

Biology of splenic and nodal marginal zone lymphomas

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Abstract: Splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL) are recognized as distinct subtypes of marginal zone lymphomas (MZLs) in the World Health Organization (WHO) classification. SMZL and NMZL share several morphological and immunophenotypic features. They are also rare and together, account for just over 3% of all B cell lymphomas. Their rarity and heterogeneity in terms of clinical presentation and biology can make their diagnosis difficult and can also complicate their molecular characterization. Despite these challenges, modern advances in high-throughput sequencing and cancer biology have granted unprecedented insights into the molecular pathogenesis of SMZL and NMZL. These techniques have provided a comprehensive overview of the genes and pathways that are deregulated in these diseases, including the identification of molecular aberrations that are associated with distinct MZL subtypes. SMZL and NMZL are characterized by mutations of genes involved in marginal zone (MZ) B cell differentiation and homeostasis including *KLF2* and components of NOTCH, NF- κ B, B cell receptor (BCR) and Toll-like receptor (TLR) signaling. Pathways involved in the differentiation of MZ B cells are also deregulated by epigenetic and post-transcriptional modifications. Although the genetic signatures of NMZL and SMZL largely overlap, the exclusive association of *PTPRD* mutations with NMZL, together with the absence of 7q deletion in this lymphoma, support the designation of NMZL and SMZL as different entities rather than different clinical presentations of the same disease. The aim of this review is to describe the molecular perturbations identified so far in SMZL and NMZL and discuss how these alterations might contribute to disease pathogenesis and inform clinical management.

Keywords: Splenic marginal zone lymphoma (SMZL); nodal marginal zone lymphoma (NMZL); NOTCH; NF- κ B; B cell receptor (BCR); Toll-like receptor (TLR); mutations; molecular pathogenesis; pathways; transcriptomic; epigenetic

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Introduction

Marginal zone lymphoma (MZL) comprises three different entities, as recognized by the World Health Organization (WHO) in the classification of lymphoid disorders: nodal MZL (NMZL), splenic MZL (SMZL) and extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma) (1).

NMZL and SMZL are infrequently occurring small B cell neoplasms; while NMZL originates in lymph nodes and subsequently infiltrates the spleen and bone marrow, SMZL originates in the spleen with frequent peripheral blood involvement. The postulated cell of origin is an antigen-experienced B cell, consistent with the homing B cells at the marginal zone (MZ). The normal MZ surrounds the

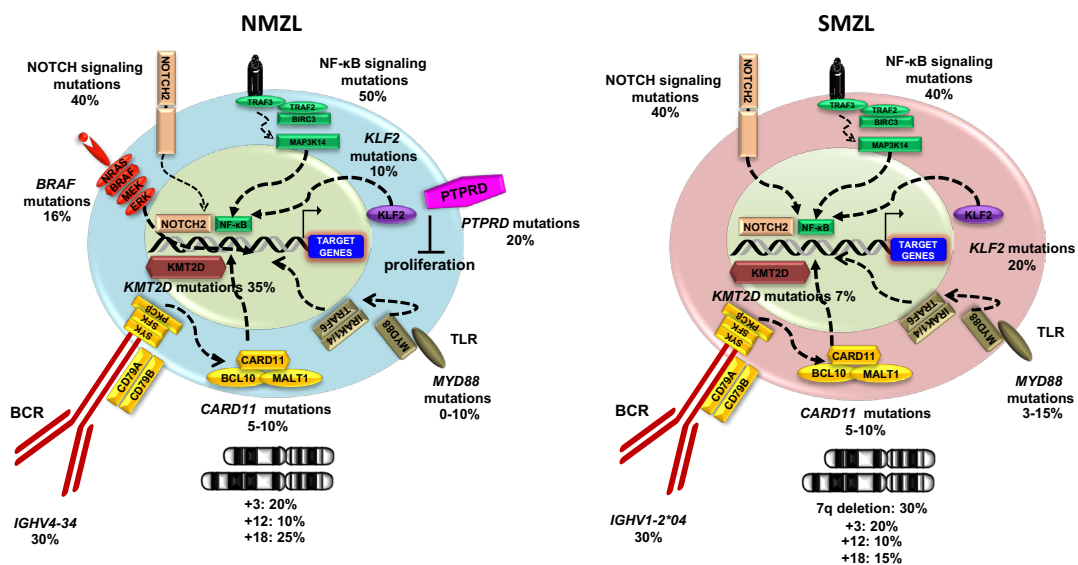


Figure 1 Key molecular alterations of SMZL and NMZL. Genes and pathways that are deregulated are schematically represented. The prevalence of molecular alterations is shown next to each gene or pathway.

secondary lymphoid follicles and is continuously exposed to extrinsic antigens that determine a rapid antibody response upon engagement of the B cell receptor (BCR).

