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Review

Inflammatory Network Architecture Across Bone Marrow Failure: An Immune-Genetic Continuum

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Abstract

Bone marrow failure (BMF) syndromes encompass inherited disorders, immune-mediated aplasia, and clonal myeloid neoplasms, which share overlapping biology but divergent clinical trajectories. Inflammation shapes hematopoietic stem and progenitor cell fate across this spectrum, yet its network organization, genetic conditioning, and therapeutic implications remain incompletely defined. An integrative, literature-based analysis of inflammatory cytokines, genetic contexts, and therapeutic targeting across major BMF disorders, including inherited BMF syndromes, aplastic anemia (AA), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), and myelofibrosis (MF). Gene–inflammation–outcome networks and co-occurrence maps were constructed with stratification by germline and somatic alterations. Therapeutic activity was mapped across cytokine-directed and pathway-targeted agents. Inflammatory signaling emerged as a conserved feature across all BMF categories, with TNF-α, IFN-γ, and IL-6 forming a recurrent core module, and TGF-β linking inflammatory programs to fibrotic remodeling. *TP53*- and *JAK2*-associated pathways appeared as central nodes integrating multi-cytokine inputs. Germline lesions in *FANCA*, *TERC/TERT*, and *GATA2* were predominantly associated with apoptotic stem-cell attrition. In contrast, somatic drivers, including *TP53*, *JAK2*, *TET2*, *DNMT3A*, and *ASXL1*, were more frequently associated with clonal expansion. Multi-cytokine convergence on shared effectors was common, suggesting pathway redundancy. The therapeutic literature predominantly focused on TNF-α/IFN-γ/IL-6 pathways, with comparatively limited exploration of TGF-β, IL-8, and IL-17. These findings support a role for inflammation as a unifying, context-dependent modifier across the BMF spectrum, and highlight *TP53*- and *JAK2*-centered circuitry as potential nodes for rational combination strategies. TGF-β, IL-8, and IL-17 axes and inherited BMF entities represent underexplored opportunities for biomarker-guided cytokine-directed intervention.

Keywords: bone marrow failure; myelodysplastic syndrome; myeloproliferative neoplasm; myelofibrosis; inflammation; cytokines; TNF-α; interferon-gamma; IL-6; TGF-β; germline mutations; somatic mutations

1. Introduction

Bone marrow failure (BMF) syndromes encompass a heterogeneous spectrum of hematologic disorders characterized by impaired hematopoietic cell production, resulting in cytopenias and elevated risks of infection, bleeding, and progression to acute leukemia [1,2]. This spectrum includes inherited conditions such as Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), severe congenital neutropenia (SCN), and dyskeratosis congenita (DKC)/telomere biology disorders (TBD), as well as acquired or clonal entities including Aplastic Anemia (AA), Myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and myelofibrosis (MF) [1,3]. While genetic abnormalities underpin many of these disorders, accumulating evidence identifies chronic inflammatory signaling as a critical pathogenic modifier that influences hematopoietic stem cell (HSC) function, clonal evolution, and disease trajectory across this continuum [4,5].

Under homeostatic conditions, immune surveillance regulates hematopoietic integrity through tightly controlled inflammatory signals [6]. Physiologic cytokines, including interferon-γ (IFN-γ), interleukin-1 (IL-1), and basal type I interferons, orchestrate emergency hematopoiesis, niche remodeling, and lineage-specific progenitor output in response to transient stressors such as infection or hemorrhage and are normally followed by anti-inflammatory resolution that restores long-term stem cell quiescence [7,8,9,10,11,12]. Clinical and experimental data support this reversibility of physiologic inflammatory responses. During recovery from severe infections, transient surges of TNF-α, IFN-γ, IL-1, and IL-6 drive emergency hematopoiesis and lineage-specific progenitor expansion, followed by anti-inflammatory resolution (IL-10, TGF-β) and restoration of HSC quiescence [6,13,14,15,16,17]. In contrast, BMF syndromes and related myeloid disorders exhibit sustained inflammatory activation without effective resolution, creating conditions that exhaust normal HSCs and favor the persistence of more resilient clonal populations.

Chronic or dysregulated inflammatory signaling fundamentally disrupts HSPC fate, as key cytokines, such as TNF-α, IFN-γ, IL-1 family members (IL-1α/β), IL-6, and IL-8, promote exit from quiescence, replication stress,

DNA damage, and TP53-mediated apoptosis or senescence [6,18,19,20,21]. In parallel, these cytokines target downstream progenitors, promoting expansion and skewing differentiation toward myeloid lineages through activation of JAK-STAT and NF-κB pathways, resulting in suppressed lymphoid and erythroid commitment and altered niche interactions [22].

Inflammasome activation, particularly via NLRP3, is a critical amplifier of chronic inflammatory dysregulation, which senses cellular stress and triggers caspase-1-dependent release of IL-1β and IL-18, alongside pyroptotic cell death [23]. This process perpetuates local cytokine storms and directly impairs HSPC function through membrane rupture, DNA fragmentation, and release of damage-associated molecular patterns (DAMPs) that further fuel inflammation. In genetically vulnerable contexts, inflammasome hyperactivity exacerbates clonal selection, favoring mutant clones with resistance to inflammatory stress [24].

A unifying feature of BMF syndromes, MDS, MPN, and MF is the persistent elevation of proinflammatory cytokines, including TNF-α, IFN-γ, IL-1β, IL-6, and TGF-β, which establishes a chronic inflammatory setting that is deleterious to marrow function and is associated with HSPC exhaustion, dysplastic hematopoiesis, and fibrotic remodeling through interconnected cytokine networks rather than isolated pathways [7,25,26,27].

This shared inflammatory signature supports an emerging view of these entities as points along an immune-driven continuum rather than discrete disorders defined solely by genetics or morphology [28]. At one end, unrelenting immune pressure depletes the HSPC reservoir, as observed in immune-mediated BMF, where autoreactive T cells target stem and progenitor compartments [29]. At the other end, accumulating data support a model in which inflammation acts as a selective pressure in genetically susceptible contexts, favoring expansion of clones with mutations (*JAK2*, *TET2*, *ASXL1*) that are relatively more tolerant of cytokine-induced stress or proliferative demands [30]. Intermediate states, such as MDS/MPN overlap syndromes, illustrate this fluidity, in which immune signals are associated with amplified clonal evolution, myeloid lineage skewing, and increased risk of leukemic transformation [31].

Consequently, the same proinflammatory cytokines exert divergent effects on HSPCs depending on genetic context [32]. In inherited BMF syndromes such as Fanconi Anemia (*FANCA/FANCC* mutations), *GATA2* deficiency, and telomere biology disorders (*TERT/TERC* variants), intrinsic DNA repair defects or transcriptional dysregulation heighten sensitivity to TNF/IFN-γ-induced replication stress and apoptosis [33,34]. Which in turn contribute to accelerated stem-cell loss, and early-onset BMF with hypocellular marrows and pancytopenia, consistent with registered data showing low clonal hematopoiesis of indeterminate potential (CHIP) prevalence in germline cohorts compared with acquired AA [35,36].

In contrast, early somatic mutations in epigenetic regulators such as *TET2*, *DNMT3A*, and *ASXL1* detected in 10–20% of healthy elderly individuals confer partial resistance to inflammation-induced apoptosis and metabolic stress [37]. Patient-derived TET2-mutant HSPCs displayed a relative clonogenic advantage over normal progenitors during chronic ex vivo TNFα exposure, accompanied by myeloid skewing and reduced apoptosis [38]. In contexts of inflammaging, chronic infection, or autoimmunity, these clones expand through a relative fitness advantage, outcompeting wild-type HSPCs as reflected by rising variant allele fractions (VAFs 1–10%) in serial samples, thereby establishing pre-myelodysplastic states that may progress upon acquisition of additional genetic lesions [39].

In myeloproliferative neoplasms (MPNs), canonical driver mutations *JAK2 V617F*, *CALR* type 1/2, and *MPL* W515L/K account for more than 90% of cases of primary myelofibrosis (PMF), essential thrombocythemia (ET), and polycythemia vera (PV), typically exhibiting variant allele fractions exceeding 50% [40]. These mutations not only render hematopoietic stem and progenitor cells (HSPCs) resistant to TNF-α and IFN-γ-mediated apoptosis but also potentiate inflammatory signaling through constitutive activation of the JAK-STAT pathway, amplifying IL-6 and IL-1 feedback loops [32,41]. In the fibrotic marrow environment, dysplastic megakaryocytes release a repertoire of growth factors and chemokines, including platelet factor 4 (PF4/CXCL4), APRIL, TGF-β, and PDGF, which drive fibroblast activation, collagen deposition, and aberrant endothelial remodeling [42,43]. Collectively, these inflammatory and stromal interactions establish a self-reinforcing microenvironment that not only sustains mutant hematopoietic stem and progenitor cells (HSPCs) but also directs their evolutionary trajectory [44]. Within this milieu, immune signaling has been proposed to function as an evolutionary selective pressure: population genetic analyses of approximately 50,000 individuals confirm that positive selection, not stochastic drift, is the dominant force shaping clonal expansion [45], while single-cell multi-omics demonstrate that DNMT3A- and TET2-mutant HSCs expand through an attenuated transcriptomic response to inflammation and aging relative to wild-type cells [46]. Experimental blockade of IL-1β reduces the fitness advantage of TP53-mutant HSPCs, directly linking the inflammatory microenvironment to clonal selection [47], manifesting clinically as hypocellular marrow failure [48]. By contrast, somatically mutated clones that better tolerate or resist these proinflammatory cues may gain a relative proliferative advantage, and observational data suggest that such clones can expand from clonal hematopoiesis of indeterminate potential (CHIP) to myelodysplastic (MDS)-like dysplasia in some patients [49]. Progressively, the most adapted mutant clones remodel and dominate the niche, culminating in myeloproliferative neoplasm (MPN) hyperproliferation and myelofibrotic transformation [50].

