CC Chemokine Ligand 25 Enhances Resistance to Apoptosis in CD4+ T Cells from Patients with T-Cell Lineage Acute and Chronic Lymphocytic Leukemia by Means of Livin Activation

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ABSTRACT

We investigated CD4 and CD8 double-positive thymocytes, CD4+ T cells from typical patients with T-cell lineage acute lymphocytic leukemia (T-ALL) and T cell lineage chronic lymphocytic leukemia (T-CLL), and MOLT4 T cells in terms of CC chemokine ligand 25 (CCL25) functions of induction of resistance to tumor necrosis factor α (TNF-α)-mediated apoptosis. We found that CCL25 selectively enhanced resistance to TNF-α-mediated apoptosis in T-ALL and T-CLL CD4+ T cells as well as in MOLT4 T cells, but CD4 and CD8 double-positive thymocytes did not. One member protein of the inhibitor of apoptosis protein (IAP) family, Livin, was selectively expressed in the malignant cells at higher levels, particularly in T-ALL CD4+ T cells, in comparison with the expression in CD4 and CD8 double-positive thymocytes. After stimulation with CCL25 and apoptotic induction with TNF-α, the expression levels of Livin in these malignant cells were significantly increased. CCL25/thymus-expressed chemokine (TECK), by means of CC chemokine receptor 9 (CCR9) ligation, selectively activated Livin to enhance resistance to TNF-α-mediated apoptosis in c-jun-NH2-kinase 1 (JNK1) kinase-dependent manner. These findings suggested differential functions of CCR9/CCL25 in distinct types of cells. CD4 and CD8 double-positive thymocytes used CCR9/CCL25 for migration, homing, development, maturation, selection, cell homeostasis, whereas malignant cells, particularly T-ALL CD4+ T cells, used CCR9/CCL25 for infiltration, resistance to apoptosis, and inappropriate proliferation.

INTRODUCTION

CC chemokine ligand 25 (CCL25), also known as thymus-expressed chemokine (TECK), together with CC chemokine receptor 9 (CCR9), efficaciously induces chemotaxis of immature CD4+CD8− double-positive, and mature CD4+ and CD8+ single-positive thymocytes, suggesting that CCL25/CCR9 interaction plays a pivotal role in T-cell migration in the thymus (1–4). CCL25/TECK delivers signals through CCR9 for developing of thymocytes (5), and developing and/or migrating of both αβ− and γδ+ T cells (6). CCR9 activation leads to phosphorylation of glycogen synthase kinase-3β (GSK-3β) and forkhead transcriptional factor (FKHR) and provides a cell-survival signal (7). In the normal human, CCR9 is restrictedly expressed at high levels on CD4+ and CD8+ T cells in the small intestine (8), providing the evidence for distinctive mechanisms of lymphocyte recruitment. The importance of CCL25/TECK is to license effector/memory cells to access anatomic sites (9, 10). Thus, CCL25/TECK is important for the homing, development, and homeostasis of T cells, particularly, mucosal T cells. The functional importance of CCR9/CCL25 in the physiologic and pathophysiologic events of T-cell trafficking and selection is not fully understood despite a considerable body of investigations.

The inhibitor of apoptosis protein (IAP) family plays a key role in apoptosis regulation and has become increasingly prominent in the field of cancer (11). Thus far, eight human IAPs have been identified: c-IAP1, c-IAP2, NAIP, survivin, XIAP, Bruce, ILP-2, and Livin (11). IAPs can block apoptosis mainly through their ability to bind and inhibit specific caspases such as caspase-3 and -7 (12, 13). A novel IAP member, designated Livin/ML-IAP/KIAP (14, 15), is suggested to mediate suppression of cell death (14–16). A key function for Livin in the transformed phenotype suggests that this protein may be an important target for immune-mediated tumor destruction (17).

A common manifestation of T-cell lineage acute lymphocytic leukemia (T-ALL) and T-cell lineage chronic lymphocytic leukemia (T-CLL) is infiltration of various organs by leukemic cells (18). We have reported that CCR9 is selectively and functionally overexpressed on T-ALL and T-CLL CD4+ T cells (19). Despite these findings, little is known about the exact mechanisms and molecule regulation in the homoing, migration, inappropriate proliferation, and resistance to apoptosis of T-ALL and T-CLL T cells.

