Review Article

Targeting pathogenic mechanisms in marginal zone lymphoma: from concepts and beyond

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Abstract: Marginal zone lymphoma (MZL) represents a group of three distinct though overlapping lymphoid malignancies that includes extranodal, nodal and splenic marginal lymphoma. MZL patients usually present an indolent clinical course, although the disease remains largely incurable, save early stage disease that might be irradiated. Therapeutic advances have been limited due to the small patient population, and have largely been adapted from other indolent lymphomas. Here, we discuss the numerous targets and pathways which may offer the prospect of directly inhibiting the mechanisms identified promoting and sustaining marginal zone lymphomagenesis. In particular, we focus on the agents that may have at least a theoretical application in the disease. Various dysregulated pathways converge to produce an overarching stimulation of nuclear factor κB (NF-κB) and the *MYD88-IRAK4 axis*, which can be thus leveraged or targeting B-cell receptor signaling through BTK inhibitors (such as ibrutinib, zanubrutinib, acalabrutinib) and PI3K inhibitors (such as idelalisib, copanlisib, duvelisib umbralisib) or via more novel agents in development such as MALT1 inhibitors, SMAC mimetics, NIK inhibitors, IRAK4 or MYD88 inhibitors. NOTCH signaling is also crucial for marginal zone cells, but no clinical data are available with NOTCH inhibitors such as the γ-secretase inhibitor PF-03084014 or the NICD inhibitor CB-103. The hypermethylation phenotype, the overexpression of the PRC2-complex or the presence of *TET2* mutations reported in MZL subsets make epigenetic agents (demethylating agents, EZH2 inhibitors, HDAC inhibitors) also potential therapeutic tools for MZL patients.

Keywords: Marginal zone lymphoma (MZL); mucosa-associated lymphoid tissue (MALT); nuclear factor κB (NF-κB); NOTCH; PI3K; *MYD88*

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Introduction

Marginal zone lymphomas (MZLs) are mature lymphoid malignancies that have undergone somatic hypermutation and isotypic switching and are derived from the "marginal zone" region surrounding lymphoid follicles. The disease is generally divided into three distinct categories based on clinical and molecular characteristics: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT); nodal marginal zone lymphoma (NMZL); and lastly, splenic marginal zone lymphoma (SMZL) (1,2). The MZLs as a whole represents the second most common type of indolent

B-cell lymphoma, comprising approximately 6% of all non-Hodgkin lymphomas (NHL) cases (3). Despite their varying clinical presentations, the three entities share common features including an association with antigen stimulation, presence of specific translocations, and importantly, the activation of the nuclear factor κB (NF-κB) pathway.

To conceptualize a new therapeutic model around how to leverage our deepening understanding of MZL pathogenesis, it is instructive to identify those unique features of MZL pathogenesis, and to consider how best to inhibit those pathways and networks in a highly disease focused fashion. In an effort to appreciate these opportunities, we have structured concepts around specific therapeutic interventions in the context of the underlying deranged biology. Genomic profiling has had a substantial impact on our understanding of the molecular pathogenesis of MZL (4-19). These experiences have identified critical aberrations in the function of the B-cell receptor (BCR), NF-κB, Janus kinase (JAK)/signal transducers and activators of transcription (STAT), and Toll-Like Receptor/Interleukin (TLR/IL) signaling, each of which has at least one therapeutic agent that could impact that biology. Herein, we underscore that biology and the agents that may have at least a theoretical application in the disease.

Pathological mechanisms driving MZL and potential therapeutic interventions

Dysregulation of NF-κB signaling

NF-κB is central to many hematological malignancies and it is a clear driver in MZL as well. The NF-κB family of transcription factors is comprised of five structurally related genes: *NFKB1* (p105 and p50), *NFKB2* (p100 and p52), *RELA* (p65), *RELB* (RelB), and *REL* (c-Rel) (20). Activation of the NF-κB family of transcription factors can occur through two distinct pathways: canonical (classical) and non-canonical (alternative). The canonical pathway is mediated through activation of BCR, Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors, and tumor necrosis factors (TNF) family receptors, leading to the phosphorylation of I-kappa-B (IκB) by IκB kinase complex, permitting NF-κB to translocate to the nucleus. Alternatively, the non-canonical pathway is induced by B-cell activating factor belonging to the TNF family (BAFF) receptor, and CD40 (21), both of which leads to the activation of NF-κB inducible kinase (NIK) and IκB kinase α (IKKα), leading to phosphorylation and proteolysis of p100 that in turn creates the active subunit, p52. The p52-RelB heterodimer translocates into the nucleus in order to induce transcriptional activation of genes involved in cycle cell progression and proliferation (20,21).

