Review

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MYD88 L265P Mutation in Lymphoid Malignancies

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Abstract

Next-generation sequencing has revealed cancer genomic landscapes, in which over 100 driver genes that, when altered by intragenic mutations, can promote oncogenesis. *MYD88* is a driver gene found in hematologic B-cell malignancies. A missense mutation (L265P) changing leucine at position 265 to proline in MYD88 is found in ~90% of Waldenström macroglobulinemia (WM) cases and in significant portions of activated B-cell diffuse large B-cell lymphomas and IgM monoclonal gammopathy of undetermined significance. Few cancers such as WM have a single amino acid substitution in one gene like MYD88 L265P that occurs in ~90% of cases, making WM paradigmatic for study of a single causative mutation in oncogenesis. In this review, we summarize the frequency and cancer spectrum of MYD88 L265P and its downstream effects in lymphoid cancers. Malignant B cells with MYD88 L265P are likely transformed from IgM-producing B cells either in response to T-cell–independent antigens or in response to protein antigens before class switching. We also discuss therapeutic strategies that include targeting Bruton tyrosine kinase and other kinases, interfering with the assembly of MYD88 and its interacting partners, and *MYD88* L265P-specific peptide-based immunotherapy. *Cancer Res; 78(10); 2457–62. ©2018 AACR.*

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Introduction

Myeloid differentiation factor 88 (*MYD88*) was discovered in the 1990s as a primary differentiation response gene in myeloid precursors that was activated following terminal differentiation and growth arrest induced by IL6 (1, 2). As a general adaptor protein, MYD88 contains three main structures: a death domain (DD) at the N terminus, an intermediate linker domain (ID), and a Toll/interleukin-1 receptor domain (TIR) at the C terminus. Following ligand binding, the cytoplasmic TIR domain of Toll-like receptors (TLR) or IL1R associates with the TIR of MYD88 (3–5). Then, the serine–threonine kinase, IL1-receptor associated kinase 4 (IRAK4), is recruited to MYD88 through the interaction of the death domains of both molecules. IRAK4 interacts and phosphorylates IRAK2 and IRAK1 to form a complex known the "Myddosome" (6). Phosphorylated IRAKs 1 and 2 interact with the E3 ubiquitin ligase TNF receptor–associated factor 6 (TRAF6), via their TRAF binding domains. TRAF6 ultimately recruits TAK1-binding protein 2 (TAB2) and activates TAB2-associated TGFβ-activated kinase 1 (TAK1), which promotes cell survival through activation of both the canonical NF-κB (p50–p65) pathway and the mitogen-activated protein kinase (MAPK) pathway (5, 7–10). In this review, we summarize the latest findings on the *MYD88* L265P mutation and highlight its role in tumor biology and treatment in hematologic malignancies. We also discuss major challenges in therapeutic development against cancers with *MYD88* L265P.

Frequency of MYD88 L265P Mutation in B-cell Neoplasms

Recurrent *MYD88* L265P mutation was first found in diffuse large B-cell lymphoma (DLBCL), which can be classified into two major molecular subtypes based on cell of origin (11). The germinal center B-cell–like (GCB) subtype possesses gene expression patterns that resemble those of nonmalignant B cells that have entered the germinal center, whereas the activated B-cell–like (ABC) subtype expresses genes induced by NF-κB during *in vitro* activation of peripheral blood cells. Patients with ABC-DLBCL have poor survival compared with GCB-DLBCL. Staudt and colleagues first found MYD88 mutations in ABC-DLBCL biopsies with L265P as the most frequent, seen in about 29% of cases (12). In contrast, this mutation was rare or absent in patients with GCB-DLBCL, primary mediastinal B-cell lymphoma, and Burkitt lymphoma. shRNA knockdown and reintroducing wild-type (WT) or mutant MYD88 revealed that the survival of ABC-DLBCL cells bearing the L265P mutation is sustained by the mutant but not WT MYD88, supporting the idea that L265P is a gain-of-function driver mutation in ABC-DLBCL (12).

Lymphoplasmacytic lymphoma (LPL) is rare, representing ~1% of all of non-Hodgkin lymphomas. LPL is characterized by predominantly small B lymphocytes in varying degrees of plasmacytic differentiation ranging from plasmacytic lymphocytes to plasma cells. Waldenström macroglobulinemia (WM) is defined as a subset of LPL in which patients have bone marrow

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involvement and produce large amounts of monoclonal IgM macroglobulin. WM represents ~95% of LPL cases, whereas other LPLs are associated with IgA or IgG paraprotein (13). In 2012, MYD88 L265P was found in tumor samples from 49 of 54 (91%) patients with WM (14). Ensuing studies indicate that the frequency of MYD88 L265P mutation in non-IgM LPL is ~25%. In contrast, MYD88 L265P was found in 87% (1,324 of a total of 1,520) of patients with WM as reported from 25 publications (Supplementary Table S1). Across all cancers, few other than WM have a missense mutation like MYD88 L265P that occurs in >85% of cases, making WM paradigmatic for study of a single causative mutation in oncogenesis (15).