Chronic cytokine signaling profoundly reorganizes the bone marrow microenvironment through a network of interconnected inflammatory and stromal mechanisms. IL-1, IL-6, and TNF stimulate TGF-β and PDGF pathways within stromal fibroblasts, driving collagen synthesis and myofibroblast differentiation characterized by α-SMA-positive cells [51]. Concurrently, endothelial dysfunction and increased vascular permeability amplify local inflammation and tissue remodeling [52]. Dysplastic megakaryocytes further reinforce these processes through paracrine interactions with stromal elements, secreting platelet factor 4 (PF4/CXCL4), APRIL, IL-1, and IL-6, which perpetuate fibroblast activation and progressive fibrosis [53]. Concomitantly, perturbed chemokine gradients (such as IL-8/CXCL8 and CCL2) together with disrupted adhesion molecule expression drive HSPC mobilization, fostering extramedullary hematopoiesis in the spleen and liver and contributing to the systemic inflammatory manifestations characteristic of advanced disease [54,55,56,57]. Myelofibrosis emerges as the endpoint of this process, a state of chronic cytokine-driven inflammation and progressive clonal evolution defined by a self-reinforcing cycle of stromal and vascular remodeling, driver-mutant expansion, reticulin and collagen fibrosis (MF grade 2–3), osteosclerosis, displacement of normal HSPCs, and continuous clinical progression [53,58,59,60].

Clinical phenotypes across the bone marrow failure-to-myeloproliferative neoplasm (BMF-MDS-MPN) spectrum reflect the dynamic interplay among inflammatory intensity, duration, and clonal fitness, as demonstrated in patient cohorts integrating genomic, cytokine, and histopathologic data [61]. BMF syndromes are characterized by profound HSPC exhaustion, manifesting as hypocellular marrows (<20-25% cellularity) with pancytopenia, driven by persistent TNF-α and IFN-γ elevation in serum and marrow plasma [35]. These cytokines disrupt stem cell quiescence and activate TP53-dependent stress responses, leading to apoptosis and senescence [62]. In contrast, MDS displays ineffective hematopoiesis and dysplastic maturation within variably cellular marrows (40-90%), sustained by chronic IL-6, IL-8, and IL-1 signaling [55]. Activation of JAK-STAT (pSTAT3/5) and NF-κB pathways favors myeloid-biased progenitor expansion while suppressing lymphoid and erythroid differentiation [63]. In contrast, myeloproliferative neoplasms (MPNs) emerge when driver-mutant hematopoietic clones harness chronic IL-6 and IL-1–mediated inflammatory signaling, converting these cytokine circuits into growth-promoting pathways that drive hematopoietic hyperproliferation, thrombocytosis, and vascular pathology [64]. Ultimately, MF represents the terminal inflammatory state, marked by extensive stromal fibrosis, extramedullary hematopoiesis with splenomegaly, and systemic constitutional symptoms resulting from sustained cytokine-driven niche remodeling [65].

Despite significant advances in understanding the inflammatory mechanisms underlying BMF and related myeloid disorders, a critical gap remains in translating these insights into clinical application [65]. While numerous studies have delineated the cytokine-mediated pathways driving hematopoietic dysfunction, comparatively few cytokine-targeted therapeutic trials have been performed, leaving uncertainty regarding the optimal inflammatory axes, disease subtypes, and patient populations to prioritize for intervention [66]. This limitation is further compounded by the insufficient integration of genetic context, particularly the distinction between germline susceptibility and somatic driver mutations in designing immunomodulatory strategies, thereby constraining opportunities for precision-directed therapeutic approaches [67].

This study integrates current understanding of how immune surveillance, inflammatory signaling, and clonal evolution intersect to shape the pathogenesis of BMF and myeloid neoplasia. Cellular and molecular evidence linking cytokine-driven immune stress to divergent disease phenotypes across BMF, MDS, MPN, and MF is synthesized, with particular emphasis on how germline predisposition and somatic mutations modulate inflammatory responses and selection pressures within the marrow niche. A structured, integrative analysis of the literature delineates inflammatory networks across the disease spectrum, evaluates immune-targeted therapeutic strategies, and highlights the role of genetic context in shaping hematopoietic fitness. The literature search and analytic approach follow a structured, reproducible strategy; search strategies, eligibility criteria, deduplication procedures, and evidence-scoring algorithms are specified in the **Supplementary Methods**.

Collectively, these entities align along a shared immune continuum in which variation in the intensity, duration, and cellular context of inflammation determines whether hematopoiesis is dominated by stem cell attrition, dysplastic inefficiency, clonal expansion, or fibrotic remodeling. This framework accounts for overlapping clinical features, disease transitions such as evolution from BMF to MDS, inflammatory flares in MPN, and heterogeneity in therapeutic response. Stage- and context-specific therapeutic principles ranging from immunosuppression in immune-dominant BMF to cytokine blockade in MDS and JAK- or niche-directed strategies in MPN and MF support a precision immunomodulation paradigm integrating cytokine profiling, genomic stratification, and microenvironmental assessment to guide adaptive treatment and clinical trial design.

2. Methods

Structured, integrative literature-mining analysis of PubMed-indexed human studies was conducted to characterize inflammatory cytokine networks, associated genetic contexts, and cytokine-directed therapies across bone marrow failure syndromes and related myeloid neoplasms.

Searches combined disease terms with synonym-expanded cytokine terms and human-study filters to construct disease-cytokine evidence matrices, cytokine co-occurrence networks, and gene-inflammation-outcome maps. Titles and abstracts were screened using predefined inclusion and exclusion criteria to retain primary human clinical or translational studies and to exclude animal-only work, purely *in vitro* studies, and non-primary publication types. All analyses were descriptive and based on bibliometric co-occurrence frequencies rather than effect sizes and were designed to be hypothesis-generating. Full details of search strategies, synonym expansion, screening algorithms, normalization procedures, network metrics, and composite evidence scoring are provided in **Supplementary Methods**.

3. Results

3.1 Inflammatory Signaling Is a Conserved Feature Across Bone Marrow Failure States

Across immune-mediated, inherited, and clonal BMF syndromes, inflammatory signaling appeared as a conserved biological feature that was contextually remodeled rather than sequentially resolved. Inflammatory programs were reported across all BMF categories, with disease-specific cytokine biases layered upon a shared background of broadly distributed immune signaling (Fig. 1A). These patterns suggest recurrent engagement of inflammatory pathways across etiologies, independent of disease origin. These findings reflect aggregated reporting patterns across the literature and do not imply uniform biological activity across all disease contexts.

3.2 Shared and Disease-Specific Cytokine Architectures

Pathway-level analysis identified concurrent representation of multiple canonical inflammatory and immune programs across all major BMF classes, including interferon signaling, TNF/NF-κB activation, inflammasome and IL-1 pathways, IL-6 signaling, TGF-β signaling, and downstream JAK–STAT cascades (Fig. 1A). The proportional band diagram in Fig. 1A depicts relative literature co-occurrence frequency across disease categories, not measured pathway activity levels; quantitative study counts per disease-cytokine pair are provided in the evidence matrix (Fig. 1C). While these pathways were broadly represented across entities, their relative literature representation differed by disease category.

Immune-mediated BMF, stratified by AA, showed dominant TNF-α signaling, with substantial contributions from IFN-γ- and IL-6-associated programs. Inherited marrow failure syndromes, including Fanconi anemia and dyskeratosis congenita, demonstrated comparatively greater proportional representation of TGF-β and IL-6 in the literature, consistent with inflammatory programs intersecting with cellular stress and tissue remodeling in these syndromes (Fig. 1B). Clonal disorders showed further stratification where MDS were most strongly associated with TNF-α (n = 309), followed by IL-6 (n = 179) and TGF-β (n = 128), whereas MPN exhibited enrichment of TNF-dominant and JAK–STAT–linked pathways. Across all entities, inflammatory signaling was broadly distributed; however, immune-mediated BMF showed more focused cytokine reporting patterns with relatively less apparent pathway redundancy. Quantitative study counts per disease-cytokine pair are provided in **Supplementary Table 1a**.

3.3 Uneven Cytokine Evidence Density Across BMF Syndromes

To contextualize these signaling patterns, structured literature mining of 1565 human patient studies was performed to construct a cytokine-disease evidence matrix summarizing cytokine reporting across entities (**Supplementary Table 1c**). Study counts were available for 92.1% of the 63-cell nine-disease matrix and 85.7% of all 70 disease-cytokine combinations, indicating broad but uneven coverage across the BMF spectrum.

Acquired and clonal disorders, including AA, MDS, MPN, and MF, accounted for most cytokine-focused publications. In MDS, TNF-α represented the largest literature volume (n = 309), followed by IL-6 (n = 179), TGF-β (n = 128), IL-1β (n = 108), IFN-γ (n = 106), IL-8 (n = 52), and IL-17 (n = 24) (Fig. 1C). MPN studies were dominated by TGF-β (n = 72), TNF-α (n = 55), IL-6 (n = 57), IL-1β (n = 35), IFN-γ (n = 22), IL-8 (n = 28), and IL-17 (n = 3). In AA, IL-6 (n = 819) and TNF-α (n = 658) were the most frequently reported cytokines, followed by IL-1β (n = 378), IFN-γ (n = 308), IL-8 (n = 198), TGF-β (n = 102), and IL-17 (n = 97) (Fig. 1C).

