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Review

Immune dysregulation and potential targeted therapy in myelodysplastic syndrome

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***Abstract*:** Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematological diseases and a high risk for transformation to acute myeloid leukemia (AML). The identification of key genetic alterations in MDS has enhanced our understanding of the pathogenesis and evolution. In recent years, it has been found that both innate and adaptive immune signaling are activated in the hematopoietic niche of MDS with aberrant cytokine secretion in the bone marrow microenvironment. It is also clear that immune dysregulation plays an important role in the occurrence and progression of MDS, especially the destruction of the bone marrow microenvironment, including hematopoiesis and stromal components. The purpose of this review is to explore the role of immune cells, the immune microenvironment, and cytokines in the pathogenesis of MDS. Insights into the mechanisms of these variants may facilitate the development of novel effective treatments to prevent disease progression.

Keywords: cytokine, immunity, microenvironment, myelodysplastic syndrome, T-cell

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Introduction

Myelodysplastic syndromes (MDS) are clonal stem cell disorders, characterized by inefficient hematopoiesis, morphologic dysplasia, and variable degrees of cytopenias.[1] Demethylation abnormality is one of the key mechanisms of MDS. It has been gradually recognized that in addition to epigenetic abnormalities, immune dysregulation also plays a key role in the development and progression of MDS. Many studies have elucidated that improper activation of the immune system is an important factor in the pathogenesis of MDS,[2] whereas the escape of mutated hematopoietic cells from immune surveillance may play a separate role in the biology of high-risk MDS and progression to acute myeloid leukemia (AML). MDS and aplastic anemia (AA) are categorized as bone marrow (BM) failure syndromes and possess several common features including immune mechanisms, partly certain clinical and laboratory features, although the impaired cell lineages and mutational abnormalities differ. AA is mainly caused by T lymphocyte-mediated autoimmune attack on hematopoietic stem and progenitor cells,[3] while MDS progresses due to serial acquisition of somatic variants, and the improper activation of the immune system is an important factor in the pathogenesis of MDS, whereas escape of mutated hematopoietic cells from immune surveillance may play a separate role in the biology of high-risk MDS and progression to AML.[4] Immunosuppressive therapy (IST) is one of the important treatment options for low-risk MDS (LR-MDS) and most AA patients.[5] Underlying clinical manifestations of MDS result from both the proliferation and aberrant differentiation of mutated malignant hematopoietic stem cells (HSCs) and their progeny, along with cloned MDS cells that replace normal BM. It is ultimately the interaction between these two groups of cells that determine the course of MDS. At present, there is accumulating evidence suggesting that the progress and/or amplification of malignant clones is highly associated with immune

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dysregulation in the tumor microenvironment, resulting in MDS cells evading immunosurveillance.[6,7] Immune cell dysfunction, aberrant cytokine production, and stromal cell destruction are the three core aspects of immune microenvironment dysfunction and are also central to the development and progression of MDS. Concurrently, the occurrence and progression of MDS is also known to be affected by the alteration of the immune checkpoint pathway, PD-1/PD-L1 or antigen presentation.[8–10]

In addition, stromal cells in the BM microenvironment play a fundamental role in disease progression through multiple mechanisms. Interactions between multiple endogenous and clonal cell populations disrupt immune surveillance and promote the progression of MDS. To date, very few reviews have explored these interactions; therefore, this review was focused on reporting the latest updates on the effects and interactions of dysregulated immune cells, stromal cells, and cytokines in the pathogenesis and progression of MDS. We also discuss several different classes of immunotherapeutic approaches, including the targeting of T-cells, direct inhibition of inflammatory cytokines, repurposing cytotoxic cells, and adoptive cell therapy, to better understand the development of new approaches for MDS treatment.

Immune cells

In MDS, immune cells in the BM microenvironment are altered, specifically T-cells, natural killer (NK) cells, macrophages, myeloid-derived suppressor cells (MDSCs), and B-cells. Many studies strongly indicate that alterations in the numbers and functions of these immune cells are associated with MDS progression, Therefore, understanding their mechanisms of dysfunction is critical in the development of new targeted therapies for MDS.

