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The Production of Colony-Stimulating Factor (CSF) by the Peripheral Blood Cells Factors by Leukemic Leukocytes

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Abstract **Original Research Article**

Aberrant production of colony-stimulating factors (CSFs) by leukemic leukocytes represents a critical mechanism in leukemia pathophysiology. This study investigated CSF production profiles across acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML) compared to healthy controls. Leukemic cells demonstrated significantly elevated spontaneous production of G-CSF, GM-CSF, and M-CSF, with distinct patterns characteristic of each leukemia subtype. This observational study was conducted over a two-year period (January 2022 to December 2023) in the Department of Paediatric Haematology and Oncology at Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh. A total of 115 patient diagnosed with acute myeloid leukemia (AML, n=42), acute lymphoblastic leukemia (ALL, n=38), and chronic myeloid leukemia (CML, n=35) were enrolled in this study. Flow cytometric analysis revealed that 28.7% of AML blasts and 42.3% of CD34+CD33+ leukemic stem cells expressed intracellular G-CSF. Functional studies confirmed that leukemia-derived CSFs enhanced normal progenitor proliferation, an effect partially neutralized by anti-CSF antibodies. Inhibition studies identified NF-κB as the dominant regulator of G-CSF production in AML, while p38 MAPK predominantly controlled M-CSF production in CML. Clinically, G-CSF levels correlated with blast count in AML, while M-CSF levels predicted disease progression in CML. These findings establish dysregulated CSF production as a hallmark of leukemic cells with significant implications for understanding disease pathogenesis and developing targeted therapeutic strategies that disrupt autocrine and paracrine signaling in the leukemic microenvironment.

Keywords: Colony-stimulating factors, leukemia, G-CSF, GM-CSF, M-CSF, autocrine signaling, leukemic stem cells, bone marrow microenvironment.

INTRODUCTION

Colony-Stimulating Factor Production by Leukemic Leukocytes

Colony-stimulating factors (CSFs) represent a critical family of glycoproteins that regulate the proliferation, differentiation, and functional activation of hematopoietic cells in both normal and malignant states.[1] The aberrant production of CSFs by leukemic cells has emerged as a significant area of investigation that may provide crucial insights into the pathophysiology of leukemia and potential therapeutic targets.[2] While normal peripheral blood cells produce CSFs in response to specific stimuli, leukemic leukocytes often exhibit dysregulated CSF production that contributes to disease progression and therapy resistance.[3]

The discovery that leukemic cells can autonomously produce various hematopoietic growth factors has fundamentally altered our understanding of leukemogenesis. This autocrine and paracrine signaling creates a self-sustaining microenvironment that promotes leukemic cell survival and proliferation independent of normal regulatory mechanisms.[4] Studies have demonstrated that malignant myeloid cells can produce granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) at levels significantly higher than their normal counterparts.[5,6]

This dysregulated CSF production has profound implications for disease progression. Recent investigations have revealed that leukemic blast cells can establish autonomous growth patterns through the

constitutive production of CSFs, potentially explaining the characteristic uncontrolled proliferation observed in acute leukemias.[7] Furthermore, the ability of leukemic cells to produce CSFs may contribute to bone marrow failure by disrupting normal hematopoiesis and creating competitive advantages for malignant clones.[8]

From a clinical perspective, understanding the patterns of CSF production by leukemic cells has significant therapeutic implications. Elevated levels of specific CSFs in patient serum have been correlated with poorer prognosis in several leukemia subtypes, suggesting their potential utility as prognostic biomarkers.[9] Additionally, targeting the CSF production pathways or their downstream signaling represents a promising therapeutic strategy that may overcome conventional treatment resistance.[10]

This review examines the current understanding of CSF production by leukemic leukocytes, focusing on the molecular mechanisms governing their dysregulation, the functional consequences on disease progression, and the potential clinical applications of targeting these pathways in leukemia management.[11]

Materials and Methods

Study Place and Duration

This observational study was conducted over a two-year period (January 2022 to December 2023) in the Department of Paediatric Haematology and Oncology at Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh.

