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Genetic, Epigenetic, and Clinical Significance of Wilms' Tumor 1 (WT-1) Gene in Acute Myeloid Leukemia

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INTRODUCTION

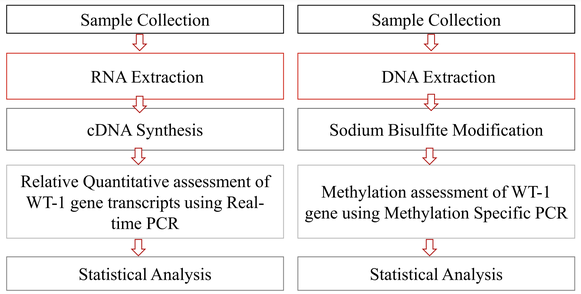
Acute myeloid leukemia (AML) is a genetically intricate hematologic malignancy characterized by aberrant differentiation and proliferation of myeloid progenitor cells in the bone marrow. The Wilms' tumor 1 (WT-1) gene serves as a crucial regulator of malignant hematopoiesis, modulating cell growth, apoptosis, and differentiation through its zinc-finger transcription factor activity. Despite its importance, the epigenetic and clinical significance of WT-1 in AML remains elusive.

AIM

This study aims to investigate the RNA expression, methylation levels, and molecular functions of the WT-1 gene in AML.

METHOD

This prospective clinical research was performed in our institution from 2020-2024. Bone marrow (BM) and peripheral blood (PB) samples were collected from 174 AML cases at diagnosis, 143 post-induction chemotherapy, and 20 non-malignant controls. WT-1 gene expression and promoter methylation status were evaluated using reverse transcription-polymerase chain reaction (RT-PCR) and methylation-specific PCR (MS-PCR). Additionally, molecular and biological functions of WT-1 were explored through Gene Set Enrichment Analysis (GSEA), and its relationship with immune checkpoint analysis was assessed using the Sangerbox database. A flow cytometric immunophenotyping study was also performed using a panel of monoclonal antibodies specific to AML.



RESULTS

Among the 174 subjects studied, 82.43% exhibited WT-1 gene overexpression at diagnosis compared to cases in complete remission or controls (P<0.001). Furthermore, robust hypermethylation of the WT-1 promoter was observed in 75.67% of AML cases at diagnosis (P<0.001). WT-1 expression and methylation levels were inversely correlated with normal hematopoiesis and positively associated with age, high marrow blast counts, adverse risk cytogenetics, and inferior outcomes. GSEA revealed WT-1's involvement in transcription misregulation of cancer and various molecular functions related to cell growth, proliferation, and apoptosis. Additionally, WT-1 expression positively correlated with immune checkpoint markers such as CD28, CD40, and CD86. The flow cytometric immunophenotyping study demonstrated that CD34, CD45, CD117, CD38, and CD56 were expressed as positive in most cases, while cCD79a, CD19, CD7, cCD3, CD123, CD11b were negatively observed.

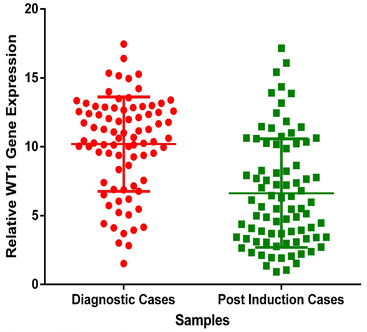
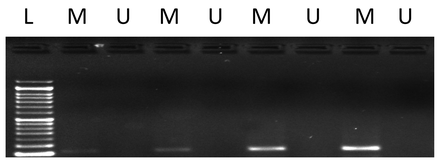
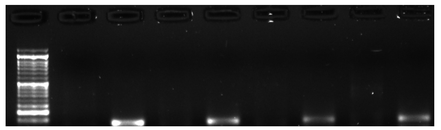


Fig 1. WT-1 Gene Expression at the time of diagnosis (day-0) and after completion of induction chemotherapy (day-28).



MSP-PCR Result of AML Patients at the Time Diagnosis (Day 0)



MSP-PCR Result of AML Patients after Induction Therapy (Day 28)

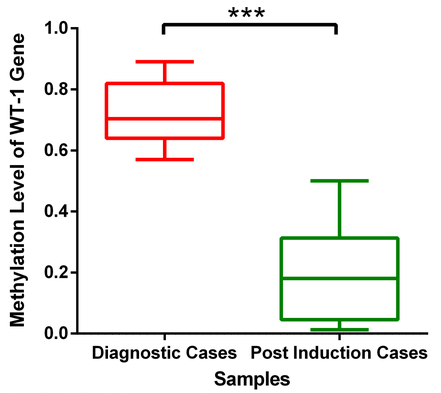


Fig 2. WT-1 Methylation Level at the time of diagnosis (day-0) and after completion of induction chemotherapy (day-28).

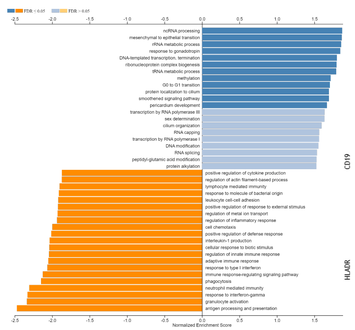


Fig 3. Molecular and Biological Functions of WT-1 identified using Gene set enrichment analysis (GSEA).

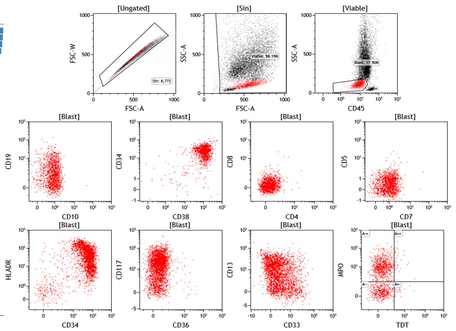


Fig 4. Flowcytometry Immunophenotyping of AML Cases

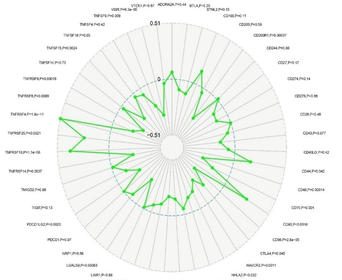


Fig 5. WT-1 gene expression and their association with immune checkpoints.

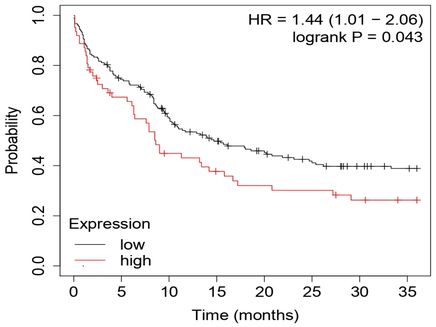


Fig 6. WT-1 gene expression and their association with Overall Survival.

CONCLUSIONS

Overexpression and hypermethylation of WT-1 are associated with increased leukemic burden in AML, suggesting its potential as a molecular marker for early diagnosis, minimal residual disease detection, and a therapeutic target against AML.