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Immune Dysregulation in MDS: The Role of Cytokines and Immune Cells

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Abstract

Myelodysplastic syndrome (MDS) is a hematopoietic stem cell disorder affecting individuals over the age of 60 years. It is characterized by ineffective hematopoiesis and extensive apoptosis of hematopoietic cells. MDS patients are at a high risk of transforming into acute myeloid leukemia. The main cause of apoptosis and escape from immune surveillance in MDS is immune dysregulation caused by a number of factors such as aberrant cytokine production and influence of various immune cells. In the past decade various pro-inflammatory cytokines and a number of immune cells such as Natural Killer cells, regulatory T cells, cytotoxic T cells, mesenchymal stem cells, myeloid derived suppressor cells and dendritic cells have been implicated in immune dysregulation leading to MDS pathogenesis. In this review we focus on the current data available on the role of these immune factors.

Keywords: myelodysplastic syndrome, cytokines, natural killer cells, dendritic cells, mesenchymal derived stem cells

1. Introduction

Myelodysplastic syndrome (MDS) is a group of clonal hematopoietic stem cell disorders with ineffective hematopoiesis, cytopenias and risk of transformation to acute myeloid leukemia (AML). Incidence of MDS is higher in older individuals (>70 years of age) [1, 2]. The severity of MDS could range from indolent disease in which no blood transfusion is required, to borderline AML. An individual can get MDS either de novo, secondary to other myeloid disorders or MDS related to therapy. There are several point mutations associated with MDS [3–5]. Few of the individuals carrying these point mutations have a risk of developing MDS in the future but the factors involved in progression of the disease have not yet been identified [6]. MDS is a multifactorial disorder arising due to factors such as genetic alterations, epigenetic changes, gene transcription dysregulation and immune dysregulation [7]. This chapter is a review of the current data available indicating the role of immune cells in immune dysregulation related to MDS pathogenesis.

2. Classification of MDS

In 1982, the French-American-British (FAB) classification was established for categorizing various MDS cases. According to this classification, all MDS patients were classified into one of the five groups based on the number of myeloblasts present in the bone marrow: refractory anemia, refractory anemia with ring sideroblasts, chronic myeloid leukemia, refractory anemia in excess of blasts (RAEB), and RAEB in transformation (RAEB-T) [8]. This was then later modified into the World Health Organization (WHO) classification which consists of the following groups: Refractory cytopenia with unilineage dysplasia (RCUD), Refractory anemia with ringed sideroblasts (RARS), Refractory anemia with multilineage dysplasia (RAMD), Refractory anemia with excess blasts-1 (RAEB-1), Refractory anemia with excess blasts-2 (RAEB-2), Unclassified myelodysplastic syndrome (MDS-U), MDS associated with isolated deletion 5q, and Refractory cytopenia of childhood (RCC). Various prognostic scoring systems are used in clinical practice to predict overall survival and risk of transformation to AML in MDS patients. Currently, the International Prognostic Scoring System (IPSS) is used for risk stratification and treatment decision making. This system divides MDS patients into 4 different risk categories: low risk, intermediate-1 risk, intermediate-2 risk and high risk, based on the number of cytopenias, the percentage of blasts and cytogenetics [9].

3. Immune dysregulation in MDS

Immune cells are typically involved in immune surveillance, however, they also play a role in disease progression. Many studies have highlighted the role of different immune cells in immune dysregulation leading to pathogenesis of MDS and progression of disease to AML (**Table 1**). These factors could range from aberrant cytokine levels, increased T helper and cytotoxic cells, lower number of regulatory T cells, and dysfunctional Natural Killer (NK) cells among others.

In MDS there is an imbalance in cell production and apoptosis of aberrant cells. The main feature of MDS is high rate of apoptosis leading to cytopenia. The disturbed immune system leads to cytopenia by not only killing the tumor cells but also normal hematopoietic precursors. The immune dysregulation mechanisms vary between the low-risk and high-risk MDS patients, wherein, low risk patients show a high rate of apoptosis resulting from an immune system that is in an activated proinflammatory state, and in high risk patients there is increase in clonality of the tumor cells which escape immune surveillance resulting in a more immunosuppressive environment [7].

