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Molecular Pathogenesis of Peripheral T Cell Lymphoma

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Abstract Understanding the molecular pathogenesis of peripheral T cell lymphomas (PTCLs) has lagged behind that of B cell lymphomas due to disease rarity. However, novel approaches are gradually clarifying these mechanisms, and gene profiling has identified specific signaling pathways governing PTCL cell survival and growth. For example, genetic alterations have been discovered, including signal transducer and activator of transcription (*STAT*)*3* and *STAT5b* mutations in several PTCLs, disease-specific ras homolog family member A (*RHOA*) mutations in angioimmunoblastic T cell lymphoma (AITL), and recurrent translocations at the dual specificity phosphatase 22 (*DUSP22*) locus in anaplastic lymphoma receptor tyrosine kinase (ALK)-negative anaplastic large cell lymphomas (ALCLs). Intriguingly, some PTCL-relevant mutations are seen in apparently normal blood cells as well as tumor cells, while others are confined to tumor cells. These data have dramatically changed our understanding of PTCL origins: once considered to originate from mature T lymphocytes, some PTCLs are now believed to emerge from immature hematopoietic progenitor cells.

Keywords T cell lymphoma · Peripheral T cell lymphomas (PTCLs) · B cell lymphomas

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Introduction

Peripheral T cell lymphomas (PTCLs) fall into more than 10 categories according to WHO classification [1]. Molecular functions underlying most of PTCLs, except for recurrent translocations at the anaplastic lymphoma receptor tyrosine kinase (*ALK*) locus in ALK-positive anaplastic large cell lymphoma (ALCL), have remained elusive until recently. However, extensive analysis of gene and micro-RNA expression profiles has identified signaling pathways regulating PTCL survival and growth.

Recent advances in sequencing technologies have also led to discovery of genetic alterations marking specific PTCL subtypes, providing clues to the molecular basis of these diseases and allowing establishment of PTCL disease models. These activities could also prove useful clinically in disease diagnosis, recognition of subtypes, or assessment of prognosis.

Furthermore, multistep acquisition of mutations has been proposed, particularly in PTCL harboring features of follicular helper T cells (Tfh) [2]. Some mutations identified in PTCL tumor cells are also found in multi-lineage hematopoietic cells, and even in hematopoietic progenitor cells [3••, 4, 5••]. These mutations may be acquired at the early phase of PTCL development, while others confined to PTCL tumor cells may be added at the late phase [2]. In this review, we describe recent progress in understanding the molecular pathogenesis of PTCL.

Peripheral T Cell Lymphoma, Not Otherwise Specified

Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS) is a heterogenous group of lymphomas that cannot be classified into specific categories [1].

PTCL-NOS Gene Expression Signatures

Gene expression profiling (GEP) has been used to identify distinct molecular subgroups in PTCL-NOS [6••, 7, 8]. A large series of GEP studies identified two major subgroups: one marked by high expression of GATA binding protein 3 (*GATA3*) and its target genes, and another characterized by high expression of T-box 21 (*TBX21*) and eomesodermin (*EOMES*) and their targets [6••]. *TBX21* and *GATA3* are master regulators of T helper cells 1 (Th1) and Th2, respectively [9]. Intriguingly, the GATA3 subgroup is associated with poor overall survival [6••].

Previous studies report that some PTCL-NOS tumors express factors common to Tfh [8, 10, 11]. A Tfh-related factors are also observed in angioimmunoblastic T cell lymphomas (AITL) [8, 11–14]. Gene mutation profiles of PTCL-NOS with Tfh features in fact resemble those seen in AITL [5••, 15], raising questions about what distinguishes PTCL-NOS with Tfh features from AITL (see section "Angioimmunoblastic T Cell Lymphoma"). Tfh-related factors are also expressed in PTCL-NOS, follicular variant (PTCL-F) [16].