Patients with monoclonal gammopathy of undetermined significance of the IgM class (IgM MGUS) are at increased risk for WM, DLBCL, and mucosa-associated lymphoid tissue (MALT) lymphoma, as well as chronic lymphocytic leukemia (16, 17). Staudt and Landgren determined the *MYD88* gene status in IgM MGUS and found MYD88 L265P expression in 5 of 9 patients (56%; ref. 18). We summarize the *MYD88* L265P mutation frequency rates in different B-cell neoplasms: MYD88 L265P mutation occurs frequently in WM (87%), primary DLBCL of the central nerve system (CNS; 70%), cutaneous DLBCL, leg-type (54%), IgM MGUS (52%), testicular DLBCL (74%), and ABC-DLBCL (24%; Fig. 1A; Supplementary Table S1). Though they are classified as independent entities of mature B-cell neoplasms, the vast majority of CNS DLBCL (19), cutaneous DLBCL, leg-type (20), and testicular DLBCL (21) are of ABC origin. Mutation of MYD88 has not been found in IgG or IgA MGUS, nor in multiple myeloma (22, 23). Therefore, IgM MGUS is more closely related to LPL and other B-cell lymphomas and is segregated from IgG or IgA MGUS, which are more closely related to multiple myeloma (23).

Origin of MYD88 L265P Mutation

Malignant B-cell neoplasms develop during various stages of normal B-cell differentiation and development (Fig. 1A; ref. 24). In humoral immune responses, B cells are activated by both protein and nonprotein antigens and secrete immunoglobulins to eliminate the antigen. In response to protein antigens, with the contribution of $CD4^+$ helper T cells, B cells in the germinal center reaction are subjected to two distinct modifications: somatic hypermutation (SHM) and heavy-chain isotype (class) switching. Class switching alters the immunoglobulin heavy-chain class from IgM to IgG, IgA, or IgE and requires the induction of activation-induced cytidine deaminase (*AID*), which is also required by SHM. Many nonprotein antigens, such as polysaccharides, membrane glycolipids, and nucleic acids, are multivalent and can activate B cells without T cell help; these T-cell independent (TI) antigens stimulate immunoglobulin responses with limited class switching. Marginal zone B cells are a distinct population of B cells that mainly respond to polysaccharides and differentiate into short-lived plasma cells producing IgM primarily. Murine B cells expressing MYD88 L265P but not those with WT MYD88 proliferate and expand in syngeneic $Rag1^{-/-}$-recipient mice, supporting that MYD88 L265P mutation promotes TI B-cell proliferation *in vivo* (25). We speculate that all malignant B cells with MYD88 L265P are transformed from IgM-producing B cells in response to TI antigens or in response to protein antigens before class switching. It is notable that most ABC-DLBCL have not undergone class switching and more ABC-DLBCL than GCB-DLBCL express IgM (26, 27). It is our hypothesis that ABC-DLBCL with MYD88 L265P predominantly express IgM. B cells with MYD88 L265P are likely transformed before or during plasmacytic differentiation, a process that occurs in all LPL forms but is infrequent in other small B-cell lymphomas like MZLs (28). Other genetic changes in *TNFAIP3*, *BCL2* (see below), and *CD79B* (29) may cooperate with MYD88 L265P to drive these IgM-producing B cells into different types of B-cell malignancies.

The pattern of *MYD88* mutations raises two important questions. First, how *MYD88* L265P mutation drives B-cell neoplasms? MYD88 DD and ID are responsible for downstream signal propagation via IRAKs, whereas the TIR domain integrates signals from upstream TLR and IL1R. The vast majority of recurrent oncogenic MYD88 mutations are mapped to its TIR domain, including a highly conserved β-sheet at the hydrophobic core where L265 resides (30, 31) and the BB loop that participates in interactions with TLR TIR domains (Fig. 1B). MYD88 mutations likely enhance TIR interactions between MYD88 and TLRs. It is possible that *MYD88* L265P mutation occurs in B-cell neoplasms where there is strong selection for aberrant NF-κB signaling. When overexpressed in BJAB cells, MYD88 L265P strongly activated an NF-κB–dependent reporter activity, whereas the S222R and T294P mutations had an intermediate effect, and WT MYD88 had only a marginal effect (12). Wang and colleagues analyze the consequences for antigen-activated mouse primary B cells of acquiring MYD88 L265P. L265P induces NF-κB activation and swift B-cell proliferation, which are nevertheless rapidly countered by the induction of *TNFAIP3* (i.e., A20) and extinguished by Bim-dependent apoptosis (25). In the presence of BCL2 overexpression or A20 inactivation, self-reactive B cells with MYD88 L265P continue to proliferate. A20 inactivation accompanies MYD88 L265P in ~24% of ABC-DLBCL (12) and A20 gene loss or inactivating mutation occurs in ~40% of WM (32). These results support that MYD88 L265P triggers the anti-apoptotic NF-κB signaling that may enable cell survival during B-cell development and yet needs a second somatic mutation to provide an advantage for continuous B-cell clonal selection (25). In WM, these second hits include *TNFAIP3*, *CXCR4*, *ARID1A/B*, and *CD79A/B* (33); among them, *CXCR4* mutation is detected in 9% of IgM MGUS (34).