The absence of diagnostic and prognostic biomarkers together with the relative rarity of these disorders makes their diagnosis and molecular investigation challenging. Genomic aberrations frequently result in the activation of survival pathways common to SMZL and NMZL. These include NF-κB activation as a result of mutation and/or deletions of *TNFAIP3*, mutations of chromatin remodeling genes, chromosomal trisomies (+3, +18), NOTCH pathway mutations and genomic aberrations affecting the *KLF2* transcription factor (2-13). In addition to shared alterations, there are also specific aberrations that characterize each subtype. In SMZL, deletions of 7q account for 30% of all chromosomal aberrations, while gains of 3/3q, 9q, 12q and 18q, and losses of 6q, 8p, 14q, and 17p occur less frequently (Figure 1) (14,15). Conversely, in NMZL deletion of 7q is absent, while trisomies of chromosomes 3, 18, 7, 12 and del6q are frequent clonal aberrations (Figure 1) (5,6,16).

Notably, unlike MALT lymphoma, neither SMZL or NMZL have specific chromosomal translocations involving the *IGH* locus and pro-survival genes. However, a higher prevalence of *KMT2D* mutations and loss of function mutations of *PTPRD* are reported for NMZL (5), and deletions affecting the long arm of chromosome 7 could be of diagnostic use in SMZL (4,17,18). Moreover, increased

expression of MNDA has been described as aiding the differential diagnosis between NMZL and follicular lymphoma (19), although the potential of MNDA as a biomarker in NMZL is yet to be determined in independent studies.

SMZL and NMZL

The lack of specific molecular biomarkers hinders precise diagnosis of SMZL or NMZL, particularly in the absence of spleen histology or in case of disseminate disease to the lymph nodes (20). Nevertheless, SMZL is characterized by a sinusoidal dissemination with a frequent nodular pattern of neoplastic cells in the bone marrow that is regarded as a possible hallmark of the disease (21). The course of MZL is usually indolent, although a fraction of patients (15–30%) progresses to a more aggressive disease (22–24). Hence, there is a clinical need for diagnostic and prognostic biomarkers that facilitate diagnosis of the disease and improve the risk stratification of patients.

The assumption that antigen stimulation could play a role in the pathogenesis and progression of MZL is supported by many studies (14,25–27). Evidence of somatic hypermutation (SHM) of the immunoglobulin heavy variable (*IGHV*) gene and the biased usage of *IGHV* gene rearrangements, point to antigen selection and expansion (14,25–27). The selective usage of immunoglobulin gene

rearrangement *IGHV1-2*04* in about 30% of SMZL cases (27,28), and the highly restricted stereotyped configuration of the BCR in about 10% of cases, suggest an antigen stimulation contribution (Figure 1). In NMZL around 30% to 40% of cases present *IGHV4-34* usage (28,29), and the mutational status of immunoglobulin gene rearrangements is significantly higher in most cases (Figure 1) (29). However, the specific antigens encountered by B cells expressing *IGHV1-2*04* or *IGHV4-34* are yet to be determined (30). Infection with the hepatitis C virus (HCV) seems to be related to the use of the *IGHV1-69* family in MZL (31-33).

Genomic landscape of SMZL and NMZL

Recent technological advances in genomics and functional genomics have significantly impacted our understanding of the molecular and biological bases of SMZL and NMZL (3-5,7-13,34). An increasingly emerging aspect from genomic studies is that malignant lymphoid cells manipulate signaling pathways that are central to the homeostasis of their normal counterparts. The most frequently mutated genes in SMZL and NMZL are physiologically involved in the normal process of differentiation of mature B cells into MZ cells, and in their trafficking between the functional compartments of lymphoid tissues. MZ development is therefore the major deregulated program in SMZL and NMZL and comprises BCR signaling, Toll-like receptor (TLR) signaling, NF- κ B, and NOTCH signaling (3-5,7-13,34).

NF- κ B pathway

Both canonical and non-canonical NF- κ B pathways play a critical role in the development of MZ B cells. The canonical NF- κ B pathway is activated by signaling from several surface receptors including BCR and TLR, and is mainly regulated by its activator *IKBKB* and inhibitor *TNFAIP3*. *IKBKB* encodes a serine kinase that plays an essential role in activation of the canonical NF- κ B pathway. The *IKBKB* protein phosphorylates inhibitors of the NF- κ B complex, causing their dissociation and subsequent activation of NF- κ B. In SMZL, up to 10% of cases harbor *IKBKB* hotspot mutations that constitutively activate the protein by changing a highly conserved amino acid of the kinase domain (2). The constitutive activation of NF- κ B pathway promotes the growth and survival of tumor cells (2,35). *TNFAIP3* encodes a zinc finger protein and ubiquitin-editing enzyme, which has both ubiquitin ligase

and deubiquitinase activities and is a principal negative regulator of NF- κ B. Frameshift mutations, nonsense mutations or deletions of the entire *TNFAIP3* gene locus are observed in about 10% to 15% of SMZL and NMZL (2,3,10). Inactivation of *TNFAIP3* causes excessive activation of NF- κ B signaling in lymphoma cells, resulting in apoptosis inhibition and oncogenic proliferation (2,36).

