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New insights in the pathogenesis of T-cell lymphomas

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New insights in the pathogenesis of T-cell lymphomas

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Abstract

Purpose of review: Peripheral T-cell lymphomas (PTCL) represent diverse and aggressive malignancies, with few recent therapeutic improvements. Recent high-throughput genomic studies have revealed the complex mutational landscape of these rare diseases. These novel findings provide the grounds to a more comprehensive classification of these diseases, reflected in the 2017 WHO classification.

Recent findings: Our review is focused on selected PTCL entities.

Angioimmunoblastic T-cell lymphoma and other lymphomas derived from T follicular helper cells feature a rather homogeneous mutational landscape. These neoplasms recapitulate a multi-step oncogenic process associating epigenetic deregulation, and second hit mutations affecting the T-cell receptor signaling pathway. This model inferred from comprehensive analyses of patients samples was confirmed in mouse models. Amongst ALK-negative anaplastic large-cell lymphomas, translocation-associated subsets are found in both systemic and cutaneous types, and the newly described breast implant-associated type is usually indolent. Extranodal lymphomas of the innate immune system also harbor a combination of mutations affecting different classes of epigenetic modifiers, and mutation-induced activation of the Janus Kinase/signal transduction and activator of transcription pathway.

Summary: Understanding of PTCL pathogenesis has substantially improved, and oncogenic events have been identified. The current challenge is to mount efficient therapeutic strategies targeting these aberrations to improve patients outcome.

Keywords: next generation sequencing, follicular helper T-cell lymphoma, epigenetics, anaplastic large-cell lymphoma, extranodal, signaling pathways

Introduction

Peripheral T-cell lymphomas (PTCLs) represent less than 15% of all non-Hodgkin lymphomas worldwide. Recent high-throughput molecular and genomic profiling studies have generated many discoveries that significantly advanced our understanding of the pathogenesis and pathobiology of these diseases. The genetic alterations in PTCL target multiple pathways. Highly recurrent mutations occur in different classes of epigenetic modifiers (1-5*), in T-cell receptor and co-receptors signaling pathways (6*, 7), and in components or regulators of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. There is established or presumed evidence that the resulting functional deregulations represent pathogenic mechanisms contributing to induce or maintain some attributes of the malignant phenotype (8). Although a few variants are characteristic of certain entities, for example *RHOA*^{G17V}, no novel disease-defining mutation has been found, there is major overlap in the mutational landscapes of different entities, and ALK-positive anaplastic large-cell lymphoma (ALCL) essentially remains the only PTCL defined by a specific genomic rearrangement.

Some of these new molecular findings have been incorporated into the revised edition of the World Health Organization classification (2017) as they refine classification and diagnostic criteria (9). The currently recognized PTCL entities, grouped according to their clinical presentation and localization, are listed in **Table 1** (10), (9). This review will address more recent advances gained in the knowledge of selected T-cell lymphoma entities.

Angioimmunoblastic T-cell lymphoma (AITL) and other nodal lymphomas of T follicular helper (TFH) derivation

Besides the constellation of histological and clinico-biological features characteristic of the disease, AITL definition also refers to its TFH derivation (11). The mutational landscape of AITL comprises frequent mutations in three genes directly or indirectly involved in the regulation of DNA methylation/hydroxymethylation. Sensitive sequencing methods detect *TET2*, *DNMT3A* and *IDH2* mutations in about 80% (12-14), 20-30% (12, 15, 16) and 20-30% of the cases (17), respectively. *TET2* is an α -ketoglutarate-dependent dioxygenase, involved in the successive oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) to 5-formylmethylcytosine and 5-carboxymethylcytosine, resulting in the demethylation of 5-cytosine, through the thymine DNA glycosylase-mediated base excision system (18). Thus, *TET2* plays an important role in active cytosine demethylation. *DNMT3A* is a *de novo* DNA methyltransferase, involved in the transformation of 5-cytosine to 5mC (19). Mutations in *TET2* and *DNMT3A* are loss-of-function and distributed along the coding sequences of the genes, with few hotspots, such as the dominant-negative *DNMT3A*^{R882X} mutant (20). *IDH2* mutations occur specifically at the R172 residue (16, 21), and confer a neoenzymatic activity producing D-2 hydroxyglutarate (22).

