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Research Article

Validation of ABO Gene Expression in Normal Tissues and Acute Myeloid Leukaemia Using In-Silico Approaches

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ABSTRACT

Background: This study investigates the association between the ABO blood group genes and acute myeloid leukaemia (AML), a cancer characterized by rapid growth of abnormal white blood cells. Prior research indicates a potential link between blood group antigens and various cancers, including leukaemia. Our objective is to assess and validate changes in ABO gene expression in AML tissues compared to normal tissues, clarifying the extent of its association with AML pathogenesis and progression.

Methods: In-silico analysis using platforms like GeneCards, HPA, ARChS4, BioGPS, and GEPIA2 was conducted to gather detailed data on ABO gene localization and its expression at RNA, mRNA, and protein levels in normal. And AML patients, aiding in understanding gene functionality.

Results: The ABO gene was expressed in almost all subcellular components and throughout normal body tissues, including the myeloid tissues. A statistically significant association was found between the ABO gene expression and AML conditions in which the expression of the ABO gene is significantly suppressed in AML. There was worse survival for the AML patient with higher ABO expression without significant statistical evidence.

Conclusions: The results reveal a reverse association between ABO gene expression and AML, highlighting the need for further research to elucidate *ABO*'s role in AML progression.

Introduction

Acute Myeloid leukemia (AML) is a highly heterogeneous disease characterized by the differentiation arrest of myeloid cells. This condition causes reduced erythropoiesis and bone marrow failure due to cancer cells accumulating in the bone marrow and peripheral blood (Shallis et al., 2019). Various factors are responsible for developing this disorder, including genetic mutations, chromosomal translocations, and alterations at the molecular level (Kawamoto & Minato, 2004; Lagunas-Rangel et al., 2017). The global prevalence of AML is intricately tied to broader trends observed in these cancers. Hematologic malignancies, including leukemia, have increased incidence globally, with 1343.85 thousand cases reported in 2019 (Zhang et al., 2023). Knowledge, treatment, and cure rates for AML have significantly improved over the last two decades with advances in sciences and targeted treatments resulting in a better prognosis of AML patients (Cairoli et al., 2012; Daver et al., 2020; Yu et al., 2020). In addition, there was a 15% increased cure rate in patients over 60 and 40% in patients under 60. However, despite advances in therapeutic regimens, the progno-

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sis remains very poor in the elderly population, and the pathogenesis of many AML subtypes remains unclear (Vakiti & Mewawalla, 2022).

Recent advances in genomics, such as bioinformatics integration of heterogeneous biological data of thousands of genes using various computational prediction tools, have enabled researchers to refine further studies regarding AML (Graubert & Mardis, 2011). The use of bioinformatics approaches, such as tissue-specific expression at both the gene and protein levels in AML, proved to be effective in diagnosing different cytogenetic subtypes, discovering novel subclasses of AML, and predicting the course of disease (Bullinger & Valk, 2005). Since genetic mutations account for most AML cases (Kumar, 2011), a better understanding of the disease requires knowledge of the genetic events that contribute to cancer pathogenesis and identification of mutations that can cause cancer and influence oncogenesis. The combination of gene expression profiling with other micro-array-based technologies and bioinformatics approaches will significantly contribute to the classification and therapeutic decision-making of AML and give insights into the true pathobiology of this type of leukaemia (Bullinger & Valk, 2005).

Several studies on the relationship between blood types to certain diseases, including leukaemia, have emerged since the relationship between stomach cancer and blood type A was identified in 1953 (Aird et al., 1953; Kumar, 2011; Risch et al., 2013; Tavasolian et al., 2014). The ABO blood group system is determined by variations in the ABO gene, which encodes a glycosyltransferase enzyme that modifies the H antigen on red blood cells. Individuals with A, B, or AB alleles express different glycosyltransferase activities, forming A or B antigens. The A antigen is formed by adding N-acetyl-galactosamine to the H antigen, while the B antigen results from the addition of galactose. The O blood group arises due to mutations in the ABO gene that lead to a loss of glycosyltransferase activity, resulting in the absence of these modifications on the H antigen. ABO blood group antigens are sugars base attached to the membrane of many cells, including lymphocytes, platelets, and white blood cells. Clinically, ABO blood group antigens are immunogenic and typically remain unchanged over time.