Innate immune cells such as cytokines and NK cells and T cells of the adaptive immunity play a major role in immunosurveillance. Since, immunosurveillance maintains the homeostasis as well as removes the aberrant cells any error in the immune regulatory pathways can lead to cancer [31]. The major cause of escape of immune surveillance in MDS is dysregulation of the immune mechanisms which involves various immune cells (**Figure 1**).

3.1 Role of cytokines in immune dysregulation in MDS

Cytokines and chemokines are soluble low-molecular-weight proteins secreted by immune cells that mediate inflammatory responses and regulate hematopoiesis by modulating bone marrow microenvironment. These are essential for the viability, proliferation and differentiation of hematopoietic stem cells. The lymphoid tissues host the effector lymphocytes in their nascent form. Upon stimulation by

chemokines released by the macrophages, the lymphocytes secrete pro-inflammatory cytokines such as IL-2, IFN-gamma, IL-17 and TNF-alpha. Additionally, cytokines such as IL-10 and TGF-Beta are also secreted which down regulate the immune

Sr. No.	Immune factor	Levels	Results	References
1	TNF- α	High	Increased rate of apoptosis	[10]
2	IL2	High	Higher levels in advanced stage MDS as compared to early stage	[11]
3	IL6, GM-CSF	High	Higher levels in advanced stage MDS as compared to early stage	[12]
4	TNF- α	High	Lower overall survival and lower event free survival	[13]
5	TNF- α	Low (<10 pg./ml)	Better overall survival and better progression free survival	[14]
6	CD ₄ ⁺ and CD ₈ ⁺	Low	Response to immunosuppressive therapy	[15]
7	CD ₃ ⁺ and CD ₈ ⁺	Low	frequent infections, lower overall survival and transformation into AML	[16]
8	CD ₈ ⁺ T cells	High	Inhibition of hematopoiesis	[17, 18]
9	CTLA-4	High	Suppression of T cell activity, escape from immune surveillance, resistance to immunotherapy	[19]
10	CTL's	High	Impairment of immune surveillance and disease progression	[20]
11	MDSC's	High	Inefficient hematopoiesis	[21]
12	MSC's	High	Increased apoptosis, immunosuppression and reduced hematopoiesis	[22]
13	MSC's	High	Poor potential for inhibition of DC differentiation and maturation in low-risk MDS patients	[10]
14	DC's	Abnormalities	Escape of tumor cell from immune recognition, Higher rate of relapse after HSCT	[23]
15	IFN- γ producing NK Cells	Low	Decreased cytolytic function leading to increased tumor load	[24]
16	CD56 ^{dim} CD16 ⁺ NK cells	High	Dysregulation of immune surveillance and ineffective hematopoiesis	[25]
17	Tregs	Low	Defective immune activation and decreased immune surveillance	[26, 27]
18	Tregs	Low	T cell cytotoxicity leading to increased apoptosis in low risk MDS	[28]
19	Tregs	High	Impaired antineoplastic immunity and immune suppression in High risk MDS	[15, 28, 29]
20	Th22 (IL22 producing T cells)	High	Increased apoptosis in high risk MDS patients	[30]

TNF- α : tumor necrosis factor-alpha; IL-2: interleukin-2, IL6: interleukin 6, GM-CSF: granulocyte macrophage colony-stimulating factor, CD4+: cluster of differentiation 4, CD8+: cluster of differentiation 8, CD3+: cluster of differentiation 3, CTLA-4: cytotoxic T-lymphocyte-associated antigen 4, CTL's: cytotoxic T lymphocytes, MDSC's: marrow derived stem cells, MSC's: mesenchymal stem cells, DC's: dendritic cells, IFN- γ : interferon gamma, NK: natural killer, CD56: cluster of differentiation 56, CD16: cluster of differentiation 16, Tregs: T regulatory cells.

