Review Article

Disease-specific mutations in mature lymphoid neoplasms: Recent advances

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Mature lymphoid neoplasms (MLN) are clinically and pathologically more complex than precursor lymphoid neoplasms. Until recently, molecular characterization of MLN was mainly based on cytogenetics/fluorescence in situ hybridization, allele copy number, and mRNA expression, approaches that yielded scanty gene mutation information. Use of massive parallel sequencing technologies has changed this outcome, and now many gene mutations have been discovered. Some of these are considerably frequent in, and substantially specific to, distinct MLN subtypes, and occur at single or several hotspots. They include the V600E *BRAF* mutation in hairy cell leukemia, the L265P *MYD88* mutation in Waldenström macroglobulinemia, the G17V *RHOA* mutation in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, not otherwise specified, and the Y640F//D661Y/V/H/I//N647I *STAT3* mutations in T-cell large granular lymphocytic leukemia. Detecting these mutations is highly valuable in diagnosing MLN subtypes. Defining these mutations also sheds light on the molecular pathogenesis of MLN, furthering development of molecular targeting therapies. In this review, we focus on the disease-specific gene mutations in MLN discovered by recent massive sequencing technologies.

Numerous technical advances have enabled us to identify abnormal genomic changes associated with cancer. A half century ago a breakthrough in our understanding of clonal evolution occurred with the discovery of the Philadelphia chromosome in chronic myeloid leukemia.[1] In MLN, several disease-specific chromosomal translocations have been identified since 1980. Translocation of proto-oncogenes to the immunoglobulin heavy chain region, or less frequently the light chain region, was identified as a prototypical mechanism driving MLN. In these translocations, the regulatory regions of immunoglobulin genes promote overexpression of those proto-oncogenes. *MYC* by the t(8;14) translocation, *BCL2* by the t(14;18) translocation, and *CCND1* by the t(11;14) translocation are seen in Burkitt lymphoma, follicular lymphoma, and mantle cell lymphoma, respectively.[2] Fusion of *ALK* and other genes, typically *NPM1* (*NPM1-ALK*), also characterizes ALK-positive anaplastic large-cell lymphoma.[2]

In addition to chromosomal translocation/inversion-based studies, cancer-associated gene mutations have been predicted by genome science-based studies and functional analysis of the genes. Mutations found by the latter often occur in genes, governing survival (e.g. *p53*),[3] or differentiation (e.g. *BCL6*).[4] Recent advances in massive parallel sequencing technology have dramatically accelerated discovery of novel mutations in the cancer genome. The function of many of these in cancer development has not been previously described. Among them are several specific to distinct categories of MLN. Not only could these mutations provide valuable diagnostic tools, but some could be considered as potential targets for anticancer drugs.

In this review, we describe newly identified mutations associated with MLN that occur frequently (>20%) in and substantially specific to disease subtypes (Table 1, Figs 1–3). We also address how to use information relevant to gene mutations for diagnostic applications as well as future therapeutic applications.

V600E *BRAF* mutation in hairy cell leukemia

Hairy cell leukemia is an indolent mature B-cell neoplasm.[2] Tumor cells with "hairy" projections are predominantly found in the BM, spleen, and circulating blood.[2] Most cases show heavy chain variable region rearrangement with somatic hypermutation in tumor cells, which suggests that the tumors arise from the cells at the post-germinal stage.[2] Heterozygous mutation in the *BRAF* gene, resulting in substitution of valine with glutamic acid at amino acid 600, has been detected in almost all HCL samples.[5–7] This mutation is highly specific to HCL among hematologic malignancies, although it has been reported at a low frequency (2.8%) in symptomatic multiple myeloma.[8]

Table 1. Disease–specific mutations in mature lymphoid neoplasms

Disease categories	Gene	Hotspot amino acids	Hotspot regions	Mutation frequency	Specificity†
Hairy cell leukemia	BRAF	V600E	—	~100%	2.8% of symptomatic MM
WM	MYD88	L265P	—	79–100%	10–87% of IgM-MGUS, 19% of non-GC DLBCL, 2.9% of CLL
AITL and AL-PTCL	RHOA	G17V	—	53–68% in AITL, 62% in AL-PTCL	Not identified in other hematologic malignances
T-LGL	STAT3	Y640F, D661Y/ V/H/I, N647I	—	28–40%	7% of AA, 3% of MDS, 1.6% of T-cell neoplasms, 3–5% of DLBCL
NK/T-cell lymphoma	JAK3	A572V, A573V, V722I	—	20–35%	4–7% of T-ALL, 0–7% of ATLL, 10% of mycosis fungoides, 9.5–10.5% of AMKL
Splenic MZL	NOTCH2	—	PEST domain	21–25%	1.5–5% of nonsplenic MZL, 3.7–7.9% of DLBCL
Burkitt lymphoma	ID3	—	HLH domain	34–68%	0–2% of DLBCL

