

Brief report

Gene expression profiling of peripheral T-cell lymphoma including $\gamma\delta$ T-cell lymphoma

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The gene expression profile of peripheral $\gamma\delta$ T-cell lymphoma ($\gamma\delta$ TCL) has not been investigated. Using oligonucleotide microarrays, we analyzed total RNA from 7 patients with $\gamma\delta$ TCL (4 hepatosplenic, 1 cutaneous, 1 intestinal, and 1 thyroidal) and 27 patients with $\alpha\beta$ TCL (11 peripheral TCL-unspecified, 15 angioimmunoblastic TCL, and 1 hepatosplenic). Unsupervised microarray analyses classified all hepato-

splenic $\gamma\delta$ TCLs into a single cluster, whereas other $\gamma\delta$ TCLs were scattered within the $\alpha\beta$ TCL distribution. We identified a T-cell receptor signature gene set, which accurately classified $\gamma\delta$ TCL and $\alpha\beta$ TCL. A classifier based on gene expression under supervised analysis correctly identified $\gamma\delta$ TCL. One case of hepatosplenic $\alpha\beta$ TCL was placed in the $\gamma\delta$ TCL grouping. $\gamma\delta$ TCL signature genes

included genes encoding killer cell immunoglobulin-like receptors and killer cell lectin-like receptors. Our results indicate that hepatosplenic $\gamma\delta$ TCL is a distinct form of peripheral TCL and suggest that nonhepatosplenic $\gamma\delta$ TCLs are heterogeneous in gene expression. (Blood. 2009;113:1071-1074)

Introduction

T cells expressing the $\gamma\delta$ T-cell receptor (TCR) heterodimer comprise only a small fraction of the peripheral blood T-cell population and differ from those expressing the $\alpha\beta$ TCR in terms of development, tissue distribution, and function.^{1,2} Mature T-cell lymphomas (TCLs) with the $\gamma\delta$ T-cell immunophenotype can be divided into hepatosplenic $\gamma\delta$ TCL³ and nonhepatosplenic $\gamma\delta$ TCL.⁴ The third World Health Organization (WHO) classification system describes hepatosplenic $\gamma\delta$ TCLs and hepatosplenic $\alpha\beta$ TCLs as a single disease entity (hepatosplenic TCL) as they exhibit nearly identical clinicopathologic and cytogenetic features.⁴⁻⁶

In contrast, nonhepatosplenic $\gamma\delta$ TCL occurs in only a limited number of anatomic sites, including cutaneous, nasopharyngeal, gastrointestinal, pulmonary, and thyroidal regions.⁷⁻¹⁰ This disease has also been called mucocutaneous $\gamma\delta$ TCL because the majority of patients show some involvement of mucocutaneous sites. Among nonhepatosplenic $\gamma\delta$ TCLs, the cutaneous form is most common and overlaps with subcutaneous panniculitis-like TCL.^{11,12} Whereas primary cutaneous $\gamma\delta$ TCL is categorized as a single disease entity in the new WHO scheme,¹³ other nonhepatosplenic $\gamma\delta$ TCLs remains an enigma.

$\gamma\delta$ TCLs are rare lymphoid malignancies and are difficult to diagnose, resulting from the lack of available monoclonal antibodies against $\gamma\delta$ TCR for use with paraffin-embedded tissue. Several studies have elucidated the gene expression profile of peripheral TCLs (PTCLs)¹⁴⁻¹⁷ but did not evaluate $\gamma\delta$ TCL. In our current study, we performed gene expression profiling in 34 PTCLs, including 7 cases of $\gamma\delta$ TCL.

Methods

Patients/samples

Our present study assessed 34 cases of PTCL, including 11 PTCL-unspecified with $\alpha\beta$ T-cell immunophenotype, 15 angioimmunoblastic TCLs, 1 hepatosplenic $\alpha\beta$ TCL, 4 hepatosplenic $\gamma\delta$ TCLs, 1 cutaneous $\gamma\delta$ TCL, 1 intestinal $\gamma\delta$ TCL, and 1 thyroidal $\gamma\delta$ TCL. All specimens were collected between 1987 and 2002 at Mie University Hospital and diagnosed according to the third WHO classification.⁶ Tumor cell expression of cell-surface antigens and TCR heterodimer ($\alpha\beta$ or $\gamma\delta$) was confirmed by immunohistochemistry using frozen sections as described previously.⁹ DNA microarray studies using specimens from patients with hematopoietic malignancies were approved by the Institutional Review Committee of Mie University Graduate School of Medicine. Informed consent was obtained from these patients in accordance with the Declaration of Helsinki. The clinicopathologic features of 6 of 7 cases of $\gamma\delta$ TCL have been reported previously.^{8,9} The single patient we examined with thyroidal $\gamma\delta$ TCL remains alive with no evidence of disease 13 years after diagnosis. Clinical data for all cases examined are presented in Table S1 (available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Gene expression profiling and analysis