MATERIALS AND METHODS

Patients and Cell Purification. All of the patients with T-ALL and T-CLL were diagnosed according to the French-American-British (FAB) Cooperative Group criteria (20) and to the guidelines of the National Cancer Institute Working Group on B-CLL (21, 22), and informed consent according to institutional guidelines. CD4+ T cells were purified by a positive selection procedure of Dynabeads (Dynal AS, Dynal, Norway). The malignancy of purified T-ALL or T-CLL CD4+ T cells was checked by expression of CD25, CD45RO, and HLA-DR (19). Human thymus tissue was aseptically obtained after consent during surgical operative procedures involving the mediastinal region. Stromal cells were prepared by enzymatic digestion of thymus tissue, as described previously (23). CD4 and CD8 double-positive thymocytes were sorted with a FACStarPlus. The cell lines were obtained from the American Type Culture Collection, Manassas, VA (MOLT4 and human embryonic kidney cells 293T). The anti-CCR9 monoclonal antibody and chemokines (CCL25/TECK, CXC (CC) chemokine ligand 12 (CXCL12)/SDF-1) were purchased from R&D Systems, Abingdon, United Kingdom.

Flow Cytometry. For detection of apoptosis, cells were stained in staining buffer with 1 μg/mL propidium iodide for 30 minutes at 4°C, then stained with FITC-conjugated annexin V with binding buffer (BD PharMingen, San Diego, CA) as described previously (7, 24). COULTER XL (Coulter, Miami, FL) was used for analyses. For detection of intracellular active caspases, cytofix/cytoperm buffer (BD PharMingen) was used to permeabilize cells, and cells...
were subsequently stained with anti-active-caspase-3 or anti-active-caspase-8 monoclonal antibody (BD PharMingen). Data were analyzed by means of the WinList program (The Syntor Research Institute, Trondheim, Norway). Cells were cultured in DMEM containing 10% fetal calf serum, penicillin, and streptomycin. Cells were harvested 2 days after the transfection.

**RESULTS**

**CCL25/TECK Selectively Rescues T-ALL and T-CLL CD4⁺ T Cells from TNF-α-Mediated Apoptosis.** The data in Table 1 showed that double-positive thymocytes, T-ALL and T-CLL CD4⁺ T cells and MOLT4 T cells expressed high levels of CCR9, which were in agreement with previous reports (1, 2, 7, 18, and 32). By knowing that activation of CCR9 led to phosphorylation of GSK-3β and JNK, we examined the protective effects of CCL25/TECK and CXCL12/SDF-1 (7) on different types of cells from tumor necrosis factor α (TNF-α)-mediated apoptosis. The number of apoptotic and necrotic cells were significantly increased on culture of double-positive thymocytes in the presence of CCL25/TECK (Fig. 1A–e), in comparison with that in malignant cells. The apoptotic responses in T-ALL and T-CLL CD4⁺ T cells as well as in MOLT4 T cells were significantly inhibited in the presence of CCL25/TECK (Fig. 1A-f, -g, and -h), CXCL12/SDF-1, to our surprise, could rescue malignant cells (Fig. 1A-j, -k, and -l), as well as double-positive thymocytes (Fig. 1A-i). Antibody against CCR9 could completely block the protective effect of CCL25/TECK (Fig. 1A-n, -o, and -p). As shown in Fig. 1B, the total dead cells (including apoptotic and necrotic) in different types of the cells tested were the same.

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patterns as the results in Fig. 1A. These results were suggesting that differential effects of CCR9 and TNF-α signaling existed between double-positive thymocytes and malignant T cells.

We examined the protective effects of CCL25/TECK on different types of malignant T cells from chemotherapy-induced apoptosis. CCL25/TECK itself induced no apoptosis in malignant T cells. Chemotherapeutic drugs induced significant apoptosis when the cells were pretreated without or with low concentration of CCL25, whereas high concentration of CCL25 significantly prevented the malignant T cells from chemotherapy-induced apoptosis (Table 2).

