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Myelodysplastic syndromes - Section 2

The role of immune response in myelodysplastic syndromes pathophysiology

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Take-home messages

- The role of immune system in MDS pathophysiology and genomic instability.
- The importance of immune-signature "switch" in disease progression.

Introduction

Myelodysplastic syndromes (MDS) are part of a larger group of diseases known as bone marrow failure syndromes (BMFs). BMFs are ranging from mainly autoimmune aplastic anemia (AA)[1] to MDS, which characterized by ineffective hematopoiesis and increased risk of transformation to acute myeloid leukemia (AML).[2,3] Like many other malignancies, a combination of environmental and genetic factors as well as immune dysregulation contribute in MDS pathophysiology. Nevertheless, the sequence of events that lead to dysplasia and subsequent malignant transformation as well as the interaction/role of other contributing factors are not fully understood in MDS.

The role of immune system in MDS pathophysiology

Despite the established role of chronic inflammation in the pathogenesis of many malignancies, its potential role in MDS remains less clear. Until recent years, autoimmune diseases (AID) were considered as coincidence rather than as a predisposing factor for MDS. However, in a comprehensive study on more than 10,000 AML and MDS patients and 43,000 healthy donors, it has been shown that a history of any infectious disease three or more years before AML/MDS, was associated with around 1.5 times increase in risk of both diseases. A previous history of any autoimmune disease was also associated with a 1.7-fold increased risk for AML and 2.1-fold increased risk for MDS.[4] On the other hand, AID can be a favorable prognostic factor in patients who have established MDS. In a collaborative study between the Moffitt Cancer Centre and King's College London, 1408 patients with MDS and AID were studied and we demonstrated that the presence of AID independently increased overall survival in MDS, which may be due to initiation of a 'protective' adaptive immune response.[5]

There is also evidence of the presence of "smouldering" inflammation in MDS in the absence of classic autoimmune diseases. It has been shown that augmented levels of pro-inflammatory cytokines (ie. TNF-α, IFN-ϒ and IL-1β) lead to bone marrow apoptosis in MDS[6-9]. Impaired clearance of apoptotic cells in MDS induces HMGB1 and TLR-4 mediated cytokine production and a vicious circle of inflammation and apoptosis[10]. The increased levels of TNF-α and IFN-ϒ lead to overexpression of an immunoinhibitory molecule, B7-H1 (CD274), which can convey a growth advantage to MDS clone[11]. Moreover, treatment of underlying MDS leads to improvement of immune mediated 'para-neoplastic' diseases like Sweets syndrome[12]. In a study on more than 200 MDS patients, we have shown that the *NLRP3* variants are enriched in MDS patients with Sweet's syndrome compared to historical data on the general population, suggesting an inflammasome-mediated chronic inflammation in these patients[13]. One of the major effects of chronic inflammation is an increased proliferation pressure on stem/progenitor cells and subsequent genetic instability and somatic mutations. In recent years, comprehensive mutational profiling has helped identify the presence of somatic mutations in nearly 80-90% of MDS patients, some of which correlate with clinical phenotype, predict outcome and response to therapy, especially hypomethylating agents[14]. These somatic mutations could lead to expression of neo-antigens which some of them are immunogenic and provoke cellular immune response. Using a combination of HLA-typing, somatic mutation analysis and antigen prediction algorithm (NetMHCpan3.0) in a cohort of 109 MDS patients, we have investigated the immunogenicity of known somatic mutations in low and high risk MDS and shown that patients with predicted neoantigens had significantly longer survival compared to the patients without neoantigens.

Cellular immune response in established MDS

Similar to the role of inflammation in the initiation of MDS, cellular immune response in established MDS is multifactorial and follows a stepwise transformation as the disease progresses toward AML. While there is enough evidence to support a relatively effective cellular immune response in low risk MDS, in high risk disease, accumulation of inflammatory derived myeloid suppressor cells (MDSCs)[15] and increase in regulatory T cells (Tregs) switch the effective immune response to a suppressive response. We have shown a significant increase in the number of Tregs in high-risk disease whereas on the low risk disease the main feature was an increase in the number of pro-inflammatory Th17 cells[16,17]. The importance of Th17 and the balance between Tregs and Th17 in the disease progression and bone marrow apoptosis has also been shown in low risk MDS. However, the difference between low and high risk MDS is not limited to $CD4^+$ T cells and similar differences are reported for other immune cells such as natural killer (NK)[18] cells, DCs[19] and MDSCs[15,20]. In summary, inflammatory environment, which is likely to be the result of a combination of chronic infection/autoimmune diseases, age related increase in pro-inflammatory cytokines and activation of inflammasome pathway in myeloid cells, plays a crucial role in MDS pathophysiology. This inflammatory environment has two overlapping effects; first is to induce apoptosis in stem/progenitor cells and subsequently increase proliferation pressure on these cells and secondly induces an auto-reactive adaptive immune response against stem/progenitor cells due to epitope spreading following apoptosis. The

