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Review Article

Recent Progress in the Understanding of Angioimmunoblastic T-cell Lymphoma

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Angioimmunoblastic T-cell lymphoma (AITL) has been classified as a subtype of mature T-cell neoplasms. The recent revision of the WHO classification proposed a new category of nodal T-cell lymphoma with follicular helper T (TFH)-cell phenotype, which was classified into three diseases: AITL, follicular T-cell lymphoma, and nodal peripheral T-cell lymphoma with TFH phenotype. These lymphomas are defined by the expression of TFH-related antigens, CD279/PD-1, CD10, BCL6, CXCL13, ICOS, SAP, and CXCR5. Although recurrent mutations in *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28,* as well as gene fusions, such as *ITK-SYK* and *CTLA4-CD28*, were not diagnostic criteria, they may be considered as novel criteria in the near future. Notably, premalignant mutations, tumor-specific mutations, and mutations specific to tumor-infiltrating B cells were identified in AITL. Thus, multi-step and multi-lineage genetic events may lead to the development of AITL.

Key words: AITL, PTCL-NOS, RHOA, TFH

INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of mature T-cell neoplasms, and accounted for 18.5% of all T- and NK-cell lymphomas in the International T-Cell Lymphoma Project.[1] Recent genetic studies and gene expression analyses have markedly altered our understanding of its classification, diagnosis, and pathogenesis. This review presents a summary of the biological and clinical aspects of AITL.

CLINICAL MANIFESTATIONS AND LABORATORY TESTS FOR AITL

Representative clinical symptoms of AITL are generalized lymphadenopathy, hepatosplenomegaly, fever, effusion/ascites, and skin rash.[2] In addition, autoimmune-like manifestations, including polyarthritis, have also been reported.[2] Laboratory tests exhibit immunological abnormalities, including hypergammaglobulinemia and positive Coomb's test.[2]

PATHOLOGY OF AITL

AITL tumor cells are typically small to medium in size, with round and slightly irregular nuclei and abundant pale cytoplasm.[2] The tumor cells express pan-T-cell antigens (i.e., CD3, CD2, and CD5). In contrast, expression of CD7, another pan-T-cell antigen, is less common,[3,4] presumably resulting from hypermethylation of its promoter region.[5] Most cases are positive for CD4 and negative for CD8.[4] In a Japanese multicenter retrospective study, CD3 was positive in 100% of the samples examined, CD4 in 90%, CD5 in 95%, and CD7 in 28%.[3] Notably, cell-surface CD3 expression is frequently negative in AITL tumor cells.[4,6] In addition, the tumor cells frequently express distinct markers that are expressed by follicular helper T (TFH) cells; in the Japanese multicenter study mentioned above,[3] CD279/PD-1 was positive in 62% of cases, CD10 in 30%, and CXCL13 in 91%. CD279/PD-1 was positive in 100%, CD10 in 89%, BCL6 in 91%, CXCL13 in 96%, and ICOS in 98% in a French-Swiss multicenter retrospective study,[7] while CD279/PD-1 was positive in 95%, CD10 in 66%, and CXCL13 in 84% in the Comprehensive Oncology Measures of Peripheral T-cell Lymphoma (COMPLETE) study, a large prospective cohort study of newly diagnosed peripheral T-cell lymphoma (PTCL) patients in the USA.[8]

Massive infiltration of accessory cells is another pathological feature of AITL. Prominent proliferation of high endothelial venules is observed in AITL.[2] An expanded follicular dendritic cell (FDC) network expressing CD21, CD23, and CD35 is usually present in areas where malignant T cells are seen.[2] B cells are closely enmeshed in the CXCL13-positive cell-rich FDC meshwork, similar with normal germinal centers.[9] Epstein-Barr virus (EBV)-infected B cells are commonly observed in AITL; EBV-infected B cells were

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found in 66% of cases in the Japanese retrospective study,[3] 91% in the French-Swiss study,[7] and 74% in the COMPLETE study.[8] Many reactive CD8-expressing T cells are often present. Other cell types (i.e., macrophages, eosinophils, and mast cells) are also seen.

REVISION OF WHO CLASSIFICATION: AN UMBRELLA CATEGORY OF NODAL T-CELL LYMPHOMAS WITH TFH PHENOTYPE

The classifications of nodal and extranodal T-cell and natural killer (NK)-cell neoplasms have been updated in the revision of WHO 2016.[10] These changes were mostly based on gene expression profiles (GEP), and the genetic landscapes of T-cell and NK-cell neoplasms.

