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EDITORIAL

MUM1: a step ahead toward the understanding of lymphoma histogenesis

G Gaidano[1] and A Carbone[2]

[1]*Division of Internal Medicine, Department of Medical Sciences, Amedeo Avogadro University of Eastern Piedmont, Novara, and* [2]*Division of Pathology, Centro di Riferimento Oncologico, IRCCS, Istituto Nazionale Tumori, Aviano, Italy*

In recent times, the field of B cell lymphoma histogenesis has progressed rapidly due to the increasing availability of histogenetic markers. Genotypic markers of B cell histogenesis are represented by mutations of IgV and *BCL*-6 genes, which are somatically acquired at the time of B cell transit through the germinal center (GC). Phenotypic markers are represented by BCL-6 and CD138/syndecan-1 protein expression and allow the distinction between GC and post-GC B cells. On this basis, lymphomas may be histogenetically distinguished into: (1) lymphomas devoid of somatic IgV and *BCL*-6 hypermutation, which derive from pre-germinal center B cells; (2) lymphomas associated with somatic IgV and/or *BCL*-6 hypermutation and BCL-6 expression, which closely reflect germinal center B cells; and (3) lymphomas associated with somatic IgV and/or *BCL*-6 hypermutation, as well as CD138/syndecan-1 positivity, representing lymphomas of post-germinal center B cells. In the March issue of *Leukemia*, Tsuboi *et al* report on the expression pattern of MUM1 in normal lymphoid tissues and in lymphoma. Because expression of MUM1 protein appears to be strictly regulated during lymphoid differentiation, and because expression of the molecule is retained upon neoplastic transformation, MUM1 may be added to the panel of phenotypic markers of B cell lymphoma histogenesis. In particular, MUM1 may provide a marker for the identification of transition from BCL-6 positivity (GC B cells) to CD138 expression (immunoblasts and plasma cells). These studies are of potential clinical value, since in some B cell malignancies, histogenesis may influence prognosis. *Leukemia* (2000) **14,** 563–566.
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Lymphomagenesis is a complex process involving a panoplia of molecular pathways causing transformation of mature lymphoid cells.[1] Each of these pathways is characterized by molecular lesions of cancer related genes and targets a specific stage of lymphoid differentiation[1] (Figure 1). Because each molecular pathway selectively associates with a given clinico-pathologic category of lymphoma, it is assumed that the genetic heterogeneity of lymphoma drives the histological, phenotypical and clinical heterogeneity of these diseases. Research performed during the last decade has been most intense in the field of lymphoma pathogenesis, and has led to the characterization of many cancer-related genes involved in the molecular pathways of lymphoma.[1] Conversely, investigations of lymphoma histogenesis have been lagging behind compared to studies of lymphoma pathogenesis and, therefore, comprehension of the precise cellular counterpart from which a given lymphoma derives is less advanced than knowledge of the genetic lesions associated with the tumor clone.

In recent times, however, the field of B cell lymphoma histogenesis has progressed rapidly due to the increasing availability of histogenetic markers of lymphoid cells.[2] In normal B cell physiology, the presence, or absence, of these histogenetic markers denotes different stages of lymphoid differentiation, allowing the distinction of mature B cells into virgin (ie pre-germinal center) B cells, germinal center B cells, and post-germinal center (ie either memory B cells or plasmacells) B cells[2] (Figure 2). Because these histogenetic markers are also retained upon neoplastic transformation, the origin and differentiation stage of a given lymphoma may be temptatively assigned based on the combination of histogenetic markers associated with the tumor clone (Figure 2). To date, well-defined histogenetic markers of B cell lymphoma include mutations of immunoglobulin (Ig) and *BCL*-6 genes, expression of the BCL-6 protein, and, at least in the context of immunodeficiency-related lymphoma, expression of the CD138/syndecan-1 antigen.[2–7] Mutations of Ig genes are accumulated at the time of B cell transit through the germinal center (GC) and are maintained thereafter upon B cell exit from the GC.[2,4] Similarly, recent evidence has shown that normal GC B cells also accumulate mutations of the noncoding regions of the *BCL*-6 proto-oncogene, which therefore parallel Ig mutations as markers of GC transit.[5–7] Because both Ig and *BCL*-6 mutations are maintained by B cells upon GC exit and further differentiation, they cannot discriminate between GC and post-GC B cells. Such distinction can be eased by phenotypic markers of histogenesis. Available phenotypic markers of histogenesis include expression of the BCL-6 protein, which is restricted to B cells reflecting a GC stage of differentiation, and CD138/syndecan-1, a proteoglycan clustering with late stages of B cell maturation.[3,8–11]