Table 1.
 The role of various immune cells in MDS pathogenesis.

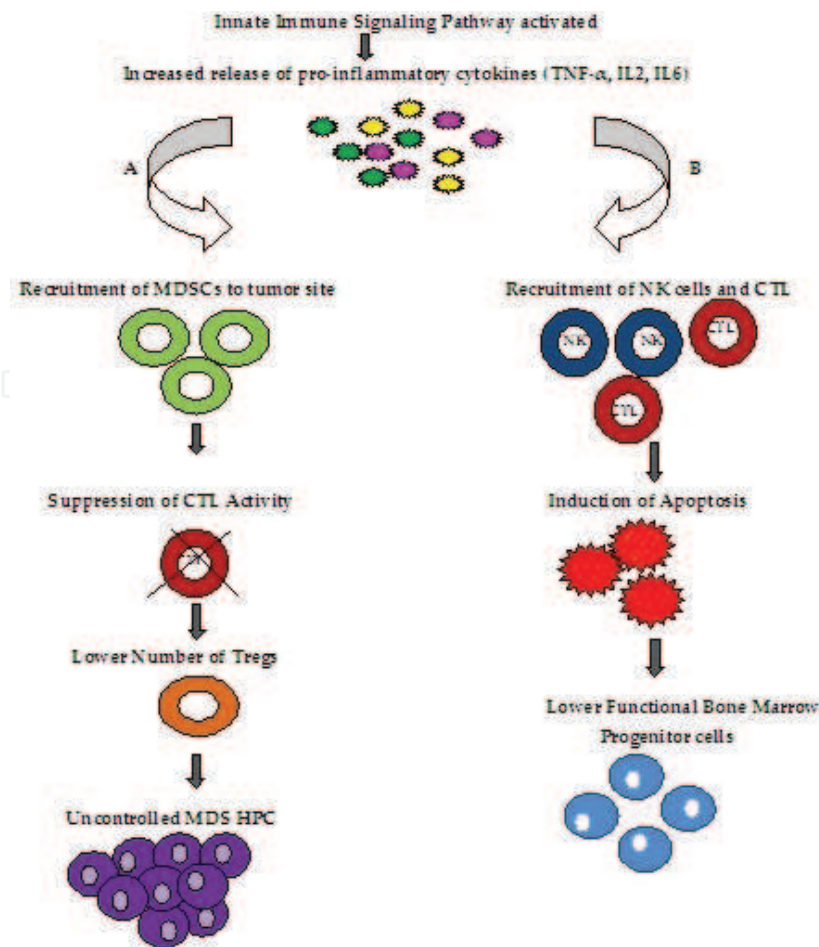


Figure 1.

The role of various immune cells in MDS pathogenesis. A. The abnormal proliferation of MDS hematopoietic cells. The increased release of various pro-inflammatory cytokines directs the recruitment of MDSC's at the tumor site. These kill the erythroid precursor cells and also lead to suppression of CTL activity. Lower number of Tregs enables the tumor cells to escape immune surveillance and leads to accumulation of uncontrolled proliferation of MDS cells. B. The decrease in normal hematopoiesis. The release of cytokines also leads to increase in the number of natural killer and cytotoxic T cells, which induces apoptosis in hematopoietic stem cells. This in turn results in lower number of functional bone marrow progenitor cells. TNF- α : tumor necrosis factor-alpha, IL2: interleukin-2, IL6: interleukin-6, MDSC: marrow derived stem cells, CTL: cytotoxic T cells, Tregs: regulatory T cells, MDS: mesenchymal stem cells, HPC: hematopoietic cells, NK: natural killer.

response and contribute in healing the tissue involved. TGF-Beta is also an inducer of regulatory T cells (Tregs). Cytokines such as TNF-alpha have been associated with pathogenesis of high risk MDS, however, their prognostic value is unknown.