As described, the normal counterparts of AITL cells are TFH cells based on the gene expression profiles and results of immunohistochemical staining.[2] Follicular T-cell lymphoma (FTCL) is a rare subtype of peripheral T-cell lymphoma that is known to have features of TFH cells.[11] Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is a heterogeneous group of lymphomas that cannot be classified into any specific categories. The tumor cells in some PTCL-NOS cases have been found to have features of TFH cells.[12,13]

The recently revised WHO classification proposed an umbrella category for nodal T-cell lymphomas with TFH phenotype to which AITL, FTCL, and nodal PTCL with TFH phenotype belong.[10] For this designation, the revision specified that the tumor cells should express at least two or three TFH-related antigens, including CD279/PD-1, CD10, BCL6, CXCL13, ICOS, SLAM-associated protein (SAP), and CXCR5.[10] Differential characterization of AITL from the other two new provisional entities has not been elucidated. Furthermore, these distinct disease categories may occur in a single patient simultaneously, or a single patient may develop distinct diseases in a time-dependent manner. Indeed, it was reported that patients with FTCL progressively developed AITL, and conversely that patients with AITL developed FTCL during the disease course.[11]

In addition, the recurrent genomic abnormalities in nodal T-cell lymphomas with TFH phenotype are described in the revised WHO classification,[10] although they are not directly used to define the entity.

TFH MARKERS

As described above, PD-1, CD10, BCL6, CXCL13, CXCR5, and ICOS are well-known markers for AITL. In contrast, SAP and CXCR5 expression in AITL tumor cells have not been fully examined; SAP was reported to be positive in 86% of AITL cases.[14]

PD-1 and ICOS, both of which are known as CD28 family members, function as T-cell co-inhibitory and co-stimulatory molecules, respectively.[16] PD-1 signaling regulates TFH functions in selection and support of germinal center B cells.[17] ICOS overexpression in T cells of *Roquin*^{san} mice with a defect in degradation of ICOS mRNA[18] results in deregulated increases in TFH cells, leading to development of AITL-like T-cell lymphoma. Of note, mutations in the *ROQUIN* gene were not present in human AITL.[19]

BCL6 functions as a transcriptional repressor, and is known as a fate determinant for TFH cells.[20] As described below, loss-of-function mutations in *TET2* encoding a demethylating protein are extremely frequent in AITL.[13] We found that the negative regulatory region of *BCL6* was hypermethylated in PTCL samples with *TET2* mutations,[21] and T-cell lymphomas with the TFH phenotype developed in *Tet2* gene-trap mice.[22] These observations suggest that the impaired TET2 function induces BCL6 upregulation by hypermethylation, leading to skewed differentiation toward TFH cells in both humans and mice.

SAP functions as an adaptor protein recruiting the Src kinase, FYN, to the SLAM family receptor proteins.[23] SAP is essential for development of TFH cells, but this biological event is not mediated by its adaptor function toward SLAM and FYN.[24] Germline mutations in *SH2D1A*, encoding SAP, are known to cause an X-linked lymphoproliferative syndrome, a type of primary immunodeficiency syndrome.[25]

The chemokine, CXCL13, and its receptor, CXCR5, are essential for the recruitment of cells that comprise follicles.[26] In AITL tumor tissues, although CXCL13 is known as a tumor cell marker, FDCs as well as tumor cells express CXCL13.[9] However, CXCR5 is found in tumor cells. The CXCL13-CXCR5 axis may account for the crosstalk between AITL tumor cells and the FDC meshwork.[9]

RECURRENT MUTATIONS IN NODAL T-CELL LYMPHOMAS WITH TFH PHENOTYPE

Among nodal T-cell lymphomas with TFH phenotype, the genetic landscape has been analyzed most intensively in AITL.[13,27,28] Importantly, many of these genetic changes discovered in AITL are shared by nodal PTCL with TFH phenotype[12, 29, 30] and FTCL[7] (Table 1). The revised WHO classification refers to recurrent mutations in *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28* mutations, as well as gene fusions, including *ITK-SYK* and *CTLA4-CD28,* in nodal T-cell lymphomas with TFH phenotype.[10] Although these mutations are not included as diagnostic criteria for this category, they may be integrated into the diagnostic criteria in the future. Moreover, all of these lesions presumably take part in the process of lymphomagenesis.

Mutations in genes encoding epigenetic modifiers in AITL

Mutations in *TET2*, *IDH2*, and *DNMT3A*, which encode epigenetic modifiers, are widely detected in hematological malignancies, both myeloid malignancies, and AITL.[31] Thus, these mutations may represent the fundamental mechanisms for hematological malignancies, although their diagnostic value for detecting these mutations is unclear.

TET2 mutations in particular were observed in up to 47% – 83% of AITL samples.[12,13] *TET2* encodes a methylcytosine dioxygenase that oxidizes 5-methylcytosine (5-mC) to

hydroxymethyl cytosine (5-hmC), formyl cytosine (5-fC), and carboxyl cytosine (5-CaC).[32] The catalytic activity of TET2 mediates active and passive demethylation processes. These modified cytosines also function as epigenetic markers.[32] *TET2* mutations, found in a wide range of hematological malignancies, were thought to be loss of function since their discovery;[33] nonsense and frameshift mutations are distributed throughout the TET2 protein, whereas missense mutations are restricted to the C-terminal catalytic domain. Remarkably, multiple *TET2* mutations (up to three mutations) were found in each sample in more than half of AITL cases.[13] In contrast, one *TET2* mutation was found in each sample of myeloid malignancies. These observations suggest that TET2 functions are more deeply repressed in AITL than in myeloid malignancies. Although TET2 loss is fundamental for a wide range of hematological malignancies, it may be especially important for the development of nodal T-cell lymphomas with TFH phenotype, as *TET2* mutations are markedly frequent in this type of lymphoma. *TET2* mutations were found in 64% of nodal PTCL with TFH phenotype, but in only 17% of PTCL without TFH phenotype.[7] Furthermore, three of four FTCL samples (75%) exhibited *TET2* mutations.[7]