In contrast, inherited BMF syndromes, including Fanconi anemia, telomere biology disorders (TBD), severe congenital neutropenia, and Diamond-Blackfan anemia, rarely exceeded 20 cytokine-focused studies per axis (Fig. 1C), despite recurrent reports of inflammatory signatures in each. TBD showed the lowest literature density of all ten entities, with most disease-cytokine pairs returning fewer than 5 deduplicated publications; this sparsity precluded TBD's inclusion in therapeutic landscape and gene-outcome network analyses (see **Supplementary Methods** for exclusion criteria). The limited TBD literature does not indicate the absence of inflammatory pathobiology; telomere dysfunction has been repeatedly linked to activation of inflammatory signaling in experimental and clinical studies, and the sparse cytokine literature more likely reflects a critical research gap in a rare and clinically distinct entity.

3.4 Cytokine Co-Reporting Networks Reveal a Core Inflammatory Module

Cytokine co-reporting network analysis based on record-level co-mention of cytokine synonym pairs within the 2207-PMID corpus showed that inflammatory mediators formed a densely interconnected literature module.

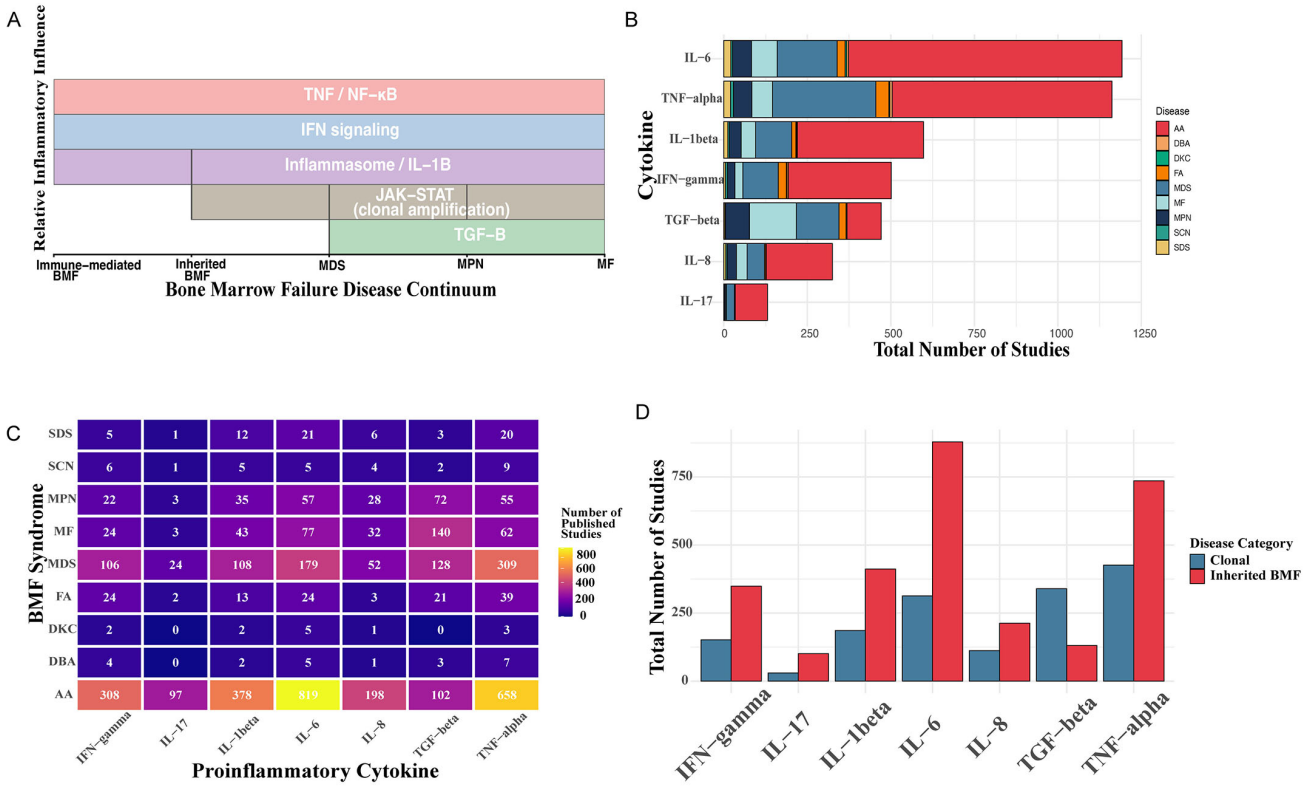

Fig. 1. Inflammatory Cytokine Landscape Across Bone Marrow Failure Syndromes. (A) Pathway-level distribution of inflammatory signaling programs across BMF categories, displayed as a proportional band diagram. Each horizontal band represents a canonical inflammatory pathway (TNF/NF-κB, IFN signaling, inflammasome/IL-1, JAK-STAT, and TGF-β); band width is proportional to the relative literature co-occurrence frequency of that pathway across the disease continuum (immune-mediated BMF, inherited BMF syndromes, and clonal myeloid disorders: MDS, MPN, MF), derived from normalized PubMed study counts per disease-pathway pair (full query strings and raw counts in **Supplementary Table 1a,b**). The y-axis reflects cumulative normalized pathway representation (0–1 scale); it does not represent a measured biological quantity. Disease categories are arranged left to right along the x-axis from immune-mediated to clonal disease. Values are log-normalized PubMed co-occurrence counts scaled 0–1 per disease category, and do not represent measured inflammatory activity. (B) Disease-specific cytokine research emphasis profiles showing differential pathway representation across BMF categories, based on proportional study counts per disease-cytokine pair. TNF-α accounts for the largest literature share in immune-mediated BMF; TGF-β and IL-6 are proportionally more represented in inherited syndromes; TNF-α represents the largest literature share in both immune-mediated AA (n = 658) and MDS (n = 309); TGF-β dominates in MF (n = 140); TGF-β and IL-6 are proportionally more represented in MPN; and inherited BMF syndromes show proportional enrichment for IFN-γ and IL-1β relative to their lower absolute literature volume. TGF-β (n = 72) and IL-6 (n = 57) are proportionally most represented in MPN, consistent with the JAK2/CALR-associated fibroproliferative biology of this entity. Values reflect relative research investment, not measured cytokine levels or statistically tested enrichment. (C) Cytokine-disease evidence matrix derived from PubMed mining across 70 disease-cytokine query combinations (total indexed records = 4380; **Supplementary Table 1a** and a structured literature selection workflow diagram, **Supplementary Fig. 1**). Cell intensity reflects publication count per disease-cytokine pair, showing 92.1% evidence coverage across the 63-cell nine-disease matrix (58/63 combinations met the minimum threshold; TBD excluded), and 82.9% across all 70 disease-cytokine combinations (58/70; including 7 TBD combinations). MDS, MPN, MF, and acquired aplastic anemia display the highest evidence density, while inherited BMF syndromes remain underrepresented. (D) Aggregate research emphasis by cytokine and disease class. Bar plots show that on a per-disease-entity basis, clonal disorders show proportionally concentrated focus for TGF-β and IL-8, while inherited BMF syndromes contribute substantially to aggregate IL-6 (n = 879, primarily AA) and TNF-α (n = 736) totals; IFN-γ and IL-1β are proportionally enriched in inherited BMF relative to clonal disease.

All 21 possible cytokine pair combinations showed co-occurrence counts above the ≥10 threshold, yielding a complete graph with density = 1.0. The most frequently co-reported pair was IL-6 and TNF-α (449 shared publications), followed by IL-1β/TNF-α and IL-1β/IL-6 (279 each) (**Supplementary Table 2**). TNF-α, IL-6, and IL-1β

showed the highest node strength (sum of co-occurrence edge weights), reflecting their broad co-reporting across BMF contexts (network metrics in **Supplementary Table 3**). This pattern reflects the structure of the BMF literature and is consistent with, but does not independently establish, biological co-regulation of these pathways. TGF-β (node strength 223) occupied a bridging position in the network, connecting records that reported inflammatory signaling with those emphasizing fibrotic and tissue-remodeling programs (**Supplementary Table 3**). IL-1β and IL-17 occupied more peripheral positions within the network, consistent with more selective disease coverage and lower overall study volume in the literature. IL-8 showed fewer co-reporting connections, consistent with both relative underrepresentation in the literature and its more focused reporting in specific disease subsets (**Supplementary Fig. 2**).

3.5 Temporal Expansion of Cytokine Research in BMF

Temporal analysis of publication trends indicated that reports linking inflammation and BMF often appeared before key molecular and genetic discoveries. IFN-γ and TNF-α were linked to AA in the mid-to-late 1990s, while IL-1 associated findings in Fanconi anemia were reported before or contemporaneously with the identification of core FA genes (**Supplementary Fig. 3**). Cytokine-focused research expanded markedly after 2000, with approximately 64.5% of studies published after 2010, coinciding with the broader adoption of sensitive immunoassays and high-throughput profiling technologies (**Supplementary Fig. 3**).

3.6 Differential Cytokine Emphasis in Inherited Versus Clonal Disorders

Aggregation of studies by disease category revealed distinct cytokine research emphases (Fig. 1D). Clonal disorders (MDS, MPN, MF) showed substantially higher publication volumes for IL-6, TNF-α, TGF-β, and IL-8. Inherited BMF syndromes contributed proportionally more to IFN-γ and IL-1β-focused studies, driven largely by AA and Fanconi anemia. Nevertheless, across inherited disorders, multiple cytokine axes, particularly IL-17, remained sparsely investigated.

3.7 Therapeutic Modality Landscape and Faceted Visualization

PubMed queries were executed with standardized parameters to identify reports of disease- specific therapeutic agents and modality groups. Searches returned 81 disease-modality combinations with non-zero counts, totaling 2838 studies. Efficacy-filtered data were identified for 9 of 10 prespecified disease entities. TBD was excluded from therapeutic and gene-outcome analyses as previously noted (**Supplementary Table 1c**). Aggregate evidence burden was highest for MDS (n = 1841), MPN (n = 1728), AA (n = 1197), and MF (n = 1129). In contrast, congenital BMF syndromes (DBA, FA, SDS, DKC, SCN, TBD) exhibited fewer efficacy-filtered reports.