Previous studies have indicated that the expression of the ABO gene is notably absent or very low in various non-erythroid tissues, including the central nervous system, muscle, heart, and connective tissue (Abegaz, 2021; Liu et al., 2023; Sano et al., 2016). This suggests that the ABO gene may have a more restricted role in these tissues compared to its well-established function in the determination of ABO blood groups. Understanding the tissue-specific expression patterns of the ABO gene is crucial for comprehensively elucidating its biological significance and potential implications in non-erythroid physiological processes. In malignant conditions the expression of ABO blood group antigens can change (Dean, 2005). A variety of cancers exhibit changes in the genes that code for ABO blood groups on chromosome 9q34.2. Studies published before 1950 that examined the association between the ABO blood group and cancer have been controversial due to their small size, inadequate controls, and incorrect analysis (Garratty, 2000). Additionally, many recent studies linking ABO groups with cancer are controversial and lack significant statistical evidence with unexplained mechanisms that need to be explored (Liumbruno & Franchini, 2014). Alternatively, the analysis of gene expression monitoring in human acute leukaemia's has revealed a striking degree of concordance between studies (Bullinger & Valk, 2005; Golub et al., 1999).

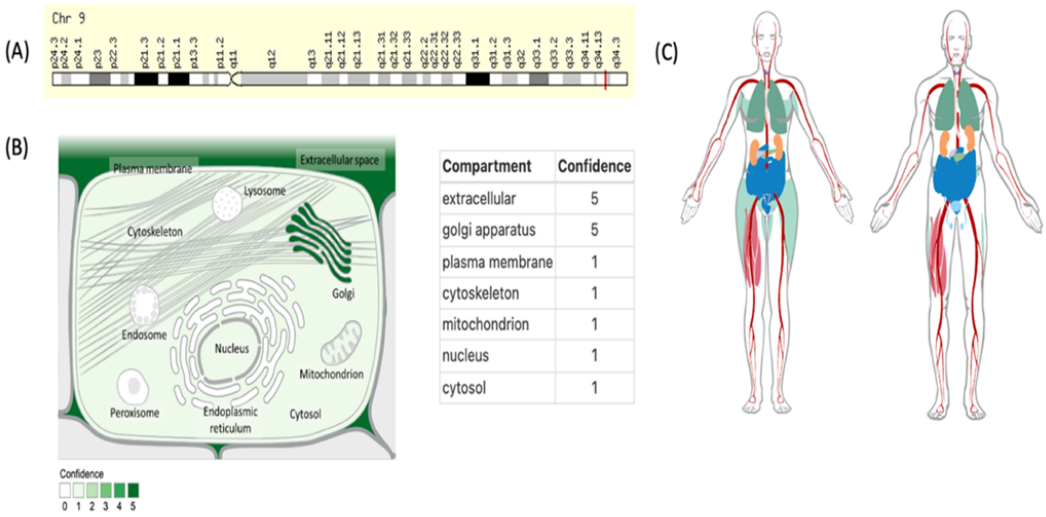
ABO antigen loss, as well as changes in expression level, were reported in many cases of acute myeloid leukaemia over the years (Bianco et al., 2001; Dobrovic et al., 1993; Nambiar et al., 2017; Prakash et al., 2021; Xiros et al., 1987). In the leukemic phase, the patient's blood group antigens were suppressed changed, and re-expressed when they reached remission (Miola et al., 2022). According to this observed pattern, blood group antigens may be involved or affected during cancer development. ABO gene status seems to be influenced during cancer in an unclear way. Therefore, this study included the following steps: verifying ABO status in normal tissues, investigating the association between ABO gene expression and leukemic conditions, and implications on survival.

