Establishing a Platform for Profiling Drug Sensitivity of Circulating Myeloma Cells

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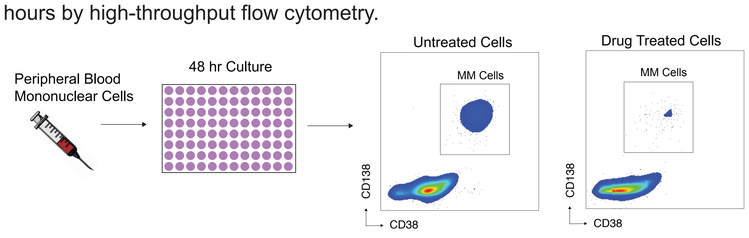
Background

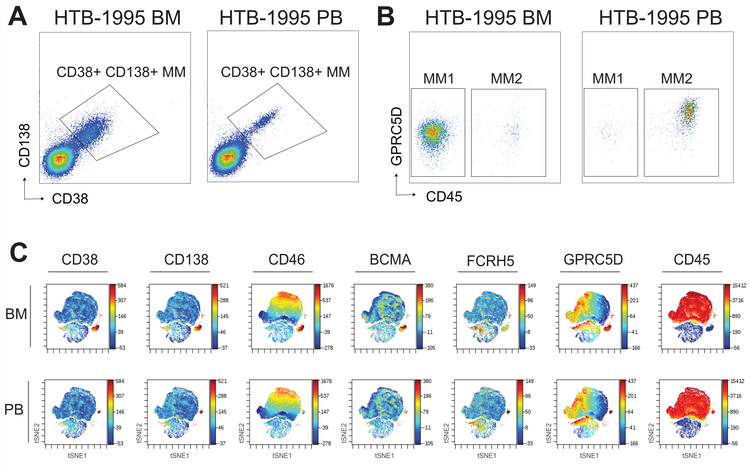
Multiple myeloma (MM) is an incurable plasma cell malignancy. Patients cycle through multiple lines of therapy and repeated relapses until ultimately succumbing to their disease. Although treatment options have greatly improved, there remains an unmet need for a platform to inform personalized treatment decisions. To address this, we previously reported an assay termed Myeloma Drug Sensitivity Testing (My-DST), which measures ex vivo viability of myeloma cells from patient-donated bone marrow (BM) samples and produces a read-out that correlates well with clinical responses. However, bone marrow biopsies are invasive and less commonly done at each relapse; thus, assaying peripheral blood (PB) offers a more accessible and routine alternative. Herein, we have adapted My-DST into a blood-based format to measure drug responses in circulating myeloma cells.

Methods

Mononuclear cells were isolated from patient-donated samples using Ficoll density gradient centrifugation. BM and PB samples were processed and ran in parallel. Primary myeloma cells in mononuclear cell culture were incubated in a 48-well plate in triplicate with clinically-available drugs, including proteosome inhibitors (PIs), immunomodulatory drugs (IMiDs), and CD38 monoclonal antibodies (mAbs). The change in myeloma cell viability was measured at 48 hours by high-throughput flow cytometry.

