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RESEARCH

Integrated transcriptome-proteome analysis in patients with myelofibrosis-related anemia

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Abstract

Objective. Myelofibrosis (MF) represents a hallmark of the advanced stage of myeloproliferative neoplasms (MPNs), and anemia serves as an independent factor for poor prognosis. Our study aimed to explore the gene and protein profile in patients with MF-related anemia through integrated transcriptome-proteome analysis. Methods. Peripheral blood was collected from 36 MPN patients, including 24 anemic individuals. Isolated mononuclear cells were analyzed for differentially expressed genes (DEGs) via transcriptomic sequencing. Plasma samples was tested for differentially expressed proteins (DEPs) using Olink proteomics technology. Potential diagnostic biomarkers for MF-related anemia were identified though combined Lasso regression, logistic regression analysis, and receiver-operating characteristic curve. Results. Gene set enrichment analysis showed that the JAK-STAT signaling pathway is generally downregulated in anemic patients, and DEGs associated with erythroid differentiation were significantly upregulated in the anemia group. Proteomics analysis indicated that TRAIL and CXCL13 were the most significantly downregulated and upregulated DEPs in anemic patients, respectively. Univariate logistic regression analysis suggested positive correlation between IL-6, IL-10, and PD-L1 with anemia, while only IL-10 remained statistically significant in multivariate analysis. ELISA assay confirmed significantly elevated plasma IL-10 levels in patients with MF-related anemia. Conclusions. DEGs associated with erythroid differentiation are highly expressed in anemic patients, confirming the involvement of ineffective erythropoiesis in the pathogenesis of MF-related anemia. Besides abnormally activated inflammatory cytokines, the anti-inflammatory factor IL-10 can also serve as a potential diagnostic biomarker for MF-related anemia, possibly due to a compensatory response arising from reduced sensitivity of monocytes to IL-10.

Keywords Myelofibrosis · Anemia · IL-10 · Transcriptomics · Proteomics · Diagnostic biomarker

Introduction

Myeloproliferative neoplasms (MPNs) are a class of clonal proliferative disorders that originate from bone marrow hematopoietic stem cells. Overactivation of Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway driven by JAK2, calreticulin (CALR), or MPL proto-oncogene, thrombopoietin receptor (MPL) mutations leads to abnormal hematopoietic clones [1]. Classical Philadelphia chromosome (Ph)-negative MPNs include primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET) [2]. Both PV and ET carry a risk of transformation into myelofibrosis (MF) in the late stage and progression to acute myeloid leukemia [3]. Approximately 1/3 of MF patients present with anemia at diagnosis [2], and new-onset or accelerated anemia is considered to be associated with JAK inhibitor therapy [4,5]. Therefore, anemia is an unavoidable therapeutic dilemma for MPN patients during the development of MF [6], and acts as an independent risk factor for poor prognosis and leukemic transformation [7].

The pathogenesis of MF-related anemia involves multiple complex mechanisms, including ineffective erythropoiesis, hepcidin-induced iron-restricted erythropoiesis, and abnormally activated inflammatory signaling pathways

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[8]. Active inflammation is a hallmark feature of MPN [8], where tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 acts as major inflammatory cytokines, collectively driving the formation of a chronic inflammatory microenvironment within the bone marrow [8–11]. Subsequently, activated fibroblasts induced by excessive fibrotic factors including transforming growth factor beta (TGF-β), and fibroblast growth factor (FGF), stimulate remodeling of the bone marrow niche [9,11]. Patients with MPN is known to have a complex network of inflammatory factors. However, current research on the association between the inflammatory profile and anemia severity remains insufficient, and their involvement in ineffective erythropoiesis have not been fully elucidated. Therefore, we conducted an integrated study of genomics and proteomics in a small cohort of MPN patients, with the aim to reveal the transcriptional profiles and abnormal immuno-oncology factors in MF-related anemia, and further identify potential diagnostic biomarkers.

Methods

Patient inclusion

Adult patients with a diagnosis of PMF, PV, and ET (including post ET / PV-MF) according to the 5th World Health Organization (WHO) criterion (2022 version) at Fujian Medical University Union Hospital were enrolled in the study [12]. Based on hemoglobin threshold (HGB = 100 g/L) defined in the Dynamic International Prognostic Scoring System (DIPSS) risk stratification [13], patients were categorized into the non-anemia group (Group 0) and the anemia group (Group 1). The anemia group excluded anemia caused by factors other than MF, including active bleeding, nutritional anemia, and anemia associated with other hematologic disorders. Transfusion dependency (TD) was defined as receiving red blood cell (RBC) transfusions at least once every eight weeks. Anemic patients with TD were assigned to Group 3, otherwise were assigned to Group 2. Data and samples from healthy donors served as the controls, and their demographic characteristics are shown in Table S1. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital.

Isolation of peripheral blood mononuclear cells (PBMCs)

Approximately 3 ml of peripheral blood with ethylenediaminetetraacetic acid (EDTA) anticoagulation was collected from each participant. After centrifugation at 2,000 rpm for 20 min, the supernatant plasma was collected and stored at -80 °C for ELISA detection and Olink proteomics analysis. PBMCs were isolated using Ficoll density gradient centrifugation with human peripheral blood lymphocyte separation medium (TBD Scientific, China), which were completely dissolved in the TRIzol reagent (Ambion, USA) and stored at -80 °C.

Total RNA isolation

Total RNA was isolated and purified with TRIzol-based methods as previously reported [14]. The quality control of the amount and purity of total RNA was performed with a NanoDrop -1000 (Thermo Fisher, USA), while the integrity of RNA was detected by Bioanalyzer 2100 (Agilent, USA).

RNA-sequencing analysis

To explore the expression of differentially expressed genes (DEGs), RNA-seq was authorized to the LC-Bio Technology CO., Ltd. (Hangzhou, China), using Illumina NovaSeq™ 6000 to conduct bipartite sequencing. The detailed protocol is provided in the Supplementary Methods.

Real time-quantitative PCR (RT-qPCR)

Total RNA was reverse transcribed into cDNA with Uni All-in-One First-Strand cDNA Synthesis SuperMix for qPCR (TransGen, China) and analyzed in technical triplicates by qPCR with SYBR probes (Vazyme, China) based on the manufacturer's instructions using a QuantStudio™ 5 System (Thermo Fisher, USA). The primer sequences are provided in Table S2. Relative expression was normalized to *GAPDH* and determined by the $2^{-\Delta\Delta CT}$ method.

Enzyme-linked immunosorbent assay (ELISA)

The levels of plasma erythropoietin (EPO), IL-10, or hepcidin were detected with Human cytokines ELISA Kit (Elabscience, China) in technical triplicates according to the manufacturer's instructions. The OD450 value was measured with SpectraMax i3X Microplate Luminometer (Molecular Devices, USA).