Gene expression profiles were generated and analyzed as previously reported.¹⁸ We used the Agilent 44K human oligonucleotide microarray (Agilent 4112F; Agilent Technologies, Palo Alto, CA), and raw gene expression data are available at the Gene Expression Omnibus (accession number GSE11946).¹⁹ For gene expression profiling supervised by TCR heterodimer phenotype, we selected genes with an average differential expression level of more than 3.0-fold and used a one-sample *t* test with a

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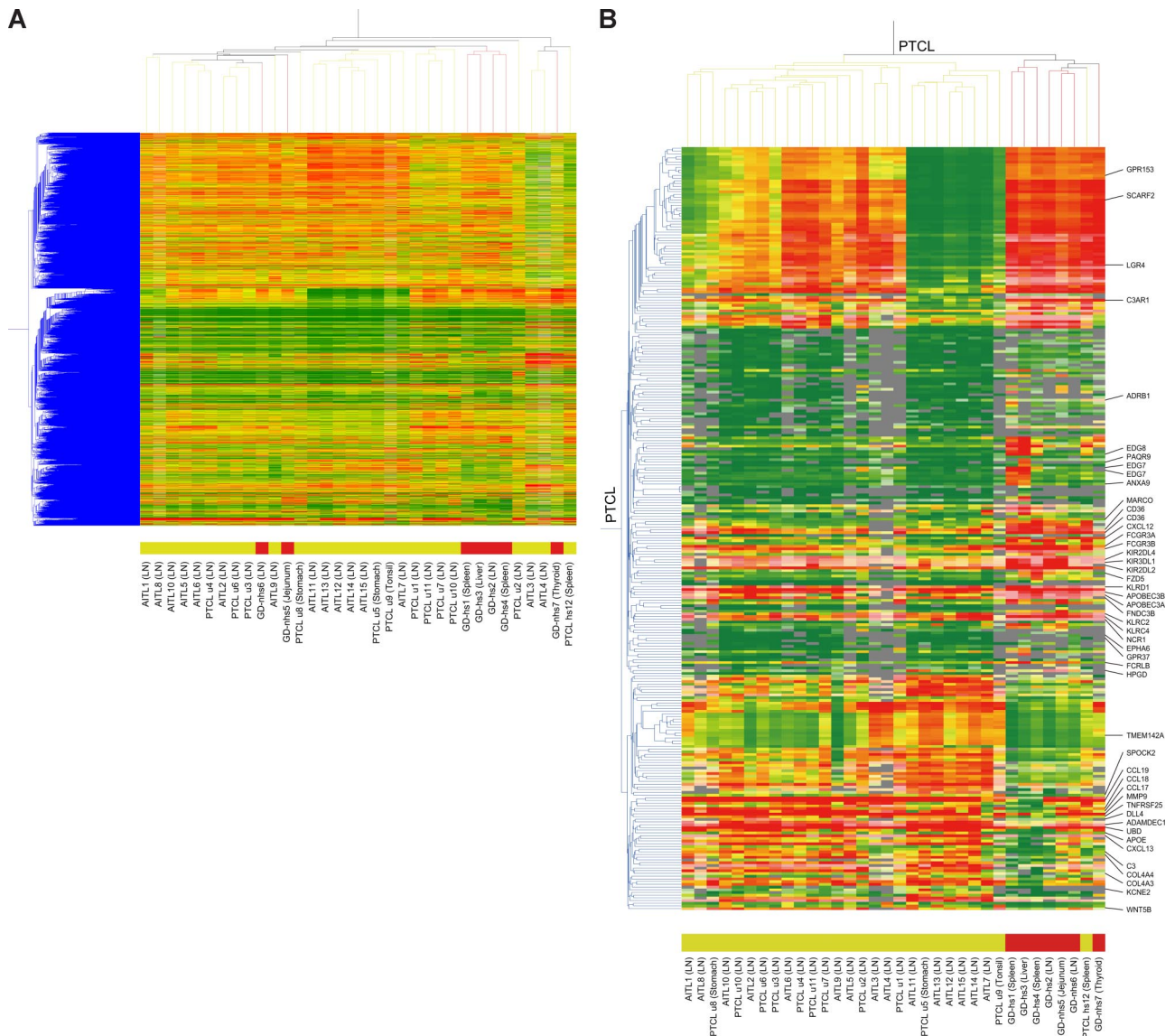


