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THE INTERSECTION OF INFLAMMATION AND GENETICS IN MYELOPROLIFERATIVE NEOPLASMS: PATHOPHYSIOLOGIC INSIGHTS

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ABSTRACT

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders characterized by somatic mutations in genes such as JAK2, CALR, and MPL, which drive excessive proliferation of myeloid lineages. Increasing evidence highlights a critical role for chronic inflammation in MPN pathogenesis, where mutant clones produce pro-inflammatory cytokines that reinforce clonal expansion, promote genomic instability, and contribute to thrombosis and fibrosis. This bidirectional interaction between genetic alterations and inflammatory signaling underpins disease progression and symptomatology. This narrative review synthesizes current insights into the intersection of genetics and inflammation in MPNs, emphasizing mechanistic pathways, clinical correlates, and therapeutic implications. Understanding this interplay provides a foundation for precision medicine strategies aimed at mitigating both proliferative and inflammatory disease components.

Keywords: *Myeloproliferative neoplasms, Inflammation, Genetics, Pathophysiology, Cytokines*

Introduction

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by excessive production of mature blood cells and include polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Traditionally, MPNs were considered primarily genetic disorders, driven by somatic mutations that constitutively activate key signaling pathways. Among these, JAK2 V617F, CALR exon 9 mutations, and MPL W515 mutations represent the predominant driver alterations, leading to activation of the JAK-STAT signaling cascade, uncontrolled proliferation, and aberrant hematopoietic differentiation [1-2]. However, recent research has highlighted the central role of chronic inflammation in MPN pathophysiology. Inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are elevated in patients, contributing not only to constitutional symptoms but also to thrombosis, bone marrow fibrosis, and clonal evolution. Notably, inflammation is not merely a secondary consequence; it actively promotes genomic instability and supports the selective expansion of mutant hematopoietic clones, creating a pathogenic feedback loop between genetics and inflammation [3-4].

Integrating the genetic and inflammatory dimensions of MPNs provides a comprehensive understanding of disease biology. While somatic mutations initiate and sustain clonal proliferation, the inflammatory microenvironment amplifies disease progression, mediates clinical complications, and influences therapeutic response. Moreover, mutations in epigenetic regulators such as TET2, ASXL1, and DNMT3A further modify inflammatory signaling by altering chromatin accessibility and transcriptional programs, linking genetic and inflammatory pathways at multiple mechanistic levels [5-6]. Targeted therapies, such as JAK inhibitors, not only suppress proliferative signals but also mitigate inflammatory cytokine production, exemplifying the translational relevance of these insights [7]. This narrative review aims to synthesize current knowledge on the intersection of inflammation and genetics in MPNs, emphasizing mechanistic pathways, clinical correlations, and translational perspectives. By elucidating the complex interplay between somatic mutations and inflammatory signaling, this review highlights emerging strategies for precision medicine approaches that address both the proliferative and inflammatory components of MPNs.

Genetic Drivers of Myeloproliferative Neoplasms

The pathogenesis of MPNs is predominantly driven by somatic mutations that confer a proliferative advantage to hematopoietic stem and progenitor cells. Among these, JAK2, CALR, and MPL mutations represent the cornerstone of MPN genetics, each contributing distinct mechanisms that promote clonal expansion and disease phenotypes [8]. The JAK2 V617F mutation is the most prevalent genetic alteration, present in nearly all polycythemia vera cases and a substantial proportion of essential thrombocythemia and primary myelofibrosis cases. This gain-of-function mutation leads to constitutive activation of the JAK-STAT signaling pathway, bypassing normal cytokine regulation and driving excessive proliferation of erythroid, megakaryocytic, and myeloid lineages. Beyond promoting cell proliferation, JAK2 V617F also stimulates the production of pro-inflammatory cytokines, linking genetic alterations directly to the inflammatory microenvironment characteristic of MPNs [9].

