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Placental Cdx2 cells and cardiac regeneration

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Introduction: Placenta is an easily available and rich source of multipotent cells. We previously reported that fetal-placental cells "home" to injured maternal hearts with 40% of these cells expressing Cdx2.

Hypothesis: Placental Cdx2 cells could be a novel source for cardiac repair.

Methods: Fetal-derived Cdx2 cells were labeled with EGFP using a cre-lox strategy wherein female virgin B6; 129S6-gt (ROSA) 26Sor<tm1 (CAG-tdTomato*,-EGFP*) Ees>/J43 mice were crossed with male B6. Cg-Tg (Cdx2-cre) 101Erf/J mice. Myocardial infarction (MI) was induced in pregnant mice at mid-gestation. Maternal hearts were analyzed 5 weeks post-MI for Cdx2-derived cardiomyocytes. Cdx2 cells from end-gestation placenta were assayed for cardiac differentiation in vitro. Proteomic analysis, vascular differentiation and immune profiling were carried out and live cell imaging was done to capture spontaneous beating. Additionally, male WT mice was subjected to MI followed by MRI to confirm MI. 1 week post-MI, the test mice received 1 million Cdx2 cells and control mice received equal volume of PBS via tail vein. MRI was repeated 1 and 3 months later to assess the cardiac function.

Results: Cdx2 cells migrated to injured maternal hearts and differentiated into cardiomyocytes. Additionally, Cdx2 cells from the late placenta differentiated into spontaneously beating cardiomyocytes in vitro and expressed cTnt, α-actinin and Cx43. The cells also differentiated into vascular cells indicative of multipotentiality. Proteomic analysis identified homing/survival signaling in Cdx2 cells compared to ES cells. Cdx2 cells further displayed a low expression of immune molecules, suggesting they can evade host immune surveillance. MRI analyses after 1 and 3 months showed a significant increase in ejection fraction (EF) in the cell-treated group [deltas: ctrl 0.355±3.421 vs test 17.18±1.05 (**p=.0093) in 1mo and ctrl 3.247±5.09 vs test 19.31±2.59 (*p=.045) in 3 mo]

Conclusion: We demonstrate for the first time that Cdx2 cells from placenta undergo trafficking upon cardiac injury to form cardiomyocytes. Our data imply that placental Cdx2 cells may represent a powerful new therapeutic strategy for cardiac repair.

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