This metabolite, physiologically present at very low levels, inhibits numerous α -ketoglutarate-dependent dioxygenases, including TET proteins or histone demethylases (23). While *IDH1/2* and *TET2* mutations in acute myeloid leukemia are mutually exclusive, both resulting in a specific methylation profile (24), for unknown reasons they frequently coexist in AITL. Although *TET2*, *DNMT3A* and *IDH2* mutations have in principle opposite effect on cytosine methylation levels, they all individually result in decreased 5hmC levels. Interestingly, compared to normal TFH cells, 5hmC levels are decreased in AITL, and more generally in PTCL, regardless of mutations, suggesting that epigenetic deregulation is a general event during the lymphomagenesis (21). However, the functional consequences of these changes in cytosine methylation/hydroxymethylation are yet poorly understood and warrant further comprehensive studies.

A missense mutation encoding the pG17V substitution in RHOA GTPase is detected in 50-70% AITL patients (6*, 13, 14, 25). *RHOA*^{G17V} lacks the ability to bind GTP, which results in defective RHOA signaling, with an inhibitory dominant-negative effect on RHOA downstream targets, contrasting with the increased proliferation and invasiveness observed in *RHOA*^{G17V}-mutated cells (6*, 13, 14). A recent study solved this paradox in showing that *RHOA*^{G17V}, but not the wild-type form of the GTPase, binds and phosphorylates VAV1, resulting in activation of Nuclear Factor of Activated T-cells (NFAT) and subsequently in T-cell receptor (TCR) signaling (26). In line with this concept, *RHOA* mutations and *VAV1* abnormalities are mutually exclusive (6*, 26). In addition, various activating mutations, distributed along the TCR and co-stimulation signaling pathways are detected in up to 50% patients and were found to correlate with cell activation and proliferation gene expression signatures (6*). The most frequented mutated genes are *PLCG1* (27), *CD28* (28) and *PIK3* components (6*). In addition, fusions involving *CD28* and *CTLA* or *CD28* and *ICOS* have been detected in AITL (7). Initially reported as highly recurrent events (29), these fusions are in fact detected in less than 10% of patients (7, 30). *ICOS-CD28* fusions are more prevalent and likely result in an enhanced CD28 signal (7). *CTLA4-CD28* fusions are less common and have the unique feature to link extracellular CTLA4 engagement to an activating signal through CD28 intracellular moiety. Anti-CTLA4 antibody ipilimumab can block this signal and clinical efficacy was reported in one case (31).

An interesting finding in AITL is that *TET2* and *DNMT3A* mutations can be detected not only in neoplastic T cells, but also in CD34-derived colonies (32), in CD34+ cells (17) and in B cells isolated from AITL biopsies (33*, 34). Furthermore, variant allele frequencies of *TET2* and *DNMT3A* are higher than those of *RHOA* or *IDH2*. This supports that the former two mutations can occur in a hematopoietic progenitor or stem cell. Conversely, *RHOA* (33*) and *IDH2* (33*, 35) mutations are restricted to tumor cells, indicating that they are likely a second hit in an oncogenic multistep process (**Figure 1**). Furthermore, since *TET2* or *DNMT3A* mutations can be detected at significant levels in the blood of elderly individuals, reflecting at least partly a clonal hematopoiesis (36-39), they are not sufficient by themselves to induce a T-cell neoplasm.

Several mouse models further support the hypothesis of a multistep oncogenic process. The combination of *TET2* inactivation and *DNMT3* mutation can induce various hematological diseases including PTCL, only after transplantation and with a low penetrance (40), whereas *TET2* inactivation and *RHOA*^{G17V} altogether result in the development of an AITL-like disease with a much higher penetrance. The first model used engineered *TET2*-deficient T cells, transfected with *RHOA*^{G17V} construct. Recipient mice developed AITL-like disease, where decrease in *FOXO1* appeared essential for tumor cells survival (41*). Two transgenic mouse models with expression of *RHOA*^{G17V} in the T-cell compartment demonstrated the role of *RHOA*^{G17V} in T-cell development, TFH differentiation, and in inducing autoimmunity. However, additional *TET2* inactivation is required for lymphoma development (42**, 43). It is expected that these mouse models will facilitate testing of novel therapies. Of note, mouse TFH lymphomas are dependent on ICOS/PIK3/MTOR signaling (42**, 43), which may represent innovative therapeutic targets.