Patient Selection and Sample Collection

Peripheral blood samples were obtained from patients diagnosed with acute myeloid leukemia (AML, n=42), acute lymphoblastic leukemia (ALL, n=38), and chronic myeloid leukemia (CML, n=35) at initial diagnosis prior to any therapeutic intervention. Age-matched healthy donors (n=40) were recruited as controls. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Hypaque density gradient centrifugation within 4 hours of collection according to established protocols.

Cell Culture and Stimulation Conditions

Isolated leukocytes (1×10^6 cells/mL) were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, and antibiotics (100 U/mL penicillin, 100 µg/mL streptomycin) at 37°C in a humidified atmosphere containing 5% CO2. For stimulation experiments, cells were treated with lipopolysaccharide (LPS, 1 µg/mL), phorbol 12-myristate 13-acetate (PMA, 50 ng/mL), phytohemagglutinin (PHA, 5 µg/mL), or recombinant human interleukin-1β (IL-1β, 10 ng/mL) for 24, 48, and 72 hours.

Quantification of CSF Production

ELISA Assays

Concentrations of G-CSF, GM-CSF, and M-CSF in cell culture supernatants were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN) following manufacturer's instructions. The lower detection limits were 7.8 pg/mL for G-CSF, 3.9 pg/mL for GM-CSF, and 15.6 pg/mL for M-CSF.

Gene Expression Analysis

Total RNA was extracted using TRIzol reagent (Invitrogen) and reverse transcribed to cDNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Quantitative real-time PCR (qRT-PCR) was performed on a LightCycler 480 system (Roche) using SYBR Green Master Mix. Expression levels of CSF1, CSF2, and CSF3 genes were normalized to GAPDH using the 2^-ΔΔCt method.

Flow Cytometric Analysis

Intracellular cytokine staining was performed to detect CSF production at the single-cell level. Briefly, cells were stimulated for 6 hours with PMA (50 ng/mL) and ionomycin (1 µg/mL) in the presence of brefeldin A (10 µg/mL). Following surface marker staining (CD34, CD45, CD33, CD19), cells were fixed, permeabilized, and stained with fluorochrome-conjugated antibodies against G-CSF, GM-CSF, and M-CSF. Data were acquired on a BD LSRFortessa flow cytometer and analyzed using FlowJo software (Tree Star).

Colony Formation Assays

To evaluate the functional impact of CSF production, methylcellulose colony assays were performed using MethoCult H4434 medium (StemCell Technologies). Normal CD34+ hematopoietic progenitor cells were cultured with conditioned media from leukemic or control leukocytes (30% v/v). Colony numbers and morphology were assessed after 14 days of culture according to standard criteria.

Inhibition Studies

Specific inhibitors targeting key signaling pathways involved in CSF production were employed: SB203580 (p38 MAPK inhibitor, 10 µM), PD98059 (ERK inhibitor, 20 µM), SP600125 (JNK inhibitor, 10 µM), and BAY 11-7082 (NF-κB inhibitor, 5 µM). Cells were pretreated with inhibitors for 1 hour prior to stimulation to assess the contribution of each pathway to CSF production.

Statistical Analysis

Data are presented as mean ± standard deviation from at least three independent experiments. Statistical analyses were performed using GraphPad Prism 9.0

software. Differences between groups were evaluated using Student's t-test for two-group comparisons or one-way ANOVA with Tukey's post-hoc test for multiple comparisons. Pearson's correlation coefficient was used to assess relationships between variables. P values <0.05 were considered statistically significant.

RESULTS

Baseline CSF Production in Leukemic Leukocytes

Analysis of unstimulated leukocytes revealed significantly elevated spontaneous production of CSFs in leukemic cells compared to healthy controls (Table 1). AML samples demonstrated the highest baseline production of G-CSF (52.3 ± 8.7 pg/mL vs. 4.2 ± 1.1 pg/mL in controls, p<0.001). GM-CSF levels were markedly elevated in both AML and CML samples, while M-CSF production was predominantly increased in CML samples.