T-cells

The dysfunction of T-cells plays an essential role in apoptosis in low-risk MDS.[11] A study has shown that the hypomethylating agent (HMA), azacitidine, enhances T-cell response to cancer-testis antigens by inducing the upregulation of cancer-testis antigens, which is a fundamental part of tumor surveillance.[12] In contrast, clinical trials have demonstrated that a similar or lower risk of progression to AML occurs after IST.[5] Through a variety of mechanisms including dysfunction of T-cells and cytokine expression, and changes in BM stromal, MDS tumor cells are able to escape tumor surveillance. Programmed death 1 (PD-1) is a T-cell surface co-inhibitory receptor that binds to Programmed Death-Ligand 1/2 (PD-L1/PD-L2) to prevent immune overactivation.[13,14] After PD-1 binds to PD-L1, it destroys a series of signaling pathways downstream of the T-cell receptor (TCR), such as the PI3K/AKT, RAS-ERK1/2, and PKC signal pathways, thereby promoting apoptosis of effector T-cells and inhibiting cell proliferation and cytokine secretion[15–18] (see Figure 1). However, this protective function of the PD-1/PD-L1 signal can also maintain an immunosuppressive tumor microenvironment and promote tumor cell proliferation.[19] Kondo *et al.*[20] revealed that PD-L1 was only observed in individuals with 5% or more blasts and found that its high expression level was related to the high-risk International Prognostic Score System for Myelodysplastic Syndrome (IPSS) category in MDS.

$CD8^+$ T-cells

In vitro studies have shown that T-cells play a role in inhibiting the growth of malignant and non-malignant hematopoietic cells, and is possibly mediated by $CD8^+$ T-cells, which target MHC-class I molecules on hematopoietic precursors.[21] In MDS, $CD8^+$ T-cells have directly cytotoxic and produce cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-1Ra, CCL3, CCL4, FAS-L, and TRAIL, with distinct characteristics. $CD8^+$ T-cells have also been found to exhibit CD39 markers associated with T-cell failure. T-cells expressing CD39 may promote the inhibitory immune microenvironment in sAML by inhibiting T-cell activation.[22,23]

Regulatory T-cells

Regulatory T-cells (Tregs) were initially found to be the key immunomodulators of autoimmunity, maintaining self-tolerance by inhibiting autoreactive T-cells.[24] Ineffective hematopoiesis and BM failure in low-risk MDS are associated with immune disorders and autoimmunity, while high-risk MDS is characterized by clonal expansion of

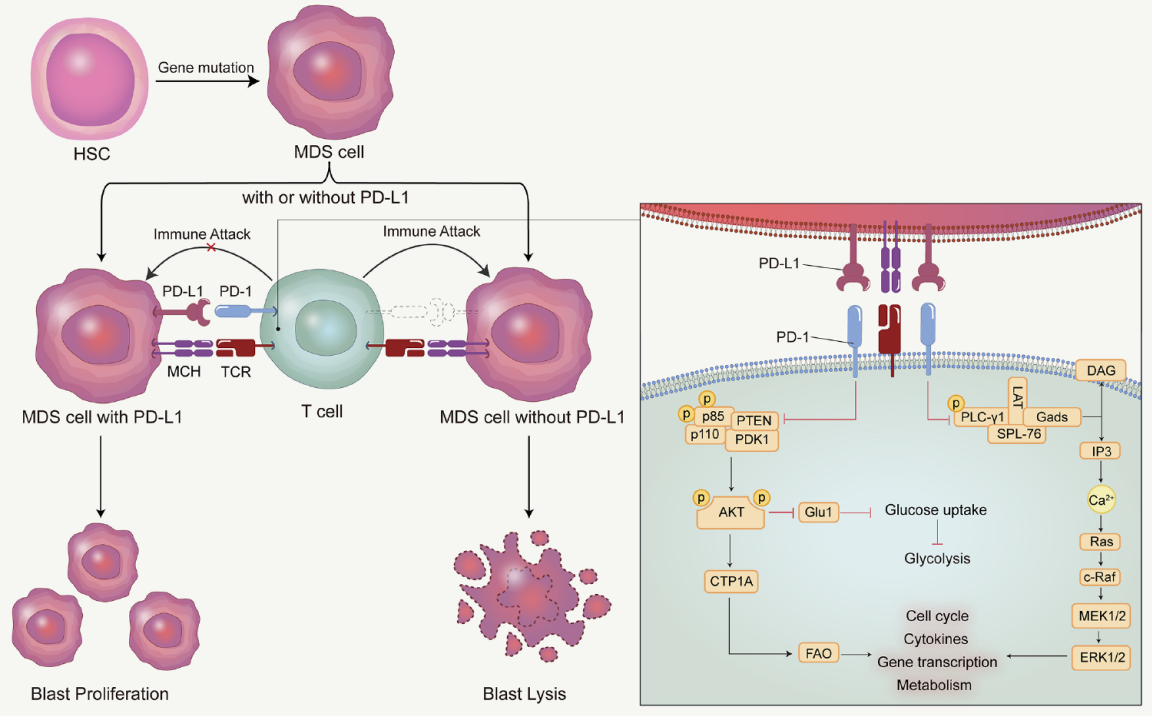

Figure 1. Schematic representation of biochemical signaling altered by T-cells and the functional implications in PD-1.
PD-1 inhibits TCR-mediated activation of the PI3K/Akt and PLCgamma-1/Ras/MEK/Erk1/2 pathways. As a consequence, T-cells are unable to progress through the S phase of the cell cycle to produce cytokines and genes responsible for the activation and differentiation programs initiated by TCR ligation. PD-1 has a major effect on the metabolic reprogramming of activated T-cells by suppressing glycolysis and promoting FAO. This altered metabolic reprogramming impacts the differentiation program of T-cells by preventing the generation of effector T cells and promoting the generation of Treg cells. It promotes the apoptosis of effector T-cells, which in turn, promotes MDS cell proliferation.
FAO, fatty acid β-oxidation; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells.

