Expression of the human germinal center-associated lymphoma (HGAL) protein, a new marker of germinal center B-cell derivation.


Department of Pathology, Stanford University School of Medicine, 300 Pasteur Dr, Stanford, CA 94305, USA. yaso@stanford.edu

Abstract

We identified the human germinal center-associated lymphoma (HGAL) in gene-expression profiling studies of diffuse large B-cell lymphoma (DLBCL). The expression of HGAL correlated with survival in patients with DLBCL. The HGAL gene is the human homolog of M17, a mouse gene expressed specifically in normal germinal center (GC) B cells. We generated a monoclonal antibody against the HGAL protein and show that HGAL is expressed in the cytoplasm of GC lymphocytes and in lymphomas of GC derivation. Among 727 lymphomas tested by immunohistochemistry on tissue microarrays, HGAL staining was found in follicular lymphomas (103 of 107), Burkitt lymphomas (40 of 40), mediastinal large B lymphomas (7 of 8), and in DLBCLs (103 of 151). Most marginal zone lymphomas lacked HGAL staining. Lymphocyte-predominant Hodgkin lymphomas (12 of 17) and, surprisingly, classical Hodgkin lymphomas (78 of 107) were found to be positive. Hierarchical clustering of comparative immunohistologic results in DLBCLs demonstrates that the expression of HGAL is similar to 2 other GC-associated proteins, BCL6 and CD10, but different from 2 markers associated with a non-GC phenotype, MUM1/IRF4 and BCL2. The restricted expression and GC specificity of HGAL protein suggest that it may have an important role in the diagnosis of specific lymphomas, and, potentially, in the identification of subtypes associated with different prognoses.
Expression of the human germinal center-associated lymphoma (HGAL) protein identifies a subset of classic Hodgkin lymphoma of germinal center derivation and improved survival.

Department of Pathology, Stanford University School of Medicine, CA, USA.

Abstract
The human germinal-center-associated lymphoma (HGAL) gene and its cognate protein are expressed in a germinal center (GC)-specific manner. Its expression in classic Hodgkin lymphoma (cHL) prompted us to address whether HGAL expression could distinguish biologically distinct subgroups of cHL. Tissue microarrays from 145 patients treated with curative intent showed HGAL staining in 75% and was closely correlated with MUM1/IRF4 (92%) expression. BCL6 (26%), CD10 (0%), BCL2 (31%), Blimp1 (0.02%), and Epstein-Barr virus (EBV) (20%) showed no specific correlation; neither did phospho-STAT6, a key mediator of IL-4 and IL-13 signaling that induces HGAL and is implicated in cHL pathogenesis. In our study cohort, the 5-year overall survival (OS) correlated with young age (less than 45 years, P < .001), low stage (stage I and II, P = .04), and low International Prognostic Score (P = .002). In univariate analysis, HGAL expression was associated with improved OS (P = .01) and failure-free survival (FFS) (P = .05) but was not independent of other factors in multivariate analysis of OS or FFS. The expression of the GC-specific marker HGAL in a subset of cHL suggests that these cHLs retain characteristics of GC-derived lymphomas. The association with improved OS in univariate but not multivariate analysis suggests that HGAL expression is related to known clinical parameters of improved survival.
Immunoarchitectural patterns in follicular lymphoma: efficacy of HGAL and LMO2 in the detection of the interfollicular and diffuse components.

Department of Pathology, Division of Oncology, Stanford University School of Medicine, Stanford, CA 94305, USA.

Abstract
Follicular lymphoma (FL) can exhibit variant histologic patterns that can lead to confusion with other B-cell lymphomas and reactive conditions. Diagnostic markers such as CD10 and BCL2 may be difficult to interpret in variant FL patterns, and are often diminished or absent in the interfollicular and diffuse components. We evaluated 2 recently characterized germinal center B-cell markers, human germinal center associated lymphoma (HGAL), and LIM-only transcription factor 2 (LMO2), in 127 FL patient biopsies (94 nodal, 33 extranodal), and correlated the findings with histologic pattern, cellular composition, grade, and additional immunostains (CD20, CD3, CD21, CD10, BCL2, and BCL6). Architectural patterns included predominantly follicular (75%) and follicular and diffuse components (25%); 10 cases showed marginal zone differentiation and 3 were floral variants. Eighty-nine cases were low grade (38 grade 1; 51 grade 2) and 38 were grade 3 (29 grade 3A and 9 grade 3B). HGAL had the highest overall sensitivity of detecting FL and was superior in detecting the interfollicular and diffuse components compared with BCL2, LMO2, CD10, and BCL6. All 28 cases that lacked CD10, expressed HGAL, and the majority also expressed LMO2. Our results show that HGAL and LMO2 are sensitive markers for FL diagnosis. The addition of HGAL and LMO2 to the immunohistologic panel is beneficial in the work-up of nodal and extranodal B-cell lymphomas and the efficacy of HGAL in detecting the follicular, interfollicular and diffuse components of FL is of particular value in the setting of variant immunoarchitectural patterns.