Significance of neutrophil elastase mutations versus G-CSF receptor mutations for leukemic progression of congenital neutropenia

Recently, Dale et al demonstrated the presence of a variety of mutations in the gene encoding the serine protease neutrophil elastase (ELA2) in a high proportion of patients with congenital neutropenia (CN). Previously, they have reported mutations in the same gene in patients with autosomal dominant and sporadic forms of cyclic neutropenia. Based on tertiary structure modeling and on the finding that ELA2 knockout mice have normal neutrophil levels, they propose that ELA2 mutations alter the structure and biological properties of neutrophil elastase. This would then lead to accelerated apoptosis of promyelocytes and their progeny in vivo. Dale et al discuss their findings in view of previous data showing the presence of acquired mutations in the G-CSF receptor (G-CSF-R) gene in patients with CN. These mutations truncate the carboxy-terminus of the G-CSF-R and are found in approximately 20% of CN patients. Increasing evidence suggests that G-CSF-R mutations are associated with leukemic progression of CN, a major complication observed in about 9% of the patients. Functional studies have indicated that truncated G-CSF-Rs have altered signaling properties and give rise to hyperproliferative responses to G-CSF, both in vitro and in vivo. In a recent study including 73 CN patients, G-CSF-R mutations were identified in 16 cases, of which 11 (69%) developed secondary leukemia. In contrast, only 1 of the 57 patients without a G-CSF-R mutation (< 2%) showed leukemic progression. Dale et al now consider it more likely that ELA2 mutations, rather than G-CSF-R mutations, contribute to leukemic progression of CN. They state that ‘current prevalence data suggest that a minority of [the CN] patients manifest [G-CSF receptor mutations], and it now seems much more likely that mutations of the gene for neutrophil elastase lead to compromised myeloid differentiation and create the risk for development of AML’.

Dale et al discuss their findings in view of previous data showing the presence of acquired mutations in the G-CSF receptor (G-CSF-R) gene in patients with CN. These mutations truncate the carboxy-terminus of the G-CSF-R and are found in approximately 20% of CN patients. Increasing evidence suggests that G-CSF-R mutations are associated with leukemic progression of CN, a major complication observed in about 9% of the patients. Functional studies have indicated that truncated G-CSF-Rs have altered signaling properties and give rise to hyperproliferative responses to G-CSF, both in vitro and in vivo. In a recent study including 73 CN patients, G-CSF-R mutations were identified in 16 cases, of which 11 (69%) developed secondary leukemia. In contrast, only 1 of the 57 patients without a G-CSF-R mutation (< 2%) showed leukemic progression. Dale et al now consider it more likely that ELA2 mutations, rather than G-CSF-R mutations, contribute to leukemic progression of CN.
leukemic transformation. Second, despite the high incidence of ELA2 mutations in cyclic neutropenia, 2 of which (16073G>A and 15862C>T) are also found in CN, none of the 132 cyclic neutropenia patients reported so far developed leukemia. How the ELA2 mutations contribute to the pathogenesis of neutropenia remains unclear until the biological properties of the various mutated neutrophil elastase proteins have been elucidated. But there is no indication that ELA2 mutations are involved in leukemic progression of CN.

References


Response:

Neutrophil elastase and congenital neutropenia

Drs Hermans and Touw have questioned the suggestion in our paper that mutations of the gene for neutrophil elastase create the risk for leukemia in patients with congenital neutropenia. We made this hypothesis based on the following:

1. Most patients with severe congenital neutropenia have mutations of the gene for neutrophil elastase (ELA2). At the recent meeting of the American Society of Hematology, we updated the information in our paper and reported that 45 of 49 patients examined have mutations of the ELA2 gene. Thus this mutation is far more common than mutations of the G-CSF receptor gene (G-CSF-R).1

2. Our report indicates that families with autosomal dominant congenital neutropenia have the same mutation in all family members. This demonstrates that these are germlinemutations and not acquired mutations. Thus far, all evidence points to the G-CSF-R mutations as being acquired mutations.2

3. We have now serially studied one patient with congenital neutropenia, having a mutation of the ELA-2 gene, who then developed leukemia. Prior to the development of leukemia, the G-CSF-R was normal, but the ELA-2 gene was abnormal. The G-CSF-R became abnormal when he developed leukemia.3

4. In our Seattle studies of patients with severe congenital neutropenia evolving to leukemia, 6 of 7 patients have had ELA2 mutations. Five of the 6 with ELA2 gene mutations evolving to leukemia have had G-CSF-R mutations.

5. In cellular studies, we have found that patients with congenital neutropenia and mutations of the ELA2 gene have accelerated apoptosis of CD34+ precursor cells. In patients evolving to leukemia and having G-CSF-R mutations, we have found that the cells manifest longer survival. It may be inferred that cells bearing the mutant receptor accumulate as part of the leukemic transformation.

Based on these data, we agree with Drs Hermans and Touw that G-CSF-R mutations are common in patients with congenital neutropenia who develop leukemia. Thus far, the data is compelling in indicating that the mutations in the gene for ELA2 come first.

References


To the editor:

Drug-dependent antibodies against the prodrug carbimazole do not react with the active metabolite thiamazole

Drug-induced immune thrombocytopenia (DITP) is a sometimes severe complication of drug treatment. Recently, we described 5 patients who presented with relatively mild thrombocytopenia after treatment with the antithyroid drug carbimazole (1-carbethoxy-3-methyl-2-thioimidazole).1 Serologic and immunochemical analysis revealed drug-dependent antibodies (DDAbs) against the platelet
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Mirjam H. A. Hermans and Ivo P. Touw