The frequencies of *DNMT3A* mutations were 20%–30% in AITL,[7,13,27] comparable to those in all PTCL-NOS (27%-29%).[13,27] *DNMT3A* mutations were present in 10% of nodal PTCL with TFH phenotype and 4% of PTCL without TFH phenotype in a French-Swiss study.[7] In addition, one of four samples of FTCL had a *DNMT3A* mutation.[7] *DNMT3A* encodes a DNA methyltransferase, which converts cytosine to methylcytosine.[34] *DNMT3A* mutations were clustered at the p.R882 position in AITL, albeit less frequently than in myeloid malignancies.[34] *DNMT3A* mutations are thought to be loss of function, but the R882H mutant was reported to have specific properties in myeloid leukemia by interacting with polycomb proteins.[35] It remains unclear whether this specific function of the R882 mutant is also important in AITL development.

DNMT3A and *TET2* mutations sometimes co-occur in both myeloid and lymphoid malignancies, although they may have opposite epigenetic effects; DNMT3A loss exacerbates DNA demethylation, whereas TET2 loss contributes to DNA methylation. Therefore, the downstream signaling of the co-occurrence of these mutations is unknown. Simultaneous deletion of *Tet2* and *Dnmt3A* results in the development of a variety of diseases in mice, including myeloproliferative neoplasm (MPN)-like diseases, B-cell lymphoma/leukemia, and T-cell lymphoblastic lymphoma.[36] The recipient mice, transplanted with *Tet2*-null hematopoietic stem/progenitor cells transduced with the R882H *DNMT3A* mutant cDNA, also developed both myeloid and T-cell malignancies, including an AITL-like disease.[37] Comprehensive epigenetic and expression studies on R882H *DNTM3A*-expressing *Tet2*-null cells identified candidate oncogenic pathways, including Notch signaling.[37]

IDH2 mutations were found in 20% – 45% of AITL samples,[13,30] but they were rare in PTCL-NOS,[13,30] even with the TFH phenotype.[7] It was also reported that none of five FTCL samples had *IDH2* mutations.[7] These observations suggest that *IDH2* mutations may confer the pathological features of AITL, which are not present in other T-cell lymphomas with the TFH phenotype. In AITL, *IDH* mutations are almost exclusively present at p.R172 IDH2,[13,30] whereas *IDH1* mutations are found in myeloid malignancies.[38] The biased distribution of *IDH* mutations may be explained by the different expression profiles of IDH1 and IDH2. *IDH1* mRNA is expressed only in myeloid cells, whereas *IDH2* mRNA is expressed in both myeloid and lymphoid cells in mice.[39] Physiologically, enzymes belonging to the IDH family convert isocitrate to alpha-ketoglutarate (α-KG), which serves as an intermediate in the tricarboxylic acid cycle (TCA) cycle and as a substrate of dioxygenases. The IDH mutants lead to the abnormal production of (R)-2-hydroxyglutarate (R-2-HG), known as an oncometabolite.[38,40] R-2-HG inhibits α-KG-dependent TET proteins and Jumonji family histone demethylases, resulting in epigenetic alterations in both DNA and histone proteins.

IDH2 and *TET2* mutations seldom coexist in myeloid malignancies.[41] It was hypothesized that the oncogenic properties of the IDH2 mutant are mainly mediated by impairment in TET2 function. Indeed, *IDH2*-mutated and *TET2*-mutated samples exhibited similar methylation profiles in myeloid malignancies.[41] In contrast, *IDH2* and *TET2* mutations coexisted in AITL samples.[13] These observations suggest that *IDH2* mutants contribute to AITL development through mechanisms other than impairment of TET2

Table 1. Frequencies of representative gene mutations in nodal T-cell lymphomas with TFH phenotype.

	AITL	PTCL-NOS			FTCL
		With TFH	Without TFH	Undetermined	
Sakata-Yanagimoto[13]	*TET2* 83% *RHOA* 71% *IDH2* 30%	*RHOA* 61%	*RHOA* 0%	*TET2* 49% *IDH2* 0%	
Dobay[7]	*TET2* 48% *RHOA* 58% *IDH2* 33%	*TET2* 64% *RHOA* 57% *IDH2* 10%	*TET2* 17% *RHOA* 0% *IDH2* 0%		*TET2* 75% *RHOA* 60% *IDH2* 0%

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; FTLC, follicular T-cell lymphoma; TFH, follicular helper T-cell phenotype.