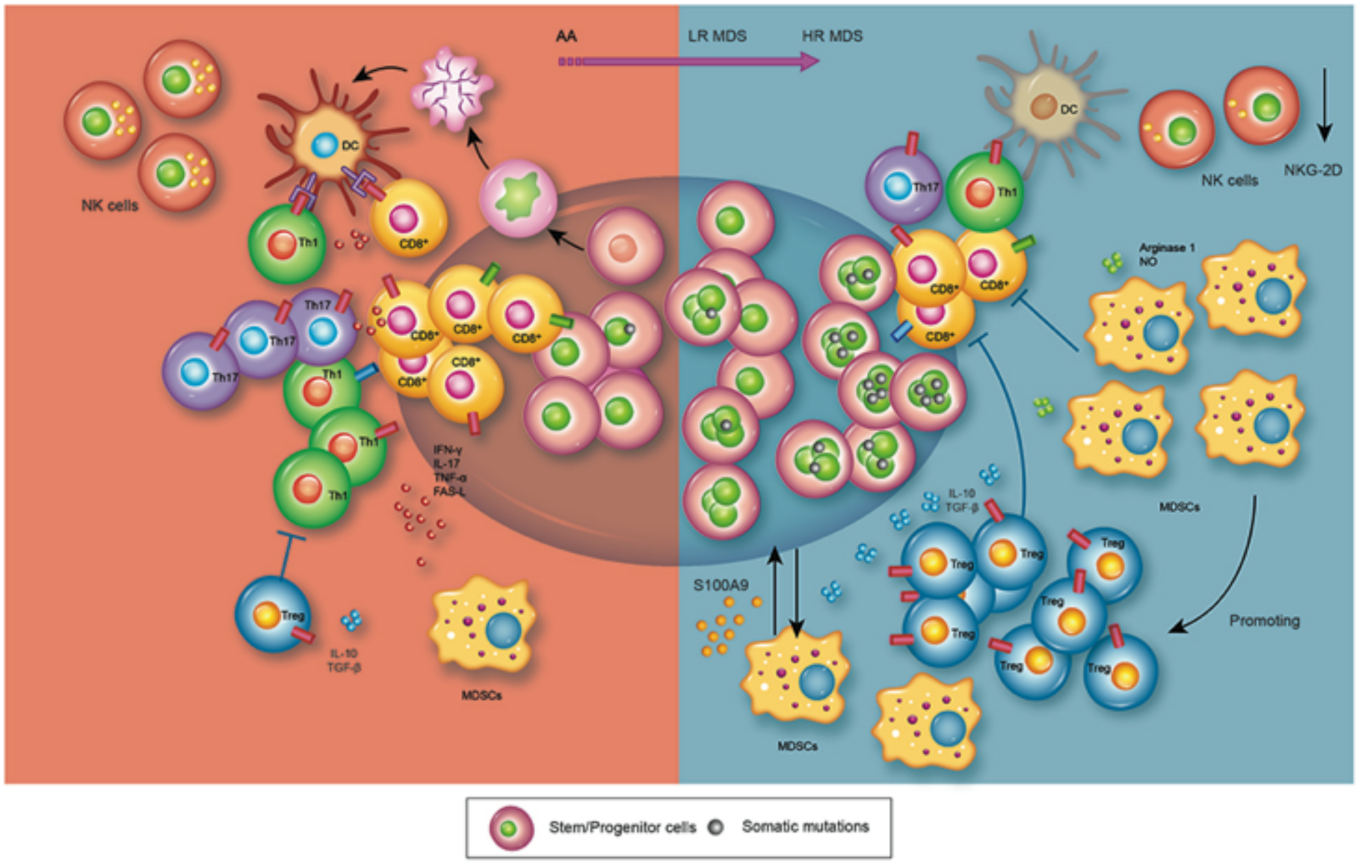

Figure 1. Immune response in MDS: The immune-signature of bone marrow failure syndromes varies and ranging from a pro-inflammatory response in AA and low-risk MDS to a more immunosuppressive environment in high risk MDS. While pro-inflammatory T cells such as Th1 and Th17 cells are more prominent in AA and low risk MDS, the suppressive immune cells such as Tregs and MDSCs play the dominant role in high risk MDS.

expansion of auto-reactive T cells would contribute further in the aforementioned proliferation pressure. Age related inefficient DNA repair mechanisms, genetic background such as detoxification genes' polymorphism and possibly HLA type as well as environmental factors are additional contributing factors into this vicious circle of inflammation-apoptosis-immune response. Adding proliferation pressure to the aged and already genetically unstable progenitor cells substantially increases the chance for acquiring additional mutations (early initiation mutations) and development of dysplasia (critical stage). At this stage while the adaptive/innate immune-surveillance (good inflammation) to some extent keep the dysplastic clone under check, the smouldering myeloid related inflammation fuels the proliferation pressure, which facilitate immune-selection and growth advantage of dysplastic clone(s). Simultaneously the inflammatory environment promotes the expansion of MDSCs, which contribute to the expansion of dysplastic clone and suppress the effective immune-surveillance both directly and indirectly through expansion of Tregs. As disease progresses, subsequent co-operating mutations appear and give growth advantage to dysplastic clones and further genetic instability. At this stage, a combination of MDSCs/ Tregs expansion and reduction in the number and function of effector immune cells and APCs lead to an ineffective immune-surveillance and immune-subversion similar to other malignancies and expedite disease progression to AML (Figure 1). It is anticipated that with advances in the immunology of MDS/AML, therapeutic strategies will evolve that will specifically affect distinctive immunological pathways so as to increase protective immunity against the early as well as evolving dysplastic/leukemic clones, the advance of immune check point inhibitors is hopefully the start of this journey.

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