CALR (calreticulin) mutations, typically frameshift insertions or deletions in exon 9, are predominantly observed in JAK2-negative essential thrombocythemia and myelofibrosis. Mutant CALR proteins aberrantly interact with the thrombopoietin receptor (MPL), activating JAK-STAT signaling and enhancing megakaryocyte proliferation. Interestingly, CALR mutations also influence cytokine profiles, contributing to the inflammatory milieu and symptomatic burden of MPNs [10]. MPL mutations, including W515L and W515K, are less common but functionally significant. These mutations activate the thrombopoietin receptor independently of ligand binding, triggering downstream JAK-STAT signaling and driving platelet proliferation. Similar to JAK2 and CALR mutations, MPL alterations are associated with increased inflammatory signaling and a heightened risk of thrombotic events [11]. Beyond these driver mutations, additional somatic alterations in epigenetic regulators, such as TET2, ASXL1, DNMT3A, and IDH1/2, contribute to disease heterogeneity and progression. Mutations in these genes disrupt DNA methylation, histone modification, and chromatin remodeling, influencing both gene expression and inflammatory signaling. For example, TET2 loss-of-function mutations enhance IL-6 and IL-1β production, providing a mechanistic link between epigenetic dysregulation and chronic inflammation in MPNs (Table 1) [12].

Table 1: Genetic Drivers of Myeloproliferative Neoplasms

Gene / Mutation	Molecular Effect	Predominant MPN Subtypes	Pathophysiologic Consequences
JAK2 V617F / exon 12	Constitutive JAK–STAT activation	PV, ET, PMF	Cytokine-independent proliferation, increased inflammation, thrombosis risk
CALR exon 9 frameshift	Abnormal CALR–MPL interaction	ET, PMF	Enhanced megakaryopoiesis, cytokine hypersensitivity, pro-inflammatory signaling
MPL (W515L/K)	Ligand-independent receptor activation	ET, PMF	Sustained thrombopoietin signaling, platelet overproduction
TET2	Epigenetic dysregulation	PV, ET, PMF	Altered DNA methylation, inflammatory gene upregulation
DNMT3A	Impaired de novo methylation	PV, ET, PMF	Clonal hematopoiesis, disease heterogeneity
ASXL1	Chromatin remodeling defects	PMF, advanced MPNs	Aggressive phenotype, fibrosis progression
SRSF2	Abnormal RNA splicing	PMF, post-MPN AML	Genomic instability, leukemic transformation
U2AF1	Spliceosome dysfunction	PMF, advanced disease	Impaired hematopoietic differentiation
LNK (SH2B3)	Loss of JAK–STAT inhibition	ET, PMF	Amplified cytokine signaling
CBL	Dysregulated signal termination	Advanced MPNs	Enhanced proliferative signaling, disease progression

Inflammatory Pathways in Myeloproliferative Neoplasms

Chronic inflammation plays a pivotal role in the pathophysiology of MPNs, acting both as a driver of disease progression and a consequence of clonal hematopoietic expansion**.** Mutant hematopoietic stem and progenitor cells, particularly those harboring JAK2, CALR, or MPL mutations**,** produce elevated levels of pro-inflammatory cytokines, creating a self-reinforcing feedback loop that perpetuates clonal dominance and contributes to disease complications [13]. Key inflammatory mediators implicated in MPNs include interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β)**.** IL-6 and TNF-α drive systemic symptoms such as fatigue, fever, and night sweats, while also promoting endothelial activation, platelet aggregation, and hypercoagulability, thereby increasing thrombotic risk. IL-1β contributes to bone marrow stromal remodeling, stimulating fibroblast proliferation and extracellular matrix deposition, which are central to myelofibrosis development. TGF-β, produced by both mutant hematopoietic and stromal cells, further enhances fibrosis and alters the bone marrow microenvironment, creating a supportive niche for mutant clones [14-15].