AA, aplastic anemia; AITL, angioimmunoblastic T-cell lymphoma; AL-PTCL, AITL-like peripheral T-cell lymphoma, not otherwise specified; AMKL, acute megakaryocytic leukemia; ATLL, adult T-cell lymphoma/leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HLH, helix–loop–helix; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MZL, marginal zone B-cell lymphoma; NK, natural killer; non-GC, non-germinal center; PEST, proline, glutamic acid, serine, threonine-rich; T-ALL, acute lymphoblastic T-cell leukemia; T-LGL, T-cell large granular lymphocytic leukemia; WM, Waldenström macroglobulinemia. †The distribution of the identical mutations in other lymphoid malignances.

The *BRAF* gene encodes a serine/threonine kinase targeting the MAPK signaling cascade. The V600E BRAF mutant is a constitutively active kinase. This mutant causes hyperphosphorylation of MEK1/2, a direct target of BRAF, and ERK1/2, substrates of MEK in HCL cells (Fig. 1).[5]

Diagnostic testing by a sensitive allele-specific PCR method,[6,9] as well as pyrosequencing,[10] has been developed. A specific antibody test for the V600E *BRAF* mutation is also useful for diagnosis[11] and detection of minimal residual HCL.[12]

Furthermore, therapeutics targeting the V600E BRAF mutant have been launched.[13,14] V600E BRAF inhibitors had already been developed for clinical use when frequent mutations of the gene were found in HCL, because the V600E *BRAF* mutations had been already known in metastatic melanoma,[15] thyroid carcinoma,[16] and colon carcinomas,[17] albeit at frequencies much lower than in HCL. Vemurafenib is an oral small-molecule serine–threonine kinase inhibitor that specifically blocks V600E BRAF kinase activity.[15] Vemurafenib has been shown effective in refractory hairy cell leukemia cases,[13,14] suggesting that the V600E *BRAF* mutation is a major driver of hairy cell leukemia. A phase II study of vemurafenib in patients with relapsed or refractory hairy cell leukemia is ongoing (NCT01711632).

L265P *MYD88* mutation in Waldenström macroglobulinemia

Waldenström macroglobulinemia is a subset of lymphoplasmacytic lymphoma, with an IgM monoclonal gammopathy.[2] Most WM cases have an indolent course.[2] Tumor cells resembling small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, infiltrate the BM and other lymphoid tissues.[2]

Mutation in the *MYD88* gene, resulting in substitution of leucine with proline at amino acid 265, has been identified in 79–100% of WM samples.[18–20] Up to 20% of WM patients show familial predisposition to the disease,[2] and the same somatic mutation is also found in these patients.[18] The L265P *MYD88* mutation status is heterozygous in most cases, although homozygous mutations have also been seen in patients who show similar clinical manifestations.[18]

MYD88 serves as an adaptor molecule in toll-like receptors and IL-1 receptor signaling. The L265P MYD88 mutant enhances nuclear factor-κB (NF-κB) signaling through increased binding to phosphorylated Bruton tyrosine kinase (BTK) (Fig. 1).[21] Such L265P MYD88 mutant-induced enhancement of NF-κB signaling is abrogated by inhibition of MYD88 homodimerization,[18] as well as by inhibition of downstream molecules, such as BTK and IL-1R associated kinases.[21]

The L265P *MYD88* mutation has also been detected in other hematologic malignancies at lower frequencies; for example, 7–10% SMZL cases are also positive for the L265P *MYD88* mutation.[20,22,23] The presence of this mutation in SMZL might be due to the diagnostic problem that it is difficult to differentiate between these two diseases.[2] Furthermore, 10–87% of IgM-type monoclonal gammopathy of undetermined significance,[18,20,22–24] 19% of non-germinal center DLBCL,[22] and 2.9% of chronic lymphocytic leukemia[25] also show the L265P *MYD88* mutation. The presence of the L265P *MYD88* mutation in several diseases makes it difficult to diagnose a given disease by this mutation only; nonetheless, it is useful in diagnosis when combined with clinical evaluation. Sensitive detection methods for the L265P *MYD88* mutation using allele-specific PCR have been investigated.[23,24]