On this basis, lymphomas may be histogenetically distinguished into: (1) lymphomas devoid of somatic Ig and *BCL*-6 mutations, which derive from naive, pre-GC B cells; (2) lymphomas associated with somatic Ig and/or *BCL*-6 mutations as well as BCL-6 protein expression, and thus closely reflecting GC B cells; and (3) lymphomas associated with somatic Ig and/or *BCL*-6 mutations as well as CD138/syndecan-1 positivity, which conceivably represent lymphomas of post-GC B cells.[2–12] According to this model, mantle cell lymphoma and a fraction of B cell chronic lymphocytic leukemia/small lymphocytic lymphoma are considered as lymphomas deriving from naive B cells[2,4] (Figure 2). Follicular lymphoma, Burkitt lymphoma and a substantial fraction of diffuse large cell lymphoma closely reflect B cells residing in the GC[2,4] (Figure 2). MALT-lymphomas are postulated to originate from B cells which have undergone a GC-like reaction and subsequently migrated to the involved extranodal site.[2,4] Lymphoplasmacytoid lymphoma, primary effusion lymphoma, and possibly a fraction of diffuse large cell lymphoma are thought to reflect post-GC B cells with a marked degreee of plasmacytoid differentiation[2–4,7,13,14] (Figure 2). Despite these advances in the histogenesis of lymphoma, several issues remain unclear. For

Correspondence: G Gaidano, Division of Internal Medicine, Department of Medical Sciences, Amedeo Avogadro University of Eastern Piedmont, Via Solaroli 17, 28100 Novara, Italy; Fax: (39) (0321) 620-421
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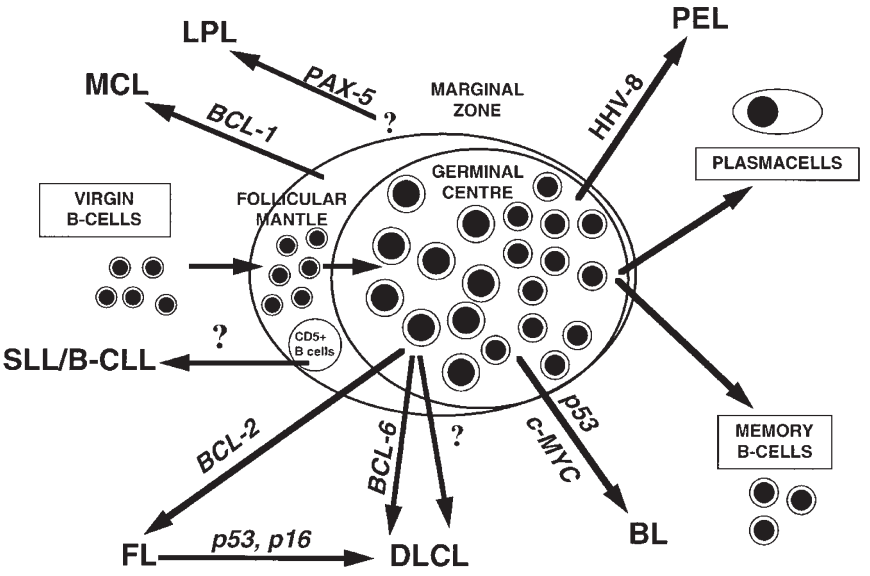

Figure 1 Genetic pathways in B cell lymphomagenesis. The major compartments of mature B cells are schematically represented as a secondary follicle containing the germinal center and the mantle zone. The $CD5^+$ B cell compartment is also shown. The major B cell lymphoma categories recognized by the WHO classification are indicated as SLL/B-CLL (for small lymphocytic lymphoma/B cell chronic lymphocytic leukemia), LPL (for lymphoplasmacytoid lymphoma), MCL (for mantle cell lymphoma), FL (for follicular lymphoma), DLCL (for diffuse large cell lymphoma), PEL (for primary effusion lymphoma), and BL (for Burkitt lymphoma). The putative histogenetic derivation of each B cell lymphoma category is indicated by an arrow originating from the relevant B cell compartment. Arrows are flanked by the molecular lesion which is selectively involved in the pathogeneis of each specific B cell lymphoma category, and, based on current knowledge, represents the genetic hallmark of the disease. In the case of SLL/B-CLL, as well as in a subset of DLCL, the relevant cancer-related gene has not been identified.

example, firm immunologic and histologic evidence indicate that the GC is a dynamic structure in which B cells progress from centroblasts, located in the GC dark zone, to centrocytes, located in the GC light zone.[2] Yet, because of the current lack of appropriate histogenetic markers, we are currently unable to precisely segregate lymphomas of GC B cells into lymphomas of centroblasts and lymphomas of centrocytes.