The second question is why does L265P heterozygous mutation predominate, particularly in WM? A possible explanation lies in the MYD88 protein structure and the disrupting power of the Proline residue. Proline is the strongest structural disruptor in the middle of α-helices and β-sheets and is commonly found in β-turns and polyproline II helices. The change of Leucine at position 265 to Proline in one of the β-sheets at the hydrophobic core (Fig. 1B) would radically disrupt the secondary structure of the TIR domain, resulting in stabilization of the core of the dimer interface of the MYD88-TIR domain (31) and an intrinsic propensity for augmented oligomerization of MYD88 to facilitate spontaneous formation of cytosolic Myddosome aggregates in lymphoma cell lines. The L265P TIR domain, but presumably less so for other MYD88 mutants, cooperates with WT MYD88 for NF-κB hyperactivation via constitutive TIR-TIR oligomer formation (35). Based on these, one allelic copy of MYD88 L265P would be sufficient to initiate potent NF-κB signaling in lymphoma cells through TIR-TIR oligomerization.

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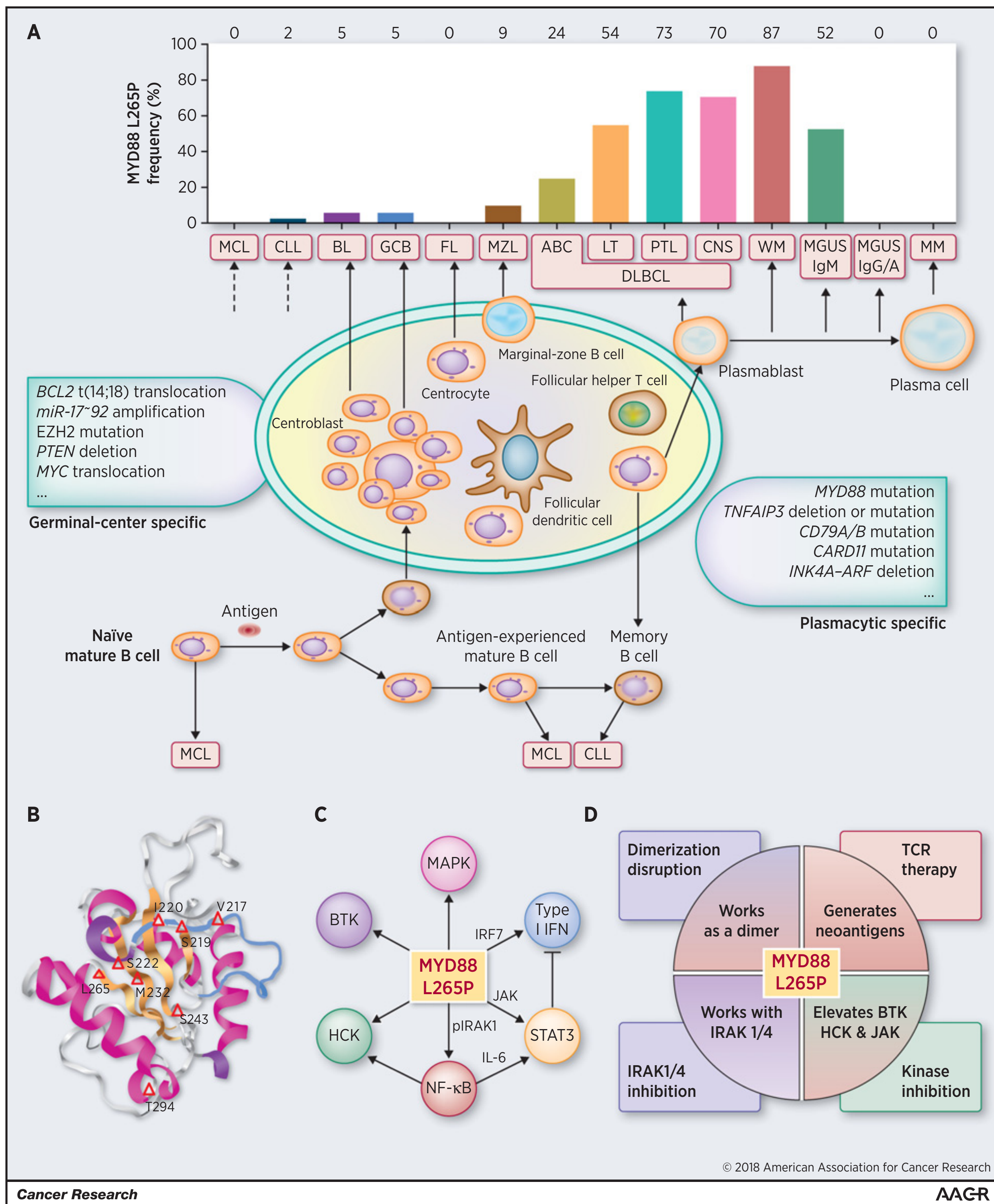