MATERIALS AND METHODS

The overall strategy for evaluating the expression and function of the ABO gene (Gene NCBI ID: 28, full name: ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) in normal and AML conditions is as follows; First, evaluate the localization and expression of ABO in human tissue. Second, identify the actual gene expression in normal and tumour tissue. Third, evaluate the difference in ABO expression between AML patients and healthy individuals. Finally, evaluate the impact of ABO expression on AML patients' survival.

ABO Validation in Normal Tissues

In this study, GeneCards was used to identify the genomic location of the ABO gene on chromosome nine using the free online platform (available at http://www.genecards.org). This online tool includes genomic data from over 150 databases such as GeneLoc, HGNC, Entrez Gene, Nature, miRBase, and a genomic view from UCSC and Ensembl (Safran et al., 2021). The validation of ABO general expression was then assessed using the DNA-seq, RNA-seq and microarray data generated internally by Human Protein Atlas (HPA) and by the Genotype-Tissue Expression project (GTEx). ARChS4 atlas (available at



Compartment	Confidence
extracellular	5
golgi apparatus	5
plasma membrane	1
cytoskeleton	1
mitochondrion	1
nucleus	1
cytosol	1

Figure 1: The expression of ABO genes in human tissue. (A) ABO Gene in genomic location: bands according to Ensembl, locations according to Entrez Gene. (B) Subcellular localization for ABO Gene in normal tissue from COMPARTMENTS wise confidence of ABO occurrence. (Generated by www.genecards.org) (C) Overview of ABO RNA expression generated from the HPA project (generated by www.proteinatlas.org).

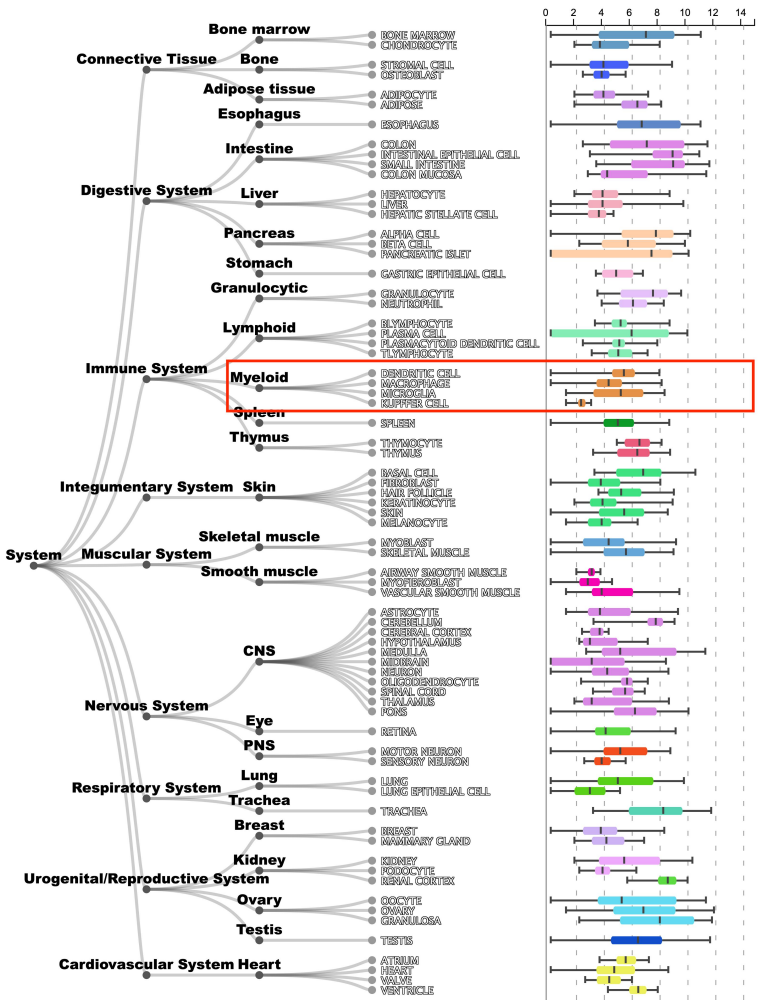


Figure 2: Overview of ABO RNA expression generated from the ARCHS4 tissue expression atlas. The tissues are grouped in multiple systemic levels and cover a wide range of different cellular contexts. The Red box shows the myeloid tissue figure available through https://maayanlab.cloud/archs4/gene/ABO.

http://maayanlab.cloud/archs4/index.html) was used to analyse ABO RNA expression in tissue. On this plat-

form, tissues are grouped into different levels and include various cellular contexts.