One of the causes of cytopenia in MDS is abnormal apoptosis. The increased expression of cytokines such as TNF-alpha, upregulates the expression of cell surface protein Fas receptor. This Fas receptor when bound to its cognate Fas ligand triggers apoptosis of the cell carrying the Fas receptor via the Fas associated death domain (FADD). Hence higher levels of TNF-alpha have been associated with rate of apoptosis in MDS patients [27].

Abnormal levels of cytokines, chemokines and growth factors in MDS patients have been reported by various researchers [32–34]. The levels of pro-inflammatory cytokines such as TNF-alpha, IFN-gamma, TGF-Beta, IL6, IL8, and granulocyte-CSF have been shown to be increased in MDS patients, highlighting the role of these immune cells in immune dysregulation related to MDS [33, 35–39]. Kornblau et al. [40] reported that MDS patients have lower levels of pleiotropic cytokines IL10 and IL4 as compared to healthy controls. Zoumbos et al. [11] have reported higher serum IL2 levels in patients with advanced MDS as compared to early stage patients. Similarly, higher serum IL6 and GM-CSF levels have been reported in patients with

advanced MDS [12]. Verhoef et al. [34] have also reported higher levels of IL-3, IL-6 and G-CSF in patients with MDS as compared to controls.

Aberrant cytokine levels have also been associated with MDS clinical outcomes. Tsimberidou et al. [13] have associated higher levels of leukocytes and lower levels of hemoglobin with lower overall survival and event free survival in high-risk MDS patients having higher TNF-alpha levels. Meyers et al. [41] have associated higher levels of TNF-alpha, IL-6, IL-1R with fatigue in MDS patients. Low TNF-alpha (<10 pg./ml) have been associated with better overall survival and better progression free survival [14]. Pardanani et al. [42] suggested the levels of IL6, IL7 and CXCL10 to be an independent prognostic factor for overall survival, wherein, patients with normal levels of these cytokines show better overall survival as compared to those with elevated levels of at least 1.

Lopes et al. [43] reported difference in cytokine profiles between low and high risk MDS cases. Also an inverse relation between IL10 and CD₈⁺ T cells has been reported and IL10 expression is much higher in patients suffering from MDS. When comparing the MDS according to the risk, patients in the low risk group show elevated levels of type I cytokines such as IL-1Beta, IL7, IL8 and IL12, whereas high-risk MDS patients show elevated levels of inhibitory factors such as IL10 and sIL2 [13, 14]. Since low-risk MDS is associated with higher apoptotic rates, the levels of cytokines such as TNF-alpha, IFN-gamma and IL-6 are higher in these patients as compared to high-risk MDS patients [35]. High risk MDS is associated with escape of tumor clones from immune recognition and hence serum of these patients have higher amounts of immunosuppressive cytokines like IL10 [44]. IFN-gamma and IL-6 are involved in apoptosis induction in BM. Hence, when they are present in higher levels, it will result in a low risk MDS [27, 32].

4. Role of immune cells

4.1 Helper and cytotoxic T cells

Cytotoxic T cells (CTLs) are cells that are capable of killing cancer cells and abnormal cells. Most of these cells have a T cell receptor (TCR) that recognizes specific antigens, hence, stimulating an immune response. Functionally stable TCRs are associated with both CD₄⁺ and CD₈⁺ glycoproteins. CD₄⁺ glycoproteins are found on cells such as dendritic cells (DC), T helper cells, etc. and are involved in communicating with antigen presenting cells (APCs). The CD₈⁺ glycoprotein is present in various cytotoxic cells such as CTL, NK cells etc. Function of CD₈⁺ glycoprotein is to recognize and destroy foreign/infectious particles. Only when the TCR is associated with CD₈⁺ glycoprotein can it bind to the specific antigens and enable presentation and destruction of these foreign antigens [45, 46].

