2020 INTERNATIONAL CONFERENCE of CANCER and AGING

Regulatory network analysis reveals the oncogenesis roles of feed-forward loops and therapeutic target in T-cell acute lymphoblastic leukemia

Mengxuan Xia#, Qiong Zhang#, Mei Luo, Pan Li, Yingxue Wang, Qian Lei*, An-Yuan Guo*

Background
T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematological malignancy. Aberrant expressed genes contribute to the development and progression of T-ALL. However, the regulation underlying their aberrant expression remains elusive. Dysregulated expression of transcription factors and miRNAs played important regulatory roles in the pathogenesis of T-ALL.
Methods
In this study, we analyzed the alteration of transcriptome profiling and regulatory networks between T-ALL sample and normal T cell samples at transcriptional and post-transcriptional levels.
Results
Our results demonstrated that genes related to cell cycle and cell proliferation processes were significantly upregulated in T-ALL comparing to normal samples. Meanwhile, regulatory network analyses revealed that FOXM1, MYB, SOX4 and miR-21/19b as core regulators played vital roles in the development of T-ALL. FOXM1-miR-21-5p-CDC25A and MYB/SOX4-miR-19b-3p-RBBP8 were identified as important feed-forward loops involved in the oncogenesis of T-ALL. Drug-specific analyses showed that GSK-J4 may be an effective drug, and CDC25A/CAPN2/MCM2 could serve as potential therapeutic targets for T-ALL.
Conclusions
This study may provide novel insights for the regulatory mechanisms underlying the development of T-ALL and potential therapeutic targets.

➢ Results

Fig.1 Differential expression analysis in T-ALL vs normal T-cells. (**a**) GO enrichment results of upregulated DEGs (red). (**b**) Venn graph of DEGs in the two comparisons. C: T-ALL Cell lines, N: Normal human T-cells, P: T-ALL patients. Numbers in the sectors are the numbers of DEGs downregulated (green) and upregulated (red). (**c**) GO enrichment results of downregulated DEGs (green)

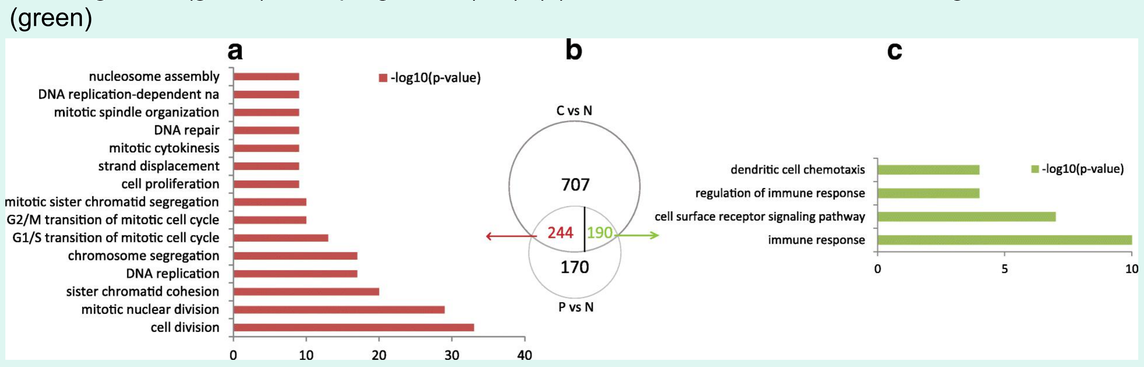


Fig.2 (a) Hierarchical clustering of miRNAs significantly differentially expressed in the comparisons of T-ALL samples (patients and cell lines) vs normal T cells (b) Hierarchical clustering of TFs. Upregulation in red and downregulation in green

