efficacy and toxicity, with more deaths due to infection on CHOP than Ld-CHOP (31% vs 18%). However, this hypothesis needs to be confirmed by competing risk analysis of the cause of death. If death due to infection on CHOP was early in the course of the trial, while subjects were on therapy and their absolute neutrophil count (ANC) was depressed, then the subject could not die due to lymphoma.

To the editor:

Analysis of the CD95 ligand gene in 20 children with autoimmune lymphoproliferative syndrome (ALPS)

The autoimmune lymphoproliferative syndrome (ALPS) is a rare disease caused by an impaired CD95-mediated apoptosis. ALPS is divided into 4 subgroups (type 0 to type III) according to the underlying defect of different CD95 pathway genes: type 0 disease is caused by homozygous mutations of the CD95 gene; type II by mutations of the caspase 10 gene. In contrast to the other subgroups, ALPS type III is characterized neither by in vitro resistance to CD95-mediated apoptosis nor by a known genetic defect. The etiology of ALPS type III is still unclear. Collectively, it is known that most ALPS cases are due to heterozygous mutations of the CD95 gene (ALPS type Ia). In 1996, a heterozygous mutation of the CD95 ligand (CD95L) in a single patient with ALPS and systemic lupus erythematosus (SLE) was detected and classified as ALPS type Ib. Very recently, a novel homozygous mutation in the CD95L has been discovered in a second patient with ALPS. Due to their findings, Del-Rey et al propose expanding the classification to include ALPS type Ic for this gene. However, there are no data on the frequency of this mutation in such a large group, we doubt if the finding by Del-Rey et al represents a novel ALPS subgroup beyond their single-case description. Therefore, the definition of 2 ALPS subgroups (Ib and Ic) based on only 2 single cases seems disputable. Moreover, the role of CD95L mutations for the pathogenesis of lymphoproliferative and autoimmune diseases might be overstated.

Table 1. CD95L mutations in lymphoproliferative diseases and healthy controls

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of cases</th>
<th>Mutation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPS</td>
<td>20</td>
<td>0</td>
<td>Own data</td>
</tr>
<tr>
<td>T-ALL</td>
<td>24</td>
<td>0</td>
<td>Own data</td>
</tr>
<tr>
<td>B-ALL</td>
<td>21</td>
<td>0</td>
<td>Own data</td>
</tr>
<tr>
<td>Controls</td>
<td>64</td>
<td>0</td>
<td>Own data</td>
</tr>
<tr>
<td>SLE</td>
<td>143</td>
<td>0</td>
<td>Kojima et al</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>111</td>
<td>1</td>
<td>Kim et al</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>70</td>
<td>0</td>
<td>Bolstad et al</td>
</tr>
</tbody>
</table>

Although the murine gld phenotype (CD95L mutation) might correspond to the report of the ALPS type Ib patient, systematic analyses to determine the frequency of CD95L mutations have challenged the impact of such mutations for the pathogenesis of lymphoproliferative and autoimmune diseases. When we analyzed the CD95L gene from 21 children with B-lineage acute lymphocytic leukemia (B-ALL) and 24 children with T-lineage ALL (T-ALL), we did not observe any genomic alteration. Accordingly, other groups did not detect any relevant mutation of the CD95L gene in different lymphoproliferative and autoimmune disorders, such as non-Hodgkin lymphoma, SLE, and Sjögren syndrome (Table 1). Therefore, we consider the CD95L gene to be of remarkable genomic stability and question its outstanding role in the pathogenesis of the disorders described above.

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E.P. and B.F. contributed equally to this work.

References

Response:

The A247E mutation in human FASL gene and the classification of autoimmune lymphoproliferative syndrome (ALPS)

Pauly et al question the role of the A247E mutation in FASL gene, recently described by us in a patient with autoimmune lymphoproliferative syndrome (ALPS),\(^1\) in the pathogenesis of the disease. The work of Pauly et al includes a valuable search of FASL mutations in groups of ALPS, B-lineage acute lymphocytic leukemia (B-ALL), and T-ALL patients and healthy individuals. As the authors do not find any mutation, they conclude that FASL gene defects are of minor importance in the pathogenesis of ALPS. Besides, they declare that data on the frequency of the A247E mutation are not available.

