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From Inflammatory Cascades to Hematopoietic Consequences; A Review of Bone Marrow Failure Mechanisms

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Abstract

Hematopoiesis plays an essential role in supporting immune cell function and different physiological processes, such as nutrient transport, hemostasis, and would healing. In inflammatory scenarios, the typically stable state of hematopoiesis shifts to emergency myelopoiesis, generating necessary effector types of cell to address acute insults. Prolonged or unusual exposure of inflammatory signals adversely affects the hematopoiesis, causing enhanced proliferation, damage to DNA, and cell death such as necrosis, apoptosis, and pyroptosis. Additionally, the microenvironment of bone marrow undergoes alterations. Collectively, such variations can results in the early impairment of hematopoiesis. Particularly in patients having immune-mediated aplastic anemia or inherited bone marrow failure syndromes (BMFS), continuous exposure to inflammatory signals can worsen cytopenias and expedite the progression of disease. Nonetheless, the comprehension of specific characteristics of inflammation in bone marrow failure is understood poorly. This review synthesizes findings from diverse mouse models exploring inflammatory mechanisms in bone marrow failure and delves into their implications for prospective research and clinical applications.

Keywords: Inflammation, Bone marrow failure syndrome, Hematopoiesis, Inflammation, Pathogenesis.

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Introduction

The process of maintaining hematopoiesis is a meticulously coordinated and closely controlled sequence, extending from the embryonic development through adulthood, with the primary goal of generating and replenishing the entire hematopoietic system within bone marrow.[1] At the core of hematopoietic hemostasis lies the hematopoietic stem cells (HSCs) self-renewal and division, characterized by significant self – renewal capacities. These HSCs undergo differentiation through lineage – committed progenitors, resulting in diverse array of mature cells of blood.[2] Though, instances of severe systemic injuries or infections, such as spinal cord injuries, sepsis, or chronic inflammatory diseases, can elicit signals of inflammation, prompting the initiation of emergency hematopoiesis. In this mechanism, pathogens are unswervingly detected by the pattern recognition receptors, including Toll – like receptors (TLRs), which are expressed on hematopoietic stem and progenitor cells (HPSCs).[3]

Inflammatory cytokines, e.g., tumor necrosis factor (TNF) and interferon (INF), play a crucial roles in amplifying signals, being secreted either locally or at peripheral active sites of immune system within bone marrow.[4] As a result, downstream signaling cascades are activated, facilitating the HSPCs mobilization to refill depleted short – lived mature hematopoietic immune effector cells and strengthen host defensive mechanism. Nevertheless, the repeated cycling of HSCs under these circumstances may lead to exhaustion, particularly in the setting of genetic disorders predisposing individuals to bone marrow failure (BMF).[3,5] Increased TNF and IFN levels have been identified in various disorders such as Fanconi anemia (FA) or aplastic anemia (AA).[6–8] However, the mere expression of these cytokines is inadequate to fully comprehend their pathological role in the intricate interplay between inflammation and disease progression.

To unravel this complex relationship, various animal models are employed to pinpoint the specific molecules responsible for inflammation and their contribution to BMF. These models lay the foundation for innovative preventive and therapeutic strategies. This perception delves into current findings that scrutinize how inflammatory signals, encompassing TGF-β, TLRs, IFN and interleukins (ILs), along with inflammatory damage of DNA, and their interfaces can precipitate BMF.

INFLAMMATORY CYTOKINE SIGNALING

Interferon (IFN)

Interferon (IFN), renowned for their interferences with viral infections, are inflammatory cytokines categorized into three types (type I-III), each comprising different categories.[9] A recent discovery had introduced a potential type IV IFN ligand – receptor system. IFNs type I are not exclusively secreted by immune cells during pathogen interactions but can also be endogenously induced in various types of cells via self – ligands, Toll – like receptors (TLR) agonists, cytokines, and host factors. Clinically, IFNs find application in treating viral diseases, autoimmune conditions, and specific cancerous conditions i.e., chronic myeloid leukemia (CML).[10,11]

