Degree of CD25 Expression in T-Cell Lymphoma Is Dependent on Tissue Site: Implications for Targeted Therapy

Dan Jones,1 Sherif Ibrahim,3 Kaushali Patel,1 Rajyalakshmi Luthra,1 Madeleine Duvic,2 and L. Jeffrey Medeiros1
Departments of 1Hematopathology and 2Dermatology, University of Texas M. D. Anderson Cancer Center, Houston, Texas, and the 3Department of Pathology, New York University School of Medicine, New York, New York

ABSTRACT

Purpose: Using concurrent tumor samples from different anatomical sites, we compared expression of the therapeutic targets CD25 and CD30 in T-cell lymphoma (TCL).
Experimental Design: We examined levels of CD25 and CD30 by flow cytometry in tumor cells from peripheral blood and lymph node in 13 cutaneous TCL patients and by immunohistochemistry in concurrent lymph node and skin biopsy specimens in 17 additional TCL cases, mostly mycosis fungoides. Tumor cell expression was correlated with patterns of expression in nonneoplastic lymphocytes in 14 reactive lymph node and 10 skin samples showing chronic dermatitis. Expression of CD25 and CD30 in all biopsy samples was compared with that of cutaneous lymphocyte antigen (CLA), a mediator of skin homing.
Results: By flow cytometry, we noted significantly decreased expression of CD25 in lymph node compared with peripheral blood in 8 of 13 TCLs, with no changes in CD30 levels in 4 cases studied. Using immunohistochemistry, CD25 was strongly expressed in epidermotropic tumor cells in 13 of 17 (76%) TCL skin specimens but was decreased in the corresponding lymph node in 12 of these cases. CD30 was expressed at roughly equal intensity in tumor cells from both sites, except in 1 case. CLA showed a similar pattern to CD25, being expressed by tumor cells in 16 of 17 (94%) skin specimens, but was largely absent in tumor cells in the corresponding lymph node in 12 of these patients. In T cells from reactive lymph node biopsy specimens, CD25 was highly expressed only in dermatopathic lymphadenitis associated with transient skin rashes.
Conclusions: We demonstrate in vivo that decreased levels of CD25 expression occur in TCL when it involves lymph node, similar to what is seen with CLA. This demonstrates variation related to anatomical localization has implications for the measurement of surface expression of CD25 and for understanding the response of patients with cutaneous TCL to interleukin 2 receptor-targeted immunotherapy.

INTRODUCTION

Lymphoma cells express a variety of cytokine receptors and signaling molecules that are current or potential targets for immunomodulatory therapy. One such agent is denileukin diftitox/ONTAK (DAB389 IL-2), a recombinant diphtheria toxin-interleukin 2 (IL-2) fusion protein, which targets the IL-2 receptor. This receptor has several isoforms with the high-affinity complex comprised of three subunits, including α chain (CD25), β chain (CD122), and γ chain (CD132). DAB389 IL-2, which preferentially targets lymphocytes bearing the high-affinity IL-2 receptor (1), has been used for treatment of mycosis fungoides (MF)/Sezary syndrome (SS) (2–4) and is in clinical trials for other T-cell and B-cell lymphoma types (5, 6). Selection of suitable patients for therapy often includes pretreatment assessment of CD25 expression in tumor cells or measurement of serum IL-2 receptor levels (7). Antibodies and chimeric ligands targeting the tumor necrosis family receptor CD30 are also under active investigation for lymphoma treatment (8–10). However, large studies comparing expression of either CD25 or CD30 on lymphoma cells at different tissue sites in vivo have not yet been reported.

We compare here the immunophenotype of T-cell tumors, mostly MF/SS, simultaneously sampled at different sites for CD25 and CD30 and compare them to expression of cutaneous lymphocyte antigen (CLA), a labile surface adhesion molecule that mediates skin homing. We show that expression of CD25, as with CLA, is highly variable in most cutaneous T-cell lymphomas (CTCLs), being expressed most intensely by lymphoma cells in the epidermis of skin and peripheral blood (PB), with moderate intensity by tumor cells within the dermis and lymph node sinusoids and lowest intensity by tumor cells in the parenchyma of lymph node. Modulation of CD25 expression in vivo by microenvironmental influences has important consequences for assessment of CD25 expression and in selecting appropriate patients for immunomodulatory therapy.

