Inflammatory Bone Marrow Microenvironment Fuels Clonal Expansion in MDS: Longitudinal Cytokine Profiling and Clonal Dynamics

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Introduction

•MDS arises in a pro-inflammatory bone marrow (BM) microenvironment, contributing to ineffective hematopoiesis and leukemic transformation.
•Chronic elevation of cytokines such as **IL-6**, **TNF-α**, and **IFN-γ** alters the hematopoietic niche.
•Inflammation-driven clonal expansion is an emerging paradigm linking aging, CHIP, and MDS.
•Prior studies suggest that cytokines may suppress normal progenitors while promoting growth of mutant clones.
•Transition from clonal cytopenias to overt MDS is accompanied by increasing inflammatory signals.
•Immune dysregulation and altered cytokine profiles may predict disease severity and progression.

Objectives

Evaluate the role of inflammatory cytokines in **clonal evolution and disease progression** in MDS.
Quantify differences in cytokine levels between **MDS**, **clonal cytopenias**, and **healthy controls**.
Assess how cytokine load correlates with **survival**, **disease risk**, and **mutational burden**.

Methods

Systematic review and meta-analysis of **11 studies (2010–2024)** involving ≈700 patients.
Supplementary analysis using public cytokine/genomic datasets (n = 111 patients + 21 controls).
Pooled data using **random-effects models** for cytokine level comparisons and survival outcomes.
Stratified by **MDS risk categories**, clonal cytopenias, and inflammatory marker load.
Evaluated mechanistic studies showing **cytokine blockade** effects on clonal dynamics.
Main cytokines analyzed: **IL-6**, **TNF-α**, **IFN-γ**, **IL-17**, **IL-1β**, and others.

Figure 1: Inflammatory Cytokine Levels in MDS vs Controls

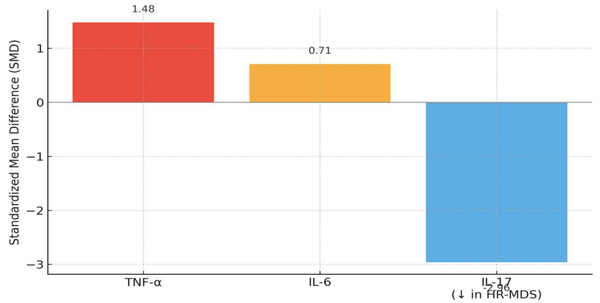


Figure 2: Impact of Inflammatory Cytokine Load on Overall Survival in MDS

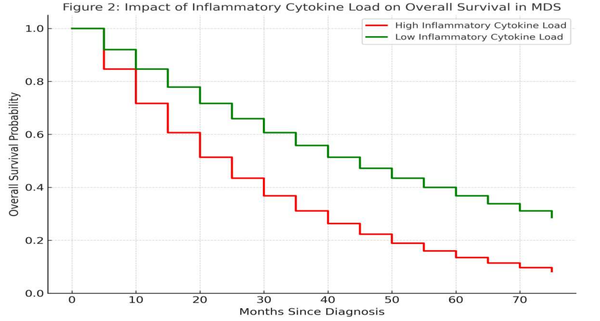
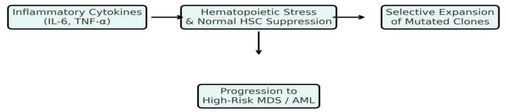


Figure 3: Mechanistic Pathway – Inflammatory Cytokines Drive Clonal Expansion in MDS



Results

IL-6 and **TNF-α** levels were significantly elevated in MDS vs. controls ($P < 0.01$).
IL-17 was significantly reduced in high-risk MDS (SMD ≈ -2.96), indicating immune skewing.
Pro-inflammatory cytokines were elevated **even in precursor states** like clonal cytopenias ($P < 0.001$).
High cytokine load associated with shorter median OS: **21 vs. 64 months** ($P < 0.0001$).
Figure 1 shows comparative SMDs for key cytokines in MDS vs. controls.
Mechanistic models confirm **IL-6 and TNF-α promote mutant clone expansion** and disease progression.

Conclusion

Inflammatory cytokine profiles are **strongly associated with clonal expansion** and adverse outcomes in MDS.
IL-6 and TNF-α act as **pro-clonal drivers**, suggesting actionable therapeutic targets.
Early inflammation is present even **before morphologic MDS**, implying a role in disease initiation.
Cytokine-based risk stratification may refine prognostication beyond molecular genetics alone.
Therapeutic blockade of inflammatory pathways may delay or prevent disease progression in early MDS.

References

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