function. Other TET family proteins and histone demethylases are likely candidates as downstream targets of IDH2 in AITL. Indeed, AITL samples with *TET2* and *IDH2* mutations demonstrated more prominent DNA hypermethylation and histone H3K27 methylation than those with *TET2*/without *IDH2* mutations.[5] AITL samples with *IDH2* mutations exhibited repression of a helper T-cell 1 (Th1)-associated gene signature and enrichment of an interleukin 12-induced gene signature.[5]

RHOA mutations

We and other groups previously reported the recurrent *RHOA* mutations in AITL (50% –70%) converting glycine to valine at amino acid 17 (G17V *RHOA*).[29,42,43] *RHOA* mutations were also found in 57% – 62% of nodal PTCL with TFH phenotype.[7,13] In addition, three of five FTCLs had *RHOA* mutations.[7] These data indicate that the G17V *RHOA* mutations are shared by all three categories of nodal T-cell lymphomas with TFH phenotype. However, the G17V *RHOA* mutations are uncommon in other hematological malignancies,[13] although *RHOA* mutations other than G17V mutations are detected in other malignant tumors (i.e., diffuse-type gastric carcinoma,[44] pediatric Burkitt lymphoma,[45] and adult T-cell leukemia/lymphoma (ATLL)[46]) (Figure 1). Therefore, the G17V *RHOA* mutation has diagnostic value for nodal T-cell lymphomas with TFH phenotype.

Functioning as a molecular switch, RHOA cycles between a GTP-bound active state and a GDP-bound inactive state.[47] The G17V RHOA mutant is thought to be loss of function in terms of classical RHOA signaling because it is not converted to the active GTP-bound form.[13,27] Intriguingly, p.K18N, confirmed to be an activating mutation, was reported in a few AITL samples.[48] Moreover, both active (p.C16R and p.G14V) and inactive (p.G17E and p.G17V) *RHOA* mutations were found in ATLL.[46] These observations suggest that the RHOA mutants may induce development of T-cell lymphomas through mechanisms other than classical RHOA signaling.

Mutations in components of the T-cell receptor (TCR) pathway

Half of the samples of AITL and nodal PTCL with TFH phenotype had mutations in genes encoding components of the T-cell Receptor (TCR) signaling pathway in an almost exclusive manner:[48] e.g., *PLCgamma*, 14%;[48] *CD28*, 9% – 11%;[48,49] *FYN*, 3% – 4%;[27,48] and *VAV1* 5%.[48] A substantial proportion of these mutations are commonly found in ATLL.[50]

PLCgamma encodes phospholipase C gamma, an enzyme that cleaves phosphatidylinositol-4,5-biphosphate ($PI_{(4,5)}P_2$) to generate inositol-1,4,5-trisphosphate (IP3), a messenger for Ca^{2+} mobilization, and diacylglycerol (DAG).[51] PLCgamma mutations are distributed throughout several functional motifs, and reporter analyses indicated them to be activating mutations.[48]

CD28 is a representative co-stimulatory molecule of the TCR, and is composed of an extracellular immunoglobulin-like domain and intracellular motifs to associate with signaling molecules.[52] Engagement of CD28 by its ligands induces sustained T-cell proliferation and cytokine production when combined with TCR stimulation.[52] Two residues, p.D124 and p.T195, are recurrently mutated.[48,49] D124 is located close to the C-terminal end of the ligand-binding site. The D124 mutant was found to have higher affinity for its ligands CD80 and CD86.[49] T195 is located between the YMNM-containing SH2-binding motif and proximal PxxP-containing SH3-binding motif. The T195 mutant was demonstrated to have higher affinity for GADS/GRAP2 and GRB2.[49,53] Both mutants activate downstream transcription of *TNFA* and *CD226*,[49] and the NF-κB reporter[49,53] in Jurkat

