PTPN2 negatively regulates oncogenic JAK1 in T-cell acute lymphoblastic leukemia

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We have recently reported inactivation of the tyrosine phosphatase PTPN2 (also known as TC-PTP) through deletion of the entire gene locus in ~6% of T-cell acute lymphoblastic leukemia (T-ALL) cases. T-ALL is an aggressive disease of the thymocytes characterized by the stepwise accumulation of chromosomal abnormalities and gene mutations. In the present study, we confirmed the strong association of the PTPN2 deletion with TLX1 and NUP214-ABL1 expression. In addition, we found cooperation between PTPN2 deletion and activating JAK1 gene mutations. Activating mutations in JAK1 kinase occur in ~10% of human T-ALL cases, and aberrant kinase activity has been shown to confer proliferation and survival advantages. Our results reveal that some JAK1 mutation–positive T-ALLs harbor deletions of the tyrosine phosphatase PTPN2, a known negative regulator of the JAK/STAT pathway. We provide evidence that down-regulation of Ptpn2 sensitizes lymphoid cells to JAK1-mediated transformation and reduces their sensitivity to JAK inhibition. (Blood. 2011;117(26):7090-7098)

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive leukemia occurring in children and adults that is characterized by the massive production of undifferentiated thymocytes of clonal origin. T-ALL arises from the neoplastic transformation of a lymphoid progenitor cell that has accumulated multiple genetic lesions that alter its differentiation and self-renewal properties and provide proliferation and survival advantages. The aberrant activation of transcription factors such as TAL1, TLX1, TLX3, MLL, and HOXA is thought to be the driving force of the transformation process and, based on the identity of the causal transcription factor, T-ALLs can be delineated in oncogenic subgroups with a characteristic immunophenotype and expression profile. In addition to the ectopic expression of these transcription factors, several other lesions have been identified, including mutations of NOTCH1 and FBXW7, inactivation of PTEN, deletion of CDKN2A (p16), mutations of PHF6, and activation of LCK, JAK1, and ABL1 tyrosine kinases.

Mutations in JAK1 and epimopal fusion of NUP214 to ABL1 are known oncogenic events that support the proliferation and survival of T-ALL cells. Whereas the chimeric NUP214-ABL1 fusion gene occurs specifically in the cortical subtype characterized by aberrant expression of homeobox transcription factors TLX1 and TLX3, mutated JAK1 kinase appears in different T-ALL subgroups. Three independent studies have reported the occurrence of JAK1 mutations in T-ALL. In 2008, Flex et al studied a cohort of Italian T-ALL patients and found the frequency of JAK1 mutations in children and adults to be 2% and 18%, respectively. That study also found a clinical association with older age at diagnosis, poor treatment response, and overall predicted outcome. Around the same time, a second group sequenced exons 5, 14, and 17 of JAK1 in 11 adult Korean T-ALL patients and identified 3 missense mutations in the coding region of JAK1 (27%). However, the latest study performed by Asnafi et al could not confirm the frequencies reported previously. Sequence analysis of the JAK1 gene in 108 adult French T-ALL patients identified only 4 individuals with JAK1 mutations. Whether JAK1 mutations occur in adult T-ALL patients at different frequencies depending on ethnic origin remains to be elucidated in future studies.

Protein tyrosine phosphorylation is a highly dynamic process that is kept in balance by the antagonistic function of protein tyrosine kinases and protein tyrosine phosphatases. Therefore, enhanced signal traffic can arise from either up-regulated protein tyrosine kinase function or loss of negative regulation. We have recently identified acquired deletions of the T-cell protein tyrosine phosphatase gene PTPN2 in ~6% of T-ALL cases. Loss of PTPN2 was restricted to an immature T-ALL subset characterized by deregulated expression of the homeobox transcription factor TLX1. Four cases also harbored the oncogenic fusion gene
and we identified NUP214-ABL1 as novel, bona fide substrate of PTPN2. Absence of the PTPN2 protein evidently enhanced NUP214-ABL1 kinase activity, thereby sensitizing cells to leukemogenic transformation. These genetic and functional data indicate that the loss of PTPN2 enhances the oncogenic properties of NUP214-ABL1 and suggest that this loss could also potentiate other oncogenic kinases such as JAK1, a known substrate of PTPN2.16-18

Methods

Cell lines

HEK293T and Ba/F3 cells were obtained from DSMZ. Cells were grown in DMEM (HEK293T) or RPMI 1640 (Ba/F3) medium supplemented with 10% FBS. The medium of cytokine-dependent Ba/F3 cells was supplemented with 1 ng/mL of recombinant IL-3 (Peprotech).