Genomic Abnormalities in Variant PTCL-NOS

Specific genetic alterations have been discovered in PTCL-NOS subtypes exhibiting distinct pathological features or unique gene expression profiles. The recurrent translocation, t(5;9) (q33;q22) has been identified in some cases of PTCL-NOS [17], predominantly in PTCL-F (PTCL-F, 18 (16)–38 % (17); all PTCL-NOS, 17 % (17)). The t(5;9) (q33;q22) translocation creates a fusion of the interleukin (*IL-2*)–inducible T cell kinase (*ITK*) and spleen tyrosine kinase (*SYK*) genes [17] and results in expression of *ITK-SYK* fusion transcript. The *ITK-SYK* transcript encodes a fusion protein with the pleckstrin homology (PH) domain and BTK homology (BH) motif (alternatively, a TEC homology (TH) domain) of ITK fused to the kinase domain of SYK [17, 18].

PTCL Disease Models Based on *ITK-SYK* Expression

Constitutive expression of the *ITK-SYK* fusion gene reportedly mimics constitutive activation of T cell receptor (TCR) signaling [18]. Tyrosine phosphorylation of lipid-raft-associated proteins (such as phospholipase C (PLC) gamma1), as well as CD69 induction and interleukin (IL)-2 production, occurs in *ITK-SYK*-expressing cells in the absence of TCR stimulation [18]. To define *ITK-SYK* function in vivo, human *ITK-SYK* complementary DNA (cDNA) was inserted into the mouse ROSA26 locus with a loxP-flanked transcriptional STOP cassette. Conditional expression of high levels of *ITK-SYK* in T cells following Cre recombinase activation under the control of *CD4* promoter induced T cell malignancies in mice at 20–27 weeks [18]; mice with lower expression of the fusion protein exhibited polyclonal T cell lymphoproliferative disease with concomitant B cell expansion by 7–9 weeks [19]. Also, transplantation of mice with bone marrow cells retrovirally transduced with an *ITK-SYK* expression vector induced T cell lymphoproliferative disease [20].

Angioimmunoblastic T Cell Lymphoma

AITL is characterized by generalized lymphadenopathy, hepatosplenomegaly, fever, and skin rash [1, 21]. Laboratory tests of AITL patients exhibit immunological abnormalities including hypergammaglobulinaemia and a positive Coomb's test [21]. Pathological examination of AITL tumors reveals proliferation of high endothelial venules and follicular dendritic cells (FDCs), and infiltration of tumors by inflammatory cells, including Epstein-Barr virus (EBV)-infected B cells [1, 21]. Tumor cells are typically so-called clear cells of medium-size and exhibiting abundant clear cytoplasm [1, 21].

AITL Gene Expression Signatures

As noted above, Tfh-related genes are enriched in GEP of AITL [8, 13, 14]. Such Tfh-like immunophenotypes have been confirmed by immunohistochemical evidence [11, 12], including high expression of B cell CLL/lymphoma 6 (BCL6), programmed death-1 (PD-1), inducible T cell co-stimulator (ICOS), chemokine (C-X-C motif) receptor 5 (CXCR5), and chemokine (C-X-C motif) ligand 13 (CXCL13). In particular, CXCL13 expression may contribute to pathological features characteristic of AITL by recruiting B cells into the germinal center and activating them [21].

AITL GEP analysis also reveals microenvironmental signatures (i.e., high expression of B cell and FDC-related genes) [8, 13] and vascular signatures [13, 14], which reflects significant infiltration of tumors by B cells and FDCs and marked endothelial cell proliferation, respectively.

Genomic Abnormalities Seen in AITL

Mutations in the epigenetic regulators, tet methylcytosine dioxygenase 2 (*TET2*) [3••, 4], DNA (cytosine-5-)-methyltransferase 3 alpha (*DNMT3A*) [4], and isocitrate dehydrogenase 2 (NADP+), mitochondrial (*IDH2*) [22] frequently occur in AITL, as they do in myeloid cancers [23, 24], suggesting that epigenetic pathway disruption is a fundamental mechanism underlying hematologic malignancies. *TET2* mutations in particular are observed in up to 83 % of AITL samples [5••]. *IDH2* mutations in AITL are confined to the R172 position [5••, 25•], while *IDH2* R140 and R172 mutations occur in myeloid cancers [23, 24].