A subset of 57 high-priority BMF-relevant trials (Phase II/III, published 2015 or later, with outcome-related keywords in title) was identified after exclusion of non-BMF false positives (**Supplementary Table 4**).

Across diseases, the most represented modality groups were biologics (anti-TNF mAbs, etanercept, IL-1Ra, anti-IL-6/IL-6R, TGF-β mAbs/traps), JAK–STAT inhibitors (JAK1/2-, JAK1-, JAK2-, JAK3-selective; STAT3 inhibitors), ATG and calcineurin inhibitors, followed by corticosteroids, mTOR, IMiDs, and NF-κB inhibitors. Therapeutic evidence was classified into five modality groups: broad immunosuppression (2899 studies, all 10 disease entities), JAK-STAT pathway inhibition (1742 studies, 8 entities), immunomodulatory drugs (826 studies, 9 entities), targeted small molecules (318 studies, 9 entities), and cytokine-specific biologics (314 studies, 8 entities). Broad immunosuppression and JAK-STAT inhibition represented the largest therapeutic literature categories, accounting for 76.1% of the summed modality-specific study counts. In comparison, cytokine-specific biologics represented fewer than 5.2% of the total corpus (Fig. 2). Additional smaller classes included inflammasome, MAPK, PI3K inhibitors, chemokine receptor antagonists, statins, and cytokine receptor kinase inhibitors (IL-6/gp130; TGF-β receptor). Faceted visualizations (Fig. 2) illustrating cytokine targets stratified by therapeutic modality, showing that AA literature is dominated by ATG, calcineurin inhibitors and corticosteroids with modest representation of JAK–STAT/TNF-directed approaches; MDS showed broad multi-axis exploration (IMiDs, JAK–STAT, IL-1/IL-6, mTOR, NF-κB, TGF-β traps); MPN/MF are dominated by JAK–STAT focused reports with smaller IL-6, mTOR, NF-κB, IMiD signals; congenital syndromes have sparse but non-zero bubbles centered on corticosteroids, ATG/calcineurin, and mTOR (Fig. 2).

3.8 Therapeutic Repurposing Timelines and Latency Patterns

Therapeutic repurposing analyses showed a median latency of ~7 years between the original FDA approval of an anti-inflammatory/pathway-targeted agent and the first reported BMF application in the literature (Fig. 3 and **Supplementary Table 4**). Across 35 prespecified agents (29 with at least one identified BMF application in the literature), repurposing latency ranged from >5 decades (late repurposing) to negative values, indicating BMF application preceded formal regulatory approval. Corticosteroids (e.g., prednisone, dexamethasone) exhibited the longest intervals (>50 years). Prednisone received FDA approval in 1955 and appeared in BMF-related contexts before modern disease classifications were established, resulting in intervals exceeding 50 years by current definitions. Thalidomide, lenalidomide, and pomalidomide were used in BMF-

Fig. 2. Therapeutic Modality Landscape and Cytokine-Targeted Interventions. Comprehensive mapping of therapeutic strategies across BMF and clonal myeloid disorders based on 2838 efficacy-filtered human studies spanning 81 disease-modality combinations. Faceted visualizations stratify interventions by therapeutic class, including biologics (anti-TNF monoclonal antibodies, IL-1 receptor antagonists, IL-6/IL-6R inhibitors, TGF-β modulators), JAK–STAT inhibitors (selective JAK1/2/3 and STAT3 inhibitors), immunosuppressive agents (antithymocyte globulin, calcineurin inhibitors), corticosteroids, mTOR inhibitors, immunomodulatory drugs, NF-κB inhibitors, and exploratory classes (inflammasome, MAPK, PI3K, and cytokine receptor kinase inhibitors). Bubble area is proportional to total study count on a $\log_{10}$ scale (legend shows absolute study counts at reference sizes of 1, 10, and 100 studies). Bubble size encodes the number of distinct therapeutic agents tested within each modality-cytokine combination (1–4+ agents, shown in the legend). Empty cells indicate no identified studies for that disease-modality-cytokine combination. Distinct disease-specific patterns were observed in the literature, aplastic anemia was represented predominantly by immunosuppressive modalities (ATG, calcineurin inhibitors, corticosteroids) with modest TNF and JAK–STAT targeting; MDS showed multi-axis exploration across IMiDs, JAK–STAT, IL-1/IL-6, mTOR, NF-κB, and TGF-β pathways; MPN and MF were characterized by concentrated reporting of JAK–STAT inhibition with smaller IL-6, mTOR, and IMiD signals; inherited BMF syndromes showed sparse exploration centered on corticosteroids, immunosuppression, and mTOR inhibition. Overall, therapeutic investment is concentrated in clonal disorders, with major gaps in inherited syndromes and underexplored cytokine axes (SCN is not shown; maximum publication count across all cytokine axes was n = 9, below the threshold for meaningful visualization in this format).

related contexts decades before formal approvals in hematologic malignancies (negative repurposing latency, indicating BMF use preceded formal regulatory approval for hematologic indications). Newer agents, including baricitinib, luspatercept, and sotatercept, also showed negative latency, reflecting early translational adoption. Target-specific patterns were evident, TNF-α inhibitors spanned the widest latency distribution, with etanercept ~4 years later than infliximab; calcineurin inhibitors aligned with IFN-γ-linked biology and showed repurposing intervals exceeding 10 years in most BMF applications; IL-6, IL-17, and JAK–STAT inhibitors were adopted more rapidly, often ≤5 years post-approval. Agents approved after 2015, especially JAK–STAT inhibitors such as filgotinib and pacritinib, exhibited significantly shorter repurposing timelines, coinciding with an era of increased mechanistic targeting and accelerated translational pathways.

3.9 Translational Gap and Therapeutic Targeting

When publication counts were compared with clinical targeting intensity, a translational gap was evident (**Supplementary Fig. 4**). TNF-α, IL-6, IFN-γ, and IL-1β had the most extensive mechanistic literature and the greatest density of approved agents and active clinical trials across BMF entities. TGF-β, IL-8, and IL-17 remain comparatively underexplored, though emerging approvals and mechanistic overlap between cytokine axes complicate a strictly binary literature-based exploited/unexploited classification. Luspatercept, an activin receptor ligand trap with TGF-β superfamily antagonism, is approved for MDS and myelofibrosis-associated anemia, representing partial clinical exploitation of the TGF-β axis [68]. Pacritinib, a *JAK2*/*IRAK1* inhibitor with downstream IL-8/CXCR2 pathway effects, is approved for myelofibrosis and may modulate IL-8 biology indirectly [69]. Imetelstat, a telomerase inhibitor approved for lower-risk MDS, has been reported to have secondary anti-inflammatory effects on the bone marrow microenvironment [70]. The translational gap for these axes, therefore, appears to reflect incomplete rather than absent clinical translation. In AA, HSCT and IST showed the highest therapeutic maturity, with cytokine-directed interventions remaining exploratory. Inherited BMF entities were dominated by HSCT, gene-directed, and supportive strategies, with limited anti-cytokine clinical evaluation. In clonal myeloid disorders, hypomethylating agents and JAK inhibitors showed the highest maturity, with inflammation-targeted approaches forming an intermediate development zone, particularly in MDS and MPN. Overall, clonal BMF received the most therapeutic investment; inherited syndromes remained under-represented.

3.10 Evidence Mapping of Inflammation-Associated Clonal Selection

A high-confidence evidence map (thresholds ≥10 disease-cytokine and ≥5 cytokine-gene publications) delineated disease-cytokine-gene associations (Fig. 4; **Supplementary Fig. 5 A–C**). Evidence Score y-axes in Fig. 4 are independently scaled per disease panel to accommodate the large variation in absolute study volume across entities. Cross-panel comparisons of absolute scores should not be made, and relative pathway emphasis within each disease panel should be interpreted independently.

TNF-α was the most frequently documented mediator, most frequently co-occurring with *TET2* in MDS and associated with dysplasia-related outcome terms, yielding one of the highest composite scores. IFN-γ associations were enriched across BMF, notably in FA, where co-occurrence with DNA-damage response genes coincided with apoptotic outcome terms. The TGF-β axis showed the highest co-occurrence with fibrotic outcome terms, most prominently in MF. Epigenetic regulators (*TET2*, *DNMT3A*, *ASXL1*) were the most recurrently reported somatic alterations in inflammatory contexts, followed by JAK–STAT pathway genes in myeloproliferative settings. Associations below the primary evidence threshold (5–9 disease-cytokine publications) suggested underexplored links: IL-17 with splicing factor mutations in MDS, and IL-1β with clonal dominance in congenital neutropenia (**Supplementary Table 5**).

3.11 Genetic Context Conditions Inflammatory Outcomes

Gene term co-occurrence analyses showed that hematopoietic consequences of inflammation were reported differently in germline vs. somatic context (Fig. 4). Somatic drivers common in myeloid disease (*TP53*, *JAK2*, *DNMT3A*, *ASXL1*, *EZH2*, *IDH1/2*, *CALR*, *MPL*, *SF3B1*) co-occurred with terms indicating inflammation-associated clonal expansion and fitness advantage. Germline BMF genes (*FANCA*, *FANCC*, *FANCD2*, *GATA2*, *SAMD9L*; *TERT*, *TERC*, *DKC1*, *RTEL1*) were more frequently co-reported with apoptosis and cell-cycle regulation and less frequently with expansion-related terms. To avoid misrepresentation of pathobiology in inherited syndromes, gene panels in **Supplementary Fig. 5** panels A–C (SDS, DKC, SCN) are restricted to disease-relevant germline drivers and the limited somatic secondary events documented in those conditions; canonical clonal myeloid genes (*CALR*, *MPL*, *SF3B1*) that appear in the full somatic gene dictionary are excluded from these panels as they do not reflect primary disease mechanisms. Under chronic inflammation, germline contexts mapped predominantly to cell death/stem-cell attrition, whereas somatic contexts were enriched for clonal expansion, proliferation, and competitive advantage; apoptotic outcomes were underrepresented in somatic contexts.