MATERIALS AND METHODS

Criteria for Diagnosis and Inclusion. All cases were drawn from the hematopathology service at The University of Texas M. D. Anderson Cancer Center (Houston, TX). Thirteen paired PB and lymph node aspirate samples from patients with MF/SS were assessed by flow cytometry, with samples from the two sites taken within 7 days of each other. Three of these patients were untreated, and the rest had received a variety of agents (median of two different therapies). No patients had received denileukin diftitox at time of sample analyzed. In all
cases, the cytomorphology of the tumor at each of the sites was assessed by Giemsa or Pap-stained smears and by H&E-stained paraffin-embedded sections of biopsies and cell-block cytolologic preparations when available. Morphology was graded as small cell/cerebriform, mixed small and large nucleolated forms, or predominantly large cells.

We also studied 17 patients with TCL who had archival paraffin tissue blocks of both skin and lymph node biopsy specimens taken within 30 days of each other. Four patients were untreated; the rest had received a variety of treatments (median of three prior agents). None had received denileukin diftitox at time of biopsy. In 16 patients, the lymph node sampled was draining the area from which the skin biopsy was taken. In the remaining case, the lymph node was obtained from a distant site. All biopsy specimens that showed evidence of histological transformation in the skin biopsy also showed transformation in the corresponding lymph node biopsy specimen. The clonal identity of the tumor, at both sites, was determined using previously described multicolor PCR analysis methods (11). In 12 cases, identical monoclonal T-cell receptor \( \gamma \) rearrangements were identified by PCR analysis in skin and lymph node, in 3 cases, different amplified products were present between the two sites, and in 2 cases, insufficient material was available for comparison.

Diagnoses were low-grade MF/SS in 5 patients, large-cell transformation of MF/SS in 8 patients, human T-cell lymphotropic virus I-positive adult T-cell leukemia/lymphoma (ATLL) in 1 patient, and CTCL unspecified type in 3 patients. A diagnosis of MF required the presence of epidermotropism and compatible clinical findings, with SS diagnosed in those patients with tumor involvement of PB. Transformed MF was diagnosed in cases in which large cells comprised \( \geq 25\% \) of the tumor cellularity, as described previously (12, 13).

For comparison of staining patterns, we studied nonneoplastic lymph nodes that showed different reactive patterns of expansion obtained from 20 patients. These included biopsy specimens showing marked follicular hyperplasia in 4 patients, progressive transformation of germinal centers in 7 patients, follicle lysis in 2 patients, paracortical immunoblastic reaction in 3 patients, and dermatopathic lymphadenitis in 4 patients. The latter diagnosis required the presence of an interfollicular to diffuse lymphohistiocytic proliferation with numerous dendritic cells containing melanin pigment. All dermatopathic lymphadenitis cases occurred in lymph nodes of patients with reactive skin rashes and were negative for monoclonal T-cell receptor \( \gamma \) chain rearrangements by PCR (11). Seven cases of chronic spongiotic dermatitis and 3 cases of psoriasis were also included.

**Flow Cytometric Analysis.** We used a standard T-cell antigen panel to assess PB and lymph node aspirate samples from 10 MF/SS patients, as described previously (14). Two-, three-, or four-color flow cytometric analysis was performed on all samples, following a standard red-cell lysis method for PB, and processed to produce 5-\( \mu \)m sections. Immunostaining was performed with mouse monoclonal antibodies directed against CD3 (CLA-HECA452; Pharmingen, San Diego, CA), CD25 (4C9; Novocastra), and CD30 (BerH2; Dako, Carpinteria, CA), as described previously (12). CD4 (1F6; Novocastra, Peterborough, United Kingdom) and CD7 (BC-272) immunostaining was also done in most cases to aid in identification of tumor cells. Immunostaining for CD1a (235; Novocastra) and S-100 (rabbit antirabbit polyclonal; Dako) was done in dermatopathic lymphadenitis to confirm the identity of dendritic cells. In a subset of cases, the lymphatic endothelium marker, D2-40 (Signet, Dedham, MA), was used to highlight lymphocytes within intranodal lymphatics. Antigen retrieval was performed in a microwave with 10 mM citrate buffer (for CLA) or Dako target retrieval buffer (for CD25 and CD30). Staining was detected using biotin-avidin-peroxidase-conjugated reagents (LSAB + kit; Dako) and diaminobenzidine or 3-amo-nino-9-ethylcarbazole as the chromogenic substrate.

