Overcoming myelodysplastic syndrome progression after frontline therapy

Analyses of primary myelodysplastic syndrome (MDS) samples from the largest cohort ever evaluated demonstrate that the hematopoietic stem cell populations that originate MDS have distinct differentiation phenotypes and associated signaling pathways. These differences can be targeted with selective therapies that could benefit patients with progressed disease.

This is a summary of:
Ganan-Gomez, I. et al. Stem cell architecture drives myelodysplastic syndrome progression and predicts response to venetoclax-based therapy. *Nat. Med*. https://doi.org/10.1038/s41591-022-01696-4 (2022).

Published online:
3 March 2022

The question

Myelodysplastic syndromes (MDSs) arise from a small population of hematopoietic stem cells (HSCs) that can persist and expand through conventional therapies and contribute to disease progression[1]. In the past decade, genomic technologies coupled with mouse genetic studies have improved understanding of the genetic elements that drive MDS initiation and progression and how such elements functionally contribute to MDS pathobiology. MDSs are typically driven by multistep processes that affect a recurrent (that is, consistently found in different patients) set of genes or cytogenetic aberrations, leading to the clonal expansion of mutant HSCs over their normal counterparts[2].

The current standard of care for patients with MDSs remains therapy with hypomethylating agents (HMAs). Although HMA therapy results in some clinical improvement in>60% of patients, the disease eventually can become resistant to HMAs and progress to secondary acute myeloid leukemia (sAML). Patients who progress to sAML have a median survival of only 4–6 months[3,4].

The biological mechanisms that drive HMA therapy failure and disease progression in MDSs are unclear. Studies with advanced sequencing technologies have shown that cells in the HSC compartment drive MDS progression[5], but how they contribute to therapy failure and disease evolution is unknown.

The discovery

To investigate the mechanistic basis of MDS progression, we elucidated the biological properties of MDS HSCs and identified survival and proliferation pathways that are specific to distinct MDS HSC populations and that could be therapeutically targeted. We analyzed the HSC compartment in ~300 bone marrow (BM) samples from patients with MDSs (before and after first-line therapy with HMAs) by using multi-omics analyses of highly purified hematopoietic stem and progenitor cell (HSPC) populations. We characterized the immunophenotypic profile of the HSPC compartment in a cohort of 123 BM samples isolated from untreated patients with MDS. We stratified the MDS samples into two main groups. Compared with the differentiation pattern of BM samples from age-matched healthy donors, the BM samples of one of the MDS groups had an abnormal differentiation pattern characterized by an increased frequency of common myeloid progenitors (CMPs) within the myeloid hematopoietic progenitor cell (MyHPC) compartment (a 'CMP pattern' of differentiation). By contrast, the BM samples of the other MDS group had an increased frequency of granulocytic–monocytic progenitors (GMPs) within the MyHPC compartment (a 'GMP pattern' of differentiation).

In both MDS types, MDS HSC populations in distinct differentiation states — long-term HSCs (LT-HSCs) in 'CMP pattern' MDS and lymphoid-primed multipotent progenitors (LMPPs) in 'GMP pattern' MDS — maintained the disease during treatment and expanded after HMA therapy failure, thereby driving disease progression. Furthermore, the expansion of each of these MDS HSC types at the time of progression depended on the selective activation of survival pathways mediated by BCL2 (in 'CMP pattern' MDS) and NF-κB (in 'GMP pattern' MDS). Pharmacologically inhibiting these pathways selectively depleted the respective MDS HSC types in vitro and decreased tumor burden in patient-derived xenograft models (Fig. 1). Consistent with these results, we observed a decrease in the number of LT-HSCs in patients with 'CMP pattern' MDS at the time of complete remission after therapy with the BCL2 inhibitor venetoclax, whereas the number of neither LT-HSCs nor LMPPs decreased in patients with 'GMP pattern' MDS. Patients with 'CMP pattern' MDS had a shorter cumulative time to complete remission and a longer relapse-free survival than that of patients with 'GMP pattern' MDS.

Future directions

Our study demonstrates that the cellular architecture of MDSs should be considered a biomarker for predicting the intrinsic vulnerabilities of the MDS HSCs that expand at progression and, therefore, could contribute to guiding the design or choice of specific therapeutic approaches targeting these cells, in the setting of anti-BCL2-based therapy.

