was not a necessary component of cutaneous homing for most T helper cells [18,19]. CCR10 is found in tissue samples of patients with psoriasis or atopic dermatitis, while skin samples of healthy individuals lack it [20]. On the other hand, malignant T cells in the MF lesional skin also express CCR10 [12]. Cutaneous T-cell Attracting Chemokine (CTACK), also called CCL27, belongs to the CC chemokine family and is a ligand for CC chemokine receptor CCR10. It selectively attracts cutaneous lymphocyte antigen positive, CCR10+ memory T cells into inflammatory sites. Serum CTACK/CCL27 levels in patients with CTCL strongly correlate with types of skin lesions, tumor burden index, serum soluble IL-2 receptor, and thymus and activation regulated chemokine/CCL17 levels, all of which are already reported to be good makers of disease activity. In addition, serum CTACK/CCL27 levels in patients with CTCL decrease after treatment [21]. Fujita et al, investigated the differences in CCR10+CD4+ expression in peripheral blood mononuclear cells and serum CTACK/CCL27 levels in 18 patients with MF and showed that the number of circulating CCR10+ CD4+ cells was significantly higher in MF peripheral blood than in controls, even during the early stages. In lesional MF skin, infiltrating tumor cells also showed considerable expression of CCR10. The serum level of CTACK/CCL27 was higher in patients with MF than normal controls, but no statistical difference was found as compared to controls; therefore, they suggested that CCR10+ CD4+ lymphocytes were significantly increased in patients with MF, regardless of clinical disease progression. An elevated concentration of serum CTACK/CCL27 was also noted in patients with MF, which together suggested an increase in lymphocyte skin-homing in the early stages of MF [22]. In contrast to CCR10, chemokine receptor CCR4 expressed by most skin-homing (CLA+) T helper cells in the circulation, CCR4 is also expressed at high levels by skin-infiltrating lymphocytes [18].

TARC/CCL17 is constitutively expressed in

the thymus and is produced by dendritic cells (DC), endothelial cells, keratinocytes (KC) and fibroblasts. TARC/CCL17 is a Th2 type chemokine and a chemoattractant for CCR4 - and CC CCR8-expressing cells. According to immunohistochemical expression of TARC, CCR4 and CXCR3 in patients with each stage of MF and also measured serum TARC levels in patients with different stages of MF, TARC is expressed in the lesional KC in the patch, plaque and tumor stages. CCR4 is expressed on the epidermotropic cells in both patch and plaque stages and on the large cell-transformed cells in the tumor stage, whereas CXCR3 is constantly expressed on the small cells in the lesional dermis. On the other hand, MF in transformation exhibits a CCR4-dominant expression [15]. Serum TARC levels in patients with tumor stage MF are markedly higher than those with the patch or plaque stage. In order to estimate the disease activity of MF, it has been reported that the thickness of the cutaneous infiltrate or serum lactate dehydrogenase (LDH) levels or soluble IL-2 receptor (sIL-2R) levels are available. Serum TARC levels significantly correlate with serum LDH, IgE, sIL-2R and MDC (macrophage-derived chemokine/CCL22) levels. These data strongly suggest that serum TARC levels are useful for assessing the disease stage of MF [9,23].

Chemokine receptor CCR7

CCR7 is the principal homing receptor directing T lymphocytes, B lymphocytes, and dendritic cells into the T cell areas of secondary lymphoid organs. CCL19 (also called ELC) and CCL21 (also called Secondary Lymphoid-tissue Chemokine, SLC), are ligands for CCR7. SLC is a CC chemokine that is constitutively expressed at high levels in high endothelial venule cells and areas of T-cell accumulation in lymph nodes, peyer's patches, and spleen and is a powerful chemoattractant for lymphocytes. CCR7 activity is essential for homing of T cells to secondary lymphoid organs through high endothelial venules (HEVs) [9,24-26].