There are several described genetic mechanisms, including recurring translocations [t(11; 18)(q21;q21); t(14;18) (q32;q21); t(1;14)(p22;q32)], that can lead to the dysregulation of the NF-κB signaling pathway in MZL (22-26). Fifteen to thirty percent of all MZL harbor inactivating mutations/deletions in *TNFAIP3* (A20), which codes for a key negative regulator of NF-κB pathway, thus representing one of the most common genetic events contributing to overactivation of the NF-κB pathway in MZL (7,9,27). As discussed below, various dysregulated pathways in MZL converge to produce an overarching stimulation of NF-κB, which can be leveraged to improve therapeutic interventions. These agents may include those targeting BCR signaling through Bruton's Tyrosine Kinase (BTK) inhibitors and phosphatidylinositol 3-kinase (PI3K) inhibitors to more novel agents in development such as MALT1 inhibitors. These pathways and their interplay are shared in *Figure 1*.

BCR and PI3K Pathway

BCR signaling plays a critical role in MZL pathogenesis, being one of several mechanisms that converge upon NF-κB activation. Chronic signaling through the BCR pathway, independent of antigen stimulation, is central for B-cell survival, and is mediated though the activation of the PI3K pathway (28,29). Engagement of the BCR induces phosphorylation of immunoreceptor tyrosine-based activation motif (ITAM) in the cytoplasmic domains of CD79A and CD79B by SRC family tyrosine kinases (LYN, FYN, and BLK) (30). Spleen tyrosine kinase (SYK) is recruited to the phosphorylated ITAMs, and in turn, augments the initial signal through further phosphorylation of ITAMs as well as autophosphorylation. Moreover, upon activation of BCR, the transmembrane protein CD19 is phosphorylated by LYN leading to PI3K recruitment and subsequent production of phosphatidylinositol-3,4,5-triphophosphate (PIP3). BTK is activated by LYN and SYK kinases, and in turn, phosphorylates phospholipase Cγ2 (PLCγ2), subsequently leading to the proteolysis of PIP2 (phosphatidylinositol 4,5-bisphosphate) into DAG (diacylglycerol) and IP3 (inositol trisphosphate), triggering an influx of calcium into the cytoplasm. Consequentially,

