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REVIEW

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Bone marrow microenvironment in myelodysplastic neoplasms: insights into pathogenesis, biomarkers, and therapeutic targets

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Abstract

Myelodysplastic neoplasms (MDS) represent a heterogeneous group of malignant hematopoietic stem and progenitor cell (HSPC) disorders characterized by cytopenia, ineffective hematopoiesis, as well as the potential to progress to acute myeloid leukemia (AML). The pathogenesis of MDS is influenced by intrinsic factors, such as genetic insults, and extrinsic factors, including altered bone marrow microenvironment (BMM) composition and architecture. BMM is reprogrammed in MDS, initially to prevent the development of the disease but eventually to provide a survival advantage to dysplastic cells. Recently, inflammation or age-related inflammation in the bone marrow has been identified as a key pathogenic mechanism for MDS. Inflammatory signals trigger stress hematopoiesis, causing HSPCs to emerge from quiescence and resulting in MDS development. A better understanding of the role of the BMM in the pathogenesis of MDS has opened up new avenues for improving diagnosis, prognosis, and treatment of the disease. This article provides a comprehensive review of the current knowledge regarding the significance of the BMM to MDS pathophysiology and highlights recent advances in developing innovative therapies.

Keywords Myelodysplastic neoplasms, Hematopoietic stem and progenitor cells, Bone marrow microenvironment, Ineffective hematopoiesis, Inflammation, Innovative therapies

Introduction

Myelodysplastic neoplasms (MDS) are a group of heterogeneous blood disorders with significant morbidity, characterized by ineffective hematopoiesis and a high risk of progression to acute myeloid leukemia (AML), which occurs in approximately 30% of patients [1]. The incidence of MDS is expected to rise due to population aging, improved diagnostic techniques, and the disease's prevalence among elderly individuals [2].

These syndromes are highly diverse in genetic and morphological characteristics, requiring accurate classification to ensure effective clinical management. The World Health Organization (WHO) 2022 classification categorizes MDS into two main groups: [1] MDS

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associated with specific genetic abnormalities, such as del(5q), SF3B1 mutations, and biallelic TP53 mutations; and [2] MDS classified based on morphological features, which encompass various subtypes identified through histopathological examination [3]. While the genetic and epigenetic drivers of MDS are well documented, the role of the bone marrow microenvironment (BMM) in disease initiation and progression remains an area of active investigation [4–9].

Chronic inflammation has been implicated in MDS pathogenesis, promoting mutagenic environments and suppressing immune effectors [10, 11]. Furthermore, MDS is often preceded by clonal hematopoiesis of indeterminate potential (CHIP), an asymptomatic phase of clonal expansion in hematopoietic stem and progenitor cells bearing somatic mutations [12, 13]. Recent evidence suggests that the BMM, which is essential for lifelong hematopoiesis, undergoes dysregulation in MDS, promoting abnormal cell proliferation and survival [14–17]. Notably, there is evidence that malignant cells are capable of remodeling the BMM to create a niche that favors disease progression at the expense of normal hematopoiesis [18, 19].

Inflammatory signals within the BMME, including cytokine release and immune cell recruitment, play a critical role in this dysregulation, creating an environment that supports tumorigenesis and impairs normal hematopoiesis. Targeting these inflammatory signals, therefore, presents an exciting therapeutic strategy to restore homeostasis and halt disease progression in MDS [20, 21].

This review explores the interplay between clonal hematopoiesis (CH), inflammation, and BMM alterations in the context of MDS, focusing on the mechanisms that drive disease progression and potential therapeutic strategies.

Inflammation, clonal hematopoiesis, and MDS progression

MDS arises from mutations and chromosomal abnormalities in hematopoietic stem and progenitor cells (HSPCs), with chronic inflammation playing a key role in disease initiation and progression. Inflammatory activation of innate immune pathways within both hematopoietic cells and the BMM contributes to preleukemic conditions such as CHIP and MDS [22, 23]. With aging, systemic inflammation—termed "inflamm-aging"—intensifies, exacerbating hematopoietic dysfunction and altering the BMM through persistent cytokine signaling and stromal remodeling. These inflammatory changes may accelerate the development of CHIP, promote MDS progression, and eventually facilitate leukemic transformation [24–26].

Hematopoiesis occurs predominantly in the bone marrow (BM), where HSPCs rely on interactions with the BMM to maintain proper function [14]. The normal BM niche consists of non-hematopoietic stromal cells that support hematopoiesis by providing critical signaling cues to adjacent hematopoietic cells [14, 16, 27]. While stromal cells support normal hematopoiesis, their dysregulation can drive inflammatory disorders and hematologic malignancies, including leukemias arising from HSPCs and myelomas and lymphomas derived from differentiated BM cells. Tumor-promoting inflammation further accelerates this process, facilitating the transition from premalignant conditions to overt malignancies [28, 29]. Moreover, chronic inflammation creates a selective pressure favoring mutant clones, leading to genetic and epigenetic alterations that increase susceptibility to hematologic malignancies [30, 31].

In MDS, excessive inflammatory activity within the BMM plays a central role in disease pathophysiology by altering hematopoietic differentiation and fostering an immune-dysregulated environment. This inflammatory milieu not only promotes clonal evolution but also increases susceptibility to systemic inflammatory and autoimmune diseases, either directly through cytokine signaling or via the stimulation of adaptive immune responses. Autoimmune conditions, in particular, can further accelerate clonal selection and impair normal hematopoiesis, exacerbating MDS progression [32]. HSPCs are highly responsive to signals from their microenvironment, where immune cells within stem cell niches regulate self-renewal, differentiation, and survival. These interactions are essential for normal hematopoiesis but can also contribute to clonal expansion and disease progression, particularly in conditions such as MDS [27]. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently identified disorder characterized by chronic, systemic inflammation. This condition establishes a critical link between rheumatology and hematology, offering valuable insights into the intersection of autoimmune diseases and MDS. The syndrome results from myeloid-restricted somatic mutations in UBA1, which drive both severe inflammatory symptoms and hematologic abnormalities, including MDS. This underscores the role of persistent inflammation in the development and progression of hematopoietic disorders, such as MDS [33].

Aging exacerbates inflammation in immunological tissues, such as the BM, contributing to "inflamm-aging," which is a hallmark of the aging process [34]. Age is the most significant risk factor for MDS, as both the immune and hematopoietic systems undergo functional

decline and dysregulation over time. In elderly populations, these age-related changes lead to increased susceptibility to infections, anemia, autoimmunity, poor vaccine responses, and a heightened risk of hematologic malignancies [25, 35]. While the molecular mechanisms underlying immune and hematopoietic aging are well characterized—including DNA damage accumulation, tumor-suppressor gene activation, telomere shortening, oxidative stress, and epigenetic alterations—the precise triggers of these changes remain an area of active research. Increasing evidence suggests that environmental stressors, such as chronic inflammation and infections, play a significant role in accelerating aging, thereby increasing the risk of preleukemic states like CHIP and MDS [23].

Inflamm-aging is characterized by an increase in pro-inflammatory mediators, such as CCL5/RANTES, IL-6, IL-1, and TNF, in the absence of overt infection. These mediators can disrupt HSPC function by altering the BMM, generating further inflammatory signals from niche cells. Severe inflammation in older individuals is associated with a higher risk of morbidity, cytopenias, and hematologic malignancies [36, 37]. Key features of inflamm-aging identified in previous studies include the expansion of myeloid progenitors in the BM, elevated pro-inflammatory cytokine production by myeloid cells, reciprocal interactions between myeloid cells and plasma cells, and non-leukemic clonal expansion of HSPCs [38–41]. During aging, HSPCs tend to differentiate into myeloid cells asymmetrically. In contrast, mesenchymal stromal cells (MSCs) undergo adipogenic differentiation instead of osteogenic differentiation, which contributes to a switch from red to yellow marrow and subsequent BM hypocellularity [42–44]. Reduced osteogenic differentiation of MSCs leads to lower osteopontin (OPN) production, which may promote HSPC proliferation and stem cell exhaustion [45]. Additionally, pro-inflammatory mediators released by adipocytes help create an inflamed BMM, further facilitating the progression of CH [46, 47].

CH was first identified in aging women through non-random X inactivation patterns, and later linked to recurrent somatic mutations in genes like TET2, DNMT3A, and ASXL1, as well as mosaic chromosomal alterations [48–51]. CH is mainly an age-related condition in which somatic mutations in HSPCs lead to clonal expansion of blood cells, increasing the risk of myeloid neoplasia, with progression influenced by factors such as clonal burden, mutation type and number, and prognostic classifications [52–54]. Both the International Consensus Classification (ICC) and the 2022 WHO Classification recognize CH as a form of hematolymphoid neoplasia [3, 55]. Next-generation sequencing (NGS) has defined the mutational landscape of CH in several cohort studies, but its relationship with aging BM remains unclear [56]. Recent research highlights the complexity and subclonal diversity of HSPCs in MDS, with leukemic clones evolving in parallel and altering hematopoietic dynamics. Investigating the dynamics of CH is critical for understanding clonal dominance and developing strategies to prevent progression to hematologic malignancies. Findings further suggest that CH exhibits genetic diversity across different hematopoietic compartments, with the inflammatory environment of BM playing a key role in shaping CH dynamics, potentially driving clonal expansion and progression toward myeloid malignancies [57].

CHIP, the most prevalent form of CH, occurs in 10–15% of individuals aged 70 and older and is associated with an increased risk of cardiovascular disease and myeloid malignancies, particularly MDS and AML [49, 53, 58, 59]. Other conditions related to CH include idiopathic cytopenia of uncertain significance (ICUS), clonal cytopenia of undetermined significance (CCUS), and idiopathic dysplasia of unknown significance (IDUS) (Table 1) [60, 61]. CHIP is defined by the presence of somatic mutations in hematologic malignancy-associated genes at a frequency $\geq$2%. Individuals with CHIP face a slightly elevated long-term risk of developing a hematologic malignancy, though the risk of leukemia is low [58, 62–66]. In contrast, CCUS involves clonal expansion of mutant HSCs and is associated with cytopenia and a higher risk of progression to hematologic malignancies [67, 68]. Recent studies have detected CH-associated mutations even in early life, shifting the focus from how these mutations arise to understanding how they are selected for in the context of aging and inflammation [69]. Table 2

Bone marrow cellular components in MDS

Mesenchymal stromal cells (MSCs)

MSCs or mesenchymal stem cells are a heterogeneous group of non-hematopoietic stem cells with immunomodulatory properties, characterized by their ability to differentiate into multiple cell types, including osteoblasts, adipocytes, chondrocytes, cardiomyocytes, and neurons [70–72]. BM-MSCs play a crucial role in both normal hematopoiesis and MDS pathogenesis by directly interacting with HSPCs and releasing regulatory factors within the BMM [73–75]. Several studies have demonstrated that MSC function and characteristics are considerably altered in AML and high-risk MDS patients compared with low-risk MDS patients [76]. Additionally, prior research has indicated that high-risk MDS patients have increased CD271+MSC density, which is correlated with poor prognosis [77]. MSCs are integral components of the HSPC niche, playing a pivotal role in HSPC maintenance and function. Studies have shown

Table 1 Definitions of CHIP, CCUS, ICUS, and IDUS

Condition	Cytopenia*	Dysplasia	Risk of progression	Mutations	Blast (%)
CHIP	No peripheral cytopenia	No or mild (< 10%)	Low to moderate risk of MDS/AML progression	One or more with a VAF of 2–30% DNMT3A, TET2, ASXL1	< 5
CCUS	Peripheral cytopenia	No or mild (< 10%)	Significant risk of progression to myeloid malignancy	One or more with a VAF of 2–30% SF3B1, SRSF2, U2AF1, ASXL1	< 5
ICUS	Mild peripheral cytopenia	No or mild (< 10%)	Low risk for hematologic malignancy	Typically, absent or low-frequency mutations	< 5
IDUS	No peripheral cytopenia	≥ 10% dysplasia in neutrophils, erythrocytes, and/or megakaryocytes	Uncertain risk of progression	Variable; can include TET2, DNMT3A	< 5