However, in our study we did not assess the role of the immune system in determining the clinical outcomes of patients given venetoclax-based therapy. Further follow-up studies will need to clarify whether the immune system contributes to disease remission, thereby explaining why 'GMP pattern' MDS eventually responds to venetoclax. These studies may open future questions to be addressed to fully elucidate the disease pathophysiology, overcome MDS progression and improve the survival of patients.

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EXPERT OPINION

"Understanding MDS remains challenging — this is a heterogeneous cancer whose pathogenesis includes stem cell damage/attrition, clonal selection of cells with mutations in different oncogenes and tumor suppressors, and an abnormal, inflammatory bone marrow microenvironment. This study, which provides new insights into stem and progenitor cell populations and their behavior in a large cohort of patients with MDS, will attract much interest in the field, raising interesting questions for follow-up studies." **Kevin Shannon, University of California San Francisco, San Francisco, CA, USA**.

FIGURE

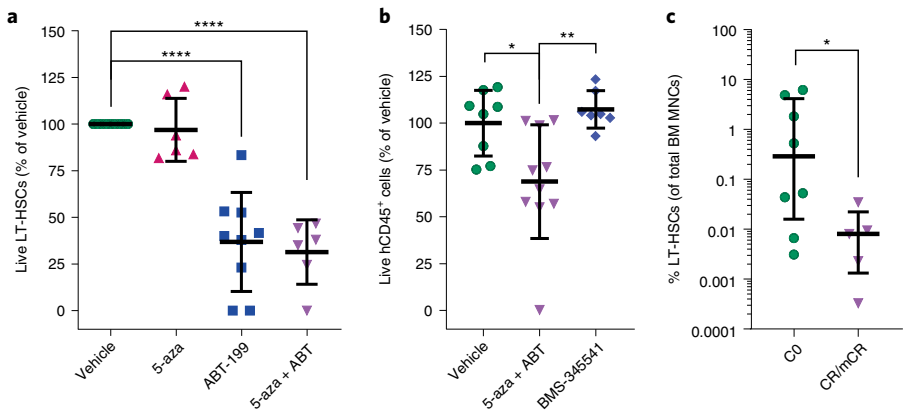

Fig. 1 | 'CMP pattern' MDS HSCs respond to venetoclax. a, LT-HSCs from patients with 'CMP pattern' MDS and blast progression after in vitro treatment with the HMA 5-azacytidine (5-aza), venetoclax (ABT-199, ABT) or both. **b**, Human cells in the BM of xenografts of a 'CMP pattern' MDS sample with blast progression. BMS-345541, an NF-κB inhibitor. **c**, BM mononuclear cell (MNC) frequencies of LT-HSCs from patients with 'CMP pattern' MDS and blast progression, before venetoclax (cycle 0 (C0)) and at the time of hematological remission (complete remission/marrow complete remission (CR/mCR)).

BEHIND THE PAPER

After I joined the Department of Leukemia at the MD Anderson Cancer Center in 2014, Dr. Garcia-Manero, the chief of the MDS section, challenged me to ask (and then answer) the right questions to improve the survival of patients with MDSs. Irene Ganan-Gomez joined me as a postdoctoral fellow, bringing her precise scientific insights, and in 2016, the team began this study on MDS progression.

In 2019, Irene and I suddenly lost our fathers and had a difficult time continuing this work. Then, the SARS-CoV-2 pandemic happened. The laboratory was closed for 3 months, and then access was restricted to a few hours a day in shifts. For 4 months, I processed samples in the morning, and Irene worked in the afternoon.

This manuscript is for all committed scientists who work tirelessly despite life's challenges with the hope of helping to cure cancer. It is also dedicated to the memory of our fathers. **S.C.**

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FROM THE EDITOR

"In this work by Irene Ganan-Gomez and colleagues, the investigators did an incredibly exhaustive analysis of samples from patients with MDSs and were able to pinpoint the biological mechanisms that are responsible for treatment failure. Taking their discoveries one step further, they identified a therapy combination that is clinically effective and has a great potential to improve the outcomes of patients in whom current standard therapies have failed." **Editorial team**, ***Nature Medicine***