Following production and secretion, IFNs bind to their receptors, activating distinct pathways of signal transduction that result in particular transcriptional responses, establishing an antiviral stage in affected cells. IFNs, notable α and γ, play roles in both developmental and adult hematopoiesis. INF-α facilitates embryonic hematopoietic stem cell (HSC) maturation during developing hematopoiesis, while IFN-γ regulates the development of HSCs positively. Apart from development of hematopoiesis, IFNs serve as apoptotic and anti-proliferative mediators in various types of cell, including HSCs.[12]

Recent research suggests that, alongside their protective effects, IFNs may compromise self-renewal capacity and long-term survival of HSPCs, resulting in diminished production of blood cells during adult phase of hematopoiesis. Continuous production of type I and II IFNs during infection has been associated with HSC exhaustion and eventual hematopoiesis failure.[13,14] Mouse infection models, like the polyinosinic – polycytidylic acid model, have been utilized to unravel the mechanisms linking inflammation to bone marrow failure (BMF) in the context of IFNs.[15]

Chronic exposure to type I and II IFNs in infection has been revealed to induced exhaustion of HSCs and hematopoietic failure.[16] Various infection models, involving pathogens like *Ehrlichia muris*, *Mycobacterium tuberculosis*, and *Mycobacterium avium*, underscore the adverse effects of continuous IFN signaling on HSC proliferation and differentiation.[17–19] Additionally, the animal model of chronic lymphocytic choriomeningitis virus (LCMV) indicates that signaling of type I and II IFN can deplete the supportive network of bone marrow mesenchymal cells.[20] Exploration into the influence of type I and II IFNs on BMF syndromes has revealed insights. Inherited BMF syndromes, especially Fanconi anemia (FA), manifest severe hematopoietic exhaustion accelerated by chronic IFN-γ singling. FA mouse models demonstrate heightened sensitivity of FA hematopoietic progenitors to IFN-γ – induced apoptosis. Models of immune – mediated aplastic anemia (AA) further elucidate IFN-γ – dependent loss of HSCs and hematopoietic failure.[20]

Recent animal models delving into immune processes of hematopoiesis contribute to understanding the pathophysiology of acquired and congenital BMFS.[21,22] These findings may pave the way for innovative therapeutic strategies aimed at targeting or preventing hematopoietic failure in such disorders. While, during acute infections, IFN-γ production transiently activates and proliferates otherwise quiescent HSCs, showcasing the dynamic effects of IFNs on hematopoiesis.[3]

Tumor Necrosis Factor (TNF)

Another important cytokine with pro–inflammatory nature in the array is tumor necrosis factor (TNF), belonging to the superfamily of 19 TNF members. Generated by antigen – stimulated monocytes and macrophages, TNF engages two distinct receptors, TNFR1 and TNFR2, initiating various pathways of signaling convoluted in cellular proliferation, differentiation, survival, and apoptosis.[23] It assumes pivotal roles in the regulation of immune responses, hematopoiesis, and tumorigenesis. Despite well – established TNF-α functions during inflammatory processes, its roles in hematopoiesis and hematopoietic stem cell (HSC) homeostasis are insufficiently characterized and subject to controversy.

TNF exhibits diverse roles in hematopoiesis, ranging from potent inhibition to the promotion of proliferation. It is likely necessary for HSC emergence during embryonic development, activated through different signaling pathway, including NF-κB pathway via signaling of TLR4-MyD88.[24] Research on zebra fish suggest that TNF endorses survival of HSCs and differentiation of myeloid cells by activation of p65/NF-κB – dependent program of genes, which mainly inhibits necroptosis. Dysregulation in the synthesis of TNF has been associated with prevention of induction and growth of apoptosis in HSCs directly,

coupled with indirect alterations in the microenvironment of bone marrow essential for homeostasis of HSCs. Increased expression of TNF is evident in the pathophysiology of various BMFS, such as FA.[24]