Recent exome sequencing has identified the disease-specific ras homologue family member A (*RHOA*) mutations in 53–71 % of AITL samples [5••, 25•, 26], resulting in conversion of glycine to valine at amino acid 17 (G17V) (Fig. 1). The RHOA GTPase undergoes conversion from a GTP-bound (active) to a GDP-bound (inactive) form and functions as a molecular switch in numerous cellular activities [27, 28]. The loss-of-function G17V RHOA mutant cannot bind GTP and thus disrupts RHOA signaling. Remarkably, there is an interesting relationship between *RHOA* mutations and *TET2* and *IDH2* mutations: All the *RHOA*-mutated samples had the *TET2* mutations, while *IDH2* mutations are found in *TET2*/*RHOA*-mutated samples [5••] (Fig. 1). Genetic evidence suggests a synergy between mutations in epigenetic regulators and the RHOA pathway in AITL development. These mutations may be acquired in a multistep manner [2] (see section "Multistep Tumorigenesis in PTCL").

Distinguishing PTCL-NOS from AITL

TET2, *DNMT3A*, and *RHOA* mutations are also found in PTCL-NOS at lower frequency [5••, 25•, 26] than in AITL (Fig. 1). Among PTCL-NOS tumors, the frequency of *TET2* [15] and *RHOA* mutations [5••] is higher in PTCL-NOS with features of AITL/Tfh than in PTCL-NOS lacking these features. The distinction between PTCL-NOS and AITL can be obscure in some cases.

AITL Disease Models

As noted, *TET2* is frequently mutated in AITL. Gene trap mice engineered to express low levels of *TET2* develop T cell lymphomas with Tfh features at a median age of 67 weeks [29]. These tumors exhibit hypermethylation of the *BCL6* locus, followed by upregulated expression of *BCL6* [29], which encodes a transcription factor critical for Tfh development. v-maf avian musculoaponeurotic fibrosarcoma oncogene homologue (*c-Maf*), which promotes differentiation of Tfh cells as *BCL6* does, is highly expressed in AITL [30]. Transgenic mice expressing *c-Maf* under control of the *CD2* promoter develop T cell lymphomas [30]. Furthermore, the ring finger protein Roquin/Rc3h1 promotes degradation of *ICOS* messenger RNA (mRNA), which encodes a protein essential for Tfh development [31]. The *sanroque* mutation in the *Roquin* gene ($Roquin^{san}$) is a missense (M199R) mutation in the Roquin ROQ domain that partially blocks *ICOS* mRNA degradation [31]. Mice heterozygous for the $Roquin^{san}$ allele develop AITL-like disease [32]. Notably, *Roquin* mutations have not been identified in human AITL [33]. Additionally, NOD/Shi-*scid*, IL-

