REVIEW

Recent advances in T-cell lymphoid neoplasms

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T Cells comprise many subtypes of specified lymphocytes, and their differentiation and function take place in different tissues. This cellular diversity is also observed in the multiple ways T-cell transformation gives rise to a variety of T-cell neoplasms. This review covers the main types of T-cell malignancies and their specific characteristics, emphasizing recent advances at the cellular and molecular levels as well as differences and commonalities among them.

HIGHLIGHTS

- T-Cell malignancies share many genetic alterations.
- Pathways repeatedly altered in T-cell malignancies include JAK/STAT, PI3K, TCR activation, and NFκB.
- The study of common alterations can provide new avenues for treatments.
- T-Cell malignancies are characterized by the resident tissue.

Mature blood cell populations are derived mostly from hematopoietic stem cells (HSCs) and multipotent progenitors (MPPs) through the progressive loss of differentiation potential and the acquisition of functional traits. These cells progressively differentiate into lymphoid and myeloid progenitors that will give rise to either T, B, and natural killer (NK) cells (lymphoid lineage) or erythrocytes, megakaryocytes, granulocytes, and monocytes/macrophages (myeloid lineage). Different phenotypical, functional, and more recently genomic classifications of the early hematopoietic progenitors have been widely and long studied and are constantly evolving [1]. Lymphoid progenitors were first identified as common lymphoid progenitors (CLPs) with the potential to become T or B lymphocytes [2], while more recent studies have provided a higher resolution of the differentiation process. MPP4 (lymphoid) cells [3] are now considered the earliest committed lymphoid progenitor, and MPP1 (short-term pluripotent), MMP2 (megakaryocyte−erythrocyte), and MPP3 (myeloid) are set for other lineages.

T-Cell differentiation initiates with T-cell commitment in the bone marrow (BM) and progresses in the thymus with proliferation, differentiation, and selection of T-cell precursors [4]. The BM T-cell progenitors are the multipotent lymphoid-primed multipotent progenitors (LMPPs) [5] (similar to MPP4). LMPPs migrate to the thymus through the blood in a chemotaxis-mediated manner [6]. LMPPs phenotypically resemble early T-cell progenitors (ETPs) [7]; however, ETPs still retain the capacity to differentiate into myeloid cells. In the thymus, ETPs differentiate into T cells owing to the epithelial stromal cells expressing high levels of Notch ligands [8], growth factors such as interleukin-7 [9], and other signaling molecules such as hedgehog [10].

The stringent selection process that T cells go through is highly dependent on the T-cell receptor (TCR) signaling. Mature T cells include distinct subpopulations including naive T cells (with potential to respond to new antigens), memory T cells (derived from antigen-activated naive cells), and regulatory T (Treg) cells (preventing exacerbated immune responses and self-damaging reactions) [11].

T cells, like other immune cells, are required to fight against pathogens and diseases such as cancer. In the latter, tumor microenvironment can impose an immunosuppressive landscape that facilitates immune evasion [12]. On this basis, reversal of T-cell function disability through blockage of immune checkpoints (i.e., using antibodies against PD1 or PDL-1) is becoming a novel and promising therapeutic option in cancer treatment [13]. However, tight regulation of the immune response is essential to preserve the integrity of the organisms. Thus, T cells with immunosenescent modifications [14], chemotactic expansion, exhaustion in response to physiological aging [15], constant TCR triggering, and co-stimulatory/inhibitory factors [16] can actually be responsible for immune dysregulation and contribute to different pathologies, including a wide variety of neoplasms [17].

Human lymphoid malignancies cover a variety of immune cell-type defects. Our main understanding of the hematopoietic system is based mainly on mouse studies for obvious reasons; however, in the case of the hematopoietic differentiation of the immune system, there are essential differences between mouse and human that should be considered, such as specialized cell types and early T-cell precursors (for review, see Parekh and Crooks [18]). This has recently been

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illustrated by single-cell RNA studies that have clarified some of these populations, including shedding some light on the corresponding human double-negative (DN) progenitor populations [19,20].

Clinical diagnostic and therapeutic studies require a more accurate characterization of the human hematopoietic and immune system. A better understanding of the human T-cell differentiation process is essential to identify the cell of origin of leukemic transformation, the subsequent evolution of these neoplasms, and the mechanisms that favor or counteract disease progression. This review focuses on the cellular and molecular characteristics of the diverse T-cell neoplasms and the differences and similarities among them. Deeper molecular studies on the variety of T-cell diseases will help to better understand the human adaptive immune system.

T-CELL LEUKEMIA

T-Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is characterized by elevated leukocyte counts followed by hematopoietic failure. The overall ALL incidence varies considerably in children (1.6/100,000) and adults (4/100,000). T-ALL is a rare subtype of ALL comprising 10%−15% of ALL cases in children and 20%−25% in adults [21], with a higher incidence in males.

Cell of origin. Despite the effort made in identifying T-ALL stem or initiating cells, their nature remains unclear. Studies using genetic mouse models in which tumor driver genes are induced at different stages of hematopoietic differentiation (from early HSCs to late CD4 T cells) suggest that there is no correlation between the cell of origin of the disease and the leukemic phenotype [22]. Through the use of patient-derived xenografts, it has been found that subpopulations of cells expressing CD1a or carrying active Notch [23] harbor leukemia initiation capacity and therapeutic resistance [24].

Genetic insight. Most genetic information comes from pediatric T-ALL [25], although data from adult patients also exist [26]. Adult and pediatric T-ALL cells share similar genetic alterations but have different outcomes, with more than 80% survival in children and about 50% in adults.

Notch1 is the most predominant tumor driver in T-ALL, with about 80% of T-ALL patients carrying activating variants imposing ligand-independent Notch activation and/or protein stabilization [27]. Further supporting the relevance of Notch as T-ALL driver, mutations in negative regulators of Notch such as Fbxw7 [28] and Vav-1 [29] are frequently mutated in T-ALL cells carrying wild-type Notch1. The importance of Notch1 in T-cell development provides a functional link between aberrant Notch signaling and T-ALL.

Apart from Notch, the mutational burden of T-ALL cells is gradually increased with age, and subclonal alterations affecting genes/pathways associated with therapy resistance and relapse have recently been detected at the time of T-ALL diagnosis [26,30]. Chromosomal rearrangements involving TCR genes, *TRD*and *TRB* being the most common, are clonally present in 50% of T-ALL patients, indicating that leukemia arose from a single cell that has experienced TCR rearrangement. These rearrangements are often juxtaposed to critical transcription factors such as Hox11 (*TLX1*), Hox11L2 (*TLX3*), and MYC, among many others, thus leading to inappropriate gene activation [31].