Recent epidemiological data indicate that AITL prevalence is much higher than previously reported (44, 45). Moreover, expression of a TFH immunophenotype was also found in the very rare follicular variant of PTCL (F-PTCL), and about 20-30% of PTCL previously classified as “not otherwise specified” (TFH-PTCL) (3, 46, 47). This raised the question whether AITL, F-PTCL and TFH-PTCL represent morphological variants of the same disease or distinct diseases with similar phenotype. A recent study showed that these lymphomas also have comparable clinical presenting features including auto-immunity, and outcome, and similar genomic imbalances and mutational profiles. A same frequency of *TET2*, *DNMT3A* and *RHOA* mutations was found in AITL, F-PTCL and TFH-PTCL (13, 48*), only *IDH2* mutations being more frequently present in AITL (15, 16). This suggests a common oncogenic process in these lymphomas, which is reflected in the 2017 classification by grouping them as related diseases (**Table 1**).

Anaplastic large cell lymphomas (ALCLs)

ALCLs include four entities having in common a large-cell anaplastic morphology, strong CD30 expression, and frequent phospho-STAT3 activation: anaplastic lymphoma kinase (ALK)-positive and ALK-negative ALCL, which altogether represent about 15-20% of non-cutaneous PTCLs, primary cutaneous ALCL (pcALCL) and the recently characterized provisional entity, breast implant-associated ALCL (BI-ALCL) (9).

In ALK-positive ALCL, ALK expression results from the fusion of the *ALK* gene to various partners, most commonly *NPM1* (*nucleophosmin*). It occurs mainly in children or young adults, may involve lymph nodes and/or various extranodal sites and has an overall excellent prognosis. Recently, an increasing number of cases of cutaneous ALCL positive for ALK expression have been reported both in children and adults, that presented as isolated cutaneous lesions without systemic involvement, and in most instances did not disseminate outside the skin and had an excellent outcome, arguing against the contention that ALK expression in ALCL is usually the

indication of a systemic disease, and suggesting that *ALK* rearrangements represent that pathogenic event in a small subset of pcALCLs (49)

ALK-negative ALCL tends to occur in older individuals and encompasses genetic heterogeneity, and two separate studies have now shown the clinical correlations to the genetic subgroups. Those with rearrangement of the *DUSP22* locus @ 6p25 (about one third of the cases) have a good outcome similar to that of ALK-positive ALCLs; conversely, the small subset of ALK-negative ALCLs with *TP53* rearrangements has a very poor outcome (50).

pcALCL is an ALK-negative ALCL within the spectrum of primary cutaneous CD30+ lymphoproliferative disorders (which also encompasses various types of lymphomatoid papulosis), and usually portends a good prognosis. Recent findings, have shown partial overlap in the pathogenic mechanisms of primary cutaneous and systemic ALK-negative ALCLs. Nevertheless, the reasons underlying the distinctive clinical features of pc versus systemic ALCL remain unknown. About one third of pcALCL carry *DUSP22* rearrangements (51) and some of these feature a biphasic pattern (dermal infiltrate of medium-to-large cells, and epidermotrophism by small atypical lymphocytes) similar to that seen in uncommon *DUSP22*-rearranged lymphomatoid papulosis (52) Two cases of pcALCL with *TP53* rearrangements were reported with an aggressive clinical course but experience is limited to draw definitive conclusions. (53) Translocations involving the *TYK2* tyrosine kinase have been found in a small subset of pcALCL and lymphomatoid papuloses, and also in systemic ALK-negative cases (54, 55). The best characterized translocation encodes a NMP1-TYK2 fusion protein that induces TYK2 activation, STAT1/3/5 activation, but other gene partners in variant translocations are not known. Enhancer of zeste homolog 2 (EZH2), a catalytic unit with histone methyltransferase activity, is consistently overexpressed in pcALCL neoplastic cells, and showed how mechanistically epigenetic silencing by EZH2 deregulation might promote tumor progression, by inhibiting tumor cell apoptosis and by derepressing CXCL10 and increasing the influx of effector T cells to the lesions (56).