Percentages of immunoreactivity in cytologically identified tumor cells were assessed by counting three \( \times \)40 high-power fields and averaging the results. Staining pattern was correlated with tumor cell localization in lymph node (sinusoidal, subcapsular, interfollicular, clustered, and diffuse) and skin (epidermal and dermal). The Kruskal-Wallis test and Spearman’s rank correlation test were used to correlate expression of markers. Statistical significance was defined as \( \alpha = 0.05 \).

**RESULTS**

**Comparison of MF/SS in PB and Lymph Node**

By flow cytometry, we examined PB and lymph node aspirate samples obtained within 7 days of each other from 13 patients with MF/SS. Eleven of 13 (85\%) of the analyzed MF/SS patients showed \( \geq 5\% \) CD25+ tumor cells in PB (Table 1). In four of these cases, there were reduced numbers of CD25+ tumor cells in the lymph node aspirate, with four cases showing a \( \geq 20\% \) decrease in the number of CD25+ tumor cells. In the four cases with \( \geq 5\% \) CD30+ tumor cells in PB...
similar numbers of CD30+/H11001 tumor cells were also present in lymph node aspirate specimens. Fig. 1 shows a comparison of tumor cells sampled from PB and lymph node within a 24-h period. Tumor cells at both sites had a CD3-dim- and CD26-negative immunophenotype that allowed separation from the (likely) nonneoplastic T cells (Fig. 1, left and middle panels). Nearly all of the tumor cells in PB were uniformly positive for CD25 (Fig. 1, top left panel), whereas tumor cells in a sampled inguinal lymph node were completely negative for CD25 (Fig. 1, bottom left panel). Comparison of a PB smear and the lymph node aspirate smears revealed similarly small to intermediate-sized cerebriform lymphocytes (Fig. 1, right panels). No other immunophenotypic variations were seen between the two populations with the tested antigens (i.e., CD3, CD4, CD5, CD7, CD8, CD19, CD26, CD56/CD16, and T-cell receptor).

### Comparison of TCL Immunophenotype in Skin and Lymph Node

We also studied 17 additional cases of TCL simultaneously involving lymph node and skin, including 8 cases of transformed MF/SS, 5 cases of lower grade MF, 1 case of ATLL, and 3 cases of CTCL, unspecified type. In two of the transformed MF cases, there was a greater percentage of large tumor cells in the lymph node as compared with the skin with a greater percentage of large tumor cells seen in skin in a third case. Otherwise, the morphological spectrum of tumor cells was similar between the two sites. Patients included 10 women and 7 men whose mean age at time of biopsy was 55 years (range, 26–80 years). Lymph node biopsies were done, on average, 15 days from the skin biopsy (range, 0–28 days). Table 2 summarizes the patterns of CLA, CD25, and CD30 immunostaining of tumor cells in skin and lymph node, and Fig. 2 illustrates a representative case.

<table>
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<th>LN % positive tumor (tumor cell size)</th>
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PB, peripheral blood; LN, lymph node.

### Table 1 Comparison of CD25 expression levels in Sezary syndrome tumor cells from simultaneously sampled PB and lymph sites

*Fig. 1* Comparison of CD25 expression in mycosis fungoides/Sezary syndrome cells sampled from lymph node and peripheral blood (PB). *Upper panels*, analysis of PB from a patient with mycosis fungoides/Sezary syndrome reveals a discrete population of CD3-dim/CD25+/H11001 tumor cells (boxed) that can be distinguished from variable CD25 positivity of nonneoplastic T cells. This CD3-dim population is also uniformly CD26-negative consistent with a neoplastic clone. PB smear demonstrates a prominent enlarged cerebriform tumor population. *Lower panels*, analysis of a fine needle aspirate from an enlarged lymph node done the same day revealed a uniform population of CD3-dim tumor cells that were completely negative for CD25. As in PB, this CD3-dim tumor cell population was also uniformly negative for CD26. Examination of the Pap-stained smears from lymph node revealed a homogeneous population of cerebriform tumor cells identical to those in the PB. This case is sample no. 1 in Table 1.
CD25 Expression

