Rewriting the Leukemic Landscape: Hypoxia and MicroRNA Interplay in AML

Mostafa Mohamed 1, Mohamed H Elbahoty 1,2, Amr Elhammsy1.
Affiliations:
Department of Pathology, University of Alabama at Birmingham, AL, USA.
Hematology Unit, Department of Internal Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Introduction

Acute Myeloid Leukemia (AML) is a biologically diverse and aggressive blood cancer marked by high relapse rates and therapeutic resistance. Hypoxia within the bone marrow niche supports leukemic stem cell survival and contributes to minimal residual disease (MRD), posing major challenges to long-term remission.

Aim

To examine how hypoxia-induced microRNAs (hypoxamirs) contribute to AML progression and therapy resistance, and to identify potential molecular targets within this regulatory network.

Design & Methods

- A retrospective, bioinformatics-based study integrating transcriptomic and miRNA expression profiles from AML cohorts. Hypoxia scoring was applied using established gene expression signatures, followed by pathway and correlation analyses.
- Over 400 AML patient samples with linked clinical data (survival and treatment response) were included. Patients were stratified based on hypoxia scores calculated from Buffa and Winter gene signatures.

Setting

Data were derived from publicly available datasets (TARGET-AML and TCGA-LAML), encompassing adult AML cases across multiple institutions. Findings are relevant to translational AML research.

Interventions

No clinical interventions were performed. Analytical methods included:

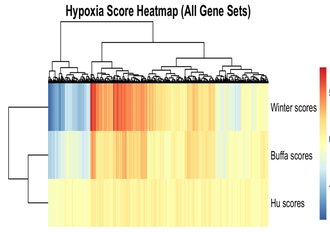
. Computation of hypoxia scores per patient
. Performing differential expression analysis for miRNAs.
. Integration of miRNA expression with hypoxia indices

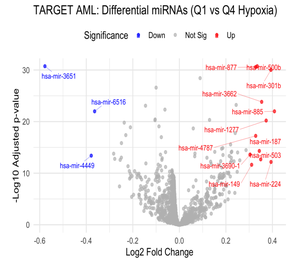
Results

- Key outcomes included identification of differentially enriched pathways and hypoxia-associated miRNAs linked to poor survival and therapeutic response.
- Hypoxia-high AML cases exhibited enrichment in stemness and proliferation-related pathways.
- Elevated hypoxia was consistently associated with increased expression of miR-3662, miR-503, and miR-877—hypoxamirs known to correlate with adverse prognosis and resistance to therapy.

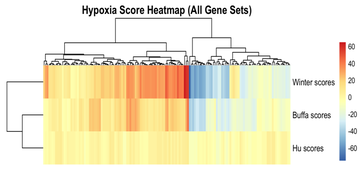
Results

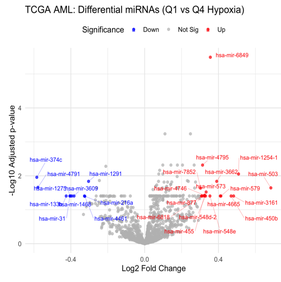
TARGET

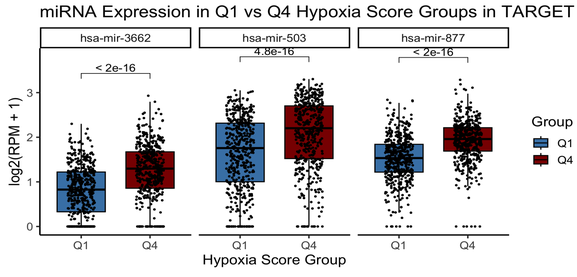


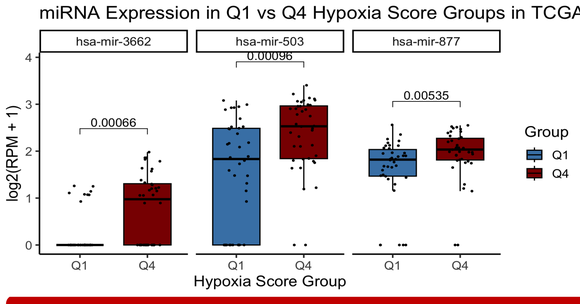


TCGA









Summary

This study highlights the hypoxia–miRNA axis as a critical regulator of AML aggressiveness and drug resistance. Hypoxia-driven miRNAs represent promising targets for therapeutic intervention. Future experimental validation and clinical exploration are warranted to leverage these insights for improved AML treatment strategies.

References

1. Shimony S, Stahl M, Stone RM. Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2023;98(3):502-26.
2. Zhou Y, Huang G, Cai X, Liu Y, Qian B, Li D. Global, regional, and national burden of acute myeloid leukemia, 1990–2021: a systematic analysis for the global burden of disease study 2021. Biomarker Research. 2024;12(1):101.
3. Bruno S, Mancini M, De Santis S, Monaldi C, Cavo M, Soverini S. The Role of Hypoxic Bone Marrow Microenvironment in Acute Myeloid Leukemia and Future Therapeutic Opportunities. Int J Mol Sci. 2021;22(13).
4. Magliulo D, Bernardi R. Hypoxic stress and hypoxia-inducible factors in leukemias. Frontiers in Oncology. 2022;12.
5. Chandraprabha Vineetha R, Anitha Geetha Raj J, Devipriya P, Sreelatha Mahitha M, Hariharan S. MicroRNA-based therapies: Revolutionizing the treatment of acute myeloid leukemia. International Journal of Laboratory Hematology. 2024;46(1):33-41.

SOHO2025