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Disordered Immune Regulation and its Therapeutic Targeting in Myelodysplastic Syndromes

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Abstract

Purpose of Review: Immune dysregulation is a defining feature of myelodysplastic syndromes (MDS). Recently, several studies have further defined the complex role of immune alterations within MDS. Herein we will summarize some of these findings and discuss the therapeutic strategies currently in development.

Recent Findings: Immune alterations in MDS are complex, heterogeneous and intertwined with clonal hematopoiesis and stromal cell dysfunction. Inflammation in MDS proceeds as a vicious cycle, mediated in large part by secreted factors, which induce cell death and activate innate immune signaling. Therapeutic targeting of this variable immune dysregulation has led to modest responses thus far, but incorporation of the growing repertoire of immunotherapy brings new potential for improved outcomes.

Summary: The immune milieu is variable across the spectrum of MDS subtypes, with a changing balance of inflammatory and suppressive cellular forces from low to high risk disease.

Keywords

myelodysplastic syndromes; inflammation; immune dysregulation; bone marrow microenvironment; immunotherapy

Introduction

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal bone marrow neoplasms defined by hematopoietic dysplasia, cytopenias, and a variable risk of transformation into secondary acute myeloid leukemia (AML). An diagnosis of MDS is based primarily on morphological dysplasia in the bone marrow and clinically documented cytopenias that can range from indolent disease with mild anemia to aggressive disease on the verge of AML.[1] Underlying these disparate clinical presentations are the phenomena

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Human and Animal Rights and Informed Consent

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Conflict of Interest

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of clonal hematopoiesis secondary to recurrent genetic alterations and a varying degree of immune and microenvironment dysregulation. Pre-clinical and clinical studies have shown that chronic or unresolved inflammation disrupts immune function and alters the bone marrow microenvironment, thus contributing to disease initiation and progression (Figure 1).[2–6] Though this environment is complex, an improved understanding of the altered immune mechanisms in MDS pathogenesis may identify new targets and lead to novel therapeutics. This article will review the recent advances in characterization of the role of the immune system in MDS pathogenesis and outline the progress of related therapeutic strategies.

Part I: New and Established Mechanisms of Immune Dysregulation in MDS

Inflammation and cell death in MDS—Abnormal cytokine secretion patterns play a major role in immune dysregulation in MDS.[7, 8] While many cytokines and growth factors have abnormal levels in MDS, among those with the greatest impact include tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and IL- 1β. Increased levels of TNFα, in particular, have been shown in the bone marrow and serum of MDS patients and are associated with several effects, including increased apoptosis, suppression of hematopoiesis, higher bone marrow cellularity, and activation of downstream signaling pathways and transcription factors.[9–13] High levels of intramedullary apoptosis have been noted across the disease spectrum and are initiated in part secondary to TNFα exposure, which increases first apoptosis signal (Fas) receptor signaling, a canonical apoptotic pathway.[14, 15, 11, 7, 16–19] Similarly, IL-6 has also been implicated in aspects of the MDS phenotype, including induction of increased cell proliferation and hypoferremia due to increased hepcidin, which contributes to anemia.[20–22] Clinically, aberrant cytokine secretion patterns, specifically elevated levels of TNFα and IL-6, are also associated with reduced quality of life and inferior leukemia-free and overall survival.[23, 24, 12] Recently, pyroptosis, a novel mode of inflammatory cell death, has been elucidated in MDS.[25, 26] Pyroptosis proceeds from the assembly of the nucleotide-binding domain and leucine-rich repeat pyrin (NLRP) domain pattern recognition receptors, specifically NLRP3. This in turn induces cell death via a caspase-1 dependent mechanism and stimulates production of IL-iβ and IL-18. Moreover, pyroptosis and resultant ineffective hematopoiesis can be reversed with blockade of S100A9 via a high affinity decoy receptor (CD33-IgG) *in vitro*.[25]

