Peripheral T-cell lymphomas: emerging and established molecular markers

L. De Leval

Institute of Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Correspondence: Laurence de Leval
E-mail: laurence.deleval@chuv.ch

Hematology Education: the education program for the annual congress of the European Hematology Association

2015;9:271-278

A B S T R A C T

The genetic and molecular aberrations underlying T-cell lymphomagenesis and the biological diversity of peripheral T-cell lymphoma (PTCL) entities remain poorly characterized. Only two entities, anaplastic lymphoma kinase ALK-positive ALCL and T-prolymphocytic leukemia (T-PLL), are characterized by specific chromosomal translocations. Over the past years, the application of genome-wide expression profiling techniques to most PTCL entities has helped refine their diagnostic criteria and identify novel diagnostic biomarkers and oncogenic pathways. Recent developments in massive parallel sequencing technologies have markedly accelerated the discovery of cancer-associated mutations and this has translated into the identification of several novel recurrent genetic alterations in PTCLs. In this review, we will summarize the current knowledge on the molecular biomarkers of PTCLs by focusing on genetic mutations and recent discoveries by virtue of their diagnostic, prognostic or therapeutic implications.

Learning goals

At the conclusion of this activity, the participant should be able to:
- describe established and emerging genetic molecular markers associated to peripheral T-cell entities;
- describe the diagnostic and prognostic value of these markers;
- understand their relevance to pathophysiology of T-cell neoplasms and their contribution to lymphomagenesis;
- understand the importance of these novel biological findings for the development of targeted therapeutic strategies.

Introduction

Peripheral T-cell lymphomas (PTCLs) constitute a heterogeneous group of uncommon neoplasias that together account for less than 15% of all non-Hodgkin lymphomas worldwide. They are listed in the WHO classification according to their major presenting features as predominantly disseminated/leukemic, extranodal or nodal diseases (Table 1).[1] With the exception of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALK+ ALCL), non-cutaneous PTCLs almost uniformly exhibit resistance to standard chemotherapy regimens and have a poor clinical outcome.[2,3]

The genetic and molecular aberrations underlying T-cell lymphomagenesis and the biological diversity of PTCL entities remain poorly characterized. Only two entities, namely anaplastic lymphoma kinase ALK+ ALCL and T-prolymphocytic leukemia (T-PLL), are characterized by specific chromosomal translocations, involving *ALK* with *NPM1* or other genes, and *TCL1* or *MTCP1* with *TCRAD*, respectively.[1] Over the past years, the application of genome-wide expression profiling techniques to most PTCL entities has helped refine their diagnostic criteria and identify novel diagnostic biomarkers and oncogenic pathways, guiding the development of novel targeted therapies (reviewed by Bisig[4]). Whereas the novel findings derived from conventional cytogenetic studies or comparative genomic hybridization methods remain limited,[5-7] recent developments in massive parallel sequencing technologies have markedly accelerated the discovery of cancer-associated mutations, and this has translated into the identification of several novel recurrent genetic alterations in PTCLs. In this review, we will summarize the current knowledge on the molecular biomarkers of PTCLs by focusing on genetic mutations and recent discoveries by virtue of their diagnostic, prognostic or therapeutic implications. We will discuss only the most common PTCL subtypes with a predominantly nodal or extranodal presentation, and will limit our consideration of cutaneous entities to the group of CD30-positive cutaneous lymphoproliferations.

Angioimmunoblastic T-cell lymphoma and other lymphomas with a T_{FH} immunophenotype

Angioimmunoblastic T-cell lymphoma (AITL), one of the most common PTCL wordwide, is the prototypic neoplasm derived from follicular helper CD4+ T cells (T_{FH} cells).[8,9] The disease affects elderly adults, and usually manifests by generalized peripheral lym-

phadenopathy, systemic symptoms, skin rash, hypergammaglobulinemia and autoimmune manifestations, with a median survival of less than three years (reviewed by de Leva *et al*.[10]). The cellular derivation of AITL from T_{FH} cells likely explains several of the peculiar pathological and biological features inherent to this disease, i.e. the presence of an abundant reactive microenvironment including B cells and follicular dendritic cells (FDCs), hypergammaglobulinemia and autoimmune manifestations. However, the molecular mechanisms underlying the neoplastic transformation of T_{FH} cells remain poorly understood.

By conventional cytogenetic analysis, detection of clonal aberrations (most commonly trisomies of chromosomes 3, 5 and 21, gain of X, and loss of 6q) has been reported in up to 90% of the cases (reviewed by de Leval *et al*.[10]).

Recurrent point mutations in *TET2, IDH2* and *DNMT3A* genes are detected in 50%-70%, 20%-30% and 20%-30% of AITL cases, respectively.[11-14] Alterations in these genes which encode enzymes involved in DNA methylation and hydroxymethylation thereby contributing to the epigenetic control of transcription, are common in various other hematologic malignancies. *TET2* mutations in AITL are often multiple and inactivating; they are associated with advanced-stage disease, high IPI scores, and a shorter progression-free survival.[11] *DNMT3A* mutations and *IDH2* mutations at the R172 residue almost always occur in association with *TET2* mutations.[13-16] *TET2* and *DNMT3* alterations are not specific for AITL as they have been also reported in a proportion of PTCLs not otherwise specified (PTCL-NOS); conversely *IDH2* mutations appear to be specific for AITL.[12]

Using next generation sequencing methods, three independent groups found somatic *RHOA* mutations encoding a p.Gly17Val in approximately 70% of AITLs.[15-17] *RHOA* encodes a small GTPase that regulates a variety of biological processes by regulating the actin cytoskeleton and cell adhesion. Mechanistically, the G17V RHOA mutant does not bind GTP and inhibits wild-type RHOA function, exerting a dominant negative effect. At the transcriptomic level, *RHOA* mutations are associated with a characteristic molecular signature including activation of the alternative nuclear factor kappa-B pathway, the phosphatidylinositol 3-kinase (PI3K), RAC1 and p38 mitogen-activated protein kinase (MAPK) pathways.[18] Subpopulation analyses indicate that *RHOA G17V* is present only in the tumor cells; conversely *TET2* and *DNMT3A* mutations have been evidenced also in hematopoietic progenitors.[14,19] Moreover, in most cases *RHOA* mutations are observed in *TET2* mutated tumors, and the allelic burden for *TET2* or *DNMT3A* mutations is higher than for *RHOA*, suggesting that the cooperation between impaired RHOA function and preceding TET2 loss of function contributes to AITL pathogenesis.[15]