Figure 1. Hierarchical clustering of gene expression data. (A) Hierarchical clustering of 34 cases of PTCL using unsupervised analysis. Color blocks indicate the characteristics of the PTCLs; red blocks, $\gamma\delta$ TCL cases; amber blocks, $\alpha\beta$ TCL cases. The anatomic site of each specimen is shown in parentheses. AITL indicates angioimmunoblastic T-cell lymphoma; GD-hs, hepatosplenic $\gamma\delta$ TCL; GD-nhs, nonhepatosplenic $\gamma\delta$ TCL; LN, lymph node; PTCL hs, hepatosplenic $\alpha\beta$ TCL; PTCL u, PTCL-unsupervised. Four cases of hepatosplenic $\gamma\delta$ TCL (GD-hs1-4) were classified into a single cluster. Nonhepatosplenic $\gamma\delta$ TCLs (GD-nhs5, intestinal; GD-nhs6, cutaneous; GD-nhs7, thyroidal) were scattered within the $\alpha\beta$ TCL distribution. (B) Hierarchical clustering of 34 cases of PTCL-based TCR signature gene expression. Genes also listed in Table 1 are shown on the right. $\gamma\delta$ TCL cases were correctly identified by the gene set, although one case of hepatosplenic $\alpha\beta$ TCL (PTCL hs12) was grouped with the $\gamma\delta$ TCLs.

P value cutoff of .005. Hierarchical clustering of genes was performed using the Pearson correlation, and hierarchical clustering of cases was obtained using an average linkage algorithm.

We chose WebGestalt using Gene Ontology (GO) hierarchies^{20,21} for categorization of functional gene groups and the Kyoto Encyclopedia of Genes and Genomes (KEGG)^{22,23} pathway for identification of signaling pathways. In both analyses, we performed a separate hypergeometric test with a *P* value cutoff of .001.

Results and discussion

Gene expression profiling is a powerful tool for establishing a molecular basis for lymphoma subtypes.²⁴ Unsupervised analysis of our PTCL cases classified hepatosplenic $\gamma\delta$ TCL as a single cluster, whereas other $\gamma\delta$ TCLs were scattered within the $\alpha\beta$ TCL distribution (Figure 1A). Since the 1980s, cumulative clinicopatho-

logic evidence has demonstrated that hepatosplenic $\gamma\delta$ TCL is a distinct clinicopathologic disease entity. Our gene expression results also confirm that hepatosplenic $\gamma\delta$ TCL is distinct from other PTCLs. Conversely, nonhepatosplenic $\gamma\delta$ TCLs appeared to be more heterogeneous. The possibility that tissue differences were responsible for these data was excluded by our observation that hepatosplenic $\gamma\delta$ TCL was classified as a single cluster, irrespective of the specimen examined (Figure 1). Angioimmunoblastic T-cell lymphoma cases were not classified as a single cluster, consistent with prior gene expression studies.¹⁴⁻¹⁷

We next compared the gene expression profiles of $\gamma\delta$ TCL and $\alpha\beta$ TCL using 291 genes showing a greater than 3.0-fold average expression difference, which we designated the TCR signature gene set (Table S2). Of note, a classifier from supervised analysis based on gene expression identified $\gamma\delta$ TCL and hepatosplenic $\alpha\beta$ TCL (Figure 1B). This finding is supported by the notion that $\gamma\delta$

Table 1. GO category analysis and KEGG pathway analysis in the TCR signature gene set