Figure 1.
MYD88 L265P mutation in B-cell malignancies and targeted therapy. **A,** Top, MYD88 L265P mutation frequency. Bottom, B-cell malignancy rises from different stages of B-cell development and differentiation. Red lines, pathogenic transformation; green lines, normal physiological B-cell development. MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; BL, Burkitt lymphoma; GCB, GCB-DLBCL; FL, follicular lymphoma; MZL, marginal zone lymphoma; PTL, primary testicular DLBCL; LT, primary cutaneous DLBCL, leg type; CNS, primary CNS DLBCL; MM, multiple myeloma. **B,** Structure of a human MYD88 TIR monomer (Protein Data Bank accession number 2JS7). The α-helices are shown in bright plum, β-sheets in light yellow, and BB loop in blue; the lymphoma-associated mutations are marked by red triangles. **C,** MYD88 L265P gain-of-function mutation drives oncogenesis through regulation of kinases and transcription factors. **D,** MYD88 L265P can be targeted directly by small-molecule inhibitors and engineered TCRs or indirectly by attenuation of MYD88 L265P-activated kinases.

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Functional Consequences of *MYD88* L265P Mutation

The primary consequence of *MYD88* L265P mutation is NF-κB activation, most likely through IRAK4 and IRAK1 (Fig. 1C; ref. 12). Phosphorylation of endogenous IRAK1 is observed in ABC- but not GCB-DLBCL cells, and phosphorylated IRAK1 (pIRAK1) interacts with *MYD88* L265P but not with WT *MYD88* or other MYD88 mutants (12). Thus, MYD88 L265P forms a signaling complex that includes pIRAK1 in ABC-DLBCL. A selective small-molecule inhibitor of IRAK1 and IRAK4 induces cell death in ABC-DLBCL cell lines but not in GCB-DLBCL and myeloma cell lines (12). Therefore, ABC-DLBCL relies upon IRAK4 and pIRAK1 to transduce signals from MYD88 L265P that promote cancer cell survival. JAK–STAT3 signaling gene signature overlapped significantly with the MYD88- and IRAK1-regulated gene signatures in ABC-DLBCL (12). Knockdown of MYD88 significantly diminished the secretion of IL6, IL10, and IFNβ and the phosphorylation of STAT3 in ABC-DLBCL cells. In addition, IL6, IL10, and IFNβ secretion was blocked by IRAK1/4 kinase inhibitor or MYD88 knockdown, indicating that MYD88 mutations, along with IRAK1/4, contribute to JAK–STAT3 and type I interferon signaling in ABC-DLBCL. IFNβ-mediated type I interferon signaling is proapoptotic. Rui and colleagues demonstrated that STAT3 is a critical transcriptional regulator of ABC-DLBCL, and STAT3 upregulates genes related to NF-κB, PI3K–AKT–mTORC1, and E2F/G_2–M cell-cycle checkpoint and downregulates the expression of *IRF7*, *IRF9*, *STAT1*, and *STAT2* in ABC-DLBCL cell lines with MYD88 L265P (36). Thus, STAT3 accentuates survival signaling pathways while dampening the lethal type I interferon pathway in ABC-DLBCL cells with *MYD88* L265P.