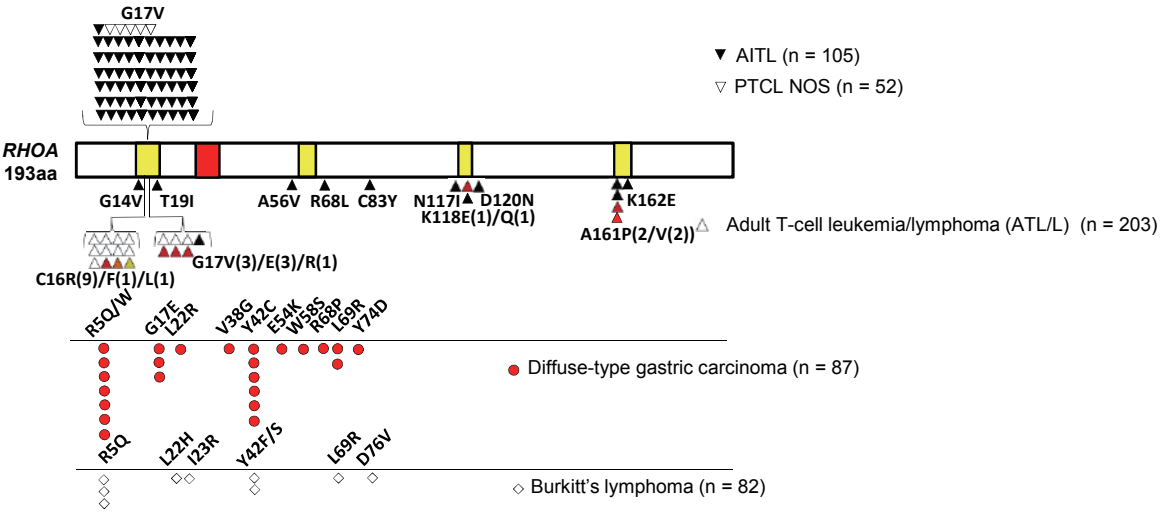

Fig. 1. Distribution of RHOA mutations in AITL and other cancers such as ATLL, Burkitt's lymphoma, and diffuse-type gastric carcinoma.
RHOA mutations are shown by integrating the published information for AITL,[13] ATLL,[46] Burkitt's lymphoma,[45] and diffuse-type gastric carcinoma.[44] Four nucleotide-binding domains are indicated by yellow boxes. The effector domain is represented with a red box.

cells. Although *CD28* mutations are found in a substantial proportion of AITL samples, they are rare in PTCL-NOS.[49] The AITL-specific distribution suggests that *CD28* mutations as well as *IDH2* mutations may account for specific pathological features of AITL. *CTLA4-CD28* fusion genes were reported to be found in 58% of AITL samples,[54] although the actual frequency of the fusion genes is uncertain because of the much lower frequency in another report.[55] *ICOS-CD28*, another fusion gene involving the *CD28* gene, was also described.[49] These fusion genes are expressed under the control of the promoters for *CTLA4* and *ICOS*, respectively. Both CTLA4 and ICOS are markedly induced after TCR stimulation, accompanied by downregulation of CD28 expression through endocytosis.[16] As a result, these genetic events may result in sustained CD28-costimulatory signaling.[50] Both fusion genes were also found in ATLL.[50]

FYN encodes a Src kinase, which mediates TCR signaling upon TCR stimulation. The *FYN* mutations are thought to be activating mutations by disruption of intramolecular inhibition.[27]

VAV1 mediates TCR signaling as a GEF protein and an adaptor for the TCR signaling complex. In addition to point mutations, novel deletion mutations were identified, resulting in in-frame deletions at the N-terminal side of the CSH3 domain by an alternative splicing mechanism.[56] *VAV1* fusion genes were also found, resulting in deletion of the CSH3 domain, which is known as a negative regulatory site.[56,57] *VAV1* fusion genes and in-frame deletions are thought to be activating mutations by disrupting intramolecular autoinhibition.[56] *VAV1* fusion genes were also reported in ATLL[50] and anaplastic large-cell lymphoma.[57]

An *ITK-SYK* fusion gene generated by the translocation t(5;9)(q33;q22) was identified predominantly in FTCL (FTCL 18%[11] – 38%;[58] all PTCL-NOS, 17%[58]). The expression of the *ITK-SYK* fusion gene was reported to constitutively activate TCR signaling.[59]

Prognostic impact of gene mutations in AITL

The prognostic impact of some of these mutations has been examined in a retrospective manner. *TET2* mutations and *CD28* mutations had negative impacts on progression-free survival (PFS)[12] and overall survival (OS),[49] respectively, whereas mutations in *IDH2*,[30] *RHOA*,[13] and genes related to the TCR pathway[48] were not associated with survival. Notably, it is uncertain whether these mutations impact survival because none were evaluated in prospective studies.

CELLULAR INFILTRATION OF AITL: MULTISTEP AND MULTI-LINEAGE ACQUISITION OF MUTATIONS IN AITL DEVELOPMENT

Among PTCL, AITL exhibits marked massive infiltration of inflammatory cells.[60] Therefore, AITL used to be considered an immune reactive process mediated by non-malignant inflammatory cells. However, Shimoyama *et al*. proposed AITL to be a T-lineage tumor, with pathological characteristics of immunoblastic lymphadenopathy (IBL).[61] Clonality was later confirmed by the rearrangement of *TCR* genes in 66% – 100% of AITL samples,[2] providing definitive evidence that AITL is a subtype of T-cell lymphoma. Tumor-infiltrating inflammatory cells were believed to be guided by cytokines and chemokines released from TFH-like tumor cells. GEPs of AITL express genes attributable to the characteristics of multiple lineage inflammatory cells in addition to those of TFH-like tumor cells;[62,63] genes of chemokines, cytokines, extracellular matrix, and immunoglobulins expressed in B-cells and follicular dendritic cells, and those related with vessels, are expressed at high levels.

Clonal expansion of B-cells

AITL contains B-cell blasts. In some cases, the atypical B-cell blasts simulate Hodgkin–Reed–Sternberg-like cells, leading to a mistaken diagnosis of classical Hodgkin lymphoma.[64,65] Rearrangement of *immunoglobulin (Ig)* genes as well as *T-cell receptor* genes is found in 0% – 40% of AITL samples.[2] As mentioned above, the cells are often EBV-positive (66% – 86%),[3,66,67] which may contribute to their clonal expansion.