Activation of the non-canonical NF- κ B pathway by CD40 receptor binding disrupts the TRAF3/MAP3K14-TRAF2/BIRC3 negative regulatory complex. Upon disruption of this complex, the central activating kinase of the pathway, MAP3K14 is released and activated to induce the phosphorylation and proteasomal processing of p100, leading to the formation of p52-RelB dimers. Translocation of p52-RelB to the nucleus enables it to positively regulate the transcription of target genes. Mutations of the TRAF3/MAP3K14-TRAF2/BIRC3 complex are observed in approximately 15% of SMZL, and in 10% of NMZL cases.

The *BIRC3* gene encodes a member of the IAP family of proteins. It consists of 3 baculovirus IAP repeats and a C-terminal RING finger domain that confers ubiquitin ligase (E3) activity. Physiologically, BIRC3 catalyzes MAP3K14 protein ubiquitination, resulting in its proteasomal degradation. The RING domain of BIRC3 is inactivated by frameshift or nonsense mutations in 10% of SMZL and 5% of NMZL. Disruption of the RING domain produces a truncated BIRC3 protein that lacks ubiquitin ligase activity, leading to functional stabilization of MAP3K14 and upregulation of NF- κ B target genes (2,37).

The *TRAF3* gene encodes a member of the TNF receptor associated factor (TRAF) protein family. Members of this family are composed of 3 structural domains: a RING finger in the N-terminal part of the protein, 1-7 TRAF zinc fingers in the central portion and a MATH domain in the C-terminal region; the latter domain is necessary for self-association and receptor interaction. TRAF3 induces MAP3K14 degradation by recruiting it to the BIRC3 ubiquitin ligase complex. In SMZL and NMZL, 5% of cases harbor *TRAF3* disrupting mutations in the C-terminal MATH domain that is required for recruiting MAP3K14 to BIRC3, resulting in MAP3K14 stabilization (2,3).

Overall, mutations of positive or negative NF- κ B regulators occur in ~40% of SMZL and ~50% of NMZL, indicating the major role of NF- κ B genetic lesions in the pathogenesis of SMZL and NMZL (Figure 1) (3-5,9,12,13). NF- κ B activation in SMZL and NMZL is also sustained by molecular alterations affecting upstream pathways that are tightly connected to NF- κ B activation in B cells, including

TLR and BCR signaling.

TLR pathway

TLRs play a critical role in NF- κ B pathway activation. Ligation to TLRs induces receptor dimerization and a conformational change that triggers downstream signaling events. Activated TLRs recruit the adaptor protein MYD88 required for propagating the signals from the TLR. MYD88 consists of an N-terminal death domain, an intermediate linker domain, and a C-terminal TIR domain. The death domain allows MYD88 oligomerization and interaction with the respective death domains of IRAKs 1-4 serine-threonine kinases, creating a protein complex called the myddosome. The myddosome complex propagates the signal and activates the NF- κ B pathway.

The TIR domain of MYD88 is crucial for signal transduction since it mediates contact with the intracellular TIR domains of TLRs upon signaling activation (38). MYD88-defective subjects are deficient in MZ B cells, suggesting that MYD88 is involved in physiological MZ B cell differentiation (39). *MYD88* is affected by somatic mutations mapping within the evolutionarily conserved $\beta\beta$ -loop of the TIR domain in 3% to 15% of SMZL and in up to 10% of NMZL cases (*Figure 1*) (40-47). These mutations change MYD88 structure, leading to spontaneous homodimerization and recruitment of IRAKs 1-4. The final result is enhanced NF- κ B activity (48). The most recurrent mutation in *MYD88* is the gain-of-function L265P variant in the toll/interleukin-1 receptor homology (TIR) domain. In SMZL the L265P variant is associated with a superior survival compared with wildtype *MYD88* (4).

The functional impact of TLR signaling on the activation and viability of MZ B cells has been demonstrated by their response to inhibitors of IRAK1/4. The TLR-mediated survival effect is blocked by IRAK1/4 inhibitors, suggesting that this pathway may represent a novel therapeutic target and supporting an important role for TLR activation in this disease (48).

BCR pathway

In normal B cells, when the BCR is ligated by an antigen, a signaling cascade is initiated, ultimately resulting in CARD11 phosphorylation and activation. CARD11 protein belongs to the membrane-associated guanylate kinase (MAGUK) family, a class of proteins that functions as molecular scaffolds for the assembly of multiprotein

complexes at specialized regions of the plasma membrane. This protein is also a member of the CARD protein family, whose characteristic feature is a caspase-associated recruitment domain (CARD). Upon BCR stimulation, CARD11 acquires an open conformation that allows BCL10 and MALT1 recruitment to activate the CBM (CARD11/BCL10/MALT1) complex, leading to the activation of IKK β kinase and initiation of NF- κ B signaling.

In SMZL and NMZL, *CARD11* is mutated in 5% to 10% of cases (*Figure 1*) (2,5,13,40). *CARD11* mutations affect the coiled-coil domain of the protein and disrupt interaction of the coiled-coil domain with the inhibitory domain by promoting spontaneous CARD11 multimerization and association with other CBM complex proteins, resulting in constitutive NF- κ B activation (49).