Somatic mutations and immune disruption—Less clear in MDS is the role of commonly associated somatic mutations in creating an inflammatory milieu within the bone marrow, though evidence for mutational effects on immune disruption is growing. It was recently reported that haploinsufficiency for the gene encoding the ribosomal protein *Rps14,* which occurs in the 5q minus syndrome, a distinct subtype of MDS, leads to upregulation of the p53 pathway and subsequent erythroid differentiation blockade.[27] Moreover, this model showed this blockade was mediated by increased expression of S100A8 and S100A9, which are danger associated molecular pattern (DAMP) proteins, leading to a reversible disruption of erythropoiesis. Another group also modeled 5q minus syndrome by knocking out mDia1 and miR-146a, found on the deleted 5q.[28] This resulted in upregulation of TNFα and IL-6 as well as expansion of myeloid derived suppressor cells (MDSCs). Overall, these studies convey the impact of mutations within the myeloid clone and the consequences

for immune regulation through both cytokine upregulation and a disrupted balance of immune regulatory components. Other commonly mutated genes in MDS, including ten-eleven translocation 2 (*TET2*) and DNA methyltransferase 3a (*DNMT3a),* also disrupt immune regulation. Recent work demonstrated that macrophages bearing a *TET2* mutation display impaired resolution of inflammation and increased production of IL-6 and IL-1β as compared to wild type *TET2* macrophages.[29] In mice with selective knockout of myeloid *Tet2,* transcripts of IL-6 and IL-1β, as well as several C-X-C motif chemokines (e.g., *Cxcl1, Cxcl2, Cxcl3*) were found to be elevated in macrophages compared to those with wild type *Tet2*.[30] This finding was reported with the groundbreaking observation that clonal hematopoiesis of indeterminate potential (CHIP), previously thought to predispose patients mainly to hematologic malignancies such as MDS and AML, also significantly increased the risk of cardiac disease, which was thought, in part, to increased inflammatory activation of macrophages in the vasculature [30]. Finally, mutations in either *TET2* or *DNMT3A* lead to increased expression of arginase-1, an enzyme found in various myeloid cells including macrophages and MDSCs that catalyzes the breakdown of arginine, a required amino acid in T cell proliferation.[31, 32] Upregulation of arginase-1 within the bone marrow appears to mimic the bone marrow microenvironment found in low risk MDS with increased inflammatory response and proliferation.

Toll-like and IL-1 Receptor Signaling in MDS—Toll-like receptor (TLR) signaling is normally involved in the immune response to foreign pathogens, however, in MDS, TLRs and their downstream effectors are aberrantly activated.[33–35] Mouse studies have demonstrated that activation of TLR signaling with low dose lipopolysaccharide (LPS) alters hematopoiesis by increasing numbers of hematopoietic stem cells (HSCs) and myeloid skewing.[36] Overexpression of a TLR4 ligand, S100A9, in a transgenic model also induced phenotypic characteristics of MDS, including cytopenias and dysplastic hematopoiesis.[37] A study of TNFα receptor-associated factor 6 (TRAF6), a downstream effector of TLR signaling, demonstrated that overexpression impairs hematopoiesis via ubiquitination of RNA splicing factors in MDS. Dysregulation of splicing led to Cdc42 activation and subsequent hematopoietic defects.[38] Moreover, *ex vivo* inhibition of TLR4 signaling in primary MDS monocytes resulted in decreased production of IL-1β, IL-6 and TNFα, indicating the importance and therapeutic potential of this pathway.[35]

IL-1 receptor (IL-1R) activation also plays a critical role in innate immune dysfunction in MDS. Stimulation of TLR and IL-1R resulted in downstream activation of IL-1 receptor associated kinase 1 (IRAK1), which bound to TRAF6 and led to activation of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), a critical transcription factor for pro-survival, pro-inflammatory and anti-apoptotic target genes.[39–41] Small molecule inhibition of IRAK1 resulted in impaired cell growth and increased apoptosis of MDS-like cells, while having a minimal effect on healthy $CD34^+$ cells.[41] In another study, transcriptional analysis of high risk MDS and AML samples identified increased transcription of IL-1 receptor associated protein (IL1RAP), a necessary part of the IL-1R signaling complex, when compared to normal controls. In another context, inactivation of TNF and IL-1β signaling sensitized leukemia stem cells to NFκB inhibition both *in vivo* and *in* wtro.[42] Oncogenic signaling and leukemic proliferation downstream of IL-1R has also

been demonstrated as a key regulator of leukemic cell expansion and progression in AML.[43] This was further shown to be attenuated by downstream inhibition of p38 mitogen associated protein kinase (p38MAPK, or p38). This pathway likely has implications for high risk MDS and leukemic progression. Indeed, p38 has been long proposed as a potential target in MDS and current trials are underway (Table 1 and discussed below). TLR and IL-1R hyperactivation ultimately result in downstream activation of signals, such as NFκB, that increase secretion of inflammatory cytokines, disrupt hematopoiesis, and cause leukemic expansion. Further elucidation of the signaling cross talk within these pathways and therapeutic potential should continue to be developed.