Bruton tyrosine kinase (BTK) is a critical node in B-cell receptor (BCR) signaling cascades, mediating the signal from BCR to downstream pathways such as NF-κB, PI3K/AKT, and NFAT (37). MYD88 is preferentially complexed to phosphorylated BTK (pBTK) in WM cells with *MYD88* L265P, yet little complexing is observed in lymphoma cells with WT MYD88 (38). The level of pBTK is higher in WM cells with *MYD88* L265P than lymphoma cells with WT *MYD88*. Importantly, inhibition of either BTK or IRAK1/4 induced WM cell apoptosis. These data not only establish BTK as a downstream target of MYD88 L265P, but also provide a novel strategy to treat WM and other *MYD88* L265P-expressing tumors (38). In an ensuing study, *MYD88* L265P is found to be associated with hematopoietic cell kinase (HCK), a member of the SRC family of protein tyrosine kinases, and one of the most aberrantly upregulated genes in WM cells (39). *MYD88* L265P overexpression triggered *HCK* and *IL6* transcription via NF-κB activation, whereas *HCK* knockdown significantly reduced cell survival and attenuated BTK, PI3K/AKT, and MAPK/ERK signaling in WM and ABC-DLBCL cells (40). Heterologous MYD88 L265P expression in HEK293 cells led to higher MAPK/ERK phosphorylation and higher NF-κB activation than that of WT MYD88 (41).

Reinhardt and colleagues generated a B-cell–specific conditional *Myd88*$^{p.L252P}$ allele (orthologous to human *MYD88* L265P) that is driven by the endogenous promoter upon Cre-mediated recombination (42). *Myd88*$^{p.L252P}$ mice develop a lymphoproliferative disease and occasional transformation into clonal lymphoma, which displays the morphologic and immunophenotypic characteristics of human ABC-DLBCL. The addition of B-cell–specific overexpression of *Bcl2* accelerates lymphomagenesis in these mice. These studies demonstrate that L265P-mutated *MYD88* is a *bona fide* oncogene. *MYD88* L265P mutation is much more common in WM than in ABC-DLBCL, so it is surprising that mice expressing *Myd88*$^{p.L252P}$ develop clonal ABC-DLBCL rather than WM (42). One explanation is that *Myd88*$^{p.L252P}$ mice are under the C57bl/6 genetic background, which predisposes mice to benign monoclonal gammopathy with higher levels of IgG (43). Crossing *Myd88*$^{p.L252P}$ mice to the Balb/c background may promote IgM MGUS and WM as aged Balb/c mice have higher levels of IgM rather than IgG (44). Compound transgenic Balb/c mice that harbor the human *BCL2* and *IL6* transgenes and lack the *Aid* gene developed, with 100% incidence and short latency (93 days median survival), a severe IgM$^+$ lymphoproliferative disorder that recapitulated many features of human WM (45). NF-κB, STAT3, and MAPK/ERK are activated, yet the *Myd88* gene is not somatically mutated in lymphomas developed in aged mice (45).

MYD88 L265P in Therapeutic Implications

Based on the functional consequence of MYD88 L265P activity, several strategies have been devised to halt its oncogenic activation by targeting IRAK1/4, JAK, and, the most successful target, BTK, or by disrupting the myddosome assembly. Moreover, MYD88 L265P-containing peptides can elicit human leukocyte antigen (HLA) class I–restricted cytotoxic T-cell responses (46, 47), supporting the potential for T-cell receptor (TCR)-based immunotherapy (Fig. 1D).

The BTK inhibitor ibrutinib (also known as PCI-32765) reduces the binding strength of BTK to MYD88 L265P. Inhibition of either BTK or IRAK1/4 induced apoptosis of WM cells, and their combination resulted in more robust inhibition of NF-κB signaling and synergistic WM cell killing (38, 48, 49). In a phase I/ II clinical trial that involved 80 patients with relapsed or refractory DLBCL, ibrutinib produced complete or partial responses in 37% of those with ABC-DLBCL (50). ABC tumors with BCR mutations responded to the drug (56%), especially those with concomitant *MYD88* mutation (80%), in agreement with *in vitro* data on BCR and MYD88 pathways (50). In a phase II trial of patients ($n = 63$) with relapsed or refractory WM, patients received ibrutinib until disease progression or unacceptable toxicity occurred (51); the objective response rate was 91%, and the major response rate was 73% (51). It was therefore concluded that ibrutinib was highly active, associated with durable responses, and safe in patients with WM who had previously received therapy (51). Based on these data, ibrutinib (Imbruvica) was approved for the treatment of WM (52). Ibrutinib is particularly effective in CNS DLBCL patients: 94% showed tumor reductions with ibrutinib alone and 86% of evaluable patients achieved complete remission with ibrutinib plus chemotherapy (53).