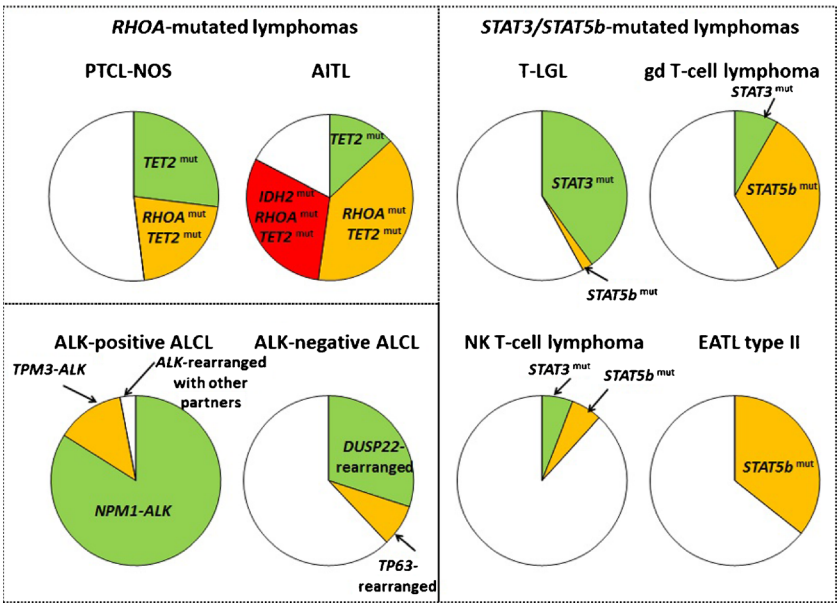

Fig. 1 Newly identified mutations associated with PTCL. *TET2* and *RHOA* mutations are seen in PTCL-NOS and AITL. Some *TET2*-mutated samples also display *RHOA* mutations. *IDH2* mutations are identified in a subset of *TET2-RHOA* mutated AITLs. *STAT3* and *STAT5b* mutations occur in various subtypes of T-NK cell neoplasms, including T-LGL, gamma delta T-cell lymphoma, NK/T cell lymphoma, and EATL type II. Mutation frequency differs among diseases. *ALK* gene translocation is seen in ALK-positive ALCL. *NPM1* is the translocation partner of *ALK* in most ALK-positive ALCLs. Recurrent *DUSP22* or *TP63* translocations are seen in ALK-negative ALCL. *Pie graphs* show mutation frequencies reported in reference [5••] for PTCL-NOS and AITL; reference [35••, 40] for T-LGL; reference [38••] for gamma delta T cell lymphoma, NK/T cell lymphoma, and EATL; reference [1] for ALK-positive ALCL; and reference [68••] for ALK-negative ALCL. *PTCL-NOS* peripheral T cell lymphoma not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma, *T-LGL* T cell large granular lymphocytic leukemia, *gd T cell lymphoma* gamma delta T cell lymphoma, *EATL* enteropathy-associated T cell lymphoma, *ALCL* anaplastic large cell lymphoma.)

2Rgamma^{null} (NOG) mice transplanted with AITL cells develop AITL-like disease [34].

T Cell Large Granular Lymphocytic Leukemia

T cell large granular lymphocytic leukemia (T-LGL) is a lymphoproliferative disorder in which large granular lymphocytes with an immunophenotype of cytotoxic T cells show persistently increased levels in peripheral blood, bone marrow, liver, and spleen [1]. Severe neutropenia with or without anemia frequently accompanies this condition, as does autoimmune-like disease [1].

Genetic Abnormalities Seen in T-LGL

Whole exome sequencing has identified *STAT3* mutations in 33–40 %[35••, 36] of T-LGL samples (Fig. 1). STAT3 proteins together Janus kinases (JAKs) positively regulate cytokine signaling. Recurrent hotspot mutations in STAT3 include Y640F (17 %), D661V (9 %), D661Y (9 %), and N647I (4 %), all activating mutations in the SH2 domain, which regulates STAT3 dimerization [35••]. *STAT3*-mutant T-LGL cells display phosphorylated STAT3 in the nucleus [35••]. STAT3 mutant protein also has greater transcriptional activity than does the wild-type protein [35••].

When they were discovered, *STAT3* mutations were predicted to be specific for T-LGL [37]; however, subsequent analysis has identified these mutations in the other PTCLs: namely, chronic lymphoproliferative disorders of natural killer cells (CLPD-NKs) [36], NK/T cell lymphoma, hepatosplenic T cell lymphomas, primary cutaneous gamma delta T cell lymphoma [38••], and CD30-positive T cell lymphomas [39]. Furthermore, mutations in *STAT5b*, another component of JAK-STAT pathway, are found in 2 % of LGL [40] (Fig. 1). *STAT5b* mutations are also seen in NK/T cell lymphoma [38••], hepatosplenic T cell lymphoma [38••, 41], primary cutaneous gamma delta T cell lymphoma [38••], enteropathy associated T cell lymphoma (EATL) type II [38••], and T cell prolymphocytic leukemia [42]. Overall, these findings suggest that activating mutations in components of the JAK-STAT pathway constitute a fundamental mechanism in PTCLs (see section "Extranodal NK/T Cell Lymphoma").

Extranodal NK/T Cell Lymphoma

Extranodal NK/T cell lymphoma (NKTL) occurs in regions of the upper aerodigestive tract, such as the nasal cavity, but is less frequent in other extranodal sites [1]. An angiocentric and angiodestructive growth pattern is frequently observed, accompanied by prominent necrosis and ulceration [1]. Tumor cells exhibit immunophenotypes of activated NK cells and less frequently of cytotoxic T lymphocytes and EBV infection of tumor cells occurs in virtually all cases [1].