Other common alterations found in T-ALL involve elements of the polycomb repressive complex 2, components of the JAK/STAT pathway, and ribosomal proteins [32]. Inactivating mutations and deletions in the *PHF6* gene were identified in 16% of the pediatric samples and 38% of primary T-ALL in adults. The location of *PHF6* on the X chromosome partly supports the higher prevalence of T-ALL observed in males [33,34]. New mutations have been described, such as *HERC1*, the splicing gene *ZRSR2*, and *PRKCZ*, functionally involved in DNA repair [35]. In 8% of adult T-ALL samples, the NO CCR4-NO3 subunit of the transcription complex (CNOT3) is inactivated. CNOT3 regulates the half-life of mRNA and participates in the control of protein translation [32]. Although most of the studies failed to correlate the presence of specific mutations with patient outcome, detection of *DNMT3A* and *RUNX1* mutations in early T-ALL (ETP) is indicative of poor OS [25,36].

T-ALL is also associated with altered NFκB signaling, characterized by mutations in the *PLCG1, PRKCB*, and *CARD11* genes. Altered Notch signaling leading to high levels of its downstream target Hes1 imposes constitutive activation of NFκB by Hes1-mediated inhibition of the NFκB negative regulator CYLD [37].

Current and new therapeutic approaches. First-line therapy for T-ALL typically involves vincristine, corticosteroids, and anthracycline [38].

The risk-based therapeutic regime incorporates alkylating agents such as cyclophosphamide, antimetabolites (methotrexate), nucleoside analogues (6-mercaptopurine, thioguanine, and cytarabine), and hydrolyzing enzymes (L-asparaginase). In patients with a poor response to treatment, the most plausible option is HSC transplantation.

Inhibition of the Notch pathway by γ-secretase inhibitors (GSIs) has been proposed as a therapeutic option in T-ALL. GSIs such as MK-0752 [39] and BMS-906024 [40] have shown clinical response, with gastrointestinal (GI) toxicity being the main associated problem. Combining GSIs with glucocorticoids reduces GI toxicity, as demonstrated in experimental murine models [41,42]. Because *NOTCH1*-mutated T-ALL cells exhibit high CXCR4 surface expression, which facilitates tumor progression and tissue colonization, CXCR4 antagonists have been proposed for treating NOTCH1-driven T-ALL [43].

Immunotherapy approaches for T-ALL include monoclonal antibodies against surface CD38 [44], which is robustly expressed in T-ALL and ETP-ALL blasts at all stages of the disease (diagnosis, chemotherapy treatment, and relapse) [45]. More sophisticated approaches, such as chimeric antigen receptor (CAR) T cells against surface CD1a [46], CD5 [47], CD7 [48], and CD38 [49], are currently being tested.

In addition, several pathway-based therapies are now under development or in clinical trials. Some examples are APR-246, which binds mutant p53 and restores its tumor-suppressor function, and MDM2 inhibitors that prevent p53 ubiquitination and proteasomal degradation. Proteasome inhibitors, such as bortezomib [50], prevent degradation of tumor suppressors and preclude NF-κB activation by stabilization of the IκB inhibitors. Increased activity of the cell cycle regulator CDK4/6 can be blocked by a CDK inhibitor (ribociclib or palbociclib) [51,52], whereas aberrant transcription induced by BRD4 can be targeted by BET inhibitors [53]. Nuclear trafficking of oncogenic mRNA and proteins can be targeted via XPO1 inhibitors (selinexor) [54]. Moreover, JAK, PIM1, PI3K, AKT, mTOR, and MEK inhibitors have demonstrated their efficacy against aberrant

IL7R signaling present in T-ALL. Finally, T-ALL cells exhibit BCLXL or BCL2 dependence, which could be therapeutically exploited using BH3 mimetics (e.g., venetoclax or navitoclax) [55–57].

T-CELL LYMPHOBLASTIC LYMPHOMA

T-Cell lymphoblastic lymphoma (T-LBL) is a subtype of aggressive non-Hodgkin lymphoma (NHL) affecting multiple organs including mediastinal masses, and there is central nervous system (CNS) involvement in 10% of cases [58]. It accounts for around 2% of all adult NHL cases [59]. Pathologic, morphologic, and phenotypic characteristics are similar to those of ALL, but some particularities are mentioned here. Peripheral involvement is minimal or typically absent [60], bone marrow infiltration is not as significant as in T-ALL [61], and its phenotype resembles more of a cortical or mature counterpart in contrast with T-ALL [60,62]. In addition, translocations involving chromosome region 9q34 are more frequent in T-LBL than T-ALL [63].

Lymphoblasts are TdT positive and variably express T-cell markers such as CD3, which is considered lineage specific, but multiple immunohistochemical antibodies and molecular detection are crucial for diagnosis. For young adult patients, the most effective treatment approaches are pediatric-like ALL-based protocols [64], with high-dose multiagent chemotherapy and CNS prophylaxis.

T-Cell prolymphocytic leukemia

T-Cell prolymphocytic leukemia (T-PLL) is an aggressive leukemia characterized by the proliferation of small to medium- sized prolymphocytes with a mature postthymic T-cell phenotype, involving peripheral blood (PB), BM, lymph nodes, liver, spleen, and skin [65]. T-PLL accounts for approximately 2% of cases of mature lymphocytic leukemia in adults, with an incidence of ≈0.6 per million in Western countries and a median overall survival (OS) of less than 3 years [66,67], and is still the most common mature T-cell leukemia in Western countries (patients aged >30 years, median age 65 years) [68].

Cell of origin. The postulated cell of origin is a postthymic $CD4^+$/$CD8^+$ T cell compatible with an intermediate stage between cortical thymocytes and PB mature T lymphocytes. T-PLL cells co-express mature T-lymphoid markers and display abnormal expression and hyperactivation of T-cell leukemia/lymphoma 1 (TCL1) [65,69].

Genetic insight. TCL1 and mature T-cell proliferation 1 (MTCP1) alterations lead to activation of protein kinase B (AKT), impairment of protein kinase C theta (PKCθ) signaling and extracellular signal-regulated kinase (ERK) [70]. Targeted and whole-exome sequencing (WES) studies have revealed recurrent activating mutations in genes of the JAK/STAT pathway. Specifically, 30%–42% of cases carry mutations in *JAK3*, 8% in *JAK1* and 21%–36% in *STAT5B*, *JAK3* mutations being the only alteration with significant negative prognosis value in T-PLL [71]. Less prevalent mutations involve genes encoding epigenetic modifiers, *EZH2* and *BCOR*, and *TP53* [72,73].

