show that among PRV-1-positive ET patients, those with normal c-Mpl levels appear to be at highest risk of thromboembolic events. The results of this retrospective analysis must now be corroborated in a large prospective trial of newly diagnosed patients such as that being implemented by the MPD Research Consortium.

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Acute Myeloid Leukemia

Mutations of PTPN11 are rare in adult myeloid malignancies

The PTPN11 gene encodes the phospho-tyrosine phosphatase protein SHP-2. Constitutional mutations of this gene are involved in Noonan’s syndrome, a developmental disorder in which children have a predisposition to develop a myeloid disorder called juvenile myelomonocytic leukemia. Recently, studies have shown that somatic mutations of PTPN11 can be found in children with myeloid malignancies. We evaluated the incidence of acquired mutation of PTPN11 in 76 adults with acute or chronic myeloid malignancies and summarized our results together with others published recently.

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The PTPN11 gene (protein-tyrosine phosphatase, non-receptor-type, 11), localized in 12q24, encodes a protein with tyrosine phosphatase activity called SHP-2 (Src homology 2 domain-containing phosphotyrosine phosphatase). The SHP-2 protein has 3 functional domains: the PT-Pase catalytic domain and two SH2 domains (src homology 2), one in the C-terminal part (C-SH2) and the other in the N-terminal part (N-SH2) of the protein. In its inactive form, the PT-Pase catalytic domain is masked by N-SH2; binding of phospho-tyrosyl peptides on N-SH2 induces a conformational change uncovering the catalytic site. SHP-2 is implicated in signal transduction pathways, particularly those induced by growth factors; activation of SHP-2 generally leads to activation of the RAS/RAF/ERK pathway. The SHP-2 protein is strongly expressed in blood cells and is implicated in the response to KIT-ligand, interleukin-3, granulocyte-monocyte colony-stimulating factor and erythropoietin. The PTPN11 alterations so far reported in human diseases were exclusively missense mutations. In Noonan’s syndrome, PTPN11 carries constitutional mutations preferentially localized in exon 3, the coding sequence for the domain of N-SH2 implicated in the inhibition of the PT-Pase catalytic site. Children with this syndrome have a developmental disorder as well as a predisposition to develop juvenile myelomonocytic leukemia (JML). Furthermore, in children, somatic mutations of PTPN11 have been reported in 34% of non-syndromic JML, 18.5% of refractory anemia with excess blasts (RAEB) in transformation, 4% of acute myeloid leukemia (AML), and 6.5% of acute lymphocytic leukemia (Table 1); 98% of those mutations were localized in exon 3.17 In this study, we performed mutational analysis of exon 3 of the PTPN11 gene to assess the incidence of mutations in adult myeloid disorders. We tested 84 patients: 38 had chronic myelomonocytic leukemia (CMLM), 18 RAEB, 4 RAEB in transformation, 4 AML with monosomy 7, 12 AML post-myelodysplastic syndrome and, as a control, 8 non-syndromic JML. After DNA extraction from bone marrow or blood samples, exon 3 of PTPN11 was amplified as previously described.3 Amplification products were purified and sequenced. As expected, 3 of the 8 cases of JML tested carried mutations (G60R, D61V and G503A). Among the 76 remaining patients, only one had a PTPN11 mutation (missense mutation: D61N). This patient had AML with monosomy
As previously described by Loh et al., in pediatric AML7, monosomy 7 is frequently associated with PTPN11 mutations. Our results confirm that alteration of PTPN11 is a rare event in the leukemogenesis of adult myeloid malignancies. Indeed, in published studies (Table 1), only 1% of CMML, 3.5% of AML and 7% of RAEB-T had somatic mutations of PTPN11. Interestingly, PTPN11 mutations occurred preferentially in leukemia with a monocytic component and/or in the presence of monosomy 7. Moreover, as in Noonan’s syndrome, all somatic mutations described were missense mutations and they were almost exclusively localized in exon 3, rarely in exon 13. As demonstrated by Tartaglia et al.,7 such mutations modify the zone of interaction between N-SH2 and PTPase domains and release enzymatic activity of SHP-2.

Contrary to pediatric myeloid malignancies in which different mechanisms can induce activation of the RAS-MEK-ERK pathway (RAS mutations, NF1 deletions or PTPN11 mutations), in adult myeloid malignancies this activation only exceptionally involves PTPN11 mutations and therefore seems related mostly to RAS mutations.

References


Malignant Lymphomas

The relative levels of cyclin D1a and D1b alternative transcripts in mantle cell lymphoma may depend more on sample origin than on CCND1 polymorphism

The relative levels of cyclin D1 (CCND1) (a) and (b) transcripts were determined by real-time reverse transcription polymerase chain reaction (RT-PCR) and found to vary according to the tissue origin in both control and tumor samples. A five-fold overexpression of both isoforms was observed in 28/38 cases of mantle cell lymphoma (MCL) and of only one isoform in 10/38 MCL. No correlation was observed between expression of cyclin D1 isoforms and CCND1 genotype at position 870.

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