Growth of both malignant and non-malignant cells in MDS is inhibited by CD₈⁺ T cells that target MHC class I molecules on the hematopoietic precursors. This response forms part of the immune surveillance. Majority of MDS patients have peripheral blood lymphopenia, which results in reduction of CD₄⁺ and CD₈⁺ cell, leading to an inverted CD₄/CD₈ ratio in these patients. In younger patients there is a decrease in both naïve CD₄⁺ and CD₈⁺ T cells which is also correlated with response to immunosuppressive treatments [15].

The distribution of CD₈⁺ T cells differs between low and high risk MDS patients. Low risk MDS patients usually show downregulated Tregs and upregulated CD₈⁺ T cells, whereas, high risk MDS patients have upregulated Tregs and downregulated CD₈⁺ T cells and NK cells. Symeonidis et al. [16] have reported association of CD₃⁺ and CD₈⁺ lymphopenia in MDS patients with frequent infections, lower overall

survival and transformation into AML. Smith et al. [17] demonstrated inhibition of hematopoiesis by CD₈⁺ T cells. This inhibition due to type-I polarization of CD₄⁺ and CD₈⁺ T cells was also confirmed by Wu et al. in 2008 [18].

Recently, a few epitopes on CD₈⁺ T cells such as Wilms tumor 1 protein (WT1), MHC Class I etc., have been implicated in activation of the CD₈⁺ T cells. Sloand et al. [47] reported that in MDS patients with trisomy 8, WT1 is highly overexpressed on CD₃₄⁺ T cells making these patients more responsive to immunosuppressive therapies. However, these immunosuppressive therapies hinder tumor surveillance by T cells resulting in disease progression.

Further, molecules such as programmed death 1 (PD1), its ligand PD1L, and T cell associated antigen CTLA-4 suppress T cell activity leading to escape of tumor cells from immune surveillance and resistance to immunotherapy [19]. Sand et al. [20] have reported a higher number of CTLs in high-risk MDS patients, however, these CTLs have a lower TCR mediated cytotoxicity, which results in impairment of immune surveillance and leads to disease progression.

A Japanese study revealed lower marrow T cells in MDS-RAEB patients and low CD₄⁺CD45RA⁺ naïve cells in MDS patients indicating impaired immune surveillance and expansion of the tumor clone [48]. Hamdi et al. [49] reported higher Th1/Th2 ratios in patients with lower risk prognostic score. Li et al. [50] have reported higher T cell count in low-risk MDS patients as compared to high-risk patients and controls.

These studies highlight the role of abnormal helper and cytotoxic T cells in autoimmunity towards hematopoietic progenitors.

4.2 Myeloid derived suppressor cells (MDSC's)

Myeloid derived suppressor cells (MDSC's) are cells belonging to the innate immunity involved in suppression of the immune system. These cells express CD33 immune receptor [51]. They are generally in few numbers in healthy individuals but increase in response to stress stimuli. They have been reported in higher frequencies in various cancers.

MDSC's are one of the cells that inhibit anti-tumor immunity. These can be differentiated based on the surface markers as monocytic (MO-MDSC) and granulocytic (PMN-MDSC). The surface markers on monocytic MDSC's are CD11b⁺CD14⁺CD15⁻CD33⁺ and HLA-DR^{low}, whereas, those on granulocytic MDSC's are CD11b⁺CD14⁻CD15⁺CD33⁺ and HLA-DR^{low/-}. MDSC's are generally induced by the pro-inflammatory nature of the tumor cells. Their function is to inhibit both adaptive as well as the innate immune system by either cell-cell contact or by releasing cytokines, which results in the inhibition of T cell proliferation and activation, induction of Tregs and NK cell impairment. MDSC's are also involved in inhibiting T cells to settle in the lymph nodes and inflammation sites. MDSC's derived from monocytes and granulocytes support tumor by releasing growth factors.