Other less frequent but recurrent genetic alterations evidenced by next generation sequencing approaches include mutations in *FYN* (activating mutations, potentially inhibited by dasatinib), *ATM, B2M, CD58, CD28, EZH2* and *VAV1*.[16,17]

A recent study identified CD28-ICOS fusion transcripts in some cases of AITL, a finding that is of interest in view of the role of these co-stimulatory molecules in the interaction between T_{FH} and B cells.[20]

Table 1. Mature T- and NK-cell neoplasms in the 2008 WHO classification of lymphoid tumors (adapted from Swerdlow *et al*.[1]).

Leukemic or disseminated
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells*
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1-positive)
Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disorders of childhood
Extranodal
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Cutaneous
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma*
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma*
Primary cutaneous small/medium CD4+ T-cell lymphoma*
Hydroa vacciniforme-like lymphoma
Nodal
Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large cell lymphoma, ALK-positive (ALK+)
Anaplastic large cell lymphoma, ALK-negative (ALK-)*
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

**Provisional entities.*

Peripheral T-cell lymphoma not otherwise specified follicular variant

Peripheral T-cell lymphoma not otherwise specified follicular variant (PTCL-F) is a rare variant of PTCL-NOS (defined by a pattern of growth related to follicular structures[21]) which comprises neoplastic CD4+ T cells with usually extensive expression of T_{FH} markers.[22] In addition to overlapping immunophenotypic features, several lines of evidence suggest a relationship to AITL; PTCL-F may present biological and clinical features overlapping with those of AITL,[22,23] and patients with F-PTCL may present with recurrent lesions resembling AITL and *vice versa*.

The t(5;9)(q33;q22) translocation, which juxtaposes the IL-2-inducible T-cell kinase *(ITK)* gene on chromosome 5 and the spleen tyrosine kinase *(SYK)* gene on chromosome 9, is found in approximately 20% of PTCL-F and was also recently found in a case of AITL, reinforcing the concept of related entities.[5,22,24] The ITK-SYK fusion protein, comprising the N-terminal pleckstrin homology domain and proline-rich region of ITK, and the tyrosine kinase domain of SYK,[5] is a catalytically active tyrosine kinase with transforming properties demonstrated *in vitro*[25] which induces a T-cell lymphoproliferative disease in mice through a signal that mimics TCR activation.[26,27] The t(5;9)/*ITK-SYK* translocation can be routinely assayed

using home-made FISH probes. Hitherto, the utility of this test in a diagnostic setting is limited, since the translocation is present in only 20% of PTCL-F[5,22] and its prognostic significance is unknown. In a series of AITL and PTCL-NOS from Taiwan, increased copy numbers of *ITK* and/or *SYK* were found in 38% and 13% of cases, respectively, in the absence of SYK-ITK fusions.[28]

Peripheral T-cell lymphoma not otherwise specified expressing TFH markers

In addition to the above-mentioned T_{FH}-derived PTCL subtypes, a subset of cases classified as PTCL-NOS on the basis of their pathological features harbor imprints of the T_{FH} signature and/or express T_{FH} markers, and frequently exhibit some AITL-like clinical and/or pathological features. Interestingly, some of the recurrent mutations demonstrated in AITL (*TET2, RHOA*) also occur in a subset of PTCL-NOS and correlate with the presence of T_{FH} -like features.[11,15] Altogether, these observations question whether PTCL-NOS with T_{FH} -like features represent AITL evolving into PTCL-NOS-like tumors, and suggest that the spectrum of AITL may be broader than is currently thought.[8,29,30]

Peripheral T-cell lymphoma not otherwise specified

Up to one-third of PTCLs lacking specific features of another entity are by default designated as unspecified PTCL (PTCL-NOS). Not unexpectedly this 'waste-basket' category comprises the most heterogeneous group of PTCL, with variable morphology, immunophenotype and genetics.

Conventional cytogenetics and comparative genomic hybridization studies have documented many genetic aberrations and complex patterns of imbalances in PTCL-NOS, but these data are on the whole difficult to interpret, and have essentially not allowed specific driver alterations to be captured (reviewed by de Leval *et al*.[7]).

Chromosomal breaks involving the *TCR* gene loci (mostly the *A/B TCR* locus at 14q11.2) occur in rare cases of PTCL-NOS. [31] Although the identity of the translocation partner(s) has not been identified in most cases, two recurrent translocations are characterized.[32-34] The t(14;19)(q11;q13) translocation fuses the poliovirus receptor-related 2 (*PVRL2*) to *TCRA* and appears to be associated with overexpression of both *PVRL2* and *BCL3* mRNAs.[35,36] The t(6;14)(p25;q11.2) involving the *IRF4* locus has been reported in 3 cases of clinically aggressive cytotoxic PTCL.[6,37]

PTCL-NOS are also heterogeneous at the molecular level, and accordingly gene expression profiling has delineated different molecular subgroups in different studies (reviewed by de Leval[7]). In a meta-analysis based on more than 300 PTCL gene expression profiles,[38] two distinct subgroups of PTCL-NOS were identified, characterized by high expression of either GATA3 or TBX21 transcription factors (master regulators of TH1 and Th2 differentiation pathways, respectively) and corresponding target genes, suggesting that a large proportion of PTCL-NOS may be segregated in relationship to either Th1 or Th2 lineage derivation. The GATA3 subgroup was associated with distinctly worse prognosis. Immunohistochemistry could be a reliable surrogate to the molecular signatures, and in independent series of cases, GATA3 expression identified a high-risk subset of PTCL-NOS.[39]