NKTL Gene Expression Signatures

GEP analysis indicates activation of Notch, aurora kinase A (AURKA) [43], JAK-STAT [44], and platelet-derived growth factor receptor (PDGFR) alpha [45] signaling in NKTL, and reagents that inhibit these pathways attenuate tumor cell growth [38••, 43, 45–47]. Micro-RNA profiles of NKTL tumors and cell lines in comparison with those of normal NK cells show downregulation of several micro-RNAs, including miR-26a, miR-26b, miR-28-5, miR-101, and miR-363 [48]. Overexpression of these micro-RNAs in NKTL cell lines reduce growth of the cells, suggesting that downregulation of these micro-RNAs contributes to tumor development [48]. Target genes by these micro-RNAs include those involved in cell cycle, mitogen-activated protein kinase (MAPK), and p53 signaling pathways; overexpression of proteins encoded by the target genes of these micro-RNAs are also confirmed by immunohistochemical staining of tumors [48].

Mechanisms Underlying Drug Resistance

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and other anthracycline-based regimens, which have been standard therapies for malignant lymphomas, are not effective for NKTL [49]. One mechanism underlying resistance is expression of the P-glycoprotein transporter, which is encoded by the multidrug resistance 1 (*MDR*) gene and transports drugs out of cells [50]. This outcome has formed the basis for development of new therapies using combinations of drugs not transported by P-glycoprotein [49]. Drug resistance may also be due to disruption of Fas-dependent apoptosis by mutations in Fas cell surface death receptor (*FAS*) gene [51] or overexpression of cellular caspase-8-like (FLICE)-inhibitory protein long form (cFLIP$_L$) [52], an inhibitor of caspase-8 activation [53].

Genomic Abnormalities Seen in NKTL

NKTL tumor cells are persistently infected with EBV, which likely contributes to tumorigenesis [49]. NKTL tumor cells display a latency II pattern, implying partial expression of viral proteins and micro-RNAs [54, 55]. For example, latent membrane protein-1 (LMP-1), an EBV protein, induces expression of survivin, antagonizing apoptosis [56]. The miR-BART20-5p, a micro-RNA encoded by EBV, inhibits translation of *TBX21* mRNA, rendering tumor cells resistant to p53-dependent apoptosis [57].

In addition, numerous genomic abnormalities have been identified in NKTL. Among them are deletion or methylation of the PR domain containing 1, with ZNF domain (*PRDM1*)

gene [58, 59], deletion of forkhead box P3 (*FOX3*) [59], or mutations in *TP53* [60], *FAS* [51], or NME/NM23 nucleoside diphosphate kinase 1 (*NME1*, alternatively *NM23-H1*) [61] . Exome sequencing has also identified *JAK3* mutations at a 20–35 % frequency in NK/T cell lymphoma [46, 47]. *JAK3* hotspot mutations include A572V, A573V, and V722I, all located in the pseudokinase domain [46, 47], resulting in constitutive tyrosine 980/981 phosphorylation and consequent *JAK3* activation. Subsequently, other groups have reported that *JAK3* mutations are not present in NKTL in particular cohorts [38••, 62], although JAK-STAT pathway activation was seen in these cases. RNA and exome sequencing revealed that activating mutations in *STAT3* and *STAT5b* were present each at a frequency of 5.9 % in NKTL cases [38••] (Fig. 1).

Inhibitors of either JAK1/2 or JAK3 reportedly repress cell growth and/or induce apoptosis in NKTL cells harboring JAK-STAT pathway mutations in in vitro studies [38••, 46, 47]. The efficacy of these inhibitors should be evaluated in future clinical studies.

