Bone marrow adipose tissue influences response to treatment and metabolism of multiple myeloma cells

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Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal expansion of malignant plasma cells within the bone marrow (BM). The disease progression is largely influenced by the bone marrow microenvironment (BMM). Bone marrow adipocytes (BMAds) are one of the most abundant cells in the BM, suggesting they might play a role in disease course. We have recently described that bone marrow adipose tissue (BMAT) contains a higher percentage of MM cells. Our aim was to investigate whether these "fat-associated" MM cells differ from the "aspirate-associated" MM.

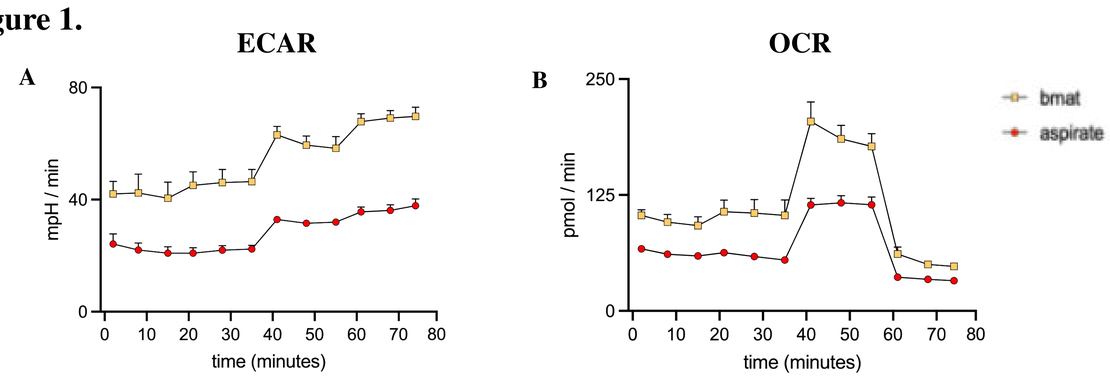
Materials and Methods

We isolated BMAT from aspirates of precursor stage (MGUS), newly diagnosed and follow-up MM patients and non-tumor controls. This BMAT fraction was then enzymatically digested to create a single-cell suspension, followed by red blood cell lysis. We then **A)** measured metabolism; **B)** compared proliferation rates of fat-associated vs aspirate-associated plasma cells; and **C)** compared the responses to conventional anti-MM drugs (bortezomib, thalidomide, melphalan, dexamethasone).

Results

We performed Seahorse assays to assess the metabolic profile of the two fractions. We found that cells derived from the BMAT exhibit a higher glycolysis (**Fig1A**) and oxidative phosphorylation (**Fig1B**) compared to the cells from the aspirate, indicating enhanced metabolic activity of cells in the vicinity of BMAds.

Figure 1.



We also performed Ki67 flow cytometric staining (**Fig2**), which revealed a lower percentage of proliferating fat-associated plasma cells in non-tumor controls but a higher percentage in MGUS. In NDMM and follow-up samples we observed mixed results (**Fig3**).

Figure 2.