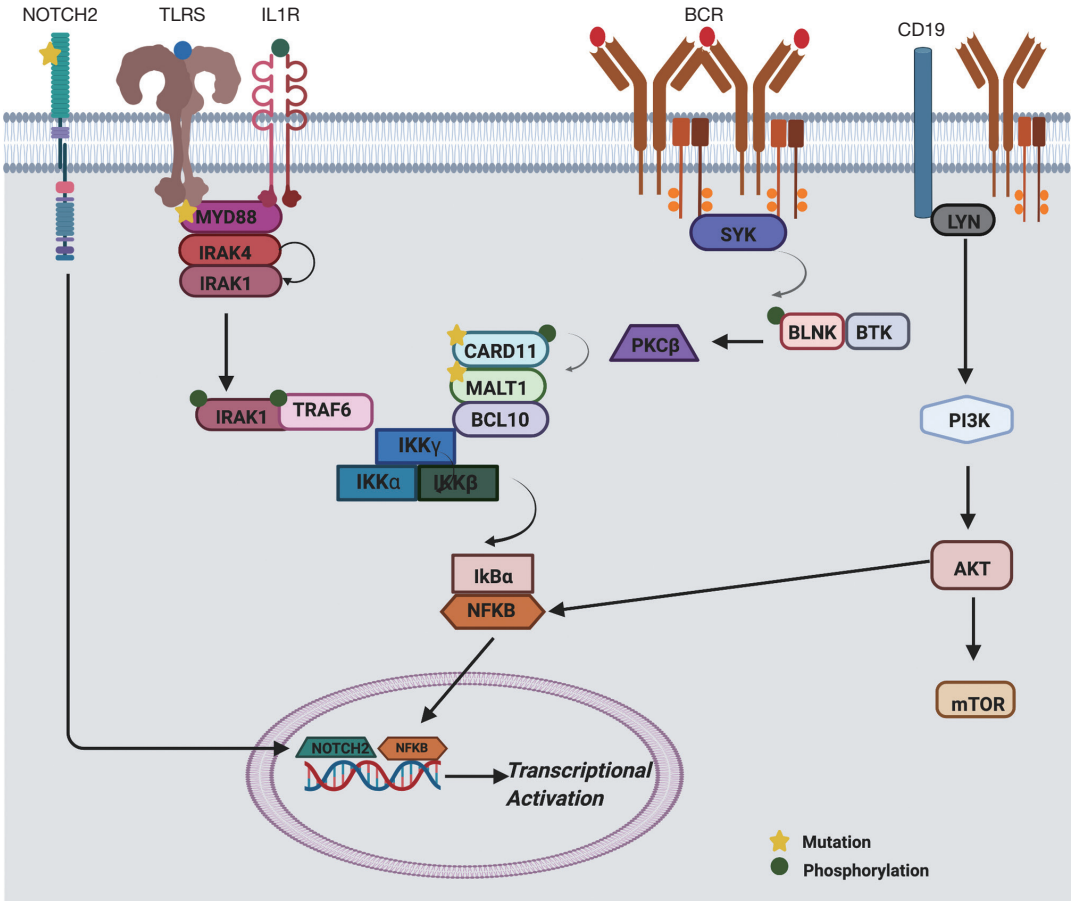

Figure 1 Driver pathways in the pathogenesis of marginal zone lymphoma. The NF-κB pathway plays a critical role in the development of MZL and can be activated by various mechanisms. BCR signaling dysregulation is a hallmark of MZL and can mimic antigen dependent BCR activation. Upon activation of BCR, SRC family proteins (i.e., LYN) phosphorylate the ITAMs of CD79A/B, which signals the recruitment of SYK in order to augment signaling. LYN is also able to activate and recruit PI3K pathway. BTK is then activated by LYN and SYK kinases, and in turn phosphorylates PLCγ2, leading to the proteolysis of PIP2 into DAG and IP3, triggering an influx of calcium into the cytoplasm that goes on to activate PKCβ. PKCβ phosphorylates CARD11, which then goes on to form the CBM complex with BCL10 and MALT1, eventually leading to downstream NF-κB activation. *MYD88* L265P mutations leads to lymphomagenesis through activation of the TLR and IL1R pathways independent of ligand stimulation. Additional mutations and overexpression in other proteins involved in BCR signaling and interrelated pathways include *CARD11*, *TNFAIP3*, *SYK*, *NOTCH2*.

protein kinase Cβ (PKCβ) is activated by the increase in calcium and DAG, and induces the phosphorylation of CARD11, leading to the formation of the CBM complex (CARD11-BCL10-MALT1), triggering the downstream activation of NF-κB, which is critical in the development and sustainment of MZL cells (31). The CBM complex ultimately activates a cascade of events that leads to the formation of p50/RelA and p50/c-Rel heterodimers, which migrate into the nucleus and induce transcriptional activation (30,32). Activating *CARD11* mutations are present in 5–10% of SMZL and NMZL, and lead to continual production or association of CBM complex components leading to IKKB activation of NF-κB pathway (12,33-35) and drives resistance in many lymphoid malignancies. Ultimately, both the BCR and PI3K pathways have the ability to promote lymphomagenesis.

Role of BTK inhibitors and PI3K inhibitors

Constitutive BCR signaling functions through a plethora of enzymes, scaffolding proteins, and protein-protein

complexes, with recent advances targeting BTK and PI3K as a means to inhibit this complex pathway. The BTK inhibitor ibrutinib (36) has been FDA approved for relapsed/refractory (R/R) MZL (37) based on a phase II trial of 63 patients who progressed after receiving a prior anti-CD20 therapy (median number of prior therapies =2, range, 1–9). After a median follow-up of 19.4 months, the overall response rate (ORR), median progression free survival (PFS) and median duration of response (DOR) were 48% (95% CI, 35–62%), 14.2 months (95% CI, 8.3 to not estimable), and not reached, respectively (38). Although the numbers of each subtype are limited, there appeared to be a difference in PFS across the MZL subtypes, where the median PFS was 19.4, 13.8, and 8.3 months in SMZL (n=14), EMZL (n=32), and NMZL (n=17), respectively (38).

