MYD88 Wild Type in IgM Monoclonal Gammopathies

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High frequencies of *MYD88*^{L265P} mutation are observed in IgM monoclonal gammopathies, and specifically in Waldenström macroglobulinemia (WM), indicating this mutation as a potential disease biomarker.

Keywords: Waldenström macroglobulinemia ; MYD88 ; wild type

1. Introduction

Mature B-cell neoplasms are clonal tumors of B-cells characterized as a group of diseases with a highly heterogeneous profile, both biologically and clinically. Depending on the entity, the clinical course may range from an indolent to an aggressive disease. Mature B-cell neoplasms constitute more than 90% of lymphoid neoplasms and, based on histology and immunophenotype, they account for 34 different entities, including diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic lymphoma (CLL), Burkitt lymphoma (BL), lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM), splenic marginal zone lymphoma (SMZL), nodal marginal zone lymphoma (NMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and hairy cell leukemia (HCL) [1]. They exhibit a broad spectrum of characteristic cytogenetic abnormalities and genetic aberrations, which are partly characteristic among different B-cell neoplasms but are (most of the time) not specific enough for a definitive diagnosis. Some of the cytogenetic abnormalities include recurrent translocations such as t(11;14) (q13;q32) seen in >95% cases of MCL, t(14;18) (q32;q21) seen in 90% cases of FL, t(8;14) (q24;q32) seen in 80% cases of BL, and 6q deletion (del6q) seen in 27% cases of WM [2][3][4][5] while genetic aberrations include gene mutations, such as *BRAF* V600E in HCL, immunoglobulin heavy chain gene (*IGHV*) in CLL, and *MYD88* L265P in WM [6][7].

IgM monoclonal gammopathy is a heterogeneous group of B-cell/plasma cell clonal diseases that includes a range of conditions from monoclonal gammopathy of undetermined significance to Waldenström macroglobulinemia, IgM multiple myeloma, and less common, other B-cell neoplasms secreting IgM.

Studies by Treon et al. and other researchers suggested the *MYD88*^{L265P} mutation is present in >90% of WM, and that it could be important for the differential diagnosis of WM [8] vs. plasma cell malignancies. This mutation is also present in various other B-cell neoplasms such as SMZL, CLL, and DLBCL, but at a lower frequency [9][10][11][12][13]. Studies have shown that WM patients lacking the *MYD88*^{L265P} may be less responsive to Bruton's tyrosine kinase (BTK) inhibitors [14], which may also be associated with a lower number of tumor cells and lower International Prognostic Scoring System score at presentation [11]. In the most recent WHO nomenclature and classification, *MYD88* wild-type (*MYD88*^{WT}) does not exclude the diagnosis of WM; however, it may be associated with a genetic profile other than *MYD88*^{L265P} WM. Hence, the prognostic impact of *MYD88*^{WT} genotype [11] requires further study.

2. *MYD88*: Role, Pathway, Origin of Mutation

MYD88 plays an important role in the functional integrity of the innate immune response. The *MYD88* gene was first described in the 1990s as a primary differentiation response gene which is upregulated during IL6-induced terminal differentiation and growth arrest. It encodes for a protein called myeloid differentiation primary response 88 (MYD88), located in the cytosol, which is involved in the signaling pathways within immune cells triggered by Toll-like receptors (TLRs) and interleukin-1 receptors (IL-1Rs). The MYD88 gene is located on human chromosome 3p22.2. It spans approximately 11.7 kilobases and consists of five exons [15]. In normal physiology, MYD88 acts as an adaptor of inflammatory signaling via the canonical NF-κB pathway. The MYD88 protein contains a death domain (DD), an intermediate linker domain (ID), and a Toll/IL-1 receptor (TIR) domain at the C-terminus. The DD enables protein–protein interactions; the absence of ID has been associated with the inability of MYD88 to support signaling [16] while the TIR domain mediates the downstream signaling cascade by interacting with TLRs and IL-1Rs. These domains are essential for MYD88's function in innate immune signaling [17][18]. Upon activation of TLRs or IL-1Rs, MYD88 is recruited to the receptor complex, leading to the formation of a signaling complex known as the Myddosome. This complex acts as a