Olink proteomics analysis

To explore the expression of differentially expressed proteins (DEPs), Olink Proteomics Target 96 Immuno-Oncology Panel was conducted at the LC-Bio Technology CO., Ltd. (Hangzhou, China) with the Proximity Extension Assay technology as previously described [15]. The detailed protocol is provided in the Supplement Methods.

Statistical analysis

Measurement data from two independent samples conforming to normal and chi-square distributions were analyzed with two-sided student's *t*-test, otherwise with Mann–Whitney test. Kruskal-Wallis test was used to evaluate differences among multiple groups, and Dunn's test was used to perform post hoc tests. Count data were analysis with Chi-square test or Fisher's exact test. Spearman's correlation is used to analyze the correlation between two continuous variables. Statistical analysis was performed via SPSS (version 25.0.0), and graphical illustrations were generated with GraphPad Prism (version 9.5) or Xiantao Academic analysis (https://www.xiantaozi.com/). A two-sided P value <0.05 was considered statistically significant (*$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$).

Results

Clinical characteristics of enrolled MPN patients

A total of 36 patients with Ph-negative MPN were enrolled in the study and clinical characteristics are summarized in Table 1. A significant decrease in platelet counts was observed in patients with anemia ($P=0.008$). Plasma EPO levels were remarkably higher in anemic patients, and were significantly negatively correlated with HGB levels ($R=-0.838$, $P<0.001$) (Figure S1), which is consistent with a recent multicenter research cohort in China [16]. Among patients without anemia ($n=12$), more than half were diagnosed with ET (58.33%) and had an MF grade of 0 (66.67%); whereas in the anemia group ($n=24$), the majority were diagnosed with PMF (79.17%) and all patients had an MF grade ≥ 2 ($P<0.001$). No significant differences were observed between non-anemic and anemic patients in terms of genetic variants or karyotype distributions due to the small sample size. As expected, JAK2 inhibitor-combined therapy is more common in patients with anemia ($P=0.003$), especially in the TD cohort, given its importance in the treatment of MF and the association with development of anemia. The proportion of HMA-combined therapy was unexpectedly greater in anemic patients without TD compared to those with TD (41.67% vs. 16.67%), which may be a result of a higher proportion of leukemia transformation (33.33% vs. 16.67%).

Transcriptional profiling in MPN patients

Transcriptomic analysis of PBMCs from patients with MPN ($n=36$) and controls ($n=13$) was performed by RNA-seq. As shown in the Venn diagram (Fig. 1A), there are 6,212 DEGs (5,176 upregulated and 1,036 downregulated) between patients and healthy controls, and 3,496 DEGs (2,434 upregulated and 1,062 downregulated) between anemic and non-anemic patients, with a total of 1,543 (18.90%) DEGs common to both pairs. Gene Ontology (GO) enrichment analysis indicated that these common DEGs were mainly associated with on the biological process (BP) of signal transduction (GO:0007165), the cellular component (CC) of cellular membrane (GO: 0016020), and the molecular function of protein binding (GO: 0005515) (Fig. 1B). Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed significant enrichment in pathway in cancer (hsa05200), cytokine-cytokine receptor interaction (hsa04060), and nuclear factor kappa-B (NF-κB) signaling pathway (hsa04064) (Fig. 1C) [17]. The correlation heatmap showed that among the common DEGs involved in the JAK-STAT signaling pathway, *IFNAR2* expression was significantly downregulated in anemic patients, while *CCND1* expression was significantly upregulated (Fig. 1D). These two DEGs showed no significance between non-anemic patients and healthy controls, suggesting that they represent characteristic genes associated with MF-related anemia. Gene set enrichment analysis (GESA) showed that the JAK-STAT signaling pathway is generally downregulated in the anemia group compared to non-anemic patients, with an enrichment score (ES) of -0.452 (Fig. 1E). Further analysis focused on the anemia group revealed that the TD cohort also exhibited a downward trend in this pathway with an ES of -0.248, though the difference was not statistically significant (Fig. 1F).

DEGs associated with erythroid differentiation significantly upregulated in MF patients with anemia

Next, we focused on the differences in transcriptomic characteristics between anemic and non-anemic patients. As shown in the volcano plot (Fig. 2A), DEGs associated with erythroid differentiation (function annotation is provided in Table S3) were significantly upregulated in anemic patients, which are involved in transcription regulators (*GATA1*, *KLF1)*, signal transduction (*EPOR*), hemoglobin synthesis and stability (*ALAS2*, *AHSP*, *TFRC*, *HBA1*, *HBA2*, *HBB*, *HBM*, *HBG1*, *HBG2*), erythrocyte membrane skeleton and membrane transport (*SPTA1*, *SPTB*, *EPB42*, *GYPA*, *GYPB*, *GYPE*, *SLC4A1*). Box plots demonstrated that these DEGs were significantly elevated in the anemia group compared to non-anemic patients and healthy controls, while no statistically significant difference was found between anemic patients with TD and without TD (Fig. 2B). We observed two individuals in the non-anemia group exhibiting high expression levels for several DEGs associated