Transcriptomics data obtained from the HPA (https://www.proteinatlas.org) was used to generate a heatmap showing the expression of ABO proteins within blood cells and tissues. Single-cell transcriptomics data was analysed on peripheral blood mononuclear cells (PBMCs). This tool uses various data sources, including data from the Single Cell Expression Atlas, the Human Cell Atlas, the Gene Expression Omnibus, the Allen Brain Map, and the European Genome-phenome Archive.

Additionally, GeneCards was used to determine the subcellular distribution of the ABO gene based on the COMPARTMENTS subcellular localisation database. The subcellular localisations are derived from database annotations, automatic text mining of the biomedical literature, and sequence-based predictions. The COMPARTMENTS result was colour-coded to indicate confidence levels, with light green (1) indicating low confidence and dark green (5) indicating high confidence. White (0) indicates no evidence of localisation. Furthermore, BioGPS free online platform (available through) was used to analyse ABO mRNA expression. This platform incorporates high-density oligonucleotide arrays obtained from the GeneAtlas (U133A, gcrma) dataset to investigate the expression of the ABO gene in 79 human tissues from 176 samples.

Analysis of ABO Expression Levels in AML

The free online Gene Expression Profiling Interactive Analysis (GEPIA2) tool (http://gepia2.cancer-pku.cn/index) was used to evaluate the differences in ABO gene expression between normal and AML patients. This platform measures the expression of the ABO gene in AML by producing box plots. Differential expression was calculated using the disease state (Tumour or Normal) as a variable. A box plot illustrates the normal vs tumour median expression using The Cancer Genome Atlas (TCGA) and GTEx data.

Survival Analysis

To view the impact of the ABO gene on the survival of AML patients, the free online GEPIA2 tool (http://gepia2.cancer-pku.cn/index) was used. The GEPIA2 platform utilized the TCGA database and presented the survival analysis through a Kaplan-Meier (KM) plotter. The ABO gene expression level was sorted from high to low expression according to the overall survival details. A log-rank value and the 95% confidence intervals in the hazard ratio (HR) were calculated and presented in the figure.

Statistical Analysis

This study utilised the available statistical tools within the following platforms: ArchS4, HPA, BioGPS, and GEPIA2. A p -value of less than 0.05 indicates a statistically significant difference between the variables. The extracted data from ARChS4, BioGPS, and GEPIA2 also used the median expression with a 95% Confidence Interval (CI).

RESULTS

ABO Gene is expressed in all normal body tissue and all cellular compartments.

Using In-silico computational analysis and free online platforms, the current study validated the expression of ABO genes in normal human tissue. According to GeneCards data, the ABO gene is located on 9q34.2 and contains seven exons (Figure 1A). GeneCards-derived subcellular compartment analysis showed that the ABO gene is expressed in almost all human cell components, such as the plasma membrane, cytoskeleton, mitochondria, nucleus, and cytosol, with a low confidence interval (CI=1). The highest expression level is found in the extracellular matrix and the Golgi apparatus (CI=5) (Figure 1B). Furthermore, data generated from HPA demonstrated that the ABO gene is expressed throughout the body, including the lymphoid and myeloid tissues (Figure 1C).

The tissue expression atlas shows a systemic measurement of normal ABO gene activity generated from the ARChS4 publicly available platform (Figure 2). Results demonstrated that the ABO gene was active in all nine major human body organ systems, including several subcategorised cell types. Under the myeloid immune system, the ABO expression was detected in dendritic cells, macrophages, microglial, and Kupffer cells.

