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EDITORIAL

Emerging immunological concepts in the pathogenesis of myelodysplastic syndromes

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Abstract

The involvement of T-lymphocytes in the pathogenesis of myelodysplastic syndromes (MDS) is now well documented by relevant clinical and experimental findings. This brief review will focus on the T-cell repertoire pattern typical of MDS patients as well as on the potential role exerted by specific T-cell subsets in this context. Future investigations should further explore the specific role played by different T-cell subsets in the bone marrow milieu typical of MDS, further clarifying which of the described changes represent either an epiphenomenon or rather a real causative factor in the pathogenesis of these disorders.

Key words: Myelodysplastic syndromes; T-cells; T-cell receptor repertoire; Regulatory T cells; Immunotherapy

Core tip: T-lymphocytes are deeply involved in the pathogenesis of myelodysplastic syndromes (MDS); patients with MDS display a typical T-cell repertoire pattern; specific T-cell subsets, such as regulatory T-cells and Th17 T-cells, play a specific riole in in this context.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematologic diseases, characterized by dysplastic haemopoiesis and by a variable degree of peripheral cytopenia. Although their pathogenesis is dominated by recurrent molecular, cytogenetic and epigenetic defects, also immune abnormalities have been often advocated in this scenario. In fact, specific laboratory and clinical immune manifestations have been described in a large percentage of patients[1] and, starting from the crucial demonstration that erythroid precursors of MDS patients can be inhibited *in vitro* by autologous T-cells[2], a number of experimental data underline the possible involvement of different T-cell subpopulations in the MDS pathogenesis[3,4]. This hypothesis has been essentially addressed by studies investigating either the profile of the T-cell receptor (TCR) repertoire, especially within the third complementarity determining region (CDR3), or the potential role of specific T-cell subsets such as for instance regulatory T-cells (Treg) and $CD3^+$ $CD4^+$ IL-17 producing (Th17) T-cells.

PATHOGENESIS OF MDS

The analysis of the TCR repertoire has now shown to offer relevant insights in a variety of haematologic malignancies[5]. Studies focussing on MDS patients have essentially demonstrated an increase in the frequency of expanded lymphocyte subpopulations expressing homogeneous TCR repertoire profiles, which tend to assume an oligoclonal pattern especially in $CD8^+$ cells[6,7]. Among the different techniques, the so called spectratyping, which has identified specific CDR3 length distributions in different immune-mediated conditions[8,9], has been the most widely

applied. The potential functional role of these lymphocyte expansions has been specifically addressed by a study showing that expanded $CD8^+$ T-cells selected by MDS patients were able to inhibit the cell growth of a dysplastic clone harbouring trisomy 8 in co-culture[10].

Considering their subtle ability to influence both autoimmunity and tumour progression, Treg have been strongly investigated in MDS patients. Noteworthy their frequency was correlated with several indicators of disease activity, such as bone marrow blast infiltration, high International Prognostic Scoring System score and history of progression[11]. Moreover, they were also shown to display a polyclonal CDR3 profile, as already observed in the post-allograft setting[12], and to belong to the naive subset, especially in high-risk patients[11]. Even more importantly significant differences were shown between low and high risk disease. In fact, Treg were shown to be impaired in their function and bone marrow homing in early stage MDS, whereas they retained their function and were expanded in late stage disease. These findings suggest that an impairment of Treg suppressive function and bone marrow trafficking could be involved in the autoimmune mechanisms typical of early stage MDS. On the contrary, the increased Treg activity observed in higher risk patients could be the expression of an impairment of anti-tumour immunity, potentially facilitating the progression towards a more aggressive disease[13]. More recently, a flow-cytometric approach based on the concomitant expression of CD25 and CD127, was able to show also in low risk MDS patients an increased frequency of Treg, pointing at a potential impairment of anti-tumor immunity even in the early stage of these disorders[14]. On the whole, these data could imply the involvement of Treg in the modulation of anti-tumour immunity and, consequently, of MDS progression.

Other T-cell subsets have been explored in this context, among which $CD4^+$ $CD8^+$ double-positive T-cells, a subset of differentiated effector memory cells with potential antiviral and immune modulating functions, showing an abnormal distribution in MDS patients, especially in those with more advanced disease[15]. Much more importantly, Th17 cells appeared to be over-represented in low risk compared with high risk MDS, being its frequency inversely correlated with that of Treg. Noteworthy, the increased Th17/Treg ratio observed in low risk patients was shown to be associated with increased bone marrow apoptosis, thus potentially explaining the increased risk of autoimmunity and the better response to immunosuppressants observed in this patient subgroup[16].

Also natural killer (NK) cells were demonstrated to display functional defects in MDS patients, even more pronounced in patients with higher risk disease[17]. More importantly, NK cells were shown to modulate cytotoxicity against dysplastic hematopoietic precursors[18]. Also myeloid derived suppressor cells, which play a potential role in regulating immune tolerance even in the context of neoplastic disorders[19], would deserve to be explored in MDS patients.

All these laboratory findings have been corroborated by relevant therapeutic experiences, starting from the well known response to antithymocyte globulin described in a relevant fraction of MDS patients[20], which is also paralleled by specific immunological effects, such as loss of the lymphocyte-mediated inhibition of colony forming unit-granulocyte macrophage and alterations in the TCR repertoire profile[21]. A number of other immunomodulating agents, among which thalidomide, infliximab, SCIO-469-a p38 a-mitogen-activated protein kinase inhibitor- and cyclosporin A[22], have shown different degree of efficacy when offered to MDS patients. Also therapeutic strategies based on more complex immunological approaches have shown a potential benefit in MDS patients, among which vaccination programs exploiting the immunogenicity of Wilms tumor gene product 1-peptide[23,24] as well astransplantation strategies based on reduced intensity or non myeloablative conditioning regimens, which typically rely on immune tolerance modulation[25].

CONCLUSION

Even though a number of clinical and laboratory findings point at the central role of molecular defects in the MDS biology, all the above mentioned data highlight the relevant involvement of different immunological players, among which undoubtedly T-lymphocytes. Future investigations should further explore the specific role played by different T-cell subsets in the bone marrow milieu typical of MDS, further clarifying which of the described changes represent either an epiphenomenon or rather a real causative factor in the pathogenesis of these disorders.

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