Current and new therapeutic approaches. T-PLL cells exhibit a poor response to conventional alkylating therapies, as well as high-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [74,75]. Alemtuzumab (α-CD52 antibody) treatment had favorable responses in 70%–80% of patients, but tumor relapse occurs in a large percentage of patients within the first year [66,76,77]. The only curative approach is allogenic HSC transplantation (allo-HSCT) following a myeloablative conditioning regimen, although it is associated with a high incidence of transplant-related morbidity and mortality, limiting its use to young patients without medical comorbidities [78]. Given the dismal prognosis of T-PLL patients, there is an urgent need for new therapeutic agents, especially in alemtuzumab-refractory/relapse disease. Recent genomic data revealed high frequencies of mutations in histone modifiers [72], and HDAC inhibitors (vorinostat, belinostat, romidepsin) are being explored [79]. The presence of *TP53* mutations in T-PLL (although rare) [80] suggested that MDM2 inhibitors might be a therapeutic option for a subset of patients [81,82]. Moderate efficacy has also been reported for JAK/STAT inhibitors such as tofacitinib (inhibitor of JAK2/3) and ruxolitinib (inhibitor of JAK1/2) [83,84]. A first report has noted partial responses after treatment with venetoclax (inhibitor of antiapoptotic Bcl2) as a single agent in two refractory patients [85]. Promising but preliminary results have also been obtained with ibrutinib (inhibitor of interleukin [IL]-2 inducible T-cell kinase [ITK]) and the purine analog pentostatin [86–88]. Current investigations include inhibitors of phosphoinositide 3-kinase (PI3K; copanlisib and duvelisib), combined JAK/STAT-SYK inhibitors (e.g., cerdulatinib), EZH2 inhibitors [89–91], and CAR-T cells [68].

T-Cell large granular lymphocytic leukemia

T-Cell large granular lymphocytic leukemia (T-LGLL) is a rare heterogeneous disorder characterized by a persistent (>6 months) increase in the number of PB large granular lymphocytes (LGLs) with azurophilic cytoplasmic granules.

T-LGLL accounts for 2%–3% of mature small lymphocytic leukemias, with comparable impact in males and females [65]. The median age of T-LGLL patients is 60 years, neutropenia being the worst prognostic factor. Mortality by T-LGLL is uncommon, with an OS of 70% at 10 years (median survival of 13 years) [92]. World Health Organization (WHO) classification recognizes three categories: chronic T-cell leukemia and NK-cell lymphocytosis, both indolent (mostly undiagnosed) diseases, and aggressive NK-cell LGLL.

Cell of origin. Most LGLL cells express CD2, $CD3^+$, CDS^+, $CD57^+$, and $\alpha\beta TCR^+$. T-LGLL diagnosis is based on the presence of an abnormal $CD3^+/CD57^+$ cell population that has clonal TCR gene rearrangement as determined by polymerase chain reaction (PCR). Clonal T-LGLL cells usually express TCR$\alpha\beta$ and have a $CD8^{+}$ $^{+}/CD4^-$ phenotype, with some $CD4^+/CD8^{-/+dim}$ cases and a minor group expressing TCR$\gamma\delta$. Other cytotoxic T-cell markers such as CD16, CD56, CD11b, and CD11c are variably expressed. LGLLs originate from $CD8^+$ cells that are oligoclonally expanded after antigen stimulation. Subsequently, T-LGLL cells are clonally selected because of constitutive upregulation of survival signals and/or downregulation of apoptotic pathways. Chronic antigen exposure resulting from autoimmune disorders (e.g., rheumatoid arthritis and Sjögren syndrome or viral infections) can trigger the disease.

Genetic insight. The hallmark of T-LGLL proliferation is constitutive activation of STAT3 [93] that induces transcription of prosurvival Bcl2-family or *Mcl-1* (myeloid cell leukemia-1) genes. STAT3 mutations are in heterozygosis and present in one-third of T-LGLL cases. They are localized mainly in the SH2 domain of the protein,

particularly affecting Y640 or D661 residues. Mutations in the SH2 domain of STAT5B have rarely been found in T-LGLL, with the N642H mutation associated with more aggressive disease [94]. Other genetic alterations found in T-LGLL involve constitutive activation of the JAK2/STAT/Mcl-1, RAS/MAPK, SFK/PI3K/AKT, and sphingolipid pathways [95,96] and dysregulated expression of Fas ligand [97].

New therapeutic approaches. There is no standard treatment for T-LGLL, but the most established protocols involve low-dose methotrexate (MTX), cyclophosphamide, and cyclosporine A as single agents [98,99]. Survival rates are independent of STAT3 mutations, but poorer survival rates are associated with more symptomatic disease and shorter time to treatment failure [100,101]. STAT3 Y640F mutation predicts the response to initial therapy with MTX [102].

New pathway-based treatments such as cytokine antagonists, antibodies against membrane receptors, JAK/STAT, NF-kB, and Ras inhibitors are currently being considered.

Aggressive NK-cell leukemia

Aggressive NK-cell leukemia (ANKL) is a subtype of T-LGLL characterized by systemic proliferation of NK cells, with an aggressive clinical course (median OS is <2 months [103,104]), and frequently associated with Epstein–Barr virus (EBV) [65]. ANKL affects mainly Asian males and females, with two incidence peaks in the third and fifth decades of life [103,105]. EBV-Negative ANKL is often seen in elderly patients [106,107].

Cell of origin. ANKL cells are likely derived from mature NK cells and express CD2, CD3ε, CD56, and EBV with a germline configuration of the TCR and Ig genes.

Genetic insight. Mutations within the JAK/STAT [108–110], Akt [108], and NF-κB [108] pathways are associated with ANKL pathogenesis. Mutually exclusive alterations in JAK and STAT have been reported in 21%–48% patients [111,112]. Although the role of EBV in the origin of ANKL is still under debate [113,114], EBV-encoded small RNAs can induce JAK/STAT downstream of interleukin (IL)-10, suggesting that the IL-10–STAT3–MYC axis is a relevant player in ANKL [115]. Other genes mutated in ANKL are *TET2* and *CREBBP*, the RNA helicase *DDX3X*, *MLL2*, *GFI1* [111,112,116], and *TP53*, with the latter representing 7%–34% of cases [111,112], in agreement with studies reporting 17p13.1 loss (including the *TP53* gene) [117]. A similar genomic landscape is found in EBV-negative patients [106,107].

New therapeutic approaches. Current therapy for ANKL is chemotherapy [118] in defined combinations such as SMILE (dexamethasone, MTX, ifosfamide, L-asparaginase, and etoposide), AspaMetDex (L-asparaginase, MTX, and dexamethasone), VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase) [119–121] or anthracycline-containing regimens [103]. Patients that are EBV negative after treatment have a better prognosis [119]. Different studies report a prolonged survival in a limited number of patients after HSC transplantation [119,120,122,123].

Targeted therapies including BCL-2 [111,116], heat shock protein 90 (HSP90), Polo-like kinase (PLK), CDK, HDACs, EZH2 [111] inhibitors, and daratumumab, a monoclonal antibody targeting CD38, which is highly expressed in ANKL, are possible therapeutic options [103,124]

Finally, it was recently reported that seven ANKL-resistant patients responded to PD-1 inhibition using pembrolizumab [125], which is consistent with the fact that PD-L1 is activated in ANKL cells [106,112,116] after EBV infection [126].

Adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasm with a dismal prognosis caused by human T-cell leukemia virus type 1 (HTLV-1), which has the highest prevalence in Japan, Africa, the Caribbean islands, Melanesia, and South America [127]. Additional genetic and/or epigenetic events contribute to ATLL [65], and individuals with HLA A26, B4002, B4006, and B4801 seem genetically predisposed [128]. The median age of Japanese patients is 60–70 years, and that in south/central America and Western countries is significantly lower (40–55 years) [129,130].

