Bioinformatic Analysis of MARCO in Multiple Myeloma Bone Marrow Microenvironment

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INTRODUCTION

Multiple myeloma (MM) is characterized by an accumulation of malignant plasma cells (PCs) within the bone marrow (BM). The BM microenvironment supports the survival of malignant cells and is composed of cellular fractions that foster myeloma development and progression by suppressing the immune response. Despite major progress in understanding the biology and pathophysiology of MM, this disease is still incurable and requires aggressive treatment with significant side effects. MARCO (Macrophage Receptor with Collagenous Structure) is a class A scavenger receptor that plays a dual role in immunity by clearing pathogens and debris while also contributing to inflammation. In MM, MARCO-expressing macrophages are a component of tumor-associated macrophages (TAMs) that shape the tumor microenvironment. MARCO-positive macrophages exhibit two phenotypes that can either support or inhibit tumor growth. However, in most cases, large amounts of MARCO suppress the immune system and promote tumor growth by inhibiting anti-tumor processes. Previous research indicates that MARCO recruits other immunosuppressive cells, including regulatory T cells (Tregs), further weakening antitumor immune responses. MARCO-positive TAMs contribute to a supportive microenvironment for cancer by promoting the M2-like macrophage phenotype, which enhances tumor growth and metastasis through the secretion of cytokines and growth factors. To better understand the impact of MARCO in MM, bioinformatic analyses were utilized. The results indicate that MARCO-positive monocytes and macrophages increase in MM patients compared to healthy individuals. High MARCO expression correlates with a poor prognosis in MM patients. Future direction of research will focus on reprogramming MARCO-positive TAMs from the immunosuppressive M2 phenotype to the immune-activating M1 phenotype to strengthen the immune response against MM.

AIM

Utilizing bioinformatic analysis the roles of MARCO in Multiple myeloma bone marrow microenvironment, tumorigenesis and potential mechanisms.

METHOD

Gene expression data for MARCO from normal and multiple myeloma patients were obtained from the CZ CELLxGENE platform, while additional gene and protein expression data were sourced from the TCGA and GTEx databases. The UALCAN portal was used to analyze MARCO's RNA and protein expression, as well as its methylation levels. Mutation data for MARCO was retrieved from CBioPortal, and survival analysis for myeloma patients was performed using the Kaplan-Meier Plotter tool. Data showing MARCO's localization in the Golgi apparatus and vesicles were obtained from the Human Protein Atlas, and information on its expression across single-cell clusters in multiple myeloma was retrieved from TISCH 2.0.

RESULTS

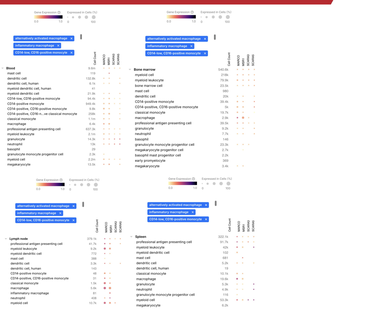


Fig. 1 Single-cell RNA-seq analysis reveals MARCO expression and gene expression distribution across various immune cell populations in blood, bone marrow, lymph node, and spleen

RESULTS

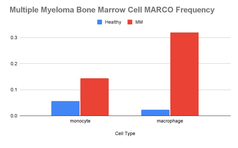


Figure 2. Comparison of MARCO Expression in Bone Marrow Cell Types: Healthy vs. Multiple Myeloma (Frequency Data)

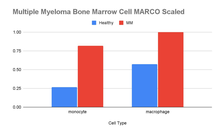


Figure 3. Scaled MARCO Expression in Bone Marrow Cell Types: Healthy vs. Multiple Myeloma

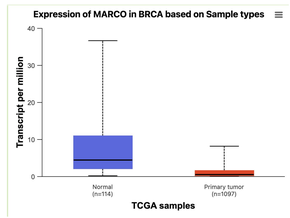


Figure 5. Differential Expression of MARCO in Normal vs. Primary Tumor Samples in Breast Cancer (BRCA)

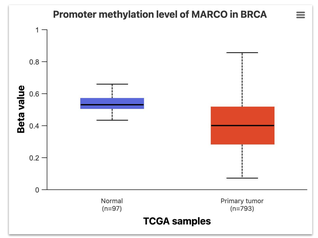


Figure 6. Promoter Methylation Levels of MARCO in Normal vs. Primary Tumor Samples in Breast Cancer (BRCA)

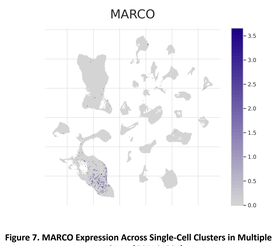


Figure 7. MARCO Expression Across Single-Cell Clusters in Multiple Myeloma (GSE161801)