Table 1 Clinical characteristics of patients with Ph-negative MPN

	Patients with Ph-negative MPN			P value		
	Non-anemic Patients(Group 0)(n=12)	Anemic Patients (Group 1) (n=24)		G1 vs G0	G2 vs G0	G3 vs G0
		Without TD (Group 2)(n=12)	WithTD(Group 3)(n=12)			
Onset Age (years)	60 (16-86)	61 (36-77)	56 (30-76)	0.856	0.715	0.928
Male, N (%)	6 (50.00)	6 (50.00)	6 (50.00)	/	/	/
Leukocytes ($\times10^9$/L)	8.50 (4.06-16.92)	8.48 (1.12-74.26)	5.18 (0.88-96.80)	0.327	0.932	0.144
NLR	4.19 (0.74-16.92)	3.72 (0.55-26.71)	3.19 (0.63-27.30)	0.631	1.000	0.443
HGB ($\times10^{12}$/L)	128.5 (102-164)	76 (59-90)	49 (35-66)	<0.001***	<0.001***	<0.0001**
Platelets ($\times10^9$/L)	441 (152-1260)	185 (5-565)	45 (14-752)	0.008**	0.019*	0.010*
Blasts in PB (%)	0	4 (0-18)	0.24 (0-20)	/	/	/
EPO (mIU/ml)	1.72 (0.69-6.71)	5.34 (2.48-29.03)	23.99 (3.93-31.58)	<0.001***	0.001**	<0.0001****
Diagnosis, N (%)						
PMF	3 (25.00)	10 (83.33)	9 (75.00)	0.003**	0.012*	0.039*
ET	7 (58.33)	0	0	<0.001***	0.005**	0.005**
PV	2 (16.67)	0	0	0.105	0.478	0.478
pET-MF	0	1 (8.33)	2 (16.67)	0.536	1.000	0.478
pPV-MF	0	1 (8.33)	1 (8.33)	0.543	1.000	1.000
Leukemic Transformation, N (%)	0	4 (33.33)	2 (16.67)	0.079	0.093	0.478
MF Grade, N (%)						
0	8 (66.67)	0	0	<0.001***	<0.001**	<0.001**
1	1 (8.33)	0	0	1.000	1.000	1.000
>= 2	3 (25.00)	12 (100.00)	12 (100.00)	<0.0001****	<0.0001****	<0.0001****
Genetic Variants, N (%)						
None	2 (20.00)	0	0	0.091	0.214	0.214
JAK2	8 (80.00)	5 (45.45)	11 (100.00)	0.072	0.183	0.214
CALR	0	4 (36.36)	0	0.283	0.090	/
MPL	0	1 (9.09)	0	1.000	1.000	/
ASXL1	1 (10.00)	5 (45.45)	3 (27.27)	0.210	0.149	0.586
TET2	2 (20.00)	0	0	0.091	0.214	0.214
TP53	0	2 (18.18)	1 (9.09)	0.534	0.476	1.000
Karyotype, N (%)						
Normal	8 (88.89)	3 (60.00)	5 (83.33)	0.591	0.505	1.000
Single Abnormity	1 (11.11)	0	1 (16.67)	1.000	1.000	1.000
Complex	0	2 (40.00)	0	0.479	0.110	/
Hepatomegaly, N (%)	2 (28.57)	7 (58.33)	8 (66.67)	0.198	0.648	0.170
Splenomegaly, N (%)	4 (57.14)	10 (83.33)	11 (91.67)	0.110	0.305	0.117
Treatment, N (%)						
Therapeutic blood cellcollection	3 (25.00)	0	0	0.031*	0.217	0.217
Hydroxyurea only	4 (33.33)	4 (33.33)	3 (25.00)	1.000	1.000	1.000
Interferon only	4 (33.33)	1 (8.33)	1 (8.33)	0.149	0.317	0.317
JAK2 inhibitor-combined	3 (25.00)	8 (66.67)	11 (91.67)	0.003**	0.100	0.003**
HMA-combined	0	5 (41.67)	2 (16.67)	0.032*	0.037*	0.478

Normally distributed measurement data are presented as the mean ± standard deviation (SD), otherwise presented as median (range), and count data are presented as number (%)

Abbreviations: *NLR* neutrophil-to-lymphocyte ratio, *HGB* hemoglobin, *PLT* platelet, *JAK2* Janus kinase 2, *CALR* calreticulin, *MPL* MPL proto-oncogene, thrombopoietin receptor, *ASXL1* ASXL transcriptional regulator 1, *TET2* tet methylcytosine dioxygenase 2, *TP53* tumor protein p53, *HMA* hypomethylating agent, *NA* not available

with erythroid differentiation, which originated from the same patients (Pt #4, Pt #10), both diagnosed with PMF and had an MF grade of 2. Enrichment analysis of via the Metascape platform revealed the significance in GO terms including erythroid differentiation (GO: 0030218), oxygen transport (GO: 0015671), and hemoglobin metabolic process (GO: 0020027) (Figure S2) [18]. RT-qPCR confirmed that the mRNA expression levels of *GATA1*, *KLF1*, *AHSP*,

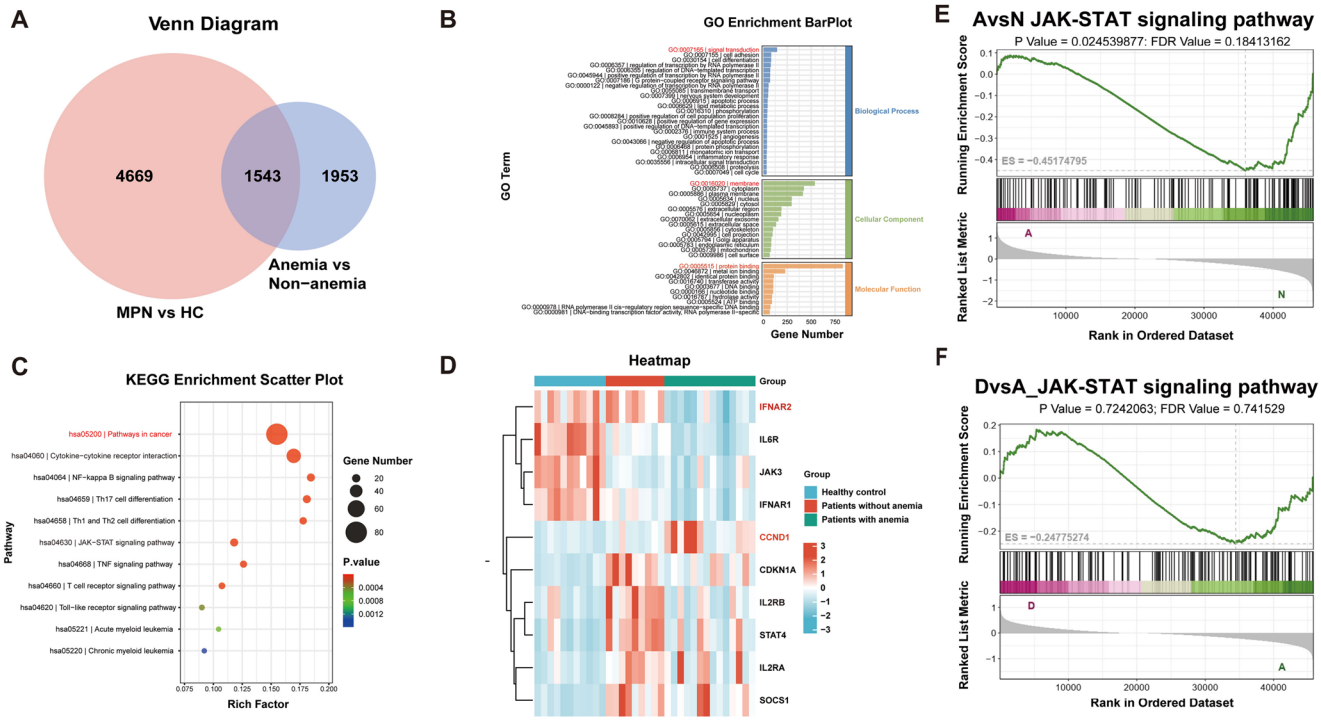


Fig. 1 DEGs based on RNA-seq analysis. (**A**) Venn diagram of DEGs with a *P* value < 0.05 and $|\log_2 FC| \geq 1$ between patients with Ph-negative MPN and healthy controls, and between anemic and non-anemic patients. (**B**) GO enrichment barplot of common DEGs based on functional categories of biological process, cellular component, and molecular function. (**C**) KEGG enrichment scatter plot of common DEGs. (**D**) Heatmap of common DEGs involved in the JAK-STAT pathway. GSEA of the JAK-STAT signaling pathway between the anemic and non-anemic patients (**E**), and between anemic patients with and without TD (**F**)

ALAS2, *HBA*, *HBB*, *HBG*, *TFRC*, and *GYPA* were significantly higher in anemic patients, especially the TD cohort (Fig. 2C). DEGs associated with erythroid differentiation formed a network composed of important nodes including ALAS2, KLF1, GATA1, HBB, SLC4A1, EPB42, GYPA, AHSP, HBG1, and HBG2 (Fig. 2D). Correlation analysis indicated that these DEGs exhibit significant positive correlations, with correlation coefficients > 0.6 except EPOR and HBM (Fig. 2E). Meanwhile, further analysis between anemic patients with and without TD showed no significant differences in the transcriptional expression of genes associated with erythroid differentiation (Figure S3).