Analytical tool	Gene no.	Gene	P
GO category			
$\gamma\delta$ TCL			
Cellular defense response	5	<i>KIR2DL4, NCR1, C3AR1, KLRC2, KLRC4</i>	1.17×10^{-4}
Signal transduction activity	29	<i>KLRD1, ANXA9, FNDC3B, GPR37, KIR2DL4, MARCO, EDG7, NCR1, MS4A5, HPGD, FCGR3A, LGR4, FCRLB, C3AR1, CXCL12, RTN4R, PAQR9, KLRC2, GPR153, FCGR3B, KIR2DL2, EDG8, ADRB1, CD36, FZD5, SCARF2, KIR3DL1, EPHA6, KLRC4</i>	5.09×10^{-6}
Receptor activity	28	<i>GPR37, KIR2DL4, ANXA9, KLRD1, FNDC3B, EDG7, HPGD, MARCO, LGR4, MS4A5, FCGR3A, NCR1, C3AR1, FCRLB, KLRC2, PAQR9, RTN4R, GPR153, EDG8, FCGR3B, KIR2DL2, ADRB1, FZD5, CD36, SCARF2, KIR3DL1, EPHA6, KLRC4</i>	7.10×10^{-8}
Transmembrane receptor activity	16	<i>ANXA9, GPR37, KIR2DL4, KLRD1, LGR4, HPGD, MARCO, EDG7, C3AR1, KLRC2, EDG8, GPR153, ADRB1, FZD5, EPHA6, KIR3DL1</i>	4.46×10^{-4}
IgG binding	2	<i>FCGR3A, FCGR3B</i>	3.07×10^{-4}
$\alpha\beta$ TCL			
Organismal physiologic process	14	<i>UBD, CXCL13, COL4A4, CCL18, KCNE2, CCL17, C3, TMEM142A, DLL4, APOE, COL4A3, TNFRSF25, MMP9, CCL19</i>	3.24×10^{-4}
Regulation of organismal physiologic process	4	<i>COL4A4, KCNE2, C3, APOE</i>	5.87×10^{-4}
Circulation	4	<i>KCNE2, DLL4, COL4A3, APOE</i>	3.14×10^{-4}
Regulation of neurophysiologic process	2	<i>COL4A4, APOE</i>	7.55×10^{-4}
Regulation of transmission of nerve impulse	2	<i>COL4A4, APOE</i>	7.55×10^{-4}
Regulation of synapse structure and function	2	<i>COL4A4, APOE</i>	8.69×10^{-4}
Regulation of synaptic transmission	2	<i>COL4A4, APOE</i>	7.55×10^{-4}
Inflammatory response	5	<i>CXCL13, CCL18, CCL17, C3, CCL19</i>	6.05×10^{-4}
Behavior	5	<i>CCL18, CXCL13, CCL17, APOE, CCL19</i>	2.47×10^{-4}
Locomotor behavior	4	<i>CXCL13, CCL18, CCL17, CCL19</i>	4.92×10^{-4}
Taxis	4	<i>CXCL13, CCL18, CCL17, CCL19</i>	4.22×10^{-4}
Chemotaxis	4	<i>CXCL13, CCL18, CCL17, CCL19</i>	4.22×10^{-4}
Receptor binding	9	<i>ADAMDEC1, CCL18, CXCL13, CCL17, C3, DLL4, APOE, COL4A3, CCL19</i>	2.76×10^{-5}
G-protein-coupled receptor binding	4	<i>CCL18, CXCL13, CCL17, CCL19</i>	1.57×10^{-5}
Chemokine receptor binding	4	<i>CCL18, CXCL13, CCL17, CCL19</i>	6.97×10^{-6}
Chemokine activity	4	<i>CCL18, CXCL13, CCL17, CCL19</i>	6.37×10^{-6}
Extracellular region	11	<i>CCL18, COL4A4, CXCL13, CCL17, C3, WNT5B, MMP9, COL4A3, APOE, SPOCK2, CCL19</i>	7.97×10^{-5}
Extracellular region part	9	<i>CCL18, COL4A4, CXCL13, CCL17, SPOCK2, APOE, COL4A3, MMP9, CCL19</i>	7.33×10^{-5}
Sheet-forming collagen	2	<i>COL4A4, COL4A3</i>	1.70×10^{-4}
Collagen type IV	2	<i>COL4A4, COL4A3</i>	1.21×10^{-4}
KEGG pathway			
$\gamma\delta$ TCL			
Natural killer cell-mediated cytotoxicity	5	<i>FCGR3A, KIR3DL1, KLRC2, KLRD1, NCR1</i>	8.10×10^{-4}
Antigen processing and presentation	4	<i>KIR3DL1, KLRC2, KLRD1, KLRC4</i>	7.53×10^{-4}
Atrazine degradation	2	<i>APOBEC3A, APOBEC3B</i>	4.42×10^{-4}
$\alpha\beta$ TCL			
Cytokine-cytokine receptor interaction	5	<i>CXCL13, CCL17, CCL18, CCL19, TNFRSF25</i>	2.65×10^{-4}