At the protein expression level, the HPA database demonstrated that the ABO protein is expressed in well-known blood cell types shown below in a heatmap (Figure 3). A main cell type was selected for each cluster after considering the expression of various markers. Based on the data, it was found that the ABO transcript expression levels were detectable in dendritic cells (z-score= 2.62), granulocytes (z-score= 2.50), macrophages (z-score=2.14), monocytes (z-score=1.61), and other blood and immune cells.

Finally, the mRNA expression/activity chart analysis from the BioGPS database summarises the data and determines the tissues where the ABO gene is positively differentially expressed (Figure 4). This chart shows various normal and tumor tissues showing variable degrees of ABO mRNA expression. Several myeloid tissues and cells, including endothelial cells (M=11.05), dendritic cells (M=8.90), myeloid (M=12.05), and monocytes (M=11.10) exhibit ABO mRNA expression. In addition, ABO mRNA expression was also detected in several different types of leukaemia, such as lymphoblastic leukaemia (M=8), chronic myelogenous leukaemia (M=9.80), Burkitt lymphoma (M=14.65) and promyelocytic leukaemia (9.90).

Figure 3: ABO expression in blood tissues/cells generated from HPA. (A) Showing a color-coded log (pTPM) z-score vis-ualization of ABO transcript expression in several PBMCs and tissues. (B) Showing fraction of ABO expression. This data suggests that ABO is expressed in all blood cells with different levels. Figure generated by www.proteinatlas.org.

Association of reduced ABO Gene expression and leukaemia

The GEPIA2 platform compared normal samples (n=70) to leukaemia samples (n=173) to investigate the correlation between ABO expression and leukemia. As shown in Figure 5, the Box blots illustrate a statistically significant association in which the expression of the ABO gene is suppressed in AML conditions. The median expression of the ABO gene in AML is (M=1.33) compared to (M=3.58) in the normal sample.

AML patients with increased expression of the ABO gene showed a lower survival rate.

The KM plotter obtained from the GEPIA2 platform demonstrates the effect of high or low ABO gene expression on the survival of AML patients (Figure 6). In this study, the overall survival of the group with higher ABO expression (n=53) has a worse outcome than people with low ABO expression (n=53). However, the statistical analysis showed a non-significant association between the two variables (p=0.17). The data shows that AML patients with high ABO expression are at higher risk of death than patients with a lower ABO expression.

DISCUSSION

Validation of ABO Gene and Protein Expression in Normal Tissues.

This study confirmed that the ABO gene and protein are subcellular localised and expressed in many normal tissues. The results of this in-Silico analysis confirm the existing evidence of ABO expression in many healthy human tissues (Dean, 2005). Most of the support of this finding does not explicitly address the full view of a subcellular location and does not specify the organs and tissues involved. However, our results provide a better understanding of how the ABO gene and protein are expressed within all body tissues. The importance of this result identifying the subcellular location of a protein is a key step toward understanding its cellular functions.

It is generally accepted that the ABO gene primarily determines an individual's blood group by modifying the oligosaccharides on the surface of the cells (Hosoi, 2008). ABO expression in cells other than blood cells may suggest a wider biological function (de Mattos, 2016). Moreover, the current study findings confirm that the ABO gene is expressed in all myeloid cells on RNA, mRNA, and protein levels. Through the actions of diverse chemokine receptors, myeloid cells such as granulocytes, monocytes, macrophages, and dendritic cells migrate rapidly to sites of damage and infection through the circulation and lymphatic system. They serve as phagocytosis cells and as secretors of inflammatory cytokines, which are crucial for the immune system's protection (De Kleer et al., 2014). The analysis of ABO expression in normal myeloid cells was particularly important because this study was also designed to investigate the expression of ABO gene in AML patients, where a massive increase in immature myeloid cells in the bone marrow and peripheral blood leads to differentiation arrest.

ABO Expression in AML is lower than that compared to normal tissue.