Among second generation BTK inhibitors, clinical data are already available for zanubrutinib (39). ORRs were 0% and 78% in two separate phase I studies enrolling two and ten R/R MZL patients, respectively, with no CRs (40-42). In a phase II study with 20 R/R MZL patients, the ORR was 80%, of which 15% attained a CR, with a median time to response of 3 months, and a 24-month PFS of 59% (43). The ORR by MZL subtype was 78% (CR, 11%) in EMZL (n.=9), 100% (CR, 40%) in NMZL (n.=5) and 67% (CR, 0%) in SMZL (n.=6) (43). Less data is available for acalabrutinib (44) which has been studied in MZL cell lines (45), and is currently being evaluated in a phase Ib/II study alone or in combination wtih rituximab (NCT02180711).

Dysregulation of the PI3K-axis has been well established as a crucial driver of malignant transformation, especially in the lymphoproliferative malignancies. Many PI3K inhibitors have emerged over the past few years, and while these drugs share class similarities, each can be differentiated from one another when one delves into the detailed pharmacology. Idelalisib was the first-in-class PI3Kδ and PI3Kd inhibitor, with essentially no activity against PI3Kα and PI3Kβ, while maintaining inhibition of PI3Kγ (albeit 40x less than PI3Kδ) (46). Idelalisib was evaluated in a phase I study which established a recommended phase 2 dose of 150 mg twice per day. This phase I study included only six patients with MZL (9% of study) (47). Across the entire population of patients in the phase I, the ORR was 47% (30/64), with a median DOR of 18.4 months and median PFS of 7.6 months (47). In the phase II study of patients with indolent lymphomas (majority with a diagnosis of FL), the ORR was 57% (71/125) with a median PFS and OS of 11 and 20.3 months, respectively (48). Only 15 patients had MZL in the phase II portion of the study. Amongst the 15 MZL patients, the median PFS was 6.6 months, ORR of 47%, CR rate of 7% and DOR of 18.4 months (49). These data led to the accelerated approval of idelalisib in patients in R/R FL and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Despite the promising activity, idelalisib was associated with a number of immune mediated toxicities, including colitis, pneumonitis and hepatitis which have limited the general use of the drug.

Subsequently, two additional PI3K inhibitors, copanlisib and duvelisib, have been developed and approved by the U.S. FDA (50,51). These drugs have slightly different patterns of selectivity for the PI3K isoforms, with copanlisib targeting preferentially PI3Kδ and PI3Kα, while duvelisib potently inhibits PI3Kγ, along with PI3Kδ and other isoforms as well (50,51). Both drugs have been approved for R/R CLL (duvelisib) and FL (copanlisib, duvelisib). In the phase II DYNAMO trial of duvelisib in R/R indolent lymphomas, Flinn *et al.* demonstrated an ORR of 47% (61/129) (52). Specifically, the ORR in MZL population was 38.9% (7/18) (52). Given the fact that the chemical structures of idelalisib and duvelisib are quite similar, it is not surprising that the safety profile of the drugs are similar with regard to the immune-mediated side effects (52). In the CHRONOS-1 trial, copanlisib was evaluated in indolent B-cell lymphomas as well as peripheral T-cell lymphoma (PTCL) and demonstrated an ORR of 43.7% (14/32), median PFS of 294 days and median DOR of 390 days in the indolent cohort. Within the indolent cohort, only 3 patients had MZL (53). In an updated analysis, the ORR was 60.6%, with a median DOR, PFS, and OS of 14.1 months, 12.5 months and 42.6 months, respectively (54). Unique to the side effect profile of copanlisib was hyperglycemia and transient hypertension; however, diarrhea, colitis, pneumonitis, and neutropenia were also present. Again, to this date, neither drug has been FDA approved for MZL.

Umbralisib, an inhibitor of PI3Kδ and CK1ε (55), is the only PI3K inhibitor specifically studied in MZL. Based on the data from a phase II registration-directed trial in MZL (n=69), Zinzani *et al.* reported an ORR of 55%, with 4 CRs, and a 12-month PFS of 71% (56). The most common adverse events (AEs) (≥20%) of any grade included diarrhea (45%), nausea (29%), fatigue (26%) and headache (26%). Thus, in general, the toxicity profile is substantially better than for idelalisib and duvelisib, with far less immune-mediated toxicity. At this time, umbralisib has been designated 'Breakthrough Therapy' status with the U.S. FDA and is being submitted for accelerated FDA approval

for MZL and FL and may represent the first PI3K inhibitor approved for MZL.