Patient samples

T-ALL samples were collected at various institutions and were obtained after informed consent following the Declaration of Helsinki and with approval from the ethical committees of all participating institutions. Diagnosis of T-ALL was based on morphology, cytochemistry, and immunophenotyping according to World Health Organization and European Group for the Immunologic Characterization of Leukemias criteria. Molecular data on 13 T-ALL cases were described previously.15 Array analysis of these cases showed no sign of cell growth were declared to be nontransforming.

Quantitative PCR

Quantitative real-time PCR was performed on a LightCycler 480 PCR instrument (Roche). Reactions were performed in a total volume of 15 μL: 2× SYBR Green I Master Mix (7.5 μL), 5pmol forward primer (1.25 μL), 5pmol reverse primer (1.25 μL), and 10ng genomic DNA template (5 μL). RNMT and CDH2 were used as control genes and normalized to a control individual with a normal PTPN2 ct) method. Primer sequences were as follows: PTPN2 for 5′-TGAGAGAATCTGGCTCCTTGAAC, reverse 5′-GCCCAAATGCTGCTTTGAAC, reverse 5′-GCCCAATGGCTGACTACA, CDH2 for 5′-TGAGAGAATCTGGCTCCTTGAAC, reverse 5′-GCCCAATGGCTGACTACA, and RNMT for 5′-TGAGAGAATCTGGCTCCTTGAAC, reverse 5′-GCCCAATGGCTGACTACA.

Sequence analysis of PTPN2 and JAK1

Sequence analysis of both PTPN2 and JAK1 were performed at the genomic DNA level. The initial screen was done with whole-genome–amplified DNA as a template. Positive hits were confirmed in an independent PCR from primary patient material. PCR composition and primer sequences for the mutational analysis of PTPN2 were described previously.15 All exons of JAK1 were amplified with Taq DNA polymerase (Promega), and PCR products were directly sequenced with internal primers at the VIB Genetics Service Facility (Antwerp, Belgium). Primer sequences will be provided upon request.

Western blotting

Cells were lysed in 4 mM HEPES, 0.1% Nonidet P-40, 0.5% sodium deoxycholate, and 0.1% sodium dodecyl sulfate, pH 7.4, and separated by 10% SDS-PAGE. Western blots were incubated with the primary antibodies overnight at 4°C. The following antibodies were used in this study: Ptpn2 (3E2) (from Medimab); JAK1 (HR-785), phospho-JAK1 (Tyr1022/1023), STAT5 (L-20), and ERK (C-16) (all from Santa Cruz Biotechnology); β-actin (AC-15; from Sigma-Aldrich); and STAT1 and STAT3 (both from Cell Signaling Technology). A

Table of contents

1. Introduction
2. Materials and Methods
3. Results
4. Discussion
5. Conclusion

Acknowledgments

References
phospho-STAT antibody sampler kit was used for the detection of STAT proteins (Cell Signaling Technology).

**AlphaScreen SureFire kinase assay**

Stat5 phosphorylation levels of Ba/F3 cells were determined using the AlphaScreen SureFire STAT5 (p-Tyr695;Tyr699) kinase assay kit (PerkinElmer). Cells (25 × 10^5) were lysed through the addition of 5X lysis buffer in a total volume of 100 μL. Lysates were simultaneously analyzed for phosphorylation levels of Stat5 and total Erk protein (loading control). All assays were performed according to the manufacturer’s instructions.

**Statistical analysis**

Significant differences were determined using Prism software Version 5 (GraphPad). The mean of 2 groups was compared with the Student t test. Normality tests were used to test the assumption of a normal distribution.