It has been well documented that AITL and B-cell lymphomas occur simultaneously as composite lymphoma, or occur serially one-by-one during the course of the disease. Although EBV was positive in the majority of B-cell lymphoma samples, a substantial proportion was negative. The combination of AITL and diffuse large B-cell lymphomas (DLBCL) accounted for 21 of 29 cases (74%) of composite lymphomas.[68] EBV was positive in only 13 of 18 cases (67%), and negative in five (33%).[68] Seven of 31 AITL patients (23%) developed EBV-positive lymphoma (DLBCL, $n = 5$; Hodgkin's lymphoma, $n = 2$), but one EBV-negative DLBCL patient was also documented.[69] Moreover, 21 patients developed B-cell lymphomas (DLBCL, $n = 16$; lymphoplasmacytic lymphoma, $n = 2$; CD30-positive lymphoma, $n = 1$; and Hodgkin's lymphoma, $n = 2$) during the study on 161 AITL patients. Nine of 20 patients (45%) were positive for EBV, while 11 (55%) were negative for EBV.[70] These data suggest that although EBV may take part in the development of B-cell lymphomas in the majority of cases, it does not explain a substantial proportion, as some were negative for EBV.

Multistep tumorigenesis in AITL

TET2 and *DNMT3A* mutations were found in normal bone marrow and blood cells in multiple lineages, in addition to in tumor tissues/cells of PTCL patients.[71-73] *TET2* and *DNMT3A* mutations were observed even in blood cells of healthy individuals.[74,75] These observations suggested that some PTCLs may originate from *TET2*- and *DNMT3A*-mutated premalignant cells.[31] *RHOA* and *IDH2* mutations were found only in tumor cells, suggesting that these mutations are acquired in the later processes of AITL development[13,76] (Figure 2).

These observations raise questions on how the tumor-infiltrating B cells are associated with clonal expansion. Considering the multistep tumorigenesis of AITL,

premalignant cells may also differentiate into tumor-infiltrating B cells. When we examined the distribution of mutations in tumor cells and tumor-infiltrating B cells in AITL samples, *TET2* and *DNMT3A* mutations were identified in both tumor cells and B cells in 15/16 and 4/7 samples, respectively.[76] In contrast, all of the *RHOA* and *IDH2* mutations were confined to the tumor cells, as described above. Notably, we identified three *NOTCH1* mutations detected only in B cells.[76] *Notch1* encodes a type I transmembrane receptor. Activating mutations were first found in 56% of T-cell acute lymphoid leukemias (T-ALL).[77] Subsequently, they were also discovered in B-cell lymphomas, including 12% of chronic lymphocytic leukemias (CLL).[78] CLL may begin from premalignant cells, phenotypically mimicking immature hematopoietic progenitor cells.[79] *NOTCH1* mutations were found in premalignant cells of CLL, suggesting that *NOTCH1* mutations are among the early events in CLL development.[80] This hypothesis is applicable to the clonal expansion of B cells in AITL because *NOTCH1* mutations seem to occur earlier than *Ig* rearrangement in some samples of AITL.[76] These findings indicate that "multi-step" and "multi-lineage" acquisition of mutations occur during AITL development.[76]

TREATMENT OPTIONS FOR AITL

AITL is a lymphoma with a poor prognosis, with a 5-year OS rate of approximately 30%.[1,3] Standard treatment strategies have not been established for AITL. Anthracycline-based CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens are used most frequently as the initial regimens for AITL.[3] However, AITL is often refractory to chemotherapy or relapses. Therefore, novel strategies are being examined. Although PTCL is a heterogeneous group of lymphomas, most trials are conducted to include "PTCL" patients because of the rarity of each subtype. Recently, the US Food and Drug Administration approved four drugs with novel mechanisms of action for the treatment of patients with relapsed or refractory PTCL. These included pralatrexate[81] in 2009, romidepsin[82,83] in 2011, and belinostat[84] in 2014. The efficacy of brentuximab vedotin (BV),[85] bortezomib+CHOP,[86] bendamustine,[87] lenalidomide,[88] and forodesine[89] for PTCL was also evaluated in a phase 2 trial. Although these drugs are available as therapeutic options for AITL, their actual impact on long-term outcome has not been well described (Table 2). To target tumor-infiltrating B cells, newly diagnosed AITL was treated with a combination of rituximab plus CHOP (R-CHOP) in a clinical trial, although the benefit of rituximab was not demonstrated.[90] Some AITL patients responded to immunosuppressive agents, including cyclosporin A and corticosteroids[91]. These agents may contribute to the suppression of autoimmune-like manifestations, and to the regression of tumors.