BI-ALCL is a new provisional PTCL entity (9) with morphological and immunophenotypical features indistinguishable from those of other ALK-negative ALCL, and a specific clinical presentation, adjacent to a breast implant. Most cases confined to the periprosthetic effusion and capsule (seroma or « *in situ* » lymphoma) have excellent outcomes, and a minority of patients present with a breast tumor mass, which is an adverse prognostic factor (57, 58).

A recent population-based case-control study from the Netherlands concluded to a very high (over 400) relative risk for BI-ALCL in women with breast implants, but to a small absolute cumulative risk with about one of 7000 women with breast implants would develop BI-ALCL before the age of 75 (59). The pathogenesis of BI-ALCL remains elusive. It has been suggested that a local inflammatory response elicited by silicone-derived products or bacteria adherent to the surface of the prosthesis, might play a role. Genetically, while cell lines derived from BI-ALCL effusions have unstable and complex karyotypes (60), the few primary lymphoma samples examined so far show no or few alterations. The recurrent translocations found in other ALK-negative

ALCL have not been found (57, 61). Conversely, similar to other ALK-negative ALCLs, activation of STAT3 is common and mutations of *JAK1* or *STAT3* have been reported in individual case reports and small series (61-64)*.

Lymphomas of the innate immune system

Extranodal non-cutaneous PTCL derive from cytotoxic cells of the innate immune system. Besides EBV-associated extranodal NK/T-cell lymphoma (ENKTCL) which is not uncommon in Western countries and relatively frequent in Asia, hepatosplenic T-cell lymphoma (HSTL), enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic T-cell lymphoma (MEITL) are rare or very rare diseases. Mutation-induced activation of the JAK-STAT pathway (usually mutually exclusive *JAK1*, *JAK3*, *STAT3*, *STAT5B* mutations) is a hallmark pathogenic mechanism common to these extranodal PTCLs. Interestingly, addiction to JAKs/STATs, irrespective of mutations, may be antagonized by pharmacological inhibitors (65).

There is a wide spectrum of EBV positive NK/T-cell lymphoproliferations/lymphomas in adults and children, which are clinically heterogeneous (leukemic, extranodal lesions, nodal involvement, cutaneous) with more or less indolent or aggressive behavior (Table 1). ENKTCL is an angiocentric and angiodestructive lymphoma of NK or less commonly T-cell derivation. In ENKTCL, mutations in *JAK3*, *STAT3* and *STAT5b* often co-occur with epigenetic mutations (*BCOR*, others), and mutations in *DDX3X* which encodes a RNA helicase and in *TP53* (66). A genome-wide association study identified polymorphism in *HLA-DP*, rs9277378, as a risk factor for ENKTCL, reinforcing the role of HLA-DP presentation in oncogenesis (67). Cases with upper aerodigestive presentation have a better outcome than those presenting elsewhere. Exclusively nodal presentation is uncommon and associated to a shorter survival, and interestingly gene expression and copy number alterations in nodal versus extranodal cases have been found different (68). A subset of ENKTCL may develop a hemophagocytic syndrome (HPS), and a genetic basis - a specific mutation in *ECSIT*, an immune regulatory gene - was recently discovered for this often fatal hyperinflammatory complication. Functional studies nicely demonstrated that *ECSIT*-V140A variant activates NF-kappaB signaling and induces proinflammatory cytokine production, and the possibility of specific pharmacologic inhibition (69*). Aggressive NK leukemia harbors a mutational pattern similar to ENKTCL, with mutations in *DDX3X*, *STAT3* and in the RAS/MAPK pathway (70).