Naive T cell lymphocytes proliferate when they travel to T-cell areas of secondary lymphoid organs and are activated by antigen presenting cells (denderitic cells), so they produce effector cells. A variety of primed T lymphocytes remains as circulating memory cells; they have a crucial role in production of an enhanced immune response. Expression of CCR7 divides human memory T cells into two subsets: CCR7– memory cells (effector or peripheral memory T cells) that express receptors for migration to inflamed tissues and CCR7+ memory cells (central memory T cells) that show lymph node-homing receptors and lake immediate effector function but can flow back to lymph nodes and into peripheral blood and look for antigens [27]. There are many evidences that support a role for specific chemokines in lymph node metastasis. Abundant expression of CCR7 on MF cells was found to be associated with homing to lymphatic tissue and metastasis of MF [28,29].

The role of chemokines in the treatment and outcome of mycosis fungoides

Alteration of serum Th1 and Th2 chemokines

Mycosis Fungoides is a T cell neoplasm with elevation of serum Th2 and Th1 chemokines. T helper1, cytotoxic T lymphocytes and natural killer cells are activated by interferon-gamma (INF-γ). Balance of the serum levels of Th1 and Th2 chemokines in patients with MF could be affected by INF-γ administration. Treatment with INF-γ increases serum levels of Th1 chemokines and slightly decreases Th2 chemokines in patients with MF. Its therapeutic effects could be interpreted by an activating effect on CTL and subsequent lyses of malignant T cells. Combination of INF-γ and narrow band UVB results in a marked increase in Th1 chemokines and therefore seems to have some beneficial effects particularly in the early stage of Mycosis Fungoides [30,31].

IFN-α and PUVA therapy by affecting lesional skin chemokine CTACK/CCL27 expression in mycosis fungoides

Chemokine CTACK (CCL27) binding to the receptor CCR10 was first reported by Homeys et al, in 2000 [32]. Tissue-selective chemokine/receptor pathways CCR4/ligands and CCR10/CTACK are involved in lymphocyte recruitment to skin in cutaneous inflammation. Inhibition of these pathways, singly or in combination, could be a reasonable suggestion for a novel approach to therapeutic modulation of cutaneous inflammatory

disorders [20,33]. It has been recently showed that combination therapy with low-dose IFN-α and PUVA may modify CTACK/CCL27 chemokine expression in sera and tissues. Although in early MF patients, complete remission did not correlate with a reduction in CTACK/CCL27 expression in the skin and some patients showed its overexpression. Low CTACK/CCL27 expression after complete remission might be related to a different clinical behavior, determining a subset of patients with a lower risk of relapse. The mechanisms involved in local CTACK/CCL27 overexpression after therapy in the other 80% of the patients with complete remission who are at greater risk of recurrence need more investigation, especially when restoration of cutaneous CTACK/CCL27 levels in early MF is assumed to be a key end-point in the treatment of the disease [34].

Special treatments in CCR4-expressing T cell tumors

Chemokine receptor expressing tumors can be successfully controlled by delivering toxins through their chemokine receptors in vitro. Expression of chemokine receptor CCR4 on cutaneous T cell lymphoma is often associated with a poor outcome, so this may be an attractive strategy to control the disease. CCL17 molecules fused to the pseudomonas exotoxin 38 (PE38) have been shown to effectively kill lymphoma cells that express CCR4. Delivery of the thymus and activation-regulated chemokine (CCL17) -expressing a truncated fragment of Pseudomonas exotoxin 38 (TARC-PE38) through the chemokine receptor CCR4 can efficiently regress the CCR4-expressing cutaneous tumors in mice [35].

Anti-CCR4 monoclonal antibody (mAb) could also represent a novel therapeutic agent against aggressive or refractory Mycosis Fungoides/ Sezary Syndrome (MF/SS). It induces enhanced antibody-dependent cellular cytotoxicity (ADCC). The therapeutic potential of this antibody against aggressive MF/SS tumor cells has been shown in vitro and in animal models in vivo [36]. According to these documents, CCR4 is a suitable target for antibody-based therapy in patients with CCR4-positive neoplasm. CCR4 immunohistochemistry that is applicable to paraffin sections will be of significant help in selecting patients suitable for such therapies [15].

Summary

Chemokine receptors are assumed to be responsible for skin-tropism, tumor metastasis, and invasion of lymphatic vessels and possibly trafficking of lymphoma cells in CTCL. More knowledge on these mechanisms and the use of receptor antagonists or anti-receptor antibodies as therapeutic agents could be a new modality for the treatment of CTCL.

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