#688 Transcriptome analyses in patients with myeloid malignancies treated with the IRAK4 inhibitor emavusertib

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Background

- Patients with hrMDS/AML present with a dynamic and diverse mutational landscape
- Splicing mutations drive overexpression of a highly active IRAK4 isoform triggering inflammation, oncogenesis and survival of cancer cells through activation of NFκB and other pathways (Fig 1)
- NFκB target genes, CCL4, IL1β and IER3 are highly expressed in patients with hrMDS and AML and are associated with a poor prognosis
- Emavusertib is a potent inhibitor of IRAK4 and FLT3 with efficacy in pre-clinical (3) and clinical studies
- **Goal**: to describe our findings from RNAseq of clinical samples from the ongoing TakeAim Leukemia trial

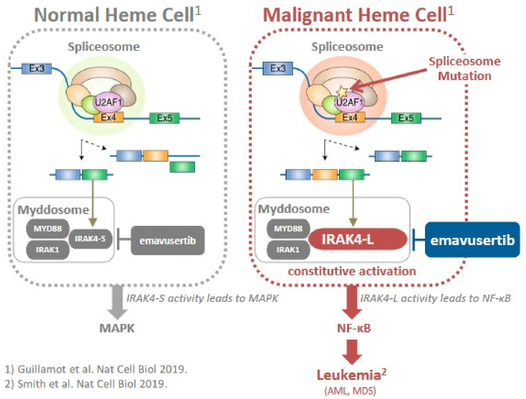


Fig 1. Spliceosome mutations (*SF3B1*, *U2AF1*) drive IRAK4-L isoform leading to overactivity of NFκB pathway

Methods

- Baseline and on treatment samples were collected from 26 AML, and 16 hrMDS patients from the ongoing TakeAim Leukemia Phase I/II Study CA-4948-102 (NCT04278768)
- Bulk RNA sequencing was performed on PBMCs and bone marrow samples
- Read depth ranged from 10.4 to 120 million reads. Percent reads aligned ranged from 67 to 92%
- QC was performed with FASTQC V0.11.8. Low quality reads were removed using Trimgalore V0.6.3
- Raw counts were normalized to total number of reads by calculating log2 Counts Per Million (CPM)

Abbreviations

MDS: Myelodysplastic neoplasms, AML: Acute Myeloid Leukemia, N.S.: non-significant, IL1β: Interleukin 1 beta, IER3: Immediate Early Response 3, CCL4 (MIP1β): C-C Motif Chemokine Ligand 4, Tx: treatment

Results

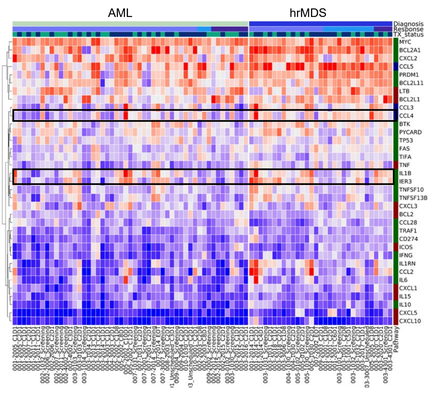


Fig 2. Differential Expression of IRAK4/NFκb pathway genes highlighting changes in gene expression by diagnosis, treatment status and response.

RNAseq data across all samples, regardless of Tx status, demonstrates predictive biomarkers of response and diagnosis in hrMDS/AML (Fig 3-4)

- *IL1β* (a known positive regulator of IRAK4 pathway) shows higher levels in hrMDS non-responder patients (P≤0.05)
- Antiapoptotic factor, *IER3*, is also expressed higher in hrMDS non-responders (P≤0.05)

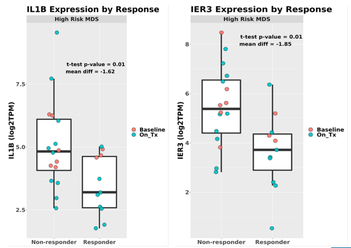


Fig 3. *IL1β* and *IER3* gene expression between responders and non-responders may serve as predictive biomarker of response

