

# Hepatosplenic and Subcutaneous Panniculitis-Like $\gamma/\delta$ T Cell Lymphomas Are Derived from Different V $\delta$ Subsets of $\gamma/\delta$ T Lymphocytes

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Gamma/delta T cell lymphomas ( $\gamma/\delta$  TCL) represent rare, often aggressive types of T cell malignancy that are clinically and pathologically diverse. Most  $\gamma/\delta$  TCL occur as a hepatosplenic or subcutaneous type. To date, analysis of the T cell receptor  $\delta$  (TCR $\delta$ ) gene repertoire of hepatosplenic  $\gamma/\delta$  TCL ( $\gamma/\delta$  HSTCL) and subcutaneous panniculitis-like  $\gamma/\delta$  TCL ( $\gamma/\delta$  SPTCL) has been reported only in a limited number of cases. In this study we analyzed 11  $\gamma/\delta$  HSTCL and 4  $\gamma/\delta$  SPTCL by polymerase chain reaction and immunostaining to determine their usage of the V $\delta$  subtypes (V $\delta$ 1–6). It is noteworthy that 10 of 11  $\gamma/\delta$  HSTCL expressed the V $\delta$ 1 gene. The remaining case also expressed T cell receptor  $\delta$  (TCR $\delta$ ) as determined by flow cytometry and TCR $\delta$  rearrangement in Southern blot. However, the V $\delta$  gene expressed by this lymphoma could not be determined, which suggests usage of an as yet unidentified V $\delta$  gene. In striking contrast to the  $\gamma/\delta$  HSTCL, all 4  $\gamma/\delta$  SPTCL expressed the V $\delta$ 2 gene. Our data demonstrate that  $\gamma/\delta$  HSTCL are preferentially derived from the V $\delta$ 1 subset of  $\gamma/\delta$  T lymphocytes, whereas  $\gamma/\delta$  SPTCL are preferentially derived from the V $\delta$ 2 subset. The pattern of V $\delta$  gene expression in HSTCL and SPTCL corresponds to the respective, predominant  $\gamma/\delta$  T cell subsets normally found in the spleen and skin. This finding suggests that  $\gamma/\delta$  TCL are derived from normal  $\gamma/\delta$  T lymphocytes which reside in the affected tissues. Furthermore, the selective, lymphoma type-specific V $\delta$  gene segment usage may provide a molecular tool to distinguish better among various types of  $\gamma/\delta$  TCL lymphoma particularly in the clinically advanced, widely disseminated cases. (*J Mol Diag* 2000; 2:11–19)

Similar to normal T lymphocytes, T cell lymphomas (TCL) may express two different types of T cell receptor (TCR),  $\alpha/\beta$  or  $\gamma/\delta$ . Four TCR genes ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) are composed in their germline configuration of noncontiguous segments of variable (V), diversity (D), joining (J), and constant (C) regions. During T cell differentiation, somatic VDJ rearrangements occur and thereby generate variability of the TCR.<sup>1</sup> Only complete in-frame TCR gene rearrangements, consisting of V, D, and J regions, may form a functional TCR. Incomplete rearrangements between two D regions (D-D), between V and D region (V-D), and between D and J region (D-J) are nonfunctional. The majority of normal T lymphocytes express the  $\alpha/\beta$  heterodimer; however, approximately 5% of the T cells express the  $\gamma/\delta$  heterodimer.<sup>2</sup> In contrast to  $\alpha/\beta$  T lymphocytes, development of  $\gamma/\delta$  T cells is not dependent on expression of major histocompatibility complex (MHC) I or MHC II molecules.<sup>3–6</sup> Unlike  $\alpha/\beta$  T cells, which develop almost exclusively in thymus,  $\gamma/\delta$  T cells can be generated in extrathymic sites such as intestinal epithelium, skin, spleen, and fetal liver.<sup>7–9</sup> The exact function of  $\gamma/\delta$  T lymphocytes has not been fully elucidated, but some studies suggest a role for these cells in early immune responses to infections, autoimmune disorders, and cancer immune surveillance.<sup>9</sup>  $\gamma/\delta$  T cells share some features with CD8+  $\alpha/\beta$  T lymphocytes and with natural killer (NK) cells. They show MHC-dependent and MHC-independent cytotoxicity, produce lymphokines, and exhibit NK-like lytic activity.

$\gamma/\delta$  TCL represent a rare type of T cell malignancy. They comprise less than 10% of peripheral T cell lymphomas<sup>10</sup> and occur mostly at extranodal sites in hepatosplenic, subcutaneous, or intestinal form. Hepatosplenic

Supported in part by grants from the Committee for Scientific Research (KBN PO5A.015.16 to G.K.P.) and the National Cancer Institute (CA76627 to M. A. W.).

Accepted for publication December 3, 1999.

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