



Landscape of Immune Cell States and Ecosystems in Patients with Myelodysplastic Syndrome to Refine Prognostic Assessment and Predict Treatment Response.

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BACKGROUND. Biological heterogeneity in Myelodysplastic Syndromes (MDS) is partly driven by tumor-associated genomic lesions, but increasing evidence suggests that immune tumor microenvironment plays a significant role. However, dissecting these cell states and understanding their clinical relevance on a large scale remains challenging.

AIMS. In this study, conducted by i4MDS consortium, we characterized the immune ecosystems in a prospective cohort of MDS patients. Specific objectives were: 1) to analyze the contribution of immune ecosystems in refining patients' prognosis; 2) to define specific immune profiles to predict probability of response to hypomethylating agents (HMA); and 3) to develop a panel for immune monitoring in clinical practice.

METHODS. We prospectively studied 286 MDS patients at Humanitas Cancer Center Milan, Italy (evaluated at diagnosis and at multiple time points throughout the disease's natural history). T lymphocytes, Natural Killer (NK) and myeloid cells were evaluated in bone marrow (BM) and peripheral blood (PB) by extensive multi-color flow cytometry (PMID:38756352). Phenograph was used to analyze immune cell subset distribution and phenotype, while HDBSCAN identified clusters of patients with homogeneous immune features (defined as ecosystems). Each ecosystem was further characterized by integrating RNA-seq data from CD34+ progenitors. A DURAClone dry pre-formulated antibody panel was designed for implementation in the clinical work-up of patients.

RESULTS. We identified five immune ecosystems in the BM, each characterized by varying functionality and maturation stages of immune cells. Two clusters exhibited features of a healthy-like immune system: one with an expanded pool of immature and plastic Naïve T cells and CD56bright NK cells (referred to as "Naïve" ecosystem); and another enriched with memory T cells and functionally activated T and NK cells, termed "Memory, activated". The other three clusters showed progressive levels of immune dysfunction: one was characterized by overall immune inactivity, labeled as "Not activated" ecosystem; another one displayed a skewing of immune cell maturation towards advanced stages accompanied by immune suppression, and was named as "Terminally differentiated, immunosuppressed", while the final group was marked by T and NK cell exhaustion and suppression, identified as "Exhausted, immunosuppressed". Transcriptome analysis of CD34+ MDS progenitors revealed distinct inflammatory signatures and immunosuppressive pathways associated with immune dysfunction.

The immune ecosystems exhibited distinct probabilities of survival ($P<0.001$) and risk of leukemic transformation ($P<0.001$). Moreover, they were able to further refine the prognosis of patients stratified according to ICC/WHO 2022 categories ($P<0.001$) and IPSS-M risk groups ($P=0.001$). In a multivariable model adjusted for age, sex and IPSS-M score, the immune ecosystems retained an independent prognostic impact ($P<0.001$, HR 1.46). Furthermore, integrating immune cell profiles with molecular profiles improved the accuracy of predicting patient outcomes, the concordance index increasing from 0.76 (IPSS-M alone) to 0.84 (IPSS-M and immune ecosystems).

In patients treated with HMA, baseline immune ecosystems identified groups with different probabilities of achieving a complete response, ranging from $>75\%$ to $<10\%$ ($P<0.001$). Correcting immune dysfunction in responding patients is a long-term process; those who recovered from immune dysfunction had a significantly higher likelihood of achieving a long-term response (>24 months) compared to MDS with persistent immune dysfunction ($P<0.01$). At relapse, most patients exhibited severe immune dysregulation.

We observed that BM immune ecosystems can be easily detected by the analysis of PB cells, providing a proof of concept for a non-invasive immune monitoring approach. We therefore assessed the reliability of the designed dry pre-formulated antibody panel for clinical work-up in 75 MDS prospectively evaluated.

CONCLUSION. Immune ecosystems capture the clinical heterogeneity of MDS within existing subtypes and extend beyond genotypic classifications. These findings provide a systems-level resolution of the MDS microenvironment and identify opportunities for patient immune monitoring in clinical practice, thereby improving the clinical decision-making process.

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Kyowa Kirin	Consultancy and Honoraria
Lava Therapeutics	Consultancy and Honoraria
Medus	Consultancy and Honoraria
Notable	Consultancy and Honoraria
Orum	Consultancy and Honoraria
Pfizer	Consultancy and Honoraria
Rigel	Consultancy and Honoraria
Servier	Consultancy and Honoraria
Sumitomo	Consultancy and Honoraria
Syros	Consultancy, Honoraria and Research Funding
Takeda	Consultancy, Honoraria and Research Funding
Vinerox	Consultancy and Honoraria

Astex	Research Funding
Shattuck Labs	Research Funding

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Name of Organization	Type of relationship
Bristol Myers Squibb	Consultancy

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