LncRNA profiling reveals that the deregulation of H19, WT1-AS, TCL6, and LEF1-AS1 is associated with higher-risk myelodysplastic syndrome

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Methods

➢ Microarray expression profiling and RT-qPCR of IncRNAs and protein-coding genes (PCGs) were performed in 183 CD34+ bone marrow cells of MDS patients and healthy controls.
➢ Expression profiles were analyzed in relation to different aspects of the disease (i.e., diagnosis, disease subtypes, cytogenetic and mutational aberrations, and risk of progression).
➢ IncRNA-PCG networks were constructed to link deregulated IncRNAs with regulatory mechanisms associated with MDS.

Results

➢ Several IncRNAs were strongly associated with disease pathogenesis (e.g., H19, WT1-AS, TCL6, LEF1-AS1, EPB41L4A-AS1, PVT1, GASS, and ZFAS1).

Figure 1. Heatmap of differentially expressed IncRNAs among MDS subtypes (FDR < 0.05). The analysis defined three clusters of samples with comparable expression profiles. The expression level is calculated as the binary logarithm of fold change (logFC) compared to the mean expression of controls. Blue - downregulation, red - upregulation, white - unchanged expression.

➢ Downregulation of LEF1-AS1 and TCL6 and upregulation of H19 and WT1-AS were associated with adverse outcomes in MDS patients. Multivariate analysis revealed that the predominant variables predictive of survival are blast count (p < 0.001), H19 level (p = 0.015), and TP53 mutation (p = 0.004).

Figure 2. (A) Expression of H19, WT1-AS, LEF1-AS1, and TCL6 IncRNAs according to IPSS-R risk score.
(B) Kaplan-Meier curves for overall survival of MDS patients stratified based on IncRNA levels.
(C) Univariate analysis for overall survival (OS) and progression-free survival (PFS) of MDS patients. Hazard ratios including 95% confidence intervals are plotted and the significance of the results is included (*p < 0.05, **p < 0.01, ***p < 0.001, n.s. - nonsignificant).

➢ Transcriptional regulation in the H19/IGF2 region is disrupted in higher-risk MDS, and discordant expression in this locus is associated with worse outcome.

Figure 4. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) in MDS patients with concordant vs. discordant expression of the H19/IGF2 and H19/miR-675 pairs.

➢ Coexpression network data suggested that prognosis-related IncRNAs are predominantly related to cell adhesion and differentiation processes (H19 and WT1-AS) and mechanisms such as chromatin modification, cytokine response, and cell proliferation and death (LEF1-AS1 and TCL6).

Conclusion

We identified specific IncRNAs contributing to MDS pathogenesis and proposed cellular processes associated with these transcripts.

Of the IncRNAs associated with patient prognosis, the level of H19 transcript might serve as a robust marker comparable to the clinical variables currently used for patient stratification.

Aim of the study

We aimed to characterize IncRNAs deregulated in MDS that are involved in disease pathogenesis and may function as novel disease biomarkers.