Immune Landscape from Low Risk to High Risk MDS—The immune disruption present in MDS also affects cell types outside of the myeloid compartment and these effects vary from low to high risk disease. Patients with low risk MDS harbored increased numbers of Th17 cells, cells which have also been strongly associated with autoimmunity.[44] Elevation in the numbers of Th17 in low risk MDS was also associated with increased levels of cytotoxic T cells and pro-inflammatory cytokines; however, in high risk MDS, Th17 cells declined while levels of inhibitory cytokines, such as IL-10 and soluble IL-2R, increased.

The role and abundance of immune suppressor cells differs greatly across the disease spectrum. Several reports have demonstrated that higher risk disease is accompanied by an increase in MDSCs (MDSCs).[2, 45, 37, 13] MDSCs and their effects were functionally important in the pathogenesis of MDS in a transgenic model.[37] Overexpression of the DAMP, S100A9, in this model resulted in accumulation of bone marrow MDSCs and CD33-dependent IL-10 and TGFβ secretion. Furthermore, disruption of MDSC function via either blockade of the CD33:S100A9 interaction or forced maturation of MDSCs with all-trans retinoic acid (ATRA) resulted in rescue of hematopoiesis.[37] MDSCs were shown to be distinct from the MDS clone via sorting and sequencing, suggesting that some MDSCs arise as a response to the mutated clone and are not mutated themselves in MDS.[37] MDSCs in MDS possessed increased in expression of CXCR4, or CD184, a critical chemokine receptor in homing to the bone marrow, along with CX3CR1.[2] Authors speculated that elevated CXCR4 increased MDSC homing and retention within the bone marrow, thus increasing marrow-specific suppressive effects of these cells. Regulatory T cells (Tregs) were also increased in high risk disease, along with MDSCs, while in low risk MDS, Tregs are less abundant.[2, 44, 3] One potential mechanism of this reduction is through increased expression of interferon regulatory factor-1(IRF-1), a suppressor of Foxp3 expression.[46] Taken together, these data indicate a dynamic role of inflammatory and suppressive cells subsets over the spectrum of MDS.

One effect of increasing suppressive cell subsets is reduction of cytotoxic anti-leukemia immunity. The activation and function of natural killer (NK) cells exert important cytotoxic activity in response to MDS and other myeloid neoplasms, but their function is reduced in high risk MDS.[6, 47] Moreover, NK cells from MDS patients lose *in vitro* anti-leukemic activity due to a TNFα-induced IL-32 secretion from stromal cells.[48] In this study, IL-32 directly inhibited the activity of NK cells, and it was found that stromal cells from MDS patients produced higher levels of IL-32. The authors concluded that IL-32 impairment of NK cells may contribute to persistence and proliferation of clonal blasts and further

progression to leukemia. Leukemic blasts also inhibit NK cell function directly via TGFβ secretion in microvesicles.[49]

Stromal Cell Contributions to MDS—Bone marrow stromal cells arise from mesenchymal stem cells (MSCs) and play a direct role in myeloid skewing and increased inflammatory response in MDS.[50] This was shown in a study that transplanted patient-derived mesenchymal stromal cells into an immunocompromised mouse model and revealed the stromal cells were critical for propagation of the MDS clone.[50] Further studies have shown that MSCs can participate in reciprocal signaling with mutated MDS hematopoietic cells, have altered epigenetic profiles as compared to non-MDS MSCs and drive disease progression starting at initiation.[51] Recent studies have shown MSC epigenetic dysregulation leads to inappropriate activation of the beta-catenin pathway and subsequent disease progression.[52] In addition to their unique epigenetic signature, the transcriptome of MDS-associated stromal cells is also distinct from healthy stromal cells. Transcriptomic analysis of stromal cells in the bone marrow of MDS patients has revealed a transcriptional signature characterized by cellular stress and upregulation of inflammation-associated secreted factors.[53] In addition, alterations of osteolineage progenitors can disrupt hematopoiesis and induce myelodysplasia.[54] The fundamental contributions of non-hematopoietic cells in MDS pathogenesis demonstrates the importance of further investigation into the hematopoietic-stromal interaction.