NOTCH pathway

Similar to NF- κ B, activation of the NOTCH signaling pathway is a crucial event, in both normal and tumoral MZ B cells. The biochemistry of canonical NOTCH signaling is well established. NOTCH is a family of heterodimeric transmembrane proteins that functions as ligand-activated transcriptional co-factors. Physiologically, differentiation and homing of B cells into the MZ is dependent on NOTCH2 signaling (50-53). *NOTCH2* encodes a co-transcription factor that physiologically promotes B cell differentiation into MZ B cells. In mice, Notch2 is critical for promoting MZ B cell differentiation and retention in the splenic MZ (54). The NOTCH2 ligand, DL1, is functionally available to B cells in the spleen (50,51). Upon activation, the cleaved intracellular portion of NOTCH (ICN) translocates into the nucleus, recruits transcriptional co-factors, and modifies expression of target genes. The PEST domain located at the C-terminus of ICN terminates signaling by directing ICN towards proteasomal degradation (52).

NOTCH2 is one of the most frequently mutated genes in SMZL and NMZL, with an occurrence of 10% to 25% and 25%, respectively (3-5,9,11-13). In SMZL, *NOTCH2* mutations are mostly represented by monoallelic stop codons or frameshift indels that truncate the PEST domain of ICN2. The loss of the PEST domain prevents proteasomal degradation of ICN2 and stabilizes its expression indicating that *NOTCH2* mutations in SMZL and NMZL are gain-of-function events (3). Indeed, genomic studies have identified other regulators of NOTCH signaling that are affected by mutations, including

NOTCH1, a paralogue of *NOTCH2*, which is targeted by similar mutations that truncate the PEST domain and stabilize the *NOTCH1* protein (55). *NOTCH1* mutations occur in approximately 5% of SMZL cases (3). Negative regulators of NOTCH signaling, including *SPEN*, *DTX1* and *MAML2*, harbor mutually exclusive mutations in around 40% of SMZL and NMZL cases (*Figure 1*) (3,13).

KLF2

KLF2 encodes a transcription factor that represses B cell activation and differentiation into MZ B cells. *KLF2* is a member of the Krüppel-like factor zinc finger transcription factor family. From a biochemical standpoint, the domains required for its transcriptional activities include three highly conserved zinc fingers at the C-terminus, which allow protein-DNA contact, and two nuclear localization sequences that mediate the localization of *KLF2* protein in the nucleus (56–58). In mice, loss of *Klf2* expression forces follicular cells of the spleen to gain a MZ-like phenotype and to migrate to the splenic MZ. *KLF2* mutations and deletions occur in 30% of SMZL cases and in 20% of NMZL (*Figure 1*) (5,7,8,34).

KLF2 frameshift and nonsense variants remove the N-terminal zinc finger domain of the protein, including the nuclear localization sequences (4,5,7,8). *KLF2* missense substitutions alter amino acids of the nuclear localization sequences, or change highly conserved codons of the first zinc finger domain involved in DNA recognition by *KLF2*. Consistently, *KLF2* mutants translocate from the nucleus into the cytoplasm. Mutated *KLF2* inhibits the ability of *KLF2* protein to suppress NF- κ B induction by upstream signaling pathways, including the BCR and the TLR pathways (7).

The development of splenic MZ B cells requires their differentiation and migration to the marginal sinus in the spleen and their retention there until they differentiate into antibody secreting plasmablasts. Together with other factors, activation of *NOTCH2* signaling and depletion of *KLF2* enables committed B cells to migrate to the MZ, where they differentiate into MZ B cells and acquire self-renewal and homing capabilities (59–63).

NOTCH2 and *KLF2* mutations co-occur in a large fraction of SMZL, suggesting that transcriptional and epigenetic programs required for physiological MZ B cell commitment are constitutively deregulated in SMZL. Deregulated transcription and differentiation are indeed recurrent themes in lymphomagenesis. Although *NOTCH2*

and *KLF2* fulfill the genetic definition of candidate cancer-driver genes, they are not biologically validated as oncogenes or tumor-suppressors in SMZL. Transgenic mice engineered to harbor either constitutive *NOTCH2* activation or lacking *KLF2* in B cells display splenomegaly due to the expansion of the MZ B cell compartment, but as yet, none have been reported to have a lymphoma phenotype (59–62).

The contribution of *NOTCH2* and *KLF2* aberrations to SMZL pathogenesis is still unclear. Some crucial questions need to be addressed by further functional studies in SMZL; firstly, there is no evidence of *NOTCH2* and *KLF2* being either independent or concomitant drivers in SMZL. Secondly, comprehensive knowledge about the genes targeted by *NOTCH2* and *KLF2* in MZ B cells is lacking, and thirdly, the consequences of *NOTCH2* and *KLF2* mutations on the signaling/epigenetic programs of SMZL are not well understood.

