Review Article

Disease-specific mutations in mature lymphoid neoplasms: Recent advances

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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. 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. Fusion of ALK and other genes, typically NPM1 (NPM1-ALK), also characterizes ALK-positive anaplastic large-cell lymphoma.

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), or differentiation (e.g. BCL6). Recent advances in massive parallel sequencing technology have dramatically accelerated discovery of novel mutations in the cancer genome. The function of many of these mutations in cancer development has not been previously described. Among them are several 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. Tumor cells with “hairy” projections are predominantly found in the BM, spleen, and circulating blood. 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. 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. 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.
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 Waldenstrom 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-kB (NF-kB) signaling through increased binding to phosphorylated Bruton tyrosine kinase (BTK) (Fig. 1).\(^21\) Such L265P MYD88 mutant-induced enhancement of NF-kB 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
symptoms such as fever, and autoimmune-like manifestations. Histologically, lymph nodes exhibit a polymorphous infiltrate accompanied by significant proliferation of high endothelial venules and follicular dendritic cells. 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. 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.
Disease-specific mutations

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 JAK2 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)

JAK/STAT pathway

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 cases.(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/A, and N647I (Fig. 3).(38,39) Activating mutations in STAT3b 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 autocrine 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, 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, 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 (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) 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 implicated 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.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ATLL | angioimmunoblastic T-cell lymphoma |
| ALK | anaplastic lymphoma receptor tyrosine kinase |
| BCL2 | B-cell chronic lymphocytic leukemia/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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