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SHORT REPORT

SOCS3 deregulation contributes to aberrant activation of the JAK/STAT pathway in precursor T-cell neoplasms

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Summary

Despite the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway being frequently altered in T-ALL/LBL, no specific therapy has been approved for T-ALL/LBL patients with constitutive signalling by JAK/STAT, so there is an urgent need to identify pathway members that may be potential therapeutic targets. In the present study, we searched for JAK/STAT pathway members potentially modulated through aberrant methylation and identified *SOCS3* hypermethylation as a recurrent event in T-ALL/LBL. Additionally, we explored the implications of SOCS3 deregulation in T-ALL/LBL and demonstrated that SOCS3 counteracts the constitutive activation of the JAK/STAT pathway through different molecular mechanisms. Therefore, SOCS3 emerges as a potential therapeutic target in T-ALL/LBL.

KEYWORDS
JAK/STAT pathway, precursor T-cell neoplasms (T-ALL/LBL), SOCS3

Abbreviations: dbGaP, Genotypes and phenotypes database; JAK/STAT, Janus kinase/signal transducers and activators of transcription; NCI, National Cancer Institute; T-ALL/LBL, T-cell acute lymphoblastic leukaemia / T-cell lymphoblastic lymphoma; TARGET, Therapeutically Applicable Research to Generate Effective Treatments; TSG, tumour suppressor gene; TSS, transcription start site.

Precursor T-cell neoplasms (T-cell acute lymphoblastic leukaemia / T-cell lymphoblastic lymphoma, T-ALL/LBL) are aggressive haematological malignancies characterized by aberrant proliferation of immature thymocytes.[1] The high toxicity associated with the current treatments and the low survival rate in case of relapse highlight the urgent need for novel therapies targeting the frequently deregulated pathways in these haematological disorders.[2,3]