Experiments involving *Fanca-/-*, *Fancc-/-*, and *Fancg-/-* mice have illustrated abnormally high TNF production in the macrophages, leading to enhanced apoptosis induced by TNF through apoptosis signal – regulating kinase 1 (ASK1).[25] Moreover, *Fancc-/-* animal model HSCs and progenitor cells have shown that overproduction of TNF contributes to hypoplasia of bone marrow. Prolonged exposure eventually results in clonal evolution and BMF-derived leukemia. Likewise, investigations of mice models with immune – mediated AA, lacking TNF or TNF receptors have indicated that BMF could be induced by infusion of TNF-/- lymph node cells or injecting lymph node cells into TNFR-/- recipients, underscoring the significance of the cytokine and such cells in the disease pathogenesis.[(26)] Further research has uncovered that receptor – interacting serine/threonine – protein kinase 1 (RIPK1) deficiency results in activation of RIPK3, leading to HSPCs loss, necroptosis, and subsequent BMF.[(27,28)]

Toll – Like Receptor (TLR)

The initial defense line in the innate immune system relies on pattern recognition receptors (PRRs) group responsible for identifying pathogen – related signatures originating from microorganisms of diverse origins. In mammals, when pathogens are recognized by PRRs, they initiate a signaling pathway cascade, culminating in the production of IFN-1 and other mediators. This well – coordinated response aims to elicit an efficient immune reaction to acute infections or injuries. Toll – like receptors (TLRs), a significant subclass of PRRs, show a crucial part in the immunity by fostering swift inflammatory response and facilitating adequate activation of T – cells in reaction to tissue damage and infection.[29]

With 10 members in humans (TLR1-10), and 12 in mice (TLR1-10, 11-13), TLRs are not confined to stromal or effector immune cells; they are likewise present in endothelial cells and HSPCs. Beyond their established function, TLRs exert effects on HSCs, impacting their differentiation and proliferation in reaction to 'danger' signals, such as infections or exposure to synthetic or purified TLR ligands that prompt the secretion of proinflammatory cytokines.[11,30] This influence aids the hematopoiesis in recognizing stressful events, prompting emergency production of blood cells.

The immune – surveillance properties of TLRs expression on HSCs activate dormant HSCs, compelling them to differentiate and proliferate into myeloid cell lineage. Conversely, dysregulated or persistent signaling of TLR, induced, can disturb the balance of stem cells, causing ineffective hematopoiesis, loss of HSCs, and ultimately, BMF.[31] Various animal models have been devised to delineate which populations of bone marrow are affected and their perspective contributions to the disease pathogenesis.

Research has brought to light the inflammatory pathogenesis mediated by TLR signaling in view of inherited BMF. The products of Fanconi genes, tasked with shielding hematopoietic cells from injury, have been identified as modulators of TLR responses in the macrophages. For instance, TLR8 and the downstream signaling intermediates like IRAK and $I_{\kappa}B$ kinase – α/β induce production of TNF in macrophages and THP – 1 cells, contributing to defects in hematopoiesis observed in *Fancc-/-* mice.[32] Likewise, another research focused on immune – mediated AA, advocates that while TLR2 and TLR4 alone may not show an indispensable part in inducing hematopoietic failure, their impact hinges on TNF and IFN-γ.[33] Treatment with a TLR2 agonist, PAM3CSK4, heightens the HSPCs phenotype but is concomitant with a decrease in function of bone marrow HSCs. Furthermore, exposure to granulocyte colony – stimulating factors (G-CSF) induces signaling and expression of TLR, causing an development and rise in of HSCs, albeit with HSC repopulation defects in animal models who lack TLR signaling adaptor MyD88, TLR2, or TLR4.[34]