PTCL-NOS is characterized by consistent overexpression of the platelet-derived growth factor receptor alpha (*PDGFRα*) mRNA and overexpression of the protein in an active phosphorylated form.[40,41] PDGFRA deregulation occurs in the absence of *PDGFRA* gene deregulation as the consequence of PDGFAA overexpression by the tumor cells resulting in an autocrine loop fostering tumor cell proliferation.[42]

Independently of the t(5;9)/*ITK-SYK* translocation, which is overall exceedingly rare, aberrant SYK expression and activation has been reported as a common feature of most PTCL histotypes (94% of cases).[43] However, these findings could not be reproduced by others who reported SYK expression to be mostly absent[44] or limited to a subset of CD30+ PTCLs.[45] Given the important implications of potential therapeutic inhibition of SYK, this issue needs to be elucidated by further research.

A recurrent mutation in the phospholipase C-gamma1 gene (*PLCG1*) encoding a protein with p.Ser345Phe (S354F) alteration that affects the catalytic domain of the protein and increases its activity, is identified in approximately 15% of PTCL-NOS and tends to correlate with lower survival, CD30 expression by the tumor cells, and markers of activation of the NF-kappaB pathway.[46] This mutation, initially discovered in cutaneous T-cell lymphomas,[47] is also present in a smaller proportion (12%) of AITLs.

Anaplastic large cell lymphoma ALK-positive

Anaplastic lymphoma kinase (ALK)-positive ALCL is characterized by usually large and pleomorphic tumor cells with strong CD30 expression and expression of ALK fusion protein derived from rearrangement of the *ALK* gene (2p23). There is a variety of *ALK* translocations, the most common fusing *ALK* to the *nucleophosmin* gene (*NPM*) (5q35). Less common partner genes include Tropomyosin 3 (*TPM3*), TRK fused gene (*TFG*), *ATIC* (Pur H gene) and Clathrin heavy chain (*CLTC*). Immunohistochemistry assesses ALK protein expression with high sensitivity and specificity. The subcellular location of the immunostaining is indicative of the type of translocation: in cases with the t(2;5)/*NPM-ALK* translocation ALK staining is both cytoplasmic and nuclear, while most variant translocations entail an ALK positivity restricted to the cytoplasm.[48] All translocations induce formation of chimeric fusion proteins which induce constitutive ALK tyrosine kinase activation and drive oncogenesis through engagement of multiple signaling pathways, including the JAK/STAT and the PI3K/Akt pathways (reviewed by Lai *et al*.[49]).

Anaplastic large cell lymphoma ALK-negative

The WHO recognizes two other entities of ALCL negative for *ALK* translocations and ALK expression: systemic ALK-negative ALCL and primary cutaneous ALCL, which is part of the spectrum of primary cutaneous CD30+ lymphoproliferations.

Systemic ALK-negative anaplastic large cell lymphoma

This (provisional) entity is defined as a large cell lymphoma with comparable morphology to classical ALK-positive ALCL, uniformly strongly positive for CD30 but lacking ALK expression.[1] Compared to ALK-positive ALCL, ALK-negative ALCL tends to occur in older individuals, and to have more preserved T-cell immunophenotype with less frequent expression of cytotoxic markers and of epithelial membranous antigen (EMA).[30,50]

Chromosomal aberrations differ from those of ALK-positive ALCL.[51] While distinct signatures have been derived from the comparison of ALK-positive and ALK-negative ALCL,[52] transcriptional profiling studies have also evidenced much in common between ALK-positive and ALK-negative ALCL, and between ALK-negative ALCL and a subset of PTCL-NOS with strong CD30 expression.[53,54] In the absence of a consistent molecular marker for ALK-negative ALCL, a three-gene model has been proposed to distinguish ALK-negative ALCL from PTCL-NOS.[55] By genome-wide DNA profiling of ALCLs with high-density, single nucleotide polymorphism arrays, the most common lesions in ALCLs were losses of *TP53* at 17p13 and/or *PRDM1* at 6q21 in 52% of ALK−ALCL, and in 29% of all ALCL cases. *PRDM1*, coding for BLIMP1, was inactivated by multiple mechanisms, more frequently, but not exclusively, in ALK−ALCL, and *in vitro* experiments supported the concept that *PRDM1* is a tumor suppressor gene in ALCL models, likely acting as an antiapoptotic agent.[56] Extra copies of *PAX-5* are detected in a subset of ALK- ALCL.[57]

Two types of recurrent translocations have been recently discovered in ALK-negative ALCL by massive parallel sequencing. The most frequent rearrangements involving the 6p25.3 locus are rather specific to systemic and cutaneous ALK- ALCLs, and virtually absent in other PTCL entities.[6,58-60] The breaks (6p25.3) involve either *IRF4* or *DUSP22* (encoding a dual-specificity phosphatase that inhibits TCR signaling) with various partners. The t(6;7)(p25.3;q32.3) translocation entails downregulation of *DUSP22* and overexpression of microRNA-coding *MIR29*, suggesting that *DUSP22* might function as a tumor suppressor and *MIR29* as an oncogene.[58] *DUSP22*-rearranged cases appear to have increased expression of the CCR8 chemokine, irrespective of the cutaneous or systemic presentation.[61] *TP63* rearrangements encoding fusion proteins homologous to ΔNp63, a dominant-negative p63 isoform that inhibits the p53 pathway, have been detected in approximately 10% of ALK-negative ALCL and PTCL-NOS.[62] The frequency of mutually exclusive chromosomal rearrangements of *DUSP22* and *TP63* in ALK-negative ALCL is 30% and 8% of the cases, respectively. In one study comparing ALK-positive ALCL with ALK-negative ALCLs, stratified according to genetic features, *DUSP22*-rearranged ALCLs had a prognosis similar to ALK-positive ALCL, *TP63* rearrangements were associated with a bad outcome (5-year OS: 17%), and cases lacking all 3 genetic markers had an intermediate prognosis.[63]

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous ALCL has overlapping clinical and pathological features with lymphomatoid papulosis, which together constitute the spectrum of primary CD30-positive cutaneous lymphoproliferative diseases. Primary cutaneous ALCL presents as solitary skin nodules or tumors that may regress and recur, and usually carries a good prognosis. The tumor comprises sheets of large anaplastic CD30+ cytotoxic T cells that are negative for EMA and ALK.