In the March issue of *Leukemia*, Tsuboi *et al*[15] report on the expression pattern of MUM1 (for *Mul*tiple *M*yeloma-1) in normal lymphoid tissues as well as in lymphoma and other lymphoid malignancies. Because expression of MUM1 protein appears to be strictly regulated during lymphoid differentiation, and because expression of the molecule is retained upon neoplastic transformation, MUM1 may be added to the panel of phenotypic markers available for the characterization of B cell lymphoma histogenesis. MUM1 originally gained attention from molecular hematologists because of its involvement in the t(6;14)(p25;q32) translocation of multiple myeloma, which causes the juxtaposition of the MUM1 gene, mapping at 6p25, to the Ig_H locus on 14q32.[16,17] Before being discovered as a protooncogene of hematologic neoplasia, though, MUM1 had been extensively investigated by immunologists who defined that MUM1 is a lymphocyte-specific member of the interferon regulatory factor family of transcription factors.[18] Hence, the various names assigned to MUM1, which include IRF4 (for *I*nterferon *R*egulatory *F*actor 4), ICSAT (for *I*nterferon *C*onsensus *S*equence binding protein for *A*ctivated *T* cells) and Pip (for *PU*.1 *I*nteraction *P*artner).[18]

Because loss of MUM1 function results in the absence of activated lymphoid cells and Ig secreting plasmacells,[19] Tsuboi and colleagues[15] reasoned that MUM1 may be developmentally regulated in lymphoid differentiation. To address this hypothesis, they have initially applied a MUM1 antiserum to reactive lymphoid tissues, showing that MUM1 expression clusters with plasma cells and, most interestingly, with a small fraction of B cells located in the light zone of the germinal center.[15] As such, MUM1 expression may denote the final step of intra-GC B cell differentiation, ie the stage known as centrocyte, as well as subsequent steps of B cell maturation toward plasmacells. Comparison of the topography of MUM1 and BCL-6 within the GC reveals substantial differences. Infact, expression of BCL-6 occurs immediately after a B cell enters the GC and is maintained until GC exit, whereas MUM1 positivity begins only at the centrocyte stage and is maintained during post-GC maturation.[8–11,15] Consequently, the histogenetic value of MUM1 may be to provide a marker for the identification of the transition from BCL-6 positivity (GC B cells) to CD138 expression (immunoblasts and plasmacells).

In agreement with the histogenetic pathways proposed to date for the major categories of lymphoma, Tsuboi *et al*[15] show that MUM1 expression is consistently absent in mantle cell lymphoma (pre-GC B cells) and in follicular lymphoma (GC B cells). Conversely, MUM1 clusters with most B lineage diffuse large lymphoma, which also frequently express BCL-6, suggesting that a large fraction of these disorders may be related to the late phases of intra-GC maturation of B cells.[15] This notion is further supported by the recent observation that B lineage diffuse large cell lymphoma fails to display ongoing mutations of Ig genes, which, conversely, are frequently observed in follicular lymphoma.[2,20] Intriguingly, Tsuboi and colleagues identify MUM1 expression also in Reed–Sternberg cells of classical Hodgkin's lymphoma and in a fraction of B cell chronic lymphocytic leukemia/small lymphocytic lymphoma.[13] MUM1 expression by Hodgkin's lymphoma is in agreement with the emerging notion that Reed–Sternberg cells are post-GC B cells, at least in the overwhelming majority of patients.[2,21] Also, the expression of MUM1 by a fraction of B cell chronic lymphocytic leukemia/small lymphocytic lym-