Due to the unfavorable outcomes for PTCL patients treated with chemotherapy alone, autologous stem cell transplantation (auto-SCT) as a consolidation treatment for first-line therapy (upfront auto-SCT) or salvage therapy for relapsed/refractory PTCL patients has been evaluated in retrospective[92-94] and prospective studies.[95-99] Again, most of these studies included both AITL and other subtypes of PTCL. A large retrospective study from the European Group for Blood and Marrow transplantation (EBMT)[93] reported 146 AITL patients who received auto-SCT. The OS at 24 and 48 months was 67% and 59%, respectively. Patients who achieved complete remission (CR) had significantly longer times to progression compared with those who did not achieve CR. The Swedish Lymphoma Registry[95] reported a population-based study of 755 PTCL (104 AITL) patients. In an intention to treat (ITT) analysis in 252 PTCL patients, including 47 AITL patients, revealed that upfront auto-SCT was associated with a superior OS and PFS (Auto-SCT ITT

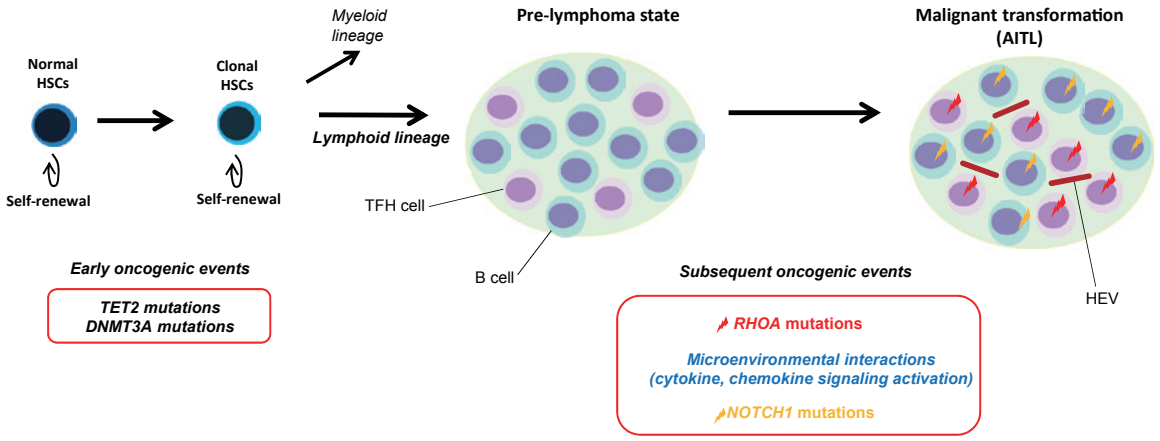

Fig. 2. Multi-step events involving epigenetic regulators and RHO pathways contributing to development of AITL. Loss-of-function mutations in *TET2* or *DNMT3A* occur in the early phase of blood differentiation. They induce the production of premalignant cells. Subsequent oncogenic events, such as *RHOA* mutations in TFH cells, microenvironmental interactions, such as cytokine expression, chemokine signaling activation, and *NOTCH1* mutations in B cells, may cause AITL development.
HSCs, hematopoietic stem cells; TFH cell, follicular helper T cell; AITL, angioimmunoblastic T-cell lymphoma; HEV, high endothelial venules.

vs Non-auto-SCT, 5 year OS, 48% vs 26%, p=0.004; 5 year PFS, 41% vs 20%, p=0.002). The Nordic Lymphoma Group reported a large prospective phase 2 study (NLG-T-01) on 160 untreated PTCL (30 AITL) patients.[96] In total, 115 PTCL patients who achieved CR/partial remission (PR) after six courses of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone) received auto-SCT. The five-year OS and PFS for all PTCL and AITL were comparable (all PTCL vs AITL, five-year OS, 51% vs 52%; five-year PFS, 44% vs 49%). The German group also reported a large prospective study on 111 untreated PTCL (37 AITL) patients.[99] Seventy-five patients who achieved CR/PR after six courses of CHOP received auto-SCT. The five-year OS and PFS for all PTCL patients were 44% and 39%, but those for AITL patients were not described. Remarkably, these prospective studies revealed that up to one-third of PTCL patients were unable to receive planned auto-SCT, mainly because they were refractory to the induction therapies. Thus, these data suggest that auto-SCT may be an option for AITL patients with chemosensitive diseases as a consolidation treatment for first-line therapy, or a salvage therapy if auto-SCT has not been performed. However, it remains unclear if upfront auto-SCT should be planned for all eligible AITL patients considering the heterogeneous clinical courses of AITL patients. Patients who achieve long-term survival after upfront auto-SCT may survive long term even without auto-SCT. Future studies are warranted to clarify any biomarkers (e.g., gene mutations or protein expression) for selecting patients who will benefit from such an intensive therapy.

Additionally, allogeneic stem cell transplan-tation (allo-SCT) using myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) has been examined as a viable option for patients with relapsed or refractory PTCL in retrospective[100-103] and prospective studies.[104] A retrospective study from EBMT[100] reported the long-term outcome in 45 patients with AITL who received allo-SCT (24 received MAC regimens and 21 RIC regimens). The estimated three-year OS and PFS were 64% and 54%, respectively. The relapse rate (RR) seemed to be lower in patients with chronic graft versus host disease (cGVHD) compared with in those without cGVHD, but the difference was not significant because of the small number of patients. A retrospective study from an Italian group reported 52 relapsed/refractory PTCL (9 AITL) patients who received allo-SCT with RIC regimens.[101] Five-year OS and PFS were 50% and 40% for all PTCL patients, and 66% and 44% for AITL patients, respectively.[101] Remarkably, donor lymphocyte infusions

Table 2. Treatment outcomes of novel agents for refractory and relapsed T-cell lymphoma.