Livin Expression in T-ALL CD4⁺ T Cells Is Selectively Increased. To examine the mechanisms of cell-type selectivity of CCL25/TECK to rescue cells from TNF-α-mediated apoptosis, we first examined the expression levels of some important substrates of apoptosis pathways in the distinct types of cells. The protein levels of one antiapoptotic member Bcl-2 and c-FLIP_L in freshly isolated different types of T cells were identical (Fig. 2A). Interestingly, Bcl-2 expression level was significantly elevated in double-positive thymocytes after stimulation with CCL25/TECK and apoptotic induction with TNF-α, but not in the malignant cells (Fig. 2A). There were no significant differences of c-FLIP_L expression in various cell types before and after stimulation (Fig. 2A). We also observed a similar expression pattern of another antiapoptotic member, Bcl-X (data not shown). One antiapoptotic member protein in the IAP family, Livin, was selectively expressed at higher levels in the malignant cells, particularly in T-ALL CD4⁺ T cells, in comparison with the level in double-positive thymocytes (Fig. 2B). For a better comparison, samples from different un-stimulated cells were loaded in the same gel that was used for examining Livin expression (Fig. 2C). The expression levels of Livin in these malignant cells were significantly increased after stimulation with CCL25/TECK and TNF-α (Fig. 2B). Stimulation with TNF-α alone slightly changed (decreased) the expression of Livin in different types of cells. The antibody against CCR9 could significantly inhibit the elevation of expression level of Livin in these cells (data not shown). Another antiapoptotic member protein in the IAP family, survivin, expressed identical levels in the different conditions in various types of cells (Fig. 2B). The expression levels of other members in the IAP protein family (c-IAP1, c-IAP2, and XIAP) were not significantly changed in various cell types before and after stimulation with CCL25/TECK and TNF-α (data not shown).

To further confirm elevated expression of Livin in T-ALL CD4⁺ T cells, we examined the expression of Livin mRNA in the distinct types of cells. The Livin mRNA was expressed at a very low level in freshly isolated double-positive thymocytes (1.1 × 10³ copies) and was not substantially altered after stimulation with CCL25/TECK and TNF-α (Fig. 3A). In contrast, Livin mRNA expression was significantly higher in T-ALL CD4⁺ T cells (3.2 × 10³ copies), whereas there were significant increases in T-ALL CD4⁺ T cells (6.2 × 10³ and 5.8 × 10³ copies, respectively) after stimulation with CCL25/TECK along or together with TNF-α (Fig. 3B). TNF-α stimulation alone slightly decreased the expression of Livin (2.5 × 10³ copies). The antibody against CCR9 could marginally inhibit the elevation in Livin mRNA expression (data not shown). The same patterns of Livin mRNA expression were seen in double-positive thymocytes (Fig. 3C) and T-ALL CD4⁺ T cells (Fig. 3D) by Northern blot. For a better comparison, samples from un-stimulated thymocytes and T-ALL CD4⁺ T cells were loaded in the same gel that was used to examine Livin mRNA (Fig. 3E). Elevated Livin mRNA expressions were also observed in other malignant cells (T-CLL CD4⁺ T cells and MOLT4 T cells) by real-time quantitative RT-PCR assay and Northern blot (data not shown). The pattern of Livin mRNA expression in normal peripheral CD4⁺CCR9⁻ T cells was similar to that in double-positive thymocytes (Fig. 3F).

The caspase-3 and caspase-8 expression is essential for this type of cell death (33). Expression levels of activated caspase-3 and caspase-8 were measured by intracellular staining of double-positive thymocytes (Fig. 4A) and T-ALL CD4⁺ T cells (Fig. 4B) with the use of cleavage-specific caspase-3 and caspase-8 antibody. Double-positive thymocytes, normal peripheral CD4⁺CCR9⁻ T cells, and T-ALL CD4⁺ T cells.
cells expressed substantially up-regulated cleaved caspase-3 and caspase-8 in TNF-α stimulation, but CCL25/TECK could only stabilize caspase-3 and caspase-8 in T-ALL CD4+ T cells, but not in double-positive thymocytes nor in normal peripheral CD4+CCR9 T cells (Fig. 4). We observed similar results in other malignant cell types (T-CLL CD4+ T cells and MOLT4 T cells; data not shown), which suggested that CCL25/TECK protection from apoptosis was limited in malignant cells.

