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Nodal peripheral T-cell lymphomas correspond to distinct mature T-cell populations

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Peripheral T-cell lymphomas (PTCL) derive from mature T-cells, but previous attempts to correlate PTCL with normal T-cell counterparts have not significantly contributed to our understanding of their biology.

Recently, reactive T-cells have been shown to sequentially change their surface molecule expression in response to antigens. These are independent of differentiation and apply equally to T_H1 and T_H2 cells, $CD4^+$ and $CD8^+$ subsets, and even to αβ and γδ T-cells.

Mature naïve T-cells continuously circulate through the blood and lymphoid organs. They are directed by lymphoid chemokines and the respective chemokine receptors expressed on the T-cell surface. Naïve T-cells express CD45RA, but not CD45R0.

The differentiation process depends on the stimulation characteristics. If stimulated with a sub-threshold amount of antigen or in the absence of polarizing cytokines, such as IL-4 or IL-12, naïve T-cells proliferate and develop into so-called central memory cells (TCM). These antigen experienced $CD45RA^-/CD45R0^+$ clonally expanded memory cells continually express CD27 and CCR7, which enables them to traffic to the T-cell areas of the lymph nodes where they may be further stimulated by professional antigen-presenting cells.[1] Following a secondary antigen challenge, TCM can activate dendritic cells, help antigen-specific B-cells, or generate a new wave of effector cells. Comparable to memory B-cells, these TCM cells represent *memory stem cells* that have the ability for both self-renewal and differentiation to effector cells.[1]

T-cells can differentiate directly to effector cells, which later undergo apoptosis or develop into effector memory cells (T_{EM}), when stimulated via their T-cell receptors in the presence of appropriate co-stimulation. T_{EM} are characterized by a lack of CD27 and CCR7 expression. Therefore, they do not recirculate to the lymph nodes, but exit the blood stream at sites of inflammation.

We investigated the expression of the antigen receptor and co-receptor molecules CD3, CD4, and CD8, and the differentiation markers CD45RA, CD45-R0, and CD27 using double and triple immunofluorescence in combination with antibodies against their respective TCRVβ segment to detect the tumor cells.[2] In addition to CCR7, which has been discussed above, we also investigated the chemokine receptors, CXCR3, and CCR4, which are related to TH1 and TH2 differentiation, and the activation-associated molecules, CD28, CTLA-4, CD69, HLA-DR, FAS, CD25, CD30, and BCL-2 using the same method. Cytotoxic features were assessed with antibodies against TIA-1, Granzyme B, perforin, and FAS-ligand. The same antigens were stained in 15 ($10\ ALK1^+$ and $5\ ALK1^-$) ALCL.

The cluster analysis revealed three distinct clusters and three unrelated cases. Our previous data suggested that the tumor cell phenotype may be masked by reactive T-cells in most cases of PTCL.[3,4] Therefore, we examined the surface molecule expression of the neoplastic cells in double and triple stained samples in order to identify the tumor cells with antibodies directed against the respective clonally rearranged TCR's Vβ segment.

All the AILT cases expressed CD4 to a varying extent or were double negative for both CD4 and CD8.[4] The AILT cases exhibited a homogeneous phenotype with respect to their stage of differentiation ($CD45R0^+/CD45RA^-/CD27^-$) that was characteristic of terminally differentiated effector or effector-memory T-cells. The absence of BCL-2 in these tumors suggests that they represent an effector population. AILT cases were

consistently negative for the chemokine receptor CCR7. CCR7$^-$ T-cells are unable to exit the blood stream via high endothelial venules in the lymph nodes due to the absence of CCR7, but do exit at sites of inflamed peripheral tissues. Based on cytokine receptor expression, AILT, which expressed the chemokine receptor CXCR3, but not CCR4, correlated with TH1 cells, which was suggested previously in studies addressing chemokine receptors and activation markers in PTCL. Our investigations do not allow to speculate about a possible correlation of AILT to so-called germinal center T-helper cells, although these tumors are generally negative for CD57[4], one of the defining markers of this T-cell population.

All five CD4$^+$ cases within PTCL-NOS clustered together. They differed from AILT in the expression of CD27, suggesting a different developmental stage. These tumors also expressed CCR7 in 4 of the 5 cases and all were BCL-2 positive. This suggests long-lived antigen-experienced T-cells that are able to recirculate to lymph nodes, that is T_{CM} cells. Therefore, a group may emerge within PTCL-NOS that is characterized by a homogeneous phenotype and corresponds to the TCM subset of antigen-experienced T-cells.

Since six of the fifteen ALCL cases analyzed expressed neither CD45RA nor CD45R0, which is unusual for reactive T-cells, the assignment of ALCL to distinct stages of development was more difficult. However, ALCL cases probably correlate to antigen-experienced T-cells because nine cases expressed the CD45R0 isoform (60%). Their consistent negativity for CD27 and rare expression of BCL-2 (20%) suggested an effector population similar to the AILT cases. Interestingly, activation markers were differentially expressed. Compared to the AILT cases, cytokine receptor expression was more heterogeneous in the ALCL cases. Most of the ALCL tumors (60%) expressed CXCR3, three coexpressed CCR4, and six showed no expression of either molecule. ALCL lack TCRs and molecules of the TCR signaling pathway, both proximally[5] and distally. Therefore, they cannot be activated via their TCR complex. Future studies are needed to clarify whether these tumors correspond to a distinct stage of T-cell development or merely share a lack of functional TCR signaling.

In summary, the differential expression of CD45 isoforms and CD27 may define the differentiation stage of tumor cells in PTCL. The scheme derived from studies on reactive T-cells seems applicable to PTCL. This scheme defines AILT as tumors with a distinct differentiation stage of effector CD4$^+$ T-cells and separates them from PTCL-NOS cases. Among the latter, a homogeneous cluster was derived from antigen-experienced CD4$^+$ central memory T-cells.

References

1. Sallusto F, Geginat J, Lanzavecchia A. Central memory and effector memory T cell subsets: function, generation, and maintenance. Annu Rev Immunol 2004;22:745-63.
2. Geissinger E, Bonzheim I, Krenacs L, et al. Identification of the tumor cells in peripheral T-cell lymphomas by combined polymerase chain reaction-based T-cell receptor beta spectrotyping and immunohistological detection with T-cell receptor beta chain variable region segment-specific antibodies. J Mol Diagn 2005;7:455-64.
3. Geissinger E, Odenwald T, Lee SS, et al. Nodal peripheral T-cell lymphomas and, in particular, their lymphoepithelioid (Lennert's) variant are often derived from CD8+ cytotoxic T-cells. Virchows Arch 2004;445:334-43.
4. Lee SS, Rüdiger T, Odenwald T, Roth S, Starostik P, Müller-Hermelink HK. Angioimmunoblastic T cell lymphoma is derived from mature T-helper cells with varying expression and loss of detectable CD4. Int J Cancer 2003;103:12-20.
5. Bonzheim I, Geissinger E, Roth S, et al. Anaplastic Large Cell Lymphomas lack the expression of T-cell receptor molecules or molecules of proximal T-cell receptor signaling. Blood 2004;104:3358-60.