CHIP: clonal hematopoiesis of indeterminate potential; CCUS: clonal cytopenia of unknown significance; ICUS: idiopathic cytopenia of unknown significance; IDUS: idiopathic dysplasia of unknown significance

* Cytopenia must continue for a minimum of four months

Table 2 Most described EV-miRNAs in MDS pathogenesis

miRNA	Alterations	Description	Refs.
miR-486-5p	Increased in MDS- MSCs-derived EVs	Enhance DNA damage and mutagenesis in HSPCs	[150]
miR-10a, miR-15a	Increased in MDS- MSCs-derived EVs	Promotes erythroid progenitor apoptosis	[149]
miR-7977	Increased in MDS-EVs	Reduce the supporting activity of MCSs in hematopoiesis	[145]
miR-103-3p	Decreased in MDS-EVs and MSC-EVs	Promotes adipogenic differentiation and blocks osteogenic differentiation in MDS-MSCs	[146]

EVs: extracellular vesicles; HSPCs: hematopoietic stem/progenitor cells; MDS: myelodysplastic syndrome; MSCs: mesenchymal stem cells

that MSCs, identified by nestin expression, constitute an essential HSC niche component. These MSCs express high levels of CXCL12, a chemokine crucial for HSPC maintenance. The close association between MSCs and HSPCs within the BMM underscores the importance of MSCs in supporting hematopoiesis [78, 79]. Alterations in MSCs can contribute to the development of malignancies, as demonstrated by a study in which selective deletion of DICER1 in mesenchymal osteoprogenitors caused significant disruption of hematopoiesis, a hallmark of MDS. Impaired osteoprogenitor function led to altered proliferation and differentiation of HSPCs and specific progenitor populations, resulting in changes to the tissue architecture [80]. In addition, Santamara et al. found that MDS-MSCs express reduced levels of DICER1 and DROSHA, miRNA processing enzymes, leading to dysregulated miRNA profiles, impaired stromal support of HSPCs, and ineffective haemopoiesis [81, 82]. MSCs from MDS patients exhibit markedly elevated miR-134 expression compared to healthy controls. miR-134 negatively regulates β1 integrin, a crucial cell adhesion molecule, leading to reduced β1 integrin protein expression in MDS-MSCs despite unchanged mRNA levels, indicating post-transcriptional regulation. This dysregulation may disrupt MSC-mediated interactions within the BMM, impair normal hematopoietic support, and contribute to MDS progression [83].

MSCs can inhibit the immune system in MDS patients. MDS-MSCs produce large amounts of transforming growth factor-β (TGF-β), which significantly suppresses T cells, B cells, and natural killer (NK) cells and stimulates regulatory T cells (Treg) cell function [76]. In high-risk MDS patients, the amount of TGF-β secreted by MDS-MSCs is markedly greater than that secreted by patients with low-risk MDS, indicating a stronger immunosuppressive impact on effector T-cell expansion in high-risk MDS patients [84]. Furthermore, BM-MSCs secrete programmed cell death ligands (PD-L1 and PD-L2) in response to proinflammatory cytokines, which suppress T cell immune responses and induce apoptosis [85]. In addition, MSCs can induce the transformation of Th17 cells into Treg cells by producing PGE2 and stimulate the growth of Treg cells by releasing IL-10 [76, 86].

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of myeloid lineage cells that originate from HSPCs as a result of aberrant myelopoiesis. These cells can inhibit immune responses against tumors, resulting in tumor metastasis, progression, therapy resistance, and immune system escape [87]. There is

evidence from previous studies that the number of MDSCs in MDS patients increases, particularly in those classified as high risk, as confirmed by the accumulation of Lin−/CD33+/CD11b+/DR− cells in the peripheral blood (PB) and BM of these patients [88]. MDSC expansion appears to be driven by the interaction of the proinflammatory molecule S100A9 produced in MDS patients with CD33. These cells produce suppressive cytokines, including IL-10, TGF-β, nitric oxide (NO), and arginase, which function as inhibitors of hematopoiesis and induce tolerance in T cells in MDS patients [89]. Tao and colleagues reported that MDSCs overexpress galectin 9 (Gal 9), which interacts with T-cell immunoglobulin and mucin-domain containing 3 (TIM3) and activates the TIM3/Gal 9 pathway, leading to CD8+ T-cell exhaustion (Fig. 1) [90]. MDS-MDSCs do not exhibit the molecular genetic abnormalities characteristic of malignant clones, suggesting their origin from nonmalignant HSPCs. The presence of recurrent mutations (CBL, EZH2, IDH1/2, N-RAS, SRSF2, U2AF1, and RUNX1) exclusively in the non-MDSC fraction indicates that MDSC expansion and activation occur before the emergence of genetically distinct MDS clones. This supports the notion that MDSCs represent a separate component of the BMM, contributing to MDS pathogenesis through non-genetic mechanisms [89, 91].

Endothelial cells

Endothelial cells (ECs) are crucial components of the BMM, where they maintain the vascular niche and support hematopoiesis. In MDS, EC dysfunction plays a significant role in disease progression. As MDS progresses, the number of BM-ECs increases, but their dysfunction becomes more severe, impairing their ability to support HSPCs and favoring the expansion of leukemia cells [92]. Endothelial progenitor cells (EPCs), another crucial EC population, exhibit dysfunction in MDS, disrupting the BM niche, impairing angiogenesis, and hindering hematopoiesis. This dysfunction not only affects the support of HSPCs but may also alter T cell trafficking and immune regulation [93, 94]. In higher-risk MDS, EPCs show progressive loss of function, marked by elevated apoptosis, increased reactive oxygen species (ROS), and reduced support for HSPCs. However, these dysfunctional EPCs promote leukemia cell proliferation and enhance leukemia colony formation [94]. Circulating endothelial cells (CECs) have also been implicated in MDS, reflecting the abnormal angiogenesis that occurs in this disease, particularly in its early stages. [95]. These findings underscore the potential for therapeutic strategies targeting EC dysfunction to restore normal hematopoiesis and slow MDS progression.

Dendritic cells

Dendritic cells (DCs) play a key role in regulating the immune system. In MDS, DCs are less frequent and exhibit functional impairments. Functionally, they exhibit decreased co-stimulatory molecule expression, weakened T-cell activation, and downregulated pro-inflammatory gene expression, contributing to immune dysregulation [96, 97]. Additionally, Saft et al. observed a significant reduction in both myeloid and plasmacytoid DC precursors in MDS patients compared to the control group, even after adjusting for age, BM cellularity, and fibrosis. The study also found that high-risk MDS subtypes have lower levels of DC subsets than low-risk subtypes, which may hinder the immune system from recognizing malignant clones [98]. Monocytes from MDS patients exhibit impaired differentiation into dendritic cells (DCs), with reduced CD1a expression and low cell yield. MDS-derived MoDCs show defective maturation in response to TNF-α, marked by decreased CD80, CD83, and CD54 expression, along with impaired endocytosis and T-cell activation [99]. In addition, DC dysfunction is associated with diminished T-cell induction and altered cytokine secretion, such as a lower level of IL-12 and a higher level of IL-10 in MDS patients [91].

NK cells

An essential component of the first line of defense against viral infections and cancer are NK cells, which are cytotoxic lymphocytes belonging to the innate lymphoid cell family [100]. Compared with those from healthy controls, NK cells from MDS patients are significantly impaired in their ability to induce cell death, even when stimulated with IL-2 in vitro [101]. In addition, NK cell functions in myeloid malignancies, including MDS, are suppressed at diagnosis, recovered at remission, and again suppressed during relapse, suggesting that these cells play an essential role in the development of these neoplasia [102]. Furthermore, the ability of AML leukemia stem cells to evade NK cell responses underscores the complexity of immune evasion in myeloid malignancies, further contributing to disease progression [103]. Previous studies have indicated that patients with MDS have disruptions in NK cells, including decreased NKp30, DNAM-1, and NKG2D receptor expression, in addition to a reduced ability to eliminate target cells [104]. Furthermore, in 2023, researchers reported that mutations detected in MDS neoplastic cells, such as TET2 and IDH1/2 mutations, were also commonly found in NK cells. As a result, NK cells with TET2 mutations are characterized by increased genomic DNA methylation and decreased

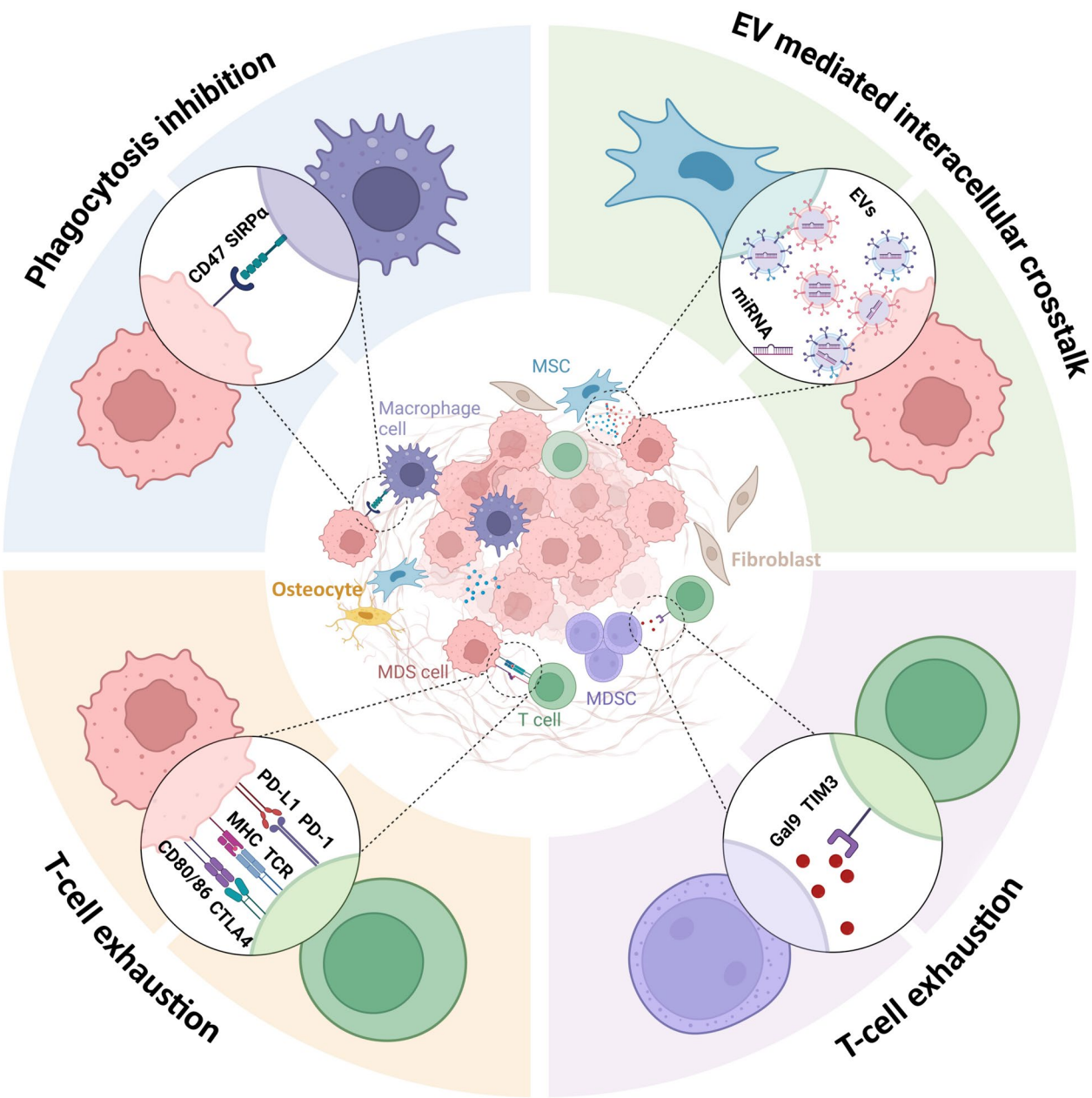

Fig. 1 Overview of the dynamic interactions among cellular components in the MDS microenvironment. T cell exhaustion results from: Excessive expression of PD-1 and CTLA-4 on T cells, which have the potential to interact with PD-L1 and CD80/86 on MDS cells, as well as elevated Gal9 levels secreted by MDSCs, which bind to TIM3 on T cells. MDS cells inhibit phagocytosis by upregulating the "don't eat me" ligand CD47, which interacts with its receptor on the surface of macrophages, SIRPα. MDS and MSCs produce EVs containing miRNAs, which play important roles in accelerating the progression of MDS. MSC: mesenchymal stromal cell; MDSC: myeloid-derived suppressor cells; EVs: extracellular vesicles; miRNAs: microRNAs; PD-1: programmed death 1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte associated protein 4; TIM-3: T-cell immunoglobulin and mucin domain 3; GAL9: galectin 9; SIRPα: signal-regulatory protein alpha

expression of killer immunoglobulin-like receptors (KIRs), TNF-α, and perforin [105].

