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Human T-cell leukemia virus type 1 (HTLV-1) infection and the chemokine system

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Abstract

Human T-cell leukemia virus type 1 (HTLV-1) is a human retrovirus that causes adult T-cell leukemia (ATL). ATL is a malignancy of mature CD4$^+$ T cells with poor prognosis. HTLV-1 genome encodes a potent transcriptional regulator, namely, Tax, which plays a critical role in CD4$^+$ T-cell transformation. However, Tax exerts its action only in the initial phase of ATL tumorigenesis because it is usually not detectable in ATL cells. A prominent role of the chemokine system is the regulation of leukocyte trafficking, including CD4$^+$ T cells. Here, we briefly summarize HTLV-1 infection and ATL and discuss the recent findings of the involvement of the chemokine system in HTLV-1 infection and ATL tumorigenesis.

Key words: HTLV-1, ATL, Tax, chemokine, chemokine receptor

Introduction

Adult T-cell leukemia (ATL) was first described in 1977 in Japan, and human T-cell leukemia virus type 1 (HTLV-1) was identified as the causative agent of ATL in 1981.[1-4] Since then, extensive studies have been performed to understand how HTLV-1 causes ATL. In the initial phase of HTLV-1 infection, one of the HTLV-1-encoded accessory proteins, named Tax, exerts a profound influence on the growth of CD4$^+$ T cells as a multipotent transcriptional regulator. However, primary ATL cells usually do not express Tax, indicating that the maintenance and proliferation of ATL cells are independent of Tax.[3,4] During the last 10 years, we have been studying HTLV-1 infection and ATL tumorigenesis from the aspect of involvement of the chemokine system, with a particular focus on the chemokine receptor CCR4. In this review, we briefly summarize HTLV-1 infection and ATL and primarily discuss the recent progress made in our studies in this field.

HTLV-1 infection and ATL

HTLV-1 is an exogenous retrovirus that infects 10~20 million people worldwide.[1-4] Although the majority of infected individuals remain lifelong asymptomatic carriers, HTLV-1 is etiologically associated with ATL and a wide range of inflammatory diseases, including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), uveitis, arthropathy, and infective dermatitis.[5] Because HTLV-1-infected lymphocytes produce very few infectious cell-free virions and because the virus is mainly transmitted via cell-to-cell contacts,[2,4,6] HTLV-1 transmission between individuals occurs by the transfer of infected lymphocytes through breast milk, semen, or blood[4,7] (Fig. 1). In vitro, HTLV-1 can transform CD4$^+$ T cells into continuously growing T-cell lines.[2,3] The potent viral transactivator Tax is known to activate both the HTLV-1 long terminal repeat (LTR) and the promoters of various cellular genes, leading to strong promotion of cell proliferation and activation.[8] However, ATL develops only after a long period of latency, usually after several decades, and during this period, tumor progression occurs through the accumulation of multiple genetic alterations[1,3,4] (Fig. 1). Notably, ATL cells usually do not express the *tax* gene and are considered to be independent of the growth-promoting effects of Tax.[3,4] This suggests that Tax is mainly involved in virus replication

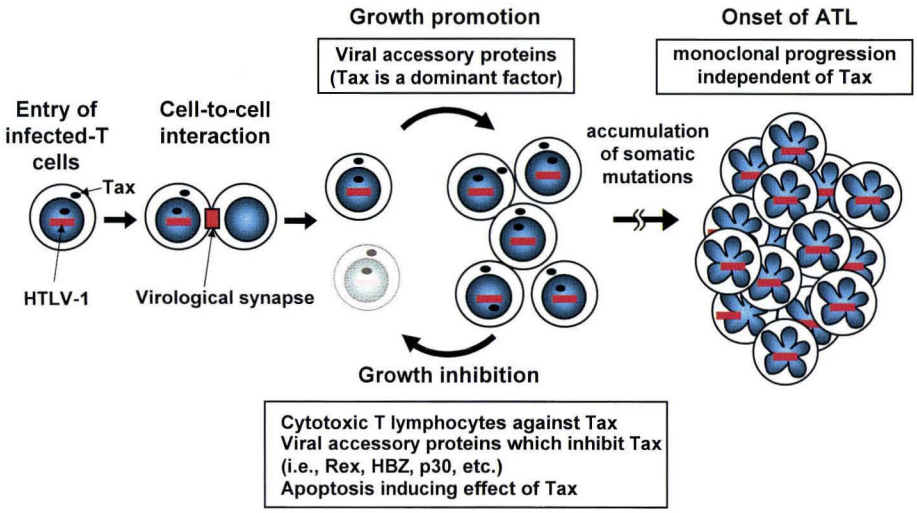

Fig. 1 Natural history of HTLV-1 infection.