Immuno-oncology proteomics profiling in MPN patients

Given the functional enrichment of common DEGs in cytokine-mediated signaling pathways (Fig. 1B and C), we presumed that proteins involved in immune-oncology interactions may play a crucial role in the development of MF-related anemia. Therefore, we subsequently conducted Olink proteomics analysis in Ph-negative MPN patients and healthy controls. Venn diagram identified 11 common DEPs (2 downregulated and 9 upregulated, details in Table S4) between patients and healthy controls, and between anemic and non-anemic patients (Fig. 3A). As shown in the volcano plot, the decrease in TRAIL levels ($P < 0.001$) and the increase in CXCL13 levels ($P = 0.004$) were most significant in anemic patients comparing to non-anemic individuals (Fig. 3B). Among the top 20 significant DEPs, the levels of ANGPT1, CCL17, CD40-L, CXCL15, EGF, FASLG, IL7, PDGF subunit B, TRAIL, TWEAK, and VEGFR-2 were downregulated, and the levels of ANGPT2, CCL3, CSF-1, CXCL13, IL-10, IL-15, IL-6, NOS3, and TNF were upregulated (Fig. 3C). GO enrichment analysis revealed that DEPs between anemic and non-anemic patients were enriched in BP of inflammatory response (GO: 0006954) and signal transduction (GO: 0007165), CC of the extracellular space (GO: 0005615) and extracellular region (GO:0005576), and molecular function of chemokine activity (GO: 0008009) and cytokine activity (GO: 0005125) (Fig. 3D). KEGG analysis also suggested the enrichment of DEPs in the cytokine-cytokine receptor interaction pathway (hsa04060) and viral protein interaction with cytokine-cytokine receptor interaction pathway (hsa04061) (Fig. 3E). Further analysis of anemic patients revealed that levels of seven proteins, including MCP-1, VEGF-2, TNF, TNFRSF4, TNFRSF9, CD28, and LAMP3, were significantly reduced in the TD cohort, with MCP-1 exhibiting the most pronounced difference (Figure S4). Except for VEGF-2, none of the others are

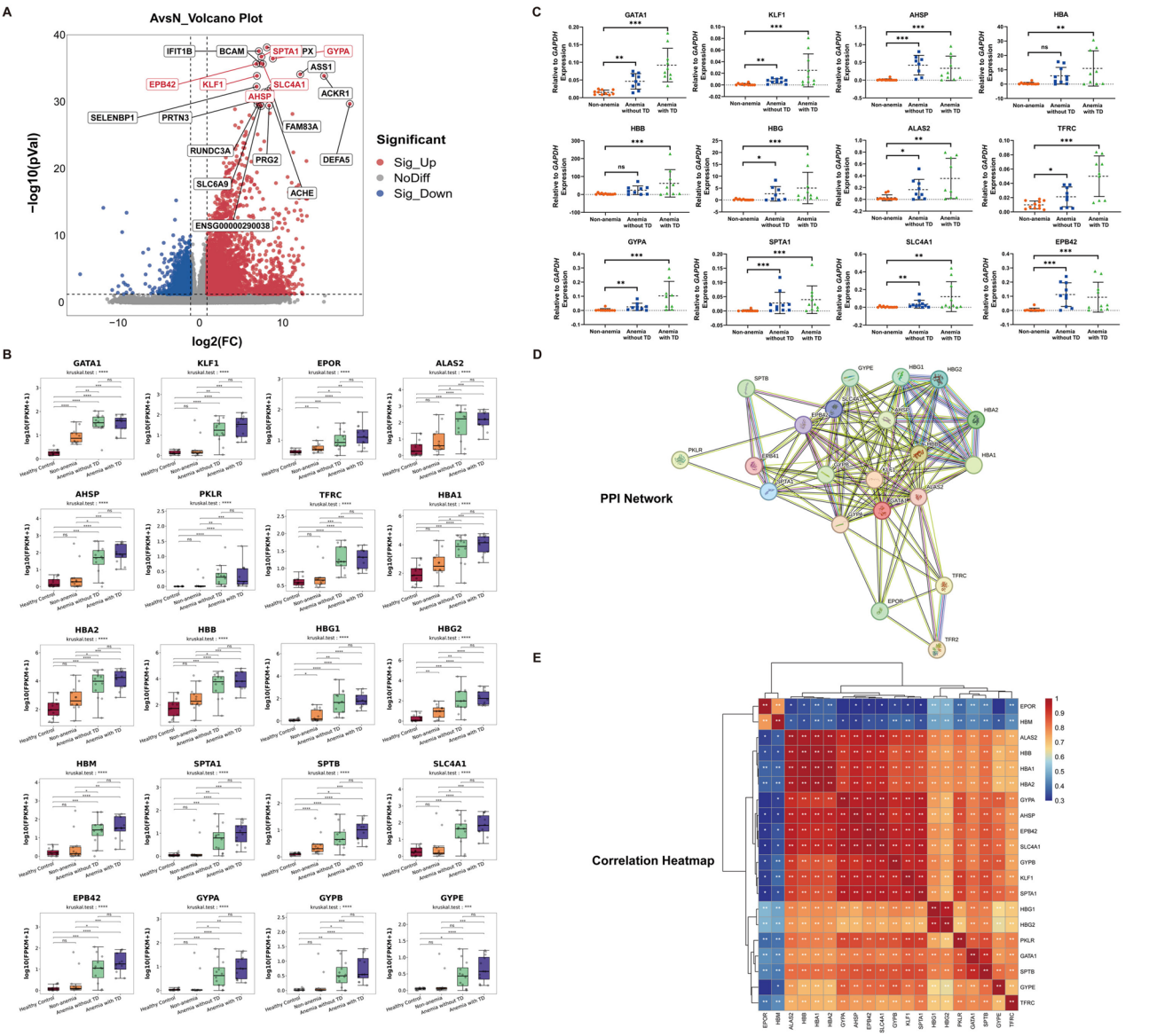


Fig. 2 DEGs associated with erythroid differentiation between anemic and non-anemic patients. (**A**) Volcano plot of DEGs in patients with anemia comparing to non-anemic patients. Top 20 DEGs are marked and those associated with erythroid differentiation are highlighted in red. (**B**) Analysis of 20 DEGs associated with erythroid differentiation among healthy control, non-anemic patients, patients without and with TD. FPKM, fragments per kilobase of exon model per million mapped fragments. (**C**) mRNA expression of 12 DEGs associated with erythroid differentiation among non-anemic patients, patients without and with TD via RT-qPCR (normalized to GAPDH). Data are presented as mean ± SD. (**D**) Protein–protein interaction (PPI) network of 20 DEGs associated with erythroid differentiation. (**E**) Heatmap of Spearman's correlation analysis for 20 DEGs associated with erythroid differentiation

DEPs between anemic and non-anemic patients, indicating that impaired angiogenesis may play a significant role in the development of MF-related anemia.