Rearrangements of the 6p25.3 locus occur in approximately30% of primary cutaneous ALCL, while they are absent in lymphomatoid papulosis of the classical type or in transformed mycosis fungoides, and are otherwise not found in other T-cell lymphoproliferative disorders involving the skin.[59,60] *DUSP22* translocation was recently described in a series of lymphomatoid papulosis patients, with a particular biphasic histological pattern, including pagetoid reticulosis-type epidermal infiltration.[64,65] Other *IRF4* FISH abnormalities (mainly extra copies of the *IRF4* locus, mutually exclusive with translocations) also occur and are more widely distributed over the T-cell lymphoproliferation subtypes.[59]

A chimeric fusion involving NPM1 (5q35) and TYK2 (19p13) that encodes an NPM1-TYK2 protein containing the oligomerization domain of *NPM1* and an intact catalytic domain in *TYK2*, was recently identified in 4% of primary cases of CD30-positive LPDs and was absent in other mature T-cell neoplasms. Functionally, NPM1-TYK2 induced constitutive TYK2, signal transducer and activator of transcription 1(STAT1), STAT3, and STAT5 activation.[66]

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTL) is an aggressive T-cell lymphoma, usually of gamma-delta(γδ) derivation, which predominantly affects young male adults and may arise in the setting of chronic immune suppression or prolonged antigenic stimulation, particularly in solid organ transplant recipients or in children treated by azathioprine and infliximab for Crohn disease.[67]

Isochromosome 7q, or i(7)(q10), is observed in the majority of the cases.[68,69] Isochromosome 7q results in deletion of the short arm of chromosome 7 which may lead to the loss of tumor suppressor genes located on 7p, as well as loss of *TRB* gene at 7p15, and duplication of the long arm, most likely causing overexpression of oncogenes located on 7q, as well as the *TRG* gene at 7q35.[69] In rare instances, extra copies of 7q are caused by ring chromosome 7.[70] Isochromosome 7q is usually thought to be the primary abnormality of this disease with a tendency to multiply the i(7)(q10) during disease progression; it may be accompanied by trisomy 8 and loss of a sex chromosome, which seem also to be associated with progression of the disease.[71,72] Isochromosome 7q is not specific for HSTL, as it is indeed one of the most common isochromosomes in malignant disorders (acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes and Wilms tumor), and it has also been found on occasions in cases of NK-/T-cell lymphomas and ALK-negative ALCLs.[34]

Mutually exclusive activating mutations in the SH2 domain of *STAT5B* (most commonly, and mainly hotspot mutations p.N642H) or *STAT3* genes (in rare cases) were recently reported in approximately one-third of cases of HSTL.[73,74] Interestingly, *STAT5B* mutations are also recur-

Table 2. Major distinguishing features of NK-/T-cell neoplasms with a disseminated/leukemic presentation.[1]

	Epidemiology	Clinical features	Morphology	Cell derivation, phenotype	Genetic and molecular features; viral association	Prognosis
T-cell prolymphocytic leukemia (T-PLL)	Adults (median age 65 yrs), rare	Splenomegaly, hepatomegaly, skin lesions (20%), generalized lymphadenopathy, lymphocytosis (usually >100x10^9/L)	Small/medium-sized mature lymphocytes, visible nucleolus, non-granular cytoplasm	αβ T cells CD2+, CD3+, CD7+, CD4+, more rarely CD4+/ CD8+ or CD8+TCL1+	nv(14)(q11;q32.1), t(14;14) (*TCL1*) or t(X;14) (MTCP1) *JAK1* mutations (<10%) *JAK3* mutations (30-40%) *STAT5B* mutations (35%)	Aggressive, median survival <1 yr Resistance to conventional chemotherapy
T-cell large granular lymphocytic leukemia (T-LGL) ,	Adults, frequent context of autoimmune disorder	Asymptomatic or cytopenia, slight lymphocytosis, moderate splenomegaly (50%)	Large granular lymphocytes (2-20x10^9/L)	Mostly αβ T cells, more rarely γδ T cells CD3+, CD8+ (more rarely CD4 -/CD8-), CD16+, CD57+ activated cytotoxic (TIA1+, GrB+, Perf+)	*STAT3* mutations (35% of the cases) *STAT5B* mutations (rare)	Indolent, non-progressive
Chronic lymphoproliferative disorder of NK cells (NK-LPD)	Adults	Asymptomatic or cytopenia, slight lymphocytosis, rare splenomegaly	Large granular lymphocytes (usually >2x10^9/L)	NK lineage CD3e+ cyt, CD3-surface, TCR-, CD2+:6, CD5-, often CD56+, CD57-, CD8 variable TIA1+, GrB+, Perf+	*STAT3* mutations (35% of the cases) *STAT5B* mutations (rare)	Indolent, non-progressive
Adult T-cell lymphoma/ leukemia (ATLL)[2]	Adults (long latency), endemic regions for HTLV1	Highly variable from leukemic variants to lymphoma forms (ADP, skin, spleen, gastrointestinal tract, lung, etc.)	Pleomorphic small to large cells, "flower" cells	αβ T cells with features of regulatory T cells (CD25+, FoxP3+), mostly CD4+, rarely CD8+, or CD4+/CD8+	Monoclonal integration of HTLV1 (role of Tax)	Poor, mostly fatal, median survival <3months in most studies
Aggressive NK-cell leukemia	Teenager/young adult, slight male predominance, Asians, Latin Americans	B symptoms, splenomegaly, cytopenia, leukemic cells, frequent hemophagocytic syndrome	Variable pleomorphic medium to large atypical cells	NK lineage CD3e+ cytoplasm, CD3/ TCR- (surface), CD5-, CD56+, CD4-/CD8-, TIA1+, GrB+, Perf+	EBV (clonal integration) 6q deletion	Aggressive, fatal