## Results

**Deletion of PTPN2 is specifically found in TLX1-positive T-ALL**

We have recently identified focal deletions of the tyrosine phosphatase gene PTPN2 in ~ 6% of T-ALL.15 Remarkably, deletion of the PTPN2 gene was strongly associated with aberrant expression of the homeobox transcription factors TLX1 (12 of 13 cases) and TLX3 (1 of 13 cases; Table 1). In addition, 30% of the PTPN2-deleted cases also harbored the NUP214-ABL1 fusion gene.15 Among the 13 identified PTPN2-deleted T-ALL individuals, 8 featured biallelic loss and 5 monoallelic loss of PTPN2. Individuals with heterozygous loss of PTPN2 showed reduced PTPN2 expression levels compared with T-ALL, along with normal PTPN2 copy numbers,15 strongly suggesting that in those cases with incomplete deletion, the loss of one copy of PTPN2 was a driving oncogenic event.

To confirm our previous findings, we screened a new set of T-ALL cases (n = 74) for deletions of the PTPN2 gene. We identified 5 cases with altered copy number status of PTPN2 (Figure 1A and Table 1), and subsequent aCGH analysis confirmed the presence of focal deletions of the entire PTPN2 gene in all cases. Two individuals featured monoallelic deletion and the 3 others showed biallelic loss of PTPN2 (Figure 1A). Sequence analysis of the coding region of PTPN2 in individuals with monoallelic deletion did not provide evidence of any nonsense, splice site, or frameshift mutation in the retained allele. In agreement with our previous observations, newly identified cases with deletion of PTPN2 belonged to the TLX1-positive T-ALL subgroup, and 2 PTPN2-deleted leukemias also harbored the NUP214-ABL1 fusion gene (Table 1). These data confirm our previous findings on the frequency of PTPN2 deletions in T-ALL, the restriction of PTPN2 inactivation to the TLX1 subgroup, and the repeated occurrence of loss of the PTPN2 gene in NUP214-ABL1-positive leukemias.

**Loss of PTPN2 can be found in JAK1 mutation–positive T-ALL**

As shown previously15 and by the results of the current study, among T-ALL individuals with deletion of PTPN2 (n = 18), one-third (6 of 18) also expressed the NUP214-ABL1–activated tyrosine kinase. Further, we have shown previously that loss of PTPN2 increases NUP214-ABL1 signaling. We speculated that cases with loss of PTPN2 but lacking NUP214-ABL1 expression could possibly express another activated tyrosine kinase that would gain further oncogenic activity due to the PTPN2 deletion. PTPN2 is an important modulator of JAK1 kinase activity, and its loss enhances JAK1-mediated cytokine receptor signaling.15,16 Therefore, we investigated whether some of the cases with deletion of PTPN2 harbored activating mutations in JAK1, a gene known to be mutated in 3%-20% of T-ALL cases.

Sequence analysis of the entire coding region of JAK1 in PTPN2-deleted cases (n = 18) identified mutations in the JAK1 kinase gene in 2 NUP214-ABL1–negative cases. One case of leukemia (individual 13) harbored the previously described c.1953T > C change in JAK1, corresponding to a p.Y652H amino acid substitution (Figure 1B and Table 1).9 The other case

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**Table 1. Characterization of T-ALL individuals with PTPN2 inactivation**

<table>
<thead>
<tr>
<th>Individual</th>
<th>Sex</th>
<th>Age, y</th>
<th>PTPN2 deletion*</th>
<th>PTPN2 mutation</th>
<th>Dereguated transcription factor†</th>
<th>NUP214-ABL1‡</th>
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<td>TLX1</td>
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<td>TLX1</td>
<td>–</td>
<td>–</td>
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<td>wt</td>
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<td>NA</td>
<td>TLX1</td>
<td>+</td>
<td>wt</td>
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</tbody>
</table>

* Determined by FISH, quantitative PCR, or aCGH; † indicates a biallelic deletion; and ‡ indicates a monoallelic deletion.

† Positivity for NUP214-ABL1 expression or rearrangement; †† indicates positive for NUP214-ABL1; and † indicates negative for NUP214-ABL1.

§ Patient results have been published previously and are consecutively numbered.15 NA indicates not applicable; and wt, wild-type.
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Role of the Funding Sponsors

The funding sponsors had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, or preparation, review, or approval of the manuscript.