PTPRD

PTPRD encodes the receptor-type-protein-tyrosine-phosphatase δ , a tumor suppressor gene involved in cell growth regulation and expressed in naïve, germinal center, and MZ B cells (5). *PTPRD* is physiologically involved in several cellular programs, including proliferation and downregulation of cytokine signaling via dephosphorylation of STAT3 at tyrosine 705 (Y705). In NMZL *PTPRD* mutations occur in ~20% of cases; in contrast *PTPRD* mutations are absent in SMZL cases (*Figure 1*) (5). *PTPRD* genetic lesions in NMZL include chromosomal deletions or missense mutations, which cause loss of the entire *PTPRD* gene or damage the protein tyrosine phosphatase function, respectively. In fact, NMZL cases harboring *PTPRD* lesions show significant enrichment of cell cycle genes compared to *PTPRD* wild type cases, including higher expression of Ki-67, indicating that *PTPRD* is involved in cell cycle regulation in normal and malignant B cells (5). Aberrations affecting *PTPRD* might therefore represent a promising biomarker for NMZL, although their prevalence has to be confirmed by additional independent studies.

Epigenetic regulator genes

Genomic studies have also identified mutations in several epigenetic regulators that occur in about 40% of SMZL and NMZL cases (*Figure 1*). Although the functional consequences of these mutations have not yet been

determined, the genes affected include *KMT2D*, *ARID1A*, *EP300*, *CREBBP*, *SIN3A* and *TBL1XR1* (3,5).

BRAF

Mutations of *BRAF* have recently been reported in NMZL (16%, 4 out of 25 cases) and might be exclusive for NMZL across MZL subtypes, suggesting a diagnostic potential of *BRAF* in NMZL (Figure 1) (34). However, since *BRAF* mutations in NMZL have only been reported in a single study, their prevalence should be validated in larger, independent series.

Transcriptomic profiles

The gene expression profiles of SMZL and NMZL have been well characterized (64-69). Overexpression of members of BCR-TLR-NF- κ B, PI3K-AKT, JAK-STAT and RHO GTPases signaling cascades, together with immune system and proliferation genes, as well as markers of normal MZ B cells, has been consistently and independently observed (64-69). The top commonly up-regulated transcripts encode B cell kinases downstream of the BCR and pro-survival genes such as *SYK*, *BIRC3*, *BTB*, *CD40*, *TLR9*, *CD79A-B*, *PLC γ 2*, *CARD11*, *RHOH*, *IL6* and *TCL1A* (Table 1). The expression patterns of SMZL and NMZL thus reveal the activation of pro-survival signatures that might contribute to the development or progression of MZL. Further, the kinases and survival genes identified in these studies provide a rationale for the use of small molecules to target therapeutic vulnerabilities.

Methylation patterns

Genome-wide epigenetic profiling of SMZL has identified aberrant promoter DNA methylation as a mechanism of deregulation that affects crucial pathways in the disease. A high degree of promoter DNA methylation is observed in 25% of SMZL cases and these patients show poorer overall survival and enriched *IGHV1-02*04* usage, *NOTCH2* mutations, 7q31-32 loss and histological transformation to aggressive lymphoma. This high methylation SMZL subset might be useful in risk stratification of patients (68).

Aberrant methylation seems to contribute to the high expression of pro-survival genes (*TCL1B*, *BCL2A1*, *FGF1*), BCR and NF- κ B signaling members (*CD79B*, *CARD11*, *PIK3CB*), PRC2-complex genes (*EZH2*, *EED*, *SUZ12*), and genes involved in JAK-STAT and PI3K/AKT

signaling pathways. Several tumor suppressor genes appear highly methylated, such as *KLF4*, *CDKN1C*, *CDKN2A/B/D*, *CDH1-2*, *WT1*, *RARB* and *GATA4*. Thus, aberrant methylation could also play a role in the pathogenesis and/or progression of SMZL (68,69). In accordance with this, genomic variants affecting epigenetic regulators have been identified in SMZL and these might be partially responsible for the aberrant methylation and subsequent development of the disease.

At the moment of writing this review there were no studies characterizing the genome-wide methylation profiles of NMZL, although promoter methylation might collaborate with loss-of-function mutations in repressing the tumor suppressor gene *PTPRD* (5).

miRNA profiles

In the last few years, a number of studies have investigated the role of miRNAs in MZL; only a few of these determined the miRNA profiles of NMZL (64,67,74,75). On the contrary, the miRNome of SMZL has been more extensively investigated in the context of the 7q LOH (15,76,77) and also in comparisons of SMZL to non-tumoral tissues (64,76,78), or to other B cell lymphomas (64,74).

The frequency of 7q loss in SMZL (~30%) is one of the highest for chromosomal aberrations in lymphomas. In the aforementioned studies focused on miRNAs located on 7q, the miR-29a/miR-29b-1 cluster was proposed as a target of the 7q LOH, involved in up-regulating the *TCL1A* oncogene (77), and miRNAs located within the minimal deleted region exhibited decreased expression in SMZL patients harboring deletion of 7q (15). Despite the prevalence of HCV infection reported in SMZL (31-33), no specific miRNA profile was associated with HCV in SMZL, although repression of miR-26b was observed in the HCV+ cases (78). In 2015, a comprehensive study compared miRNA expression patterns between indolent NMZL, transformed NMZL and diffuse large B cell lymphoma (DLBCL). Interestingly there were no significant differences between the miRNA profiles of indolent and transformed NMZL, although the authors identified decreased expression of miRNAs in transformed NMZL compared to DLBCL, including members of the miR-183/96/182 polycistron (75). Most recently reviewed was the involvement of miRNAs in the pathogenesis of SMZL, where miRNAs located at 7q or those targeting the 7q31 gene *CAV1*, were proposed as promising candidates for further investigation (79).