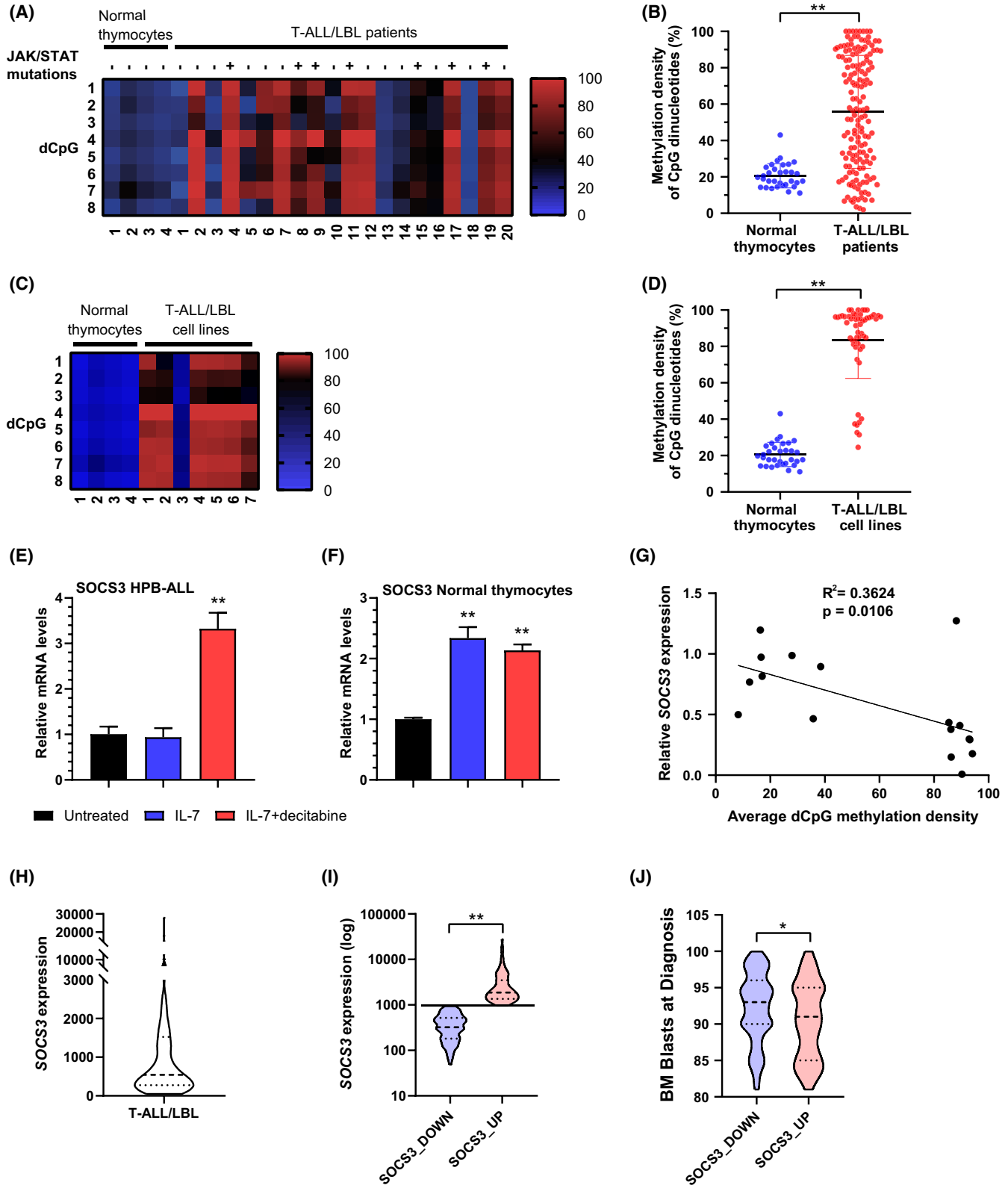
The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is the second most deregulated signalling pathway in T-ALL/LBL only after the NOTCH1 pathway. Consequently, a significant proportion of T-ALL/LBL patients show constitutive activation of the JAK/STAT pathway, which leads to sustained phosphorylation of STAT proteins and tumour development.[4] While previous studies have reported the efficacy of inhibiting certain JAK/STAT pathway members,[5,6] no specific therapy has been officially approved yet for T-ALL/LBL patients with constitutive activation of the JAK/STAT pathway.[7] Therefore, characterizing the molecular alterations responsible for the sustained phosphorylation of STAT proteins is essential to identify new pathway members which could be used as potential therapeutic targets. However, most genetic alterations identified so far through whole-exome-sequencing are restricted to positive regulators of the pathway and have a low incidence, suggesting the presence of additional alterations which remain to be identified.[4]

In the present study, we wondered whether epigenetic alterations and specifically an aberrant methylation profile could have an impact on the JAK/STAT pathway signalling. To this end, we focused on the CpG islands frequently appearing near the transcription start site (TSS) and colocalizing with cis-regulatory elements because tumour suppressor genes (TSG) are often silenced in cancer cells due to hypermethylation of such islands.[8] We recurrently identified hypermethylation of the *SOCS3* gene, a member of the SOCS family which regulates the JAK/STAT pathway in a negative feedback loop.[9] Additionally, we explored the possible implications of SOCS3 in T-ALL/LBL and demonstrated that SOCS3 counteracts the constitutive activation of the JAK/STAT pathway through different molecular mechanisms. Finally, we revealed the oncogenic role of multiple JAK1 mutations and showed their ability to induce SOCS3 phosphorylation at higher levels than $JAK1^{WT}$ in the absence of cytokines.

Primary samples of precursor T-cell neoplasms (n = 20) were obtained through the Spanish Hospital Biobanks Network (RetBioH; www.redbiobancos.es) (Table S1). Human postnatal thymocytes (n = 4) were isolated from thymuses removed during cardiac surgery of paediatric patients. Institutional review board approval was obtained for these studies (CEI 98–1825) and the participants provided written informed consent in accordance with the Declaration of Helsinki.