Genetic insight. ATLL is characterized by gain-of-function alterations in the TCR/NF-κB pathway, including mutations in *PLCG1*, *PRKCB*, *CARD11*, and *Vav-1* genes and CTLA4–CD28 or ICOS–CD28 fusions [131]. These mutations together with inactivation of TP53 and CDKN2A can drive T-cell transformation [132]. Immune surveillance–associated molecules such as HLA-A/B, CD58, and FAS are recurrently mutated, deleted, or hypermethylated [131], and overexpression of PD-L1 is also frequently observed. Other mutational targets found in ATLL include the T-cell transcription factors IRF4, IKZF2, and GATA3 and chemokine receptors (CCRs) such as CCR4, CCR7, and GPR183 [133,134]. Some ATLL cases exhibit increased H3 methylation and DNA hypermethylation [135].

Current treatment and new approaches. Chemotherapy combination regimens remain the first-line treatment for ATLL, despite limited long-term efficacy. Prospective clinical trials in Japan using CHOP or aggressive regimens including etoposide had a median OS benefit of 8.3 to 10.6 months [136,137]. Combination of the proteasome inhibitor bortezomib with chemotherapy did not improve response [138,139]

Lenalidomide as a single agent had a 42% overall response rate in relapsed or refractory ATLL with a median disease-free survival (DFS) of 4 months and median OS of 20 months [140]. Because of the high relapse rates, consolidation of first remission with allo-HSCT is strongly considered [141]. The anti-CCR4 antibody mogamulizimab had a 50% response rate and median OS of 13.7 months [142], and CCR4 mutation predicted better response [133].

Aberrant *PD-L1* expression found in 27% of ATLL cases, similar to other T-cell leukemias, supports the use of immune checkpoint therapy [143]. Unfortunately, three patients treated with nivolumab had aggressive progression [144].

NON-HODGKIN T-CELL LYMPHOMAS

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is an aggressive subtype of extranodal lymphoma characterized by a hepatosplenic presentation without lymphadenopathy, poor response to therapy, and high mortality [65]. HSTCL constitutes less than 1% of all NHLs and 1%–2%

of all T/NK cell lymphomas [145]. It is rare, but its incidence is currently increasing [146].

Cell of origin. This neoplasm derives from cytotoxic CD8+ T-cell expansion, usually of the $\gamma\delta$ -TCR type [147], mainly Vδ1 [148], with rare cases expressing the α/β subunits. The neoplastic HSTCL population is usually composed of medium-sized lymphoid cells presenting with sinusoidal infiltration of the spleen, liver, and BM [149].

Genetic insight. Some patients display rearranged TCRγ locus genes and biallelic rearrangement of the TCRδ locus. Next-generation sequencing has revealed recurrent genetic alterations affecting epigenetic regulators, JAK/STAT, and PI3K elements [109]. Missense mutations in *STAT5B* and, more rarely, *STAT3* have been found in about 40% of HSTCL cases [109,150] associated with JAK/STAT target gene upregulation [151]. Chromatin modifiers such as SETD2, INO80, and ARID1B are mutated in 62% of cases [152]. Other recurrent alterations include mutations in *TET3, SMARCA2, TP53, UBR5*, and *IDH2*; overexpression of NK-related antigens (including Ig-like receptors), oncogenes (*MYBL1, VAV3*), cell-trafficking genes (*S1PR5*), or multidrug resistance 1 (*MDR-1*) genes; and downregulation of tumor suppressors such as AIM1 [151]. P-Glycoprotein-1 (Pgp-1) and MDR1 amplifications explain some chemotherapy-resistant phenotypes [151].

Current and new therapeutic approaches. Patients are generally treated with chemotherapy and initially respond to platinum–cytarabine [149] and pentostatin [153]. However, tumor relapse is very frequent, and median survival is <2 years [149,154]. Early treatment with high-dose chemotherapy followed by HSC transplantation (especially allo-HSC) may improve survival [155]. Regimes of gemcitabine, carboplatin, and dexamethasone have been determined to increase the efficacy of subsequent allo-HSCT [156]. Etoposide, methylprednisolone, excessive-dose cytarabine, cisplatin, alemtuzumab, and purine analogs [157] have also been effective. However, the increased risk of cytopenia, infections, and difficulties in HSC mobilization may limit the general application of these therapeutic schemes. Standard anthracycline-containing induction regimens have been disappointing [145,149,154,155], as have CHOP or CHOP-like regimens [149,154].

Preclinical results indicated that concomitant use of a STAT5B and a PI3Kδ inhibitor had a synergic effect on cell viability [152]. Alemtuzumab may also be considered as an alternative strategy given the ubiquitous expression of CD52 [158].

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) comprises a group of CD30+ T-cell NHLs with overlapping clinical, histological, and immunohistochemical phenotypes that differ in their clinical behavior and genetic profiles. Four distinct ALCL entities are recognized in the WHO classification: anaplastic lymphoma kinase (ALK^+ ALCL, ALK^- ALCL), breast implant–associated (BIA-ALCL), and primary cutaneous ALCL (pcALCL).

ALK^+ ALCL carries ALK gene rearrangements and has a favorable prognosis. The presence of combined nuclear and cytoplasmic ALK strongly suggests underlying t(2;5) translocation resulting in the fusion of ALK and nucleophosmin (NPM1). Cytoplasmic ALK is mainly associated with other ALK fusion partners such as TRAF1, ATIC, and TPM3.

ALK^- ALCL lacks ALK gene rearrangement but carries other alterations, such as 6p25 rearrangements involving the *IRF4/DUSP22* locus. DUSP22-Rearranged cases have favorable outcomes similar to those of ALK^+ ALCL. In contrast, patients with rearrangements in *TP63* have a dismal prognosis. Absence of *ALK*, *DUSP22*, and *TP63* rearrangements results in an intermediate prognosis.

BIA-ALCL are rare ALK^- NHLs with an overall favorable prognosis. A recent report identified deletions at chromosome 20q13.13 in two-thirds of cases. Similar to other T-cell lymphomas, mutations affecting the IL-6–JAK1/STAT3 pathway are observed (13%–26% of cases). Other genetic alterations include point mutations of *DNMT3A* and *TP53* [159].

Intestinal T-cell lymphoma

Intestinal T-cell lymphoma is a subtype of peripheral T-cell lymphoma (PTCL) that was categorized as types I and II in the 2008 WHO classification based on epidemiologic and clinicopathologic differences [160]. A better understanding of disease biology has led to a change in terminology, with the designation enteropathy-associated T-cell lymphoma (EATL) (former type I) now reserved to intestinal T-cell lymphomas occurring in individuals with celiac disease, and a reclassification of EATL type II as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). Intestinal T-cell lymphomas, which no longer fulfill the standards for both EATL type 1 and MEITL, are often defined as intestinal T-cellular lymphoma, not otherwise specified (ITL-NOS) [65]. The classification and naming of EATL and its subtypes have been extensively debated [161–164].