In terms of therapeutic approaches for L265P *MYD88* mutation-positive WM, inhibitors targeting factors downstream of L265P MYD88 signaling, such as the BTK inhibitor ibrutinib (PCI-32765), have already been developed, although reagents that block the mutant itself have not been developed.[26] Phase II trials to evaluate ibrutinib as a single reagent in 63 patients with relapsed or refractory WM shows that the best overall response rate is 81% (four very good partial response, 32 partial response, 15 minor response), with a major response rate (partial response or better) of 57.1% (NCT01614821).[27] Moreover, phase I trials to evaluate it in combination with other drugs are ongoing.[28]

G17V *RHOA* mutation in angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma is a distinct subtype of PTCL characterized by generalized lymphadenopathy, systemic
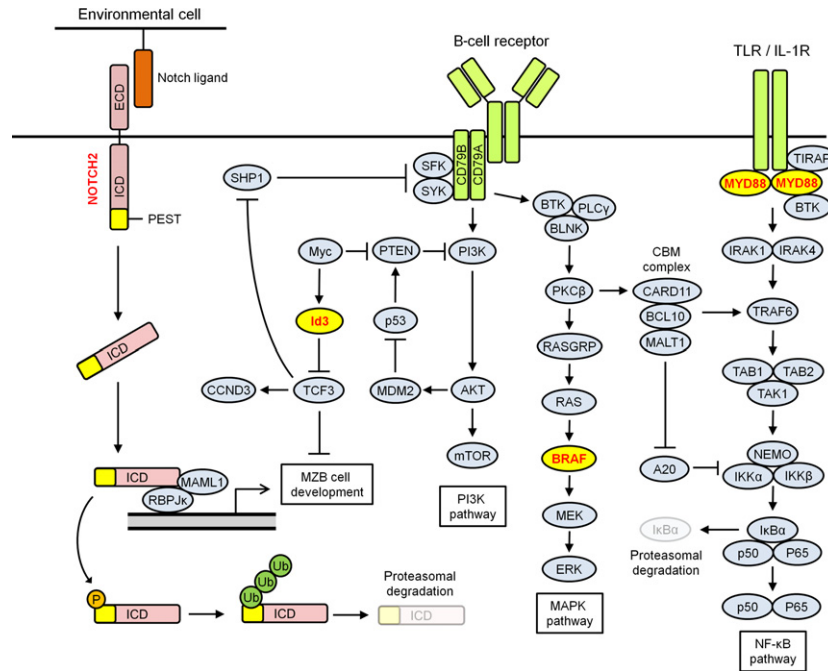
Fig. 1. Disease-specific mutations in B-cell lymphoid neoplasms. V-raf murine sarcoma viral oncogene homolog B (BRAF) is a serine/threonine protein kinase that mediates the MAPK pathway. B-cell receptor signaling triggers activation of BRAF. Activated BRAF phosphorylates MEKs, which, in turn, leads to activation of ERKs. The V600E BRAF mutant in hairy cell leukemia possesses constitutive kinase activity, resulting in overactivation of downstream targets. Myeloid differentiation primary-response gene 88 (MYD88) is an adaptor protein that plays an essential role in signaling by the Toll-like receptors (TLRs) and interleukin-1 receptor (IL-1R). On cell stimulation, MYD88 is directly recruited to the Toll/IL-1R (TIR) domain in TLRs/IL-1R, binds to Bruton tyrosine kinase (BTK) and acts to recruit IL-1R-associated protein kinases. This leads to activation of the nuclear factor-κB (NF-κB) signaling. The L265P MYD88 mutant in Waldenström macroglobulinemia contributes to constitutive activation of the NF-κB signaling by preferential binding to BTK. Inhibitor of DNA binding (ID3) is a member of the Id helix–loop–helix proteins, which lack a DNA-binding region and function as dominant negative antagonists of basic helix–loop–helix transcription factors, including transcription factor 3 (TCF3). TCF3 plays a role in germinal center B-cell development and promotes cell growth by activating the B-cell receptor signaling pathway, phosphatidylinositol 3-kinase (PI3K) signaling pathway, and positive cell cycle regulator cyclin D3 (CCND3). Gain-of-function mutations in *TCF3* and loss-of-function mutations in *ID3*, the negative regulator of TCF3, in Burkitt lymphoma enhance the TCF3 pathway. NOTCH2 is a single transmembrane receptor. Following NOTCH ligand binding, NOTCH receptor is cleaved in the transmembrane region, resulting in the release of the intracellular domain (ICD) from the plasma membrane. Then ICD is translocated to the nucleus, and activates the transcription of target genes. This signal is terminated by phosphorylation (P) of the proline, glutamate, serine, and threonine (PEST) domain of the ICD, followed by proteasomal degradation. NOTCH2 mutants in splenic marginal zone lymphoma lack the degradation signals in the PEST domain and act in a gain-of-function manner. AKT, v-akt murine thymoma viral oncogene homolog; BCL10, B-cell lymphoma 10; BLNK, B-cell linker; CARD11, caspase recruitment domain family, member 11; ECD, extracellular domain; IKK, IκB kinase; IRAK, I interleukin-1 receptor-associated kinase; MALT1, mucosa associated lymphoid tissue lymphoma translocation gene 1; MAML1, mastermind-like 1; MDM2, MDM2 oncogene, E3 ubiquitin protein ligase; mTOR, mammalian target of rapamycin; MZB, marginal zone B cell; PLCγ, phospholipase C, gamma; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma viral oncogene homolog; RASGRP, RAS guanyl releasing protein; RBPJk, recombination signal binding protein for immunoglobulin kappa J region; SFK, Src family kinases; SHP1, Src homology region 2 domain-containing phosphatase-1; SYK, spleen tyrosine kinase; TAB, TAK1 binding protein; TAK, TGF beta-activated kinase; TIRAP, TIR adaptor protein; TRAF6, TNF receptor-associated factor 6; Ub, ubiquitin.