EBV: Epstein-Barr. ADP: adenopathies.

rent in non-hepatosplenic γδTCLs, including primary cutaneous γδTCL and a subset of type II enteropathy-associated TCL.[74]

Extranodal NK-/T-cell lymphoma

Extranodal NK-/T-cell lymphoma (ENKTCL) nasal type is an Epstein-Barr virus (EBV)-associated aggressive cytotoxic lymphoma, most common in Asia, Mexico and South America. It is derived from NK cells or, more rarely, T cells. Epstein-Barr virus is clonally present in an episomal form in the tumor cells and exerts oncogenic effects through the production of cytokines such as IL-9 and IL-10, upregulation of IP10/MIP2 chemokines that may contribute to vascular damage and secondary necrosis,[75] while TNFα production may explain the common hematophagocytic syndrome. Partial deletion of chromosome 6 (6q21-25) is a recurrent aberration in ENKTCL. Several candidate tumor suppressor genes, such as *PRDM1, ATG5, AIM1* and *HACE1*, are mapping to that region and their inactivation by deletion and/or methylation might be involved in lymphomagenesis.[76,77] The molecular signature of ENKTCL, irrespective of the cellular derivation, is distinct from that of other PTCLs, including overexpression of granzyme H. Compared to normal NK cells, extranodal NKTCL is characterized by activation of PDGFRA, and of the AKT, JAK/STAT, and nuclear factor-kappaB pathways.[77,78]

Constitutive activation of STAT3 is a characteristic oncogenic feature in NKTCL, associated to constitutive JAK3 activation. In a subset of cases, JAK/STAT deregulation can be ascribed to *JAK3* somatic-activating mutations (found in 20%-30% of cases) or STAT3 mutations (in less than 10% of cases).[74,79,80] Other genes found recurrently mutated in ENKTCK include *TP53, CCND1, FAS*.

Enteropathy-associated T-cell lymphoma

Enteropathy-associated T-cell lymphoma (EATL) defines an intestinal tumor derived from intestinal intraepithelial lymphocytes (IEL). EATL type I is most common and occurs as a complication of gluten-sensitive enteropathy. Type II EATL is overall very rare and in the majority of cases there is no association with celiac disease.[81] Both types share common recurrent chromosomal imbalances and also distinctive genetic alterations. 9q33-q34 gains and 16q21.1 deletions are common to both types. However, gains or partial trisomy of 1q22-44 and 5q (commonly found in type I EATL) are rare in type II, while gains of the *MYC* oncogene locus at 8q24 are frequent.[82] The recent discovery of recurrent *STAT5B* mutations in a subset of type II cases offers the possibility of applying targeted treatment to this highly aggressive, and usually rapidly fatal, disease.[74]

Mature T-cell neoplasms with a leukemic/disseminated presentation

The epidemiology, clinical features and outcome, morphology, immunophenotype, and main genetic features of these disease entities are summarized in Table 2.

The vast majority of T-PLL are characterized by translocations or inversions with the *TRA* gene, involving the *TCL1* and *TCL1b* genes at 14q32 [inv(14)(q11;q32.1) or t(14;14)(q11;q32.1)], or the *MTCP1* gene at Xq28 [t(X;14)(q28;q32.1)], which are over-expressed as a consequence of juxtaposition to the *TRA* locus.[83] TCL1 binds to AKT1, enhances its activity and promotes its transport to the nucleus; TCL1 overexpression confers resistance to activation-induced cell death and growth arrest in T-PLL cells and derived cell lines. Transgenic mice over-expressing either activated TCL1 or MTCP1 gene in T cells develop mature T-cell leukemias. *TCL1* gene rearrangements are specific for T-PLL and are not observed in other categories of T-cell neoplasms.[34] In addition, recent sequencing analyses have evidenced recurrent mutually exclusive gain-of function mutations in *JAK1, JAK3, STAT5B*, in less than 10%, 30%-40%, and 35% of the cases, respectively.[84-86]

Chronic lymphoproliferative disorders of NK cells and T-large granular lymphocyte leukemia, two indolent lymphoproliferative disorders, were found to have in common a relatively high frequency (approx. one-third of cases) of *STAT3* mutations.[87,88] *STAT5B* mutations are conversely rare in these entities and appear to correlate with aggressive variants of the disease.[89]

Conclusion

The application of next generation sequencing methods to different PTCL entities has led to the discovery of an increasing number of recurrent mutations associated with these disorders, some being rather specific to certain disease entities and others being common to several entities. The cell of origin as a determinant of T-cell lymphoma biology correlates to some extent with the type of mutations demonstrated. The molecular pathways that are recurrently targeted by these alterations include the JAK/STAT, TCR, and PDGFR pathways. The functional consequences of these mutations are not fully understood, and for many of them, whether they have a 'driving' role in lymphomagenesis remains unclear. Interestingly, however, there are several potential inhibitory compounds that are antagonistic in terms of activating mutations, which may represent promising novel therapeutic approaches.