Many signaling events of binding of certain chemokines to chemokine receptors were included, such as phosphoinositide-3 kinase (PI3K), mitogen-activated protein kinase (MAPK), or protein kinase C (PKC), which appeared to be involved in chemokine-mediated chemotaxis in certain cell types (7, 34–36). To determine whether these kinases were responsible for CCL25/TECK-mediated chemotaxis, T-ALL CD4+ T cells were pretreated with various concentrations of pertussis toxin, an inhibitor of PKC; wortmannin, a potent PI3K inhibitor; PD98059, a MAPK inhibitor; or vehicle, DMSO. As seen in Fig. 5A, pertussis toxin and wortmannin significantly inhibited cell migration toward CCL25/TECK; PD98059 did not inhibit T-ALL CD4+ T cell migration toward CCL25/TECK, which was in agreement with those who observed similar results in MOLT4 T cells (7). We observed similar results in other malignant cell types (T-CLL CD4+ T cells and MOLT4 T cells; data not shown). To determine whether these kinases were responsible for CCL25/TECK-mediated protection from apoptotic response, we pretreated the cells with the inhibitors mentioned above. As seen in Fig. 5B, only pertussis toxin significantly inhibited the apoptotic protection effect in T-ALL CD4+ T cells. Neither PD98059 nor wortmannin inhibited apoptotic protection effect in T-ALL CD4+ T cells, suggesting that CCL25/TECK went through different signaling pathway to carry out chemotaxis and apoptosis.

### Table 2. Apoptotic analysis in malignant T cells under different chemotherapeutic drug treatments in vitro

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>0.1</th>
<th>100</th>
<th>0</th>
<th>0.1</th>
<th>100</th>
<th>0</th>
<th>0.1</th>
<th>100</th>
</tr>
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<tbody>
<tr>
<td>Nontreated</td>
<td>9 ± 2</td>
<td>8 ± 1</td>
<td>9 ± 6</td>
<td>6 ± 3</td>
<td>10 ± 2</td>
<td>7 ± 2</td>
<td>8 ± 3</td>
<td>9 ± 3</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Comp.</td>
<td>62 ± 12</td>
<td>55 ± 17</td>
<td>13 ± 6</td>
<td>57 ± 9</td>
<td>52 ± 12</td>
<td>9 ± 5</td>
<td>67 ± 3</td>
<td>59 ± 6</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Cyclop.</td>
<td>65 ± 8</td>
<td>62 ± 9</td>
<td>12 ± 2</td>
<td>65 ± 7</td>
<td>61 ± 11</td>
<td>10 ± 5</td>
<td>59 ± 8</td>
<td>60 ± 10</td>
<td>14 ± 6</td>
</tr>
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**NOTE.** Cells were pretreated for 2 hours in the presence (at concentration of 0.1 or 100 ng/mL) or absence (0) of CCL25, then were treated in the presence of camptothecin (Comp., 5 μmol/L) or cyclophosphamide (Cyclop., 7.5 mmol/L; ref. 48) for 12 hours, followed by apoptotic analysis by flow cytometry. The data for apoptotic cells are mean values ± SD of six experiments performed in each group.
apoptotic protection in T-ALL CD4⁺ T cells. The inhibitors themselves had no apoptotic effects on the T-ALL CD4⁺ T cells (Fig. 5B-g, -h, -i, and -j). Z-VAD-FMK rescued T-ALL CD4⁺ T cells from TNF-α-mediated apoptosis. We observed similar results in other malignant cell types (T-CLL CD4⁺ T cells and MOLT4 T cells; data not shown).