malignant tumor cells and immune escape. Tregs are dysfunctional in the early stages of MDS due to the downregulation of CXCR4, which seriously affects BM homing of Tregs through the CXCL12/CXCR4 axis.[25] Many studies have shown that effective inhibition of the local immune response can promote the selective migration of Tregs to the inflammatory site and retain them by changing the homing receptor of Tregs.[26] However, in late MDS, both systemic and local Tregs maintain function and migration ability. Studies have suggested that Treg amplification may be driven by tumor-associated antigens because Treg clones result from the uncontrolled growth of pre-leukemic clones and a large number of tumor antigens, thus tumor-specific Tregs can effectively inhibit the specific immune response of tumor-associated antigens.[27,28] The lack of Treg inhibition and dysregulated BM transport can play a fundamental role in the development of early MDS, while an increase in Treg activity can promote the progression of leukemic clones in advanced diseases. In addition, Treg subtypes may also be transformed. A study demonstrated that a subset of the high-risk MDS patients displayed a significant shift from central memory Treg cells ($Treg^{CM}$) to effector memory Treg cells ($Treg^{EM}$).[29]

NK cells

NK cells play an important role in the host's defense against malignant transformation by secreting cytokines and through their cytolytic activity.[30] Decreased numbers of NK cells have been observed in high-risk MDS patients, allowing for further clonal evolution. However, in low-risk MDS, it appears that NK cells are cytotoxic to cloned MDS precursors, thus inhibiting progression. In addition to a quantitative change, it has been observed that the expression of NK-activated receptors is significantly decreased

and NK cells with a non-cytotoxic phenotype (CD56bright) increase in MDS, which plays an immunomodulatory role in both early and late stages of the disease,[31] and provides an opportunity for the treatment of myeloid malignant tumors, including MDS.[32]

Macrophages

Macrophages may also be involved in the progression of MDS. Recent studies have shown that the increased phagocytosis of granulocyte/monocyte progenitor cells by macrophages may lead to periodic and specific loss of granulocyte/monocyte progenitor cell populations in the BM of low-risk MDS patients. This deregulated phagocytosis is thought to be controlled by the interaction between calreticulin on the surface of target cells and the low-density lipoprotein receptor-related protein (LRP1) receptor on macrophages.[33] Macrophages also mediate angiogenesis, which is elevated in high-risk MDS.[34,35] Furthermore, high-risk MDS macrophages have characteristics such as low IL-12 expression, high IL-10 expression, low tumor-killing activity, and promotion of tissue remodeling and angiogenesis, which are M2-related characteristics.[36]

Myeloid-derived suppressor cells

MDSCs are a heterogeneous population of immature myeloid cells that are recruited by chemokines and regulate immunosuppression, providing immunosuppressive signals in MDS. Previous studies have shown that MDSCs interfere with immunity by inhibiting cytotoxic T-cells,[37] and the interaction of pro-inflammatory S100A9 with CD33 promotes MDSC expansion. A study found that S100A9 and CD33 form a functional ligand/receptor pair that recruits components to CD33's immunoreceptor tyrosine-based inhibition motif (ITIM), inducing secretion of the suppressive cytokines, IL-10 and TGF-β.[38] In addition to these immunomodulatory actions, the inflammatory mediators secreted by MDSCs in MDS can directly disrupt erythropoiesis and promote disease progression.[39]

B-cells

Multiple studies have demonstrated that many patients with early MDS present with abnormalities in the B-cell progenitor compartment. A feature of early MDS may be the reduced expression of genes principally expressed in B-cell progenitors.[40] Compared with those with normal BM, MDS patients had significant levels of apoptosis in BM CD19+ cells.[41] Furthermore, the number of *B*-cells or their precursors have been found to be significantly reduced, and the frequency of pro-B ($CD34^+19^+$) cells has also been found to be significantly reduced in patients with 5q-syndrome compared with those with normal cells.[42]