References

1. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press. 2008.
2. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30.
3. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. Blood. 2011;117(25):6756-67.
4. Bisig B, Gaulard P, de Leval L. New biomarkers in T-cell lymphomas. Best Pract Res Clin Haematol. 2012;25(1):13-28.
5. Streubel B, Vinatzer U, Willheim M, Raderer M, Chott A. Novel t(5;9)(q33;q22) fuses ITK to SYK in unspecified peripheral T-cell lymphoma. Leukemia. 2006;20(2):313-8.
6. Feldman AL, Law M, Remstein ED, Macon WR, Erickson LA, Grogg KL, et al. Recurrent translocations involving the IRF4 oncogene locus in peripheral T-cell lymphomas. Leukemia. 2009;23(3):574-80.
7. de Leval L, Bisig B, Thielen C, Boniver J, Gaulard P. Molecular

classification of T-cell lymphomas. Crit Rev Oncol Hematol. 2009 Feb 23. [Epub ahead of print]
8. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood. 2007;109(11):4952-63.
9. Iqbal J, Weisenburger DD, Greiner TC, Vose JM, McKeithan T, Kucuk C, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood. 2010;115(5): 1026-36.
10. de Leval L, Gisselbrecht C, Gaulard P. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Br J Haematol. 2010;148(5):673-89.
11. Lemonnier F, Couronne L, Parrens M, Jais JP, Travert M, Lamant L, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood. 2012;120(7):1466-9.
12. Cairns RA, Iqbal J, Lemonnier F, Kucuk C, de Leval L, Jais JP, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood. 2012;119(8):1901-3.
13. Couronne L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. N Engl J Med. 2012;366(1):95-6.
14. Odejide O, Weigert O, Lane AA, Toscano D, Lunning MA, Kopp N, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood. 2014;123(9):1293-6.
15. Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46(2):171-5.
16. Palomero T, Couronne L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet. 2014;46(2):166-70.
17. Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, et al. A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46(4):371-5.
18. Manso R, Sanchez-Beato M, Monsalvo S, Gomez S, Cereceda L, Llamas P, et al. The RHOA G17V gene mutation occurs frequently in peripheral T-cell lymphoma and is associated with a characteristic molecular signature. Blood. 2014;123 (18):2893-4.
19. Quivoron C, Couronne L, Della Valle V, Lopez CK, Plo I, Wagner-Ballon O, et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. Cancer Cell. 2011;20(1):25-38.
20. Guo s, Kucuk C, Iqbal J, Rohr J, Bi C, Wang C, et al. Novel Fusion Transcripts Identified in Angioimmunoblastic T Cell Lymphoma. Modern Pathol. 2013;26(S2):330A.
21. de Leval L, Savilo E, Longtine J, Ferry JA, Harris NL. Peripheral T-cell lymphoma with follicular involvement and a CD4+/bcl-6+ phenotype. Am J Surg Pathol. 2001;25(3):395-400.
22. Huang Y, Moreau A, Dupuis J, Streubel B, Petit B, Le Gouill S, et al. Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. Am J Surg Pathol. 2009;33(5):682-90.
23. Moroch J, Copie-Bergman C, de Leval L, Plonquet A, Martin-Garcia N, Delfau-Larue MH, et al. Follicular peripheral T-cell lymphoma expands the spectrum of classical Hodgkin lymphoma mimics. Am J Surg Pathol. 2012;36(11):1636-46.
24. Attygalle AD, Feldman AL, Dogan A. ITK/SYK translocation in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol. 2013;37(9):1456-7.
25. Rigby S, Huang Y, Streubel B, Chott A, Du MQ, Turner SD, et al. The lymphoma-associated fusion tyrosine kinase ITK-SYK requires pleckstrin homology domain-mediated membrane localization for activation and cellular transformation. J Biol Chem. 2009;284(39):26871-81.
26. Pechloff K, Holch J, Ferch U, Schweneker M, Brunner K, Kremer M, et al. The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma. J Exp Med. 2010;207(5):1031-44.
27. Dierks C, Adrian F, Fisch P, Ma H, Maurer H, Herchenbach D, et al. The ITK-SYK fusion oncogene induces a T-cell lymphoproliferative disease in mice mimicking human disease. Cancer Res. 2010;70(15):6193-204.
28. Liang PI, Chang ST, Lin MY, Hsieh YC, Chu PY, Chen CJ, et al. Angioimmunoblastic T-cell lymphoma in Taiwan shows a frequent gain of ITK gene. Int J Clin Exp Pathol. 2014;7(9): 6097-107.
29. Rodriguez-Pinilla SM, Atienza L, Murillo C, Perez-Rodriguez A, Montes-Moreno S, Roncador G, et al. Peripheral T-cell Lymphoma With Follicular T-cell Markers. Am J Surg Pathol. 2008 Sep 5. [Epub ahead of print]
