1. BIOLOGY AND PRECLINICAL

INTERACTION BETWEEN MYELOMA AND BONE MARROW MESENCHYMAL STEM CELLS

H. Ahmed[1|2], J. Vorwerk[2], M. Hussein[2], P. Kumar Patnana[1|2], A. Kumar Rout[3], U. Guenther[3], N. Von Bubnoff[2], W. Mansour[4], C. Khandanpour[1|2]

[1]Department of Internal Medicine, Hematology and Oncology, University Medicine Oldenburg, Germany; [2]Department of Hematology and Oncology, University Hospital of Schleswig-Holstein, University of Lübeck, Germany and Universitäres Cancer Center Schleswig-Holstein, Germany; [3]Institute of Chemistry and Metabolomics, University of Lübeck, Germany; [4]University Medical Center Hamburg-Eppendorf, Oncology Center, Department for Radiotherapy and Radio-Oncology, Germany

https://doi.org/10.3324/haematol.2026.s2.14104

Introduction. Multiple myeloma (MM) is a malignancy of B-cells marked by excessive proliferation and accumulation of malignant plasma cells within the bone marrow (BM). Mesenchymal stromal cells (MSCs) are vital components of the BM microenvironment, facilitating interactions that influence disease progression and therapeutic resistance through cytokine secretion and direct cell-cell contact.

Objectives. MM remains an incurable disease so far. This study explores the unique role of BM-derived MSCs in MM, aiming to uncover key gene sets and signaling pathways in MSCs that contribute to MM pathogenesis, treatment response, and to identify potential therapeutic targets.

Methods. To investigate these dynamics, BM-MSCs were isolated from MM patients at diagnosis (MM-Act-MSC s) and in remission (MM-Rm-MSCs), as well as from patients with other malignancies (CTR-MSCs). Comparative analyses were performed using RNA sequencing, Western blotting, and functional assays assessing cellular proliferation, metabolic activity, DNA damage, and proteomic expression profiles.

Results. Our results indicate that MM-Act-MSCs promote MM cell line proliferation approximately threefold more effectively ($p<0.01$) than MM-Rm- and CTR-MSCs. Metabolic profiling revealed that MM-Act-MSCs exhibit elevated glycolytic activity and reduced oxidative phosphorylation compared to CTR-MSCs, suggesting a shift in metabolic programming associated with MM pathophysiology. Additionally, MM-Act-MSCs demonstrated increased DNA damage and reduced DNA repair capacity, as evidenced by immunofluorescence assays, implying a state of genomic instability that may influence MM cell support. Gene expression analysis highlighted significant enrichment of the PI3K-AKT-mTOR signaling pathway in MM-Act-MSCs relative to CTR-MSCs (NES = 1.75, $p<0.001$), suggesting a key role for this pathway in MM-associated MSC functionality. Proteomic validation further confirmed the upregulation of pathway components, including PI3Kα, AKT, phosphorylated AKT, and mTOR, in MM-Act-MSCs when compared to other MSC types ($p<0.05$). To test therapeutic relevance, we treated both MM-Act-MSCs and MM cell lines (MM.1S, SKMM2) with the PI3K inhibitor GDC-0941. This treatment attenuated PI3Kα, AKT, and mTOR signaling in both MSCs and MM cells, reducing MM cell proliferation when co-cultured with MM-Act-MSCs by 32–34% ($p=0.04$), suggesting a heightened therapeutic impact in the MM-BM microenvironment.

Conclusions. Our findings reveal functionally and molecularly distinct properties in MM-Act-MSCs compared to MM-Rm- and CTR-MSCs, highlighting their role in disease progression and response to therapy. The PI3K-AKT-mTOR axis emerges as a critical target within MM-Act-MSCs, underscoring the potential of PI3K inhibitors to disrupt the MM-BM niche interaction. This study advances our understanding of MSC contributions to MM and suggests that targeting MSCs may offer new avenues to improve patient outcomes by effectively mitigating MSC-mediated support of MM cells.