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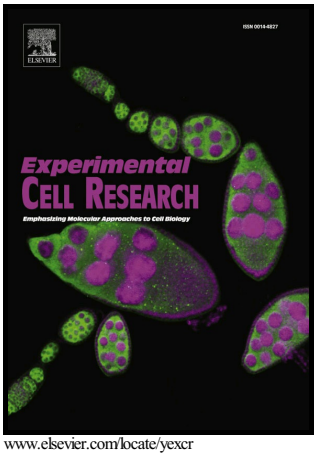

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Orthogonal Potency Analysis of Mesenchymal Stromal Cell Function During Ex Vivo Expansion

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Abstract

Adult bone marrow mesenchymal stromal cells (MSCs) have cross-functional, intrinsic potency that is of therapeutic interest. Their ability to regenerate bone, fat, and cartilage, modulate the immune system, and nurture the growth and function of other bone marrow hematopoietic stem/progenitor cells have all been evaluated by transplant applications of MSCs. These applications require the isolation and expansion scaled cell production. To investigate biophysical properties of MSCs that can be feasibly utilized as predictors of bioactivity during biomanufacturing, we used a low-density seeding model to drive MSCs into proliferative stress and exhibit the hallmark characteristics of *in vitro* aging. A low-density seeding method was used to generate MSCs from passages 1 to 7 to simulate serial expansion of these cells to maximize yield from a single donor. MSCs were subjected to three bioactivity assays in parallel to ascertain whether patterns in MSC age, size, and shape were associated with the outcomes of the potency assays. MSC age was found to be a predictor of adipogenesis, while cell and nuclear shape was strongly associated to hematopoietic-supportive potency. Together, these data evaluate morphological changes associated with cell potency and highlight new strategies for purification or alternatives to assessing MSC quality.

Keywords: Mesenchymal stromal cell; Aging; Cell morphology; Adipogenesis; Hematopoiesis: Immuno-suppression

Introduction

There are currently over 200 active mesenchymal stromal cell (MSCs) clinical trials for regenerative medicine and immunomodulatory applications (www.clinicaltrials.gov; keyword: mesenchymal stem cell). Bone marrow-derived MSCs have been a long standing cornerstone in cell therapy and contain a subpopulation of stem cells that possess the innate ability to repopulate connective tissue cells in the bone marrow (BM) cavity [1-4]. This adipogenic, osteogenic, or chondrogenic capacity, when induced *in vitro*[5], has led to orthopedic applications to replace or reconstruct tissue defects as a local injection. These stem cell-containing MSCs also support the bone marrow compartment through the nurture and trafficking of hematopoietic stem cells (HSCs) as well as their differentiated progeny [6-8]. This hematopoietic supportive function has been harnessed clinically through an MSC:bone marrow co-infusion to enhance the transplant

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