LEADING OPINIONS

Hämatologie & Onkologie

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Grosse und kleine Fortschritte in der Krebstherapie

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2. Schweizer Jahrestagung
New Data in the Molecular Pathology of T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCLs) comprise a heterogeneous group of malignancies derived from mature T- or natural killer (NK) cells, representing less than 10% of all non-Hodgkin lymphomas. With few exceptions, PTCLs are usually aggressive. Recent findings in molecular pathology have led to a significant improvement of disease subtype classification and understanding of cancer signaling.

There are about 30 PTCL entities in the current WHO classification of lymphomas, grouped according to their clinical presentation into predominantly leukemic, or as primarily nodal, extranodal or cutaneous diseases (Table 1).

Novel data derived from high-throughput genomic studies have contributed to refining diagnostic and classification criteria of PTCLs and to a better understanding of their pathogenesis (Figure 1).2 Mutations and copy number variations (CNV) frequently target different classes of epigenetic modifiers, T-cell receptor and co-receptors signaling pathways, and components or regulators of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Although a few variants are characteristic of certain PTCL subtypes, there is an overlap in the mutational landscapes of different entities. Immune evasion has also emerged as another oncogenic mechanism in PTCLs. Programmed cell death-1 ligand-1 (PD-L1) is expressed at variable frequencies in different diseases, suggesting that PD-1 blockade may represent an efficient therapy in some patients; however, because PD-1 also acts as a tumor suppressor which is inactivated in a fraction of PTCLs, PD-1 checkpoint inhibition may also potentially lead to unwanted effects.3 Constitute genetic background may confer susceptibility to PTCL development, as suggested by HLA associations to celiac disease and enteropathy-associated T-cell lymphoma; also demonstrated by the recent finding of germline hepatitis A virus cellular receptor 2 (HAVCR2) mutations altering T-cell immuno-globulin and mucin-domain containing-3 (TIM-3) in subcutaneous panniculitis-like T-cell lymphomas with hemaglobocytic lymphohistiocytic syndrome.4

Cell of origin is a major determinant of PTCL biology. Neoplasms of the innate lymphoid cells (NK, NK-like T- and gamma-delta T-cells) are predominantly extranodal, cytotoxic and – with the exception of T-cell large granular lymphocytic and chronic NK cell leukemias – frequently highly aggressive. Lymphomas of the adaptive immune system (derived from alpha-beta CD4+ or CD8+ T-cells) constitute the majority of PTCLs and often involve lymph nodes. This review will focus on nodal PTCLs.

Nodal lymphomas of T-follicular helper (TFH) derivation

Cell derivation from CD4+ TFH cells is the defining feature of the most prevalent group of nodal lymphomas including angioimmunoblastic T-cell lymphoma (AITL) and related entities (follicular T-cell lymphoma and nodal lymphoma with a TFH phenotype). AITL typically manifests with systemic symptoms and biological abnormalities and consists of a polymorphous infiltrate comprising of TFH neoplastic cells within an abundant polymorphous microenvironment associated with proliferation of veinsides and follicular dendritic cells.5 In addition to sharing a TFH immunophenotype and gene expression signature,6 these lymphomas disclose a rather homogeneous mutational landscape which recapitulates a multi-step oncogenic process. This typically consists of epigenetic deregulation (ten-eleven translocation-2 [TET2] +/- DNA (cytosine-5)-methyltransferase 3A [DNMT3A] mutations, often occurring at early stages in hematopoietic progenitors),7,8 and second hit mutations including a hotspot Ras homolog gene family, member A (RHOA)G17V mutation in up to 80% of cases and other gain-of-function mutations targeting the T-cell receptor signaling pathway (phospholipase C, gamma 1 [PLCG1], CD28, PIK3 components, caspase recruitment domain-containing protein 11 [CARD11], ...).9, 10 Moreover, fusions involving spleen tyrosine kinase (SYK) and interleukin-2-inducible T-cell kinase (ITK), CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or CD28 and inducible T-cell co-stimulator (ICOS) are detected at lower frequency.11 Dihydrate dehydrogenase 2 (IDH2) mutations at the R172 residue resulting in production of an oncometabol...
Mature T-cell neoplasms

Challenges and novelties

Angiogenic/immunostimulatory T-cell lymphoma

Lymphoma of TFH, the prototypic and largest entity in the spectrum of nodal lymphomas of TFI origin, is an umbrella category which encompasses follicular T-cell lymphoma and nodal peripheral T-cell lymphoma with TFH phenotype.

Follicular T-cell lymphoma

Formerly classified as a variant of PTCL-NOS, now classified as an entity in the spectrum of nodal TFH lymphomas.

Nodal peripheral T-cell lymphoma with TFH phenotype

Formerly not identified as an entity and included in PTCL-NOS.

Anaplastic large cell lymphoma, ALK-negative

Formerly provisional, now a definitive entity. Genetic subsets (DUSP22 rearrangements, TP63 translocations) with distinctive molecular and 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.