and transmission as well as in the early stages of tumorigenesis. Because Tax is the main target of cytotoxic T lymphocytes (CTLs) of the host, cells that cease Tax expression have an advantage in evading immunosurveillance and are preferentially selected for in vivo during disease progression.[9]

The potent transactivator Tax has an oncogenic activity

Upon HTLV-1 infection of a $CD4^+$ T cell, the randomly integrated provirus is expressed at low levels. For efficient viral protein production, it is essential that the potent transactivator Tax induces viral gene expression at high levels, especially in the initial phase. Tax-mediated activation of viral LTR requires 3 imperfect 21-bp repeats termed the Tax-response elements.[10,11] Tax has also been shown to activate or repress cellular gene expression by recruiting or interacting with cellular transcription coactivators such as CBP/p300, by indirectly activating the NF-κB activation pathway, or by modulating the activity of many cellular proteins.[12–15] Many of the cellular genes modulated by Tax are involved in cell growth, differentiation, apoptosis, or cell cycle regulation.[16–20] Thus, these effects of Tax on cellular processes are suggested to be required for the transforming or oncogenic capacity of HTLV-1.[21,22] Indeed, mutational analysis in the context of a replicating virus directly demonstrated that Tax is essential for virus-mediated cellular transformation of primary human T cells and that Tax activation of NF-κB and CREB/ATF signaling plays a key role in the malignant process.[23–25]

A well-known cancer paradox is that the overexpression of oncoproteins not only provides proliferative advantages to cells but also frequently triggers cellular apoptosis.[26] Tax may share such duality. In the run-up to ATL establishment, HTLV-1-infected cells continuously repeat growth promotion and inhibition (Fig. 1). In this stage, HTLV-1-infected cells may be eliminated by Tax-induced apoptosis as well as by Tax-specific CTLs. There is evidence that Tax protects cells from stress-induced cell cycle arrest or apoptosis,[27–30] but it can also sensitize cells to stress-induced apoptosis.[30–32] This phenomenon may be because the transforming activity develops by opposing the effects of the cellular tumor suppressor genes, which often induce cell cycle arrest and/or apoptosis. To transform a cell, an oncoprotein must defeat the cellular apoptotic response, and this would explain why Tax exerts antiapoptotic activity probably through activation of NF-kB,[33] Bcl-XL,[34] c-FLIP,[35] and other unknown factors. In addition, the selection between life and death is influenced by cell background, cell milieu, and whether tumor suppressor functions have been defeated. In ATL, these multiple complexities may account for the long duration required by HTLV-1 to cause ATL.[36]

Chemokines and chemokine receptors

I would like to briefly describe the chemokine system before discussing the relationship between HTLV-1 and chemokines. Chemokines are a family of small cytokines that induce directed chemotaxis in nearby responsive cells via G-protein-coupled receptors (GPCRs).[37] Thus far, approximately 50 chemokines and 20 chemokine receptors have been identified (Table

Table 1 Diversity of chemokine system classified by chemokine receptors, their cognate ligands, and expressing leukocytes.