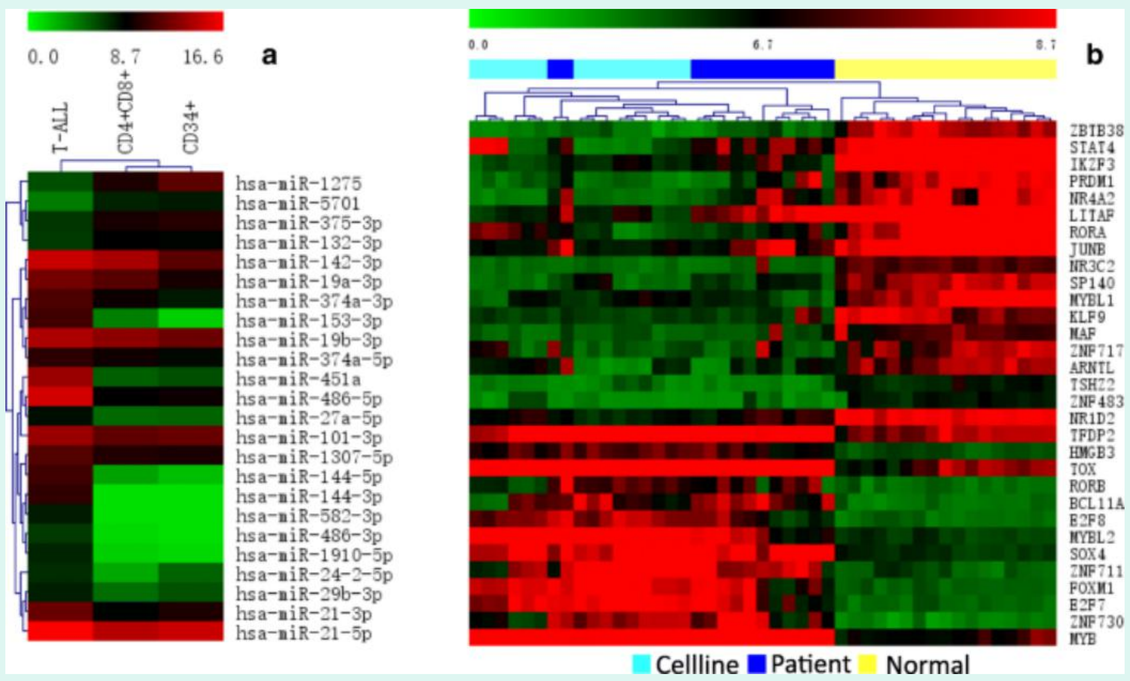


Fig.3 The regulatory network of DEGs and DEMs. Green, downregulated genes and miRNAs. Red, upregulated genes and miRNAs. The diamond nodes, TFs; Ellipse nodes, DEMs; Round Rectangle, DEGs. The size of the nodes represents the degree of the nodes

