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Inhibiting Fatty Acid Binding Protein Family Members Decreases Multiple Myeloma Cell Proliferation Through Effecting the myc Pathway

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FABP inhibition leads to increased survival of myeloma bearing mice and decreased cell growth by inhibiting MYC signaling

Inhibiting fatty acid binding protein family members decreases multiple myeloma cell proliferation through effecting the myc pathway

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Introduction

- Multiple myeloma (MM) is currently an incurable cancer of the plasma cells, and ultimately results in only 53% of patients surviving after 5 years.
- FABP signaling is instrumental in various cancers leading to tumorigenesis, metastasis, and poor prognosis
- FABP5 is the only family member to display a strong dependency in hundreds of cancer cell lines according to the Cancer Dependency Map database (Broad Institute).

Methods

- Using OncoMine, the Zhan et al. dataset (GSE132604) was analyzed for FABP5 expression in patient MM cells and analyzed using Graphpad Prism.
- MM patient cells were fixed and permeabilize prior to staining with CD38 (Biolegend), DAPI and FABP5/secondary AF647.
- Myeloma cell number was measured using a bioluminescence imaging (BLI) assay, Cell Titre Glo, or RealTime Glo and measured on a GLOMAX microplate reader.
- Eight-week old female Scid-beige mice were inoculated tail vein with 5 million Luc+MM1S cells. Next day, 5 mg/kg BMS309403, 1 mg/kg SBFI-26, and the combination were injected IP and continued 3x weekly for the duration of the study. BLI imaging started on day 12 and continued 2x weekly.
- RNA sequencing was performed on MM1S samples that were exposed to vehicle, 50 μM BMS, SBFI or the combination for 24 hours. Sequencing was completed by VIGR to receive a list of counts per million and differentially expressed genes for each treatment group. Data was then submitted to Morpheus (Broad Institute) for heatmaps.

Results

- Primary patient myeloma cells that contain a high level of FABP5 is indicative of poor overall survival.
- Most human and mouse myeloma cell lines have a dose dependent response to FABP inhibitors BMS309403 (BMS) and SBFI-26 (SBFI) after 72 hours of exposure.
- Immunodeficient mice inoculated with Luc+ MM1S cells have reduced tumor burden and increased survival when treated with 5 mg/kg BMS, 1 mg/kg SBFI or the combination compared to the vehicle treated cohort.
- RNA sequencing that the largest change in expression in the combination treatment was MYC, with similar trends in the single treatments.
- Downstream MYC regulated genes are also have decreased expression with treatment, with the combination exhibiting the greatest decrease among the treatment groups.

Discussion

- Myeloma is currently an incurable cancer, and ultimately results in all patients succumbing to the disease.
- While there has been an explosion in the amount of treatments in the past decade, all patients still relapse, demonstrating a need for new treatments
- Clinical data reveals that FABP5 levels are indicative to patient outcomes and that inhibition *in vivo* or *in vitro* of FABPs lead to decrease tumor growth and increased survival.
- This in part is due to decreased MYC signaling
- Creating new treatments against FABP5 that can be used in MM patients could extend patient survival.

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Graphs and Figures