Receptor	Systematic/General names	Major leukocyte subsets	Inflammatory	Homeostatic
CXC chemokine				
CXCR1	CXCL6/GCP-2, CXCL8/IL-8	Neu[a], CTL, NK	○	
CXCR2	CXCL1/GROα, CXCL2/GROβ CXCL3/GROγ, CXCL5/ENA-78 CXCL6/GCP-2, CXCL7/NAP-2 CXCL8/IL-8	Neu, CTL, NK	○	
CXCR3	CXCL9/Mig, CXCL10/IP-10 CXCL11/I-TAC	act. T, Th1	○	○
CXCR4	CXCL12/SDF-1	T, B, PC, DC		○
CXCR5	CXCL13/BLC	folicular helper T, B		○
CXCR6	CXCL16	Th1, NK, NKT, PC		
CXCR7	CXCL12/SDF-1, CXCL11/I-TAC	B, Mo		
CC chemokine				
CCR1	CCL3/MIP-1α, CCL5/RANTES CCL7/MCP-3, CCL14/HCC-1 CCL16/LEC	Mo, memory T, iDC	○	
CCR2	CCL2/MCP-1, CCL7/MCP-3 CCL8/MCP-2(?), CCL16/LEC	Mo, memory T, iDC	○	
CCR3	CCL5/RANTES, CCL7/MCP-3 CCL8/MCP-2, CCL13/MCP-4 CCL11/Eotaxin, CCL24/Eotaxin-2 CCL26/Eotaxin-3, CCL28/MEC	Eo, Ba, (Th2)[b], PC, iDC	○	
CCR4	CCL17/TARC, CCL22/MDC	Th2, Th17, (Treg), skin-homing T	○	○
CCR5	CCL3/MIP-1α, CCL4/MIP-1β CCL5/RANTES	act. T, Th, Mo, iDC	○	
CCR6	CCL20/LARC	B, iDC, gut-homing T	○	○
CCR7	CCL19/ELC, CCL21/SLC	naive T, central memory T, B, mDC		○
CCR8	CCL1/I-309	Th2, (Treg), Mo	○	○
CCR9	CCL25/TECK	gut-homing T, intraepithelium T small intestine-homing IgA PC	○	○
CCR10	CCL27/ILC, CCL28/MEC	skin-homing T, PC	○	
C chemokine				
XCR1	XCL1/Lymphotactin	CTL, NK	○	
CX3C chemokine				
CX3CR1	CX3CL1/fractalkine	Mo, CTL, NK, intraepithelium T	○	
Receptor unknown				
	CXCL4/PF4	Ba, mast cells	○	
	CCL18/PARC	naive T	○?	○?
	CXCL14/BRAK	iDC		○?

[a]Abbreviations; Neu, neutrophils; CTL, cytotoxic T lymphocytes; NK(T), natural killer (T) cells; Th, helper T cells; DC, dendritic cells; Mo, monocytes; iDC, immature DC; Eo, eosinophils; Ba, basophils; Treg, regulatory T cells; mDC, mature DC.

[b]Parenthesis means some population of those cells express the corresponding chemokine receptor.

1). Chemokines are classified into 4 subtypes according to the number and spacing of cysteine residues in the amino-terminal region : C, CC, CXC, and CX3C. All chemokines are secreted, except CX3CL1 and CXCL16, which have transmembrane and cytoplasmic domains.[37-41] Chemokines are highly basic proteins, and this property may help to mediate stable gradient formation by promoting interactions with sulfated proteins and proteoglycans at extracellular matrices. All chemokine receptors reported to date belong to the GPCR family, which are transmembrane receptors that cross the cell membrane seven times and couple to heterotrimeric GTP-binding proteins (G proteins). Induction of migration up a chemokine gradient (chemotaxis) and subsequent adhesion to endothelial cells require activation of pertussis toxin (PTX)-sensitive G proteins (Gi).[37]

Some chemokines are considered proinflammatory (named "inflammatory" chemokines) and can be induced during an immune response to recruit cells of the immune system to the site of infection, while other chemokines are considered homeostatic (named "homeostatic" chemokines) and are involved in controlling the migration of cells during normal processes of tissue maintenance or development (Table 1).[37,42] Chemokines are found in all vertebrates, some viruses, and some bacteria, but no chemokines have been reported in other invertebrates.

The major role of chemokines is to act as a chemoattractant to guide the migration of cells. "Inflammatory" chemokines such as CXCL8/IL-8, CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, and CCL5/RANTES are released by a wide variety of cells in response to bacterial and viral infection and agents that cause physical damages.[37,42] Their release is often stimulated by proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). These "inflammatory" chemokines function mainly as chemoattractants for leukocytes and recruit monocytes, neutrophils, and other effector cells from the blood to sites of infection or tissue damage. Certain "inflammatory" chemokines activate cells to initiate an immune response or promote wound healing. They are released by many different cell types and serve to guide cells of both the innate immune system and adaptive immune system. On the other hand, "homeostatic" chemokines such as CXCL12/SDF-1, CXCL13/BLC, CCL19/ELC, and CCL21/SLC control cells of the immune system during processes of immune surveillance, for example, directing lymphocytes to the lymph nodes so that they can screen for invasion of pathogens by interacting with antigen-presenting cells residing in these tissues.[37,42-44] These "homeostatic" chemokines are produced and secreted without any need to stimulate their source cell(s). Some chemokines, including "homeostatic" chemokines secreted from the cells of the bone marrow and thymus or in embryo, play roles in development ; they promote not only cell differentiation but also angiogenesis, organogenesis, and even tumor growth and metastasis.[37,42,45] Recent findings, however, indicate that several chemokines cannot be assigned clearly to either of the 2 functional categories. Therefore, some researchers referred to such chemokines as "dual-function" chemokines[42].