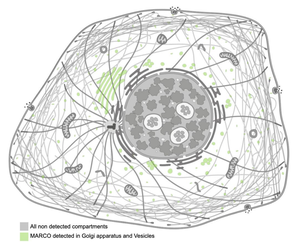
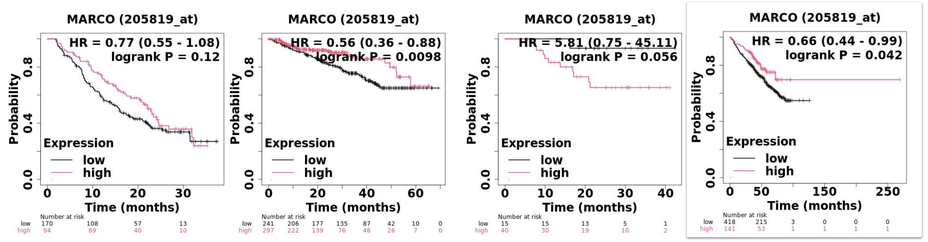


Figure 11. Subcellular Localization of MARCO: Detected in Golgi Apparatus and Vesicles



GSE: GSE9782
n=264
Treated With Bortezomib

GSE: GSE4202
n=538
Pre-Treatment

GSE: GSE57317
n=55
Previously Treated

GSE: GSE24080
n=559
Untreated

Figure 4. Higher MARCO expression in multiple myeloma is associated with a lower overall survival rate.

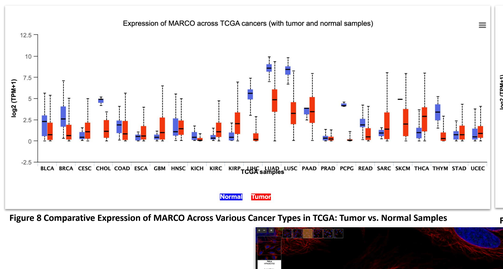


Figure 8 Comparative Expression of MARCO Across Various Cancer Types in TCGA: Tumor vs. Normal Samples

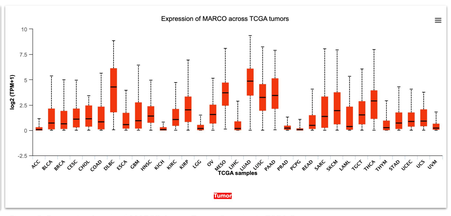


Figure 9. Expression Levels of MARCO Across Tumor Samples in TCGA Cancers

Figure 10. Domain Structure and 41 Mutation Distribution of MARCO Protein Across Pan Cancer Patients

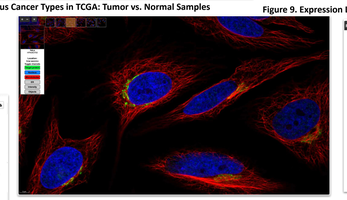


Figure 12. Immunofluorescence Staining of MARCO in HeLa Cells: Localization to the Golgi Apparatus

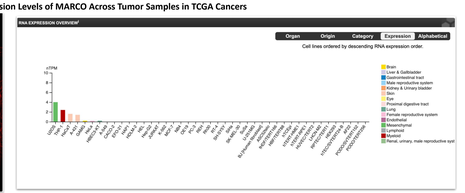


Figure 13. RNA Expression Levels of MARCO Across Various Human Cell Lines

CONCLUSIONS

1) The MARCO gene plays a key role in cancer progression and immune suppression in multiple myeloma and other cancer types.
2) Single-cell RNA-seq analysis (Figure 1) shows that MARCO is highly expressed in macrophages that create an immune-suppressive environment, particularly in alternatively activated and inflammatory macrophages, which contribute to tumor development.
3) In multiple myeloma, MARCO expression is significantly higher in bone marrow from patients compared to healthy individuals (Figures 2 and 3). This higher expression correlates with a worse prognosis and lower survival rates (Figure 4).
4) In breast cancer, MARCO is more highly expressed in normal tissues than in tumors (Figure 5), while tumor samples show lower promoter methylation (Figure 6), which increases MARCO activity in cancer progression.
5) Across different cancer types, MARCO shows variable expression between normal and tumor tissues (Figures 9 and 10), emphasizing its role in the tumor microenvironment.
6) Structural and mutation analysis (Figure 11) highlights MARCO's protein domain organization, providing insight into how its structure influences its function in cancer.
7) Subcellular localization show that MARCO is found in the Golgi apparatus and vesicles (Figure 8), with immunofluorescence staining in HeLa cells (Figure 12) confirming this localization.
8) RNA expression analysis across human cell lines (Figure 13) shows that MARCO expression varies by cell type.

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