T cells partially share a cytotoxic immunophenotype with cytotoxic $\alpha\beta$ T cells.^{1,2} Among 30 patients for whom survival data were available, the prognosis for 8 cases with a $\gamma\delta$ TCL gene profile (7 $\gamma\delta$ TCLs and 1 hepatosplenic $\alpha\beta$ TCL) was not significantly poorer than that of 22 patients with an $\alpha\beta$ TCL gene profile ($P = .152$; Figure S1). The unusual case of thyroidal $\gamma\delta$ TCL in the $\gamma\delta$ TCL gene profile group may affect the result because the P value was .009 when we excluded this patient from the survival analysis (data not shown). Future analyses will probably reveal the relationship between our TCR signature gene set and prognostic indicators.

In $\gamma\delta$ TCL, genes of natural killer (NK) cell-associated molecules, such as killer cell immunoglobulin (Ig)-like receptor (KIR) genes (*KIR3DL1*, *KIR2DL4*, and *KIR2DL2*), and killer cell lectin-like receptors (*KLRC4*, *KLRD1*, and *KLRC2*) were found to be overexpressed (Figure 1; Table S2). These NK receptors are expressed by a subset of NK cells, $\gamma\delta$ T cells, and CD8⁺ $\alpha\beta$ T cells.²⁵ *KIR3DL1* and *KIR2DL2* exhibit inhibitory functions, and *KIR2DL4* has potentially both inhibitory and activating roles.²⁵

KIR3DL1, *KIR2DL2*, and *KLRD1* are reported to be expressed in some cases of hepatosplenic $\gamma\delta$ TCL.^{26,27} Although *KLRC4*, a top 10 feature gene that characterizes $\gamma\delta$ TCL and its protein, NK2G2F, is expressed in human NK cells,²⁸ its expression in normal $\gamma\delta$ T cells has not been determined. CD16 is also frequently expressed in cases of hepatosplenic $\gamma\delta$ TCL,^{4,27} and its genes (*FCGR3B* and *FCGR3A*) were among the $\gamma\delta$ TCL signature genes identified in this study.

To search for functionally important genes overexpressed in $\gamma\delta$ TCL, we performed GO and pathway analysis using 139 of 204 and 53 of 87 known genes in the $\gamma\delta$ TCL and $\alpha\beta$ TCL groups, respectively. By WebGestalt, 5 and 20 GO categories were enriched in $\gamma\delta$ TCL and $\alpha\beta$ TCL, respectively (Table 1). The enriched GO categories in $\gamma\delta$ TCL were cellular defense response, signal transduction activity, receptor activity, transmembrane receptor activity, and IgG binding. Three $\gamma\delta$ TCL pathways and 1 $\alpha\beta$ TCL pathway were found to be altered in KEGG-signaling analyses (Table 1). No $\gamma\delta$ TCL and $\alpha\beta$ TCL signature genes were

shared in a GO category or KEGG pathway, indicating different functional profiles between $\gamma\delta$ TCL and $\alpha\beta$ TCL. Four of the 5 $\gamma\delta$ TCL-enriched GO categories and 2 of the 3 KEGG-signaling pathways altered in $\gamma\delta$ TCL contained genes encoding KIRs and killer cell lectin-like receptors, a finding that suggests that the expression of these genes may be important for the differential diagnosis of $\gamma\delta$ TCL and $\alpha\beta$ TCL.

In conclusion, our current gene expression data confirm that hepatosplenic $\gamma\delta$ TCL is a distinct lymphoma entity in PTCLs and reveal differences in the gene expression profiles of $\alpha\beta$ TCL and $\gamma\delta$ TCL. Further investigations of our newly identified TCR signature genes are warranted to identify novel therapeutic targets and facilitate the diagnosis of $\gamma\delta$ TCL.