Macrophages

Macrophages are another type of immune cell that may contribute to the progression of MDS. In low-risk MDS, macrophages enhance phagocytosis of granulocyte–macrophage progenitors (GMPs) due to the upregulation of

calreticulin (CRT) on GMPs, which binds to low-density lipoprotein receptor-related protein 1 (LRP1) on macrophages, a pro-phagocytic receptor, promoting phagocytosis. This increased phagocytosis depletes GMPs in the BM and contributes to neutropenia. In contrast, high-risk MDS is marked by macrophage dysfunction, where the elevated expression of CD47 on myeloid progenitors binds to signal regulatory protein alpha (SIRPα) (Fig. 1) on macrophages, inhibiting phagocytosis and impairing proper regulation of hematopoiesis, thereby promoting disease progression and poor prognosis [106–108]. Additionally, in MDS, impaired macrophage clearance of apoptotic cells leads to the release of high-mobility group box 1 (HMGB1), which functions as a damage-associated molecular pattern (DAMP), activating Toll-Like Receptor 4 (TLR4) on BM macrophages and triggering pro-inflammatory cytokine production. This inflammatory response disrupts normal hematopoiesis and accelerates disease progression [109]. According to a study that compared macrophages from MDS patients with those from healthy controls, there was a significant increase in the number of CD68-positive macrophages [110, 111]. Additionally, in MDS patients, hematopoietic cells display high levels of FAS and TNF receptor-1 (TNFR-1) expression, whereas macrophages overexpress their ligands FAS-L and TNF-α, respectively. TNFR-1/TNF-α and FAS/FASL interactions may contribute to increased apoptosis in MDS BM [112, 113]. Moreover, BM-macrophages contribute to ineffective hematopoiesis by creating an inflammatory microenvironment, which may influence T cell activity through cytokine release and antigen presentation [114].

Lymphocytes

In many patients with low-risk MDS, there is an aberrant B-cell progenitor compartment. A malfunction in the development of B-cell progenitors has been shown to be a characteristic of early MDS, which could serve as the basis for a diagnostic test [115]. Several components of the adaptive immune system are regulated by T cells, including reactions to infections, allergies, and cancers. T cells are essential for the development and maintenance of homeostasis, immune responses, and memory [116]. In a study in MDS patients, researchers reported an activated state of lymphocytes, characterized by increased frequencies of effector cytotoxic T lymphocytes (CTLs), decreased percentages of regulatory T cells, and greater skewing of the T-cell receptor (TCR)-Vβ repertoire than in healthy controls [117]. Furthermore, effector CTLs, particularly CD8+/CD28− and CD8+/CD28−/CD57+ subsets, are significantly elevated in MDS compared to healthy controls. Their increased levels, especially in untreated patients and those unresponsive to immunosuppressive therapy, suggest a persistent immune response against hematopoietic cells, underscoring their role in MDS pathophysiology [118, 119]. On the basis of their functional characteristics, different populations of T cells act against tumor cells, such as CD4+T cells (helper T cells), which coordinate the immune response against tumor cells; CD8+T cells (CTLs), which directly kill tumor cells; and Tregs, which suppress the immune response.

CD8+T cells can induce apoptosis in tumor cells by producing cytotoxic substances after identifying tumor antigens displayed by malignant cells via MHC class I molecules [120]. Despite the greater number of CD8+T cells found in the BM of MDS patients, these cells from high-risk MDS patients display reduced cytotoxic capabilities. A reduction in adhesion molecules and the formation of fewer conjugates with target cells were observed in CD8+T cells from MDS patients, who presented the lowest level of cytotoxicity [119]. Furthermore, CD8+T cells in high-risk MDS patients exhibit increased expression of PD-1 (programmed death 1), which interacts with PD-Ligand 1 (PD-L1) produced by tumor cells, thereby reducing CD8+T-cell immune responses to tumor cells and causing T-cell exhaustion [106, 121]. Furthermore, a clonal expansion of CD8+T cells is observed in the BM of patients with low-risk MDS. There is a skewed TCR repertoire associated with this expansion, suggesting a clonal expansion of tumor-specific CD8+T cells [122].

CD4+T cells play a crucial role in the adaptive immune system by expressing CD4, TCRs, and TCR coreceptors that bind to the β2 domain of MHC class II molecules, facilitating peptide-MHC II interactions on antigen-presenting cells (APCs). Through these interactions, CD4+T cells support CD8+T cell activation, enhance antibody-mediated immunity, and secrete cytokines such as TNF-α and IFN-γ, contributing to the adaptive immune response against tumor cells [123]. Different subgroups of CD4+T cells, including Th1 (IFN-γ, TNF-α, and IL-2), Th2 (IL-4, IL-5, IL-10, and IL-13), Th17 (IL-17 and IL-23), and Th22 (IL-22, IL-13, and TNF-α) [121, 122]cells, are identified on the basis of their cytokine secretion. There is an imbalance in the ratio of Th1 to Th2 cells in MDS patients compared with healthy controls due to a reduction in the number of Th1 cells. In addition, there is a contrasting relationship between a decrease in the number of Th1 cells in the BM of patients with MDS and an increase in blast cells [124]. Patients with low-risk MDS exhibit a higher frequency of Th17 cells and increased IL-17 levels compared to those with high-risk MDS. This elevated Th17 response may reflect an immune-mediated mechanism that restricts the expansion of dysplastic clones, thereby slowing disease progression.

Additionally, the enhanced Th17 presence could contribute to the increased incidence of autoimmune manifestations in low-risk MDS and may explain their better response to immunosuppressive therapies compared to high-risk patients [125]. In addition, a significant increase in the Th22 subgroup was observed in the PB of patients with MDS compared with healthy controls, whereas it was greater in low-risk MDS patients than in early-stage MDS patients. These findings suggest that Th22 cells may be involved in MDS immune escape, ultimately resulting in MDS development [126].

Treg cells are a specific type of CD4+ T-cell that express high levels of CD25. These cells are capable of regulating autoimmunity and maintaining immunological homeostasis [127]. However, Treg cells may interfere with immune responses to tumor cells because of their ability to inhibit self-antigen responses [128]. Treg proliferation occurs as the disease progresses in patients with high-risk MDS. Conversely, in low-risk MDS, the number of Treg cells is often lower, which enables the immune system to respond to dysplastic clones more effectively [129]. In one study, some MDS patients presented an increase in the number of effector memory Tregs ($Treg^{EM}$), which do not express CD27 and have a greater capacity to suppress the immune system. As a result, increased numbers of $Treg^{EM}$ cells appear to have independent prognostic significance for survival [130].

A hallmark of malignant cell expansion is immune evasion, which is particularly relevant in patients with MDS, whose aged immune system is more susceptible. The overexpression of immune checkpoint molecules, such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and PD-1 on T cells, results in T-cell exhaustion, which results in malignant cells being able to evade the immune system (Fig. 1) [121]. The PD-1 receptor on activated T cells functions as a coinhibitory receptor to block the stimulation signal triggered by TCR interactions. Furthermore, PD-1 is expressed on B cells, monocytes, and NK cells [131]. In patients with MDS, PD-1 and PD-L1 expression are significantly altered, and CD34+HSPCs upregulate PD-L1, while Treg cells and effector T cells overexpress PD-1. MDS-associated inflammatory cytokines, such as S100A9, TNF-α, and IFN-γ, which are produced at high levels in BMM of MDS patients, induce the overexpression of PD-1 and/or PD-L1 on the BM cells of MDS patients, allowing malignant cells to evade the immune system [121, 132]. Similarly, CTLA-4, present on both CD4+ and CD8+ T cells, serves as another coinhibitory receptor that modulates T-cell activation, thereby suppressing the immune response and facilitating tumor progression [133]. Aref et al. reported higher serum CTLA-4 levels in MDS patients than in healthy controls. Furthermore, high-risk MDS patients exhibited higher CTLA-4 levels than intermediate-risk patients. According to the results of this study, high CTLA-4 serum concentrations in patients with MDS are associated with increased mortality rates and a greater risk of developing AML [134]. T-cell immunoglobulin and mucin domain 3 (TIM-3) is a checkpoint receptor found on the surface of Th1 cells, CTLs, Tregs, and several other immune cells, including NK cells, DCs, and monocytes. GAL9 is the most well-known ligand for TIM3, which triggers apoptotic signals in Th1 cells and regulates the release of cytokines, such as IFN-γ and TNF-α. MDS is characterized by increased levels of TIM-3 in Th1 cells, CTLs, Treg cells, and HSPCs, which contributes to blast expansion and immunological evasion [135, 136]. Additionally, T-cell immunoglobulin and ITIM domain (TIGIT) molecules are other coinhibitory receptors that are extensively produced by T cells and NK cells. TIGIT levels are increased in higher-risk MDS patients, resulting in a reduction in the responsiveness of CD4+ T, CD8+ T, and NK cells to stimulation and a decrease in their ability to secrete effector cytokines such as TNF-α, IFN-γ, and CD107a, which leads to the clonal expansion of malignant cells and tumor escape [137, 138].

Bone marrow derived extracellular vesicles in MDS

Extracellular vesicles (EVs) are a diverse range of secreted membrane-enclosed vesicles that vary in size, composition, content, density, and cellular origin [139]. Almost all cell types release EVs, which play crucial roles in facilitating communication between cells [140]. EVs carry various types of cargo, such as proteins, metabolites, messenger RNAs (mRNAs), and miRNAs [141]. Since EVs are abundant in biofluids such as blood, plasma, and serum, they may serve as valuable minimally invasive diagnostic biomarkers for hematologic malignancies because of their ability to carry and protect biologically active molecules that reflect their cell of origin [142]. It has been suggested that tumor cell-derived EVs contribute significantly to the remodeling of niches in MDS [143]. Hayashi et al. reported that MDS neoplastic cells prevent the differentiation of MSCs into osteolineages via MDS-derived EVs, which ultimately reduce supportive niche function and lead to BM failure. Furthermore, encapsulated miRNAs contribute to at least one of the critical processes involved in MSC impairment, which is commonly observed in MDS patients (Fig. 1) [144]. EV miR-7977 derived from MDS and AML cells can be transferred into BM-MSCs and inhibit the capacity of MSCs to support HSPCs by suppressing poly(rC)-binding protein 1 (PCBP1). Therefore, EV miR-7977 may contribute to hematopoiesis dysfunction in patients with MDS and AML [145]. In addition, it has been demonstrated that the expression of EV miR-103-3p in MDS

patients is lower than that in healthy controls. The same results were obtained when miR-103-3p expression was measured in MDS-MSCs. These results also indicate that low miR-103-3p expression suppresses the osteogenic differentiation of MDS-MSCs and promotes adipogenic differentiation, explaining the ineffective hematopoiesis associated with MDS [146].