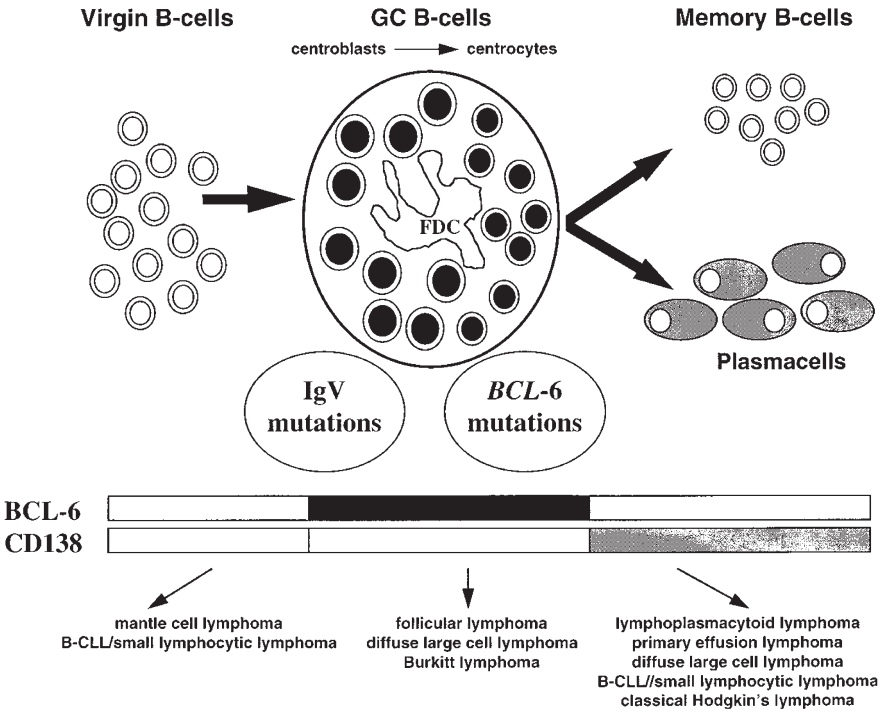

Figure 2 A proposed model for the histogenesis of B cell lymphoma. The model is derived from the mutation pattern of Ig and *BCL*-6 genes (identified by circles in the figure) and from the expression profile of BCL-6 and CD138/syndecan-1 proteins (identified by rectangles in the figure) throughout physiologic B cell maturation. Virgin B cells do not display Ig and BCL-6 mutations and lack protein expression of BCL-6 and CD138/syndecan-1. At the time of B cell transit through the germinal center (GC), B cells acquire Ig and *BCL*-6 mutations which are maintained during further differentiation, thus constituting genotypic markers of GC transit. B cells within the GC, ie centroblasts and centrocytes, express BCL-6 but not CD138/syndecan-1. Post-GC B cells undergoing maturation toward the plasmacell stage switch off BCL-6 expression and stain positive for CD138/syndecan-1. The putative histogenesis of the different categories of B cell lymphoma are indicated in the lower part of the figure. Some lymphoma categories, namely B cell chronic lymphocytic leukemia/small lymphocytic lymphoma and diffuse large cell lymphoma, are characterized by histogenetic heterogeneity. Based on the results of Tsuboi *et al*[15] presented in the March issue of *Leukemia*, the histogenetic model presented in the figure may be enriched by the addition of the MUM1 marker, which is expressed by late stages of intra-GC differentiation, ie centrocytes, and by post-GC B cells undergoing plasmacell maturation.

phoma reinforces very recent evidence indicating that this disorder is histogenetically heterogeneous and that a proportion of cases reflect post-GC B cells.[22,23]

If MUM1, as it appears, is indeed a solid marker of lymphoma histogenesis, several applications may be envisaged to refine our understanding of lymphomagenesis. Intuitively, MUM1 studies need to be performed for lymphoma categories not analyzed by Tsuboi *et al* and MUM1 staining pattern needs to be compared to that of other available histogenetic markers within individual clinico-pathologic categories of lymphoma. Also, whereas the MUM-1 antibody used by Tsuboi *et al* is a polyclonal antiserum, the availability of an anti-MUM-1 monoclonal antibody[26] will conceivably increase the experimental power of MUM-1 immunohistochemistry. The combination of MUM1, BCL-6, CD138/syndecan-1, mutations of Ig and *BCL*-6 genes, as well as other potential novel markers (eg TCL-1; Ref. 24) will conceivably provide a powerful tool to understand the histogenesis of lymphoma. In addition, MUM1 may offer advantage in refining classification of lymphoma entities thought to be non homogeneous and in identifying specific disease subsets within lymphoma categories characterized by histogenetic heterogeneity.[25] These studies are of potential clinical value, since histogenesis may influence prognosis, as recently proposed for B cell chronic lymphocytic leukemia/small lymphocytic lymphoma.[22,23]

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