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

Authors : Manali Jain, Neeta Singh, Raunaq Fatima, Soniya Nityanand, Mandakini Pradhan, Chandra Prakash Chaturvedi

Abstract : Isolated Congenital Heart Defect (ICHD) is the major cause of neonatal death worldwide among all forms of CHDs. A significant proportion of fetuses with ICHD die in the neonatal period if no treatment is provided. Recently, stem cell therapies have emerged as a potential approach to ameliorate ICHD in children. ICHD 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 ICHD (ICHD AF-MSCs) has been evaluated and compared with that of AF-MSCs of structurally normal fetuses (normal AF-MSCs). Normal and ICHD 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 ICHD AF-MSCs have significantly lower expression of cardiac progenitor markers VEGFR-2 (0.14% ± 0.6 vs.48.80% ± 0.9; p <0.01), SSEA-1 (70.86% ± 2.4 vs. 88.36% ±2.7; p <0.01), and PDGFR-α (3.92% ± 1.8 vs. 47.59% ± 3.09; p <0.01) in comparison to normal AF-MSCs. Upon induction with 5'-azacytidine for 21 days, ICHD 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 ICHD AF-MSCs. Overall, these results suggest that the ICHD-AF-MSCs have a defective cardiomyogenic differentiation potential and that the defects in these stem cells may have a role in the pathogenesis of ICHD.

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