Down-regulated FOXO1 in refractory/relapse childhood B-cell acute lymphoblastic leukemia

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Abstract

Background

Refractory/relapsed acute lymphoblastic leukemia (RR-ALL) remains to be a leading cause of treatment failure and subsequent death. Forkhead box O1 (FOXO1) belongs to the forkhead family of transcription factors, its specific role in RR-ALL has not yet been determined in B-cell ALL (B-ALL). The purpose of this study was to investigate the expression and prognostic value in ALL.

Methods

RNA sequencing was applied to an ALL case with induction failure to identify the causal events. The transcription activity was examined with luciferase reporter assay. FOXO1 mRNA expression level was examined using real-time quantitative PCR. Association analysis was performed to correlate FOXO1 transcription with childhood B-ALL prognosis and relapse.

Results

In this ALL case with induction failure, we successfully identified a novel MEIS1-FOXO1 fusion gene. The transcription activity of MEIS1-FOXO1 was significantly abolished as compared to wild-type FOXO1. Low FOXO1 expression level was strongly associate with unfavorable subtype, MRD positivity and relapse.

Conclusions

FOXO1 loss of function associates with ALL high-risk stratification and relapse, which might be due to drug resistance.

Background

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with an overall prevalence of 4/100,000, accounting for 25–30% of all childhood cancers[1]. The cure rate for childhood ALL has exceeded 80% in most countries, and even higher than 90% in developed countries with contemporary therapy[2], but refractory/relapsed ALL remains a leading cause of treatment failure and subsequent death[3]. Though most patients achieve quick and long-term response to contemporary chemotherapy, a non-ignorable part of childhood ALL patients do not respond well or relapse during chemotherapy. Cumulating convincing evidences have pointed out that the long-term
outcome for those patients with relapsed ALL and especially with induction failure, is very poor. Thus, early recognition this population and then assign them to optimal therapy is highly needed. In this regard, recently, many novel significant somatic alterations have been increasingly reported. Of importance, genomic lesions play deterministic role in refractory/relapsed ALL. For example, patients with Philadelphia chromosome (Ph) translocation, Ph-like related PDGFRB-rearrangement, MEF2D-rearrangement, MLL-rearrangement, TP53 mutation, and E2A-HLF are classified into the high- or very-high risk population[4]. In the meanwhile, gene expression profile can also predict the therapeutic response and relapse, e.g., Philadelphia chromosome-like signature [5]. Many findings above have been translated into drug discovery and improving clinical application, e.g., a milestone BCR-ABL1 targeted tyrosine kinase inhibitor, imatinib[6]. However, a portion of clinical failure cannot be explained by our current knowledge. Thus, more focus on ALL biology and refractoriness/relapse prediction can definitely assist us in early identifying them and then precisely treating them with more aggressive strategies, e.g., chimeric antigen receptor (CAR) T-cell therapy or hematopoietic stem cell transplant (HSCT)[7].

In this study, we identified a novel FOXO1 fusion gene in an induction failure B-ALL patient, namely MEIS1-FOXO1, which promoted leukemogenesis in vitro. MEIS1-FOXO1 fusion protein showed significantly reduced activity to promote transcription of its target genes as compared to its wild-type FOXO1 protein. Further gene expression association study revealed that the FOXO1 was lower expressed in high-risk group B-ALL as well as in those relapse patients, expanding our knowledge towards precision medicine.

Methods
Patients
Twenty-six patients with B-ALL (one with induction failure, five with relapse, and twenty with newly diagnosis) were enrolled into this study. The clinical research protocol was approved by our Institutional Review Board (IRB) and registered in Clinical Trial (ChiCTR-IPR-14005706). Informed consents were received from their parents.

Leukaemic Transformation Assay In Ba/f3 Cells
The full-length MEIS1-FOXO1 and NRASG12D were amplified from the patient and cloned into the
cL20c-IRES-GFP and cl20c-IRES-mCherry lentiviral vector respectively, and lentiviral supernatants were produced by transient transfection of 293 T cells (ATCC) using calcium phosphate. Ba/F3 cells (gift from Jun J Yang at St. Jude Children’s Research Hospital) were maintained in medium supplemented with 10 ng/ml recombinant mouse IL3. Ba/F3 cells were transduced with lentiviral supernatants with MEIS1-FOXO1 and/or NRAS$^{G12D}$. GFP and mCherry double positive cells were sorted 48 h later, and washed three times and grown in the absence of cytokine. Cell growth and viability were monitored daily by Trypan blue using a TC10 automated cell counter (BIO-RAD). Each experiment was performed three times.