Part II: Therapeutic Targeting of the Immune System in MDS

Immune Suppression in the Treatment of MDS—Therapies such as anti-thymocyte globulin (ATG) and cyclosporine, both T cell directed therapies, have been found to be effective for some patients with MDS, particularly in the hypoplastic subtype.[55–57] Published studies report response rates to both of these therapies vary greatly (0–100% response with ATG and 33–82% for cyclosporine) and combination therapy is not superior to monotherapy.[58, 59] A single center study of immunosuppressive therapy (IST), including ATG and cyclosporine, demonstrated response rate in low risk disease similar to other standard therapies, however high risk disease patients did not respond as well to IST.[60] A more recent study presented in abstract form was one of the largest studies of immunosuppressive therapy in MDS. Immunosuppressive therapy in this large cohort showed overall response rate of 45%, leading to transfusion independence in 39% of patients.[61] A correlation of response with MDS subtype or other factors was not observed. Over the past decade more has been discovered regarding the role of the immune system in MDS and with these discoveries comes the advent of directed immunotherapies. These therapies fall into distinct groups: targeting of the inflammatory components of MDS, directing cytotoxic cells (including T cells and NK cells) against the MDS clone and targeting the mutant myeloid cells via immune-mediated mechanisms.

Direct Inhibition of Cytokines and Downstream Targets—Early strategies to target abnormal cytokine levels in MDS focused on anti-TNFα therapy.[62] Single agent studies of etanercept, a TNFαreceptor mimetic, and infliximab, a monoclonal antibody to TNFα, showed some early activity, however a phase II trial of infliximab reported low activity and insufficient responses.[62, 63] Combinations with anti-TNF agents have also been

underwhelming. Azacitidine, a DNA methyltansferase inhibitor (DNMTi), and etanercept were combined with a reported 72% overall response rate after 3 months of therapy; however, this was a single arm study and response criteria differed from key historical controls with azacitidine alone.[64] Another phase II study of 25 patients combined etanercept with ATG showed the combination was effective in low risk MDS with overall response rate of 56%.[65] Unfortunately, TNFα inhibitors have not been as successful as once hoped and they are not considered standard therapy in MDS at present. IL-6, another cytokine implicated in MDS pathogenesis, has also been used in MDS, with similarly poor results. Siltuximab, a monoclonal antibody to IL-6, was studied in a phase II trial in 2012, but this was terminated early due to lack of efficacy in the primary endpoint (transfusion reduction).[20] Some therapeutic potential, however, exists in newer strategies to target cytokine signaling. Luspatercept, a TGFβ superfamily ligand trap, inhibits downstream SMAD2/3 signaling and improves erythropoiesis in preclinical and early phase studies.[66, 67] This therapy seems to be particularly useful in MDS with a splicing factor 3B subunit 1 (*SF3B1*) mutation, which is enriched in MDS with ringed sideroblasts. In a phase II study of luspatercept in lower risk MDS showed a 63% rate of hematologic improvement and a 38% of red blood cell transfusion independence. Despite underwhelming evidence in support of cytokine targeting, pre-clinical evaluation of IL-8 inhibition suggests it may be a more effective target than other cytokines, given that high levels of its receptor, CxC chemokine receptor 2 (CXCR2), are associated with adverse prognosis and increased transfusion dependency.[68] Additionally blockade of IL-8 could decrease recruitment of inflammatory cells to the bone marrow and reduce inflammation in MDS.

More recent and ongoing efforts to target innate immune signaling have focused on TLR, IL-1, and DAMP signaling. Overexpression and activation of p38 within the bone marrow is a unifying feature in low risk MDS patients.[69] This molecule, as discussed above, is downstream of the IL-1R and preclinical inhibition has anti-leukemic activity in *ex vivo* treatment of primary samples.[70, 43] Therefore it is an attractive target as it can be part of many treatment regimens, regardless of mutation subtype. Three small molecule inhibitors of p38 have been used preclinically and clinically: SCIO-469, pexmetinib (ARRY614) and ralimetinib. SCIO-469, inhibits TNFα secretion from myeloid cells and decreases the expression of TNFα and IL-1β from stromal cells in the bone marrow.[71] Data from a phase I/II study, however, indicated rare bone marrow and/or cytogenetic responses, suggesting that clinically this drug may not be as effective as *in vitro* (NCT00113893).[72] Recent preclinical studies of pexmetinib, a dual inhibitor of p38 and Tie2, the angiopoietin receptor, also demonstrated some hematologic responses.[73] Similar results were seen in the phase I trial of low and intermediate-1 risk MDS, with 5/7 (71%) achieving platelet transfusion independence. However, only three patients (12%) achieved red blood cell transfusion independence (NCT00916227).[74] The newest p38 inhibitor, ramlitinib, has shown some promise as it leads to decreased IL-1 and reduced proliferative effects in an AML model.[43] Targeting p38, thus appears to be of potential utility, especially in low risk MDS, though many studies have only reported preliminary results at this time.