Mutations were generated using the QuickChange Site-Directed-Mutagenesis kit (Agilent). Cell transfection was accomplished using Lipofectamine™ 2000 (ThermoFisher) while virus production and cell transduction were performed as previously described.[10] Cells were counted with trypan blue and TC10 Automated Cell-Counter (Bio-Rad). Reagents and equipment from Bio-Rad were used for electrophoresis and Western blot. Immunoprecipitation of SOCS3 was accomplished using Dynabeads™ Protein G Immunoprecipitation Kit (Invitrogen). Additional information is available in Methods S1.

In search for JAK/STAT pathway genes modulated by aberrant methylation, we analysed the CpG islands associated with the TSS of genes from SHP, SOCS and PIAS families. Such genes are considered as potential negative regulators of the JAK/STAT pathway and their methylation status remains unexplored in T-ALL/LBL except for the case of *SOCS5*.[11,12] We first evaluated the extension or size of the CpG islands (Figure S1) and their colocalization with cis-regulatory elements (Figure S1). Next, the Infinium Methylation-EPIC array was employed to assess for the presence of hypermethylated CpG dinucleotides within the selected CpG islands in three T-ALL/LBL-derived cellular models (Figure S1). Following these criteria, we identified different candidates potentially modulated by aberrant methylation (Table S2). Among them, we focused on *SOCS3* since (i) it has been found hypermethylated in other malignancies[13,14]; (ii) does not show genetic alterations in T-ALL/LBL[4]; and (iii) it is essential for T-cell development.[9] We employed bisulphite treatment followed by DNA-pyrosequencing to study the methylation density of CpG dinucleotides within the CpG island of *SOCS3* in our patient-cohort and we observed *SOCS3* hypermethylation in more than 50% of the analysed samples (Figure 1A). Moreover, the methylation status of *SOCS3* was significantly higher in T-ALL/LBL patients when compared to that of normal thymocytes (Figure 1B). *SOCS3* hypermethylation was independent of different parameters such as the subgroup, the immunophenotype and the age (Figure S1). We corroborated that *SOCS3* hypermethylation was not limited to our patient cohort by analysing its methylation density in seven T-ALL/LBL-derived cells lines (Figure 1C). The corresponding results were also compared with those previously obtained from normal thymocytes (Figure 1D). Since *SOCS3* hypermethylation promotes its deregulation in other malignancies,[13,14] we confirmed this is also the case for T-ALL/LBL-derived cells by analysing the expression of *SOCS3* in HPB-ALL cells, which respond to interleukin-7 (IL-7) and display *SOCS3* hypermethylation, in the absence or presence of the demethylating agent decitabine (Figure 1E). The results showed decitabine induced a specific effect on *SOCS3* expression in HPB-ALL cells and were further validated using normal thymocytes as a negative control (Figure 1F). Moreover, we observed a negative correlation between *SOCS3* methylation and expression levels when evaluating normal thymocytes, T-ALL/LBL-derived cell lines and the T-ALL/LBL tumour samples with available RNA material (Figure 1G). Using data from the TARGET cohort, we observed that *SOCS3* expression follows a variable pattern, with heterogeneous levels of *SOCS3* (Figure 1H) and with around 60% of T-ALL/LBL



tumour samples showing downregulation of *SOCS3* relative to normal thymocytes (Figure 1I). Remarkably, T-ALL/LBL patients with reduced *SOCS3* expression exhibited significantly higher levels of blasts in bone marrow at diagnosis (Figure 1J). Additionally, *SOCS3* expression was independent of the immunophenotype but not of the molecular classification (Figure S1). In this respect, the HOXA, NKX2_1, TLX1 and TLX3 groups showed significantly lower levels of *SOCS3*.