symptoms such as fever, and autoimmune-like manifestations.[2] Histologically, lymph nodes exhibit a polymorphous infiltrate accompanied by significant proliferation of high endothelial venules and follicular dendritic cells.[2,29] The normal counterparts of AITL tumor cells are proposed to be follicular helper T cells, a subset of helper T cells.[30]

We and others recently identified hotspot mutations in the *RHOA* gene, which almost invariably cause substitution of glycine with valine at the RHOA amino acid 17.[31–33] This mutation was detected in 53–68% of AITL patients.[31–33] All G17V *RHOA* mutation-positive cases also showed mutations in *TET2*, encoding a methylcytosine dioxygenase, which are commonly identified in diverse hematologic malignancies.[31] In AITL, one-third of *RHOA/TET2* mutant cases also have mutations in *IDH2*.[31,32]

Functioning as a molecular switch, RHOA cycles between a GTP-bound active state and a GDP-bound inactive state.[34] The G17V RHOA mutant functions as a dominant-negative to inhibit conversion of wild-type RHOA protein to an active state (Fig. 2).[31–33] Molecular mechanisms underlying the association of the G17V RHOA mutant with T-lymphomagenesis remain to be elucidated.

Peripheral T-cell lymphoma, not otherwise specified, is a more heterogeneous category of lymphoma. Some PTCL-NOS cases share features with AITL. Peripheral T-cell lymphoma, not otherwise specified with AITL features can be defined when two or more of the following four features are positive: PD1 staining (in tumor cells); CD10 staining (in tumor cells); follicular dendritic cell meshwork formation; and Epstein–Barr virus-infected B cells indicated by EBER mRNA staining.[31,35,36] Under this definition, the G17V *RHOA* mutation is found in 62% of samples in PTCL with AITL features, but it is undetectable in PTCL-NOS cases without AITL features.[31] Based on the mutational profile, it is highly likely that G17V *RHOA* mutation-positive AITL and G17V *RHOA* mutation-positive PTCL-NOS harboring features of AITL constitute a single disease entity.