ATL and the chemokine receptor CCR4

Studies by our group and other researchers have shown that most malignant cells from ATL patients frequently and highly express CCR4,[46,47] which is known to be expressed by Th2 cells, some regulatory T cells, and skin-homing memory/effector T cells[37] (Fig. 2). Thus, ATL may be preferentially derived from any one of these T-cell subsets. Indeed, several recent studies have demonstrated that FOXP3, a forkhead/winged-helix transcription factor and a specific marker of regulatory T cells[48], is expressed in a fraction of ATL cases.[49-51] Furthermore, ATL cells often express the cutaneous lymphocyte-associated antigen (CLA), which is a marker for skin-homing memory/effector CD4$^+$ T cells. Intriguingly, these skin-homing T cells also frequently express FOXP3.[52] Collectively, these findings suggest that some ATL cells might originate from CCR4$^+$CLA$^+$ skin-homing Treg cells.

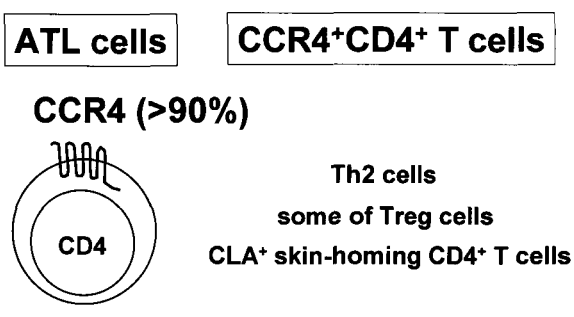

Fig. 2 ATL cells frequently express chemokine receptor CCR4.

Does CCR4$^+$ phenotype appearing in ATL cells result from HTLV-1 infection? We have recently found a clue to this question. Thus far, HTLV-1-infected T cells have been reported to produce various chemokines mostly through transcriptional activation by Tax.[53–58] Therefore, HTLV-1-infected T cells may use the chemokine-chemokine receptor system for promoting recruitment and cell-to-cell interactions with uninfected target CD4$^+$ T cells. In our previous report, we demonstrated that Tax does not induce CCR4 expression in a T-cell line[46] but robustly promotes the expression of a CCR4 ligand, namely, CCL22 (also known as macrophage-derived chemokine/MDC), which attracts and interacts with CCR4$^+$CD4$^+$ T cells in peripheral blood mononuclear cells (PBMCs)[59] (Figs. 3 and 4). Because CCR4$^+$CD4$^+$ T cells migrated toward HTLV-1-infected T cells more robustly than other T-cell subsets in PBMCs, this initial selectivity at the time of primary infection may partly explain the strong bias toward the CCR4$^+$ phenotype in HTLV-1-infected CD4$^+$ T cells and eventually in ATL cells. These findings propose a new mechanism by which Tax-expressing HTLV-1-infected T cells preferentially transmit HTLV-1 to CD4$^+$ T cells where the CCL22-CCR4 pathway plays an important role in promoting recruitment and cell-to-cell interactions. Even though HTLV-1 infection would be critically dependent on the expression of HTLV-1 Env receptors such as HSPG and/or GLUT-1,[60–62] we may also include the CCL22-CCR4 system as an important biological factor that promotes HTLV-1 tropism to CCR4$^+$CD4$^+$ T cells.[59]

Recently, Igakura et al.[63] have reported the formation of a highly organized structure at the cell-cell junction, termed "virological synapse (VS)," between HTLV-1-infected CD4$^+$ T cells and uninfected autologous or allogeneic CD4$^+$ T cells. The adhesion adaptor protein talin and the microtubule-organizing center (MTOC) are polarized to the cell-cell junction in HTLV-1-infected T cells, together with the accumulation of the HTLV-1 Gag protein and the HTLV-1 genome. This leads to the transfer of both the Gag protein and the HTLV-1 genome to unin-