Activation of TLR signaling within MDS makes the TLR axis a promising therapeutic target and there are several ongoing efforts to test this hypothesis. OPN-305 is a humanized IgG4 monoclonal antibody to TLR2. In a phase I setting for a separate indication it was safe and

tolerable, while a phase I/II study is underway in patients with MDS (NCT02363491).[4] [75] Additional mechanisms to target TLR signaling include direct inhibition with CX-01, a heparin-derived polysaccharide. CX-01 disrupts TLR4 interactions with high-mobility group box protein 1 (HMBGP1) and other leukocyte/ adhesion molecules.[76] A phase I trial has begun to evaluate efficacy of CX-01 with azacitidine in relapsed or refractory (R/R) MDS (NCT02995655). Another mechanism to inhibit TLR signaling is through its downstream effectors, the IRAK molecules. Currently only preclinical data has shown IRAK¼ inhibition suppresses mutant myeloid cells through downstream inhibition of NF-kB signaling.[41] Moreover, PF-06650833, an IRAK4 inhibitor, is currently only in phase I clinical trial for rheumatoid arthritis (NCT02996500).[77]

MDSCs are also a targetable source of immune dysregulation; however, only preclinical studies have been done to evaluate these cells as a potential therapeutic target. CD33 is a marker of some MDSCs and therefore a logical target.[78] BI836858 is a Fc-engineered CD33 antibody that binds to the CD33 receptor and 1) prevents the release of immune-suppressive cytokines, 2) reduced reactive oxygen species commonly seen in MDSCs and 3) induce antibody-mediated cytotoxicity to MDSCs.[78] A phase I/II trial of BI836858 is ongoing (NCT02240706).

Vaccine Therapy—Vaccinations against cancer antigens are a novel strategy to resensitize the adaptive immune system to tumor-associated epitopes, thus turning on tumor-directed immune response. Wilms tumor 1 (WT1) is a protein expressed on abnormal cells in MDS and AML and vaccines to the antigen have been in development for some time. Studies using WT1 as a vaccine target have shown mixed results, but some encouraging responses in MDS. [79, 80]. CDX-1401,a vaccine featuring the fusion protein of CD205(DEC-205), a marker on dendritic cells, and cancer-testis antigen 1 (CTAG1 or NY-ESO-1), was shown to effectively induce cytotoxic response from T cells when examined *ex vivo* and has recently concluded phase I with no clinical outcomes reported to date.[81] Another vaccine target includes the PR1 peptide, an HLA-A2 restricted peptide on myeloid leukemia cells, Initially developed in 2008, the first phase I trial displayed both safety and efficacy of the PR1 vaccine.[82] Last year another phase I/II trial also demonstrated robust immune response (53% patients had at least doubled PR1-specific cytotoxic T cells (CTLs)) and objective clinical response (24% patients had complete, partial or hematological improvement) (NCT00004918).[83] Interestingly, the initial trial has now found that repeated vaccinations lead to the expansion of low-avidity PR1-specific CTLs and loss of high-avidity PR1-specific CTLs.[84] Therefore in the future, vaccine schedules will be carefully considered as more frequent schedules could lead to loss of the high-avidity CTLs.