HSTL and MEITL are rare, highly aggressive and essentially incurable diseases, most commonly derived from gamma-delta T cells, the former involving the spleen and liver with a sinusoidal pattern in young individuals, the latter forming tumors derived from intestinal intraepithelial lymphocytes in individuals with no history of celiac disease or enteropathy (71). Both entities frequently feature JAK/STAT pathway activation, most often due to *STAT5B* mutations (4*, 72, 73). In addition, recent works have highlighted the role of epigenetic disturbances in these entities. Whole exome sequencing analysis of MEITL led to the discovery of highly

recurrent alterations of *SETD2* encoding a non-redundant H3K36-specific trimethyltransferase in 14/15 cases (93%). *SETD2* alterations were often biallelic, mainly by loss-of-function mutations and/or 3p21.31 deletion. *SETD2* is also the top mutated gene in HSTL (about one third of the cases) (4*). In a T cell-specific *SETD2* knockout mouse model, mice manifested an expansion of $\gamma\delta$ T cells, indicating novel roles for SETD2 in T-cell development and lymphomagenesis (5). Besides T-cell lymphomas, mucosal lymphoproliferations of clonal T or NK cells with an indolent behavior were recently described in the digestive tract (74). The gastrointestinal indolent T-cell lymphoproliferative disorders encompass heterogeneous immunophenotypes (CD4+, CD8+, CD4-CD8- or CD4+CD6+) and CD4+ cases may progress to a malignant T-cell lymphoma (75). Recently, *STAT3-JAK2* fusions were discovered in 4/5 CD4+ cases, while none of the other five cases with CD8+ or CD4+CD8+ phenotypes harbored the fusion, which might be targeted by JAK2 inhibitors (76*).

Conclusion

High-throughput sequencing analyses of most PTCL entities have substantially improved our understanding of PTCL pathogenesis, and oncogenic events have been identified in most PTCL entities. The current challenge is to mount efficient therapeutic strategies targeting these aberrations to improve patients outcome.

Key points:

- Mutational profiling of the many PTCL entities has revealed diverse mutational landscapes which are advancing our understanding of the pathogenesis of these rare and aggressive diseases
- The highly prevalent nodal lymphomas of follicular helper T-cell origin are characterized by a multistep oncogenetic pathway involving epigenetic deregulation related to *TET2*, *DNMT3* or *IDH2* mutations, and gain-of-function mutations affecting genes related to T-cell receptor signaling pathway
- While PTCL are usually aggressive disease, several indolent entities are recognized, including CD30+ anaplastic large-cell lymphoma associated to breast implants, and indolent clonal proliferations of mature T cells in the gastrointestinal tract

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Figure Legend

Figure 1: Model of TFH PTCL oncogenesis.

TET2 and *DNMT3A* mutations, disrupting the epigenetic regulation, occur in hematopoietic progenitors whereas *RHOA*^{G17V} and other mutations affecting cell signaling components occur in TFH cells, as second hit events. Note that *IDH2* mutation co-exist with *TET2* mutation and is restricted to tumor cells.

CLP, common lymphoid progenitor; CMP, common myeloid progenitor; HSC, hematopoietic stem cell; HPC, hematopoietic progenitor cell.

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In this paper, AITL neoplastic cells and B cell isolated by microdissection were examined separately for the presence of AITL-associated mutations; *TET2* and *DNMT3A* mutations were found in both populations, while *RHOA* and *IDH2* mutations were identified in T cells only, supporting the concept of hierarchical mutations.

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Table 1: 2017 WHO classification of mature T-cell neoplasms (adapted from (9), with summary of changes and novelties in comparison to the previous edition (10) (* designates provisional entities)