3.12 Disease-Specific Inflammation-Gene Coupling

Hierarchical path analyses of high-confidence disease-cytokine-gene-outcome chains identified disease-specific architectures (Table 1). Full-resolution multi-

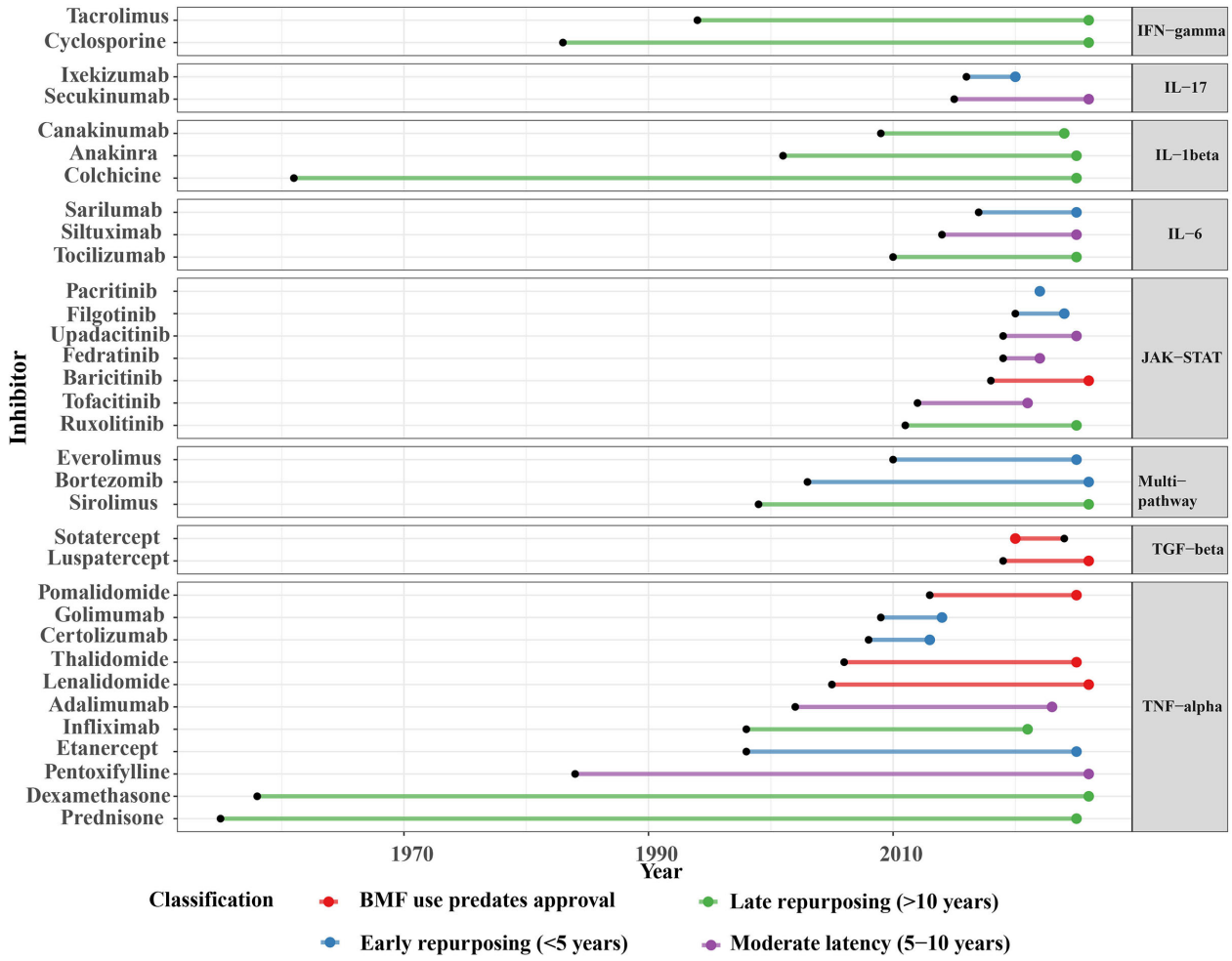

Fig. 3. Therapeutic Repurposing Timelines and Translational Latency. Temporal analysis of drug repurposing from initial FDA approval to first reported bone marrow failure application among 33 of 35 prespecified anti-inflammatory and pathway-targeted agents. The x-axis depicts repurposing latency (in years), and the y-axis groups agents by target class IFN-γ pathway agents (tacrolimus, cyclosporine), IL-17 inhibitors, IL-1β inhibitors (canakinumab, anakinra, colchicine), IL-6/IL-6R antagonists, JAK–STAT inhibitors, multipathway agents (everolimus, bortezomib, sirolimus), TGF-β modulators, and TNF-α/broad anti-inflammatory agents (including IMiDs and corticosteroids). The median repurposing latency is approximately seven years. Prednisone and dexamethasone show the longest positive repurposing latency (>50 years), listed within the TNF-α/broad anti-inflammatory group, reflecting their use long after initial approval for non-hematologic indications. IMiDs (thalidomide, lenalidomide, pomalidomide) and select JAK inhibitors (baricitinib) and TGF-β modulators (luspatercept, sotatercept) show negative repurposing latency, meaning BMF-related clinical use was documented before their formal FDA approval, classified as 'Pre-approval BMF use documented' in the figure. TNF-α inhibitors show broad latency variability; IL-6, IL-17, and JAK–STAT inhibitors translate most rapidly (≤5 years post-approval). Agents approved after 2015 display significantly compressed translation timelines, reflecting increased mechanistic targeting and translational efficiency.

layered visualizations are provided in (**Supplementary Figs. 7,8**) for detailed exploration.

In MDS, *TNF-α* and *TGF-β* co-occurred most frequently with *TP53* and, to a lesser extent, *DNMT3A* and *TET2*, with these co-occurrence chains predominantly associated with apoptotic and attrition-related outcome terms in the literature. In MPN/MF, interferon-associated terms co-occurred most frequently with *JAK2*, with these chains associated in the literature with fibrotic and apoptotic outcome terms. In AA, *TNF-α* co-occurrence with *TP53* and apoptosis-related terms ranked among the most prominent, while IFN-γ/*JAK2* co-occurrence was associated with fibrotic and apoptotic outcome terms. FA displayed a distinct TGF-β/*TP53* apoptotic co-occurrence pattern with reduced TNF-α involvement and modest IFN-γ/*JAK2* co-occurrence.

3.13 TP53 and JAK2 as Integrative Hubs

Network co-occurrence analysis identified *TP53* and *JAK2* as the genes most frequently associated