In addition to stimulating MSCs with MDS-derived EVs during MDS progression, MDS-MSCs also release EVs that influence dysplastic cells, resulting in leukemogenesis [4, 147]. In a study, MSC-derived EVs from MDS patients were shown to inhibit the proliferation of MDS cells, prevent differentiation, promote apoptosis, and arrest cell cycle progression. Additionally, these EVs may play a role in the transformation of MDS into leukemia by activating the TNF-α/ROS-Caspase3 pathway [148]. Furthermore, MSC-derived EVs from MDS patients have been shown to enhance the clonogenicity of CD34+ cells, suggesting their role in disease progression. These EVs contain several miRNAs, including miR-10a and miR-15a, which are involved in regulating critical cellular functions such as the cell cycle and apoptosis. Additionally, the increased erythroid progenitor apoptosis observed in this study in MDS patients may be driven by EVs from the BMM carrying miRNAs that activate the TP53 pathway [149]. Meunier et al. demonstrated that EV miR-486-5p derived from MDS-MSCs increases ROS levels, damages DNA, and promotes HSPC apoptosis. These results support the idea that BMM may contribute to MDS progression by inducing genotoxic stress in HSPCs through EV-mediated cell-to-cell communication [150]. EVs from patients with MDS are generally involved in the cross-talk between malignant cells and BMM components, and their microRNA contents differ from those of healthy controls. These EVs also suppress healthy hematopoiesis either by directly affecting hematopoietic cells or by reprogramming the BMM [151].

Inflammatory signaling pathways in MDS

Inflammatory signaling and its therapeutic targeting in MDS have emerged as critical areas of research [152–154]. Systemic inflammation drives HSPCs from quiescence to rapid proliferation, enhancing their differentiation capacity, particularly toward myeloid lineages. This process, known as emergency myelopoiesis, facilitates the essential replenishment of leukocytes during systemic inflammation [155]. Activation of the innate immune system plays a significant role in hematopoietic senescence and MDS pathophysiology [156]. Specifically, inflammation in the BMM represents a complex interplay between inflammatory mediators produced by malignant cells, antitumor immunity, and the remodeling of the extracellular matrix (ECM) alongside tissue damage [28]. Stressed/dying cells generate a proinflammatory state by releasing DAMPs, which bind and activate pattern recognition receptors (PRRs), such as TLRs, CD33, and nucleotide-binding domain leucine-rich repeat containing (NLR) proteins [157–159]. Due to the high density of PRRs on their surface, specifically TLRs, MDS-HSPCs are more susceptible to modulation by DAMPs [160, 161]. The activation of PRRs by DAMPs induces pyroptosis, a form of caspase-1-dependent programmed cell death, which suggests ineffective hematopoiesis in MDS [162, 163].

TLR

Aberrant TLR signaling plays a crucial role in the dysregulation of innate immune pathways in MDS, contributing to disease pathogenesis [164]. TLR activation recruits cytoplasmic MYD88 and initiates a signaling cascade leading to interleukin receptor-associated kinase-1 (IRAK1) and IRAK4 activation. Phosphorylated IRAK-1 triggers tumor necrosis factor receptor-associated factor 6 (TRAF6) to activate the NF-κB pathway [165].

Overexpression of TLR1, TLR2, and TLR6 was identified in MDS BM-CD34+ cells, along with a recurrent genetic variant, TLR2-F217S, present in 11% of patients. TLR2-F217S enhanced NF-κB activation and gene expression in response to TLR2 agonists. Inhibition of TLR2 in lower-risk MDS CD34+ cells increased erythroid colony formation, indicating that deregulated TLR2 signaling contributes to MDS and may serve as a potential therapeutic target [160]. One study analyzed TLR expression and global histone H3/H4 acetylation in BM-CD34+ cells from lower-risk and higher-risk MDS patients. It found that excessive apoptosis of hematopoietic precursors in MDS is associated with abnormal TLR signaling. Specifically, elevated TLR1, TLR2, and TLR6 expression, along with increased histone H4 acetylation, were observed in lower-risk MDS patients. TLR2 activation induced apoptosis via β-arrestin1-mediated recruitment of p300, leading to enhanced histone acetylation and transcriptional changes. These findings further suggest that TLR signaling may contribute to ineffective hematopoiesis in MDS [166].

MYD88 assembles with IRAK4 and IRAK2 to form a macromolecular complex called the myddosome, which contains six to eight subunits of MYD88 and, precisely, four subunits of each kinase (Fig. 2) [167, 168]. Abnormally overexpressed MYD88 plays a role in MDS pathogenesis. Furthermore, MYD88 blockade induced erythroid differentiation in patients with lower-risk MDS and negatively regulated IL-8 secretion [169]. An oncogenic long IRAK-4 isoform (IRAK4-L), which interacts with MYD88 to activate NF-κB excessively, has been shown to be overexpressed in AML/

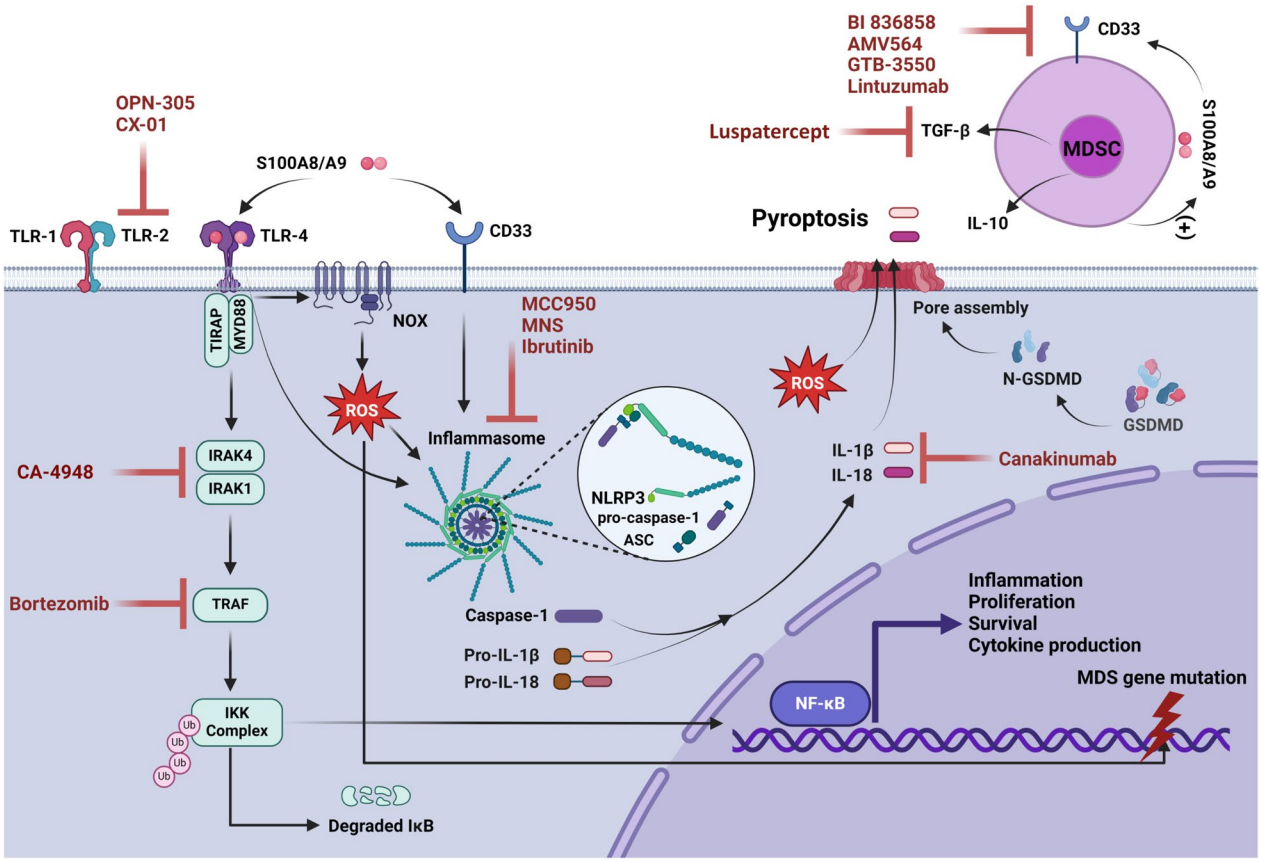

Fig. 2 Inflammatory signaling pathways involved in MDS and associated therapeutic targets. S100A8/A9 bind to TLR4 and CD33 and initiate the assembly of the NLRP3 inflammasome. The binding of S100A8/A9 to TLR4 also activates NF-kB through IRAK1/TRAF6/NF-κB signaling pathway, which results in the production of proinflammatory cytokines (pro-IL-1β and pro-IL-18). S100A8/A9 promote NOX activation, leading to excessive production of ROS and the subsequent activation of NLPR3 and inflammasome assembly. Inflammasomes recruit ASCs to form complexes that facilitate the conversion of pro-caspase-1 to caspase-1. Mature and activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their bioactive forms, which induce pyroptosis. TLR: toll-like receptor; TIRAP: toll-interleukin-1 receptor domain-containing adaptor protein; IRAK: interleukin receptor-associated kinase; TRAF: tumor necrosis factor receptor-associated factor; IκK: inhibitor of κB kinase; NF-κB: nuclear factor kappa B; NLRP3: nucleotide-binding domain and leucine-rich repeat pattern recognition receptor; ASC: apoptosis-associated speck-like protein containing a caspase-recruitment domain; GSDMD: gasdermin D; NOX: nicotinamide-adenine dinucleotide phosphate oxidase; ROS: reactive oxygen species; Ub: ubiquitin; TGF-β: transforming factor-β; IL: interleukin

MDS, whereas the shorter form (IRAK4-S) has less binding ability to MYD88 [170, 171]. Splicing mutations in U2AF1 and SF3B1 have been shown to generate IRAK4-L, facilitating myddosome formation and NF-κB activation [171, 172]. IRAK1 is overexpressed and activated in MDS, and its genetic or pharmacological inhibition induces apoptosis, cell-cycle arrest, and improves survival in a human MDS xenograft model. A collaborative cytotoxic effect was observed with combined IRAK1 and BCL2 inhibition. This study also indicates that targeting IRAK1 may offer a potential therapeutic approach for MDS [173, 174].

Another study demonstrated that inhibiting IRAK4 in leukemic cells leads to compensation by IRAK1, and cotargeting both IRAK1 and IRAK4 is necessary to suppress leukemic stem/progenitor cell (LSPC) function and induce differentiation. IRAK1 and IRAK4 act through noncanonical, MyD88-independent pathways to maintain the undifferentiated state of MDS/AML LSPCs by regulating pathways including polycomb repressive complex 2 and JAK/STAT signaling. A dual IRAK1/IRAK4 inhibitor, KME-2780, effectively suppresses LSPCs in vitro and in xenograft models. These findings support cotargeting IRAK1 and IRAK4 as a therapeutic strategy for MDS/AML [175].

NF-κB serves as a key mediator of the TLR signaling pathway in MDS, contributing to disease pathogenesis. Chronic inflammation can drive a shift from canonical to noncanonical NF-κB signaling, facilitated by TLR-TRAF6-mediated activation of protein A20 [176]. MDS

patients exhibit reduced A20 levels and increased proinflammatory cytokines, indicating heightened inflammatory responses [177]. NF-κB activation in mesenchymal cells is linked to impaired hematopoiesis and cytopenia in low-risk MDS patients [178]. A study identified a significant correlation between NF-κB signaling, leukemic stem cell (LSC) signature pathways, oxidative stress, and a high-risk immune cell scoring system (ICSS). It also demonstrated that constitutive NF-κB activation is a hallmark of high-risk MDS, contributing to disease progression and promoting the acquisition of M2-like macrophage phenotypes [179].