ROLE OF TGF-β IN BONE MARROW FAILURE

Previously, scientists uncovered a polypeptide called Sarcoma Growth Factor (SGF) in cultured fibroblasts of rat kidney that had undergone transformation. This polypeptide consisted of both TGF-α and TGF-β.[35] Superfamily TGF-β encompasses a multitude of proteins, participating not only in fibroblast growth and collagen production but also in functions such as the inhibition of cell proliferation. TGF-β has been identified as a contributor to suppression of hematopoiesis, particularly in conditions like FA and other myelodysplastic diseases (MDS)[36] Investigations utilizing mouse models disrupted TGF-β signaling in FA HSPCs through the application of a

neutralizing antibody named 1D11. This disruption meaningfully enhanced the cellular survival and proliferation, concurrently decreasing the activity of the harmful non – homologous end – joining (NHEJ) machinery and augmenting homologous recombinant (HR) activity. Remarkably, the therapeutic TGF-β pathway inhibition has exhibited effectiveness in animal models.[37]

ROLE OF INTERLEUKINS IN HEMATOPOIESIS

Interleukins (ILs) constitute a diverse cytokine group with intricate immunomodulatory functions originating from various cell types, including leukocytes and lymphocytes. Their engagement extends across an extensive range of actions, such as cellular differentiation, proliferation, and activation, though also playing pivotal role in the pathogenesis of numerous diseases. ILs can be categorized into four different groups based on the structural characteristics. IL-1, recognized as a key inflammatory mediator, has been acknowledged for its influence on HSCs and HSPCs regulation. Its effects encompass growth, radioprotection , differentiation, and modulation of cell adhesion and migration.[38] Studies indicate that the IL-1 administration prior to lethal radiation doses shields mice models from fetal hematopoietic disorder, attributed to the IL-1's role in activation of cell cycle via myeloid precursor and HSPCs expression.[39] However, persistent exposure to IL-1 causes an impaired HSC activity, and the underlying processes of such effects remain mainly unidentified (Table I).

Another interleukin influencing hematopoietic process is IL-6, with diverse functions in malignancies, chronic inflammation, and autoimmunity. Investigations have suggested that the T cells with absent IL-6 may result in BMF and pancytopenia, while IL-6 gene deletions induce varying degrees of immune – mediated BMF.[40] Though, these findings do not definitively establish a noteworthy or direct action of IL-6 in BMF animal models. In reaction to heightened inflammatory signals, HSCs transition from their quiescent homeostatic state and undergo proliferation to produce more cells. This increased cellular division heightens like likelihood of acquiring and accumulating cellular mutations. Prolonged IFN-α, TLR, and TNF exposure to mimic chronic inflammatory stimuli has been associated with elevated reactive oxygen species (ROS) – induced DNA damage in mitochondria of HSCs, potentially contributing to BMF.[41] Chronic exposure to polyinosinic – polycytidylic acid, inducing an IFN-1 response, results in increased mitochondrial ROS – induced DNA damage in *Fanca-/-* mice having an inactive FA DNA repair pathway.[42] Additionally, extended stimulation with lipopolysaccharide (LPS) or *Salmonella typhimurium* infection induces DNA damage in HSCs through the pathway of TLR4-TRIF-ROS-p38, rather than MyD88 signaling.[43] ROS accumulation and oxidative damage of DNA induced by TNF encourages immature HSCs and progenitor cells senescence in wild – type mice. Moreover, *Fancc-/-* mice treated with TNF exhibit aberrations in chromosomes alongside impaired pathways of oxidative DNA damage repair.[44] Thus, it is imperative to recognize that such inflammatory signals can instigate DNA injury, leading to HSC depletion. In certain disorders, impaired pathways of DNA repair may cause BMF.

ASK1, apoptosis signal – regulating kinase 1; Batf2, basic leucine zipper ATP-like transcription factor 2; BM, bone marrow; BMF, bone marrow failure CFU, colony – stimulating unit; FA, Fanconi anemia; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell; IFN, interferon; IRF, interferon regulatory factor; LSK, lineage – negative, Sca-1 positive, c-Kit-positive; MPP, multipotent progenitor; RBC, red blood cell; RIPK1, receptor – interacting protein kinase 1; ROS, reactive oxygen species; TGF-β, transforming growth factor – β, TNF, tumor necrotic factor;