Anaplastic Large Cell Lymphoma

Based on the WHO classification, ALCLs are classified as ALK-positive or ALK-negative subtypes, and molecular mechanisms underlying each differ [1]. ALK-positive ALCL is most frequent in younger patients (<30 years old). ALK-positive patients often have a favorable outcome, although most present with advanced disease and fever [1]. ALK-negative ALCL is more frequent in middle-aged individuals, and its clinical outcome is poorer [1]. In both types, tumor cells display pleomorphic nuclei and express CD30 and cytotoxic molecules, including TIA1, granzyme B and/or perforin, while CD3, the most widely used T cell marker, and other T cell-specific molecules are frequently downregulated [1]. Downregulation of the latter in nucleophosmin (*NPM*)-*ALK*-positive (see the following paragraph) ALCL reportedly occurs via hypermethylation caused by ALK-mediated STAT3 activation [63].

Genomic Abnormalities Seen in ALCL

ALK-positive ALCL tumors almost always harbor a translocation at the *ALK* 2p23 locus [64]. The most frequent is t(2;5)(p23;q35), resulting in creation of the *NPM-ALK* fusion gene [64, 65] (Fig. 1). NPM-ALK fusion protein is distributed in both the nucleus and cytoplasm, as NPM-ALK protein forms heterodimers with wild-type NPM1 through the NPM1 oligomerization domain, which in turn imports NPM-ALK into nucleoli [65]. By contrast, most other ALK fusion proteins are restricted to the cytoplasm [64]. Several ALK inhibitors, including crizotinib (PF-02341066), an orally available small-molecule ALK inhibitor, are currently in clinical trials (https://clinicaltrials.gov). The discovery of *ALK* translocations in solid tumors has accelerated investigation of ALK inhibitors [66].

Remarkably, a novel recurrent translocation (6;7)(p25.3;q32.3) has been discovered in ALK-negative ALCL [67] (Fig. 1). 6p25.3 breakpoints are located in *DUSP22* locus in most cases, and interferon regulatory factor (*IRF*) *4* locus in fewer cases. *DUSP22* and *IRF4* loci are only 40 kb apart. *DUSP22* gene, encoding a phosphatase, is disrupted in some cases, while its expression is reduced even when breakpoints are located closed to *IRF4* locus [67]. In contrast, *IRF4* expression is not affected regardless of translocation loci [67]. Those tumors showed upregulation of miR-29a and miR-29b on 7q32.3 [67].

Rearrangement of *DUSP22* is found in 30 % of ALK-negative ALCL cases, and prognosis of those patients is as favorable as that of ALK-positive ALCL patients [68••]. Rearrangements involving *TP63* also reportedly occur in ALK-negative ALCL (8 %) [68••, 69], although that rearrangement is also seen in other PTCL subtypes, including PTCL-NOS (9.4 %) and primary cutaneous ALCL (10.5 %) [69]. Unlike cases showing *DUSP22* rearrangement, prognosis of *TP63*-rearranged, ALK-negative ALCL is quite poor (5-year overall survival in ALK-positive vs *DUSP22*-rearranged vs *TP63*-rearranged vs triple-negative ALCL; 85 vs 90 vs 17 vs 42 %) [68••]. From these data, ALK-negative ALCLs are subclassified by existence of particular translocations.

Downstream Signaling in ALCL

GEP and proteome studies combined with analysis of disease models indicate that signaling pathways significant in ALK-positive ALCL include ALK-STAT3 [70], RAS-extracellular signal-regulated kinase (ERK) [71], and phosphoinositide 3 kinase (PI3K)-AKT- mammalian target of rapamycin (mTOR) pathways [71]. Inhibitors of STAT3 [72], Ras/ ERK [71], or mTOR [71, 73] suppress growth and increase apoptosis of tumor cells. In addition, Jun and cJunB mediates NPM-ALK-driven lymphoma development through transcriptional regulation of PDGFRbeta [74]. Imatinib, a tyrosine kinase inhibitor, inhibits growth of these tumors in an in vivo disease model by blocking a PDGFRbeta positive feedback loop [74].

GEP has been also used to examine differences in ALK-positive and -negative ALCL [6••, 70, 75]. Analysis indicates enrichment of IL-10, H-Ras/K-Ras, and hypoxia inducible factor (HIF)1-alpha pathways in ALK-positive relative to ALK-negative ALCL [6••].

