T-cell lymphomas of follicular helper T-cell derivation: pathology, mechanisms and therapeutic implications

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Lymphomas derived from CD4+ follicular helper T-cells (TFH cells) represent the largest group of nodal T-cell lymphomas. They comprise three entities, namely angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma (F-TCL) and nodal lymphoma with a TFH phenotype (PTCL-TFH). AITL typically manifests with systemic symptoms and biological abnormalities and consists of a polymorphous infiltrate comprising a usually small population of TFH neoplastic cells within an abundant polymorphous microenvironment associated to proliferation of veinules and follicular dendritic cells. F-TCL and PTCL-TFH usually lack a prominent microenvironment. F-TCL shows a nodular pattern of growth reminiscent of follicular lymphoma or progressive transformation of germinal centers, and PTCL-TFH may feature an interfollicular "T-zone" patter. In addition to sharing a TFH immunophenotype and gene expression signature, the three TFH lymphomas disclose a homogeneous mutational landscape which recapitulates a multi-step oncogenic process. This typically consists of epigenetic deregulation (*TET2 +/- DNMT3A* inactivating mutations, often occurring at early stages in hematopoietic progenitors), and second-hit mutations including a hotspot *RHOA*^{G17V} mutation (50-80% of cases) or other gain-of-function mutations targeting the TCR signaling pathway (*PLCG1, CD28, PIK3* components, C*ARD11*…). Moreover, fusions involving *SYK* and *ITK, CD28* and *CTLA4* or *CD28* and *ICOS* are detected at lower frequency and *IDH2*^{R172} mutations resulting in production of an oncometabolite are found in 25-30% of AITLs. The prognostic impact of the variations in the mutational landscape appears limited. Transgenic mouse models with expression of *RHOA*^{G17V} in the T-cell compartment demonstrated the role of RHOA^{G17V} in TFH differentiation, and in inducing autoimmunity. However, additional TET2 inactivation is required for lymphoma development, and these mouse tumors are dependent on ICOS/PIK3/MTOR signaling. In humans there is now evidence that AITL emerges in a background of *TET2* and/or *DNMT3* mutated clonal hematopoiesis, a scenario which explains the co-occurrence of AITL and myeloid neoplasms in some patients. Our current understanding of TFH lymphomas pathogenesis supports therapeutical targeting epigenetic changes in these diseases, and promising results have been yet reported with the use of hypomethalyting agents (5-azacytidine) or histone deacetylase inhibitors in relapsed/refractory patients.