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Alternative Splicing Factor Rbm17 Affects Proliferation and Aging of MDS-HSPC

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INTRODUCTION

Myelodysplastic syndrome (MDS) is a diverse clonal hematopoietic stem cell disorder. The gene expression profile of hematopoietic stem cells and progenitor cells (HSPC) was analyzed in MDS patients by using single-cell sequencing to reveal a new pathogenesis of MDS and provide new strategies for the treatment of blood diseases such as MDS.

AIM

This study analyzed the gene expression profile of HSPC in MDS patients (MDS-HSPC) using single-cell sequencing (scRNA-seq) and explored the role of variable splicing factor Rbm17 in the pathogenesis of MDS.

METHOD

We used scRNA-seq, CUT&Tag, CRISPR/cas9, and FCM technologies, with a focus on elucidating the upstream regulatory factors and the downstream pathways regulated by Rbm17.

RESULTS

MDS-HSPC exhibit impaired differentiation into myeloid and lymphoid lineages. By comparing the KEGG signaling pathways of quasi-temporal processes, we found the differentiation-related notch signaling pathway was significantly reduced in MDS patients (Figure a). In addition, signaling pathways related to cellular biologic functions such as DNA replication were decreased in MDS patients (Figure b). Compared to the normal group‘s HSC (hematopoietic stem cell) and MPP (multipotent progenitor), upregulated genes of HSC and MPP in MDS are mainly enriched in "cell burial effect" and "Wnt signaling pathway“ . The downregulated genes are mainly enriched in OXPHOS and DNA repair, indicating that MDS-HSPC are in an aging state (Figure c). We discovered proliferation-related genes (such as CDK1) in MDS-HSPC by comparing differentially expressed genes. The expression of CDK4 and Mki67 was decreased, while HK2 expression was increased (Figure d). Further analysis combining single-cell sequencing and transcriptomics data showed that Rbm17 was significantly downregulated in MDS-HSPC (Figure d). We constructed SKM-1 cell lines with Rbm17 knockout using CRISPR-Cas9 technology. SKM-1 cells with Rbm17 deficiency have high expression of aging-related genes (IL27RA) and HK2, with low expression of CDK1, CDK4, and Mki67. Intracellular lactate concentration in cells with Rbm17 deficiency was increased. In addition, P300 is upregulated in MDS-HSPC, while HDAC1 and HDAC3 are downregulated (Firgure d).

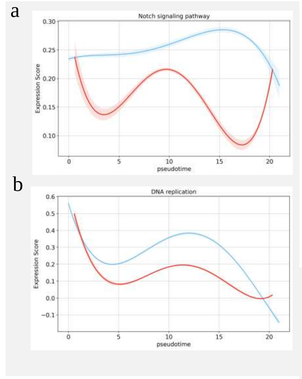


Figure a and b. By comparing the KEGG signaling pathways of quasi-temporal processes, the notch signaling pathway was significantly reduced in MDS patients. DNA replication signaling pathway were decreased in MDS patients.

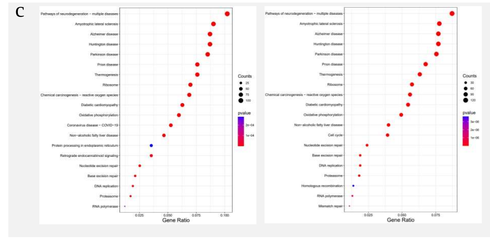
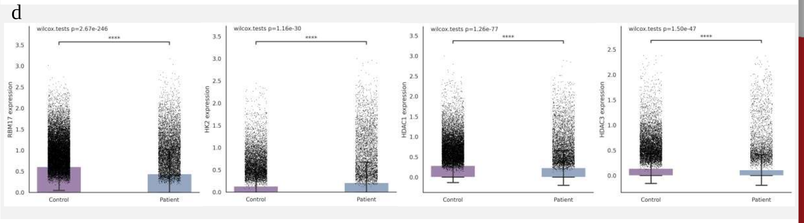


Figure c. The downregulated genes of HSC (right) and MPP (left) are mainly enriched in OXPHOS and DNA repair.

Figure d. Rbm17 was significantly downregulated in MDS-HSPC. The expression of glycolysis-related gene HK2 was increased. The expression of protein lactate related genes HDAC1 and HDAC3 was decreased



CONCLUSIONS

- RBM17 regulates disease progression in leukemia[1].
- In MDS-HSPC, Rbm17 downregulation promotes differentiation disorders by regulating aging and proliferation genes, resulting in increased aging markers and altered proliferation potential. Further research is needed to elucidate its mechanisms.

REFERENCES

1 Liu L, Vujovic A, Deshpande NP, et al. The splicing factor RBM17 drives leukemic stem cell maintenance by evading nonsense-mediated decay of pro-leukemic factors. *Nat Commun*. 2022;13(1):3833.

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