platform for the recruitment of downstream signaling molecules; activated MYD88 recruits IL-1 receptor-associated kinases (IRAKs), a serine-threonine kinase, and together they phosphorylate IRAK1 and IRAK2 which, in turn, interact with TNF receptor-associated factor 6 (TRAF6), initiating the activation of various signaling pathways, including transforming growth factor beta-activated kinase 1 (TAK1), mitogen-activated protein kinase (MAPK), and TAK1-binding protein (TAB) [18][19]. Activation of MYD88-dependent signaling pathways leads to the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), as well as the expression of co-stimulatory molecules necessary for an effective immune response [19]. Ngo et al. were the first to identify that inhibition of MYD88 signaling via a non-synonymous, gain-of-function mutation in *MYD88* gene, leading to an amino acid change of leucine to proline at position 265 (NM_002468.5) (in the TIR domain), resulted in decreased NFκB activity and enhanced survival of activated B-cell-type diffuse large-cell lymphoma cell lines [12]. Other recurrent mutations in *MYD88* have also been reported, although the impact of these mutations is still under investigation due to their low prevalence [20]. As previously mentioned, MYD88 DD and ID are responsible for downstream signal propagation via IRAKs, whereas the TIR domain integrates signals from upstream TLR and IL1R [21][22][23]. In the case of the $MYD88^{L265P}$ mutation, the TIR domain of *MYD88*, where this mutation resides, is highly activated compared to the $MYD88^{WT}$, and this increases downstream signaling and formation of the Myddosome complex. It has been shown that mutated MYD88 recruits IRAK1 and, together with IRAK4, promotes the survival of activated B-cell-(ABC)-diffuse large B-cell lymphoma (DLBCL) cell lines [12]. Hence it has been hypothesized that $MYD88^{L265P}$ occurs in B-cell neoplasms where there is a strong selection for aberrant NFκB signaling [23]. Since $MYD88^{L265P}$ constitutively activates the NFκB pathway, it is contemplated as an important oncogenic driver in B-cell lymphomas [12][24][25]. Non-L265P mutations (M232T, S243N, S222R, and T294P) have an intermediate effect on NFκB pathway signaling compared to the $MYD88^{WT}$, which shows the lowest activity [12]. In addition to NFκB activation, L265P induces B-cell proliferation, which is accompanied with the induction of TNFAIP3 [26]. However, although studies have shown that L265P triggers the anti-apoptotic NFκB signaling that, in turn, enables cell survival during B-cell development, is not capable of providing a continuous B-cell clonal selection on its own, and for this reason, a second somatic mutation is required [26]. In WM, these mutations usually reside in genes such as *CXCR4*, which is the second most mutated gene, *TNFAIP3*, *CD79 A/B*, and *ARID1 A/B* [27][28]. In WM, patients who harbor the L265P mutation have also been reported to bear a mutation in the 196 tyrosine residue of *CD79B* gene, leading to a better response to BTK-based therapies [29].

In addition to NFκB pathway signaling, the BCR pathway also plays an important role in B-cell survival and proliferation and the oncogenesis of various B-cell lymphomas in combination with *MYD88* mutations [30]. Within the BCR signaling cascade, BTK acts as an integral protein which forms complexes with $MYD88^{L265P}$ but not $MYD88^{WT}$ cells [31]. Furthermore, the level of phosphorylated BTK is higher in WM cells with L265P mutation than lymphoma cells with WT *MYD88* [31]. Therefore, inhibition of BTK would result in the disruption of the $MYD88^{L265P}$ complex but would not significantly affect the $MYD88^{WT}$ cells.

3. *MYD88* Mutation Detection Assays

Currently used methods to detect $MYD88^{L265P}$ mutation most often involve allele-specific polymerase chain reaction (AS-PCR), ddPCR and Sanger sequencing, or use of NGS-based protocols in unsorted or sorted (for Sanger sequencing or NGS) bone marrow (BM) aspirates of patients with IgM monoclonal gammopathies [32][33][34][35][36][37][38]. The sensitivity of the molecular assay for the detection of $MYD88^{L265P}$ should not exceed a detection limit of 10^{-3}. It has been shown that conventional polymerase chain reaction (PCR) and Sanger sequencing–based methods for MYD88 mutational detection have a low sensitivity of 25%, and although fairly described, should be considered especially when used in non-selected B-cells [39][40]. Non-L265P *MYD88* mutations have also been identified in patients with WM, including S219C, M232T, and S243N [41][42]. Furthermore, the evaluation of cell-free DNA (cfDNA) for the mutational characterization and monitoring of disease burden has recently been described in several hematological malignancies, including IgM monoclonal gammopathies, and has shown remarkable results [43][44][45]. It is a less invasive, patient-friendly test that could provide a good diagnostic yield, even comparable to BM, but the challenges in the detection sensitivity should be evaluated. Data so far have shown that only highly sensitive techniques such as ddPCR or Cast-PCR should be used for the detection of $MYD88^{L265P}$ mutation in cfDNA [36][38]. However, all these techniques, although promising, need to be standardized and implemented in prospective studies before they can be used in clinical practice; therefore, the current recommendation for molecular analysis is to perform BM aspiration at diagnosis [3].