30. Attygalle A, Cabeçadas J, Gaulard P, Jaffe ES, de Jong D, Ko YH, et al. Peripheral T- and NK-cell lymphomas and their mimics: taking a step forward - Report on the Lymphoma Workshop of the XVI meeting of the European Association for Haematopathology in Lisbon 2012. Histopathology. 2013 [In press]
31. Nelson M, Horsman DE, Weisenburger DD, Gascoyne RD, Dave BJ, Loberiza FR, et al. Cytogenetic abnormalities and clinical correlations in peripheral T-cell lymphoma. Br J Haematol. 2008;141(4):461-9.
32. Gesk S, Martin-Subero JI, Harder L, Luhmann B, Schlegelberger B, Calasanz MJ, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17(4):738-45.
33. Leich E, Haralambieva E, Zettl A, Chott A, Rudiger T, Holler S, et al. Tissue microarray-based screening for chromosomal breakpoints affecting the T-cell receptor gene loci in mature T-cell lymphomas. J Pathol. 2007;213(1):99-105.
34. Feldman AL, Law M, Grogg KL, Thorland EC, Fink S, Kurtin PJ, et al. Incidence of TCR and TCL1 gene translocations and isochromosome 7q in peripheral T-cell lymphomas using fluorescence in situ hybridization. Am J Clin Pathol. 2008;130(2):178-85.
35. Martin-Subero JI, Wlodarska I, Bastard C, Picquenot JM, Hoppner J, Giefing M, et al. Chromosomal rearrangements involving the BCL3 locus are recurrent in classical Hodgkin and peripheral T-cell lymphoma. Blood. 2006;108(1):401-2; author reply 402-3.
36. Almire C, Bertrand P, Ruminy P, Maingonnat C, Wlodarska I, Martin-Subero JI, et al. PVRL2 is translocated to the TRA@ locus in t(14;19)(q11;q13)-positive peripheral T-cell lymphomas. Genes Chromosomes Cancer. 2007;46(11):1011-8.
37. Somja J, Bisig B, Bonnet C, Herens C, Siebert R, de Leval L. Peripheral T-cell lymphoma with t(6;14)(p25;q11.2) translocation presenting with massive splenomegaly. Virchows Arch. 2014;464(6):735-41.
38. Iqbal J, Wright G, Wang C, Rosenwald A, Gascoyne RD, Weisenburger DD, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood. 2014;123(19):2915-23.
39. Wang T, Feldman AL, Wada DA, Lu Y, Polk A, Briski R, et al. GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood. 2014 Feb 4. [Epub ahead of print]
40. Piccaluga PP, Agostinelli C, Zinzani PL, Baccarani M, Dalla Favera R, Pileri SA. Expression of platelet-derived growth factor receptor alpha in peripheral T-cell lymphoma not otherwise specified. Lancet Oncol. 2005;6(6):440.
41. Piccaluga PP, Agostinelli C, Califano A, Rossi M, Basso K, Zupo S, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J Clin Invest. 2007;117(3):823-34.
42. Piccaluga PP, Rossi M, Agostinelli C, Ricci F, Gazzola A, Righi S, et al. Platelet-derived growth factor alpha mediates the proliferation of peripheral T-cell lymphoma cells via an autocrine regulatory pathway. Leukemia. 2014;28(8):1687-97.
43. Feldman AL, Sun DX, Law ME, Novak AJ, Attygalle AD, Thorland EC, et al. Overexpression of Syk tyrosine kinase in peripheral T-cell lymphomas. Leukemia. 2008;22(6):1139-43.
44. Pozzobon M, Marafioti T, Hansmann ML, Natkunam Y, Mason DY. Intracellular signalling molecules as immunohistochemical markers of normal and neoplastic human leucocytes in routine biopsy samples. Br J Haematol. 2004;124(4):519-33.
45. Geissinger E, Sadler P, Roth S, Grieb T, Puppe B, Muller N, et al. Disturbed expression of the T-cell receptor/CD3 complex and associated signaling molecules in CD30+ T-cell lymphoproliferations. Haematologica. 2010 May 29. [Epub ahead of print]
46. Manso R, Rodriguez-Pinilla SM, Gonzalez-Rincon J, Gomez S, Monsalvo S, Llamas P, et al. Recurrent presence of the PLCG1 S345F mutation in nodal peripheral T-cell lymphomas. Haematologica. 2015;100(1):e25-7.
47. Vaque JP, Gomez-Lopez G, Monsalvez V, Varela I, Martinez N, Perez C, et al. PLCG1 mutations in cutaneous T-cell lymphomas. Blood. 2014;123(13):2034-43.
48. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood. 1999;93(8):2697-706.
49. Lai R, Ingham RJ. The pathobiology of the oncogenic tyrosine kinase NPM-ALK: a brief update. Ther Adv Hematol. 2013;4(2):119-31.
50. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK-negative anaplastic large-cell lymphoma (ALCL) is clinically and immunophenotypically different from both ALK-positive ALCL and peripheral T-cell lymphoma, not otherwise