FIGURE 1 Aberrant methylation of *SOCS3* in T-cell acute lymphoblastic leukaemia / T-cell lymphoblastic lymphoma (T-ALL/LBL). (A) Heatmap showing the methylation density of dCpG within the CpG island of *SOCS3* in primary T-ALL/LBL samples and in normal thymocytes eight dCpG have been analysed for each sample). To account for possible variations due to intratumour heterogeneity and contamination with normal cells, only dCpG with a methylation density higher than 40% were considered as truly hypermethylated. The presence or absence of somatic mutations affecting genes belonging to the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway in these samples is indicated by + or − respectively. (B) The methylation density of dCpG was compared between primary T-ALL/LBL samples and normal thymocytes. *, $p < 0.05$; **, $p < 0.01$. (C) Heatmap showing the methylation density of dCpG within the CpG island of *SOCS3* in T-ALL/LBL-derived cell lines (from 1 to 7: ALL-SIL, HPB-ALL, HSB2, MOLT4, PEER, KARPAS and Jurkat) and normal thymocytes (eight dCpG have been analysed for each sample). dCpG with a methylation density higher than 80% were considered as hypermethylated. (D) The methylation density of dCpG was compared between T-ALL/LBL-derived cell lines and normal thymocytes. *, $p < 0.05$; **, $p < 0.01$. (E) mRNA expression levels of *SOCS3* in HPB-ALL cells untreated or treated with IL-7 (10 ng/ml) and decitabine (1 μM). (F) mRNA expression levels of *SOCS3* in normal thymocytes untreated or treated with IL-7 (10 ng/ml) and decitabine (1 μM). For panels (E) and (F), data are referred to untreated cells and show the mean ± standard deviation (SD) after three independent experiments. *, $p < 0.05$; **, $p < 0.01$. (G) A significant negative correlation between methylation density of *SOCS3* CpG island and *SOCS3* transcriptional expression in control healthy thymocytes ($n = 3$), primary T-ALL/LBL samples ($n = 9$) and cell lines ($n = 5$). The value for *SOCS3* methylation density is the average of eight dCpG analysed for each sample. *SOCS3* mRNA levels were determined by quantitative reverse transcription polymerase chain reaction (RT-PCR). The results from three technical replicates were normalized using the $2^{-\Delta\Delta CT}$ method, referring *SOCS3* expression to those of *B2M* and *PPIA*, and referenced to the average value of the control group. Both parametric (Pearson: $r = -0.6020$, p-value = 0.0106) and non-parametric (Spearman: $r = -0.6642$, p-value = 0.0046) analyses revealed statistical significance. (H) Violin plot representing *SOCS3* expression (DESeq2 normalized counts) in 264 patients from the TARGET cohort. For optimal appreciation of the heterogeneous data, the Y-axis is shown in three segments (bottom from 0 to 3000, 75%; center from 3000 to 15 000, 7%; top from 15 000 to 30 000, 18%). (I) Violin plots representing *SOCS3* expression (DESeq2 normalized counts, shown in logarithmic scale) in two groups of T-ALL/LBL samples from the TARGET cohort ($n = 264$) that were established according to their *SOCS3* expression compared to that of control healthy thymocytes ($n = 2$). Samples with *SOCS3* values below the average of the controls (which is indicated by the horizontal line) constituted the SOCS3_DOWN group ($n = 169$) and those above the average constituted the SOCS3_UP group ($n = 95$). *, $p < 0.05$; **, $p < 0.01$. (J) Violin plots representing the number of bone marrow blasts at diagnosis in patients belonging to the SOCS3_DOWN and SOCS3_UP groups (as defined previously in Figure 1I). *, $p < 0.05$; **, $p < 0.01$.

To explore the relevance of SOCS3 for the constitutive activation of the JAK/STAT pathway, we specifically focused on IL-7 signalling and JAK/STAT pathway mutations since they are inductors of the JAK/STAT pathway which contribute to the sustained phosphorylation of STAT proteins in T-ALL/LBL.[4,15] To study the effects of SOCS3 on IL-7 signalling, we employed complementary cellular models with and without SOCS3 expression (Figure S2A). We observed that SOCS3 attenuates the signalling through IL-7, as shown by a reduction in STAT5 phosphorylation, a target of IL-7, as well as in PIM1, a target of phosphorylated STAT5 and a proto-oncogene (Figure 2A).