Plasma IL-10 identified as an independent diagnostic biomarker for MF-related anemia

To identify diagnostic biomarkers for MF-related anemia, we further performed Least Absolute Shrinkage and Selection Operator Regression (Lasso) regression analysis on DEPs between anemic and non-anemic patients (Fig. 4A and B). 12 DEPs remained in the final model are involved in the inflammatory response, angiogenesis, cell proliferation, apoptosis and migration (function annotation is provided in Table S5). Risk factor analysis revealed that elevated levels of TRAIL, FASLG, VEGFR-2, and EGF were associated with a lower risk score of anemia, while elevated IL-6, IL-8, IL-10, IL-15, CXCL13, ANGPT2, TNFRSF4, and PD-L1 levels were associated with a higher risk score (Fig. 4C). Spearman's correlation analysis with major DEGs associated

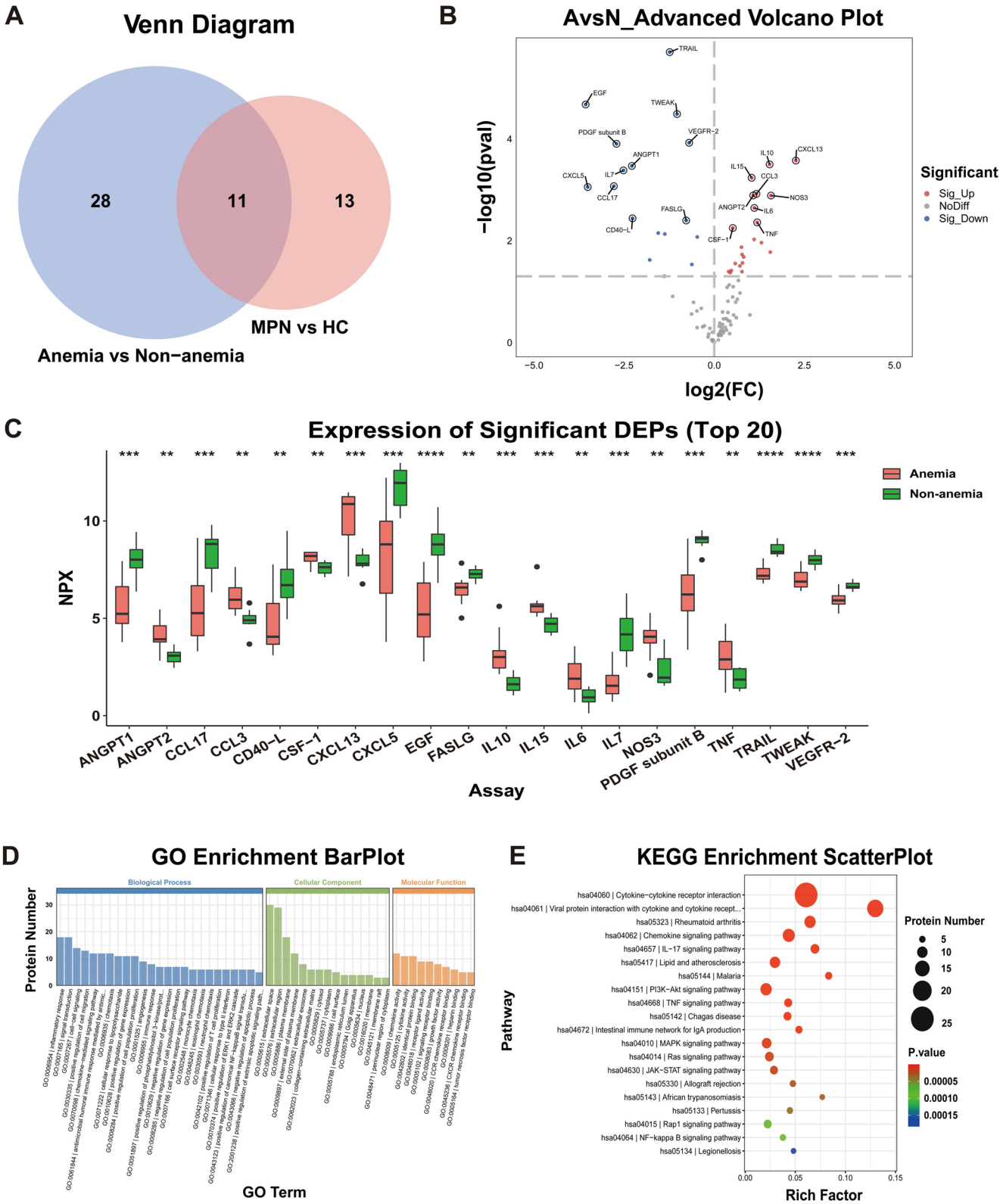
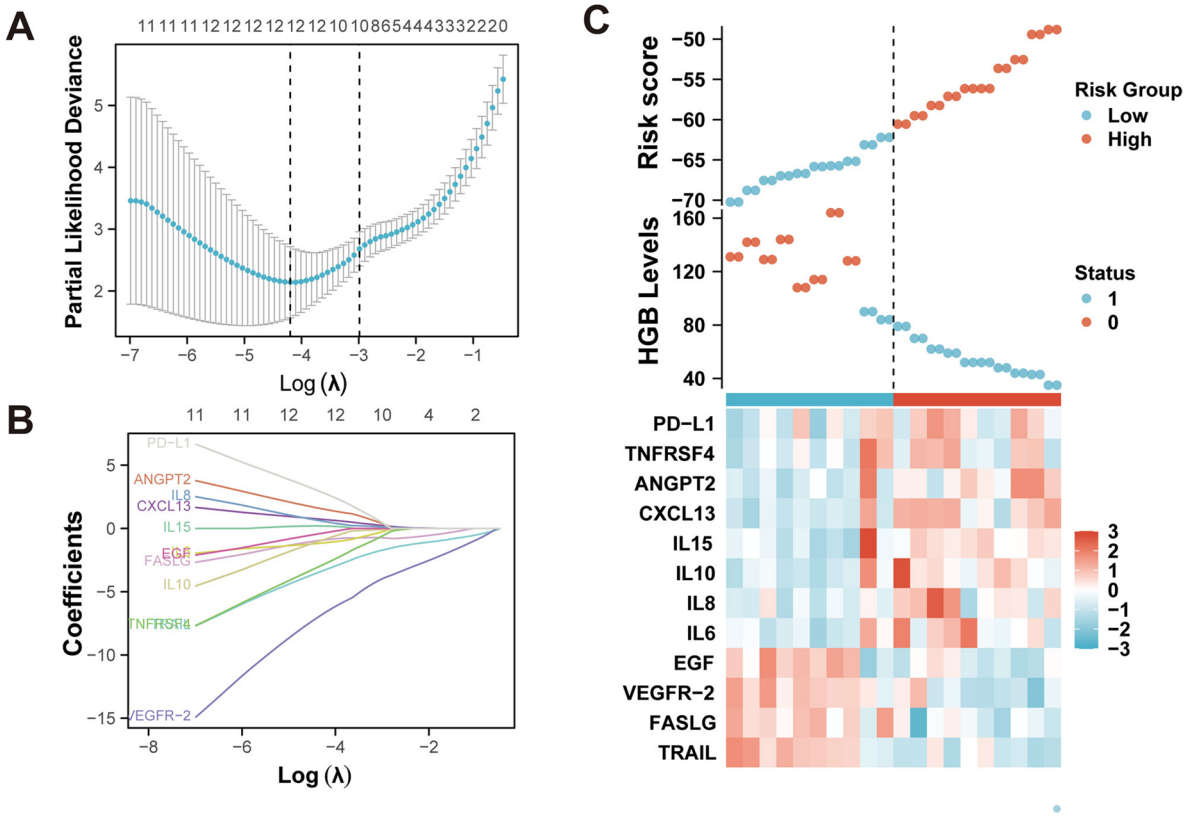
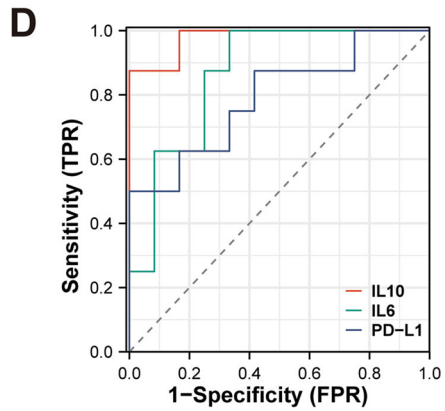