CCL25/TECK via CCR9 Activates Livin in JNK1 Kinase-Dependent Manner. The inhibitor of apoptosis family of proteins was found to protect against the broadest spectrum of apoptotic signals (37, 38). We further investigated the ability of the IAP family members to induce downstream kinase activation for protection from apoptosis by CCL25/TECK in the cells. CCL25/TECK selectively activated Livin (Fig. 6A). The phosphorylation of ATF-2 substrate was dose-dependent on expression level of Livin in the system. In contrast, none of c-IAP1, c-IAP2, XIAP, or survivin showed activation. In the system with JNK1 transfection lacking, Livin could not be activated, phosphorylation of ATF-2 substrate was also dose-dependent on expression level of JNK1 (Fig. 6B), suggesting CCL25/TECK activating Livin was JNK1 kinase-dependent. To further elucidate whether the activation of JNK1 was also important for the protective activity of the IAPs against TNF-α-induced apoptosis. All examined kinases (p38, extracellular signal-regulated kinase (ERK2), JNK1, or PI3K) were activated in MOLT4 T cells by CCL25/TECK, but they were inhibited by stimulation with TNF-α (Fig. 7), except for JNK1, which was constantly activated (Fig. 7C), suggesting that TNF-α could not interfere in the interaction of CCR9 and JNK1, which might be important for induction of protection of cells from TNF-α-mediated apoptosis.

To be sure that the results of correlation between Livin activation and CCL25/TECK-induced resistance to TNF-α-mediated apoptosis, we applied short hairpin RNA of Livin (shRNALivin) to knockdown Livin expression and activation in MOLT4 T cells before assay of CCL25/TECK-induced resistance to TNF-α-mediated apoptosis. The results (Fig. 8A) showed that culture with shRNALivin at high concentration completely abolished expression of Livin in MOLT4 T cells at both mRNA and protein levels, whereas low-concentration shRNALivin or DNALivin or vector had no such effect. Only high-concentration shRNALivin significantly blocked the effects of CCL25/TECK on induction of resistance to TNF-α-mediated apoptosis (Fig. 8B and C) and on stabilization of caspase-3 and caspase-8 in MOLT4 T cells (Fig. 8D and E). We observed similar results for shRNALivin in T-ALL and T-CLL CD4⁺ T cells (data not shown). These results in MOLT4 and in T-ALL and T-CLL CD4⁺ T cells confirmed experimentally the observations that CCL25/TECK, via CCR9, activated Livin to induce resistance to TNF-α-mediated apoptosis.

Thus, CCL25/TECK rescued T-ALL and T-CLL CD4⁺ T cells as well as MOLT4 T cells from TNF-α-mediated apoptosis, but double-positive thymocytes did not. CCL25/TECK selectively activated Livin to induce resistance to TNF-α-mediated apoptosis in JNK1 kinase-dependent manner.
DISCUSSION

A majority of the G protein-coupled receptor supergene family has been shown to be capable of activating MAPK, which is an indication of providing proliferative or antiapoptotic signaling. Several chemokines are able to activate MAPK to function as proliferative or antiapoptotic signals (39). For example, CXCL12/SDF-1 is an important cytokine that, acting together with thrombopoietin, enhances the development of megakaryocytic progenitor cells and activates circulating CD34+ cells and platelets (40, 41). CXCL1 and CXCL4 are able to support the survival of endothelial cells and monocytes.
respectively (42, 43). Chemokine receptor signaling may be able to provide antiapoptotic activity to hematopoietic cells in a natural context (44). A solid report shows that CCR9/CCL25 interaction provides a cell survival signal to the receptor-expressing cells (7). However, there are some controversial, even contradictory, reports. For example, CXCR4 has induced programmed cell death of human peripheral CD4\(^+\) T cells, malignant T cells, and CD4/CXCR4 transfectants (45). The interaction between HIV R5 Env and CCR5 activates the Fas pathway and caspase-8, as well as triggering FasL production, ultimately causing CD4\(^+\) T cell death (46). CCR3 expression, induced by interleukin (IL)-2 and IL-4, functions as a death receptor for B cells (24). We have investigated four different types of cells: double-positive thymocytes, T-ALL and T-CLL CD4\(^+\) T cells, and MOLT4 T cells. We have found that, even through all types of cells are CCR9 rich-expressing cells, the responsiveness to CCL25/TECK-mediated protection from apoptosis is quite differential; double-positive thymocytes use CCR9/CCL25 for migration, homing, development, maturation, selection, and cell homeostasis. Meanwhile, malignant cells, particularly T-ALL CD4\(^+\) T cells, take advantages of CCR9/CCL25 for infiltration, resistance to apoptosis, and inappropriate proliferation. To our knowledge, this study is the first report on differential functions of CCR9/CCL25 in distinct types of cells and is the direct evidence of the pathophysiologic activity of T-ALL and T-CLL CD4\(^+\) T cells induced by CCL25/TECK.