Next, we studied the possible association between JAK/STAT pathway mutations and *SOCS3* hypermethylation in our patient cohort. Patients with JAK/STAT pathway mutations displayed higher methylation levels of *SOCS3* (Figure 2B), suggesting that SOCS3 deregulation may be important for the oncogenic activity of these mutations. To validate this hypothesis, we aimed to investigate the relationship between SOCS3 and JAK1 oncogenic mutants and we started with a comprehensive characterization of multiple JAK1 mutations identified in T-ALL/LBL but whose functional effects had not been previously addressed (Tables S3 and S4). Among them, $JAK1^{F805V}$ was identified for the first time in our patient cohort (Figure 2C). We analysed the ability of the selected mutations to activate the JAK/STAT pathway in the absence of cytokines and observed that $JAK1^{D604Y}$, $JAK1^{L653F}$ and $JAK1^{F805V}$ mutants induced STAT1 phosphorylation to a greater extent than $JAK1^{WT}$ and similarly to $JAK1^{V658F}$, which in this case acts as a positive control[10] (Figure 2D). The oncogenic role of $JAK1^{D604Y}$, $JAK1^{L653F}$ and ^{F805V} mutations was further confirmed by their ability to induce cell growth and viability in the absence of cytokines (Figure 2E). Moreover, both events correlated with an increase in the levels of STAT5 phosphorylation (Figure 2F). Treatment with the JAK1/2-inhibitor ruxolitinib significantly reversed the previously observed effects on cell growth, viability and STAT5 phosphorylation (Figure S2B,C), indicating they were the specific result of $JAK1^{D604Y}$, $JAK1^{L653F}$ and $JAK1^{F805V}$ mutants.

Finally, we analysed the effects of SOCS3 on the JAK1 mutations that we had comprehensively characterized as oncogenic and observed that SOCS3 attenuates the activity of these mutants, as shown by a reduction in STAT1 phosphorylation, a specific target of JAK1 (Figure 2G). The results were corroborated when evaluating the global levels of JAK1-induced tyrosine phosphorylation (Figure 2H). Notably, the appearance of a particular band at approximately 25 kDa (indicated with an arrow in Figure 2H) prompted us to examine whether it may correspond to phosphorylated SOCS3, since SOCS3 has a predicted molecular weight of 27 kDa and can be phosphorylated at two tyrosines, Tyr^{204} and Tyr^{221}, by different protein tyrosine-kinases including JAK1.[16] To prove such hypothesis, we performed immunoprecipitation of SOCS3 followed by detection of phosphorylated tyrosines. Our results show that JAK1 oncogenic mutants induce SOCS3 phosphorylation to a greater extent than $JAK1^{WT}$ (Figure 2H, Figure S2D) and that such phosphorylation occurs specifically at Tyr^{204} and Tyr^{221}, as demonstrated when the $SOCS3^{Y204\&221F}$ mutant was used instead of $SOCS3^{WT}$ (Figure 2I, Figure S2E).

Our results identify the hypermethylation of the CpG island associated with the TSS of *SOCS3* as a recurrent event in T-ALL/LBL. Contrary to most alterations affecting other members of the JAK/STAT pathway, we observed that *SOCS3* hypermethylation has a notable incidence in T-ALL/LBL and was identified in more than 50% of the analysed samples. Additionally, we explored the possible implications