Table 1 Up-regulated signature in SMZL and NMZL across different gene expression profiling studies

Gene	Pathway	Description	References
<i>POU2AF1</i>	B cell development	POU class 2 homeobox associating factor 1	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>LTB</i>	MZ B cells	Lymphotoxin beta	Ruiz-Ballesteros, <i>Blood</i> , 2005 (65); Arribas, <i>Blood</i> , 2012 (67)
<i>TNFRSF13B</i>	MZ B cells	TNF receptor superfamily member 13B	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>IRTA1</i>	MZ B cells	Immune receptor translocation-associated protein 1	Arribas, <i>Mod Pathol</i> , 2013 (64); Ikeda, <i>Hum Pathol</i> , 2017 (70)
<i>CD1D</i>	MZ B cells	CD1d molecule	Arribas, <i>Mod Pathol</i> , 2013 (64); Kotsianidis, <i>Am J Clin Pathol</i> , 2011 (71)
<i>SYK</i>	B cell receptor	Spleen associated tyrosine kinase	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>PTPRC</i>	B cell receptor	Protein tyrosine phosphatase receptor type C	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>BTK</i>	B cell receptor	Bruton tyrosine kinase	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>BLNK</i>	B cell receptor	B cell linker	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>BLK</i>	B cell receptor	B lymphoid tyrosine kinase	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>PLCG2</i>	B cell receptor	Phospholipase C gamma 1	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>CARD11</i>	B cell receptor	Caspase recruitment domain family member 11	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>CD79A</i>	B cell receptor	CD79a molecule	Trøen, <i>J Mol Diagn</i> , 2004 (72); Arribas, <i>Mod Pathol</i> , 2013 (64)
<i>CD79B</i>	B cell receptor	CD79b molecule	Trøen, <i>J Mol Diagn</i> , 2004 (72); Arribas, <i>Mod Pathol</i> , 2013 (64)
<i>TLR9</i>	Toll like receptor	Toll like receptor 9	Arribas, <i>Mod Pathol</i> , 2013 (64); Verney, <i>Oncotarget</i> , 2018 (66)
<i>CXCL9</i>	Toll like receptor	C-X-C motif chemokine ligand 9	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>AKT1</i>	PI3K-AKT	AKT serine/threonine kinase 1	Thieblemont, <i>Blood</i> , 2004 (73); Arribas, <i>Blood</i> , 2012 (67)
<i>AKT3</i>	PI3K-AKT	AKT serine/threonine kinase 3	Arribas, <i>Blood</i> , 2015 (68)
<i>EIF4B</i>	PI3K-AKT	Eukaryotic translation initiation factor 4B	Ruiz-Ballesteros, <i>Blood</i> , 2005 (65); Arribas, <i>Blood</i> , 2012 (67)
<i>PIK3CB</i>	PI3K-AKT	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	Arribas, <i>Blood</i> , 2015 (68)
<i>UBD</i>	NF-κB	Ubiquitin D	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>BIRC3</i>	NF-κB	Baculoviral IAP repeat containing 3	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>CD40</i>	NF-κB	CD40 molecule	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>PDE4B</i>	NF-κB	Phosphodiesterase 4B	Ruiz-Ballesteros, <i>Blood</i> , 2005 (65); Arribas, <i>Blood</i> , 2012 (67)
<i>JUNB</i>	NF-κB	Jun proto-oncogene	Trøen, <i>J Mol Diagn</i> , 2004 (72); Arribas, <i>Blood</i> , 2012 (67)
<i>JUN</i>	NF-κB	Jun proto-oncogene	Trøen, <i>J Mol Diagn</i> , 2004 (72); Arribas, <i>Blood</i> , 2012 (67)
<i>PTPN1</i>	JAK-STAT	Protein tyrosine phosphatase non-receptor type 1	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
<i>IL6</i>	JAK-STAT	Interleukin 6	Arribas, <i>Mod Pathol</i> , 2013 (64); Trøen, <i>J Mol Diagn</i> , 2004 (72)
<i>IL2RA</i>	JAK-STAT	Interleukin 2 receptor subunit alpha	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
<i>HLA class II</i>	Immune system	Major histocompatibility complex, class II	Ruiz-Ballesteros, <i>Blood</i> , 2005 (65); Trøen, <i>J Mol Diagn</i> , 2004 (72)

Table 1 (continued)

Table 1 (continued)

