Transcriptomic and Proteomic Analyses of Bone Marrow of Patients with Extramedullary Multiple Myeloma Reveals Key Proteins Associated with Transendothelial Migration

The 11th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

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INTRODUCTION

Extramedullary multiple myeloma (EMD) is a highly aggressive manifestation of multiple myeloma (MM) (1). It is characterized by the spread of malignant plasma cells outside the bone marrow microenvironment to distal organs and tissues (2,3). EMD is present at the time of diagnosis in 6-10% of patients; however, this increases to 13-26% in patients with disease progression and relapse (4). EMD is associated with poor prognosis and significantly reduced overall survival (OS) compared to MM confined to the bone marrow (4,5). Yet, the molecular mechanisms of how myeloma progresses to non-bone marrow components and how the immune microenvironment sustains EMD progression is poorly understood.

The aim of this study, is to use an integrated proteomic and transcriptomic approach to understand extramedullary multiple myeloma.

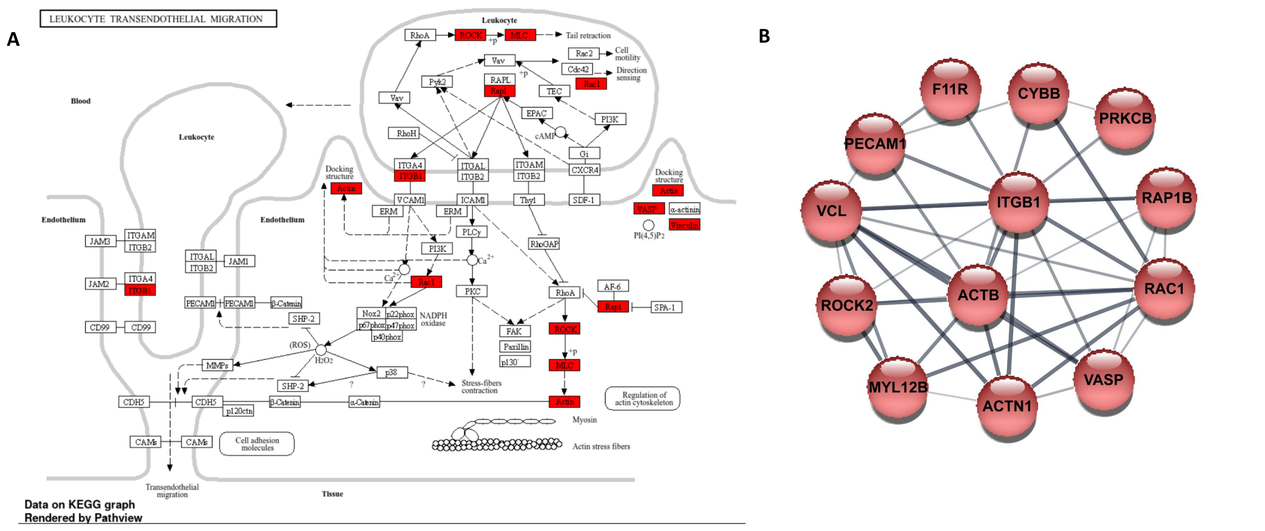
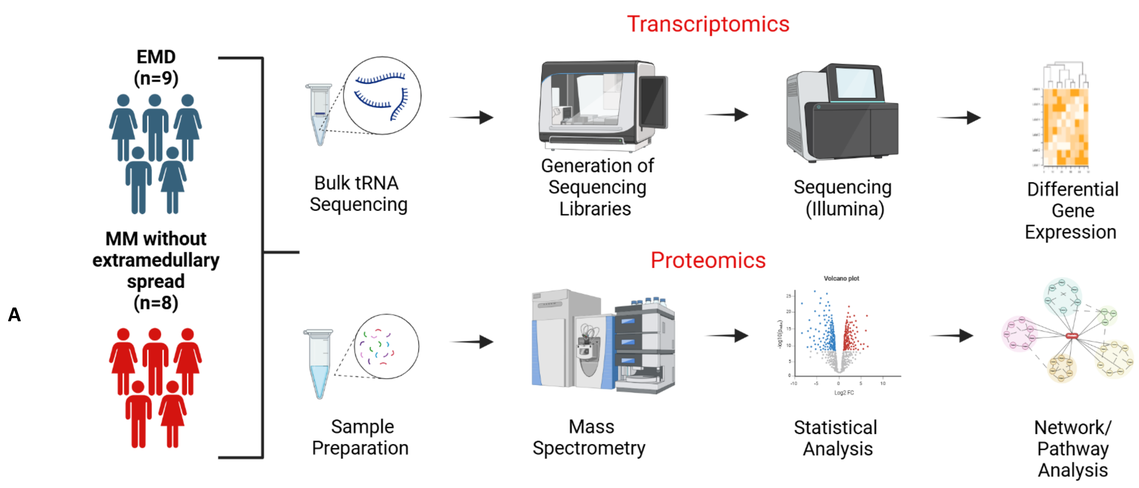


Fig 3: A) KEGG pathway highlighting proteins associated with leukocyte transendothelial migration. A number of proteins significantly increased in abundance in EMM, which are involved in the leukocyte transendothelial migration pathway are highlighted (red). **B)** Protein-protein interaction of proteins significantly increased in abundance in EMD in leukocyte transendothelial migration

METHODS



BMNCs were obtained from MM patients with (n=9, two samples from same patient at different time points) and without (n=8) extramedullary spread. Proteome Discover 2.5 (Thermo Scientific) was used for protein identification. Perseus (1.6.14) was used for statistical analysis.(FDR p-value ≤ 0.1, FC > 1.5. For total RNA analysis, libraries were prepared and sequenced using TruSeq Rapid PE Cluster Kit, TruSeq Rapid SBS (Illumina) and run on a NextSeq500.