ALCL subtypes also exhibit different micro-RNA profiles. miR-101, which targets mTOR, is downregulated in ALK-positive and -negative ALCL, while miR-101 downregulation has a growth-promoting effect only in ALK-positive ALCL [76]. miR-155, an oncogenic micro-RNA, is specifically expressed in ALK-negative ALCL [76–78], and miR-155 antagonists block growth of ALK-negative ALCL in a xenograft

model [78]. ALK/STAT3-dependent expression of miR-135b mediates production of IL-17, a cytokine expressed in Th17 cells [79]. ALK-dependent downregulation of miR-16 promotes tumor cell growth by upregulating expression of vascular endothelial growth factor (VEGF) [80]. Expression of miR-29a is downregulated in ALK-positive ALCL due to ALK-dependent hypermethylation of CpG sites near the miR-29a locus [81]. miR-29a downregulation antagonizes apoptosis by allowing expression of antiapoptotic protein myeloid cell leukemia (MCL)-1 [81].

ALCL Disease Models

Mice expressing *NPM-ALK* cDNA under control of the *lck* promoter develop CD30-positive T cell lymphomas at 5–15 weeks [82], while those expressing *NPM-ALK* cDNA under control of the *CD4* promoter develop CD30-positive T cell lymphomas and plasma cell neoplasms at 5–25 weeks [83]. In contrast, mice expressing *NPM-ALK* cDNA under control of either the *VAV1* [84] or *CD2* promoters [85], develop B cell malignances. When bone marrow cells are retrovirally transduced with *NPM-ALK* cDNA and transplanted into lethally irradiated recipients, the latter develop both myeloid and B cell malignancies [86]. These data suggest that *NPM-ALK* does not determine tumor-cell lineage but rather provides a growth-promoting signal. Additionally, immunodeficient SCID/bg mice transplanted with ALCL tumor cells develop ALCL-like disease [87].

Multistep Tumorigenesis in PTCL

T cell lymphomas have been thought to originate from mature T lymphocytes, because immunophenotypes of tumor cells resemble those of mature T lymphocytes. Rearrangements of *T cell receptor* genes, which are detected in most PTCL cases, provide further evidence for clonal expansion of T lineage cells. Intriguingly, however, recent genetic findings suggest that PTCL tumor cells may emerge from immature hematopoietic cells rather than from mature T lymphocytes [2].

TET2 and *DNMT3A* encode enzymes that function in DNA methylation [88, 89]. As described, mutations in both are frequently observed in PTCL with Tfh features [5••, 15, 25•], as well as in myeloid cancers [23, 24]. Strikingly, *TET2* and *DNMT3A* mutations seen in tumor cells are also sometimes detected in apparently normal blood cells in PTCL [3••, 4, 5••] and acute myeloid leukemia (AML) patients [90, 91], respectively. Several groups also report *TET2* and *DNMT3A* mutations in elderly individuals without hematologic malignancies [92–95], suggesting that these mutations are acquired with aging. Impaired activity or expression of these epigenetic factors may confer a clonal advantage to mutated over non-mutated cells, considering that deletion of either gene in mice increases self renewal capacity of hematopoietic stem cells [88, 89]. These pieces of evidence suggest that the mutated cells have the potential to differentiate into multi-lineage blood cells, but finally they may evolve into premalignant cells [2]. PTCLs and myeloid cancers both may occur from these premalignant cells. Additional genetic events, such as *RHOA* mutations seen in PTCL with Tfh features, may determine the fate of premalignant cells towards each subtype of tumor cells [2].

A multistep model has been proposed in PTCL with Tfh features [2]. Future studies will address what other kinds of PTCLs proceed via a multistep model.

Conclusion

Molecular analysis of PTCL is now in the forefront of cancer research. Discovery of aberrant gene and micro-RNA expression signatures, gene mutations, and chromosomal translocations in PTCLs, has enabled us to establish disease models, which have further uncovered underlying molecular pathogenesis of PTCL. Advances in our understanding of molecular pathogenesis of PTCL may reveal novel therapeutic strategies by directly or indirectly targeting the newly discovered oncogenic molecules in PTCL in the near future.

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Compliance with Ethics Guidelines

Conflict of Interest Mamiko Sakata-Yanagimoto and Shigeru Chiba have a patent pending for detection technology for T cell lymphoma (PCT/JP2014/62112).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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