There is sparing data available regarding the role of MDSC in MDS. The increase in MDSC's in MDS patient results in suppression of normal hematopoiesis and leads to progression of the disease. Chen et al. [21], reported an association of inefficient hematopoiesis with increased MDSC's in the bone marrow of patients with MDS. Graft versus host disease (GvHD) is the number one cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation. Low levels of MO-MDSC's have been reported in association with onset of aGvHD [52]. The levels of both MO-MDSCs and PMN-MDSCs are increased in the peripheral blood soon after transplant and are reported to lower the risk of acute GvHD (aGvHD) as well as response to steroid therapy [53].

Lechner et al. [54], reported the role of various cytokines in the development of MDSC's. In MDS there are irregular levels of cytokines which indicates that targeting the cytokine levels can lead to loss of immunosuppression by the MDSC's. Jiang et al. [55], reported increased levels of circulating MDSC's in MDS patients. The immature myeloid cells induce secretion of cytokines such as IL-10 and TGF-Beta which increase the levels of MDSC's.

4.3 Mesenchymal stem cells

MSC's are self-renewing cells with the ability to differentiate into a number of cells such as adipocytes, and chondrocytes. The main role of MSC's is maintaining normal hematopoiesis, however, they are also implicated in MDS pathogenesis. The role of MSC's in MDS is different in low risk and high-risk patients. In high risk patients MSC's induce apoptosis and suppress the immune system by secreting various cytokines like TGF-B, whereas, in low risk patients they reduce the efficiency for inhibiting DC differentiation. Since MSC's have an immunomodulatory role, they have been investigated for their role in MDS disease progression. However, most of the studies have reported contradictory results and a consensus on the involvement of MSC's in MDS is not yet sought.

Han et al. [56] have demonstrated MSC's with normal morphology and phenotype, but with deficient immunomodulatory function that could not inhibit in vitro T cell activation and proliferation. Klaus et al. [57], did not find any difference in the differentiation potential and immunosuppressive potential of MSC's in MDS patients and controls. In high-risk MDS patients, Zhao et al. [22] reported MSC's with an increase in apoptosis, immunosuppressive rate and reduced hematopoiesis, whereas, Wang et al. [10] reported MSC's with poor potential for inhibition of DC differentiation and maturation in low-risk MDS patients.

4.4 Dendritic cells

The site of origin of DC's is the bone marrow. There are four different types of dendritic cells present in the peripheral blood: plasmacytoid DCs (pDCs), two types of myeloid DCs and slan DC's. The main function of DC's is pathogen and tumor recognition and antigen presentation [58, 59]. Hence, any defect in DC's could mean that the tumor cells will escape immune recognition [28, 29]. DC's upregulate and activate co-receptors on T cells. In MDS patients the ability of DC's to activate T cells is much lower as compared to healthy controls [60]. Ma et al. [61], reported similarities in cytogenetic abnormalities in DC's of MDS patients and in their malignant clones indicating that these abnormalities belonged to the malignant clone.

DC's are equipped with Toll-like receptors and C-type lectin receptors which help in recognition of pathogens. DC's are usually in a nascent state and upon contact with potential pathogens they mature. During maturation there are morphological changes due to which the function of DC's changes from pathogen capturing to cytokine secretion and antigen presentation. The processed antigens on MHC's are presented by DC's to naïve T cells which then elicit an immune response.

Various researchers have reported aberrant immune response by DC's in different cancer types [62–66]. This defect could be in the frequency of DC's, maturation, cytokine secretion profile, and ability to induce T cell proliferation [7]. Abnormalities and defects in number of dendritic cells lead to escape of tumor cell from immune recognition, hence, resulting in higher rate of relapse after allogeneic HSCT [23]. The number and frequency of DC's in the peripheral blood of MDS cases is much reduced as compared to healthy individuals [60, 61, 67]. Further their capability to stimulate T cells is also reduced due to lower surface expression of

molecules such as CD54, CD80 and CD86 [60]. Ma et al. [68] have reported lower IL12 secretion and higher IL10 secretion in DC's from MDS patients. Saft et al. [23] reported lower myeloid and plasmacytoid precursor DC's in high-risk MDS as compared to low-risk MDS patients.