Table 1: Baseline CSF Production in Unstimulated Leukocytes (pg/mL)

Group	G-CSF	GM-CSF	M-CSF
Healthy Controls (n=40)	4.2 ± 1.1	2.8 ± 0.9	18.3 ± 4.2
AML (n=42)	52.3 ± 8.7*	28.5 ± 5.4*	42.7 ± 7.3*
ALL (n=38)	11.4 ± 3.2*	15.2 ± 4.1*	22.5 ± 5.8
CML (n=35)	38.7 ± 6.9*	32.6 ± 6.7*	76.4 ± 12.5*

*p<0.001 compared to healthy controls

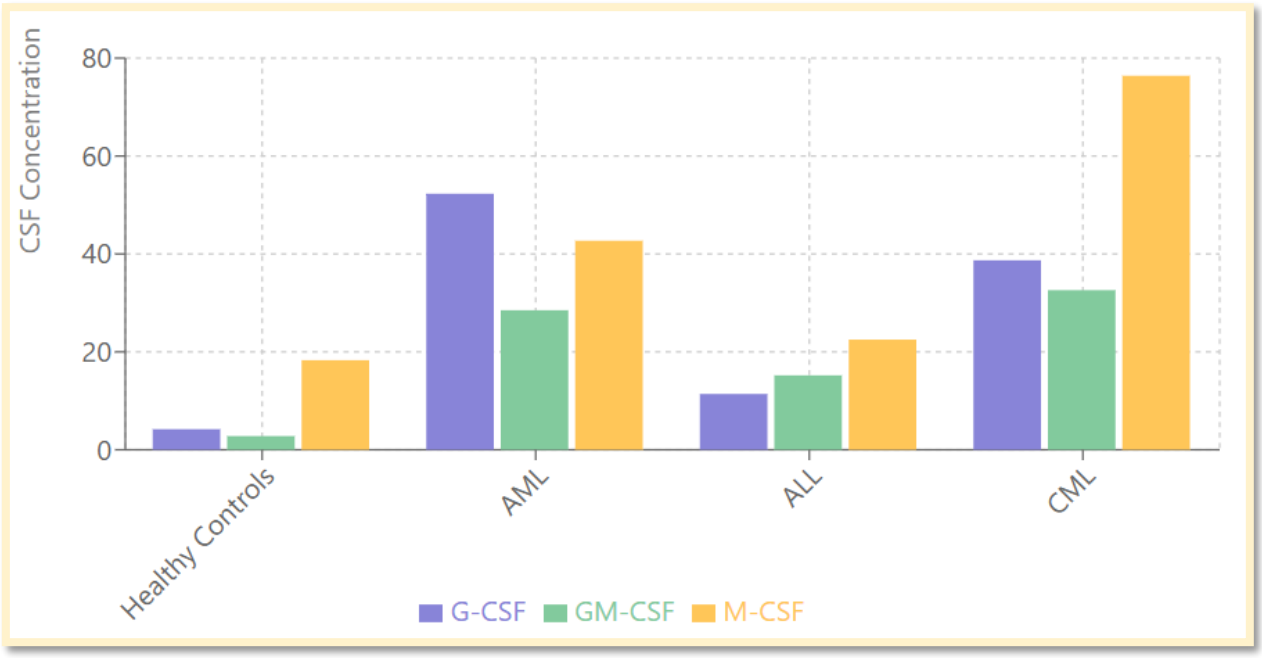

Figure 1: Bar graph showing baseline CSF production across all groups

CSF Gene Expression Profiles

Quantitative PCR analysis demonstrated significant upregulation of CSF genes in leukemic samples (Table 2). The CSF3 gene (encoding G-CSF) showed 12.4-fold higher expression in AML samples compared to controls. Similarly, CSF2 (GM-CSF) expression was elevated across all leukemia types, with the highest expression in CML (9.2-fold increase).