A study of the clinical application of the G17V *RHOA* mutation as a diagnostic marker of AITL is in preparation (Rie
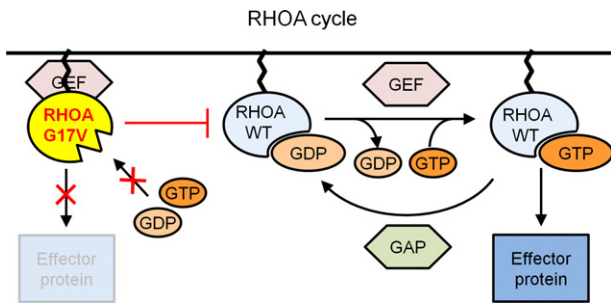
Fig. 2. Disease-specific mutations in angioimmunoblastic T-cell lymphoma and its related cancers. Ras homolog gene family, member A (RHOA) acts as a molecular switch, cycling between a GDP-bound inactive state and a GTP-bound active state. RHOA is activated by specific guanine-exchange factors (GEFs) and inactivated by GTPase-activating proteins (GAPs). The G17V RHOA mutant in angioimmunoblastic T-cell lymphoma impairs binding capacity for GTP/GDP and inhibits activation of WT RHOA by sequestering the upstream activator GEFs.
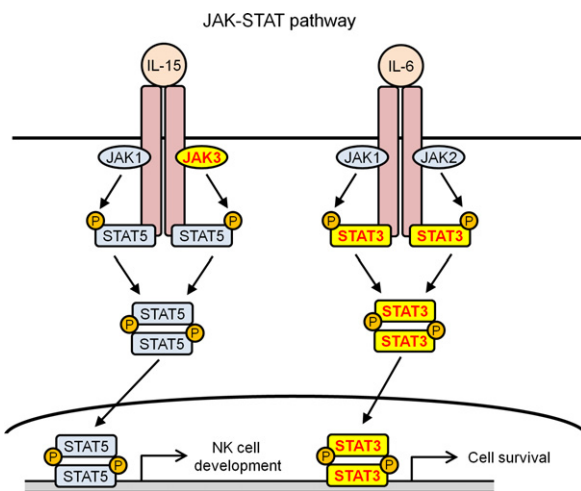

Fig. 3. Disease-specific mutations in T-cell large granular lymphocytic leukemia and natural killer (NK)/T-cell lymphoma. Both JAK and signal transducer and activator of transcription (STAT) are mediators of diverse cytokine signaling. After binding of the cytokine to the receptor, JAK proteins are activated, followed by phosphorylation (P) of STATs. Activated STATs are dimerized and enter the nucleus to initiate target gene transcription. Both JAK3 mutation in NK/T-cell lymphoma and STAT3 mutation in T-cell large granular leukemia enhance the JAK/STAT signaling pathway.

Nakamoto-Matsubara, Mamiko Sakata-Yanagimoto and Shigeru Chiba, manuscript in submission, 2014). Therapeutic strategies targeting G17V RHOA might be developed.

Mutations of STAT3 in T-cell large granular lymphocytic leukemia

T-cell large granular lymphocytic leukemia (T-LGL) is a chronic lymphoproliferative disease characterized by an increased number of large granular lymphocytes, which retain functional properties of cytotoxic T cells, in circulating blood, BM, liver, and spleen.[2] Most T-LGL cases have an indolent course and are frequently accompanied by severe neutropenia with or without anemia, and autoimmune-like manifestations including rheumatoid arthritis, autoantibodies, and hyperglobulinemia.[2]

Signal transducer and activator of transcription 3 (STAT3) mediates cytokine signaling activated by JAKs. Activation of STAT3 signaling has been known to play fundamental roles in cancer development.[37] Recent studies report STAT3 mutations in 28–40% of T-LGL samples.[38,39] All mutations were restricted to the Src-like homology 2 domain, mediating dimerization and activation of the STAT3 protein,[38,39] especially in three hot spots: Y640F, D661Y/V/H/I, and N647I (Fig. 3).[38,39] Activating mutations in STAT5b were also reported in 2% of T-LGL cases,[40] further emphasizing the role of STAT signaling in T-LGL pathogenesis. Hyperphosphorylation of STAT3 was observed in mutation-positive BM cells,[38] indicative of STAT3 activation.

STAT3 mutation-positive cells were also identified in 7% of aplastic anemia and in 3% of myelodysplastic syndrome samples displaying a lower BM cellularity, suggesting that autoimmune activation by clonal T cells similar to T-LGL cells might facilitate immunological destruction of blood cells.[41] STAT3 mutations are quite rare in other malignancies,[42] although 1.6% of T-cell neoplasms[42] and 3–5% of DLBCL samples[42,43] harbor these mutations.