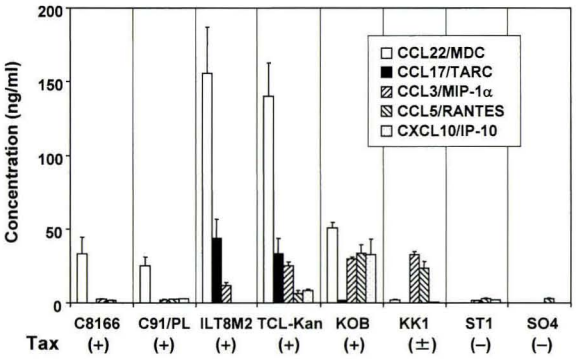

Fig. 3 Tax-dependent chemokine expressions in various HTLV-1-infected and ATL-derived T cell lines.

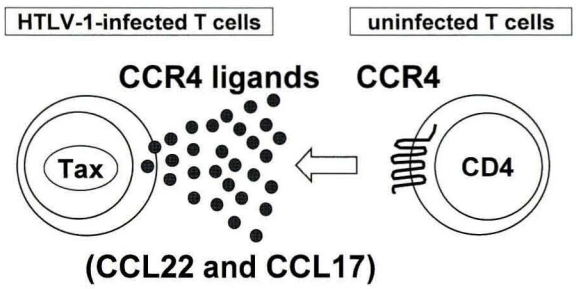

Fig. 4 Role of CCR4 in the primary HTLV-1 infection.

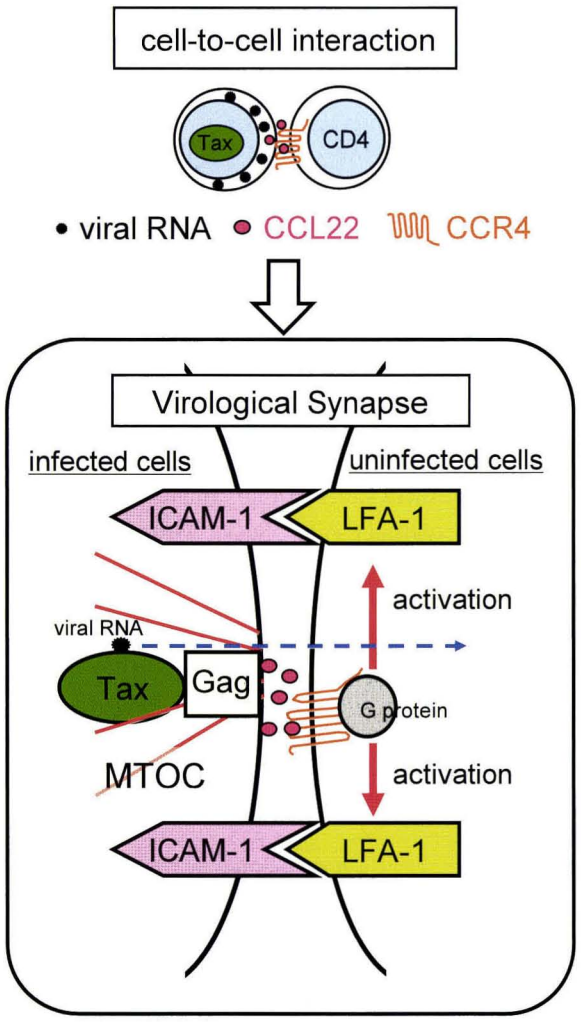

Fig. 5 Role of CCL22-CCR4 system in the formation of virological synapse.

fected T cells through VS.[6,63] However, it was still unknown whether the attraction and initial interaction of target $CD4^+$ T cells with HTLV-1-infected T cells are mostly random processes.[59] In our previous report, we demonstrated that Tax-inducible CCL22 in HTLV-1-infected T cells preferentially attracts $CCR4^+CD4^+$ T cells in PBMCs and promotes the transmission of HTLV-1 to these cells. In this instance, HTLV-1-infected T cells engage in close cell-to-cell contacts with $CCR4^+CD4^+$ T cells, resulting in the formation of VS (Fig. 5). Interestingly, CCR4 colocalizes with both MTOC and CD4 at a cell-cell junction. It remains uncertain whether CCR4 plays an important role in HTLV-1 transmission to uninfected T cells in addition to its primary role in cell migration and subsequent interaction.