Compared with WT MYD88, mutated MYD88 protein has enhanced IRAK4 and pIRAK1 binding and can form the myddosome without external stimuli, thus heightening canonical NF-κB signaling in *MYD88* L265P WM cell lines (12, 38). Using minipeptides designed to compete with MYD88 TIR and DD domain interactions to disrupt the myddosome self-assembly, Liu and colleagues found that expression of two MYD88 minipeptides (MYD88$^{181\text{-}202}$ and MYD88$^{40\text{-}85}$) blocked the growth of *MYD88* L265P BCWM.1 and MWCL-1 cells, but not that of WT *MYD88* Ramos cells (54). Furthermore, these minipeptides induced apoptosis, reduced IRAK1 phosphorylation, and attenuated NF-κB activation in *MYD88* L265P WM cells (54). Inhibition of MYD88 homodimerization

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using another peptide IMG-2005-5 (IMGENEX) reduced NF-κB activation in WM cell lines (BCWM.1 and MWCL-1) expressing MYD88 L265P (14). Olson and coworkers performed high-throughput computational screening to identify drug-like inhibitors of MYD88 homodimer formation; biochemical and cellular assays revealed that a promising compound, T6167923, disrupts MYD88 homodimer formation by targeting its TIR domain, though its efficacy for *MYD88* L265P was not tested (55). These data indicate that interference of myddosome assembly is an attractive option for developing target therapies for WM and other lymphoproliferative disorders driven by *MYD88* L265P.

Tumor-specific neoepitopes, derived from protein-altering mutational events like missense mutations, may be perceived as foreign by the human immune system and induce tumor-specific T-cell immunity (56, 57). Growing evidence demonstrates that therapeutic peptide-vaccines that target tumor neoepitopes elicit specific immune responses and improve outcome (58, 59). MYD88 L265P is one such tumor-specific mutation. Based on *in silico* predictions, Nelde and colleagues identified potential MYD88 L265P-containing ligands of HLA for several HLA class I restrictions (46). A few MYD88 L265P-derived ligands elicited specific cytotoxic T-cell responses for HLA-B*07 and -B*15. The HLA-B*15–restricted peptide is HQKRPIPIKY (named $P4_{B*15}$; the L265P is underlined). $P4_{B*15}$-specific $CD8^+$ T cells from healthy blood donors showed IFNγ and TNFα secretion after stimulation with the peptide $P4_{B*15}$ but not with the WT peptide. Furthermore, $P4_{B*15}$-specific $CD8^+$ T cells elicited mutant peptide-restricted cytotoxicity (46). In a separate study, Nielsen and colleagues assessed T cells from healthy donors for recognition of MYD88 L265P-containing peptides and identified CD8+ T cells against RPIPIKYKA when presented by HLA-B*07:02 (47). In both cases, healthy individuals harbor T cells with specific TCRs that recognize L265P-containing neoantigens restricted by MHC, highlighting the potential of TCR recognition of *MYD88* L265P-derived peptides as a novel personalized therapeutic strategy.