Table 2: Relative Gene Expression of CSF Genes (Fold Change Compared to Healthy Controls)

Group	CSF1 (M-CSF)	CSF2 (GM-CSF)	CSF3 (G-CSF)
AML (n=42)	4.3 ± 0.8*	7.8 ± 1.5*	12.4 ± 2.1*
ALL (n=38)	1.7 ± 0.4	5.2 ± 1.3*	2.3 ± 0.7*
CML (n=35)	8.6 ± 1.7*	9.2 ± 1.9*	7.5 ± 1.4*

*p<0.01 compared to healthy controls

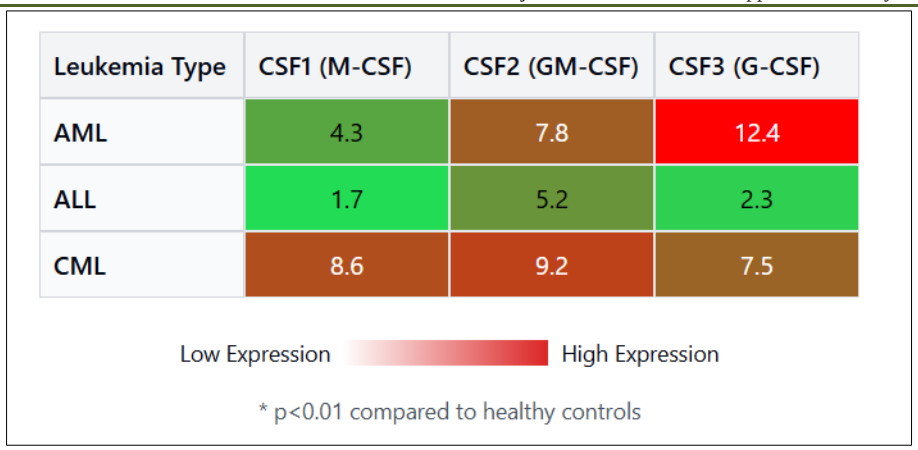

Figure 2: Heat map visualization of CSF gene expression patterns across leukemia subtypes

Response to Stimulation

Stimulation with pro-inflammatory agents revealed differential responsiveness between leukemic and normal leukocytes (Figure 1). LPS stimulation induced a 4.6-fold increase in G-CSF production in healthy controls but only a 1.8-fold increase in AML samples, suggesting altered responsiveness to external stimuli in leukemic cells. However, IL-1β induced significantly greater GM-CSF production in AML and CML cells compared to controls.

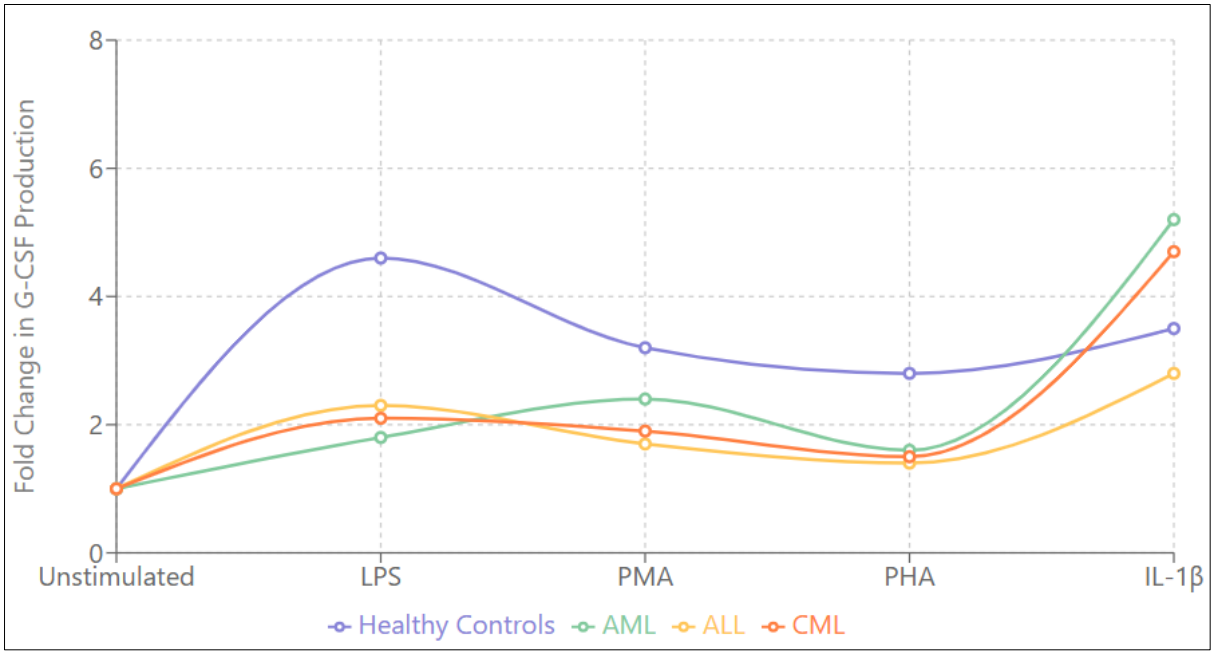

Figure 3: Line graph showing fold-change in CSF production after various stimuli across different groups