RESULTS

PROTEOMICS

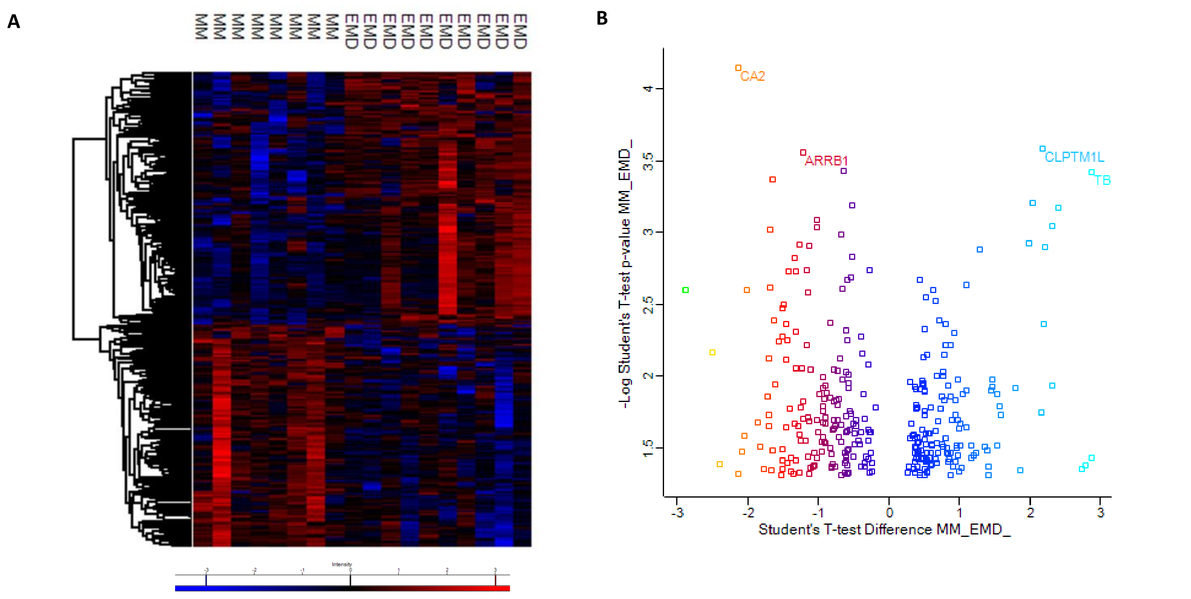


Fig 1: Proteomic Profile of **A)** Hierarchical Cluster profile of BMNCs. The colors from blue to red represent the relative protein levels between the two groups. **B)** Volcano plot representing statistically significant differentially abundant (SSDA) proteins in BMNCs between MM and EMD patients

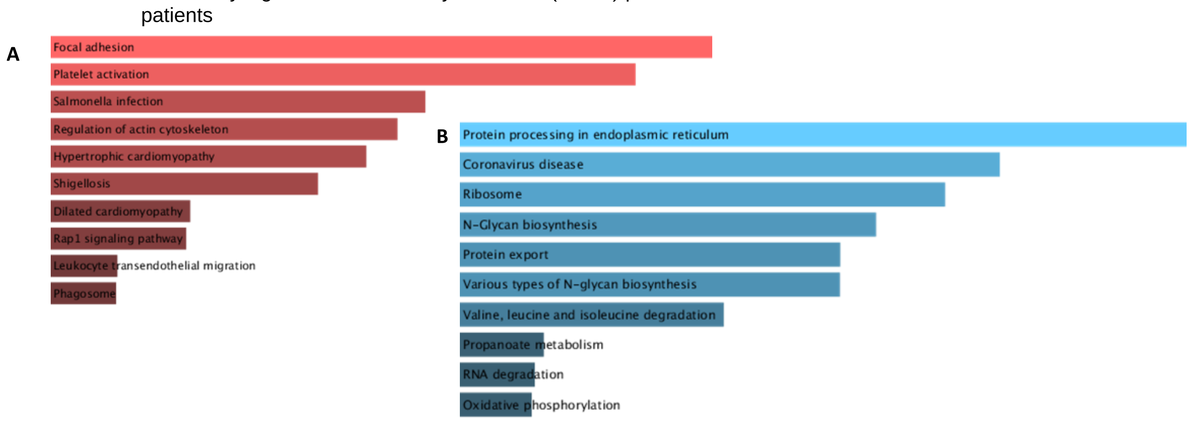


Fig 2: Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis of SSDA proteins found to be **A)** increased (red) and **B)** decreased (blue) in EMD MM. Proteins increased in abundance in EMD patients are enriched in pathways associated with platelet activation, cell-matrix adhesion and migration. Proteins decreased in abundance in EMD compared to MM are enriched in several metabolic pathways including amino acid metabolism and oxidative phosphorylation.