specified: report from the International Peripheral T-Cell Lymphoma Project. Blood. 2008;111(12): 5496-504.
51. Salaverria I, Bea S, Lopez-Guillermo A, Lespinet V, Pinyol M, Burkhardt B, et al. Genomic profiling reveals different genetic aberrations in systemic ALK-positive and ALK-negative anaplastic large cell lymphomas. Br J Haematol. 2008;140(5): 516-26.
52. Lamant L, de Reynies A, Duplantier MM, Rickman DS, Sabourdy F, Giuriato S, et al. Gene-expression profiling of systemic anaplastic large-cell lymphoma reveals differences based on ALK status and two distinct morphologic ALK+ subtypes. Blood. 2007;109(5):2156-64.
53. Piva R, Agnelli L, Pellegrino E, Todoerti K, Grosso V, Tamagno I, et al. Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. J Clin Oncol. 2010;28(9):1583-90.
54. Bisig B, de Reynies A, Bonnet C, Sujobert P, Rickman DS, Marafioti T, et al. CD30-positive peripheral T-cell lymphomas share molecular and phenotypic features. Haematologica. 2013;98(8):1250-8.
55. Agnelli L, Mereu E, Pellegrino E, Limongi T, Kwee I, Bergaggio E, et al. Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma. Blood. 2012;120(6):1274-81.
56. Boi M, Rinaldi A, Kwee I, Bonetti P, Todaro M, Tabbo F, et al. PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. Blood. 2013 Sep 4. [Epub ahead of print]
57. Feldman AL, Law ME, Inwards DJ, Dogan A, McClure RF, Macon WR. PAX5-positive T-cell anaplastic large cell lymphomas associated with extra copies of the PAX5 gene locus. Mod Pathol. 2010;23(4):593-602.
58. Feldman AL, Dogan A, Smith DI, Law ME, Ansell SM, Johnson SH, et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood. 2011;117(3):915-9.
59. Wada DA, Law ME, Hsi ED, Dicaudo DJ, Ma L, Lim MS, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol. 2010;24(4):596-605.
60. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E, Vergier B, Jouary T, Beylot-Barry M, et al. IRF4 gene rearrangements define a subgroup of CD30-positive cutaneous T-cell lymphoma: a study of 54 cases. J Invest Dermatol. 2010;130(3):816-25.
61. Xing X, Flotte TJ, Law ME, Blahnik AJ, Chng WJ, Huang G, et al. Expression of the Chemokine Receptor Gene, CCR8, is Associated With DUSP22 Rearrangements in Anaplastic Large Cell Lymphoma. Appl Immunohistochem Mol Morphol. 2014 Nov 11. [Epub ahead of print]
62. Vasmatzis G, Johnson SH, Knudson RA, Ketterling RP, Braggio E, Fonseca R, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. Blood. 2012;120 (11):2280-9.
63. Parrilla Castellar ER, Jaffe ES, Said JW, Swerdlow SH, Ketterling RP, Knudson RA, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood. 2014;124(9): 1473-80.
64. Karai LJ, Kadin ME, Hsi ED, Sluzevich JC, Ketterling RP, Knudson RA, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. Am J Surg Pathol. 2013;37(8):1173-81.
65. Kluk J, Child F, Robson A. Lymphomatoid papulosis with 6p25.3 rearrangement: a further case of the newly described variant. Br J Dermatol. 2014;171(6):1590-2.
66. Velusamy T, Kiel MJ, Sahasrabuddhe AA, Rolland D, Dixon CA, Bailey NG, et al. A novel recurrent NPM1-TYK2 gene fusion in cutaneous CD30-positive lymphoproliferative disorders. Blood. 2014;124(25):3768-71.
67. Belhadj K, Reyes F, Farcet JP, Tilly H, Bastard C, Angonin R, et al. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood. 2003;102(13):4261-9.
68. Macon WR, Levy NB, Kurtin PJ, Salhany KE, Elkhalifa MY, Casey TT, et al. Hepatosplenic alphabeta T-cell lymphomas: a report of 14 cases and comparison with hepatosplenic gammadelta T-cell lymphomas. Am J Surg Pathol. 2001;25(3): 285-96.
69. Wlodarska I, Martin-Garcia N, Achten R, De Wolf-Peeters C, Pauwels P, Tulliez M, et al. Fluorescence in situ hybridization study of chromosome 7 aberrations in hepatosplenic T-cell lymphoma: isochromosome 7q as a common abnormality accumulating in forms with features of cytologic progression. Genes Chromosomes Cancer. 2002;33(3):243-51.
70. Tamaska J, Adam E, Kozma A, Gopcsa L, Andrikovics H, Tordai A, et al. Hepatosplenic gammadelta T-cell lymphoma with ring chromosome 7, an isochromosome 7q equivalent clonal chromosomal aberration. Virchows Arch. 2006;449(4): 479-83.
71. Alonsozana EL, Stamberg J, Kumar D, Jaffe ES, Medeiros LJ, Frantz C, et al. Isochromosome 7q: the primary cytogenetic abnormality in hepatosplenic gammadelta T cell lymphoma. Leukemia. 1997;11(8):1367-72.
72. Jonveaux P, Daniel MT, Martel V, Maarek O, Berger R. Isochromosome 7q and trisomy 8 are consistent primary, non-random chromosomal abnormalities associated with hepatosplenic T gamma/delta lymphoma. Leukemia. 1996;10(9):1453-5.
73. Nicolae A, Xi L, Pittaluga S, Abdullaev Z, Pack SD, Chen J, et al. Frequent STAT5B mutations in gammadelta hepatosplenic T-cell lymphomas. Leukemia. 2014;28(11): 2244-8.
74. Kucuk C, Jiang B, Hu X, Zhang W, Chan JK, Xiao W, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 2015;6:6025.
75. Teruya-Feldstein J, Jaffe ES, Burd PR, Kanegane H, Kingma DW, Wilson WH, et al. The role of Mig, the monokine induced by interferon-gamma, and IP-10, the interferon-gamma-inducible protein-10, in tissue necrosis and vascular damage associated with Epstein-Barr virus-positive lymphoproliferative disease. Blood. 1997;90(10):4099-105.
76. Iqbal J, Kucuk C, Deleeuw RJ, Srivastava G, Tam W, Geng H, et al. Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. Leukemia. 2009;23(6): 1139-51.
77. Huang Y, de Reynies A, de Leval L, Ghazi B, Martin-Garcia N, Travert M, et al. Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type. Blood. 2010;115(6):1226-37.
78. Coppo P, Gouilleux-Gruart V, Huang Y, Bouhlal H, Bouamar H, Bouchet S, et al. STAT3 transcription factor is constitutively activated and is oncogenic in nasal-type NK/T-cell lymphoma. Leukemia. 2009;23(9):1667-78.
79. Koo GC, Tan SY, Tang T, Poon SL, Allen GE, Tan L, et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012;2(7):591-7.
80. Bouchekioua A, Scourzic L, de Wever O, Zhang Y, Cervera P, Aline-Fardin A, et al. JAK3 deregulation by activating mutations confers invasive growth advantage in extranodal nasal-type natural killer cell lymphoma. Leukemia. 2014;28(2):338-48.
81. Delabie J, Holte H, Vose JM, Ullrich F, Jaffe ES, Savage KJ, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood. 2011;118(1):148-55.
82. Deleeuw RJ, Zettl A, Klinker E, Haralambieva E, Trottier M, Chari R, et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology. 2007;132(5):1902-11.
83. Brito-Babapulle V, Catovsky D. Inversions and tandem translocations involving chromosome 14q11 and 14q32 in T-prolymphocytic leukemia and T-cell leukemias in patients with ataxia telangiectasia. Cancer Genet Cytogenet. 1991; 55(1):1-9.
84. Bellanger D, Jacquemin V, Chopin M, Pierron G, Bernard OA, Ghysdael J, et al. Recurrent JAK1 and JAK3 somatic mutations in T-cell prolymphocytic leukemia. Leukemia. 2014;28 (2):417-9.
85. Bergmann AK, Schneppenheim S, Seifert M, Betts MJ, Haake A, Lopez C, et al. Recurrent mutation of JAK3 in T-cell prolymphocytic leukemia. Genes Chromosomes Cancer. 2014;53(4):309-16.
86. Kiel MJ, Velusamy T, Rolland D, Sahasrabuddhe AA, Chung F, Bailey NG, et al. Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood. 2014;124(9):1460-72.
87. Koskela HL, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmaki H, Andersson EI, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012;366(20):1905-13.
88. Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012;120(15): 3048-57.
89. Rajala HL, Eldfors S, Kuusanmaki H, van Adrichem AJ, Olson T, Lagstrom S, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood. 2013;121(22):4541-50.