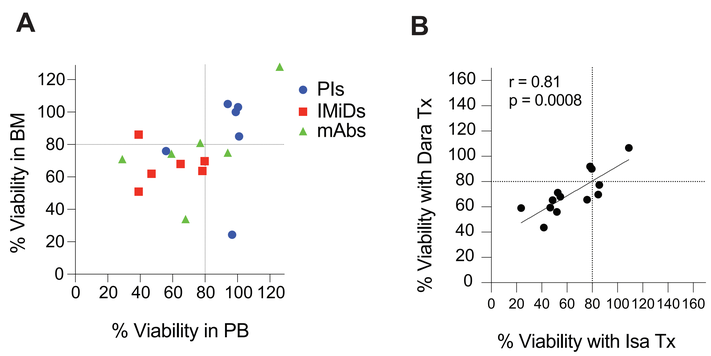


Similar Populations in Different Abundance



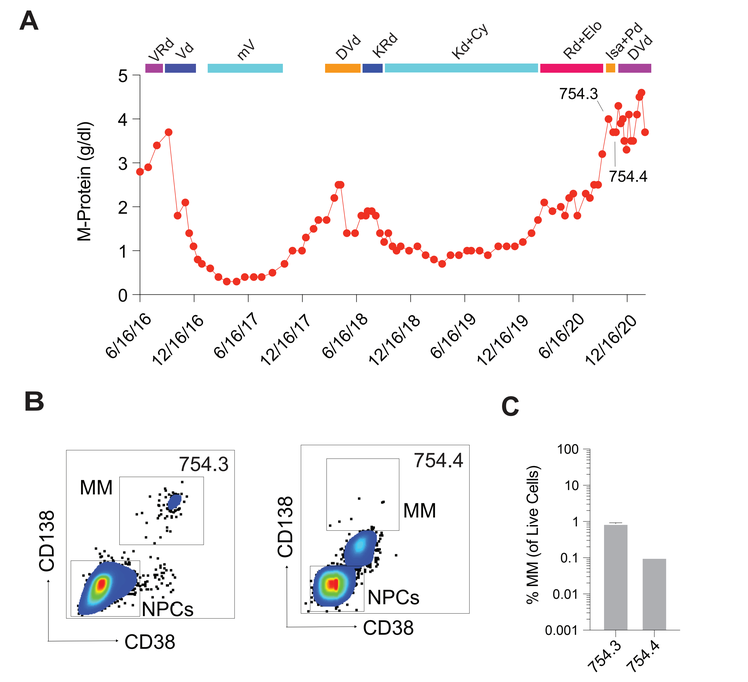
A) Representative flow plot for matched BM and PB from a multiple myeloma patient. **B)** Gating from the previous MM gate, showing 2 subpopulations named MM1 and MM2.The subpopulations are CD45+ and CD45- respectively, but have different abundance in the BM and PB. **C)** tSNEs showing marker expression for all live cells, including the MM1 and MM2 subpopulations.

High Correlation in Drug Sensitivity



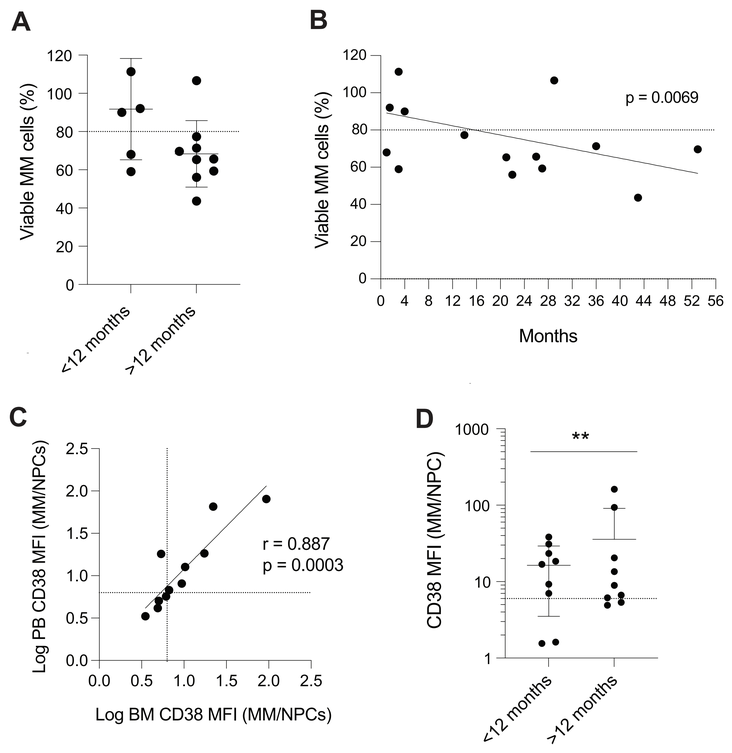
A) Normalized viability of MM cells in paired BM and PB samples from the same patients showing correlation between resistance and sensitivity of the combined drug classes. **B)** Normalized viability of MM cells in PB samples showing significant correlation of drug sensitivity between the two CD38 monoclonal antibodies, Daratumumab and Isatuximab.

Measuring MM Over Time



A) Monoclonal (M) protein levels and sequential lines of therapy shown over disease course for patient, HTB-0754. Timepoint 754.3 occurred at relapse. Timepoint 754.4 occured after treatment with Isatuximab. **B)** Flow plots showing decrease in myeloma population after treatment. **C)** Bar graph showing decrease in %MM population out of all live cells.

Antigen Expression and Daratumumab Treatment



A) Normalized viability of MM cells grouped by months post-Dara. **B)** Normalized viabilty of MM cells over time since last Dara treatment. **C)** CD38 MFI from matched BM and PB samples. **D)** CD38 MFI grouped by months post-Dara.

Conclusions and Future Directions

- MM in the BM and PB have similar populations that differ in relative abundances.
- My-DST PB correlates well with BM drug sensitivity when compared in paired samples from the same patient and timepoint.
- Serial sampling shows differences in the myeloma cell population when monitored over cycles of clinical treatment.
- Antigen expression, such as CD38 and BCMA, is measurable on myeloma cells in the peripheral blood.

Future directions include testing if this rapid functional assay could complement current clinical testing and help guide clinical decision making.

Acknowledgments

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