Based on our investigation of the association between the ABO gene and AML, patients with AML have lower expression of the ABO gene than normal people. The significance of this study lies in its potential to unravel novel aspects of AML pathogenesis. Lower ABO gene expression in AML patients compared to healthy individuals could lead to new diagnostic markers or therapeutic targets, enhancing our understanding and treatment of AML. These findings are consistent with those reported in several case reports describing AML and chronic myeloid leukaemia (Bianco et al., 2001; Dobrovic et al., 1993; Nambiar et al., 2017; Prakash et al., 2021; Xiros et al., 1987). A case report found

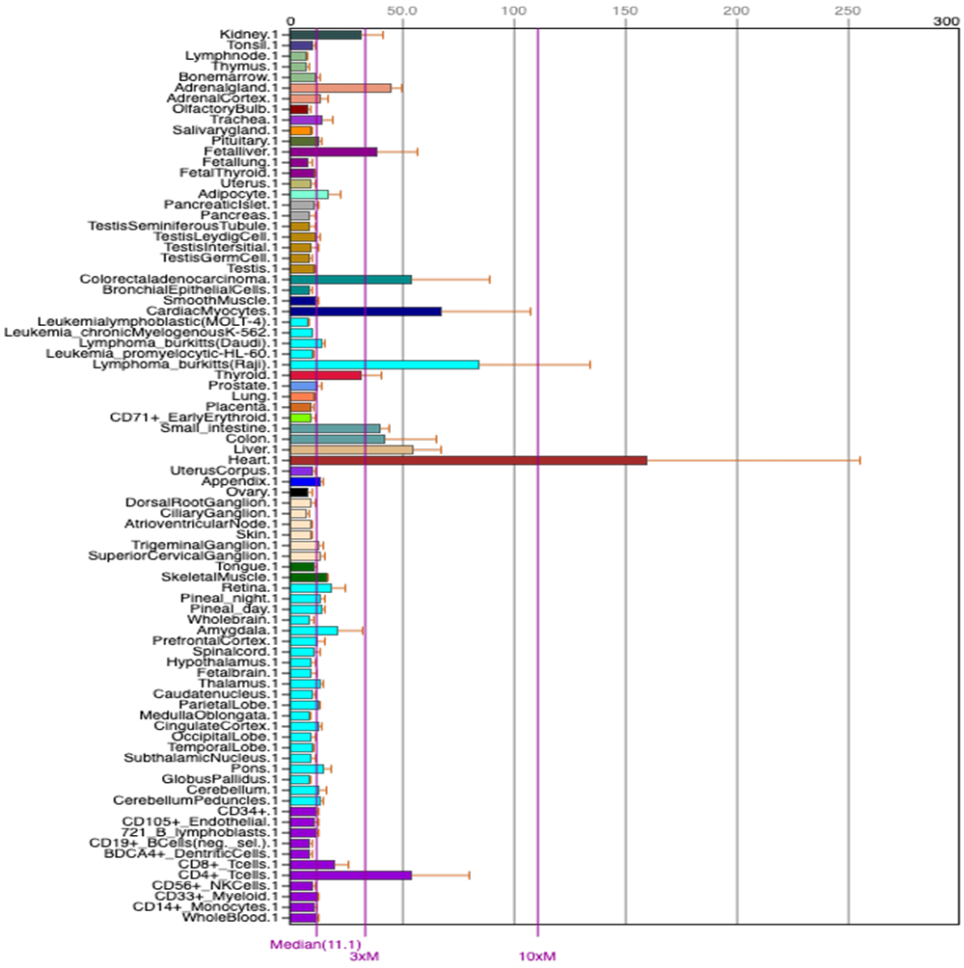


Figure 4: Expression levels of ABO gene in normal tissues and different types of tumors generated from Bi-oGPS. The BioGPS database contains a coherent collection of expression profiles in more than 70 human tissue types, including myeloid tissues. (Available through http://biogps.org/). The data presented in the bar box indicates the median mRNA expression in the tissue ± Standard deviation. The median, 3X median, 10X median, and 30X are defaults of the BioGPS presentation sketched by the lines.