Fig. 3 DEPs based on immuno-oncology proteomics analysis. (**A**) Venn diagram of DEPs with a *P* value < 0.05 and $|\log_2 FC| \geq 1$ between patients with MPN and healthy controls, and between anemic and non-anemic patients. (**B**) Volcano plot of DEPs in patients with anemia compared to non-anemic patients (Top 20). (**C**) Expression of significant DEPs between anemic (red) and non-anemic (green) patients (Top 20). NPX, normalized protein expression. (**D**) GO enrichment barplot of DEPs between anemic and non-anemic patients based on functional categories of biological process, cellular component, and molecular function. (**E**) KEGG enrichment scatterplot of DEPs between anemic and non-anemic patients





Biomarker	Cut-off value	AUC	95% CI
IL-10	2.135	0.979	0.956-1.000
IL-6	1.546	0.865	0.787-0.942
PD-L1	5.127	0.792	0.688-0.896

Combined Biomarker	AUC	95% CI	*P* -value
IL-10+PD-L1	0.979	0.945-1.000	0.012
IL-10+IL-6	0.979	0.946-1.000	0.052
IL-6+PD-L1	0.885	0.782-0.989	0.399

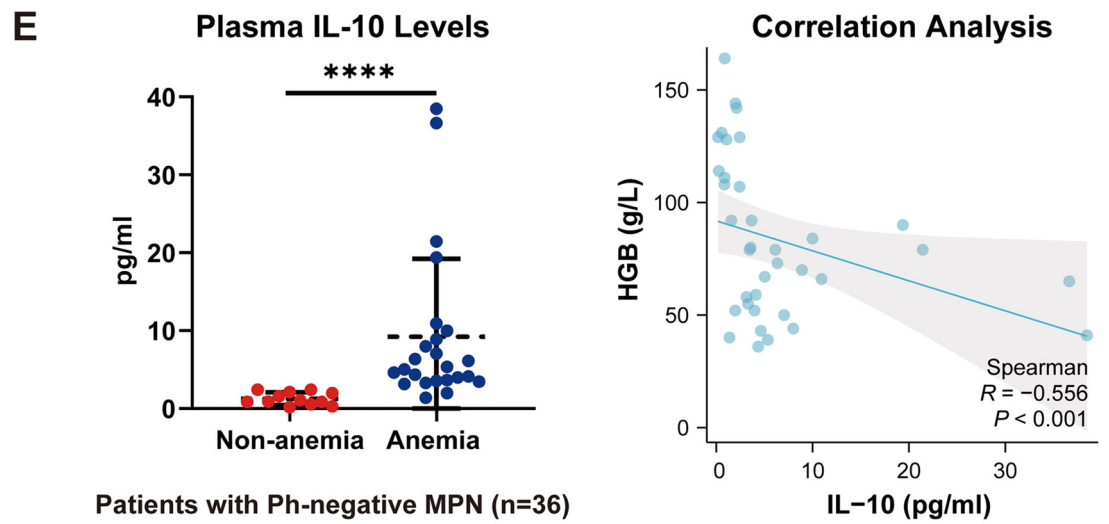


Fig. 4 Potential diagnostic biomarkers for MF-related anemia. The 10-fold cross-validation curve (**A**) and coefficient path diagram (**B**) in Lasso regression analysis. (**C**) Risk factor chart of selected12 DEPs. (**D**) Receiver-operating characteristic (ROC) curve analysis evidences the diagnostic value of IL-10, IL-6, and PD-L1, and tables show area under curve (AUC), 95% confidence interval (CI), and *p*-value for single or combined biomarkers. (**E**) Plasma IL-10 levels in Ph-negative MPN patients detected by ELISA and their correlation with HGB levels. Data are presented as mean ± SD

with erythroid differentiation revealed significant negative correlations for TRAIL, FASLG, and VEGFR-2, while IL-15, CXCL13, and PD-L1 showed significant positive correlations (Table 2, Figure S5A). Meanwhile, the protein levels of TRAIL ($P<0.001$), FASLG ($P=0.006$), VEGFR-2 ($P<0.001$), EGF ($P=0.003$), TWEAK ($P<0.001$), IL-10 ($P=0.007$), IL-15 ($P=0.001$), and CXCL13 ($P=0.013$) were significantly linearly correlated with HGB levels (Figure S5B). In addition, we observed that TRAIL serves as the most significant correlation factor for selected DEGs and HGB levels ($P<0.001$). After excluding genes with high collinearity, univariate logistic regression backward stepwise analysis demonstrated that IL-6 ($P=0.005$), IL-10 ($P=0.025$), and PD-L1 ($P=0.003$) were significant diagnostic biomarkers for MF-related anemia. However, only IL-10 remained significant in the multivariate analysis ($P=0.035$). ROC curve analysis indicated that the AUC for IL-6, IL-10, and PD-L1 to predict MF-related anemia were 0.865 (95% CI: 0.787–0.942), 0.979 (95% CI: 0.956-1.000), and 0.792 (95% CI: 0.688–0.896), respectively (Fig. 4D). Combined analysis of IL-10 and PD-L1 remained significant ($P=0.012$), but the AUC was not superior to that of IL-10 alone. Furthermore, ELISA confirmed that plasma IL-10 levels in anemic patients were significantly elevated compared to non-anemic patients ($P<0.0001$) and showed a significant negative correlation with HGB levels (R=-0.556, $P<0.001$) (Fig. 4E).