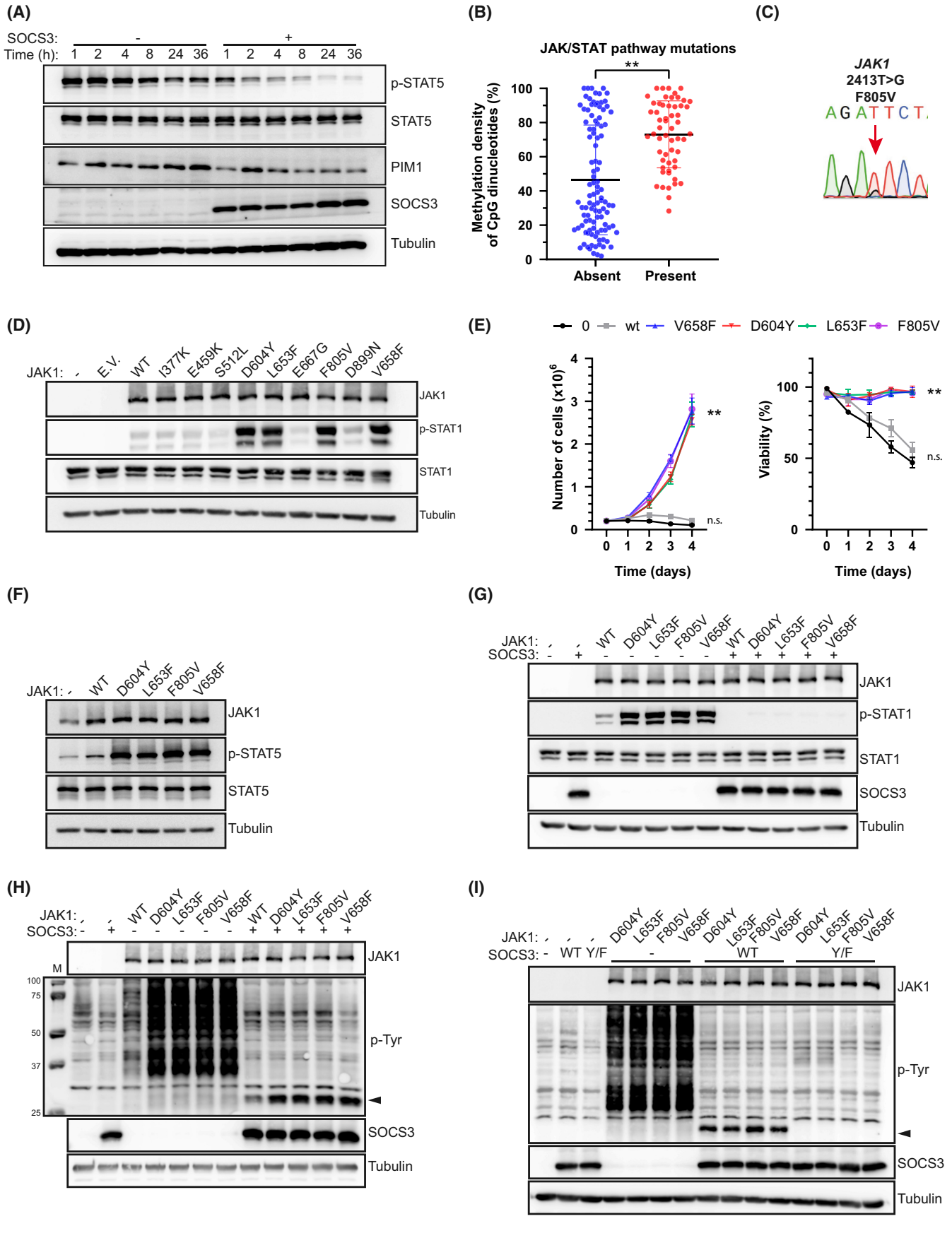


FIGURE 2 Functional consequences of SOCS3 deregulation in T-ALL/LBL. (A) Western blot for p-STAT5, STAT5, PIM1 and SOCS3 in HPB-ALL cells untransduced or transduced with SOCS3 and treated with IL-7 (10 ng/ml) for different time periods. (B) The methylation density of CpG dinucleotides was compared between patients with and without Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway mutations. *, $p < 0.05$; **, $p < 0.01$. (C) Electropherogram confirming the presence of a new single-point mutation in *JAK1* that causes the amino acid substitution at codon 805. The mutation was heterozygous so it appears as a double peak (indicated with an arrow). (D) Western blot for JAK1, p-STAT1 and STAT1 in U4A cells untransfected (–) or transfected with empty vector (E.V.), $JAK1^{WT}$ or JAK1 mutants. (E) Cell growth (left) and viability (right) assays of Ba/F3 cells untransduced (0) or transduced with $JAK1^{WT}$ or JAK1 mutants. Data show the mean ± standard deviation (SD) after three independent experiments. *, $p < 0.05$; **, $p < 0.01$. (F) Western blot for JAK1, p-STAT5 and STAT5 in Ba/F3 cells untransduced (–) or transduced with $JAK1^{WT}$ or JAK1 mutants. (G) Western blot for JAK1, pSTAT1, STAT1 and SOCS3 in U4A cells untransfected (–) or transfected with $JAK1^{WT}$ or JAK1 mutants in combination with SOCS3. (H) Western blot for JAK1, p-tyrosine and SOCS3 in U4A cells untransfected (–) or transfected with $JAK1^{WT}$ or JAK1 mutants in combination with SOCS3. The first lane contains the molecular weight marker and is named as M. Lanes corresponding to cells expressing JAK1 along with SOCS3 and analysed with anti-p-tyrosine show a specific band around 25 kDa which is indicated with an arrow and may be attributed to SOCS3 (27kDa). (I) Western blot for JAK1, p-tyrosine and SOCS3 in U4A cells untransfected (–) or transfected with JAK1 mutants in combination with $SOCS3^{WT}$ *or* $SOCS3^{Y204\&221F}$. Lanes corresponding to cells expressing JAK1 along with $SOCS3^{WT}$ but not $SOCS3^{Y204\&221F}$ and analysed with anti-p-tyrosine show a specific band which is indicated with an arrow and may be attributed to SOCS3 (27kDa). Western blots are representative examples of at least three independent experiments.