**Real Time Quantitative PCR**
For quantitative reverse transcription-PCR (qRT-PCR), total RNA was extracted using the RNeasy Micro kit (Qiagen) according to the manufacturer’s protocol. Total RNA (500 ng) was reverse transcribed into cDNA using oligoT primers and the SuperScript III reverse transcriptase kit (Invitrogen). Quantitative real-time PCR was performed by using ABI Prism 7900HT detection system (Applied Biosystems) with Faststart SYBR Green master mix (Roche). Relative expression was calculated as a ratio of FOXO1 to GAPDH. Primer sequences of FOXO1 and GAPDH were as follows: FOXO1 (forward: 5’-GAAGAAAGCATCTCTCCAGTC-3’; reverse: 5’-GATCATCCTGTTCGGTCATAAT-3’); GAPDH (forward: 5’-ACATCAAGAAGTGGTGTAAG-3’; reverse: 5’-TGACAAAGTGTCGTTGAG-3’).

**Gene Expression Analysis**
The raw gene expression data and clinical data from four cohorts of childhood ALL patients were provided by other research groups [8–10]. To perform interarray comparisons, the CEL files were analyzed using Affymetrix MAS 5.0 software. The FOXO1 expression level relative to that of GAPDH was calculated as log2. Two-tailed t tests were used to validate the significance of the observed differences.

**Statistics**
Correlation analysis of the FOXO1 expression level with clinic pathological variables was performed by two-sided Chi-square test. The statistical software SPSS16.0 was used for all the statistical analysis.

**Results**
Identification of novel MEIS1-FOXO1 fusion gene in an induction failure ALL case
A 2-year-old boy was diagnosed with precursor B-cell ALL in March 2018. Enrolled into CCCG-ALL-2015 clinical trial (ChiCTR-IPR-14005706), this patient was refractory to conventional chemotherapeutic agents and failed to achieve complete remission at the end of induction therapy (Fig. 1A). Regular clinical tests showed an B-Cell precursor ALL (BCP-ALL) with abnormal 46,XY,del(17)(p11)[15]/46,XY,i(17)(q10)[2]/46,XY[3] karyotype, and without any identified fusion genes (Supplementary Fig. 1). A land-scale capture sequencing identified the NRAS\(^{G12D}\), TP53\(^{R273H}\), ABCC1\(^{R1176X}\), PHGR1\(^{H37P}\), HOXA3\(^{P219L}\), and DST\(^{P4606L}\) mutation (Fig. 1B and supplementary Fig. 2). By performing RNA sequencing, we identified a novel MEIS1-FOXO1 fusion gene: in-frame fusion of exon 1-6 of MEIS1 with exon 2 of the FOXO1 gene, which was confirmed by Sanger sequencing (Fig. 1C and Supplementary Fig. 3).

**The Oncogenic Potential Of MEIS1-FOXO1**

By using an IL3-dependent growth mouse hematopoietic progenitor cell line Ba/F3, we tested the oncogenic potential of MEIS1-FOXO1. Ectopic expression of the fusion gene in combination with NRAS\(^{G12D}\) efficiently induced Ba/F3 cells IL3-independent growth and transformation in a faster fashion as compared to NRAS\(^{G12D}\) alone (Fig. 2A), suggesting its oncogenic effect. Using the same cell model, we tested the impact of MEIS1-FOXO1 on cell cycle distribution and found that MEIS1-FOXO1 potentiated S-phase entry in comparison with NRAS\(^{G12D}\) alone (Fig. 2B).

**Low FOXO1 Expression Level Associated With Unfavorable All Subtype**

We first examined their expression in human and mouse hematopoiesis and in B-ALL patient samples and found gradual up-regulation of FOXO1 expression was observed during B cell differentiation while no characteristic pattern was identified in MEIS1, suggesting the tumor suppressor role of FOXO1 in B cell development (Fig. 3A). As shown in Fig. 3B and supplementary Fig. 4, FOXO1 was constitutively expressed in B-ALL cells while MEIS1 was merely expressed, suggesting that FOXO1 but not MEIS1 played an important role in B-ALL leukemogenesis. As shown in Fig. 3C and supplementary Fig. 5, the FOXO1 transactivation activity was completely abolished in MEIS1-FOXO1 as compared to wild-type FOXO1, suggesting that the FOXO1 was totally loss of function in this induction failure patient. We then tested the association of FOXO1 expression with risk stratification in multiple datasets. We
retrieved the FOXO1 expression data from Pediatric Cancer Genome Project (PCGP)[8] and found that FOXO1 was highest expressed in ETV6-RUNX1 fusion cases while lowest expressed in infantile leukemia (Fig. 3C). Next, we applied the same strategy to analyze data from the Ma-Spore ALL cohort [9] and reached the same correlation pattern (Supplementary Fig. 6). Moreover, in the Ma-Spore ALL cohort, we found that lower FOXO1 expression was associated with higher minimal residual disease (MRD) burden post induction therapy ($P = 3.8 \times 10^{-4}$ by Wilcox test, Fig. 3D).