INFLAMMATION – RELATED PROGRAMMED CELL DEATH IN BONE MARROW FAILURE

Programmed cell death (PCD) is a fundamental mechanism that preserves the normal homeostasis of hematopoietic and various other processes. The two primary types of PCD, i.e., apoptosis, and necroptosis, operate with distinctive mechanisms. Apoptosis is non – immune – related, whereas necroptosis triggers inflammation via release of damage – associated molecular patterns (DAMPs).[63] As previously stated, HSPCs react to DAMPs by generating diverse cytokines to mitigate hematopoietic impairment and sustain homeostasis. Investigations employing various mouse models have revealed that an upsurge in necroptotic bone marrow cell death results in the depletion of HSPCs, concurrent SLAM – HSCs proliferation, leading to exhaustion of stem cell, and ultimately culminating in BFM.[64]

Table I: Implementation of Inflammatory Signals in Bone Marrow Failure.

Disease	Inflammatory Signal	Pathway / Mechanism	Target cell	Ref.
Aplastic anemia	IFN-γ	Suppression of MPP generation and hindrance of differentiation in lineages	RBCs B cells HSCs	(45)
	IFN-γ	Macrophages act as IFN-γ sensors, contributing to HSC loss and hematopoietic failure	HSCs Macrophages	(46)
	TNFαR	TNF and TNFαR play a crucial role in the pathophysiology of immune-mediated disorders in animal models	Macrophages BM cells T cells	(7)
	TLR2 TLR4	Impact of TLR2 and TLR4 depends on TNF and IFN-γ	BM cells T cells	(40)
Fanconi Anemia	Batf2	Hematopoietic progenitors in FA are vastly susceptible to apoptosis induced by IFN-γ through Fas apoptotic mechanism	HSPCs MPPs	(47,48)
	TNF ASK1	Macrophages produce excessive TNF, thereby contributing to increased TNF-induced apoptosis	HSCs HSPCs	(49,50)
	TGF-β	Dysfunctional HSPC causing BMF	HSPCs	(37)
	IFN ROS	Multiplication and depletion of HSCs within CFUs Elevated mitochondrial ROS – mediated DNA damage in HSCs	HSCs	(51,52)
HSC functional loss/ BMF	IRF2	Diminish ability of HSCs for multi-lineage differentiation and self–renewal	HSCs	(51)
	IFN-γ RIPK1	Type I IFN induced collapse in HSC/HSPC through reduced proliferation and enhanced RIPK1- dependent cell death during *Ehrlichial* infection with shock – like characteristics	HSCs Macrophages	(53–55)
	IFN-γ	IFN-γ influences macrophages, leading to the depletion of BM and HSC s during infection	HSCs Macrophages	(56)
	Batf2	IFN-γ signaling impairs the transcription program and proliferation of HSCs	HSCs LSKs	(57)
	Batf2	Signaling through Type I and II IFNs mediates the depletion of supportive BM mesenchymal CXCL12 – abundant reticular cells network	Mesenchymal CXCL12 – abundant reticular cells	(58)
	TRIF TLR2 TLR4 ROS	Inefficient blood cell formation, depletion of HSCs, and resulting BMF TLR4-TRIF-ROS-p38 pathway mediates DNA damage in HSCs	HSCs HSPCs	(43,59,60)
	TGF-β	Neutralizing TGF-β with an antibody enhances proliferation	HSPCs	(37)
	IL-1	Impairs HSC function, preventing PU.1 hyperactivation	HSCs MPPs	(61)
	IL-6	T cells without IL-6 or gene deletion result in pancytopenia and BMF with varying degrees of immune – mediated BMF	T cells	(33)
	IL-18	BM aplasia induced by IL-18 through MLKL signaling	HSCs HSPCs	(16)
HSC depletion	Batf2	IFN-γ signaling leads to significant depletion of HSCs and HSPCs, causing defects in self – renewal	HSCs HSPCs	(62)