Aberrant expression of AP-1 Fra-2 causes enhanced CCR4 expression in ATL cells

Notably, primary ATL cells express CCR4 at levels considerably higher than those of normal resting $CD4^+CD25^+$ T cells.[64] Given the Tax-independent CCR4 expression,[46] transcription factor(s) constitutively active in ATL cells may be responsible for CCR4 expression. This notion led to the recent report on the regulation of the CCR4 promoter, where we demonstrated that Fra-2, one of the AP-1 family members,[65,66] is aberrantly expressed in primary ATL cells and that the Fra-2/JunD heterodimer plays a major role in both CCR4 expression and cell proliferation in ATL cells (Fig. 6). We also found that the proto-oncogenes c-*myb*, *BCL-6*, and *MDM2*[67–69] are the downstream target genes of the Fra-2/JunD heterodimer and are highly expressed in primary ATL cells. Thus, aberrantly expressed Fra-2 in association with JunD may be involved in ATL oncogenesis.[70]

Anti-CCR4-based therapy of ATL

Recently, Ueda's group at Nagoya City University reported that the administration of anti-CCR4 monoclonal antibody (KM2760) to anticancer drug-resistant ATL patients had a good therapeutic effect in a phase I clinical trial.

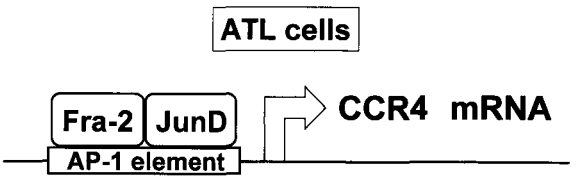

Fig. 6 Aberrant expression of transcription factor AP-1 Fra-2 promotes CCR4 gene expression in ATL cells.

KM2760 is a chimeric IgG1 whose Fcγ regions are artificially defucosylated in their asparagine-linked oligosaccharides to enhance antibody-dependent cellular cytotoxicity (ADCC) activity by increasing its binding affinity to FcγR on effector cells.[77,78] CD20 is expressed on all mature B cells and is a good target of the monoclonal antibody Rituximab for the treatment of B-cell lymphomas and leukemias.[79] Likewise, CCR4 is expressed on "mature" $CD4^+$ T cells in the periphery, suggesting that the anti-CCR4-based therapy is promising for the treatment of CCR4-expressing malignancies, including ATL, cutaneous T-cell lymphoma (CTCL),[80] and a portion of Hodgkin's lymphoma.[81] Furthermore, the possible depletion of CCR4-expressing Treg cells particularly may result in enhancement of antitumor effect. Thus, anti-CCR4 monoclonal antibody could be an ideal treatment agent for many different malignancies, not only to directly kill CCR4-expressing malignant cells but also to overcome the suppressive effect of CCR4-expressing Treg cells on the host immune response to malignant cells.

CCR7 expression and lymphoid organ infiltration of ATL cells

CCR7 has been identified as a key regulator of homeostatic T-cell trafficking to secondary lymphoid organs. In humans, 2 T-cell subsets can be defined according to their expression levels of CCR7 and CD62L,[76] both these markers being necessary for entry into the peripheral lymph nodes through high endothelial venule,[37] where 2 CCR7 ligands, i.e., CCL19/ELC and CCL21/SLC, are expressed. The $CCR7^+$ $CD62L^+CD45RO^+$ central memory T cells (T_{CM}) recirculate through the lymphoid organs and do not exhibit immediate effector functions if they do not receive a secondary stimulus, whereas the $CCR7^-CD62L^-CD45RO^+$ cells are effector memory T cells (T_{EM}) that reside within or recirculate through peripheral tissues and have immediate effector functions. All these subsets can be found in the blood and spleen. Thus, CCR7 is an important regulatory molecule with an instructive role in determining the migration of cells to secondary lymphoid organs.