The stromal microenvironment

MDS is a functional disorder of the whole BM, including hematopoietic cells and mesenchymal components. The study of BM function in patients with MDS has shown that there is a close relationship between hematopoietic cells and stromal cells.[43] Colony-forming unit (CFU-F) analysis of human BM fibroblasts has indicated that mesenchymal stem cells (MSCs) from MDS patients have reduced CFU-F counts when compared with those purified from healthy controls. Furthermore, MSCs from MDS samples did not maintain a high passage in culture when compared with healthy control samples.[44] The dicer1-deficient mouse model demonstrated that a dysfunctional stromal environment may initiate myelodysplasia.[45] Another study demonstrated that a mouse model of MDS could be more efficiently transplanted into aged recipient mice than into young recipient mice, suggesting that aged BM stroma are more favorable for the development of MDS.[39] In an MDS mouse model, an increase in the WNT/ β-catenin signal in MSCs, and the activation of β-catenin in osteoblasts derived from MSCs led to the occurrence of AML, indicating that the WNT signal from BM stroma also promote the progression of MDS.[46,47] Furthermore, some of the MSC genetic pathways (Wnt/β-catenin, Jagged-1, proinflammatory genes, miR-155) identified in mouse cancer models are also correlated with human clinical outcomes[46,48–51] Transcriptome analysis has revealed the transcriptional signature of BM stromal cells from MDS patients with cellular stress and upregulation of inflammation-associated secreted factors.[52] Thus, some aspects of MDS may be driven by MSCs, while others may be a mechanism of MDS progression and transformation to leukemia.

Production of inflammatory and aberrant cytokine

In recent years, the main pathogenic factors of MDS have been found to be malignant cloning and abnormal innate immune activation, as well as pro-inflammatory signal transduction in the BM microenvironment.[53] Toll-like receptor (TLR) signaling is involved in immune response; however, in MDS, TLRs and their downstream effectors are aberrantly activated.[54,55] Studies have shown that low-dose lipopolysaccharide (LPS) activates TLR signaling and alters hematopoiesis.[56] In addition, a study using a transgenic mouse model demonstrated that overexpression of S100A9 also induces cytopenia and dysplastic hematopoiesis.[38] Furthermore, S100A9-mediated inflammatory activation of nod-like receptor protein 3 (NLRP3) leads to a pyroptotic cell death, which is the basis of many typical features of the disease.[57] This pathway, and the accompanying release of other risk-related molecular patterns, expands MDSCs, creating a feedforward process that magnifies inflammatory body activation. In the inflammatory body family, NLRP3 is related to the pyroptosis of MDS cells. Furthermore, pyroptosis-associated gene transcripts and inflammasome assembly are profoundly upregulated in MDS.[57] Somatic gene mutations of different functional categories cause NLRP3 to share a common phenotype, including the excessive production of reactive oxygen species, proliferation induced by Wnt/β-catenin, cell swelling induced by cation flux, and caspase-1 activation. Although these findings contradict the observed competitiveness of MDS cells, the relationship between NLRP3 as drivers of MDS amplification need to be further explored.

High-Mobility Group Box 1 (HMGB 1) is a nuclear protein involved in chromatin folding, transcription, and signaling in inflammatory states. It can be passively shed by necrotic cells or actively released by mononuclear cells, further amplifying inflammation. Aberrant inflammatory signaling induces apoptosis, NLRP3 inflammasome activation, and pyroptosis of BM progenitors, which may induce anemia by interfering with hemoglobin homeostasis and EPO signaling.[58,59] Circulating HMGB1 has been found to be increased in MDS but not in other BM failure syndromes, which further suggests that HMGB1 is involved in the immune pathogenesis of MDS.[60] Inhibitors of HMGB1 and neutrophil elastase have been used in combination with azacitidine to reduce the expansion of abnormal (but unhealthy) MDS CFU *in vitro*. Inhibition of HMGB1 has also been shown to reduce the expression of TLR and NF-κB in LR-MDS cells;[61] therefore, it may be a therapeutic target for MDS. Recent studies have shown that aspirin may play a role in reducing inflammation by inhibiting the activity of HMGB1.[62,63] Thus, the possible beneficial effects of aspirin in reducing inflammation in MDS are worth exploring.

Abnormal cytokines play a complex and important role in immune dysregulation in MDS.[64,65] In BM samples from patients with MDS, the levels of many cytokines and growth factors were found to be abnormal.[66] Furthermore, in the BM and serum of MDS patients, elevated levels of TNF-α in particular were associated with multiple effects such as increased apoptosis, an increased number of BM cells, suppression of hematopoiesis, and activation of downstream signaling pathways and transcription factors.[67–70] Cytokines play vital roles in regulating cell-cell interactions, and the behavior and functions of immune cells are also regulated by the interplay with cytokines. For example, T-helper 17 (Th17) T-lymphocytes act by producing IL-17, which is a cytokine that in turn, activates macrophages and DCs to produce additional pro-inflammatory cytokines. Studies have shown that IL-17 levels are elevated in low-risk MDS, and may play a role in the induction of apoptosis.