Beyond its inflammatory functions, TNF can activate apoptosis (caspase – 8 – dependent apoptosis) as well as RIPK1 – dependent necroptosis. Numerous researches underscore the RIPK1's role in immune-mediated and emergency homeostasis. For example, *Ehlichia* infection, RIPK1 activation reduces caspase – 8 expression, resulting in BMF and suppression of hematopoiesis after induction of IFN-α/β.[65] Other studies have illustrated the necessity of IFN-α/β for upregulation of IL-18 expression throughout infection processes, causing depletion of short – term HSCs.[66] The absence of IL-18 prevents bone marrow aplasia and enhances HSCs/HSPCs. Moreover, RIPK3 has been identified as playing an essential role in producing necroptotic DAMPs and fostering the production of inflammatory cytokines.[67] In addition to necroptosis and apoptosis, pyroptosis, also called caspase – 1 – dependent death, has been demonstrated to induce cytopenias in HSPCs on activation of NLRP1a inflammasome.[68] Hence, such varied processes propose

that both pyroptosis and necroptosis hold promise as treatment targets for preventing BMF.

Clinical Application

Together, the investigations underscore the vital role played by diverse inflammatory signaling pathways in the regulation of hematopoiesis. Prolonged exposure to inflammation results in functional impairment and diminished self – renewal capacity of HSCs, heightening the risk of developing BMF. Inflammation significantly expedites failure of hematopoiesis in of inherited BMFS animal models, including immune-mediated AA and FA.(69) It is possible that inflammatory signals may also influence the onset of cytopenia among individuals with these disorders. Notably, individuals with inherited BMF syndromes and immune – mediated AA are predisposed to leukemia. Accumulating evidence suggests that both inflammation and infectious diseases lead to the progression of hematological malignancies. Consequently, inflammation not only fosters hematopoietic failure but also holds the potential to instigate malignant transformation, potentially through ROS-induced DNA damage.[70]

A thorough comprehension of the characteristics of essential inflammatory signaling pathways and their interplay in hematopoietic system could pave the way for innovative therapeutic approaches intended at modifying the immune inflammatory response in order to prevent BMF. Regulating pro-inflammatory IFNs, TLRs, TNF, and ROS may provide treatment advantages for BMF patients. The use of neutralizing antibodies targeting essential molecules or gene deletion / silencing to counteract the adverse properties of inflammatory factors on proliferation of HSCs may revive the capability of progenitor cells to restore compromised bone marrow, thereby averting that lethal consequences associated with BMF. Additionally, inhibiting the production of ROS may offer potential for salvaging suppressed cellular function of hematopoiesis. For instance, the dietary flavonoid Fisetin has exhibited antioxidant activities, mitigating multi-organ injuries caused by cecal ligation and puncture (CLP) through the reduction of TNF expression and dose – dependent inhibition of the p38 MAPK and MK2 phosphorylation.(71) Rapamycin has proven efficacy in animal studies of immune – mediated BMF by decreasing TNF and IFN-γ, fostering the extension of functional regulatory T cells, eradicating effector $CD8^+$ T cells, and conserving HSPCs. Alternatively, targeting downstream effects of inflammation, such as inhibiting necroptosis or pyroptotic cell death, may be predominantly promising for preventing failure of hematopoiesis in immune-mediated AA and inherited BMFS.[72]

Conclusion

This comprehensive review intricately explores the relationship between inflammation, hematopoiesis, and bone marrow failure (BMF), drawing upon insights derived from mouse models. The thorough investigations of diverse inflammatory signaling pathways accentuates their essential role in regulation of hematopoiesis and provides illumination on the repercussions of sustained inflammation in HSCs. Through a meticulous examination of mouse models that mirror inherited BMF syndromes for example Fanconi anemia (FA) and immune – mediated aplastic anemia (AA), a valuable perspective on the hastening of hematopoietic failure and potential implications for the onset of cytopenia in human patients can be established. Moreover, it emphasizes the dual impact of inflammation, not merely fostering hematopoietic failure but also augmenting the risk of malignant transformation, potentially via RNA damage induced by reactive oxygen species (ROS). The insights gleaned from these investigations present novel therapeutic avenues aimed at alleviating the repercussion of inflammation on hematopoietic function and averting the severe consequences linked with BMF.

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