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Immune dysregulation in myelodysplastic syndrome: Clinical features, pathogenesis and therapeutic strategies

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ABSTRACT

Myelodysplastic syndrome (MDS) is a heterogeneous hematological malignancy, characterized by cytopenia and accompanied by a risk of transformation into acute myeloid leukemia (AML). Epidemiological studies for decades have shown association between autoimmune diseases (AIDs) and MDS. Specifically, patients with antecedent AIDs tends to have an increased risk of developing MDS, and these patients display different clinical characteristics and outcomes. Importantly, immune dysregulation has been the common driving force between MDS and AIDs pathogenesis. Both innate and adaptive immune systems are overly active in the hematopoietic niche of MDS. It has been observed that in addition to many cytokines secreted in the bone marrow (BM) microenvironment, almost all types of immune cells and their downstream signaling pathways participate in MDS pathogenesis and evolution. Currently, growth factor therapy and hypomethylating agents (HMAs), along with supportive care, are the mainstay for MDS treatment. As information about the contribution of immune system has started emerging in different subtypes of MDS, we need to highlight the value of immunomodulatory therapies. Immune activation seems to participate specifically in the development of lower-risk MDS, and therefore, use of immunosuppressive therapies would be an ideal treatment option for this type. However, in high-risk MDS, escape from immune surveillance appears to contribute to its progression, and thus, several immune-activating treatment options, including immune checkpoint inhibitors and vaccines, are being considered. HMAs have been approved for use in treating high-risk MDS for many years based on their cytotoxicity, but since they also display an epigenetic-immunomodulatory role, they can be an option for lower-risk MDS. Thus, in this review, we discuss the immune dysregulation in MDS, including its clinical features, pathogenic mechanism and immunomodulatory therapeutic options.

1. Introduction

Myelodysplastic syndrome (MDS) is a group of heterogeneous clonal hematopoietic stem cell malignancies, characterized by cytopenia associated with defective hematopoiesis, myeloid dysplasia and intramedullary apoptosis, with an increased risk of progression to acute myelogenous leukemia (AML) (Corey et al., 2007). In recent years, a large spectrum of point mutations related to MDS clinical phenotypes has been identified (Kim et al., 2015; Aslan et al., 2016). These mutations have the potential to reflect clinical outcomes and thus could very likely be incorporated into a future prognostic scoring system (Papaemmanuil et al., 2011). Interestingly, no somatic mutations have been shown to be specifically associated with pathognomonic of MDS, as they were also detected in patients with other myeloid malignancies, and even in healthy people (Kwok et al., 2015).

However, recent clinical and molecular studies (Fozza and Longinotti, 2012; Fozza and Longinotti, 2013; Komrokji et al., 2016) have yielded accumulating evidence about the contribution of different immune pathways in MDS pathogenesis and evolution. From the clinical perspective, a variety of autoimmune manifestations and diseases seem to be associated with MDS, and some patients even appear to be sensitive to immunosuppressive treatments. In addition, it has been suggested that aplastic anemia, the pathogenesis of which is driven by immune-mediated mechanisms, can evolve into a typical MDS with specific genetic lesions, like trisomy 8 or monosomy (Dazzi et al., 2006). Specifically, it has been observed at the molecular level that immune dysregulation in MDS primarily causes apoptosis and immune surveillance escape (Sugimori et al., 2010; Epling-Burnette and List, 2009). Thus, this highlights the importance of understanding the various immune dysregulation mechanisms involved in MDS pathogenesis,

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which can eventually help to establish accurate diagnostic criteria and effective targeted therapies. In this review, we have tried to summarize the results of the most recent and significant MDS studies and discuss their clinical implications and therapeutic applications.

2. Association between MDS and AIDs

For a very long time, it has been shown that there is an association between MDS and autoimmune diseases (AIDs) (Anderson et al., 2009; Dalamaga et al., 2002). Multiple MDS patients with AIDs display a range of symptoms starting from limited clinical manifestations to systemic disease affecting multiple organs (Fozza, 2017). In some recent studies, it was observed that AIDs patients (antecedent) have an increased MDS risk, with an odds ratio (OR) from 1.5 to 3.5 (Kristinsson et al., 2011; Wilson et al., 2014). Specifically, the large cohort study by Kristinsson et al. (2011) in Sweden, including 1662 MDS patients and 42,878 matched controls, revealed that previous history of AIDs increased the risk of MDS by 2.1-fold. In addition, it was noticed that some AIDs patients had a particularly very high risk, with an OR for idiopathic thrombocytopenic purpura (ITP) of 23.9, as well as ORs of 7.9 for myasthenia gravis and 5.4 for giant cell arteritis. Overall, these observations indicate that chronic immune stimulation can act as a trigger for MDS development, but the potential molecular mechanism is still unclear.