that both AML patients (male and female) lost their blood group B antigen during the leukemic phase but regained it after remission (Bianco et al., 2001). Another chronic myeloid leukemia case report observed the patient's (female) past blood group was A-positive. After her underlying leukaemia, subsequent blood testing showed that the expression of A antigens was diminished (Shafiq Karim, 2015). Furthermore, many types of cancers have also been reported to exhibit a loss and alteration of ABO antigens (Bryne et al., 1991; Lee et al., 1991; Wolf et al., 1990), which has led several studies to investigate the causes of this suppression. Consequently, to gain a deeper understanding of the suppression pattern, it is necessary to establish whether the changes are caused at the gene or protein level.

One of the suggested explanations is regarding the production of ABO antigens which may have been affected by a mutation in the stem cells. According to the degree of mutation, there may be a complete or partial loss of antigen expression (Bianco et al., 2001). Another suggested explanation is based on molecular studies which examined DNA methylation as a possible modifier of ABO gene expression in leukaemia. According to Bryne et al., methylation of the ABO promoter and expression of ABO mRNA are negatively cor-related (Bryne et al., 1991). Furthermore, Bianco-Miotto and colleagues found that methylation of the ABO promoter strongly correlated with the loss of the ABO allelic expression (Bianco-Miotto et al., 2009). Therefore, DNA methylation played a pivotal role in reducing ABO antigens in the acute leukaemia (Bianco-Miotto et al., 2009; Shao et al., 2016).

Kronstein-Wiedemann and colleagues reported that changes in glycosyltransferase gene expression could lead to a change in A/B antigen expression (Kronstein-Wiedemann et al., 2020). The study found that miRNAs are essential regulators of ABH antigens, which may, among other effects, contribute to the loss of ABO antigen expression in both physiological and abnormal circumstances.

Investigation of the impact of ABO expression on AML patient survival

This study's importance lies in challenging existing perceptions about ABO gene expression's role in AML. The finding that higher ABO gene expression correlates with increased mortality risk, despite its suppression in AML, could redefine our understanding of AML's molecular mechanisms and influence future research directions in targeted therapies and prognosis. This result remains obscure as no data or previous research of similar findings were found. This can be due to the small sample size (n=58), limiting the accuracy of interpretation. However, repeating the analysis with a larger dataset is advisable for a more accurate assessment. Thus, if a significant relationship exists between the high expression of ABO and worse survival, it would be beneficial to address its molecular involvement. This can be achieved by conducting further molecular studies to investigate the degree of gene expression in each AML subtype and at each disease progression stage. Another approach would be to examine the survival analysis with a different targeted tumor , such as the thyroid gland , and determine if a similar observation is found. Also, the current data does not explain the relationship between the reduction of ABO gene. So, the loss or reduction of expression cannot be explained in terms of cause and effect. The antigen loss could be due to disease progression and not a cause of this progression, and the reverse can be true.

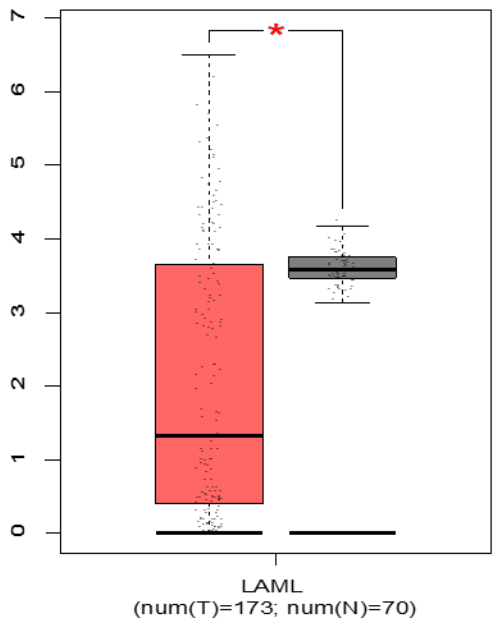


Figure 5: The median expression of the ABO gene is reduced in AML patients. Box plots with jitter for comparing ABO gene expression (expression-log2 (TMP+1)) in normal (n=70, black) and AML cancer (n=173, red). The red star indicates a significant correlation where $p < 0.05$. Figure generated from https://gepia.cancer-pku.cn/.