NLRP3

Analysis of BM-derived mononuclear cells (BM-MNCs) from MDS patients demonstrated that pyroptosis is a predominant type of cell death rather than apoptosis [159]. Pyroptosis is executed through the formation of cytosolic multiprotein complexes known as inflammasomes, which are composed of NLRPs. NLRP3, the best characterized form of NLRP, is activated in response to different DAMPs, stimulating the recruitment of an apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD) (ASC) and a pyrin domain (PYD). In addition, the inflammasome complex facilitates the conversion of the inflammatory cytokines IL-18 and IL-1β into their active forms through a caspase 1-dependent process during pyroptosis [162, 163]. Gasdermin D (GSDMD), the pore-forming protein that mediates cytolysis, is proteolytically cleaved by caspase-1 in inflammasomes, causing membrane permeability, swelling, and passive release of IL-18 and IL-1β (Fig. 2) [20, 180, 181].

Conditional knockout of Nucleophosmin 1 (NPM1), a crucial regulator of HSC aging and inflammation, in a mouse model accelerates aging and activates mitochondrial pathways. This leads to aberrant NLRP3 inflammasome activation, which plays a central role in the development of an MDS-like phenotype, underscoring the key contribution of NLRP3 in MDS pathogenesis [182]. TIM3/CEACAM1, highly expressed on MDSCs and CD8+ T cells in MDS patients, contributes to CD8+ T-cell exhaustion and may activate the NF-κB/NLRP3/Caspase-1 pathway in MDSCs. This activation leads to the production and secretion of proinflammatory cytokines IL-18 and IL-1β, promoting inflammation in the BMM and driving MDS pathogenesis [183]. A study on the miR-223-3p/NLRP3 signaling axis in MDS demonstrated that overexpression of miR-223-3p effectively inhibited NLRP3, resulting in reduced cell proliferation, migration, and invasion. In vivo, miR-223-3p reduced tumor volume, while co-overexpression with NLRP3 promoted tumor growth. These findings highlight the pivotal role of NLRP3 in MDS and suggest that targeting the miR-223-3p/NLRP3 axis could offer a promising therapeutic strategy for MDS [184]. Furthermore, pyroptosis-induced extracellular oxidized mitochondrial DNA (ox-mtDNA), a DAMP in MDS cells, directly activates the NLRP3 inflammasome and indirectly activates it via the TLR9-MYD88 pathway [185].

S100A8/A9

The cytosolic DAMP proteins S100A8 and S100A9 are inflammatory mediators that play significant roles in the development and progression of different malignancies [186]. S100A8 and S100A9 induce inflammatory responses by promoting the release of proinflammatory cytokines such as IL-6, IL-8, and IL-1β through ROS-dependent mechanisms. S100A9 is a more potent stimulator than S100A8 [187].

Some studies have produced inconsistent findings regarding S100A9 levels in MDS patients, likely due to heterogeneity within patient subgroups, which are influenced by distinct genetic mutations and variations in the activation of specific inflammatory pathways. In a previous study, S100A9 was overexpressed in lower-risk MDS patients, promoting cellular senescence in MSCs through the formation of the TLR4-NLRP3 inflammasome, leading to increased production and secretion of the proinflammatory cytokine IL-1β [188]. However, another study found that despite high levels of S100A8 in lower-risk MDS patients, the circulating levels of S100A9 were not significantly different from those in healthy controls [189]. A recent study reported that the protein levels of S100A9 in BM samples from MDS patients were lower than those in healthy controls. The findings highlighted the presence of diverse inflammatory states associated with distinct disease entities, which may influence S100A9 expression patterns and have implications for stratifying patients for emerging anti-inflammatory treatments. Notably, SF3B1-mutant MDS exhibited a clear trend toward higher S100A9 gene expression and protein levels, despite an overall lower inflammatory state in MDS patients [190].

Moreover, the S100A9/CD33 signaling pathway plays a crucial role in promoting the expansion of MDSCs bearing the CD33+ /Lin-/HLA-DR- phenotype, which impairs hematopoiesis and contributes to MDS development. In S100A9 transgenic mice, MDSCs accumulated and became activated in the BM, leading to cytological dysplasia and progressive multilineage cytopenias [191]. Additionally, in two del(5q) MDS mouse models, hematopoietic defects are associated with elevated expression of S100A8 and S100A9, which activate the innate immune system. RPS14 deletion (mouse model 1) causes erythroid differentiation defects, anemia, and

megakaryocyte dysplasia, while combined haploinsufficiency of Rps14, Csnk1a1, and miR-145/146a (mouse model 2) results in anemia and macrophage activation, disrupting the BMM. Overall, elevated S100A8 and S100A9 expression impairs hematopoiesis and underscores their critical role in MDS pathogenesis [192, 193]. There is also evidence that the overexpression of PD-1 and PD-L1, which are induced by S100A9 on the surface of HSPCs and MDSCs, respectively, contributes to HSPC death in MDS [194]. Additionally, activation of the p53-S100A8/9-TLR signaling pathway in mesenchymal cells appears to be a reliable predictor of leukemic evolution and progression-free survival in patients with MDS [195].

Elevated S100A8/A9 levels have been identified as an independent poor prognostic factor in MDS. Higher S100A8/A9 levels in the bone marrow were associated with a disrupted microenvironment, characterized by an enhanced MDSC signal and impairments in both the function and quantity of CD8+ T cells and NK cells. Finally, the S100A8/A9 level is a well-established independent poor prognostic factor in patients with MDS. Based on these findings, S100A8/A9 has been proposed for integration into current risk stratification systems and prospective evaluation in clinical trials [196].

Inflammatory cytokine profile of MDS

Overproduction and hyperactivity of proinflammatory cytokines in the MDS microenvironment contribute to hematopoietic defects and clonal proliferation, driven by cytokines such as TGF-β, IL-6, IL-1, IL-17, TNF-α, and IFN-γ [197]. Analyses of cytokine profiles across large MDS cohorts have yielded conflicting results [23, 198], likely due to variations in inflammatory involvement across MDS subgroups, influenced by genetic factors, disease progression, and the BMM composition. Despite these inconsistencies, several cytokines, including tumor necrosis factor α, TGF-β, IL-6, interferon γ, IL-8, IL-1β, and granulocyte–macrophage colony-stimulating factor, are consistently elevated in MDS patients, with some correlating to disease outcomes [198–200].

TGF-β

TGF-β is a critical factor in the BM and is produced by various cells, including Tregs, macrophages, and DCs. It binds to the TGF-β receptors, which subsequently activate SMAD molecules [201]. The TGF-β/SMAD signaling pathway is triggered when the TGF-β receptors are phosphorylated, initiating a downstream regulatory network involving both receptor-regulated SMAD (R-SMAD) and inhibitory SMAD (I-SMAD) molecules. This cascade has been shown to perform several functions, such as promoting erythroid differentiation through SMAD2/3 and inhibiting cell proliferation via SMAD6/7 [202].

A study indicated that the gelatinase MMP9 plays a novel role in the pathogenesis of the del(5q) subtype of MDS by activating the TGF-β/SMAD signaling pathway [203]. Additionally, several polymorphisms associated with elevated expression of TGF-β1 are overrepresented in MDS patients, suggesting that increased activity of this cytokine may contribute to the susceptibility and/or pathogenesis of MDS [204]. Furthermore, there is considerable evidence linking the overexpression of TGF-β1, SMAD3, and SMAD4 with BM fibrosis in MDS patients, regardless of genomic abnormalities or mutations [205–207]. Interestingly, MDS-MSCs suppress immune responses by secreting TGF-β1, which inhibits T-cell proliferation and dendritic cell differentiation and function [208].

Pharmacological inhibition of the TGF-β signaling pathway has been shown to enhance late-stage erythroid differentiation and maturation [209, 210]. During the early stages of MDS, the miR-21-mediated loss of SKI (a TGF-β antagonist) activates TGF-β signaling, resulting in the loss of a competitive advantage for normal HSPCs [211]. Moreover, the miR-21-mediated suppression of SMAD7 activates the TGF-β signaling pathway in BM progenitor cells, leading to ineffective hematopoiesis in MDS patients [212]. Additionally, the deficiency of miR-143/145 triggers SMAD-dependent activation of TGF-β in the del(5q) subtype of MDS [213].

IL-6

IL-6 is a crucial inflammatory cytokine that likely plays a significant role in the development of CHIP and MDS, not only by influencing clonal dynamics but also by directly contributing to hematopoietic dysfunction. Specifically, IL-6 is involved in promoting the expansion of mutated TET2 and DNMT3A clones [214, 215].

In a mDia1/miR-146a double knockout (DKO) mouse model that mimics del(5q) MDS, aging BMM contributes to ineffective erythropoiesis through increased levels of DAMPs, which upregulate IL-6 and TNFα in MDSCs. Elevated IL-6, along with TNFα, inhibits erythroid colony formation and disrupts terminal erythropoiesis via ROS-mediated caspase-3 activation, ultimately leading to apoptosis. This highlights the central role of IL-6 in MDS pathology, exacerbating anemia and ineffective hematopoiesis [26]. In a follow-up study, DKO mice were crossed with IL-6 knockout mice to investigate the role of IL-6 in the pathogenesis of MDS in the DKO model. The resulting mDia1/miR-146a/IL-6 triple knockout (TKO) mice showed a significant reversal of the leukemic transformation observed in the DKO mice [216].

As previously noted, cytokine profile analyses in MDS cohorts have yielded inconsistent results, likely

attributed to genetic heterogeneity and the complex composition of BMM. In this context, a cohort study on cytokine expression in MDS and AML identified distinct dysregulated profiles with overlapping patterns between the two, alongside elevated levels of IL-6, IL-9, IFN-γ, and CXCL10 in normal controls compared to prior studies [198]. Moreover, some studies have indicated that elevated levels of IL-6 are associated with the progression of MDS to AML; however, another study reported no correlation between the stage of the disease and IL-6 levels [217–219].

IL-1β

Single-cell RNA sequencing of MDS-DCs revealed high expression of IL-1β and TLR1/2, suggesting that activated TLR1/2 signaling may result in HSPC dysfunction by increasing IL-1β expression in the perivascular niche [220]. In addition, IL-1β and IL-18 are secreted by MDS-HSPCs through aberrantly activated NLRP3 complexes that trigger caspase-1-dependent pyroptotic cell death [221]. Moreover, high expression of the IL-1 receptor accessory protein (IL1RAP) is associated with poor overall survival (OS) and poor prognosis in patients with high-risk MDS and AML [222]. In patients with low-risk MDS, inflammatory cytokines are generally elevated, but the NLRP3/IL-1β pathway may have a significant effect on disease progression. Therefore, IL-1β serum levels might be a reliable indicator of prognosis in MDS patients [223]. RNA-sequencing analysis identified distinct IL-1β production patterns across different low-risk MDS subgroups, suggesting that anti-inflammatory therapies could be personalized. Further analysis revealed that inflammasome-related genes, including IL1B, were mainly expressed in monocytes, playing a key role in the inflammatory bone marrow environment. Treatment with the IL-1β-neutralizing antibody canakinumab increased colony-forming activity in HSPCs exposed to monocytes from low-risk MDS patients, indicating its potential to improve erythropoiesis in MDS [190]. In addition, there is a link between the IL-1β polymorphism (rs16944) GG and decreased hemoglobin levels, which indicates its potential as a novel biomarker for MDS patients [224].

IL-17

A meta-analysis on inflammatory cytokine levels in MDS found that IL-17 levels are lower in high-risk MDS patients [225]. Conversely, low-risk MDS patients exhibit higher IL-17 levels, potentially linked to IL-17-induced apoptosis [197, 226]. Analysis of bone marrow mononuclear cells (BM-MNCs) showed significantly higher levels of both IL-17 and its receptor (IL-17R) in lower-risk MDS patients compared to higher-risk patients and healthy controls. Additionally, treatment with recombinant human IL-17 (rhIL-17) in lower-risk MDS patients increased TNF-α and IFN-γ production, which could play a role in MDS pathogenesis [227].

TNF-α

Studies of elevated serum TNF-α levels in MDS patients have provided evidence that TNF-α may contribute to a cytopenic phenotype in these patients. Furthermore, the observation of increased levels of TNF-α during MDS progression suggests that TNF-α might also play a role in the leukemic transformation of genetically altered HSPCs [228]. TNF-α has been reported to play a direct and/or indirect role in inducing intramedullary apoptosis by upregulating Fas expression on CD34+ progenitor cells in MDS patients [229].