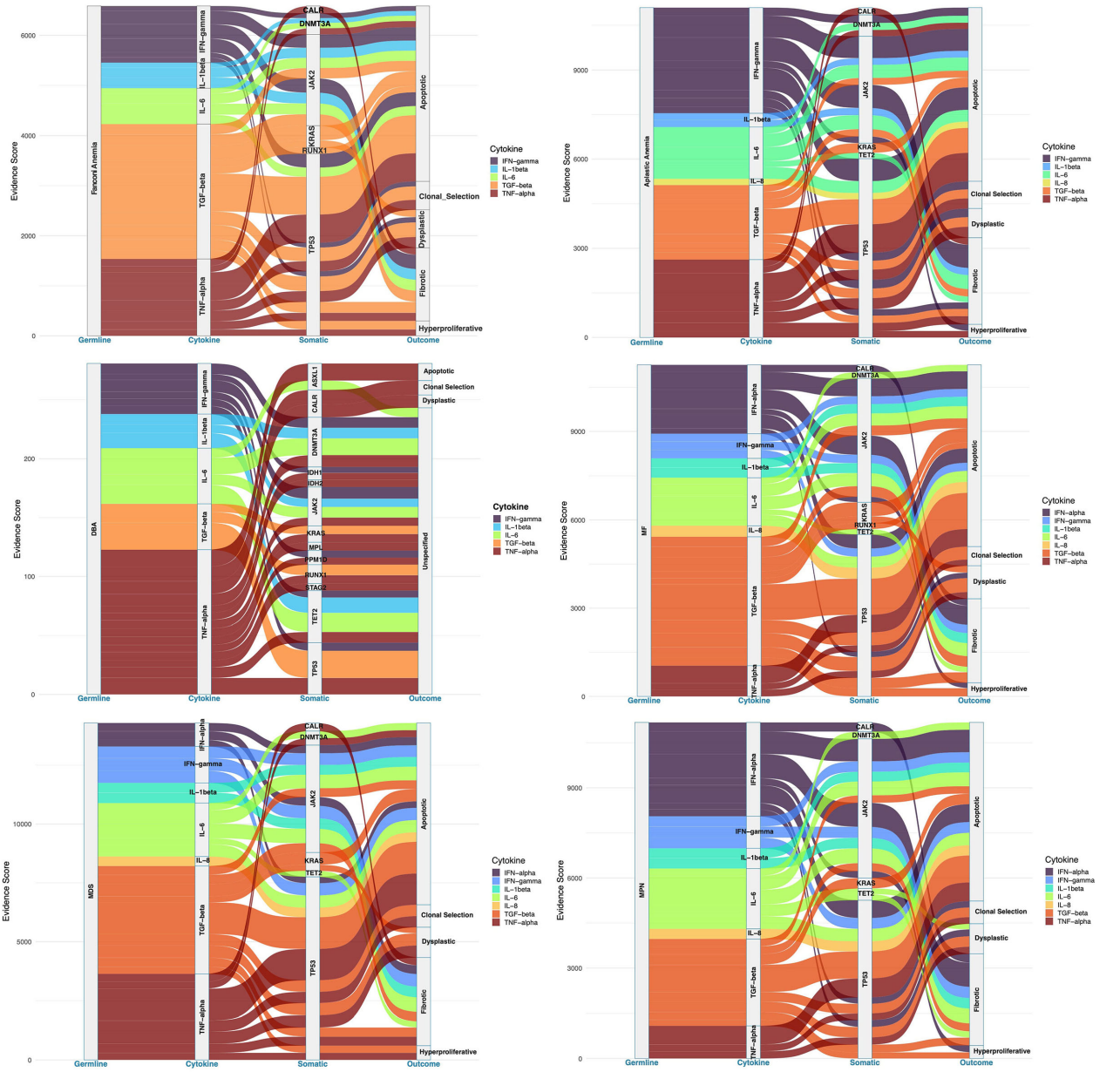

Fig. 4. Disease-Specific Inflammation-Gene-Outcome Networks. Sankey flow diagram of high-confidence evidence maps linking germline context, inflammatory cytokines, somatic genetic drivers, and hematopoietic outcomes for each disease entity. Only chains meeting dual inclusion thresholds (≥10 deduplicated publications per disease-cytokine pair; ≥5 per cytokine-gene pair) are shown. Flow width is proportional to composite evidence score. The Evidence Score y-axis is scaled independently per panel to reflect the absolute evidence volume available for each disease; scales are not comparable across panels. Aplastic anemia (AA), Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), Myelofibrosis (MF), Myelodysplastic syndromes (MDS), and Myeloproliferative neoplasms (MPN).

with cytokine-disease-outcome chains across the corpus (**Supplementary Figs. 7,8**). In MDS, *TP53* co-occurred most prominently with *TNF-α* and *TGF-β* inputs and with downstream apoptotic and dysplastic outcomes; in AA, *IL-6-TP53* co-occurrence was comparatively more prominent. *JAK2* showed broader co-occurrence across disease contexts: in MPN, it was most tightly linked to interferon-associated chains and fibrotic/hyperproliferative outcomes, while in MDS, its associations were concentrated around *IL-6*-related inputs. The 20 highest-confidence chains, ranked by composite evidence score, are presented in **Supplementary Table 6**. *TP53*-associated chains occupied 10 of the top 20 positions, predominantly linking TGF-β and TNF-α inputs to apoptotic and attrition-related outcomes across MDS, MF, MPN, AA, and FA. *JAK2*-associated chains accounted for the remaining 9 of the top 20, predom-

Table 1. Top 20 High-Confidence Disease-Cytokine-Gene-Outcome Co-occurrence Chains Across the BMF Spectrum.

Rank	Disease	Cytokine	Gene	Outcome Category	Composite Score
1	MDS	TGF-β	*TP53*	Apoptotic/Attrition	1346
2	MDS	TNF-α	*TP53*	Apoptotic/Attrition	1330
3	MF	TGF-β	*TP53*	Apoptotic/Attrition	1228
4	AA	TNF-α	*TP53*	Apoptotic/Attrition	959
5	MPN	TGF-β	*TP53*	Apoptotic/Attrition	897
6	AA	TGF-β	*TP53*	Apoptotic/Attrition	839
7	MPN	IFN-α†	*JAK2*	Fibrotic	801
8	AA	IFN-γ	*JAK2*	Fibrotic	779
9	FA	TGF-β	*TP53*	Apoptotic/Attrition	755
10	MPN	IFN-α†	*JAK2*	Apoptotic/Attrition	749
11	AA	IFN-γ	*JAK2*	Apoptotic/Attrition	728
12	MF	IFN-α†	*JAK2*	Fibrotic	645
13	MPN	TNF-α	*TP53*	Apoptotic/Attrition	623
14	MDS	IL-6	*JAK2*	Fibrotic	615
15	MF	IFN-α†	*JAK2*	Apoptotic/Attrition	603
16	MF	TNF-α	*TP53*	Apoptotic/Attrition	599
17	MDS	IL-6	*JAK2*	Apoptotic/Attrition	575
18	FA	TNF-α	*TP53*	Apoptotic/Attrition	562
19	MDS	IFN-γ	*JAK2*	Fibrotic	532
20	MDS	TGF-β	KRAS‡	Apoptotic/Attrition	522

Chains ranked by composite evidence score [$\sqrt{(C1 \times C2 \times C3)}$], where C1 = deduplicated disease-cytokine co-occurrence count, C2 = cytokine-gene co-occurrence count within the disease corpus, C3 = global gene-outcome co-occurrence count across PubMed without disease restriction. Only chains meeting dual inclusion thresholds are shown (≥10 deduplicated disease-cytokine publications; ≥5 cytokine-gene publications). Chain notation denotes analytical node sequence, not experimentally validated causal directionality.

†IFN-α and IFN-γ were captured as separate synonym sets during literature mining. IFN-α predominance in MPN and MF reflects the larger published literature on pegylated interferon therapy in these entities.

‡KRAS at rank 20 reflects high background cancer literature volume in the C3 component rather than disease-specific BMF pathobiology;

Outcome shading: red = Apoptotic/Attrition; purple = Fibrotic.

AA, aplastic anemia; FA, Fanconi anemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MF, myelofibrosis. Full chain data provided in **Supplementary Data File**.

inantly linking IFN and IL-6 inputs to fibrotic and apoptotic outcomes in MPN, MF, MDS, and AA. The only exception was rank 20 (*KRAS*), which reflects background publication volume rather than disease-specific pathobiology.

An important interpretive caveat applies: *TP53* and *JAK2* are among the most extensively published genes in hematologic malignancy research, and their high co-occurrence scores are partly a function of overall publication volume rather than exclusively reflecting disease-specific biological centrality. To address this, co-occurrence frequencies were normalized against each gene's total PubMed citation volume across the BMF corpus. After normalization, *TP53* and *JAK2* retained their top-ranked positions for cytokine co-occurrence within MDS and MPN, respectively, while *GATA2* and *TERT/TERC* emerged as proportionally more prominent in inherited BMF syndromes than suggested by raw counts alone (**Supplementary Table 3**). These normalized results are consistent with established biological roles and support the interpretation that the hub designation reflects both bibliometric prominence and genuine pathway convergence, while acknowledging that lower-volume genes in inherited syndromes may be underrepresented in raw rankings.

3.14 Redundant Cytokine Convergence on Shared Pathways

Convergence analysis identified extensive overlap among cytokine pathways. Distinct cytokines, including *TNF-α*, *TGF-β*, and *IL-6*, frequently mapped to overlapping gene-outcome trajectories, particularly those involv-

ing TP53-mediated apoptosis (Fig. 4 and Table 1). Approximately one-third of high-confidence co-occurrence chains (Table 1; **Supplementary Table 3**) showed multi-cytokine convergence. This pattern suggests that multiple inflammatory inputs are frequently co-reported with shared molecular effectors, as literature co-occurrence indicates that several cytokine pathways share downstream gene-outcome associations, including *TP53*- and *JAK2*-associated pathways. Whether this reflects true biological redundancy or preferential reporting requires experimental validation.

3.15 Integrated Inflammatory Flows

Integrated Sankey and circular network visualizations synthesized disease, cytokine, gene, and outcome relationships into directional flows (**Supplementary Figs. 7,8**). High-confidence co-occurrence chains included TNF-α/*JAK2*/MPN/clonal advantage, IFN-γ/*TP53*/*ASXL1*/MDS/proliferation-apoptosis, TGF-β/*TP53*/MDS-MF/apoptotic-fibrotic, and IL-6/*JAK2*/MPN-MF/fibrotic remodeling.

Literature-level co-occurrence patterns across 1565 studies are consistent with inflammation operating as a context-dependent modifier of clonal trajectories; whether hematopoiesis collapses via attrition or shifts toward clonal dominance appears associated in the literature with underlying genetic context, though causal directionality cannot be inferred from bibliometric co-occurrence alone.

To assess whether the observed disease-cytokine-gene-outcome patterns depended on the assumed directional ordering of analysis nodes, a form of structural bias inherent to Sankey flow diagrams, two complementary orderings were constructed and compared: (i) germline → cytokine → somatic → outcome (Fig. 4 and **Supplementary Fig. 7**), which positions cytokines as intermediaries between germline predisposition and somatic evolution; and (ii) germline → somatic → cytokine → outcome (**Supplementary Fig. 8**), which instead positions somatic mutations as the context-setting layer before cytokine association. If the observed cytokine enrichments, hub genes, and outcome patterns were artifacts of node placement rather than genuine signals, they would be expected to differ substantially between orderings.

Both architectures yielded concordant cytokine enrichments, hub gene associations, and outcome distributions across all six disease entities (Table 1, **Supplementary Figs. 5,6,7,8**). Germline lesions showed consistent co-occurrence with apoptotic and exhaustion-related outcome terms in the literature, whereas somatic drivers, particularly those associated with *TP53* and *JAK2*, showed stronger co-occurrence with competitive advantage and clonal expansion terms. Whether this reflects direct mechanistic coupling or differential reporting emphasis requires prospective experimental validation. This preservation of pattern across two structurally distinct orderings argues against ordering-dependent artifact and supports the interpretation that genetic context, rather than the analytical sequencing of nodes, plays a primary role in shaping the inflammatory outcome profile. It does not, however, establish causal directionality between germline lesions, somatic mutations, and cytokine signaling, which would require longitudinal experimental validation.