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Authorship

Contribution: K.M. and M. Yamaguchi designed and performed the study, collected data and samples, interpreted data, and wrote the paper; H.I. and S.T. performed the study and collected samples; M. Yuda and H.S. contributed analytical tools and supervised the research; K.N. collected samples and wrote the paper; and T.K. and N.K. supervised the research and wrote the paper.

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References

- Hayday AC. $\gamma\delta$ cells: a right time and a right place for a conserved third way of protection. *Annu Rev Immunol*. 2000;18:975-1026.
- Carding SR, Egan PJ. $\gamma\delta$ T cells: functional plasticity and heterogeneity. *Nat Rev Immunol*. 2002;2:336-345.
- Farcet JP, Gaulard P, Marolleau JP, et al. Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor $\gamma\delta$. *Blood*. 1990;75:2213-2219.
- Vega F, Medeiros LJ, Gaulard P. Hepatosplenic and other $\gamma\delta$ T-cell lymphomas. *Am J Clin Pathol*. 2007;127:869-880.
- Macon WR, Levy NB, Kurtin PJ, et al. Hepatosplenic $\alpha\beta$ T-cell lymphomas: a report of 14 cases and comparison with hepatosplenic $\gamma\delta$ T-cell lymphomas. *Am J Surg Pathol*. 2001;25:285-296.
- Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer; 2001.
- Arnulf B, Copie-Bergman C, Delfau-Larue MH, et al. Nonhepatosplenic $\gamma\delta$ T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. *Blood*. 1998;91:1723-1731.
- Yamaguchi M, Ohno T, Kita K. $\gamma\delta$ T-cell lymphoma of the thyroid gland. *N Engl J Med*. 1997;336:1391-1392.
- Yamaguchi M, Ohno T, Nakamine H, et al. $\gamma\delta$ T-cell lymphoma: a clinicopathologic study of 6 cases including extrahepatosplenic type. *Int J Hematol*. 1999;69:186-195.
- Jaffe ES. Pathobiology of peripheral T-cell lymphomas. *Hematology*. 2006;317-322.
- Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood*. 2003;101:3407-3412.
- Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood*. 2008;111:838-845.
- Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer; 2008.
- Ballester B, Ramuz O, Gisselbrecht C, et al. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. *Oncogene*. 2006;25:1560-1570.
- Cuadros M, Dave SS, Jaffe ES, et al. Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. *J Clin Oncol*. 2007;25:3321-3329.
- de Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (T_{FH}) cells. *Blood*. 2007;109:4952-4963.
- Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. *J Clin Invest*. 2007;117:823-834.
- Miyazaki K, Yamaguchi M, Suguro M, et al. Gene expression profiling of diffuse large B-cell lymphoma supervised by CD21 expression. *Br J Haematol*. 2008;142:562-570.
- National Center for Biotechnology Information. GEO: Gene Expression Omnibus. <http://www.ncbi.nlm.nih.gov/geo/>. Accessed July 1, 2008.
- Zhang B, Kirov S, Snoddy J. WebGestalt: an integrated system for exploring gene sets in various biological contexts. *Nucleic Acids Res*. 2005;33:W741-W748.
- Vanderbilt University. WebGestalt. <http://bioinfo.vanderbilt.edu/webgestalt/>. Accessed May 2, 2008.
- Kanehisa M, Goto S. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. 2000;28:27-30.
- Kanehisa Laboratories. KEGG: Kyoto Encyclopedia of Genes and Genomes. <http://www.genome.ad.jp/kegg/>. Accessed May 2, 2008.
- Staudt LM, Dave S. The biology of human lymphoid malignancies revealed by gene expression profiling. *Adv Immunol*. 2005;87:163-208.
- Lanier LL. NK cell recognition. *Annu Rev Immunol*. 2005;23:225-274.
- Haedicke W, Ho FC, Chott A, et al. Expression of CD94/NKG2A and killer immunoglobulin-like receptors in NK cells and a subset of extranodal cytotoxic T-cell lymphomas. *Blood*. 2000;95:3628-3630.
- Morice WG, Macon WR, Dogan A, Hanson CA, Kurtin PJ. NK-cell-associated receptor expression in hepatosplenic T-cell lymphoma, insights into pathogenesis. *Leukemia*. 2006;20:883-886.
- Kim DK, Kabat J, Borrego F, Sanni TB, You CH, Coligan JE. Human NKG2F is expressed and can associate with DAP12. *Mol Immunol*. 2004;41:53-62.