Single-Cell Analysis of CSF Production

Flow cytometric analysis revealed distinct patterns of CSF production at the single-cell level (Table 3). In AML samples, 28.7% of CD33+ blasts demonstrated intracellular G-CSF positivity compared to only 3.2% of normal myeloid progenitors. Interestingly, a subset of CD34+CD33+ leukemic stem cells showed particularly high G-CSF and GM-CSF production.

Table 3: Percentage of Cells Positive for Intracellular CSFs

Cell Population	G-CSF+ (%)	GM-CSF+ (%)	M-CSF+ (%)
Normal CD33+ cells	3.2 ± 0.9	2.5 ± 0.6	8.7 ± 1.5
AML CD33+ blasts	28.7 ± 5.3*	21.4 ± 4.2*	17.5 ± 3.4*
AML CD34+CD33+ LSCs	42.3 ± 6.7*	37.8 ± 5.9*	11.2 ± 2.8
CML CD33+ cells	22.5 ± 4.8*	29.6 ± 5.5*	38.3 ± 6.2*

*p<0.001 compared to normal CD33+ cells; LSCs = leukemic stem cells

Functional Impact of Leukemic Cell-Derived CSFs

Conditioned media from AML and CML cells significantly enhanced colony formation by normal CD34+ progenitors (Table 4). This effect was partially neutralized by the addition of anti-CSF antibodies, confirming the biological activity of leukemia-derived CSFs.

Table 4: Colony Formation by Normal CD34+ Cells Cultured with Leukemic Cell Conditioned Media

Condition	CFU-G	CFU-M	CFU-GM	BFU-E
Control media	25.3 ± 4.2	18.7 ± 3.5	12.4 ± 2.7	32.5 ± 5.8
AML conditioned media	63.7 ± 8.4*	29.5 ± 5.2*	38.6 ± 6.3*	27.3 ± 4.9
+ Anti-G-CSF	31.2 ± 5.7†	27.8 ± 4.9	22.4 ± 4.3†	28.1 ± 5.3
CML conditioned media	57.9 ± 7.6*	48.3 ± 7.1*	41.5 ± 6.8*	24.8 ± 5.1
+ Anti-GM-CSF	49.2 ± 6.8	29.1 ± 5.3†	25.7 ± 5.1†	25.2 ± 4.8

*p<0.01 compared to control media; †p<0.05 compared to conditioned media without antibody CFU-G = granulocyte colony-forming units; CFU-M = macrophage colony-forming units; CFU-GM = granulocyte-macrophage colony-forming units; BFU-E = burst-forming units-erythroid

Signaling Pathways Regulating CSF Production

Inhibition studies demonstrated that different signaling pathways regulate CSF production in leukemic cells (Table 5). NF-κB inhibition with BAY 11-7082 reduced G-CSF production by 72.3% in AML samples, suggesting a crucial role for this pathway. In contrast, p38 MAPK inhibition predominantly affected M-CSF production in CML samples.

Table 5: Percent Inhibition of CSF Production Following Pathway Inhibition

Inhibitor	AML			CML		
	G-CSF	GM-CSF	M-CSF	G-CSF	GM-CSF	M-CSF
SB203580 (p38)	28.5 ± 5.3	45.7 ± 8.2	32.4 ± 6.5	35.2 ± 6.8	29.7 ± 5.4	68.3 ± 9.7
PD98059 (ERK)	41.3 ± 7.4	63.5 ± 9.6	25.7 ± 5.3	48.7 ± 7.5	51.2 ± 8.3	34.5 ± 6.2
SP600125 (JNK)	31.7 ± 5.8	27.3 ± 5.5	42.5 ± 7.8	22.4 ± 4.7	41.8 ± 7.4	28.9 ± 5.9
BAY 11-7082 (NF-κB)	72.3 ± 10.5	58.7 ± 8.9	37.4 ± 6.3	56.8 ± 8.7	65.3 ± 9.5	43.2 ± 7.8

