Received: 16 January 2023 | Accepted: 17 January 2023

DOI: 10.1111/ejh.13931

European Journal of Haematology WILEY

RESPONSE

The potential etiopathogenetic role and diagnostic utility of $CD3^+CD56^+$ regulatory T lymphocytes in Myelodysplastic Syndromes

Novelty statements

What is the new aspect of your work?

The confirmation, by an independent study, of the key role of $CD3^+CD56^+$ regulatory T cells in MDS pathogenesis/progression.

What is the central finding of your work?

The relevance of a deranged CTL control in BM, by defective $CD3^+CD56^+$ regulatory T cells, for MDS pathogenesis/progression.

What is (or could be) the specific clinical relevance of your work?

Possibility to consider $T_{R3\text{-}56}$ cells as an additional diagnostic/prognostic marker of MDS.

To the Editor,

Serio et al.[1] show a significant reduction of $CD3^+CD56^+$ regulatory T cells ($T_{R3\text{-}56}$) in bone marrow (BM) of low-risk myelodysplastic subjects, as compared with the high-risk and the AML group; in addition, the BM frequency of mature granulocytes, a recognised marker of residual effective haematopoiesis, was observed to inversely correlate with $T_{R3\text{-}56}$ in the MDS cohort. Such data are of great interest and confirm and extend, in an independent MDS cohort, the trend-increase of BM $T_{R3\text{-}56}$ from very low/low risk to high/very high risk MDS and the inverse correlation with the cytotoxic T-cell (CTL) activity, likely fostering the escape of leukaemic blasts to immune-surveillance, by us recently described.[2] Authors also observed BM $T_{R3\text{-}56}$ frequency as negatively correlated with WT1 expression in AML, but not in MDS patients. Moreover, analysis of $T_{R3\text{-}56}$ frequency after treatments in MDS patients, showed a persistent increase of this cell subset, regardless of therapy. Serio et al. conclude that BM $T_{R3\text{-}56}$ frequency could be a flow-cytometry marker for MDS diagnosis, since consistently increased in high-risk MDS and AML, highlighting the role for this cell subset in promoting expansion of the dysplastic precursor/s with consequent ineffective myelopoiesis.[1]

Serio et al. data support the etiopathogenetic role of $T_{R3\text{-}56}$ in MDS and the possible use of this population as diagnostic/prognostic marker of the disease. We previously suggested that type 1 diabetes (T1D) progression is associated with the loss of $T_{R3\text{-}56}$-dependent control of CTL effector functions[3] and, as commented by Serio et al., we highlighted the trend-increase of BM $T_{R3\text{-}56}$ cells, with concomitant reduction of cytotoxic T-cell activity in MDS.[2] The cytofluorimetric approach allows, in MDS, the evaluation of immune profile in BM, the microsite in which deranged precursor/s maturation takes place; thus, the possibility that the analysis of $T_{R3\text{-}56}$ might contribute to improve homogeneity of the diagnostic framing for MDS patients in whom an immune-mediated etiopathogenesis is conceivable, has to be also considered.[4–7]

Deranged activation and clonal expansion of the BM CTL represent a key element in the MDS pathogenesis.[2,4–7] In very-low/low-risk MDS patients, activated CTL and a pro-inflammatory environment contribute to impairment of polyclonal haematopoiesis, fostering the selection of dysplastic clones and their escape from immune control. Conversely, an immunosuppressive environment could disable CTL functions and favour the expansion/progression of dysplastic clones in the advanced stages of MDS.[2,4–7] In very-low/low-risk MDS subjects, the inverse correlation between BM $T_{R3\text{-}56}$ amount and BM CTL activation and expansion[2] suggest the possible participation of defective control of CTL effectors by the $T_{R3\text{-}56}$ subset in immune-mediated mechanisms involved in the emergence of dysplastic clones, as proposed for the Treg subset.[5] Mature granulocytes are significantly reduced in high-risk compared to low-risk MDS. Thus, the observation that the BM mature granulocytes frequency is inversely correlated with BM $T_{R3\text{-}56}$,[1] intriguingly draws attention to the role of this regulatory subset in the etiopathogenesis and diagnosis of MDS.

AUTHOR CONTRIBUTIONS

All the authors wrote the manuscript and provided substantial contribution to the manuscript review and final approval.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Valentina Rubino[1]
Stefania Leone[2]
Flavia Carriero[3]
Fabrizio Pane[2]
Giuseppina Ruggiero[1]
Giuseppe Terrazzano[3]

[1]*Dipartimento di Scienze Mediche Traslazionali, Università di Napoli "Federico II", Naples, Italy*
[2]*Divisione di Ematologia, Dipartimento di Medicina Clinica e Chirurgia, Università di Napoli "Federico II", Naples, Italy*
[3]*Dipartimento di Scienze, Università della Basilicata, Potenza, Italy*

Correspondence
Giuseppina Ruggiero, Università di Napoli "Federico II" Dipartimento di Scienze Mediche Traslazionali, Via Pansini,5 - 80131 Napoli, Italy.
Email: giruggie@unina.it

ORCID

Giuseppina Ruggiero https://orcid.org/0000-0002-8975-6001

REFERENCES

1. Serio B, Bertolini A, Gorrese M, et al. Persistent decreased bone marrow CD3+CD56+ T lymphocytes are inversely associated with mature granulocytes in myelodysplastic syndromes. *Eur J Haematol*. 2022;XX:XX-XXX.
2. Leone S, Rubino V, Palatucci AT, et al. Bone marrow CD3+CD56+ regulatory T lymphocytes (TR3-56 cells) are inversely associated with activation and expansion of bone marrow cytotoxic T cells in IPSS-R very-low/low risk MDS patients. *Eur J Haematol*. 2022;109(4):398-405. doi:10.1111/ejh.13822
3. Terrazzano G, Bruzzaniti S, Rubino V, et al. T1D progression is associated with loss of CD3+CD56+ regulatory T cells that control CD8+ T cell effector functions. *Nat Metab*. 2020;2(2):142-152. doi:10.1038/s42255-020-0173-1
4. Winter S, Shoaie S, Kordasti S, Platzbecker U. Integrating the "Immunome" in the stratification of myelodysplastic syndromes and future clinical trial design. *J Clin Oncol*. 2020;38(15):1723-1735. doi:10.1200/JCO.19.01823
5. Giovazzino A, Leone S, Rubino V, et al. Reduced regulatory T cells (Treg) in bone marrow preferentially associate with the expansion of cytotoxic T lymphocytes in low risk MDS patients. *Br J Haematol*. 2019;185(2):357-360. doi:10.1111/bjh.15496
6. Glenthøj A, Ørskov AD, Hansen JW, Hadrup SR, O'Connell C, Grønbæk K. Immune mechanisms in myelodysplastic syndrome. *Int J Mol Sci*. 2016;17(6):944-957. doi:10.3390/ijms17060944
7. Komrokji RS, Kulasekararaj A, Al Ali NH, et al. Autoimmune diseases and myelodysplastic syndromes. *Am J Hematol*. 2016;91(5):E280-E283. doi:10.1002/ajh.24333

How to cite this article: Rubino V, Leone S, Carriero F, Pane F, Ruggiero G, Terrazzano G. The potential etiopathogenetic role and diagnostic utility of $CD3^{+}CD56^{+}$ regulatory T lymphocytes in Myelodysplastic Syndromes. *Eur J Haematol*. 2023;1-2. doi:10.1111/ejh.13931