Hasegawa et al. reported that ATL cells from patients with lymphoid organ involvement showed substantially higher expression of CCR7 than control $CD4^+CD45RO^+$ T cells and ATL cells from patients without lymphoid organ involvement.[77] It really makes sense for ATL

cells to enter the lymphoid organs because CCR7 is a homing receptor for these organs. Hasegawa et al. also compared the expression levels of CCR7 and CXCR4 in ATL cells from patients with and without lymphoid organ infiltration and demonstrated that increased expression of CCR7 but not CXCR4 correlates with infiltration of the lymphoid organs by ATL cells. By far, CXCR4 is probably the most common chemokine receptor expressed by many cancer cells. The sole ligand of this receptor, namely, CXCL12/SDF-1, is strongly expressed in the lung, liver, and bone marrow—the common metastatic destinations of many cancers.[78] Therefore, CXCR4 expression in ATL cells may be involved in these tissue metastases that are often observed as a complication of ATL.

A potential autocrine antiapoptotic loop between CCR8 and its ligand CCL1/I-309 in ATL cells

CCR8 is a chemokine receptor expressed on thymocytes and a subset of $CD4^+$ memory T cells enriched for Treg and Th2 cells, which have the potential for recruitment into sites of allergic inflammation.[79–81] The sole ligand of this receptor, namely, CCL1/I-309, was one of the first chemokines discovered, and numerous target cells and cellular responses have been reported, including those related to tumor cell apoptosis, angiogenesis, and HIV-1 infection as well as blood and tissue cell chemotaxis. However, the cloning of CCR8 revealed the scarcity of this chemokine receptor, notably in peripheral blood leukocytes.[82,83] Recent reports demonstrated that CCL1/I-309 is constitutively expressed within the dermal microvasculature as well as by epidermal Langerhans cells and melanocytes and that healthy skin is a major reservoir of $CCR8^+$ T cells. Surprisingly, these skin-homing $CCR8^+$ T cells secrete TNF-α and interferon-γ (IFN-γ) but not IL-4, IL-10, and transforming growth factor-β (TGF-β), thereby arguing against a strict association of CCR8 expression with either Th2 or Treg subsets. Further studies are required to fully define the role of CCR8 in $CD4^+$ T-cell subsets.

Ruckes T et al. systematically compared the gene expression of cultured cells from acute ATL patients with that of stimulated peripheral blood T lymphocytes and found that CCL1/I-309 is one of the overexpressed genes in the cells from acute ATL patients and is secreted sufficiently in HTLV-1-infected cell culture supernatants.[84] An earlier study reported that CCL1/I-309 protects thymoma lines against dexamethasone-induced apoptosis.[85] HTLV-1-infected T cells also express CCR8, and their cell culture supernatants exhibited an antiapoptotic activity that could be specifically inhibited by antibodies directed against CCL1/I-309. Inhibition of CCR8 signaling by PTX increased the apoptosis rate of HTLV-1-infected T-cell cultures in the presence and absence of external apoptotic stimuli. Both the CCL1/I-309-specific antiapoptotic activity and the proapoptotic effect of inhibitors of CCL1/I-309 signaling suggest the existence of an antiapoptotic autocrine loop in ATL cells.

Given the constitutive expression of CCL1/I-309 within the dermal microvasculature, CCR8, together with CCR4, may allow ATL cells to recruit to and/or localize in the skin. However, the other role of CCR8 in ATL cells in vivo remains uncertain.

Tax-dependent CCR9 expression and intestine-infiltrating ATL cells

The chemokine receptor CCR9 is specifically expressed by $CD4^+CD8^+$ (double positive) thymocytes, $\alpha4\beta7^+$ gut-homing effector/memory T cells, intraepithelial T cells, and IgA-producing antibody secreting cells (IgA-ASCs) among blood leukocytes. Basically, $CCR9^+\alpha4\beta7^+$ gut-homing and $CCR4^+CLA^+$ skin-homing phenotypes are mutually exclusive. However, recently, our group demonstrated that CCR9 is expressed in $CCR4^+$ ATL cells probably through indirect CCR9 promoter activation by Tax, even though Tax is usually undetectable in ATL cells circulating in the peripheral blood. It might be possible to express Tax in ATL cells because Tax induction in some ATL cells remains intact after cultivation in vitro. Contrary to the blood circulating ATL cells, CCR9 is often positive in ATL cells that invade the gastrointestinal tract where CCL25 is abundantly produced.[86,87] Thus, CCR9 may play a role in invasion and/or localization of ATL cells in the gastrointestinal tract. However, given that certain $CCR9^-$ ATL cells invade the gastrointestinal tract, CCR9 may not be essential for ATL invasion of the gastrointestinal tract. Since circulating ATL cells hardly express surface CCR9, ATL cells may be induced to express CCR9 either in lymphoid tissues such as Peyer's patches or after infiltration into the gastrointestinal tract through upregulation of Tax in situ[88,89] or by other stimulatory factors such as cytokines and cell adhesion molecules