To build upon the potential platform of PI3K inhibition in MZL, Tarantelli *et al.* performed combination cell-viability screening using copanlisib as the basis in a panel of lymphomas cell lines, including MZL and mantle cell lymphoma models (57). This study revealed that amongst 15 compounds tested, venetoclax in conjunction with copanlisib was the most synergistic, and the combination was then validated using a MZL xenograft model. Based on this pre-clinical data, a phase I trial investigating this combination is underway (NCT03886649), and is again representative of a non-chemotherapeutic predicated regimen that simultaneously targets various oncogenic mechanisms.

Moreover, Arribas and colleagues have recently reported on preclinical SMZL models of secondary resistance to idelalisib. This resistance is driven by epigenetic changes leading to the upregulation of tyrosine kinase receptors (PDGFRA or ERBB4) and secretion of factors (IL6 or HBEGF), therefore, providing the basis for novel combinations in this setting that target these resistant pathways (58).

SYK inhibitors

Development of small molecule SYK inhibitors is another method in order to mitigate constitutive BCR signaling found in MZL. As stated previously, upon BCR stimulation, Syk is recruited and leads to activation of BTK, PLCγ2, and PI3K. SYK has been found to be upregulated in all three MZL subtypes, making it a rationale therapeutic target upstream from the already more established BTK inhibitors and PI3K inhibitors (4-6).

Several SYK inhibitors, including fostamatinib (59-61), entospletinib (60,62), and cerdulatinib (inhibitor of SYK, JAK1/3 and TYK2) (63,64), have entered clinical trial development based on the rationale shared above. Much of the data available has been performed in DLBCL as well as CLL/SLL with little experience in MZL. The oral Syk inhibitor fostamatinib was evaluated in R/R DLBCL and indolent lymphomas in a phase I/II trial (59). Three patients with MZL were included in the phase II portion, with 1 patient with stable disease in a composite group of MZL and lymphoplasmacytic lymphoma. The most common AEs in the phase II portion was fatigue, diarrhea, transaminitis, and cytopenias (59). In a phase II study of entospletinib, 114 patients were enrolled, of that 17 subjects had a diagnosis of MZL (60). The ORR in the MZL subgroup was 11.8% (2/17), all of which were PRs, with 12 patients achieving stable disease (60). The most common grade ≥3 treatment emergent AEs included ALT elevation (15.8%), anemia (11.4%), fatigue (10.5%) and AST elevation (8.8%). Hamlin and colleagues evaluated cerdulatinib, a multi-kinase inhibitor, in patients with R/R B- and T-cell lymphomas, with an ORR of 61% in CLL/SLL, 50% in FL and 43% in PTCL (63); it is unclear how the MZL patients fared (n=8). Although a promising target, and perhaps due to the small numbers enrolled in the aforementioned studies, SYK inhibition has demonstrated limited activity as a single agent in MZL.

Immunomodulatory drugs

Lenalidomide is an immunomodulatory drugs (IMiD) shown to influence the ubiquitination and degradation of Ikaros, Aiolos and CK1α (65-68). The drug, possibly via pleotropic effects, including those on NF-κB and the microenvironment, has demonstrated an ORR of 61% and a CR of 33% as monotherapy in EMZL (69). To investigate a chemotherapy-free platform, the addition of lenalidomide to rituximab (R^2 regimen) in untreated MZL demonstrated a remarkable ORR 93%, with CR/CRu of 70%, and a median PFS of 59.8 months and 5-year OS of 96% (70). The R^2 regimen was further validated in the AUGMENT trial, which was a phase III, multicentered, randomized trial of R^2 *vs.* rituximab in conjunction with a placebo in patients with R/R follicular lymphoma (FL) or MZL (n=358) (71). At a median follow-up of 28.3 months, the PFS was significantly improved in the R^2 arm (39.4 months) compared to rituximab plus placebo cohort (14.1 months) [HR, 0.46; 95% CI, 0.34–0.62, P<0.0001]. Subgroup analysis evaluating MZL patients (n=63) demonstrated that there was no statistically significant difference between the two treatment arms (HR 1.0; 95% CI, 0.47–2.13), which was attributed to a small sample size and an imbalance in baseline characteristics, with many high-risk/advance features notably in the R^2 investigational arm. Nevertheless, based on the AUGMENT trial, the FDA approved R^2 regimen for both R/R FL and MZL patients. Extrapolating from this platform, a single-center phase II study is currently underway evaluating the merits of the combination of ibrutinib, lenalidomide and rituximab (iR^2) in previously untreated MZL and FL (NCT02532257). Results thus far have demonstrated an estimated 2-year PFS of 76% (95% CI: 60–96%), with a ORR of 80% and CR rate of 60% in MZL (n=10; 4 NMZL; 3 SMZL; 3 EMZL) (72). This data suggests that the combination of novel, targeted