4.5 Natural killer cells

Natural Killer cells (NK) play an important role in innate immunity. NK cells secrete cytokines and play an important role in host defense [69]. Their main role is to kill non-self cells, i.e., cells that lack self-major histocompatibility complex (MHC). NK cell cytotoxicity can either be activated or inhibited based on the sum of the activating and inhibitory receptors present on their surface. The inhibitory receptors could either be Killer immunoglobulin like receptors (KIR) or CD94/NKG2A dimer which protect self-cells from NK cell lysis by binding to their cognate MHC Class I ligands [70], whereas, the activating receptors are the natural cytotoxic receptors (NCRs), namely, NKp46, NKp44, NKp30 and NKG2D [69, 71].

The role of NK cells in immune dysregulation in MDS results from reduction in total number or functional NK cells leading to defects in immune surveillance and hence disease progression. Since NK cells eliminate the aberrant cells from the system, deficiency of NK cell functionality has been associated with poor prognosis in MDS, hence, in older patients, where in the NK cell activity is already low due to aging, the NK cell activity decreases further.

Various reports have measured NK cells in MDS patients [72–74]. Epling-Burnette et al., reported 2 types of NK cells based in their cytotoxicity: low function NK cells which have been associated with high-risk MDS, and normal function NK cells. Furthermore, they also reported defects in number of activating NK receptors such as NKG2D leading to progression of disease. They observed reduced NK cell cytolytic activity in MDS patients as compared to healthy donors. The activating receptors NKp30 and NKG2D was downregulated in these patients [74].

Fujii et al. [24], reported deficiency of IFN-gamma producing NK T cells in blood and marrow of MDS patients. This led to decreased cytolytic function leading to tumor load. Zhang et al. [25], report lower expression of CD3⁻CD56⁺CD16⁺ NK cells in MDS patients as compared to healthy individuals. CD16⁺ NK cells play an important role in tumor surveillance, and hence decreased count of these cells correlate with the tumor cell load in MDS patients [75, 76].

CD56⁺ is a marker for NK cells that produce high levels of cytokines. Circulating NK cells usually exhibit CD56^{dim} which produce lower amounts of cytokines as compared to CD56^{bright} NK cells. Hence, CD56^{bright} are known to have a more immunomodulatory role as compared to CD56^{dim} which are mostly cytotoxic in nature [77]. In patients with MDS, there is a higher prevalence of CD56^{dim}CD16⁺ cells as compared to healthy controls which results in dysregulation of immune surveillance and ineffective hematopoiesis [25]. Hejazi et al. [72] conducted a study on 75 MDS patients, wherein it was observed that majority of the patients in the high risk group had a NK Cell deficiency, moreover, in another group, it was observed that although NK cells were present, they were non-functional. CD56^{dim} NK cells were predominantly present which result in reduction of cytotoxicity.

4.6 Regulatory T cells

Tregs are T helper cells that are involved in immune tolerance and modulation of immune reactions. Regulatory T cells (Tregs) cells are CD4⁺CD25^{high}FOXP3⁺ or CD4⁺CD25^{high}CD127^{low}. Tregs carry out immune tolerance as well as modulation of immune response and are the important for immune surveillance [27] by secreting IL10

and TGF-Beta which are immunosuppressive cytokines [78]. Any impairment in Tregs results in defective immune activation and decreased immune surveillance against the tumor cells [26]. Lower numbers of functional Tregs result in autoimmunity.