CD25 was expressed in ≥5% of cytologically atypical lymphocytes in skin in 13 of 17 (76%) cases, with a median of 20% CD25+ tumor cells across all cases. In seven of these cases, CD25 was more highly expressed in the intraepidermal tumor component than in the tumor cells in the dermis. In 12 of these CD25+ tumors (92%), the number of CD25+ tumor cells was decreased in lymph node as compared with skin (Fig. 2, B and E). There was often a staining intensity gradient in lymph node with the strongest CD25+ staining located within the sinusoidal and subcapsular components. Using the antibody D2–40 to highlight intranodal lymphatics, we noted that in four cases (2 transformed MF, 1 ATLL, and 1 CTCL), the only strongly CD25+ tumor cells were present in lymph node sinusoids (Fig. 2H and data not shown). In another four cases, the CD25+ tumor cells were located primarily in the subcapsular region in association with CLA+/S100+ dendritic cells. In 4 of 17 cases (24%), CD25 was expressed by <5% of tumor cells in skin. In three of these cases, tumor cells in lymph node were also negative for CD25. However, in one case, intrasinusoidal tumor cells were strongly CD25+.

CD30 Expression

CD30 was expressed in >5% of tumor cells in skin of 5 of 17 (29%) cases (range, 5–50% of CD30+ tumor cells; median, 15%). In 12 (71%) skin cases, CD30 was not expressed or was positive in only rare tumor cells. CD30 expression was similar between skin and lymph node samples, with the number of positive cells within 5% of each other in 16 of 17 cases (94%). The one exception was a transformed MF/SS case, which showed 50% CD30+ tumor cells in skin and only rare CD30+ cells in lymph node.

CLA Expression

Tumor cells in skin strongly expressed CLA in 9 cases, variably expressed CLA in 7 cases (Fig. 2, C and I), and were completely negative for CLA in a single transformed MF case. CLA was more strongly expressed in low-grade MF and expressed at lower levels in transformed MF. Similar to the results with CD25, CLA staining of tumor cells in lymph node was decreased in 12 of 16 cases as compared with staining levels in skin. As with CD25, the strongest CLA+ tumor cells were frequently in the sinusoids or subcapsular areas of lymph node (Fig. 2F and data not shown). In cases with numerous CLA+ dendritic cells, it was often difficult to distinguish their strong positivity from the weak positivity of adjacent tumor cells.

By pairwise rankings, expression of CLA, CD25, and CD30 were not significantly correlated. There was, however, a statistically significant association between those cases with the largest decreases in CLA staining in lymph node as compared with skin and those tumors that had the most variable CD25 expression (r = 0.61). CLA expression was also inversely correlated with CD30 staining levels (r = −0.40). Besides the association of CD30 and decreased CLA expression with transformed MF, there was no significant association of CD25 or CLA modulation with specific diagnostic categories, although the limited numbers of cases in some categories precluded meaningful subset analysis.

CD25 and CD30 Expression in Nonneoplastic Lymphocytes in Skin and Lymph Node

Nonneoplastic Lymph Nodes. We correlated the levels of CD25 and CD30 expression in T cells in nonneoplastic tissues. In cases showing follicular hyperplasia or immunoblastic paracortical expansion, CD25 was highly expressed only in scattered interfollicular clusters of histiocytes and lymphocytes and in rare germinal center cells, overall comprising much less than 1% of lymphocytes (Fig. 3A). In cases with progressively transformed germinal centers, focal increases in CD25+ cells were present in association with transformed follicles, marking up to 5% of lymphocytes in these areas (data not shown). In four cases of dermatopathic lymphadenitis, there was marked expression of CD25 by interfollicular T cells (up to 30% of lymphocytes) and weaker expression by dendritic cells at various stages of maturation (Fig. 3B). These cases all occurred in lymph nodes of patients’ draining transient severe skin rashes and, in contrast to lymphomatous involvement, showed expansion of only the...
interfollicular nodal regions with no encroachment on the follicular compartment (Fig. 3C). The density of CD25+ T cells in dermatopathic lymphadenitis was related to the number of CD1a+/S100+ dendritic cells, with cases showing only focal melanin deposition having the lowest numbers of CD25+ lymphocytes (Fig. 3D).