Many registry studies have focused on the associations between MDS and AIDs by recording clinical characteristics and outcomes of MDS patients with AIDs, as shown in Table 1. A large clinical cohort study 8 last year concluded that AIDs was more prevalent among MDS patients, as 391 of the 1408 (28%) patients had AIDs. Moreover, it was indicated that MDS patients with AIDs typically had higher refractory anemia (RA) or refractory cytopenia with multilineage dysplasia (RCMD) WHO subtype and were less dependent on red blood cell transfusion. They displayed better overall survival (OS) and had less AML transformation. In contrast, another multicenter retrospective study (Mekinian et al., 2016) in France showed that MDS patients with AIDs had less favorable clinical features, but experienced similar outcomes in comparison to patients without AIDs. However, the interesting observation from this study was that hypomethylating agents (HMAs), especially azacitidine, had a positive effect on AID symptoms in MDS patients. Another retrospective cohort study by Lee et al., (2016), conducted in Korea last year, mainly focused on identifying the association of autoimmune manifestations (AIMs) with specific karyotype and prognosis in MDS patients. Neutrophilic dermatosis (ND) was the most prevalent AIM (36%) observed in this study and was associated with 5q deletion. Surprisingly, ND was associated with a 1.8-fold increase in mortality of MDS patients, in comparison to patients without AIMs.

The information in Table 1 indicates that MDS is significantly associated with AIDs. Among the 9 studies, only one showed concurrent AID as a beneficial predictor of longer survival and less progression to AML. Besides this, all other studies did not detect any significant differences (Komrokji et al., 2016; Mekinian et al., 2016). Generally, MDS patients with concurrent AIDs fail to demonstrate consistent epidemiological, clinical and prognostic features, potentially reflecting differences in the study designs, statistical methods, and therapeutic advances for both MDS and AIDs. Hence, additional large prospective studies are required to understand the underlying mechanisms as well as their clinical and biologic significance.

3. Mechanisms of immune dysregulation in MDS

Both innate and adaptive immune systems have been implicated in MDS pathogenesis. The activated innate immune system by directly affecting cytokine levels, inflammatory signaling and immune cells, contribute to abnormal hematopoiesis along with unbalanced cell death and proliferation. On the other hand, $CD8^+$ T cells, part of the adaptive immune system, are activated by expanded malignant MDS stem cells, and results in suppression of hematopoiesis and escape from tumor surveillance. Here, we have tried to extensively review the contribution of cytokines, immune and inflammatory signaling pathways and immune cells in the immune dysregulation of MDS (Fig. 1).

3.1. Cytokines

Abnormal expression of at least 30 cytokines has been observed in the peripheral blood and bone marrow (BM) of MDS patients (Barreyro et al., 2012; Pardanani et al., 2012; Kornblau et al., 2010). Among these, a few have been related to MDS clinical subtypes and outcomes

Table 1
Studies comparing clinical features and outcomes between MDS patients with and without AIDs/AIMs.

Authors	Years/ Country	MDS Patients with AID/Total	Types of AIDs/AIMs	Clinical features (patients with AID/AIM)	Impact on Survival
Giannouli et al. (2004)	2004/ Greece	13/70(18%)	Vasculitis (38%) Polymyalgia rheumatic (23%)	NA	No differences
Dalamaga et al. (2008)	2008/ Greece	21/84(25%)	Vasculitis (24%) ND (10%)	Higher risk group Hypergammaglobulinemia	NA
De Hollanda et al. (2011)	2011/ France	46/235(20%)	Arthritis (13%) Peripheral neuropathy (10%)	NA	No differences Poorer prognosis in MDS patients with vasculitis
Komrokji et al. (2016)	2016/USA	391/1408(28%)	Hypothyroidism (44%) ITP (12%)	More female and RA[b]/RCMD/Less red blood cell (RBC) transfusion	Better OS 60 m vs 45m AML Transformation 23% vs 30%
Fraison et al. (2016)	2016/ France	123/788(15.6%)	Vasculitis (32%) CTD (25%)	Younger/poorer karyotype/ Higher IPSS scores	No differences
Lee et al. (2016)	2016/Korea	67/201(33%)	ND (36%) RA [a](13%)	More 5q-and + 8	No differences Higher death rate in MDS patients with ND
Williamson et al. (2016)	2016/ British	11/252(4.4%)	Vasculitis (36%) Arthritis (27%)	More RA[b]/RCMD/ Lower risk groups	No differences
Kipfer et al. (2017)	2017/ Bernese	30/95(35%)	Arthritis (20%) Vasculitis (17%)	More RAEB More cardiovascular comorbidities	No differences
Zahid et al. (2017)	2017/USA	77/377CMML(20%)	RA [a](10%) Thyroiditis (9%)	Less immature myeloid cells/ Lower risk groups	No differences

Abbreviations: AID, autoimmune disease; AIM, autoimmune manifestation; RA[a], rheumatoid arthritis; RA[b], refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; IPSS, international prognostic scoring system; ITP, Idiopathic thrombocytopenic purpura; CTD, Connective tissue disease; ND, Neutrophilic dermatosis.