3.16 Cross-Cutting Principles

Cross-cutting analysis revealed six overarching principles that unify inflammatory mechanisms across BMF entities. First, conserved TNF-α and interferon-driven signaling axes were consistently reported in the literature across all disease categories, but with discernible disease-specific biases. Immune-mediated BMF favored *TNF-α* dominant architectures, while clonal disorders showed more interferon-skewed signaling, and inherited syndromes showed stronger representation of TGF-β and IL-6 pathways. This pattern is consistent with a shared inflammatory backbone that appears remodeled according to disease context. This architectural conservation raises the possibility that anti-inflammatory strategies targeting the core TNF-α/IFN axis may have cross-entity therapeutic applicability.

Second, convergence analyses identified *TP53*- and *JAK2*-associated pathways as the most frequent recipients of multi-cytokine inputs within this literature corpus. These genes linked inflammatory signaling to downstream phenotypes encompassing apoptosis, clonal expansion, fibrosis, and dysplasia. Their prominence reflects both established biological roles and high publication volume in myeloid research; normalization analyses confirmed relative enrichment above baseline (**Supplementary Table 3**). Third, inflammatory outputs demonstrated strong genetic-context dependence. Germline-based lesions, such as those seen in inherited marrow failure syndromes, showed preferential co-occurrence with apoptotic and attritional responses. In contrast, somatic driver mutations characteristic of clonal and malignant evolution were associated with proliferative or fibrotic expansion, consistent with pre-existing genomic context conditioning.

Fourth, network-level examination identified extensive overlap among upstream cytokine pathways, with multiple ligands including TNF-α, TGF-β, and IL-6 converging on overlapping downstream effectors such as *TP53* and *JAK2*. Approximately one-third of high-confidence co-occurrence chains displayed multi-cytokine convergence, consistent with limited responsiveness to single-axis cytokine blockade, given that multiple cytokine pathways share downstream gene-outcome associations in the literature. This redundancy supports combination cytokine-targeting strategies in future trials, although this hypothesis requires prospective experimental validation.

Fifth, evidence mapping demonstrated a translational bottleneck, with therapeutic development and clinical investigation concentrated on a narrow subset of cytokines, primarily TNF-α, IFN-γ, and IL-6, despite bibliometric

and experimental evidence implicating additional pathways such as TGF-β and IL-1β (Fig. 2; **Supplementary Table 4**). This imbalance highlights a gap between available mechanistic and associative evidence and current translational exploitation.

Sixth, comparative analysis across disease categories revealed entity-level disparities in therapeutic engagement, with clonal disorders receiving greater investment in cytokine-targeted approaches than inherited BMF syndromes (Fig. 2; **Supplementary Table 4**). Collectively, these findings provide a literature-based framework for positioning current therapies in relation to inflammatory pathways, expose potentially actionable translational gaps, and nominate underexplored but biologically plausible targets, including TGF-β, IL-8, and IL-1β axes in inherited BMF for future clinical investigation.

4. Discussion

Inflammation has long been recognized as a central yet context-dependent determinant of pathogenesis in BMF syndromes [71]. In this integrative synthesis, integrating literature-derived genetic, molecular, and therapeutic evidence, these analyses support a conceptual model in which inflammatory signaling intersects with both germline susceptibilities and somatic drivers to influence divergent hematopoietic outcomes. Rather than functioning as a uniform stressor, inflammation represents a multidimensional network of signaling axes whose effects, ranging from stem cell attrition to clonal expansion, are dictated by disease context, underlying genetic architecture, and stage of evolution.

Across inherited and acquired BMF conditions, cytokine axes such as *TNF-α*, *IL-6*, *IFN-γ*, and *TGF-β* recur consistently as mediators of hematopoietic dysfunction [72]. However, the biological consequences of these signals differ sharply across contexts. In germline predisposition syndromes such as Fanconi anemia or telomere biology disorders, chronic inflammatory stress has been reported to exacerbate intrinsic defects in DNA repair, replication stress tolerance, and oxidative balance, consistent with apoptotic, exhaustion, and differentiation-blockade outcomes observed in the literature [73]. In contrast, in MDS and MPN, inflammatory signaling co-occurs in the literature with the expansion of somatic mutant clones [74]. This dual behavior reconciles inflammation's paradoxical roles, where in some settings it is associated in the literature with marrow failure through stem cell attrition, while in others with clonal evolution [75,76].

These integrative analyses highlight that germline and somatic variants fundamentally determine the hematopoietic response to inflammatory stress. Germline lesions consistently mapped to apoptotic or exhaustion phenotypes, whereas somatic drivers, particularly those associated with *TP53* and *JAK2* pathways, showed stronger co-occurrence with competitive advantage and clonal expansion outcomes. This pattern was preserved after normalization for gene-level publication volume, supporting a genuine contextual difference rather than a purely bibliometric artifact. Disease-specific network architecture further illustrated these distinctions. In MDS, *TP53* was chiefly associated with TNFα and TGFβ-rich contexts in the literature, consistent with established models in which inflammatory stress promotes TP53-mediated apoptosis and subsequent clonal selection. In MPN/MF, interferon-driven *JAK2* pathways are frequently co-reported with both fibrotic remodeling and apoptotic attrition, suggesting that outcome specification may depend on additional cell intrinsic or microenvironmental modifiers. Importantly, the associations described here are derived from literature co-occurrence and should be interpreted as indicators of consistent reporting patterns rather than direct mechanistic validation.

These findings provide a framework for interpreting key clinical observations across bone marrow failure and clonal myeloid disorders. In aplastic anemia, published reports of *TP53*-mutant clone expansion following immunosuppressive therapy are co-occurring in the literature with studies of inflammatory microenvironments, consistent with but not directly demonstrating a model of p53-dependent apoptotic resistance conferring competitive advantage [77]. In myelofibrosis, activation of the interferon-*JAK2* axis appears to operate as a fibrotic switch, linking dysregulated megakaryopoiesis to extracellular matrix remodeling [53]. The clinical efficacy of *JAK* inhibitors, characterized by symptomatic improvement and reduction in splenomegaly with limited impact on mutant allele burden, can thus be interpreted as functional attenuation of the interferon-*JAK2*-fibrosis circuit rather than direct eradication of malignant clones, recognizing that alternative explanations remain possible [78].

A defining insight from this analysis is the extent of redundancy across inflammatory pathways. TNF-α, TGF-β, and IL-6 frequently converged on identical downstream gene-outcome pairs, most prominently TP53-mediated apoptosis and stem cell attrition (Table 1). This architectural redundancy in the co-occurrence literature is consistent with and may help to contextualize the limited efficacy of single cytokine blockers reported to date, though formal mechanistic validation of this inference would require controlled intervention studies and underscores the potential value of targeting convergent downstream nodes, including *JAK–STAT* or NF-κB, or employing rational cytokine combination strategies.

Despite strong mechanistic evidence implicating additional cytokines such as IL-8, IL-17, and TGF-β across BMF conditions, direct cytokine-targeted clinical translation remains limited. Notably, the TGF-β axis has seen partial exploitation through luspatercept (approved for MDS and MF-associated anemia), and *IL-8* pathway signaling may be indirectly modulated by pacritinib via JAK2/IRAK1 inhibition. These examples illustrate that the translational

gap is incomplete rather than absolute, and that pathway redundancy may enable cytokine axis targeting through agents with pleiotropic mechanisms (i.e., agents that simultaneously modulate multiple cytokine pathways, such as JAK inhibitors or corticosteroids). This gap reflects both the complexity of inflammatory circuitry and the challenge of achieving selective immunomodulation without compromising essential host defense functions. Nonetheless, the relative safety and mechanistic specificity of TNF-α and IL-6 blockers support their candidacy for early phase trials, particularly in contexts where inflammation is prominent early in disease evolution. Promising translational directions include the cytokine-genetic architecture described here, which enables more specific therapeutic mapping.

The following conceptual frameworks are intended as hypothesis-generating maps linking bibliometric patterns to existing therapeutic classes; they do not constitute treatment recommendations and require prospective validation before clinical application. Three actionable frameworks emerge (**Supplementary Figs. 9,10**): These frameworks do not incorporate cytokine directionality, measured protein levels, or functional pathway activation data; it maps bibliometric evidence density onto existing therapeutic categories to identify axes warranting prospective cytokine-stratified trial design.

4.1 Framework 1: Immunosuppression-Dominant BMF (AA, Early Inherited Syndromes)

The TNF-α/IFN-γ/TP53 co-occurrence pattern that characterizes immune-mediated AA is compatible with current use of ATG/calcineurin inhibitor-based immunosuppression as the primary strategy, and suggests that TNF-α blockade (including etanercept, infliximab) or IL-6 pathway inhibition (tocilizumab) could be explored as adjuncts in refractory or relapsed settings in carefully designed trials (**Supplementary Table 6**). For inherited syndromes where *IFN-γ* and *TGF-β* co-occur with germline gene-attrition chains, anti-TGF-β approaches (luspatercept) may reduce inflammatory attrition before stem cell exhaustion, warranting prospective evaluation. If such approaches are pursued, patient selection might reasonably incorporate baseline cytokine profiling (TNF-α, IFN-γ, IL-6 levels) and germline genotyping to distinguish immune-driven from genetically determined attrition as potential stratification variables.

4.2 Framework 2: Clonal Dysplasia With Active Inflammation (MDS)

The broad multi-cytokine landscape of MDS with co-occurrence signals across IL-6, IL-8, IL-1β, TNF-α, and TGF-β supports consideration of rational combination approaches rather than single-axis targeting, recognizing that this inference is based on co-occurrence patterns rather than comparative trial data. The *TET2*- and *DNMT3A*-associated co-occurrence patterns suggest that epigenetic modifier mutations may modulate cytokine sensitivity, providing a basis for genotype-stratified cytokine blockade trials. Specific combinations that emerge from this mapping as candidates for early-phase evaluation include hypomethylating agent + luspatercept (for TGF-β-high, lower-risk MDS); hypomethylating agent + IL-6 blockade (for IL-6-high, *DNMT3A*-mutant MDS); and canakinumab (IL-1β blockade) in *NLRP3*-inflammasome-active MDS subtypes (**Supplementary Table 6**).