Extranodal

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Monomorphic epithelioid intestinal T-cell lymphoma

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 immunophenotypic may be encountered; some cases may progress to overt lymphomas.

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; no translocations.

Note: There are in present about one third of TFF cases. Transgenic mouse models with expression of RIG-I/STING in the T-cell compartment demonstrated the role of RIG-I/STING in T-cell development and in THF differentiation and in inducing autostimulatory T-cell IFN-γ. However, additional TFE3 inactivation is required for lymphoma development, and these mouse tumors are dependent on ICOS/PISK mechanism of target rapamycin (MTOR) signaling.

Anaplastic large cell lymphoma (ALCLs)

ALCLs have in common a large-cell anaplastic morphology, strong CD30 expression, and frequent phospho-STAT3 activation. Systemic cases (anaplastic lymphoma kinase (ALK)-positive and ALK-negative) represent 15–20% of non-c cutaneous PTCLs. In ALK-negative ALCL, which occurs mainly in children or young adults and has an excellent overall prognosis, ALK fusion proteins resulting from the fusion of ALK to various gene partners, most frequently nucleophosmin (NPM), drive lymphomagenesiathrough several mechanisms, among which activation of STAT3 plays a prominent role. ALK-negative ALCL also includes T-cell larger individuals and encompasses clinical and genetic heterogeneity. Those with rearrangement of the dual specificity phosphatase 22 (DUSP22) locus at 16q22.1 represent 8% of the cases) have unique molecular features – lack of STAT3 activation, DNA hypomethylation and an immunophenotypic type (CD42–) – and frequently harbor a hotspot M33C3C mutation in the musculus gene, which drives cell cycle progression, and can be targeted by brentuximab-vedotin and extra- terminal motif (BET) protein inhibitors. DUSP22-rearranged ALCLs have been reported to usually have a good outcome, but this was not confirmed in a recent study. The small subset of ALK-negative ALCL with tumor protein 63 (TP63) rearrangements (2–4% of the cases) has a very poor outcome. In addition, a subpopulation of ALK-negative ALCL has STAT3 activation resulting from rearrangements of other tyrosine kinase genes (non-exzept tyrosine-protein kinases as ITK, ROS1, and its related family tyrosine kinase (EKR1) and/or JAK and/or STAT3). Downregulation Wiskott-Aldrich syndrome protein (WASP) was recently identified as another oncogenic pathway in ALCLs, which could be exploited as a therapeutic vulnerability by increasing mitogen-activated protein kinase (MAPK) activation. Breast implant-associated (BIA)-ALCL is a peculiar form of ALK-negative ALCL occurring as a rare complication of breast implants. Most cases confirmed so far the paracrine effusion and capsule (seroma or a "fat nodule" lymphoma) have excellent outcomes; a minority of patients present with a tumor mass, which is an adverse prognostic factor. BIA-ALCL does not harbor recurrent translocations found in other ALK-negative ALCL. Conversely, activation of STAT3 is common and recurrent mutations of STAT3 or, less commonly, JAK1 or suppressor of cytokine signaling 1 (SOCS1) have been reported. Chronic inflammation elicited by silicone-derived products or bacteria adherent to the prosthesis (in particular, Bakersian pickett) likely play a role in triggering polyclonal lymphocyte activation, proliferation and expansion through the release of cytokines like interleukin (IL) 6 and 10. Suppression genetic alterations would represent an additional step in the transformation process to a malignant monoclonal proliferation.

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

PTCL-NOS is a heterogeneous group of cases not fulfilling the criteria for more specific PTCL entities. Some cases are associated with infection by the Epstein-Barr virus (EBV). Gene expression profiling has unraveled molecular subgroups with differential expression of cytokine signature 1, a lymphoid progenitor signature 2 and TH1-like associated transcription factors (TF-Box transcription factor (TFX) and GATA3, respectively) and their associated target genes. GATA3-positive PTCL-NOS and those with a cytotoxic phenotype were associated with a worse outcome in comparison to TFX-positive or non-cytotoxic lymphomas. Genetically, PTCL-GATA3 exhibit greater genomic complexity with frequent loss or mutation of tumor suppressors genes targeting the cyclin-dependent kinase Inhibitor 2A/B (CD274/273) and phosphatase and tensin homolog (phosphatase and tensin homolog) 3-kineses (PTEN/P38K) pathway. The PTCL-TGB subgroup has fewer CNVs, and is enriched in mutations of genes regulating DNA methylation. Loss of CDKN2A is a factor of adverse prognostic in PTCL-NOS in general and in the GATA3 subgroup.

Figure 5: Overview of the main nodal TPTCL entities. TCR, T-cell receptor

Table 1: Main nodal and extranodal mature T-cell neoplasms according to the 2017 WHO classification of lymphomas (adapted from 3, with summary of changes and novelties in comparison to the previous edition).

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<th>Clinical features</th>
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Literature:
1. IARC. WHO classification of tumours of the haematopoietic and lymphoid tissues (Revised 4th edition). Lyon 2017