[haematologica reports]
2006;2(7):66-67

Gene expression analysis of peripheral T-cell lymphoma not otherwise specified reveals two distinct subgroups and recurrent PDGFR-alpha deregulation

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Peripheral T-cell lymphomas (PTCLs) represent approximately 12% of lymphoid neoplasms.[1] Their incidence varies in different countries and races, being higher in HTLV-1 endemic areas (Asia, Caribbean basin and some parts of the United States).[2] PTCLs are a heterogeneous group of tumours that in the REAL/WHO Classification are roughly subdivided into specified and unspecified (or not otherwise specified, NOS) forms.[1,3] In particular, the latter – corresponding to about 50% of T-cell lymphomas – cannot be further classified on the basis of morphology, phenotype and conventional molecular studies. Immunohistochemistry does generally show T-cell associated molecule expression, although the phenotypic profile is aberrant in about 80% of cases, CD5 and CD7 being the most frequently defective antigens.[4] The nodal cases are more often $CD4^+$, whereas the extra-nodal ones frequently carry CD8. However, the latter two antigens are co-expressed or even not expressed in some instances (double-positive and double-negative cases, respectively). Clonal rearrangements of T-cell receptor encoding genes are generally detected.[5] The karyotype is aberrant in more than 80% of cases and often characterized by complex abnormalities.[6] However, specific alterations have not been identified. Recently, some recurrent lesions have been documented by comparative genomic hybridization such as deletions at 13q, 6q, 9q, 10q, 12q and 5q, and gains at 7q, 17q, 16q, 8q, 9q, 3p, 1q, 11q.[7] The molecular patho-biology of PTCLs/NOS, as in general of all T-cell neoplasms, is poorly understood. In particular, only few studies deal with their gene expression profile.[8-10] On clinical grounds, PTCLs/NOS are among the most aggressive non-Hodgkin lymphomas (NHL).[11-13] Their response to conventional chemotherapy is indeed frustrating, with relapse free and overall survival rates at five years of 26% and 20%, respectively. Neither the morphology nor the international prognostic index (IPI) significantly correlates with the outcome. A new mixed clinico-biological score has recently been reported.[4]

Using gene expression profiling, we show that PTCL/NOS displays a gene expression pattern which is clearly distinct from that of normal T-cells and other lymphoid malignancies. Comparison with the profiles of purified normal T-cell subpopulations [$CD4^+$, $CD8^+$, resting (HLA-DR-), and activated ($HLA\text{-}DR^+$)] reveals that PTCLs/NOS are more related to activated peripheral T-lymphocytes, either $CD4^+$ or $CD8^+$. Interestingly, the global gene expression profile cannot be surrogated by the immunohistochemical determination of CD4 and CD8 in routine sections. When compared with normal T-cells, PTCLs/NOS display deregulation of functional programs often involved in tumorigenesis (e.g. apoptosis, proliferation, cell adhesion, and matrix remodelling). Several genes are specifically expressed in PTCLs/NOS, whose products can be detected by immunohistochemistry with an ectopic, paraphysiologic or stromal location. Among others, PTCLs/NOS aberrantly express CYR61, a molecule involved in drug resistance, and PDGFRα, a tyrosine kinase receptor whose deregulation is often related to a malignant phenotype. Notably, both phosphorylation of PDGFRα and sensitivity of cultured PTCL cells to imatinib-mesylate and other tyrosine-kinase inhibitors are found. These results are provided with biological implications relevant to the tumour pathogenesis and clinical management.

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