A genetic change that leads to blocking apoptosis may allow a cell to acquire additional mutations, survive inappropriately and eventually become malignant. Additionally, a defect in the inherent ability of a cell to undergo apoptosis may account for much of the resistance observed in leukemic cells. Therefore, much effort has gone into understanding how apoptosis is altered in leukemia cells and how it can be modulated to overcome resistance and improve clinical outcomes. Recent reports that CCR9 is selectively and functionally overexpressed on T-ALL and T-CLL CD4\(^+\) T cells (19) prompted us to investigate more closely the additional functions of CCR9 with regard to these malignant cells, which often manifest inappropriate survival and resistance to various clinical therapies. We have found that one antiapoptotic member protein in IAP family, Livin, is selectively expressed at higher levels in the malignant cells, particularly in T-ALL CD4\(^+\) T cells, in comparison with double-positive thymocytes. After stimulation with CCL25/TECK and apoptotic induction with TNF-\(\alpha\), the expression levels of Livin in these
cells are significantly increased (Fig. 2B). With sufficient and direct evidence, we have shown that Livin, but not other IAP members (c-IAP1, c-IAP2, XIAP, and survivin), has been directly activated by CCL25/TECK in JNK1-dependent manner and that, subsequently, T-ALL and T-CLL CD4+ T cells, as well as MOLT4 T cells, inappropriately survive. Originally characterized in a number of melanoma cell lines (14, 15), Livin is a potent antiapoptotic protein and is not detectable in most normal adult tissues. Elevated expression of Livin renders melanoma cells resistant to apoptotic stimuli and potentially contributes to the pathogenesis of this malignancy (47). Our findings, together with those of others, indicate that Livin may be one of the critical cellular factors the increased expression of which confers resistance to apoptotic stimuli, thereby contributing to the pathogenesis and progression of malignant cells, such as melanoma cells and T-ALL and T-CLL CD4+ T cells. The observation interestingly indicates that Livin may be a suitable therapeutic target for gene therapy. Moreover, the results may strengthen the strategic ideal of identifying Livin as antigen linked with immune-mediated tumor destruction (immunotherapy; ref. 17).

PI3K, but not MAPK, is required for CCR9-mediated chemotaxis (7). Costimulation of MOLT4 T cells with CCL25/TECK and CXCL12/SDF-1 significantly blocks CHX-mediated apoptosis, whereas stimulation with only CCL25/TECK only partially blocks Fas-mediated apoptosis. Akt, GSK-3β, FKHR, and MAPK have been involved in cell survival signals in response to an array of death stimuli. Our results showing that CCL25/TECK rescues T-ALL and T-CLL CD4+ T cells, as well as MOLT4 T cells, from TNF-α-mediated apoptosis are largely in agreement with these observations. Of note, we have not been able to show that stimulation of CCR9 with CCL25/TECK can directly activate p38, ERK2, or PI3K in the presence of stimulation with TNF-α (Fig. 7) in our applied experimental system, except JNK1 is constantly activated (Fig. 7C). Taking into account that CCL25/TECK can directly activate JNK1, and subsequently Livin, to induce resistance to TNF-α-mediated apoptosis, we...
suggest that TNF-α can interfere with the activation of p38, ERK2, and PI3K, which is a necessary signal for cell survival. However, CCL25/TECK can bypass the obstacle, and directly activate JNK1. With facilitation of the environment of activated JNK1, Livin can, therefore, be activated to initiate a rescuing mechanism in the cells.

On the basis of our findings, we suggest that there are differential functions of CCR9/CCL25 in distinct types of cells: Double-positive thymocytes use CCR9/CCL25 for migration, homing, development, maturation, selection, and cell homeostasis. Meanwhile, the malignant cells use CCR9/CCL25 for infiltration, resistance to apoptosis, and inappropriate proliferation. The observation indicates that Livin may be a suitable therapeutic target for gene therapy.

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