Drugs	PTCL subtype	Primary endpoint	Design	ORR	CR*	PR	Median PFS (months)	Median OS (months)	Reference
Pralatrexate	Relapsed/refractory PTCL n = 109 (PTCL-NOS n = 59 (53%), AITL n = 13 (12%))	ORR	Phase II, open-label, multicenter	27%	8%	18%	NA	NA	Malik *et al*. (2010)
Pralatrexate	Relapsed/refractory PTCL n = 115 (PTCL-U n = 59 (53%), AITL n = 13 (12%))	ORR	Phase II, open-label, multicenter	29%	11%	18%	3.5	14.5	O'Connor *et al*. (2011) PROPEL trial
Romidepsin	Relapsed/refractory PTCL and CTCL n = 47 (PTCL-U or NOS n = 27 (57%), AITL n = 7 (15%))	ORR	Phase II, multicenter	38%	18%	20%	13.0 for CR+PR, 4.6 for SD and 1.4 for PD+NE	NA	Piekarz *et al*. (2011)
Romidepsin	Relapsed/refractory PTCL n = 130 (PTCL-NOS n = 67 (53%), AITL n = 27 (21%))	CR/CRu	Phase II, multicenter	25%	15%	11%	4	NA	Coiffier *et al*. (2012)
Belinostat	Relapsed/refractory PTCL n = 120 (PTCL-NOS n = 77 (64%), AITL n = 22 (18%))	ORR	Phase II, open-label, multicenter	26%	11%	15%	1.6	7.9	O'Connor *et al*. (2015) BELIEF (CLN-19) Study
Brentuximab vedotin	Relapsed/refractory PTCL n = 35 (PTCL-NOS n = 22(63%), AITL n = 13(37%))	ORR	Phase II, open-label, multicenter	41% (PTCL-NOS 33%, AITL 54%)	24%	18%	6.7(AITL), 1.6 (PTCL-NOS)	NA	Holwitz *et al*. (2014)
Lenalidomide	Relapsed/refractory PTCL n = 54 (PTCL-NOS n = 20(37%), AITL n = 26(48%),ALCL n = 10(26%))	ORR	Phase II, open-label, multicenter	22% (PTCL-NOS 20%, AITL 31%)	11%	11%	2.5	NA	Morschhauser *et al*. (2013) EXPECT trial
Bendamustine	PTCL n = 60 (PTCL-NOS n = 23 (38%), AITL n = 32 (58%))	ORR	Phase II, open-label, multicenter	50%	28%	22%	3.6	6.2	Damaji *et al*. (2013) BENTLY trial
Bortezomib +CHOP	Stage III/IV primary PTCL n = 46 (PTCL-NOS n = 16(34.8%), AITL n = 8(17.4%),ALK-negative ALCL n = 6(13%))	-	Phase II, open-label, multicenter	76%	65%	11%	8.8	26.6	Kim *et al*. (2012) CISL

Abbreviations: ORR, overall response rate; CR, complete response; CRu, complete response, unconfirmed; PR, partial response; PFS, progression-free survival; OS, overall survival; NA, not analyzed; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; PTCL-U, peripheral T-cell lymphoma unclassified; ALCL, Anaplastic large cell lymphoma. * included CR and CRu.

(DLIs) were given for 12 patients who relapsed after allo-SCT.[101] Five patients including one AITL patient achieved CR by DLIs.[101] The report from the Center for International Blood and Marrow Transplant Research (CIBMTR) included 12 AITL patients who received allo-SCT.[102] The three-year OS and PFS for AITL patients were 83% and 67%, respectively.[102] A retrospective study from a French group reported 77 PTCL (11 AITL) patients who received allo-SCT (57 MAC and 20 RIC).[103] The five-year OS and PFS were 57% and 53% for all PTCL patients, and 80% and 80% for AITL patients, respectively.[103] A prospective phase 2 study on 17 PTCL patients who received allo-SCT with RIC regimens reported that the three-year OS and PFS were 81% and 64%, although only four AITL patients were included in this study.[104] Overall, these data suggest that some relapse/refractory AITL patients may benefit from allo-SCT, presumably because of graft-versus-lymphoma effects.

CONCLUSION

The GEP and genetic landscape has clarified a new distinct entity of T-cell lymphoma with TFH phenotype, involving AITL as a representative. The importance of genetic events has increased in diagnosis of and treatment strategies for AITL; "precision medicine" will be implemented for AITL, leading to improved management. Moreover, evidence of "multi-step" and "multi-lineage" genetic events in AITL will provide insights into the origins and evolution of this unusual subtype of T-cell lymphoma.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

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