Inflammation and immune dysregulation are crucial in the initiation and progression of MDS. MDS and chronic myelomonocytic leukemia (CMML) are frequently associated with autoimmune disorders (ADs) and inflammatory responses of the immune system.[71] The development of AD in the context of cytopenia should be considered in association with MDS, especially in elderly patients. In addition, cytopenias appear to be the result of complex autoreactive immune activity in some patients with MDS and may respond to IST. The increased release of inflammatory cytokines, such as TNF-α and interferons, triggers apoptosis of BM precursor cells, leading to cytopenia.[72] Impaired function of immune cells, including cytotoxic Treg, Th17, and NK cells, is also predictive of the IST response, and AD outcome and occurrence. Vacuolated, E1 enzyme, X-linked

autoinflammatory, somatic mutation of UBA1 (VEXAS) syndrome is a newly described episodic inflammatory syndrome in adults that overlaps with MDS and AD.[73] Mutations result in the loss of the canonical cytoplasmic isoform of UBA1, reduced ubiquitination, and activation of innate immune pathways and systemic inflammation. A previous study demonstrated that anti-inflammatory drugs did not improve VEXAS syndrome in any of the study subjects; however, all subjects were high-dose glucocorticoid dependent.[74] Recently, a study involving 11 MDS patients with confirmed VEXAS syndrome reported a 46% response rate to azacitidine treatment.[75] Of note, clonal T-cell large granular lymphocyte (T-LGL) proliferation associated with MDS was not uncommon. In a larger study, Huh *et al.*[76] described nine patients who had both MDS and T-LGL, and proposed an etiologic relationship between the two, rather than simple coincidence. A study comparing MDS patients with and without T-LGL proliferation found that T-LGL proliferation in patients with MDS may be associated with BM cytopenia and lineage hypoplasia. Moreover, autoreactive T-cells may inhibit hematopoietic function and lead to cytopenia in T-LGL and some MDS patients, which may lead to the occurrence of T-LGL/MDS.[77] IST may be beneficial for the elimination of T-LGL cells in MDS patients with T-LGL proliferation.[78]

Therapeutic targeting of the immune system in MDS

MDS is highly heterogeneous, which presents unique challenges in developing novel treatments. Correcting the immune microenvironment alone is not enough to treat MDS, thus immunotherapy in combination with other drugs may be necessary to ultimately halt disease progression. Since the immune characteristics of different stages of MDS are not the same, several trials have investigated the potential effects of immune regulation in low- and high-risk MDS patients, which will be briefly reviewed in Table 1.

Immunosuppressive treatment

Therapies targeting T-cells, anti-thymocyte globulin (ATG), and cyclosporine (CSA) have been found to be effective in some MDS patients, especially those with dysplasia.[79–81] Studies have shown that response rates vary widely between the two treatments and that combination therapy is not superior to monotherapy.[82,83] In a phase II study, 25 patients with transfusion-dependent MDS were treated with a single course of ATG, which resulted in hematopoietic recovery in some of the patients, especially those with refractory anemia, and was well-tolerated.[84] In addition, the results of a single-center study of immunosuppressive treatment with ATG and CSA demonstrated similar response rates to other standard treatments in early MDS, but poor responses to IST in patients with late MDS.[85] A large, multicenter international cohort retrospectively examined 207 patients with MDS receiving IST, and reported an overall response rate (ORR) of 48.8% and suggested that the preferred IST regimen to be used in patients' hypocellular BMs was horse ATG in combination with CSA.[5] An open-label randomized phase III trial also demonstrated that ATG and CSA treatment was associated with a hematologic response and had no apparent impact on TFS and OS, where dysplastic MDS had a higher ORR of 50%.[86] Several studies have also demonstrated that treatment with IST significantly favored survival,[87] with conflicting results reported. Immunosuppressive drugs are still controversial in MDS. The relevance of IST for MDS depends on whether the BM failure of a particular subtype has an autoimmune component. Some studies have indicated that it may benefit certain MDS patients with specific characteristics: dysplasia, HLA-DR15, trisomy 8 syndrome, young (<60 years), absence of somatic mutations, and low transfusion burden.[5,88]

Direct inhibition of inflammatory cytokines

Anti-TNF-α therapy is one of the main strategies used in early MDS to target abnormal cytokine levels.[89] Some studies on etanercept and infliximab demonstrated early activity; however, a phase II trial also demonstrated low activity and low response.[89,90] Studies on combinations with other medicines have also been underwhelming. Etanercept in combination with azacitidine, which is a DNA methyltransferase inhibitor (DNMTi), resulted in an overall response rate of 72% after 3 months; however, the criteria used to assess the response in this study were critical to those of azacytidine alone.[91] Unfortunately, TNF-α inhibitors have not been as successful as expected and are not currently used as a standard treatment for MDS. As an important cytokine

Table 1. Selected ongoing trials of immune therapeutic in myelodysplastic syndrome.