Low FOXO1 expression level was specifically found in relapsed B-ALL

To further assess the impact of FOXO1 on B-ALL relapse, we first examined the FOXO1 mRNA level using diagnostic and relapsed B-ALL samples in our GWCMC ALL cohort under CCCG-ALL-2015 protocol using real-time quantitative PCR assay. As shown in Fig. 4A, the FOXO1 transcription was significantly higher in the diagnosed ALL samples than in the relapsed samples, suggesting that FOXO1 loss of function might be an important factor in B-ALL relapse. This expression pattern was also observed in the St. Jude PCGP dataset (Fig. 4A). To further validate this finding, we next tested the FOXO1 transcription level among the matched diagnosis-relapse samples in our study cohort and identified an extremely low FOXO1 expression in the relapsed samples as compared to their diagnostic counterparts (Fig. 4B). This result was again confirmed in another matched diagnosis-relapse dataset (Supplementary Fig. 7), consolidating the role of FOXO1 in B-ALL poor prognosis. In order to preliminarily explore how lower FOXO1 expression contributes to higher MRD level and relapse, we performed the drug resistance association analysis using the datasets published by Paugh SW et al[10]. Interestingly, we did find that lower FOXO1 expression was significantly correlated with glucocorticoid resistance (Fig. 4C), a very key component in the ALL therapy.

Discussion

Refractory/relapsed ALL (RR-ALL) is the first priority issue to clinicians and translational researchers. Multiple layers of factors, e.g., somatic genomic lesions, inherited variation, micro-environment, and acquired mutations, played important roles in RR-ALL. Recent studies showed that FOXO1 was a predominant transcription factor in B-lineage-restricted progenitor cells. Pre-BCR signaling activation can suppress FOXO1 transcription activity and subsequent B-ALL cells maintenance. However, no
report has been focus on the role of FOXO1 in B-ALL prognosis.
In this study, we identified a novel FOXO1 fusion gene in an induction failure B-ALL patient, namely MEIS1-FOXO1. FOXO1 gene belongs to the forkhead family of transcription factors, which play roles in myogenic growth and differentiation, cancer development, and therapy [11-14]. Translocation of FOXO1 with PAX3 and PAX7 has been reported in pediatric alveolar rhabdomyosarcoma [8, 15]. In the meanwhile, two cases of FOXO1 fusions with unknown genes have been identified in BCP-ALL [8], while the role of FOXO1 in B-ALL remains clarified. Using an IL3-dependent growth mouse hematopoietic progenitor cell line Ba/F3, we found that MEIS1-FOXO1 in combination with NRASG12D efficiently induced Ba/F3 cells IL3-indepdent growth and transformation in a faster fashion as compared to NRASG12D alone, suggesting its oncogenic effect. Also we observed that MEIS1-FOXO1 potentiated S-phase entry.
Robert and Mark et al have demonstrated that Foxo1 is a key regulator B cells development, in which Foxo1 inactivation cause differentiation blockage at the pro-B cell stage, suggesting Foxo1 function as a tumor suppressor in mouse[16, 17]. To initially probe the role of MEIS1 and FOXO1 in hematopoiesis and leukemogenesis, especially in B cells differentiation, we first analyzed their expression during hematopoiesis and B-ALL [18-20]. Interestingly, gradual up-regulation of FOXO1 expression was observed during B cells differentiation while no characteristic pattern was identified in MEIS1, suggesting the important role of FOXO1 in B cells development. In combination with the result that the FOXO1 transcription activity was almost completely abolished in the MEIS1-FOXO1 protein, while it MEIS1 transcription activity was normal. Our novel fusion gene finding and its FOXO1 loss of function supported FOXO1 also functioned as a tumor suppressor.
The FOXO1 transactivation activity was completely abolished in MEIS1-FOXO1 as compared to wild-type FOXO1, suggesting that the FOXO1 was totally loss of function in this induction failure patient. FOXO1 has been reported as a predominant transcription factor in B-lineage-restricted progenitor cells [16, 17]. Pre-BCR signaling activation can suppress FOXO1 transcription activity and subsequent B-ALL cells maintenance [21, 22], however, the role of FOXO1 in B-ALL risk stratification and relapse
remains unclear. To address this question, we used sets of dataset to associate the FOXO1 expression with risk stratification. The FOXO1 was highest expressed in ETV6-RUNX1 fusion cases (a well-known excellent prognosis group) while lowest expressed in infantile leukemia, this pattern was confirmed by different cohort studies [9]. Interestingly, we also identified the correlation between lower FOXO1 expression and higher minimal residual disease (MRD) burden post induction therapy ($P = 3.8 \times 10^{-4}$). All these evidences suggested that lower FOXO1 expression might be one of the independent prognostic factor in childhood B-ALL.