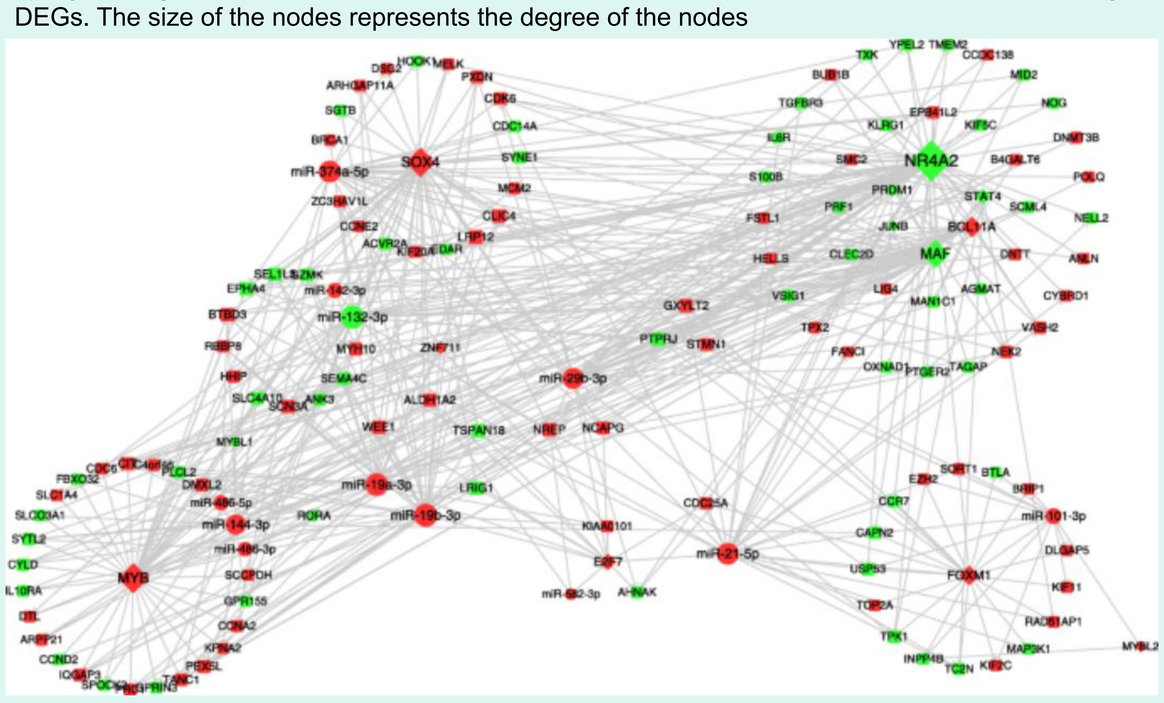


Fig.4 TF and miRNA regulatory subnetwork of cell cycle and cell proliferation genes. Light blue Round Rectangle, enriched GO terms; Grey line, regulatory relationship of TFs and miRNAs to genes; Blue line, relationship of mRNAs to GO terms. The means of nodes are the same as Fig. 3