Discussion

In this study, we combined genomics and proteomics analysis to reveal the transcriptional profiles and plasma diagnostic biomarkers for MF patients with anemia. DEGs involved in the JAK-STAT signaling pathway indicated significant upregulation of *CCND1* and downregulation of *IFNAR2* in anemic patients in contrast to non-anemic patients and healthy controls. We also observed that *IFNAR1*, another subunit of the type I interferon receptor (IFNAR), was significantly reduced in the anemia group compared to non-anemic patients, while its expression levels in the latter were also lower than those in healthy controls (Figure S6), potentially represented as a feature associated with MF progression in MPN patients. Cathrin-dependent endocytosis of IFNAR is essential for activating JAK-STAT signaling pathway [19], and downregulation of both subunits reflects a negative feedback regulatory response to inhibit pathway activation. IFNAR1 drives initial signal transduction by binding to TYK2 and triggering its cross-phosphorylation with JAK1, while IFNAR2 is responsible for promoting STAT recruitment, STAT phosphorylation, and target gene activation, which indicates their distinct roles in initiating type I interferon-induced JAK-STAT signaling [20]. Downregulation of *IFNAR2* expression may indicate a more sustained and effective negative feedback on the JAK-STAT signaling pathway.

Further analysis of MPN patients revealed that DEGs associated with erythroid differentiation were predominantly

Table 2 Correlation analysis between selected DEPs and DEGs associated with erythroid differentiation

	TRAIL	FASLG	VEGFR-2	EGF	IL-6	IL-8	IL-10	IL-15	CXCL13	ANGPT2	PD-L1	TNFRSF4
GATA1	-0.846	-0.604	-0.548	-0.425	0.546	0.670	0.665	0.648	0.604	0.445	0.760	0.583
	(<0.001***)	(0.355)	(0.974)	(1.000)	(0.997)	(0.085)	(0.098)	(0.142)	(0.357)	(1.000)	(0.006**)	(0.529)
KLF1	-0.783	-0.486	-0.802	-0.683	0.598	0.288	0.614	0.646	0.454	0.511	0.612	0.506
	(0.003**)	(1.000)	(0.001**)	(0.061)	(0.400)	(1.000)	(0.295)	(0.151)	(1.000)	(1.000)	(0.309)	(1.000)
ALAS2	-0.778	-0.669	-0.564	-0.528	0.598	0.552	0.678	0.764	0.721	0.574	0.632	0.578
	(0.003**)	(0.088)	(0.739)	(0.021*)	(0.402)	(0.902)	(0.071)	(0.005**)	(0.022*)	(0.623)	(0.200)	(0.584)
AHSP	-0.760	-0.577	-0.759	-0.540	0.554	0.471	0.649	0.701	0.548	0.410	0.681	0.565
	(0.006**)	(0.591)	(0.006**)	(1.000)	(0.887)	(1.000)	(0.139)	(0.038*)	(0.969)	(0.115)	(0.066)	(0.736)
HBB	-0.761	-0.759	-0.649	-0.622	0.657	0.430	0.663	0.820	0.652	0.617	0.552	0.506
	(0.006**)	(0.006**)	(0.138)	(0.253)	(0.117)	(1.000)	(0.100)	(<0.001***)	(0.131)	(0.276)	(0.909)	(1.000)
TFRC	-0.857	-0.540	-0.603	-0.425	0.514	0.646	0.622	0.608	0.574	0.519	0.668	0.478
	(<0.001***)	(1.000)	(0.368)	(1.000)	(1.000)	(0.150)	(0.251)	(0.329)	(0.621)	(1.000)	(0.091)	(1.000)
GYPA	-0.770	-0.519	-0.763	-0.592	0.547	0.450	0.646	0.709	0.490	0.500	0.615	0.498
	(0.004**)	(1.000)	(0.005**)	(0.450)	(0.992)	(1.000)	(0.151)	(0.030*)	(1.000)	(1.000)	(0.288)	(1.000)
SLC4A1	-0.789	-0.582	-0.771	-0.577	0.526	0.435	0.670	0.684	0.506	0.447	0.589	0.505
	(0.002**)	(0.545)	(0.004**)	(0.591)	(1.000)	(1.000)	(0.085)	(0.060)	(1.000)	(1.000)	(0.474)	(1.000)

Partial correlation analysis (age-controlled) was used to calculate correlation coefficients. Data was shown as Rho (Bonferroni-adjusted *P*-value)

upregulated in the anemia group compared to non-anemic patients and positively correlated with anemia severity. TGF-β family members, as the major fibroblast growth factors in the pathogenesis of MF, induces apoptosis of late-stage erythrocytes by activating the bone morphogenetic protein / small mother against decapentaplegic (BMP/SMAD) signaling pathway [8,9]. Although plasma EPO levels were compensatorily elevated in anemic patients, whose receptor is crucial for activating JAK-STAT signaling pathway to drive early erythropoiesis [21], such effect is typically ineffective in late-stage hematopoietic defect [8]. Therefore, our data support ineffective erythropoiesis as a prominent feature of MF-related anemia. We propose that in MF patients with anemia, the body may compensate for EPO-induced activation of the JAK-STAT signaling pathway by inhibiting *IFNAR* expression (especially *IFNAR2*) through an unknown negative feedback mechanism.

Meanwhile, functional enrichment analysis revealed that common DEGs between patients with MPN and healthy controls, as well as between anemic patients and non-anemic patients were enriched in the cytokine-cytokine receptor interaction pathway and NF-κB signaling pathway. Previous studies on transcriptional analysis in different MPN subtypes similarly reported enrichment of inflammatory GO terms and activation of TNF-α and NF-κB signaling pathway in the MF cohorts [22,23]. To identify plasma biomarkers for MF-related anemia, we subsequently performed Olink proteomics, which revealed that TRAIL and CXCL13 were the most decreased and increased cytokines in the anemia group compared to non-anemic patients, respectively. CXCL13 has been identified as an inferior prognostic biomarker in systemic lupus erythematosus (SLE)-related autoimmune hemolytic anemia [24]. TRAIL, as an apoptosis-inducing factor, has been reported to be overexpressed in aplastic anemia, Fanconi anemia, and myelodysplastic syndrome (MDS) [25–27]. Elevated TRAIL levels in the bone marrow are associated with erythropoiesis impairment due to direct cytotoxicity and inhibition of erythroid maturation [28,29]. However, TRAIL can also promote erythroid survival by activating the NF-κB signaling pathway under starvation conditions in vitro [30]. In addition, TRAIL was found to induce macrophage polarization toward the pro-inflammatory/tumor-fighting M1 phenotype, thereby enhancing their cytotoxicity [31]. In our study, plasma TRAIL levels were decreased in anemic patients and positively correlated with HGB levels. This phenomenon may be a compensatory protective mechanism to reduce the cytotoxicity on erythrocyte precursors and alleviate the inhibition of inflammation on erythropoiesis, which requires further exploration. Furthermore, DEPs between anemic patients with and without TD suggested negative feedback regulation of inflammatory cytokines (downregulation of TNF, TNFRSF4, TNFRSF9) in the former. MF-related anemia may induce T-cell exhaustion and immune paralysis, thereby accelerating disease progression.

