Co-inhibition of *ATM* and *IKBKG* with JAK-STAT effectors *STAT1* and *STAT4* could present a Novel Therapeutic Outlet for treating elderly Acute Myeloid Leukemia

Hassan Rizwan[1], Usama J AlDallal[1], Adnan Mansoor[2]. RCSI-MUB[1]
University of Calgary, Department of Pathology[2]

The authors report no conflicting financial relations or conflicts of interest.

Word count

- Background: 87
- Materials and Methods: 69
- Results: 75
- Conclusion: 51

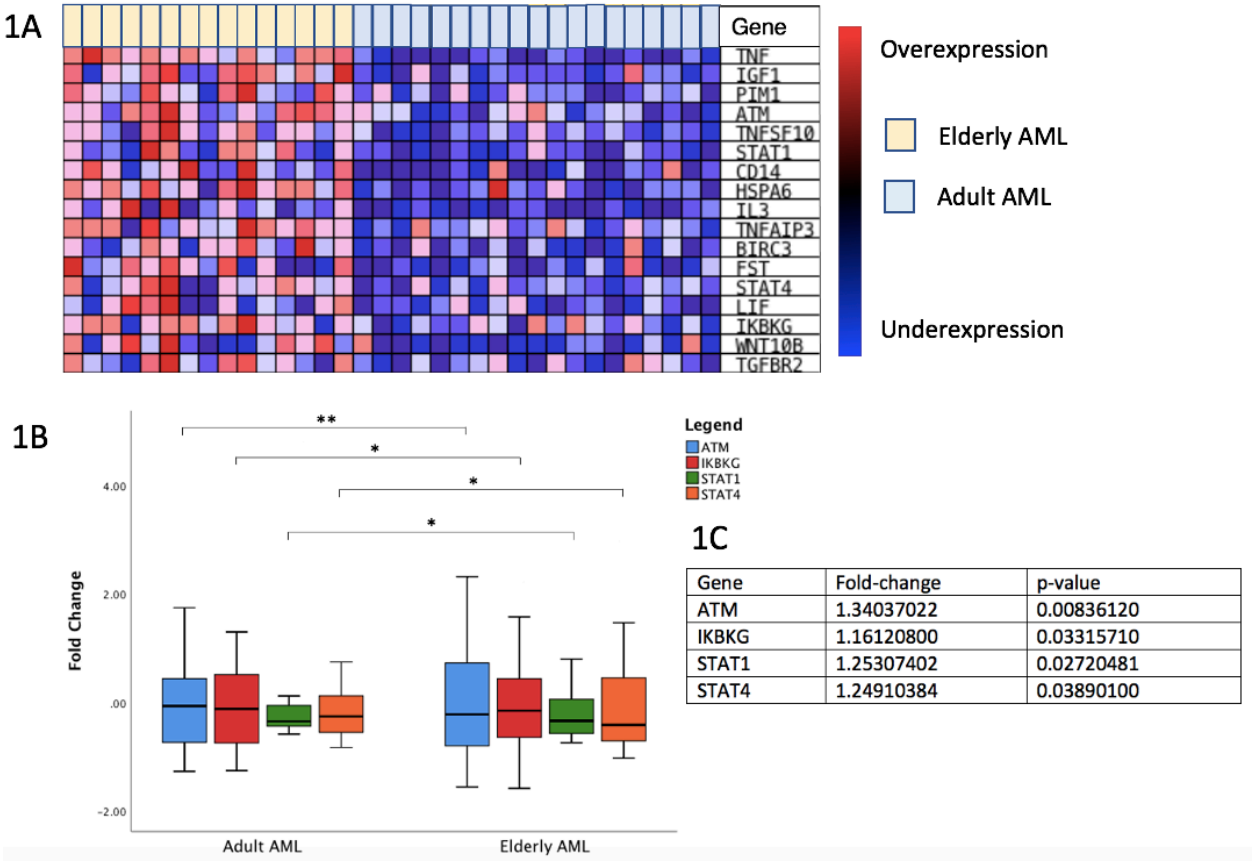
Background: Acute Myeloid Leukemia (AML) is the most prevalent leukemia in adults. Elderly AML patients experience disproportionally adverse clinical prognosis and treatment outcomes relative to younger cohorts, yet the underlying factors remain under investigated. The benefits of modern therapies are limited by aberrations of the genomic structure, patient comorbidities, and toxicity of treatments. Hence, new treatment strategies are required for treating elderly AML. Differences among patterns of genetic expression between age groups can identify therapeutic targets, as regulating the activities of genes could sensitize AML to contemporary treatments.

