DNMT3A CO-MUTATION AND IMMUNE EXCLUSION SIGNATURES DEFINE OUTCOMES IN AML WITH IDH2 MUTATIONS

Feng-Ming Tien, Chi-Yuan Yao, Hsin-Yu Lu, Min-Yen Lo, Xavier Cheng-Hong Tsai, Wan-Hsuan Lee, Chien-Yuan Chen, Yuan-Yeh Kuo, Bor-Sheng Ko, Ming Yao, Hsin-An Hou, Wen-Chien Chou, Hwei-Fang Tien

[1]Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan [2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University Taipei, Taiwan [3]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan

INTRODUCTION

- Isocitrate dehydrogenase (IDH) exists in 3 isoforms: IDH1, IDH2 and IDH3, which convert isocitrate to α-KG and regulate cell functions.
- IDH2 mutations are recurrent genetic alterations in acute myeloid leukemia (AML), defining a subgroup with distinct co-mutation patterns as well as metabolic and epigenetic features.
- Although IDH1-mutated tumors have been associated with an immune exclusion phenotype (1), the transcriptomic basis of immune dysfunction and its prognostic relevance in IDH2-mutated (IDH2mut) AML remain incompletely understood.

AIM

- Utilize genomic and transcriptomic profiling to dissect the heterogeneity of IDH2mut AML.
- Clarify immune exclusion phenotype in IDH2mut AML.

METHOD

We analyzed 1,039 de novo non-M3 AML patients treated with standard intensive chemotherapy, with targeted mutational profiling and bulk RNA-seq analysis. Single-cell RNA sequencing (scRNA-seq) (GSE116256) were used to delineate the cell-type specific dysregulations (2).

CONCLUSIONS

- DNMT3A co-mutation confers adverse prognosis in IDH2-R140 AML.
- IDH2 mutations are associated with immune exclusion, particularly in T cells and progenitor cells, highlighting the relevance of host immunity in shaping prognosis.

RESULTS

- IDH2 mutations were identified in 11.9% of patients (R140 7.9%, R172 3.0%). Patients with IDH2-R140 and IDH2-R172 mutations exhibited distinct co-mutational patterns. (Fig.1)
- Concurrent DNMT3A mutations were associated with worse OS (P=0.010) and EFS (P=0.004) in those with IDH2-R140 but not those with R172 mutations, which were validated in AMLSG cohort. (Fig.2)

Fig.1

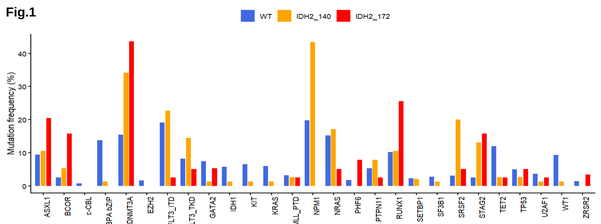
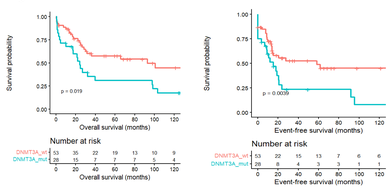


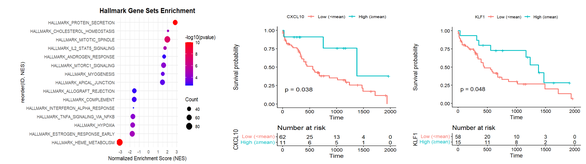
Fig.2



- Compared to IDH2wt AML, IDH2mut AML displayed significant negative enrichment of interferon-α (IFN-α) (NES -1.76, FDR 2.25E-3), IFN-γ signaling (NES -2.07, FDR 2.65E-8), and allograft rejection signatures (NES -2.31, FDR 2.50E-9), consistent with an immune exclusion phenotype. (Fig.3)
- IDH2mut patients with short EFS (<2 years) showed stronger immune exclusion, with CXCL10, KLF1, and CTSL identified as key DEGs that also stratified OS in BEAT-AML cohort. (Fig.4)

Fig.3

Fig.4



- In scRNA-seq analyses, a total of 10722 cells derived from 5 healthy donors (HD), 9 IDH2wt and 2 IDH2mut patients were analyzed. A higher proportion of T cells was observed in IDH2mut than IDH2wt AML. (Fig.5)
- IFN-γ pathway module scores were higher in monocytes, and T cells than progenitor cells. IDH2mut AML exhibited reduced IFN-γ module scores within cell subpopulations.(Fig.6)

Fig.5

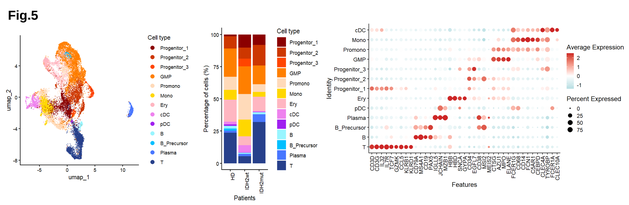
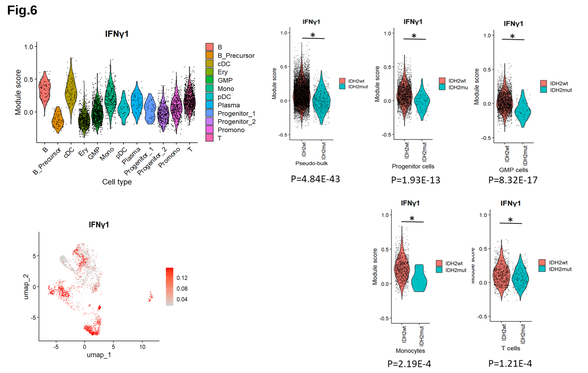
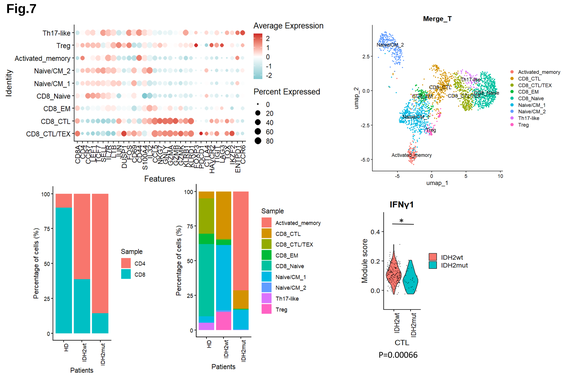


Fig.6



- T cells were subclustered. IDH2mut AML exhibited reduced CD8 T cell fractions within the CD3+ T cell compartment, IFN-γ module scores were significantly lower in the CTL clusters. (Fig.7)

Fig.7



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CONTACT INFORMATION

Feng-Ming Tien, M.D., M.Sc.

Attending Physician and Assistant Professor

Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

b92401007@gmail.com

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