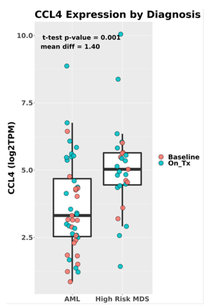
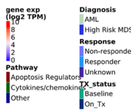


Fig 4. *CCL4* expression is significantly increased hrMDS patients compared to AML patients

- CCL4, a chemokine associated with heme malignancies, is expressed higher in hrMDS patient samples than AML



- CCL4 is a known chemokine associated with the pathophysiology of heme malignancies
- Patients with hrMDS demonstrate higher expression of *CCL4* (P≤0.05) when compared to AML at baseline and on Tx patient samples
- Other chemokines (CCL3) downstream of IRAK4, and associated with AML/hrMDS, present a similar differential expression pattern (N.S)

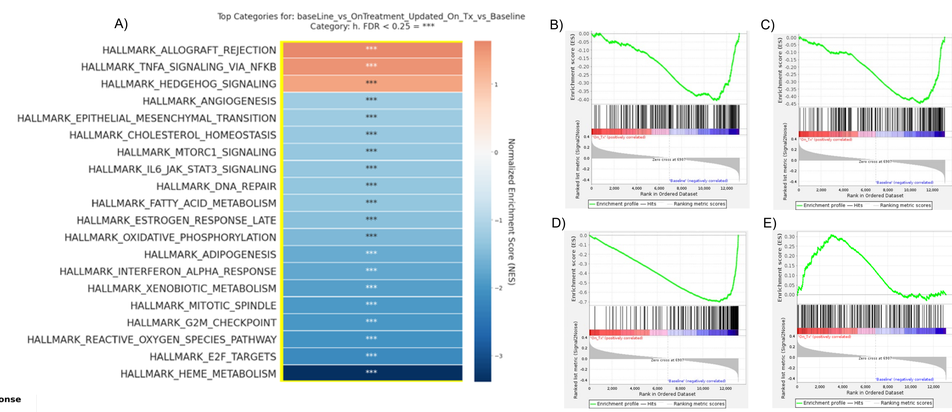


Fig 5. Hallmark pathway analysis, for AML and hrMDS patients treated with emavusertib (A). Gene Enrichment plots for Hallmark G2M Checkpoint pathway (B), Hallmark E2F Targets pathway (C), Hallmark Heme Metabolism pathway (D), and TNFα/NFκB signaling (E)

- G2M Checkpoint, E2F and heme metabolism pathways present the lowest enrichment scores in AML/hrMDS patients treated with emavusertib indicating decrease in cell cycle proliferation and metabolic markers
- TNFα/NFκB signaling pathway exhibits a higher enrichment score after data normalization indicating an increase in apoptosis
- Data indicates a decrease in the expression of cell cycle related factors and an increase in apoptosis via TNFα signaling

Conclusions

- hrMDS shows specific predictive biomarkers associated with clinical responses to emavusertib, with non-responders presenting higher expression of *IL1β* and *IER3* when compared to responders
- Chemokine CCL4, associated with heme malignances (4), demonstrates a higher expression in hrMDS when compared to AML. This reflects an associated increase in inflammatory status
- G2M checkpoint, E2F targets and heme metabolism Hallmark pathways are negatively enriched in AML/hrMDS patients treated with emavusertib compared to baseline. This suggests that these pathways are downregulated by emavusertib, while TNFα/NFκB signaling is upregulated suggesting an increase in apoptosis
- Future research will examine correlation of gene expression, mutational data and proteomics
- The data presented here demonstrates that emavusertib increases apoptosis/cell death and decreases cell proliferation and cell cycle (5,6). Overall, this data supports targeting the IRAK4/NFκB pathway with emavusertib in heme malignancies

References

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