
Bone Marrow Transplantation

Elevated thrombopoietin levels and alterations in the sequence of its receptor, c-Mpl, in patients with Diamond-Blackfan anemia

In the study of the possible thrombopoietin (TPO)-c-Mpl pathway involvement in the pathogenesis of Diamond-Blackfan anemia, repeatedly increased serum TPO levels were identified in 7/14 patients and changes in c-mpl sequence in 3/14 patients. While elevated TPO levels can represent a compensatory mechanism for impaired erythropoiesis, c-Mpl mutations could influence the disease severity.

Thrombopoietin (TPO) is the major stimulator of megakaryopoiesis and platelet production. Besides its function in megakaryopoiesis, TPO and its receptor c-Mpl are also involved in the production of progenitors of other hematopoietic lineages. TPO acts synergistically with erythropoietin, greatly expanding the number of erythroid progenitors in vitro, as well as in mice after myelosuppressive therapy. Its plasma level is inversely correlated to the mass of megakaryocytes and platelets, which degrade TPO following its binding to c-Mpl.

Diamond-Blackfan anemia (DBA) is a congenital red cell aplasia characterized by normochromic macrocytic anemia, reticulocytopenia, normocellular bone marrow with a selective deficiency of erythroid precursors, normal or slightly decreased leukocyte count, and normal or slightly increased platelet count. To elucidate the possible role of the TPO-c-Mpl pathway in the pathogenesis of DBA we measured TPO serum levels and screened c-mpl for mutations in these DBA patients.

In 7/14 (50%) of DBA patients, serum TPO levels were repeatedly higher than in age-matched controls (Table 1). Two of three patients with a mutation in RPS19 also showed elevated TPO levels. Interestingly, all patients had normal or slightly changed platelet counts, indicating that the general TPO level control mechanism may be altered in DBA patients and/or the increase in the TPO level may represent a compensatory mechanism for the promotion of their impaired erythropoiesis.

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age (years)</th>
<th>Type of anemia (treatment)</th>
<th>Associated anomalies</th>
<th>Platelet count (×10^9/L)</th>
<th>Plasma TPO (pg/mL)</th>
<th>Age-matched controls (pg/mL); Average±SD</th>
<th>Mutation in RPS19</th>
<th>Mutation in c-mpl</th>
</tr>
</thead>
<tbody>
<tr>
<td>CZ2 (M)</td>
<td>28</td>
<td>mild (S) thenar hypoplasia</td>
<td>no</td>
<td>225</td>
<td>52±20.7</td>
<td>n = 22</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>CZ3 (F)</td>
<td>21</td>
<td>remission kidney aplasia</td>
<td>174*</td>
<td>178; 199</td>
<td>52±20.7</td>
<td>n = 22</td>
<td>Leu524Leu (C1570T)</td>
<td>Val556Phe (G1666T)</td>
</tr>
<tr>
<td>CZ7 (F)</td>
<td>14</td>
<td>severe (TD)</td>
<td>no</td>
<td>174</td>
<td>52±20.7</td>
<td>n = 22</td>
<td>R56Q</td>
<td>G167A</td>
</tr>
<tr>
<td>CZ9 (F)</td>
<td>18</td>
<td>mild (S)</td>
<td>293</td>
<td>178; 211; 235</td>
<td>52±20.7</td>
<td>n = 22</td>
<td>Del(196-206)</td>
<td>no</td>
</tr>
<tr>
<td>CZ19 (M)</td>
<td>8</td>
<td>mild (S) short stature</td>
<td>530*</td>
<td>209; 215</td>
<td>88.4±19.5</td>
<td>n = 7</td>
<td>Val114Met (G340A)*</td>
<td>no</td>
</tr>
<tr>
<td>CZ21 (M)</td>
<td>5</td>
<td>severe (TD)</td>
<td>no</td>
<td>290*</td>
<td>80.5±23.8</td>
<td>n = 7</td>
<td>Val114Met (G340A)</td>
<td>no</td>
</tr>
<tr>
<td>CZ23 (F)</td>
<td>3</td>
<td>severe (TD)</td>
<td>no</td>
<td>139*</td>
<td>90.8±29.1</td>
<td>n = 9</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

* TPO levels in all of these patients were at least 6 standard deviations above the average level in age-matched controls. Individual c-mpl exons were amplified by polymerase chain reaction (PCR); amplicons were purified and used as templates for sequencing using an ABI310 Genetic Analyzer (Perkin Elmer). Nucleotide numbering: A in the first start codon is considered +1. TD: transfusion dependency, S: steroid dependency, *: increased platelet count in infant age; x: mutations in the same allele (proved by PCR cloning of the region spanning exons 11 and 12, and by sequencing); #: the same substitution found also in a patient with a normal level of TPO; SD: standard deviation.
Letters to the Editor

Thrombopoietin (TPO) is a cytokine that is involved in the regulation of megakaryocytic and erythroid progenitors. The receptor for TPO, c-Mpl, is a key player in the process of platelet production and is essential for normal hematopoiesis. Mutations in the c-Mpl receptor have been linked to various hematologic disorders, including congenital amegakaryocytic thrombocytopenia (CAMT) and Diamond-Blackfan anemia (DBA).

In a recent study, researchers analyzed TPO serum levels and c-Mpl mutations in patients with DBA to better understand the pathogenesis of this disease and to identify potential therapeutic targets. They noted that elevated TPO levels were present in 50% of DBA patients, suggesting a compensation mechanism for the c-Mpl receptor deficiency. However, no specific mutations in the c-Mpl gene were identified in these patients.

The relevance of the Val114Met substitution for the function of c-Mpl remains to be determined. In the third patient, two novel point mutations were identified in the c-Mpl gene, leading to amino acid substitutions that could influence the protein's function. Further functional studies are needed to determine the impact of these mutations.

The researchers also highlighted the importance of longitudinal studies with larger cohorts of patients to better understand the natural history of DBA and to identify potential novel therapeutic strategies.

References


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Key words: thrombopoietin, c-Mpl, Diamond-Blackfan anemia.

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Myelodysplastic Syndromes

Latency of onset of de novo myelodysplastic syndromes

The latency of onset of de novo myelodysplastic syndromes (MDS) is unknown. We report a retrospective analysis of blood counts from patients with MDS and acute myeloid leukemia (AML), and demonstrate temporal differences in rates of change of hematocrit and hemoglobin concentration and mean cell volume within 2–3 years of diagnosis, indicative of the earliest evidence of disease.

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(http://www.haematologica.org/2004/11/1392)

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders, whose etiology is largely unknown, except for the relatively few cases presenting after exposure to cytotoxic chemotherapy. Definition of the latency of onset of de novo MDS and acute myeloid leukemia may inform future epidemiologic studies of the etiology of these diseases.

We have collected all known blood counts from 109 patients with MDS and AML over a 20-year period prior to the date of their diagnosis (all diagnosed after 1995). Sources of data were hospital case notes, computer databases, and community general practice notes. Co-existent...