A meta-analysis indicated that the TNF-α G308A polymorphism might serve as a valuable biomarker to aid the development of personalized prevention strategies for MDS patients [230, 231]. In addition, TNF and IL6 gene polymorphisms affect cytopenia severity in MDS, with high-producing genotypes linked to increased anemia and earlier transfusion dependence. Patients carrying both high-producing TNF and IL6 variants exhibited more severe bicytopenia, highlighting the role of cytokine polymorphisms in disease progression and their potential as therapeutic targets [232].

Other

In addition to those mentioned above, other cytokines contribute to MDS pathogenesis. Serum cytokine profile analysis revealed elevated C-X-C motif chemokine ligand 8 (CXCL8)/IL-8 and CXCL10 levels in patients with MDS [218, 233]. MDS patients, especially those over the age of 75, exhibited increased IL-8 and NF-κB levels, indicating age-related cytokine dysregulation. A significant positive correlation was found between IL-8 and NF-κB, suggesting that they function together as part of a complex network of immune factors involved in MDS [234]. In addition, a significant increase in the IL-8 receptor C-X-C motif chemokine receptor 2 (CXCR2) was observed in MDS progenitor cells. Activation of the IL-8/CXCR2 signaling axis stimulated the MAPK and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways in MDS samples, whereas inhibition of CXCR2 resulted in G0/G1 cell cycle arrest and suppressed leukemic cell growth [235].

According to a previous study, the levels of IL-18, IL-18 binding protein (IL-18BP), and free IL-18 (fIL-18) are higher in MDS patients than in healthy controls.

Although MDS patients exhibited increased levels of free IL-18, the concurrent expression of IL-18BP effectively neutralized its biological activity, rendering the elevated IL-18 concentrations functionally inactive. Moreover, CD8+ T cells express low levels of IL-18 receptor α (IL-18Rα), thus allowing less influence from fIL-18, which contributes to an immunosuppressive state by impairing CD8+T cells [236].

Furthermore, cytokines such as TNF-α and IFN-α activate p38 MAPK downstream signaling in MDS-HSPCs, which enhances apoptotic signaling in these cells [237]. In addition, elevated serum TNF-α levels may serve as a negative prognostic marker in high-risk MDS, correlating with increased leukocyte counts and higher concentrations of β2-microglobulin, creatinine, uric acid, and alkaline phosphatase [238]. Moreover, TNF-α levels have been linked to the severity of fatigue in MDS patients [239]. Lower levels of IL-33 were found in patients with more advanced stages of MDS. The role of IL-33 in MDS remains unclear mainly, although aberrant signaling by IL-33 has been reported in some cancers and chronic inflammatory diseases [240].

Therapeutic targeting of bone marrow microenvironment in MDS

MDS consists of an extremely heterogeneous myeloid malignancy originating from HSPCs. Consequently, patient management and treatment are also heterogeneous. Allogeneic- hematopoietic stem cell transplantation (allo-HSCT) is the only potential cure for MDS. Still, despite increased donor availability and better management, challenges remain in reducing the risk of relapse, which is the leading cause of transplant failure. Lower-risk MDS patients are mostly treated to improve cytopenia, especially anemia, and quality of life. Anemia in lower-risk MDS patients with no chromosomal abnormalities has been treated with erythropoiesis-stimulating agents (ESAs) for many years. In the case of ESAs ineligibility or failure, treatment will be individualized according to the main molecular mechanism of the disease. In this context, luspatercept, lenalidomide, and immunosuppressive therapy are medications used for MDS with ring sideroblasts, low-risk del(5q) MDS, and hypoplastic MDS (hMDS) without high-risk gene abnormalities, respectively. In addition, hypomethylating agents (HMAs) are first-line treatments for higher-risk MDS [241, 242]. In general, fewer approved therapeutic options are available for MDS than for other hematologic malignancies. Since BMM plays a key role in MDS pathogenesis, recent research has explored various potential treatments, particularly targeting its immune components (Table 3).

Cytokine inhibitors

A therapeutic alternative that may be efficient in MDS is the blockade of cytokine signaling. The Food and Drug Administration (FDA) approved luspatercept, which interferes with the TGF-β signaling pathway and represents an effective treatment option for lower-risk MDS patients with ring sideroblasts (RS) and SF3B1 mutations for whom ESAs have failed [243, 244]. In addition, KER-050, which is a TGF-β superfamily signaling inhibitor, stimulates multiple stages of the erythropoiesis cascade and increases erythropoietin (EPO) within the milieu of elevated RBCs in mouse models. Consequently, it may be an effective therapeutic candidate for diseases characterized by inefficient erythropoiesis, such as MDS [245]. The KER-050 is currently being evaluated in a phase II clinical trial in very low-, low-, or intermediate-risk MDS patients (NCT04419649). The updated results show that the KER-050 is generally well tolerated. The findings support that the KER-050 contributes to improving hematopoiesis, reducing the transfusion burden, and minimizing iron overload, a significant clinical complication in patients with MDS. In addition, data indicate the potential of KER-050 as a treatment for multilineage cytopenia in MDS patients by targeting multiple stages of hematopoiesis [246, 247]. Galunisertib is an oral inhibitor of the TGF-β receptor type 1 kinase (ALK5), which has an acceptable safety profile and improved hematological findings in patients with very low-, low-, and intermediate-risk MDS, who are transfusion-dependent and exhibit early stem cell differentiation block [248]. Additionally, researchers developed a mouse model of MDS that underwent leukemic transformation and demonstrated the clinical significance of blocking IL-6 signaling as a treatment strategy for high-risk MDS. The inhibition of IL-6 signaling with tocilizumab, a monoclonal antibody against IL-6R, markedly reduced the clonogenicity of MDS-CD34+cells as well as the progression of MDS to AML in a mouse model [219]. However, a phase II, randomized, double-blind study revealed that the anti-IL-6 agent siluximab did not reduce transfusion dependence in lower-risk MDS patients [249]. The monoclonal antibodies infliximab and etanercept, which inhibit TNF-α, have been investigated in different clinical trials and have displayed modest efficacy in patients with MDS [250–253].

Signaling pathway inhibitors

There is evidence that signaling pathways can be exploited for therapeutic purposes in patients with MDS. In a phase I/II study investigating tomaralimab (OPN-305), a humanized anti-TLR2 monoclonal antibody, some MDS patients who previously experienced HMA therapy failure achieved hematologic

Table 3 Emerging therapeutic agents targeting BM microenvironment

Therapeutic category	Agent	Target	Clinical trial phase	Patients/test model	Clinical trial ID-refs.
Cytokine inhibitors	Luspatercept (ACE-536)	TGF-β	III-Completed FDA approved	Lower-risk MDS	NCT02631070 [243, 278]
			II-Ongoing	Very low, low, or intermediate-risk MDS	NCT04477850 [30] NCT05732961 [70] NCT05181592 [70] NCT05732961 [70] NCT06045689 [100] NCT05925504 [36]
	Luspatercept + Lenalidomide	TGF-β	I/II-Ongoing	Nondel(5q) MDS	NCT04539236 [50]
	Luspatercept Injection (Reblozyl) + Eprex	TGF-β	I/II-Ongoing	Lower-risk MDS without RS (Failed or Being Ineligible to ESA)	NCT05181735 [150]
	Roxadustat + Luspatercept	TGF-β	IV-Not yet recruiting	Refractory MDS-RS	NCT06006949 [62]
	Ker-050	TGF-β	II-Ongoing	Lower-risk MDS	NCT04419649
	Galunisertib	TGF-β R	II-Completed	Lower-risk MDS	NCT02008318 [248]
	Vactosertib + Fludarabine Phosphate + Cyclophosphamide + IL-2 + Natural Killer Cells	TGF-β R	I-Ongoing	MDS Other hematologic malignancies	NCT05400122 [12]
	Siltuximab	IL-6	II-Completed	Lower-risk MDS	NCT01513317 [249]
	Infliximab	TNF-α	II-Completed	Lower-risk MDS	NCT00074074 [253]
	Etanercept	TNF-α R	I/II-Completed	MDS	NCT00118287 NCT00217386 NCT00093366 NCT00005853
	BMS-986253	IL-8	I/II-Ongoing	MDS	NCT05148234
	Canakinumab	IL-1β	I-Completed	Very low-, low-, and intermediate-risk MDS	NCT04810611
			II-Ongoing	Low- or intermediate-risk MDS CML	NCT04239157 [263]
	Canakinumab Injection + Darbepoetin Alfa	IL-1β	II- Ongoing	Lower-risk MDS	NCT04798339 [41]

Table 3 (continued)

Therapeutic category	Agent	Target	Clinical trial phase	Patients/test model	Clinical trial ID-refs.
Signaling pathway inhibitors	Tomaralimab (OPN-305)	TLR2	I/II-Completed	Lower-risk MDS (HMA failure)	NCT02363491 [254]
	CX-01	TLR2/4	I-Completed	R/R MDS AML	NCT02995655
	Emavusertib (CA-4948)	IRAK4	I/II-Ongoing	Higher-risk MDS R/R AML	NCT04278768 [153, 279]
	R289	IRAK1/4	Ib- Ongoing	Lower-risk MDS	NCT05308264 [34]
	Bortezomib	TRAF6	I/II-Completed	Lower-risk MDS (HMA failure)	NCT01891968 [280]
	Ibrutinib	ASC/NLRP3	I-Completed	Higher-risk MDS (Refused standard therapy)	NCT03359460 [259]
	Ibrutinib	ASC/NLRP3 Caspase-1	I-Ongoing	Higher-risk MDS (HMA failure) HMA-naive higher-risk MDS	NCT02553941 [260]
	DFV890	NLRP3	I-Ongoing	Very low-, low- or intermediate-risk MDS Lower risk CMML	NCT05552469 [80]

Table 3 (continued)

Therapeutic category	Agent	Target	Clinical trial phase	Patients/test model	Clinical trial ID-refs.
Immune checkpoint inhibitors	Sabatolimab	TIM-3	II-Ongoing	Lower-risk MDS	NCT04823624 [20, 281]
	Sabatolimab + Azacitidine + Decitabine	TIM-3	II-Ongoing	Higher-risk MDS	NCT04878432 [39]
	Sabatolimab + NIS793 + canakinumab	TIM-3	I-Completed	Lower-risk MDS	NCT04810611 [33]
	Sabatolimab + azacytidine + venetoclax	TIM-3	II-Ongoing	Higher-risk and very higher-risk MDS	NCT05020912 [281]
	Sabatolimab + HMAs	TIM-3	Ib-Completed	Higher-risk MDS AML	NCT03066648 [121]
	Sabatolimab + HMAs	TIM-3	II-Ongoing	Higher-risk MDS	NCT03946670 [121]
	Sabatolimab + azacytidine + Placebo	TIM-3	III-Ongoing	Higher-risk MDS	NCT04266301 [282]
	Ligufalimab (AK117)	CD47	I/II-Ongoing	MDS	NCT04900350 [283]
	Magrolimab + Azacitidine, Placebo + Azacitidine	CD47	III-Completed	MDS	NCT04313881 [269]
	Magrolimab + Azacitidine	CD47	Ib-Completed	MDS R/R AML	NCT03248479 [284, 285]
	Magrolimab + Decitabine/Cedazuridine	CD47	II-Completed	Intermediate-, high- or very high-risk MDS	NCT05835011 [100]
	IBI188 + Azacitidine	CD47	I-Ongoing	Higher-risk MDS	NCT04485065
	TQB2928 Injection + Azacitidine	CD47	I-Ongoing	MDS AML	NCT06008405
	ALX148 + Azacitidine	CD47	I/II-Ongoing	Higher-risk MDS	NCT04417517 [286]
	Pembrolizumab	PD-1	Ib-Completed	Lower- and higher-risk MDS (HMA failure)	NCT01953692 [121]
	Pembrolizumab + azacytidine	PD-1	II-Ongoing	HMA failure MDS	NCT03094637 [121]
	BI 836858	CD33	II-Completed	Low- and intermediate 1- risk MDS	NCT02240706 [287]
	Nivolumab and/or ipilimumab ± azacytidine	PD-1 (Nivo) CTLA-4 (Ipi)	II-Ongoing	HMA failure MDS	NCT02530463 [121]
	Nivolumab and ipilimumab ± azacytidine	PD-1 (Nivo) CTLA-4 (Ipi)	Basket exploratory phase II	HMA failure MDS	NCT02530463 [121]