Therapy	Impact on MDS development and progression	Therapy	NCT	Phase	Condition or disease	Study Population	Outcomes
Inhibition of NLRP3	Improves hematopoietic failure, suppresses pyroptosis	Ibrutinib and Azacitidine	NCT02553941	I	CML/*de novo* MDS; previously treated MDS/refractory anemia with excess blasts in transformation/ secondary MDS/	21	43% ORR
		CG-806	NCT04477291	I	AML/MDS	80	NA
Antibody against IL-8	Promotes the differentiation of $CD34^+$ erythrocytes in MDS bone marrow	BMS-986253	NCT05148234	I/II	MDS	NA	NA
TLR2 inhibitory antibody	Suppresses pyroptosis	OPN-305	NCT02363491	I/II	Low and intermediate-1 risk MDS	22	50% ORR
Monoclonal antibody to PD-1	Inhibits the production of growth factors and cell proliferation, and restores the immune killing function of T cells	Pembrolizumab and entinostat	NCT02936752	I	Patients with MDS who are not responding to hypomethylating agents	27	NA
		Pembrolizumab	NCT01953692	I	R/R hematologic malignancies	28	4% ORR; The mOS was 23 weeks
		Nivolumab and Ipilimumab with or without Azacitidine	NCT02530463	II	MDS	26	36% ORR in HMA-failure cohort; 67% ORR in frontline cohort; In HMA-failure cohort, mOS was 11.4 months; In frontline cohort, mOS was 12 months
		Azacitidine and Pembrolizumab	NCT03094637	II	High-risk MDS/ Intermediate-1 MDS	37	76% ORR and 18% CR (in the 17 previously untreated patients, cohort 1); 25% ORR and 5% CR (in the 20 HMA-failure patients, cohort 2); mOS not reached (cohort 1), and mOS was 5.8 months (cohort 2)
Monoclonal antibody to CD33	Induces MDS cell death	GO and liposome-encapsulated Daunorubicin–Cytarabine	NCT03672539	II	R/R AML and post-HMA failure HR-MDS	24	55% ORR; The mOS was 5 months
Macrophag-e immune checkpoint inhibitor that targets CD47	Phagocytosis and elimination of tumor cells	Magrolimab with or without Azacitidine	NCT04313881	III	Higher-risk MDS	520	NA
		Magrolimab with Azacitidine	NCT03248479	I	AML/MDS	43	The objective response rate was 74.7%

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CR, complete response; GO, gemtuzumab ozogamicin; HMA, hypomethylating agent; IL, interleukin; mCR, marrow complete response; MDS, myelodysplastic syndromes; MDS-RS, MDS with ring-sideroblastic; mOS, median overall survival; NLRP3, nod-like receptor protein 3; ORR, overall response rate; PD-1, programmed death 1; TLR, toll-like receptor.

involved in the pathogenesis of MDS, IL-6 has also been used in the treatment of MDS, but the results have also been poor. A double-blind, phase II study assessed siltuximab, a chimeric anti-IL-6 monoclonal antibody, but this was terminated early due to a lack of efficacy in reducing red blood cell (RBC) transfusions.[92] However, newer strategies to target cytokine signaling still have some therapeutic potential. Luspatercept, a recombinant fusion protein that exhibited promising results in a phase II study, is able to bind transforming growth factor beta superfamily ligands to reduce SMAD2 and SMAD3 signaling and improves erythropoiesis. A placebo-controlled, double-blind, phase III trial on luspatercept in MDS demonstrated a transfusion independence in 38% patients over 8 weeks or longer.