Repurposing Cytotoxic Cells—Harnessing the cytotoxic immune response to target transformed cells has been a successful approach for many solid tumors and lymphomas, however it has unclear utility in myeloid malignancies. Targeted approaches include both stimulating the endogenous system and reengineering lymphoid-derived cells to target the mutant cells. Checkpoint inhibitors are the most prominent current class of immunotherapy and act through binding of a soluble protein to either the checkpoint receptor (e.g., cytotoxic t-lymphocyte associated protein 4 (CTLA4) and programmed death-1 (PD-1)) or ligand

(e.g., PD-L1) and blocking the receptor-ligand interaction which would normally act as an "off" switch, causing a T cell to become anergic or exhausted.[85, 86] Preclinical data suggests that this treatment strategy may be useful in MDS where there is increased expression of PD-1.[87] Additionally, epigenetic modifications of the PD-1 promoter site resulting in increased expression have been implicated patients with DNMTi-resistance.[88] Initial studies using pembrolizumab, a monoclonal antibody against PD-1, were disappointing with the first study showing only 4% overall response rate.[89] However, due to data showing upregulation of PD-1 following hypomethylating agents (HMA), more recent trials have investigated the role of PD-1 therapy in HMA-refractory disease as well as in combination with other therapies.[90] Nivolumab, an IgG4 anti PD-1 antibody, is part of a trial comparing standard of care without and without nivolumab (NCT02464657). Additional trials are enrolling patients following HMA failure (NCT02530463) and in combination with traditional chemotherapies and other immunotherapies (table 1). While currently only theoretical, evidence from melanoma suggests that MDSCs found in the microenvironment could be particularly susceptible to combination PD-1 and c-KIT blockade.[91]

A new class of molecules including bi-specific killer engager (BIKE), bispecific T cell engager (BITE), trispecific killer engager (TriKE) and Dual Affinity Re-targeting (DART) antibodies engage specific epitopes both on malignant cells and cytotoxic cells, bringing these two cell types together in close proximity for target cell killing. The first successful *in vitro* studies with BIKE therapy in MDS used a CD16xCD33 BIKE to reverse MDSC immunosuppression of NK cells and induce MDSC target cell lysis. This therapy was effective in all patient samples, regardless of disease stage.[92] In AML, addition of a modified IL-15 cross-linker to a CD16xCD33 backbone created a CD16xCD33xIL-15 TRiKE. This therapeutic not only increases NK cell mediated killing but concurrently stimulates NK cell proliferation with IL- 15.[93] *In vivo* TRiKEs are superior to BIKEs. A phase I/II trial of CD16xCD33xIL-15 TRiKE for AML and high risk MDS is planned (NCT03214666). Unlike BiKEs and TriKES, which are one conjugate polypeptide, DARTs consist of two polypeptide chains linked by a disulfide bond. They have been potent against myeloid malignancies *in vitro* and in early clinical trials.[94] Results from a phase I study of flotetuzumab (MGD006), a CD123xCD3 DART, in AML and high risk MDS were recently reported to have some anti-leukemic activity with an overall response rate of 43% and enrollment for this study continues (NCT02152956).[95] Future combinations with anti-PD-1 therapy may be advantageous as synergistic toxicity has been observed in an *in vitro* model with flotetuzumab and check point inhibition.[95]

Engineered NK cell cytotoxicity against dysplastic clones is a new area of research and has shown some effect in AML and high risk MDS.[96, 97] There are multiple potential sources of NK cells for patients, including cord blood, matched donors and autologous harvests.[98] Regardless of type of donation, *ex vivo* expansion in the presence of K562 leukemia cell line prior patient engraftment to produces immature NK cells with greater cytotoxicity and receptor diversity than unexpanded samples.[99, 100] The ideal method of ex vivo expansion is not yet clear; however, priming with IL-15 did improve NK cell cytotoxicity in a murine myeloma model.[101] A recent trial in Sweden demonstrated NK cell therapy was effective in AML and high risk MDS with 6/16 patients (38%) achieving complete or partial

remission following low-intensity lymphodepleting agents and haploidentical NK cell infusion. Additionally, 6 refractory patients became eligible for HSCT, suggesting the NK cell therapy may act as a bridge to transplant in otherwise refractory patients.[97] Trials currently enrolling with NK cells are shown in table 1. Chimeric-antigen receptor (CAR) T cells work similarly to NK cell therapy in that they both are endogenous immune regulators coopted to target malignant clones. The role of CAR T cells in MDS has primarily been explored *in vivo* with promising results. Early preclinical data showed anti-CD123 CAR T cell therapy eliminates MDS clones in a patient derived xenograft (PDX) model.[102] Additionally, a phase I trial of CAR T cells engineered to recognize NKG2D-ligands, commonly found on MDS clones, is underway (NCT02203825).