CD30 in all nonneoplastic lymph nodes was expressed in a small number (less than 1%) of intrafollicular lymphocytes, most with immunoblastic morphology. CD30 was also weakly expressed in some plasma cells. In all nonneoplastic lymph nodes, CLA was expressed in less than 1% of interfollicular lymphocytes, CLA was highly expressed in high endothelial venules as well as a small subset of migrating dendritic cells and clusters of plasmacytoid monocytes, located primarily around HEV (not shown). In 4 lymph nodes with benign dermatopathic lymphadenitis, CLA was variably and weakly expressed in numerous dendritic cells, particularly in subcapsular areas.

**Skin Biopsies with Inflammatory Infiltrates.** We studied seven skin biopsy specimens from patients with chronic dermatitis. CD25 positivity in lymphocytes ranged from 5 to 20%, with the scant lymphocytes in the epidermis more strongly positive for CD25 than the dermal lymphocytes. CD25 was highly expressed in 30–50% of the lymphocytes in three psoriasis biopsy specimens in both dermis and epidermis. In both types of lesions, CD25 expression was characteristic of larger, activated-appearing lymphocytes (data not shown). CD30 expression was not detected in lymphocytes in any of the biopsy specimens. In all chronic dermatitis and psoriasis samples, the majority of infiltrating lymphocytes in the dermis and epidermis expressed CLA (data not shown).

**DISCUSSION**

We demonstrate here that IL-2 receptor-α/CD25 is expressed in TCL cells at varying levels in simultaneous samples of different tissue sites. Among the 13 CD25+ TCLs in skin studied by immunohistochemistry, there was decreased expression by the tumor cells in lymph nodes in 12 (92%). In 13 additional patients with TCL studied by flow cytometry, 8 (61%) had decreased CD25 expression in the tumor cells from lymph node samples, as compared with those in PB. We
observed lower expression of CD25 in tumor cells from lymph node samples even in a human T-cell lymphotropic virus I-positive ATLL patient who had uniformly strongly CD25+ tumor cells in skin. Among cases of reactive lymphadenitis, high CD25 expression by T cells was associated with reactive dermatopathic lymphadenitis, occurring in lymph nodes that are draining sites of transient skin rashes, and suggesting a transient pattern of CD25 expression by lymphocytes recently entering the lymph node.

The pattern of immunostaining observed for CLA was similar to CD25. In the 16 cases of TCL with CLA+ tumor cells in skin, 12 cases (75%) showed decreased expression of CLA in the lymph node tumor cells. This could not be readily attributed to morphological changes because the cytomorphology of lymph node tumor cells was similar in all but three cases. This pattern of CLA staining in tumor cells was paralleled by the observed pattern of CLA expression in lymph node-dendritic cells. These cells were frequently strongly CLA+ in the sinuses and in areas directly adjacent but were much more weakly positive or negative in deeper paracortical areas. We observed a reproducible microanatomical pattern of CD25 and CLA expression by tumor cells within lymph node, namely high in sinusoidal and subcapsular locations with loss in the deeper paracortex. This gradient of decreased CD25 and CLA expression in lymph node suggests both proteins can be modulated on tumor lymphocytes during their passage through the lymph node, although the presence of multiple immunophenotypically stable or genetically distinct tumor populations cannot be completely excluded.