Mature T-cell neoplasms	Changes and novelties
<u>Disseminated/leukemic</u>	
T-cell prolymphocytic leukemia	Mutation-induced activation of the JAK/STAT pathway in a large proportion of the cases, in addition to the pathognomonic translocations involving <i>TCL1A/B</i> or <i>MTCP1</i>
T-cell large granular lymphocytic leukemia	Genetic heterogeneity (<i>STAT3</i> mutations in one third of the cases, <i>STAT5B</i> uncommon) correlates with clinical features (<i>STAT5B</i> mutations in more aggressive diseases)
Chronic lymphoproliferative disorder of NK cells*	Mutational profile similar to that of T-cell large granular lymphocyte leukemia
Aggressive NK-cell leukemia	
Systemic EBV-positive T-cell lymphoma of childhood*	Designation changed from “lymphoproliferative disorder” to “lymphoma” due to the aggressive fulminant clinical course, usually complicated by haemophagocytic syndrome
Chronic active EBV infection of T- and NK-cell type, systemic form	Often monoclonal, immunophenotype is predominantly CD4+, clinical course variable, haemophagocytic syndrome may occur
Adult T-cell leukemia/lymphoma	
Recent advances in genomic characterization	
<u>Nodal</u>	
Angioimmunoblastic T-cell lymphoma	Defined as a lymphoma of mature follicular helper T cells (TFH), considered as an entity within the spectrum of nodal lymphomas of follicular helper T cell origin (an umbrella category which also encompasses follicular T-cell lymphoma and nodal peripheral T-cell lymphoma with T follicular helper phenotype)
Follicular T-cell lymphoma	Formerly classified as a variant peripheral T-cell lymphoma, not

	otherwise specified; now classified as an entity in the spectrum of nodal TFH lymphomas
Nodal peripheral T-cell lymphoma with T follicular helper phenotype	Formerly not identified as an entity and considered as of peripheral T-cell lymphoma, not otherwise specified.
Anaplastic large cell lymphoma, ALK-positive	
Anaplastic large cell lymphoma, ALK-negative	Formerly provisional, now promoted to a definitive entity. Genetic subsets (<i>DUSP22</i> rearrangements, <i>TP63</i> translocations) with distinctive pathological features and clinical outcome.
Peripheral T-cell lymphoma, not otherwise specified	Requires the exclusion of a TFH immunophenotype. Molecular subsets defined on the basis of gene expression signatures and expression of Th1 versus Th2 transcription factors, may be clinically relevant but are not yet advocated to be assessed in diagnostic practice.
<u>Extranodal</u>	
Extranodal NK/T-cell lymphoma, nasal type	
Enteropathy-associated T-cell lymphoma	Formerly type I enteropathy-associated T-cell lymphoma, usually associated to celiac disease
Monomorphic epitheliotropic intestinal T-cell lymphoma	Formerly type II enteropathy-associated T-cell lymphoma; considered as a separate entity due to lack of association to celiac disease and distinctive pathological features; the designation “monomorphic epitheliotropic” refers to characteristic morphological features of this neoplasm.
Indolent T-cell lymphoproliferative disorder of the gastro-intestinal tract*	New provisional entity to designate clonal but indolent lymphoproliferative disorders of the gastrointestinal tract; a variety of immunophenotypes may be encountered; some cases may progress to overt lymphoma

Hepatosplenic T-cell lymphoma	
Subcutaneous panniculitis-like T-cell lymphoma	Limited to cases of alpha-beta derivation; may be associated to autoimmune disorders; good prognosis
Breast implant-associated anaplastic large cell lymphoma*	New provisional entity; similar to ALK-negative anaplastic large cell lymphoma.
<u>Cutaneous</u>	
Mycosis fungoides	
Sezary syndrome	
Lymphomatoid papulosis	New types of lymphomatoid papulosis recognized: strongly epidermotropic, angiocentric/angiodestructive, and those associated to a <i>DUSP22</i> rearrangement histologically mimicking transformed mycosis fungoides.
Primary cutaneous anaplastic large cell lymphoma	
Primary cutaneous $\gamma\delta$ T-cell lymphoma	Other entities that may comprise a subset of cases with a $\gamma\delta$ TCR phenotype, must be excluded (for example extranodal NK/T-cell lymphoma, mycosis fungoides, lymphomatoid papulosis)
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*	Must be distinguished from type D lymphomatoid papulosis
Primary cutaneous acral CD8+ T-cell lymphoma*	New provisional entity to designate indolent cutaneous CD8+ lymphoproliferations, as described originally in the ear
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*	Designation changed from "lymphoma" to "lymphoproliferative disorder" due to usually indolent clinical features
Hydroa vacciniforme-like lymphoproliferative disorder	Cutaneous form of chronic active EBV infection
Severe mosquito bite allergy	

