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Strategies to induce cardiac differentiation of Mesenchymal Stem Cells

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Introduction:

Loss of cardiomyocytes during myocardial infarction leads to decreased heart function. Replacing the injured myocardium with a muscle tissue created in vitro has gained increasing attention. Yet, the optimal cell source to engineer a functional and contractile cardiac tissue has to be defined. In this regards, mesenchymal bone marrow stem cells (MSCs) present numerous advantages: easy accessibility, large expansion capacity, high plasticity and aptitude to differentiate into cardiomyocytes. In the present study we investigated different strategies to induce the differentiation of rat MSCs into cardiac-like cells.

Methods:

Isolated from tibial and femoral rat bone marrow, MSCs were separated from hematopoietic stem cells by their capacity to adhere to plastic. MSCs were cultured for 14 days with 20% FBS and FACS analysis were performed. To induce their differentiation into cardiomyocytes, different strategies were evaluated: (1) chemical treatments with 5-azacytidin, TSA or ascorbic acid; (2) culture with cardiomyocytes (CM)-conditioned medium. Phenotype characterization was evaluated by immunostaining for specific cardiac proteins: cTnT, cMHC, alpha-actinin sarcomeric and titin, and by RT-PCR for specific transcription factors (GATA4, Nkx2.5) and structural proteins (cTnT, beta-MHC).

Results:

After 14 days, at least 98% of the cell population was positive for CD90, CD29, and CD44, negative for CD109, CD31, and about 40% were positive for CD45. Cells rapidly spread in culture and punctuated localization of alpha-actinin was detected by immunofluorescence in pseudopods and at the periphery of spreading cells. We detected an increased gene expression of cTnT, beta-MHC, desmin and Nkx2.5 after 4 weeks compared to initially seeded cells. There was no difference between non-treated cells, chemical and conditioned medium treatments. This expression decreased after 12 weeks. The immunostaining revealed only a weak presence of related proteins in a small number of cells.

Conclusions:

Our results showed that cardiac differentiation of MSCs was initiated independently of the treatments and concerned only a sub-population of the heterogeneous MSCs population. Further investigation will be
undertaken to define this sub-population with cardiac progenitor characteristics. Differentiation of cells toward cardiocytes was mainly observed at the gene levels. Additional stimuli such as mechanical stretch may be necessary to promote further cell differentiation and maturation.