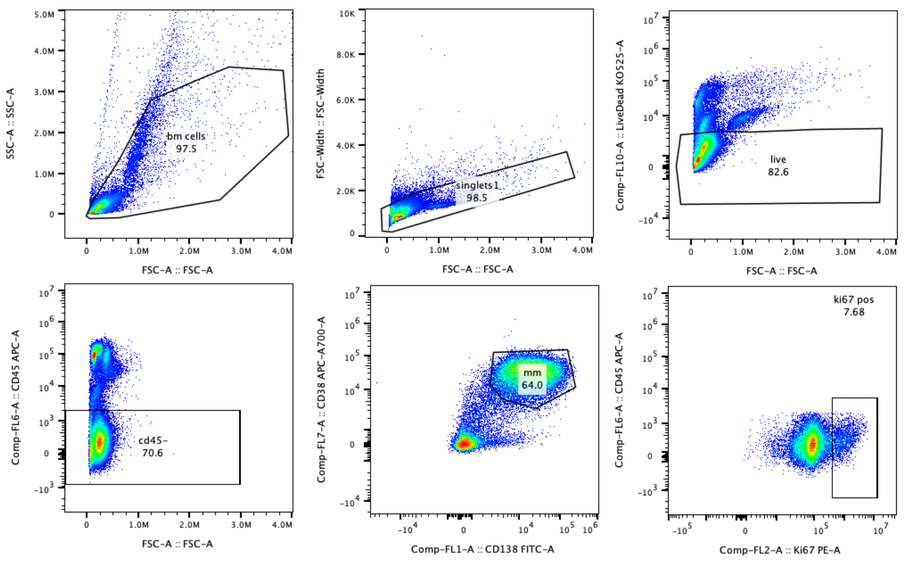
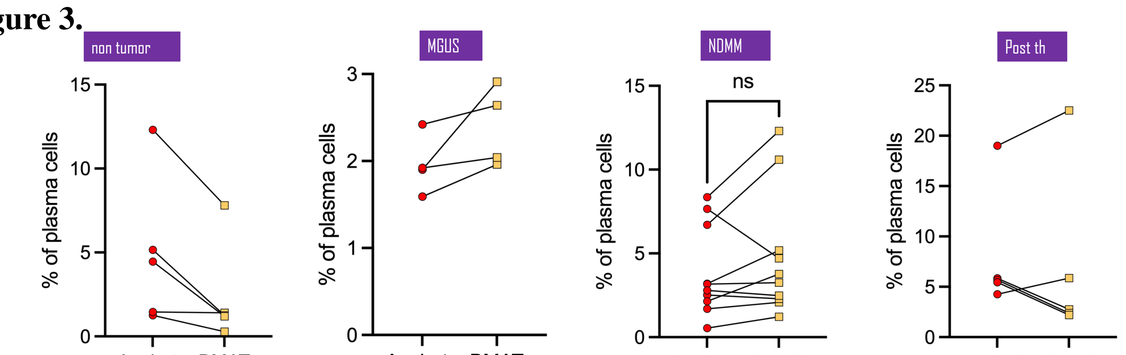
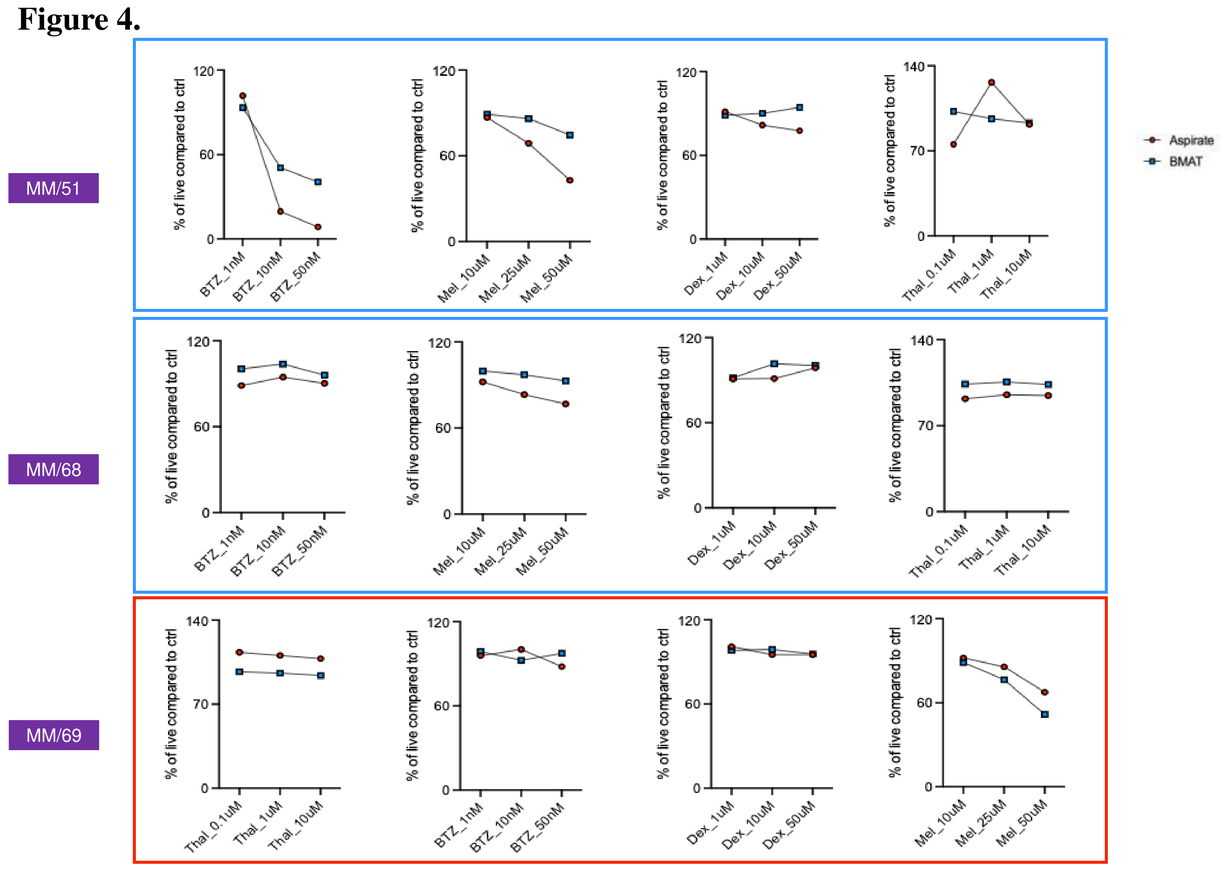


Figure 3.



After the 4 hours treatment we found that in a subset of patients BMAT-associated MM cells responded less to drugs compared to aspirate-associated MM (MM/58 and MM/51, **Fig4**). Meanwhile, in one patient it had the opposite effect (MM/69, **Fig4**).

Figure 4.



Conclusions

Our data suggests that the BMAT might act as a supportive niche for MM by influencing MM cell metabolism, proliferation, and response to therapy. We plan to perform transcriptomic studies and *in vivo* mouse experiments to identify the exact molecular interactions between BMAds and MM cells.

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