Authorship

The authors declare that they have no relevant financial interests.

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Supplementary Material

Supplementary Plateau 1 and Plateau 2 are available with the online version of this article.


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LOSS OF PTPN2 IN JAK1 MUTATION–POSITIVE T-ALL

7093
Discussion

T-ALL is an aggressive T-cell malignancy that is most common in children and adolescents. Current treatment for T-ALL consists mainly of multi-agent combination chemotherapy. Improvements in treatment regimens has led to significant increases in survival, but the long-term survival rates for adult T-ALL patients are still below 40% for those < 60 years of age and even lower in older patients. These observations indicate that, especially for older T-ALL patients, new and less toxic drugs are needed to improve overall survival. JAK1 may be an interesting drug target in this subgroup of T-ALL patients. JAK1 is mutated in up to 20% of older T-ALL patients, and new JAK inhibitors are under clinical development. In addition to JAK1 mutations, we have recently identified deletion of the tyrosine phosphatase PTPN2 in 6% of T-ALL cases. PTPN2 is a negative regulator of the JAK/STAT pathway, and its loss sensitizes T cells to cytokine stimulation. The results of the present study confirm the relationship between loss of PTPN2 and JAK1 by demonstrating that down-regulation of Ptpn2 makes mouse lymphoid cells more susceptible to transformation.

It is currently unclear whether the loss of PTPN2 is an independent oncogenic event or if it occurs along with other mutations in signaling proteins. We have shown herein that the loss of PTPN2 occurs in a subset of JAK1 mutation–positive T-ALL patients.
cases and that down-regulation of Ptpn2 increases the activation status of both wild-type and mutant JAK1, resulting in increased activation of the JAK/STAT pathway and increased cytokine-independent cell proliferation. Therefore, inactivation of PTPN2 in T-ALL may cause increased JAK/STAT signaling and, especially in JAK1 mutation–positive T-ALL, the loss of PTPN2 may further assist in activation of proliferation and survival signals within leukemic cells. This increased activation of JAK1 is associated with reduced responsiveness to JAK inhibition, suggesting that T-ALL individuals with JAK1 mutation in combination with loss of PTPN2 may respond less well to JAK inhibitors. The direct implication of JAK1 mutations in the pathogenesis of leukemia, together with our current results, warrant further studies into the use of JAK inhibitors for the treatment of leukemia.
We provide genetic and functional evidence for the concomitant appearance of mutations in JAK1 kinase with inactivation of its negative regulator PTPN2, with each potentiating the oncogenic capacity of the other. These data, together with our previous findings in NUP214-ABL1-positive PTPN2-negative T-ALL individuals, suggest that PTPN2 inactivation may appear mainly in association with deregulated tyrosine kinase signaling, the oncogenic activity of which is further increased by the absence of the negative regulator PTPN2. The presence and identity of other oncogenic kinases in T-ALLs featuring loss of PTPN2 but negative for both the NUP214-ABL1 fusion and activating JAK1 mutations remain to be determined. We speculate that other tyrosine phosphatases may be mutated or lost in T-ALL cases, whereas JAK1 mutations are specifically found in TLX1-positive T-ALLs. This is also to be expected, because deletions of PTPN2 are specifically found in TLX1-positive cases, whereas JAK1 mutations are not restricted to any particular subtype of T-ALL.

Constitutively activated tyrosine kinases activate a variety of signaling pathways that provide proliferation and survival advantages to cancer cells. Both our current results and those from a previous study suggest that cancer cells may have the pressure to lose additional negative regulators of oncogenic kinases to further strengthen these proliferation and survival signals, and that cells with such increased proliferation capacity may be selected for during the development and progression of tumors. We have provided evidence for such evolution during the development of T-ALL, but this is likely to also occur in most, if not in all, tumor types. Full genome sequencing of tumors is likely to provide further insights into this issue.

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References


Authorship

Contribution: M.K. designed the study, performed experiments, analyzed data, and wrote the manuscript; V.A. and N.M. performed experiments and analyzed data; J.S., T. Hornakova, L.K., S.C., F.S., J.P.M., P.V., M.T., R.F., E.M., and T. Haferlach provided reagents and wrote the manuscript; and J.C. designed the study, analyzed data, and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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