The absence of FASL mutations in the group of 20 ALPS patients does not necessarily imply that defects in that gene do not participate in the pathogenesis of the disease. To clarify this question, it would be essential to analyze a broad series of patients who completely fulfill the ALPS criteria as well as those with milder or related phenotypes. Patients with different genetic backgrounds should be studied, since some genetic defects arise and accumulate in human groups with a common ethnic origin, whereas they are undetectable in other populations.

Regarding frequency of the A247E mutation, in our paper\(^1\) we analyzed a total of 155 individuals: 104 race-matched healthy donors and 51 race-matched patients with systemic lupus erythematosus (SLE), as SLE was the clinical phenotype associated with the first human FASL mutation described. We did not find the A247E mutation in the FASL gene in any of the individuals tested, and in the “Abstract” we stated that “FASL abnormalities cause an uncommon apoptosis defect.”\(^1\)

It should also be taken into account that, at present, unidentified genes, not only the genes that Pauly et al’s group has tested (CD95, FASL, FADD, and CASP10), code for proteins that participate in a cascade of events that finally result in apoptosis. Consequently, while the causative genetic defect for the ALPS patients studied remains unknown, they should be classified as ALPS type III.

Finally, ALPS categorization takes into account the genes mutated as well as homozygosity or heterozygosity (type 0, homozygous FAS mutation; type Ia, heterozygous FAS mutation; type Ib, heterozygous FAS deletion; etc). In this sense, the new homozygous FASL mutation found by Del-Rey et al\(^1\) together with the indistinguishable clinical ALPS phenotype in comparison with ALPS type Ia patients argue for this case to be included as a new ALPS type Ic subgroup. Other primary immunodeficiencies referred to in a single reported case, such as CD8 deficiency,\(^2\) are included as individual conditions in the Classification of Primary Immunodeficiency Diseases.\(^3\)

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References


To the editor:

Subtype preference of the BCL6\(^{397G/C}\) polymorphism in germinal-center and non–germinal-center subtypes of diffuse large B-cell lymphoma

The BCL6 gene encodes a POZ/Zinc finger sequence–specific transcription inhibitor important for T- and B-cell maturation, cell-cycle control, apoptosis, and inflammation. Recent studies indicate that high BCL6 expression correlates with good prognosis for diffuse large B-cell lymphoma (DLBCL) patients.\(^1,2\) Moreover, mutations and polymorphisms, such as the BCL6\(^{397G/C}\) polymorphism, in the 5’ regulatory region of the BCL6 gene have been suggested to increase BCL6 expression and to be involved in lymphoma progression and transformation from follicular lymphoma (FL) to diffuse large B-cell lymphoma.\(^3,5\) whereas no correlation was evident for de novo DLBCL.\(^6\) DLBCL can now be classified into 2 major subgroups: one derived from germinal-center B cells, the GC subtype, often with a high expression of BCL6, and one derived from B cells, often with a lower expression of BCL6, the non-GC subtype.\(^1,2\)

To investigate the impact of the BCL6\(^{397G/C}\) polymorphism, we screened 120 de novo DLBCLs from Uppsala and Umeå University Hospitals regarding their BCL6\(^{397G/C}\) genotype and compared the allele and genotype frequencies with samples from 230 healthy donors. Subclassification into GC and non-GC DLBCL according to Hans et al\(^1\) was available for all 120 tumors.

In the present material, the frequency of the BCL6\(^{397G}\) allele did not differ significantly in our DLBCL patients compared with the control group, which is in accordance with previous data.\(^6\) Furthermore, we did not find any difference in overall survival between patients with the BCL6\(^{397GG}\) genotype and BCL6\(^{397G/C/C}\) genotypes.
Analysis of the CD95 ligand gene in 20 children with autoimmune lymphoproliferative syndrome (ALPS)

Eva Pauly, Benedikt Fritzsching, Markus Dechant, Joerg Fellenberg, Christian Gerold Scheuerpflug and Klaus-Michael Debatin