Conclusions

Immune dysregulation defines MDS across the broad spectrum of disease (Figure 1). Dysregulated immune signaling stems from elevated levels of inflammatory cytokines and mutations that activate innate immune signaling. The combination of these two events leads to an environment that promotes further mutations, clonal hematopoiesis, increased cell proliferation and abnormal cell death. As the inflammation progresses the immune and stromal compartments become transformed as well and cooperate with further decreased anti-leukemic immunity and increased proliferation of blasts. Regulatory and suppressive cells accumulate, ostensibly to quiet the disrupted immune environment, but also likely contribute to immune suppression and leukemia progression. To alter this disrupted phenotype, several strategies have been attempted. The lack of response to cytokine therapy in MDS has been disappointing, but current strategies and emerging rational clinical trial designs hold some promise. Eventually, given the complexity of the disease, combination of multiple immune focused therapies will likely be needed. Lastly, it must be noted that our current armament of immunotherapies is far more sophisticated than just five years ago, thus, we anticipate an ever-quickening pace of discovery in this burgeoning field.

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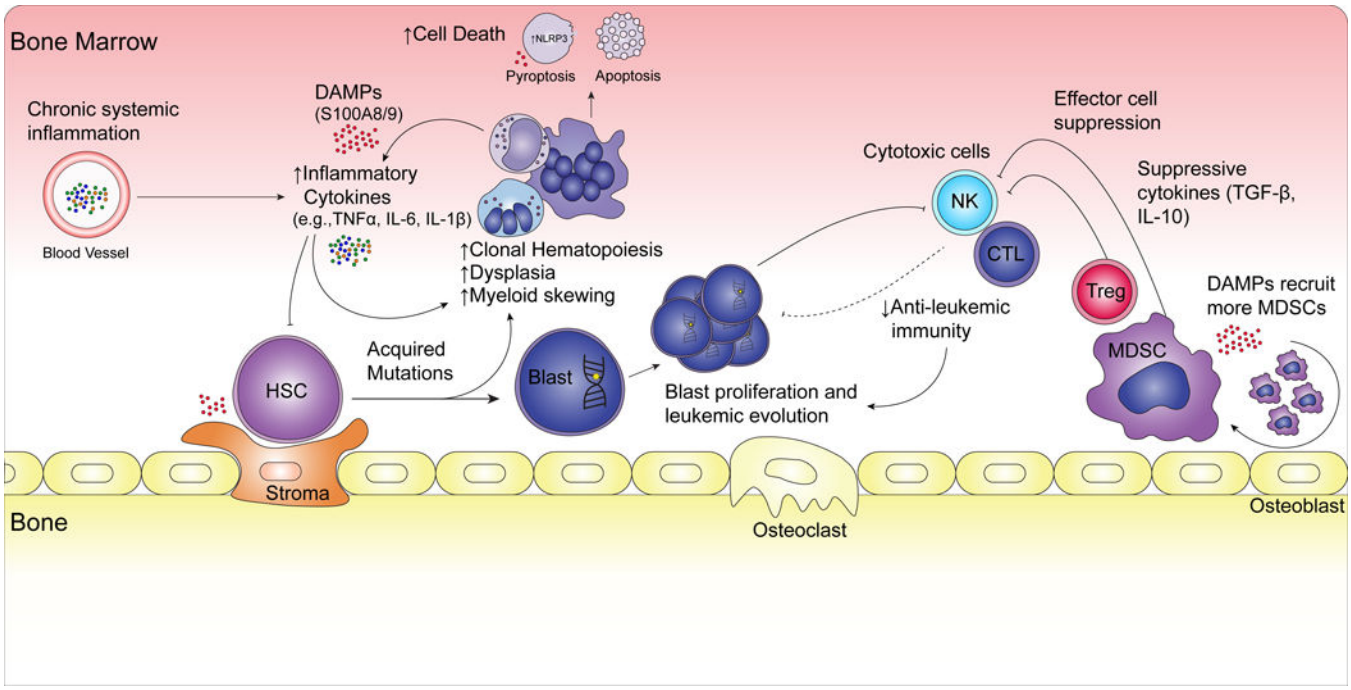

Figure 1.
Overview of Immune Dysregulation in MDS.

Table 1:

Therapies evaluating various immune targets in MDS.