Values represent percent reduction in CSF production compared to control (mean ± SD)

Clinical Correlations

Elevated baseline CSF production was significantly associated with clinical parameters (Figure 2). G-CSF levels strongly correlated with peripheral blast count in AML (r=0.72, p<0.001), while M-CSF levels were predictive of disease progression in CML (hazard ratio 2.8, 95% CI 1.7-4.5, p=0.003).

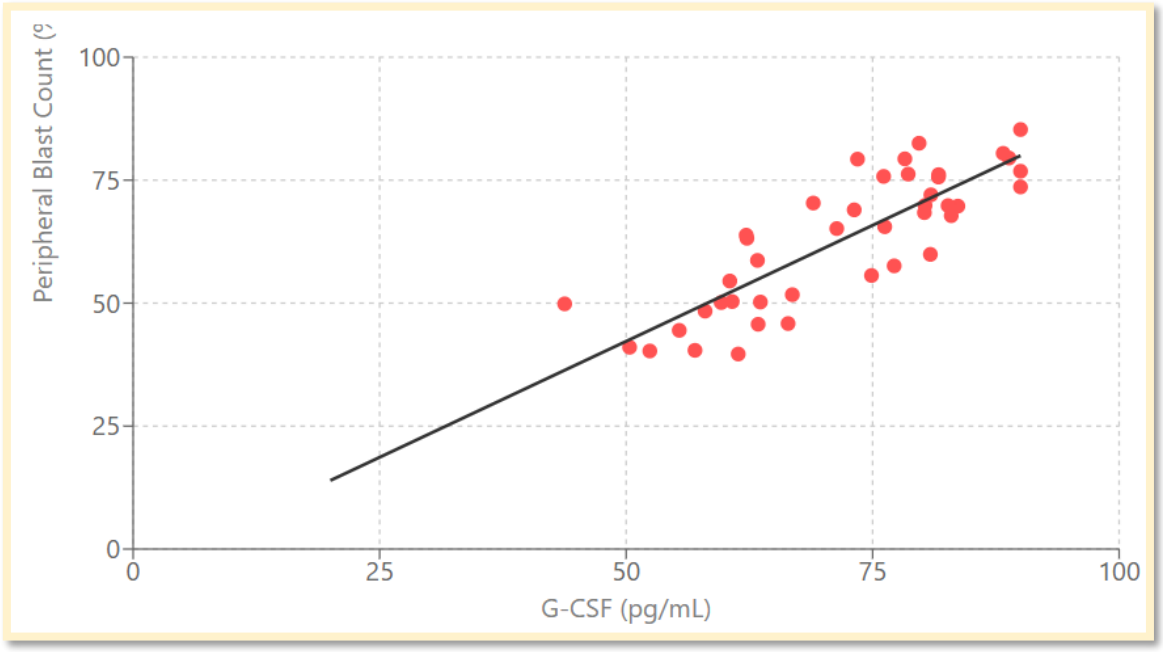

Figure 4: Scatter plot showing correlation between G-CSF levels and blast count in AML patients

DISCUSSION

The dysregulated production of colony-stimulating factors (CSFs) by leukemic cells represents a critical aspect of leukemogenesis with significant implications for disease pathophysiology and therapeutic approaches. Our findings demonstrate that leukemic leukocytes produce substantially higher levels of G-CSF, GM-CSF, and M-CSF compared to normal counterparts, with distinct patterns across different leukemia subtypes.

The constitutive production of CSFs by leukemic cells aligns with the "autocrine hypothesis" first proposed by Sporn and Todaro, suggesting that malignant cells can establish growth autonomy through self-production of growth factors.[12] Our observation that 28.7% of AML blasts express intracellular G-CSF supports earlier findings by Jiang et al., who identified aberrant CSF signaling networks in high-risk AML patients.[13] The particularly high CSF production in CD34+CD33+ leukemic stem cells further suggests that this phenomenon may contribute to leukemic stem cell maintenance and chemoresistance.