present in the local milieu. In this context, Iwata et al. demonstrated that all-trans retinoic acid (ATRA) is a potent inducer of CCR9 in memory T cells.[90] Given the CCL25-induced antiapoptotic effect on CCR9-expressing cells,[91] the expression of CCR9 may also promote survival of ATL cells infiltrating into the gastrointestinal tract.[64]

CCR10, another T-cell skin-homing receptor, and ATL cells

The chemokine receptor CCR10 is expressed by CLA^+ memory T cells, plasmablasts, and/or plasma cells. Previously, our group reported that CCR10 is expressed by human bone marrow-derived plasma cells,[92] myeloma cells,[92] and IgA-ASCs.[93] CCR10-expressing IgA-ASCs home to mucosal immune tissues, where one of the CCR10 ligands, CCL28/MEC, is abundantly expressed and serves to establish a common mucosal immune system[93,94]. In this review, I will discuss only CCR10 expression in T cells. CCL27 is another CCR10 ligand selectively expressed by keratinocytes of the epidermis (the superficial epithelial lining of the skin) and thus is thought to mediate the "epidermotropism" (chemoattraction to the epidermis) of $CCR10^+$ T cells from the dermis—the underlying subepithelial skin layer.[95,96] In addition to such epidermotropism, CCR10 and CCL27 may influence the retention of T cells in or near the epidermis and can participate in (but are not required for) the homing of T cells from the blood into the vascular dermis.[95,97]

Previously, Harasawa et al. performed a comprehensive survey on the chemokine receptor expression in blood circulating ATL cells[98]. ATL cells expressed CCR1, CCR4, CCR7, CCR8, CCR10, and CXCR4 but hardly expressed CCR2, CCR3, CCR5, CCR6, CCR9, CXCR1, CXCR2, CXCR3, and CXCR5. Notably, patients who have skin lesions showed substantially higher levels of CCR10 mRNA expression than patients without skin lesions. ATL cells migrated efficiently to the CCR4 ligand CCL22 and moderately to the CCR10 ligands CCL27 and CCL28. Moreover, ATL skin lesions consistently contained transcripts of CCR10 and its ligands CCL27 and CCL28 in addition those of CCR4 and its ligands CCL17 and CCL22.[46] Taken together, the frequent coexpression of CCR4 and CCR10, which are the known pair of skin-homing chemokine receptors, and conceivably CCR8, may play an important role in ATL invasion into the skin.

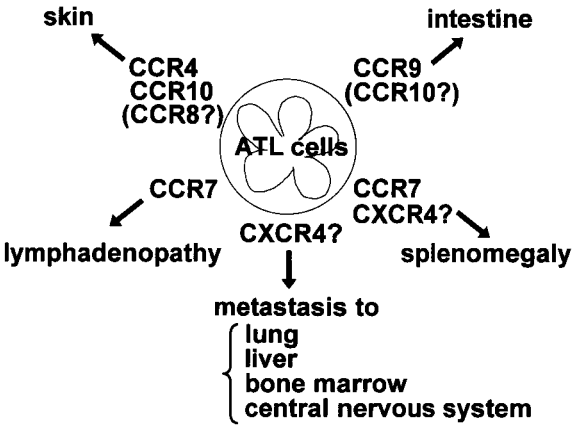

Fig. 7 Relationship between chemokine receptor expression in ATL cells and their tissue invasion.

Closing remarks

Profiling of chemokine-chemokine receptor expression in tumor cells provides many beneficial outcomes in cancer research. By analyzing chemokine-chemokine receptor expression patterns, we can understand the origin of tumor cells through analogy with normal cells during development and functional maturation and the distribution of tumor cells. CCR4 expression in ATL cells is a good example of such cases. Summary of the relationship between chemokine receptor expression pattern in ATL cells and their tissue invasion is shown in Fig. 7. Elucidation of the involvement of the chemokine system in HTLV-1 infection and ATL is useful to fully understand the pathophysiology of this disease and to provide a useful application of ATL therapy in the near future.

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