

Comparison of Cardiomyogenic Potential of Amniotic Fluid Mesenchymal Stromal Cells Derived from Normal and Isolated Congenital Heart Defective Fetuses

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Abstract : Isolated Congenital Heart Defect (ICHHD) is the major cause of neonatal death worldwide among all forms of CHDs. A significant proportion of fetuses with ICHHD die in the neonatal period if no treatment is provided. Recently, stem cell therapies have emerged as a potential approach to ameliorate ICHHD in children. ICHHD is characterized by cardiac structural abnormalities during embryogenesis due to alterations in the cardiomyogenic properties of a pool of cardiac progenitors/ stem cells associated with fetal heart development. The stem cells present in the amniotic fluid (AF) are of fetal origin and may reflect the physiological and pathological changes in the fetus during embryogenesis. Therefore, in the present study, the cardiomyogenic potential of AF-MSCs derived from fetuses with ICHHD (ICHHD AF-MSCs) has been evaluated and compared with that of AF-MSCs of structurally normal fetuses (normal AF-MSCs). Normal and ICHHD AF-MSC were analyzed for the expression of cardiac progenitor markers viz., stage-specific embryonic antigen-1 (SSEA-1), vascular endothelial growth factor 2 (VEGFR-2) and platelet-derived growth factor receptor-alpha (PDGFR- α) by flow cytometry. The immunophenotypic characterization revealed that ICHHD AF-MSCs have significantly lower expression of cardiac progenitor markers VEGFR-2 ($0.14\% \pm 0.6$ vs. $48.80\% \pm 0.9$; $p < 0.01$), SSEA-1 ($70.86\% \pm 2.4$ vs. $88.36\% \pm 2.7$; $p < 0.01$), and PDGFR- α ($3.92\% \pm 1.8$ vs. $47.59\% \pm 3.09$; $p < 0.01$) in comparison to normal AF-MSCs. Upon induction with 5'-azacytidine for 21 days, ICHHD AF-MSCs showed a significantly down-regulated expression of cardiac transcription factors such as GATA-4 (0.4 ± 0.1 vs. 6.8 ± 1.2 ; $p < 0.01$), ISL-1 (2.3 ± 0.6 vs. 14.3 ± 1.12 ; $p < 0.01$), NK-x 2-5 (1.1 ± 0.3 vs. 14.1 ± 2.8 ; $p < 0.01$), TBX-5 (0.4 ± 0.07 vs. 4.4 ± 0.3 ; $p < 0.001$), and TBX-18 (1.3 ± 0.2 vs. 4.19 ± 0.3 ; $p < 0.01$) when compared with the normal AF-MSCs. Furthermore, immunocytochemical staining revealed that both types of AF-MSCs could differentiate into cardiovascular lineages and express cardiomyogenic, endothelial, and smooth muscle actin markers, viz., cardiac troponin (cTNT), CD31, and alpha-smooth muscle actin (α -SMA). However, normal AF-MSCs showed an enhanced expression of cTNT ($p < 0.001$), CD31 ($p < 0.01$), and α -SMA ($p < 0.05$), compared to ICHHD AF-MSCs. Overall, these results suggest that the ICHHD-AF-MSCs have a defective cardiomyogenic differentiation potential and that the defects in these stem cells may have a role in the pathogenesis of ICHHD.

Keywords : amniotic fluid, cardiomyogenic potential, isolated congenital heart defect, mesenchymal stem cells

Conference Title : ICCR 2022 : International Conference on Cardiac Regeneration

Conference Location : Barcelona, Spain

Conference Dates : December 15-16, 2022