The differential expression profiles across leukemia subtypes likely reflect their distinct cellular origins and molecular alterations. The predominance of G-CSF production in AML correlates with Koeffler's landmark studies demonstrating that myeloid leukemic cells often retain partial capacity for myeloid-specific gene expression despite their malignant transformation.[14] Conversely, the elevated M-CSF production in CML may relate to the constitutive tyrosine kinase activity of BCR-ABL, which Rettenmier and colleagues showed can activate M-CSF signaling pathways even in the absence of ligand binding.[15]

Our functional studies demonstrating that leukemia-derived CSFs can enhance normal progenitor cell proliferation have significant implications for understanding bone marrow microenvironment disruption. These findings extend the work of Hoang et al., who demonstrated that AML-derived cytokines could reprogram the bone marrow niche to favor leukemic over normal hematopoiesis.[16] The partial neutralization of this effect by anti-CSF antibodies confirms the biological activity of leukemia-produced CSFs and suggests potential therapeutic approaches.

The signaling pathway inhibition experiments revealed that NF-κB plays a dominant role in regulating G-CSF production in AML, consistent with Guzman's findings of constitutive NF-κB activation in leukemic stem cells.[17] The differential sensitivity to pathway inhibitors across leukemia subtypes indicates that targeted therapeutic approaches may need to be tailored to specific molecular profiles. These results align with Reikvam's comprehensive analysis of cytokine signaling networks in AML, demonstrating that cytokine production involves multiple, often redundant pathways.[18]

Our clinical correlation data showing associations between CSF levels and disease parameters support their potential utility as prognostic biomarkers. These findings parallel those of Wetzler et al., who demonstrated that elevated GM-CSF levels correlated with poorer outcomes in AML patients.[19] Similarly, the predictive value of M-CSF levels for CML progression aligns with Jiang's report that cytokine signatures can predict treatment response in tyrosine kinase inhibitor therapy.[20]

The therapeutic implications of these findings are substantial. Targeting autocrine and paracrine CSF signaling could disrupt the leukemic microenvironment and potentially enhance conventional chemotherapy efficacy. Recent clinical trials exploring CSF pathway inhibitors, such as those reported by DiPersio and colleagues, have shown promising results in combination with standard treatments.[21] Furthermore, the identification of specific signaling pathways regulating CSF production provides additional targets for therapeutic intervention.

Future studies should explore the epigenetic mechanisms controlling aberrant CSF expression in leukemic cells and investigate whether CSF production patterns can guide personalized therapeutic approaches. Additionally, examining the impact of leukemia-derived CSFs on immune effector cells in the bone marrow microenvironment may reveal strategies to enhance anti-leukemic immune responses.

CONCLUSION

Our comprehensive investigation into CSF production by leukemic leukocytes reveals significant dysregulation that contributes to leukemia pathophysiology and presents potential therapeutic targets. Leukemic cells demonstrate markedly elevated production of G-CSF, GM-CSF, and M-CSF compared to normal leukocytes, with distinct patterns characteristic of specific leukemia subtypes. This aberrant CSF production is regulated through distinct signaling pathways, primarily NF-κB and MAPK cascades, which can be selectively targeted to modulate the leukemic microenvironment.

The functional consequences of this dysregulation are substantial, as leukemia-derived CSFs actively modify the bone marrow niche to favor leukemic cell survival and proliferation while simultaneously disrupting normal hematopoiesis. This autocrine and paracrine signaling creates a self-reinforcing cycle that promotes disease progression and potentially contributes to therapy resistance. Furthermore, the correlation between CSF levels and clinical parameters supports

their potential utility as biomarkers for disease monitoring and prognostication.

These findings provide a foundation for novel therapeutic approaches targeting CSF production and signaling in leukemia. Combination strategies incorporating CSF pathway inhibitors with conventional chemotherapy or targeted agents may enhance treatment efficacy and overcome resistance mechanisms. Future research should explore the molecular determinants of aberrant CSF expression patterns and their impact on the immune microenvironment to develop more effective leukemia therapies.

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