therapies may lead to chemotherapy-free platforms that aim to inhibit multiple oncogenic pathways in MZL.

MALT1 inhibitors

The development of MALT1 inhibitors is being intensively investigated mostly for DLBCL (73-80), though there is preclinical evidence of anti-tumor activity in MZL models as a single agent or in combination such as with the PI3K inhibitor, copanlisib (57,81). A phase I study (NCT03900598) is currently on-going with the oral MALT1 inhibitor JNJ-67856633 in R/R B-cell lymphoma and CLL patients.

SMAC mimetics

The *BIRC3* gene, fused to *MALT1* in the t(11;18) of EMZL, and recurrently mutated in the other MZLs, codes for the cellular inhibitor of apoptosis 2 (cIAP2) protein, an E3 ubiquitin ligase important for the activation of the CBM complex (82). Different SMAC mimetics have been developed (83-86). LCL-161 has shown anti-tumor activity in MZL primary cells (87). Some SMAC mimetics are under clinical investigation as single agents or in combination for different oncological indications (83), but not specifically for MZL patients (83,87).

NIK inhibitors

NIK inhibitors, which would target both the classical and alternative NF-κB pathways, have been developed (88-95). As noted above, NIK activation correlates with increased activity of the NF-κB pathway and has been an attractive target as a means to downregulate this oncogenic driver. Although several inhibitors have been developed and studied, including in multiple myeloma models (96), no agent to date has entered clinical evaluation.

MYD88-IRAK4 Axis

TLR/ILR signaling is mediated through the recruitment of MYD88, an adaptor molecule, which forms the core of the Myddosome complex along with IRAK4 and serves as another method to which the canonical NF-κB pathway is stimulated (97-99). Upon ligand binding with lipopolysaccharide (LPS), lipoproteins, and IL-1, TLR/ILR dimerize or oligomerize, leading to the recruitment of MYD88 which then interfaces with IRAK4 through death domains (97) (*Figure 1*). The formation of the Myddosome is hierarchal. After ligand stimulation of TLR/IL1R, MYD88 recruits IRAK4, and subsequently, the MYD88-IRAK4 complex recruits IRAK1 or IRAK2 to form the Myddosome (97). IRAK1/2 is phosphorylated by IRAK4 and subsequently dissociates from the Myddosome in order to interact with TRAF6 (100), in turn, leading to the activation of downstream transcription factors such as NF-κB and AP-1 (101). Gain of function *MYD88* mutations are found in approximately 10–15% SMZL, NMZL and EMZL, and leads to constitutive activation of this pathway independent of ligand binding (8,102-105).

Attempts to target MYD88 has largely been unsuccessful as it is difficult to inhibit given the fact that it is an adaptor protein with no catalytic activity. ST2825 is a small molecule inhibitor that prevents dimerization of MYD88, however, it requires micromolar concentrations (>15 μM) in order to suppress the growth of lymphoma cell lines, and was found to have off target effects (106,107). T6167923, another MYD88 dimerization inhibitor, was found to protect mice from toxic-shock induced death in a dose dependent manner but has not been fully explored in malignancies addicted to MYD88 activation as a treatment option (108). On the contrary, targeting IRAK4, a key member of the Myddosome, has become a recent area of investigation. IRAK4 kinase inhibitors have been developed, including CA-4948, which is currently under investigation for patients with R/R B-cell lymphomas (NCT03328078) (109). More recently, IRAK4 degraders have been developed (110), with the thought that as IRAK4 serves as both a scaffolding and catalytic protein, the elimination of IRAK4 as a whole would lead to improved therapeutic efficacy compared to IRAK4 kinase inhibitors. To date, we await further clinical results of IRAK4 targeting, which may be a promising area of development.

