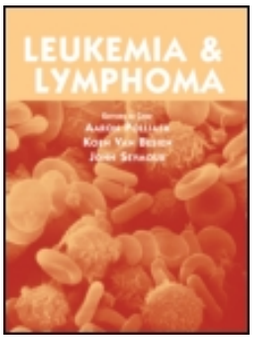

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COMMENTARY

What is Waldenström macroglobulinemia?

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In this issue of ***Leukemia and Lymphoma***, Varettoni *et al*. analyze immunoglobulin heavy chain rearrangements in patients with Waldenström macroglobulinemia and immunoglobulin M (IgM) monoclonal gammopthy of undetermined significance (MGUS) [1]. They detect that immunoglobulin heavy chain variable (IGHV) subgroup usage is much greater for IGHV3 than in normal peripheral blood, and IGHV gene usage is much greater for IGHV3-23. The heavy chain complementarity determining region (HCDR) clusters do not occur with an appreciable frequency, and do not support a B-cell receptor-driven pathogenesis for Waldenström macroglobulinemia.

Precursor B-cells that mature in the bone marrow may undergo apoptosis or develop into mature naive B-cells that, following exposure to antigen, develop into short-lived plasma cells, or may alternatively enter the germinal center, where somatic hypermutation and heavy chain class switching occur. The transformed cells of the germinal center then either undergo apoptosis or develop into centrocytes. Post-germinal center cells include long-lived plasma cells and memory or marginal zone B-cells. B-cells are activated within the germinal center. Activation can also occur outside of the germinal center and leads to memory type B-cells. Somatic hypermutation introduces mutations in the variable region of immunoglobulin genes with a frequency one million times higher than the spontaneous mutation rates seen in somatic cells. Mistargeting of somatic hypermutation can result in the development of B-cell malignancies [2].

Lymphomas that derive from a naive pre-germinal center B-cell will lack somatic hypermutation. Germinal center-derived lymphomas such as large cell lymphoma and follicular lymphomas display somatic hypermutation. A post-germinal center B-cell, which has been stimulated to differentiate into an immunoglobulin-secreting plasma cell, is believed to be the precursor to lymphoplasmacytic lymphoma. Secretion of monoclonal IgM gives rise to the symptom complex known as Waldenström macroglobulinemia (WM) [3]. WM is defined as lymphoplasmacytic lymphoma with an IgM monoclonal protein of any concentration. The neoplastic cells express monotypic IgM and light chain and pan-B-cell antigens and are usually negative for CD5 and CD10 [4].

Decades ago, WM was simply considered a low-grade lymphoproliferative disorder; however, it is a distinct entity, and t(9;14), as is seen in other lymphomas and immunoglobulin heavy chain translocations, is often not observed. The t(11;18) that defines marginal zone lymphoma (MZL) is absent; and the t(11;14), evident in mantle cell lymphoma, is also absent. Deletions of chromosome 13q14, as reported in myeloma and chronic lymphocytic leukemia (CLL), are uncommon; t(14;18), as seen in follicular lymphoma, is not encountered. The most common cytogenetic abnormality is deletion of the long arm of chromosome 6, rarely seen in other lymphomas, suggesting a truly distinct entity [5]. WM, clinically, is often difficult to diagnose and can be confused with splenic marginal zone lymphoma, type II cryoglobulinemia, mucosal-associated lymphoid tumors and amyloidosis [6].

Fortunately, the recent detection of MYD88 L265P somatic mutation, as a defining genetic event in WM, reaffirms that this is a truly unique form of lymphoma that is not related to any of the other lymphomas in the World Health Organization classification. This mutation that stimulates nuclear factor κB (NFκB) has been reported in over 90% of patients with WM, and assays to detect and quantify the expression of the mutation show the mutation to be present in 93% of cases of WM but in only 10% of patients with splenic MZL and in 4% of patients with CLL. This will allow the genetic tests to be used diagnostically, and the possibility exists that the expression of the mutation may allow response assessment akin to Bcr–Abl expression in monitoring the response of chronic myelogenous leukemia to tyrosine kinase inhibitors [7]. The MYD88 L265P somatic mutation is also present in IgM MGUS, suggesting that this is the precursor disease to WM and that a transforming mutation converting MGUS to WM is not necessary. MYD88 L265P is probably a driver mutation, providing a growth advantage to the WM clone [8].

Recently, immunoglobulin heavy chain variable gene features were also analyzed, and the occurrence of MYD88

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mutations was explored in splenic marginal zone lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma and Waldenström macroglobulinemia. Patients with Waldenström macroglobulinemia were associated with IGHV-23 over-representation, as reported in the current article [1], and with a high IGHV mutation rate and short CDR3 segments. This suggests that antigenic exposure of the four lymphoproliferative entities is different, and the high frequency of MYD88 mutation suggests that Waldenström is functionally associated with NFκB activation. In this study, MYD88 was expressed in 67% of patients [9]. Comparative genomic analysis indicates that Waldenström macroglobulinemia has a very stable karyotype, that trisomy 4 is unique to Waldenström, and abnormalities in interleukin-1 receptor-associated kinase 4 (IRAK4) likely plays a role in the pathogenesis of the disease [10]. Not only does the MYD88 serve as a confirmatory diagnostic test but it may yield a therapeutic target in the future. Targeting the signaling induced by this mutation could be envisioned to have anti-tumor effects using small molecule inhibitors [11].

In conclusion, the current trial on IGHV subgroup usage and gene usage, as well as genetic surface marker and gene studies, all indicate that Waldenström macroglobulinemia is a unique, independent entity unrelated to any other type of lymphoma, and likely all arise from an antecedent IgM MGUS. MYD88 may become the key to curative therapy. Consequentially, therapeutic studies on other indolent lymphomas may not have applicability to Waldenström due to its unique etiopathogenesis, and treatment trials specifically targeted to this population are desperately needed.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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