Gene	Pathway	Description	References
CD20	Immune system	B-Lymphocyte Antigen CD20	Arribas, <i>Mod Pathol</i> , 2013 (64); Trøen, <i>J Mol Diagn</i> , 2004 (72)
SP140	Immune system	SP140 nuclear body protein	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
AMPD3	Immune system	Adenosine monophosphate deaminase 3	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
E2F5	Proliferation	E2F transcription factor 5	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
TCL1A	Proliferation	T cell leukemia/lymphoma 1A	Fresquet, <i>Br J Haematol</i> , 2012 (14); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
AIM2	Proliferation	Absent in melanoma 2	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
CDK14	Proliferation	Cyclin dependent kinase 14	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
TFEB	Proliferation	Transcription factor EB	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
ARHGAP24	RHO GTPases	Rho GTPase activating protein 24	Arribas, <i>Mod Pathol</i> , 2013 (64); Arribas, <i>Blood</i> , 2012 (67)
RHOH	RHO GTPases	Ras homolog family member H	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)
RASSF2	RHO GTPases	Ras association domain family member 2	Arribas, <i>Mod Pathol</i> , 2013 (64); Ruiz-Ballesteros, <i>Blood</i> , 2005 (65)

Only a few miRNAs have been found consistently de-regulated across these studies and different factors likely contribute to this variability, including the high degree of heterogeneity in SMZL and differences in experimental designs. Additionally, we are still far from fully understanding the biology of non-coding RNAs. In the following paragraphs we will discuss in more depth the miRNAs that have been identified in various independent studies.

High expression levels of miR-155 have been reported in both SMZL and NMZL (64,74,76,78), while overexpression of miR-21 is found in SMZL compared to reactive spleen and is also associated with aggressive SMZL (64,76,78). The overexpression of miR-21 and miR-155 seems to contribute to the activation of survival signaling pathways in B cell lymphoma. An elevated expression of miR-21 has been extensively reported in hematopoietic disorders (80-84). Mechanistically, miR-21 downmodulates tumor suppressor genes, including *PDCD4* and *PTEN*, which negatively regulate MAPK and PI3K-AKT pathways respectively (80,84). In a similar manner to miR-21, miR-155 is strongly up-regulated across B cell lymphoma subtypes (84-89). miR-155 is one of the most well studied miRNAs in B cells and plays a role in the regulation of many crucial processes. For example, miR-155 is involved in B cell differentiation (85) and plays a fundamental role in the regulation of BCR signaling. Ligand engagement by BCR induces miR-155 expression (90), and directly targets negative regulators of downstream BCR signaling, such as *SHIP1* and *FOXO3*

(88,91,92). BCR signaling leads to activation of NF- κ B, which then induces expression of both miR-155 and miR-21. This positive feedback loop likely sustains high levels of these miRNAs (93,94).

Conversely, miRNAs with potential tumor suppressor capabilities have been reported in SMZL. Mir-136 is repressed in SMZL compared to non-tumoral spleen (64) but exhibits higher expression when compared to NMZL and MALT lymphoma (74), suggesting a specific expression pattern of miR-136 in MZL subtypes. Although the mechanistic role of miR-136 has not yet been characterized in lymphoma, in solid tumors miR-136 acts as a tumor suppressor that regulates proliferation, migration and invasion (95), and targets *BCL2* to promote apoptosis (96). Experiments in rats have shown that miR-136 regulates the activation of NF- κ B, since its forced expression induces secretion of pro-inflammatory cytokines and inhibits the expression of the NF- κ B negative regulator *TNFAIP3* (97).

The expression levels of miR-127 are lower in SMZL compared to non-tumoral spleen (64), and in accordance with the expansion of the MZ in SMZL, miR-127 is not expressed in normal memory B cells (98). Indeed, miR-127 targets crucial regulators of B cell development, including *BCL6* and *CD10* (99), whose expression is absent in SMZL tumors.

Very few miRNAs are differentially expressed in NMZL. Compared to non-tumoral tissue, mir-370 and miR-513 are downregulated in NMZL and conversely, miR-221 and miR-223 appear up-regulated in NMZL when compared

to other B cell lymphomas (67,74). Lack of epigenetic regulation resulting from the loss of miRNAs may play a role in immune escape of tumor cells. Disruption of miR-513 induces PD-L1 protein expression, and transfection of miR-513 into Jurkat cells eradicates PD-L1 expression and inhibits apoptosis (100). Secretion of pro-inflammatory cytokines, including IL6 and IL1 β , is abolished by miR-370 (101). Downmodulation of miR-370 in DLBCL increases the expression of members of BCR and PI3K signaling cascades and its expression is associated with sensitivity to rituximab and doxorubicin (102). Furthermore, aberrant homing and differentiation of tumor cells may also be partly due to epigenetic de-regulation. In this context, miR-221 and miR-223 are thought to have roles in B cell differentiation and homing (103,104); NMZL clinical specimens express genes related to the normal MZ B cell signature and thus lack expression of germinal center markers such as *LMO2* and *CD10*, which are targeted by miR-223 and miR-221 (67). Additionally, studies in DLBCL have reported high expression of miR-223 compared to non-tumoral lymph nodes (105), and miR-221 is overexpressed in activated B cell-like compared to the germinal center B cell-like DLBCL subtypes (85). Therefore, profiles of miR-221 and miR-223 in B cell lymphoma are consistent with the notion that both miRNAs might contribute to the specific signature of post germinal center B cells. Lastly but of clinical interest, miR-223 may represent a novel prognostic biomarker since longer survival of DLBCL (105) or CLL (106) patients correlates with high expression of miR-223.