At the molecular level, chronic inflammation in MPNs engages multiple signaling pathways, including JAK-STAT, NF-κB, and inflammasome activation. JAK2 V617F and MPL-mutant cells amplify cytokine production via constitutive STAT signaling, which in turn sustains proliferation and survival of malignant clones. NF-κB activation in both hematopoietic and stromal cells mediates transcription of pro-inflammatory genes, while inflammasome complexes contribute to IL-1β maturation and secretion, linking innate immune signaling to disease progression [16]. Moreover, inflammation promotes reactive oxygen species (ROS) generation and oxidative stress, which can induce DNA damage and further somatic mutations, fostering clonal evolution. This interplay between inflammatory signaling and genomic instability exemplifies how genetic and inflammatory mechanisms converge to drive MPN pathophysiology [17-18]. Clinically, the inflammatory milieu in MPNs correlates with symptom burden, thrombotic complications, fibrotic progression, and risk of transformation to acute leukemia. Targeting these pathways, particularly with JAK inhibitors, has demonstrated both symptomatic relief and reduction in cytokine levels, highlighting the therapeutic relevance of modulating inflammation alongside addressing the underlying genetic drivers (Table 2) [19-20].

Table 2: Inflammatory Pathways in Myeloproliferative Neoplasms

Inflammatory Pathway	Key Mediators	Cellular Targets	Pathophysiologic Role in MPNs
JAK–STAT signaling	JAK2, STAT3, STAT5	Hematopoietic stem and progenitor cells	Drives cytokine hypersensitivity, clonal expansion, and systemic inflammation
NF-κB pathway	TNF-α, IL-1β, IL-6	Myeloid cells, stromal cells	Sustains chronic inflammation, promotes survival of malignant clones
TNF-α signaling	TNF-α, TNFR1/2	Hematopoietic stem cells, endothelium	Selective advantage for mutant clones, endothelial activation
TGF-β pathway	TGF-β1, SMAD proteins	Megakaryocytes, fibroblasts	Bone marrow fibrosis, extracellular matrix deposition
Interferon signaling	IFN-α, IFN-γ	Immune cells, stem cells	Immune modulation, effects on clonal suppression
Inflammasome activation	NLRP3, IL-1β, caspase-1	Monocytes, macrophages	Amplification of inflammatory cascades, symptom burden
NET formation	Neutrophil elastase, MPO	Endothelium, platelets	Thrombosis, vascular inflammation
Angiogenic signaling	VEGF, PDGF	Endothelial cells	Increased marrow angiogenesis, disease progression

Clinical Correlates of Genetic-Inflammatory Interplay

The dynamic interaction between somatic mutations and chronic inflammation in MPNs manifests in a spectrum of clinical features and disease complications. Understanding this interplay is critical for risk stratification, disease monitoring, and therapeutic decision-making [21]. Symptom burden in MPNs, including fatigue, pruritus, night sweats, and fever, is strongly linked to elevated levels of pro-inflammatory cytokines such as IL-6, TNF-a, and IL-1β. Patients with JAK2 V617F-positive polycythemia vera or myelofibrosis frequently report severe constitutional symptoms, reflecting the combined effects of proliferative and inflammatory signaling [22]. Thrombotic risk is another clinically significant outcome of the genetic-inflammation nexus. Mutant clones enhance platelet production and activation, while pro-inflammatory mediators induce endothelial dysfunction and a hypercoagulable state. This dual contribution explains the high incidence of arterial and venous thromboses in MPN patients, particularly in those with JAK2 mutations and elevated inflammatory markers [23].

Fibrotic progression represents a hallmark of disease evolution, particularly in primary myelofibrosis. Cytokines such as TGF-β and IL-1β, produced by both malignant hematopoietic cells and stromal elements, drive fibroblast activation and extracellular matrix deposition in the bone marrow. This inflammatory-fibrotic environment not only disrupts normal hematopoiesis but also fosters clonal expansion and extramedullary hematopoiesis [24]. Clonal evolution and leukemic transformation are further consequences of the genetic-inflammation feedback loop. Chronic inflammation induces reactive oxygen species (ROS) and genomic instability, increasing the likelihood of additional somatic mutations. Patients with concomitant mutations in epigenetic regulators such as TET2, ASXL1, or DNMT3A exhibit a higher propensity for disease progression and transformation to secondary acute myeloid leukemia [25].