4.3 Framework 3: Fibrotic and Proliferative Disease (MPN/MF)

The IFN-γ/*JAK2*/fibrosis co-occurrence pattern that dominates MPN/MF provides a conceptual framework consistent with JAK inhibitor monotherapy (ruxolitinib, fedratinib, pacritinib) serving as the backbone strategy in current practice (**Supplementary Table 6**). The additional TGF-β/fibrosis co-occurrence signal in MF supports combination strategies pairing JAK inhibition with anti-TGF-β agents (sotatercept) or anti-fibrotic approaches. IL-6 blockade may have additive value in MF patients with elevated IL-6 and constitutional symptom burden. Response prediction framework could integrate baseline *JAK2* variant allele fraction (VAF), IL-6 and IFN-γ levels, and TGF-β1 quantification as biomarkers, subject to validation.

5. Conclusion and Future Directions

Inflammation emerges from this synthesis as a central context-shaping force that unifies inherited marrow failure syndromes, immune-mediated aplasia, and clonal myeloid neoplasms within a shared immune-genetic landscape. Across this continuum, recurrent cytokine axes, including TNF, IFN-γ, IL-1, IL-6, and TGF-β, are repeatedly reported as exerting pressure on hematopoietic stem and progenitor cells (HSPCs) through partially overlapping and redundant signaling circuits, although the precise mechanisms remain incompletely defined. The consequences of these signals, however, diverge markedly by genetic background. Germline vulnerabilities are more frequently associated in the literature with apoptotic depletion and stem-cell attrition, whereas somatic drivers such as *TP53*, *JAK2*, and other recurrent myeloid mutations are often co-reported with competitive advantage, clonal expansion, and fibrotic remodeling.

This immune genetic vantage offers a framework for viewing BMF, MDS, MPN, and MF not as discrete disorders but as dynamic states along a continuum of dysregulated immune surveillance, in which inflammatory pressure and clonal fitness are, in the literature, associated with evolving disease trajectories. Stage and genotype-dependent predominance of specific cytokine axes helps explain both clinical overlaps, such as progression from immune-mediated aplasia to MDS, and heterogeneity in responses to immunosuppressive therapy. Early disease states show a predominant co-occurrence in the literature, with TNF-α, interferon-associated attrition outcome terms,

and genomic stress. In contrast, later-stage MPN and MF show increasing co-occurrence with interferon-*JAK2* and fibrotic outcome terms in the literature. Framing disease in terms of immune versus clonal dominance, thus, may support more adaptive, time-sensitive therapeutic decision-making beyond categorical diagnoses.

5.1 Translational Outlook

The translational potential of an integrated immune-genetic framework is substantial. Biomarker-guided immunomodulation anchored in cytokine profiling, clonal architecture, and microenvironmental context has the potential to refine therapeutic timing and enhance response durability. Early immune-dominant states (high TNF-α or IFN-γ, germline context, absent somatic drivers) appear, within this framework, to align most directly with ATG/calcineurin inhibitor-based immunosuppression with adjunct anti-TNF or anti-IL-6 strategies as candidates for evaluation in carefully designed trials. Intermediate states with evolving clonal architecture (*TET2*, *DNMT3A* mutations, elevated IL-6 or IL-1β) may represent an optimal window for cytokine-genotype-integrated interventions combining epigenetic therapy with targeted cytokine blockade before full clonal dominance is established. Late fibrotic states (high TGF-β, IFN-γ, *JAK2* VAF >50%) may be best approached, in current practice, with JAK inhibitor backbone therapy, and anti-TGF-β or anti-fibrotic co-treatment could be explored as adjunct strategies. A proposed clinical decision framework linking cytokine signature to therapeutic strategy is outlined in (**Supplementary Figs. 9,10**) as a hypothesis-generating tool and not as a prospective treatment algorithm.

Drug repurposing offers a potentially direct and efficient translational pathway. Agents targeting IL-6, TNF, and the JAK-STAT axis already validated in other inflammatory diseases remain attractive candidates for early-phase, mechanism-informed evaluation in BMF and clonal myeloid disorders. Combination approaches aimed at convergent downstream nodes, such as JAK-STAT, NF-κB, or TP53-associated stress circuits, may be necessary in some settings to overcome the compensatory redundancy evident across inflammatory pathways. Realizing these strategies will require a harmonized clinical framework that integrate cytokine quantification, single-cell transcriptomics, and dynamic assessment of variant allele fractions to guide patient-specific therapeutic adaptation.

5.2 Research Gaps and Priorities

Quantitative mapping across more than 70 disease-cytokine axes underscores marked asymmetry in the existing evidence base. Clonal myeloid neoplasms are comparatively well characterized, whereas inherited BMF syndromes remain understudied despite strong mechanistic plausibility. IL-17 and IL-8 biology in severe congenital neutropenia, dyskeratosis congenita, and Fanconi anemia represents a notable gap, as does early-stage TGF-β activation in precursor MPN states and low-risk MDS. Addressing these gaps will require coordinated mechanistic and translational efforts.

Key priorities include:

• Prospective, multi-center cytokine profiling to delineate inflammatory trajectories across inherited and acquired BMF syndromes (**Supplementary Table 6**).

• Longitudinal single-cell and clonal tracking under cytokine modulation to quantify how immune interventions reshape clonal competition.

• Integration of germline and somatic genotyping in immunomodulatory clinical trials, enabling genotype-informed stratification and response prediction.

• Construction of disease-stage reference atlases linking cytokine signatures with clinical outcomes to support predictive modeling and early-intervention strategies.

These initiatives will not only clarify mechanisms in underrepresented syndromes but also accelerate translation through harmonized biobanking, registry-based platforms, and adaptive trial designs.

6. Limitations and Future Innovation

The approach presented here is subject to methodological constraints inherent to literature-derived analyses, including publication bias, uneven disease representation, and limited capacity to resolve bidirectional interactions. Hierarchical network models inevitably simplify recursive biology, particularly in settings where mutations such as *JAK2* or *CALR* can themselves amplify cytokine production. Outcome categories, while mechanistically motivated, compress complex, staged, and compartment-specific processes.

A critical limitation is the profound asymmetry in evidence base across disease entities. Clonal disorders, MDS (n = 906 across all cytokine axes), MPN (n = 272), MF (n = 381), and AA (n = 2560 across all cytokines; n = 308 for IFN-γ alone) are represented by substantially larger literature volumes than inherited syndromes, where DKC (maximum n = 5 studies per cytokine axis), DBA (maximum n = 7), and SCN (maximum n = 9 per cytokine axis) provide very sparse co-occurrence data. This disparity has three specific consequences for interpretation that readers should weigh: First, composite evidence scores for inherited syndromes are inherently lower than for clonal disorders, not because inflammatory mechanisms are less operative, but because fewer studies have been performed. Cross-disease comparisons of absolute composite scores are therefore not equivalent comparisons of biological importance. Second, the cytokine-gene-outcome network architectures derived for MDS, MPN, and MF are supported by robust multi-study evidence, whereas equivalent architectures for DKC, DBA, SCN, and SDS rest on sparse bibliographic foundations and should be regarded as hypothesis-generating rather than hypothesis-confirming.

Third, the high-confidence threshold (≥10 disease-cytokine publications; ≥5 cytokine-gene publications) by design excludes most inherited syndrome data from the primary network analysis, which concentrates interpretive emphasis on clonal disorders. Conclusions regarding conserved inflammatory features across the full BMF spectrum should be understood as strongest for clonal entities and most provisional for rare inherited syndromes, where mechanistic plausibility inferred from germline biology often outpaces the available clinical literature [79].

Emerging technologies offer avenues to substantially refine these models. Single-cell multi-omics, cytokine spatial profiling, and longitudinal sampling now allow mechanistic reconstruction of how immune-genetic interactions evolve during disease progression and treatment [80]. Dynamic network inference integrating transcriptomic, proteomic, and clinical parameters may identify transitional states such as shifts from immune attrition to clonal expansion that represent actionable therapeutic windows [81]. Finally, all cytokine-gene-outcome 'trajectories' described in this study reflect co-occurrence patterns in the published literature and should not be interpreted as experimentally validated causal mechanisms; the directional flow notation used in Sankey and sunburst visualizations represents analytical node sequencing, not established biological causality. Validation of predicted circuits, including the interferon-JAK2-fibrosis and TNF-α-TP53-apoptosis pathways, will be essential in both preclinical systems and translational cohorts [82].

Together, these insights support the view of dysregulated immune surveillance as a modifiable determinant of marrow failure and clonal myeloid evolution. Inflammation can be conceptualized as a dominant ecological pressure shaping hematopoietic resilience, influencing trajectories from stem-cell attrition to clonal dominance and fibrosis. Integrating immune, genetic, and stromal perspectives thus provides a conceptual foundation for precision immunogenetic medicine in marrow failure and myeloid neoplasms. Continued integration of structured pathway analysis with real-world, patient-derived multi-omic data may ultimately transform inflammation from a driver of pathology into a therapeutically tractable axis capable of restoring hematopoietic equilibrium.

Author Contributions

SB conceived and designed the study, developed the search strategy and Boolean query framework, performed all automated literature mining, data extraction, network construction, gene-outcome chain analysis, and statistical analyses, generated all figures and Supplementary Tables, drafted the manuscript, and takes full responsibility for the integrity of the analysis and the accuracy of the reported findings. The author read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author used AI and AI-assisted technologies to assist with the grammar and spelling checking of the Methods, Results, Discussion, and figure legend sections and for the structural review of sentence clarity in the Introduction and Discussion. All AI-generated suggestions were reviewed, evaluated, and edited by the author. The author takes full responsibility for the scientific content, data integrity, analytical decisions, and accuracy of all findings reported in this publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL50689.

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