TRANSCRIPTOMICS

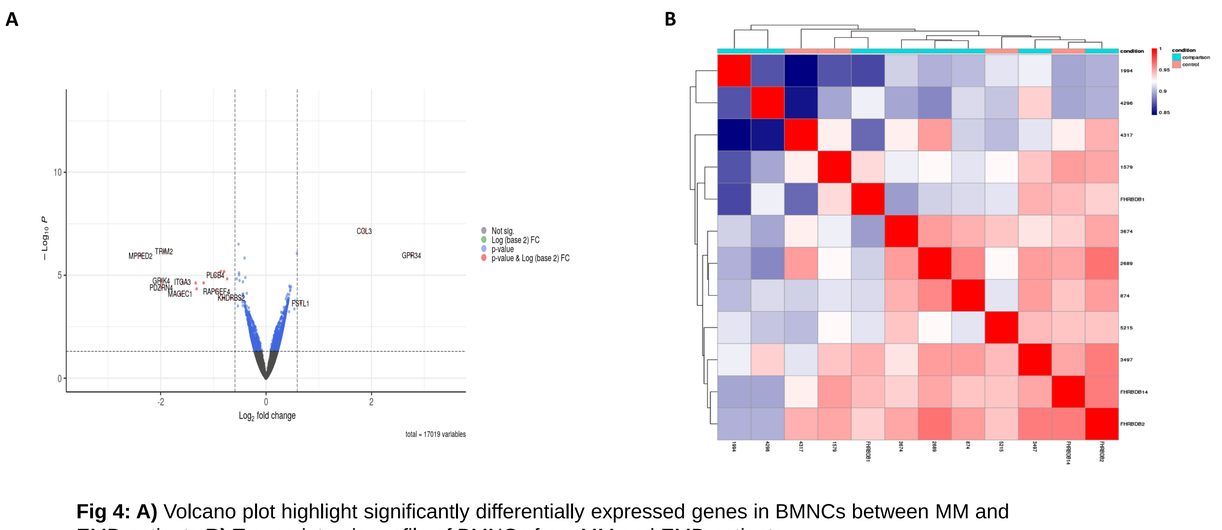


Fig 4: A) Volcano plot highlight significantly differentially expressed genes in BMNCs between MM and EMD patients **B)** Transcriptomic profile of BMNCs from MM and EMD patients

- Genes found to be increased in both transcriptomics and proteomics; S100A6 and TMEM183A
- S100A6 is highly expressed in MM patients and is associated with poor prognosis (6)
- TMEMs have been implicated in tumor progression (7)

CONCLUSION

- This study highlights distinct transcriptomic and proteomic profiles in MM patients with aggressive EMD, aiming to inform personalised therapies in future larger cohort studies.
- Cell adhesion, invasion, and migration proteins including those involved in leukocyte transendothelial migration were significantly increased in abundance in the EMD cohort highlighting their role in tumour dissemination
- Omics profiling identifies proteins linked to transendothelial migration, providing insight into how myeloma cells potentially evade the bone marrow microenvironment.
- Transcriptomic analysis revealed increased expression of S100 Calcium Binding Protein A6 in the EMD patient cohort, correlating with shorter overall survival and resistance to proteasome inhibitors such as bortezomib and carfilzomib.

REFERENCES

1.Bhutani, M., et al., *Extramedullary multiple myeloma. Leukemia, 2020.* ***34(1): p. 1-20.***

2. Beksac, M., et al., *A real world multicenter retrospective study on extramedullary disease from Balkan Myeloma Study Group and Barcelona University: analysis of parameters that improve outcome. haematologica, 2019.* ***105(1): p. 201.***

3. van de Donk, N., C. Pawlyn, and K.L. Yong, *Multiple myeloma. Lancet, 2021.* ***397(10272): p. 410-427.***

4. Bladé, J., et al., *Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer Journal, 2022.* ***12(3): p. 45.***

5. Bansal, R., S. Rakshit, and S. Kumar, *Extramedullary disease in multiple myeloma. Blood Cancer J, 2021.* ***11(9): p. 161.***

6. Bao, H.Y., et al., *[Expression Level of S100A6 mRNA in MM and Its Clinical Significance]. Zhongguo Shi Yan Xue Ye Xue Za Zhi, 2016.* ***24(5): p. 1466-1469.***

7. Schmit, K. and C. Michiels, *TMEM Proteins in Cancer: A Review. Frontiers in Pharmacology, 2018.* ***9.***

ACKNOWLEDGEMENTS

We are grateful to the Finnish Hematology Registry and Clinical Biobank (FHRB) and the patients in this study.

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