Presence of N regions in the clonotypic DJ rearrangements of the immunoglobulin heavy-chain genes indicates an exquisitely short latency in t(4;11)-positive infant acute lymphoblastic leukemia

Karin Fasching, Simon Panzer, Oskar A. Haas, Arndt Borkhardt, Rolf Marschalek, Frank Griesinger, and E. Renate Panzer-Grümayr

Childhood acute lymphoblastic leukemia (ALL) is frequently initiated in utero at a time of developmentally regulated insertion of N regions into the DJH rearrangements of immunoglobulin heavy-chain (IgH) genes. Here it is shown that N regions are present in the clonotypic DJH rearrangements in 11 of 12 infant ALLs with t(4;11). These data are compared with the 122 previously published DJH sequences and were found to have a pattern similar to that of ALL in children older than 3 years at diagnosis but were unlike that in children younger than 3 years who predominantly lack N regions. These findings, therefore, indicate that t(4;11)-positive infant ALL is initiated later in fetal development than most B-cell precursor ALL from children younger than 3 years and that they have a shorter latency period already in utero. (Blood. 2001;98:2272-2274)

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BCP ALL and their ages at diagnosis...

...common as in children older than 3 years.15,18,19 Figure 1 illustrates the use of D H and J H families, similar to that reported previously.16,18,19

The results from this study indicate that most DJ H regions from t(4;11) infant leukemias. There are 2 groups of BCP ALL that have N regions in their clonotypic DJ H junctions, namely t(4;11) infant ALL with a manifestation mostly in the first year of life and other leukemias with a clinical manifestation after the 3rd year of life.18,19 Both rearrange their DJ H segments at a similar time during gestational development. It is obvious, however, that t(4;11) ALL has a remarkably shorter latency than the others.

Results and discussion

We identified 16 Ig H rearrangements in 13 infants with t(4;11) ALL (Figure 1A). Ten leukemias had 1 rearrangement, and 3 leukemias (patients 4, 8, 10) had 2 rearrangements. We considered only 1 of the 2 rearrangements (in patients 4 and 10) because they had identical DJ H regions. We excluded the DJ H rearrangement in patient 1 because the sequence between DJ H and J H was homologous to the J1 pseudogene. Thus, 13 unique rearrangements were analyzed for the inclusion of N regions. We observed in patient 4 a D-D fusion, but only the DJ H gene segment most proximal to the J H region was included in the analysis. As depicted in Figure 1, only 1 of the 13 unique sequences lacked N nucleotides at the DJ H junction.

Table 1. Occurrence of N regions between the DJ H junction of children with BCP ALL and their ages at diagnosis

<table>
<thead>
<tr>
<th>Age at diagnosis (y)</th>
<th>No. of ALLs</th>
<th>N + n</th>
<th>N - n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 1 year</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>This study</td>
</tr>
<tr>
<td>Younger than 3 years</td>
<td>16</td>
<td>2</td>
<td>18</td>
<td>Wassermann et al16</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>Steenbergen et al13</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>4</td>
<td>12</td>
<td>Schneider et al15</td>
</tr>
<tr>
<td>Older than 3 years</td>
<td>46</td>
<td>41</td>
<td>10</td>
<td>Wassermann et al18</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>35</td>
<td>12</td>
<td>Steenbergen et al13</td>
</tr>
</tbody>
</table>

The data from this study indicate that most DJ H regions from infant ALL with t(4;11) contain N nucleotides that lack N regions at the DJ H junction.13,18,19 Figure 1 illustrates the use of D H and J H families, similar to that reported previously.16,18,19

The data from this study indicate that most DJ H regions from infant ALL with t(4;11) contain N nucleotides that developed at a time of TdT activity; hence, they were more mature than those without N regions. Interestingly, other leukemias, diagnosed in children before the age of 3, do not have N regions in their DJ H junctions15,18,19 and thus have a longer latency period than the t(4;11) infant leukemias. There are 2 groups of BCP ALL that have N regions in their clonotypic DJ H junctions, namely t(4;11) infant ALL with a manifestation mostly in the first year of life and other leukemias with a clinical manifestation after the 3rd year of life.18,19 Both rearrange their DJ H segments at a similar time during gestational development. It is obvious, however, that t(4;11) ALL has a remarkably shorter latency than the others.

We propose a model for the relation between the time of initiation of the leukemia, characterized by the clonotypic DJ H rearrangements, and the age of the children at clinical manifestation of BCP ALL (Figure 2). Ig H rearrangements that lack N regions occur during a narrow time window—the first weeks of B lymphopoiesis in fetal liver that is TdT negative. Transformed cells with such rearrangements most likely acquire additional mutations, leading to leukemias during the first 3 years of life. Ig H rearrangements with the addition of N nucleotides in the DJ H junction occur later in gestation, when TdT has already been activated. These leukemias become clinically apparent during the first year of life if a t(4;11) chromosomal translocation started leukemogenesis or, in its absence, after the 3rd year of life. Alternatively, the (t;4;11) translocation arises in a TdT-negative primitive cell without Ig H rearrangements. This target cell may represent a B-plus myeloid lymphoid stem cell, as described by Cumano et al20 in mouse fetal liver, which would be unique in specific stages of in utero hematopoiesis. The N region–positive DJ H rearrangement may be a later addition during progression to leukemia. Then, unrelated rearrangements are expected, such as in t(9;22) B lymphoid blast crisis of chronic myeloid leukemia.16 However, in our series, no leukemia had multiple unrelated Ig H rearrangements, but 2 leukemias had related rearrangements. In addition, the target cell for the t(4;11) translocation may be a rare progenitor with TdT expression at earlier stages of fetal lymphopoiesis than common B precursor cells. No such cells have been identified thus far in humans.

Figure 2. Time frame. Development of N- and N+ BCP leukemias in childhood.
It is assumed that a chromosomal translocation is an initiating event in leukemogenesis,9,21 which can be induced by apoptotic stimuli that lead to the generation of gene fusions in B precursor cells, thus rescuing a cell programmed to die.22 This assumption is supported by the findings that most IgH rearrangements in ALL are either incomplete or not potentially productive,16 underlying the immaturity of these cells, which would not survive without a transformation. It is further hypothesized that additional mutations are required for the development of leukemia. However, our findings support the hypothesis that the t(4;11) is either sufficient for leukemogenesis or provokes efficiently further changes that lead eventually to leukemia in infancy.1,11

Acknowledgment

This article is dedicated to Helmut Gadner for his 60th birthday.

References

22. Stanulla M, Wang J, Chernivska DS, Thandla S, Aplan PD. DNA cleavage within the MLL breakpoint cluster region is a specific event which occurs as part of higher-order chromatin fragmentation during the initial stages of apoptosis. Mol Cell Biol. 1997;17:4070-4079.
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