Therapeutic Implications

The intricate interplay between genetic mutations and chronic inflammation in MPNs has significant therapeutic implications, shaping both current treatment strategies and future precision medicine approaches. Effective management requires targeting not only the proliferative drive of mutant clones but also the inflammatory microenvironment that perpetuates disease progression and complications [26]. JAK inhibitors represent the cornerstone of targeted therapy in MPNs. Agents such as ruxolitinib and fedratinib inhibit the hyperactive JAK-STAT signaling induced by JAK2, CALR, and MPL mutations, reducing clonal proliferation. Beyond their anti-proliferative effects, these inhibitors also attenuate cytokine production, alleviating systemic symptoms such as fatigue, pruritus, night sweats, and fevers. The dual action of JAK inhibitors highlights the therapeutic benefit of addressing both genetic and inflammatory pathways concurrently [27].

Anti-inflammatory approaches are emerging as complementary strategies. Targeting specific cytokines, including IL-1β, IL-6, and TNF-α, may mitigate fibrosis, thrombotic risk, and symptom burden. Early-phase studies exploring IL-1 or IL-6 blockade suggest potential benefits in reducing marrow fibrosis and systemic inflammation, particularly in high-risk or symptomatic patients [28]. Epigenetic therapies offer another avenue, especially for patients harboring mutations in TET2, ASXL1, or DNMT3A. These agents aim to restore normal chromatin and transcriptional regulation, indirectly modulating inflammatory signaling and clonal expansion. Such strategies are particularly relevant in myelofibrosis or in patients demonstrating disease progression despite conventional therapy [29]. Combination strategies that simultaneously target genetic drivers and inflammatory mediators are increasingly recognized as essential for modifying disease trajectory. For instance, combining JAK inhibitors with anti-fibrotic agents, immunomodulators, or epigenetic therapies holds promise for more durable responses, reduced symptom burden, and delayed progression to secondary acute leukemia [30]. Personalized therapy is the ultimate goal, guided by integrated genomic profiling and assessment of inflammatory biomarkers. Patients with high-risk mutations, elevated cytokine levels, or significant symptom burden may benefit from tailored treatment regimens that address both clonal proliferation and inflammation, optimizing outcomes and minimizing toxicity [31].

Conclusion

Myeloproliferative neoplasms are defined by a dynamic interplay between genetic mutations and chronic inflammation, each reinforcing the other in a pathogenic feedback loop. Driver mutations in JAK2, CALR, and MPL activate proliferative and inflammatory pathways, while pro-inflammatory cytokines enhance clonal expansion, genomic instability, and disease progression. Recognizing the intersection of genetics and inflammation provides critical insights into MPN pathophysiology, symptomatology, and clinical complications, while guiding the development of targeted therapies that address both proliferative and inflammatory components. Integrating molecular and inflammatory biomarkers into clinical practice holds promise for precision medicine approaches that improve patient outcomes and alter the natural history of these complex hematologic malignancies.

Abbreviations and Meanings

ASXL1 – Additional sex combs–like 1
BET – Bromodomain and extra-terminal domain
CALR – Calreticulin
CBL – Casitas B-lineage lymphoma proto-oncogene
DNMT3A – DNA methyltransferase 3 alpha
ET – Essential thrombocythemia
IL – Interleukin
JAK – Janus kinase
JAK2 – Janus kinase 2
JAK–STAT – Janus kinase–signal transducer and activator of transcription
LNK – Lymphocyte adaptor protein (SH2B3)
MPL – Myeloproliferative leukemia virus oncogene (thrombopoietin receptor)
MPN – Myeloproliferative neoplasm
NET – Neutrophil extracellular trap
NF-κB – Nuclear factor kappa B
PMF – Primary myelofibrosis
PV – Polycythemia vera
STAT – Signal transducer and activator of transcription
TET2 – Ten-eleven translocation 2
TGF-β – Transforming growth factor beta
TNF-α – Tumor necrosis factor alpha
U2AF1 – U2 small nuclear RNA auxiliary factor 1
SRSF2 – Serine/arginine-rich splicing factor 2

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