Next, Lasso regression analysis identified 12 DEPs as candidate risk variables, which were also closely correlated with erythroid differentiation-associated DEGs and HGB levels. Subsequent logistic regression analysis and ROC curve analysis identified IL-10 as an independent diagnostic biomarker for MF-related anemia. Multiple pro-inflammatory cytokines are spontaneously secreted in MF patients, and monocytes are the most responsible cell population [32]. IL-8, IL-2R, IL-12, and IL-15 have been identified as independent adverse prognostic biomarkers in PMF patients, and elevated levels of IL-2R and IL-12 correlate with transfusion need [33]. A bidirectional Mendelian-randomization study revealed that genetically predicted MPN promoted the expression of IL-10 and monokine induced by interferon-gamma (MIG) [34]. IL-10 is a well-known anti-inflammatory cytokine, and exogenous IL-10 can inhibit the autonomous myelopoiesis in MF patients in vitro, especially the formation of colony-forming unit-granulocyte-macrophage (CFU-GM) [35,36]. The monocytes of patients with MPN are reportedly insensitive to IL-10, leading to the loss of negative regulation of TNF-α induced by Toll-like receptor signaling activation [37]. In the bleomycin-induced pulmonary fibrosis mouse model, IL-10 deficiency aggravated cell senescence and susceptibility to fibrosis, while the administration of recombinant IL-10 significantly rescued the phenotypes [38]. In addition, IL-10 can exert anti-inflammatory and antifibrotic effects by enhancing the functions of FOXP3 + regulatory T cells to maintain immunotolerance [39], which also presents a risk of immune escape in neoplasms [40,41]. Therefore, elevated IL-10 levels in MF patients with anemia may represent a compensatory anti-inflammatory response due to reduced sensitivity, or a marker of disease progression and an immunosuppressive microenvironment.

Recently, novel targeted agents including momelotinib, gecacitinib (both a dual inhibitor of JAK and activin A receptor, type I [ACVR1]), and luspatercept (a TGF-β ligand trap) have shown great efficacy and safety in MF patients with anemia [42–44]. Although the importance of abnormal inflammatory signaling in the pathogenesis of MF has been widely recognized, current treatment options remain limited. The NF-κB pathway, rather than the JAK-STAT pathway, has been identified to play a dominant role in driving the cytokine storm [32]. Inflammation is also involved in the regulation of hepcidin [8]. Functional iron deficiency presents in nearly 35% of MF patients with anemia, and increased hepcidin levels are associated with anemia severity, transfusion need and increased DIPSS-plus risk [45–47]. Given the importance of hepcidin in iron-restricted erythropoiesis, we conducted a supplementary analysis of plasma hepcidin

levels via ELISA assay. Results indicated that hepcidin levels were significantly elevated in anemic patients without TD compared to non-anemic patients ($P=0.006$), while no significance was observed between anemic patients with TD and non-anemic patients (Figure S7A). Correlation analysis also barely supported the association between hepcidin levels and HGB levels (Figure S7B). Repeated blood transfusions carry a risk of iron overload, so theoretically, hepcidin levels should be elevated in such cohort. However, our results did not show a significant difference, which may be attributed to the fact that some individuals in the TD cohort once received iron chelation therapy.

Due to the small sample size and high heterogeneity of MF patient in this study, the following limitations are unavoidable. First, although no significant difference was observed in age distribution between anemic and non-anemic patients, healthy controls were relatively younger than MPN patients. Age-induced differential expression should be excluded given that age is a risk factor of increased somatic variants in MF[23]. Second, a higher proportion of patients receiving JAK inhibitors or HMA treatment was observed in the anemia group, and part of patients in the non-anemia group underwent cytoreductive therapy. Study on the inflammatory factor profile in MF-related anemia should ideally be conducted in newly diagnosed patients to avoid treatment-induced interference. Third, to explore the molecular characteristics of MF-related anemia, the most suitable control group should consist of MF patients without anemia, who constitute only 25% in this study. The non-anemia group primarily comprised ET and PV patients, while patients with post ET / PV-MF accounted for only 20.83% in the anemia group. Therefore, variations stemming from the heterogeneity of the primary disease are also unavoidable. Fourth, the presence of anemia is considered as one of the characteristics distinguishing genuine ET from pre-fibrotic PMF [48,49]. However, since all PMF patients were in the overt fibrotic phase in our study, further research is warrant to explore genomic and inflammatory characteristics among pre-PMF, overt-PMF, and secondary MF. In addition, given that all samples in our study were obtained from the peripheral circulation, the applicability of these findings in the bone marrow microenvironment remains to be discussed.

Conclusions

In conclusion, our study combined transcriptomics and Olink proteomics to preliminarily reveal the transcriptional landscape and expression patterns of oncology-immune-related proteins in MF patients with anemia. The results confirmed that ineffective erythropoiesis and abnormally activated inflammatory cytokines are hallmark features of MF-related anemia. Furthermore, we identified a significant negative correlation between TRAIL and DEGs associated with erythroid differentiation, and confirmed the anti-inflammatory factor IL-10 as a potential diagnostic biomarker for MF-related anemia. Despite the small sample size, our study innovatively clarifies the role of oncology-immune-related proteins in MF-related anemia and their correlation with genes associated with erythroid differentiation and anemia severity. Future studies are needed to confirm these findings and the importance of IL-10 in MF-related anemia.

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Author contributions Liqing Yang performed the research, analysed the data, and write the original draft. Yuanzhong Chen supervised the research and revised the draft. Yong Wu guided the composition and made a revision. All the authors read and approved the final manuscript.

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Data availability The data supporting the findings of this study are available in the results and supplementary files. Additional data are available upon reasonable request from the corresponding author.

Declarations

Ethics approval statement This study was approved by the ethics committee of Fujian Medical University Union Hospital (Approval no. 2025YF022-01) and was performed in accordance with the Declaration of Helsinki.

Patient consent statement Written informed consent for data collection and publication was obtained from each participant prior to the enrollment of the study.

Competing interests The authors declare no competing interests.

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