Enteropathy-associated T-cell lymphoma

EATL is an aggressive type of peripheral T-cell lymphoma with increasing incidence [65,165]. EATL is the most common oncologic complication of celiac disease, with a prevalence of ~1% in those patients [166], and usually occurs in older (60–70 years) Northern European individuals [167–170]. Histologically, EATL cells have a medium-large size, usually associated with the HLADQ2 or HLA-DQ8 haplotype, also linked to celiac disease [167,171].

Genetic insight. The genetic basis of EATL remains poorly understood, but copy number alterations are recurrently observed, including gains at chromosome 1q, 5q35 (21%), 7q22, or 9q31 and losses at 8p, 13q22, 18q22, 16q12.1, and 9p21 [172,173]. Microsatellite instability was also observed in a significant fraction of EATLs [172].

WES of 69 EATL tumors [174] revealed that the JAK/STAT pathway is the most commonly mutated, with frequent activating mutations in *STAT5B* (29%), *JAK1* (23%), *JAK3* (23%), and *STAT3* (16%) and frameshift mutations in the negative regulator of the pathway, *SOCS1* (7%). *TP53* was found to be mutated in 10% of cases, in addition to other DNA damage-related genes such as *BCL11B*, a known tumor suppressor in T-cell lymphomas, and *BRIP1*, a DNA helicase involved in the repair of double-strand breaks [174]. Chromatin modifiers such as *TET2* and *YLPM1* were mutated in a significant number of cases and typically exhibit loss-of-function mutations [174].

Prognosis and current treatment. The poor prognosis of EATL is explained by multifocal involvement of the small intestine and

frequent dissemination, which make complete resection difficult [175]. The median survival is about 10.5 months with chemotherapy, and the estimated OS and DFS at 5 years are around 20% and 4%, respectively [167]. Initial cytoreductive surgery combined with systemic chemotherapy is considered the standard treatment [176,177], CHOP being the most used regimen [176] with total remission rates around 46% [162]. Multiagent anthracycline-based chemotherapy alone is associated with poor long-term outcomes with a median OS of 7 months [169,178]. In patients who respond to first-line therapy and are eligible for autologous HSC transplantation (auto-HSCT), the 5-year median OS can be improved up to 50%–60%.

Based on the fact that 50% of EATL cases express CD30 [179], targeted therapy with brentuximab vedotin has been tested with promising outcomes [180,181]. In addition, a single patient with relapsed EATL achieved durable remission after CD30 CAR T-cell therapy and allo-HSCT [179].

Monomorphic epitheliotropic intestinal T-cell lymphoma

MEITL constitutes less than 5% of all GI lymphomas. However, it is the most common primary T-cell lymphoma affecting the small bowel in Asia and also is frequent in Hispanics [182]. MEITL is twice more common in males than in females. It disseminates and has a poor prognosis with a median survival of 7 months [183].

Genetic insight. MEITL cells are $CD3^+$, $CD5^-$, $CD8^+$, $CD56^+$, and TCR-$\gamma\delta^+$ [166] and express cytotoxic markers [166,184]. Seventy-five percent have extra copies of 8q24 (including *MYC*) and 9q34.3 [173,185]. The most common genetic alterations are activating mutations of STAT5B [109] and loss-of-function mutations of SETD2 [164], a lysine methyltransferase catalyzing H3K36 methylation. Loss of SETD2 in mice leads to expansion of $\gamma\delta$ T cells, suggesting a role for SETD2 not only in oncogenesis but also in T-cell development [186,187]. Mutations in JAK3 or SH2B3 are also useful in distinguishing MEITL from indolent T-cell lymphoproliferative disease (IT-LPD) of the GI tract.

Prognosis and treatment. There is no standardized therapy for MEITL, and most studies in Europe are tailored from EATL or PTCL therapies. MEITL treatment usually consists of surgery in combination with chemotherapy, radiotherapy, and allo-HSCT. Anthracycline-based polychemotherapy followed by allo-HSCT (in younger patients) has demonstrated some improvement in OS [188]. Alternative therapies including alemtuzumab (anti-CD52) or L-asparaginase-based regimens have had higher complete remission rates than CHOP or anthracycline-based chemotherapy [189]. Failure of CHOP chemotherapy in aggressive lymphomas is linked to CD56 expression or elevated levels of P-glycoprotein, which are seen in both MEITL and NK/T-cell lymphoma [190]. Higher DFS and OS rates have been obtained in patients receiving IVE/MTX polychemotherapy (ifosfamide, vincristine, etoposide/methotrexate) compared with those receiving anthracycline-based chemotherapy [169].

Indolent T-cell lymphoproliferative disease of the GI tract

Indolent T-cell lymphoproliferative disease of the GI tract (GI-IT-LPD) is a rare low-grade clonal lymphoproliferative disease occurring in the GI tract and is included as a provisional entity in the current WHO classification [65]. GI-IT-LPD is more common in males than females in a wide range of adult ages [191]. Indolent GI-T-LPD cases is occasionally misdiagnosed as EATL or MEITL.

Genetic insight. ITLPD cells may derive from $CD8^+$ T cells and less often from $CD4^+$ T cells, the former phenotype being the most frequently reported [65]. Neoplastic lymphocytes are mature small lymphocytes that are CD56 negative, suggesting that they do not originate from NK cells. In general, GI-IT-LPD tumors exhibit a non-invasive pattern and indolent clinical behavior with a proliferative index of ~5% $Ki67^+$ cells [183].

Six nonactivating mutational hotspots in the SH2 domain of STAT3 have been identified in five indolent GI-IT-LPD cases [183]. STAT3/JAK2 fusions have been specifically found in four of five CD4 + GI-IT-LPD cases, which were not detected in $CD8^+$ or $CD4^+$/$CD8^+$ cases [192]. If confirmed, STAT3/JAK2 gene fusions genes may represent a novel diagnostic biomarker for genetic tests.

Prognosis and treatment. GI-IT-LPD is usually an indolent disease with rare cases progressing to aggressive lymphomas [193]. Factors that predict tumor progression in GI-ITLPD are unknown, but one of five $CD4^+$ cases with STAT3/JAK2 fusion was found to develop T-cell lymphoma [192]. Mechanistically, ectopic STAT3/JAK2 promotes cytokine-independent growth of $CD4^+$ T cells and pro-B cells by activating STAT5. Moreover, STAT3/JAK2 promotes in vivo tumor growth that is inhibited by JAK inhibitors [194].

Promoter methylation leading to tumor suppressor silencing [195], aberrant histone methylations [196], and altered miRNA expression [197] are also useful biomarkers for diagnosis, prognosis, and therapeutic prescription in indolent GI-IT-LPD.

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) cells phenotypically resemble T follicular helper (TFH) cells and are characterized by inflammatory/autoimmune reactions accompanying reactive follicular hyperplasia or B-cell neoplastic proliferation. AITL is characterized by mutations in *RHOA* (50%–70% of cases), *TET2, DNMT3A*, and *IDH2* (about 80% of cases) and mutations in the TCR-related genes *CD28* and *PLCG1* [198–200]. All these genes, except *IDH2*, are mutated at similar frequencies in AITL, follicular T-cell lymphoma (FTCL), and a subset of T-cell lymphomas of TFH origin. The 2016 WHO classification included three diseases, namely, AITL, FTCL, and the newly defined nodal PTCL with TFH phenotype (nPTCL-TFH).

Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL), is an aggressive lymphoma that is strongly associated with EBV infection and arises primarily, but not exclusively, in nasal and paranasal areas. Typically, this aggressive lymphoma appears in adult patients from Caribbean or South and East Asian countries. Despite variations in geographic distribution, the genetic landscape of ENKTCL is characterized by mutations in the JAK/STAT components; tumor suppressors such as *TP53* or *MGA*, immune evasion elements; *MYC* [201]; the epigenetic modifiers *KMT2D, ARID1A,* and *EP300*; and loss-of-function mutations of the BCOR corepressor [202,203]. Gain of 2q and losses in chromosomes 6q16-q27 or 11q22-q23 are also present in ENKTCL and distinguish ENKTCL from ANKL.

A provisional distinct entity in the WHO classification is the primary EBV-positive nodal T/NK cell lymphoma without nasal or

extranodal involvement. It is characterized by losses in 14q11, which are suggestive of TCR rearrangement and T-cell origin.

Peripheral T-cell lymphoma, not otherwise specified

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a heterogeneous category of nodal and extranodal mature T-cell lymphomas different from other mature T-cell lymphoma entities in the current classification [65]. This group accounts for almost 30% of PTCLs in Western countries [204].

Genetic insight. PTCL-NOS is a diagnosis of exclusion and the most common subtype of PTCL. Recurrent mutations detected in PTCL-NOS include the epigenetic regulators KMT2C and ARID1A and the TCR signaling molecules PLCG1 and CD28. A subset of PTCL-NOS exhibits TFH markers such as PD-1, CD10, CXCL13, BCL6, and ICOS and shares pathologic characteristics with AITL [65,205]. *TET2, RHOA, DNMT3A*, and *IDH2* mutations are also present among PTCL-NOS [198,199,206,207]. Importantly, RHOA G17V mutation induces TFH lineage specification and promotes T-cell lymphomas in cooperation with TET2 loss in vivo [208]. In the revised WHO classification, this subset of PTCL-NOS is categorized as PTCL with TFH cell phenotype as a provisional entity [65].

Recent genetic studies identified a new non-TFH PTCL-NOS subtype that carries TP53 and/or CDKN2A mutations and deletions [209,210] and exhibits distinct genetic features associated with genomic instability specifically involving the HLA-A and HLA-B loci [209].

Current therapy. PTCL-NOS are aggressive, chemoresistant neoplasms [211–213], and the only prognosis factors are the stage and the International Prognostic Index (IPI) score [204]. CHOP-like regimens remain the most frequently used frontline strategy with overall response rates (ORRs) of 50%–60%, and complete response rates of 20%–30%. The efficacy of anthracyclines remains controversial and non–anthracycline-containing regimens are being investigated. Long-term survival remains poor with a median 5-year OS not higher than 30% [211,214,215]. Upfront auto-HSCT seems to significantly improve both OS and DFS [188].

In the last decade, four agents have been approved by the U.S. Food and Drug Administration (FDA) for treating relapsed and refractory PTCL-NOS: pralatrexate, the HDAC inhibitors romidepsin and belinostat, and the anti-CD30 antibody brentuximab vedotin with ORRs around 20%–30% [211,215,216]. Current clinical trials are investigating their efficacy in combination with other drugs [211,217].

Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) comprises a heterogeneous group of T-cell malignancies that arise from skin-resident T cells and may involve skin and lymph nodes and eventually extend to viscera. Collectively, CTCLs are classified under extranodal NHL with an estimated incidence in Western countries of 10 new cases per million people per year [218].

Mycosis fungoides and Sézary syndrome

Mycosis fungoides (MF) represents 50% of all primary cutaneous lymphomas with confined skin lesions that include patches, papules, and plaques and lesions with tumor appearance. Sézary syndrome (SS) is classically manifested by pruritic erythroderma, generalized lymphadenopathy, and atypical large circulating mononuclear cells with convoluted nuclei (Sézary cells). SS is observed almost exclusively in adults and elderly patients. It is an aggressive disease (OS = 30% at 5 years), similar to advanced MF [219].

Cell of origin. MF and SS are usually CD4+ T-cell malignancies with a T-helper memory phenotype (CD45RO). MF cells reside in the skin at early stages, but nodal and PB involvement are common in advanced stages, when the clonal expansion of malignant T cells within the PB is also associated with loss of TCR repertoire, increased T-regulatory activity, and diminished CD8 counts. SS malignant T cells, which have been postulated to derive from a distinct T-cell population, co-express the lymph node–homing molecules CCR7, CD62L, and L-selectin and the central memory T-cell marker CD27. In contrast, T cells isolated from MF lesions lack CCR7/L-selectin, CD103, and CD27 but express CCR4, CD69, and CLA, a phenotype of skin-resident effector memory T cells [220]. WES studies in MF patients have identified multiple clonotypes of TCRγ, TCRα, and TCRβ genes, suggesting that MF malignization occurs in T-lymphocyte progenitors before TCRβ or TCRα rearrangements [221].

Genetic and epigenetic insights. The mutational landscape of advanced MF and the SS obtained by NGS [222–224] identified recurrent genomic alterations, including mutations in the TCR signaling effectors *PLCG1* (9%–21%), *NFATC2*, and *NFAT5*; the NF-κB elements *CARD11* (7%), *GLI3*, or *TNFRSF1B* (4%); and the DNA damage/repair elements *TP53* (18%) and *ATM*. Copy number variations in *DNMT3A* (≤6%), *ARID1A, TRRAP, CTCF, NCOR1, KDM6A, SMARCB1, ZEB1, PRKCB, PTPRN2,* and *RLTPR* were also detected. Copy number variations appeared to be more prevalent than somatic mutations in *TNFAIP3, CSNK1A1,* and several JAK/STAT pathway elements [225,226]. The mutational signature in SS is characterized by a high percentage of >T transitions, a signature associated with UV exposure [227].

Current and new therapeutic strategies. Most patients with MF have an indolent clinical course that is managed with a combination of oral and skin-directed treatments. However, patients with extensive nodal or visceral involvement require systemic immuno- or biomodulatory-based therapies, conventional chemotherapy regimens, and allo-HSCT in selected advanced cases.

Moreover, targeted therapies such as PI3K (duvelisib) and NF-κB inhibitors (bortezomib) are the focus of research, and clinical trials have revealed relatively good tolerance and durable responses. The HDAC inhibitors vorinostat and romidepsin are currently approved in the United States for MF treatment, and resminostat is in phase III clinical trials in Europe. Currently, phase II clinical trials are ongoing for alisertib, an oral Aurora A kinase inhibitor, and cobomarsen, an oligonucleotide inhibitor of miR-155. JAK/STAT inhibitors also represent promising drugs for further clinical development in CTCL [228,229]. The presence of immune evasion-related gene alterations leading to abnormal expression of PD1, PD-L1, and PD-L2 and co-stimulatory elements such as CD28-ICOS have also spurred the investigation of anti-PD1/PD-L1 antibodies for MF and SS patient treatment [230]. In addition, because of the high clonal heterogeneity detected in the tumor populations, targeting of the microenvironment is being considered as an alternative therapeutic opportunity in MF and other CTCLs [221,231].