Through real-time quantitative PCR assay, we found that the FOXO1 transcription was significantly lower in relapsed samples, suggesting that FOXO1 loss of function might be an important factor in B-ALL relapse. We performed this association analysis again using serial datasets and reached the same pattern. To gain a more convincing evidence, we tested the FOXO1 transcription level among the matched diagnosis-relapse paired samples to further confirm our findings. Using our study cohort, PCGP data and GSE28642, we uniformly confirmed that FOXO1 was significantly lower expressed in relapse samples than their primary diagnosis samples. Question still remained that how lower FOXO1 expression did contribute to higher MRD level and relapse, we found that lower FOXO1 expression was significantly correlated with glucocorticoid resistance, a very key component in the ALL therapy.

Conclusions
In this study, we identified a novel fusion gene of MEIS1-FOXO1 and systemically characterized the prognostic impact of FOXO1 in B-ALL. Importantly, this is the first report that FOXO1 loss of function was associated with ALL high-risk stratification and relapse, which might be due to drug resistance. Our findings provide new insights into the application of genomic information may to guide our B-ALL risk stratification and relapse prediction, which is conducive to precision medicine.

Abbreviations
FOXO1, Forkhead box O1
ALL, acute lymphoblastic leukemia
qRT-PCR, Quantitative real-time polymerase chain reaction
Ph, Philadelphia chromosome
CAR-T, chimeric antigen receptor (CAR) T-cell therapy
HSCT, hematopoietic stem cell transplant
BCP-ALL, B-Cell precursor acute lymphoblastic leukemia
CCCG-ALL-2015, Chinese Childhood Cancer Group-Acute lymphoblastic leukemia-2015

Declarations

Ethical Approval and Consent to participate
This study was approved by the institutional ethics committee of Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, and performed in accordance with the Declaration of Helsinki. Written informed consent to participate this study was obtained from patients or their guardians.

Consent for publication
Not applicable.

Availability of data and material
Not applicable.

Competing interests
The authors declare no competing financial interests.

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Authors' contributions
H.Z., C.J., H.L., and Q.Z. designed the research; H.Z., C.J., Z.L., and J.Q. performed experiments; H.Z., P.W., W.H., H.H., and Q.Z. recruited and followed up the patient; H.Z, J.C., H.L., M.Q., and Q.Z.
analyzed results; and H.Z., C.J., H.L., and Q.Z. wrote the paper. All authors have read and approved this manuscript.

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**Figures**

Identification of novel MEIS1-FOXO1 fusion gene in an acute lymphoblastic leukemia patient with induction failure. (A) Plot of therapeutic response in this induction failure ALL case. (B) Somatic mutations identified this case. (C) Schematic representation of novel MEIS1-FOXO1 rearrangement.
Oncogenic potential of MEIS1-FOXO1 fusion gene. (A) MEIS1-FOXO1 potentiated leukemia transformation in BaF3 cell model. (B) MEIS1-FOXO1 triggered S-phase cell cycle entry.
Lower FOXO1 transcription associated with poor prognosis. (A) FOXO1 transcription was increased within human (left panel) and mouse (right panel) B lymphocyte development. (B) The transcription activity of MEIS1-FOXO1 was completely destroyed. (C) FOXO1 was constitutively expressed among B-ALL, with the highest expression in ETV6-RUNX1 subtype. (D) Lower FOXO1 expression conferred higher MRD burden in children with B-ALL.
Figure 4

Lower FOXO1 transcription correlated with ALL relapse. (A) Lower FOXO1 expression was found in relapsed B-ALL as compared to primary samples in our institutional data (left panel) and St. Jude Children’s Research Hospital data (right panel). (B) The FOXO1 transcription was extremely low in relapsed B-ALL among the diagnosis-relapse matched paired samples. (C) Lower FOXO1 expression associated with dexamethasone resistance.

Supplementary Files

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MEIS1-FOXO1 Fusion gene_2018.8.15.pdf
Supplementary Figure.pdf