4. $MYD88^{WT}$ Genotype in IgM Monoclonal Gammopathies

Patients with $MYD88^{WT}$ genotype have not been studied extensively due to the low prevalence of this genotype; hence, the effect of this genotype on the disease outcome of patients with IgM monoclonal gammopathies is still unclear. While

most WM cases have mutated *MYD88* gene, 5–10% do not carry *MYD88* mutations. Some studies show that WT WM patients may have a shorter overall survival (OS) (10-year OS of 73% in WT versus 97% in mutated patients) [46][47] while other studies indicate that the OS is not affected in this subgroup of patients [28][48]. Treon et al. suggested that although *MYD88*^{WT} patients with suspected WM fulfil the WHO criteria for WM diagnosis, around 30% have an alternate diagnosis [49] such as IgM MM, where the predominant plasma cell compartment and the high IgM levels are the main characteristics [50]. A study by Lee et al. showed that DLBCL patients with L265P had a statistically significant inferior overall survival compared to DLBCL patients with the WT genotype [51]. In other subtypes of B-NHL, such as CLL and SMZL, *MYD88*^{L265P} is associated with superior survival compared to WT *MYD88* [52][53][54]. In IgM-MGUS patients, although the presence of *MYD88*^{L265P} mutation has been associated with greater risk of progression to WM [34][55], most IgM-MGUS patients never progress to WM or other lymphoproliferative disorders, so this mutation cannot be considered a unique pathogenic factor in WM, and other WM precursors might exist rather than the transformation from IgM-MGUS [56] [57]. In contrast to the “classic” IgM-MGUS cases that typically evolve to WM or even MZL, IgM-MGUS cases with a plasma cell infiltrate, rather than a predominant B-cell clone, may serve as precursors to IgM MM [49]. A study by Treon et al. showed that among patients with suspected *MYD88*^{WT} WM, 10% had findings consistent with IgM myeloma characterized by predominant plasma cell clone and a significantly higher IgM level compared to *MYD88*^{WT} WM patients [49].

Few studies have compared the clinical and laboratory features of *MYD88*^{WT} versus *MYD88*^{L265P} cases in WM. Patkar et al. found that WT patients had lower hemoglobin and IgM paraprotein levels, lower tumor burden in the bone marrow, lower prognostic score, higher total leukocyte counts (TLC), and higher platelet counts compared to *MYD88* mutated cases [11]. Treon et al., in a study which included 150 patients with B-cell neoplasms, also showed lower serum IgM levels, TLC, and bone marrow infiltration, but also an association with older age in WT patients. Given the low prevalence of WT genotype across patients with IgM monoclonal gammopathies, some experts in the WM field consider the disease with this genotype to be an entirely separate clinicopathological entity, distinct from the typical WM associated with *MYD88* gene mutation, and are proposing that the presence of the L265P mutation should be considered as a WM-defining feature [46]. However, since the WM disease characteristics and severity assessed by the IPSS-WM, the bone marrow involvement, and patients’ performance status are similar between the two subgroups, the diagnosis could not be other than an active WM with a different genotype status. Therefore, more studies on *MYD88*^{WT} patients need to be conducted, wherein the combination of high throughput molecular assays, such as single-cell RNA seq analysis and a close follow-up of these patients, will lead to a better understanding of this genetically distinct subgroup of patients at both the biological and the clinical level.

In terms of the genomic landscape of WM patients harboring the *MYD88*^{WT} genotype, Hunter et al. provided the first—and, to date, only—study, aiming to explore the genomic and transcriptomic characteristics of WM WT patients in a cohort of patients that included 18 *MYD88*^{WT} patients [58]. Data from this analysis were compared with previous genome and transcriptome data from *MYD88*^{L265P} WM patients [8][42][49][59]. This analysis in WT WM patients identified the presence of somatic mutations in NFκB-related genes, in genes that impact epigenomic dysregulation, and in genes that impair DNA damage repair. Transcriptionally, *MYD88*^{WT} patients showed similarities to the *MYD88*^{L265P} patients, justifying the many overlapping disease characteristics noted between the two subsets of patients [46][49]. Transcriptomic studies have also shown that *MYD88*^{WT} WM clonal cells represent an earlier stage of B-cell differentiation compared to the *MYD88*^{L265P} clonal cells [59] which is also consistent with the lower rate of *IgH* somatic hypermutation previously described in *MYD88*^{WT} WM patients [35].

WM patients with *MYD88*^{WT} have also been shown to have an increased risk of disease transformation and resistance to ibrutinib monotherapy [49][58][60]. A study by Treon et al. showed a higher incidence of disease transformation to DLBCL in *MYD88*^{WT} WM patients, which also contributed to 36% of the death events observed in these patients [49]. Furthermore, this study showed that associated DLBCL events in *MYD88*^{WT} patients were also associated with shortened survival. In terms of response to ibrutinib therapy, IgM and hemoglobin responses were more frequent and deeper in *MYD88*^{L265P} WM cases, and significantly lower in *MYD88*^{WT} WM cases [61]. Response to therapy was also affected by the *CXCR4* mutational status, where patients with the *CXCR4*^{WT} genotype achieved better response rates compared to those with the *CXCR4*^{WHIM} genotype. Given the above data, it is suggested that patients with WT genotype should be followed closely due to the higher risk of histological transformation and higher resistance to BTK-based therapies [48][49][58][62][63].

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