Table 3 (continued)

Therapeutic category	Agent	Target	Clinical trial phase	Patients/test model	Clinical trial ID-refs.
Bi and Tri-specific antibodies	Flotetuzumab (MGD006)	CD3 + CD123	I/II-Completed	Intermediate- and higher- risk MDS AML	NCT02152956 [288]
	JNJ-67571244	CD3 + CD33	I-Completed	MDS AML	NCT03915379 [289]
	Vibecotamab	CD3 + CD123	II-Ongoing	MDS AML	NCT05285813 [290]
	AMV564	CD3 + CD33	I-Completed	Intermediate-2 and high-risk MDS	NCT03516591 [291]
	APVO436	CD3 + CD123	Ib-Ongoing	MDS AML	NCT03647800 [292]
	GTB-3550	CD16 + IL-15 + CD33	I/II-Completed	Higher-risk MDS R/R AML	NCT03214666 [293]
Chimeric Antigen Receptor (CAR) cells	CATCHAML (CAR-T cell)	CD123	I-Ongoing	AML/MDS	NCT04318678 [269]
	ARC-T (CAR-T cell)	CD123	I-Ongoing	Higher-risk MDS and AML	NCT05457010 [269]
	CLL1-CD33 cCAR- T-cell	CLL1 + CD33	I-Ongoing	Refractory higher-risk MDS	NCT03795779
	APVO436 (CAR-T cell)	CD123 + CD3	I-Ongoing	MDS AML	NCT03647800 [294]
	MP0533 (CAR-T cell)	CD33 + CD123 + CD70 + CD3	I/II-Ongoing	MDS AML	NCT05673057 [294]
	IPH6101/SAR443579 (CAR-T cell)	CD123 + CD16 + NKp46	I/II-Ongoing	MDS AML	NCT05086315 [294]
	NKX101 (CAR-NK cell)	NKG2D-Ls	I-Ongoing	Adult with MDS Adult with AML	NCT04623944 [61]
	CAR.70/IL15-transduced CB-NK cells (CAR-NK cell)	IL15-transduced	I-Ongoing	MDS and other hematologic malignancies	NCT05092451 [269]
Vaccines	TAA whole-cell vaccine (K562-GM-CSF-CD40L Vaccine) + lenalidomide + GM-CSF	TAA	I-Completed	Intermediate- and higher-risk MDS (Failed-HMA treatment)	NCT00840931 [266]
	TAA whole-cell vaccine (GVAX vaccine)	TAA	II-Completed	MDS, CMML, or AML	NCT01773395 [266]
	PR-1Peptide vaccine + Montanide + GM-CSF	Proteinase-3 + neutrophil elastase (PR-1)	I/II-Completed	MDS-RAEB	NCT00004918 [266]
	WT-1 peptide vaccine + montanide + GM-CSF	Wilms' Tumor 1 (WT1) antigen	I-Completed	MDS Other hematologic malignancies	NCT00665002 [266]
	WT-1 and PR-1 Peptide vaccine + montanide + GM-CSF	Combined PR1 and WT1	I-Completed	Montanide + GM-CSF	NCT00313638 [266]
	RHAMM Peptide vaccine + Incomplete FreudAdjuvant + GM-CSF	The receptor for hyaluronic acid-mediated motility (RHAMM)	I/II-Completed	MDS Multiple myeloma	ISRCTN32763606 [266]
	DEC-205/NY-ESO-1 Fusion Peptide vaccine + Decitabine + Nivolumab	DEC-205/NY-ESO-1 fusion protein CDX-1401	I-Completed	Intermediate- and higher-risk MDS	NCT01834248 [266]
	NY-ESO-1, MAGE-A3, PRAME, WT-1 Peptide vaccine + Azacitidine	Long peptide sequences from NY-ESO-1, PRAME, MAGE-A3, WT-1	I-Completed	Higher-risk MDS	NCT02750995 [266]

HMA, hypomethylating agent; TGF-β: transforming growth factor beta; TGFBR1: TGF-β receptor 1; TNF-α: tumor necrosis factor α; TRAF: tumor necrosis factor receptor associated factor; CML: chronic myeloid leukemia; TLR: toll-like receptors; IRAK: interleukin-1 receptor-associated kinase; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain; NLRP3: NLR family pyrin domain containing 3; R/R: refractory/relapsed; RS: ring sideroblast; PD-1: programmed death 1; CTLA-4: cytotoxic T-lymphocyte associated protein 4; TIM-3: T-cell immunoglobulin mucin-3; TAA: tumor associated antigen; Nivo: nivolumab; Ipi: ipilimumab; cCAR: compound chimeric antigen receptor; NKG2D: natural killer group 2; GM-CSF: granulocyte–macrophage colony-stimulating factor; CMML: chronic myelomonocytic leukemia; RAEB: refractory anemia with excess blasts

improvement and became transfusion independent. In lower-risk MDS patients, OPN-305 was well tolerated and had no serious toxicity [254]. Additionally, follow-up clinical research on OPN-305 in patients with lower-risk MDS for whom HMA treatment failed was conducted in 2018. The results of this study demonstrated that OPN-305 has a 50% overall response rate (ORR) in highly pretreated, transfusion-dependent HMA-failed patients, suggesting a possible treatment option for these patients [255]. CA-4948 (emavusertib), which inhibits IRAK4, a key component of the myddosome complex, has shown promise in the treatment of heavily pretreated high-risk MDS and AML patients, particularly those who carry U2AF1/SF3B1/FLT3 mutations [153]. Furthermore, targeting IRAK1 with a small-molecule IRAK1 inhibitor (IRAK1/4-Inh) reduces cell expansion and increases apoptosis in MDS cells, which is associated with the inhibition of the TRAF6/NF-κB pathway, indicating that IRAK1 may be a druggable target for MDS [256]. Moreover, multiple promising therapeutic strategies have been developed to target NLRP3 inflammasome to treat MDS. BTK, a positive and direct regulator of the NLRP3 inflammasome, appears to be an effective target for inhibiting NLRP3-dependent inflammation. In this context, the combination of lenalidomide and ibrutinib, an inhibitor of BTK, demonstrated a tolerability profile in a small cohort of MDS patients whose standard therapy failed [257–259]. However, preliminary results of another clinical trial combining ibrutinib and azacitidine showed promising efficacy, such as responses in higher-risk MDS patients with prior HMA exposure [260]. Additionally, several agents that directly inhibit NLRP3 ATPase activity, such as MCC950, 3,4-methylenedioxy-β-nitrostyrene (MNS), and CY-09, are in the preclinical stage of development [257, 261, 262]. Given the central role of IL-1β in triggering inflammasome activation and contributing to MDS pathogenesis, anti-inflammatory therapy with IL-1β neutralizing antibody canakinumab was investigated for lower-risk MDS. This study's results indicate that canakinumab effectively targets IL-1β signaling pathway in these patients [263]. In addition, several therapeutic agents, such as the recombinant IL-1 receptor (IL-1R) antagonist anakinra and the soluble decoy IL-1R rilonacept, target IL-1β signaling. Although there are no clinical trials evaluating these agents for MDS and AML, they have potential as future treatment approaches [264].

Vaccines

Cancer vaccines are immunotherapy approaches designed to stimulate effector immune cells to target cancer cells specifically. This strategy is based on effectively presenting tumor-associated antigens (TAAs) to the host's immune system, activating the immune response against them [265]. Several studies and trials have examined the effectiveness of vaccinations in the treatment of MDS. The most well-known vaccine approaches are whole-cell, DC, and peptide vaccines, which are being investigated for their potential therapeutic benefits in patients with MDS and other malignancies [266]. Granulocyte–macrophage colony–stimulating factor (GM-CSF)-transduced tumor cell vaccines (GVAXs) are whole tumor cell-based vaccines that are irradiated to inhibit proliferation before autologous delivery, stimulating specific, potent, and persistent antitumor immunity. Preclinical findings have shown that the GM-CSF gene stimulates the immune system when it is transfected into tumor cells and employed as a vaccine (Fig. 3A). Tumor suppression and increased survival rates have been observed in animal models that have undergone this vaccination [267]. Moreover, DCs are professional APCs that trigger adaptive immune responses to antigens presented by their MHC-I/II molecules, which makes them ideal immune cells for the development of cell-based vaccines. To prepare DC vaccines, TAAs can be expressed on MHC-I/II in DCs loaded with peptides, viral vectors, apoptotic tumor bodies, or nucleic acids before reinfusion in patients (Fig. 3B)[266]. Peptide vaccines can be synthesized from leukemia-associated antigens (LAAs) or TAAs to induce immune responses against tumors. Several LAAs and TAAs have been identified in MDS, in which notable targets are Wilms' tumor 1 (WT-1) antigen, NY-ESO-1 peptide, receptor for hyaluronic acid-mediated motility (RHAMM), preferentially expressed antigen of melanoma (PRAME), and proteinase-3+neutrophil elastase (PR-1) (Fig. 3C)[266, 268]. Several clinical trials have been conducted in MDS patients at different phases, the results of which are summarized in Table 3.

CAR-T/NK cells

Another therapeutic approach that relies on immune cells to treat MDS patients is the use of chimeric antigen receptor (CAR)-T and natural killer (NK) cells. To prevent complications, these engineered cells must be specific enough to target malignant cells while maintaining healthy progenitors for BM regeneration. In this context, several CAR-T cells have been engineered to target CD123, which is expressed by high-risk MDS stem cells (Table 3) [269, 270]. In addition, a phase I trial of NKX101, an allogeneic CAR-NK cell that targets NKG2D ligands, was initiated in 2020 to determine its safety and tolerability in adults with MDS and AML (Fig. 3D). The primary completion of this research is expected to occur in late 2024, with the study being completed in 2039. The