Class	Therapy	Target	Mechanism	Clinical Trial	Status
TLR signaling	OPN-305	TLR2	Humanized anti-TLR2 mAB	NCT02363491: second-line treatment for lower risk MDS	Phase I/II, recruiting
	CX-01	TLR4	Heparin-derived polysaccharide disrupts interaction between TLR4 and HMGB1	NCT02995655: combination therapy with azacitidine in R/R MDS and AML	Phase I, recruiting
Cytokine inhibitors	Etanercept	TNFα	Soluble TNFa receptor	NCT00118287: combination azacitidine and Etanercept in MDS	Phase I/II, completed
	Siltuximab	IL-6	Chimeric monoclonal antibody to IL-6	NCT01513317: siltuximab vs. placebo with best supportive care in anemic patients with IPSS low or intermediate-1 risk MDS	Phase II, terminated
	Luspatercept	TGFβ			
p38 inhibitor	Talmapimod (SCIO-469)	p38	Inhibitor of p38α	NCT00113893: open label study for any patient with MDS	Phase II, completed
	ARRY-614	p38/Tie2	Inhibitor of p38 and Tie2	NCT00916227: ARRY-614 in patients with IPSS low or intermediate-1 risk MDS	Phase I, completed
Checkpoint inhibitor	Pembrolizumab (MK-3475)	PD-1	Monoclonal antibody to PD-1	NCT01953692: Pembrolizumab in patients with blood cancers	Phase Ib, active not recruiting
	Nivolumab	PD-1	Monoclonal antibody to PD-1	NCT02464657: safety and efficacy of nivolumab in combination with idarubicin and cytarabine in MDS and AML	Phase I/II, recruiting
	Nivolumab	PD-1	Monoclonal antibody to PD-1	NCT 03417154: nivolumab and cyclophosphamide in R/R AML and high risk MDS	Phase II, not yet recruiting
	Ipiliumab	CTLA-4	Monoclonal antibody to CTLA-4	NCT02530463: nivolumab and/or ipililumab, with or without azacitidine in MDS	Phase II, recruiting
Trispecific Killer Cell Engager	CD16/IL-15/CD33 TRiKE	CD16/CD33	anti-CD16 single chain variable fragment (scFv) to engage NK cells and anti-CD33 scFv with a modified IL-15 linker	NCT03214666: CD16/IL-15/CD33 TRiKE for CD33 hematological malignancies	Phase I/II, not yet recruiting
Dual Affinity Retargeting molecule	Flotetuzumab (MGD006)	CD123/CD3	DART recognizing CD123 and CD3	NCT02152956: safety of MGD006 in R/R AML or IPSS intermediate-2 or high risk MDS	Phase I, recruiting
Monoclonal Antibody	BI 836858	CD33	Monoclonal antibody to CD33	NCT02240706: BI836858 vs. best supportive care in patients with IPSS low or intermediate-1 risk MDS	Phase I/II, recruiting
Vaccine therapies	PR1 Leukemia Peptide Vaccine		Stimulates host's immune system to mount a cytotoxic T lymphocyte response to tumor cells	NCT00004918: Vaccine Immune Adjuvant in Chronic Myeloid Leukemia (CML), AML or MDS	Phase I/II, completed

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Class	Therapy	Target	Mechanism	Clinical Trial	Status
	DEC-205/NY-ESO-1 Fusion Protein CDX-1401		Stimulates host's immune system to mount a cytotoxic T lymphocyte response to tumor cells	NCT03358719: DEC-205/NY-ESO-1 Fusion Protein CDX-1401, Poly ICLC, Decitabine, and Nivolumab in Treating Patients With MDS or AML	Phase I, not yet recruiting
NK cellular therapy	Lirilumab	KIR2DL½L3	Monoclonal antibody to KIR2DL½L3	NCT 02599649: nivolumab and/or lirilumab, with or without azacitidine in MDS	Phase II, recruiting
	Activated NK cells	-	Expansion of NK cells ex vivo in presence of irradiated K562 cell line	NCT02123836: NK cell therapy in AML and MDS	Phase I, recruiting
	Activated NK cells	-	Donor NK cell transfusion	NCT01898793: Cytokine-induced Memory-like NK Cells in Patients With AML or MDS	Phase I/II, recruiting
	Activated NK cells		Donor NK cell transfusion	NCT02890758: Universal Donor NK Cell Therapy in Combination with ALT803	Phase I, recruiting
	CAR T cell targeting NKG2D-ligand		CART T cells targeting NKG2D-ligands on myeloid cells	NCT02203825: Safety Study of Chimeric Antigen Receptor Modified T-cells Targeting NKG2D-Ligands in MDS/AML/MM	Phase I, not yet recruiting