In nonneoplastic T cells, regulation of the CD25/IL-2 receptor-γ gene is complex, with established roles for CD25 in early thymic T-cell maturation and as an activation marker in mature T cells. CD25 is an essential component of the three-chain high-affinity IL-2 receptor; however, IL-2 signaling can still occur through the medium-affinity CD122/CD132 complex (16). We show here that wide variations in the levels of CD25 occur in different benign lymph node conditions and inflammatory dermatoses (Fig. 3). Recently, there has been great emphasis on the role of bright CD25+ CD4+ T cells as mediators of the regulatory/suppressor T-cell response, with CD25 loss leading to overexpansion of normal T-cell populations (16, 17). Our findings suggest that bright CD25+ CD4+ tumor cells isolated from PB or seen in the lymphatic sinuses may have the capacity to become negative for CD25 once they enter the lymph node parenchyma. This suggests that CD25 levels on normal T cells may also be rapidly regulated because they appear to be on CTCL cells and might not be a stable feature of regulatory T cells. Indeed, bright CD25+ T cells can be isolated in great numbers from lymph nodes that are draining sites of inflammation (18, 19) but were seen in much lower numbers in most of the reactive lymph node conditions analyzed here. Strong CD25 expression on CD4+ T cells within the lymph node itself was common only in dermatopathic lymphadenitis.

We demonstrate here, for the first time, differential expression of CD25 in vivo between TCL tumor cells in skin, lymph node, and PB. This differential expression occurred even in a case of human T-cell lymphotropic virus I-positive ATLL, which is commonly regarded as uniformly, strongly positive for CD25 (20). This is of interest because CD25 is currently a therapeutic target in T-cell tumors, using agents such as DAB389 IL-2 (21). Our results demonstrate that the expression level of CD25 by tumor cells measured as a possible indicator of therapeutic response will depend on the site sampled. Thus, overall systemic measures of IL-2 receptor levels, such as by soluble serum assay, may give a more accurate median expression level and better predictor of therapeutic response (7). Our results also suggest that drugs targeting CD25 may be more effective in treating skin disease than tumors with predominantly lymph node involvement. Previous studies measuring IL-2 receptor levels in serum have also suggested lower systemic levels of IL-2 receptor in patients with nodal disease (22). However, given the multiple topical and systemic treatments that most of the patients studied here had undergone, it is possible that...
modulations in CD25 expression may be affected by certain treatments more than others.

We also demonstrated parallel patterns of expression of CD25 and CLA in most CTCL cases. CLA is expressed by the vast majority of skin-homing T cells as well as by a small subset of circulating benign lymphocytes, especially in patients with chronic dermatitis (23–26). CLA is a modified selectin ligand that mediates binding of a subset of circulating lymphocytes to dermal endothelium (27, 28). We have previously demonstrated that CLA is highly expressed in tumor cells in skin at all stages of CTCL (12). CLA can also be expressed in MF/SS in PB, but analysis of sorted cell populations has demonstrated that circulating tumor cells are present in both the CLA+ and CLA-negative T-cell populations (29). This suggests that CTCL may shed or rapidly modulate CLA once outside of the skin microenvironment as has been demonstrated for nonneoplastic T cells (30, 31).

The differential expression of CLA and CD25 is contrasted with the relatively uniform pattern of CD30 expression by tumor cells at different sites observed here. Only 1 of 17 cases showed substantial differences in the expression of CD30 between lymph node and skin. This suggests that induction of CD30 expression may be a more stable, likely transformation-related property of the tumor cells, rather than being more transiently influenced by tissue microenvironment. We have previously observed that CD30 up-regulation in transformation of MF is associated with many other phenotypic changes, including expression of cytotoxic proteins (e.g., perforin) and chemokine receptors (e.g., loss of CXCR3) that would be consistent with a stable change in tumor phenotype (12).

However, the majority of T-cell tumors do show tissue-specific variations in CD25 and CLA levels in a manner resembling patterns of antigen modulation in nonneoplastic T cells. Therefore, it may be useful to define those markers used for targeted therapies as being either relatively labile (as with CD25) or as being relatively stably expressed by tumors (such as CD30). Because the pattern of antigen expression in normal cells may not always directly mimic the pattern observed in tumors, microenvironmental influences need to be directly confirmed on involved tumor samples from different sites. For these reasons, we believe that for lymphoid tumors, in vivo monitoring of the microenvironmental regulation of a therapeutic marker is an important component of understanding the consequences of targeting that antigen.

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