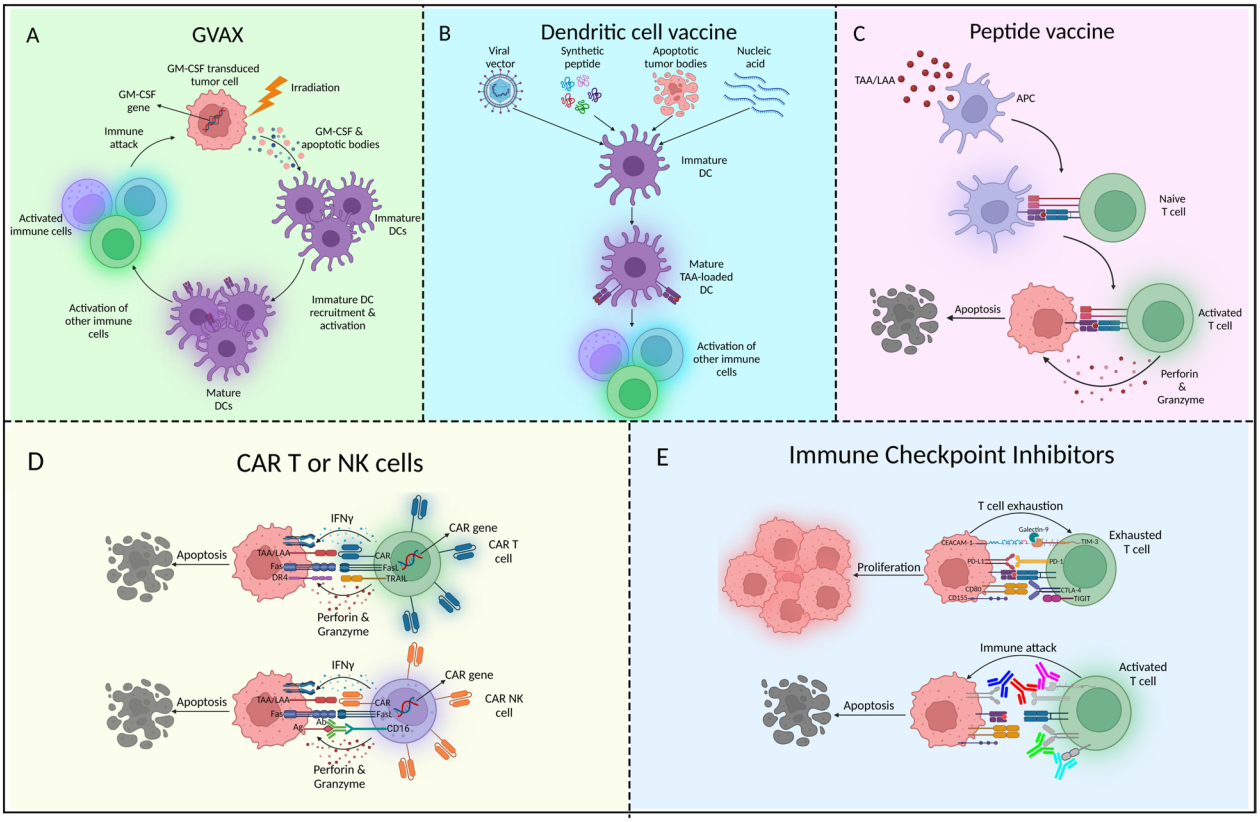

Fig. 3 Novel immunotherapy approaches in MDS. **A** Genetically modified tumor cells are used in GVAX vaccine to release GM-CSF, which enhances the immune response against tumor cells. GVAX promotes DC recruitment and activation to increase the ability of the immune system to recognize and destroy tumor cells. Apoptotic bodies produced by irradiated tumor cells are taken up by DCs, contributing to DC maturation. **B** Dendritic cell vaccines are generated by loading patient-derived DCs with TAA/LAA to trigger a targeted immune response against tumor cells. These vaccines can be prepared by expressing TAA/LAA on MHC-I/II in DCs loaded with peptides, nucleic acids, viral vectors, or apoptotic tumor bodies. **C** Peptide vaccines are based on the identification of epitopes that cause antitumor immune responses specific to TAA/LAA. **D** CAR-T or -NK cells are genetically engineered cells designed to express CARs targeting TAA/LAA on tumor cells. CAR immune cells induce apoptosis in tumor cells by releasing cytotoxic molecules such as IFNγ, perforin, and granzymes and activating death receptor pathways (Fas-FasL and TRAIL-DR4). **E** ICIs inhibit ICPs such as PD-L1, TIGIT, TIM-3, and CTLA-4, which tumor cells use to exhaust T cells and avoid detection. By inhibiting these immune checkpoints, T cells can recognize and attack tumor cells. GM-CSF, granulocyte–macrophage colony–stimulating factor; GVAX: GM-CSF-transduced tumor cell vaccines; DC: dendritic cell; TAA: tumor-associated antigen; LAA: leukemia-associated antigen; MHC: major histocompatibility complex; CAR: chimeric antigen receptor; FasL: Fas ligand; TRAIL: Tumor necrosis factor (TNF)-related apoptosis-inducing ligand; DR: death receptor; ICIs: Immune checkpoint inhibitors; ICPs: immune checkpoint proteins; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; TIM-3: T cell Ig- and mucin-domain-containing molecule-3; TIGIT: T cell immunoreceptor with immunoglobulin and ITIM domain; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4

latest data from this ongoing study indicate that treatment with NKX101 led to an optimal complete remission (CR) rate of 67% in patients (NCT04623944).

Immune checkpoint inhibitors

Dysregulation of immune checkpoints, such as PD-1/PD-L1, TIM-3, CD47/SIRPα, CTLA-4, and TIGIT, plays a critical role in immune evasion by tumor cells. Blocking these checkpoints is a promising therapeutic strategy in MDS (Fig. 3E). Immune checkpoint inhibitors are monoclonal antibodies designed to disrupt the interaction between immune inhibitory receptors and their ligands, thereby reactivating immune responses against tumor cells [121, 269]. Notably, recent clinical trials have begun to investigate the potential of these inhibitors in MDS, such as the phase I trial exploring nivolumab (PD-1 inhibitor) combined with the IL-6 inhibitor tocilizumab for patients with relapsed MDS after allogeneic transplantation. Although this trial was terminated, it underscores the ongoing exploration of immune checkpoint inhibition as a treatment option for MDS. Additionally, the 2023 phase III STIMULUS-MDS2 trial (NCT04812548) demonstrated that sabatolimab, an anti-TIM-3 antibody, combined with azacitidine, significantly

improves survival in higher-risk MDS patients [271]. A randomized phase II trial of durvalumab (PD-L1 inhibitor) combined with azacitidine as first-line therapy for high-risk MDS revealed feasibility, but with greater toxicity and no significant improvement compared to azacitidine alone [272].

Cell-derived EVs have characteristics that make them suitable for the treatment of different malignancies, such as low immunogenicity, high stability, and low toxicity [273]. Additionally, the use of EVs derived from CAR-T cells is being investigated for the treatment of solid tumors and hematologic malignancies to reduce the risk of uncontrollable cytokine storms associated with CAR-T-cell therapy [274]. Nevertheless, very few studies have investigated the use of EVs as a treatment for hematologic malignancies, particularly MDS. Although targeting miRNA cargo in EVs, which is critical in MDS pathogenesis, may offer hope for future therapeutic interventions in leukemia [275]. For example, since elevated levels of miR-21 in MDS decrease the expression of SMAD7, a negative regulator of TGF-β receptor I kinase (TGFBR1), the suppression of miR-21 with a chemically modified inhibitor prevents TGF-β pathway activation, leading to improved erythropoiesis and increased hematocrit levels in patients with MDS [276]. An effective method of inhibiting aberrantly expressed miRNAs involves the use of other nucleic acid analogs, such as locked nucleic acids (LNAs), peptide nucleic acids, and anti-miRNAs [277].

Potential diagnostic and prognostic biomarkers in MDS

Considering the heterogeneity of MDS clinical manifestations, it is essential to establish accurate diagnostic and prognostic indicators. To predict the outcomes of patients with MDS, several prognostic scoring systems have been developed, including the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R). Moreover, the WHO classification-based Prognostic Scoring System (WPSS) and IPSS-Molecular (IPSS-M) are used, although not as frequently as IPSS and IPSS-R [295]. The IPSS-R stratifies MDS patients into risk categories (very low, low, intermediate, high, and very high) based on prognostic factors such as cytogenetics, BM blast%, and hemoglobin levels. It serves as a critical tool for guiding treatment decisions, ranging from supportive care to stem cell transplantation, based on the patient's individual risk profile [296]. It has also been suggested that the analysis of inflammatory biomarkers such as ASC specks and S100A8/S100A9 might be valuable in patients with MDS; however, further validation of their diagnostic and prognostic potential is needed [226, 297]. In addition, TNF-α and IL-2 levels are associated with MDS progression, as are IL-6 and IL-1β levels with time to the first blood transfusion [297, 298]. IL-4 levels at the time of diagnosis have been shown to be indicators of poor prognosis in MDS patients. Importantly, the serum IL-4 level was an independent risk factor for low-risk and medium- to high-risk patients according to IPSS and medium- to high-risk patients according to IPSS-R scoring systems [299]. Additionally, there is evidence that a higher concentration of TNF-α has a negative prognostic effect on MDS, as it is associated with lower hemoglobin levels and higher levels of leukocytes, creatinine, and β2-microglobulin [229]. MDS/AML patients with high levels of IL8 receptor CXCR2 reportedly have poor prognoses [235]. In this context, some investigators have used MDS cytokine profiles to assess patient prognosis, but owing to the heterogeneity and varying characteristics of MDS subtypes, their reliability has not been proven [197].

Since EVs can be considered a liquid biopsy source in hematologic malignancies without the need for BM aspiration, they are helpful for monitoring disease progression. In patients with high-risk MDS, EVs carrying CD13 (EV-CD13) are found at higher concentrations than in patients with low-risk MDS, suggesting that EV-CD13 may be a reliable indicator of MDS progression [142]. Hrustincova et al. reported that miR-1237-3p and miR-548av-5p in EVs were significantly correlated with poor OS in MDS patients [300]. In another study, a specific miRNA signature was identified in serum EVs from MDS patients. Compared with healthy controls, MDS patients presented decreased expression of miR-16, miR-17, miR-20a, miR-21, miR-126, miR-146a, miR-155, and miR-181a, suggesting their potential as reliable biomarkers for the progression of MDS [301].

Conclusion

MDS represents a complex and heterogeneous group of disorders, with current treatment strategies primarily focused on symptom management. HSCT remains the only potentially curative therapy, though its use is limited by patient eligibility. Advancing treatment requires a deeper exploration of the disease's pathophysiology, biology, and underlying causes. Research in this area is progressing rapidly, with ongoing studies offering promising new therapeutic strategies and a more thorough understanding of the disease. Recent technological breakthroughs have significantly expanded our knowledge of the BMM in MDS, revealing the complex interactions between stromal, hematopoietic, and malignant cells. These interactions contribute to the disruption of hematopoiesis and immune function, positioning immune modulation—through cytokine inhibitors, immune checkpoint blockade, and T cell regulation—as a promising approach to enhance patient outcomes. Notably,

inflammation is a hallmark of both high-risk and especially low-risk MDS, with distinct cytokine signatures and immune dysregulation patterns characterizing each, highlighting the intricate crosstalk between inflammatory pathways and disease progression. EVs play a key role in MDS progression, transferring miRNAs and other bioactive molecules that influence disease progression and support malignant cell growth by reprogramming stromal cells. While EVs show potential as both biomarkers and therapeutic targets, their clinical use is constrained by their complexity and heterogeneity. The impairment of hematopoiesis and immune function in MDS is closely associated with disturbances in the BMM. Gaining further insight into these altered BMM interactions could lead to novel therapeutic approaches aimed at restoring healthy hematopoiesis. However, the development of targeted therapies for MDS faces significant challenges, including genetic heterogeneity and limitations of current preclinical models, underscoring the need for more comprehensive studies to overcome these obstacles. In conclusion, this review emphasizes the critical role of immune dysfunction and the aberrant BMM in MDS pathogenesis, with continued research into these mechanisms offering substantial potential for developing more effective and individualized treatments for MDS patients.

Abbreviations

MDS	Myelodysplastic neoplasms
MPN	Myeloproliferative neoplasm
MM	Multiple myeloma
AML	Acute myeloid leukemia
AML/MRC	Acute myeloid leukemia/myelodysplasia-related changes
HSPC	Hematopoietic stem and progenitor cell
BM	Bone marrow
BMM	Bone marrow microenvironment
CH	Clonal hematopoiesis
CHIP	Clonal hematopoiesis of indeterminate potential
ICUS	Idiopathic cytopenia of uncertain significance
CCUS	Clonal cytopenia of undetermined significance
IDUS	Idiopathic dysplasia of unknown significance
EV	Extracellular vesicle
MSC	Mesenchymal stromal cell
NGS	Next-generation sequencing
GM-CSF	Granulocyte–macrophage colony-stimulating factor
LSC	Leukemic stem cell
MDSC	Myeloid-derived suppressor cell
DC	Dendritic cell
MoDC	Monocyte-derived dendritic cell
DAMP	Damage-associated molecular pattern
PRR	Pattern recognition receptor
OS	Overall survival
AD	Autoimmune disorder
VEXAS	Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic
ESA	Erythropoiesis-stimulating agent
FDA	Food and drug administration
ICSS	Immune cell scoring system
IPSS	International prognostic scoring system
IPSS-R	Revised IPSS
IPSS-M	IPSS-molecular
WHO	World Health Organization
WPSS	WHO classification-based prognostic scoring system

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