Summary and Future Directions

To summarize, *MYD88* L265P is a prevalent somatic mutation in patients with WM, IgM MGUS, ABC-DLBCL, and other non-Hodgkin lymphomas. The discovery of this somatic mutant affords us numerous opportunities to improve lymphoma diagnosis and treatment. Further dissection of *MYD88* L265P at the molecular and cellular levels and using mouse models will produce insights into the underlying mechanisms of its oncogenic action and devise novel avenues for drug development against lymphoid malignancies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Lord KA, Hoffman-Liebermann B, Liebermann DA. Nucleotide sequence and expression of a cDNA encoding MyD88, a novel myeloid differentiation primary response gene induced by IL6. Oncogene 1990;5:1095–7.
2. Bonnert TP, Garka KE, Parnet P, Sonoda G, Testa JR, Sims JE. The cloning and characterization of human MyD88: a member of an IL-1 receptor related family. FEBS Lett 1997;402:81–4.
3. Burns K, Martinon F, Esslinger C, Pahl H, Schneider P, Bodmer JL, et al. MyD88, an adapter protein involved in interleukin-1 signaling. J Biol Chem 1998;273:12203–9.
4. Dunne A, Ejdeback M, Ludidi PL, O'Neill LA, Gay NJ. Structural complementarity of Toll/interleukin-1 receptor domains in Toll-like receptors and the adaptors Mal and MyD88. J Biol Chem 2003;278:41443–51.
5. Muzio M, Ni J, Feng P, Dixit VM. IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling. Science 1997;278:1612–5.
6. Lin SC, Lo YC, Wu H. Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. Nature 2010;465:885–90.
7. Li X, Commane M, Jiang Z, Stark GR. IL-1-induced NFkappa B and c-Jun N-terminal kinase (JNK) activation diverge at IL-1 receptor-associated kinase (IRAK). Proc Natl Acad Sci U S A 2001;98:4461–5.
8. Qian Y, Commane M, Ninomiya-Tsuji J, Matsumoto K, Li X. IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NFkappa B. J Biol Chem 2001;276:41661–7.
9. Wesche H, Henzel WJ, Shillinglaw W, Li S, Cao Z. MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. Immunity 1997;7:837–47.
10. Hu J, Jacinto R, McCall C, Li L. Regulation of IL-1 receptor-associated kinases by lipopolysaccharide. J Immunol 2002;168:3910–4.
11. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–11.
12. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, et al. Oncogenically active MYD88 mutations in human lymphoma. Nature 2011; 470:115–9.
13. Cao X, Medeiros LJ, Xia Y, Wang X, Thomas SK, Loghavi S, et al. Clinicopathologic features and outcomes of lymphoplasmacytic lymphoma patients with monoclonal IgG or IgA paraprotein expression. Leuk Lymphoma 2016;57:1104–13.
14. Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med 2012;367: 826–33.
15. Kapoor P, Ansell SM, Braggio E. Waldenstrom macroglobulinemia: genomic aberrations and treatment. Cancer Treat 2016;169:321–61.
16. Kyle RA, Therneau TM, Rajkumar SV, Remstein ED, Offord JR, Larson DR, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. Blood 2003;102:3759–64.
17. Tsai H-T, Caporaso NE, Kyle RA, Katzmann JA, Dispenzieri A, Hayes RB, et al. Evidence of serum immunoglobulin abnormalities up to 9.8 years before diagnosis of chronic lymphocytic leukemia: a prospective study. Blood 2009;114:4928–32.
18. Landgren O, Staudt L. MYD88 L265P somatic mutation in IgM MGUS. New Engl J Med 2012;367:2255–6; author reply 56–7.
19. Camilleri-Broet S, Criniere E, Broet P, Delwail V, Mokhtari K, Moreau A, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood 2006;107:190–6.
20. Hoefnagel JJ, Dijkman R, Basso K, Jansen PM, Hallermann C, Willemze R, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671–8.
21. Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. Blood 2014;123:486–93.
22. Xu L, Hunter ZR, Yang G, Zhou Y, Cao Y, Liu X, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood 2013;121:2051–8.

23. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–90.
24. Lenz G, Staudt LM. Aggressive lymphomas. N Engl J Med 2010;362: 1417–29.
25. Wang JQ, Jeelall YS, Beutler B, Horikawa K, Goodnow CC. Consequences of the recurrent MYD88(L265P) somatic mutation for B cell tolerance. J Exp Med 2014;211:413–26.
26. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 2003;100: 9991–6.
27. Lenz G, Nagel I, Siebert R, Roschke AV, Sanger W, Wright GW, et al. Aberrant immunoglobulin class switch recombination and switch translocations in activated B cell-like diffuse large B cell lymphoma. J Exp Med 2007;204:633–43.
28. Swerdlow SH, Kuzu I, Dogan A, Dirnhofer S, Chan JK, Sander B, et al. The many faces of small B cell lymphomas with plasmacytic differentiation and the contribution of MYD88 testing. Virchows Arch 2016;468:259–75.
29. Wang JQ, Jeelall YS, Humburg P, Batchelor EL, Kaya SM, Yoo HM, et al. Synergistic cooperation and crosstalk between MYD88(L265P) and mutations that dysregulate CD79B and surface IgM. J Exp Med 2017; 214:2759–76.
30. Zhan C, Qi R, Wei G, Guven-Maiorov E, Nussinov R, Ma B. Conformational dynamics of cancer-associated MyD88-TIR domain mutant L252P (L265P) allosterically tilts the landscape toward homo-dimerization. Protein Eng Des Sel 2016;29:347–54.
31. Vyncke L, Bovijn C, Pauwels E, Van Acker T, Ruyssinck E, Burg E, et al. Reconstructing the TIR Side of the Myddosome: a Paradigm for TIR-TIR Interactions. Structure 2016;24:437–47.
32. Braggio E, Keats JJ, Leleu X, Van Wier S, Jimenez-Zepeda VH, Valdez R, et al. Identification of copy number abnormalities and inactivating mutations in two negative regulators of nuclear factor-kappaB signaling pathways in Waldenstrom's macroglobulinemia. Cancer Res 2009;69:3579–88.
33. Hunter ZR, Yang G, Xu L, Liu X, Castillo JJ, Treon SP. Genomics, signaling, and treatment of Waldenstrom macroglobulinemia. J Clin Oncol 2017; 35:994–1001.
34. Varettoni M, Zibellini S, Defrancesco I, Ferretti VV, Rizzo E, Malcovati L, et al. Pattern of somatic mutations in patients with Waldenstrom macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica 2017;102:2077–85.
35. Avbelj M, Wolz OO, Fekonja O, Bencina M, Repic M, Mavri J, et al. Activation of lymphoma-associated MyD88 mutations via allostery-induced TIR-domain oligomerization. Blood 2014;124:3896–904.
36. Lu L, Zhu F, Zhang M, Li Y, Drennan AC, Kimpara S, et al. Gene regulation and suppression of type I interferon signaling by STAT3 in diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 2018;115: E498–505.
37. Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. Nat Rev Drug Discov 2013;12:229–43.
38. Yang G, Zhou Y, Liu X, Xu L, Cao Y, Manning RJ, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. Blood 2013;122:1222–32.
39. Gutierrez NC, Ocio EM, de Las Rivas J, Maiso P, Delgado M, Ferminan E, et al. Gene expression profiling of B lymphocytes and plasma cells from Waldenstrom's macroglobulinemia: comparison with expression patterns of the same cell counterparts from chronic lymphocytic leukemia, multiple myeloma and normal individuals. Leukemia 2007;21:541–9.
40. Yang G, Buhrlage SJ, Tan L, Liu X, Chen J, Xu L, et al. HCK is a survival determinant transactivated by mutated MYD88, and a direct target of ibrutinib. Blood 2016;127:3237–52.
41. Rousseau S, Martel G. Gain-of-function mutations in the toll-like receptor pathway: TPL2-mediated ERK1/ERK2 MAPK activation, a path to tumorigenesis in lymphoid neoplasms? Front Cell Dev Biol 2016;4:50.
42. Knittel G, Liedgens P, Korovkina D, Seeger JM, Al-Baldawi Y, Al-Maarri M, et al. B-cell-specific conditional expression of Myd88p.L252P leads to the development of diffuse large B-cell lymphoma in mice. Blood 2016;127: 2732–41.
43. van den Akker TW, de Glopper-van der Veer E, Radl J, Benner R. The influence of genetic factors associated with the immunoglobulin heavy chain locus on the development of benign monoclonal gammapathy in ageing IgH-congenic mice. Immunology 1988;65:31–5.
44. Kalpaktsoglou PK, Hong R, Good RA. The five classes of immunoglobulins in normal C3H and BALB/c mice. Immunology 1973;24:303–14.
45. Tompkins VS, Sompallae R, Rosean TR, Walsh S, Acevedo M, Kovalchuk AL, et al. Transgenic mouse model of IgM(+) lymphoproliferative disease mimicking Waldenstrom macroglobulinemia. Blood Cancer J 2016;6: e488.
46. Nelde A, Walz JS, Kowalewski DJ, Schuster H, Wolz OO, Peper JK, et al. HLA class I-restricted MYD88 L265P-derived peptides as specific targets for lymphoma immunotherapy. Oncoimmunology 2017;6:e1219825.
47. Nielsen JS, Chang AR, Wick DA, Sedgwick CG, Zong Z, Mungall AJ, et al. Mapping the human T cell repertoire to recurrent driver mutations in MYD88 and EZH2 in lymphoma. Oncoimmunology 2017;6:e1321184.
48. Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107:13075–80.
49. Herman SE, Gordon AL, Hertlein E, Ramanunni A, Zhang X, Jaglowski S, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood 2011;117:6287–96.
50. Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21:922–6.
51. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med 2015;372:1430–40.
52. Raedler LA. Imbruvica (Ibrutinib): first drug approved for the treatment of patients with Waldenstrom's macroglobulinemia. Am Health Drug Benefits 2016;9(Spec Feature):89–92.
53. Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell 2017;31:833–43.e5.
54. Liu X, Hunter ZR, Xu L, Chen J, Chen JG, Tsakmaklis N, et al. Targeting myddosome assembly in waldenstrom macroglobulinaemia. Br J Haematol 2017;177:808–13.
55. Olson MA, Lee MS, Kissner TL, Alam S, Waugh DS, Saikh KU. Discovery of small molecule inhibitors of MyD88-dependent signaling pathways using a computational screen. Sci Rep 2015;5:14246.
56. van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol 2013;31:e439–42.
57. Coulie PG, Lehmann F, Lethe B, Herman J, Lurquin C, Andrawiss M, et al. A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma. Proc Natl Acad Sci U S A 1995;92:7976–80.
58. Bian Y, Zhang Z, Sun Z, Zhao J, Zhu D, Wang Y, et al. Vaccines targeting PreS1 domain overcome immune tolerance in HBV carrier mice. Hepatology 2017;66:1067–82.
59. Schumacher T, Bunse L, Pusch S, Sahm F, Wiestler B, Quandt J, et al. A vaccine targeting mutant IDH1 induces antitumour immunity. Nature 2014;512:324–7.

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