Methods: A gene expression profile analysis was performed using formalin fixed paraffin embedded (FFPE) diagnostic bone marrow samples from elderly AML patients (≥60 years, n = 34), adults (60-18 years, n = 32) and pediatric samples (<18 years, n = 34) in this retrospective, cross-sectional study. mRNA expression levels were quantified via the nCounter Pathway panel (Nanostring Technologies) and analyzed via Gene Set Enrichment Analysis (GSEA) version 4.1.0 ($p< 0.05$).

Results: 6 effectors pertaining to cellular apoptosis and 4 mediators of the JAK-STAT signal transduction pathway were differentially expressed in one gene set of the Molecular Signatures Database (MSigDB) via GSEA. The anti-apoptotic genes *ATM* and *IKBKG*, and JAK-STAT intermediaries *STAT1* and *STAT4* were overexpressed in the elderly cohort relative to the adult group. These findings were not replicated within the other age groups nor when comparing the expression of genes between the other age cohorts.

Conclusion: Crosstalk between the aforementioned apoptotic and JAK-STAT effectors might induce AML tumorigenesis. The impact of their therapeutic (co)inhibition should be investigated in AML tumor models for treating the disease. Furthermore, their upregulation could be monitored in future studies to assess the clinical progression of AML, patient survival and disease relapse outcomes.

If multiple figures are permitted as one figure:



1C

Gene	Fold-change	p-value
ATM	1.34037022	0.00836120
IKBKG	1.16120800	0.03315710
STAT1	1.25307402	0.02720481
STAT4	1.24910384	0.03890100

Figure 1A: Heatmap illustrating the expression of functionally enriched signal transduction pathway genes in elderly acute myeloid leukemia (AML) patients compared to the adult cohort. 1B: Box and whiskers plot depicting comparisons of log expression of key anti-apoptotic genes (*ATM, IKBKG*) and JAK-STAT genes (*STAT1, STAT4*) between the elderly and adult AML patient cohorts (* = $p < 0.05$, ** = $p < 0.01$ on 2-tailed independent sample *t*-test). 1C: Table depicting the statistical data for the aforementioned anti-apoptotic and JAK-STAT effectors.

If there is too much information here the other figure below can be used instead:

If only 1 figure is permitted:

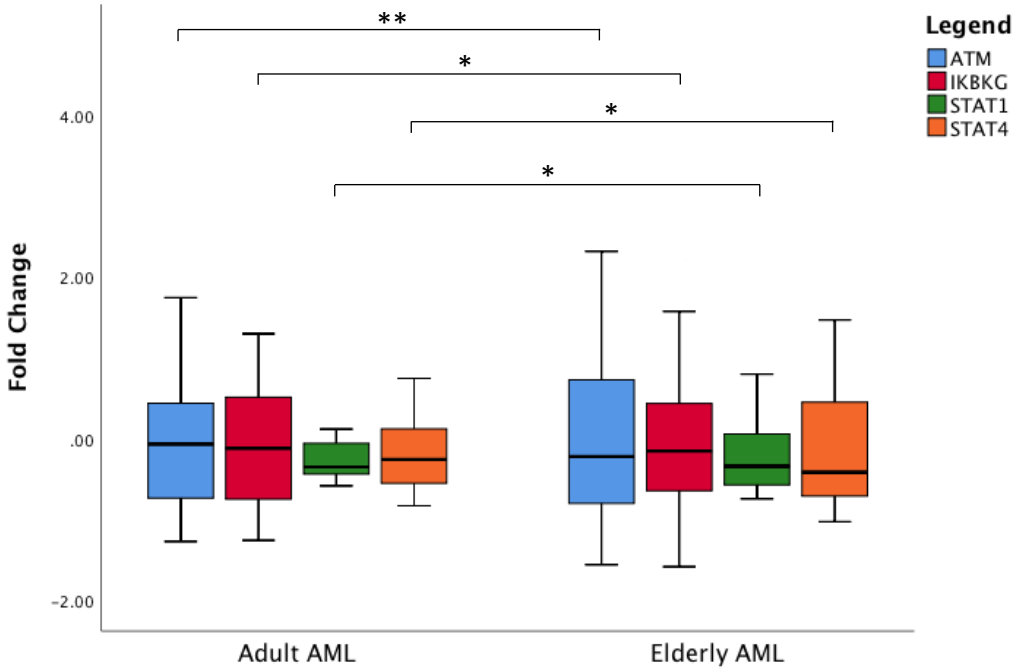


Figure 1: Box and whiskers plot depicting comparisons of log expression of key Anti-apoptosis genes (*ATM, IKBKG*) and JAK-STAT genes (*STAT1, STAT4*) between the elderly and adult AML patient cohorts (* = $p < 0.05$, ** = $p < 0.01$ on 2-tailed independent sample *t*-test).