Other CTCLS distinct from MF AND SS

Additional clinical variants of CTCL have been recognized in the WHO classification, including the indolent primary cutaneous $CD30^+$ lymphoproliferative disorders (LPDs) and the more aggressive cytotoxic CTCL subtypes: extranodal natural killer T-cell lymphoma; primary cutaneous $\gamma\delta$ T-cell lymphoma; primary cutaneous $CD8^+$ aggressive epidermotropic lymphoma (pcAETCL), and the subcutaneous panniculitis-like T-cell lymphoma (SPTCL) [65,232].

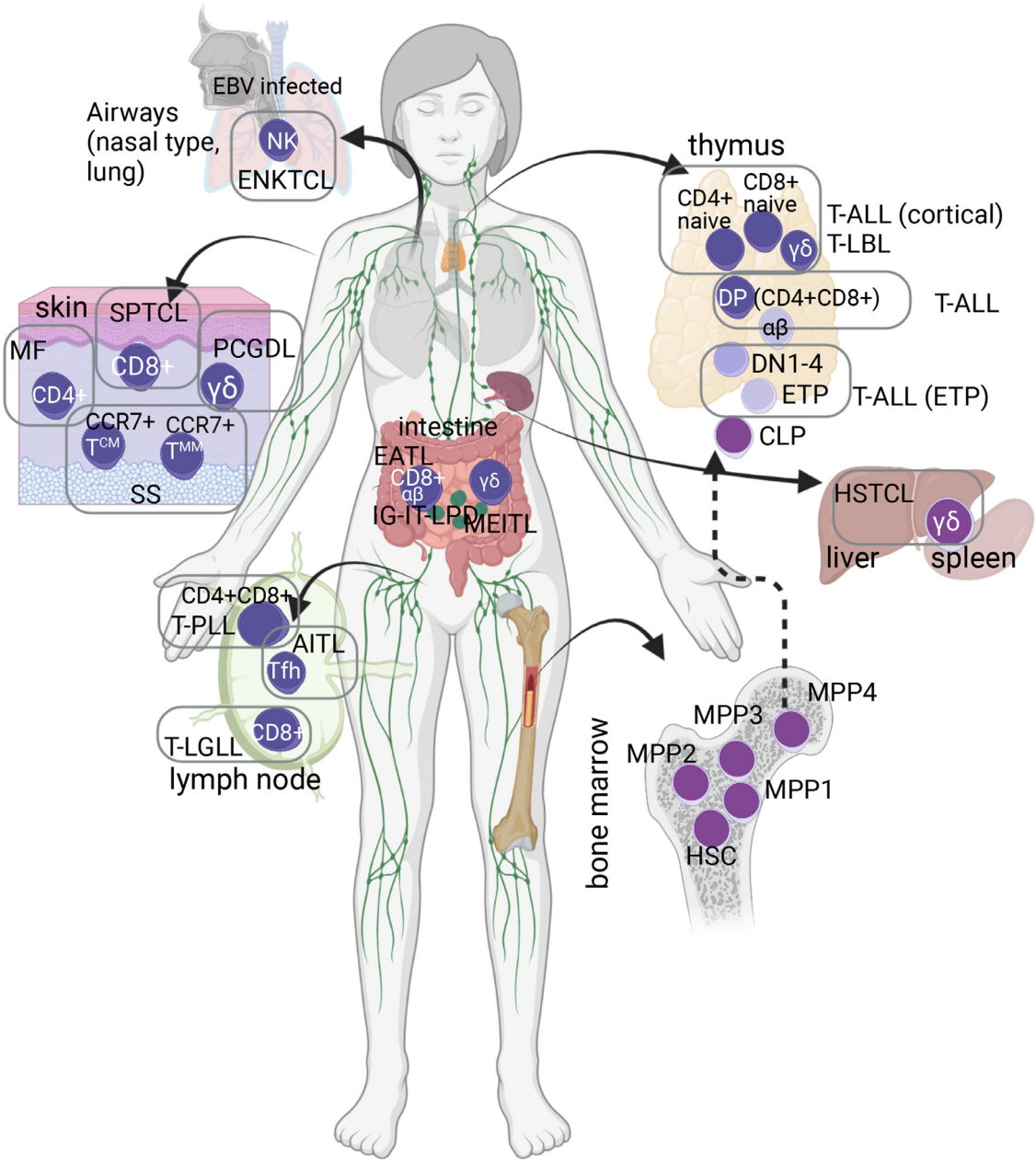

Figure 1 Subtypes of T-cell malignances characterized by the resident tissue of neoplastic cells. The cartoon integrates the different T-cell neoplasms in the affected tissue and represents the most characteristic cell phenotype for disease. AITL = angioimmunoblastic T-cell lymphoma; CLP = common lymphoid progenitor; DP = double positive; EATL = enteropathy-associated T-cell lymphoma; EBV = Epstein–Barr virus; ENKTCL = extranodal natural killer/T-cell lymphoma, nasal type; ETP = early T-cell progenitors; HSC = hematopoietic stem cell; HSTCL = hepatosplenic T-cell lymphoma; IT-LPD = indolent T-cell lymphoproliferative disease of the gastrointestinal track; MEITL = monomorphic epitheliotropic intestinal T-cell lymphoma; MF = mycosis fungoides; MPP = multipotent progenitor; PCGDL = primary cutaneous $\gamma\delta$ T-cell lymphoma; SPTCL = subcutaneous panniculitis-like T-cell lymphoma; SS = Sezary syndrome; T-ALL = T-cell acute lymphoblastic leukemia; T^{CM} = T central memory; Tfh = T follicular helper cells; T^{MM} = T migratory memory; T-LGLL = T-large granular lymphocytic leukemia; T-PLL = T-cell prolymphocytic leukemia.