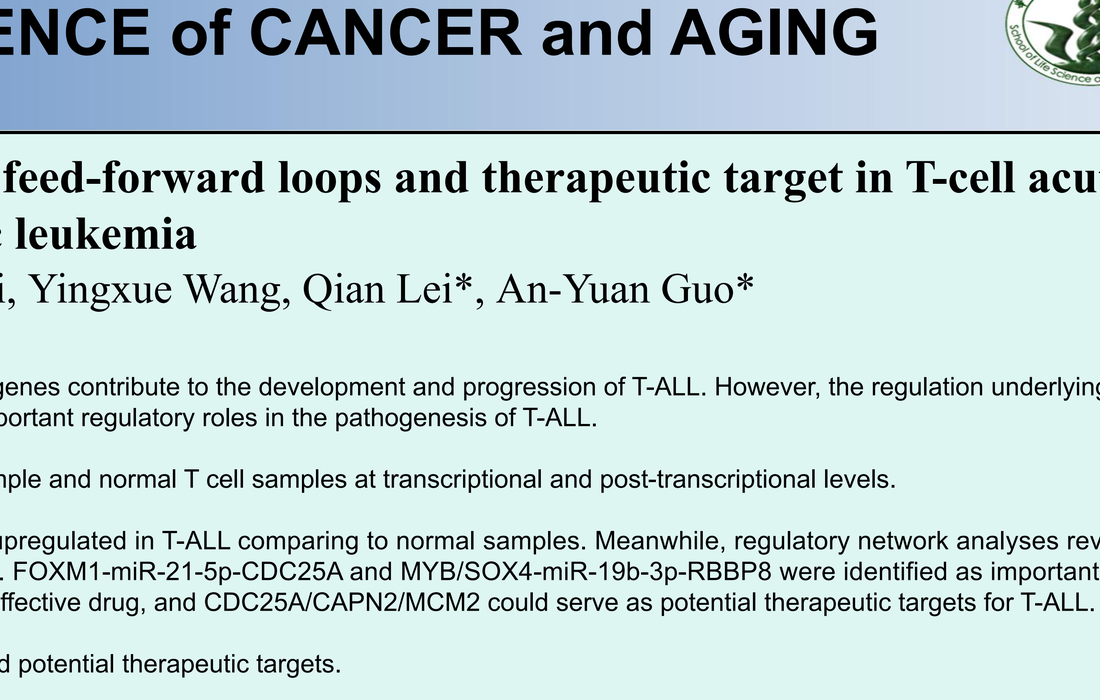


Fig.5 FFLs for *FOXM1*-miR-21-*CDC25A* and *MYB*/*SOX4*-miR-19b-*RBBP8* and their enriched GO terms. The means of nodes are the same as Fig. 3

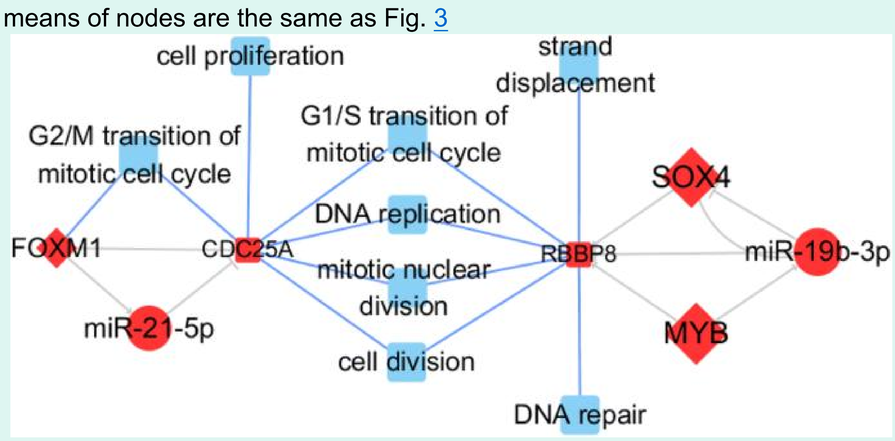
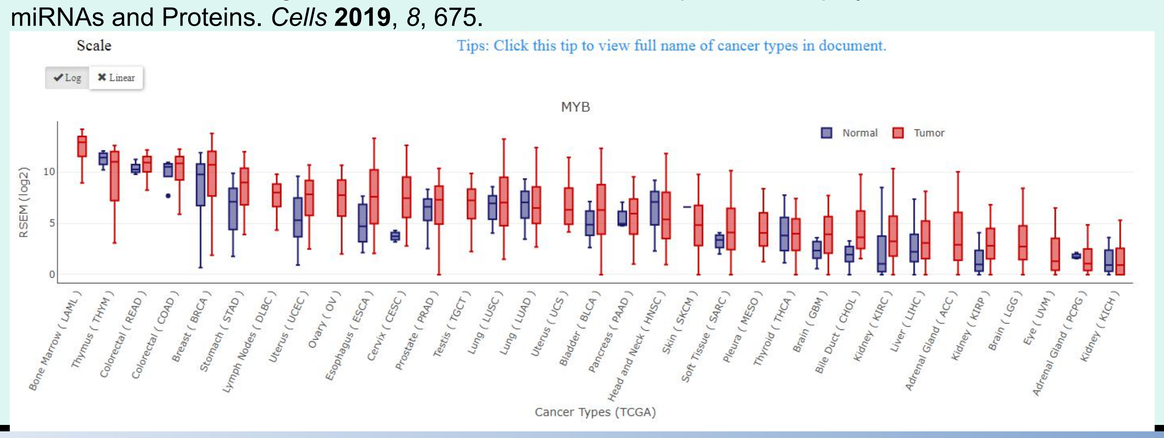
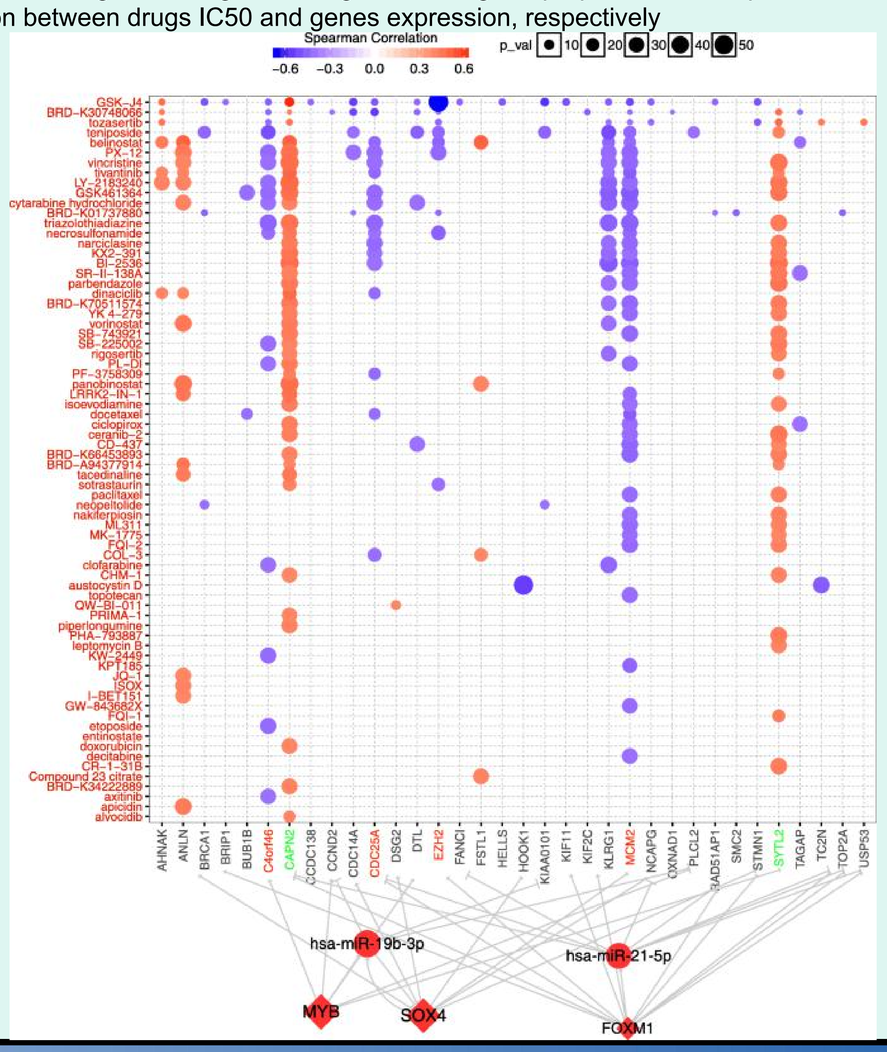


Fig.6 The correlation of drugs IC50 and genes in the regulatory network of FOXM1, MYB, SOX4, miR-21-5p and miR-19b-3p. Drug names are in red font. Upregulation significance genes are red; downregulation significance genes are green. Orange or purple dots mean positive or negative correlation between drugs IC50 and genes expression, respectively

Fig.7 MYB expressed highest expression in LAML cancer.
Displayed by GEDS (http://bioinfo.life.hust.edu.cn/web/GEDS/)
Xia, M.; Liu, C.-J.; Zhang, Q.; Guo, A.-Y. GEDS: A Gene Expression Display Server for mRNAs, miRNAs and Proteins. *Cells* **2019**, *8*, 675.





Supervisor: Jianfeng Liu
Key Laboratory of Molecular Biophysics of Ministry of Education,
School of Life Science and Technology,
Huazhong University of Science and Technology
Email: jfliu@mail.hust.edu.cn