Rescuing Aged Mesenchymal Stem Cells by Exposure to a Young Extracellular Matrix
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Introduction

Bone marrow mesenchymal stem cells (MSCs) are capable of self-renewal and differentiation into multiple cell lineages including osteoblasts, chondrocytes, adipocytes, muscle cells, neurons and hepatocytes. The quantity and quality of MSCs decrease with aging, which is associated with the progressive failure of function of tissues and organs. Recently, we reported that in both mouse and human a native extracellular matrix (ECM) generated by bone marrow cells dramatically promoted MSC proliferation, preserved the stem cell properties, and enhanced their capacity for skeletogenesis (1;2). This led us to investigate whether culture of aged MSCs on such ECM could improve their number and quality. In particular, we wanted to take advantage of this established model to address whether the effect of age on MSC themselves (intrinsic theory), or changes to MSCs by the surrounding ECM (extrinsic theory) occurs, or both.

Materials and Methods

A cell-free ECM was prepared from cultured femoral marrow cells from either 3-month-old (young) or 18-month-old C57BL/6 mice (young-ECM, or old-ECM, respectively). The replication and osteogenesis of young or old MSCs maintained on young-ECM versus old-ECM as well as plastic were examined in vitro and in vivo. The detailed procedures have been previously described (1).

Results

The number of MSCs in marrow of old mice, as measured by their ability to form a colony of osteoblastic cells (CFU-OB), was 5-10% lower as compared to young mice (Fig.1). However, they failed to increase in number during 6 days of culture, as measured by a re-plating assay; whereas CFU-OB from young mice increased by 2.3 fold. When cultured on young-ECM for 6 days, the number of MSCs from young and old mice increased by ~16-, and ~13-fold, respectively (Fig.1). Furthermore, old as well as young MSCs pre-cultured on young-ECM formed the same amount of bone as determined by bone mineral density (BMD), which was ~ 2 to 3 times more than that formed by the cells pre-cultured on plastic or old-ECM (Fig.2). In contrast, defects in the self-renewal and bone formation capacity of old MSCs were not corrected by exposure to an old-ECM (Fig.1&2).

Discussion and Conclusions

Here, we propose for the first time a unique model to study the roles of MSC aging (cell intrinsic) and ECM or niche aging (cell extrinsic). Our studies revealed that defects in replication and bone formation capacity of aged MSCs were very remarkable. Importantly, this study indicates that aging negatively impacts the formation of an ECM that normally preserves MSC function, and MSCs from aged animals can be improved by culture on ECM made by stromal cells from young mice. We suggest that culture of aged MSCs on a young-ECM may optimize the effectiveness of autologous MSC administration for future therapeutic applications for aging-related diseases.

![Figure 1](image1.png)  Correction of a defect in the replication of MSCs from old mice by exposure to an ECM made by marrow stromal cells from young mice.

![Figure 2](image2.png)  Increased skeletal tissue formation by MSCs, from either young or old mice, cultured on young-ECM.

References


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Disclosures

Authors have nothing to disclose.