Based on specificity of the STAT3 mutations in T-LGL, testing for STAT3 mutations should increase the accuracy of T-LGL diagnosis, although 60% of mutation-negative T-LGL cases could not be diagnosed by this approach.

Regarding therapeutic approaches, several classes of STAT3 inhibitors have been investigated for other types of cancers.[44] Future studies should address their efficacy in blocking STAT3 signaling in T-LGL.

Mutations of JAK3 in extranodal natural killer/T-cell lymphoma

Extranodal natural killer (NK)/T-cell lymphoma often affects the upper aerodigestive tract, especially the nasal cavity.[2] Patients often present with symptoms of local invasion, such as nasal obstruction or extensive midfacial destruction.[2] Histologically, the condition is characterized by diffuse lymphomatous infiltration, accompanied by angiodestruction and prominent necrosis.[2] The tumor cells are definitely positive for Epstein–Barr virus infection.[2] The normal counterparts of NK/T-cell lymphoma cells are postulated to be activated NK cells or cytotoxic T cells.[2]

JAK3 mediates diverse types of cytokine receptor signaling by interacting with the common gamma chain of IL receptors for IL-2, -4, -7, -9, -15, and -21. Recurrent mutations in JAK3 gene have been found in 20–35% of extranodal NK/T-cell lymphoma samples.[45,46] Most identified JAK3 mutations are missense mutations, A572V or A573V, and less frequently V722I in the pseudokinase domain.[45,46] JAK3 mutations result in constitutive phosphorylation of JAK3 tyrosine 980[46] and activation of downstream signaling, such as phosphorylation of STAT5,[46] STAT3, AKT, and ERK (Fig. 3).[45] Activation of JAK3 signaling by these mutations enhances proliferation[45,46] and invasiveness of NK/T-cell lymphoma cell lines,[45] which is abrogated by chemical inhibitors or siRNAs targeting mutant JAK3.[45,46]

Later, several groups reported that JAK3 mutations were rare in NK/T-cell lymphoma.[47] Hence, further studies are needed to clarify mutation profiles in NK/T-cell lymphoma. Nonetheless, many of NK/T-cell lymphoma samples showed phosphorylation of JAK3 tyrosine 980, even when the JAK3 mutations were not identified.[45] This data suggests that activation of JAK3 plays fundamental roles in development of NK/T-cell lymphoma.

JAK3 mutations have been found in other hematologic malignancies at lower frequencies, especially in T-lymphoid

and myeloid malignancies. For example, 4–7% of acute lymphoblastic T-cell leukemia,[48,49] up to 7% of adult T-cell lymphoma/leukemia (ATLL),[50,51] 10% of mycosis fungoides,[52] and 9.5–10.5% of acute megakaryoblastic leukemia samples[53,54] were reported to harbor *JAK3* mutations, whereas mutations are quite rare in B cell malignancies. Notably, all *JAK3* mutations found in ATLL are located in the alternative N-terminal FERM domain,[50] which might contribute to discrimination between extranodal NK T-cell lymphoma and ATLL. In clinical settings, JAK3 inhibitors have been applied as immunomodulators,[55] although the efficacy of these inhibitors in NK/T cell lymphomas remains to be elucidated.

Mutations of *NOTCH2* in splenic marginal zone lymphoma

Splenic marginal zone lymphoma, the most common primary lymphoma of the spleen,[56] is a low-grade extranodal B-cell lymphoma. It often involves BM and splenic hilar lymph nodes, and lymphoma cells may be found in the peripheral blood as villous lymphocytes.[2] Histologically, the spleen in SMZL is characterized by prominent nodular involvement of the white pulp along with focal infiltration of red pulp.[2] Clinical and epidemiologic data indicate an association with hepatitis C virus in 15–20% of SMZL cases.[57]

Notch2 is a NOTCH family protein important for cell fate decisions and differentiation of various tissues.[58] In hematopoietic cells, *NOTCH2* is predominantly expressed in mature B cells and is indispensable for marginal zone B-cell differentiation.[59–61] Recently, recurrent mutations in *NOTCH2* have been found in 21–25% of SMZL.[62,63] In most cases, nonsense or frameshift mutations cluster within a hotspot region in the last exon, resulting in truncated NOTCH2 proteins that lack degradation signals in the proline, glutamic acid, serine, threonine-rich domain and thus act in a gain-of-function manner (Fig. 1).[64] Importantly, although *NOTCH2* mutations occur infrequently in 1.5–5% of non-splenic MZL and 3.7–7.9% of DLBCL, they are rare in other B cell lymphoproliferative disorders,[62,63,65] indicating that *NOTCH2* mutations can serve as a diagnostic marker for SMZL.