of SOCS3 in T-ALL/LBL and demonstrated that SOCS3 counteracts the constitutive activation of the JAK/STAT pathway by attenuating the signalling through IL-7 and the oncogenic activity of JAK1 mutants. Moreover, we revealed the oncogenic role of JAK1 mutations $JAK1^{D604Y}$, $JAK1^{L653F}$ and $JAK1^{F805V}$ and their sensitivity to ruxolitinib. Finally, we show that such mutations induce SOCS3 phosphorylation at Tyr^{204} and Tyr^{221} at higher levels than $JAK1^{WT}$, suggesting they could promote the aberrant hyperactivation of the JAK/STAT pathway not only by phosphorylating STAT proteins but also SOCS3. In conclusion, SOCS3 emerges as a potential therapeutic target for T-ALL/LBL patients with constitutive activation of the JAK/STAT pathway and future studies will be needed to determine the efficacy of SOCS3 mimetics[17,18] against this malignancy.

AUTHOR CONTRIBUTIONS

Antonio Lahera designed, performed and analysed experiments; Antonio Lahera, José Fernández-Piqueras and María Villa-Morales conceived the project and the experimental plan; Pilar López-Nieva and Agustín F. Fernández performed and analysed the methylation studies; José L. López-Lorenzo and María Á. Cobos-Fernández helped with flow cytometry and cell culture; Hernán Alarcón contributed to the generation of DNA constructs; Pablo Fernández-Navarro. advised on statistical analyses; Sara Ruiz-García and Isabel Sastre helped with qPCR experiments; María Villa-Morales analysed data from TARGET; Laura Vela-Martín assisted with scientific figures preparation; Pilar Llamas, José L. López-Lorenzo and Javier Cornago collected human primary samples and clinical data; Antonio Lahera, José Fernández-Piqueras, María Villa-Morales and Pilar López-Nieva prepared and wrote the manuscript; Javier Santos assisted with review and editing of the manuscript; and all authors approved the manuscript in its final format.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data corresponding to the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative that support the findings of this study are available from the National Cancer Institute (NCI). Restrictions apply to the availability of these data, which were used under licence for this study. Data are available at the genotypes and phenotypes database (dbGaP, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study) with the permission of the NCI. Additional data that support the findings of this study are available in the supplementary material of this article and/or from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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