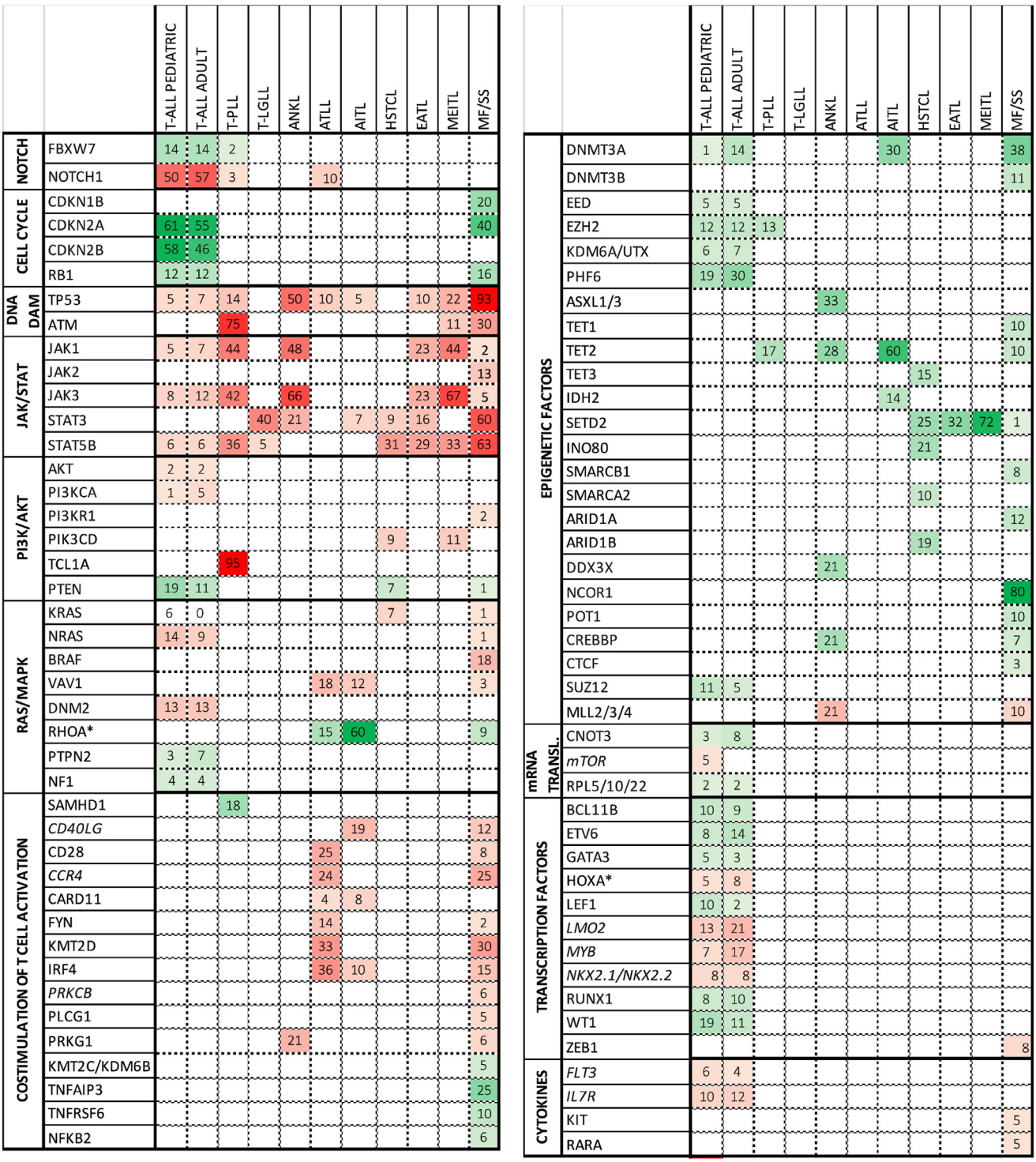

Figure 2 Elements of different pathways and functions altered by mutations, chromosomal rearrangements, deletions, or duplications in the indicated T-cell malignancies. Gain-of-function alterations are in *red*, and loss-of-function alterations are in *green*. Color intensity reflects the maximal incidence found for this alteration. HoxA* = altered expression by CALM-AF10, MLL-ENL, or SET-NUP214; RHOA* = active mutation in G17V and gain of function in ATLL.

Cutaneous CD30+ lymphoproliferative disorders. Cutaneous CD30+ lymphoproliferative disorders (LPDs) comprise two different entities: lymphomatoid papulosis (LyP), a benign lymphoproliferative disease with spontaneously regressing papules, and pcALCL, which is characterized by the presence of isolated or multiple skin tumors with low propensity to disseminate. pcALCL cases have a favorable prognosis and lack the genetic alterations found in systemic ALCL, although 20% carry rearrangements at the *IRF4/DUSP22* locus. NGS technology detected genetic alterations of the JAK/STAT pathway in 50% of $CD30^+$ LPDs, thus uncovering JAK/STAT as a candidate target for novel personalized treatments [233,234].

Subcutaneous panniculitis-like T-cell lymphoma. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare primary cutaneous lymphoma composed of cytotoxic $\alpha\beta$ CD8 T cells that mimics inflammation of the adipose tissue. SPTCL differentiates from the more aggressive primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGDTL). Autoimmune diseases such as lupus erythematosus panniculitis occur in approximately 20% of PCGDTL cases. Most cases have an indolent (good prognosis) clinical course, with 15%–20% of cases developing hemophagocytic syndrome (HPS). Approximately 60%–80% of SPTCL cases contain germline or somatic loss-of-function mutations in TIM-3, an immune response modulator [235]. Additional mutations in SPTCL cells involve epigenetic regulation and signal transduction [236].

Primary cutaneous $\gamma\delta$ T-cell lymphoma. Primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGDTL) usually exhibits systemic symptoms and lymphadenopathy, with features of HPS appearing in 50% of cases. PCGDTL is a poor-prognosis disease with a 5-year OS of 10%. NGS and TCR sequencing indicate that the cell-of-origin of PCGDTL depends on the tissue in which it arises, Vδ1 cells being predominant in epidermis and dermis and Vδ2 cells in the panniculitic lymphomas. Vδ1 and Vδ2 lymphomas exhibit similar targetable mutations in the JAK/STAT, MAPK, MYC, and chromatin editing pathways [237].

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (pcAETCL) is a rare fatal subtype of T-cell NHL with a complex karyotype and clonal evolution that reflects genomic instability. No specific profile of recurrent copy number variations has been reported but gains and losses of 7q, 8q24.3, and 17q and losses of 9p21.3 (*CDKN2A–CDKN2B*) and 17p including the *TP53* gene [238,239].

Primary cutaneous T-cell lymphoma, not otherwise specified. Primary cutaneous T-cell lymphoma, not otherwise specified (pcPTCL-NOS) is an aggressive CTCL showing immunohistochemical heterogeneity that is difficult to distinguish from other CTCL variants [240]. The identification of some cases with mTOR mutations may benefit from targeted therapy [241].

CONCLUSIONS

The heterogeneity of T-cell malignancies parallels the multiple types of specialized T cells and their specific tissue distribution (Figure 1). However, many recurrent hotspot and damaging mutations are shared by CTCL and other T-cell cancers, including ATLL, AITL, PTCL-NOS, and ALCL without ALK, EATL, and ENKTCL (nasal-type) [198,199,223] (summarized in Figure 2). Pathways that are repeatedly altered in the different types of malignancies include the JAK/STAT, PI3K, TCR activation, or NFκB pathways. Mutations in the Notch pathway, which is crucial at different stages of T-cell differentiation, are highly restricted to the leukemic variants. As in many other cancer types, genetic alteration in chromatin regulators such as *TET*, *IDH*, and *DNMT3* are also frequent. Identification of recurrent alterations in CTCL may help in the design of new genetic screening panels for better diagnosis and provide new opportunities for the development or repurposing of therapeutic strategies to fight CTCLs.

Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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