Recently, many types of NOTCH inhibitors have been investigated in clinical trials in other types of cancers.[66] These inhibitors should be tested for their efficacy in clinical trials specifically dedicated to SMZL.

Mutations of *ID3* in burkitt lymphoma

Burkitt lymphoma is a highly aggressive B-cell lymphoma frequently presenting in extranodal sites or as a leukemia.[2] The tumor has an extremely high mitotic rate and apoptotic activity. A "starry sky" appearance of tumor tissue is usually present due to scattered tingible body macrophages. Burkitt lymphoma is characterized by translocation and deregulation of the *MYC* oncogene.[2] However, *MYC* translocations are not restricted to BL but also occur in other aggressive B-cell lymphomas.[2] Furthermore, *IgH-MYC* translocation can be found even in healthy individuals,[67,68] albeit at very low frequencies, suggesting that deregulation of *MYC* alone is not sufficient to drive lymphomagenesis.

Inhibitor of DNA binding proteins regulate normal cellular development.[69] These proteins lack a DNA-binding domain and inhibit transcription through the formation of non-functional heterodimers with other basic helix–loop–helix proteins. Recent studies showed that recurrent loss-of-function mutations in the

dominant negative helix–loop–helix protein *ID3* gene occurred in 34–68% of BL.[70–72] *ID3* mutations were usually biallelic, and nearly all alterations in *ID3* affected the highly conserved HLH domain, resulting in impaired interaction with binding partner proteins (Fig. 1). Importantly, *ID3* mutations are extremely rare in DLBCL, including those containing the *MYC* translocation. These observations suggest that *ID3* mutation is a particularly useful marker for distinguishing BL from DLBCL.

Additionally, although the mutation frequency is lower than that of *ID3*, recurrent activating mutations in *TCF3*, which is negatively regulated by ID3, were also identified in BL (18.3%).[72] Transcription factor 3 is important for normal B-cell development by regulating B-cell-restricted genes through E-box motifs.[69,73] TCF3 promotes survival of BL cells by activating B-cell receptor signaling and PI3K signaling pathways and by modulating cell cycle regulators such as *CCND3*, which is also mutated in BL (Fig. 1).[72] These studies implicate *TCF* or its negative regulator *ID3* in a commonly deregulated pathway, which cooperates with *MYC* in BL. Targeting this pathway could provide more effective and less toxic treatment for BL in the future.

Conclusion

Newly found mutations characteristic of MLN subtypes are reviewed in Table 1. Importantly, mutations in five of seven genes reviewed occur at hotspots. In the other two genes, mutations are found in short restricted regions (Table 1). Therefore, all mutations reported here may soon be proven to be useful for diagnostic testing. Given disease specificity, molecular diagnosis is undoubtedly important, not only to create a treatment strategy today but also as a biomarker for future treatment using newly developed drugs.

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

AITL	angioimmunoblastic T-cell lymphoma
ALK	anaplastic lymphoma receptor tyrosine kinase
BCL2	B-cell chronic lymphocytic leukaemia/lymphoma 2
BL	Burkitt lymphoma
BM	bone marrow
BRAF	v-raf murine sarcoma viral oncogene homolog B
BTK	Bruton tyrosine kinase
CCND1	cyclin D1
DLBCL	diffuse large B-cell lymphoma
HCL	hairy cell leukemia
ID	inhibitor of DNA binding
IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial
IL	interleukin
MLN	mature lymphoid neoplasm
MYC	v-myc avian myelocytomatosis viral oncogene homolog
MYD88	myeloid differentiation primary response 88
NPM1	nucleophosmin 1

PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
RHOA	*Ras* homolog gene family, member A
SMZL	splenic marginal-zone lymphoma
STAT3	signal transducer and activator of transcription 3
TCF3	transcription factor 3
TET2	tet methylcytosine dioxygenase 2
T-LGL	T-cell large granular lymphocytic leukemia
WM	Waldenström macroglobulinemia

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