

iPSC-derived MSCs to study Multiple Myeloma stroma-interactions.

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## Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled growth of clonal plasma cells within the bone marrow, leading to severe bone damage and a complex tumor microenvironment. The interaction between MM cells and the bone marrow stroma plays a crucial role in pathophysiology of the disease, i.e. promoting MM cell growth and survival. Traditionally, primary stromal cells derived from patient samples are used to study MM-stroma interactions. However, these cells present notable challenges, such as limited availability and significant cellular heterogeneity, both within and across samples, making standardization difficult.

## Methods

In this study, we investigate the potential of using induced pluripotent stem cell (iPSC)-derived mesenchymal stromal cells (iMSCs) to replicate the supportive function of primary bone marrow stromal cells in promoting MM growth and drug resistance.

## Results

To address this, we developed an efficient protocol for generating iMSCs from iPSCs and validated their multipotency in vitro, along with their bone-forming capacity in vivo. Furthermore, when assessing their ability to support MM cell proliferation and survival, we found that these iMSCs can effectively promote MM cell growth and induce resistance to common MM drugs such as melphalan, carfilzomib, and pomalidomide. These effects were further amplified by the overexpression of interleukin-6 (IL-6).

## Conclusion

Taken together, our findings show that iMSCs can effectively replace primary stromal cells for studying MM-stroma interactions in vitro, offering a more standardized alternative. Additionally, their ease of genetic manipulation makes them a valuable tool for advancing research into the complex interactions between MM and the bone marrow microenvironment.