Repurposing cytotoxic cells

The role of the cytotoxic immune response to target transformed cells in myeloid malignancies, including stimulating the endogenous system and reengineering lymphoid-derived cells to target the mutant cells, is currently unclear. With the successful use of immune checkpoint inhibitors in the clinical treatment of solid tumors,[93,94] the concept of immune checkpoint blockade therapy has been applied to hematological tumors.[95,96] Blocking immune checkpoints may be an effective and reasonable strategy in treating late MDS, including inhibiting the role of the PD-1/PD-L1 pathway in immune escape and cytotoxic T-cell failure in MDS.[97,98] Pembrolizumab (MK-3475) is a humanized monoclonal antibody that can block the interaction between PD-1 and its PD-L1 ligand. In 28 MDS patients who exhibited failed responses to HMA, the ORR of pembrolizumab monotherapy was only 4% and the OS rate was 49% after 24 weeks.[99] The reason for the contradiction between preclinical studies and clinical trials is still unclear; however, the dynamic changes in the BM immune microenvironment may be the key. Another phase II trial assessed the synergistic effects of pembrolizumab and AZA in 37 MDS patients with IPSS intermediate-1 or higher-risk disease. The ORRs were 76% in the HMA-untreated cohort ($n = 17$) and 25% in the HMA-failure cohort ($n = 20$), with a CR of 18% and 5%, respectively. Furthermore, the median overall survival (mOS) was not reached after a median follow-up of 12.8 months in the HMA-untreated cohort and 5.8 months in the HMA-failure cohort.[100] These results show that HMAs and PD-1/PD-L1 inhibitors have a potentially synergistic effect, but there are still obvious challenges in the treatment of MDS based on PD-1/PD-L1 inhibitors.

Adoptive cell therapy

Engineered NK cell cytotoxicity for the treatment of dysplastic clones is a new therapeutic approach and has exhibited some positive effects in AML and late MDS.[101,102] A trial on NK-cell therapy demonstrated that high-risk MDS patients responded to treatment, which supports the use of haploidentical NK-cell infusions as a bridge therapy for HSCT in refractory patients.[102] A phase II randomized trial in high-risk AML and MDS patients after haploidentical HCT also demonstrated the benefits of NK-cell therapy after haploidentical HCT in reducing disease progression.[103] Following the successful treatment of lymphoma, several trials have evaluated the role of chimeric CAR (chimeric antigen receptor)-T cells in MDS and other advanced myeloid neoplasms. CAR-T cells need to have a certain degree of specificity for malignant cells to ensure that there are healthy progenitors to repopulate the BM in time to avoid complications. Several CAR products have been developed and target CD123, which delineates high-risk MDS stem cells derived from normal progenitor cells.[104] A first-in-human phase I study (NCT02159495), which included 40 participants, examined the antitumor activity and safety of MB-102 (CD123-targeted CAR-T cell) and demonstrated complete responses in people with AML and BPDCN without dose-limiting toxicities. Treatment with CD33-targeted CAR-T cell therapy demonstrated that the CAR-T cell infusion caused severe toxic side effects in one patient, including aggravation of pancytopenia and an increase in serum cytokine levels. The patient's BM blasts were significantly reduced after 2 weeks of CAR-T cell therapy. However, 9 weeks later, significant disease progression resumed.[105] There have also been evaluations of combinatorial targets such as CD123–CD33 cCAR-T cells (NCT04156256), CLL1–CD33 (NCT03795779), or CD33–IL15 constructs (NCT03927261). Another study on CAR-T cells that had been engineered to recognize NKG2D-ligands did not yield significant clinical activity in AML and MM.[106] In addition, a phase I trial on anti-NKG2D CAR–T cells,

Table 2. Selected clinical trials of CAR-NK/T cells in myelodysplastic syndrome.

Therapy	Target	Condition or disease	Phase	Status	NCT
CAR-NK cell	CAR.70/IL15-transduced CB-NK cells	B-cell lymphoma/MDS/AML	I	Recruiting	NCT05092451
CAR-T cell	CD123	BPDCN;	I/II	Recruiting	NCT04109482
		AML/ALL/BPDCN/MDS	I	Recruiting	NCT04318678
		AML/MDS	I	Recruiting	NCT05457010
	CD33	Myeloid leukemia/AML	I	Unknown	NCT01864902
		Myeloid malignancies	I/II	Unknown	NCT02958397
	CD33-IL15 constructs	AML/MDS	I	Completed	NCT03927261
	NKG2D-ligand	AML/MDS;	I	Recruiting	NCT04167696
		AML/MDS/MM	I	Completed	NCT02203825
	CD123-CD33	Hematologic malignancy/ AML/MDS/ MPN/CML;	Early phase I	Unknown	NCT04156256
	CLL1-CD33	Hematologic malignancy/ AML/MDS/ MPN/CML	Early phase I	Recruiting	NCT03795779

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CAR-NK, chimeric antigen receptor-natural killer; CAR-T, chimeric antigen receptor-T; CML, chronic myeloid leukemia; IL, interleukin; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasm.

which are commonly found on MDS clones, is currently underway (NCT04167696). One of the major challenges associated with current CAR-T cell therapies is the lack of a specific antigen. Many tumor-associated antigens are expressed on normal myeloid cells, which exert myeloablative effects on non-MDS target cells. We briefly reported some CAR-NK/T cells therapies that are currently under investigation in Table 2.