NOTCH signaling

NOTCH proteins are transmembrane receptors, which are comprised of four regions: an extracellular domain (NECD), a transmembrane domain, an intracellular domain (NICD), and a PEST domain (111-114). After binding with Notch ligands, the NOTCH proteins are first cleaved by an ADAM metalloproteinase, leading to the release of the NECD, and, later, by a γ-secretase, which then initiates the translocation of NCID from the cell membrane to the nucleus. In the nucleus, NCID recruits transcriptional co-factors, and acts as transcriptional factor. The PEST domain contains a ubiquitination site critical for the proteasomal degradation of the NCID. In B-cells, active NOTCH2 signaling is fundamental for the differentiation of B-cells versus the

MZ phenotype (115-117), and, indeed, NOTCH signaling is activated by genetic events in MZL, especially in SMZL and NMZL (up to 40% of the cases) (8,11,12,16-18,103). Oncogenic mutations affecting the PEST domain, which induces the loss of negative regulation mediated via proteasomal degradation, are observed especially in the NOTCH2 gene (SMZL, 10–25%; NMZL, 25%; EMZL, <5%) and less frequently in NOTCH1. Notch activation is also sustained by recurrent inactivating mutations in genes coding for negative regulators such as DTX1, SPEN, and MAML2.

NOTCH inhibitors acting at different levels of the Notch signaling are available (111-114). Limited single agent anti-tumor activity has been observed using the γ-secretase inhibitor PF-03084014 (118) and the NICD inhibitor CB-103 (119) in SMZL cell lines with or without *NOTCH2* mutation. More promising results are seen combining the γ-secretase inhibitor with PI3K, BTK and EZH2 inhibitors, or with the hypomethylating agent, decitabine (118). However to date, no clinical data is available with compounds targeting NOTCH in MZL patients.

Methylation and chromatin remodeling

There are genomic and preclinical data supporting the use of demethylating agents in MZL.

First, one quarter of SMZL cases are associated with a very high degree of promoter hypermethylation, leading to silencing of tumor suppressor genes and over-expression of potential therapeutic targets (NF-κB, PI3K and BCR signaling; PRC2-complex, that is EZH2, EED, and SUZ12). This phenotype is associated with inferior outcomes and a higher risk of histologic transformation (118). In fact, exposure of SMZL cell lines to the demethylating agent decitabine demonstrates a strong *in vitro* and *in vivo* anti-tumor activity in SMZL cell lines (118), and can, at least partially, revert the methylation-related phenotype observed in primary clinical specimens (118).

Another set of data supporting the importance of methylation in MZL comes from the recently observed high prevalence of somatic mutations in the *TET2* gene in primary thyroid EMZLs (8,13). This gene encodes for a methylcytosine dioxygenase, which catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), a fundamental and critical role in DNA demethylation (120,121). Importantly, the presence of the *TET2* mutations in primary thyroid EMZLs is associated with increased DNA promoter methylation in genes targeted by the PRC2 complex members (EZH2, EED and SUZ12) (8). Interestingly, the transcriptome of *TET2* DLBCL mutants have important overlaps with the transcriptome of *CREBBP* DLBCL mutants (122), and CREBBP mutants are sensitive to HDAC3 inhibitors (123). In fact, silencing of TET2 sensitizes DLBCL cells to HDAC3 inhibitors. Therefore, considering that *CREBBP* mutations are also common in MZL, there is a clear rationale to explore HDAC3 and other epigenetic drugs in MZL.

Conclusions

Taken together, the three MZL subtypes share common pathological mechanisms, including prominent TLR, BCR and PI3K pathway dysregulation that cumulate to induce NF-κB activation, as well as clear epigenetic deregulation. Our understanding of the deeper molecular biology of MZL, although with some overlapping themes with other indolent lymphomas, can lead to the unique targeted platforms that leverage a precision-medicine approach, which will likely require combinations of two or more novel agents to achieve the optimal therapeutic outcome of long durable responses with limited toxicity.

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