The exact role of Tregs in MDS progression is not very clear. However, variation in number of Tregs has been reported to be associated with disease progression, risk of transformation to AML and overall survival in MDS patients [29, 31, 49, 79]. The very first study for the involvement of Tregs in MDS was demonstrated by Kordasti et al. [29], wherein, an association between increased CD₄⁺ Tregs and disease progression was shown. Low number of Tregs in bone marrow have been linked to increased CD₈⁺ T cells and the recruitment of Th17 proinflammatory cells [44, 80]. The number of Tregs differs based on the disease stage. In low-risk MDS, lower numbers of Tregs or impaired Tregs have been reported in association with T cell cytotoxicity leading to increased apoptosis, whereas, higher number of Tregs are seen in high-risk MDS patients and are associated with impaired antineoplastic immunity and immune suppression [15, 28, 29].

Costantini et al. [81] conducted a study to investigate the effect of 5-azacytidine on Tregs functionality in intermediate/high risk MDS patients. Following treatment, lower numbers and Tregs with lower suppressive function were observed in these patients. Alfinito et al. [80] reported an inverse relationship between levels of Tregs and the degree of dyserythropoiesis. Hamdi et al. [49], reported an inverse ratio between Treg and CD₈⁺ frequencies in MDS patients. Low risk MDS patients have higher number of Th17 cells which is inversely correlated with Tregs numbers. Hence in these patients the Th17/Tregs ratio is found to be increased [44]. Shao et al. [30] have shown increased number of Th22 (IL22 producing T cells) in high-risk MDS patients. This increased number of Th22 is correlated with release of pro-inflammatory cytokines leading to increased apoptosis.

5. Immunosuppressive therapy

The most curative treatment for MDS is allogeneic hematopoietic stem cell therapy; however, since MDS develops mostly later in life, most patients are rendered ineligible for transplantation and supportive care is their only option for treatment. As previously discussed, many researchers have shown the involvement of immune cells in the pathogenesis of MDS and hence, immunosuppression involving targeting these cells has evolved as one of the treatment modalities.

Molldrem et al. and Jonasova et al. [82, 83] were the first to report the use of immunosuppressive therapy (IST) in MDS with Antithymoglobulin (ATG) in 1997 and Cyclosporin (CsA) in 1998 respectively. Jonasova et al. [83] reported positive response in MDS-RA patients treated with CsA. On the contrary, another study showed no advantage to CsA and also reported CsA related renal toxicity [84]. CsA acts by blocking IL-2 production which leads to inhibition of expansion of CTLs and suppression of cytokines like TNF- α which are involved in apoptosis [85]. ATG has a role in depleting T cells and restoring normal hematopoiesis [86]. It acts by interfering with the normal function of DC's and hence inhibiting the interaction between the T cell and the antigen presenting cell. Moreover, ATG restores normal hematopoiesis by diminishing cytokine release by activated T cells [87].

Since reduced number of Tregs are associated with disease progression in low-risk MDS, introduction of ex-vivo expanded Tregs is a potential targeted therapy in such patients. Not only the number but also the function of Tregs is important, hence, it is absolutely necessary to be sure that the ex-vivo expanded Tregs population do not have non-regulatory effector cells. Functional Tregs can be also be induced by vaccination using tolerizing DC's [88].

6. Conclusions

It is now well known that genetic, epigenetic and aberrant immune factors play a major role in the pathogenesis of MDS, making it one of the most challenging disorders to design therapies for. Leaving aside the MDS patients in whom the major factor is genetic mutations, there is a group of patients in whom immune cells play a major role in the disease progression. In these patients, immunosuppressive therapies (IST) form part of the major treatment strategy. It is known that there is improved marrow function and increased survival in patients undergoing IST. However, identifying patients that will respond favorably is a challenge. Some targeted therapies involve introducing tolerogenic DC's and expansion of Tregs. The therapeutic approach becomes more difficult because of the difference in the immune environment that exists between low-risk and high-risk MDS cases. For this the exact immune mechanisms involved and the specific immune cells responsible for the pathogenesis in the particular group of patients need to be identified in order to establish targeted therapies in the future.

Conflict of interest

The authors declare that there is no conflict of interest.

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