Molecular pathogenesis of SMZL and NMZL

The genomic and transcriptomic landscapes of SMZL and NMZL indicate a role for NF- κ B activation in the pathogenesis of MZL (20,64,67,107). Not surprisingly, signals from NF- κ B are necessary for normal establishment and maintenance of the MZ (108). Together with the high prevalence of molecular lesions targeting NF- κ B pathway components in ~40-50% of SMZL and NMZL patients, these findings underscore NF- κ B pathway activation as a hallmark of these MZL subtypes (2-6,10,12,13). Overexpression of genes involved in NF- κ B signaling has been reported in a number of genomic studies (64,65), including upstream signals from BCR (*SYK*, *BTK*, *CD79A-B*), TLR (*TLR9*, *CXCL9*) and *CD40*, as well as a number of NF- κ B related transcripts (*UBD*, *BIRC3*, *TRAF3*, *IL6*, *JUN*, *FOS*). Supporting the transcriptional

activation of the NF- κ B signaling cascade, approximately half of SMZL patients show nuclear expression of p50 and/or p52 (2).

The up-regulation of BCR/TLR/NF- κ B in MZL might be the consequence of concomitant genomic and epigenetic events. Somatic mutations in key regulators of the NF- κ B pathway, aberrant DNA methylation and de-regulated miRNAs likely function in concert to activate the NF- κ B cascade. In such a scenario, mutations of NF- κ B pathway members and upstream signaling components (*TNFAIP3*, *BIRC3*, *CARD11*, *MAP3K14*, *TRAF3*, *MYD88*), *KLF2* genomic lesions, low methylation of promoters regulating BCR/TLR/NF- κ B members and aberrant miRNA expression (overexpression of miR-155, repression of miR-27b, miR-370 and miR-377), lead to constitutively active signaling downstream of the BCR.

Although NF- κ B is probably the most relevant survival pathway activated in SMZL and NMZL, other signaling cascades have been reported with enhanced activity, which might have therapeutic implications. Members of the PI3K/AKT and JAK/STAT signaling pathways are unmethylated and highly expressed in SMZL (68) and in NMZL (67). In SMZL up-regulation of miR-21, which targets *PTEN*, might work together with the low methylation levels of PI3K signaling genes (*AKT1*, *AKT3*, *PIK3CB* and *CXCR4*) to determine the overexpression and activation of the pathway.

A consequence of continuous NF- κ B signals is the secretion of pro-inflammatory cytokines, such as IL6 and IL2 (109,110), which induces the NF- κ B transcription machinery resulting in a positive feedback loop that can over activate NF- κ B signaling (111). Release of IL6 and/or IL2 also initiates a cascade of kinases whose phosphorylating action triggers the JAK/STAT pathway. Since members of the JAK/STAT pathway are reported to be unmethylated in SMZL (68), and upregulated in both SMZL and NMZL (67), it is possible that these perturbations establish a cancer-related pro-inflammatory circuit (111).

Biomarkers for diagnosis/prognosis

Diagnosis, prognosis and development of new therapeutic approaches might take advantage of molecular lesions and potential biomarkers so far identified in MZL. Loss of 7q or *TNFAIP3*, together with the presence of trisomies 3 and 18 indicate a diagnosis of MZL. Mutations of NF- κ B members might not have a diagnostic value in SMZL or NMZL since they are not specific for these entities within the spectrum of B cell lymphomas (107). Mutations affecting *NOTCH2*

suggest a NMZL or SMZL diagnosis with the possible exclusion of MALT lymphoma (19,20). Nevertheless, these molecular biomarkers might not be adequately sensitive and are not specific for SMZL or NMZL.

A number of retrospective studies have described biomarkers of prognosis in NMZL, although they should be considered with precaution due to the limited number of patients and different therapeutic approaches (112). Despite these caveats, molecular lesions with a high prevalence in SMZL show some promise as prognostic biomarkers, including *KLF2* and *NOTCH2* mutations that are linked to poorer outcome in SMZL (4,8,13).

Future perspectives

The classification of lymphoma by the WHO recognized SMZL and NMZL as distinct entities with specific phenotypical, morphological and clinical features. Nonetheless, similar incidences and common aspects in the biology of SMZL and NMZL are consistent with a common origin in MZ B cells. Many studies have improved diagnosis and shed light on the biology of these tumors however, the causes and pathogenic mechanisms of SMZL and NMZL are yet to be clarified. The genetic landscapes of SMZL and NMZL exhibit common genomic aberrations of crucial players in MZL that are mostly regulated upon NF- κ B activation, such as *NOTCH2* and *KLF2*. These common lesions present opportunities for novel therapeutic approaches that might benefit both SMZL and NMZL patients. Additionally, these mutated genes might be promising biomarkers for SMZL and/or NMZL, including *NOTCH2*, *KLF2*, *PTPRD* and *BRAF*, although their diagnostic and prognostic relevance requires further investigations.

At present, current therapies for NMZL patients are still based on immunochemotherapy, while many SMZL cases still undergo splenectomy or rituximab monotherapy as a valid treatment. The expectation is that novel personalized medicine approaches will provide molecularly targeted therapies that match the unique genetic, epigenetic and clonal composition of each individual tumor.

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