Conclusion and future prospective

Immune cells, inflammatory signals producing abnormal cytokines, and the stromal microenvironment are important contributors to the disease phenotype and clinical manifestations of myelodysplastic syndrome. Figure 2 depicts the possible mechanisms of these factors. As the use of multi-omics approaches in the BM microenvironment, further the mechanisms for MDS pathogenesis will be elucidated in more detailed. The mutation and clinical heterogeneity of MDS is a challenge when it comes to successfully treating MDS. Improving the hematopoietic microenvironment may promote the recovery of hematopoiesis and inhibit disease progression in some patients. Therefore, it is necessary to understand the changes in inflammation and microenvironment in the different disease stages in order to construct targeted therapy, combat the pro-inflammatory environment of the disease, and ultimately stop disease progression. Concurrently, given the complexity of the disease, a combination of treatments may be needed. Significant efforts have been made to find ways for the therapeutic to immune system, both the activation of quiescent immune effector cells and the amelioration of an aberrant inflammatory microenvironment. Additional work on predictive indicators that can be used to evaluate the response to immunotherapy, including CAR-T, is also greatly warranted.

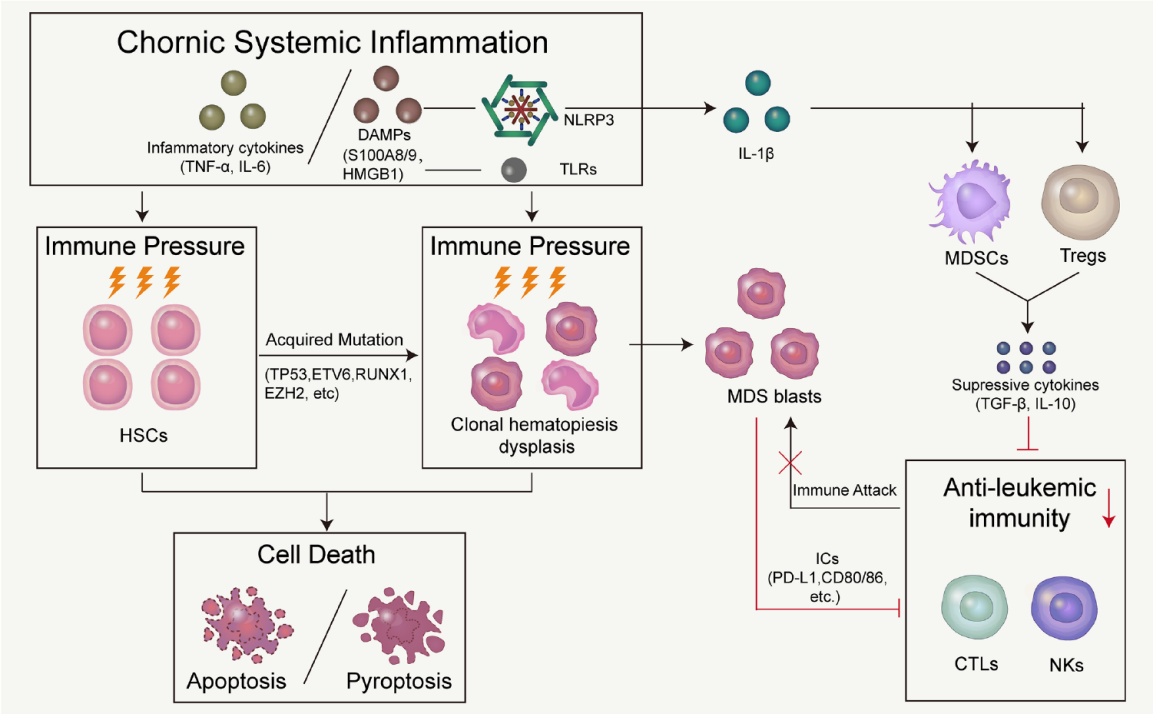

Figure 2. Overview of immune dysregulation in MDS.
Immune dysregulation in MDS proceeds as a vicious cycle, disrupts immune function, and alters the BM microenvironment, thus contributing to disease initiation and progression. Chronic or unresolved inflammation, which is mediated in large part by secreted factors, induces cell death and activate innate immune signaling. Furthermore, the s100A9-mediated nod-like Receptor protein 3 (NLRP3) inflammasome is also activated, resulting in pyroptosis. The release of the NLRP3 pathway and other associated danger-associated molecular patterns extend MDSCs. Extended MDSCs cooperate with Tregs, which subsequently release suppressive cytokines and inhibit the NK and CTL killing effect, inhibiting the anti-leukemia effect, and leading to MDS blast and leukemic evolution.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Xiaoying Zhang: Conceptualization; Investigation; Writing – original draft.

Xingcheng Yang: Investigation; Writing – original draft.

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Yicheng Zhang: Conceptualization; Methodology; Project administration; Writing – review & editing.

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Availability of data and materials

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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