This study pioneers the exploration of the ABO gene's role in AML, offering initial insights into molecular mechanisms, and potentially guiding future targeted therapies. A major limitation of this study was that the large amounts of data are time-consuming and require careful selection and examination, as well as the challenge of the heterogeneous nature of data. Thus, resulting in a limitation in including all aspects that can be assessed regarding the correlation between the ABO gene and AML. Understanding ABO gene expression in normal and cancer cells lacking A/B antigens requires identifying the molecular pathways controlling their transcription, such as protein integrations. Also, there are many subtypes of AML; this study investigated the association between the ABO gene and AML in general. A detailed study of the ABO expression pattern in each subtype of AML can provide more details on the relationship between the ABO gene in this disease. Further study can help explain the role played by the expression or regression of the ABO gene throughout different stages of AML. Moreover, this study is considered an introductory phase to studying the relationship between AML and the ABO gene. Additional detailed analysis methods can help reveal a deeper understanding of this gene function. Investigating protein interactions, molecular studies, and other genes with similar expression patterns that are likely to have related functions can further predict the role that the ABO gene plays in AML.

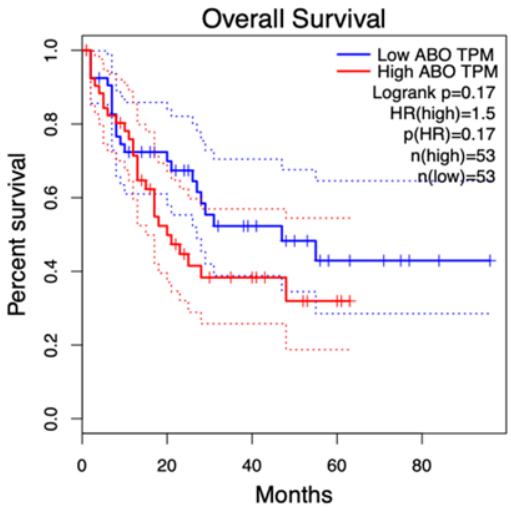


Figure 6: Relationship between ABO gene expression and survival of patients with AML. Overall Survival Kaplan-Meier analysis was performed using the GEPIA2 online application. The solid and dotted lines represent the survival curve and 95% confidence interval. The p values of a log-rank test for trend and the High Risk (HR) were shown in the plot. Figure generated from https://gepia.cancer-pku.cn/.

CONCLUSION AND RECOMMENDATION

Our analysis confirms the cellular localization and expression of the ABO gene throughout body tissues, including in the lymphoid and myeloid cells. Moreover, the result of this research highlights the presence of ABO proteins in the blood and myeloid cells. Additionally, the study demonstrated a significant correlation between ABO expression and AML status. According to the survival data, individuals with higher levels of ABO expression have a greater risk of death and a worse outcome than those with lower levels. However, this finding is not statistically significant. Moreover, future studies should focus on a detailed analysis of ABO gene expression across AML subtypes, explore molecular pathways influencing ABO transcription in cancer cells, and investigate protein interactions to elucidate ABO's role in AML progression and patient prognosis. Further research is also needed to translate the current findings into practical diagnostic tools for AML.

AUTHOR CONTRIBUTION

SK conceived and designed the study. WB, MA, AlM, and RA, contributed to data collection and draft writing; SK, AA, AF, AM, AJH, and AAO conducted data cleaning and analysis. All authors interpreted the results. SK, AM, and FA revised the manuscript. All au-thors proofread and finalized the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the contents.

ETHICAL APPROVAL

Ethical approval was obtained from the Biomedical Ethical Committee at Umm Al-Qura University (HAPO-02-K-012-2023-03-1531).

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DECLARATIONS

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose. The authors declare no conflict of interest.

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